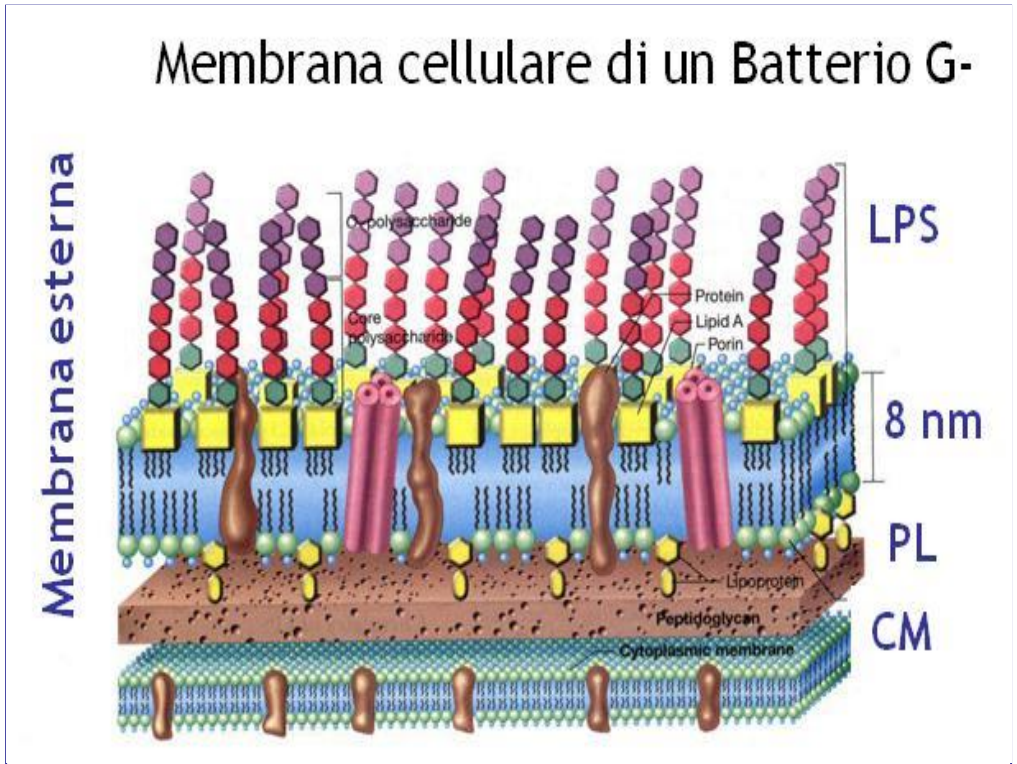
European Association of Cardiothoracic Anaesthesiologists

POLYMIXYN B *per chi e quando*

ITACTA
ITALIAN ASSOCIATION OF CARDIOTHORACIC ANAESTHESIOLOGISTS

Gianluca Paternoster
SAN CARLO HOSPITAL POTENZA ITALY

LIPOPOLISACCARIDE (LPS)

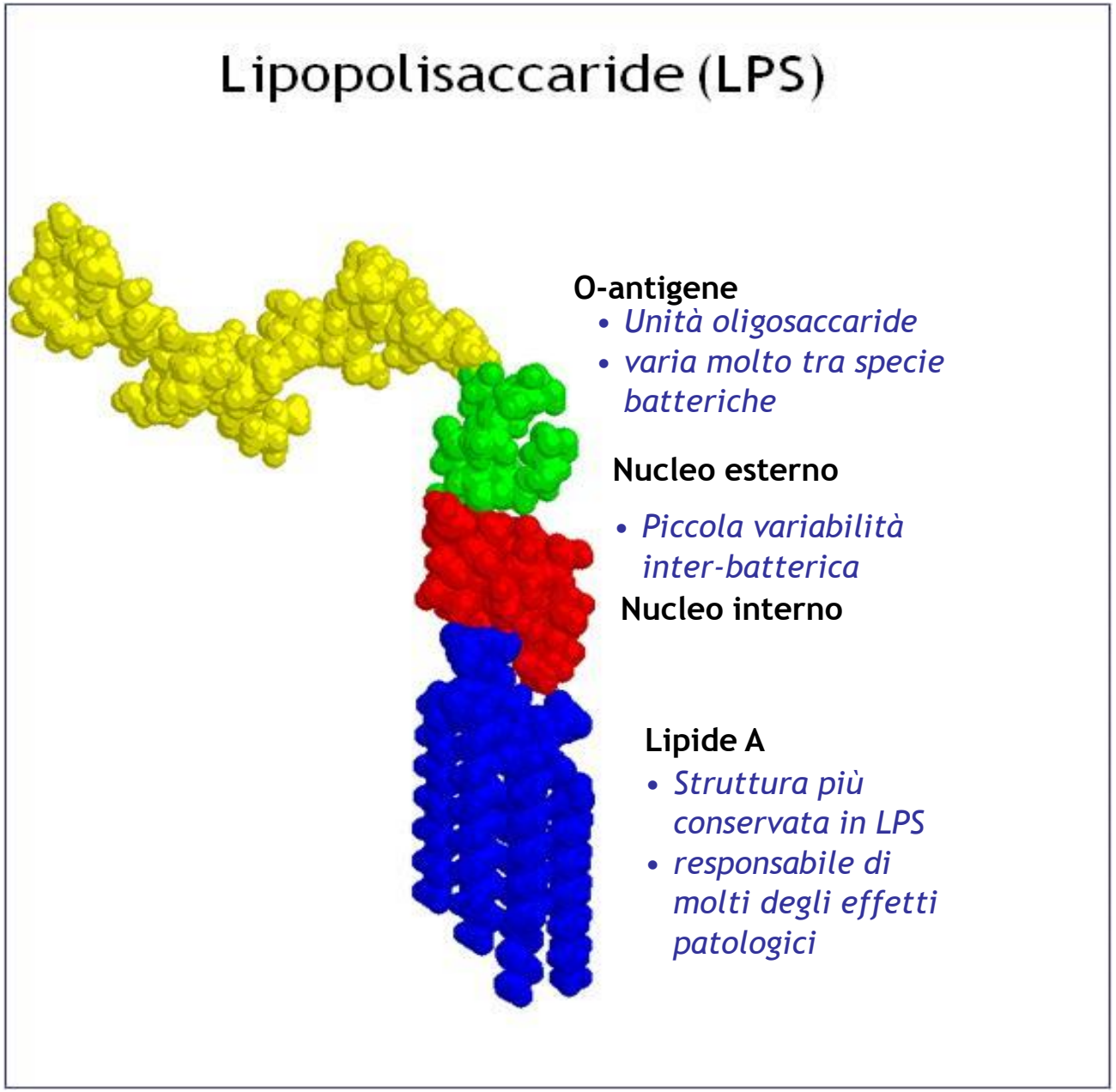


Tre strati:

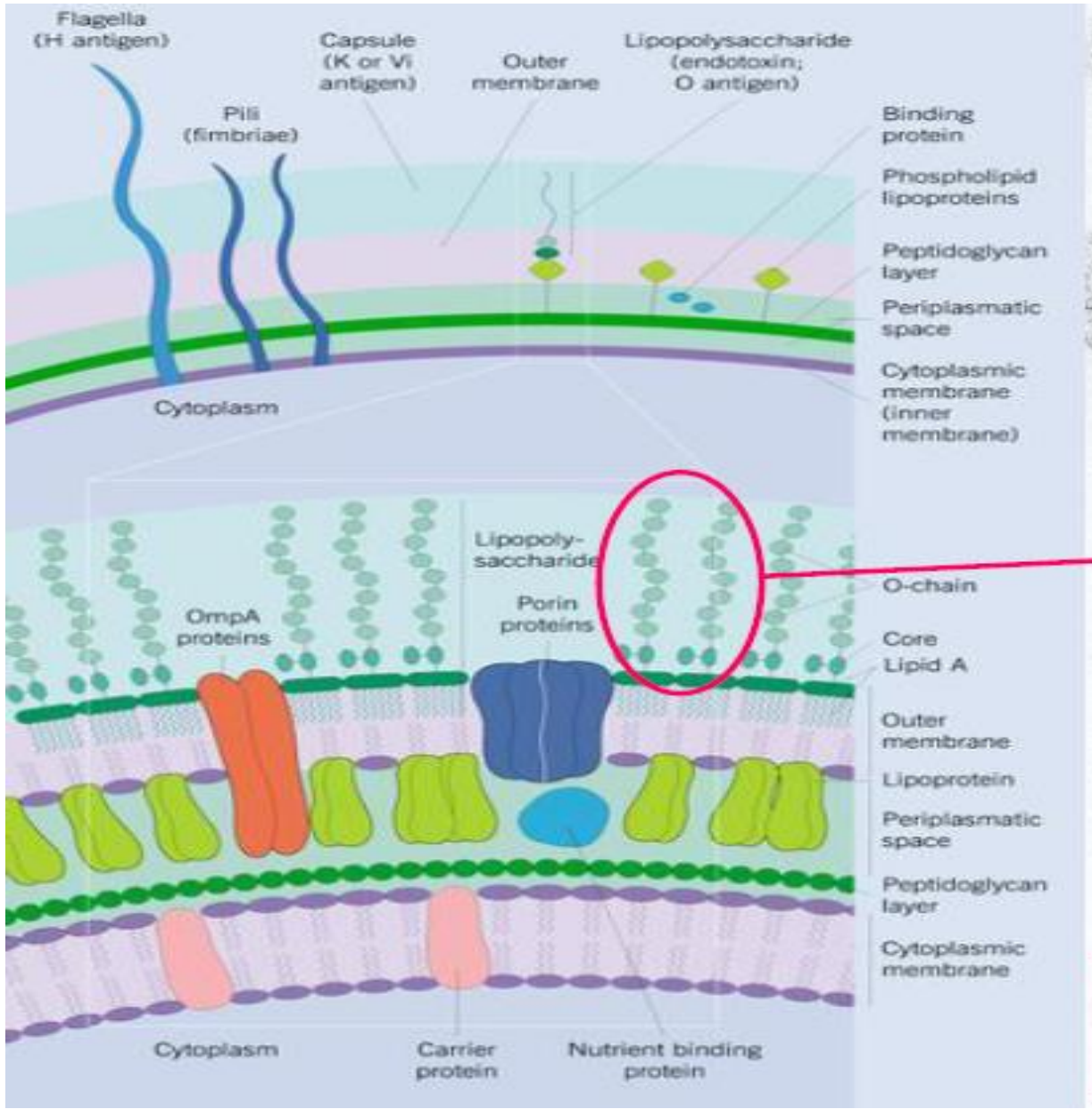
Membrana citoplasmatica (CM)

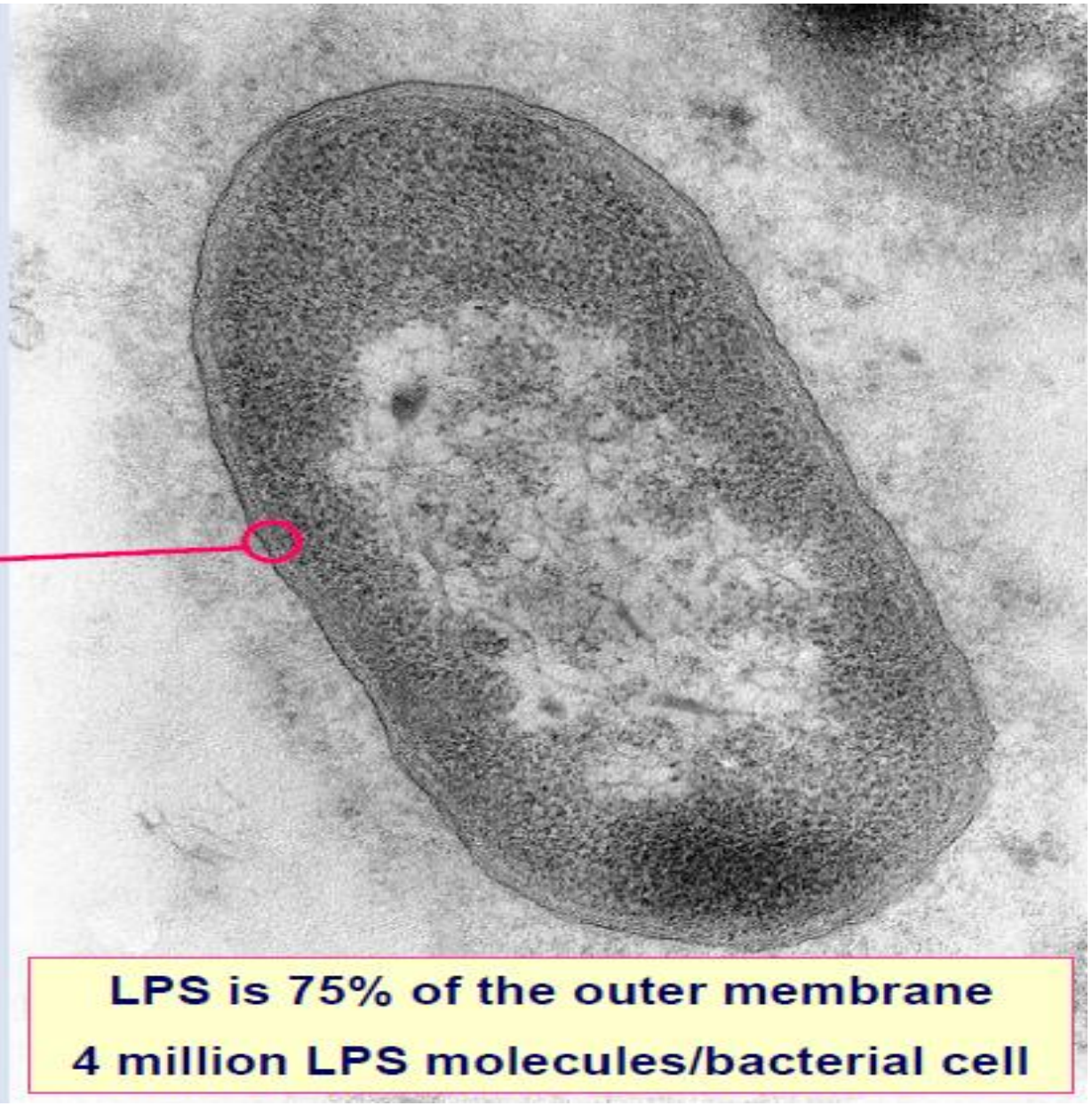
Strato peptidoglicano (PL)

Membrana esterna (LPS)



STRUTTURA MOLECOLARE DEL LIPOPOLISACCARIDE (LPS)

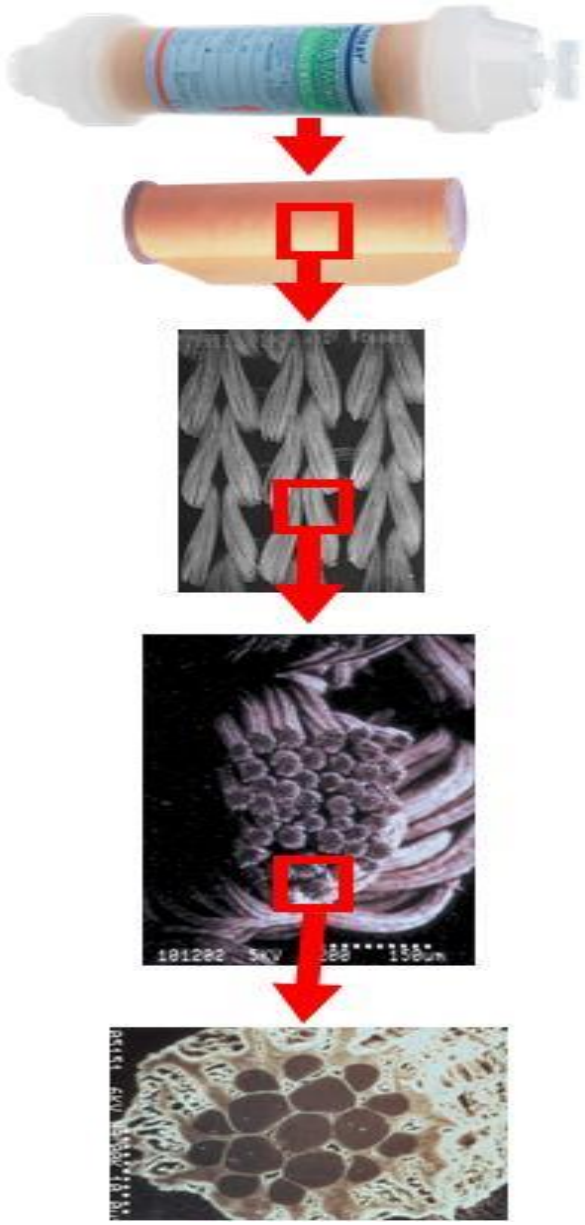


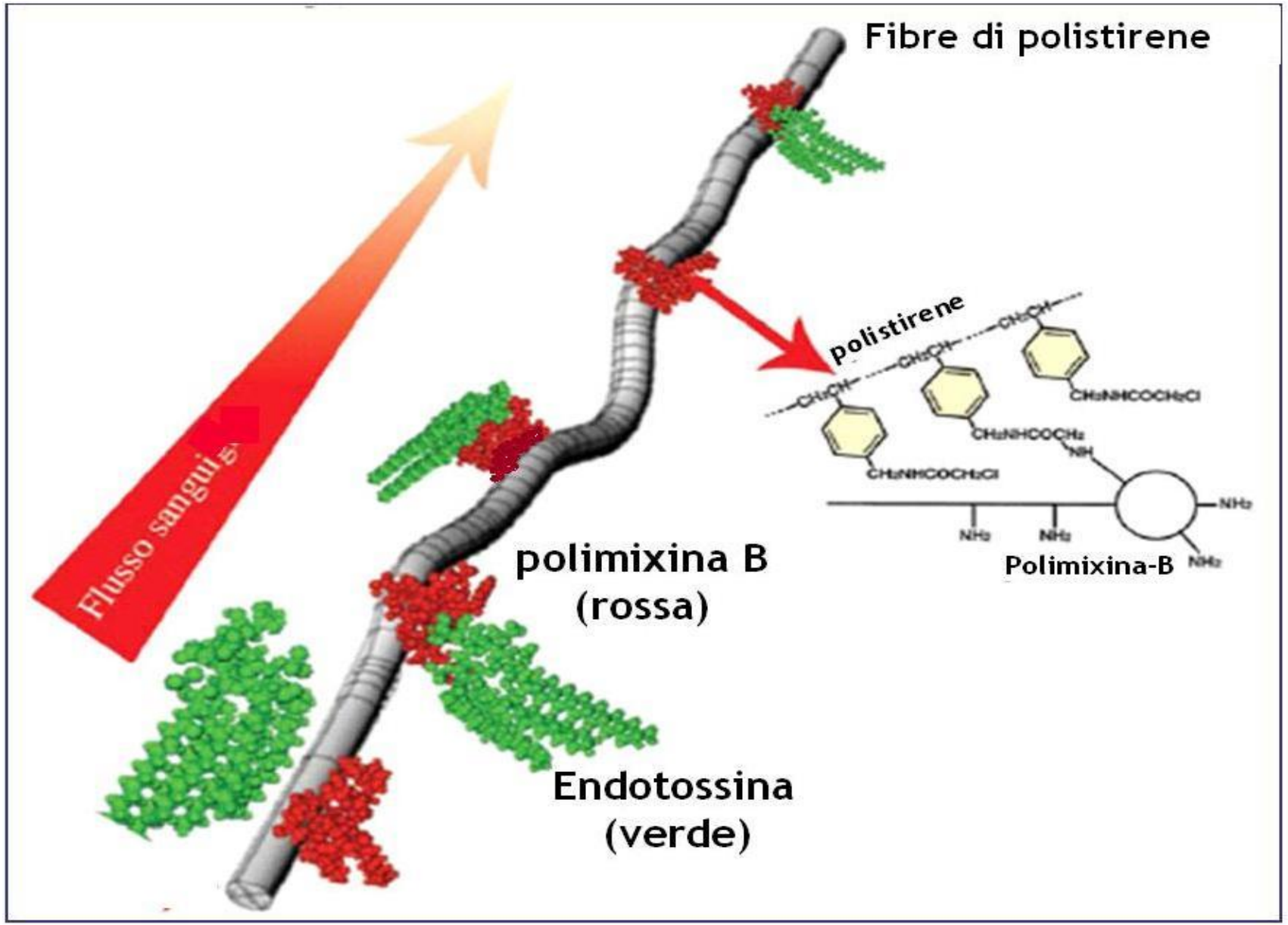


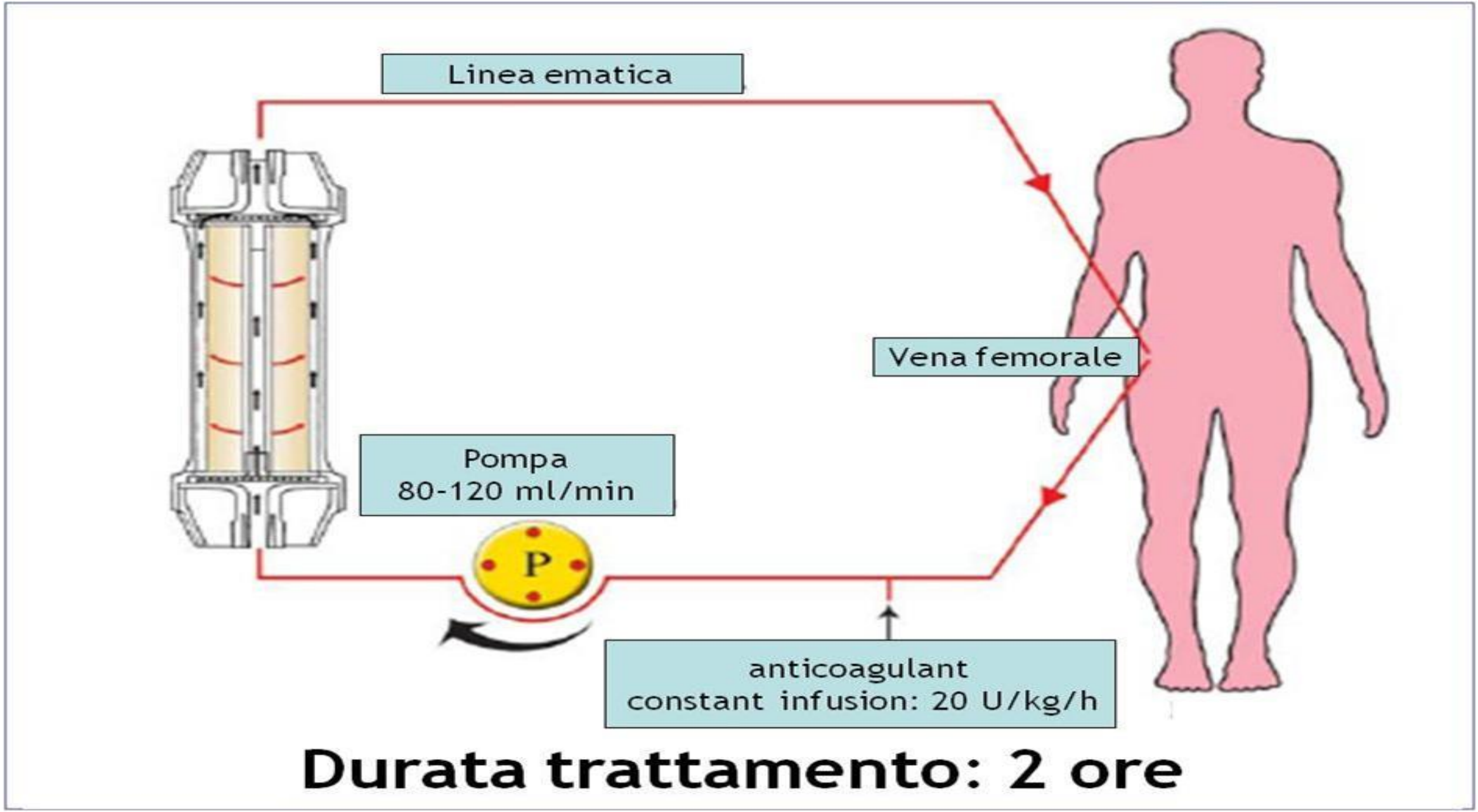
LPS is 75% of the outer membrane

4 million LPS molecules/bacterial cell

POLYMYXINA B: RIMOZIONE EXTRACORPOREA DI ENDOTOSSINE

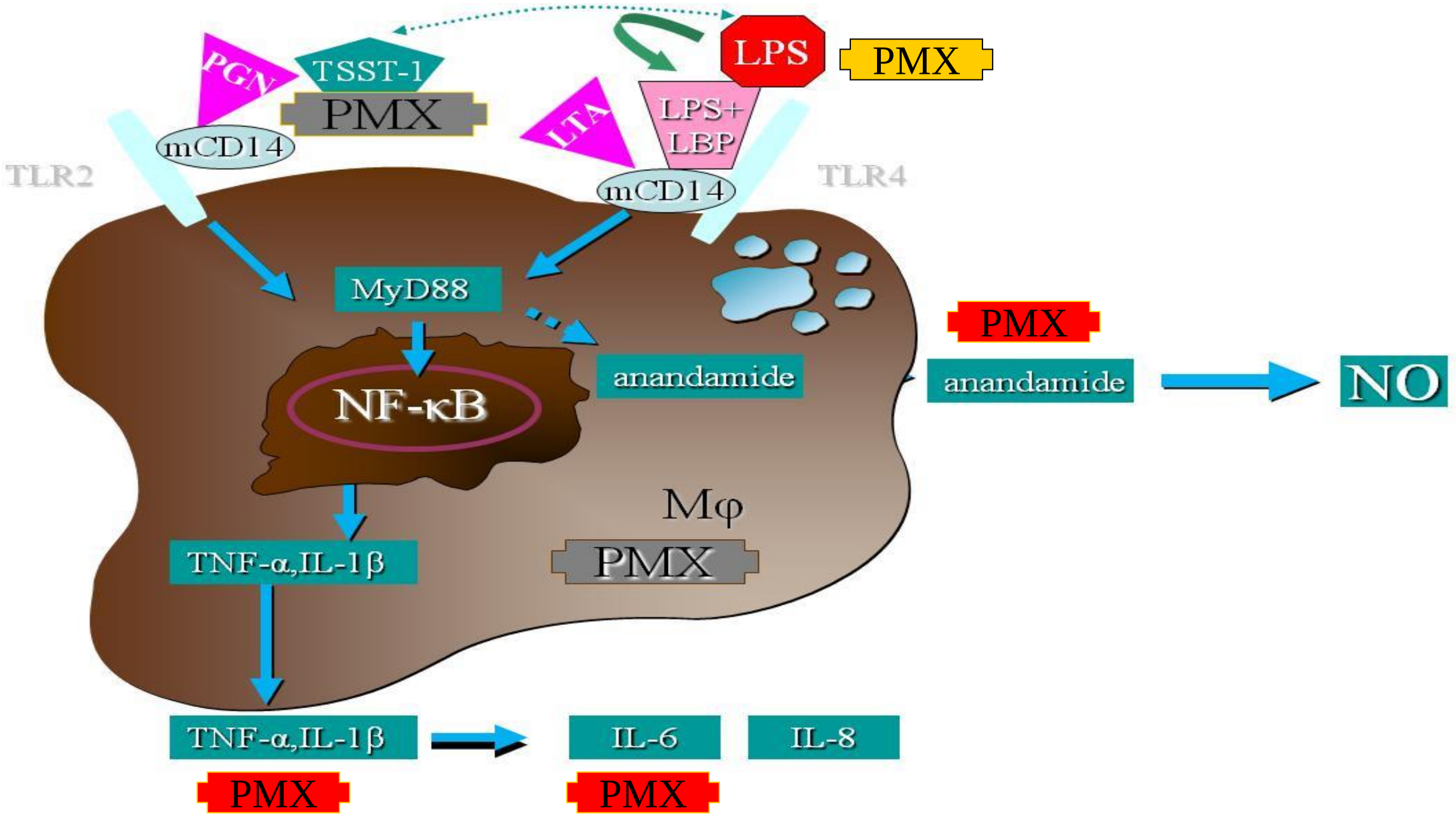




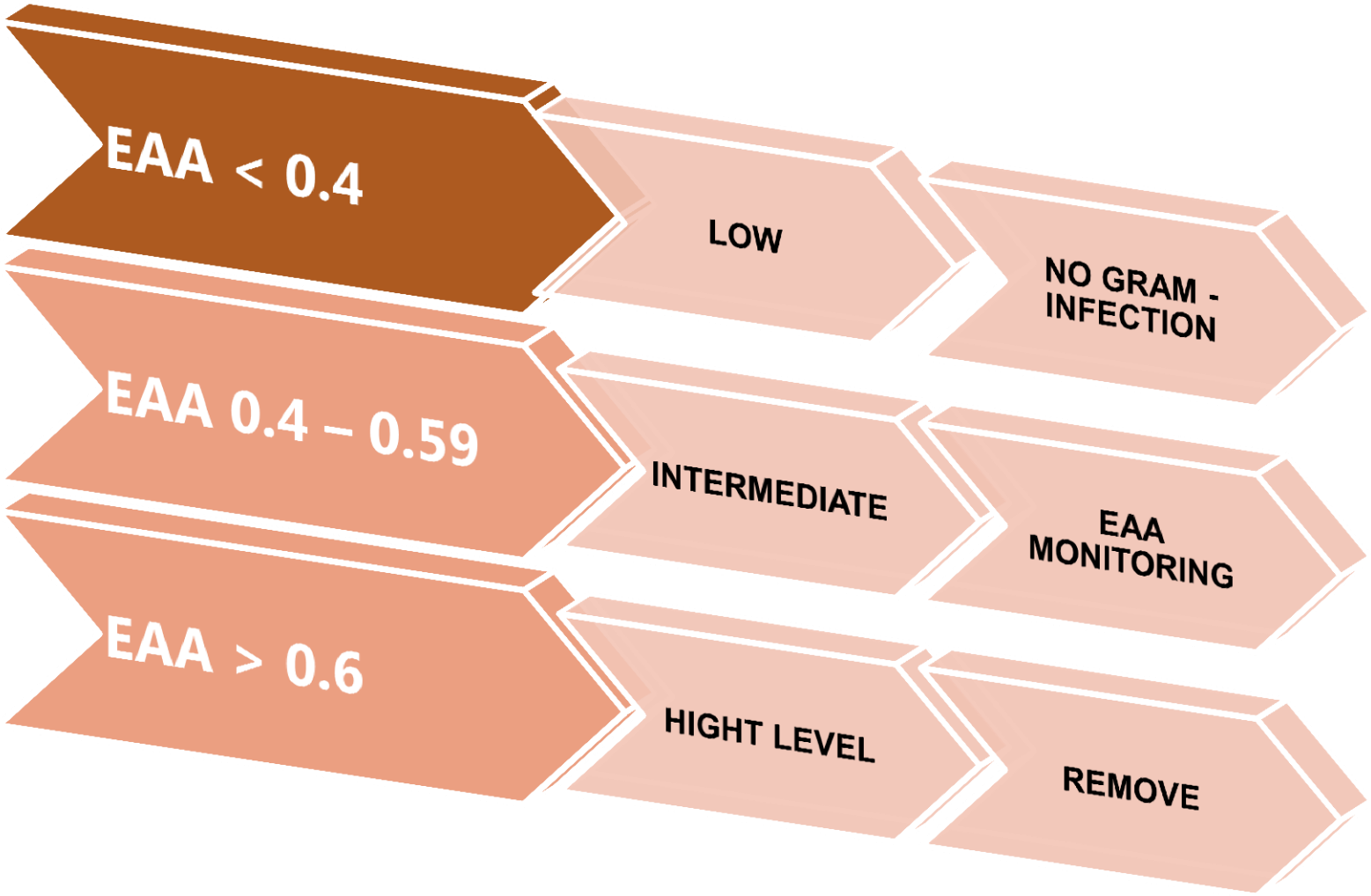


Durata trattamento: 2 ore

AZIONE MOLECOLARE DEL PMX



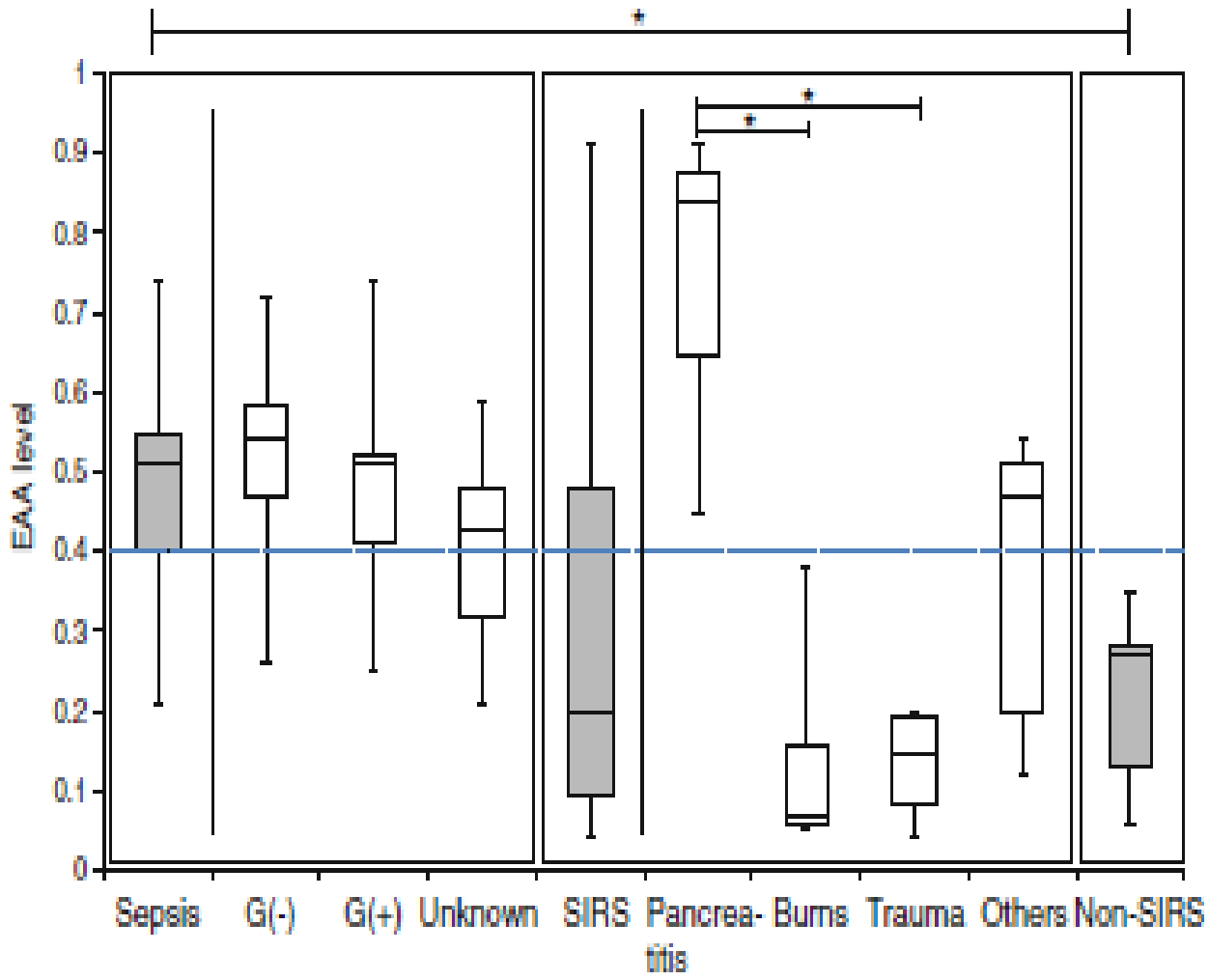
ENDOTOXIN ACTIVITY ASSAY



EAA AND ENDOTOXIN LEVELS

*CORRELATION WITH **INNATE***

***IMMUNE** SYSTEM REACTIVITY*



DEFINITION

ENDOTOXIN PLAY A PIVOTAL ROLE IN PATHOGENEIS OF **MODS**

ORGAN DISFUNCTION IS TRIGGERED BY ENDOTOXIN INTERACTION WITH IMMUNE CELLS

THE EFFECTS OF THIS INTERACTION ARE:

- APOPTOSIS
- AUTOPHAGY
- CELL CYCLE ARREST
- MICRO RNAs ACTIVATION

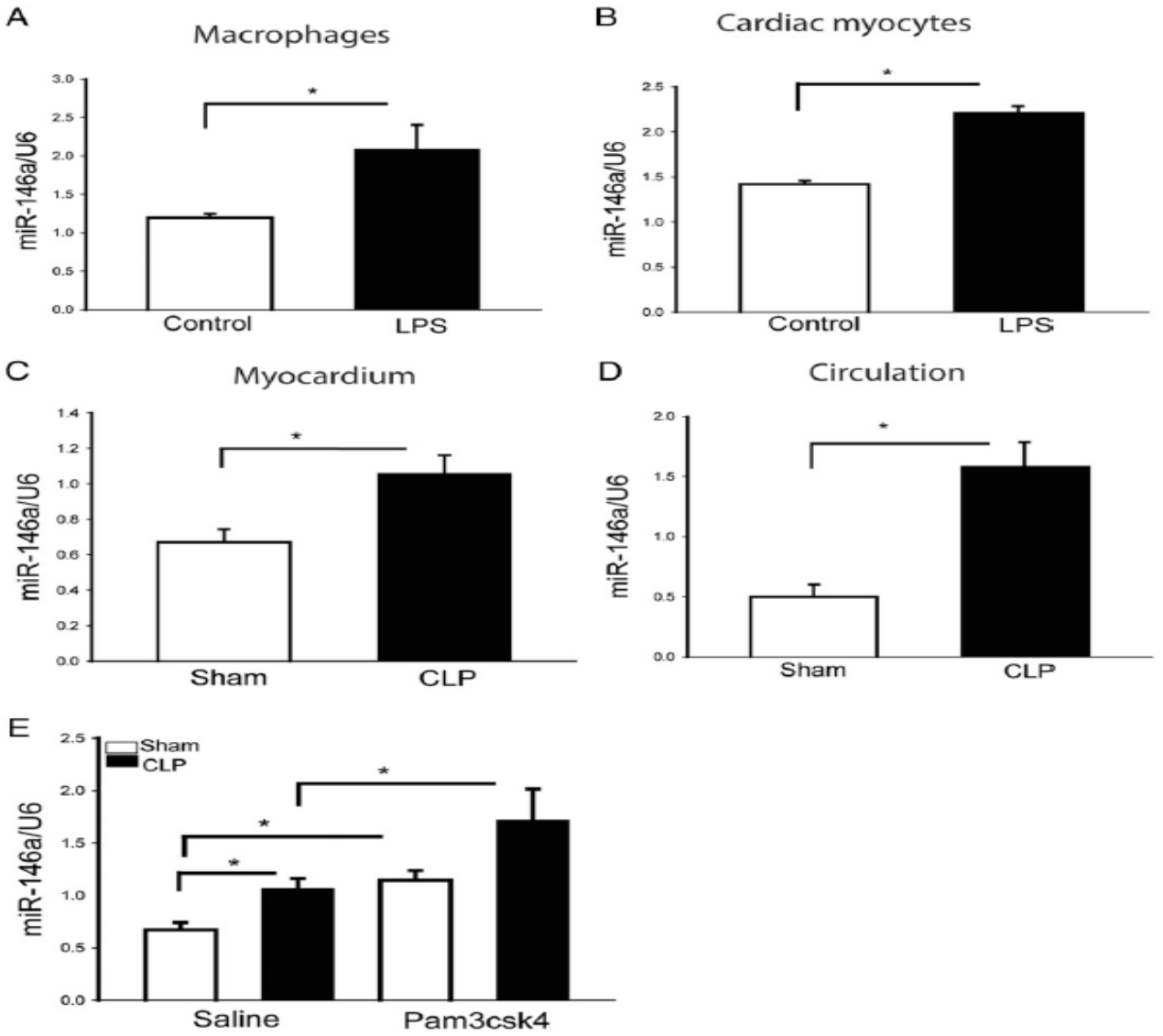
IMMUNE AND INFLAMMATORY RESPONSE

MACROPHAGES

CARDIAC MYOCYTES

MYOCARDIUM

CIRCULATION



Published June 5, 2015, doi:10.4049/jimmunol.1403155

The Journal of Immunology

Attenuation of Cardiac Dysfunction in Polymicrobial Sepsis by MicroRNA-146a Is Mediated via Targeting of IRAK1 and TRAF6 Expression

Ming Gao,*·[1] Xiaohui Wang,*·[1] Xia Zhang,* Tuanzhu Ha,*·† He Ma,* Li Liu,‡ John H. Kalbfleisch,†·§ Xiang Gao,¶ Race L. Kao,*·† David L. Williams,*·† and Chuanfu Li*·†

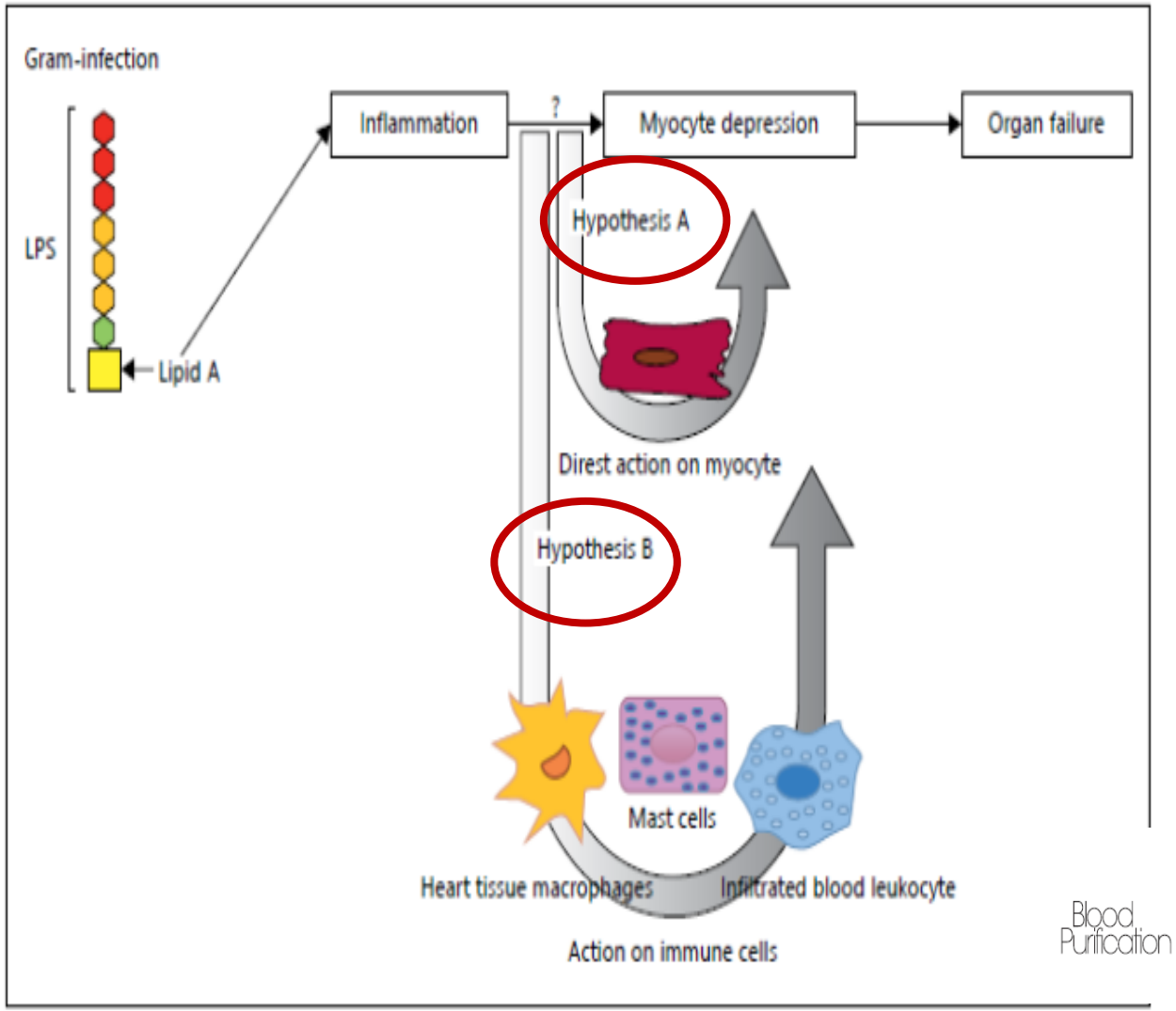
ATTENTION

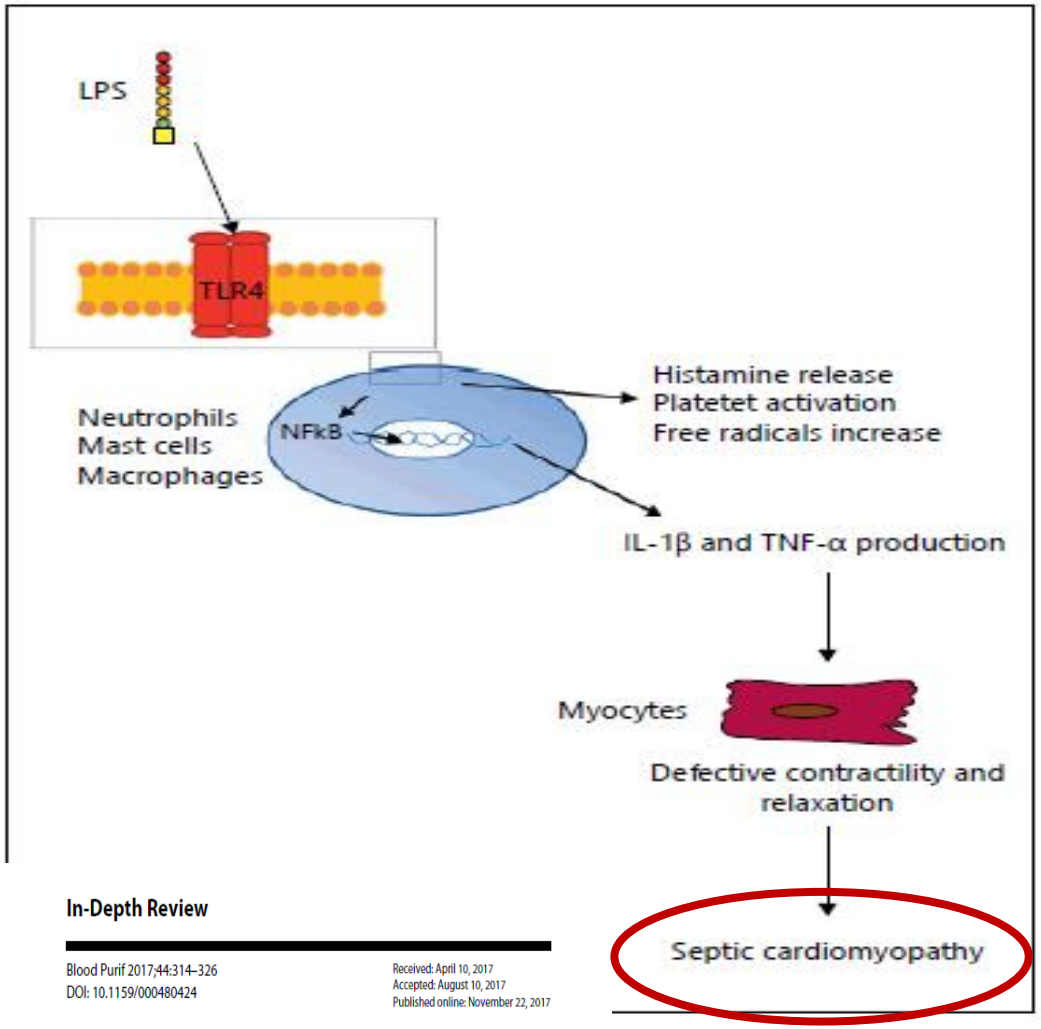
THE **EARLY INDENTIFICATION** OF ORGANE DAMAGE IMPROVE OUTCOME

- **HEART:** DIRECT TLR4 ACTIVATION INDUCE IL- 6 & TNF-ALFA ACTIVATION WITH A DIRECT CARDIAC INJURY

- **KIDNEY:** NOT CLEAR INVOLVED MECHANISM;IMPAREMENT OF RENAL BLOOD FLOW,GLOMERULAR FILTRATION RATE,TUBULAR DISFUNCTION

ORGAN DAMAGE





In-Depth Review
Blood Purif 2017;44:314–326
DOI: 10.1159/000480424
Received: April 10, 2017
Accepted: August 10, 2017
Published online: November 22, 2017

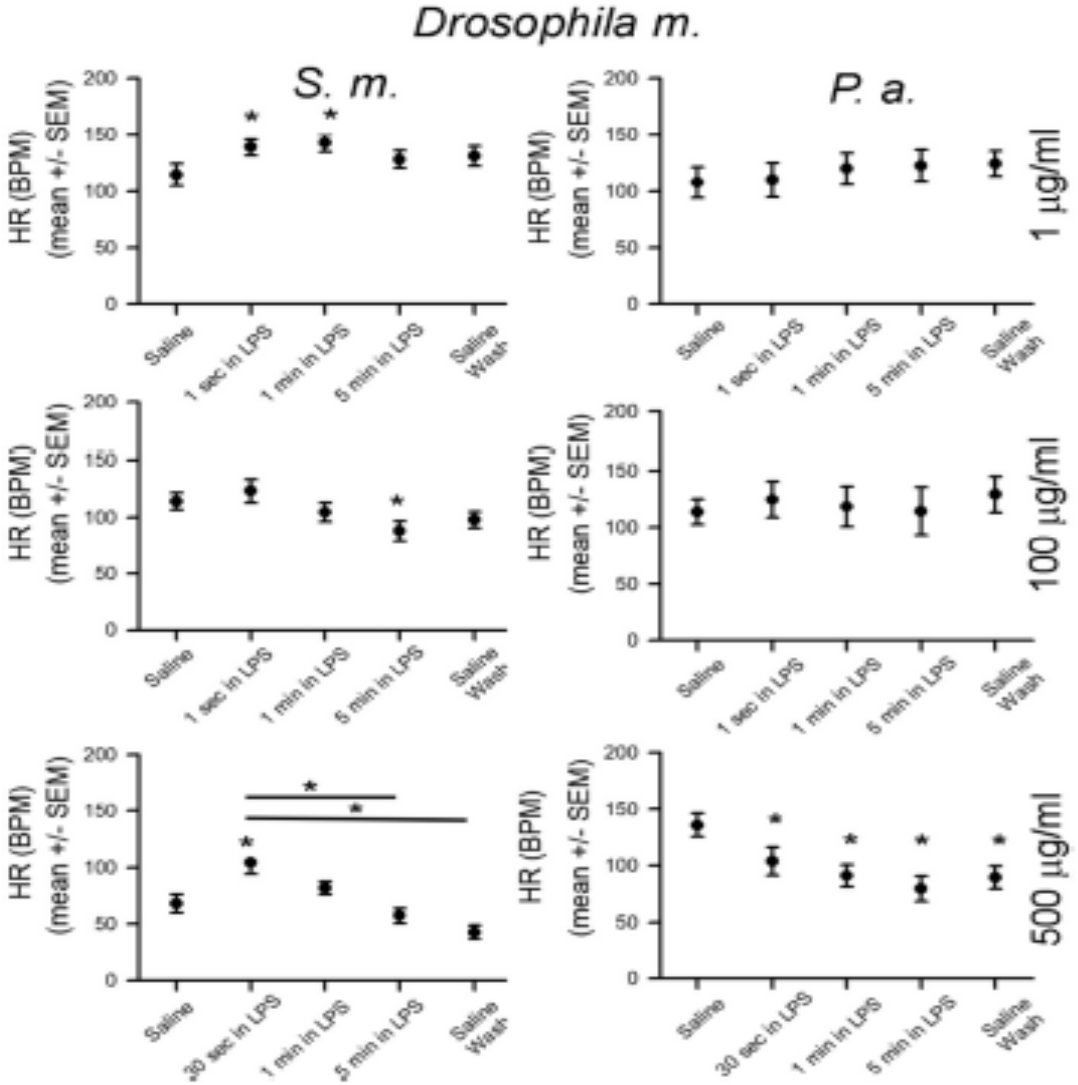
ENDOTOXIN AND HEART

ENDOTOXIN ITESELF CAUSE **MYOCARDIAL DISFUNCTION** DUE TO IS EFFECT ON SARCOPLASMATC LEAK

- *REDUCE SYSTOLIC Ca 2+ TRANSIENT*
- *REDUCE MYOCITE CONTRACTION*

COMMON HYPERCALCEMIC CONDICTION DURING SPETIC SHOCK

INCREASE ProCT



Comparative Biochemistry and Physiology, Part C 217 (2019) 15–24

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journal homepage: www.elsevier.com/locate/cbpc

CARDIOCIRCULATORY HOMEOSTASIS

HEART

- IMPAIRED CARDIAC FUNCTION
- MICROVASCULAR BLOOD FLOW
- MYTOCHONDRIAL ABNORMALITIES
- AUTONOMIC DISFUNCTION

ENODOTOXIN HEART EFFETCS

- LOAD DEPENDENT INDEX
- LEFT VENTRICULAR PRESSURE
- EJECTION FRACTION

CARDIAC LOADING CONDICTIONS

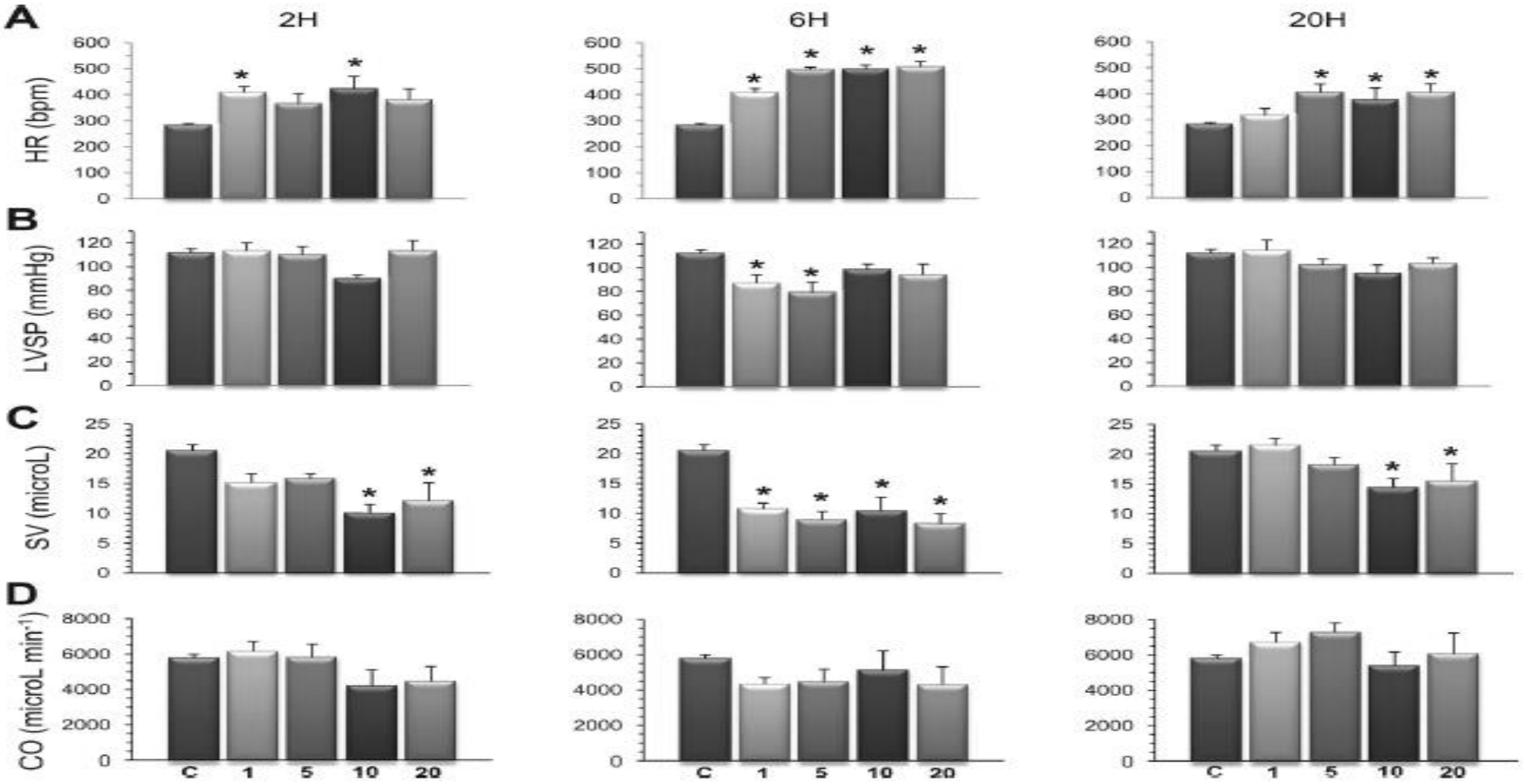
ENDOTOXIN AND HEART

MAJOR HEMODYNAMICS VARIABLES

Endotoxin impairs cardiac hemodynamics by affecting loading conditions but not by reducing cardiac inotropism

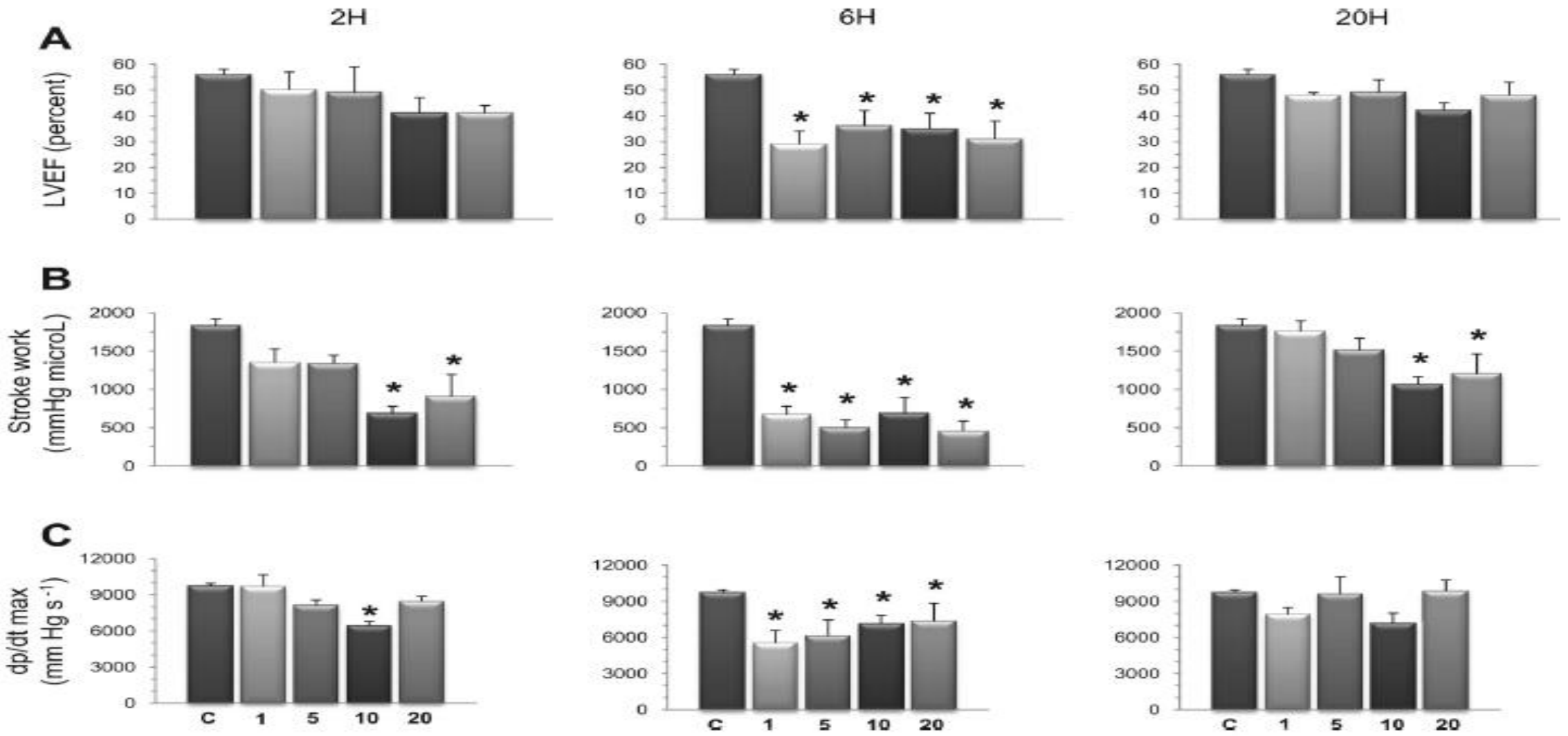
Li Jianhui, Nathalie Rosenblatt-Velin, Noureddine Loukili, Pal Pacher, François Feihl, Bernard Waeber and Lucas Liaudet

Am J Physiol Heart Circ Physiol 299:H492-H501, 2010. First published 4 June 2010;
doi: 10.1152/ajpheart.01135.2009



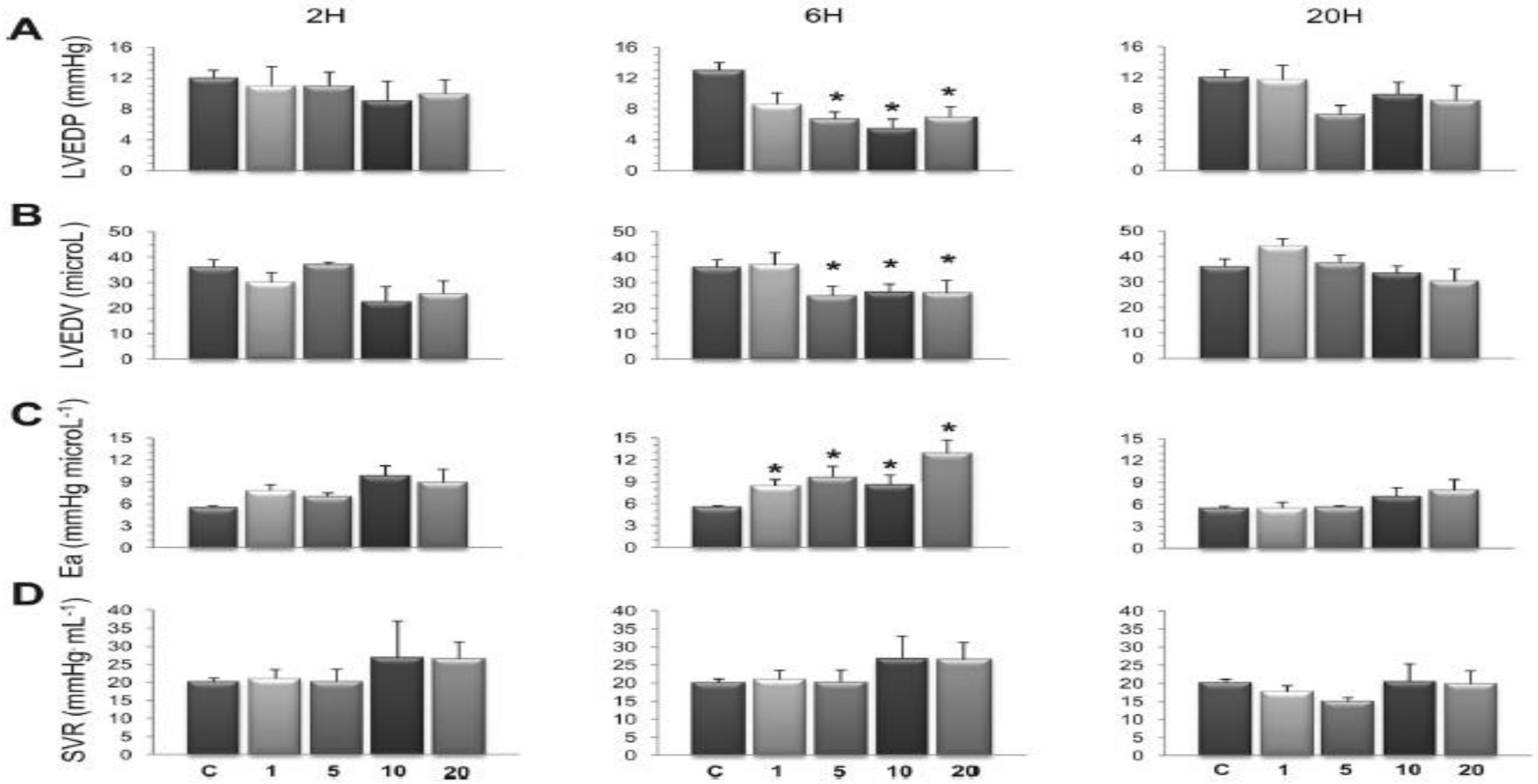
ENODOXIN AND HEART

LOAD DEPENDENT INDEX



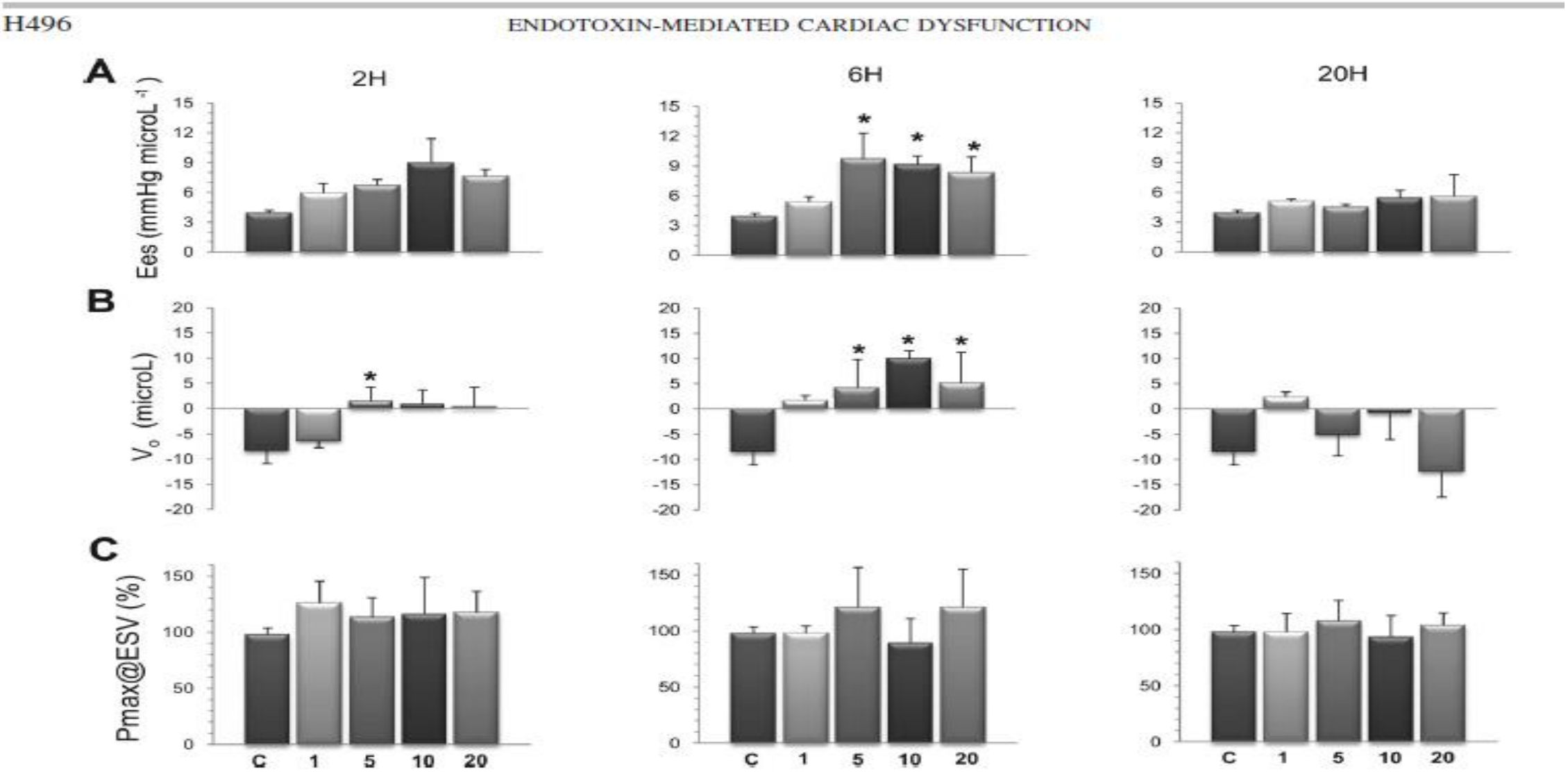
ENDOTOXIN AND HEART

LOADING CONDICTION OF LV

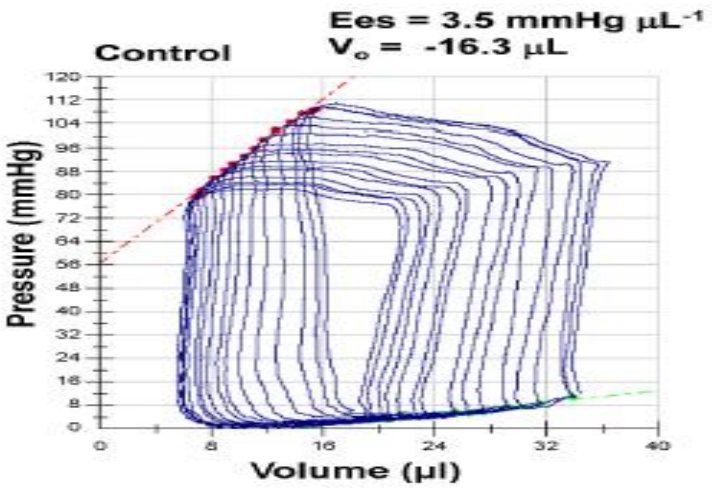


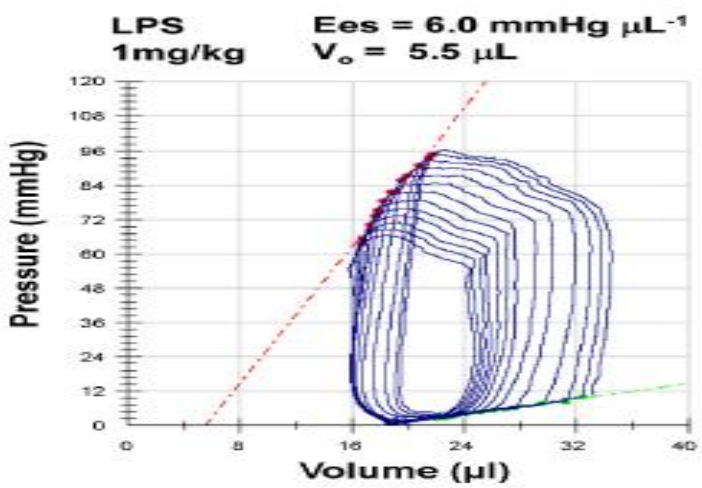
ENDOTOXIN AND HEART

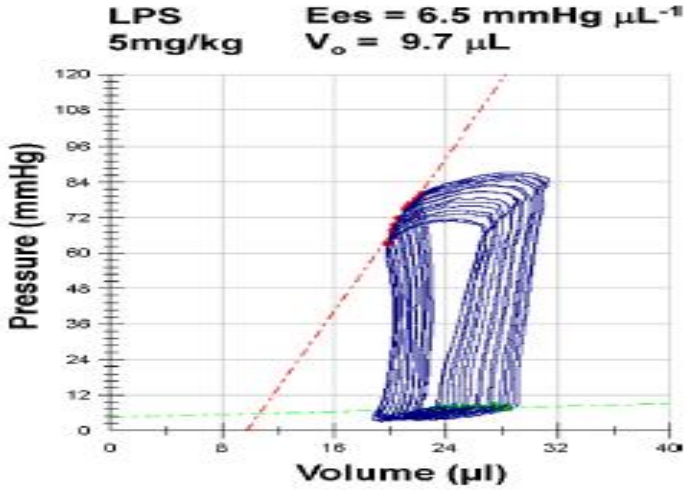
END SYSTOLIC PRESSURE VOLUME

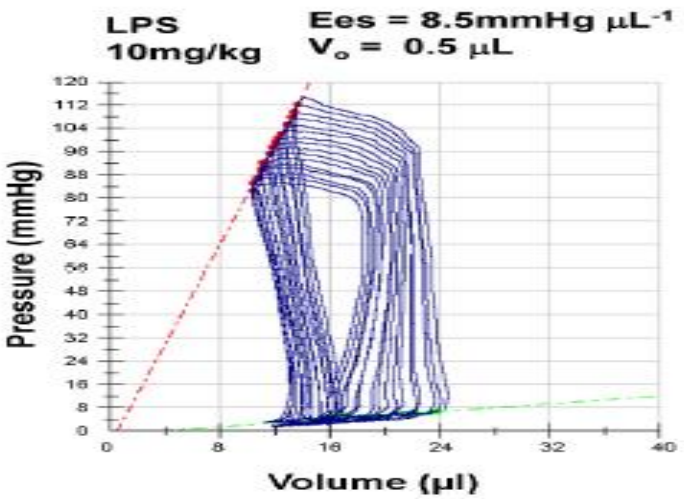


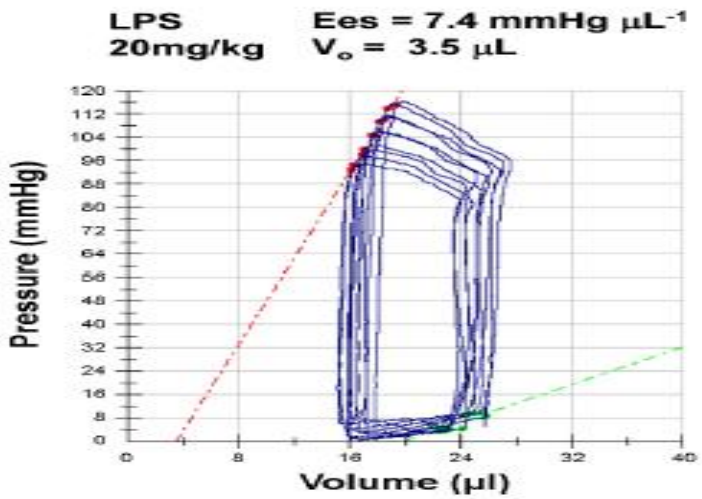
PV LOOPS


Control
Ees = 3.5 mmHg µL⁻¹
Vo = -16.3 µL
Pressure (mmHg)
Volume (µl)


LPS
1mg/kg
Ees = 6.0 mmHg µL⁻¹
Vo = 5.5 µL
Pressure (mmHg)
Volume (µl)

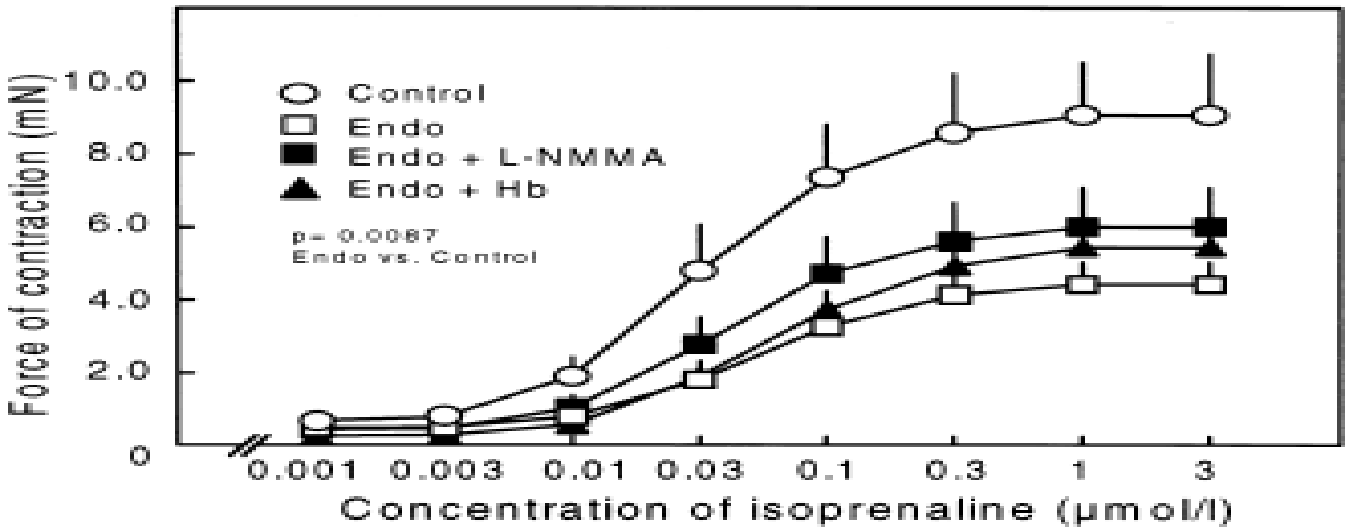

LPS
5mg/kg
Ees = 6.5 mmHg µL⁻¹
Vo = 9.7 µL
Pressure (mmHg)
Volume (µl)

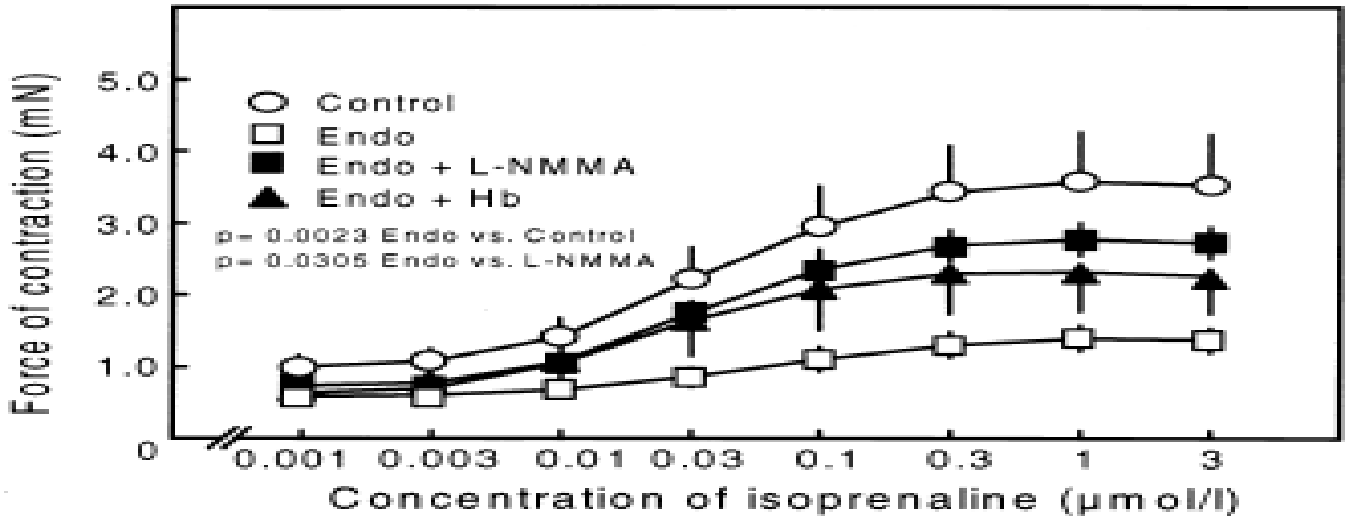

LPS
10mg/kg
Ees = 8.5mmHg µL⁻¹
Vo = 0.5 µL
Pressure (mmHg)
Volume (µl)


LPS
20mg/kg
Ees = 7.4 mmHg µL⁻¹
Vo = 3.5 µL
Pressure (mmHg)
Volume (µl)

LEFT VENTRICULA FAILURE

ENDOTOXIN EFFECT ON FORCE OF CONTRACTION





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PII S0735-1097(98)00660-3

EXPERIMENTAL STUDY

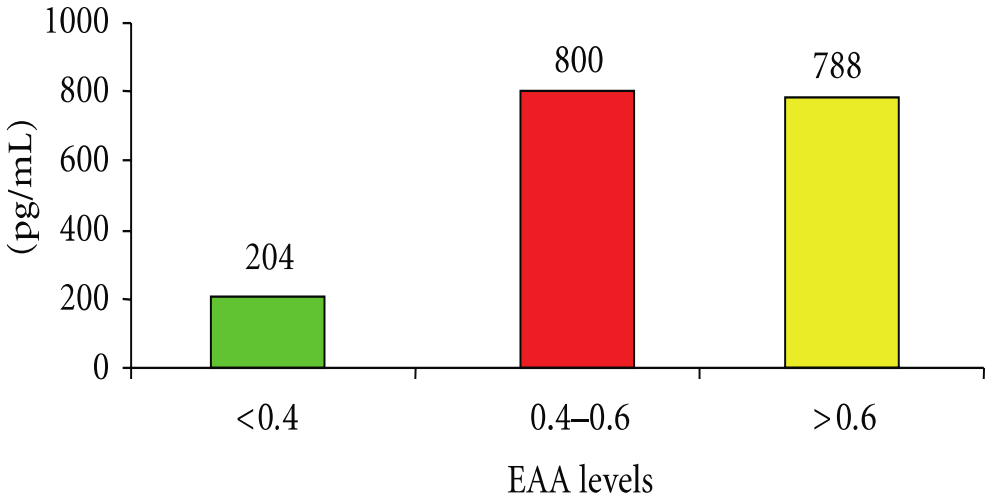
Effects of Endotoxin on Human Myocardial Contractility
Involvement of Nitric Oxide and Peroxynitrite

Markus Flesch, MD, Heiko Kilter, MD, Bodo Cremers, MS, Ulrich Laufs, MD, Michael Südkamp, MD,*
Monika Ortmann, MD,† Frank U. Müller, MD,‡ Michael Böhm, MD
Cologne and Münster, Germany

B-TYPE NATRIURETIC PEPTIDE

SEPTIC MYOCARDIAL DISFUNCTION

Crit Care Res Pract. 2012;2012:856401



(b) BNP, $P = 0.02$

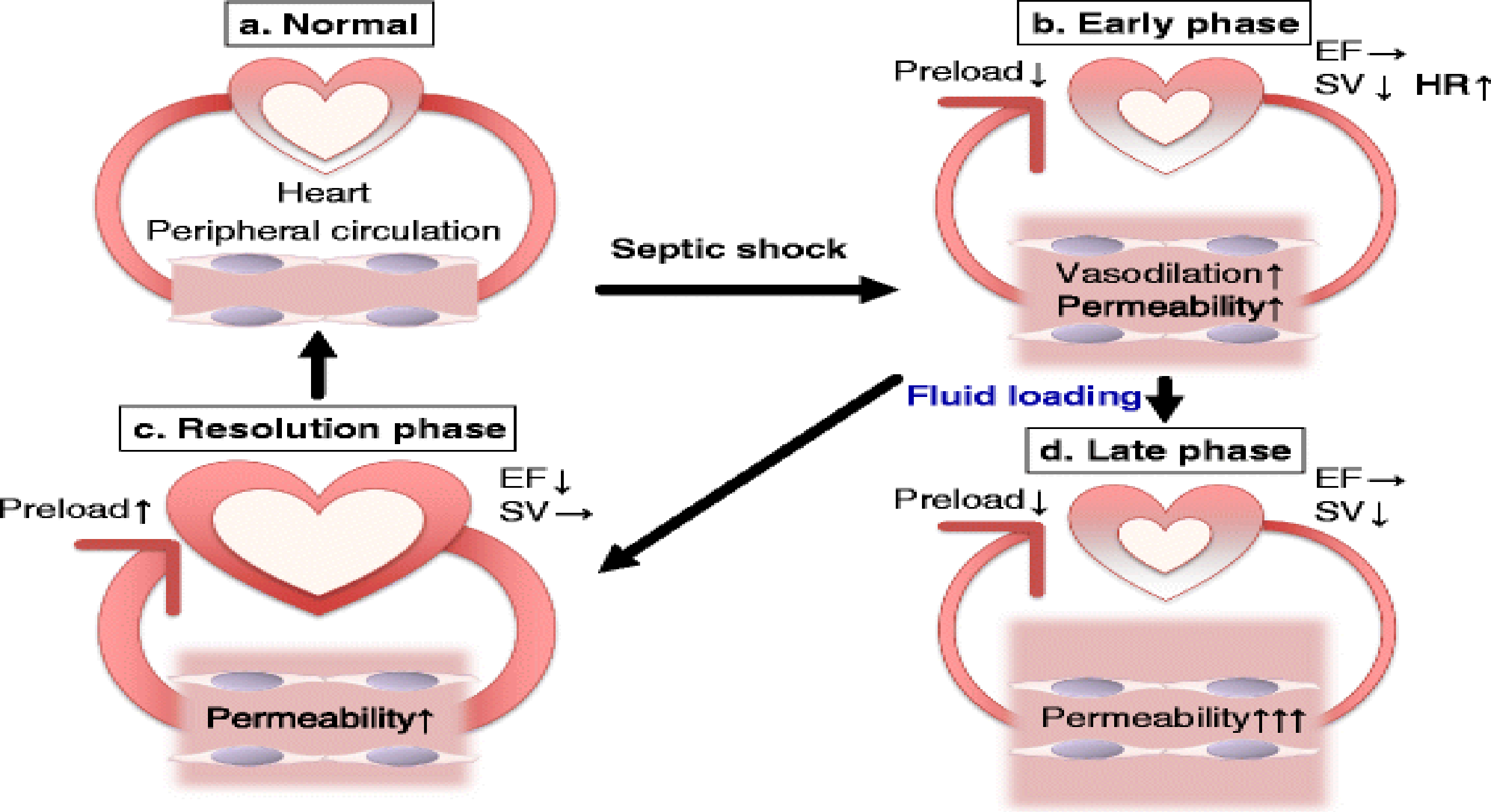
Table 3. Markers Before and After Polymyxin B-Immobilized Fiber Hemoperfusion Treatment

	Before	After Second Treatment	Following Day
Endotoxin (pg/ml)	48.6 ± 22.4	8.4 ± 2.2*	4.0 ± 1.6†‡
IL-6 (pg/ml)	6,240 ± 2840	224 ± 62*	88 ± 26†§
ANP (pg/ml)	120.6 ± 26.8	38.6 ± 10.6*	28.4 ± 6.5*‡
BNP (pg/ml)	328.5 ± 68.0	80.0 ± 34.0*	32.0 ± 14.0†§
EF (%)	40 ± 12	52 ± 10*	58 ± 8†‡

Versus before: * $p < 0.01$ and † $p < 0.001$. *Versus* after second treatment ‡ $p < 0.05$ and § $p < 0.01$.

IL-6, interleukin-6; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; EF, ejection fraction.

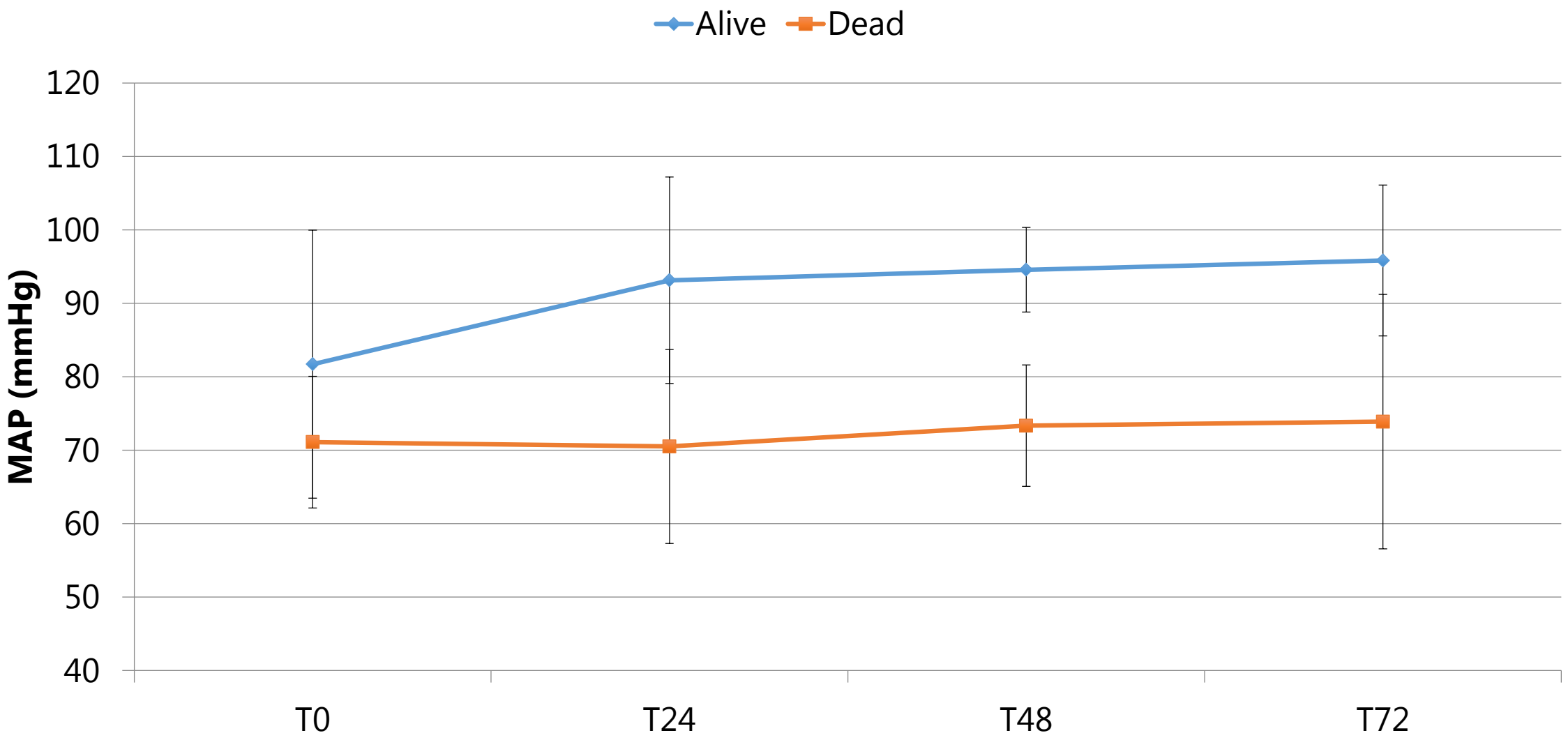
ASAIO Journal 2008; 54:210–213.


a. Normal
Heart
Peripheral circulation
Septic shock
b. Early phase
Preload↓
EF→
SV↓ HR↑
Vasodilation↑
Permeability↑
Fluid loading
c. Resolution phase
Preload↑
EF↓
SV→
Permeability↑
d. Late phase
Preload↓
EF→
SV↓
Permeability↑↑↑

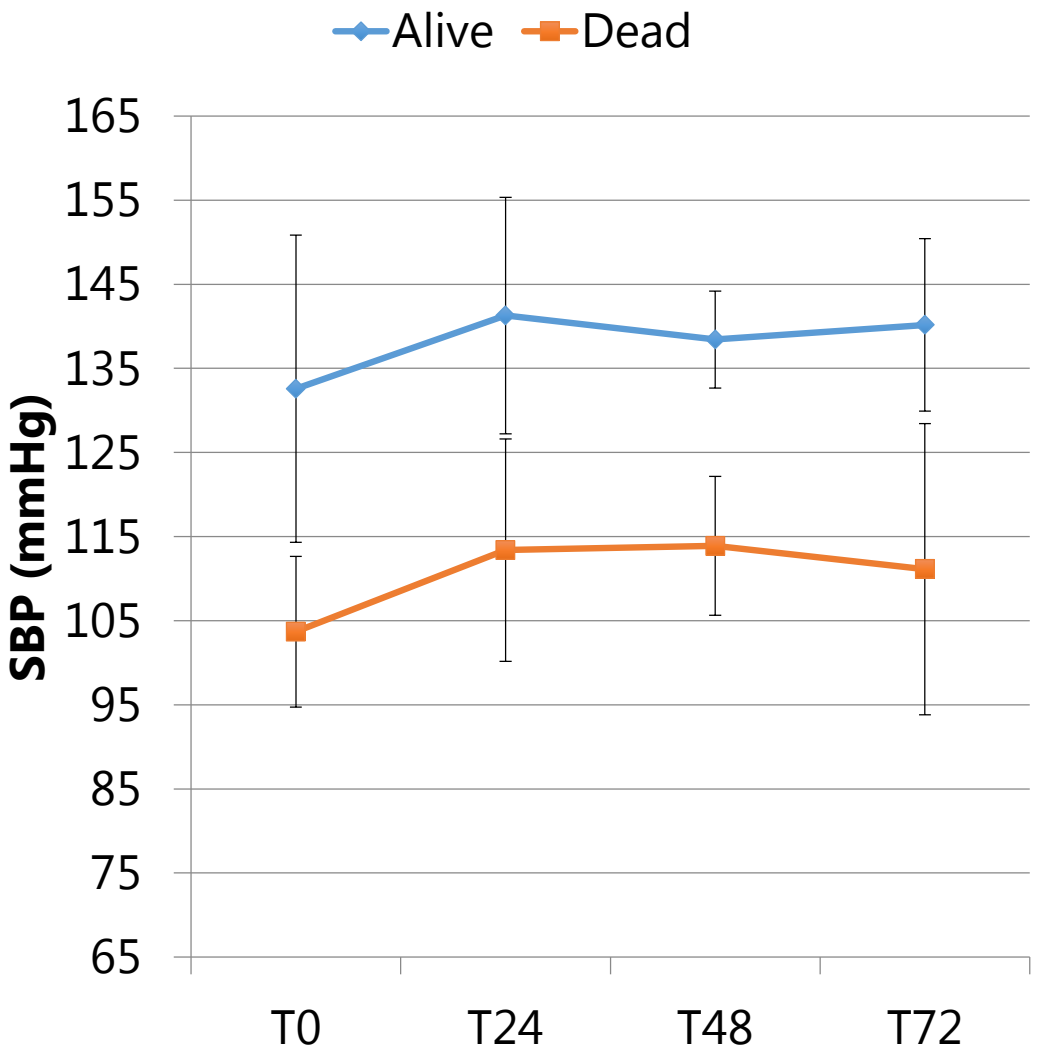
CLINICAL PARAMETERS: SURVIVORS vs NON-SURVIVORS

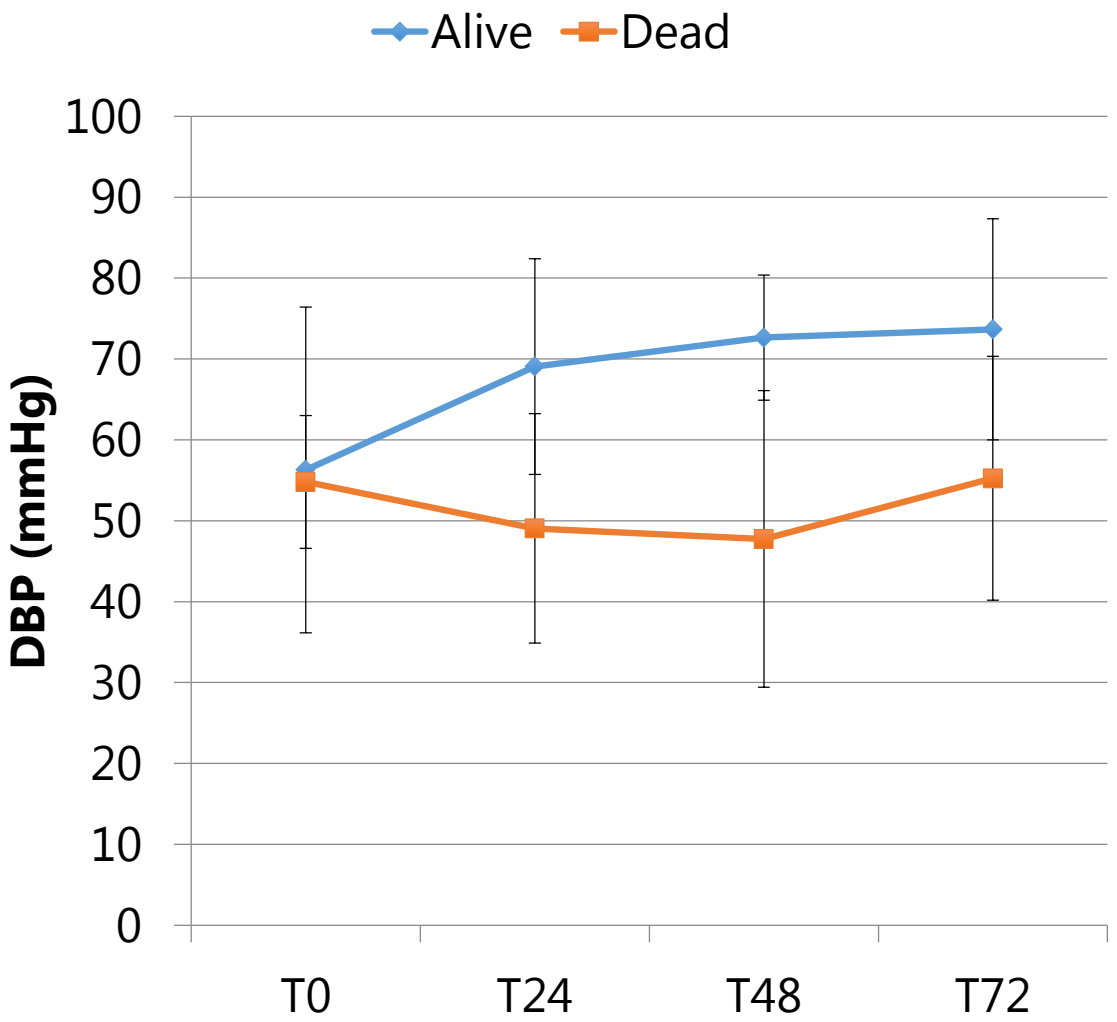
	NON-SURVIVORS	SURVIVORS	P-VALUE
SAPS II	53.4 ± 15.7	50.0 ± 11.0	0.67
SOFA SCORE	14.1 ± 3.8	12.4 ± 4.0	0.44
MEAN ARTERIAL PRESSURE (MAP)	71.1 ± 9.0	81.7 ± 18.3	0.13
INOTROPIC SCORE (IS)	20.6 ± 15.2	15.9 ± 19.3	0.55
SYSTOLIC BLOOD PRESSURE (SBP)	**103 ± 16**	**133 ± 21**	***0.005***
DIASTOLIC BLOOD PRESSURE (DBP)	54.8 ± 8.2	56.3 ± 20.1	0.83
HEART RATE (HR)	**102±22**	**81 ± 8**	***0.005***

MEAN ARTERIAL PRESSURE:SURVIVORS vs NON-SURVIVORS

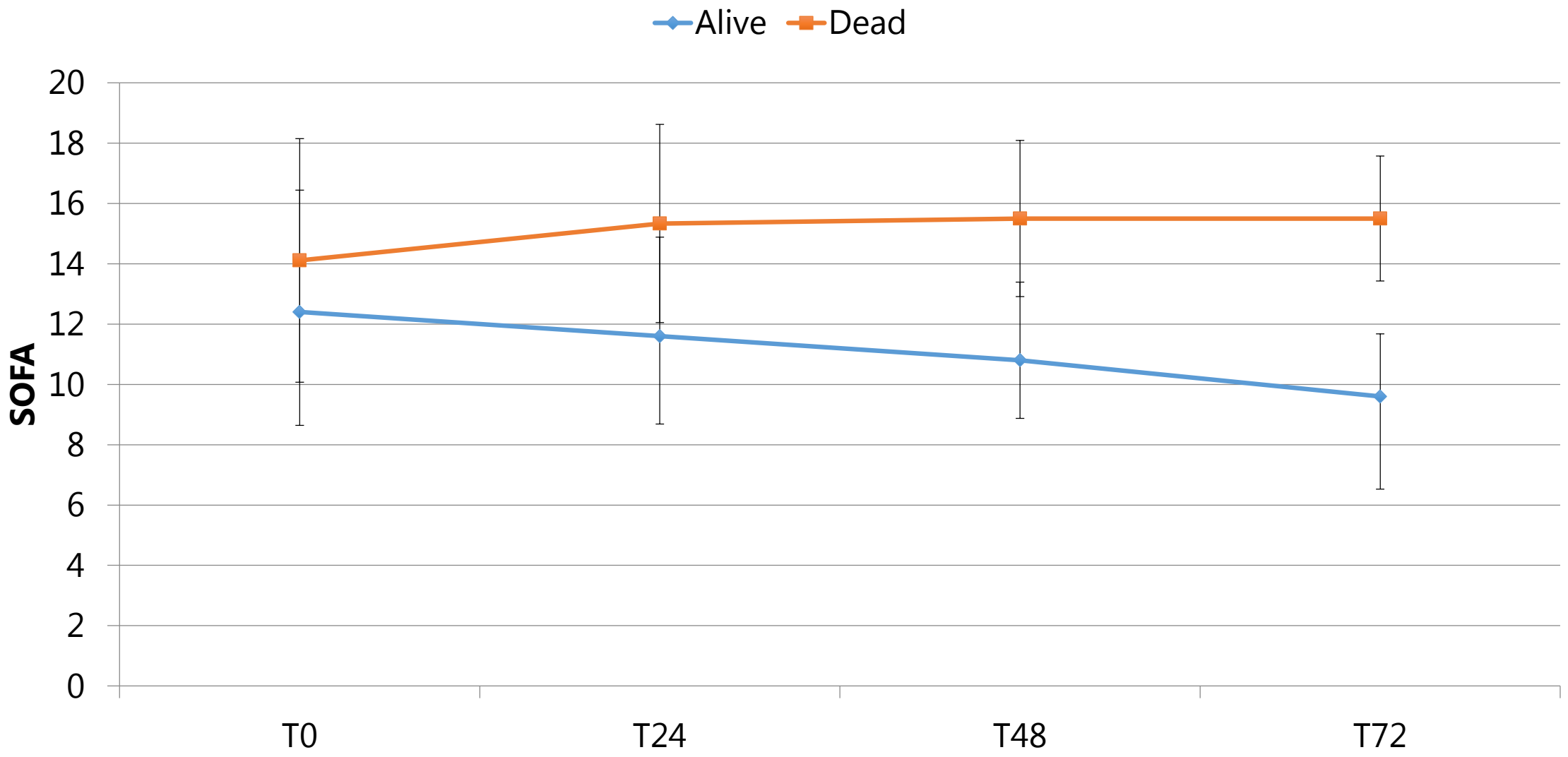


SYSTOLIC AND DIASTOLIC PRESSURES: SURVIVORS vs NON-SURVIVORS





SOFA SCORE:SURVIVORS vs NON-SURVIVORS

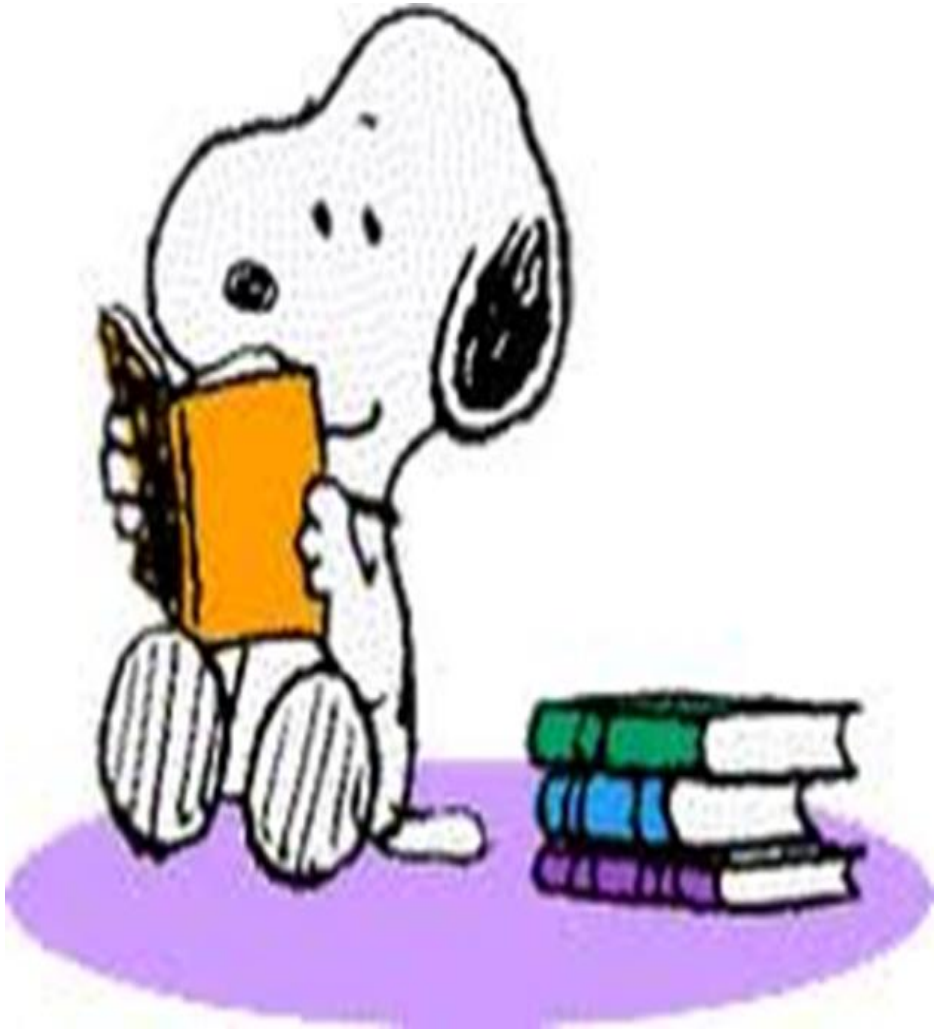


EAA CBP AND RENAL FUNCTION

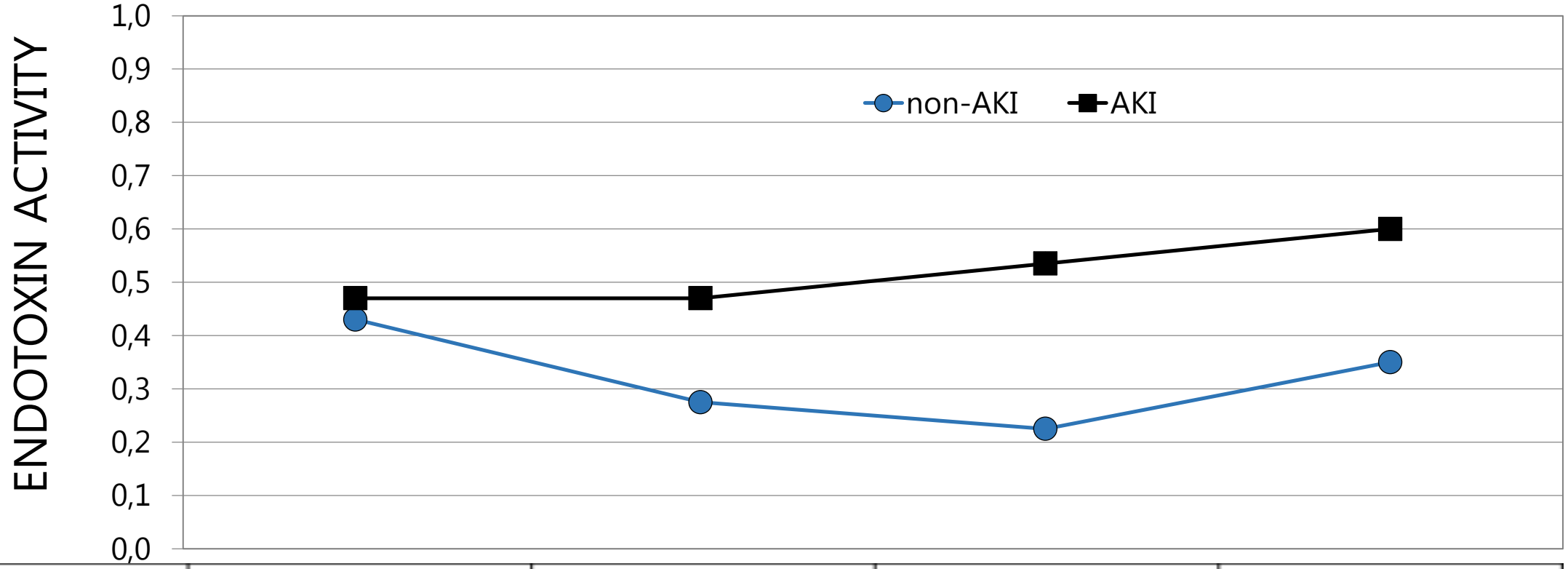
Association between Endotoxin Activity and Acute Kidney Injury in Cardiac Patients Undergoing Cardiopulmonary Bypass

Gianluca Paternoster[a] Gianni Rubino[b] Antonio Balducci[c] Rosmunda Maiorano[b] Nicola Brienza[b]

[a]U.O.C. Cardioanesthesia and Cardio-Intensive Care, San Carlo Hospital, Potenza, [b]Anesthesia and Critical Care Division, Department of Emergency and Organ Transplantation, Università degli Studi Aldo Moro, Bari, [c]Estor S.p.A. Pero, Italy



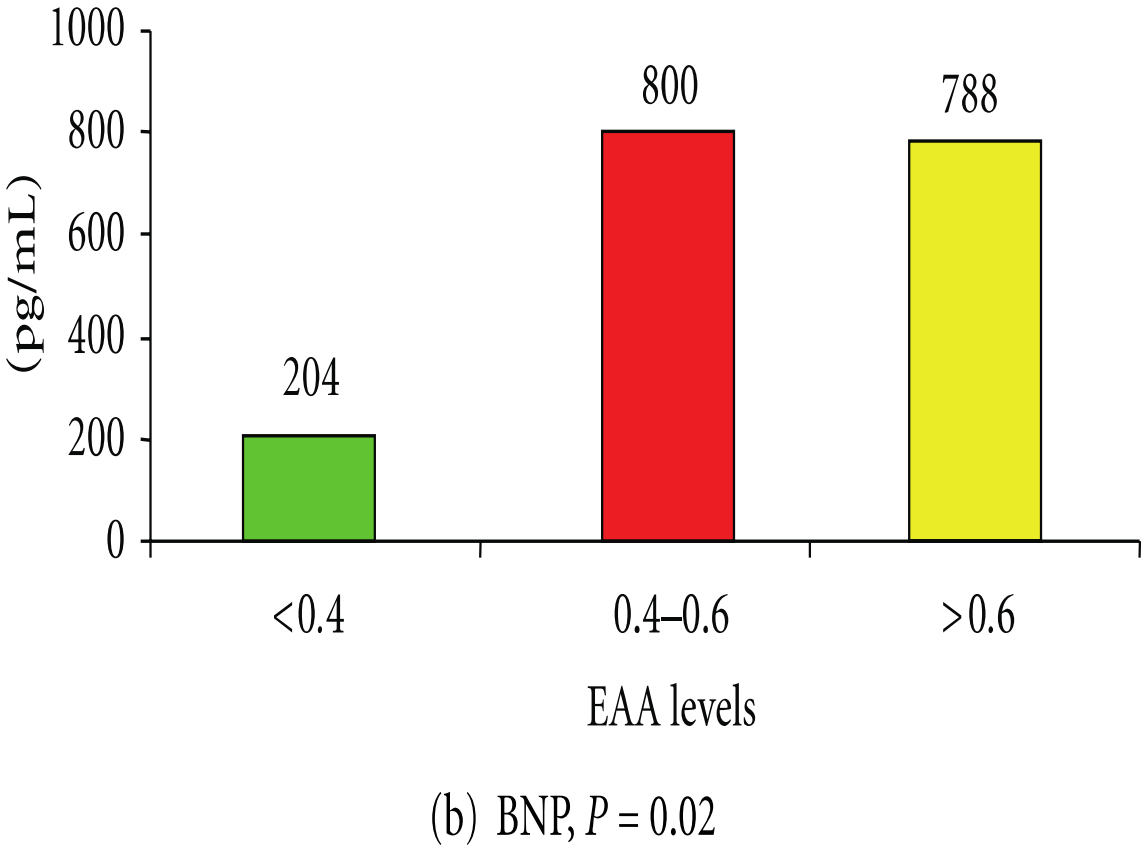
ENDOTOXEMIA IN AKI AND NON-AKI



	T0	T1	T2	T3
EA non-AKI	0.43 [0.15-0.79]	0.28 [0.05-0.67]	0.23 [0.13-0.51]	0.47 [0.16-0.60]
EA AKI	0.47 [0.04-0.78]	0.47 [0.03-0.78]	0.54 [0.07-0.71]*	0.60 [0.32-1.0]§ #

§ p=0.004 T3 vs. T0 Wicoxon signed rank test for paired data
* p=0.0044 non-AKI vs AKI at T2: Wincoxon (Mann-Whytney test for unpaired data)
# p=0.014 non-AKI vs AKI at T3: Wincoxon (Mann-Whytney test for unpaired data)

ENDOTOXIN AND ORGANE FAILURE

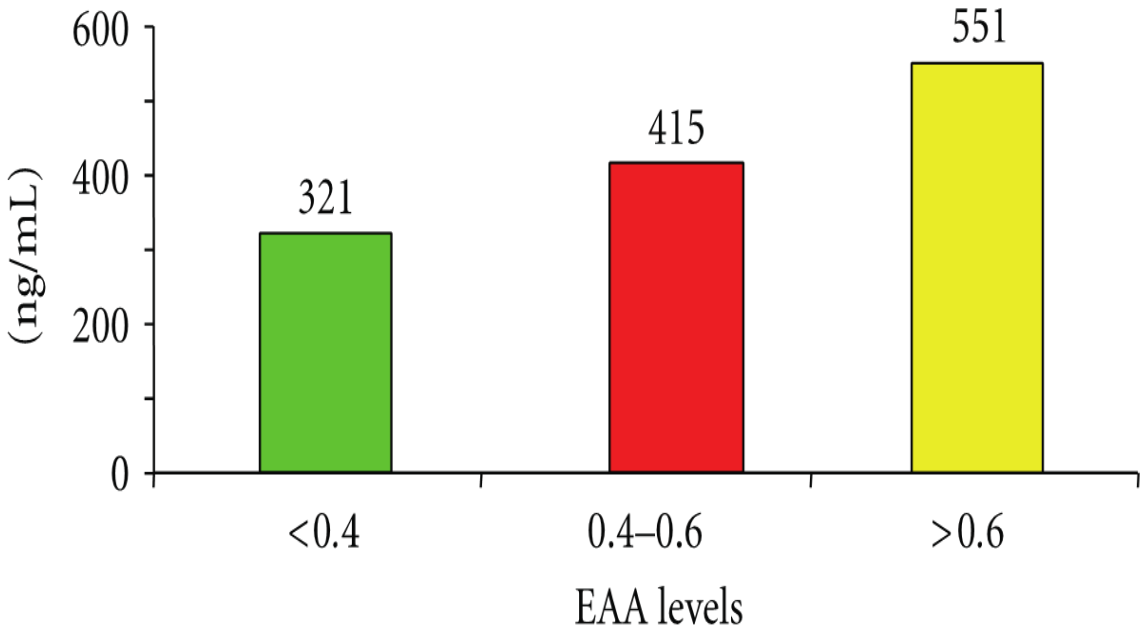


(b) BNP, $P = 0.02$

Research Article

Sepsis and AKI in ICU Patients: The Role of Plasma Biomarkers

Paolo Lentini,[1,2] Massimo de Cal,[2,3] Anna Clementi,[3] Angela D'Angelo,[2] and Claudio Ronco[3]



(a) NGAL

Critical Care Research and Practice Volume 2012, Article ID 856401, 5 pages doi:10.1155/2012/856401

CLINICAL SCENARIO

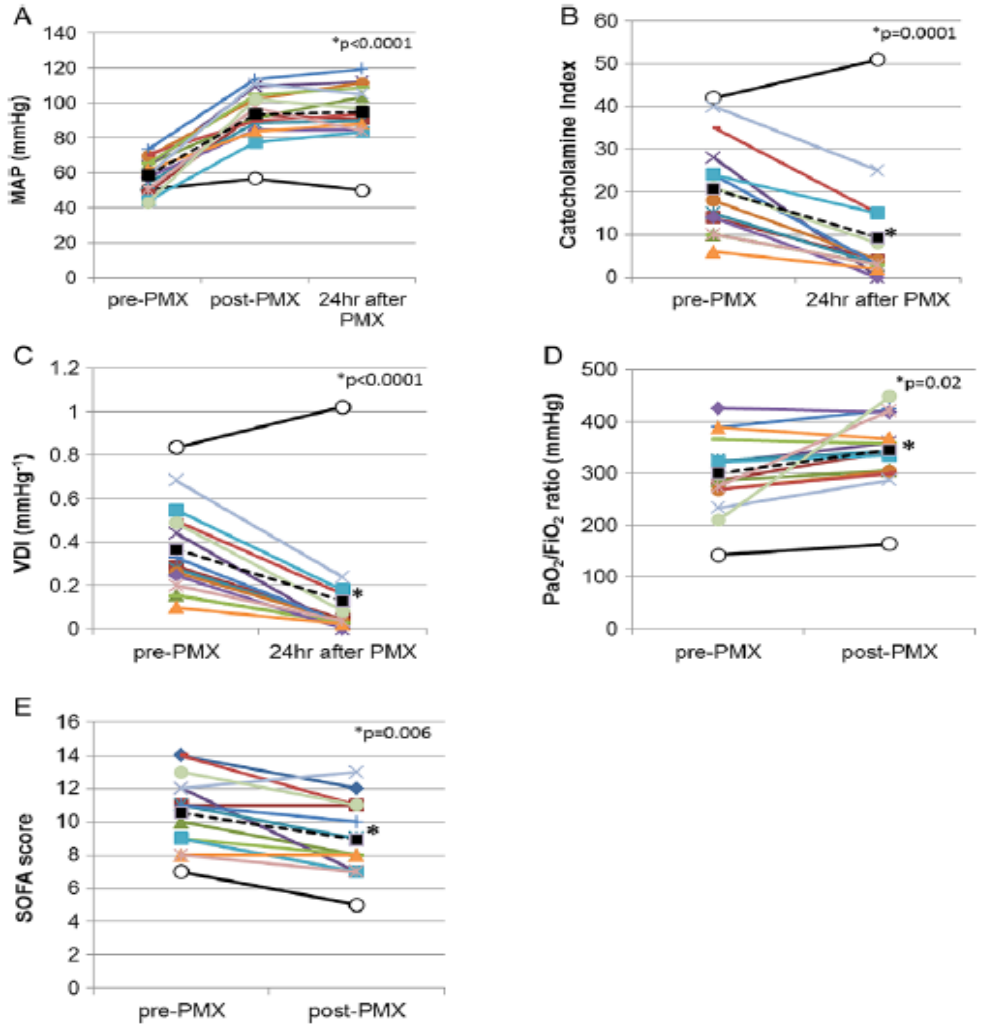


FIG. 1. Effect of PMX-DHP on MAP (A), CAI (B), VDI (C), PaO_2/FiO_2 ratio (D), and SOFA score (E) before (pre-) and after (post-) or 24 h after completing (24 h after) PMX-DHP. The data of all of cases are plotted. A solid line with open circle is a nonsurvivor (case 1). A dotted line with filled square is average. CAI, catecholamine index; MAP, mean arterial pressure; PaO_2/FiO_2, partial pressure of oxygen/inspired fraction of oxygen; PMX-DHP, direct hemoperfusion with polymyxin B-immobilized fiber; SOFA, Sequential Organ Failure Assessment; VDI, vasopressor dependency index.

Therapeutic Apheresis and Dialysis 2018
doi: 10.1111/1744-9987.12746

Clinical Effects of Polymyxin B Hemoperfusion in Patients With Septic Shock Caused by Urinary Tract Infection

Yasushi Suzuki,[1] Masahiro Kojika,[1] Hisaho Sato,[1] Yoshihiro Inoue[1,2], and Shigeatsu Endo[3]

[1]*Iwate Prefectural Advanced Critical Care and Emergency Center,* [2]*Department of Critical Care, Disaster and General Medicine, School of Medicine, Iwate Medical University and* [3]*Morioka Yuai Hospital, Iwate, Japan*

Combined Extracorporeal Therapy for Severe Sepsis in Patients after Cardiac Surgery

M. Yaroustovsky M. Abramyan N. Krotenko D. Popov M. Plyushch
E. Rogalskaya H. Nazarova
Bakoulev Scientific Centre for Cardiovascular Surgery, Moscow, Russia

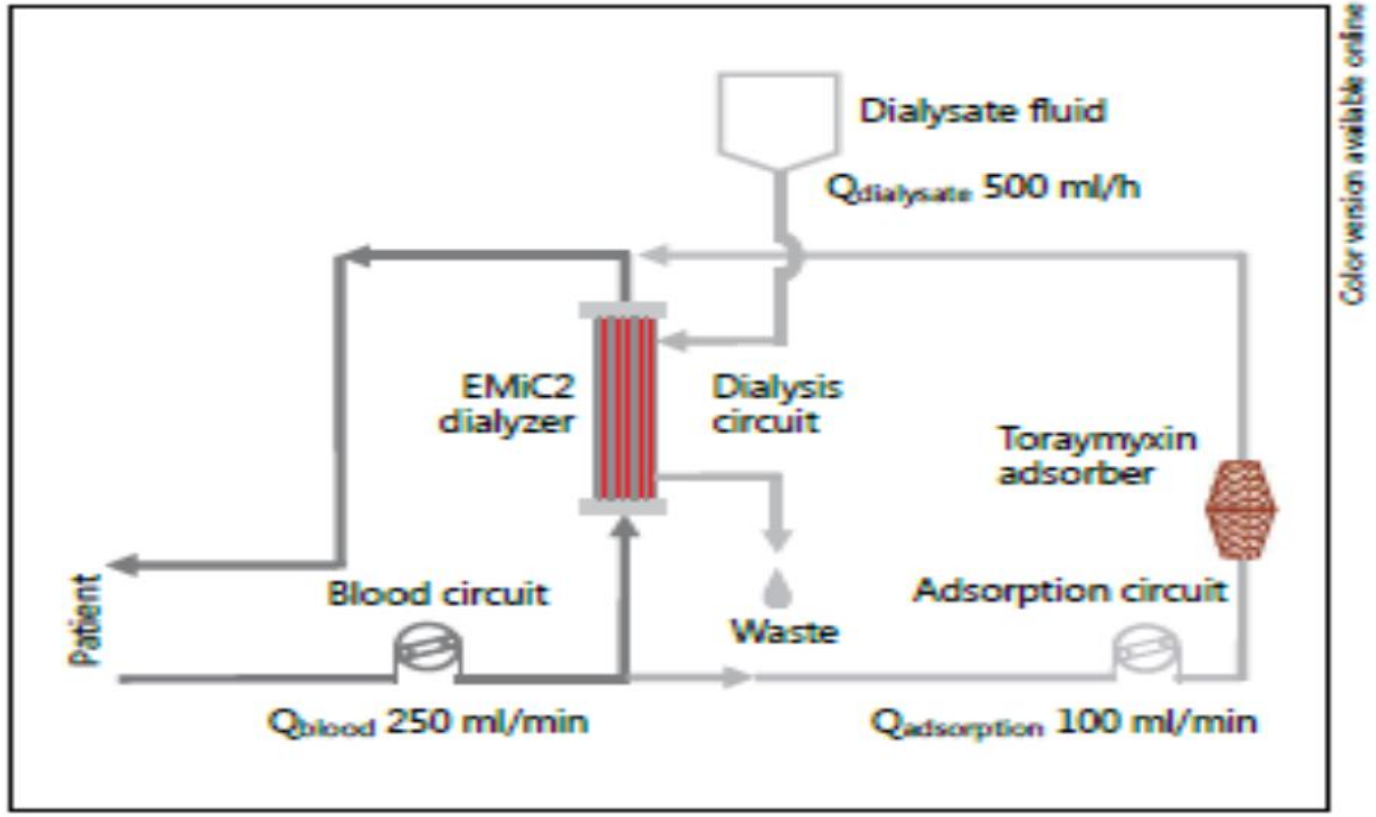


Fig. 1. Schematic of the extracorporeal circuit.

Table 1. Initial clinical characteristics of the patients in the study and control groups

Characteristics	Study group	Control group	p
Number of patients	26	30	NA
Age, years	57 (48–62)	57 (51–61)	0.7
Male/female	18/8	19/11	NS
Body weight, kg	81 (78–96)	78 (67–91)	0.08
CPB duration, min	158 (136–220)	208 (148–266)	0.1
Aorta cross-clamping time, min	104 (83–121)	112 (90–150)	0.3
MAP, mm Hg	76 (65–81)	80 (75–85)	0.14
LVEF, %	29 (27–32)	31 (29–33)	0.22
Heart rate, bpm	101 (91–110)	100 (88–107)	0.57
Thrombocytes, 1×10^9/litre	121 (73–156)	116 (74–150)	0.75
White blood cells, 1×10^9/litre	17.1 (10.6–19)	15.3 (9.7–19.5)	0.9
Body temperature, °C	38.4 (37.7–38.9)	38.2 (37.7–38.9)	0.5
PCT, ng/ml	8.19 (3.87–19.03)	5.59 (2.84–15)	0.26
EAA	0.73 (0.68–0.79)	0.66 (0.6–0.7)	0.062
Epinephrine, µg/kg/min	0.07 (0.05–0.1)	0.08 (0.05–0.1)	0.69
Norepinephrine, µg/kg/min	0.1 (0.05–0.2)	0.08 (0.06–0.11)	0.92
Dopamine, µg/kg/min	5 (2–6)	5 (3.5–8)	0.12
PaO_2/FiO_2	226 (127–285)	224 (165–262)	0.89
IABP use	4/26 (15%)	8/30 (26%)	0.48
Dialysis-dependent AKI	23/26 (88%)	24/30 (84%)	0.9
APACHE-II scores	28 (25–31)	27 (24–32)	0.73
SOFA scores	13 (11–14)	13 (12–14)	0.95
Positive blood culture	16/26 (61.5%)	19/30 (63.3%)	NS

NA = Not applicable; NS = not significant.

CLINICAL SCENARIO

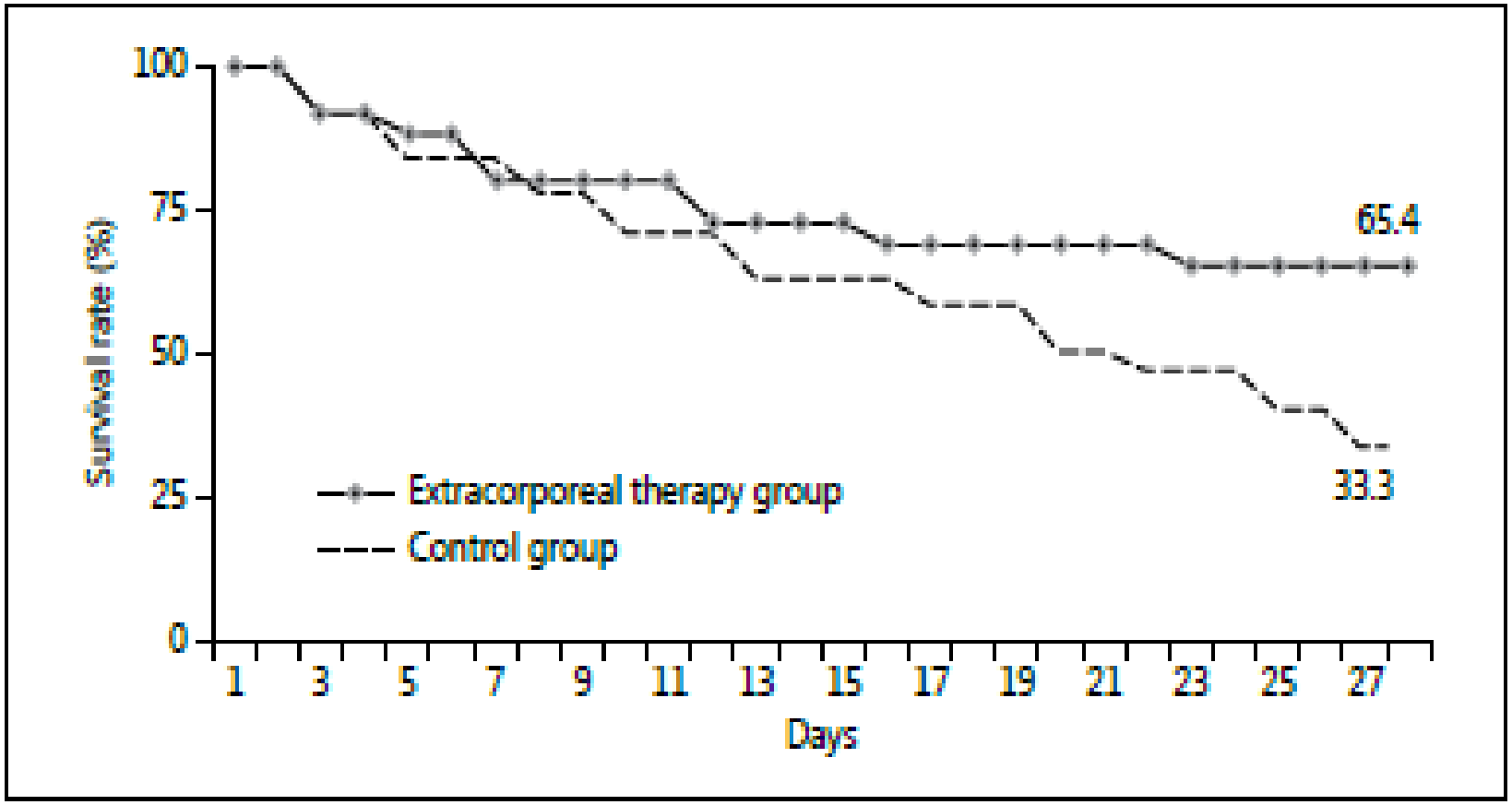
Table 2. Laboratory data before and after the combined extracorporeal therapy for sepsis in the study group patients

Characteristics	Extracorporeal therapy		p
	before	after	
EAA	0.73 (0.68–0.79)	0.59 (0.5–0.62)	<0.01
LAL test, IU/ml	1.44 (0.72–1.44)	0.36 (0.36–0.72)	<0.01
PCT, ng/ml	8.19 (3.8–19.03)	2.44 (0.58–5.25)	<0.01
TNF-α, pg/ml	4.5 (2.5–12)	5.1 (2.6–28.5)	0.8
IL-1β, pg/ml	37.4 (23.4–338)	54.17 (16–119.8)	0.409
IL-6, pg/ml	8.6 (6.25–38.1)	10 (5.5–15.4)	0.83
IL-8, pg/ml	5.3 (4.5–5.5)	8.5 (6–9)	0.182
IL-10, pg/ml	28 (119–60)	34 (21.7–77.5)	0.598

Table 3. Clinical and laboratory characteristics of the patients in the study group upon completion of the extracorporeal therapy and in the controls on day 3 after the initiation of standard therapy

Characteristics	Study group	Control group	p
MAP, mm Hg	90 (85–102)	81 (73–87)	0.0004
Heart rate, bpm	96 (86–99)	94 (85–100)	0.9
Epinephrine, μg/kg/min	0.065 (0.03–0.1)	0.1 (0.04–0.12)	0.06
Norepinephrine, μg/kg/min	0.05 (0–0.1)	0.07 (0.03–0.1)	0.22
Dopamine, μg/kg/min	3 (2–4)	5 (3–8)	0.11
PaO_2/FiO_2	291 (220–367)	229 (190–262)	0.01
Body temperature, °C	37.2 (36.7–37.7)	37.8 (37.1–38.5)	<0.01
White blood cells, 1×10^9/litre	12.7 (7–16.5)	12.4 (8.8–14.5)	0.1
PCT, ng/ml	2.44 (0.58–5.25)	3.41 (1.51–10.65)	0.15
EAA	0.59 (0.5–0.62)	0.67 (0.59–0.88)	0.05
SOFA scores	10 (8–13)	12.5 (10–14)	0.063
Renal recovery on 28 day, %	13/23 (56.5)	3/24 (12.5)	0.049
Length of ICU stay, days	9 (4.5–28.5)	12 (7.5–17)	0.5

MORTALITY


100
75
50
25
0
Survival rate (%)
65.4
33.3
Extracorporeal therapy group
Control group
1
3
5
7
9
11
13
15
17
19
21
23
25
27
Days

EAA LEVELS

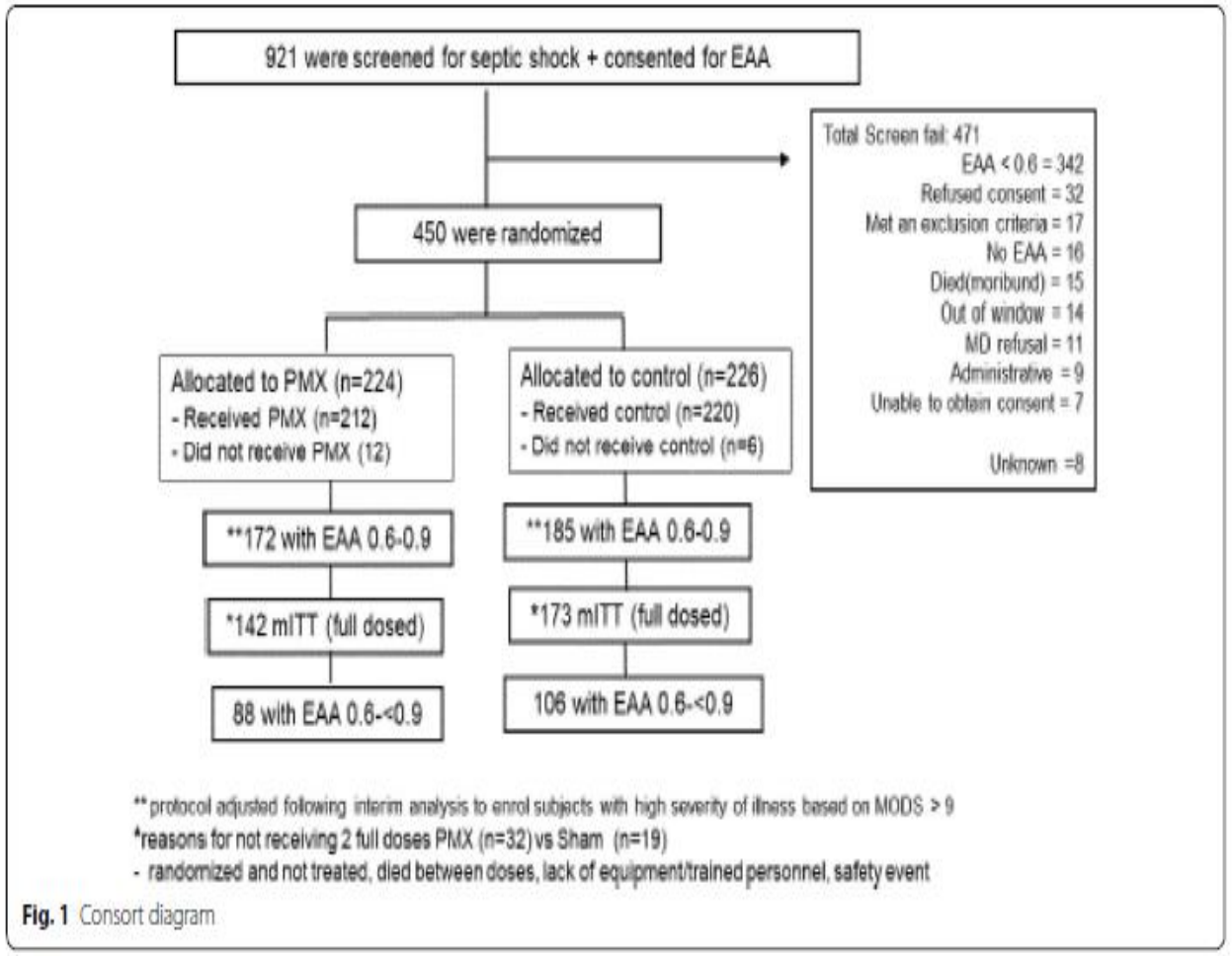


Fig. 1 Consort diagram

Intensive Care Med
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ORIGINAL

Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial

D. J. Klein[1*], D. Foster[2], P. M. Walker[2], S. M. Bagshaw[3], H. Mekonnen[4] and M. Antonelli[5]

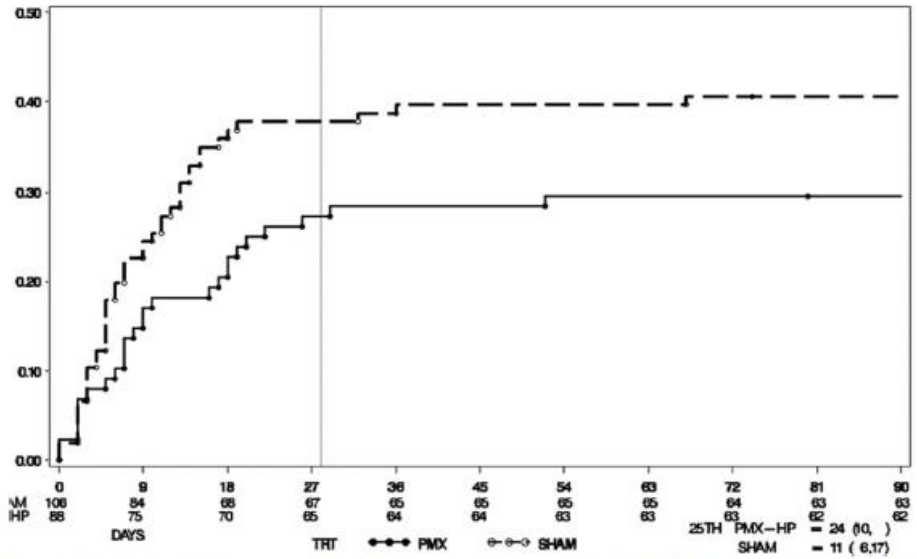
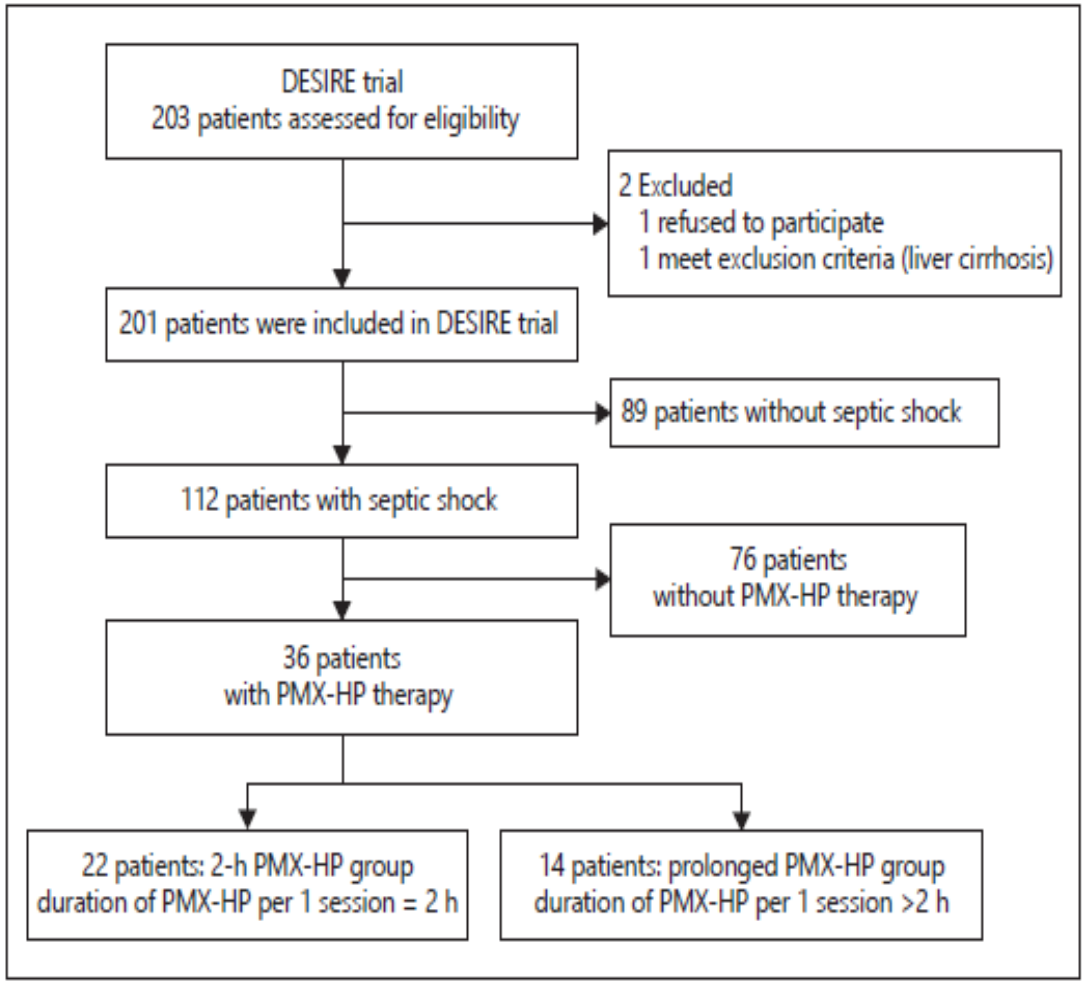


Fig. 2 Time to death within 90 days for PMX versus sham. Kaplan-Meier estimates of the probability of survival to day 90 among 194 per-protocol patients with MODS > 9 and EAA between 0.6 and 0.89, by treatment groups. The 90-day results of Cox proportional hazards adjusted for baseline MAP and APACHE II score are the hazard ratio [0.57, 95% CI (0.35, 0.93), *P* value = 0.02]. The vertical line represents the 28-day interval. The 28-day adjusted Cox proportional hazard ratio for death in the PMX group compared with the sham group is 0.58 (95% CI, 0.35 to 0.98; *P* = 0.04). *TRT* treatment, *25th* 25th percentile at 90 days

PROLONGED THERAPY



Original Paper

Blood Purification

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Published

Mortality Effects of Prolonged Hemoperfusion Therapy Using a Polymyxin B-Immobilized Fiber Column for Patients with Septic Shock: A Sub-Analysis of the DESIRE Trial

Yu Kawazoe[a] Tetsuya Sato[b] Noriko Miyagawa[b] Yuta Yokokawa[b]
Shigeki Kushimoto[a] Kyohei Miyamoto[c] Yoshinori Ohta[d] Takeshi Morimoto[e]
Hitoshi Yamamura[f]

Table 2. Primary and secondary outcomes

	2-h PMX-HP group (n = 22)	Prolonged PMX-HP group (n = 14)	p value
28-Day mortality	7 (31.8)	0 (0)	0.019
Ventilator-free days during initial 28 days	11.5 (10.5)	15.6 (8.3)	0.23
Vasopressor-free days during initial 7 days	2.5 (0.46)	3.1 (0.58)	0.41

Data are reported as numbers (%).
PMX-HP, hemoperfusion therapy using a polymyxin B-immobilized fiber column.

POLYMIXIN AND LEUKOCYTE

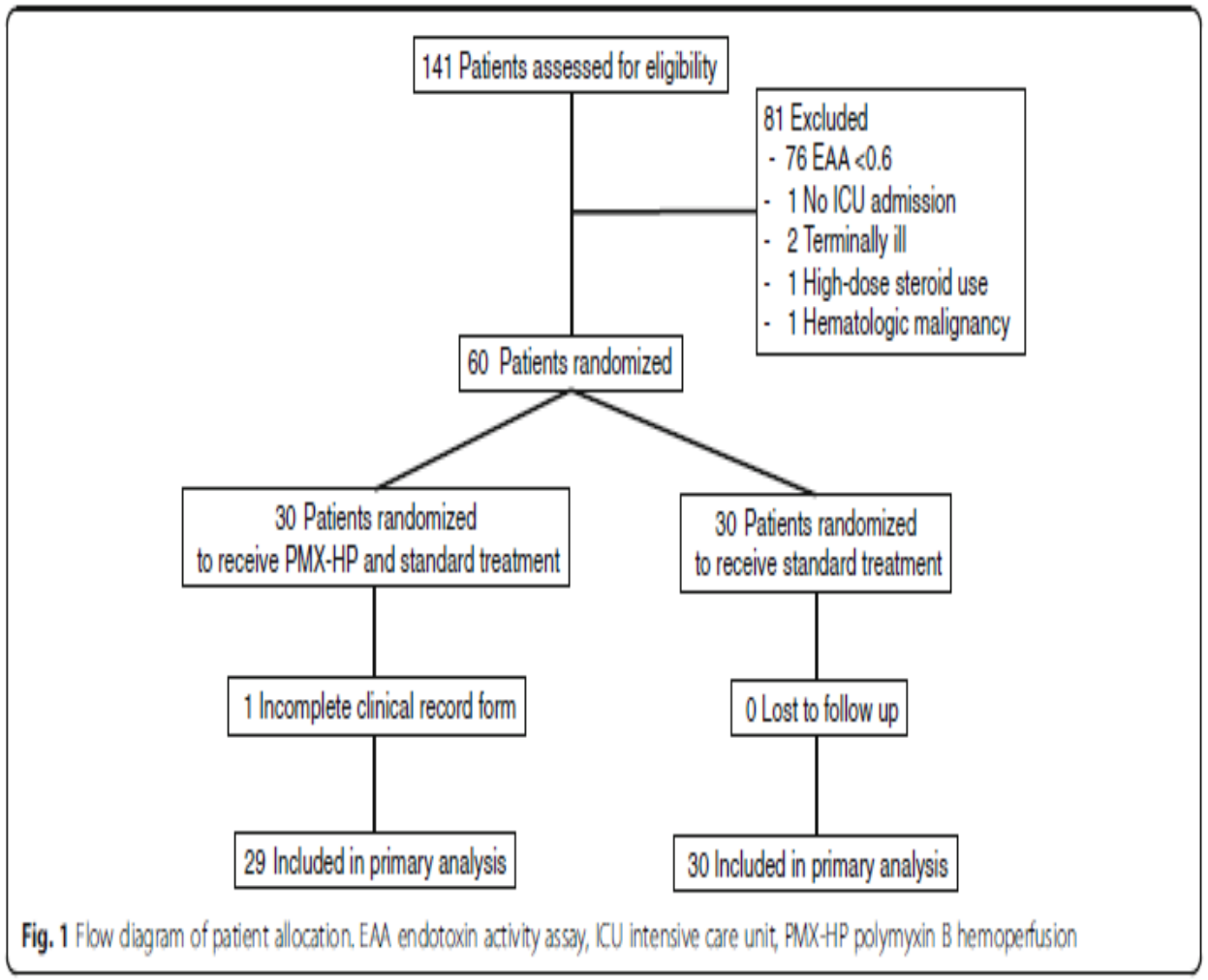


Fig. 1 Flow diagram of patient allocation. EAA endotoxin activity assay, ICU intensive care unit, PMX-HP polymyxin B hemoperfusion

Srisawat *et al. Critical Care* (2018) 22:279
https://doi.org/10.1186/s13054-018-2077-y

Critical Care

RESEARCH Open Access

The effect of polymyxin B hemoperfusion on modulation of human leukocyte antigen DR in severe sepsis patients

Nattachai Srisawat[1,2,3*], Somkanya Tungsanga[1], Nuttha Lumlertgul[1,2], Chalermchai Komaenthammasophon[1,2], Sadudee Peerapornratana[1,2,3], Nicha Thamrongsat[1,2], Khajohn Tiranathanagul[1], Kearkiat Praditpornsilpa[1], Somchai Eiam-Ong[1], Kriang Tungsanga[1] and John A. Kellum[3]

POLYMIXIN B AND LEUKOCYTE

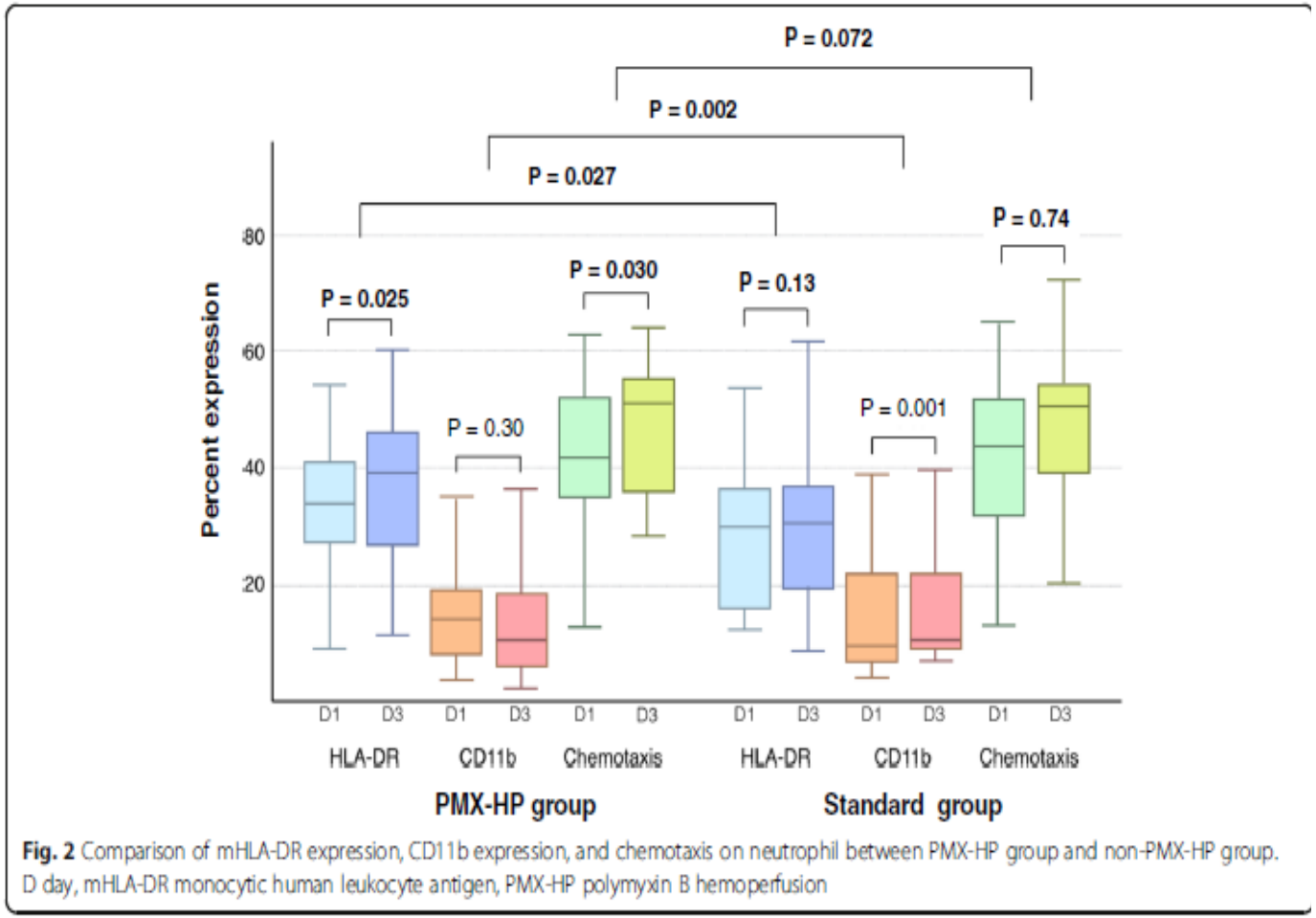


Fig. 2 Comparison of mHLA-DR expression, CD11b expression, and chemotaxis on neutrophil between PMX-HP group and non-PMX-HP group. D day, mHLA-DR monocytic human leukocyte antigen, PMX-HP polymyxin B hemoperfusion

Table 4 Clinical outcomes by treatment group

	PMX-HP group	Non PMX-HP group	*P* value[a]
Overall	*n* = 29	*n* = 30	
Mortality on day 3, *n* (%)	3 (10.3)	10 (33.3)	0.058
Mortality on day 7, *n* (%)	6 (20.7)	12 (40.0)	0.11
Mortality on day 28, *n* (%)	17 (58.6)	15 (50.0)	0.51
MAKE 28[b] (%)	22 (75.9)	22 (73.3)	1.00
Alive on day 28	n=13[c]	*n* = 15	
ICU-free days (Q1, Q3)	0 (0, 10)	0 (0, 8)	0.99
Ventilator-free days (Q1, Q3)	0 (0, 8)	0 (0, 0)	0.28
RRT, *n* (%)	7 (53.8)	6[d] (50.0)	0.85
Serum creatinine (mg/dl) (Q1, Q3)	1.4 (1.1, 2.2)	2.1 (1.3, 2.5)	0.59
Vasopressor free days (Q1, Q3)	0 (0, 25)	11.5 (0, 25)	0.47
AKI at baseline	*n* = 25	*n* = 25	
Renal recovery[e], *n* (%)	5 (20.0)	3 (12.0)	0.70

OTHER SCENARIO

- ECMO

- CADIAC ARREST

HIGHTLIGHTS

CYTOKINETIC MODEL

- EARLY EAA MOBILIZATION
- CLEARANCE
- ANTOBIOTICS

Plasma Concentrations of Inflammatory Cytokines Rise Rapidly during ECMO-related SIRS due to the Release of Pre-formed Stores in the Intestine

Britt McILwain[1,2], Joseph Timpa[1], Ashish R. Kurundkar[3], David W. Holt[2], David R. Kelly[4], Yolanda Hartman[3], Mary Lauren Neel[3], Rajendra K. Karnatak[3], Robert L. Schelonka[5], G. M. Anantharamaiah[6], Cheryl R. Killingsworth[6], and Akhil Maheshwari[3,4,7]

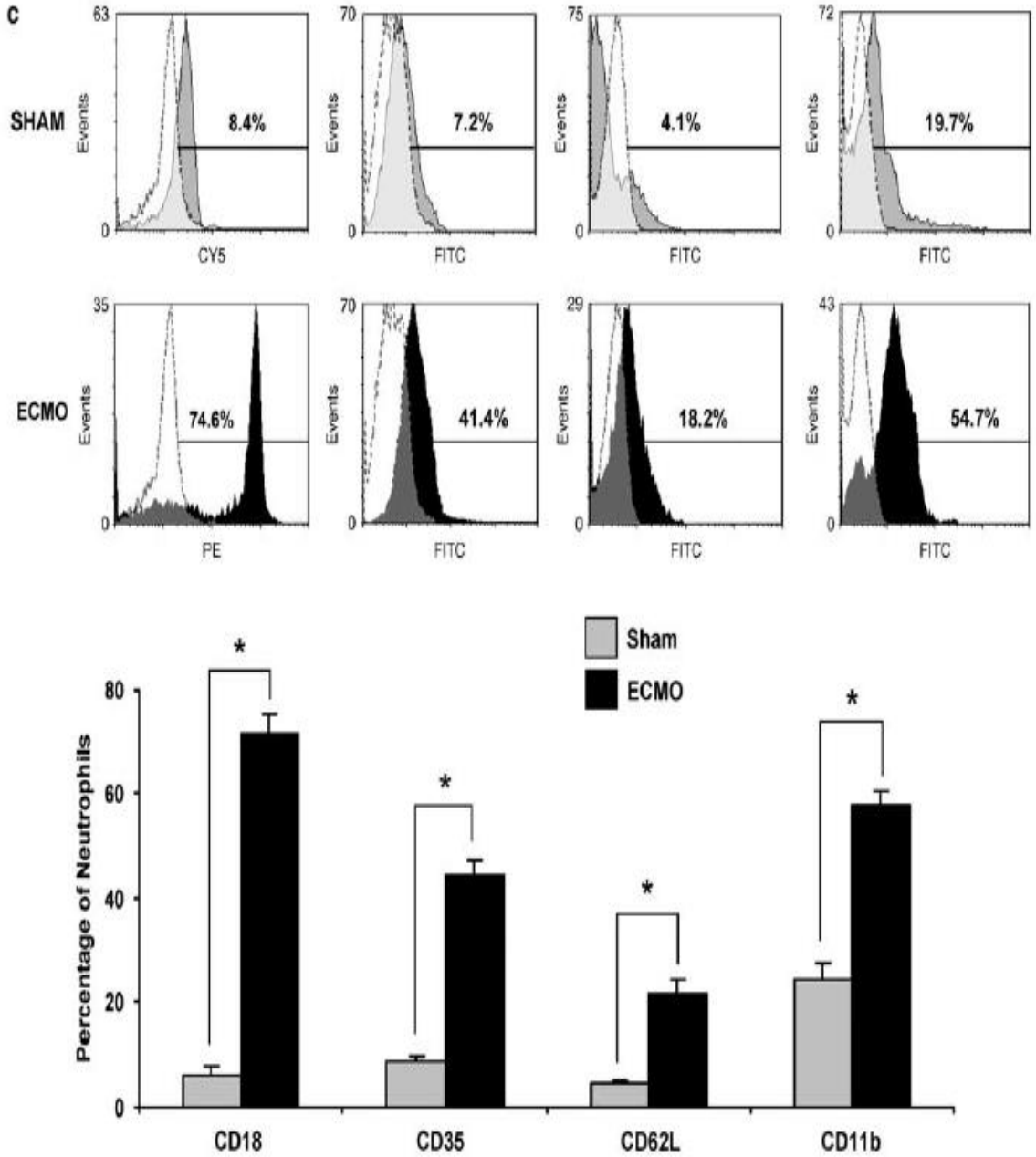
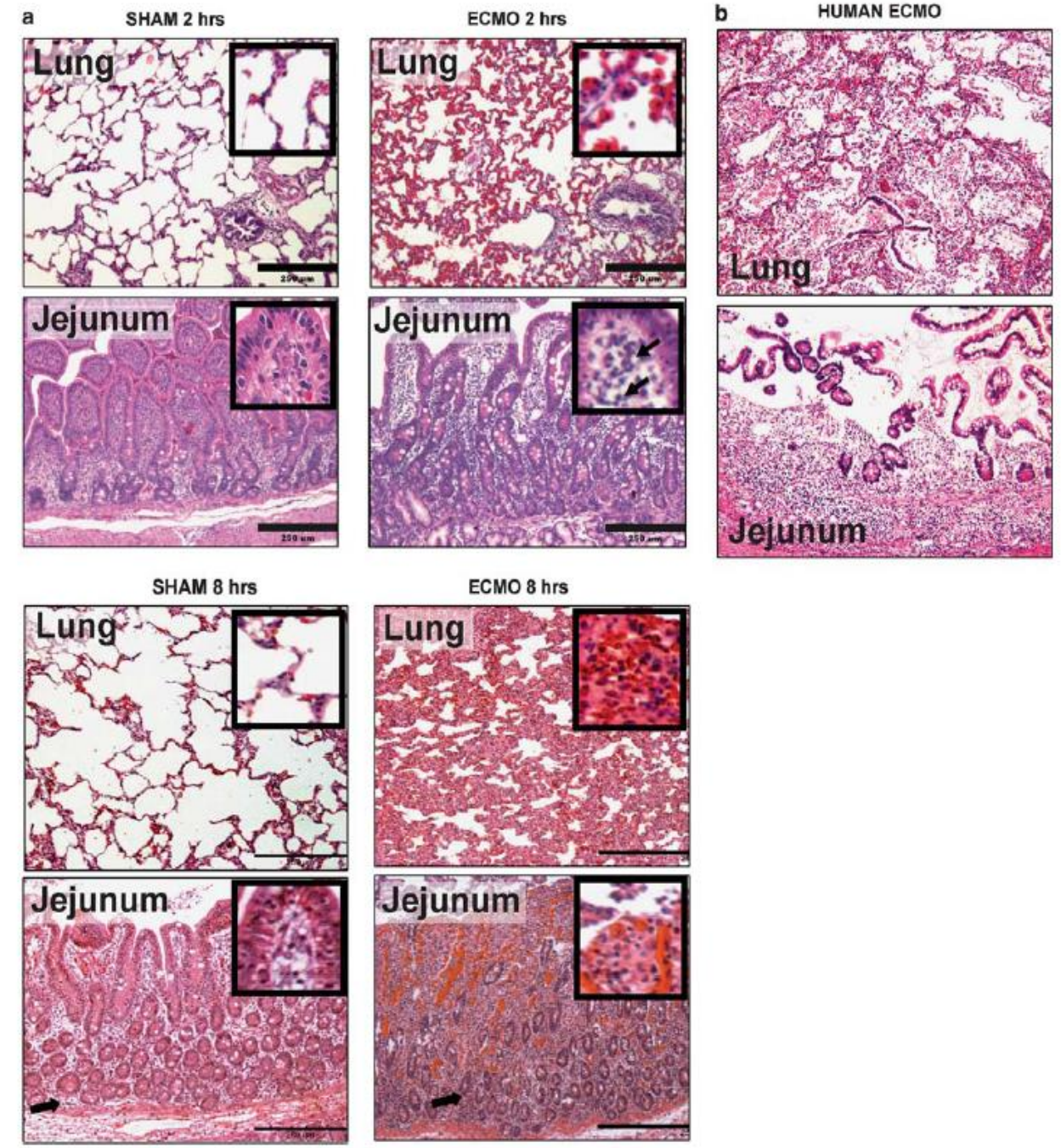
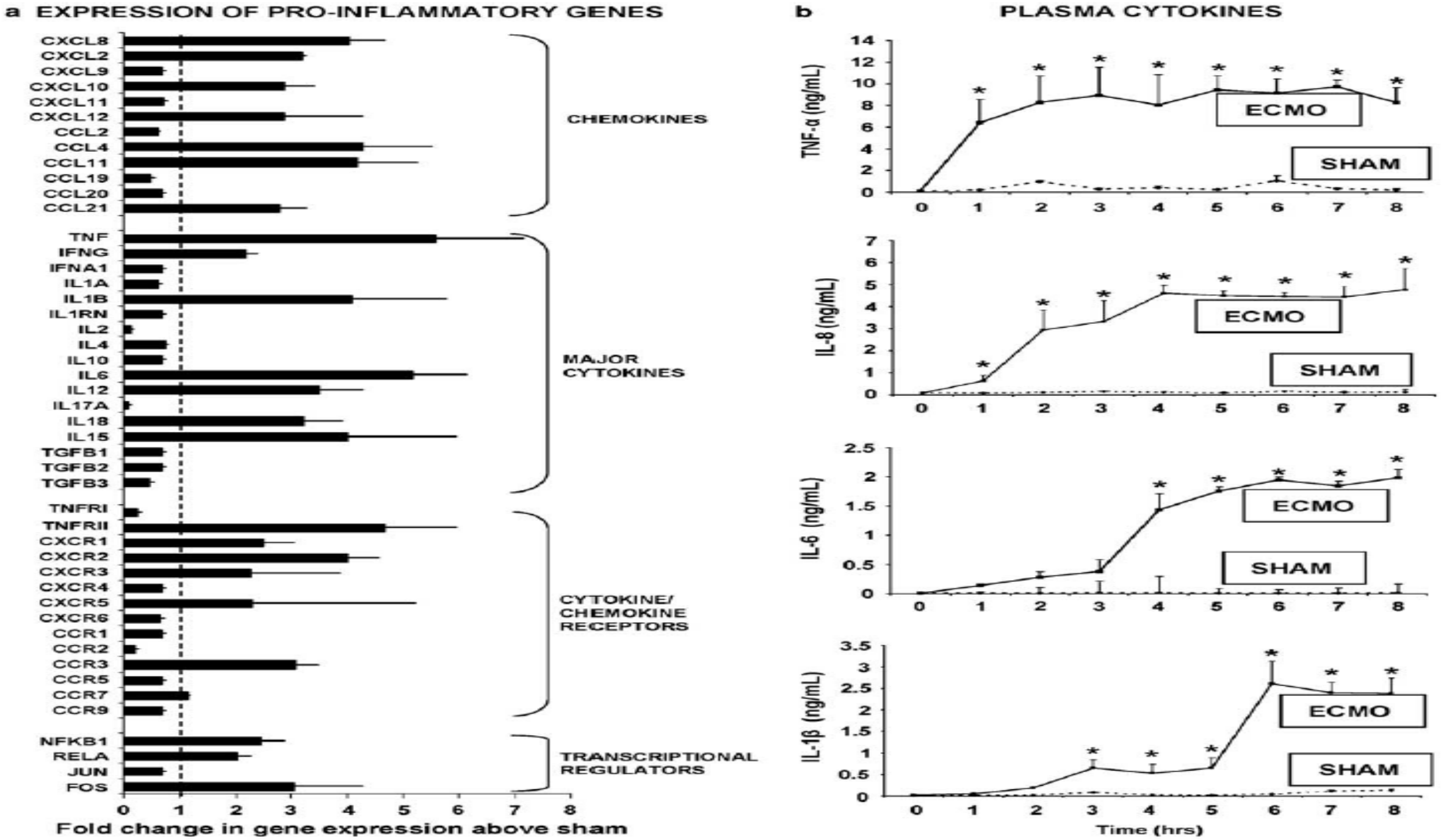
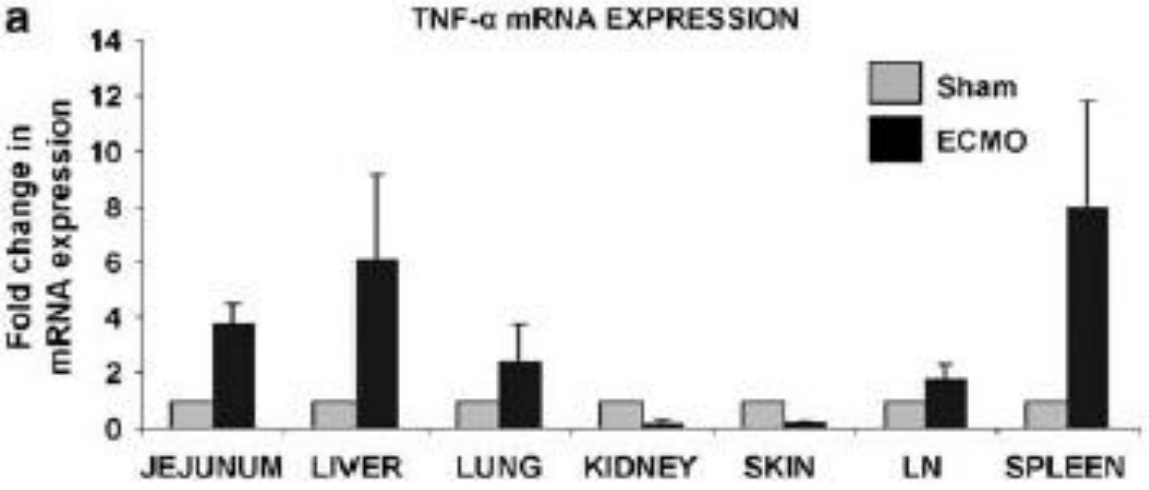
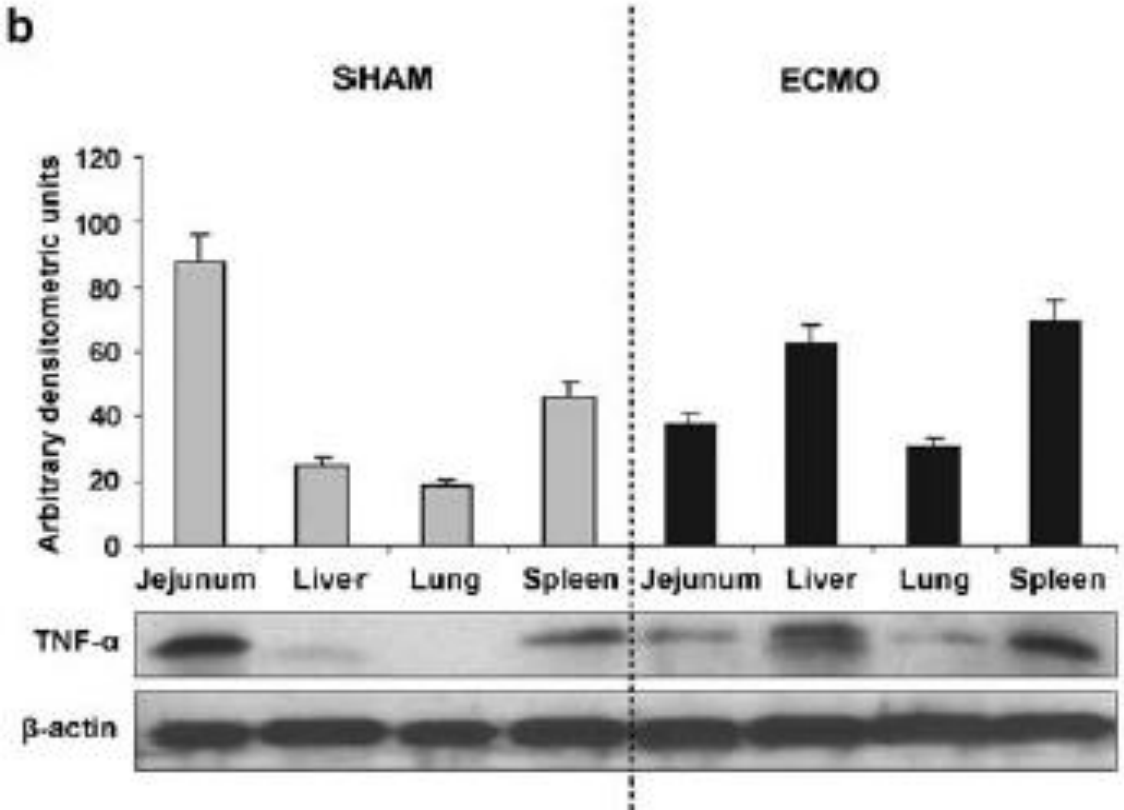


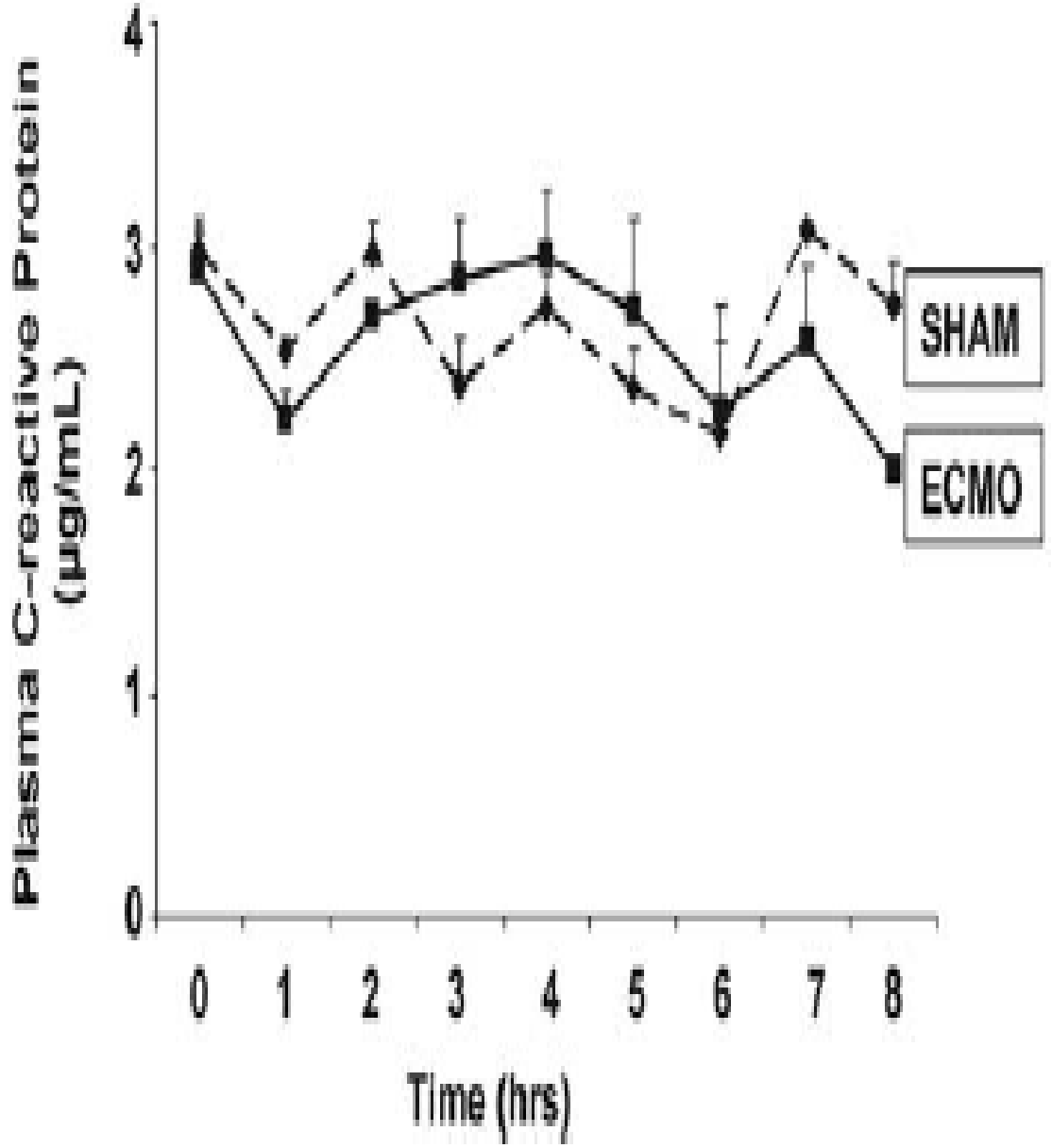
Figure 1 continued.

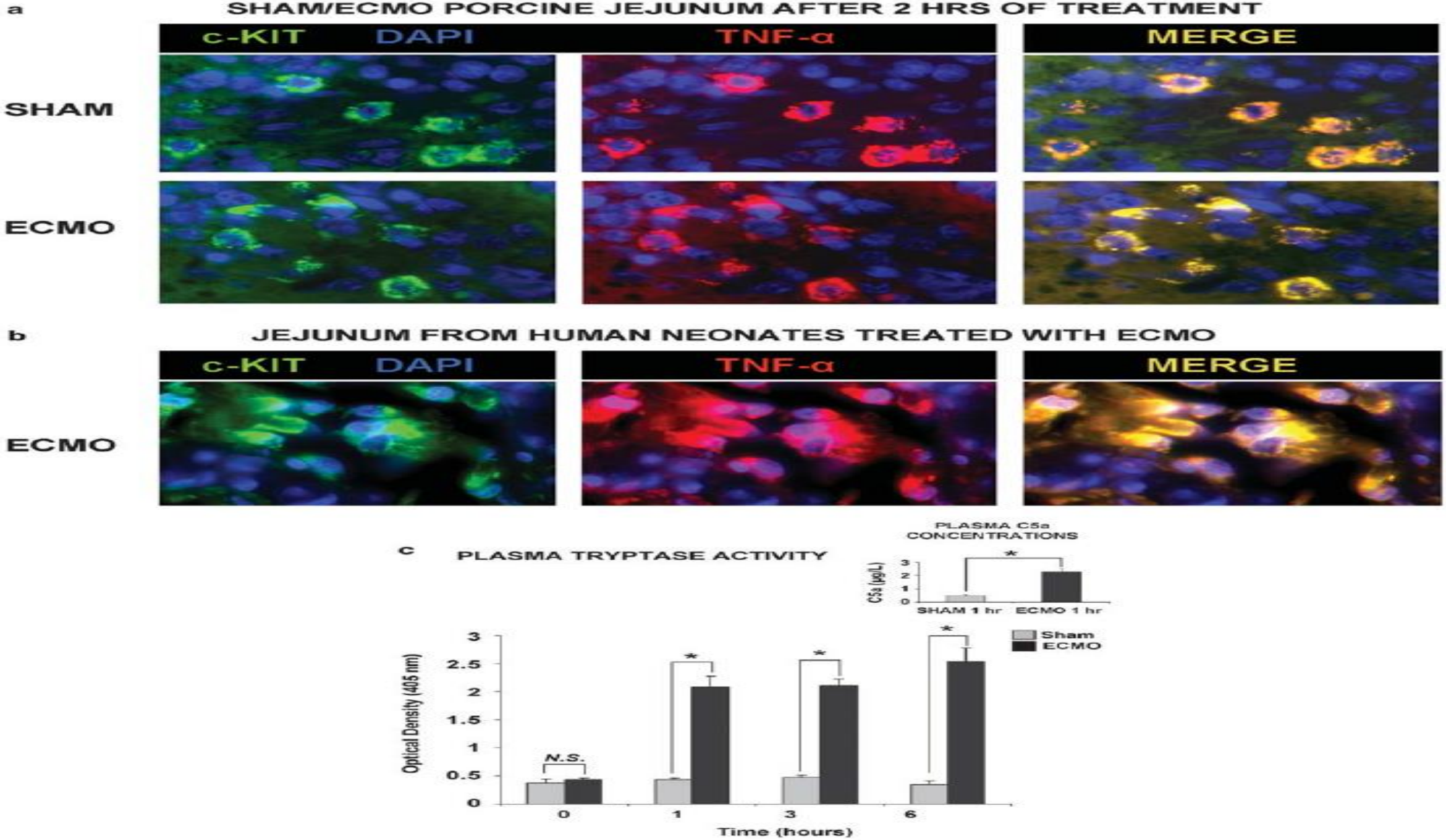



a EXPRESSION OF PRO-INFLAMMATORY GENES
CXCL8
CXCL2
CXCL9
CXCL10
CXCL11
CXCL12
CCL2
CCL4
CCL11
CCL19
CCL20
CCL21
CHEMOKINES
TNF
IFNG
IFNA1
IL1A
IL1B
IL1RN
IL2
IL4
IL10
IL6
IL12
IL17A
IL18
IL15
TGFB1
TGFB2
TGFB3
MAJOR CYTOKINES
TNFRI
TNFRII
CXCR1
CXCR2
CXCR3
CXCR4
CXCR5
CXCR6
CCR1
CCR2
CCR3
CCR5
CCR7
CCR9
CYTOKINE/ CHEMOKINE RECEPTORS
NFKB1
RELA
JUN
FOS
TRANSCRIPTIONAL REGULATORS
0 1 2 3 4 5 6 7 8
Fold change in gene expression above sham
b
PLASMA CYTOKINES
TNF-α (ng/mL)
ECMO
SHAM
IL-8 (ng/mL)
ECMO
SHAM
IL-6 (ng/mL)
ECMO
SHAM
IL-1β (ng/mL)
ECMO
SHAM
Time (hrs)

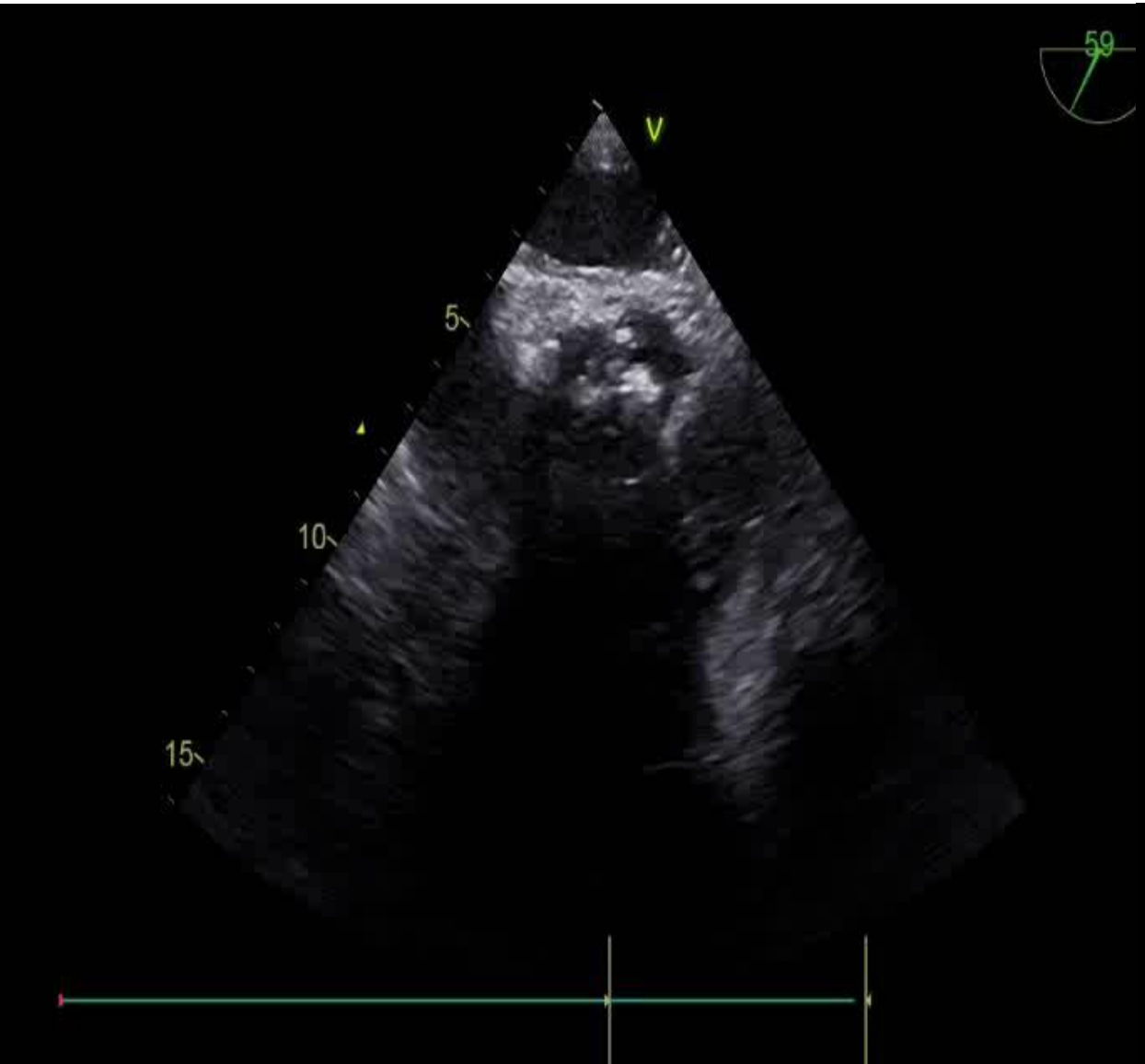

a
TNF-α mRNA EXPRESSION
Sham
ECMO
Fold change in mRNA expression
14
12
10
8
6
4
2
0
JEJUNUM
LIVER
LUNG
KIDNEY
SKIN
LN
SPLEEN

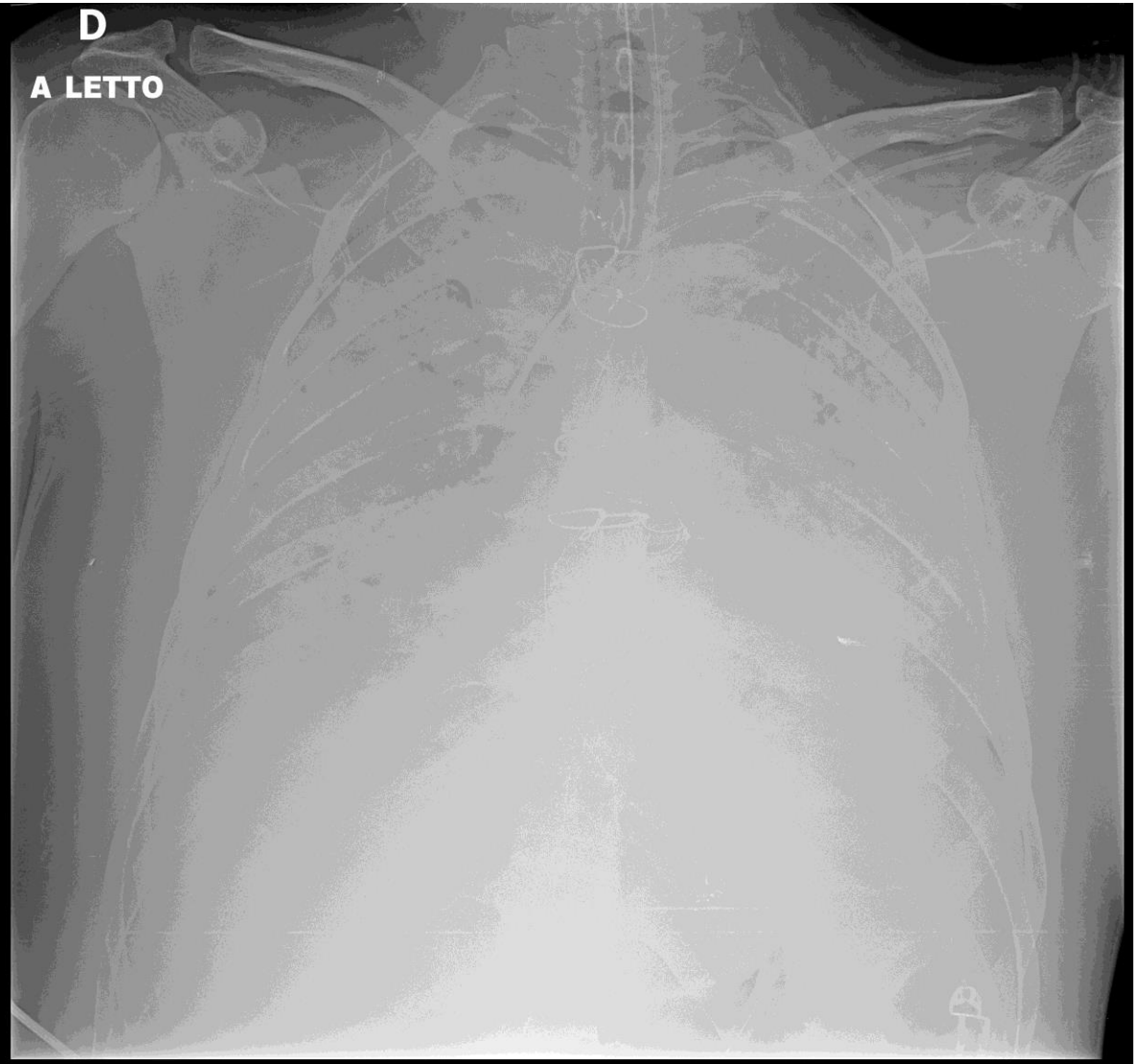

b
SHAM
ECMO
Arbitrary densitometric units
120
100
80
60
40
20
0
Jejunum
Liver
Lung
Spleen
Jejunum
Liver
Lung
Spleen
TNF-α
β-actin


Plasma C-reactive Protein (µg/mL)
4
3
2
1
0
0
1
2
3
4
5
6
7
8
Time (hrs)
SHAM
ECMO


a
SHAM/ECMO PORCINE JEJUNUM AFTER 2 HRS OF TREATMENT
c-KIT
DAPI
TNF-α
MERGE
SHAM
ECMO
b
JEJUNUM FROM HUMAN NEONATES TREATED WITH ECMO
c-KIT
DAPI
TNF-α
MERGE
ECMO
c
PLASMA TRYPTASE ACTIVITY
Optical Density (405 nm)
N.S.
Time (hours)
PLASMA C5a CONCENTRATIONS
C5a (pg/L)
SHAM 1 hr
ECMO 1 hr
Sham
ECMO

CASE REPORT

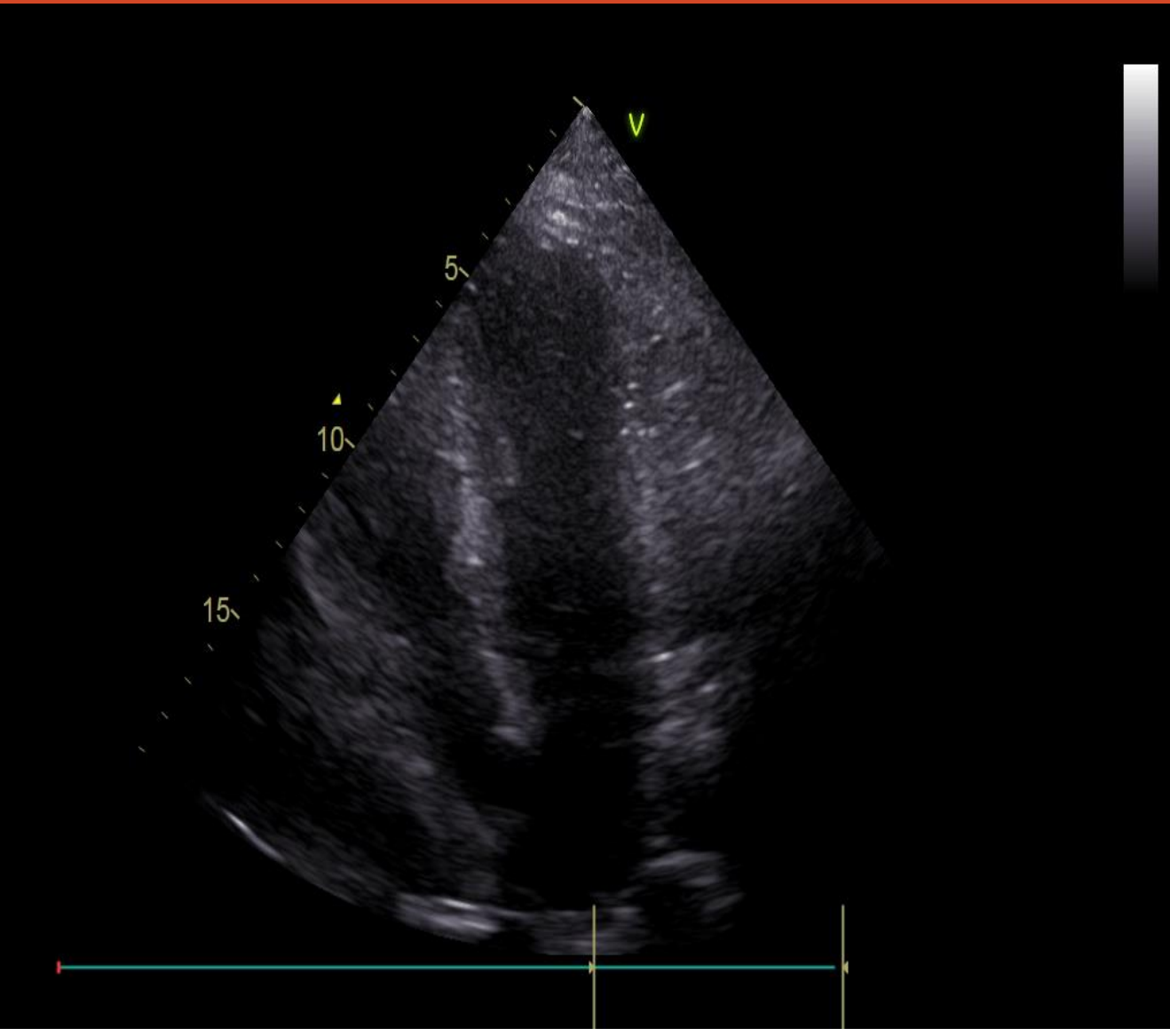


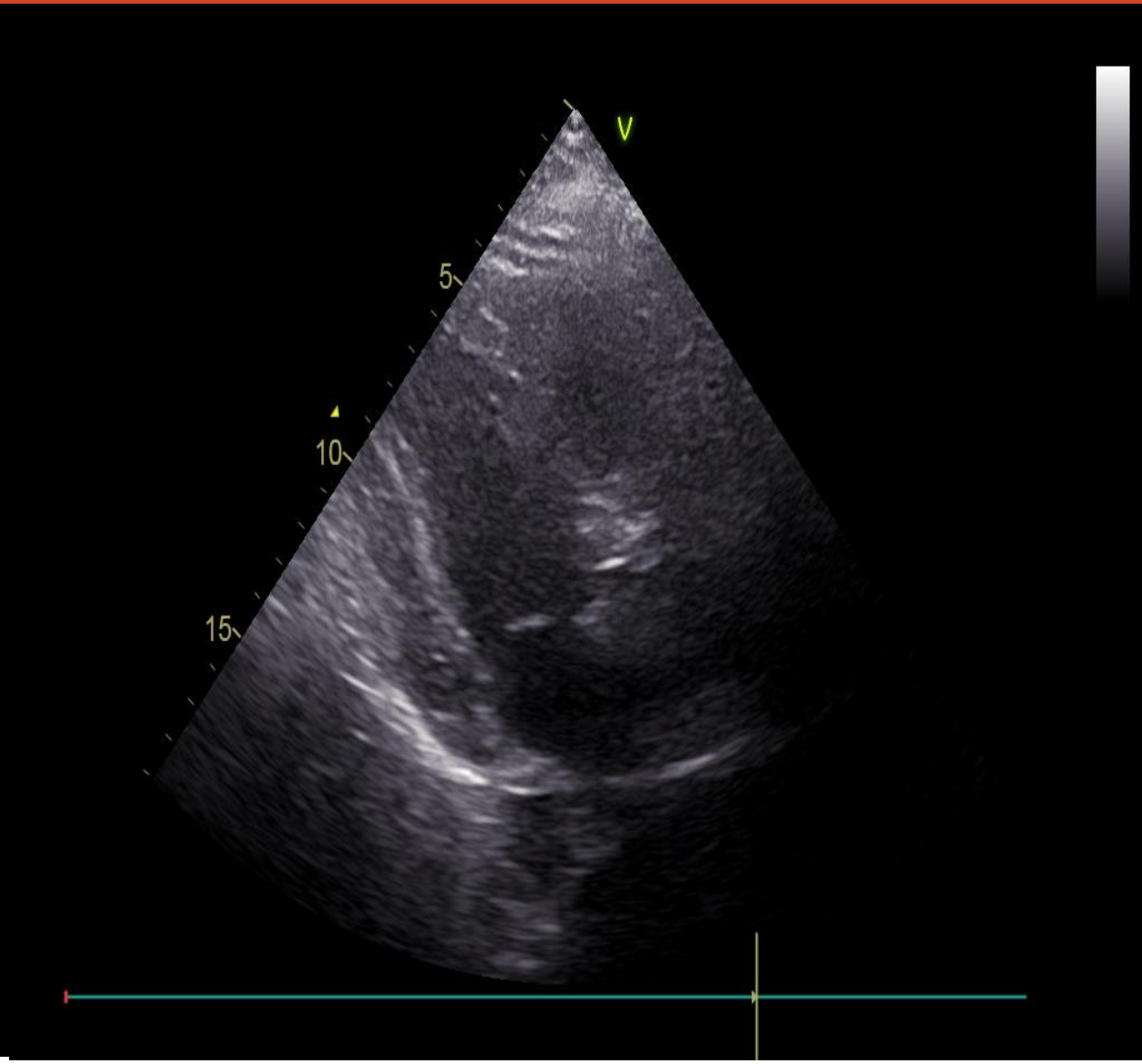


LAB PANEL

LAB PANEL	ADMIS	PRE TREAT	48 HOURS	POST TREAT	
IL 6	5.2	3.2	2.7	1	
IL 10	3.5	7.3	9.5	15.3	
PCT	10.4	9.87	6.56	5.03	
EAA	0.9	0.9	0.7	0.6	
WBC	38.45	32	23.46	12.57	

ECHO POST ECMO





CARDIAC ARREST

IN PATIENTS SUCCEFULLY RESUSCITATED FROM CARDIAC ARREST WITH **A POST CARDIAC ARREST SHOCK HIGHT EAA LEVELS** IS INDIPENDENT ASSOCIATED WITH DURATION OF POST CARDIAC ARREST SHOCK AND **AMOUNT OF VASOACTIVE DRUGS**

High Level of Endotoxemia Following Out-of-Hospital Cardiac Arrest Is Associated With Severity and Duration of Postcardiac Arrest Shock*

David Grimaldi, MD, PhD[1]; Bertrand Sauneuf, MD[2]; Elise Guivarch, MD[2]; Sylvie Ricome, MD[2]; Guillaume Geri, MD[2,3,4]; Julien Charpentier, MD[2]; Benjamin Zuber, MD[1]; Florence Dumas, MD, PhD[3,4,5]; Christian Spaulding, MD, PhD[4]; Jean-Paul Mira, MD, PhD;[2,3] Alain Cariou, MD[2,3,4]

CARDIAC ARREST

TABLE 1. Characteristics of Patients With Postcardiac Arrest Shock According to Endotoxemia Level at ICU Admission

Characteristics	Whole Population ($n = 60$)	Low Etx (< 0.4 EA) ($n = 31$)	Intermediate Etx (0.4–0.59 EA) ($n = 18$)	High Etx (≥ 0.6 EA) ($n = 11$)	p^a
Female, *n* (%)	19 (32)	8 (26)	6 (33)	5 (45)	0.48
Age	64 (53–75.5)	65 (59–75)	59.5 (46–77)	57 (52.5–75)	0.72
Place: public, *n* (%)	24 (40)	16 (52)	6 (33)	2 (18)	0.12
Witnessed, *n* (%)[b]	37 (62)	22 (73)[b]	10 (56)	4 (36)	0.08
Nonshockable rhythm	25 (41.7)	12 (39)	7 (39)	7 (64)	0.32
Time to return of spontaneous circulation (min), median (IQR)	22 (15–35)	21 (14–34.5)	25 (17–38.5)	25 (20–33)	0.49
Epinephrine dose (mg), median (IQR)	2 (0–5)	1 (0–2.5)	3 (0–7)	4 (1.5–7)	0.05
Simplified acute physiology score-II	80.5 (71–92)	75 (70–93)	81.5 (74–95)	82 (71–90.5)	0.79
Sequential organ failure assessment day 1	11 (9–15)	11 (9–13)	10 (8–15)	16 (13–17)	0.01
Dobutamine use, *n* (%)	7 (11.7)	3 (9.7)	3 (16.7)	1 (9.1)	0.73
Mechanical circulatory assistance, *n* (%)	6 (10)	4 (12.9)	2 (11.1)	0 (0)	0.46
Infection during ICU stay, *n* (%)	39 (65)	20 (64.5)	11 (61)	7 (64)	0.97
Vasopressor-free days, median (IQR)	2 (0–6)	4 (2–7)	2 (0–4)	0 (0–1)	0.02
Mean daily vasopressor dose (mg), median (IQR)	13 (8–61)	11 (6–26)	12.5 (9–78)	75.5 (33–249)	0.02
ICU length of stay (days), median (IQR)	5 (3–8)	7 (4–10)	5 (3–6)	4 (1–6)	0.05
ICU mortality	46 (77)	21 (68)	14 (78)	10 (91)	0.30

Etx = endotoxin, EA = endotoxin assay, IQR = interquartile range.
[a]*p* value was determined using χ^2 or Kruskall-Wallis test as appropriate.
[b]One missing data.

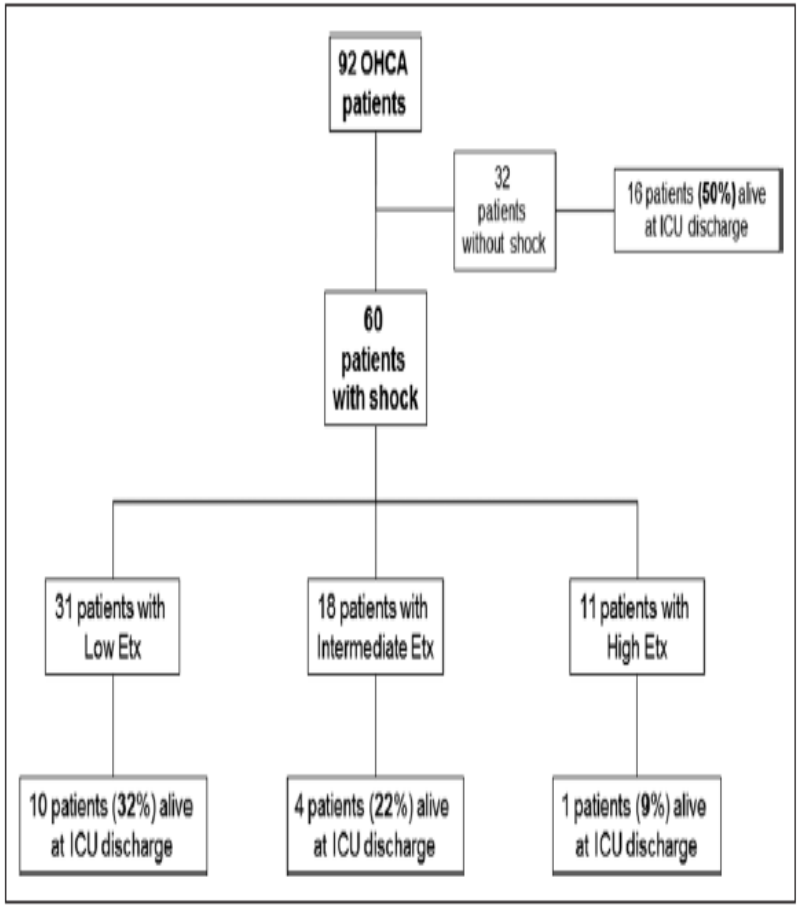


Figure 1. Flow chart of the study. Endotoxin measurement was performed in 92 patients. Sixty of them developed a postcardiac arrest shock. Etx = endotoxin, OHCA = out-of-hospital cardiac arrest.

CARDIAC ARREST

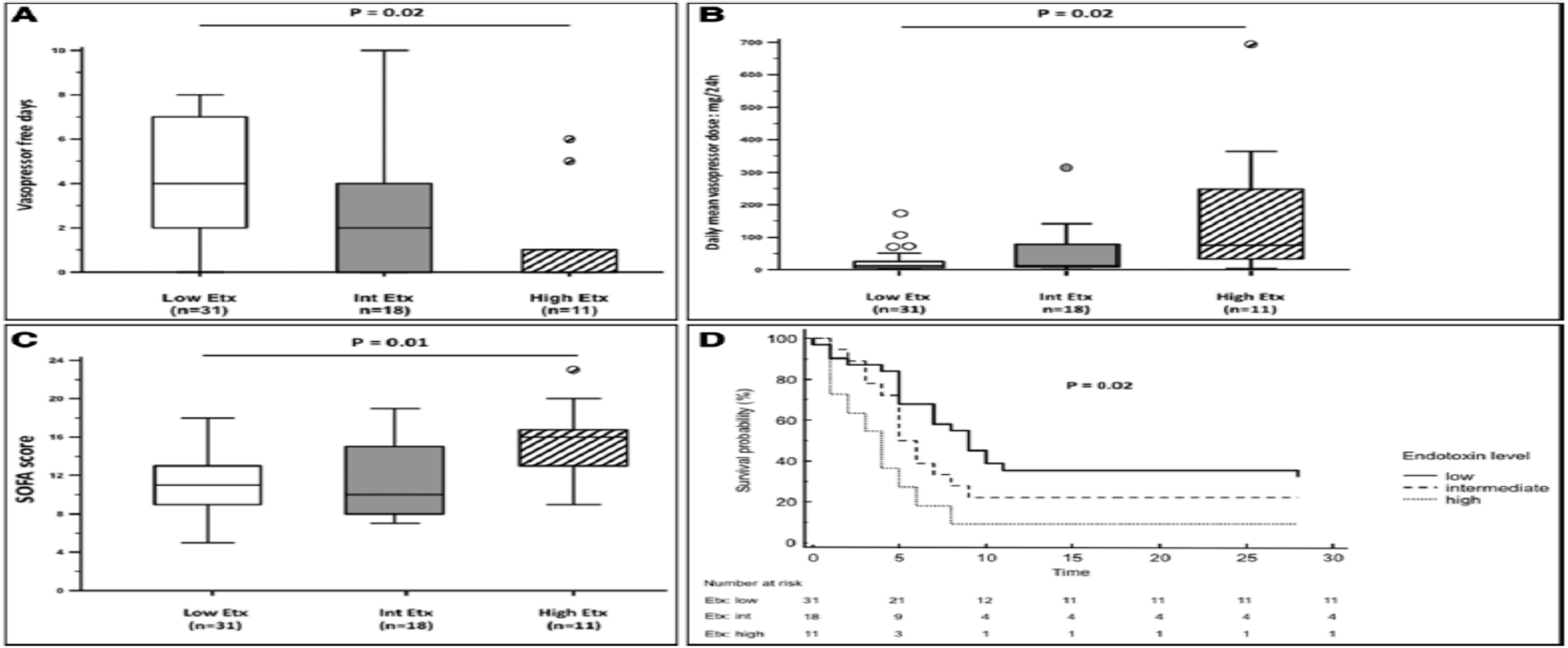


Figure 2. Comparison of vasopressor-free days (**A**), mean daily vasopressor dose (**B**), day-1 sequential organ failure assessment (SOFA) score (**C**), and survival (**D**) according to endotoxin class in the 60 patients with postcardiac arrest shock. Data of A, B, and C are shown as box plots, comparison among groups of patients were made using Kruskall-Wallis test. D, Depicts the survival curves during the 672 patient-days follow-up. *Continuous line* = low endotoxin level, *dashed line* = intermediate level, and *dotted line* = high endotoxin level. Follow-up is in days; survival curves were compared using log-rank test, $p < 0.001$.

CARDIAC ARREST

TABLE 2. Determinants of Vasopressor-Free Days (Bivariate and Multivariate Analyses)

Baseline Characteristics	Crude Estimate (95% CI)	p	Adjusted Estimate (95% CI)	p
Female gender	−0.22 (−1.95 to +1.50)	0.80		
Age	−0.016 (−0.07 to +0.038)	0.56		
Public place of cardiac arrest	**+2.33 (0.82 to 3.85)**	**0.003**	**1.47 (0.007 to 2.93)**	**0.05**
Witnessed	−0.043 (−1.68 to +1.59)	0.96		
Nonshockable rhythm	−0.86 (−2.46 to +0.75)	0.29		
Time to return of spontaneous circulation (/min)	**−0.093 (−0.14 to −0.045)**	**< 0.001**	**−0.08 (−0.13 to −0.03)**	**0.001**
Epinephrine dose (/mg)	−0.12 (−0.41 to +0.16)	0.39		
Etx class low (ref)	**0**		**0**	
Int	**−1.01 (−2.86 to +0.83)**	**0.28**	**−0.16 (−1.79 to 1.46)**	**0.84**
High	**−1.36 (−2.36 to −0.36)**	**0.009**	**−2.00 (−3.90 to −0.11)**	**0.04**

Etx = endotoxin.
First, bivariate linear regression was performed to determine the variables associated with vasopressor-free days. All variables associated with vasopressor-free days with a $p < 0.15$ were included in the multivariate model. Multivariable linear regression was performed using backward selection.
Bold values indicate variables with significant association.

TABLE 3. Determinants of Mean Daily Vasopressor Dose (Bivariate and Multivariate Analyses)

Baseline Characteristics	Crude Estimate (95% CI)	p	Adjusted Estimate (95% CI)	p
Female gender	−46.2 (−107.8 to +15.3)	**0.138**	34.3 (−91.1 to +22.5)	0.23
Age	−0.30 (−2.27 to +1.68)	0.76		
Public place of cardiac arrest	26.8 (−19.9 to +73.4)	0.22		
Witnessed	14.4 (−46.23 to +75.1)	0.64		
Nonshockable rhythm	72.4 (16.6 to 128)	**0.01**	**59.9 (6.23 to 113.7)**	**0.007**
Time to return of spontaneous circulation (/min)	1.19 (−0.76 to +3.14)	0.23		
Epinephrine dose (/mg)	9.16 (−1.08 to +19.4)	**0.08**	6.5 (−3.7 to +16.7)	0.21
Etx class low (ref.)	**0**		**0**	
Int	**23.04 (−9.67 to +55.76)**	**0.16**	**10.43 (−52.6 to 73.5)**	**0.33**
High	**68.26 (29.2 to 107.3)**	**0.001**	**97.95 (20.5 to 175.4)**	**0.01**

Etx = endotoxin.
First, bivariate linear regression was performed to determine the variables associated with mean daily vasopressor dose. All variables associated with mean daily vasopressor dose with a $p < 0.15$ were included in the multivariate model. Multivariable linear regression was performed using backward selection.
Bold values indicate variables with significant association.

PROGNOSTIC VALUE OF EAA IN CARDIAC SURGERY

EAA **CORRELATES** WITH ENDOTOXIN LEVELS

MIGHT BE USEFUL FOR RECOGNISING PATIENTS WHO HAVE AN **INCREASE RISK OF MORTALITY**

Prognostic value of endotoxin activity assay in patients with severe sepsis after cardiac surgery

Michail Yaroustovsky, Marina Plyushch, Dmitry Popov*, Natalia Samsonova, Marina Abramyan, Zakhar Popok and Nickolay Krotenko

PROGNOSTIC VALUE OF EAA IN CARDIAC SURGERY

Table 1 Patient characteristics

Parameters		Overall population, n = 81	Survivors, n = 44	Non-survivors, n = 37	p-value*
Age, years		56 (47.5-64.5)	53 (42–61)	59 (52–66)	0.06
Male sex		45/81 (56%)	23/44 (52%)	22/37 (59%)	0.67
APACHE II scores		20 (10–30)	11 (8–26)	28 (15–31)	0.0008
Renal failure		41/81 (50.6%)	20/44 (45.5%)	24/37 (64.9%)	0.19
Dialysis requirement		19/81 (23.5%)	6/44 (13.6%)	13/37 (36.4%)	0.44
Epinephrine	Receivers	74/81 (91.4%)	40/44 (90.9%)	34/37 (91.9%)	0.81
	Dose, mcg/kg/min	0.08 (0.05-0.1)	0.07 (0.05-0.1)	0.09 (0.06-0.1)	0.31
Dopamine	Receivers	53/81(65.4%)	29/44 (65.9%)	24/37 (64.9%)	0.89
	Dose, mcg/kg/min	5 (4–7)	5.5 (5–8)	5 (3–6)	0.06
Dobutamine	Receivers	26/81(32%)	14/44(31.8%)	11/37(29.7%)	0.97
	Dose, mcg/kg/min	5.75 (4–8)	5.15 (4.25-7)	6 (4–8)	0.64
Norepinephrine	Receivers	12/81(14.8%)	5/44(11.4%)	9/37(24.3%)	0.02
	Dose, mcg/kg/min	0.07 (0.05-0.1)	0.08 (0.05-0.15)	0.06 (0.05-0.09)	0.46
WBC, $x10^9$/l		13.2 (10.5-19.3)	13 (10.6-20.8)	13.4 (10–18.9)	0.83
LAL,EU/mL		0.72 (0.36-0.72)	0.72(0.36-0.72)	0.72 (0.36-1.08)	0.65
PCT, ng/mL		5.07 (1.25-13.72)	3.06 (0.72-8)	5.69 (3.19-23.34)	0.05
EAA		0.49 (0.39-0.66)	0.45 (0.33-0.58)	0.6 (0.45-0.69)	0.009

* between survivors and non-survivors.

PROGNOSTIC VALUE OF EAA IN CARDIAC SURGERY

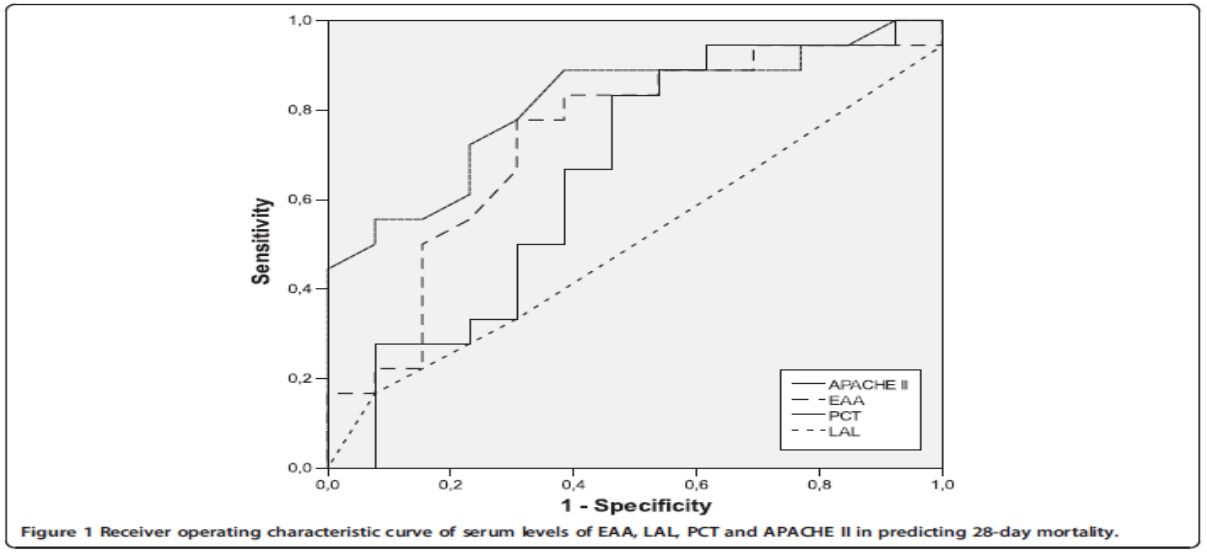


Figure 1 Receiver operating characteristic curve of serum levels of EAA, LAL, PCT and APACHE II in predicting 28-day mortality.

Table 3 ROC analysis data

Parameter	AUC (95% CI)	Optimal cut-off value	Se,%	Sp,%
APACHE II	0.81 (0.66-0.96)	11.5	78	69
EAA	0.73 (0.55-0.92)	0.65	72	69
PCT	0.66 (0.45-0.87)	4.76	67	62

Se sensitivity, *Sp* specificity, *AUC* area under the curve.

Table 2 Clinical and laboratory indices

Group	EAA	LAL,EU/mL	PCT, ng/mL	APACHE II	28-day mortality,%
Group I, n = 20	0.3 (0.26-0.34)	0.36 (0.36-0.72)	3.49 (1.25-8.75)	10 (6–13)	20
Group II, n = 35	0.48* (0.44-0.52)	0.72 (0.36-0.72)	3.68 (0.95-7.7)	15 (9–20.5)	43
Group III, n = 26	0.69** (0.65-0.73)	0.72** (0.7-1.44)	9.3** (4.2-28.3)	30,5** (28–32)	54**

* $p_{I\text{-}II} < 0.05$.
** $p_{I\text{-}III} < 0.05$.

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http://www.journal-inflammation.com/content/10/1/8

OUTCOME CORRELATION

biomedicines
MDPI
Article

Comparative Evaluation of Endotoxin Activity Level and Various Biomarkers for Infection and Outcome of ICU-Admitted Patients

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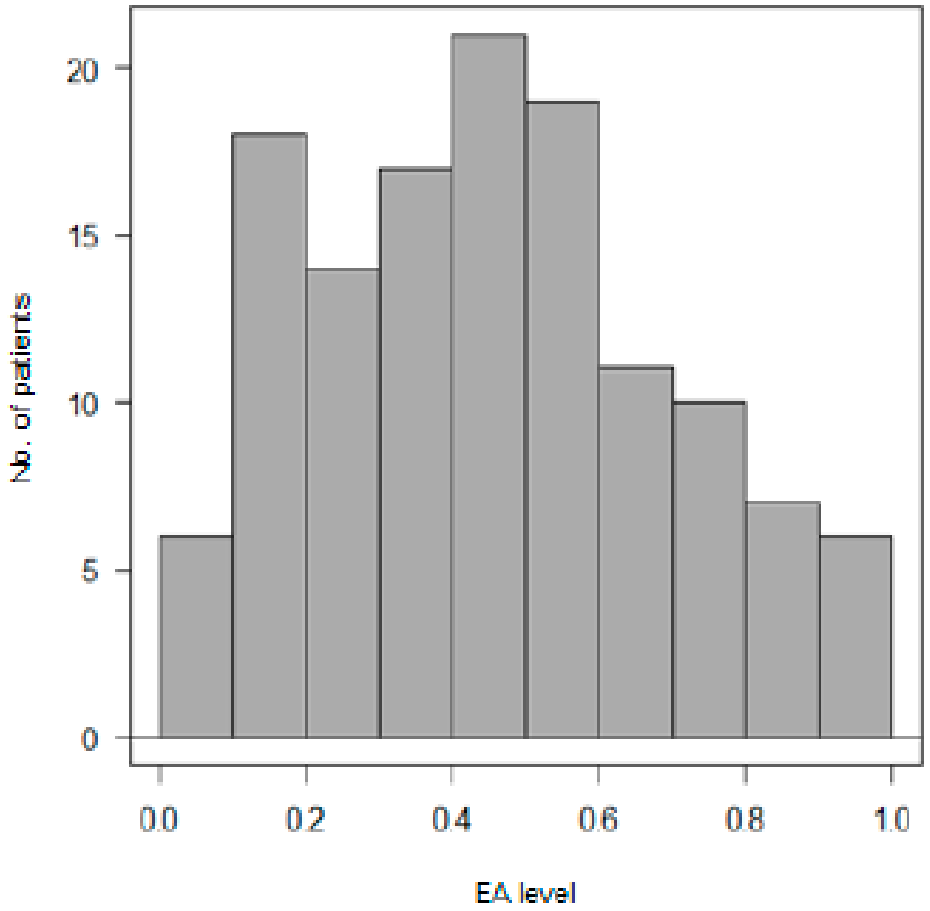
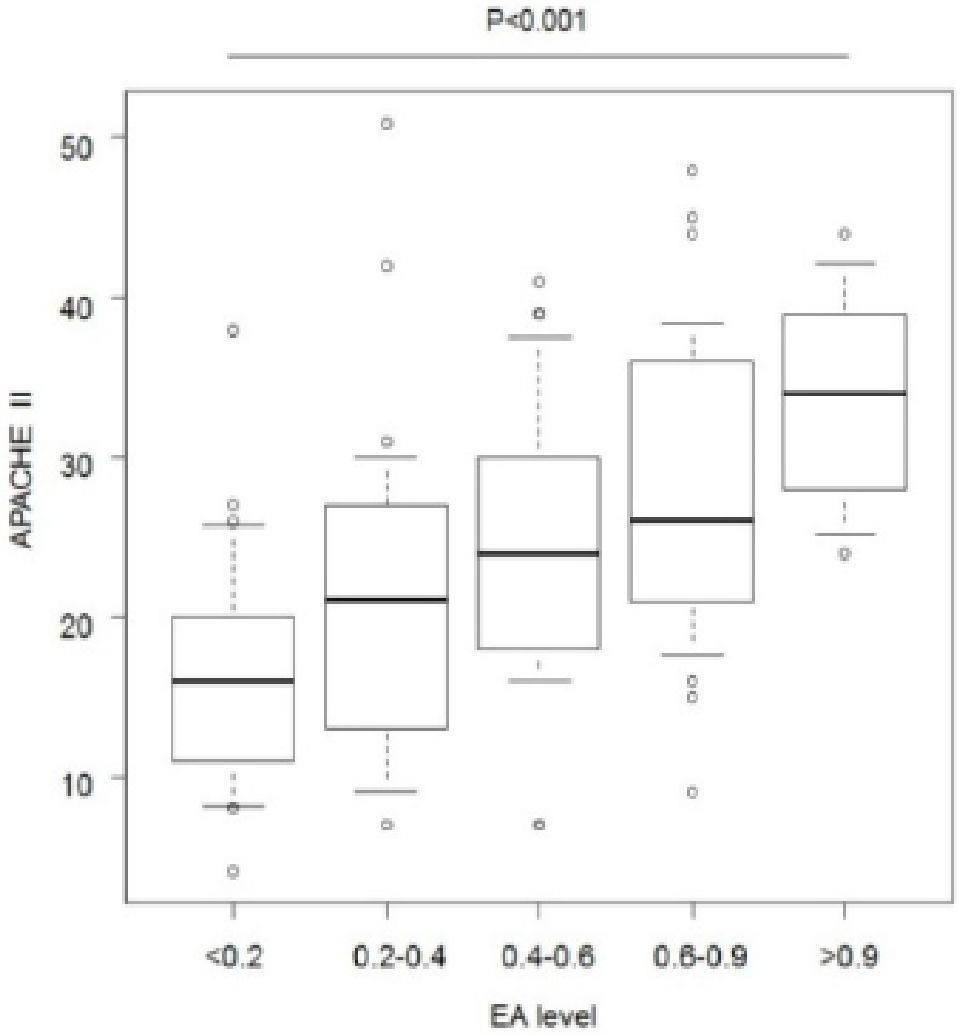
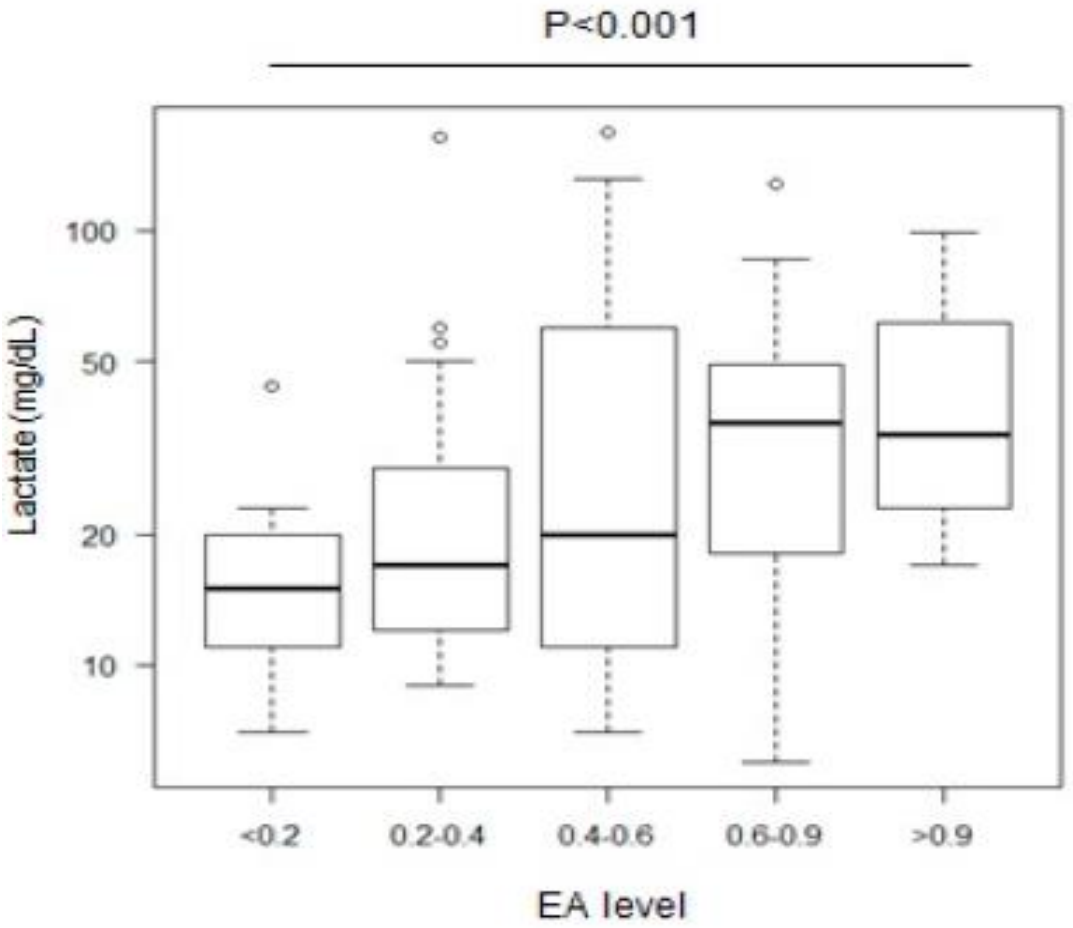
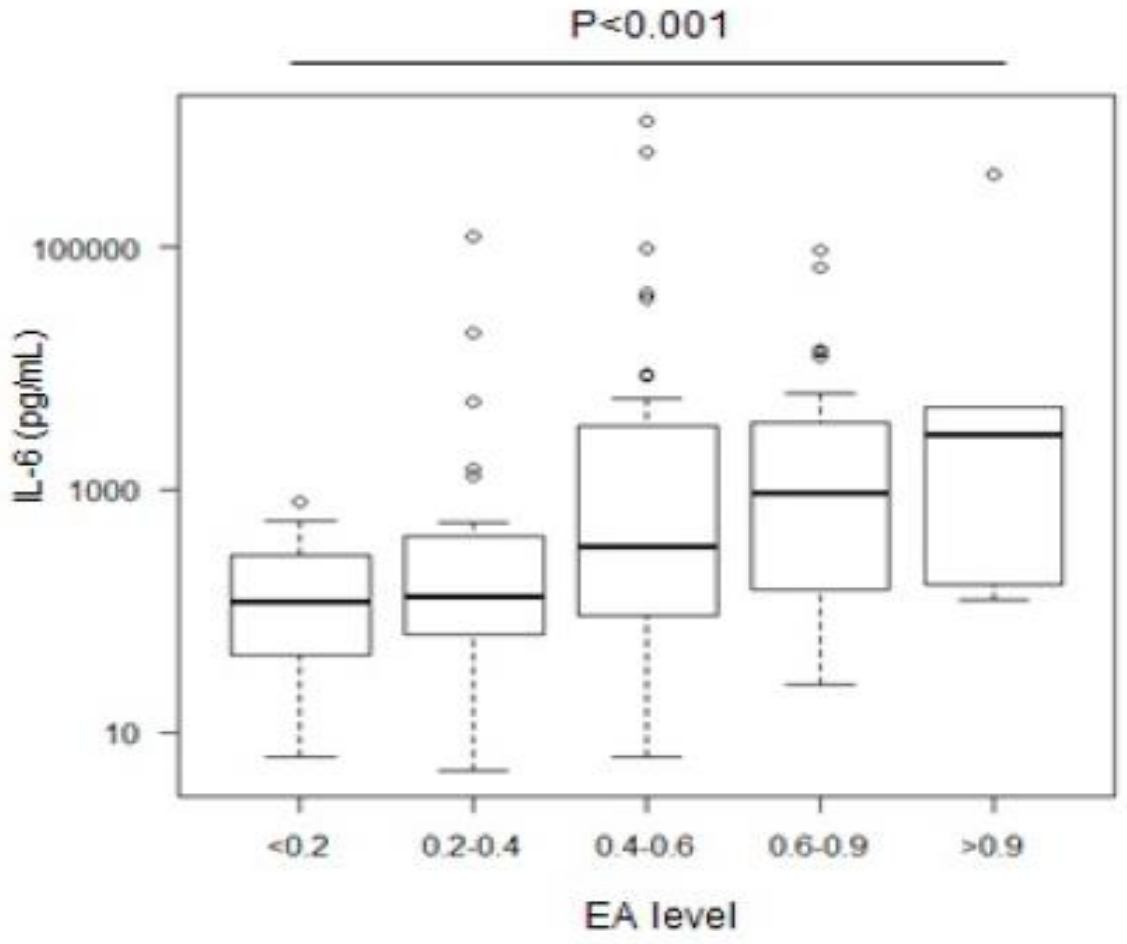


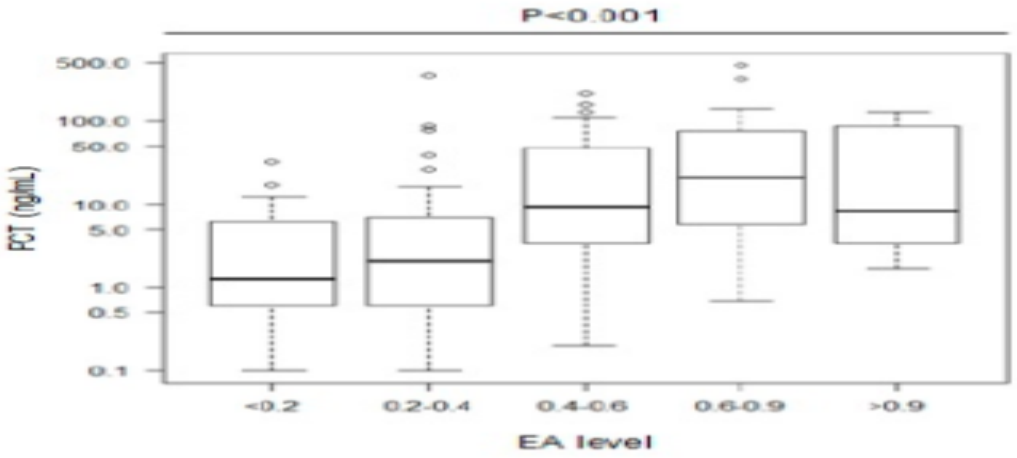


OUTCOME CORRELATION

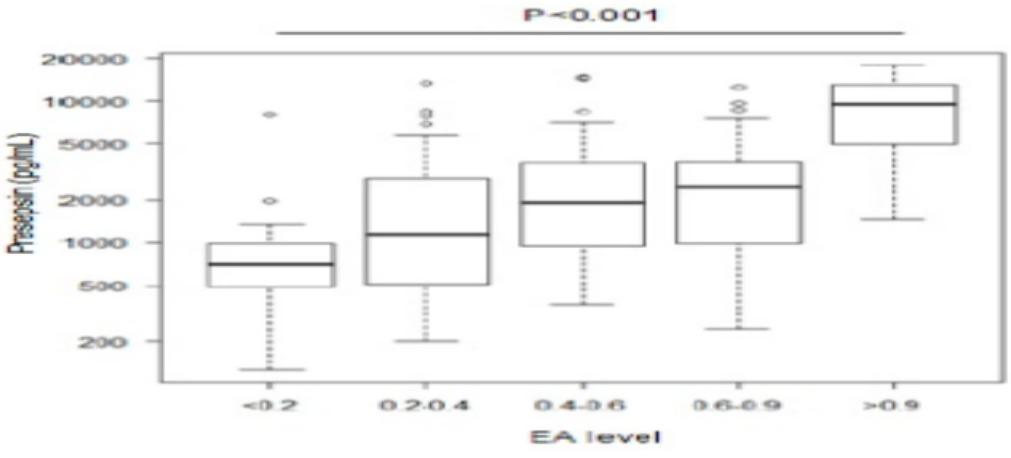




BIOMARKERS CORRELATION



(a)



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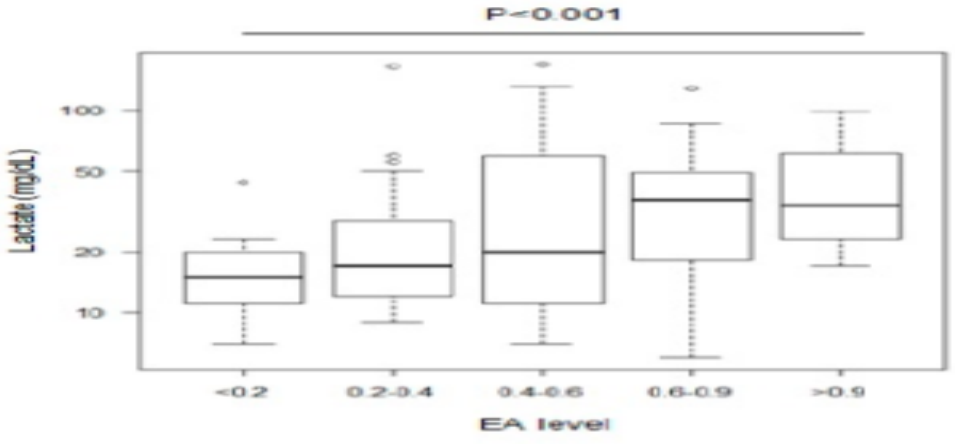

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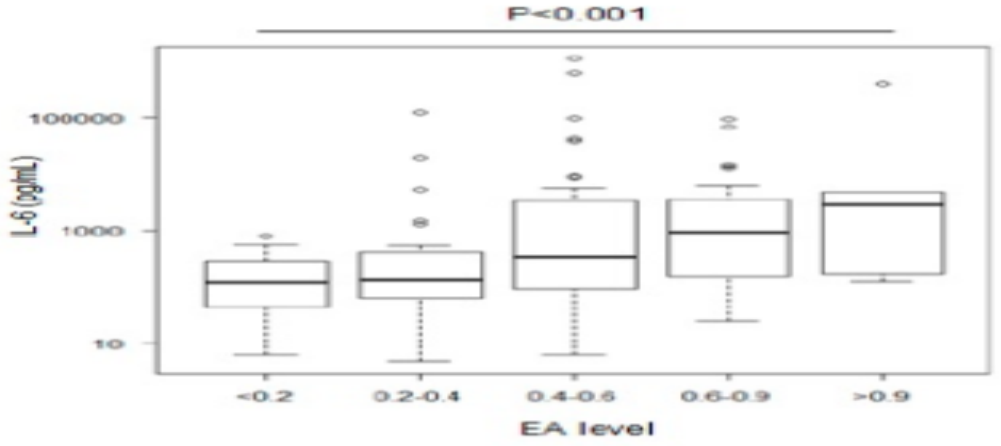

(d)

ATTENTION

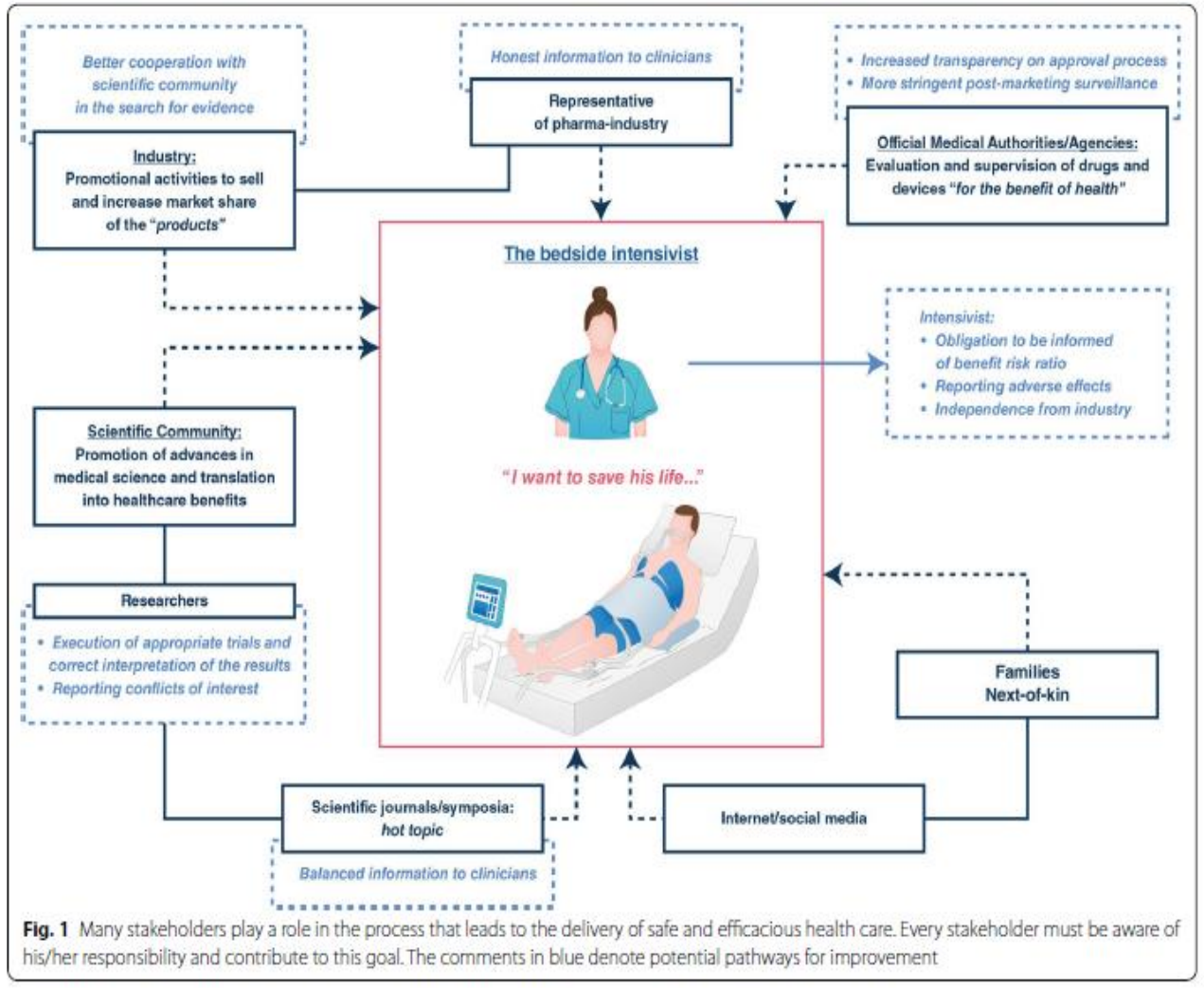

Fig. 1 Many stakeholders play a role in the process that leads to the delivery of safe and efficacious health care. Every stakeholder must be aware of his/her responsibility and contribute to this goal. The comments in blue denote potential pathways for improvement

LESS IS MORE IN ICU

When more could be industry-driven: the case of the extracorporeal treatment of sepsis

Miet Schetz[1*] and Thomas Bein[2]

CONCLUSIONS

NOT ONLY GRAM INFECTION

ECMO

CARDIAC ARREST

IMMUNOMODULATION

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