Etat de choc septique Réfractaire

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Medical ICU
European Georges Pompidou Hospital,
APHP, Paris

Conflicts of interest:

- Advisory Board: F4-Pharma, FindImmune, Lascco Getinge

- PHRC *A0R19017*

- PHRC N-23-042

60 ans. Tabagisme 40 PA + éthylisme chronique +/- Cirrhose
Pneumonie aiguë communautaire-> urgences
O_2, ATB par claforan
H12: Dégradation respiratoire puis hémodynamique
IOT/VM, ATBthérapie par Tazocilline+ Rovamycine
Optimisation volémie, noradrénaline , HSHC+Fludro.
HFVVC
Dobutamine FeVG 30%, ITvssAo 12 cm
H24: Dobu 10 µg/kg/min+ Noradrénaline 32 mg/h (6,2 µg/kg/min)
Fc 116/min. PA 77/60/48
FiO2 80% PEP +10 cm H2O Pplat 28 , P/F 146
pH 7,03 HCO3 18 mmol/L Lactatémie 9,5 mmol/L
ASAT 9694 U/L ALAT 1737 U/L TP 15%

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ASAT 9694 U/L ALAT 1737 U/L TP 15%

Quel traitement supplémentaire instaurez-vous?

- Aucun

- Vasopressine

- Angiotensine-II

- Bleu de méthylène

- ECMO veino-artérielle

Septic Shock…Refractory?

Outcome of patients with septic shock and high-dose vasopressor therapy

Thomas Auchet[1,2], Marie-Alix Regnier[3], Nicolas Girerd[4] and Bruno Levy[1,2,5*]

106 patients, retrospective

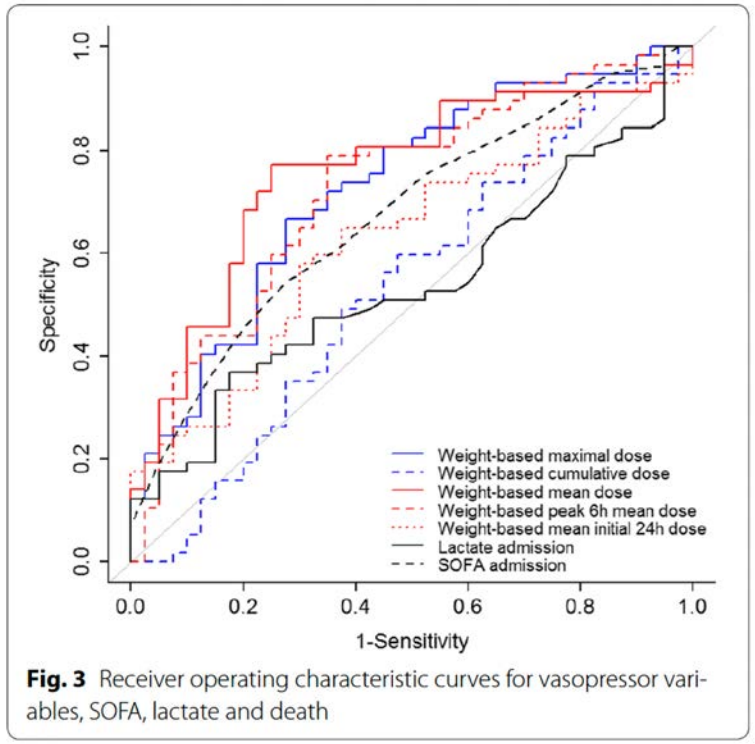
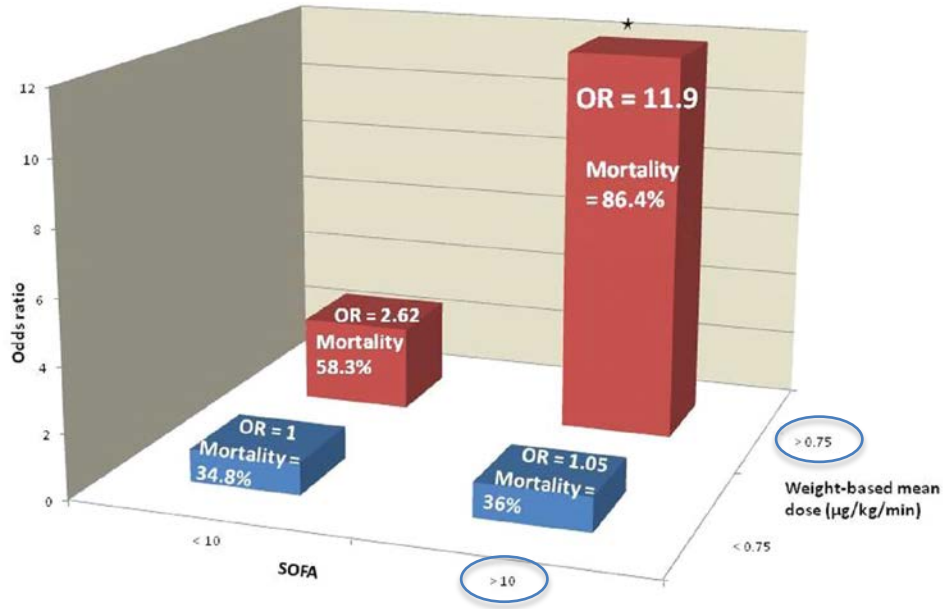


Fig. 3 Receiver operating characteristic curves for vasopressor variables, SOFA, lactate and death



Auchet, AOIC 2017

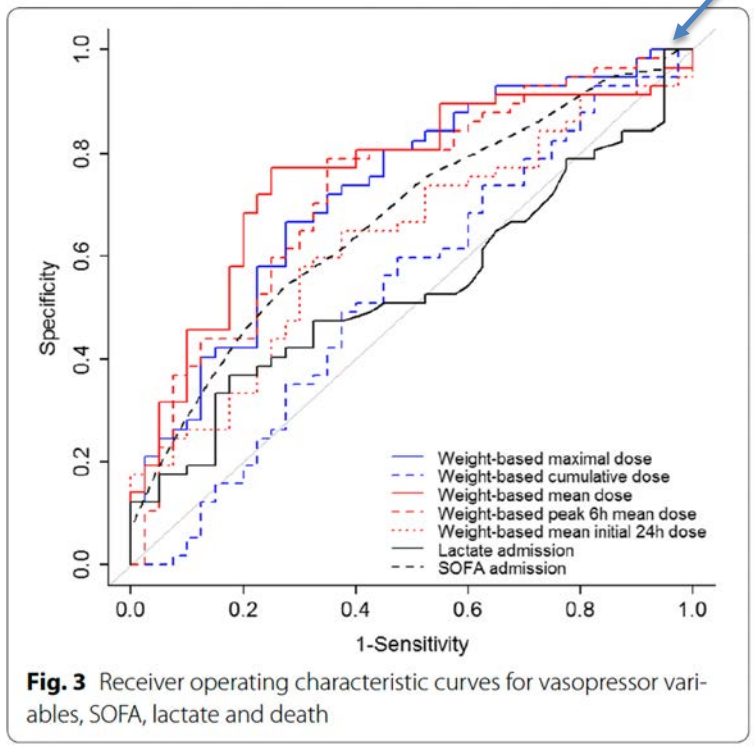
Septic Shock…Refractory?

Outcome of patients with septic shock and high-dose vasopressor therapy

Thomas Auchet[1,2], Marie-Alix Regnier[3], Nicolas Girerd[4] and Bruno Levy[1,2,5*]

2,2 µg/kg/min?
3,8 µg/kg/min?

106 patients, retrospective



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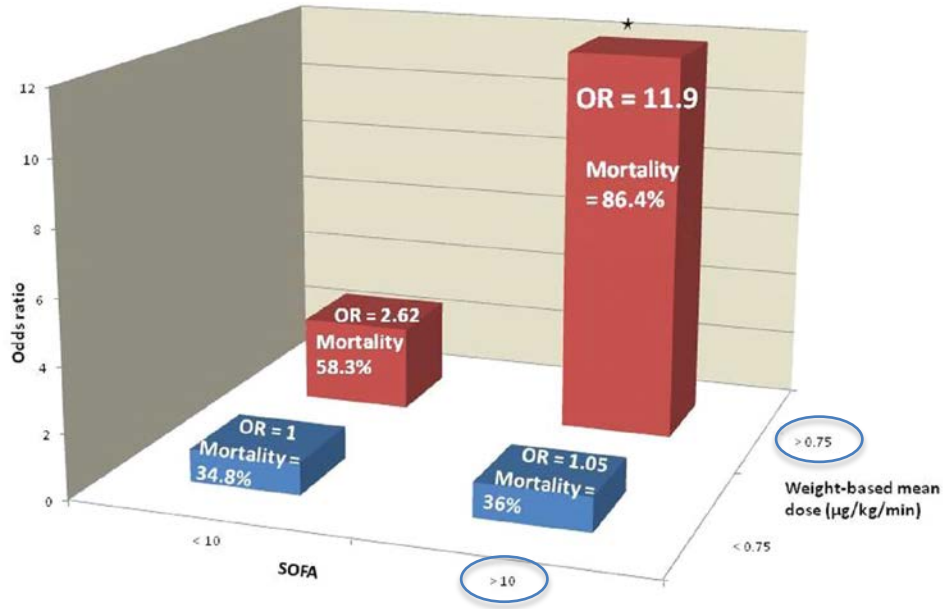
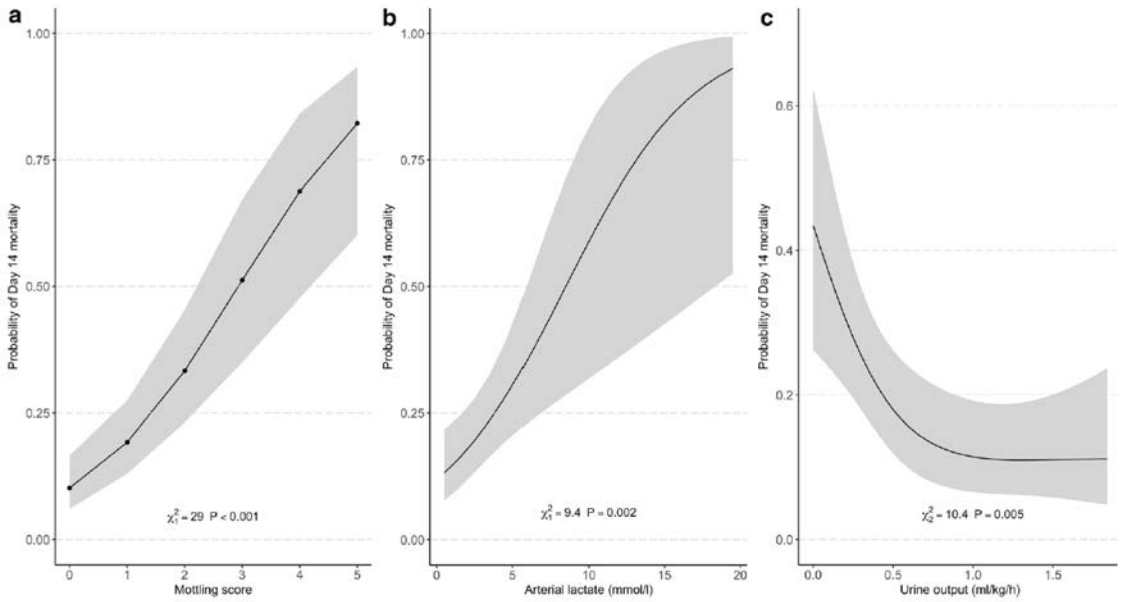
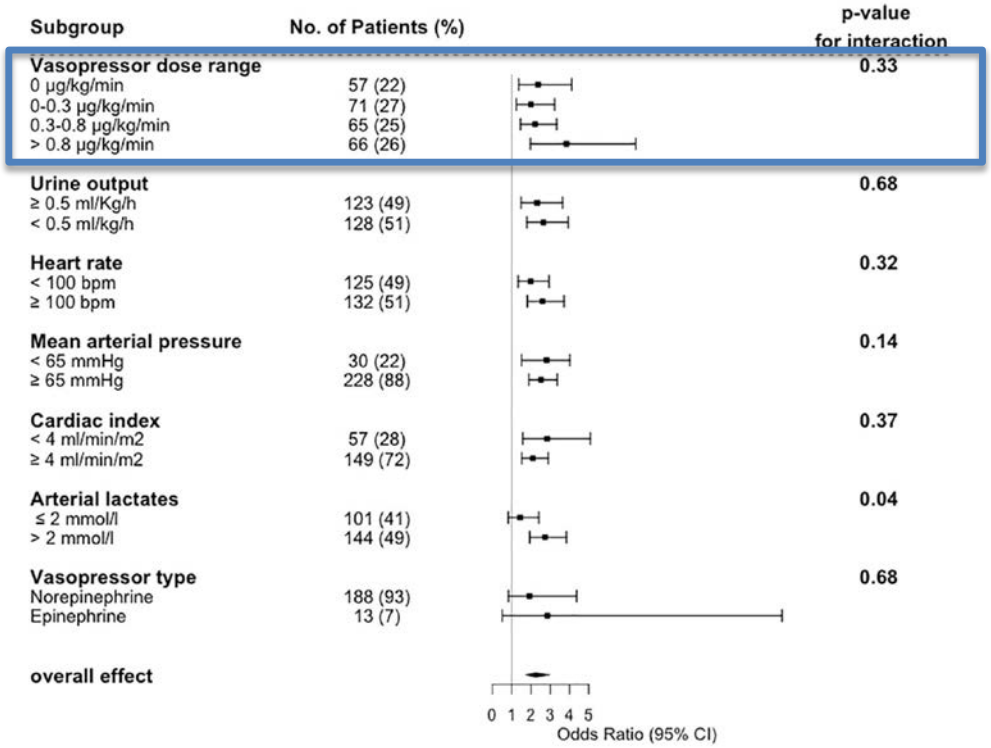


Auchet, AOIC 2017

Septic Shock…Refractory?

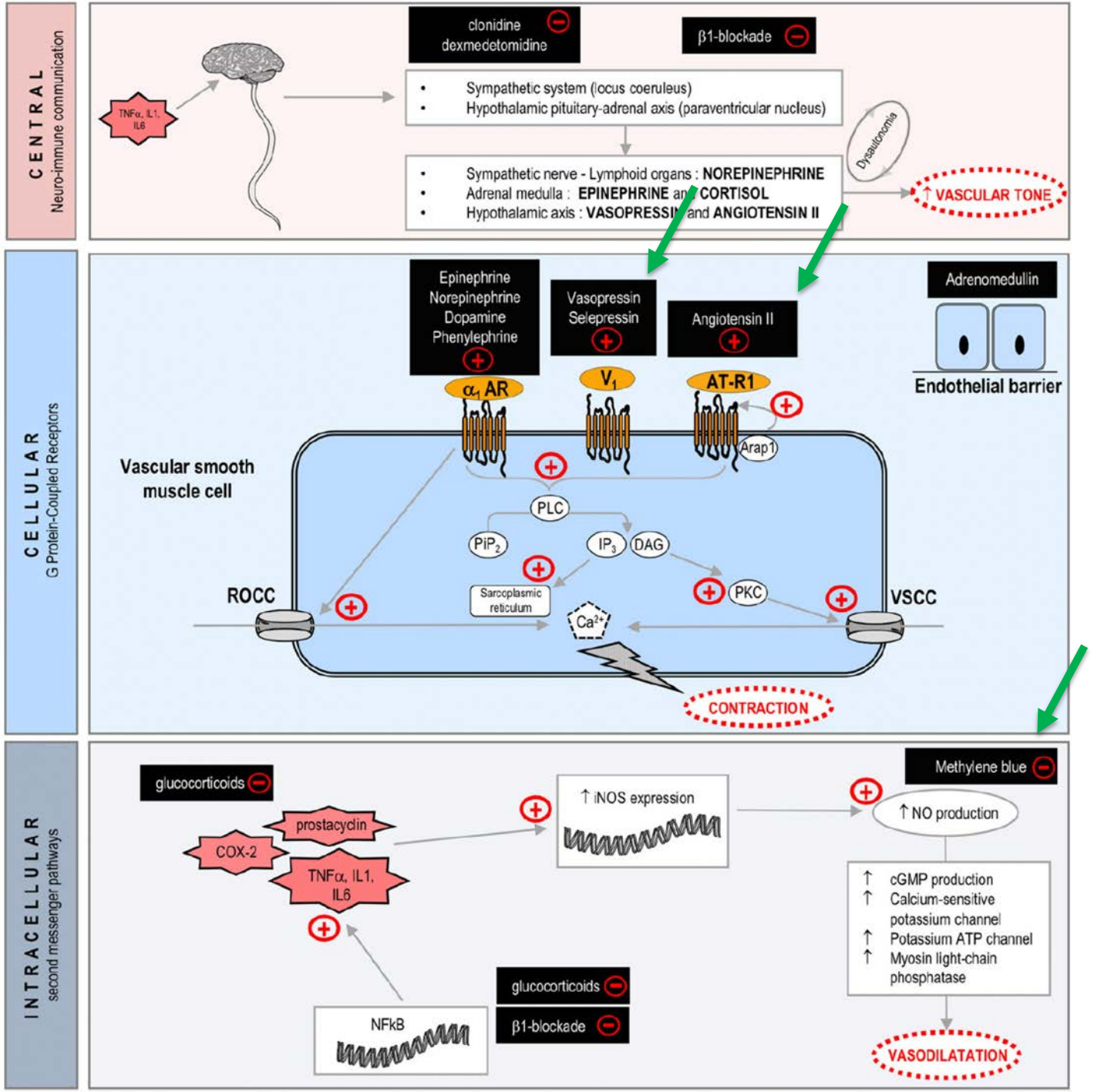
Mottling score is a strong predictor of 14-day mortality in septic patients whatever vasopressor doses and other tissue perfusion parameters





259 Patients, H6

Dumas, Crit Care 2019


CENTRAL
Neuro-immune communication
clonidine
dexmedetomidine
β1-blockade
TNFα, IL1, IL6
Sympathetic system (locus coeruleus)
Hypothalamic pituitary-adrenal axis (paraventricular nucleus)
Dysautonomia
Sympathetic nerve - Lymphoid organs : NOREPINEPHRINE
Adrenal medulla : EPINEPHRINE an CORTISOL
Hypothalamic axis : VASOPRESSI and ANGIOTENSIN II
↑ VASCULAR TONE
CELLULAR
G Protein-Coupled Receptors
Epinephrine
Norepinephrine
Dopamine
Phenylephrine
Vasopressin
Selepressin
Angiotensin II
Adrenomedullin
Endothelial barrier
α1 AR
V1
AT-R1
Arap1
Vascular smooth muscle cell
PLC
PiP2
IP3
DAG
Sarcoplasmic reticulum
PKC
ROCC
VSCC
Ca2+
CONTRACTION
INTRACELLULAR
second messenger pathways
glucocorticoids
prostacyclin
COX-2
TNFα, IL1, IL6
↑ iNOS expression
Methylene blue
↑ NO production
↑ cGMP production
↑ Calcium-sensitive potassium channel
↑ Potassium ATP channel
↑ Myosin light-chain phosphatase
NFkB
glucocorticoids
β1-blockade
VASODILATATION

Vasopressin

Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

RDZ, multicenter, double-blind
>5 µg/min norepinephrine-> Vasopressin 0.01-0.03 U/min vs. norepinephrine

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)	Relative Risk (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)	1.04 (0.83 to 1.3)
90-day mortality	105/199 (52.8)	103/199 (51.8)	0.84	1.0 (−8.8 to 10.8)	0.98 (0.81 to 1.18)
Less severe septic shock					
28-day mortality	65/182 (35.7)	52/196 (26.5)	0.05	9.2 (−0.1 to 18.5)	0.74 (0.55 to 1.01)
90-day mortality	83/180 (46.1)	69/193 (35.8)	0.04	10.4 (0.4 to 20.3)	0.78 (0.61 to 0.99)

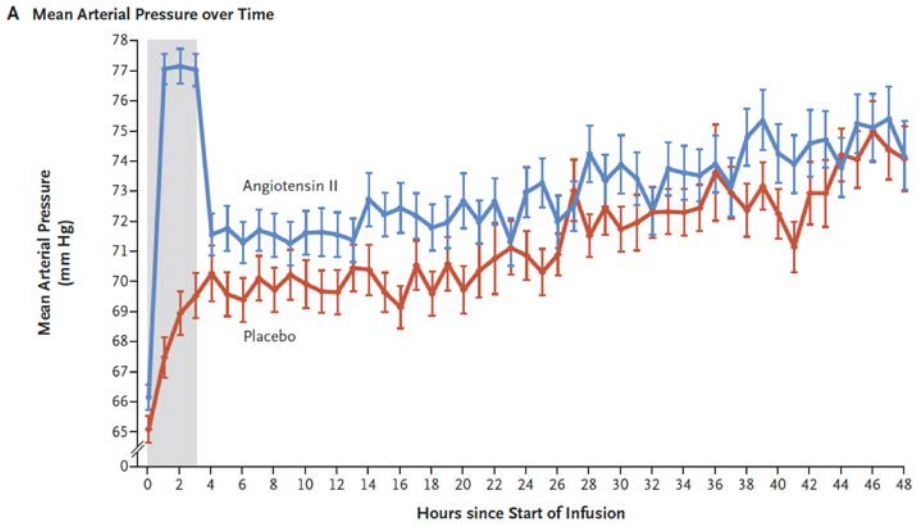
Norepi <15 µg/min

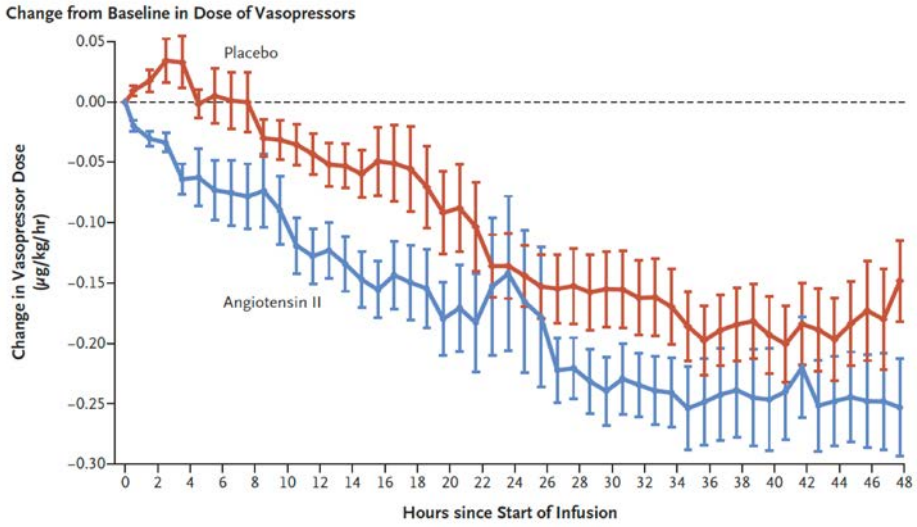
Russel, NEJM 2008

Angiotensin II

Angiotensin II for the Treatment of Vasodilatory Shock

RDZ, multicenter, blinded
344 Patients
>0.2 µg/kg/min norepinephrine-> Angiotensin-II 20-200 ng/kg/min vs. Placebo





Response to Angiotensin II: 78% norepineprine< 0.5 µg/kg/min
50% norepinephrine > 0.5 µg/kg/min, p<0.0001

Khanna, NEJM 2017

Angiotensin II

Post-hoc analysis of ATHOS-3

Primary outcome, 28-day survival in the Low-NED (≤ 0.25 µg/kg/min) subgroup			
Placebo (n = 48)	**AT II (n = 56)**	**HR (95% CI)**	***p*-value**
48% (33%–61%)	64% (50%–75%)	0.51 (0.27, 0.95)	0.03
Secondary outcome, 28-day survival in the High-NED (> 0.25 µg/kg/min) subgroup			
Placebo (n = 110)	**AT II (n = 107)**	**HR (95% CI)**	***p*-value**
45% (36–54%)	49% (39–58%)	0.93 (0.64, 1.35)	0.71

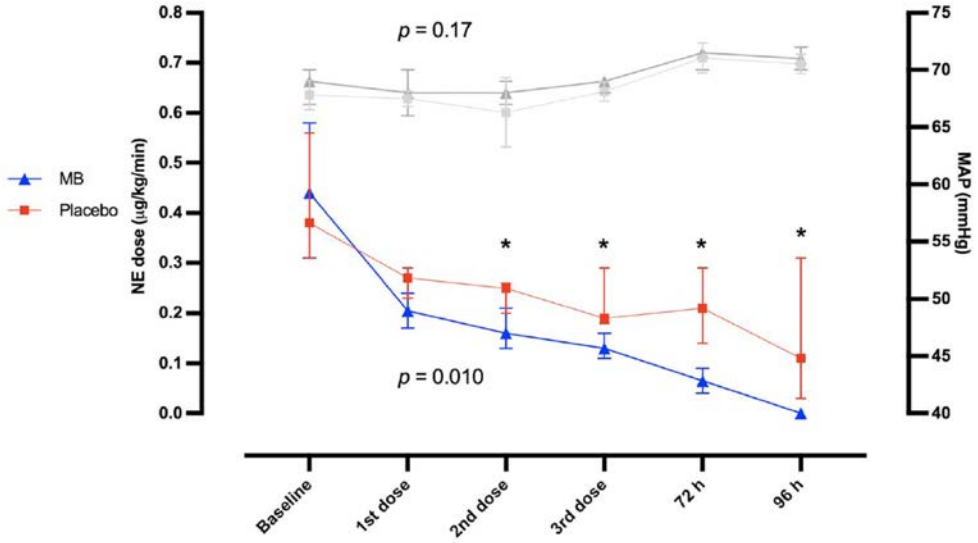
Wieruszewski, Critical Care 2023

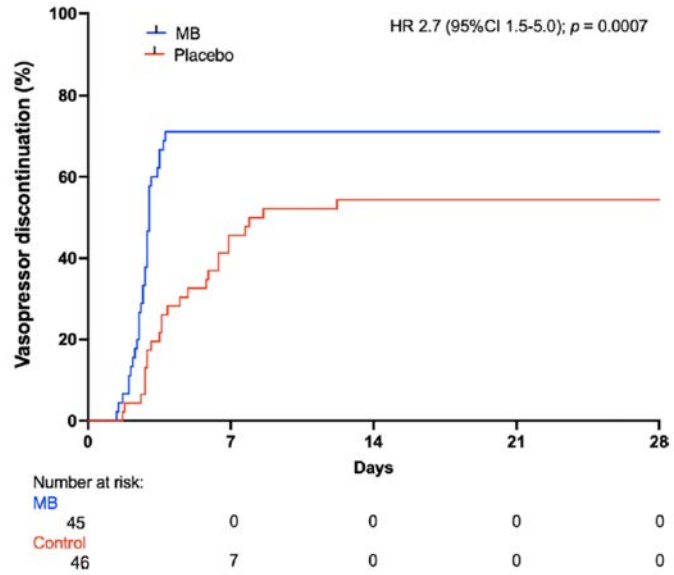
Methylene Blue

RESEARCH Open Access

Early adjunctive methylene blue in patients with septic shock: a randomized controlled trial

91 pts. 100 mg/J sur 6h, 3 doses





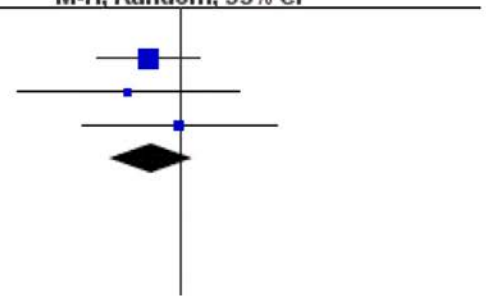
Ibarra-Estrada, Crit Care 2023

Methylene Blue

Study or Subgroup	MB Events	MB Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
8.1.1 septic shock						
Ibarra-Estrada 2023	15	45	21	46	47.9%	0.60 [0.25, 1.39]
Kirov 2001	5	10	7	10	13.2%	0.43 [0.07, 2.68]
Memis 2002	4	15	4	15	16.6%	1.00 [0.20, 5.04]
Subtotal (95% CI)		**70**		**71**	**77.7%**	**0.62 [0.31, 1.25]**
Total events	24		32			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.50$, df = 2 (P = 0.78); $I^2 = 0\%$

Test for overall effect: Z = 1.32 (P = 0.19)



Huang, BMJ Open 2024

Refractory septic shock: VA-ECMO

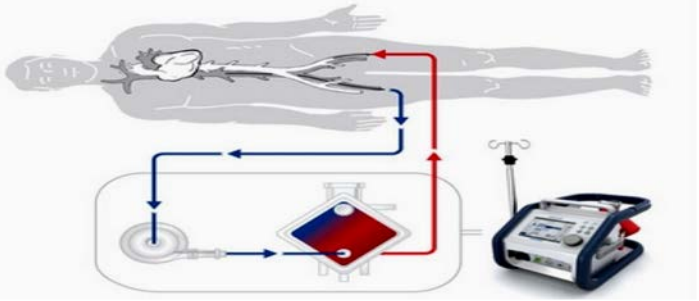


TABLE 3. Clinical parameters before extracorporeal membrane oxygenation

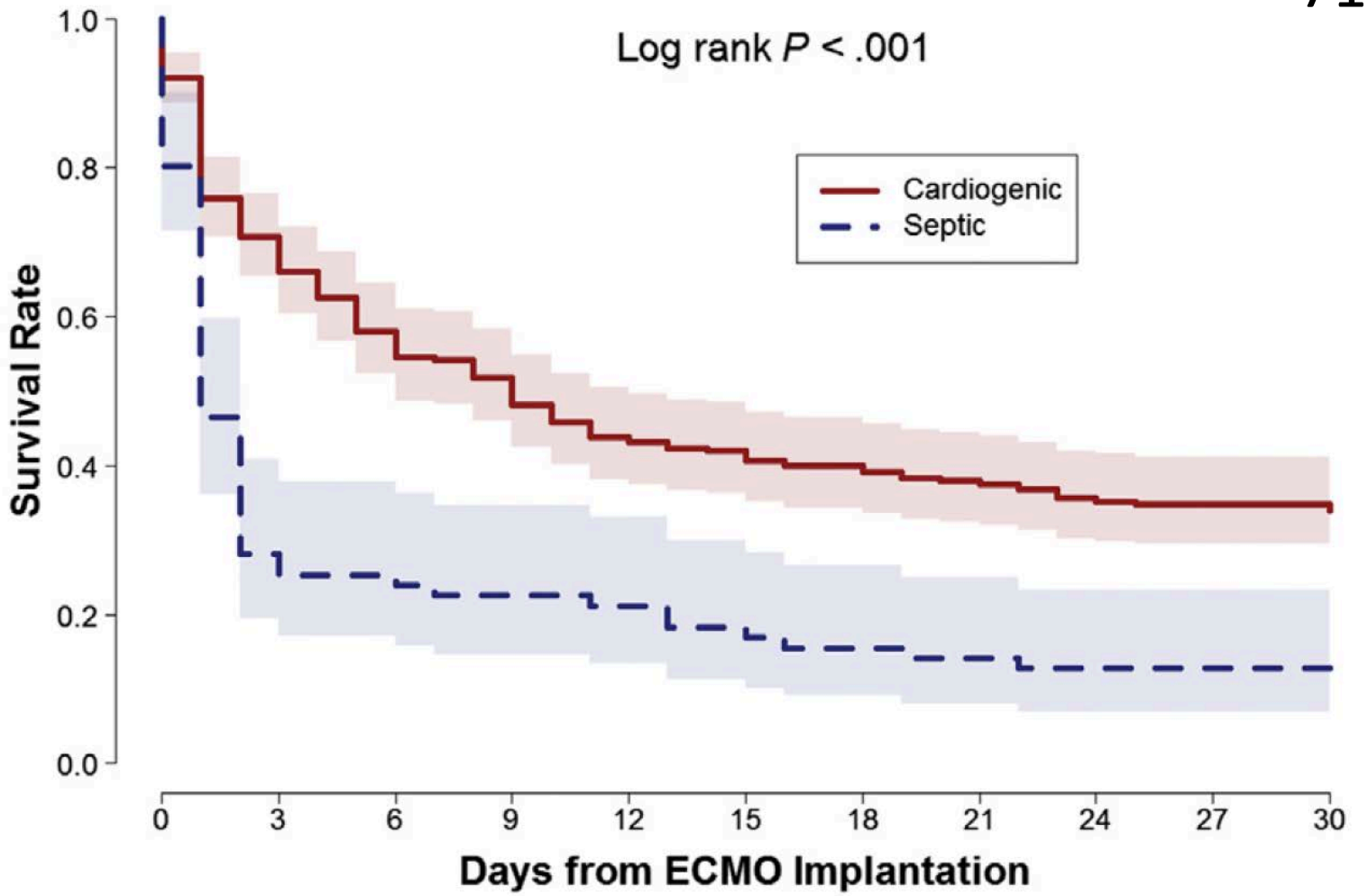
Variable	Survivors (n = 8)	Nonsurvivors (n = 44)	*P* value
Circulatory			
Mean arterial pressure (mm Hg)	57.0	55.5	.424
Inotropic equivalent* (mcg/kg/min)	52.8	56.0	.275
Urine output in hour before ECMO (mL/kg/h)	0.07	0.02	.493
Left ventricular ejection fraction (%)	56.5	55.5	.657
Ventilatory			
Peak airway pressure (cm H_2O)	30	30	.980
Mean airway pressure (cm H_2O)	17	15	.341
Positive end-expiratory pressure (cm H_2O)	11	8	.150
F_{IO_2}	0.65	0.60	.552
Laboratory			
pH	7.32	7.30	.960
P_{aO_2}/F_{IO_2}	89	112	.233
P_{aCO_2} (mm Hg)	37.6	38.1	.704
Base excess (mmol/L)	–6.6	–6.3	.899
Arterial lactate (mmol/L)	5.3	8.8	.089

Survival 15%

Huang. JTCVS 2012

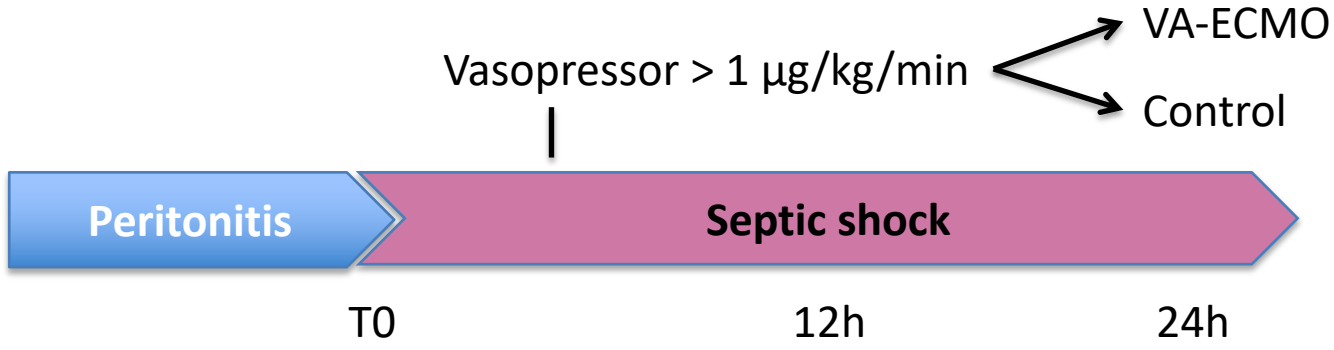
Extracorporeal life support for adults with refractory septic shock

71 patients

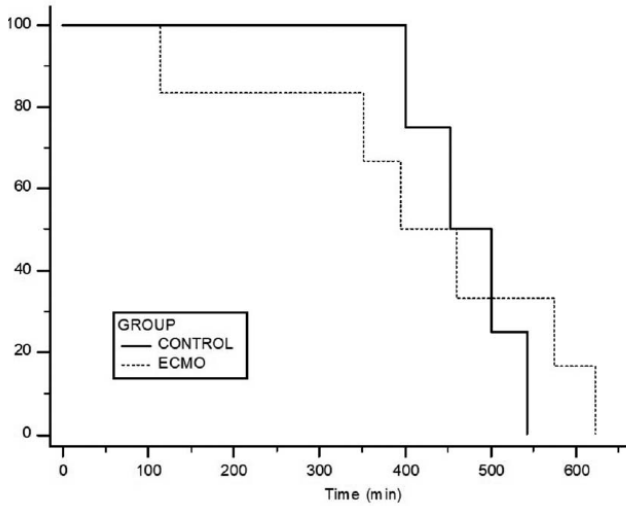


Ro. JTCVS 2018

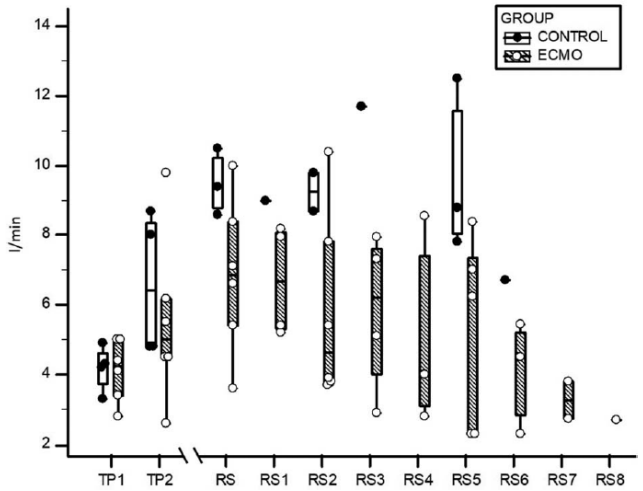
VA-ECMO during severe vasoplegia



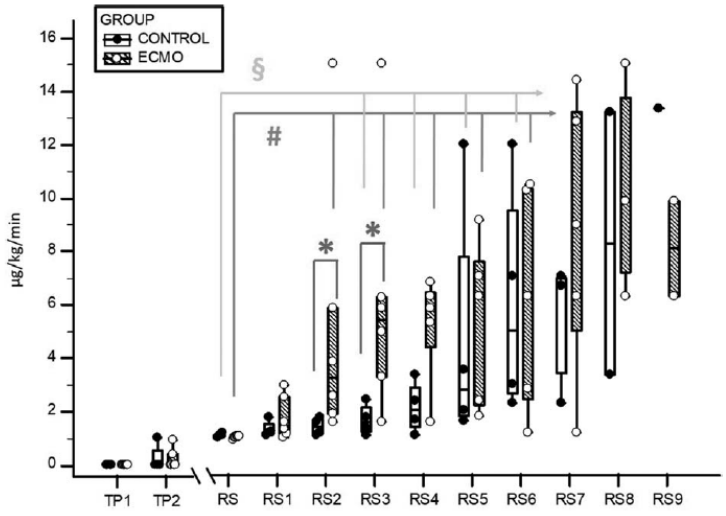
Survival



Native Cardiac Output



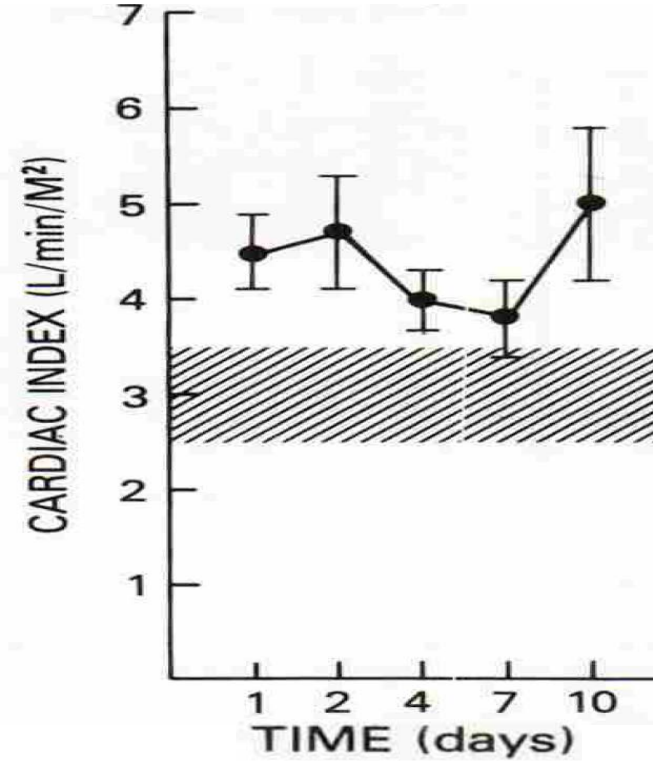
Norepinephrine

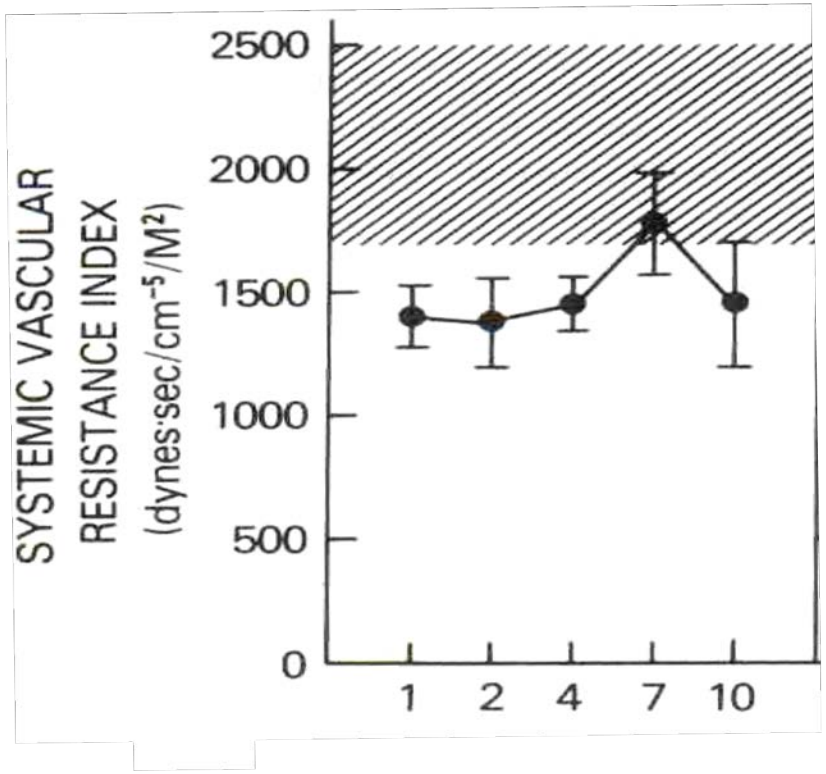


Chvojka. Shock 2020

Reversible myocardial dysfunction during sepsis

20 pts

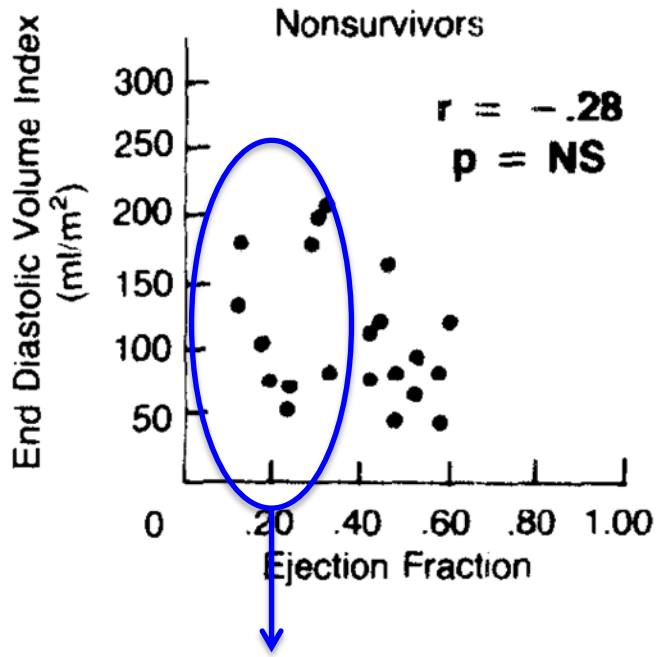




Parker MM, Ann Intern Med 1984

Refractory myocardial dysfunction during sepsis

54 pts, 21->death



"**Half of the nonsurvivors** developed a decreasing cardiac index, with no change in heart rate or ejection fraction, (..) and become those nonsurvivors who die of a **cardiogenic shock-like state**."

Causes?

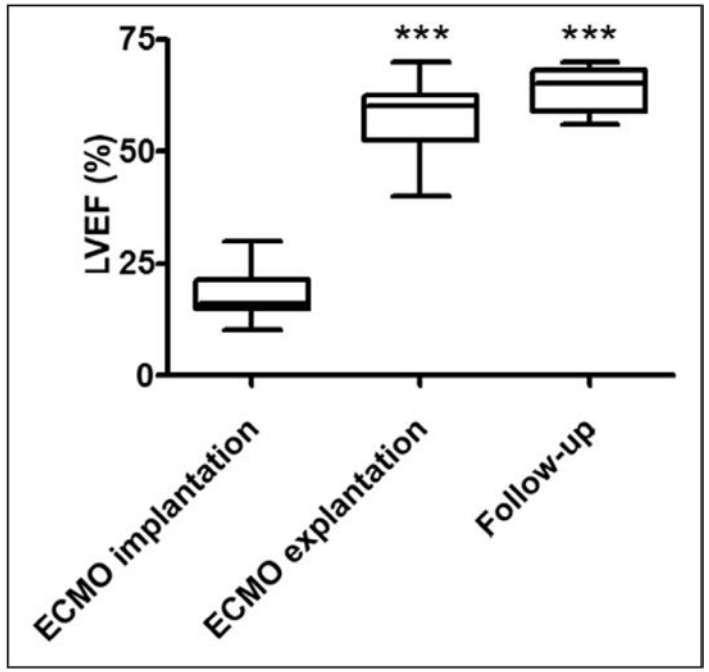
Incidence?

Impact?

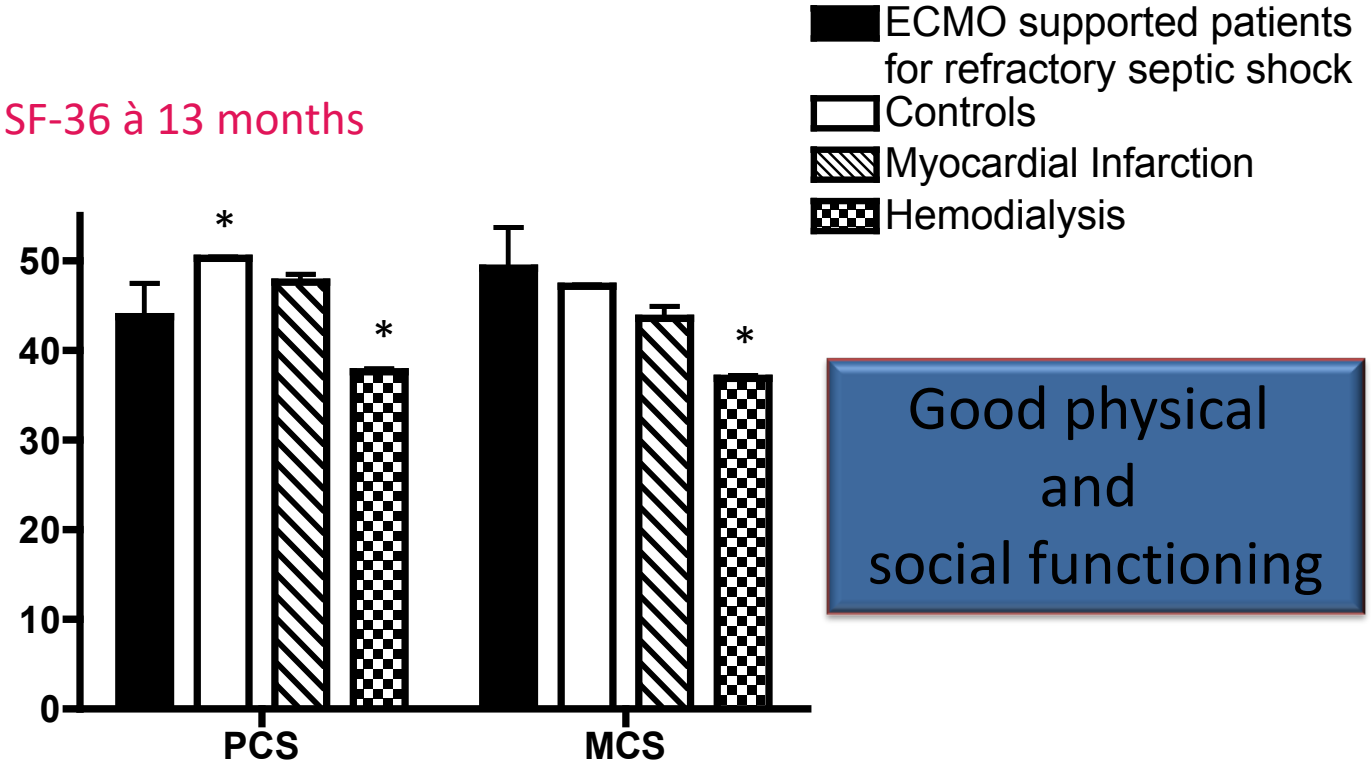
Parker MM, J Crit Care 1989

Venoarterial Extracorporeal Membrane Oxygenation Support for Refractory Cardiovascular Dysfunction During Severe Bacterial Septic Shock

Longterm Survivors
10/14 (71%)



SF-36 à 13 months



Good physical and social functioning

Bréchot. Crit Care Med 2013

THE LANCET

Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study

Nicolas Bréchot, David Hajage, Antoine Kimmoun, Julien Demiselle, Cara Agerstrand, Santiago Montero, Matthieu Schmidt, Charles-Edouard Luyt, Guillaume Lebreton, Guillaume Hékimian, Erwan Flecher, Elie Zogheib, Bruno Levy, Arthur S Slutsky, Daniel Brodie, Pierre Asfar, Alain Combes*, for the International ECMO Network*

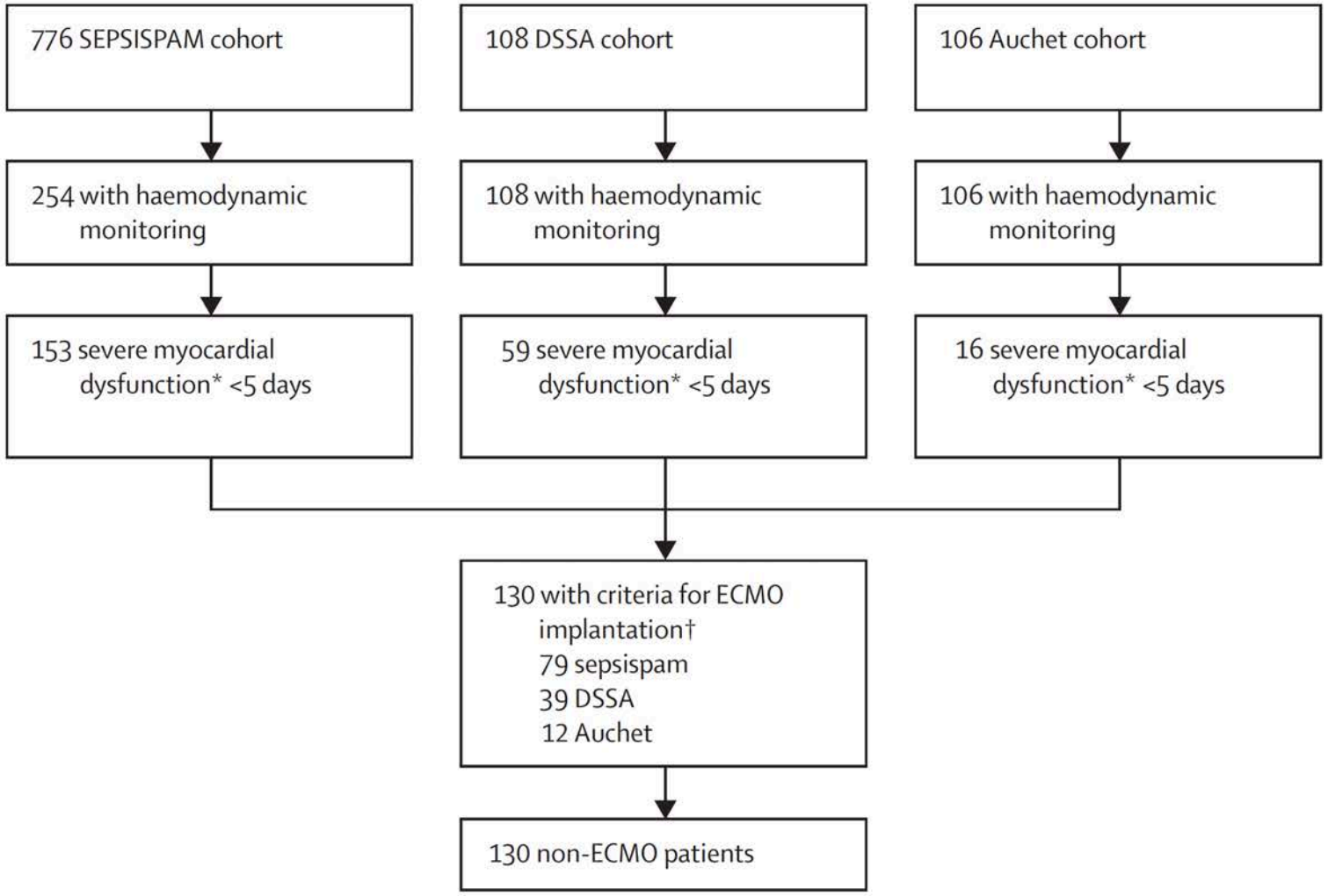
***Lancet* 2020; 396: 545–52**

Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study

Sepsis-induced cardiogenic shock

CI ≤ 3L/min/m² or LVEF≤ 35%
Inotrope score >75 µg/kg/min
Lactatemia>4 mmol/L

Sepsis-induced cardiogenic shock
130/990 (13%)



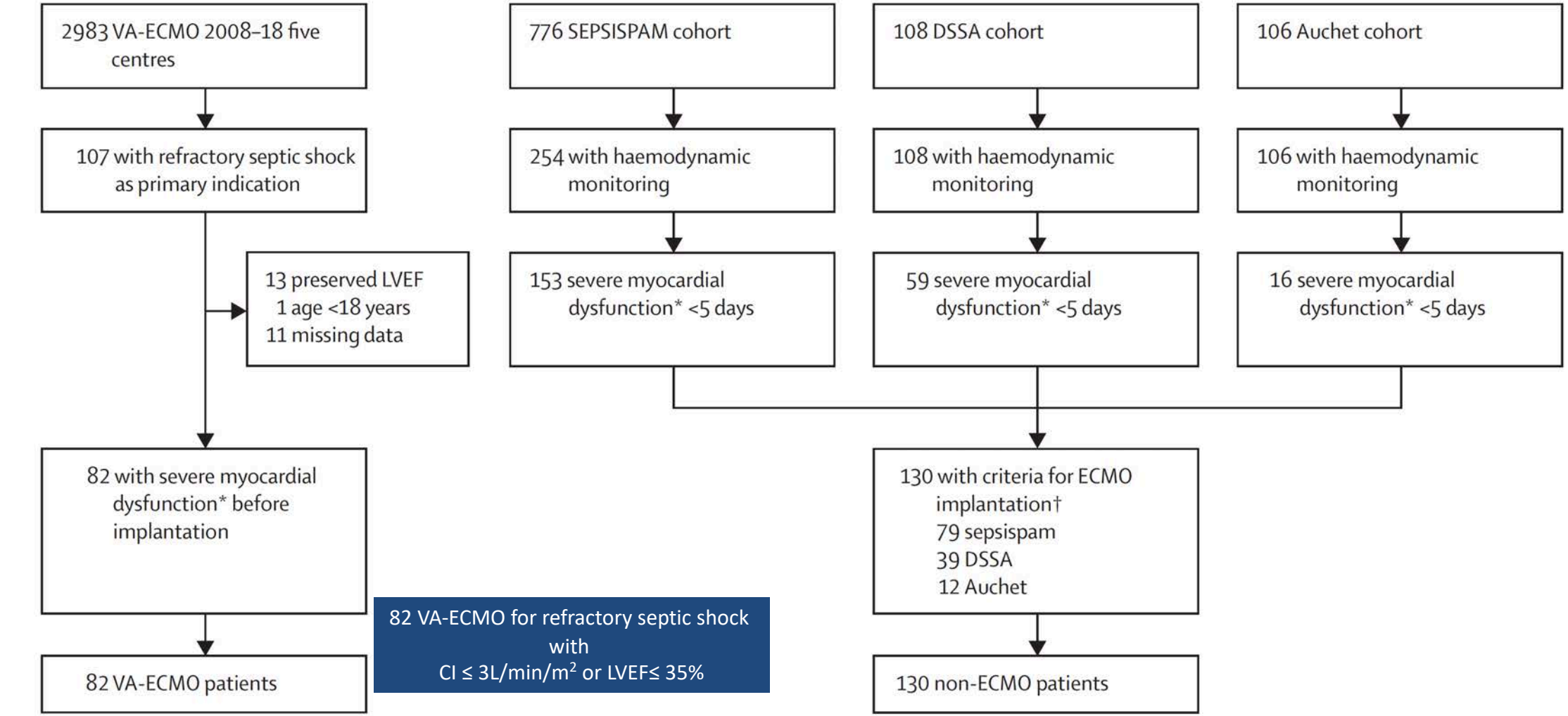
Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study

Parameters (%; mean (SD)	Non-ECMO (n=130)
Age	66 (16)
Charlson score	1.6 (1.2)
Immunodeficiency	26 %
Source of infection: lung	50 (38)
Delay shock-inclusion, d	0.7 (1.0)
Pre-inclusion cardiac index, L/min/m2	2.21 (0.59)
LVEF (%)	28 (6)
Inotrope score, µg/kg/min =Dobu+100*(Epi+Norepi)	145 (128)
pH	7.23 (0.16)
Blood lactate	6 (4)
Fluids before inclusion	1654 (1952)
SOFA	13 (4)
SAPS II	68 (19)

SURVIVAL at 90 days
33/130 (25.4%)

Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study

PARIS NEW-YORK NANCY AMIENS RENNES



82 VA-ECMO for refractory septic shock with
CI ≤ 3L/min/m^2 or LVEF≤ 35%

Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study

Parameters (%; mean (SD)	Non-ECMO (n=130)	ECMO (n=82)
Age	66 (16)	48 (15)
Charlson score	1.6 (1.2)	1.1 (1.3)
Immunodeficiency	26 %	16 %
Source of infection: lung	50 (38)	64 (78)
Delay shock-inclusion, d	0.7 (1.0)	1.1 (0.9)
Pre-inclusion cardiac index, L/min/m2	2.21 (0.59)	1.5 (0.5)
LVEF (%)	28 (6)	17 (7)
Inotrope score, µg/kg/min =Dobu+100*(Epi+Norepi)	145 (128)	279 (247)
pH	7.23 (0.16)	7.13 (0.15)
Blood lactate	6 (4)	9 (4)
Fluids before inclusion	1654 (1952)	4925 (2886)
SOFA	13 (4)	17 (3)
SAPS II	68 (19)	78 (16)

Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study

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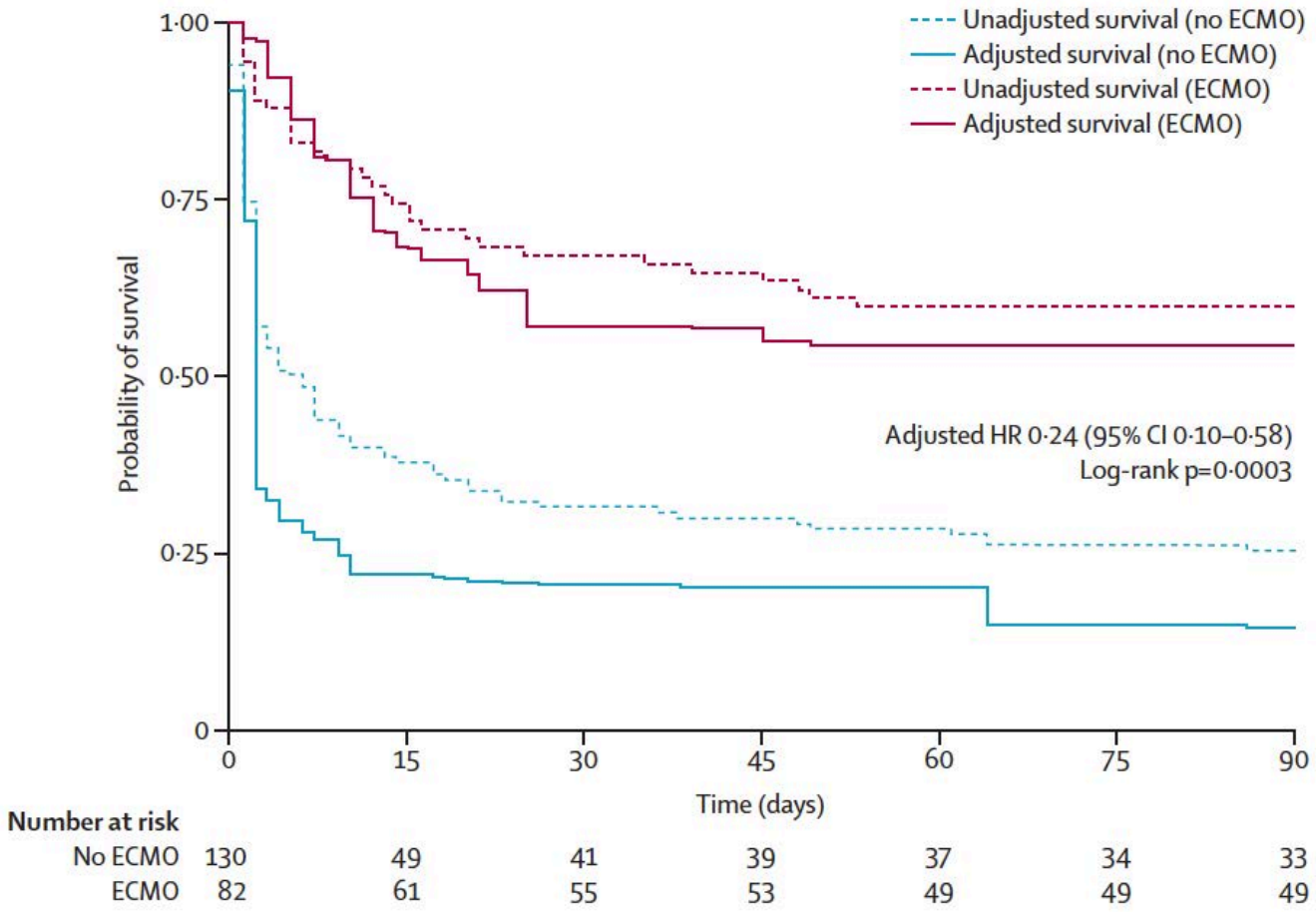
SAPS II	68 (19)	78 (16)

SURVIVAL at 90 days
49/82 (60%)
p<0.001 vs. Non ECMO

Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study



Day 90 Relative risk of Mortality
(ECMO vs. non ECMO)

0.47 (95% CI [0.34 – 0.67]; p<0.0001)

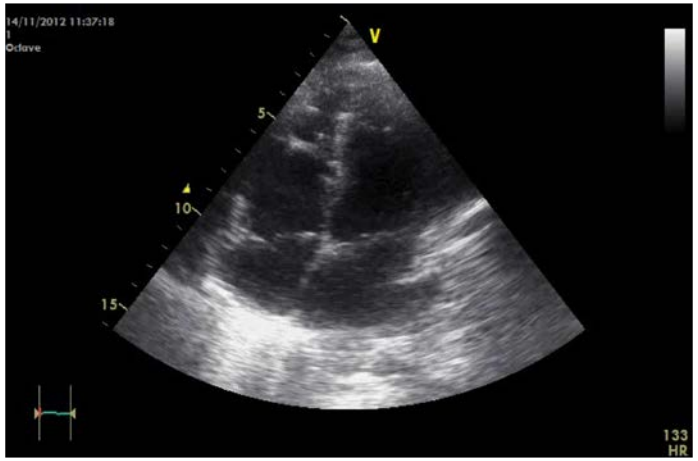
Mrs U.

- 52 years, no medical condition
- Septic shock due to E.Coli pyelonephritis
- Ureteral drainage
- Refractory septic shock with profound myocardial dysfunction and MOF
  - Epinephrine 5mg/h, MV
  - LVEF 20%, CI 1.5 l/min/m2
  - ABP 70/61/57 HR 130/min
  - pH 7.15 Blood Lactate 8 mmol/L
  - Anuric, CRRT
  - PT 29%
  - SAPS II 92

PVA ECMO at Day 1

Mrs U.

D0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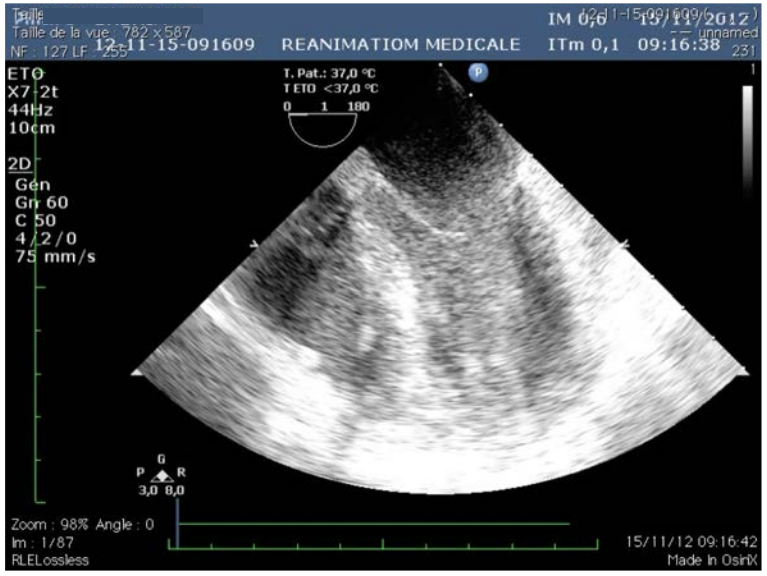
Octave
V
5
10
15
133
HR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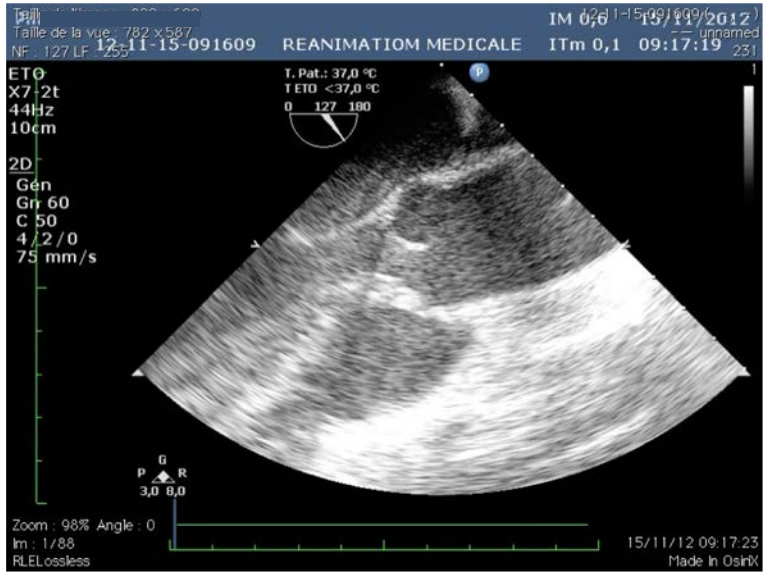
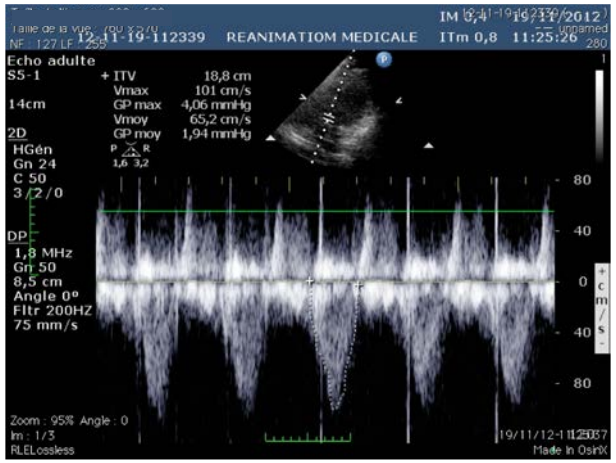
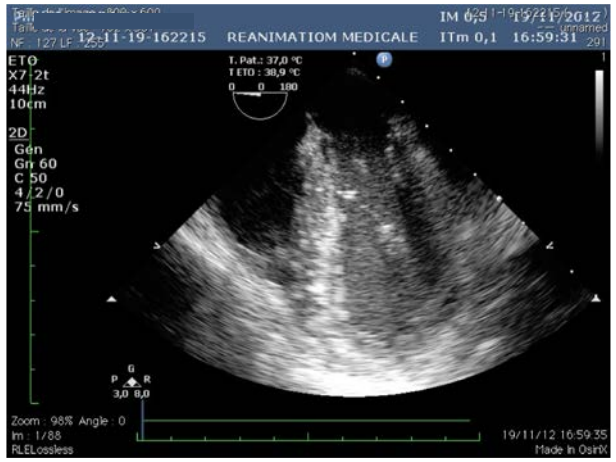
NF : 127 LF : 255
12-11-15-091609
REANIMATIOM MEDICALE
IM 0,6 15/11/2012
ITm 0,1 09:16:38
unnamed
ETO
X7-2t
44Hz
10cm
2D
Gén
Gn 60
C 50
4/2/0
75 mm/s
T. Pat.: 37,0 °C
T ETO <37,0 °C
0 1 180
G
P R
3,0 8,0
Zoom : 98% Angle : 0
Im : 1/87
RLELossless
15/11/12 09:16:42
Made in OsiriX

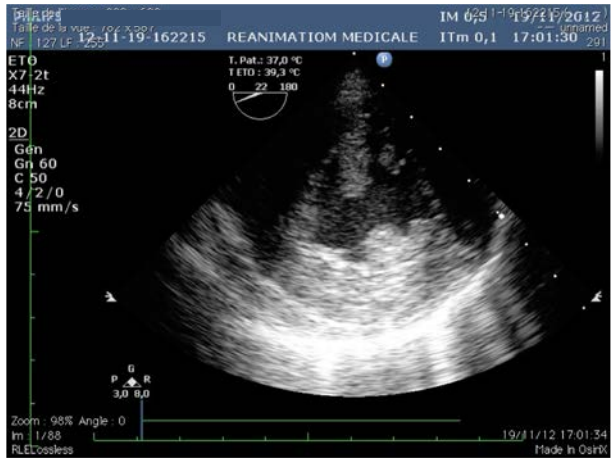

Taille de la vue : 782 x 587
NF : 127 LF : 255
12-11-15-091609
REANIMATIOM MEDICALE
IM 0,6 15/11/2012
ITm 0,1 09:17:19
unnamed
ETO
X7-2t
44Hz
10cm
2D
Gén
Gn 60
C 50
4/2/0
75 mm/s
T. Pat.: 37,0 °C
T ETO <37,0 °C
0 127 180
G
P R
3,0 8,0
Zoom : 98% Angle : 0
Im : 1/88
RLELossless
15/11/12 09:17:23
Made in OsiriX

Mrs U.

D4

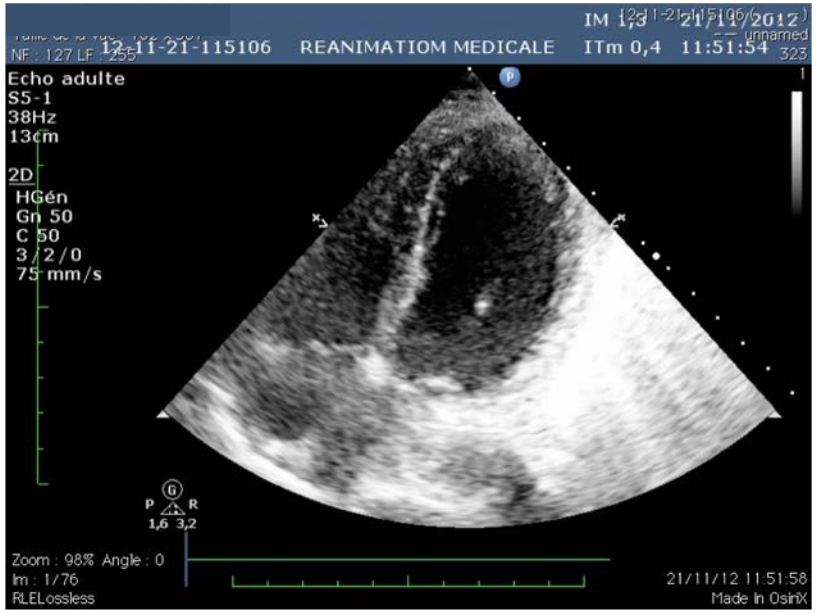

REANIMATIOM MEDICALE
Echo adulte
S5-1
14cm
2D
HGén
Gn 24
C 50
3/2/0
DP
1,8 MHz
Gn 50
8,5 cm
Angle 0°
Fltr 200HZ
75 mm/s
+ ITV 18,8 cm
Vmax 101 cm/s
GP max 4,06 mmHg
Vmoy 65,2 cm/s
GP moy 1,94 mmHg
Zoom : 95% Angle : 0
Made in OsirX


REANIMATIOM MEDICALE
ETO
X7-2t
44Hz
10cm
2D
Gén
Gn 60
C 50
4/2/0
75 mm/s
T. Pat.: 37,0 °C
T ETO : 38,9 °C
Zoom : 98% Angle : 0
Made in OsirX


REANIMATIOM MEDICALE
ETO
X7-2t
44Hz
8cm
2D
Gén
Gn 60
C 50
4/2/0
75 mm/s
T. Pat.: 37,0 °C
T ETO : 39,3 °C
Zoom : 98% Angle : 0
Made in OsirX

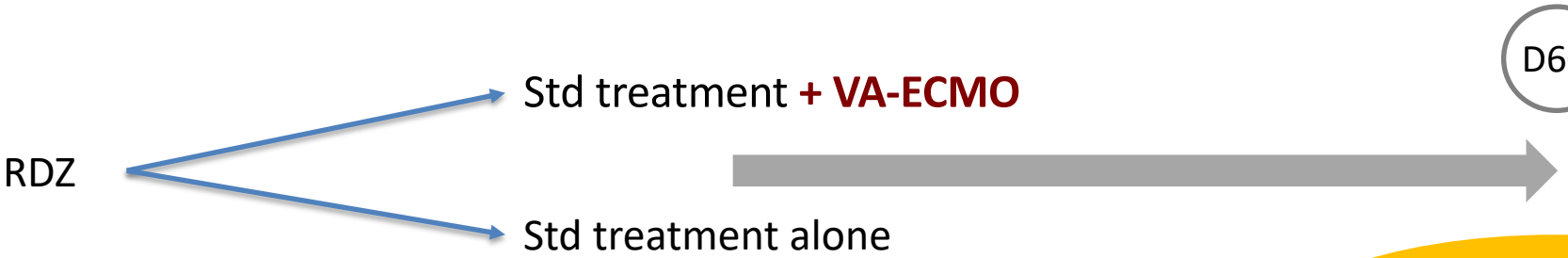
Mrs U.

D6


12-11-21-115106
REANIMATIOM MEDICALE
ITm 0,4 11:51:54
Echo adulte
S5-1
38Hz
13cm
2D
HGén
Gn 50
C 50
3/2/0
75 mm/s
1,6 3,2
Zoom : 98% Angle : 0
Im : 1/76
RLELossless
21/11/12 11:51:58
Made in OsiriX

CRESCENDO multicenter RDZ Trial

Veno-arterial extra-**C**orporeal membrane oxygenation to **RESC**u**E** sepsis-i**ND**uced cardiogenic sh**O**ck



N = 116*

Sepsis-induced CS:
Sepsis
+ CI<2.5 L/min/m2
+ LVEF<35%
+ Dobu>10 µg/kg/min
+ IS>75µg/kg/min
+ Lactatemia>4 mmol/L

12 Units

Primary endpoint:

All cause Mortality

* ↘ 70% to 50% ECMO group

Secondary Endpoints:

Mortality at 2, 7, 30, 60 days and 1 year

Evolution of hemodynamic parameters from D1 to D7

Catecholamine-free days at D30

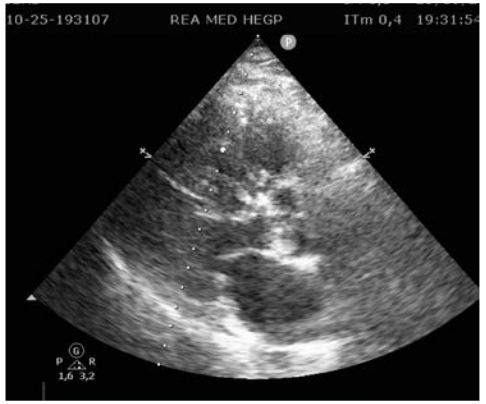
Daily SOFA score from D1 to D7

Catecholamine, Mechanical ventilation & RRT free days at D30

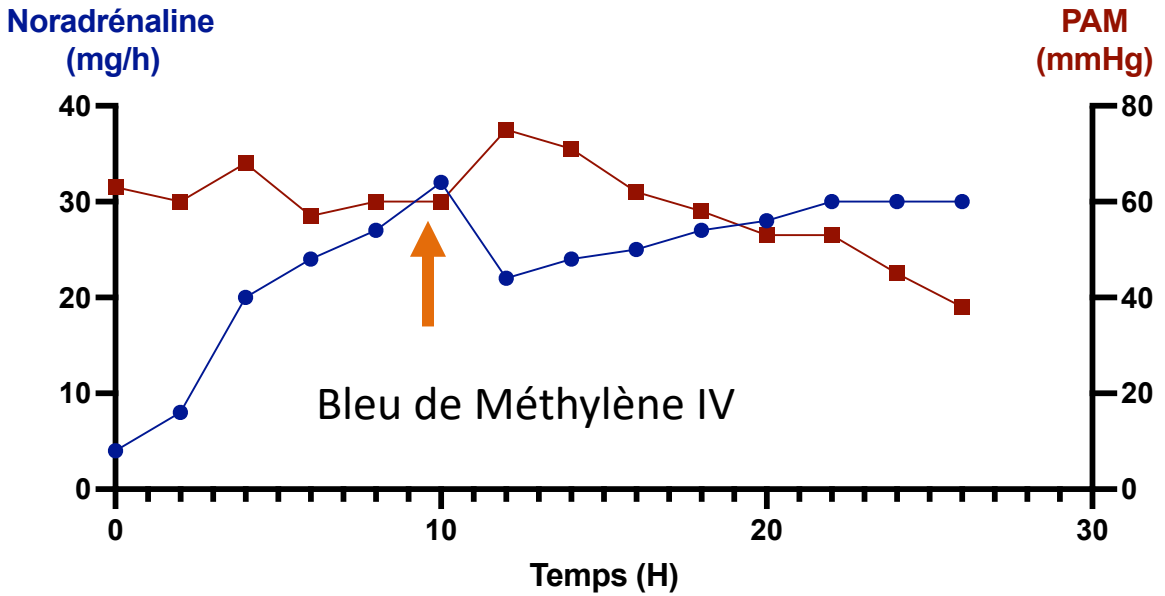
Quality of life at 1 year

Adverse events

60 ans. Tabagisme 40 PA + éthylisme chronique +/- Cirrhose
Pneumonie aiguë communautaire-> urgences
O_2, ATB par claforan
H12: Dégradation respiratoire puis hémodynamique
IOT/VM, ATBthérapie par Tazocilline+ Rovamycine
Optimisation volémie, noradrénaline , HSHC
HFVVC
Dobutamine FeVG 30%, ITvssAo 12 cm
H24: Dobu 10 µg/kg/min+ Noradrénaline 32 mg/h (6,2 µg/kg/min)
Fc 116/min. PA 77/60/48
FiO2 80% PEP +10 cm H2O Pplat 28 , P/F 146
pH 7,03 HCO3 18 mmol/L Lactatémie 9,5 mmol/L
ASAT 9694 U/L ALAT 1737 U/L TP 15%



ITVssAo 15 cm
IC 3,2 L/min/m^2



Choc septique “réfractaire”
Conclusions

- **Définition? Dose ponctuelle de vasopresseurs peu informative**
- **Pas de traitement de sauvetage ayant fait la preuve de son efficacité au cours des vasoplégies réfractaires à la noradrénaline**
- **Intérêt potentiel d’une ‘décatécholaminisation’ (vasopressine, angiotensine II, bleu de méthylène?)**
- **L’ ECMO-VA semble reverser l’évolution du choc cardiogénique induit par le sepsis -> Intérêt majeur de la réévaluation du profil hémodynamique**

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