Lactate

Dr John Vogel

OA Critical Care
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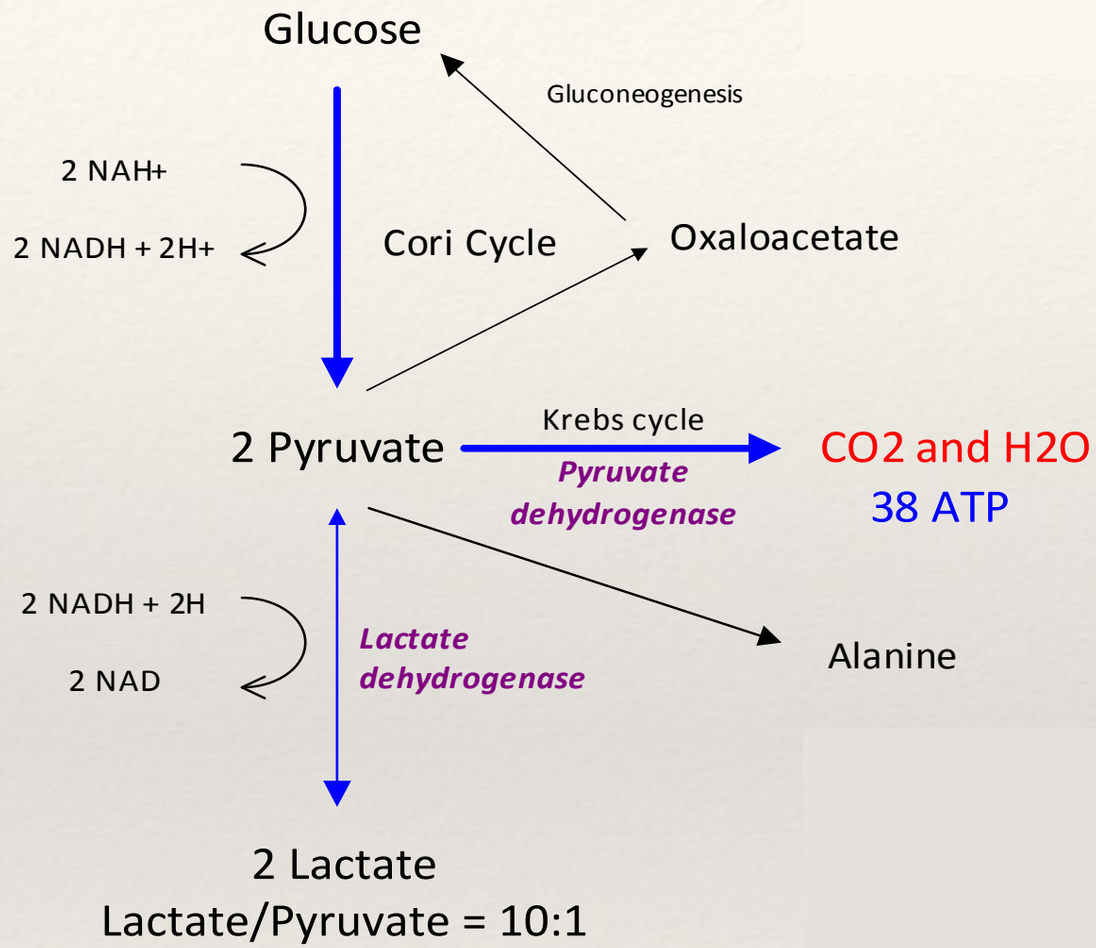
Critical review

Lactate clearance as a target of therapy in sepsis: a flawed paradigm

PE Marik[1]*, R Bellomo[2]


Glucose
Gluconeogenesis
2 NAH+
2 NADH + 2H+
Cori Cycle
Oxaloacetate
2 Pyruvate
Krebs cycle
Pyruvate dehydrogenase
CO2 and H2O
38 ATP
2 NADH + 2H
2 NAD
Lactate dehydrogenase
Alanine
2 Lactate
Lactate/Pyruvate = 10:1

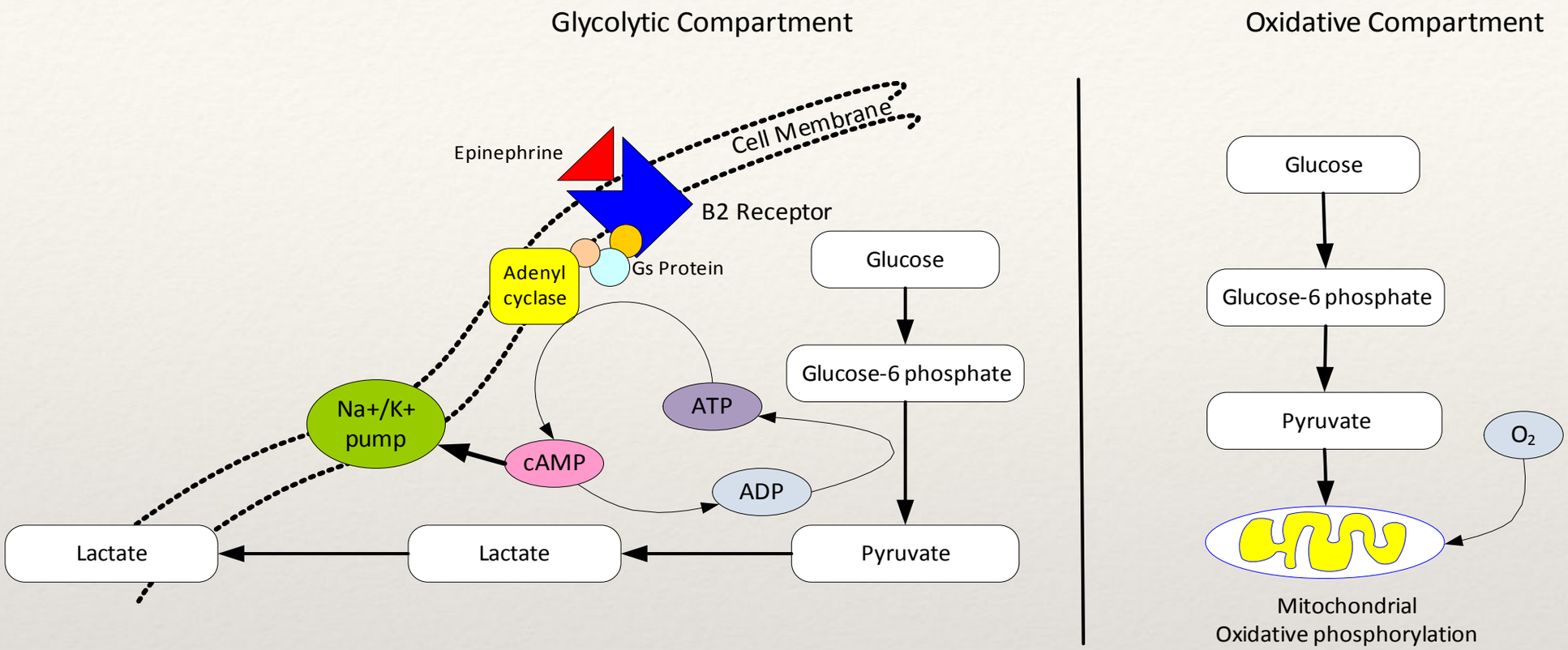


Figure 2. Glycolytic pathway. Epinephrine-increased glycolysis is coupled to Na^+/K^+ ATPase activity. *From James et al*[39].

Clinical Utility of Lactate levels

Jan Bakker

Chair dept Intensive Care Adults

Intensive Care Med
DOI 10.1007/s00134-007-0788-7

ORIGINAL

E. J. O. Kompanje
T. C. Jansen
B. van der Hoven
J. Bakker

The first demonstration of lactic acid in human blood in shock by Johann Joseph Scherer (1814–1869) in January 1843

- 1780 Scheele: first description of lactic acid found in sour milk
- 1808 Berzelius: found lactic acid in fluid extracted from meat
- 1843 Scherer: lactic acid is increased in human blood of patients that died of septic shock
- 1858 Folwarczny: first measurement of lactic acid in blood of a living patient (leukaemia)
- 1891-1892 Araki and Zillessen: interruption of oxygen supply to muscles result in lactic acid production and increased levels
- 1907 Fletcher and Hopkins: muscle contraction is accompanied by anaerobic formation of lactic acid that is removed aerobically at a rate depending on the level of exposure to oxygen

Predictive value of lactate

- **Survivors decrease lacate levels within 60 minutes after start of therapy** (Vincent et al Crit Care Med 1983;11:449-451)
- **Increased area under the time-lactate curve is associated with organ failure and mortality in septic shock** (Bakker et al Am J Surg 1996;171:221-226)
- **Lactate levels predict mortality in Metformin-associated lactic acidosis** (Misbin et al N Engl J Med 1998;338:265-266)
- **Lacate levels predict survival in paracetamol-induced liver failure** (Bernal et al Lancet 2002;359:558-563)
- **Increasing lactate levels in Asthma are associated with persistent severe obstruction** (Appel et al Am J Med 1983;75:580-584)
- **Lactate production by the lung is related to lung injury** (Kellum et al Chest 1997;111:1301-1305)
- **Lactate levels predict Injury Severity Score, Survival and OF in Trauma** (Cerović et al Intensive Care Med 2003;29:1300-1305) (Manikis et al. Am J Emerg Med 1995;13:619-622)

- **Survivors decrease lacate levels within 60 minutes after start of therapy** (Vincent et al Crit Care Med 1983;11:449-451)
- **Increased area under the time-lactate curve is associated with organ failure and mortality in septic shock** (Bakker et al Am J Surg 1996;171:221-226)
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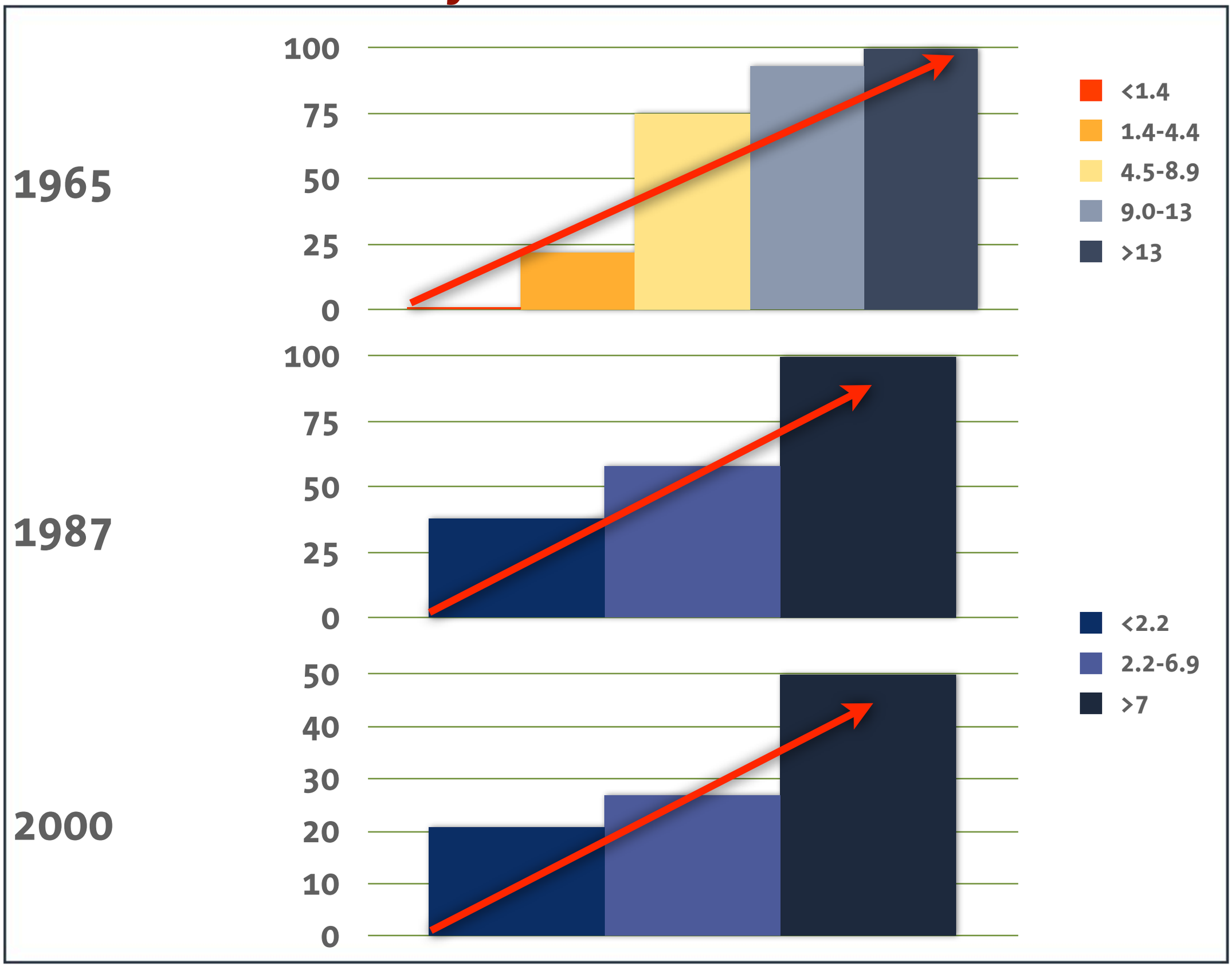
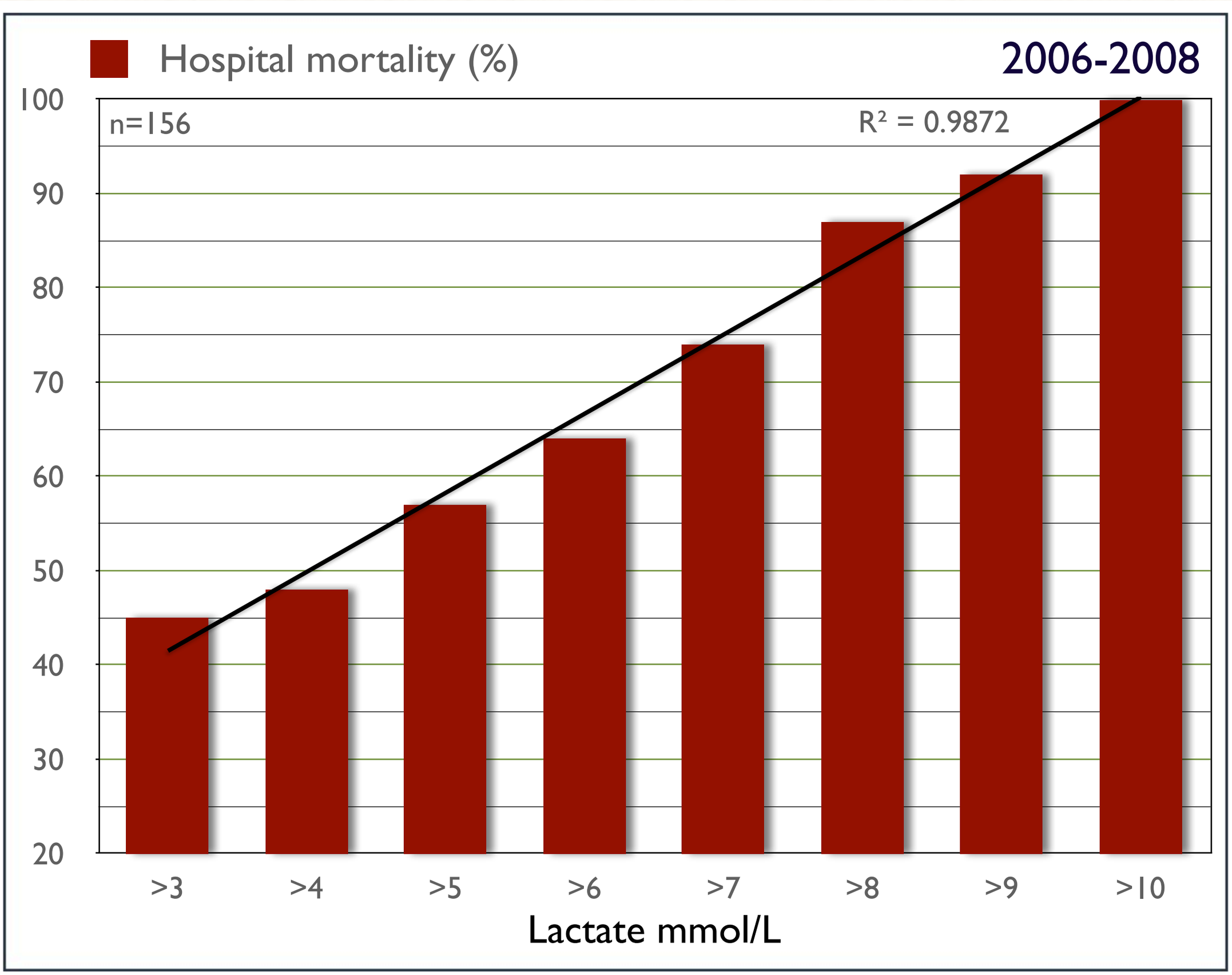
Lactate and mortality



Peretz et al. Ann NY Acad Sci 1965;119:1133-1141

Kruse et al. Am J Med 1987;83:77-82


Hospital mortality (%)
2006-2008
n=156
R² = 0.9872
100
90
80
70
60
50
40
30
20
>3
>4
>5
>6
>7
>8
>9
>10
Lactate mmol/L

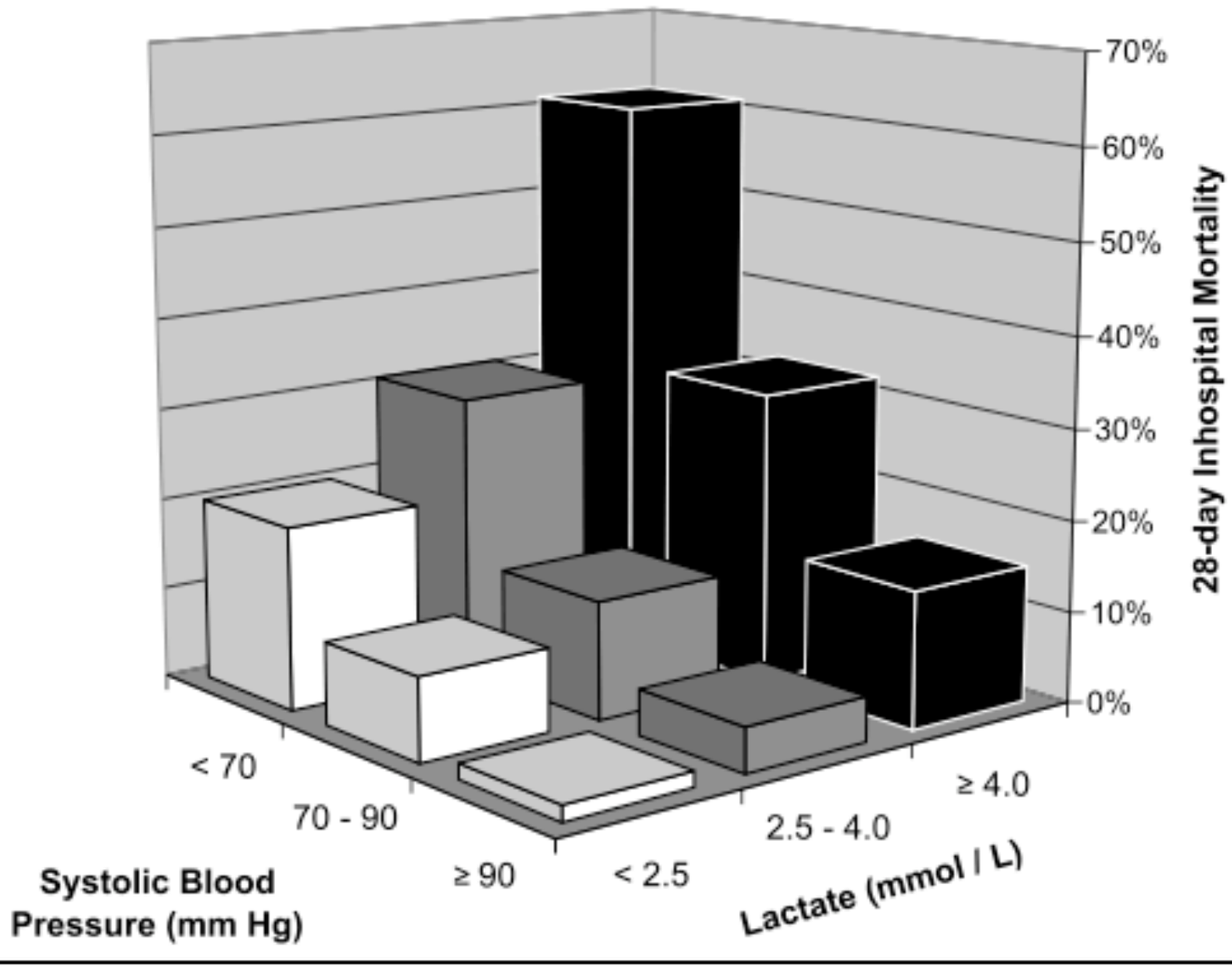
Intensive Care Med (2007) 33:1892–1899
DOI 10.1007/s00134-007-0680-5

ORIGINAL

Michael D. Howell
Michael Donnino
Peter Clardy
Daniel Talmor
Nathan I. Shapiro

Occult hypoperfusion and mortality in patients with suspected infection

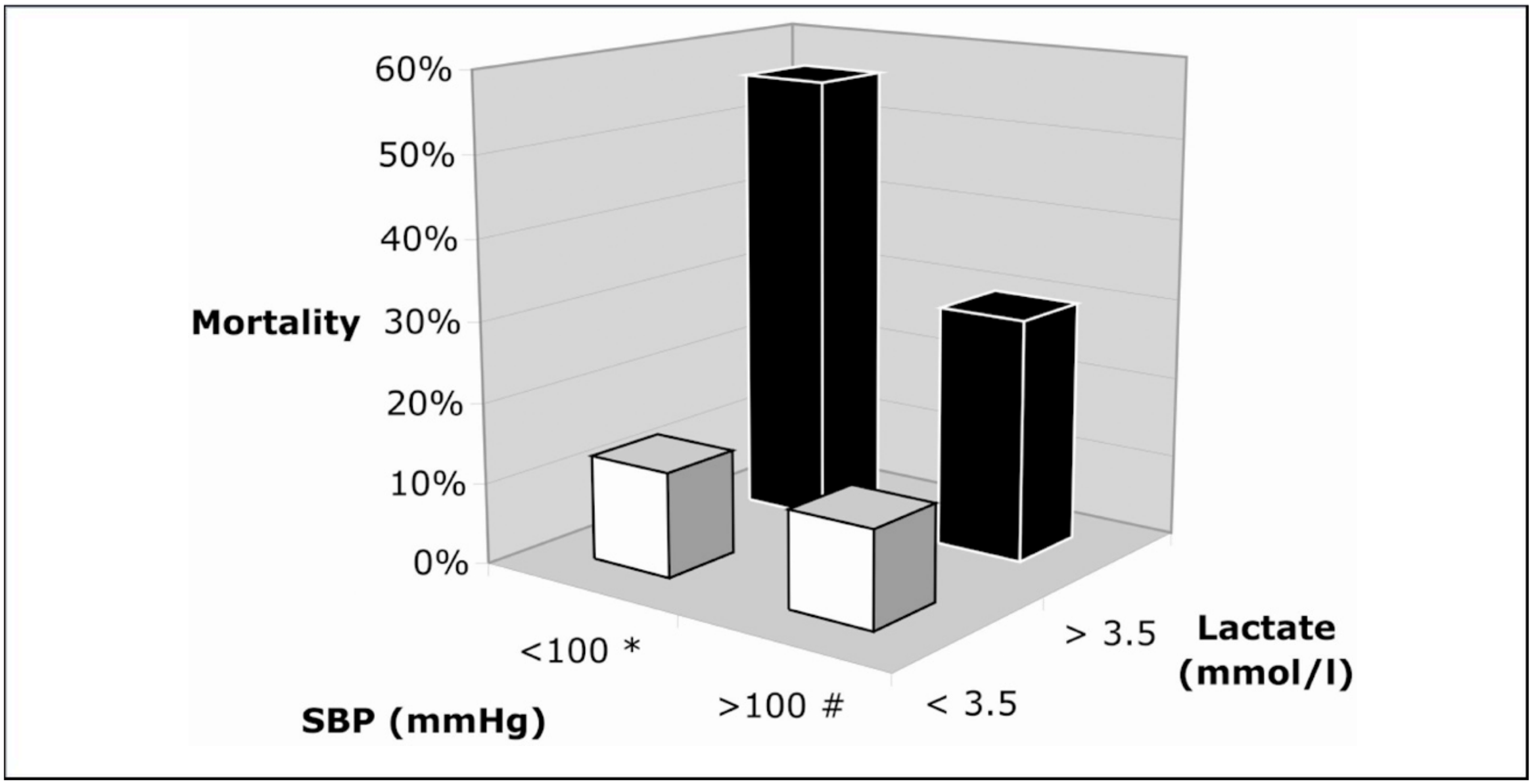
Emergency Room



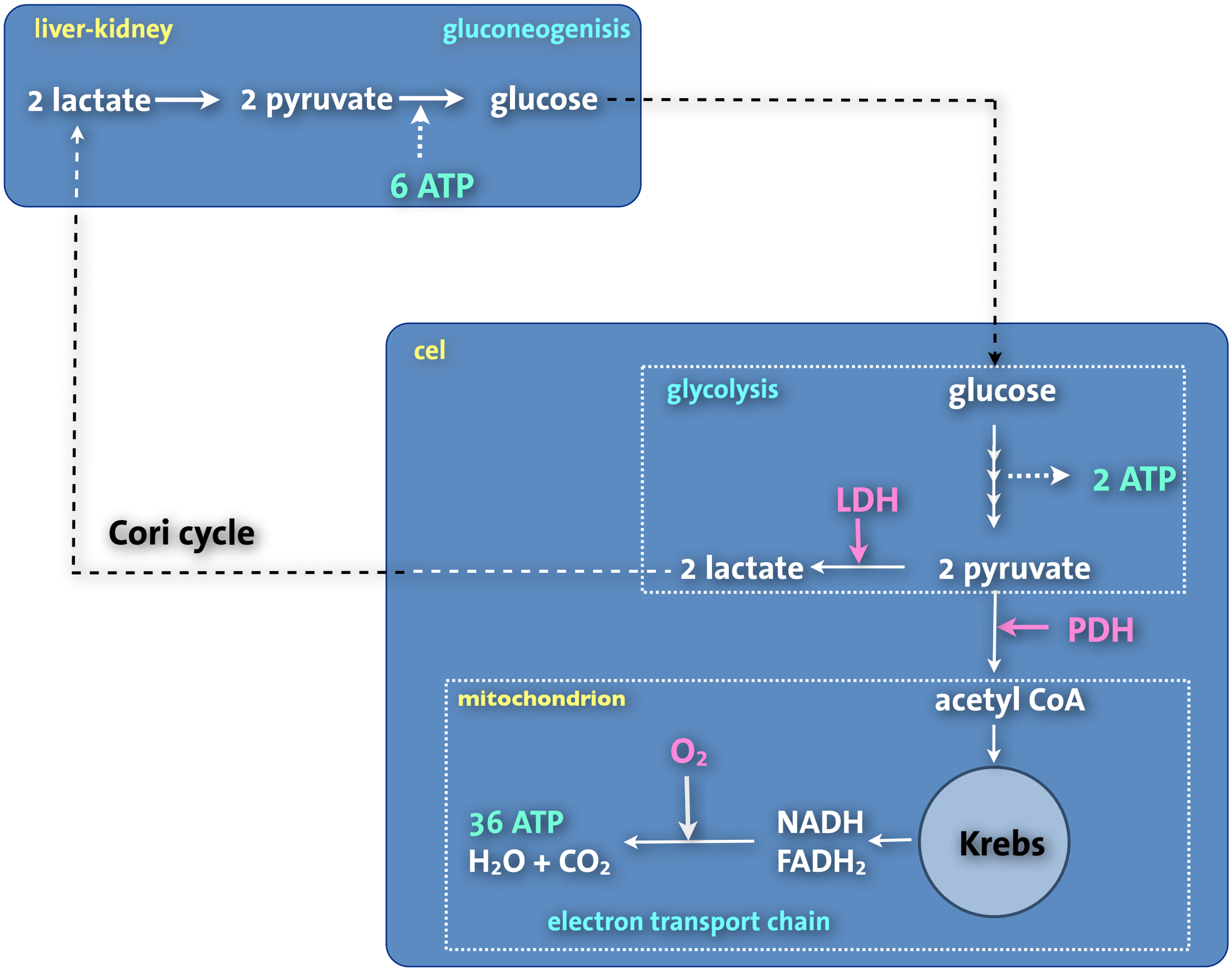
The prognostic value of blood lactate levels relative to that of vital signs in the pre-hospital setting: a pilot study

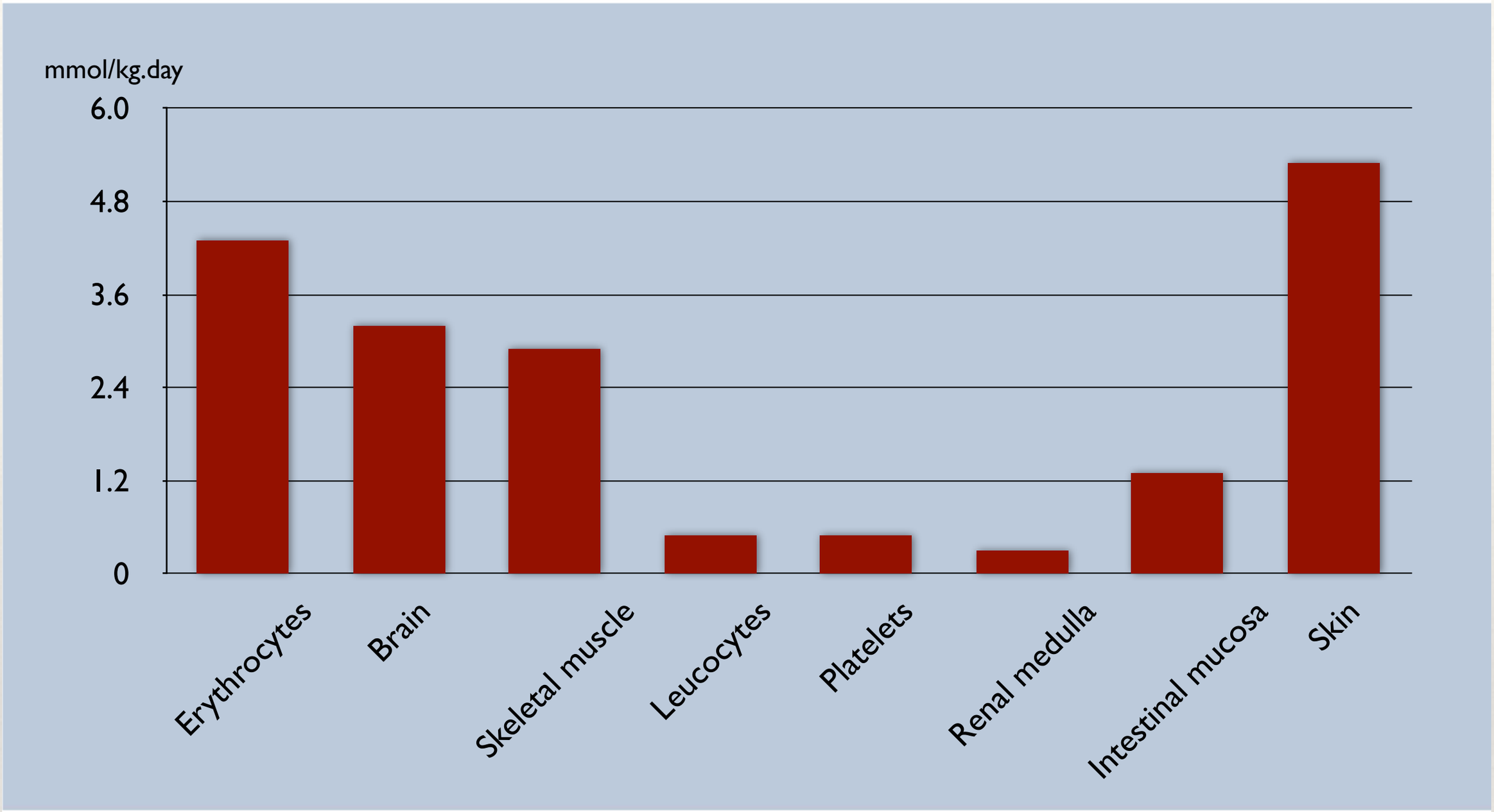
Tim C Jansen[1], Jasper van Bommel[1], Paul G Mulder[2], Johannes H Rommes[3], Selma JM Schieveld[3] and Jan Bakker[1]

Critical Care 2008, **12**:R160 (doi:10.1186/cc7159)



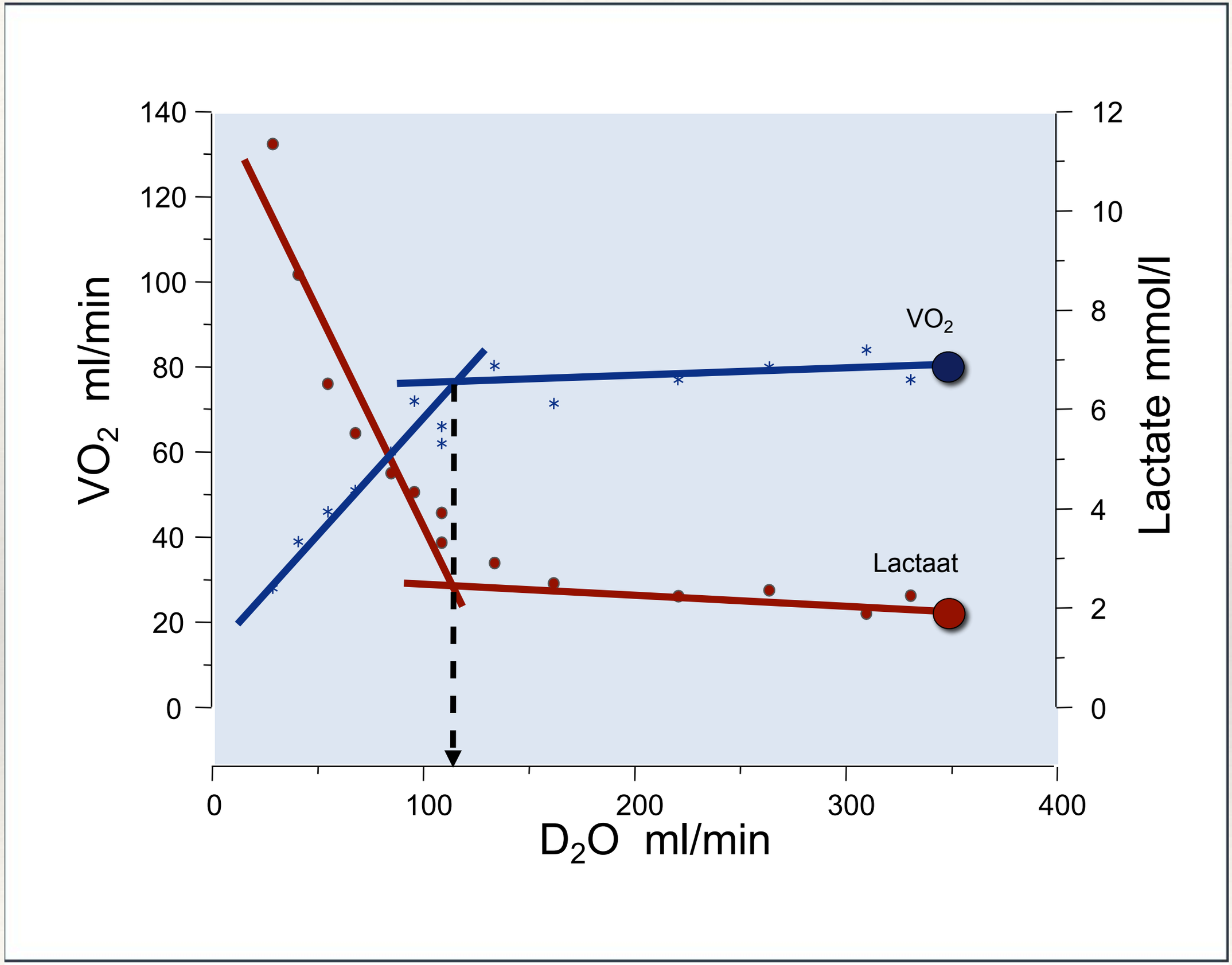
• SAP < 100 mmHg OR 30 ≤ RR < 10 /min OR GCS<14


liver-kidney
gluconeogenisis
2 lactate
2 pyruvate
glucose
6 ATP
Cori cycle
cel
glycolysis
glucose
2 ATP
LDH
2 lactate
2 pyruvate
PDH
mitochondrion
acetyl CoA
O_2
36 ATP
$H_2O + CO_2$
NADH
$FADH_2$
Krebs
electron transport chain



Production of lactate

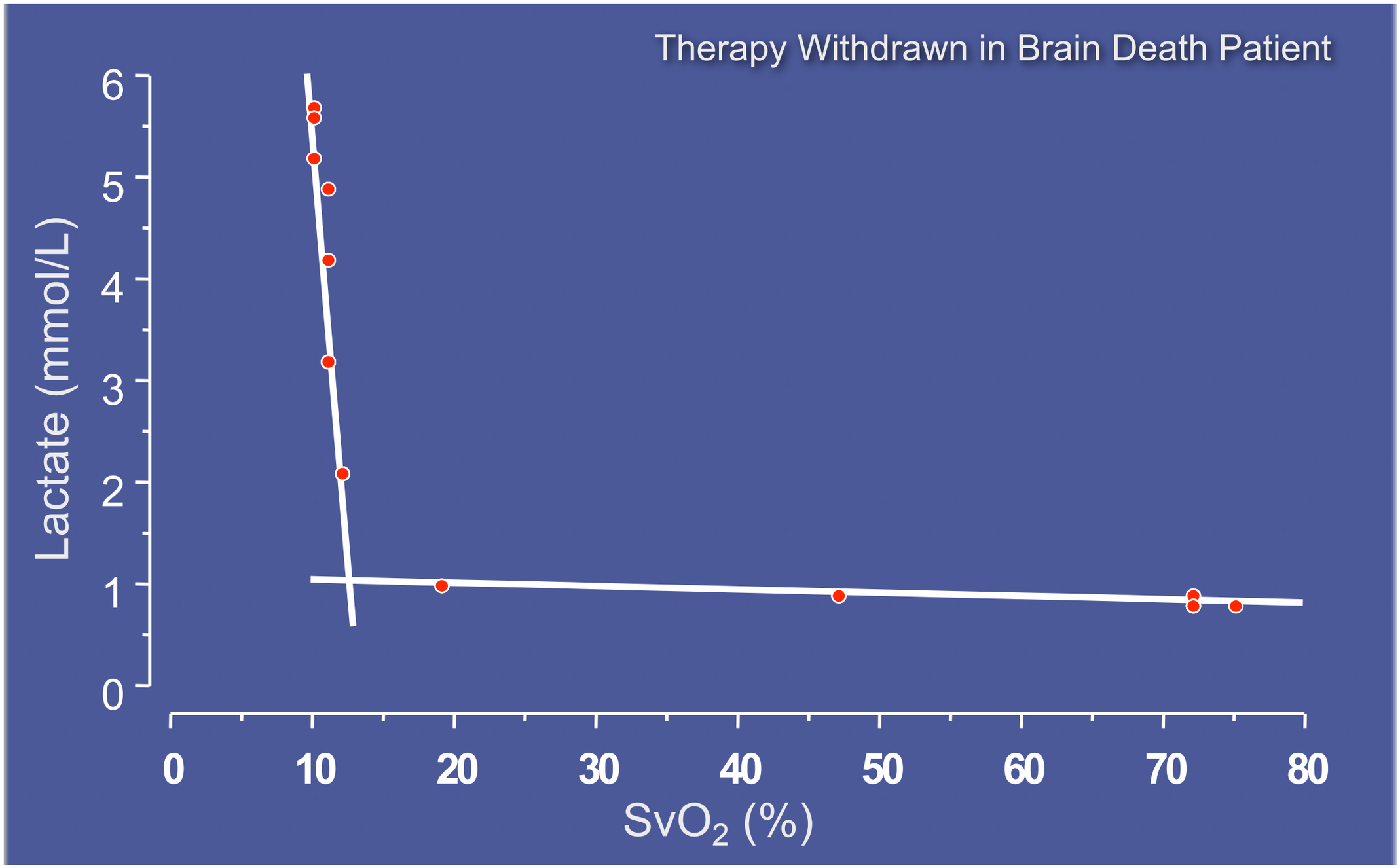
Kreisberg et al. N Engl J Med 1972;287(3):132-137



Zhang et al. Amr Rev Respir Dis 1993;148:867-871 Θ De Backer et al. Shock 1995;4(2):107-112

Oxygen extraction

Decreased DO_2



Aerobic production and clearance

Increased activity of the Na^+-K^+ pump increased lactate production

(James et al J Clin Invest 1996;98:2388-2397 Levy et al Lancet 2005;365:871-875)

Decreased lactate clearance in patients with Sepsis and following CABG

(Levraut et al Am J Respir Crit Care Med 1999;157:1021-1026 – Intensive Care Med 2003;29:1279-1285)

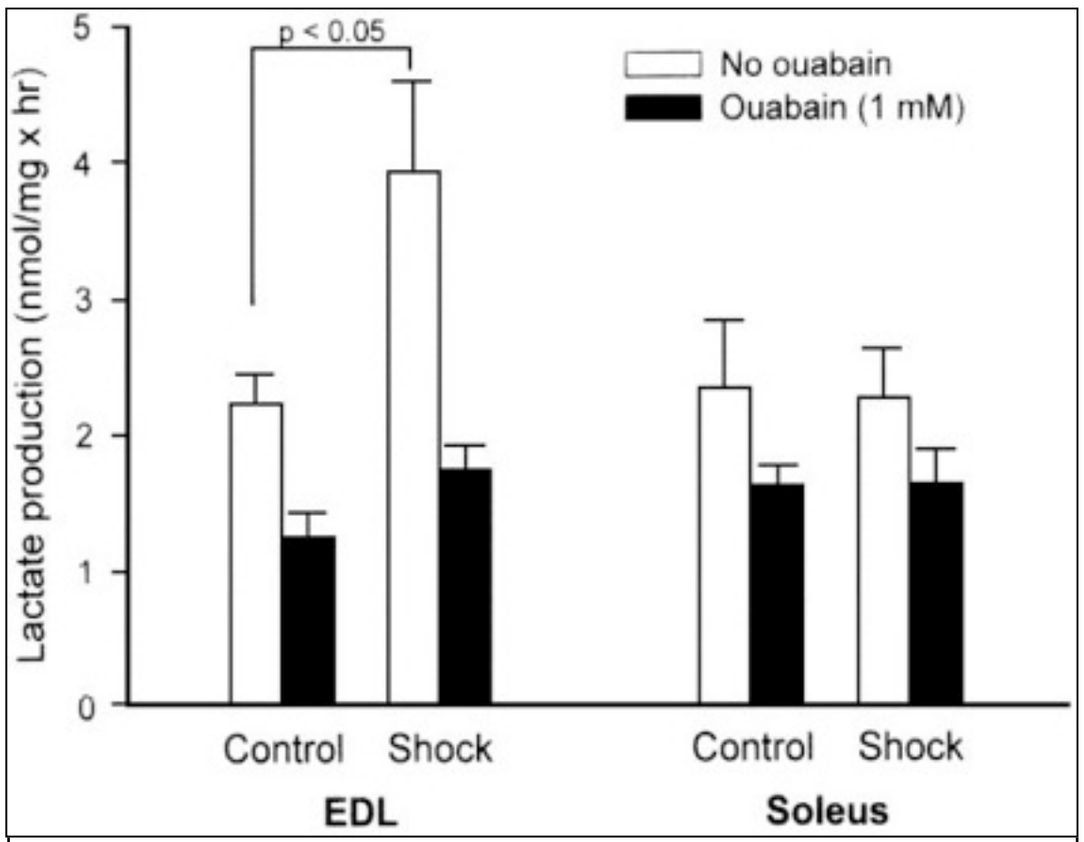
Decreased lactate clearance in patients with liver dysfunction

(Almenoff et al Crit Care Med 1989;17:870-873)

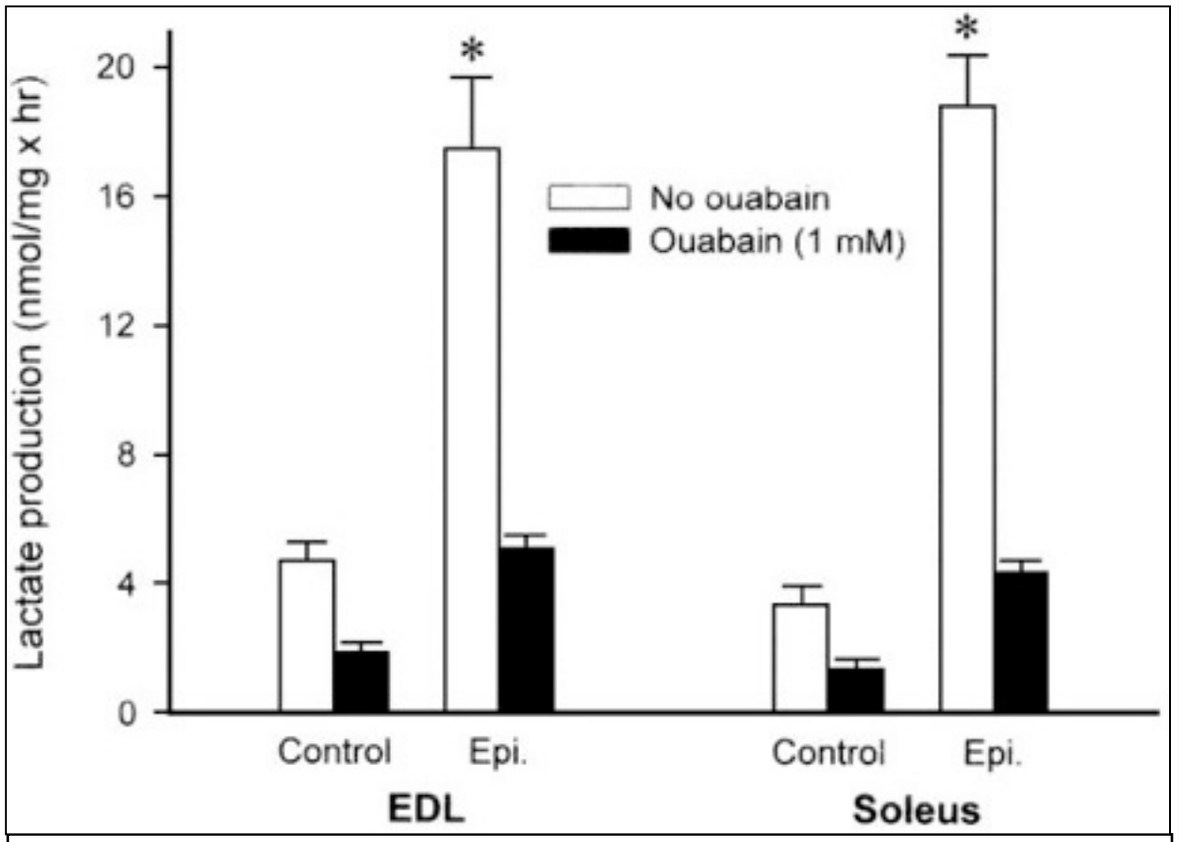
The effect of sepsis on activity of PDH-complex in skeletal muscle and liver

(Vary Am J Physiol 1986;250:E634-E640)

$Na^+K^+ATP^{ase}$ and Lactate in Shock



In hemorrhage Lactate production is increased more in the absence of Ouabain

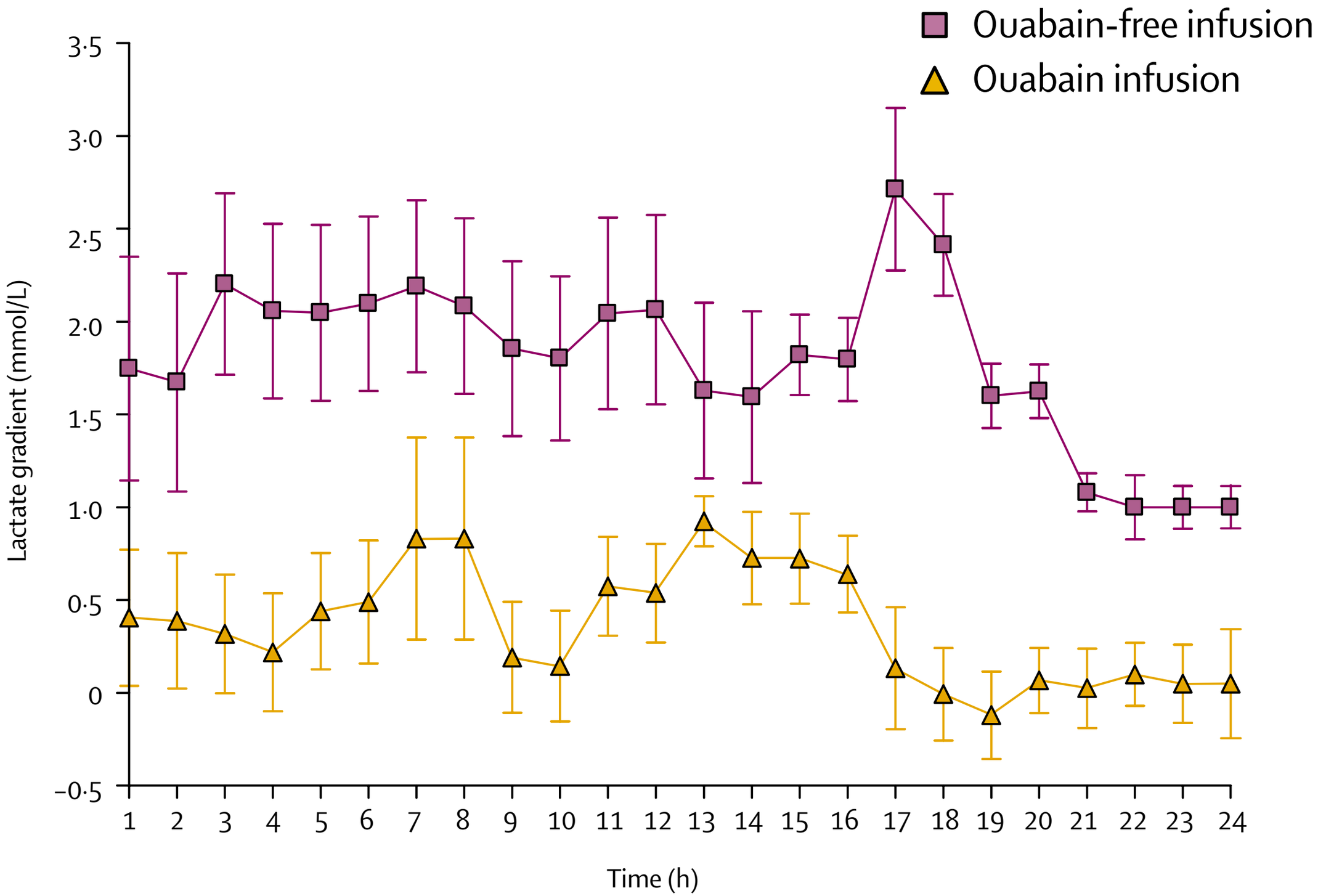


During Epinephrine: Lactate production is increased more in the absence of Ouabain

Luchette et al. J Trauma 1998;44(5):796-801

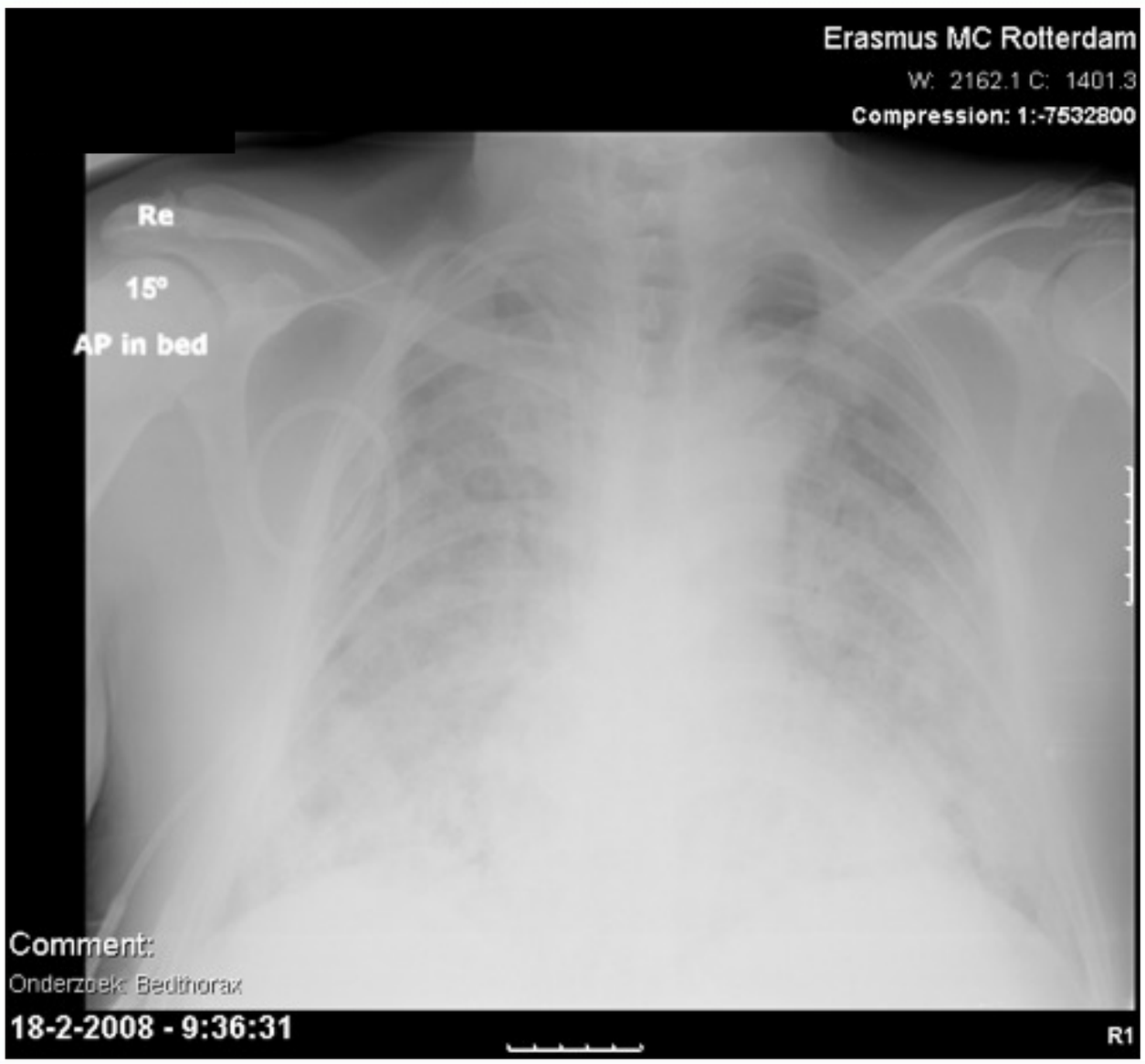
Relation between muscle Na^+K^+ ATPase activity and raised lactate concentrations in septic shock: a prospective study

Bruno Levy, Sébastien Gibot, Patricia Franck, Aurélie Cravoisy, Pierre-Edouard Bollaert



Lactate in B-cel lymphoma

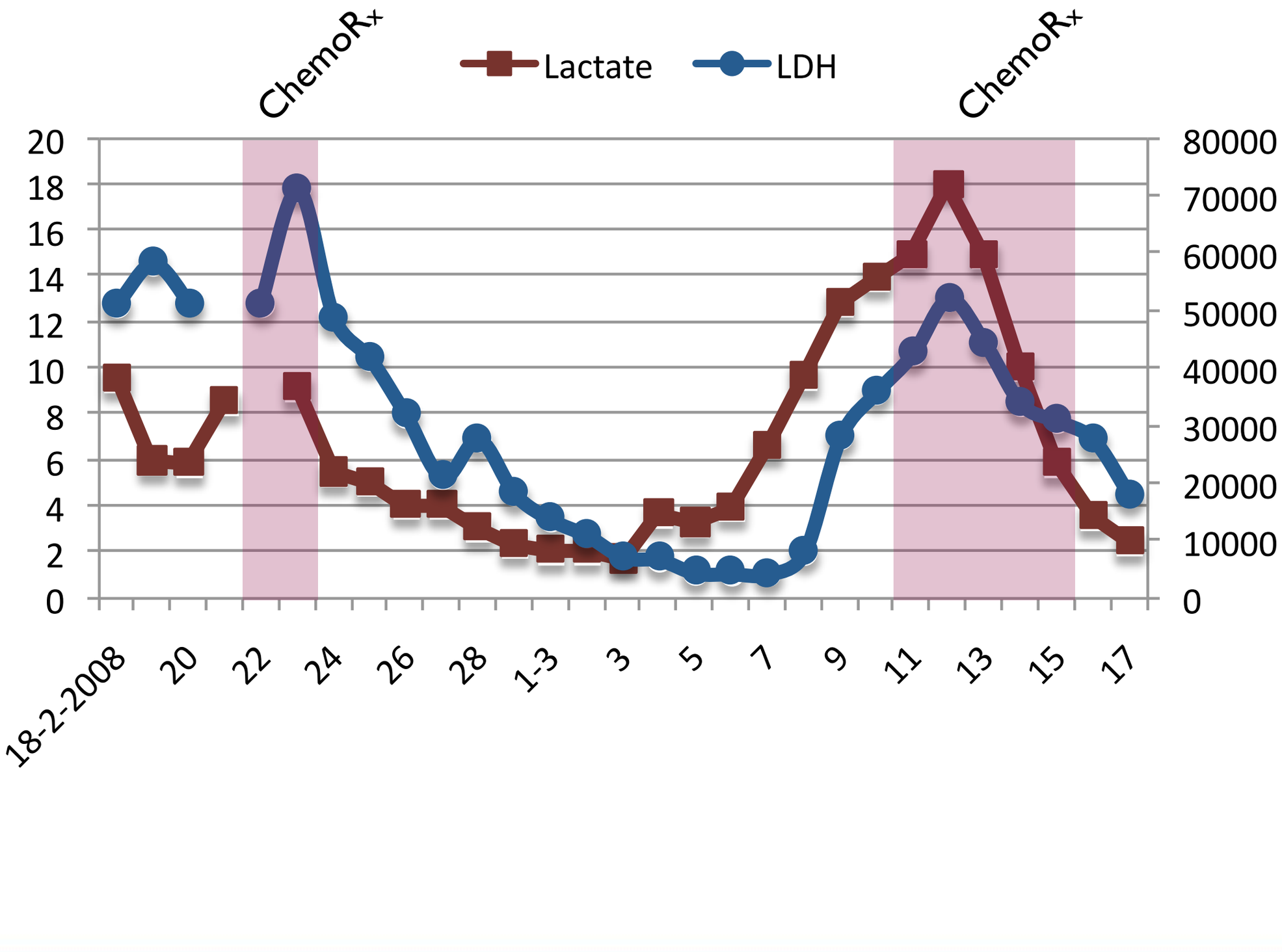
The Warburg effect



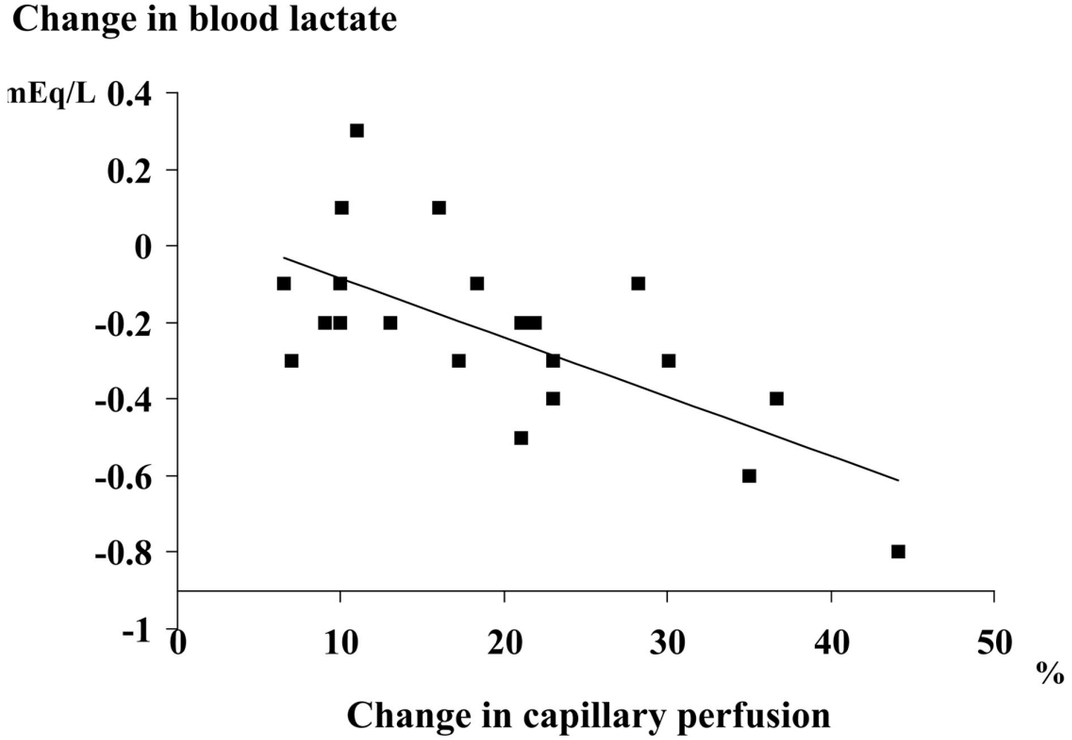
62 yr old male
admitted with respiratory failure following 1st chemtherapy for B-cell lymphoma

High lactate levels

Text


ChemoR+
Lactate
LDH
ChemoR+
20
18
16
14
12
10
8
6
4
2
0
80000
70000
60000
50000
40000
30000
20000
10000
0
18-2-2008
20
22
24
26
28
1-3
3
5
7
9
11
13
15
17

Effect of Dobutamine on microcirculatory flow



De Backer et al. Crit Care Med 2006;34(2):403-408 § Creteur et al. Intensive Care Med 2006;32:516-523

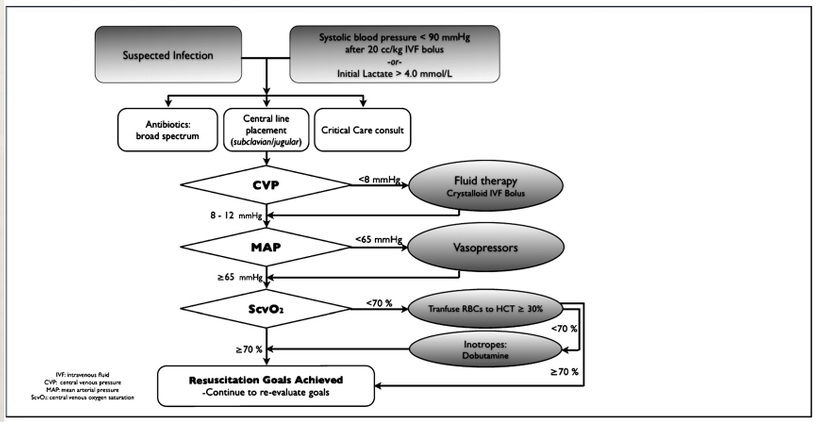
Multicenter Study
Lactate levels as a guide to therapy

USA

MULTICENTER STUDY OF EARLY LACTATE CLEARANCE AS A DETERMINANT OF SURVIVAL IN PATIENTS WITH PRESUMED SEPSIS

Ryan C. Arnold,* Nathan I. Shapiro,† Alan E. Jones,‡ Christa Schorr,§ Jennifer Pope,† Elisabeth Casner,‡ Joseph E. Parrillo,§ R. Phillip Dellinger,§ Stephen Trzeciak,* and on behalf of the Emergency Medicine Shock Research Network (EMShockNet) Investigators

SHOCK, Vol. 32, No. 1, pp. 35–39, 2009



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SHOCK, Vol. 32, No. 1, pp. 35–39, 2009

TABLE 2. **Lactate clearance versus lactate non-clearance**

	Lactate clearance (n = 151)	Lactate non-clearance (n = 15)	*P*
Age, mean (SD), y	67 (15)	62 (16)	0.22
SBP <90 mmHg despite i.v. fluids, n (%)	50 (33)	13 (87)	0.02
Initial serum lactate, mean (SD)	4.5 (2.7)	3.9 (1.7)	0.08
Serial serum lactate, mean (SD)	2.3 (1.8)	5.1 (2.9)	<0.001
Vasopressor usage, n (%)	87 (58)	11 (73)	0.39
Individual organ failure, n (%)			
Cardiovascular	50 (33)	13 (87)	<0.001
Pulmonary	25 (17)	3 (20)	0.94
Renal	48 (32)	6 (40)	0.73
Hepatic	12 (8)	2 (13)	0.86
Coagulopathy	18 (12)	5 (33)	0.06
Total SOFA score, mean (SD)	3.6 (2.6)	4.1 (2.3)	0.47
Continuous $ScvO_2$ monitoring, n (%)	134 (81)	14 (93)	0.42
$ScvO_2$ ≥70% achieved	114 (85)	11 (79)	0.84
Mortality, n (%)	29 (19)	9 (60)	<0.001

Lactate clearance: >10% in 6h

A lactate clearance of less then 10% in 6h off initial resuscitation is occurring infrequently (9% of the patients)

MULTICENTER STUDY OF EARLY LACTATE CLEARANCE AS A DETERMINANT OF SURVIVAL IN PATIENTS WITH PRESUMED SEPSIS

Ryan C. Arnold,* Nathan I. Shapiro,† Alan E. Jones,‡ Christa Schorr,§ Jennifer Pope,† Elisabeth Casner,‡ Joseph E. Parrillo,§ R. Phillip Dellinger,§ Stephen Trzeciak,* and on behalf of the Emergency Medicine Shock Research Network (EMShockNet) Investigators

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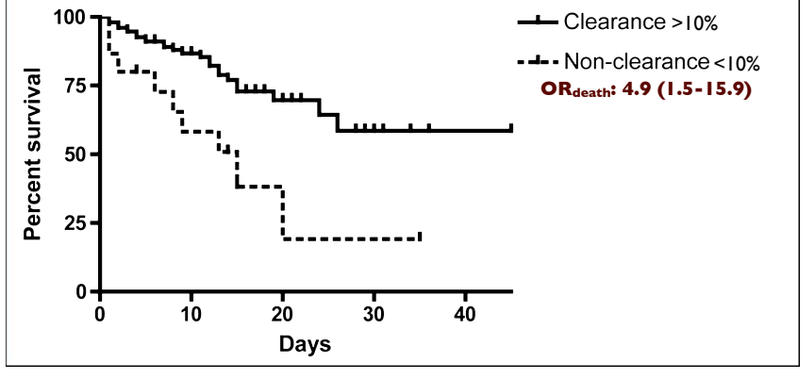


Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy

Alan E. Jones, MD

Interventions We randomly assigned patients to 1 of 2 resuscitation protocols. The $ScvO_2$ group was resuscitated to normalize central venous pressure, mean arterial pressure, and $ScvO_2$ of at least 70%; and the lactate clearance group was resuscitated to normalize central venous pressure, mean arterial pressure, and lactate clearance of at least 10%. The study protocol was continued until all goals were achieved or for up to 6 hours. Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment.

My problems with the design

- why would lactate or $ScvO_2$ be specific for sepsis
- would a patient with a lactate of 5.0 mmol/L be sufficiently treated when it decreases to 4.5 mmol/L
- is there no more than dobutamine and Ht to optimize the balance between oxygen delivery and oxygen demand?
- what if lactate does not decrease and $ScvO_2$ and Ht are optimal?

JAMA. 2010;303(8):739-746 (doi:10.1001/jama.2010.158)

Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy

Alan E. Jones, MD

Table 5. Hospital Mortality and Length of Stay

Variable	Lactate Clearance Group (n = 150)	$ScvO_2$ Group (n = 150)	Proportion Difference (95% Confidence Interval)	*P* Value[b]
In-hospital mortality, No. (%)[a]				
Intent to treat	25 (17)	34 (23)	6 (–3 to 15)	
Per protocol	25 (17)	33 (22)	5 (–3 to 14)	
Length of stay, mean (SD), d				
ICU	5.9 (8.46)	5.6 (7.39)		.75
Hospital	11.4 (10.89)	12.1 (11.68)		.60
Hospital complications				
Ventilator-free days, mean (SD)	9.3 (10.31)	9.9 (11.09)		.67
Multiple organ failure, No. (%)	37 (25)	33 (22)		.68
Care withdrawn, No. (%)	14 (9)	23 (15)		.15

JAMA. 2010;303(8):739-746 (doi:10.1001/jama.2010.158)

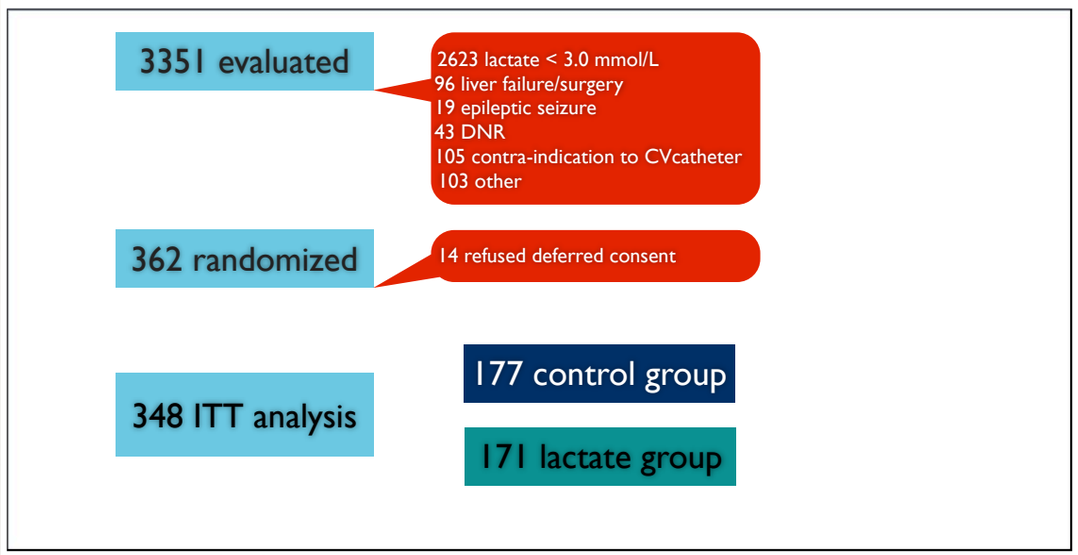
Netherlands

Early Lactate-Guided Therapy in Intensive Care Unit Patients

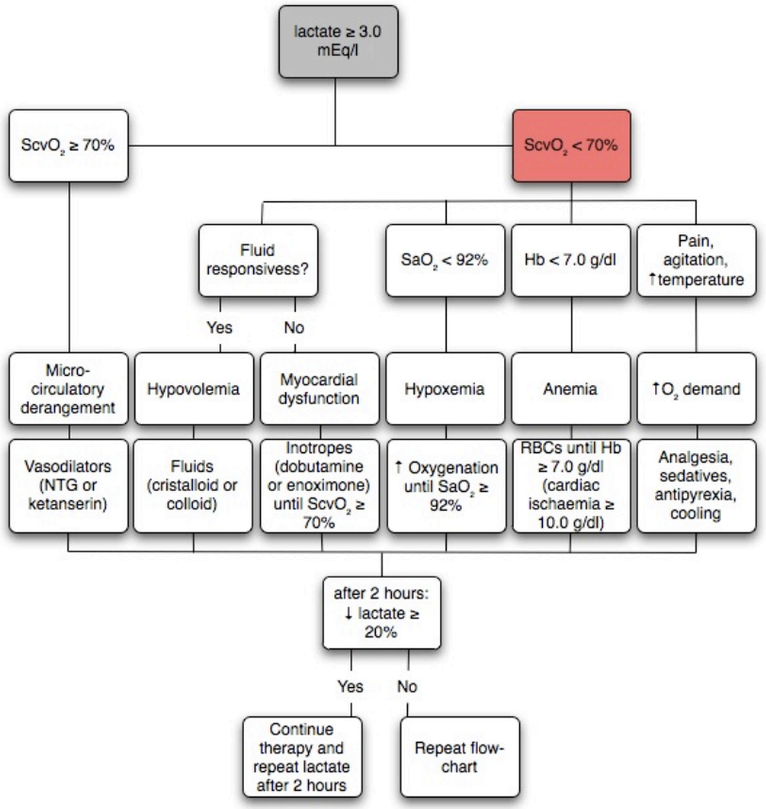
A Multicenter, Open-Label, Randomized Controlled Trial

Tim C. Jansen[1], Jasper van Bommel[1], F. Jeanette Schoonderbeek[3], Steven J. Sleeswijk Visser[4], Johan M. van der Klooster[5], Alex P. Lima[1], Sten P. Willemsen[2], and Jan Bakker[1], for the LACTATE study group*

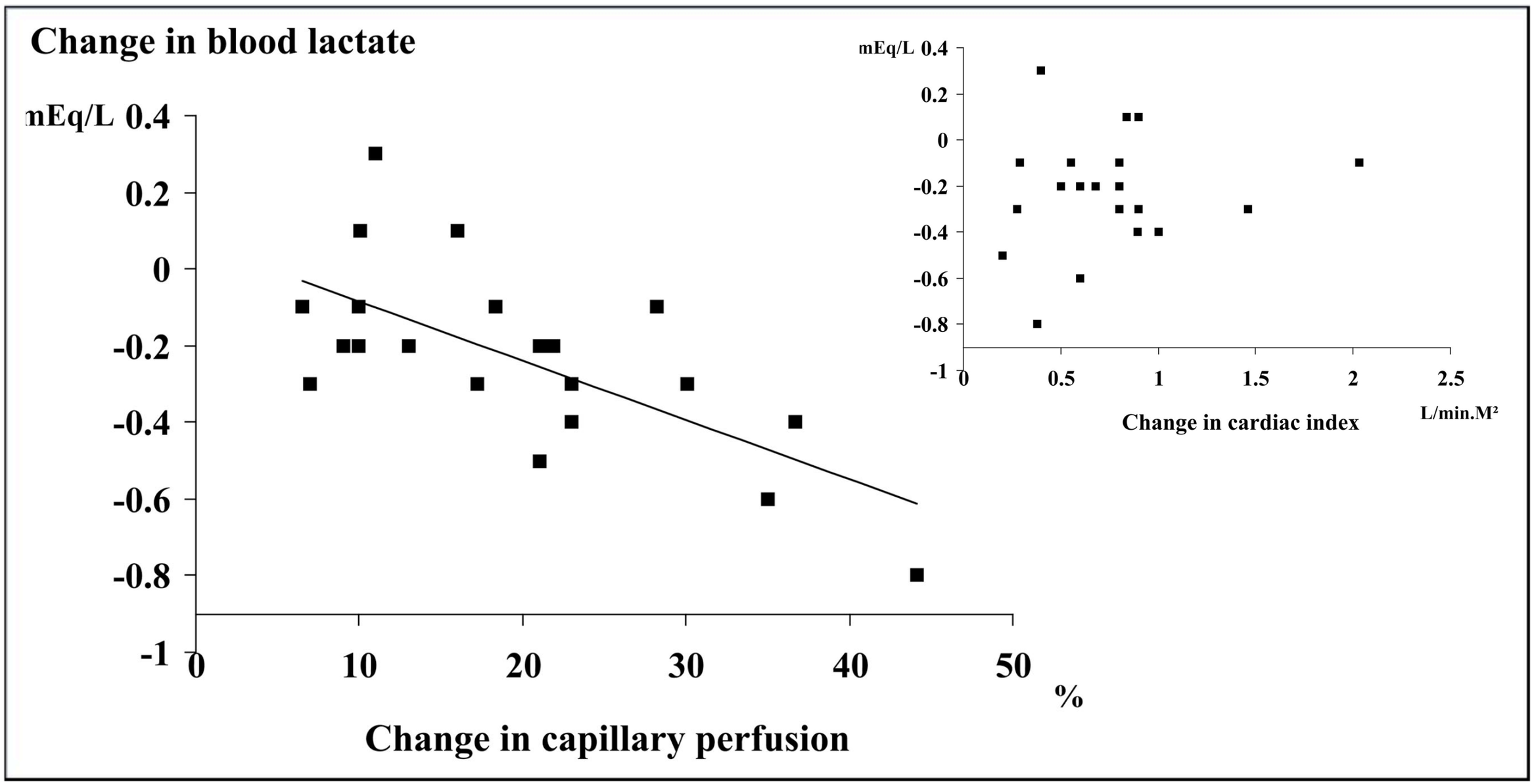
[1]Department of Intensive Care, Erasmus MC University Medical Centre, Rotterdam, The Netherlands; [2]Department of Biostatistics, University Medical Centre Rotterdam, Rotterdam, The Netherlands; [3]Department of Intensive Care, Ikazia Hospital, Rotterdam, The Netherlands; [4]Department of Intensive Care, Reinier de Graaf Hospital, Delft, The Netherlands; and [5]Department of Intensive Care, St. Franciscus Gasthuis, Rotterdam, The Netherlands



Am J Respir Crit Care Med Vol 182. pp 752–761, 2010

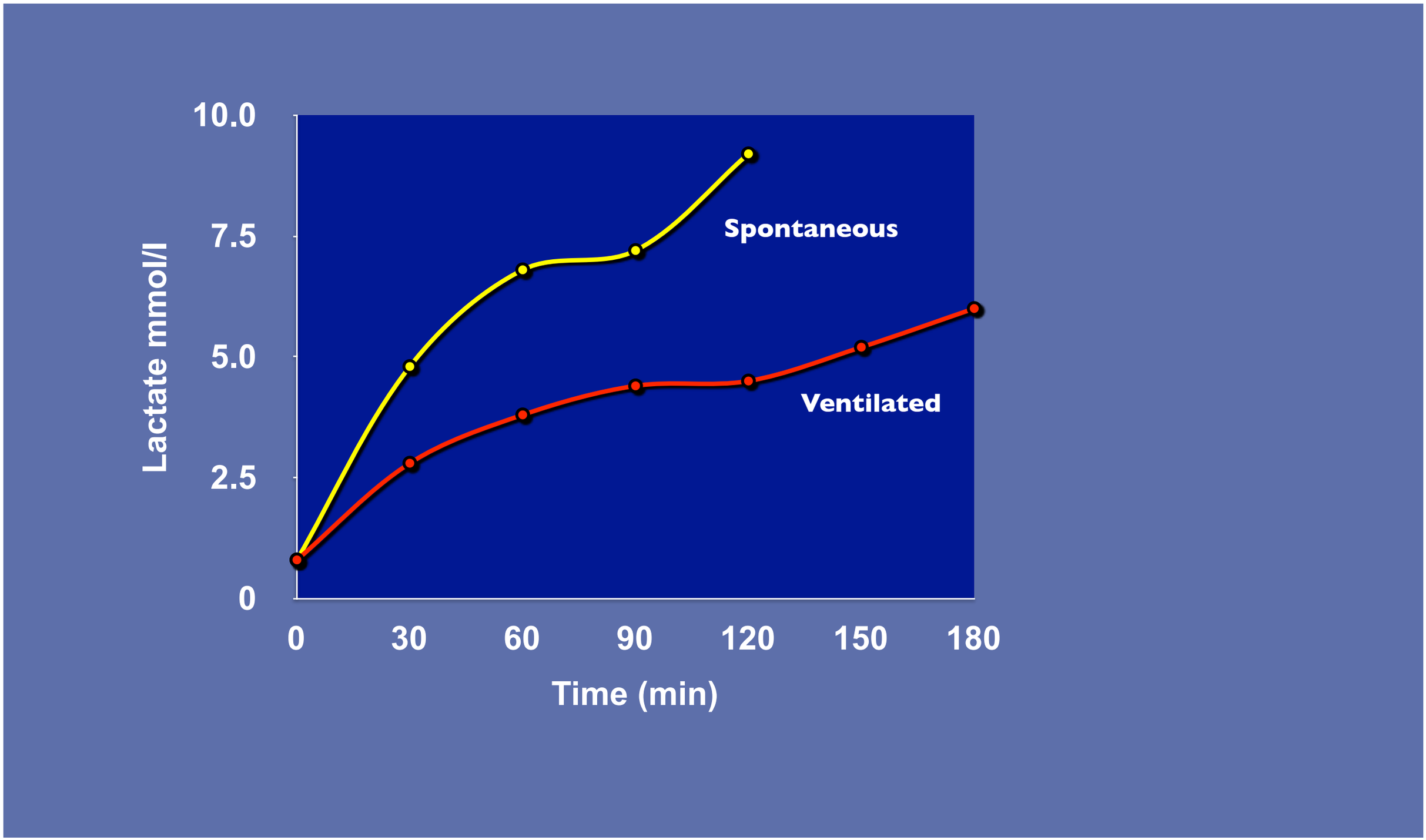


Effect of Dobutamine on microcirculatory flow



De Backer et al. Crit Care Med 2006;34(2):403-408

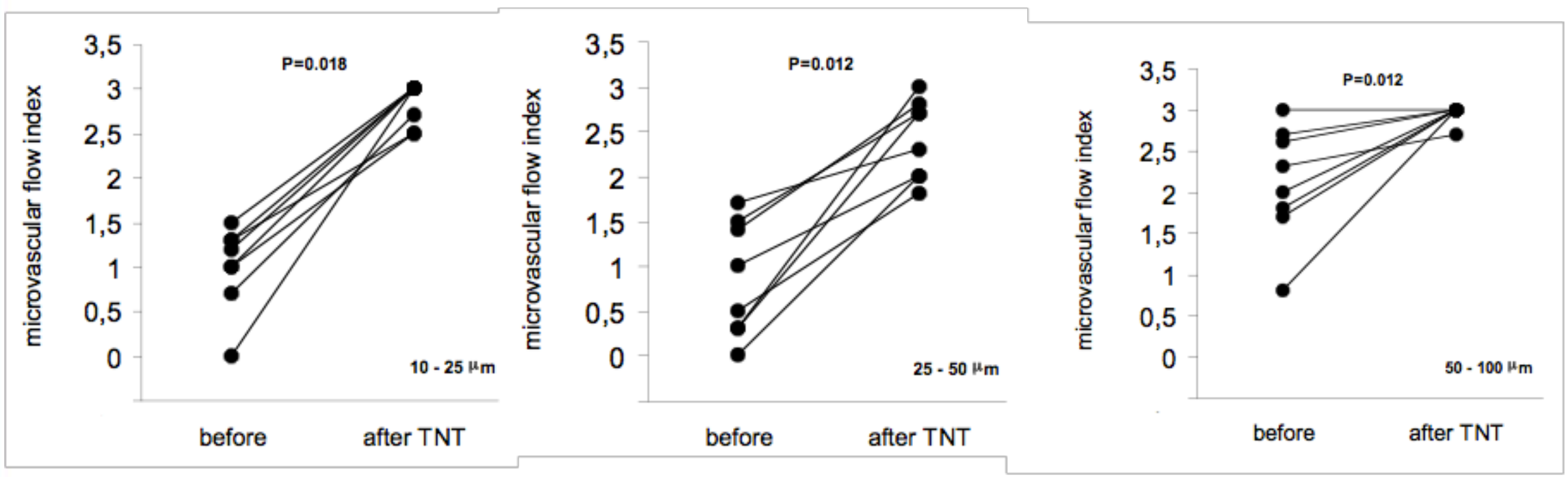
O_2 costs of breathing in low output state



Aubier et al. Am Rev Respir Dis 1982;126:648-652

Microcirculatory effect of NTG

NTG used in patients with microcirculatory dysfunction (high $ScvO_2$ and no decrease in lactate levels)



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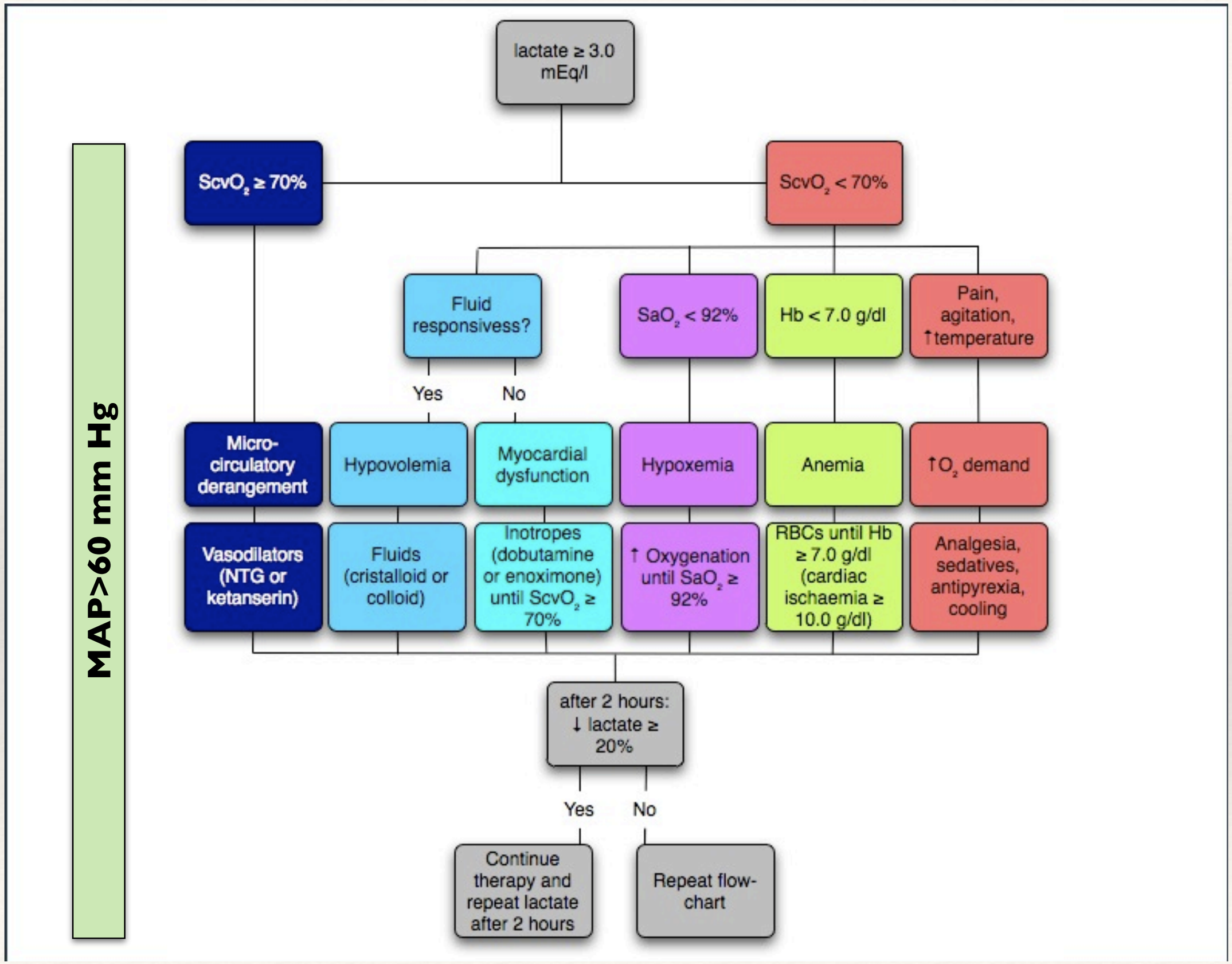
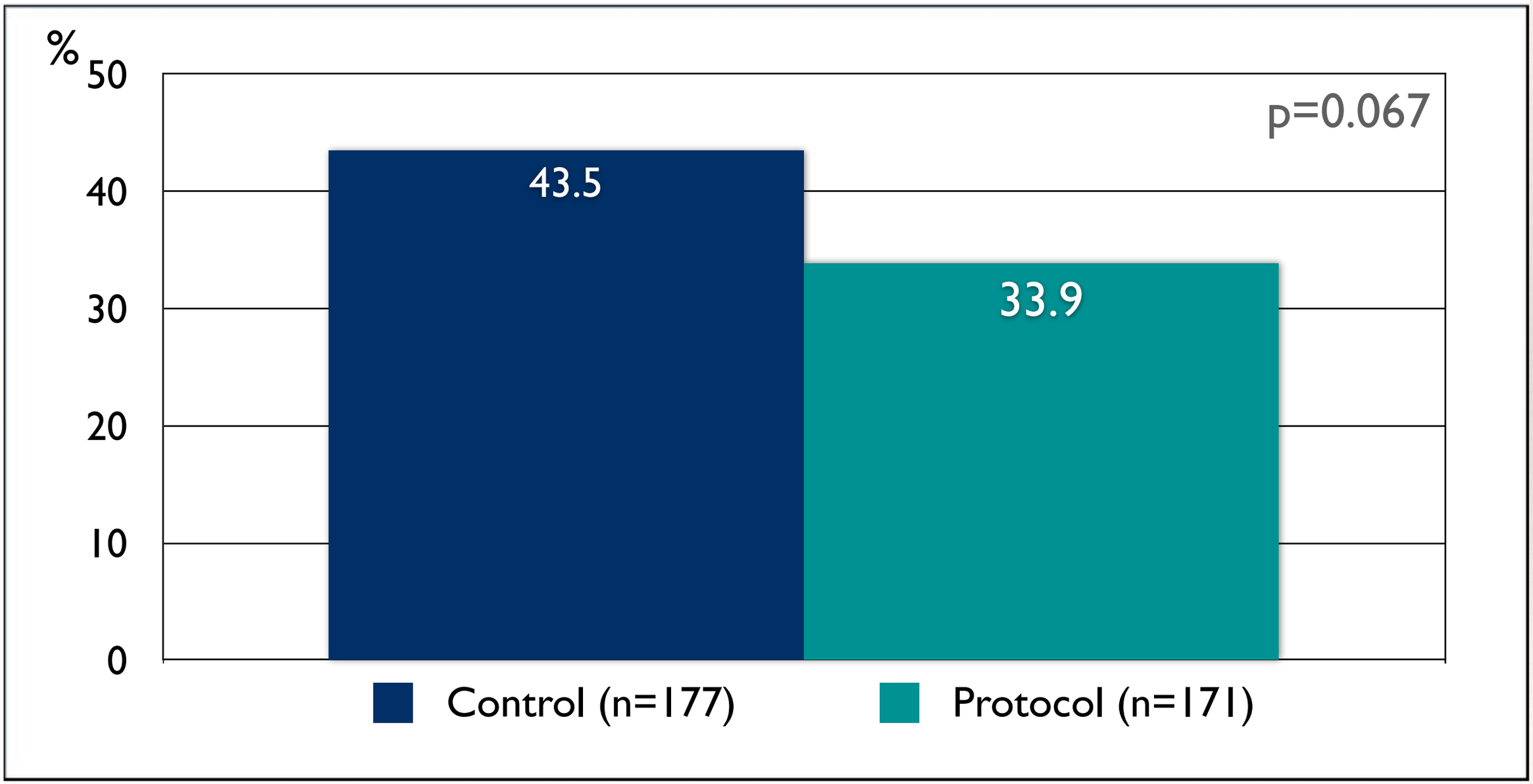
Lancet 2002;360:1395

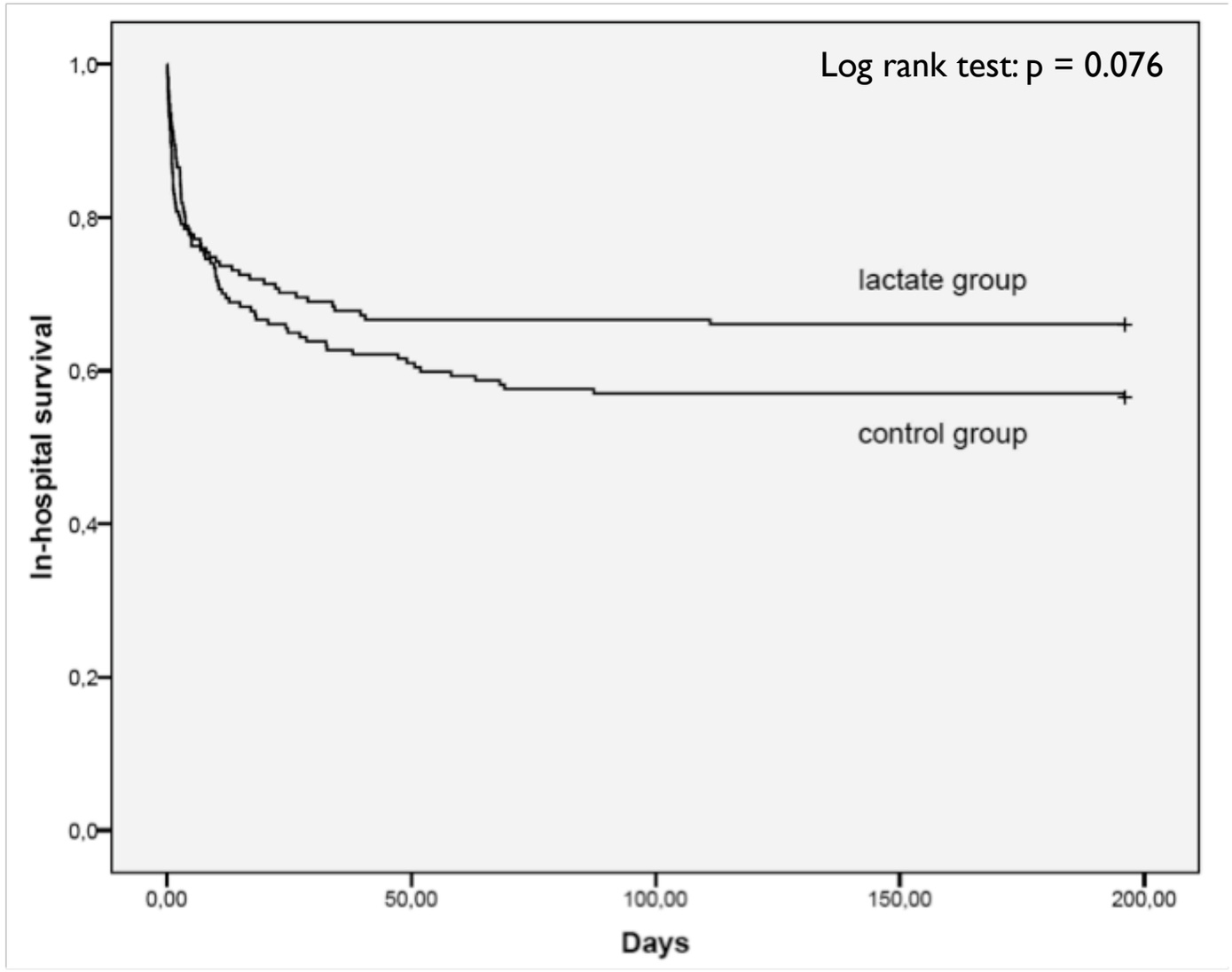

MAP>60 mm Hg
lactate ≥ 3.0 mEq/l
ScvO2 ≥ 70%
ScvO2 < 70%
Fluid responsivess?
SaO2 < 92%
Hb < 7.0 g/dl
Pain, agitation, ↑temperature
Yes
No
Micro-circulatory derangement
Hypovolemia
Myocardial dysfunction
Hypoxemia
Anemia
↑O2 demand
Vasodilators (NTG or ketanserin)
Fluids (cristalloid or colloid)
Inotropes (dobutamine or enoximone) until ScvO2 ≥ 70%
↑ Oxygenation until SaO2 ≥ 92%
RBCs until Hb ≥ 7.0 g/dl (cardiac ischaemia ≥ 10.0 g/dl)
Analgesia, sedatives, antipyrexia, cooling
after 2 hours: ↓ lactate ≥ 20%
Yes
No
Continue therapy and repeat lactate after 2 hours
Repeat flow-chart

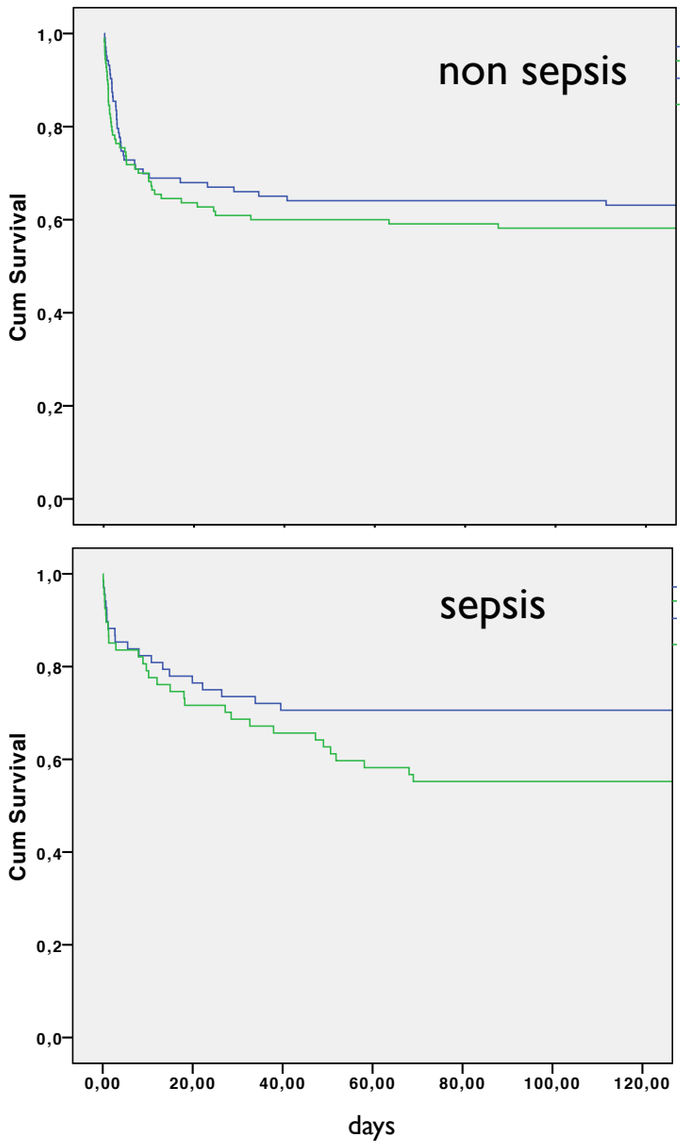
Result

Unadjusted Hospital Mortality



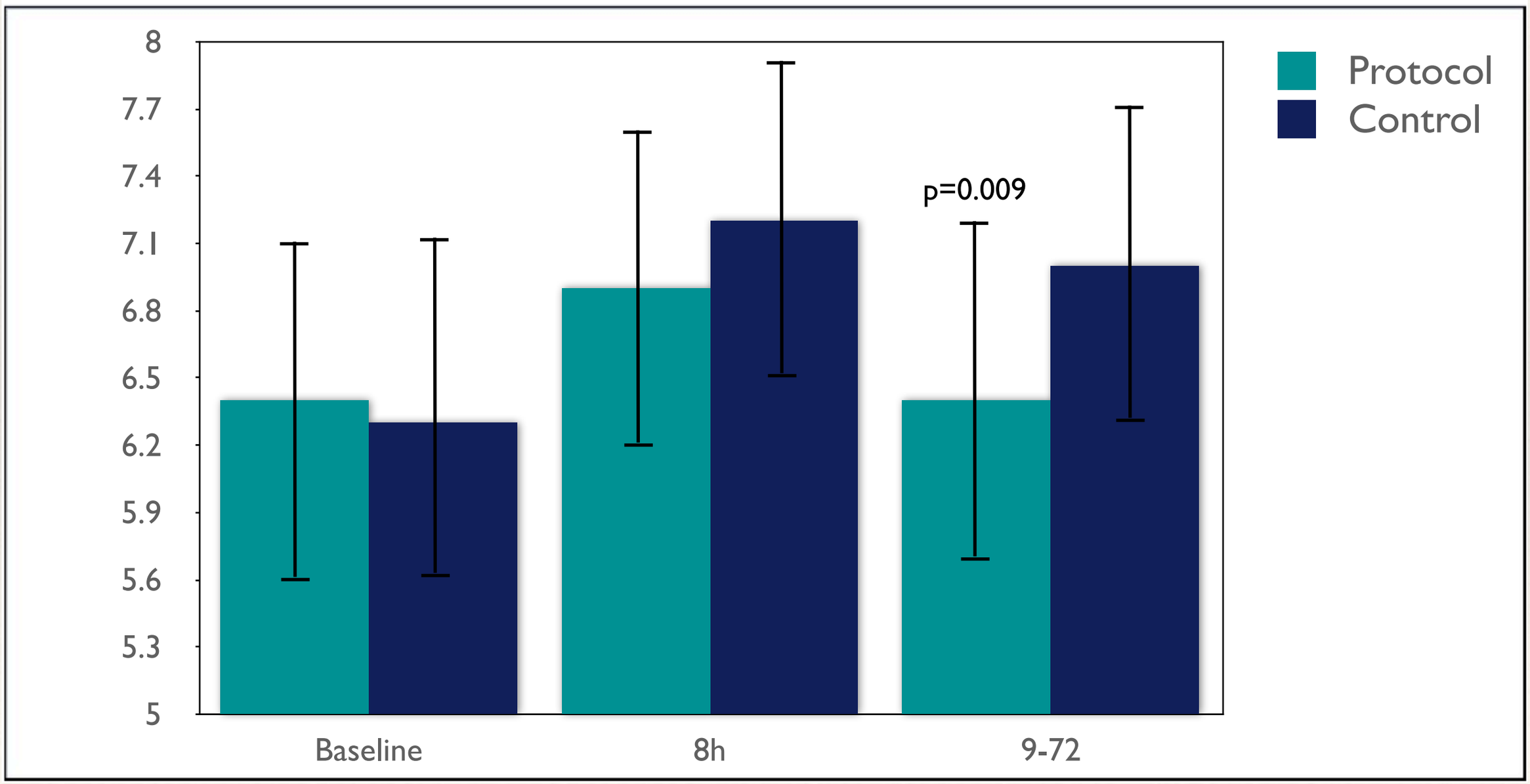
Mortality


Log rank test: p = 0.076
lactate group
control group
In-hospital survival
1,0
0,8
0,6
0,4
0,2
0,0
0,00
50,00
100,00
150,00
200,00
Days


non sepsis
sepsis
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0,00
20,00
40,00
60,00
80,00
100,00
120,00
days

Effect on organ failure

SOFA score



New end-points of resuscitation?

The prognostic value of the subjective assessment of peripheral perfusion in critically ill patients

Alexandre Lima, MD; Tim C. Jansen, MD; Jasper van Bommel, MD, PhD; Can Ince, PhD; Jan Bakker, MD, PhD

(Crit Care Med 2009; 37:934–938)

- 50 critically ill patients following initial resuscitation and stabilization
- Abnormal peripheral circulation was defined as
  - increase in capillary refill time (> 4.5 sec) or cool skin (subjective)
- Measurements: Forearm-Finger Skin temperature difference, Central-Toe temperature difference, Peripheral Perfusion Index, SOFA score

Clinical significance

- Odds for increase in SOFA score during first 48h of admission are 7.4 times higher (CI: 2-19, P<0.05) in patients with abnormal peripheral perfusion

- Odds to have increased lactate levels following initial resuscitation are 4.6 times higher (CI: 1.4-15, P<0.05) in patients with abnormal peripheral perfusion

Low tissue oxygen saturation at the end of early goal-directed therapy is associated with worse outcome in critically ill patients

Alexandre Lima, Jasper van Bommel, Tim C Jansen, Can Ince and Jan Bakker

Critical Care 2009, **13(Suppl 5):**S13 (doi:10.1186/cc8011)

Patients with circulatory failure (increased lactate) enrolled in EGDT protocol (8 hours) immediately following admission

Patient demographic data	
Number of patients	22
Age (years)	62 (57 to 71)
Male/female	16/6
Sequential Organ Failure Assessment score	7 (5 to 9)
Acute Physiology and Chronic Health Evaluation II score	23 (16 to 30)
Admission category	
Septic shock	3 pneumonia, 3 abdominal sepsis, 1 meningitis
Circulatory failure not associated with sepsis	3 hypovolemic/hemorrhagic, 3 cardiogenic, 4 postoperative, 2 trauma
Without circulatory failure or sepsis	1 cerebrovascular accident, 2 postoperative
Noradrenaline use	16 (72%)
Noradrenaline dose (µg/kg/minute)	0.16 (0.07 to 0.24)
Dobutamine use	8 (36%)
Dobutamine dose (µg/kg/minute)	4.3 (3.6 to 6.3)
Mechanical ventilation	15 (68%)
Survivor/nonsurvivor	17/5

Data expressed as number, as median (25th to 75th percentile), or as *n* (%).

n=22

abnormal peripheral perfusion

n=14

29%

n=8

n=2

50%

StO_2 ±60%

2 hours

8 hours

Mortality

normal peripheral perfusion

n=8

13%

n=6

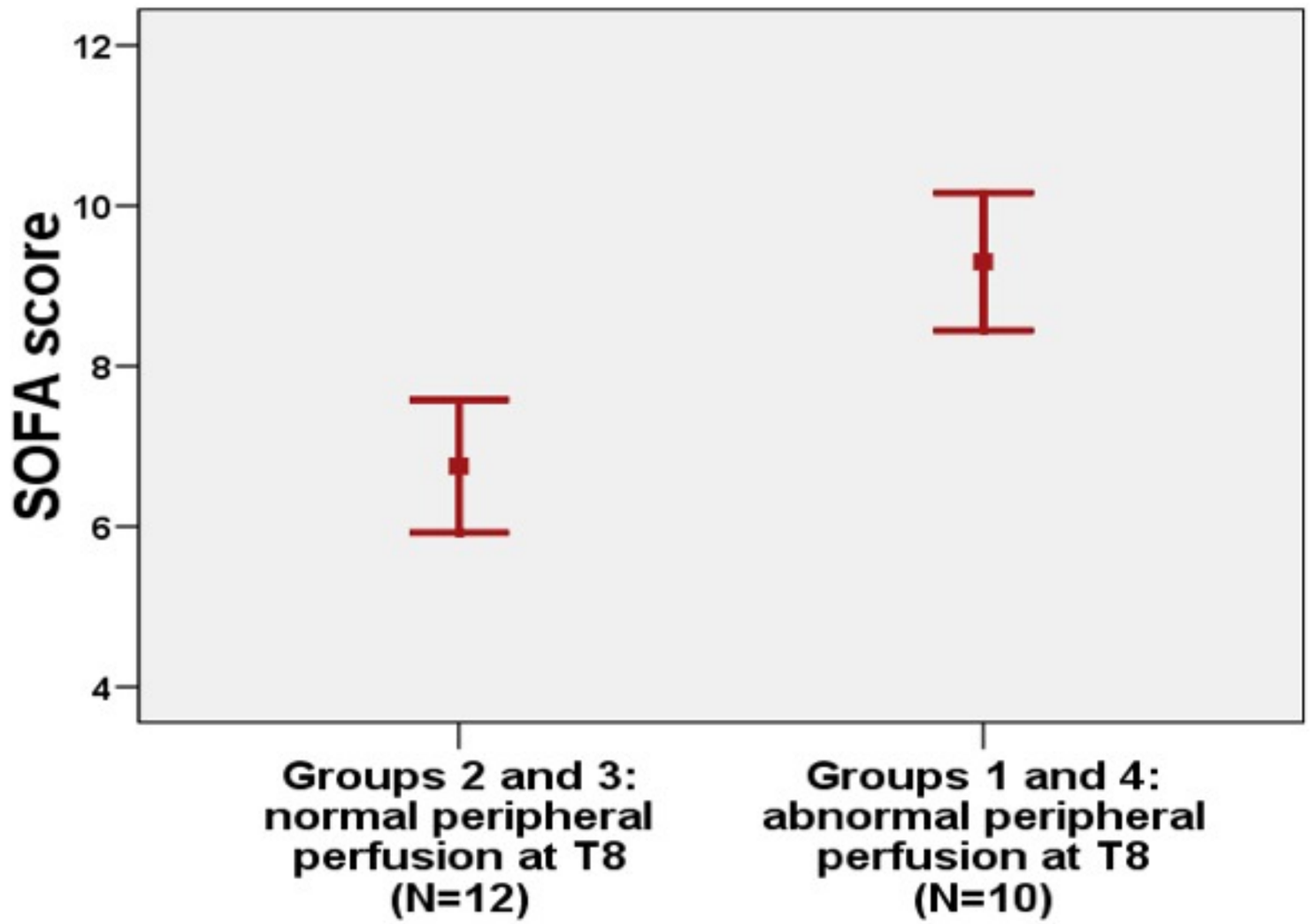
n=6

0%

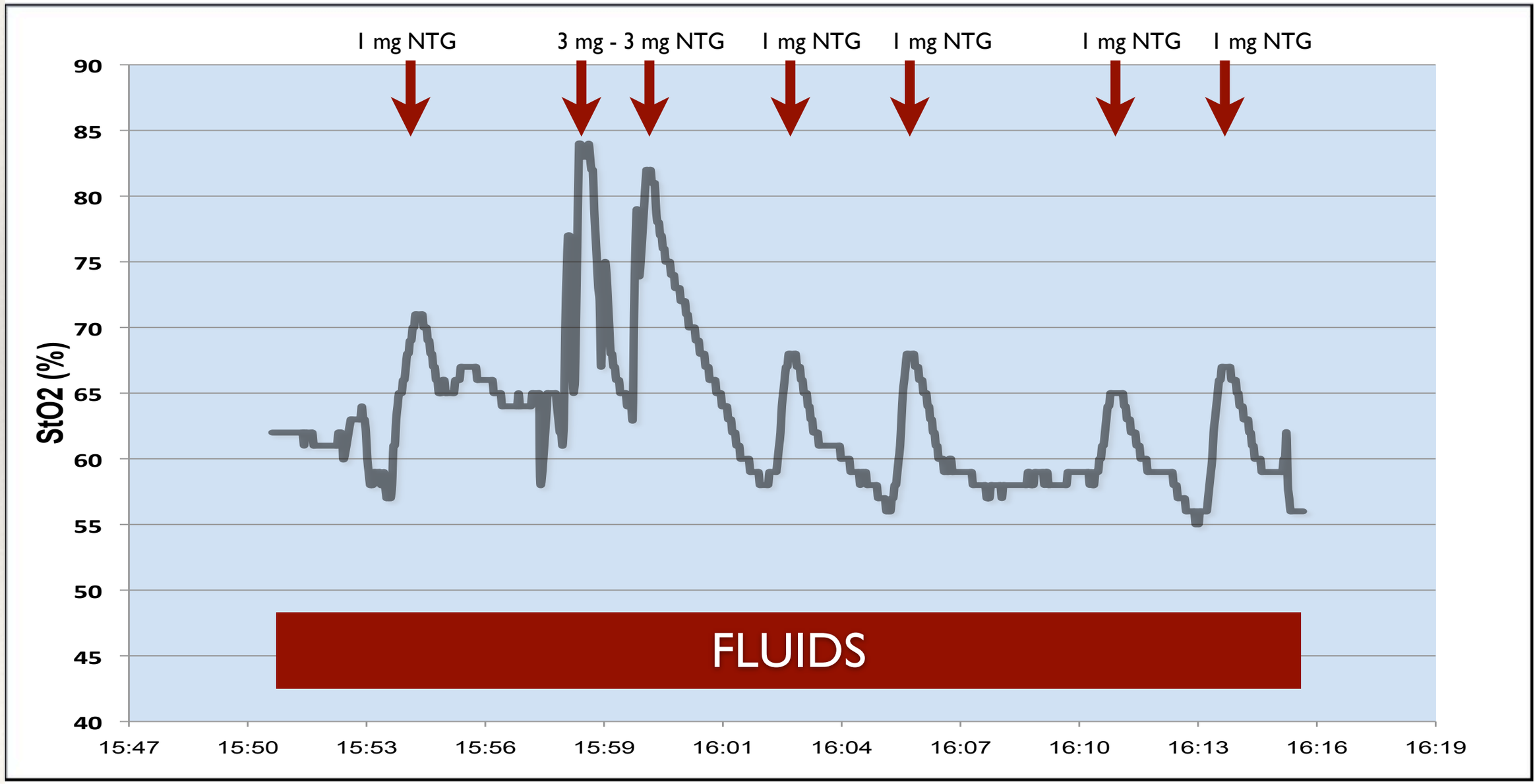
StO_2 ±80%

Clinical significance of low StO_2 in patients with shock

patients with abnormal peripheral circulation following EGDT have more organ failure



NTG in Septic Shock



Conclusions

- Increased lactate levels or failure to clear associated with morbidity and mortality for more than 150 years
- Delivery dependent oxygen consumption, present early in the course of disease, is associated with increased lactate
- Improvement in tissue oxygen delivery is associated with a decrease in lactate levels and ultimate survival
- However other (aerobic) metabolic processes result in increased lactate levels
- Therapy aimed to improve the balance between oxygen demand and oxygen supply improves outcome in patients with increased lactate levels

LACTATE : A REVIEW OF ITS METABOLISM IN SHOCK STATES

Pr Levy Bruno

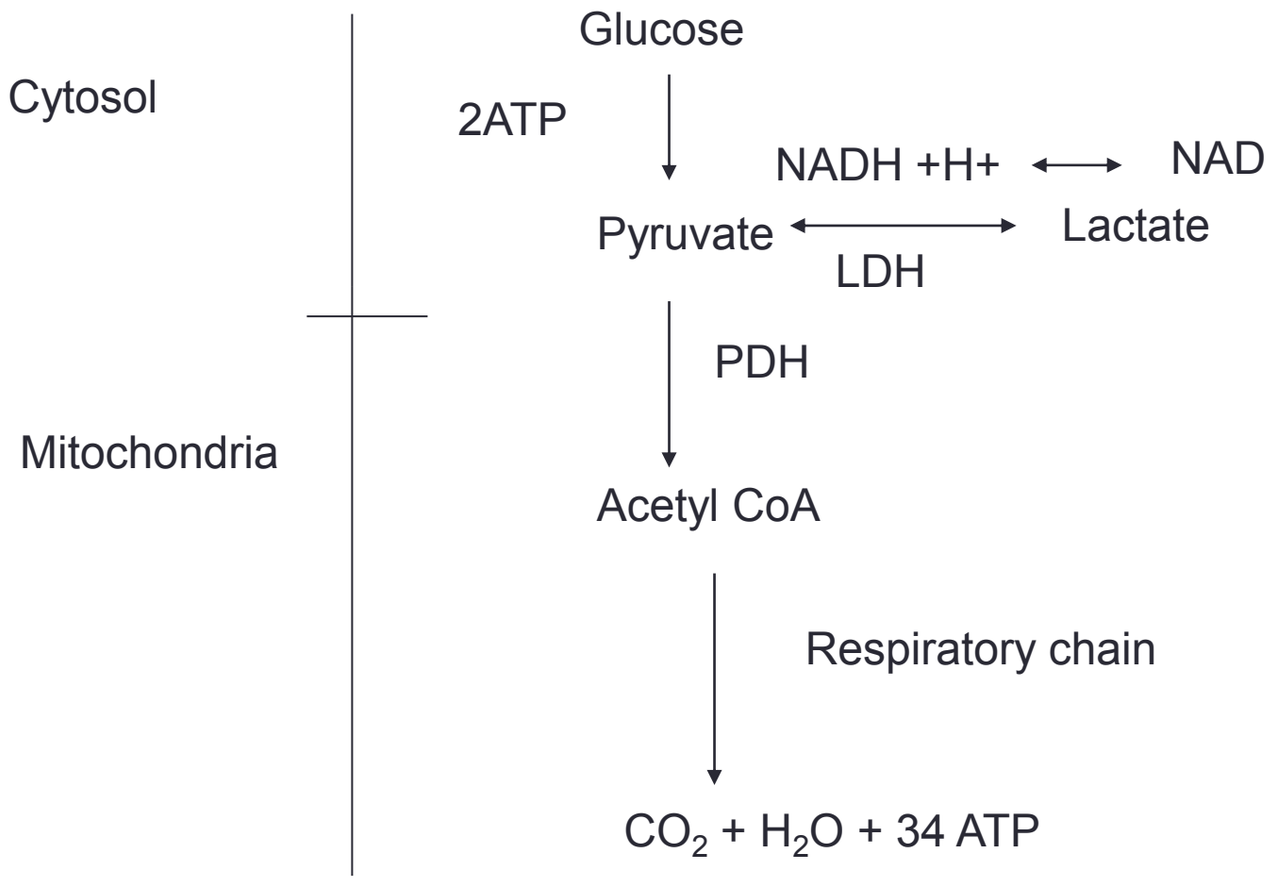
Réanimation Médicale Nancy

Groupe Choc, Inserm

Normal lactate metabolism

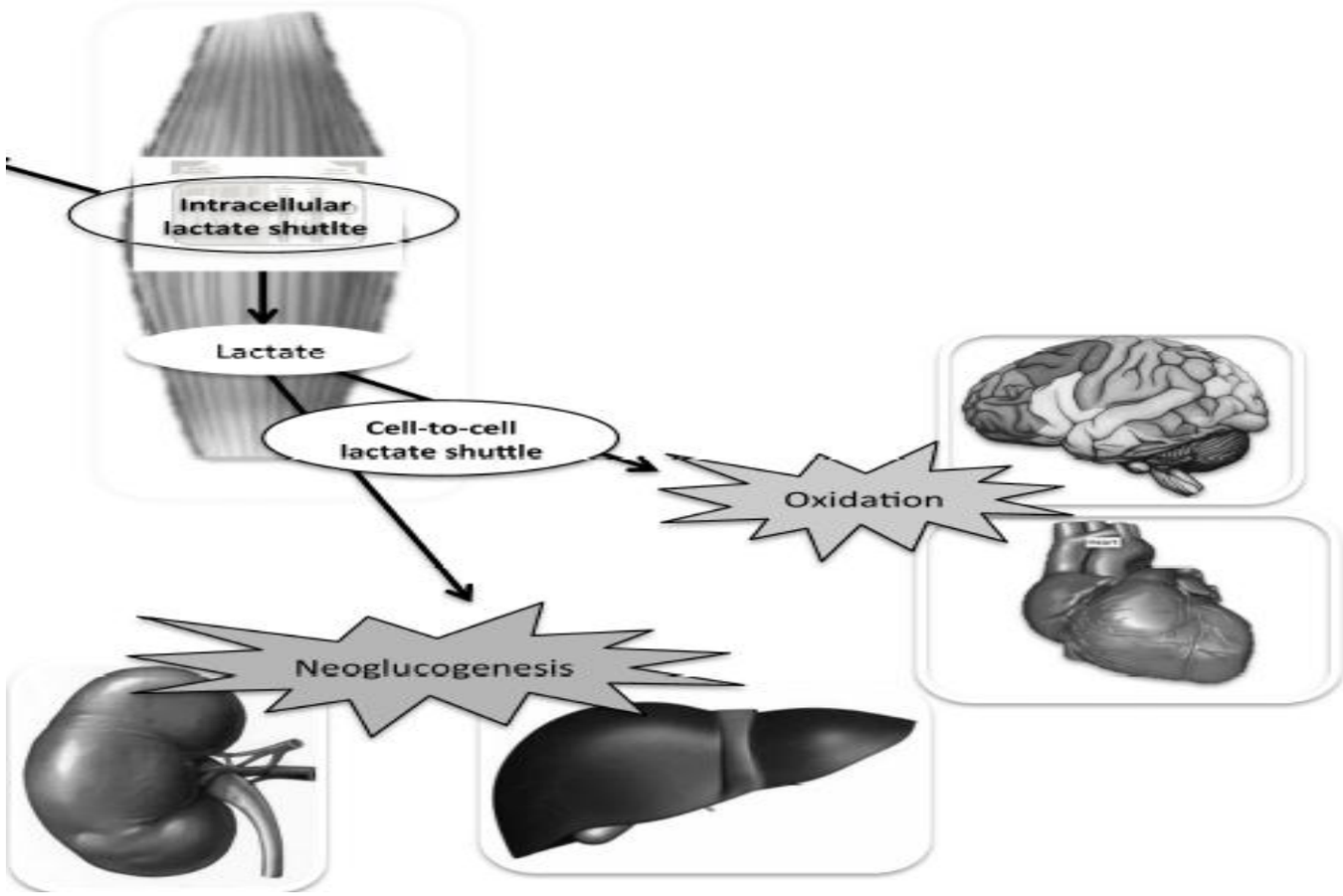
- Normal value less than 2 mmol/l
- Released by skeletal muscle, adipose tissue, brain+++
  - but also lung, heart and gut.
- Daily production : 20 mmol/kg per day
- Lactate clearance : 800-1800 ml/min
  - Every 3-4 minutes all of the blood can be cleared of lactate
- Lactate released into the bloodstream is transported to the liver and the kidney where it is subsequently metabolised
  - Oxydation (50% at rest and 75 % during exercise)
  - Neoglucogenesis

Simplified glycolysis

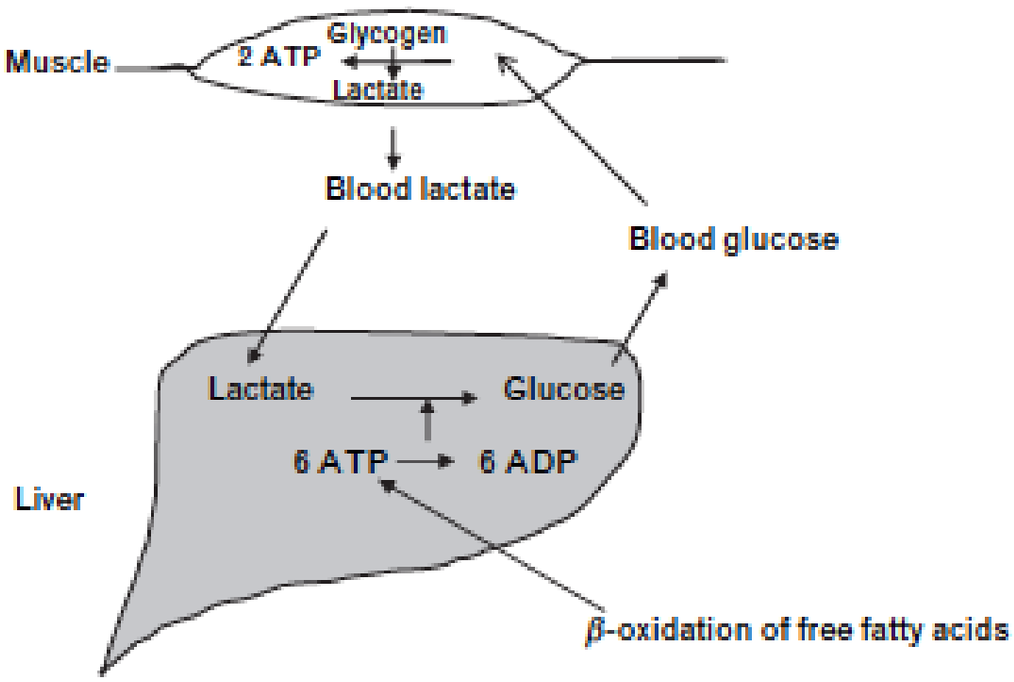


Lactate therefore increases when production of pyruvate exceeds its utilization by the mitochondria

Removal : Oxidation and Cori Cycle



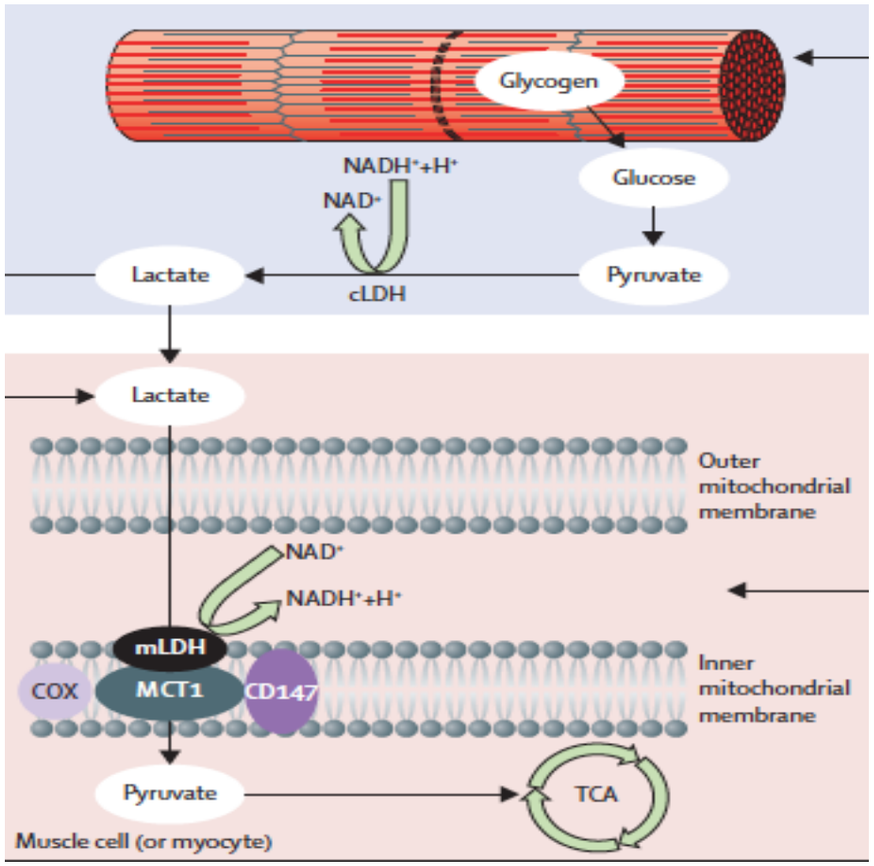
Cori Cycle



- Lactate reaches the liver where it enters the Cori cycle and becomes glucose
- The energy for such gluconeogenesis is supplied by b-oxidation of fatty acids
- Conversion of slow energy stored as fat into fast energy that is readily available as glucose.
- Energy is used to sustain the increased glycolytic flux necessary to meet the metabolic demands of severe sepsis

Lactate oxydation

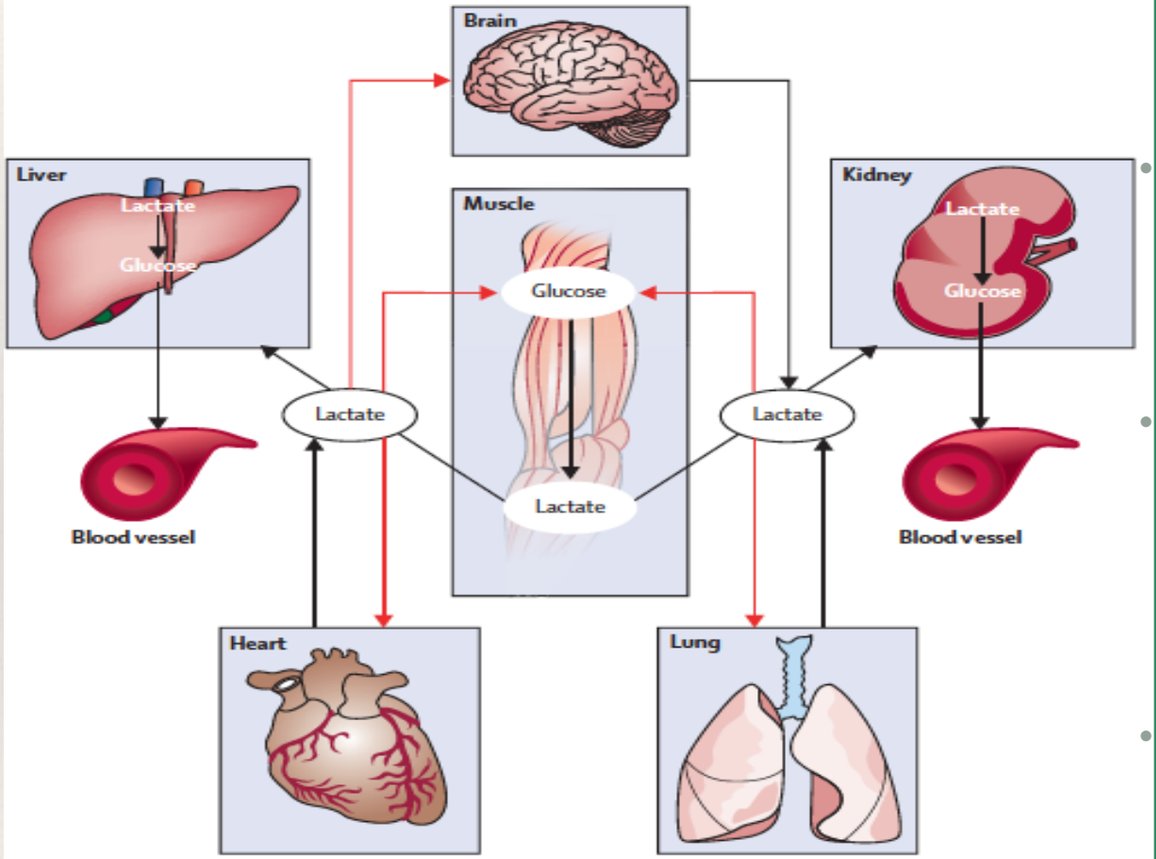
Cytosol



Mitochondria

Lactate oxydation complex

Cell-to-cell lactate shuttle

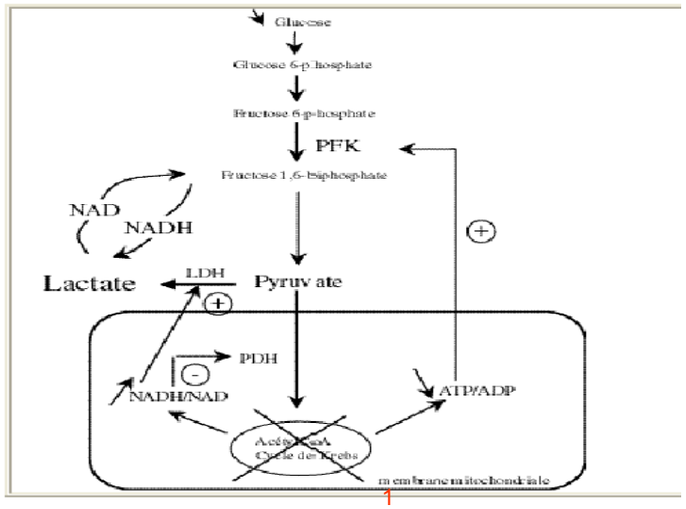


- Hypothesis : Lactate is not only produced in muscle and disposal within the same myocyte
- Lactate serve as a substrate in highly oxidative cells (eg, heart and brain) or contribute to gluconeogenesis (in the liver and kidney)
- Lactate is also released by brain, lung, and heart.

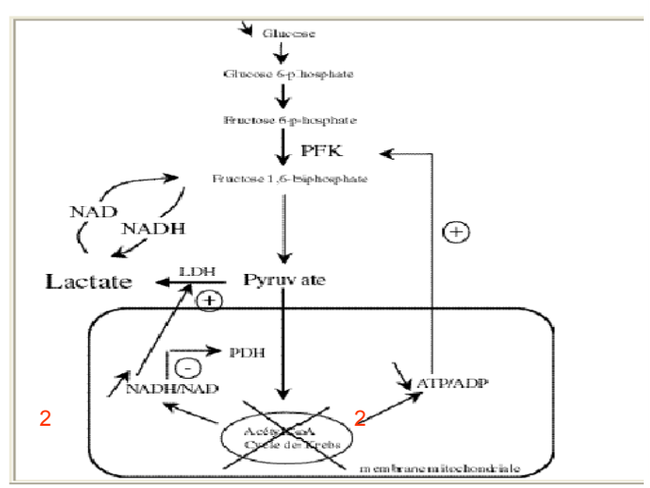
LACTATE AND SHOCK

THE CLASSICAL PARADIGM

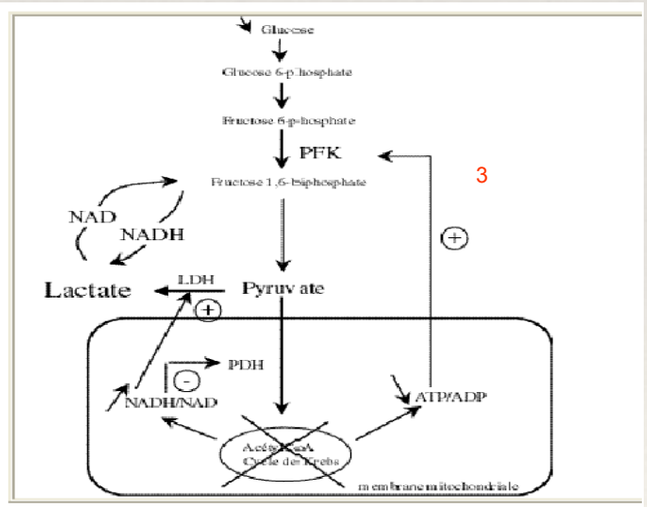
Hyperlactataemia during shock is a marker of tissue hypoperfusion or tissue hypoxia, and is indicative of the onset of anaerobic glycolysis



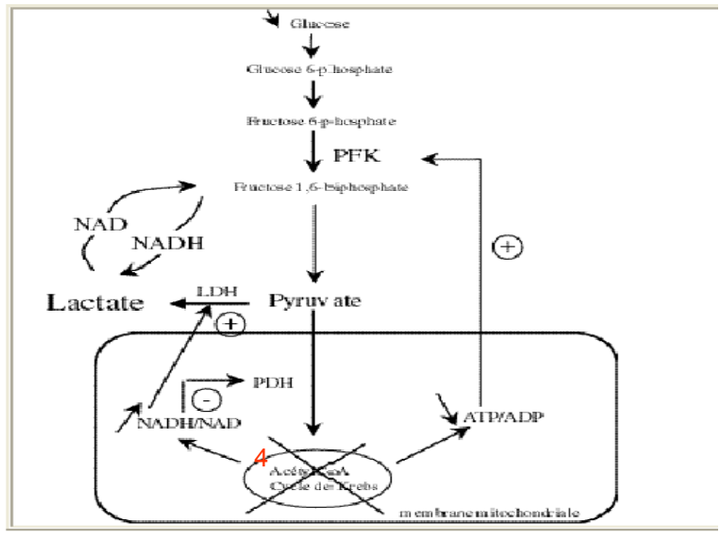
1. Absence of O_2 : stoppage or decrease in ATP production by mitochondrial electron transfer



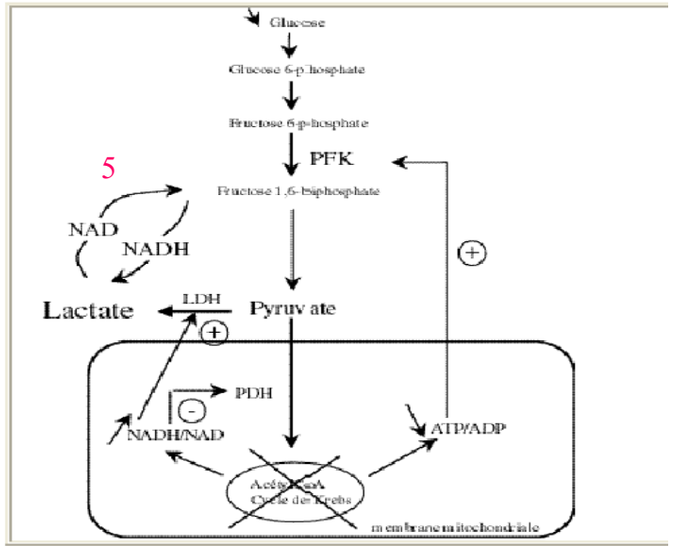
2. Decrease in ATP/ADP ratio and increase in NADH/NAD ratio



3. The decrease in ATP/ADP ratio induces an increase in PFK activity



4. The increase in NADH/NAD ratio decreases in PDH and increased LDH activity in favour of lactate formation



5. The conversion allows NAD regeneration and ATP production (2 ATP for one glucose)

Anaerobic metabolism

- Hyperlactatemia and elevated L/P ratio
- Accelerated aerobic glycolysis
- Low energy production
- Adaptive mechanism in crisis situation

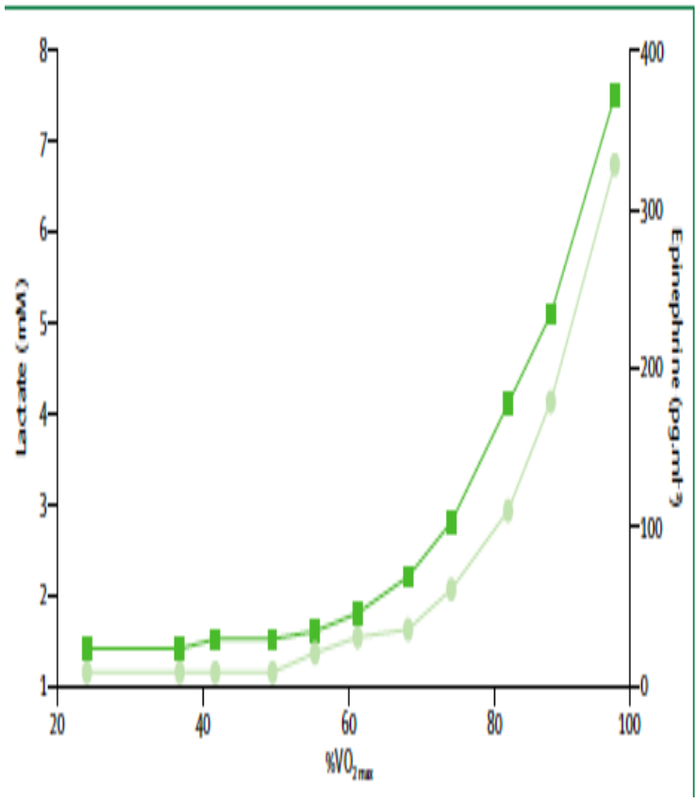
THE NEW PARADIGM

Shock induced hyperlactataemia should no longer be seen as a biomarker of hypoxia or anaerobic glycolysis, but as a major protective component of the stress response.

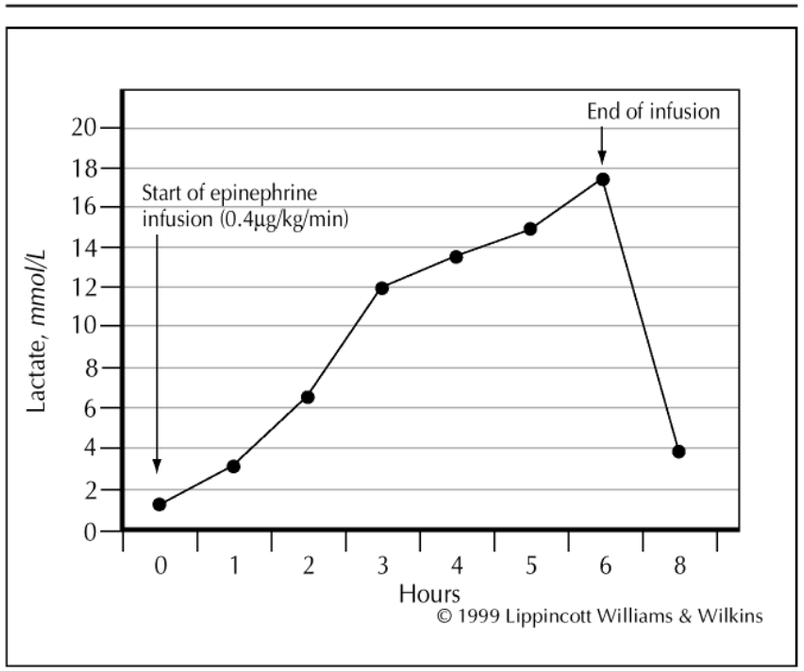
Proof against hypoxia induced hyperlactatemia in septic shock

- Oxygen delivery after initial resuscitation is generally elevated
- Increasing oxygen delivery does not decrease lactate level in all patients
- Muscular ATP and PO_2 level are normal or elevated.
- Splanchnic production is scarce (De Backer et al)
- Lungs produce lactate

Relationship between epinephrine and lactate

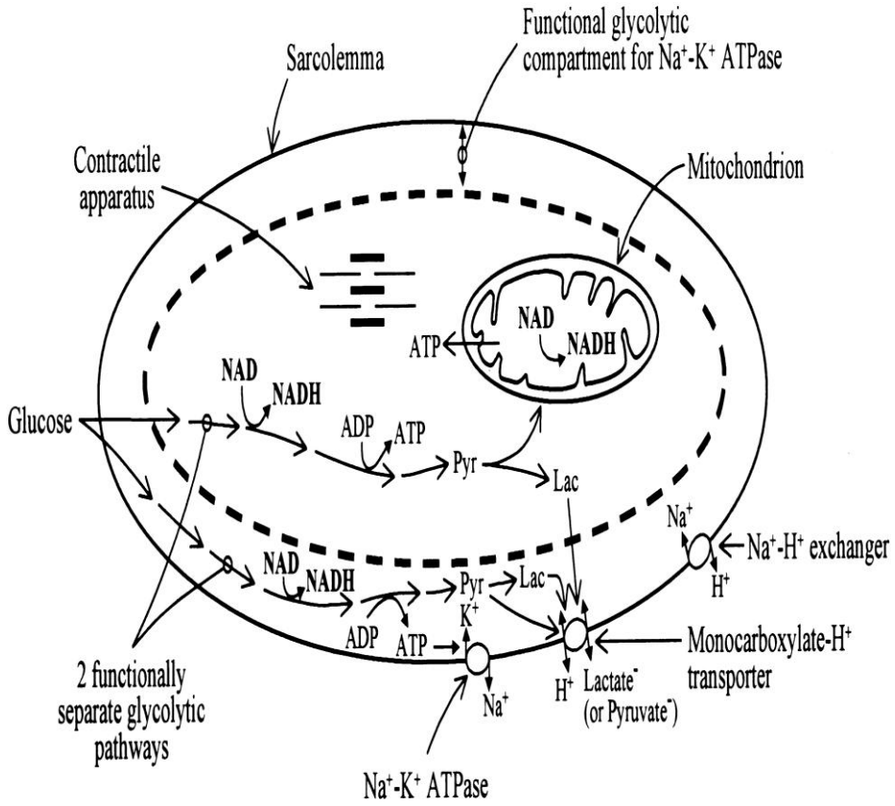


Mazzeo RS, Marshall P. *J Appl Physiol* 1989; **67:** 1319–22.



As can be seen, epinephrine infusion induces marked hyperlactatemia. During this time, systemic oxygen delivery is approximately doubled. This severe hyperlactatemia cannot be secondary to tissue hypoxia.

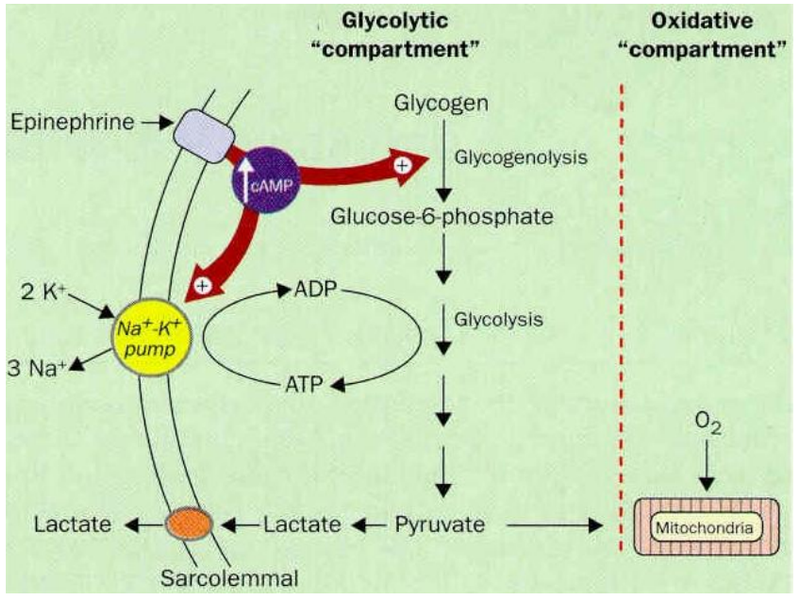
Glycolysis compartmentalisation and Na+-K+ase activity



- Two glycolytic pathways with separate sets of glycolytic pathways enzyme
- The enzyme of the first pathway have been shown to be associated with NaK ATPase activity.
- Accelerated aerobic glycolysis provide ATP to sustain Na+K+ ATPase activity in cells with intact oxydative activity
- The two compartments are independent.

Aerobic production of lactate under epinephrine stimulation

- Epinephrine binds to muscle adrenergic β 2 receptors and raises AMP production
  - Stimulation of glycogenolysis and ATP production
  - ATP is used to fuel the sarcolemmal Na+-K+ATPase that consumes ATP and increases ADP level
  - ADP increases PFK activity and thus pyruvate production
- Epinephrine increases glycogenolysis with a net increase in pyruvate production and thus an increase in lactate concentration

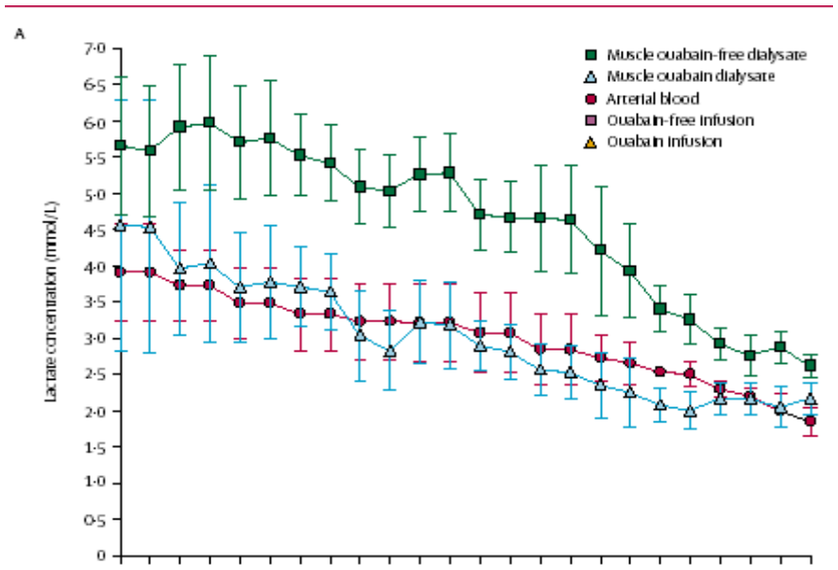


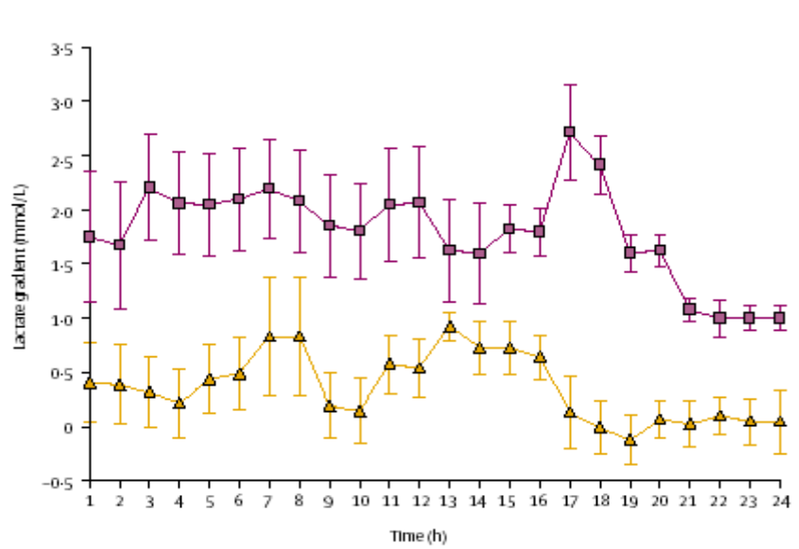
James et al, Lancet 1999, 354 : 505-508.

Relation between muscle Na^+K^+ ATPase activity and raised lactate concentrations in septic shock: a prospective study

Bruno Levy, Sébastien Gibot, Patricia Franck, Aurélie Cravoisy, Pierre-Edouard Bollaert

Lancet 2005; 365: 871–75





SHOCK, Vol. 30, No. 4, pp. 417–421, 2008

INCREASED AEROBIC GLYCOLYSIS THROUGH β2 STIMULATION IS A COMMON MECHANISM INVOLVED IN LACTATE FORMATION DURING SHOCK STATES

Bruno Levy, Olivier Desebbe, Chantal Montemont, and Sebastien Gibot
Groupe CHOC, Contrat AVENIR INSERM 2006, Faculté de Médecine, Nancy Université, Vandoeuvre les Nancy, France

SHOCK, Vol. 34, No. 1, pp. 4–9, 2010

EARLY INCREASE IN ARTERIAL LACTATE CONCENTRATION UNDER EPINEPHRINE INFUSION IS ASSOCIATED WITH A BETTER PROGNOSIS DURING SHOCK

Yann Wutrich,* Damien Barraud,* Marie Conrad, Aurélie Cravoisy-Popovic,* Lionel Nace,* Pierre-Edouard Bollaert,* Bruno Levy,*† and Sébastien Gibot*†

Intensive Care Med (2010) 36:1703–1709
DOI 10.1007/s00134-010-1938-x

ORIGINAL

Bruno Levy
Pierre Perez
Sebastien Gibot
Alain Gerard

Increased muscle-to-serum lactate gradient predicts progression towards septic shock in septic patients

LACTATE METABOLISM MODIFICATION DURING SHOCK

Lactate and glucose metabolism in severe sepsis and cardiogenic shock*

Jean-Pierre Revelly, MD; Luc Tappy, MD; Alexandro Martinez, MD; Marc Bollmann, MD; Marie-Christine Cayeux, RN; Mette M. Berger MD, PhD; René L. Chioléro, MD

	Healthy	Septic	Cardiac
Baseline			
Glucose rate of appearance, µmol/kg/min	7.2 ± 1.1	14.8 ± 1.8[a]	15.0 ± 1.5[a]
Plasma lactate concentration, mmol/L	0.9 ± 0.20	3.2 ± 2.6[a]	2.8 ± 0.4[a]
Lactate infusion 10 µmol/kg/min			
Lactate clearance, mL/kg/min	12.0 ± 2.6	10.8 ± 5.4	9.6 ± 2.1
Endogenous lactate production, µmol/kg/min	11.2 ± 2.7	26.2 ± 10.5[a]	26.6 ± 5.1[a]
Lactate oxidation, % lactate load	65 ± 15	54 ± 25	43 ± 16
Glucose rate of appearance, µmol/kg/min	6.7 ± 0.9	14.3 ± 3.2[a]	13.1 ± 1.2[a]
Gluconeogenesis from lactate, % lactate load	10 ± 7	15 ± 15	9 ± 18
Lactate infusion 20 µmol/kg/min			
Glucose rate of appearance, µmol/kg/min	6.6 ± 0.8	14.3 ± 3.5[a]	12.9 ± 2.1[a]
Gluconeogenesis from lactate, % lactate load	11 ± 5	17 ± 6	10 ± 5

[a]Different from the healthy subjects ($p < .05$).

Mild Hyperlactatemia in Stable Septic Patients Is Due to Impaired Lactate Clearance Rather Than Overproduction

JACQUES LEVRAUT, JEAN-PIERRE CIEBIERA, STEPHANE CHAVE, OLIVIER RABARY, PATRICK JAMBOU, MICHEL CARLES, and DOMINIQUE GRIMAUD

TABLE 3

BLOOD LACTATE DATA FOR SEPTIC PATIENTS WITH NORMAL OR SLIGHTLY INCREASED BLOOD LACTATE CONCENTRATIONS

	Normal Blood Lactate ($n = 20$)	Increased Blood Lactate ($n = 10$)	p Value
Blood lactate concentration, mmol/L	1.2 ± 0.2	2.6 ± 0.6	—
Maximum Δblood lactate, mmol/L*	3.4 ± 0.8	3.7 ± 0.5	0.22
Plasma lactate clearance, ml/kg/h	1,002 ± 284	473 ± 102	< 0.0001
Lactate production, μmol/kg/h	1,181 ± 325	1,194 ± 230	0.90
Half-life of infused lactate, min	17.9 ± 10.2	28.7 ± 8.9	0.008
Central distribution volume, ml/kg	122 ± 32	100 ± 17	0.052
Total distribution volume, ml/kg	264 ± 116	259 ± 61	0.91

Lactate and heart

- Heart is an omnivore
  - Fatty acids : 60-90%
  - Pyruvate : 10-40%
    - Lactate oxydation
    - Glycolysis
- Septic shock (Dhainault JF, 1988)
  - Fatty acids :12 % vs 54% in control group
  - Lactate : 36% vs 12% in control group

Effects of substrate selection on contractile function

- Better if the heart oxidizes more glucose and lactate than FFA.
- Preferential FFA utilization increases MVO_2 without changes in cardiac efficiency
- During ischemia, high dependance of cardiac function to glycolytic flux

Bruno Levy
Arnauld Mansart
Chantal Montemont
Sebastien Gibot
Jean-Pierre Mallie
Veronique Regnault
Thomas Lecompte
Patrick Lacolley

Myocardial lactate deprivation is associated with decreased cardiovascular performance, decreased myocardial energetics, and early death in endotoxic shock

Conclusions

- Stress induced lactate formation is a ubiquitous phenomenon in shock state
- During shock, the heart uses lactate as a preferential fuel
- Reconsideration of the signification and the role of lactate in septic shock
  - Adapted mechanism
  - Preferential fuel for heart and brain
  - Metabolic signal

Stress hyperlactataemia: present understanding and controversy

Mercedes Garcia-Alvarez, Paul Marik, Rinaldo Bellomo

www.thelancet.com/diabetes-endocrinology

Lactate and shock state: the metabolic view

Bruno Levy

Curr Opin Crit Care 12:315–321.

Current Trends in Lactate Metabolism: Introduction

L. BRUCE GLADDEN

Lactate:
any beneficial role?

Antonio Pesenti
University of Milano Bicocca
Italy

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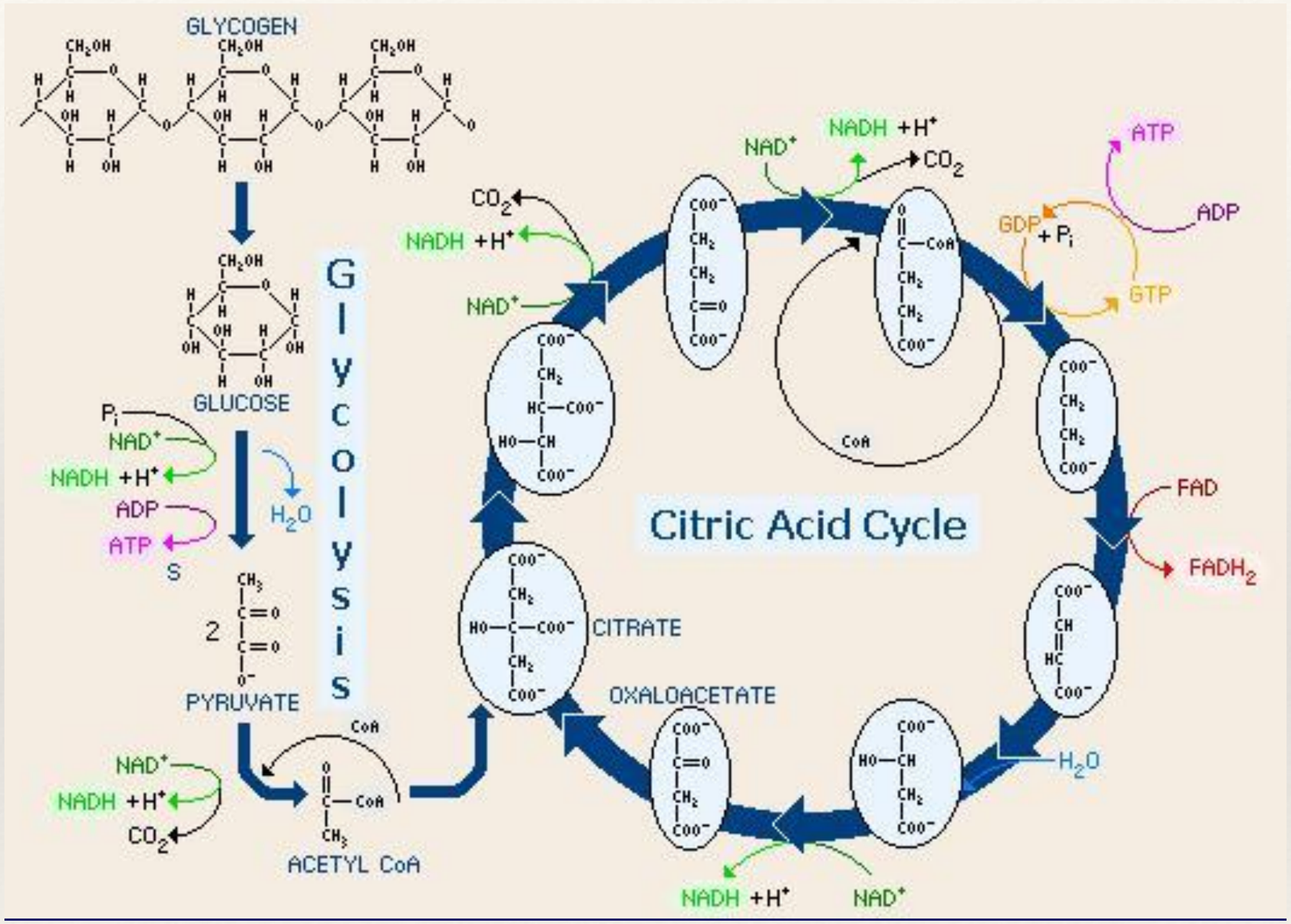
ISICEM 2014

Lactate

- What is lactic acid?
- A physiological metabolite

- Does it have any function?
- Restoring NAD/ NADH ratio


GLYCOGEN
GLUCOSE
Glycolysis
PYRUVATE
ACETYL CoA
CITRATE
OXALOACETATE
Citric Acid Cycle
NAD+
NADH +H+
CO2
H2O
ATP
ADP
GDP + Pi
GTP
FAD
FADH2
Pi
S
2
CoA

Lactate

- Its level may increase due to:
  - Increased production : increased glycolysis (e.g. sepsis, exercise, catecholamines, inflammation etc)
  - Decreased clearance :
    - Intracellular (lack of oxygen ; mitochondrial dysfunction)
    - Intercellular (e.g. Liver failure)

Oxygenation what for?

- Oxydative Phosphorylation
- End products of anaerobic metabolism (glycolysis, beta oxydation,) enter the Krebs cycle as Acetil CoA to produce (some) ATP and reduce NAD FAD to NADH FADH
- Glycolysis only can proceed without oxygen because of the conversion Pyruvate to lactate, which reconverts NADH to NAD

Glyco ATP summary

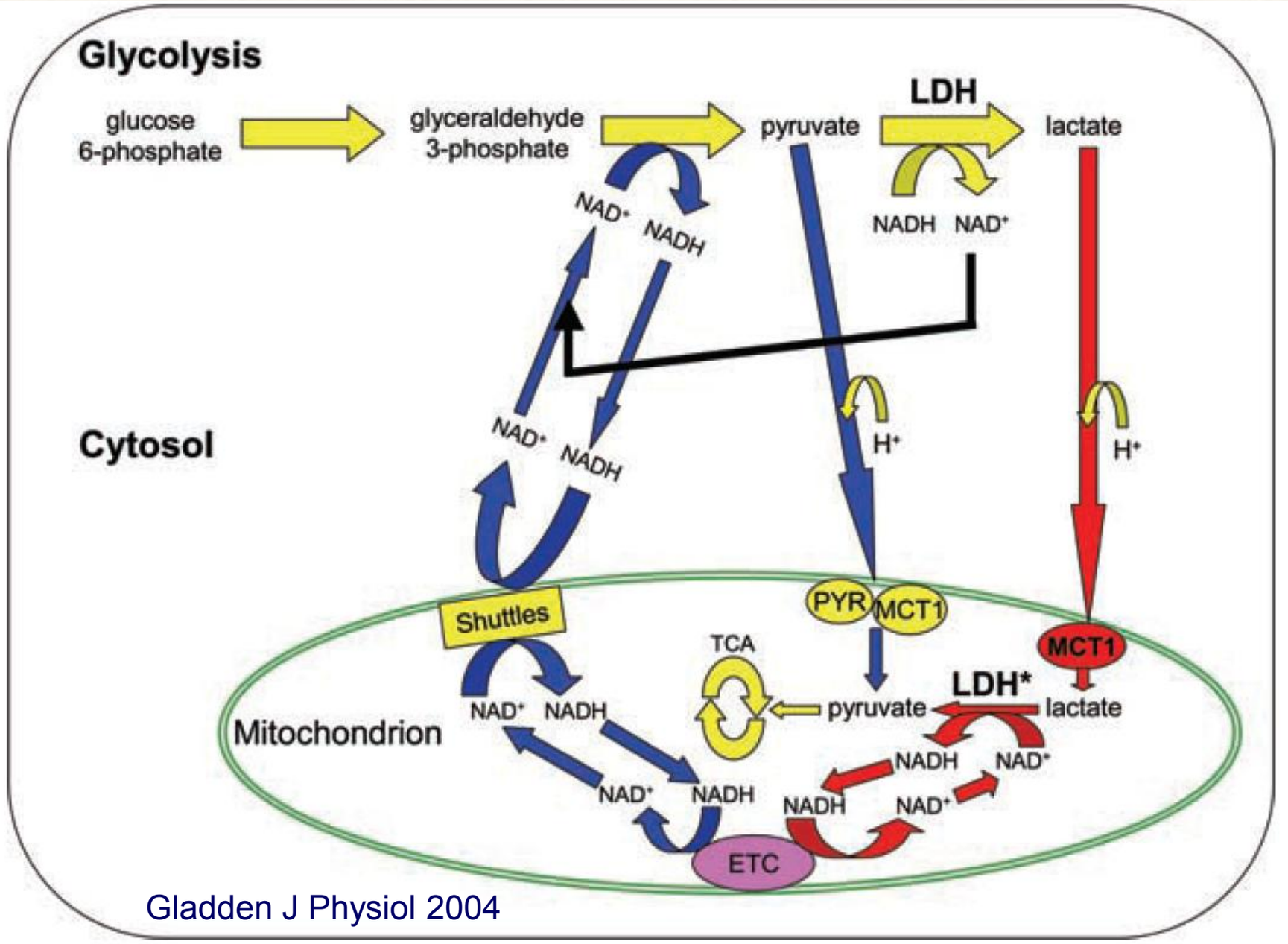
- Glucose > 2 Lactate = 2 ATPs
- Glucose + O_2> CO_2+ H_2O = 36 ATPs
- 2 Lactate > Glucose = - 6 ATPs
- Glucose > Lactate > Glucose = - 4 ATPs

Lactate

- Is lactate a toxic waste product?
- Apparently not. It may be useful
- Turbo fuel for many tissues

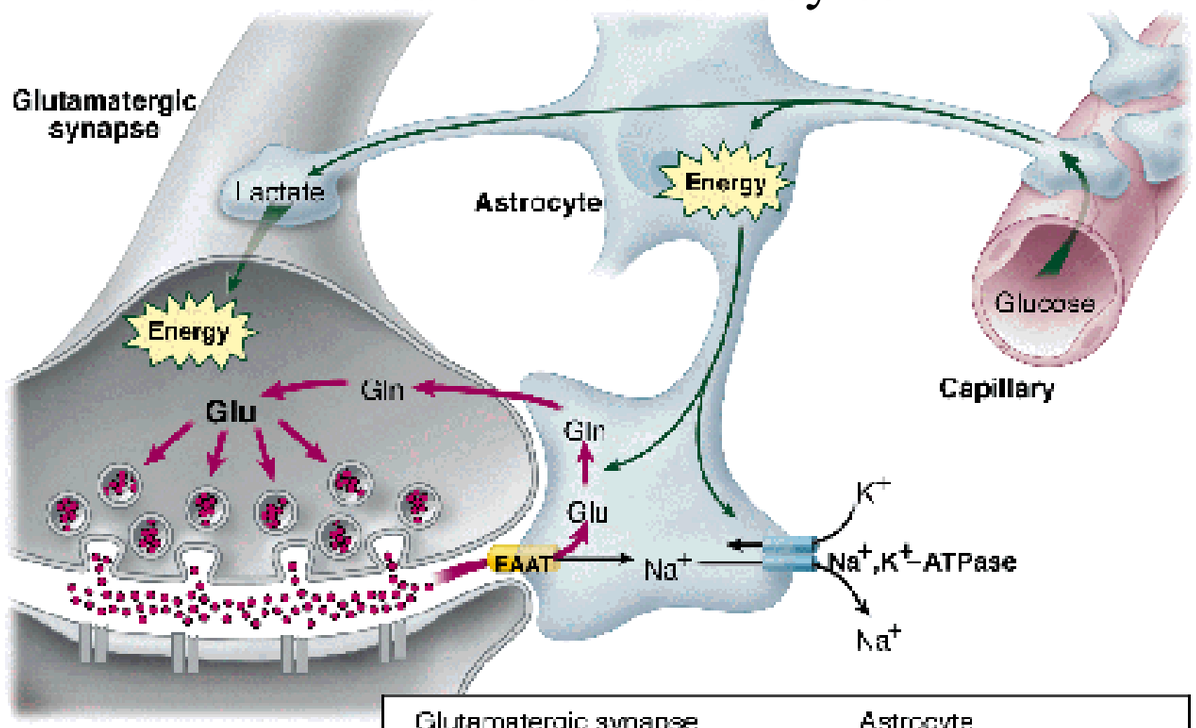
LACTATE

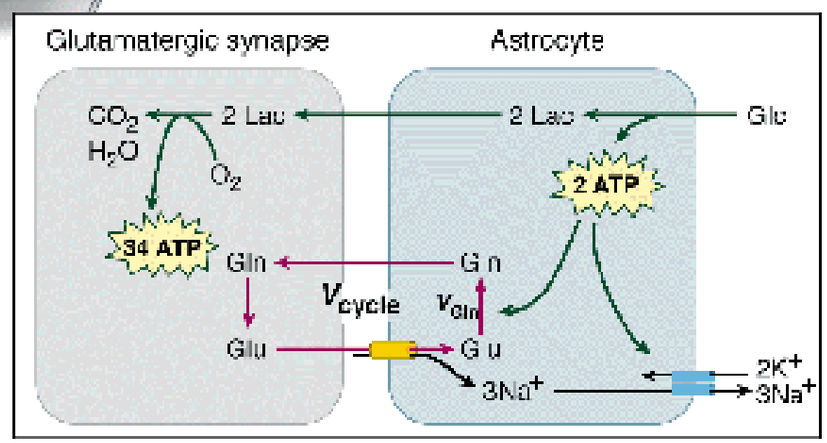
- LACTATE SHUTTLE:
  - »Within cells
  - »Between cells
  - »Between Organs



Gladden J Physiol 2004

Glucose and Lactate: a metabolic dialogue between neurons and astrocytes





Magistretti, Science

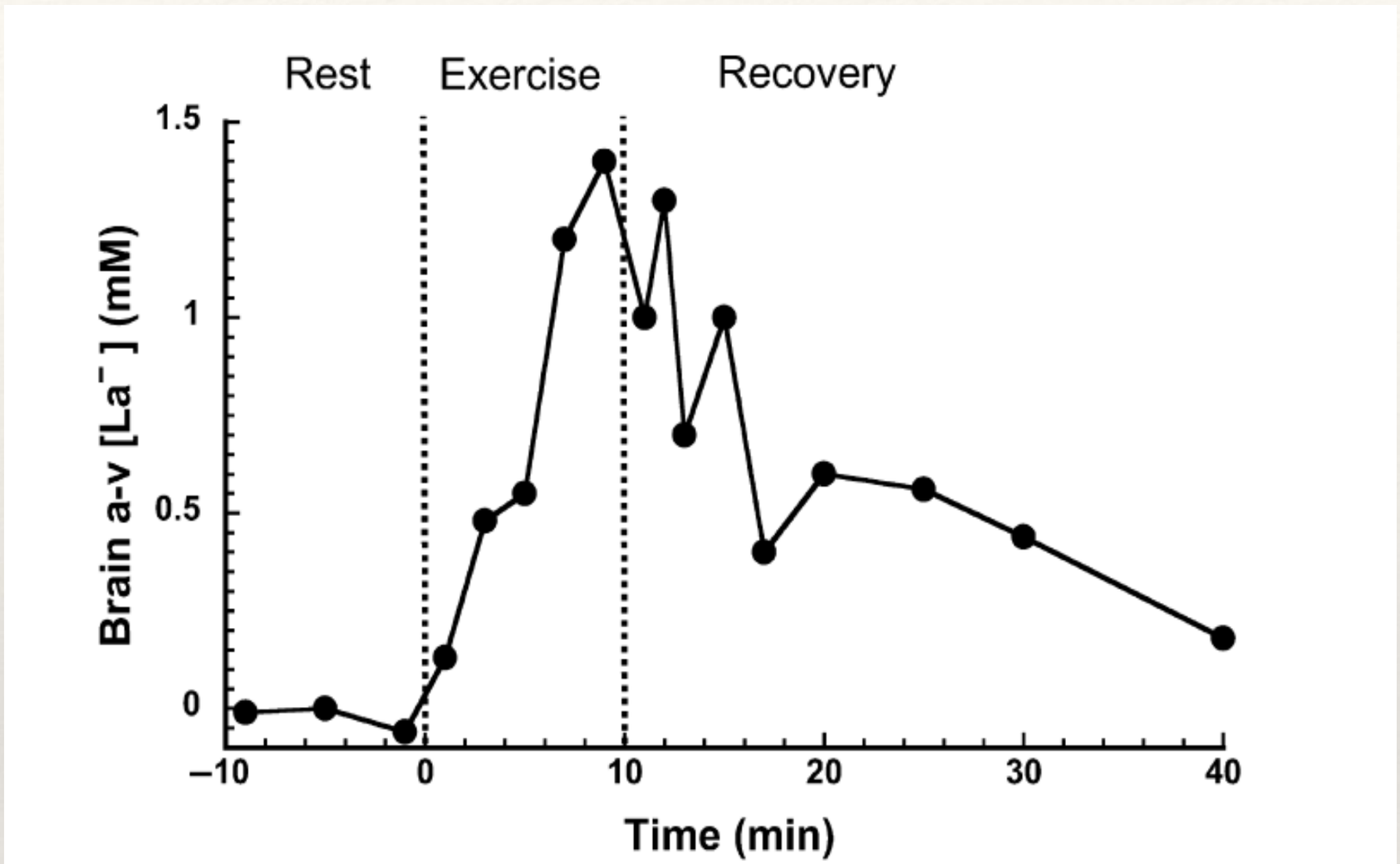


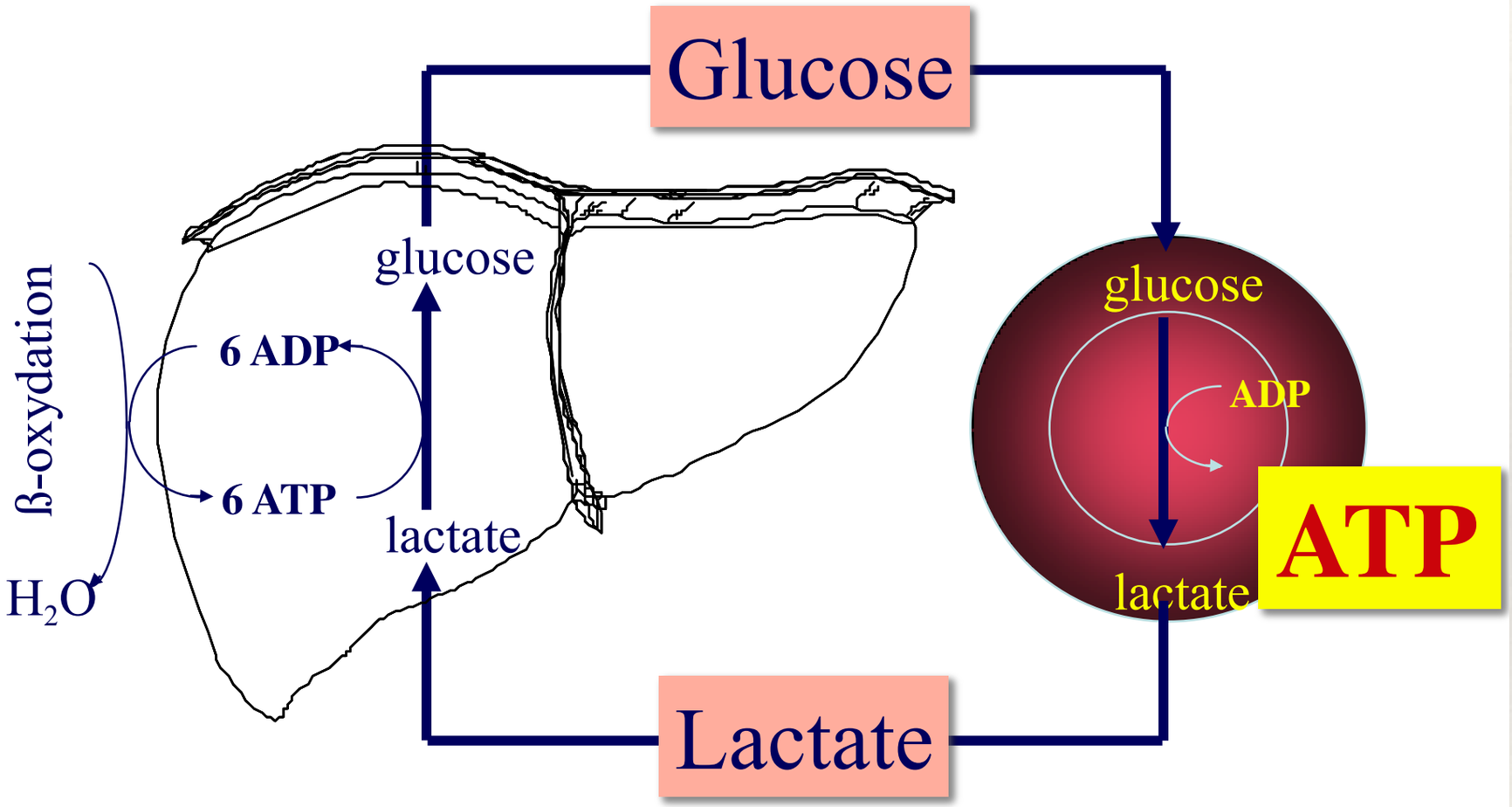
FIGURE 3—Global cerebral arteriovenous [La^-] difference during rest, progressive incremental exercise, and recovery. Redrawn with permission from Dalsgaard et al. (17).

Gladden Medicine and Science Sport Exercise 2008

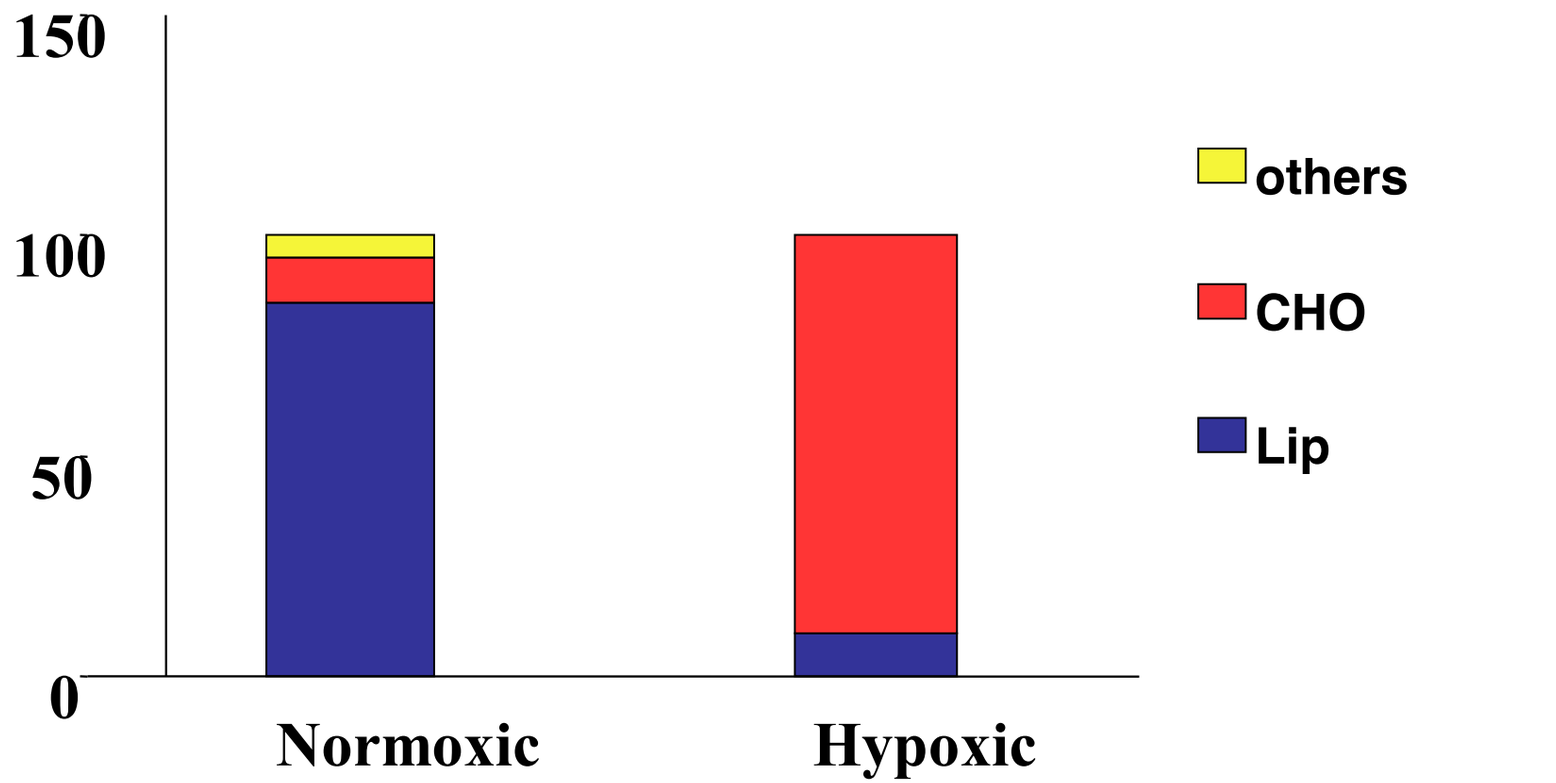
ANAEROBIC MAN

- Some organs or cells are anaerobic:
- Red Cells (no mitochondria) a good example:
- Approx 3.5 Kg of anaerobic cells: the liver breaths for them

Glucose-Lactate recycling: the Cori's Cycle



Miocardial metabolism in humans under normoxic and hypoxic conditions



Hochachka et al, PNAS 2001

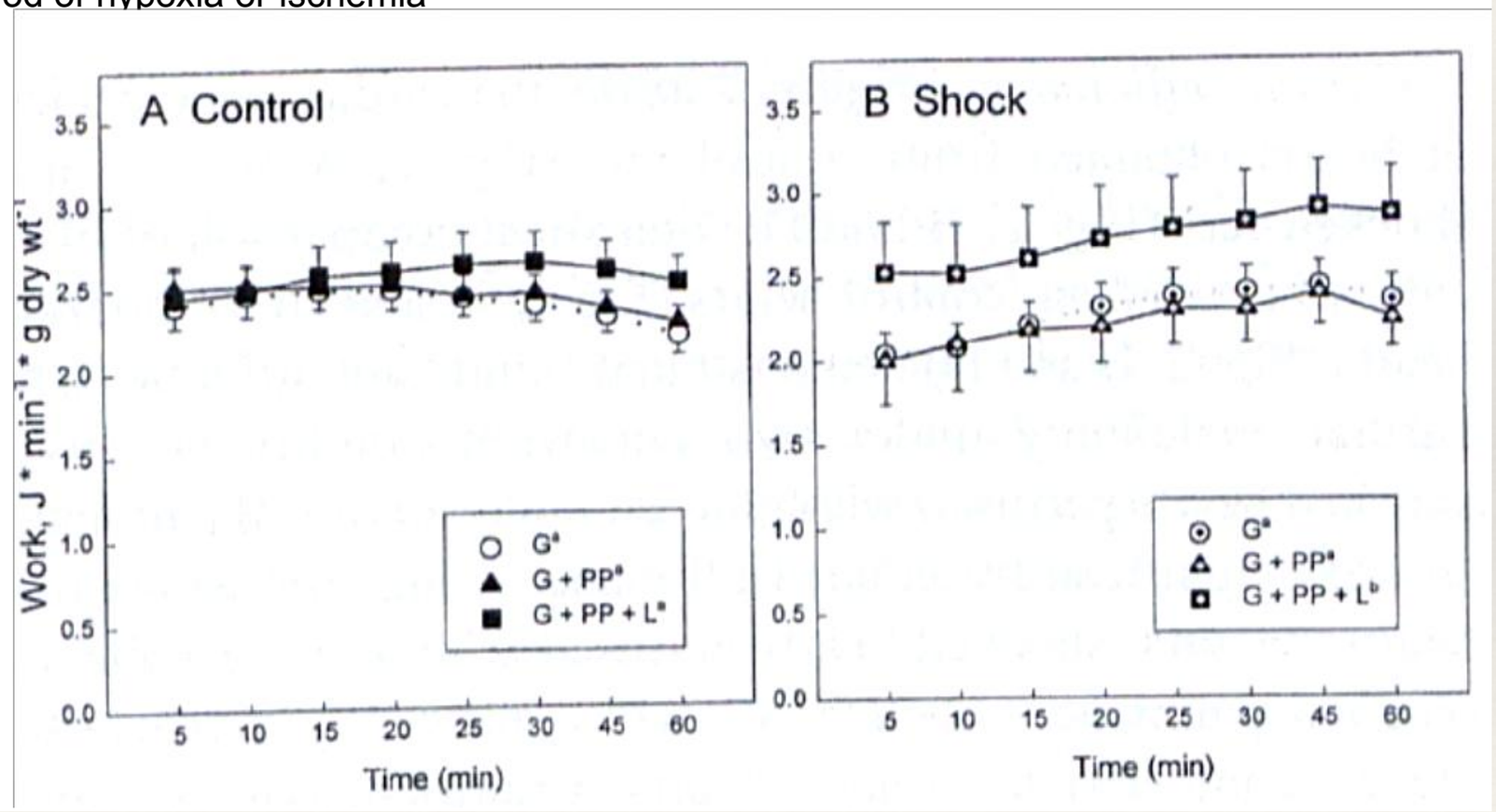
SHOCK, Vol. 14, No. 2, pp. 215–221, 2000

LACTATE IMPROVES CARDIAC EFFICIENCY AFTER HEMORRHAGIC SHOCK

With this in mind, the increased lactate concentration

permits an increase of a substrate readily oxidizable even after a transient

period of hypoxia or ischemia



Lactate and wound healing

- Healing wounds produce and accumulate Lactate (10-15 mMol/l)
- Lactate produced by rapidly multiplyng cells
- Lactate enhances collagen deposition
- Lactate enhances angiogenesis

Glucose paradox of cerebral ischemia

- Preischemic hyperglycemia associated to increased [Lac] associated to increased brain damage.
- Does Lac cause damage?

- Lac used up by neural tissue post ischemia : it is there were it is most needed

Relation between muscle Na^+K^+ ATPase activity and raised lactate concentrations in septic shock: a prospective study

Bruno Levy, Sébastien Gibot, Patricia Franck, Aurélie Cravoisy, Pierre-Edouard Bollaert

Lancet 2005; 365: 871–75

Service de Réanimation

Interpretation :
Skeletal muscle could be a leading
source of lactate formation as a result of exaggerated aerobic glycolysis through NaK ATPase stimulation during septic shock.

Lactate
Conclusions

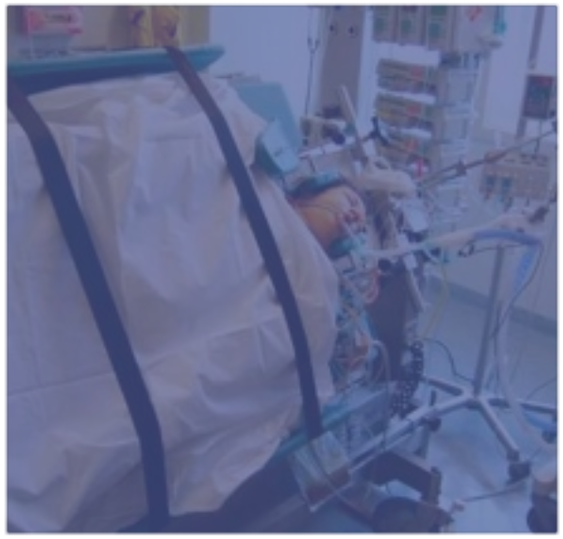
- Is not a bad guy, but a friend of the physician
- It is not dangerous in itself
- Most often it indicates that something is wrong: perfusion, oxygenation, sepsis, inflammation
- Energy failure
- Guide to therapy
- We still have to exploit all the potential advantages of lactate as a therapeutic agent

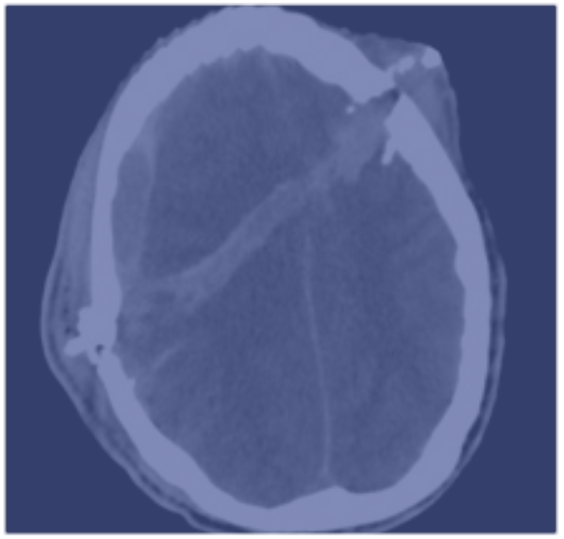
Lactate

Time course in septic shock

Jan Bakker MD PhD

jan.bakker@erasmusmc.nl





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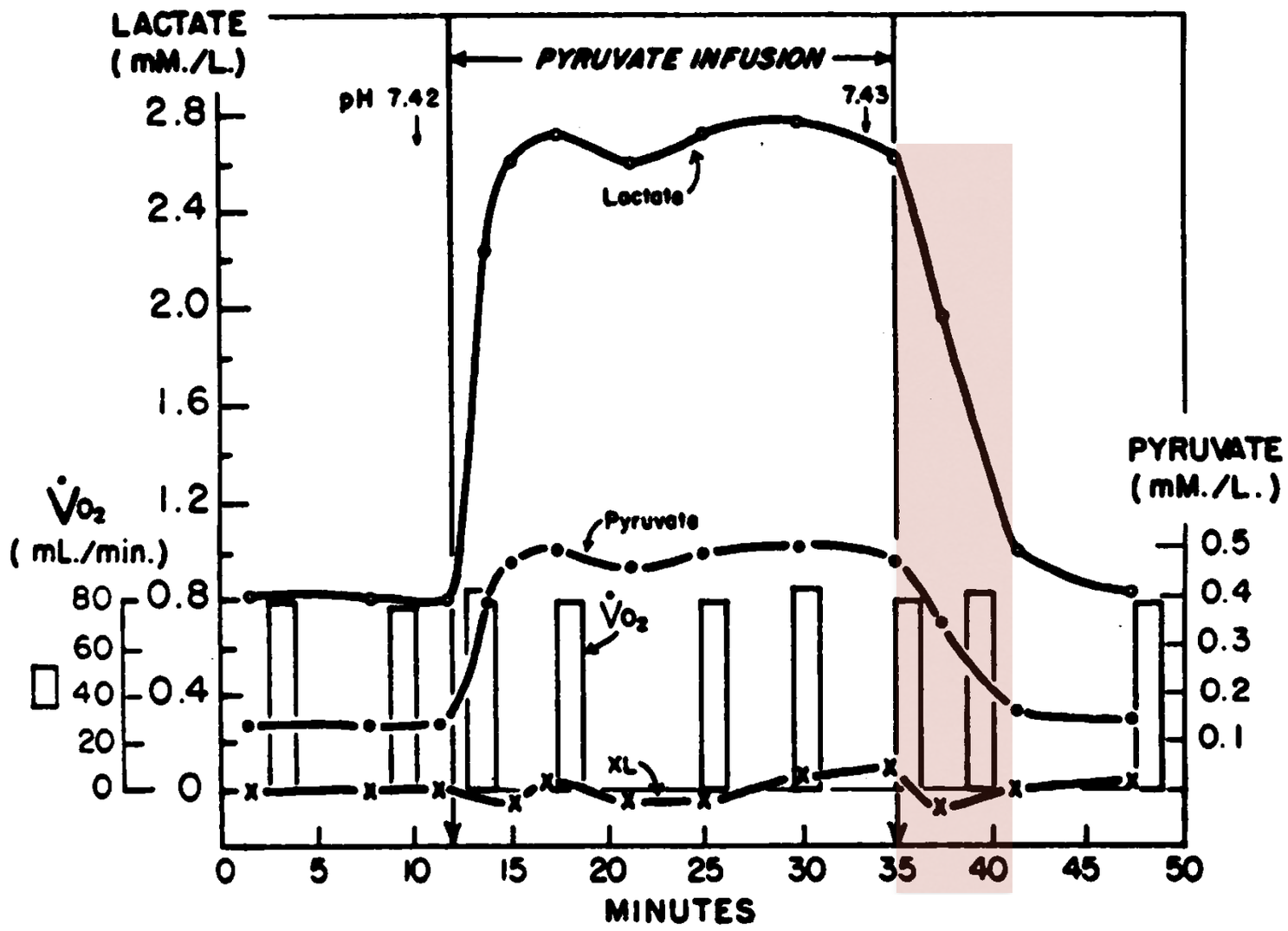
University Medical Center Rotterdam

RELATIONSHIPS OF PYRUVATE AND LACTATE DURING ANAEROBIC METABOLISM. I. EFFECTS OF INFUSION OF **PYRUVATE** OR GLUCOSE AND OF HYPERVENTILATION

WILLIAM E. HUCKABEE



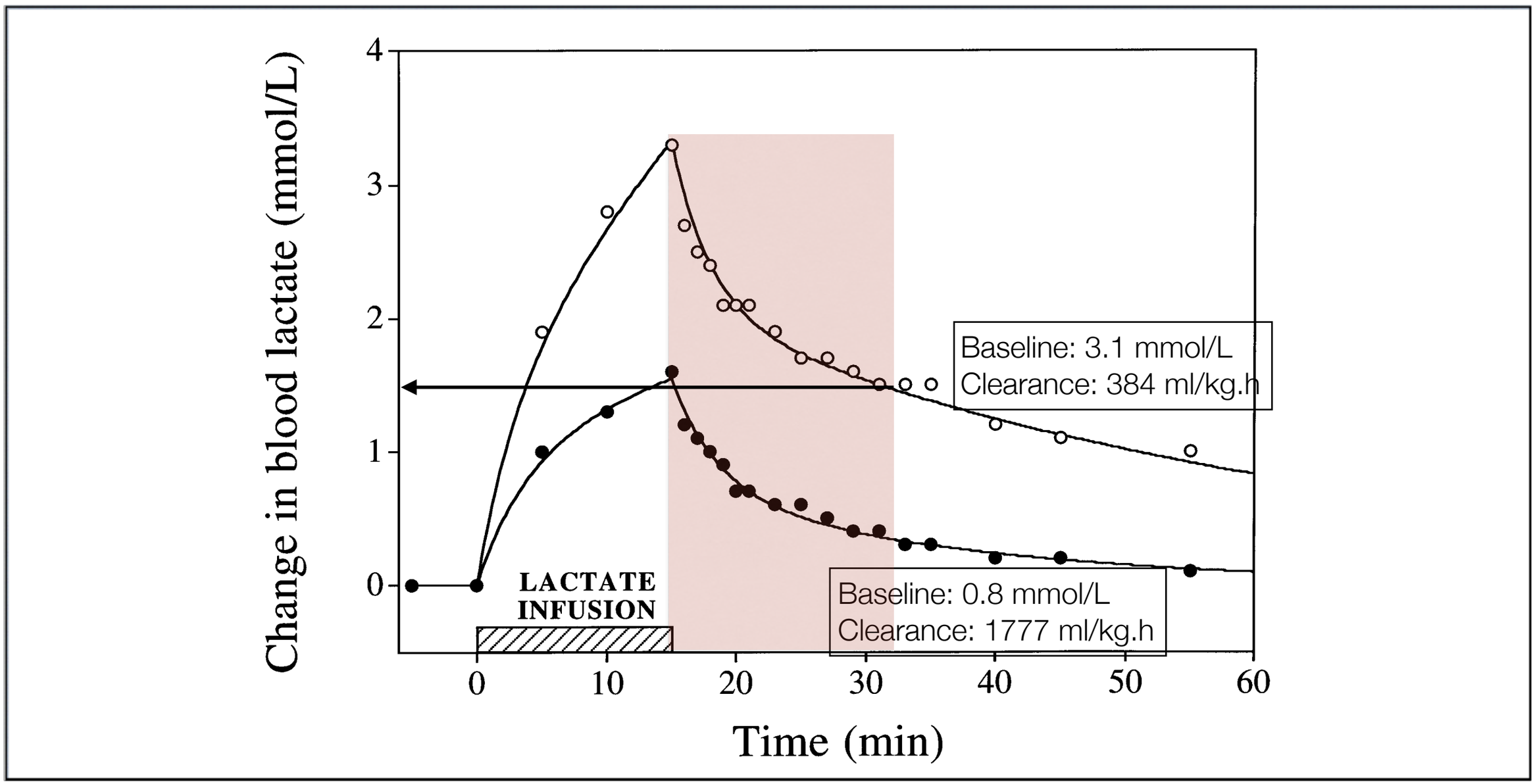
Lactate production theoretically is not controlled exclusively by the adequacy of cellular oxygenation, and is demonstrably affected to a very significant extend by the pyruvate changes of over-ventilation or pH alterations of the body, of blood glucose changes and probably other stimuli. **It would, therefore, seem quite inadvisable to draw any conclusions about tissue oxygen supply from determinations of lactate alone.**

J Clin Invest. 1958 Feb.;37(2):244-254

Mild Hyperlactatemia in Stable Septic Patients Is Due to Impaired Lactate Clearance Rather Than Overproduction

JACQUES LEVRAUT, JEAN-PIERRE CIEBIERA, STEPHANE CHAVE, OLIVIER RABARY, PATRICK JAMBOU, MICHEL CARLES, and DOMINIQUE GRIMAUD

AM J RESPIR CRIT CARE MED 1998;157:1021–1026.



The prognostic value of blood lactate levels relative to that of vital signs in the pre-hospital setting: a pilot study

Tim C Jansen[1], Jasper van Bommel[1], Paul G Mulder[2], Johannes H Rommes[3], Selma JM Schieveld[3] and Jan Bakker[1]

Critical Care 2008, **12**:R160 (doi:10.1186/cc7159)

- 124 patients enrolled
  - inclusion criteria
    - SAP<100 mm Hg
    - 29 < RR < 10 /min
    - GCS < 14
  - cap or venous lactate on arrival at the scene (T1) and just before arrival at the hospital (T2)
  - Outcome: hospital mortality

The prognostic value of blood lactate levels relative to that of vital signs in the pre-hospital setting: a pilot study

Tim C Jansen[1], Jasper van Bommel[1], Paul G Mulder[2], Johannes H Rommes[3], Selma JM Schieveld[3] and Jan Bakker[1]

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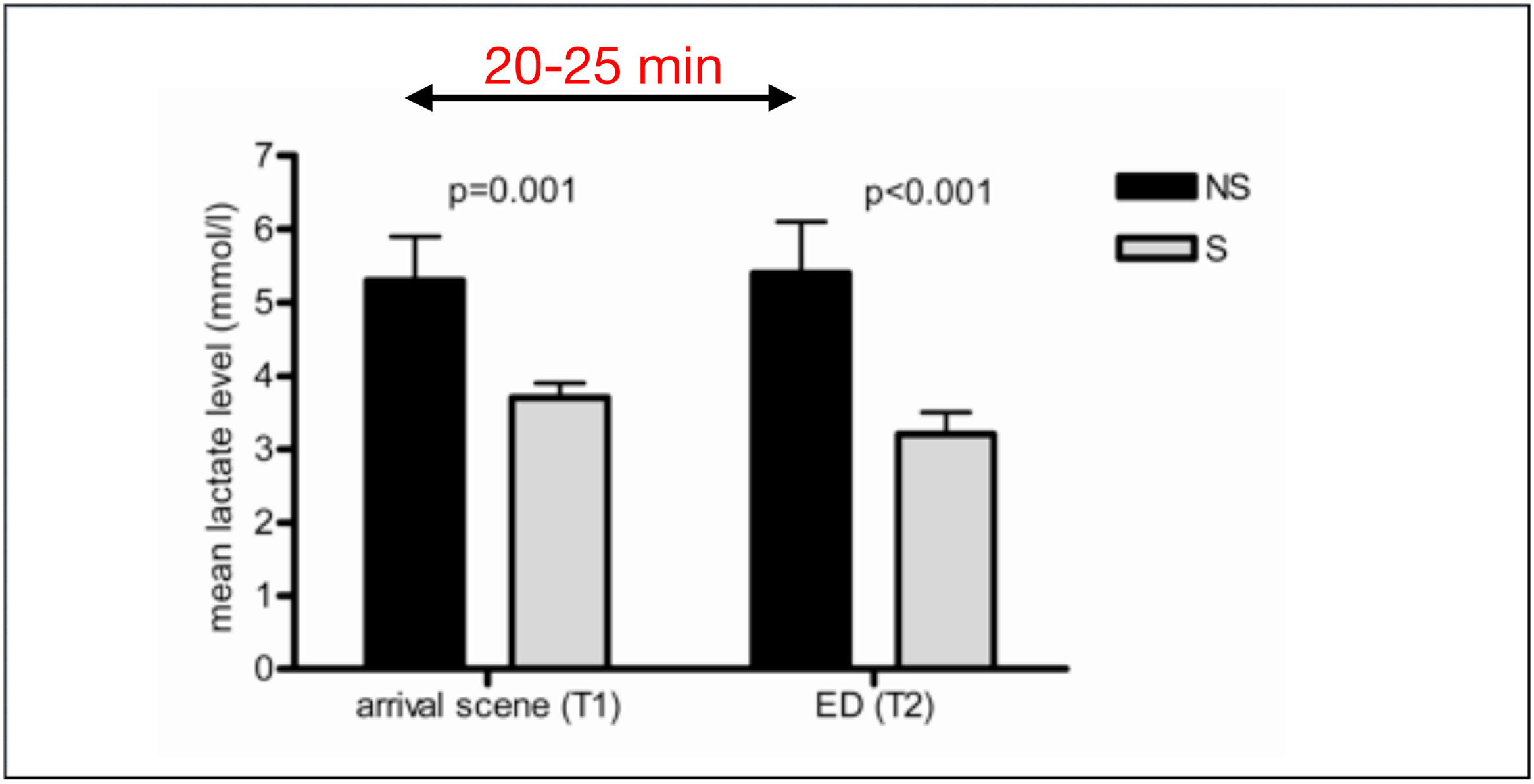
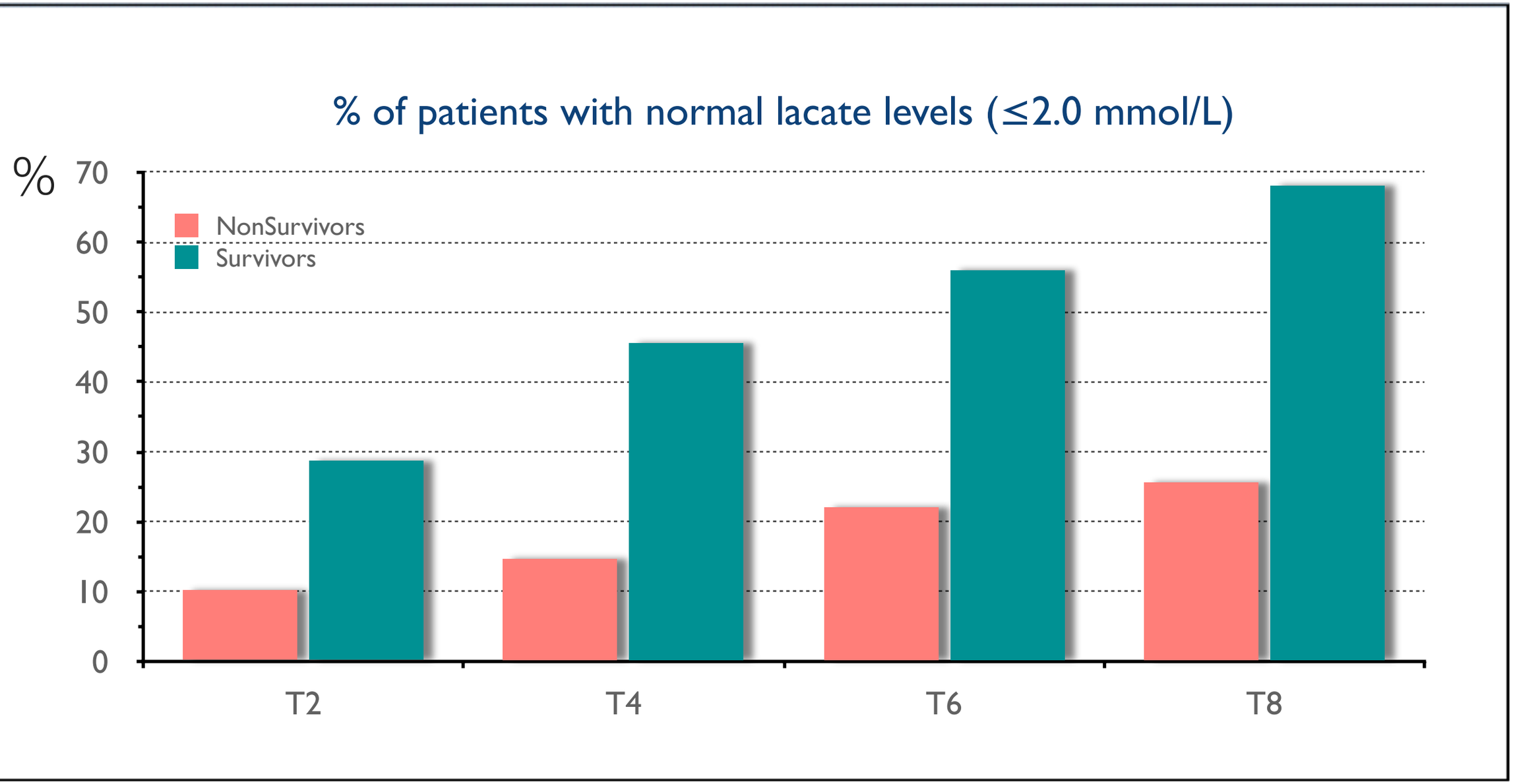


Critical Care 2008, **12**:R160 (doi:10.1186/cc7159)

Change in lactate levels

data from MC lactate study



Jansen et al. Am J Respir Crit Care Med 2010;182:752-761

Conclusions

- The metabolic process of lactate production is fast
- When metabolic production ceases lactate levels fall rapidly
- Lactate levels in shock rise rapidly
- Clearance of exogenous lactate is limited, though still fast, in sepsis, liver dysfunction of SIRS
- Treatment of hypo perfusion results in a rapid decrease in lactate levels
- In sepsis there may be a flow-dependent phase in lactate clearance that may have important clinical consequences

EGDT

lactate

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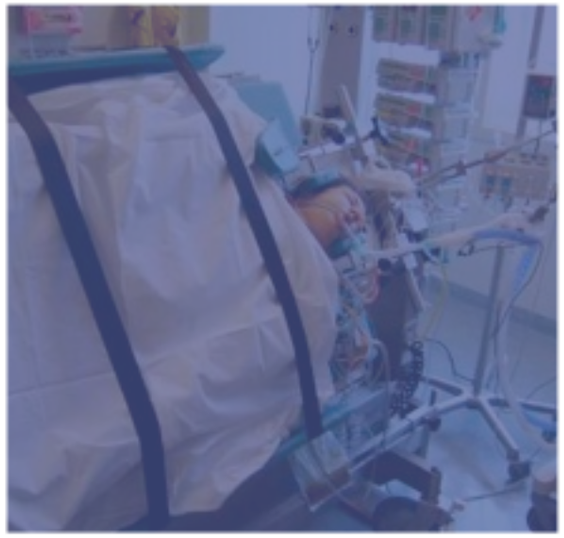

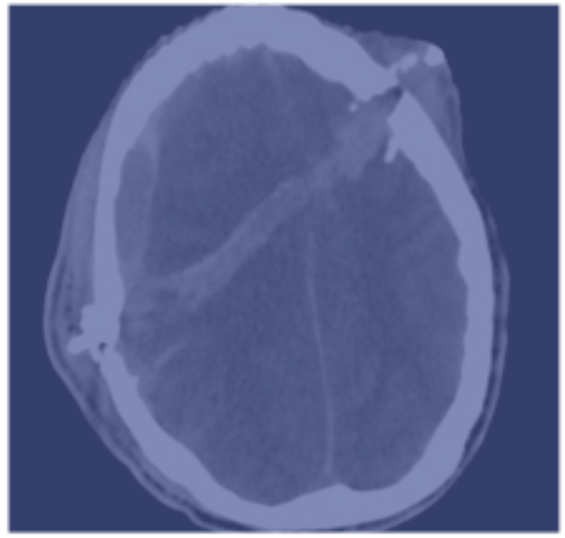

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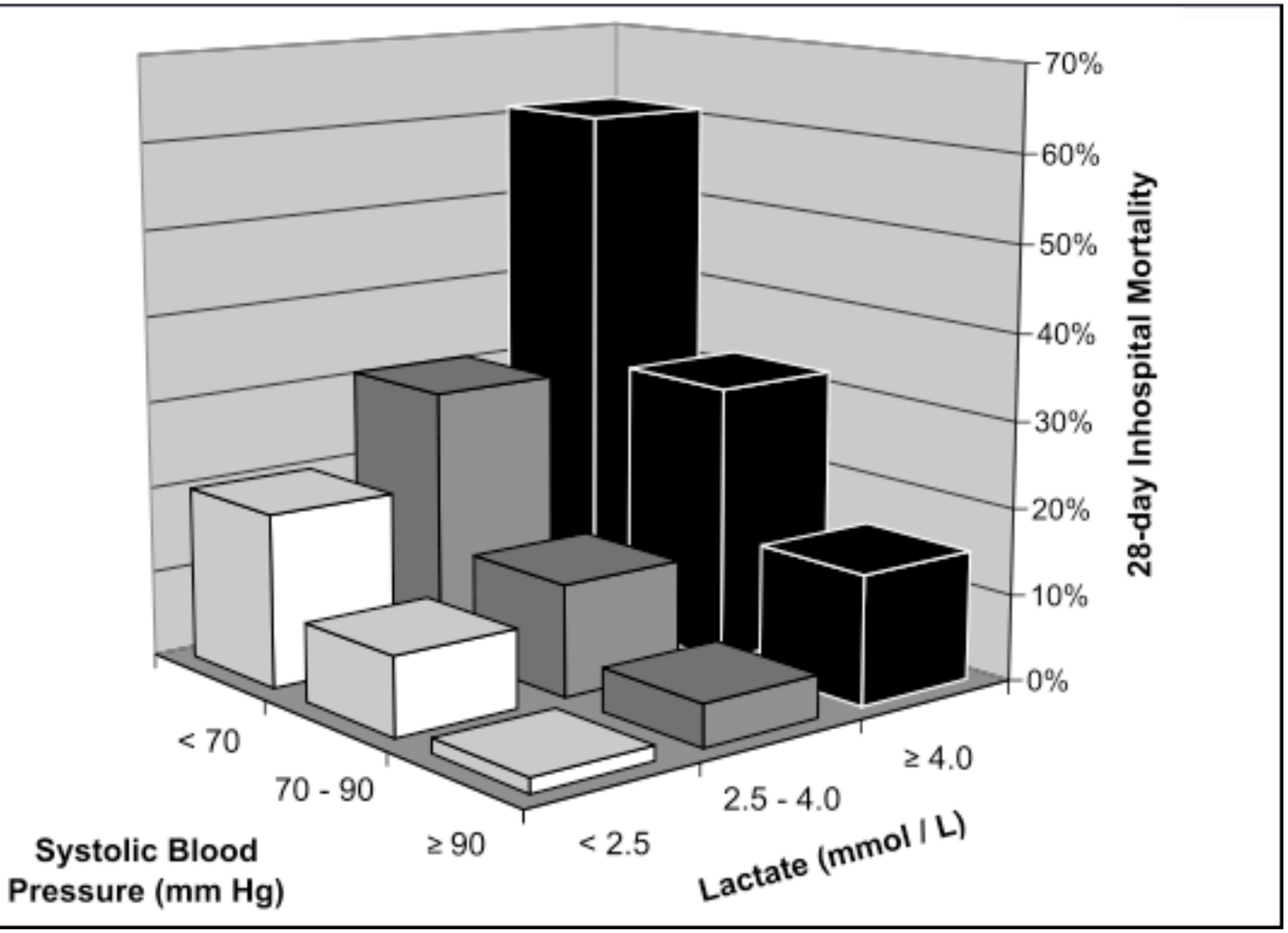
Intensive Care Med (2007) 33:1892–1899
DOI 10.1007/s00134-007-0680-5

ORIGINAL

Michael D. Howell
Michael Donnino
Peter Clardy
Daniel Talmor
Nathan I. Shapiro

Occult hypoperfusion and mortality in patients with suspected infection

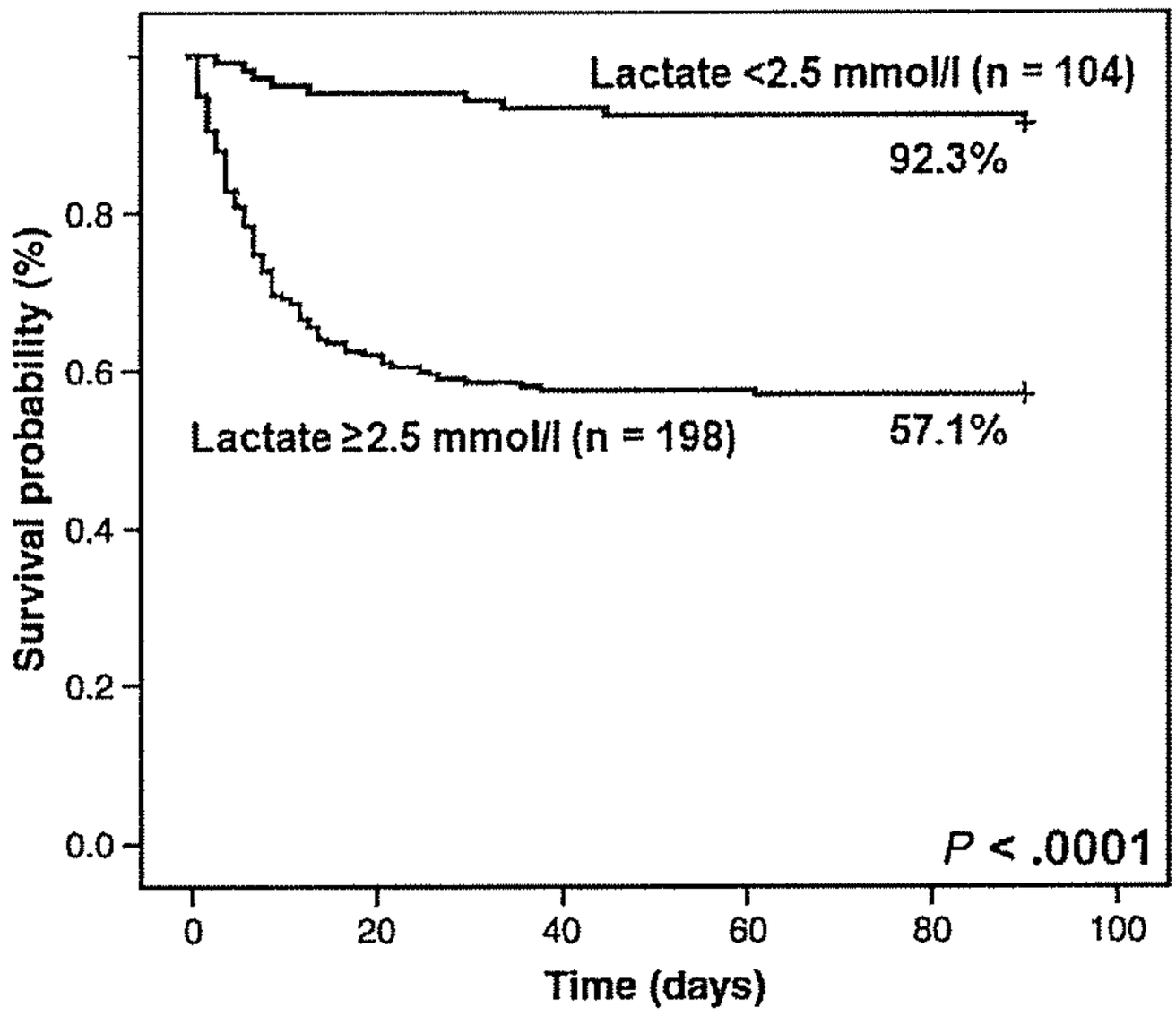
Emergency Room



Persistent sepsis-induced hypotension without hyperlactatemia: Is it really septic shock?

Glenn Hernandez*, Ricardo Castro, Carlos Romero, Claudio de la Hoz, Daniela Angulo, Ignacio Aranguiz, Jorge Larrondo, Andres Bujes, Alejandro Bruhn

J Crit Care 2011;26:435



Persistent sepsis-induced hypotension without hyperlactatemia may not constitute a real septic shock.

Our results support the need to review the current definition of septic shock.

Hyperlactatemia could represent an objective parameter worth to be explored as a potential diagnostic criterion for septic shock

MULTICENTER STUDY OF EARLY LACTATE CLEARANCE AS A DETERMINANT OF SURVIVAL IN PATIENTS WITH PRESUMED SEPSIS

Ryan C. Arnold,* Nathan I. Shapiro,† Alan E. Jones,‡ Christa Schorr,§ Jennifer Pope,† Elisabeth Casner,‡ Joseph E. Parrillo,§ R. Phillip Dellinger,§ Stephen Trzeciak,* and on behalf of the Emergency Medicine Shock Research Network (EMShockNet) Investigators

SHOCK, Vol. 32, No. 1, pp. 35–39, 2009

OR_{death}: 4.9 (1.5-15.9)

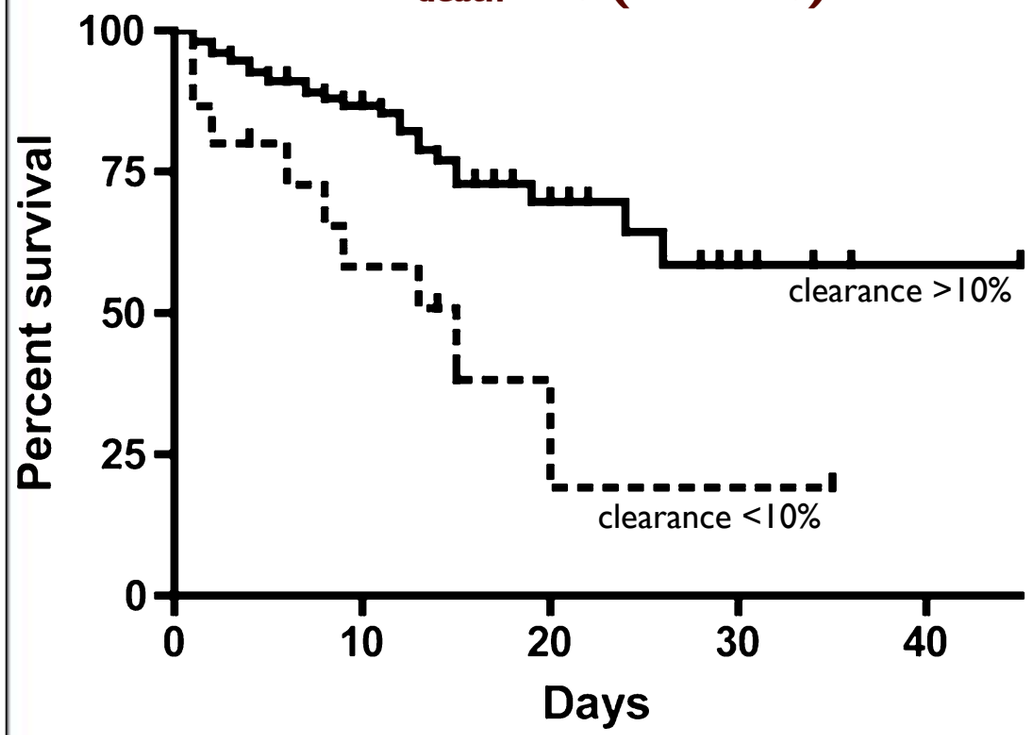
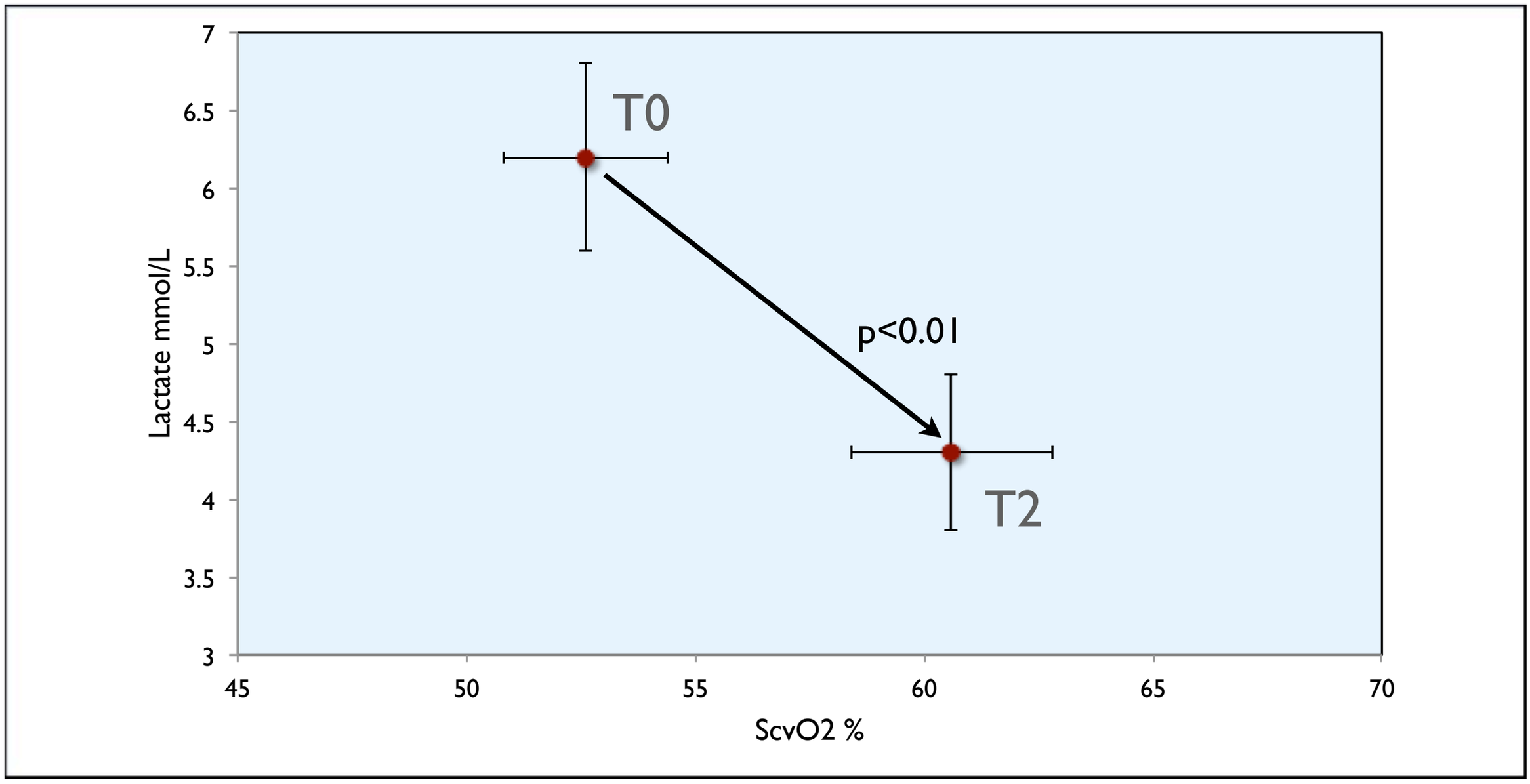


TABLE 4. **Survivors versus nonsurvivors (n = 166)**

	Survivors (n = 128)	Nonsurvivors (n = 38)	*P*
Age, mean (SD), y	66 (15)	66 (16)	1.00
SBP <90 mmHg despite i.v. fluids, n (%)	42 (33)	21 (55)	0.02
Initial serum lactate, mean (SD)	4.3 (2.6)	4.7 (2.8)	0.41
Serial serum lactate, mean (SD)	2.2 (1.6)	3.6 (2.8)	<0.001
Individual organ failure, n (%)			
Cardiovascular	42 (33)	21 (55)	0.02
Pulmonary	20 (16)	8 (21)	0.64
Renal	43 (34)	11 (29)	0.70
Hepatic	9 (7)	5 (13)	0.40
Coagulopathy	15 (12)	8 (21)	0.26
Total SOFA score, mean (SD)	3.6 (2.6)	3.7 (2.7)	0.84
Continuous $ScvO_2$ monitoring, n (%)	112 (87)	36 (95)	0.28
$ScvO_2$ ≥70% achieved, n (%)	99 (88)	26 (72)	0.03
Lactate clearance ≥10%, n (%)	122 (95)	29 (76)	0.001

$ScvO_2$ and Lactate

$ScvO_2 \leqq 60\%$ § n=15



Early Lactate-Guided Therapy in Intensive Care Unit Patients

A Multicenter, Open-Label, Randomized Controlled Trial

Tim C. Jansen[1], Jasper van Bommel[1], F. Jeanette Schoonderbeek[3], Steven J. Sleeswijk Visser[4], Johan M. van der Klooster[5], Alex P. Lima[1], Sten P. Willemsen[2], and Jan Bakker[1], for the LACTATE study group*

[1]Department of Intensive Care, Erasmus MC University Medical Centre, Rotterdam, The Netherlands; [2]Department of Biostatistics, University Medical Centre Rotterdam, Rotterdam, The Netherlands; [3]Department of Intensive Care, Ikazia Hospital, Rotterdam, The Netherlands; [4]Department of Intensive Care, Reinier de Graaf Hospital, Delft, The Netherlands; and [5]Department of Intensive Care, St. Franciscus Gasthuis, Rotterdam, The Netherlands

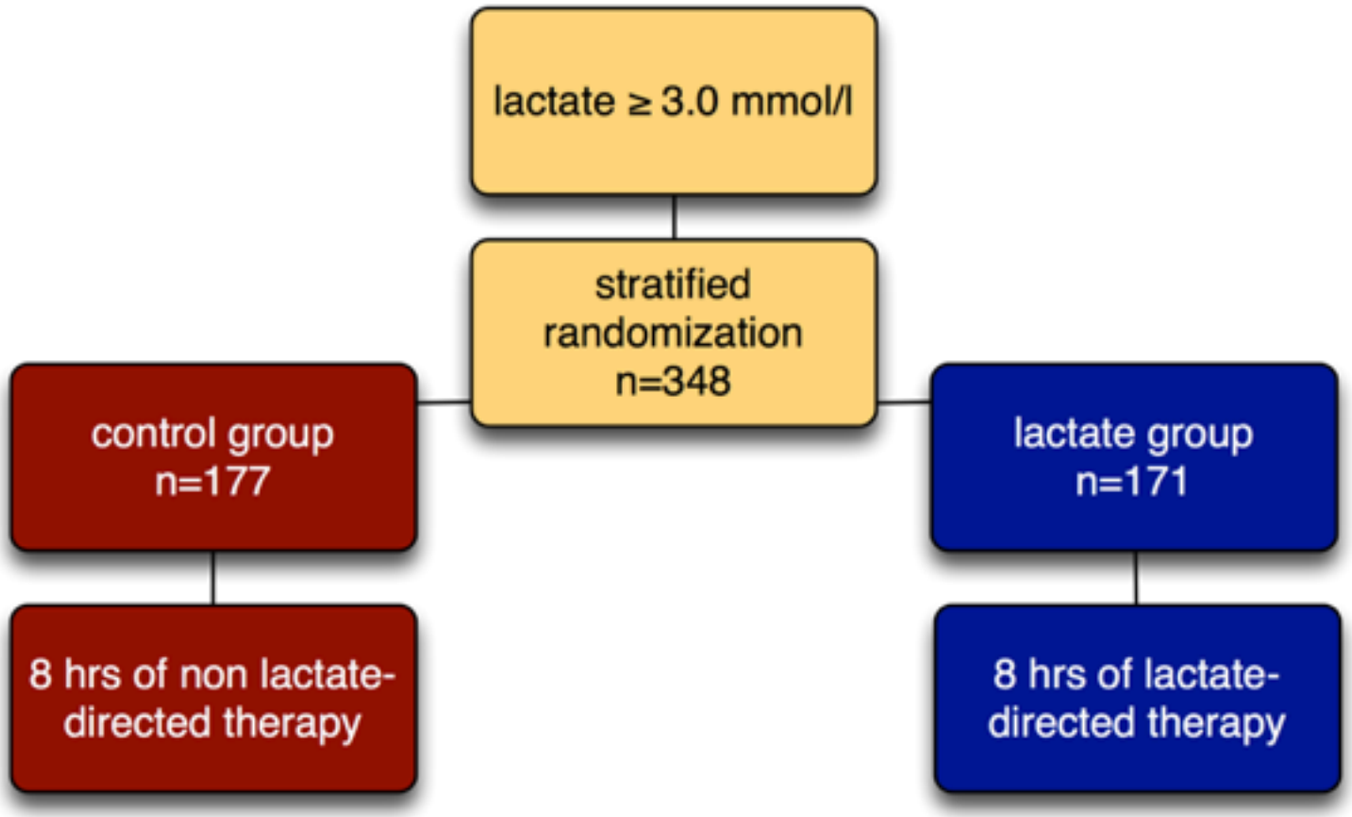
LACTATE study group

D Gommers[1], B v.d Hoven[1], W Thijsse[1], C Groeninx Van Zoelen[1], J Weigel[1], P Gerritsen[1], B v.d Berg[1], J Lenoble[1], D Reis Miranda[1], J Rischen[1], B. Dellen[1], M Zijnen[1], C Ince[1], E Kompanje[1], C Birsak[1], H de Geus[1], J Epker[1], M Muller[1], W Mol[1], W in t Veld[1], C. Bruning[1], E forman[1], E Klijn[1], P Mulder[2], M Middelkoop[3], J Zandee[3], Wilma Smit[3], G Burggraaff[3], I Meynaar[4], L Dawson[4], M v Spreuwel[4], P Tangkau[4], E Salm†[4 5], M. Ruijters[4], N Verburg[4], R. Kleijn[4], A Rietveld[5], P de Feiter[5] and A Brouwers[5]

Ikazia hospital Rotterdam
St. Fransiscus Gasthuis hospital Rotterdam
Reinier de Graaf hospital Delft
Erasmus MC Rotterdam

ClinicalTrial.gov number NCT00270673

Am J Respir Crit Care Med Vol 182. pp 752–761, 2010



No lactate levels
standard therapy

every 2h lactate level
goal: ⬇20%
$ScvO_2$ mandatory
goal > 70%

Conclusion

- Therapy aimed to optimize the balance between oxygen demand and oxygen supply **($ScvO_2$)** and decrease lactate levels by 20% /2h for 8h in patients with increased lactate levels reduced in-hospital mortality **(when corrected for predefined risk factors)** and it decreased organ failure and use of health care resources.