Do we need new vasopressors or less of old ones?

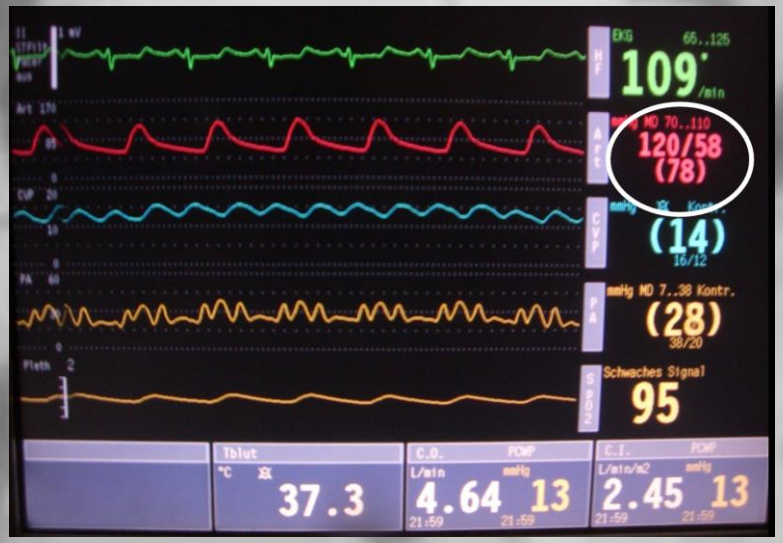
Martin Dünser

Department of Anesthesiology and Intensive Care Medicine
Kepler University Hospital and Johannes Kepler University
Linz/Austria

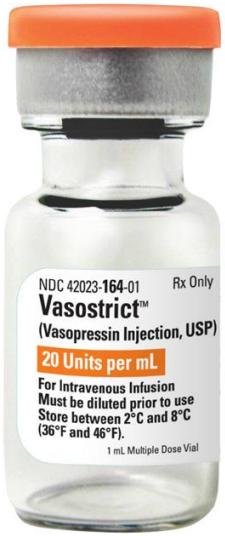
Kepler Universitäts Klinikum

JOHANNES KEPLER UNIVERSITÄT LINZ

Conflicts of Interest


EKG
65..125
109
/min
MD 70..110
120/58
(78)
(14)
16/12
mmHg MD 7..38 Kontr.
(28)
38/20
Schwaches Signal
95
Tblut
37.3
C.O.
PCWP
4.64
13
C.I.
PCWP
2.45
13

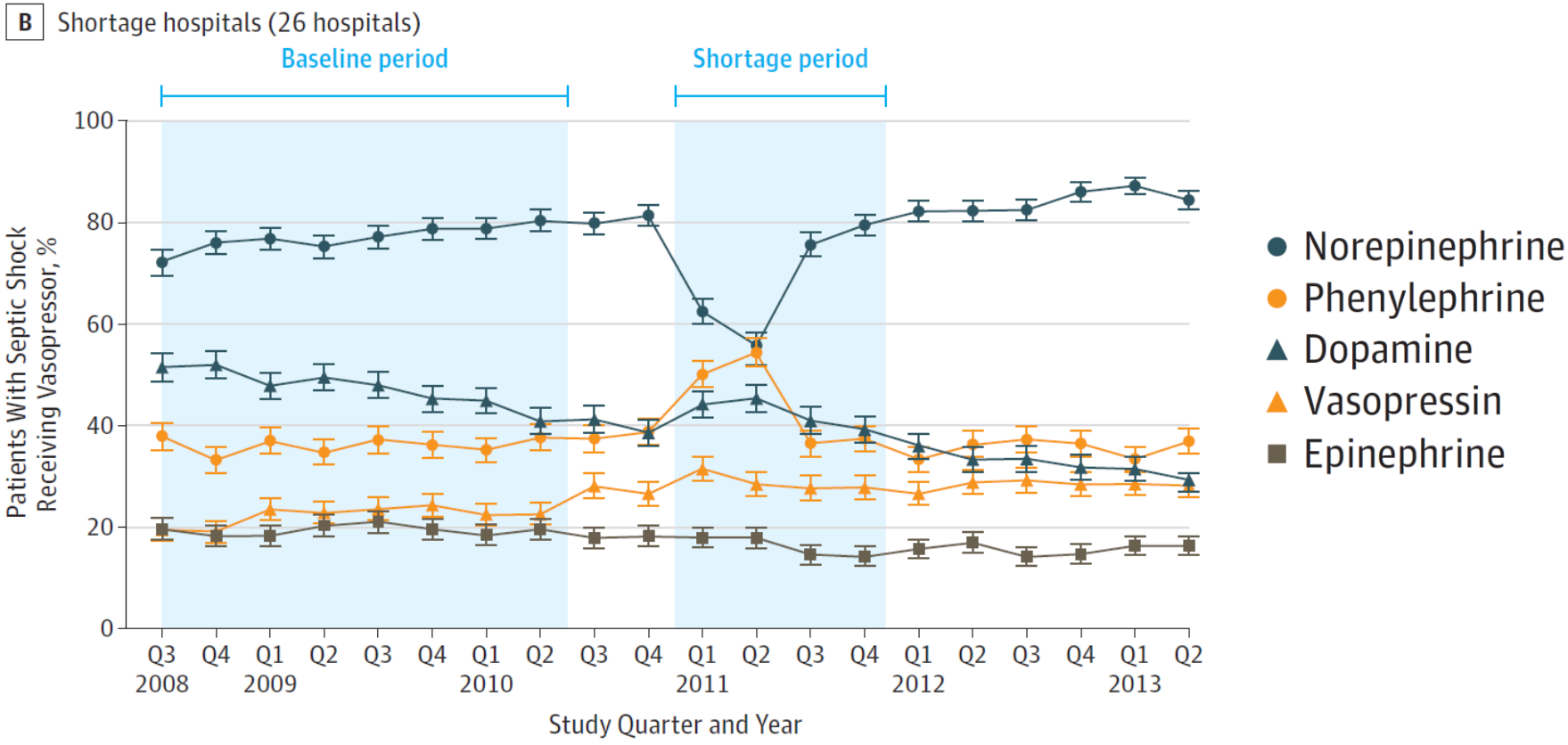
Which „old“ vasopressors do we have?



JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock

Emily Vail, MD; Hayley B. Gershengorn, MD; May Hua, MD, MSc; Allan J. Walkey, MD, MSc; Gordon Rubenfeld, MD, MSc; Hannah Wunsch, MD, MSc



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Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock

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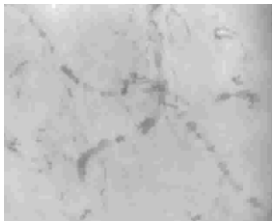
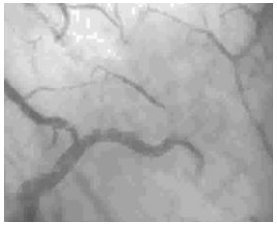
Cohort	Deaths, No./Total Patients, No. (%)	Absolute Mortality Difference, % (95% CI)[a]	Adjusted Odds Ratio (95% CI)[b]	*P* Value
Patients with septic shock receiving vasopressors				
Primary model[c]				
Admission to shortage hospitals during a nonshortage quarter	9283/25 874 (35.9)	NA	1 [Reference]	
Admission to shortage hospitals during a quarter of 2011 in which norepinephrine use decreased >20% below baseline	777/1961 (39.6)	3.7 (1.5-6.0)	1.15 (1.01-1.30)	.03

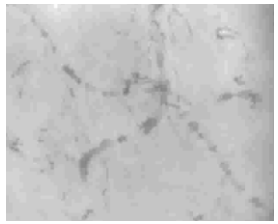
CONCLUSIONS AND RELEVANCE Among patients with septic shock in US hospitals affected by the 2011 norepinephrine shortage, the most commonly administered alternative vasopressor was phenylephrine. Patients admitted to these hospitals during times of shortage had higher in-hospital mortality.

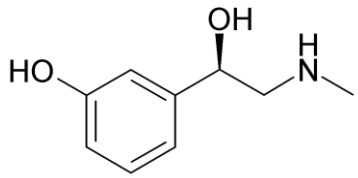
Safety margins: Phenylephrine vs. Norepinephrine

Heart failure — **Microcirc. failure**

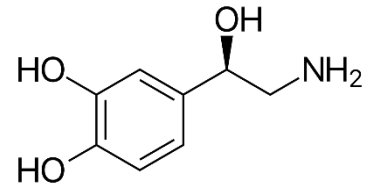






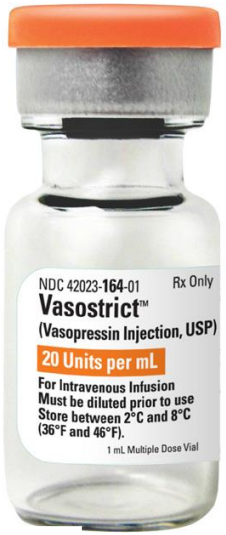


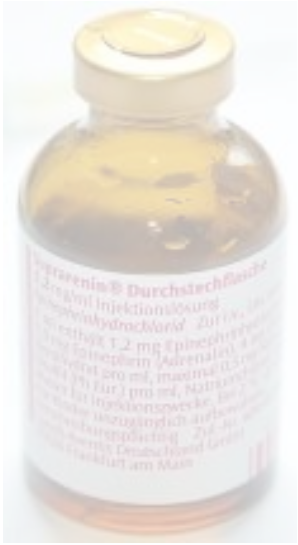
Phenylephrine

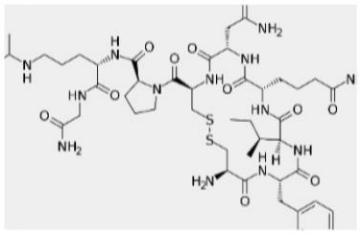


Norepinephrine

Which „old“ vasopressors do we have?

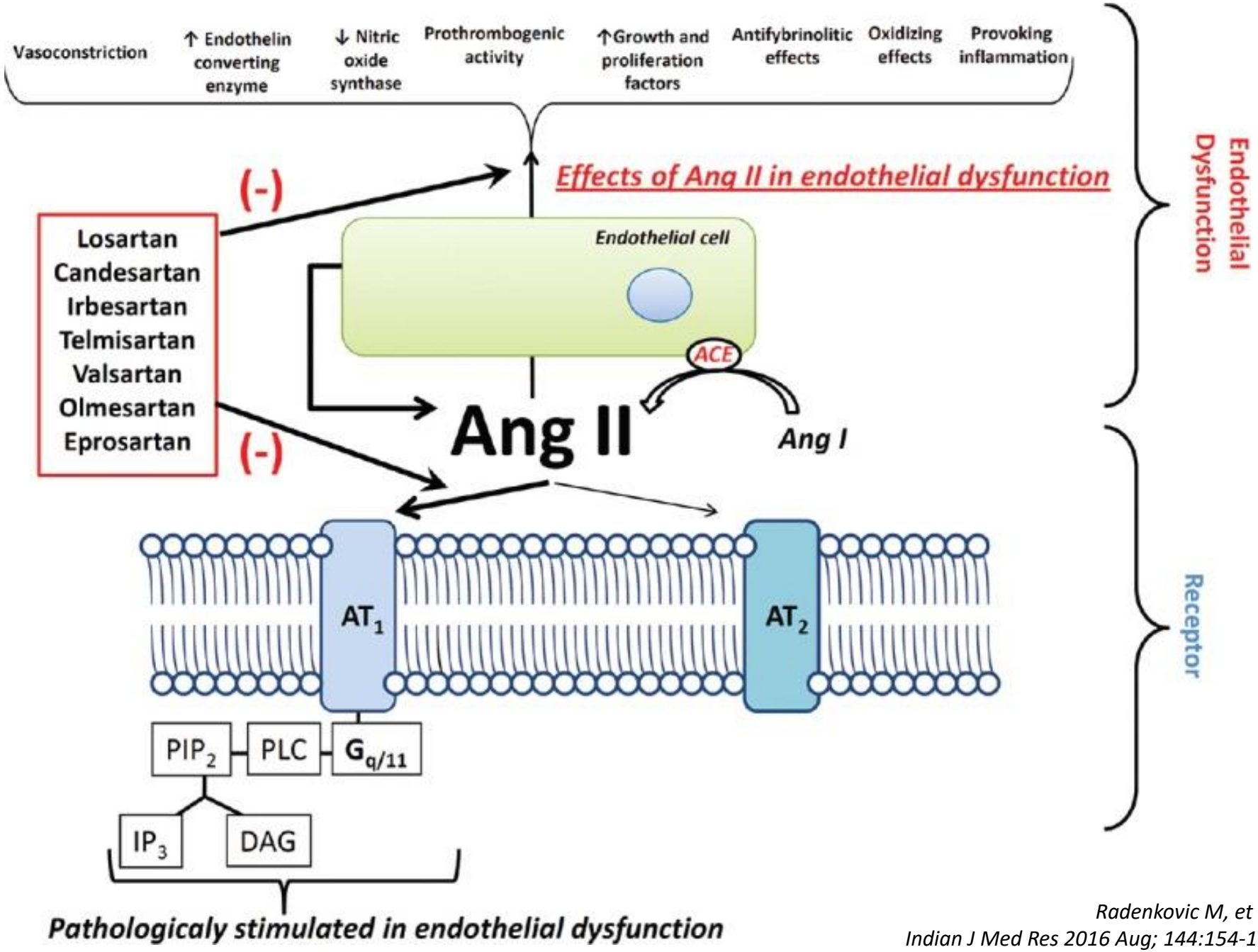






Selepressin

Angiotensin II

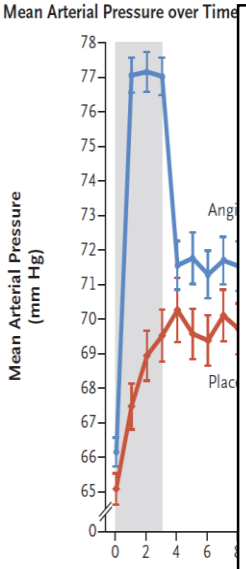


Radenkovic M, et al.
Indian J Med Res 2016 Aug; 144:154-168

ORIGINAL ARTICLE

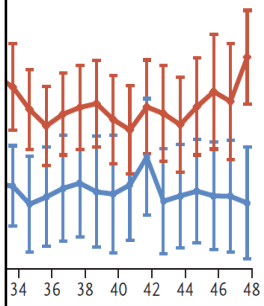
Angiotensin II for the Treatment of Vasodilatory Shock

Ashish Khanna, M.D., Shane W. English, M.D., Xueyuan S. Wang, M.D.,



	Angiotensin II	Placebo	P-value
MAP ≥75 mmHg	69.9%	23.4%	<0.001

Angiotensin II	NE <0.5 µg/kg/min	NE >0.5 µg/kg/min	P-value
MAP ≥75 mmHg	77.8%	50%	<0.001

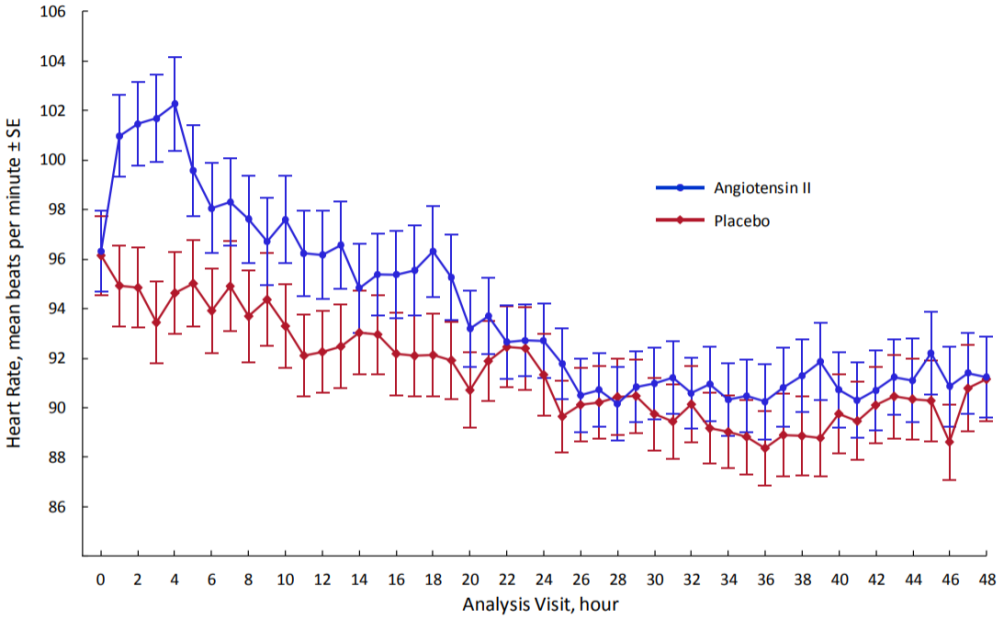


Event	Angiotensin II (N=163)	Placebo (N=158)
	no. of patients (%)	
Adverse event of any grade†	142 (87.1)	145 (91.8)
Adverse event leading to discontinuation‡	23 (14.1)	34 (21.5)
Serious adverse event with frequency ≥1% in either study group		

ORIGINAL ARTICLE

Angiotensin II for the Treatment of Vasodilatory Shock

Ashish Khanna, M.D., Shane W. English, M.D., Xueyuan S. Wang, M.D.,



Cardiac output

Tissue perfusion

Organ function

Trial data were collected by the investigators with the assistance of a contract research organization and were analyzed by the sponsor. Study oversight was provided by an independent data and safety monitoring board. The writing committee, which included investigators and representatives of the sponsor, drafted the manuscript and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. A professional medical writer funded by the sponsor assisted with manuscript revisions. All the authors made the decision to submit the manuscript for publication.

CONCLUSIONS

Angiotensin II effectively increased blood pressure in patients with vasodilatory shock that did not respond to high doses of conventional vasopressors. (Funded by La Jolla Pharmaceutical Company; ATHOS-3 ClinicalTrials.gov number, NCT02338843.)

Clinical Experience With IV Angiotensin II Administration: A Systematic Review of Safety

Laurence W. Busse, MD[1]; Xueyuan Shelly Wang, MD[2]; Divya M. Chalikonda, MD[3]; Kevin W. Finkel, MD[4]; Ashish K. Khanna, MD[5]; Harold M. Szerlip, MD[6]; David Yoo, MD[7]; Sharon L. Dana, PhD[8]; Lakhmir S. Chawla, MD[8,9]

1124 Studies included (31,281 patients receiving angiotensin II)

Conclusion: Adverse events associated with angiotensin II were infrequent; however, exacerbation of asthma and congestive heart failure and one fatal cerebral hemorrhage were reported. This systematic review supports the notion that angiotensin II has an acceptable safety profile for use in humans. (*Crit Care Med* ; XX:00–00)

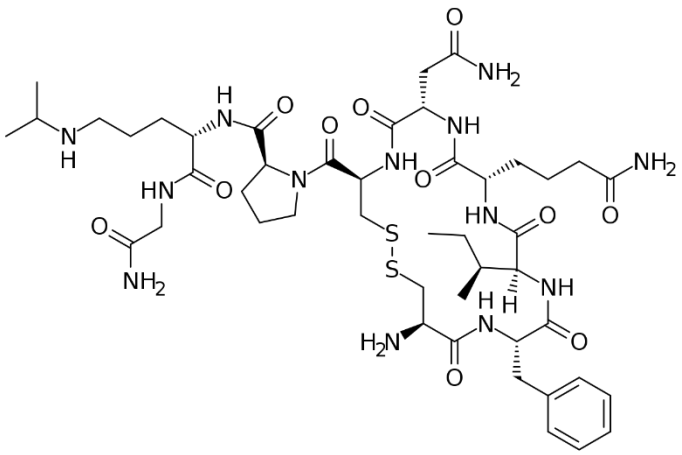
0022-3565/11/3373-786–796$25.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Copyright © 2011 by The American Society for Pharmacology and Experimental Therapeutics
JPET 337:786–796, 2011

Vol. 337, No. 3
178848/3690289
Printed in U.S.A.

Pharmacological Characterization of FE 202158, a Novel, Potent, Selective, and Short-Acting Peptidic Vasopressin V_{1a} Receptor Full Agonist for the Treatment of Vasodilatory Hypotension

Régent Laporte, Arash Kohan, Joshua Heitzmann, Halina Wiśniewska, Jeannine Toy, Erin La, Hiroe Tariga, Sudarkodi Alagarsamy, Brian Ly, John Dykert, Steve Qi, Kazimierz Wiśniewski, Robert Galyean, Glenn Croston, Claudio D. Schteingart, and Pierre J.-M. Rivière

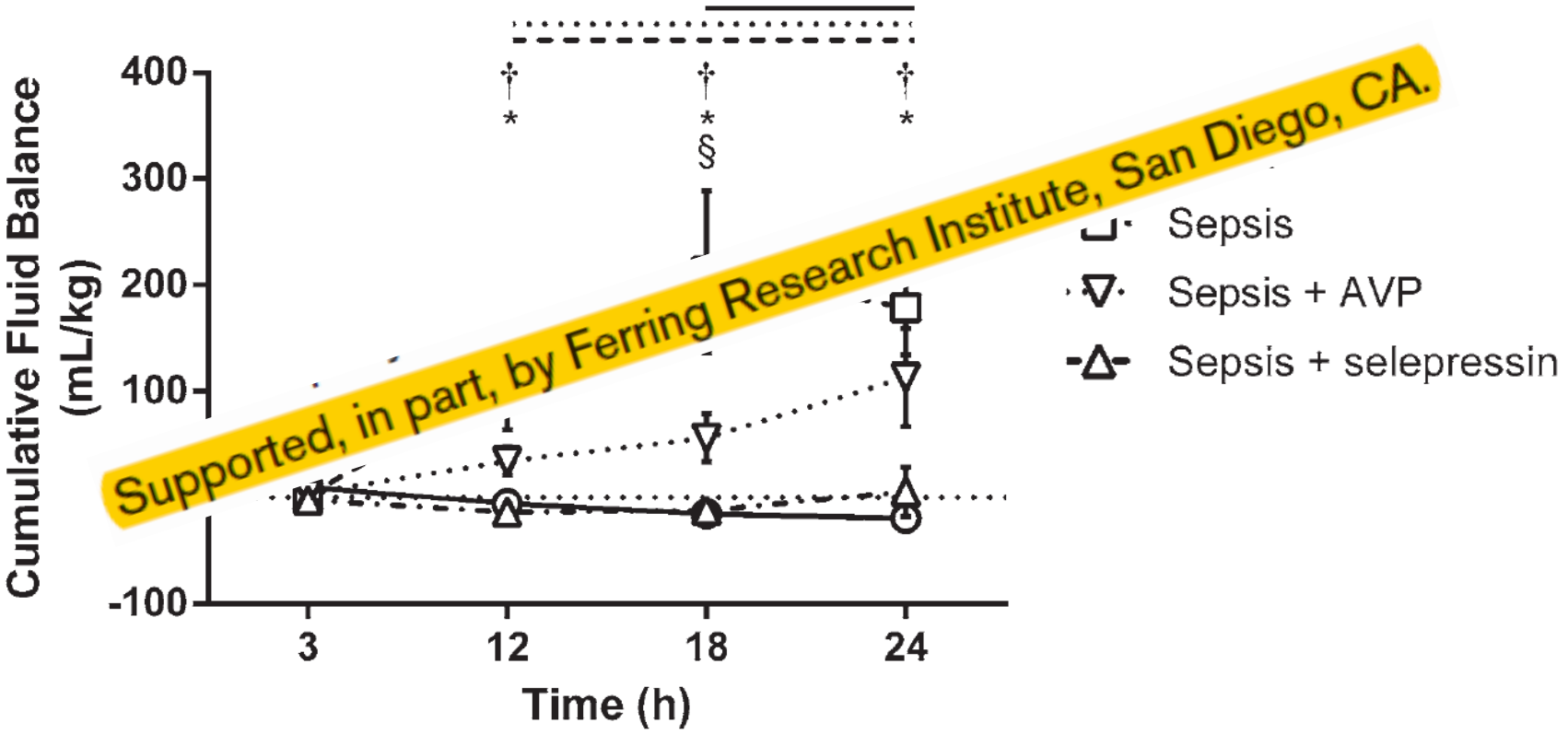
Ferring Research Institute, Inc., San Diego, California



Receptor	EC_{50}	
	Mean	95% CI
	nM	
FE 202158		
$V_{1a}R$	2.4	1.73–3.35
$V_{1b}R$	340	130–888
V_2R	2656	2083–3387
OTR	1057	269–4153
AVP		
$V_{1a}R$	0.24	0.22–0.25
$V_{1b}R$	4.3	3.9–4.7
V_2R	0.05	0.04–0.07
OTR	22	15–33

The Selective Vasopressin Type 1a Receptor Agonist Selepressin (FE 202158) Blocks Vascular Leak in Ovine Severe Sepsis*

Marc O. Maybauer, MD, PhD, EDIC, FCCP[1,2]; Dirk M. Maybauer, MD, PhD[1,2];

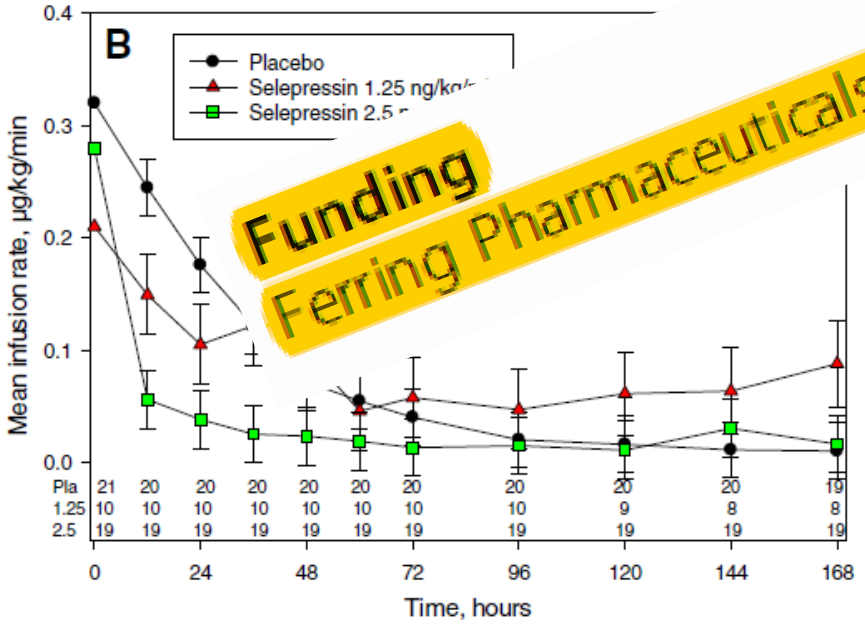


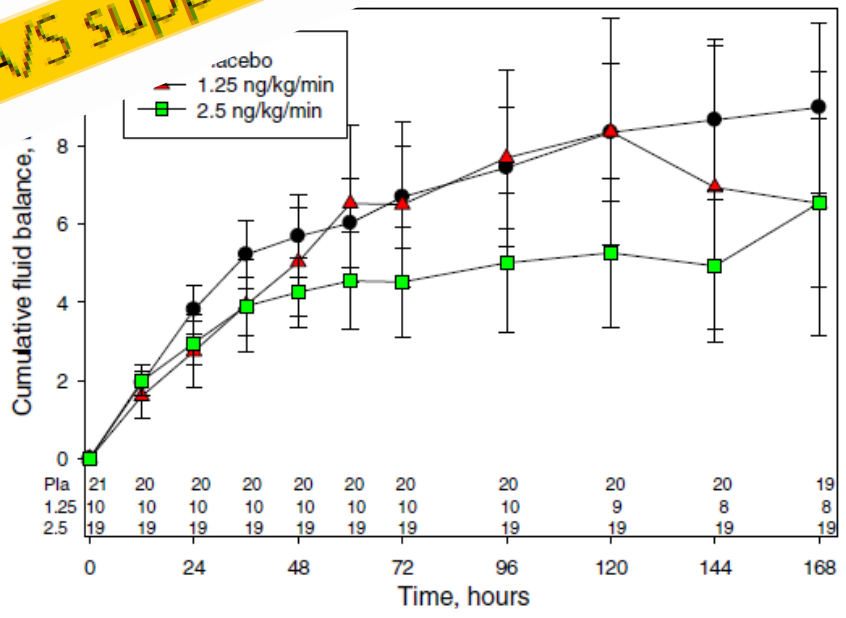
Supported, in part, by Ferring Research Institute, San Diego, CA.

Selepressin, a novel selective vasopressin V_{1A} agonist, is an effective substitute for norepinephrine in a phase IIa randomized, placebo-controlled trial in septic shock patients

James A. Russell[1*], Jean-Louis Vincent[2], Anne Louise Kjølbye[3], Håk- ert Spapen[4], Peder Carl[5], Pierre-Francois Laterre[6] and Lars Grundemar[3]

Funding
Ferring Pharmaceuticals A/S supported this work





Rationale and Design of an Adaptive Phase 2b/3 Clinical Trial of Selepressin for Adults in Septic Shock

Selepressin Evaluation Programme for Sepsis-induced Shock—Adaptive Clinical Trial

Roger J. Lewis[1,2,3,4], Derek C. Angus[5,6], Pierre-François Laterre[7], Anne Louise Kjølbye[8], Egbert van der Meulen[8], Allan Blemings[8], Todd Graves[4], James A. Russell[9], Jan E. Carlsen[10], Karsten Jacobsen[8], Donald M. Yealy[11], Steven M. Opal[12], Nis A. Windeløv[8], Bruno François[13], Anders Perner[14], Peter Pickkers[15], and Scott M. Berry[4]

Inclusion criteria

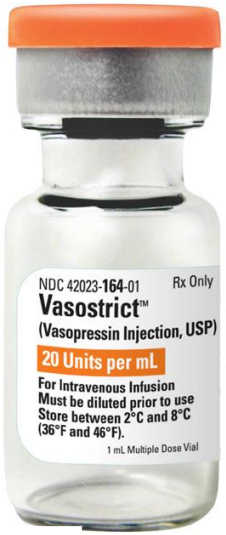
- 18 yr of age or older
- Proven or suspected infection
- Septic shock defined as hypotension (systolic blood pres… n 90 mm Hg *or* MAP less than 65 mm Hg) requiring vasopress… ose of norepinephrine/noradrenaline base … uate fluid resuscitation (at least 1 L …
- Informed consent …

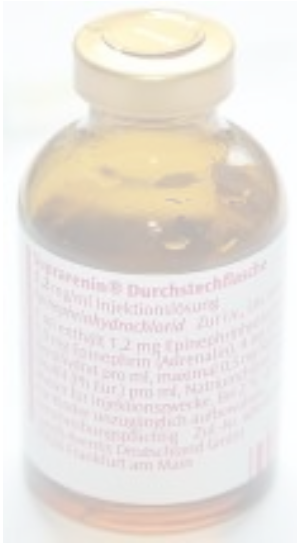
Acknowledgment: The authors thank Helena Andersson, Senior Medical Writer at Ferring Pharmaceuticals A/S, for invaluable assistance in the drafting of many trial-related documents.

Name	Starting Infusion Rate (ng/kg/min)	
Placebo	0*	0*
Arm 1	1.7	2.5
Arm 2	2.5	3.75
Arm 3	3.5	5.25
Arm 4†	5.0	7.5

Endpoints. The primary endpoint for the trial is the number of pressor- and mechanical ventilator-free days (P&VFDs) up to Day 30. We define this composite

What is the problem of the old vasopressors? Why do we need new ones?



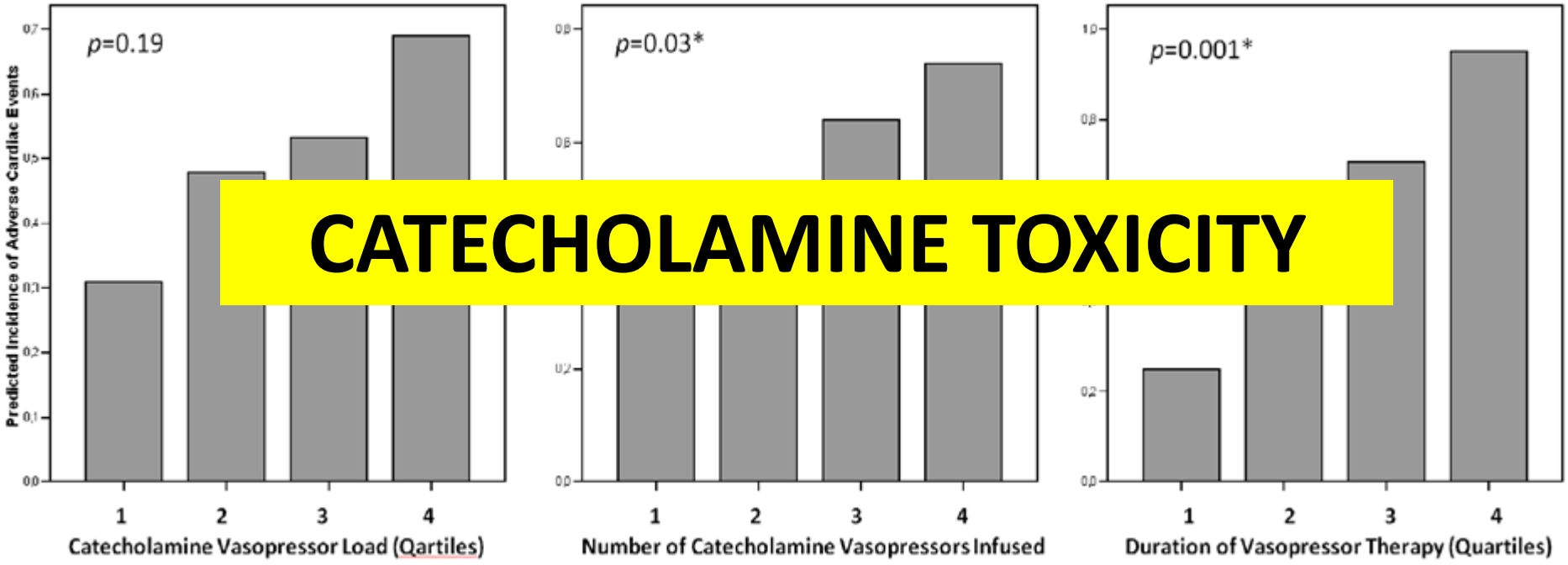


Intensive Care Med (2012) 38:950–958
DOI 10.1007/s00134-012-2531-2

ORIGINAL

Christian A. Schmittinger
Christian Torgersen
Günter Luckner
Daniel C. H. Schröder
Ingo Lorenz
Martin W. Dünser

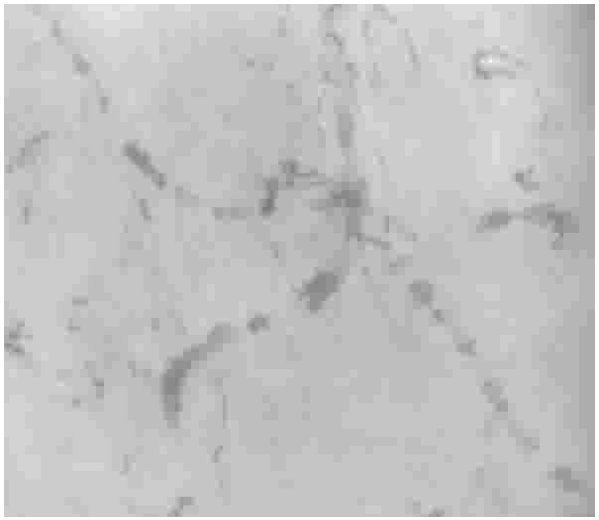
Adverse cardiac events during catecholamine vasopressor therapy: a prospective observational study



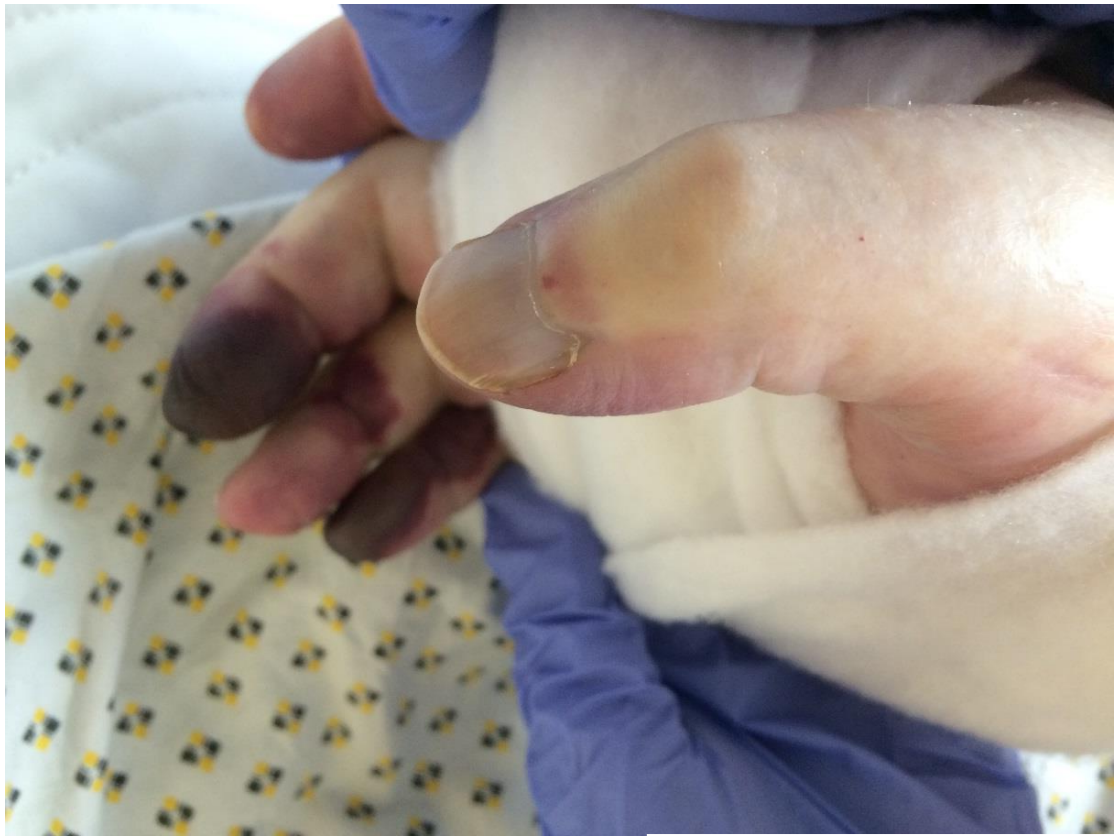
CATECHOLAMINE TOXICITY

Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: Incidence and risk factors*

Martin W. Dünser, MD; Andreas J. Mayr, MD; Andreas Tür; Werner Pajk, MD; Friesenecker Barbara, MD; Hans Knotzer, MD; Hanno Ulmer, PhD; Walter R. Hasibeder, MD



septic




EKG
65..125
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/min
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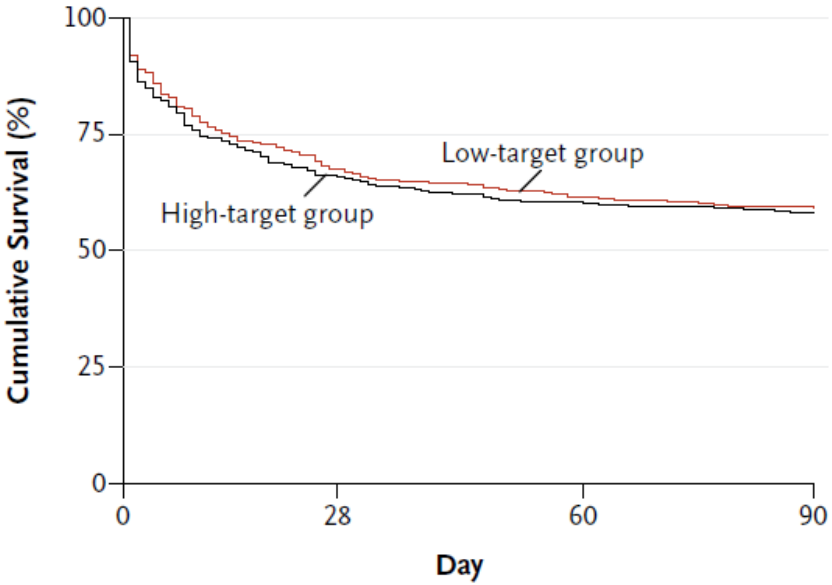
(78)
(14)
16/12
MD 7..38 Kontr.
(28)
38/20
Schwaches Signal
95
Art 170
CVP 20
PA 60
Pleth
Tblut
°C
37.3
PCWP
mmHg
4.64
13
21:59
21:59
C.I.
PCWP
L/min/m2
mmHg
2.45
13
21:59
21:59

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 24, 2014 VOL. 370 NO. 17

High versus Low Blood-Pressure Target in Patients with Septic Shock

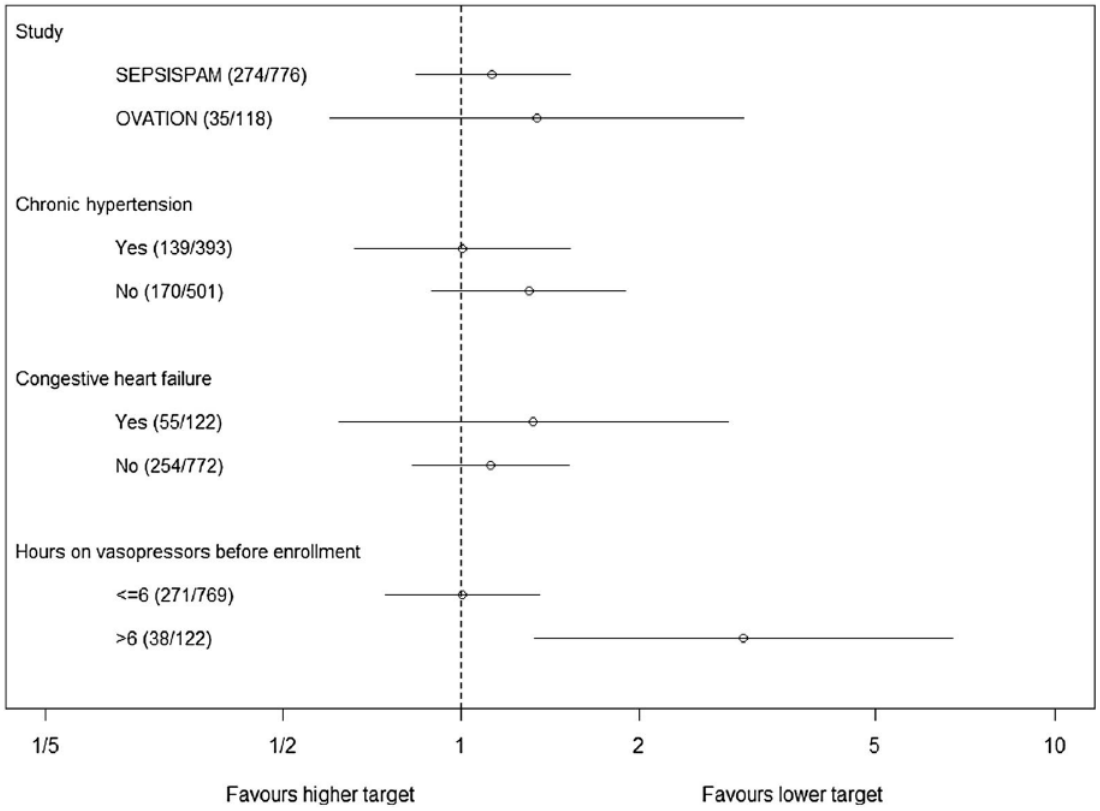
Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D.,



No. at Risk				
Low target	379	256	233	225
High target	375	249	227	219

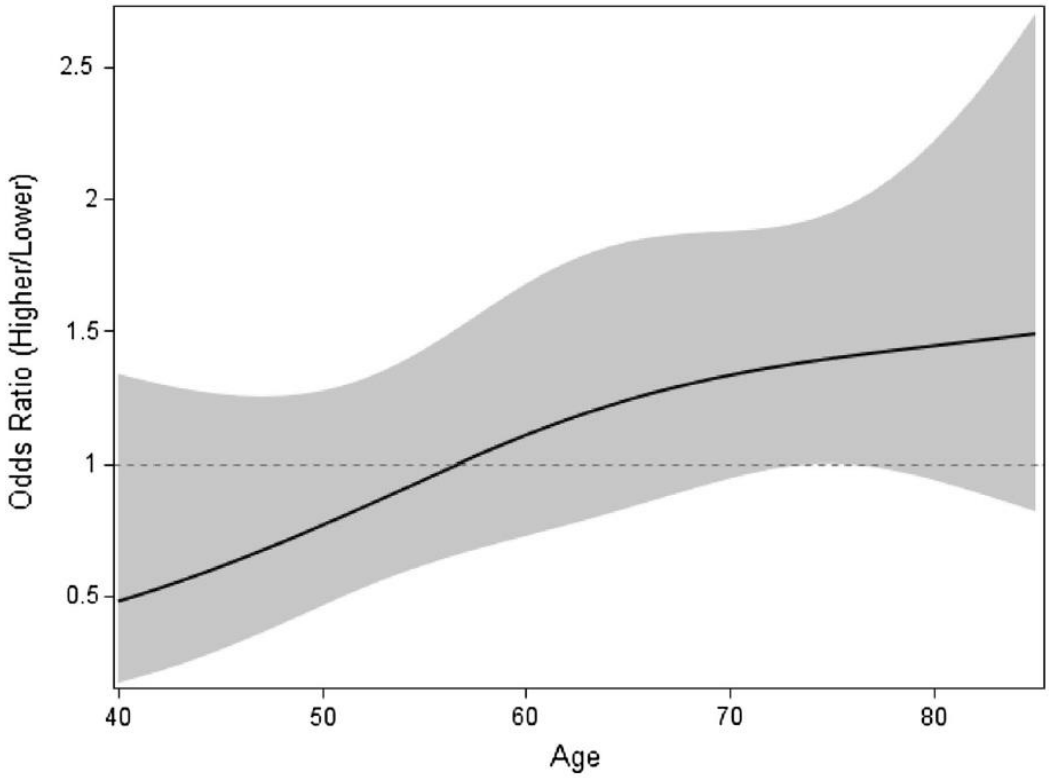
Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock

François Lamontagne[1,2*], Andrew G. Day[3], Maureen O. Meade[4,5], Deborah J. Cook[4,5], Gordon H. Guyatt[5], Mathieu Hylands[6], Peter Radermacher[7], Jean-Marie Chrétien[8], Nicolas Beaudoin[9], Paul Hébert[10], Frédérick D'Aragon[1,2], Ferhat Meziani[11] and Pierre Asfar[12]

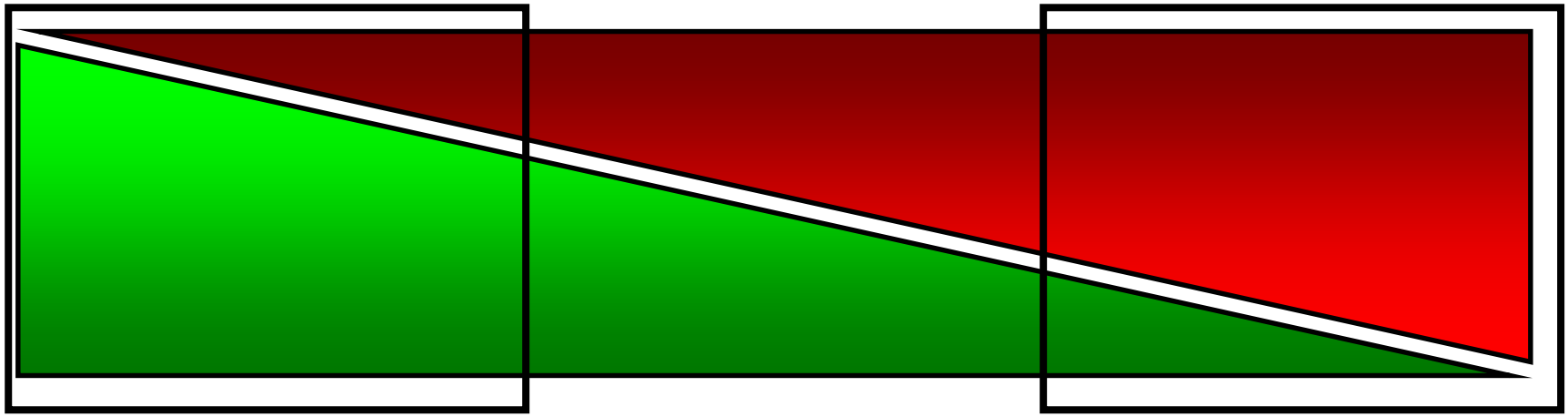


Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock

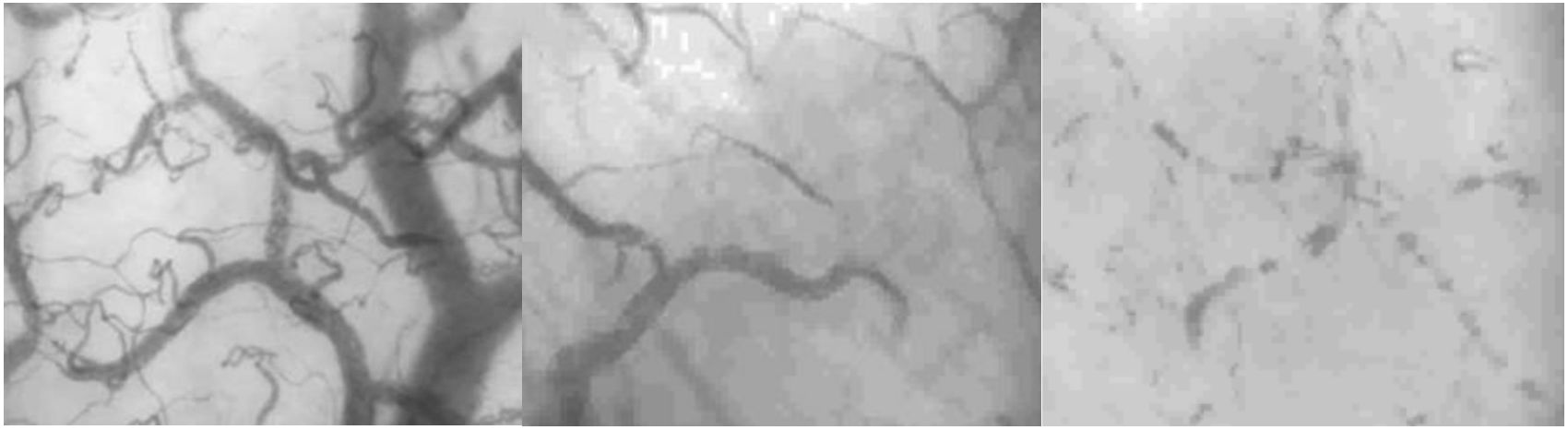
François Lamontagne[1,2*], Andrew G. Day[3], Maureen O. Meade[4,5], Deborah J. Cook[4,5], Gordon H. Guyatt[5], Mathieu Hylands[6], Peter Radermacher[7], Jean-Marie Chrétien[8], Nicolas Beaudoin[9], Paul Hébert[10], Frédérick D'Aragon[1,2], Ferhat Meziani[11] and Pierre Asfar[12]



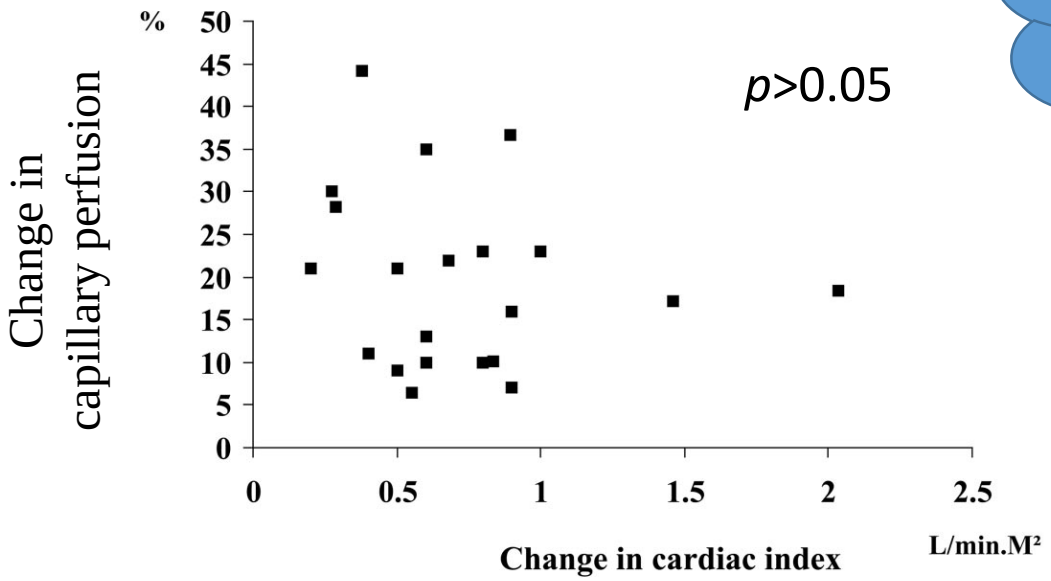
Pressure = Flow x Resistance



CO MAP 65 mmHg SVR



Absolute CO vs. adequacy



p>0.05

Is the cardiac output enough to adequately perfuse the tissues?

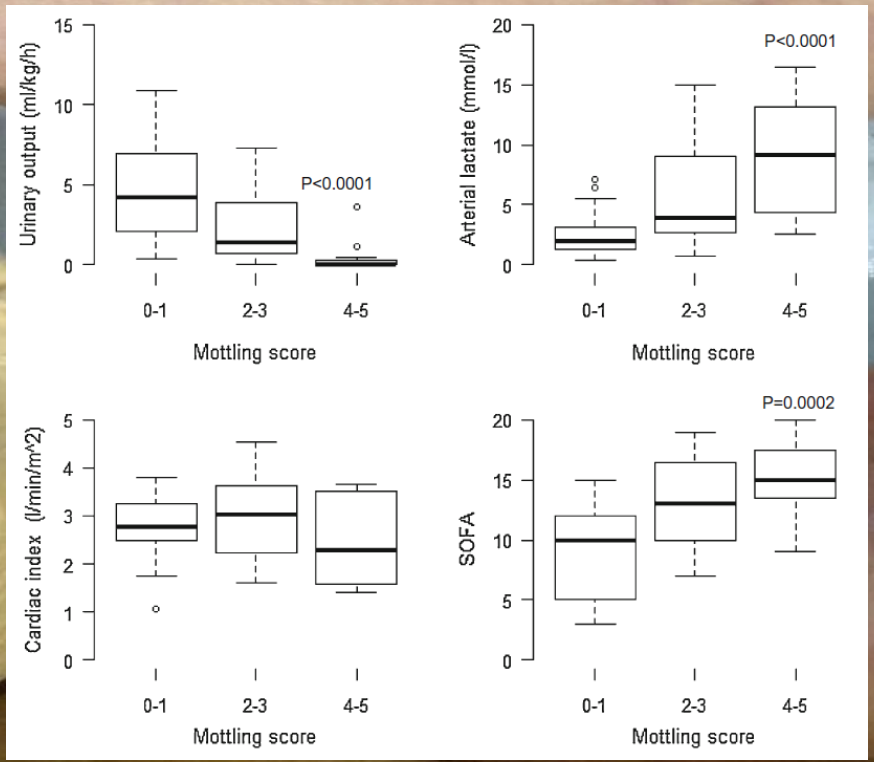
De Backer D, et al. Crit Care Med 2006;34:403-408

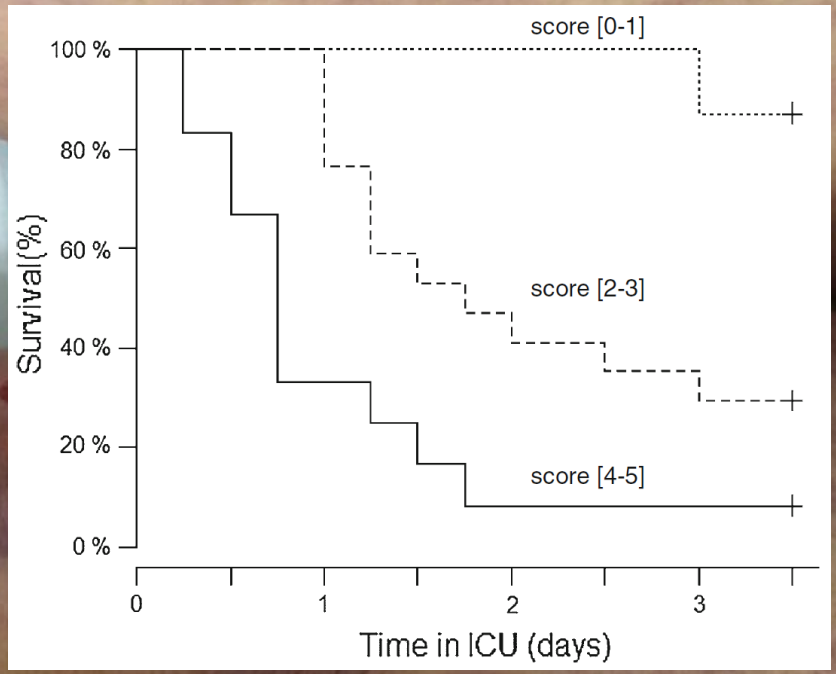
Intensive Care Med (2011) 37:801–807
DOI 10.1007/s00134-011-2163-y

ORIGINAL

H. Ait-Oufella
S. Lemoinne

Mottling score predicts survival in septic shock

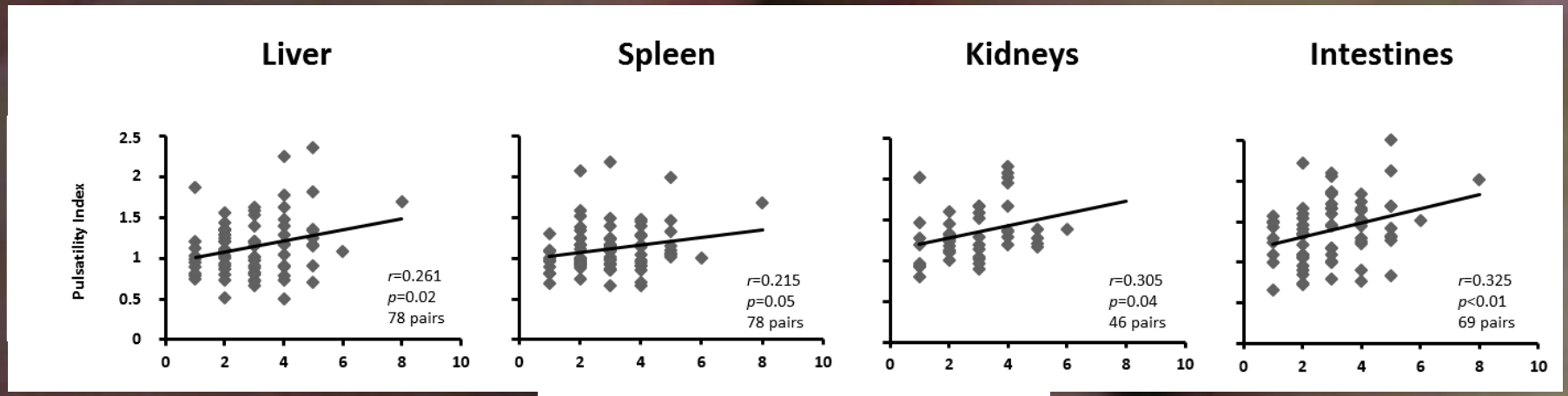




Ait-Oufella H, et al. Intensive Care Med 2011; 37:801-807

Changes in peripheral perfusion relate to visceral organ perfusion in early septic shock: A pilot study☆

Andreas Brunauer, MD [a], Andreas Koköfer, MD [a], Otgon Bataar, MD, PhD [b], Ilse Gradwohl-Matis, MD [a], Daniel Dankl, MD [a], Jan Bakker, MD, PhD [c,d,e], Martin W. Dünser, MD [a,*]

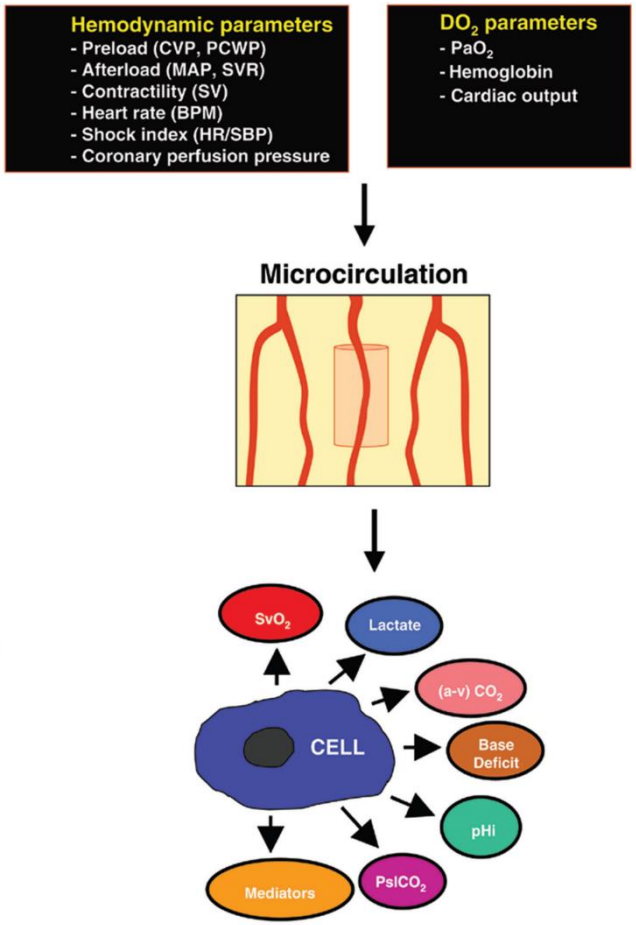


Capillary refill time

Brunauer A, et al. J Crit Care 2016

Re-thinking resuscitation: leaving blood pressure cosmetics behind and moving forward to permissive hypotension and a tissue perfusion-based approach

Martin W Dünser*[1], Jukka Takala[2], Andreas Brunauer[1] and Jan Bakker[3]



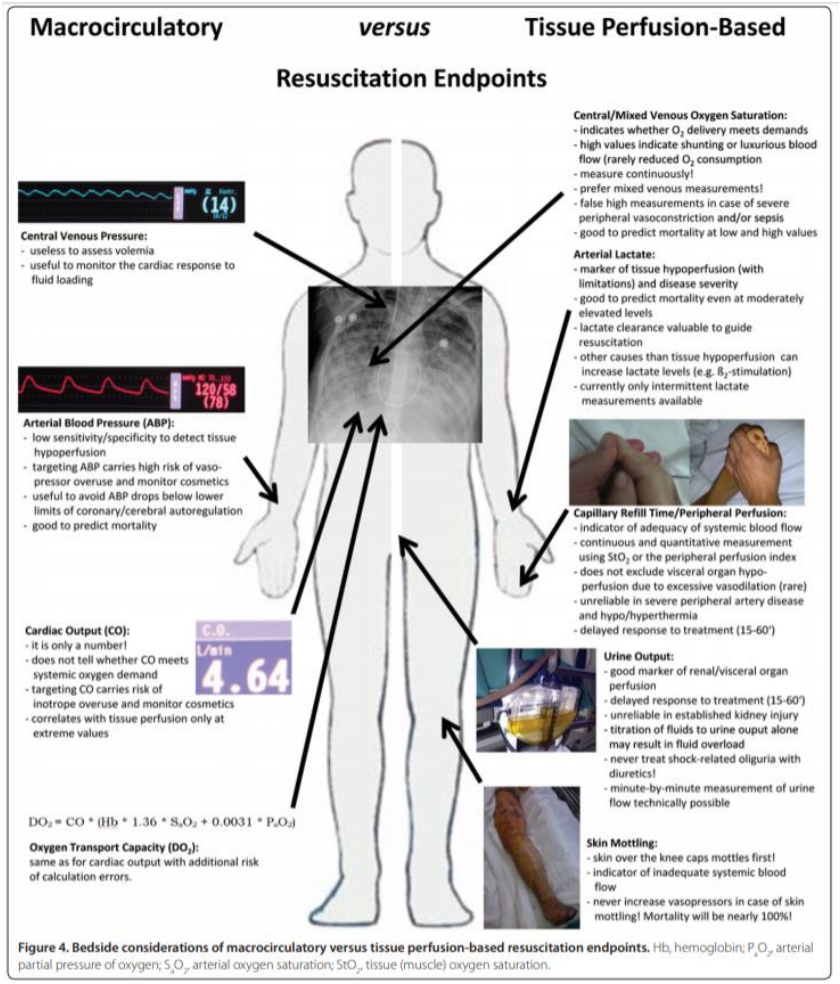
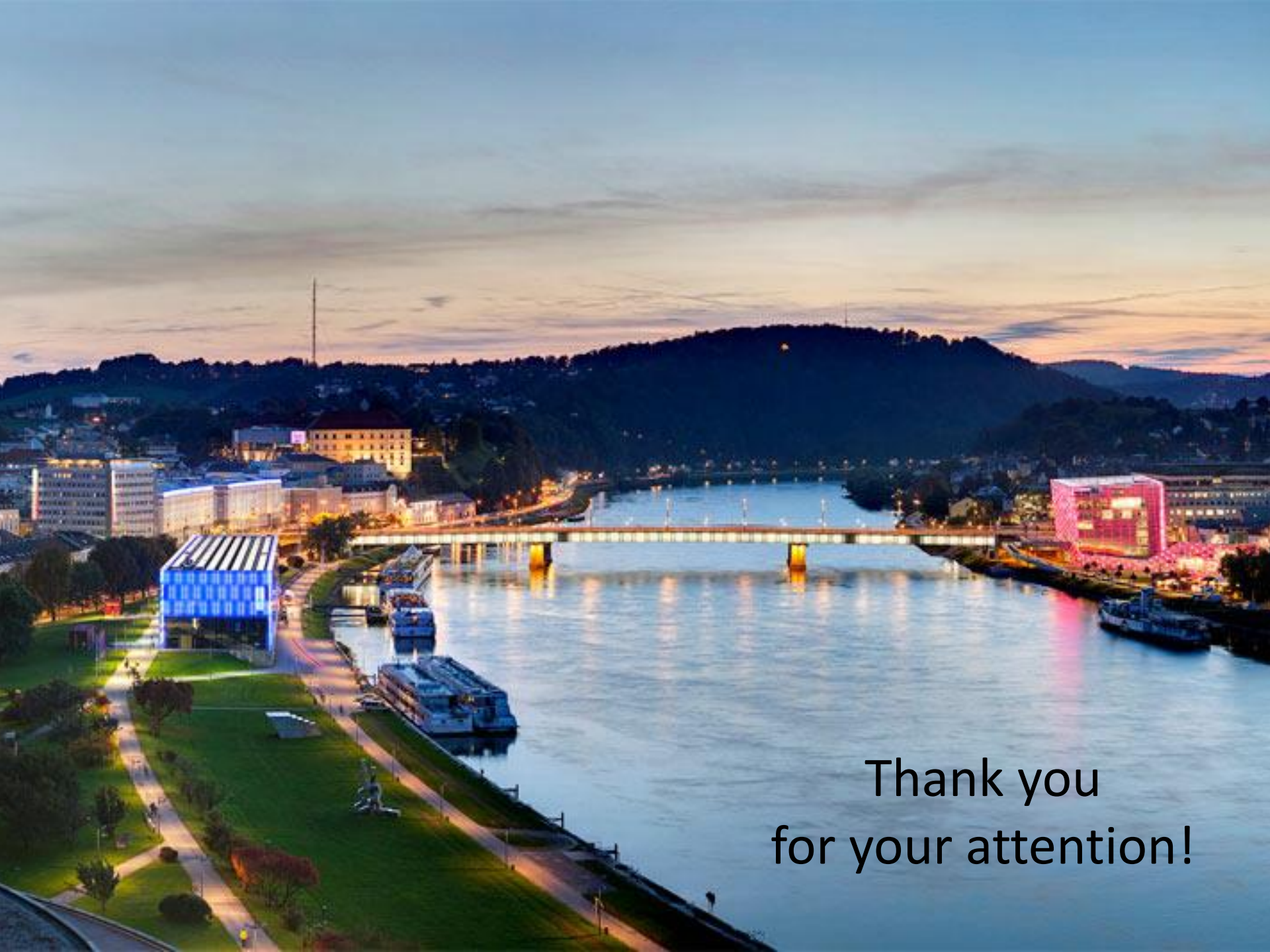


Figure 4. Bedside considerations of macrocirculatory versus tissue perfusion-based resuscitation endpoints. Hb, hemoglobin; P_aO_2, arterial partial pressure of oxygen; S_aO_2, arterial oxygen saturation; StO_2, tissue (muscle) oxygen saturation.

Conclusions

- **Norepinephrine is a safe vasopressor when used correctly at low doses.**
- **New vasopressors are coming …**
- **… but there are more important questions to be solved than simply playing with a new drug which we do not know how to steer.**


Thank you
for your attention!