AER 2019

AER

ACTUALITÉS EN RÉANIMATION

25ème AER : 19 & 20 novembre 2020

COMMENT INTERPRÉTER UNE HYPERLACTATÉMIE

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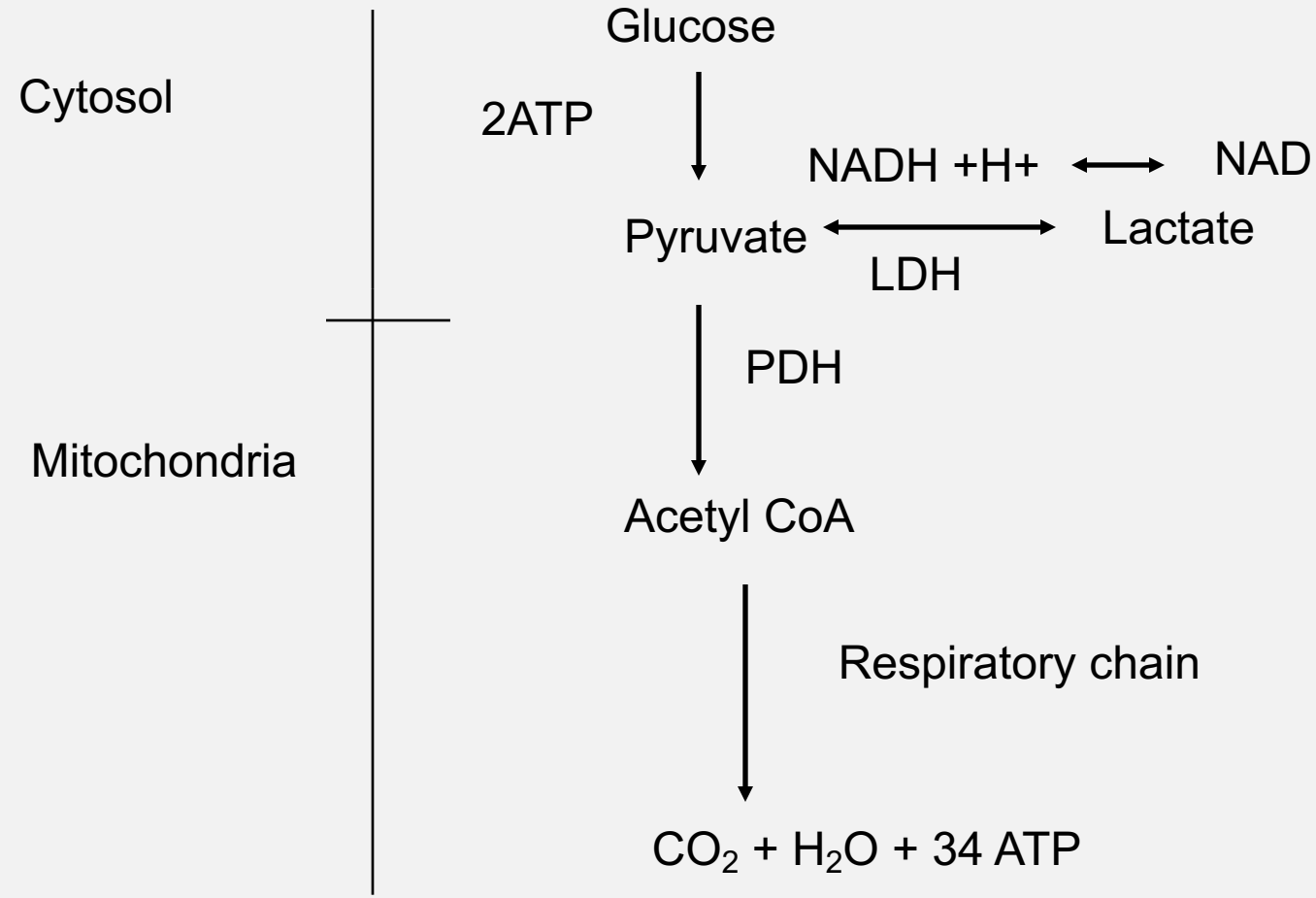
SUMMARY OF NORMAL LACTATE METABOLISM

- **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**

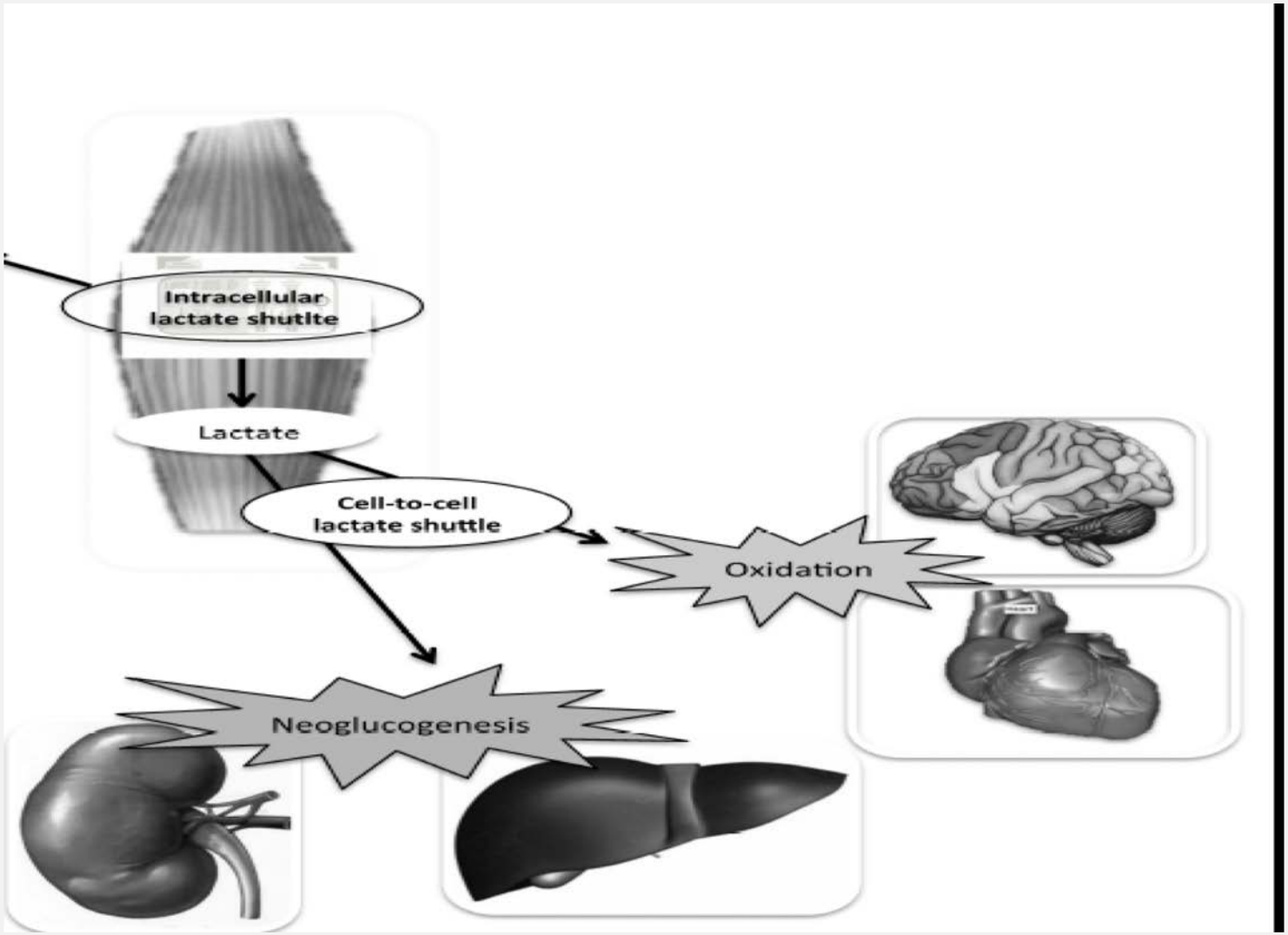
- **Lactate released into the bloodstream is transported to the liver and the kidney where it is subsequently metabolised**
- **Oxydation (50% at rest and 75 % during exercise) and neoglucogenesis**

SIMPLIFIED GLYCOLYSIS

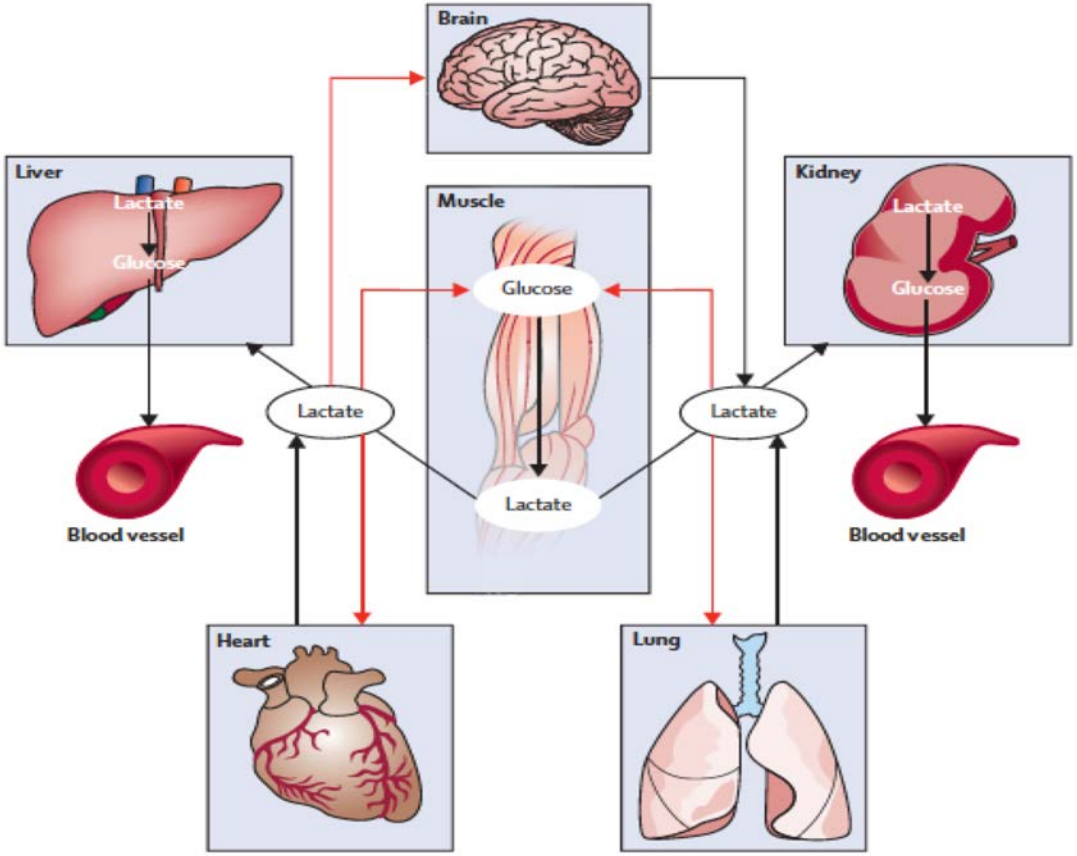


Lactate therefore increases when production of pyruvate exceeds its utilization by the mitochondria

REMOVAL : OXIDATION AND CORI CYCLE

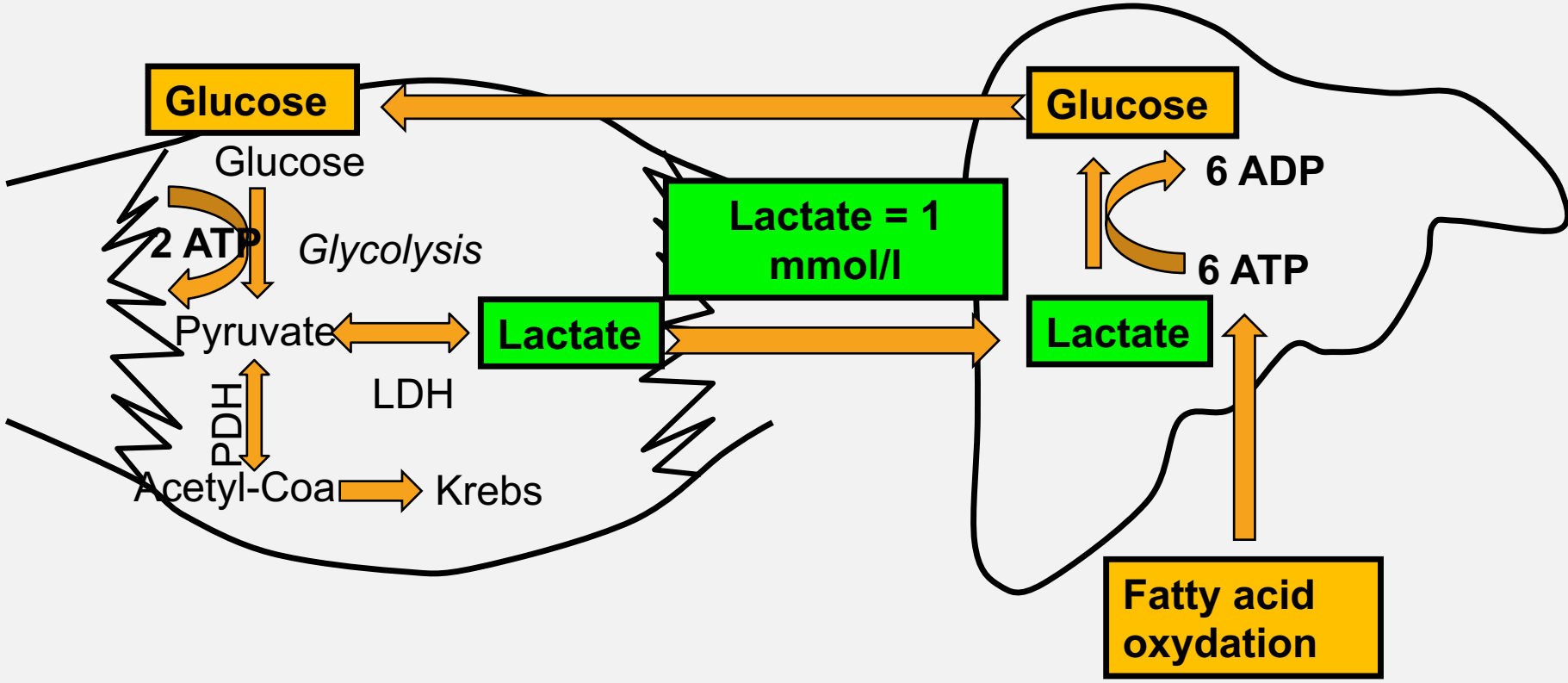


CELL-TO-CELL LACTATE SHUTTLE

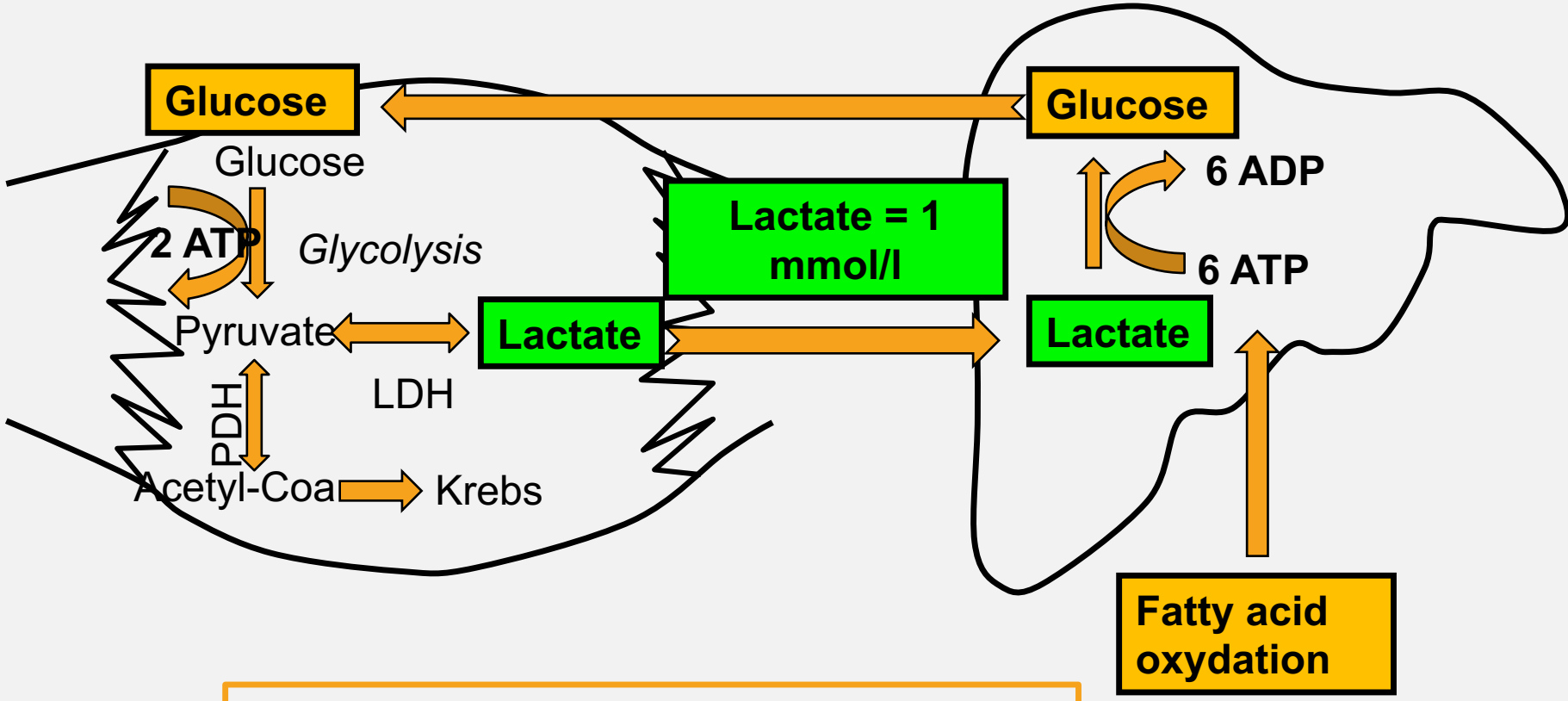


- **Hypothesis : Lactate is not only produced in muscle and used within the same myocyte**
- **Lactate serves as a substrate in highly oxidative cells (eg, heart and brain) or contributes to gluconeogenesis (in both the liver and kidney)**

CORI CYCLE



- Lactate reaches the liver where it enters the Cori cycle and becomes glucose
- The energy for such gluconeogenesis is supplied by beta-oxidation of fatty acids

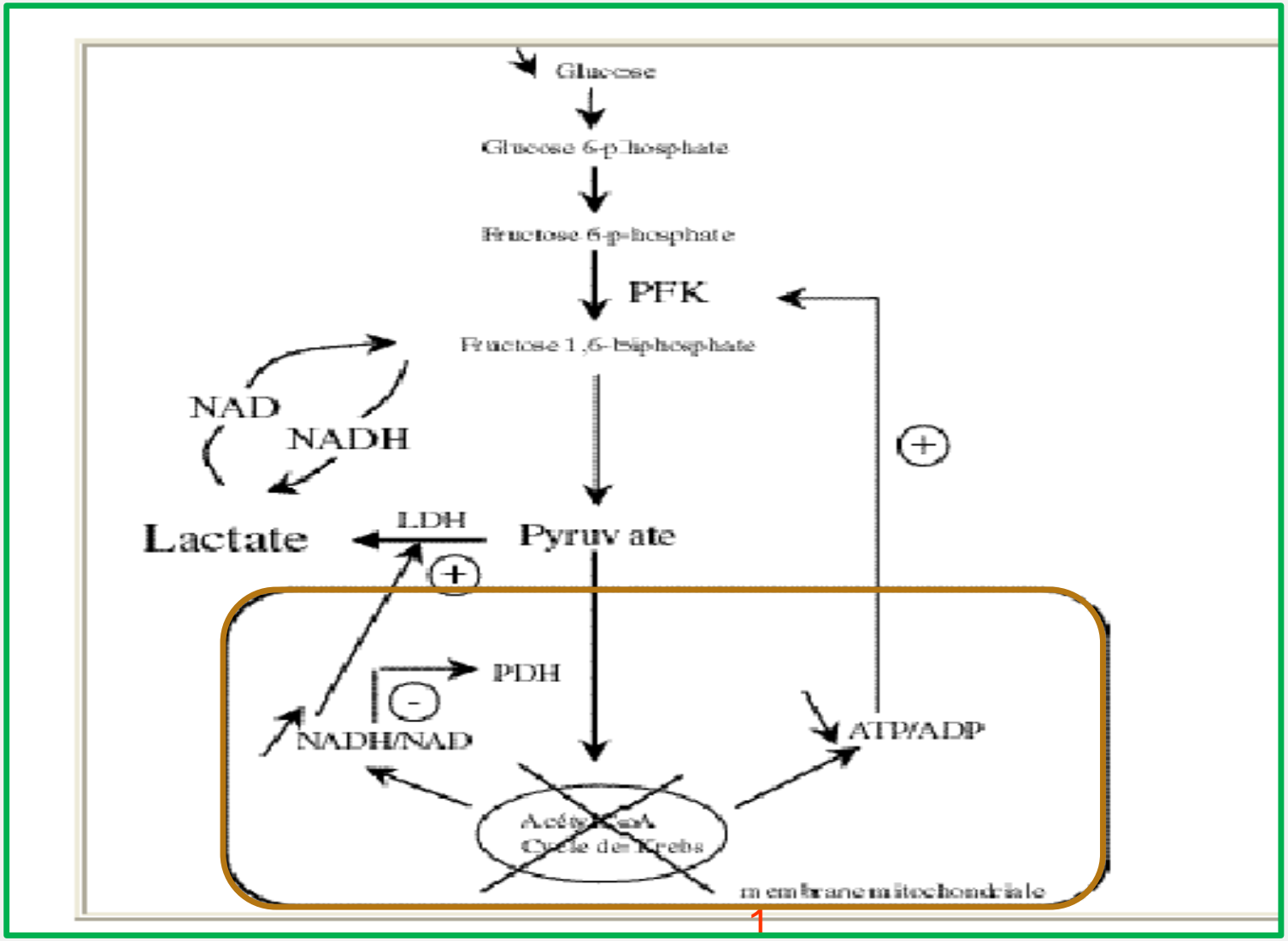


- **Conversion of slow energy stored as fat into fast energy that is readily available as glucose.**
- **Energy is used to sustain the increased glycolytic flux necessary to meet the metabolic demands of severe sepsis**

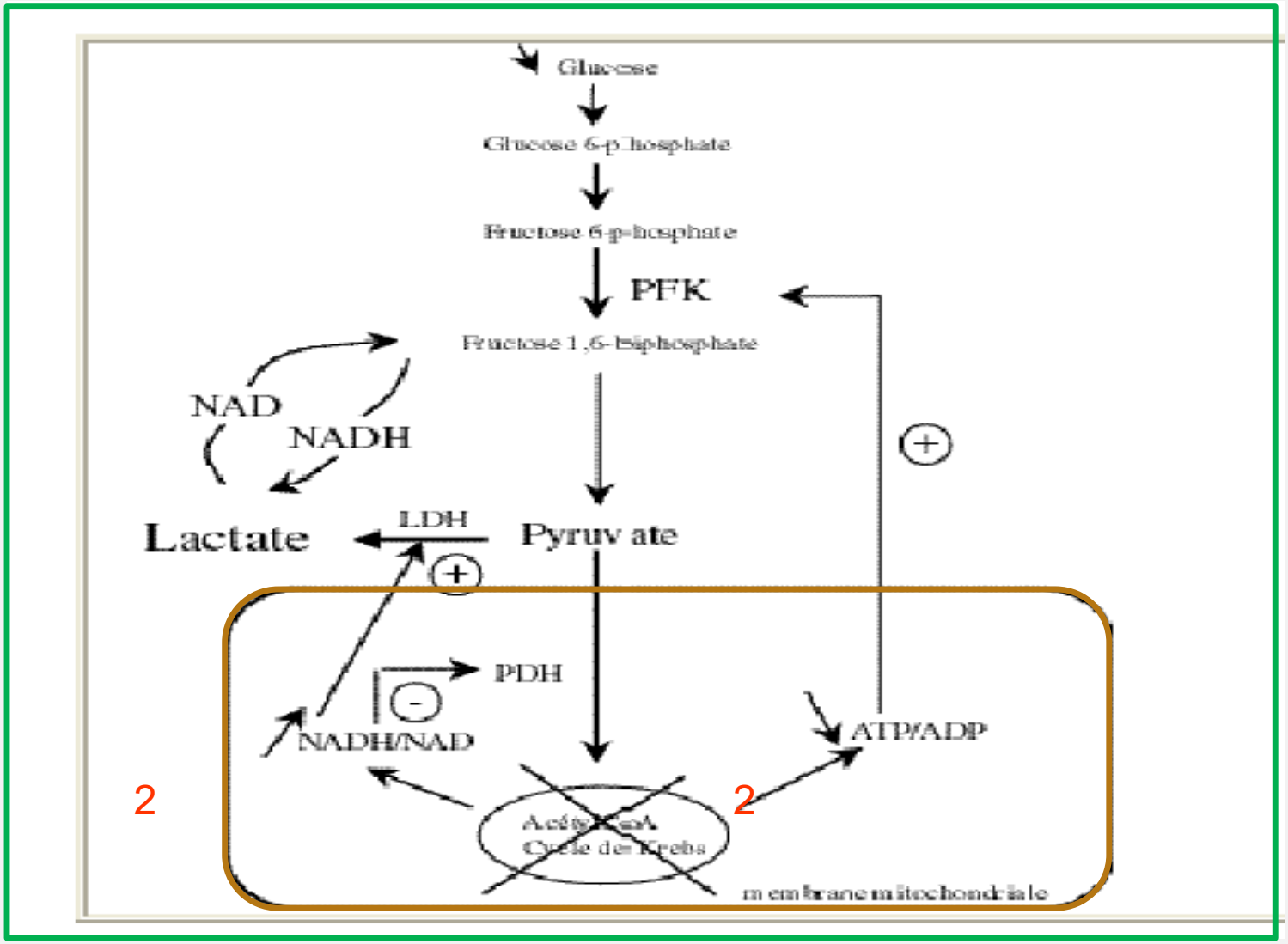
LACTATE AND SHOCK

THE CLASSICAL PARADIGM

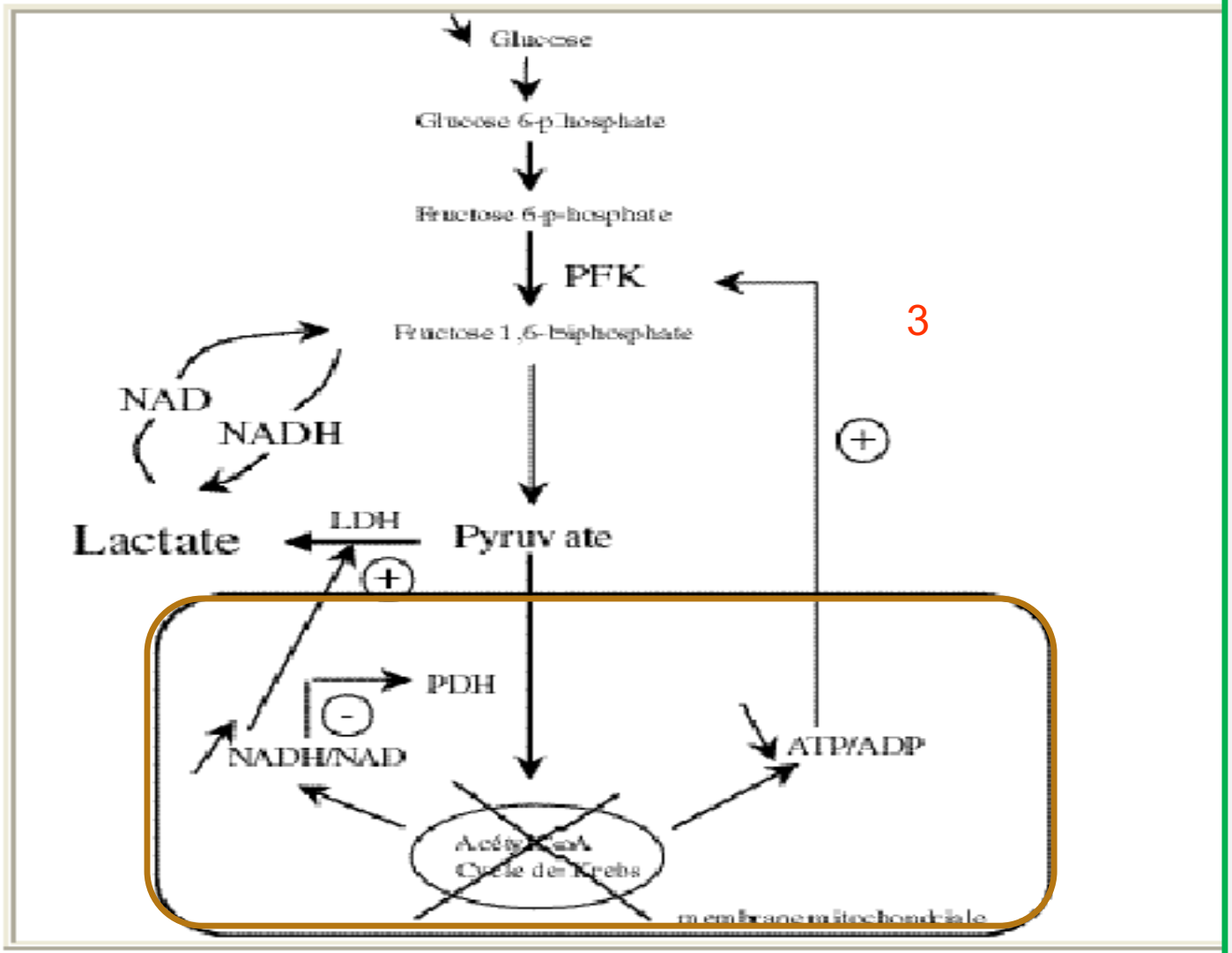
Hyperlactataemia during shock is a marker of tissue hypoperfusion or tissue hypoxia, and is indicative of the onset of anaerobic glycolysis



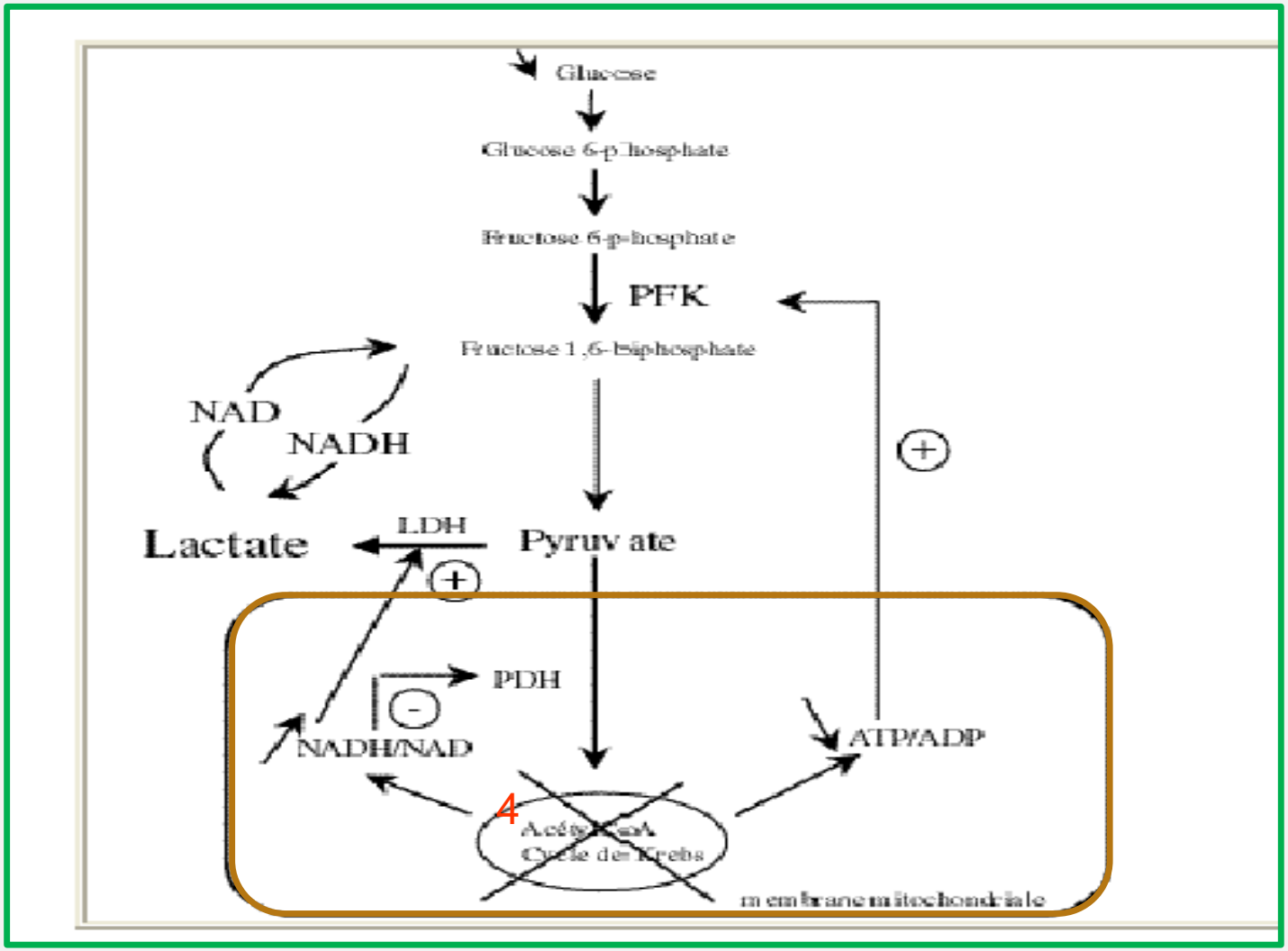
1. Absence of O_2 : stoppage or decrease in ATP production by mitochondrial electron transfer



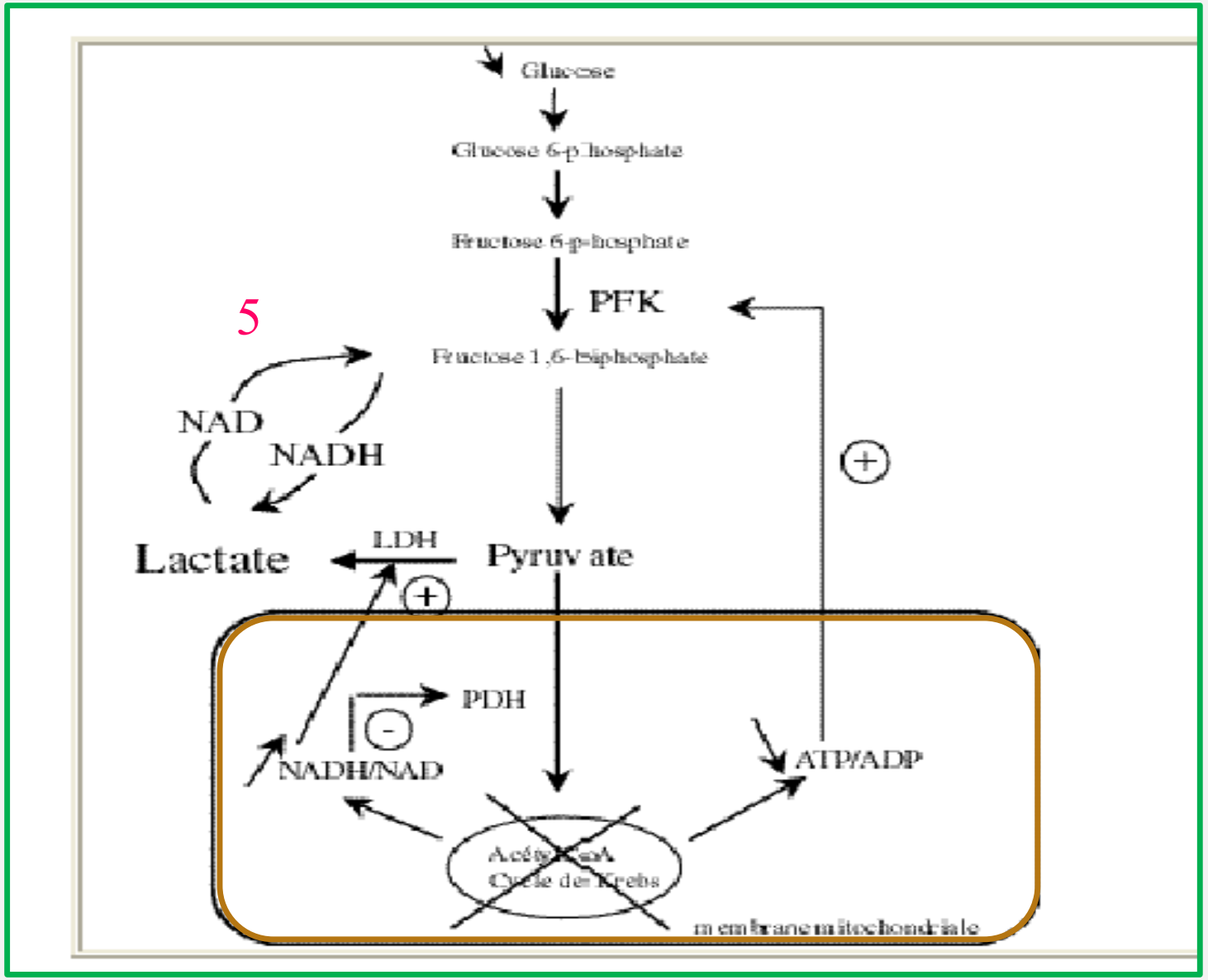
2. Decrease in ATP/ADP ratio and increase in NADH/NAD ratio



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



4. The increase in NADH/NAD ratio decreases in PDH and **increases** 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

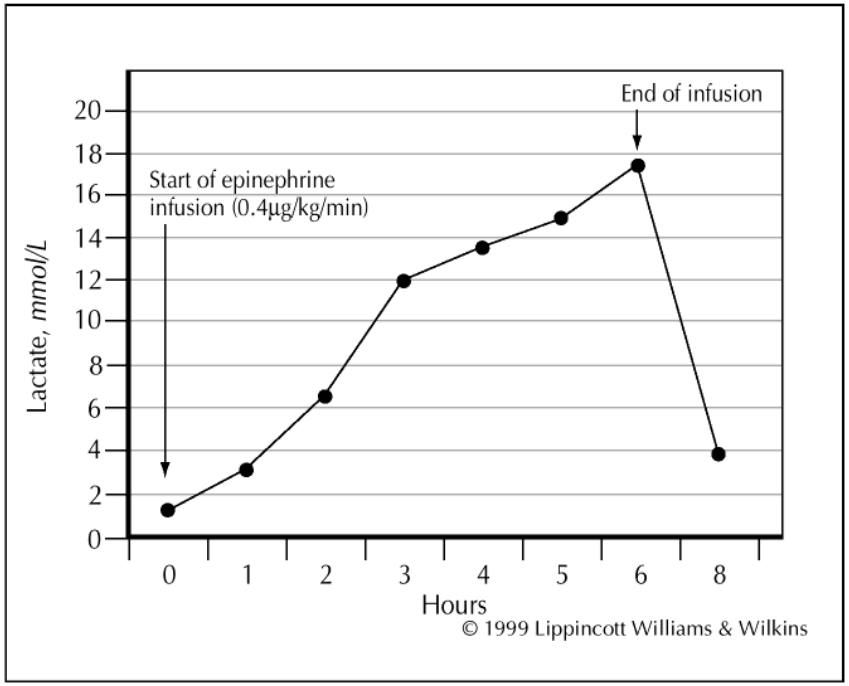
THE NEW PARADIGM

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 high.
- 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

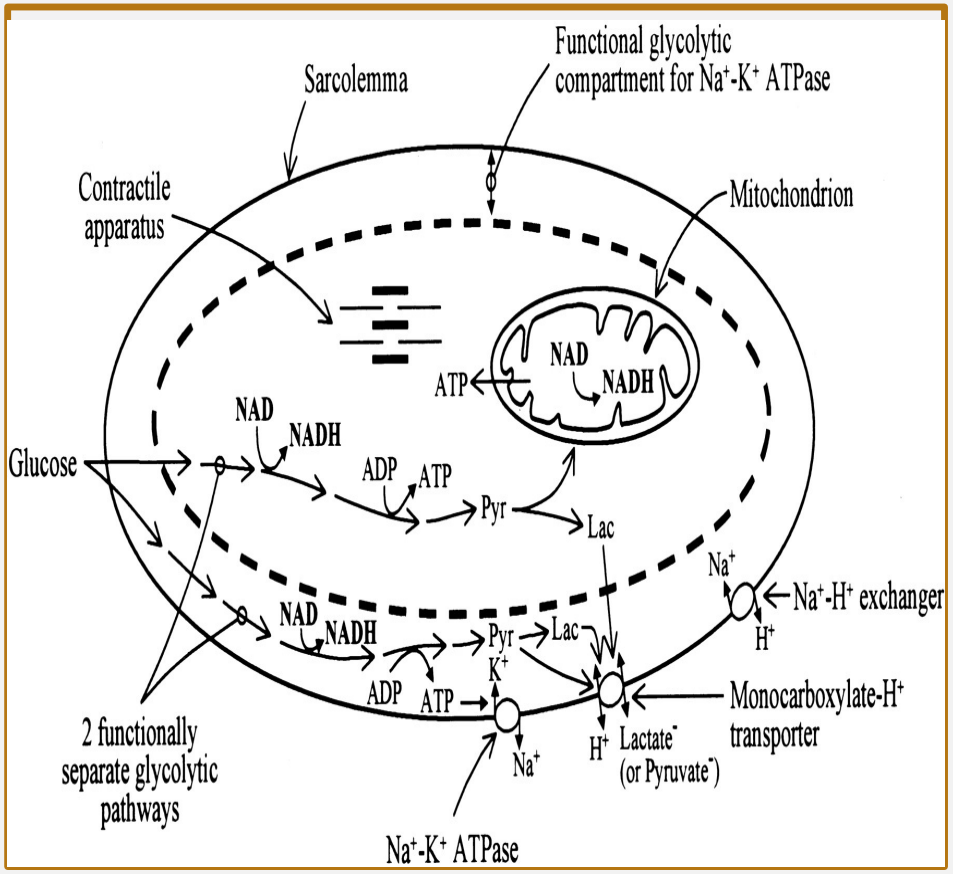
RELATIONSHIP BETWEEN EPINEPHRINE AND LACTATE



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.

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

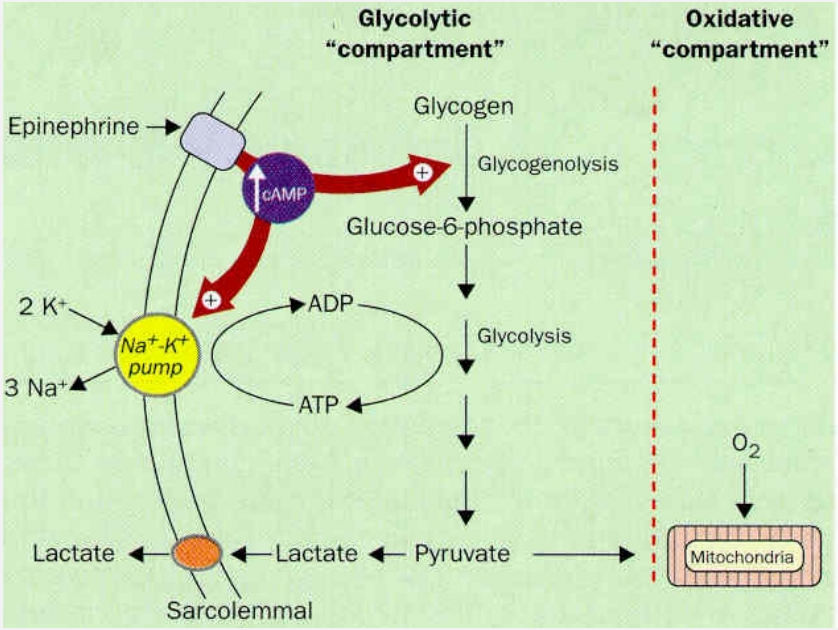
GLYCOLYSIS COMPARTMENTALISATION AND NA+-K+ASE ACTIVITY



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

Aerobic production of lactate under epinephrine stimulation

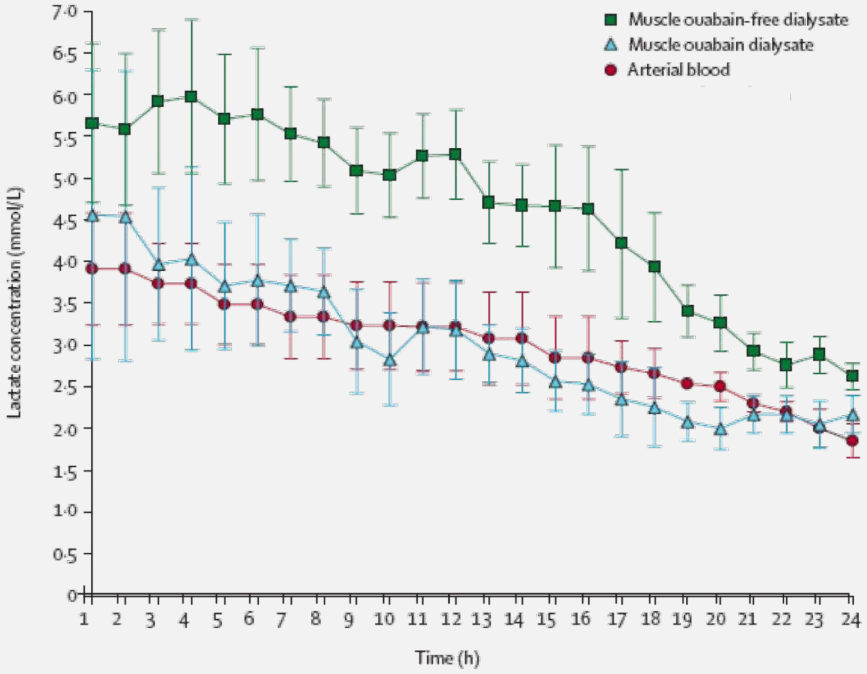
- Epinephrine binds to muscle adrenergic β 2 receptors and raises AMP production
  - Stimulation of glycogenolysis and ATP production
  - ATP is used to fuel the sarcolemmal Na+-K+ATPase that consumes ATP and increases ADP level
  - ADP increases PFK activity and thus pyruvate production
- Epinephrine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



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

DURANT L'ÉTAT DE CHOC LA PRODUCTION DE LACTATE N'EST PAS QU'HYPOXIQUE

Prospective, monocentrique, 14 choc septique, micro-dialyse, mesure du lactate musculaire en présence ou non d'inhibiteurs



Lactate musculaire > lactatémie

Production musculaire bloquée par la ouabaïne (inhibiteur NA/K ATPase)

Production dépendante de la stimulation β2 adrénergique

Production indépendante de l'hypoxie

Levy al. Lancet 2005

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

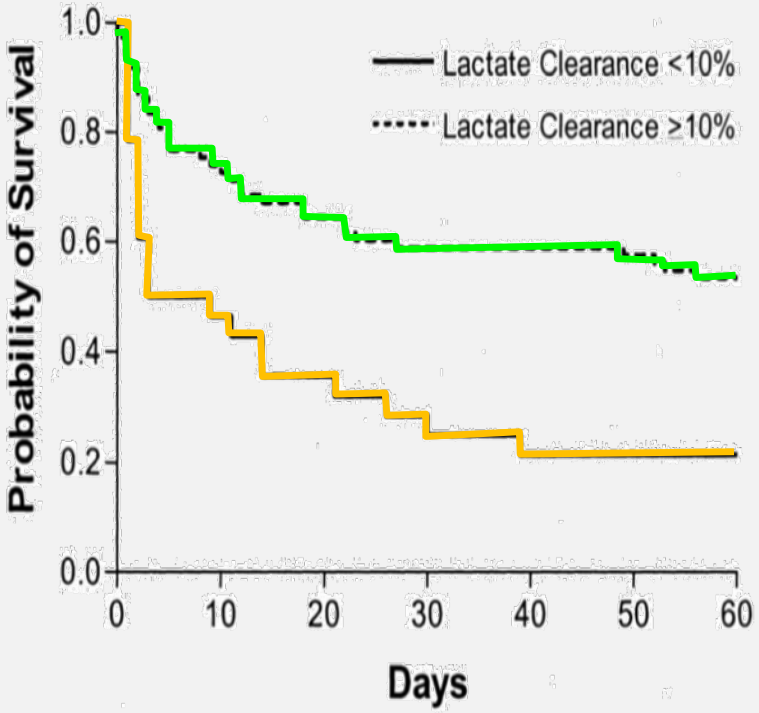
LACTATE CLEARANCE

Observational study, 111 patients with sepsis or septic shock, 6H clearance , D60 mortality

Lactate clearance

$$= \frac{(\text{Lactate}^{\text{ED Presentation}} - \text{Lactate}^{\text{Hour 6}}) \times 100}{\text{Lactate}^{\text{ED Presentation}}}$$

Variable	OR (95% CI)	*p* Value
Septic shock	2.473 (0.927–6.600)	.07
Platelet	0.999 (0.994–1.004)	.69
Prothrombin time	1.140 (0.988–1.315)	.07
Albumin	0.569 (0.267–1.212)	.14
Total bilirubin	1.045 (0.855–1.276)	.67
Lactate	1.057 (0.945–1.182)	.34
Lactate clearance	0.989 (0.978–0.999)	.04[a]



Nguyen et al. Crit care med 2004

Hernandez et al. Annals of Intensive Care 2014, 4:30
http://www.annalsofintensivecare.com/content/4/1/30

Annals of Intensive Care
a SpringerOpen Journal

RESEARCH Open Access

When to stop septic shock resuscitation: clues from a dynamic perfusion monitoring

Glenn Hernandez[1*], Cecilia Luengo[2], Alejandro Bruhn[1], Eduardo Kattan[1], Gilberto Friedman[3], Gustavo A Ospina-Tascon[4], Andrea Fuentealba[1], Ricardo Castro[1], Tomas Regueira[1], Carlos Romero[2], Can Ince[5] and Jan Bakker[5]

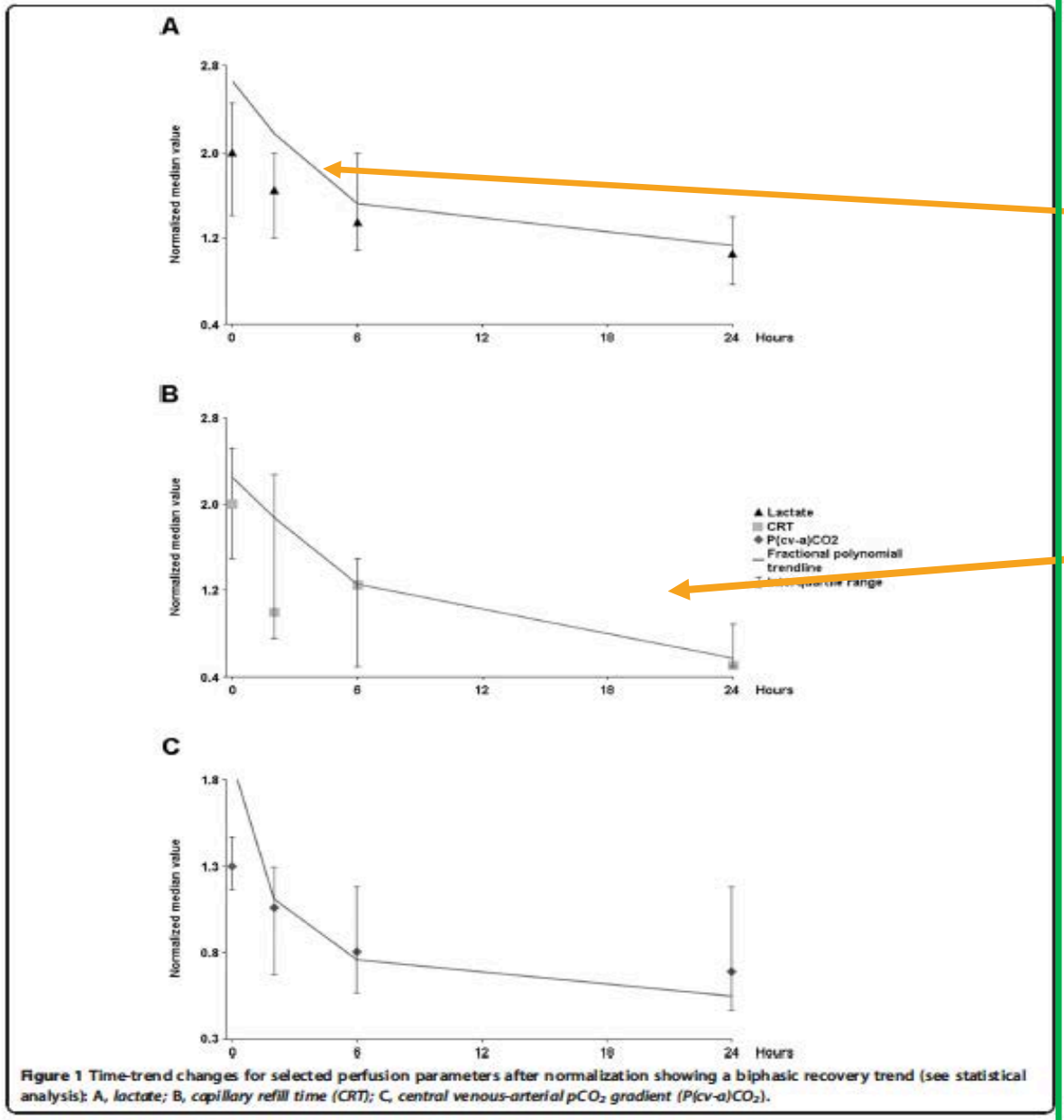


Figure 1 Time-trend changes for selected perfusion parameters after normalization showing a biphasic recovery trend (see statistical analysis): A, *lactate*; B, *capillary refill time (CRT)*; C, *central venous-arterial pCO_2 gradient ($P(cv\text{-}a)CO_2$)*.

To-T6 hours
Flow dependant part

T6-T24 hours
Not flow dependant
Metabolic part?

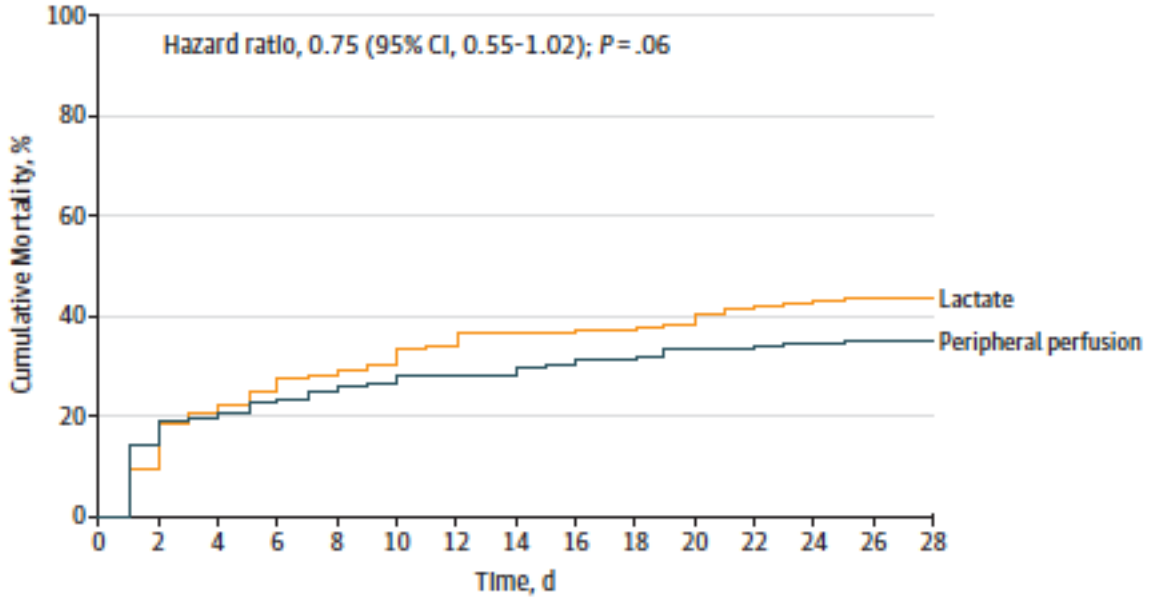
Biphasic response with an initial rapid improvement, followed by a much slower trend thereafter

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

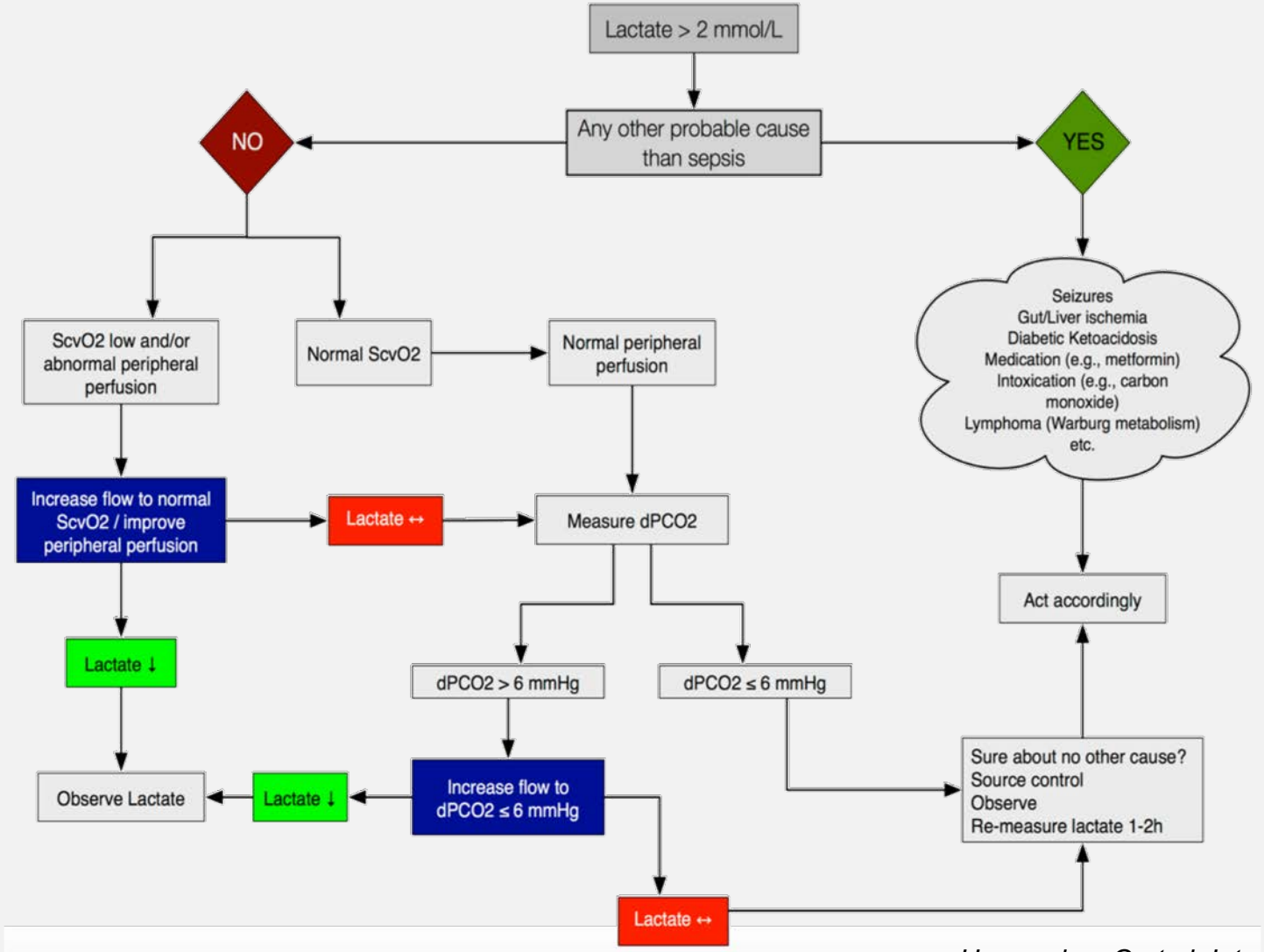
Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock

The ANDROMEDA-SHOCK Randomized Clinical Trial

Glenn Hernández, MD, PhD; Gustavo A. Ospina-Tascón, MD, PhD; Lucas Petri Damiani, MSc; Elisa Estenssoro, MD;



LACTATE MONITORING YES, BUT NOT ALONE



Hernandez G et al. Intensive Care Med 2018

ACIDOSE LACTIQUE DE TYPE B

ETIOLOGIES POSSIBLES

TABLE 1. Etiologies of Type B Lactic Acidosis*

- Malignancy
- Other medical diseases
  - Liver failure
  - Renal failure
  - HIV
  - Diabetes mellitus
- Medications or toxins
  - Metformin or historically phenformin
  - Nucleoside reverse transcriptase inhibitors
    - Stavudine
    - Zidovudine
    - Lamivudine
  - Salicylates
  - Isoniazid
  - Alcohol
  - Cyanide
- Hereditary disorders
  - Glucose 6-phosphate deficiency (type I glycogenolysis)
  - Fructose-1,6-diphosphatase deficiency
  - Pyruvate carboxylate deficiency
  - Pyruvate dehydrogenase deficiency
  - Oxidative phosphorylation deficiencies

LACTATE ET CONVULSION

Arterial blood samples 5–60 min after the convulsions (e.g. lactate-1) and 30–60 min after the first sample (e.g. lactate-2).

Pt	pH-1	pH-2	pO_2-1 torr [kPa]	pO_2-2 torr [kPa]	pCO_2-1 torr [kPa]	pCO_2-2 torr [kPa]	Bicarbonate-1 mmol l^{-1}	Bicarbonate-2 mmol l^{-1}	BE-1 mmol l^{-1}	BE-2 mmol l^{-1}	Lactate-1 mmol l^{-1}	Lactate-2 mmol l^{-1}
1	6.9	7.12	218 [29]	210 [28]	26 [3.5]	33 [4.4]	5.7	10.5	−23	−17	22.4	15.1
2	7.25	7.42	74 [9.9]	501 [66.8]	35 [4.7]	37 [4.9]	16.2	24.6	−10.3	−0.1	12.3	3.5
3	6.8	7.32	118 [15.7]	68 [9.0]	71 [9.4]	49 [6.5]	9.0	23.0	−22.4	−0.9	?	1.6
4	7.41	7.42	107 [14.3]	113 [15.0]	39 [5.3]	44 [5.9]	25.7	28.0	1.5	4.3	3.8	1.4
5	7.12	7.35	71 [9.4]	61 [8.1]	36 [4.8]	34 [4.5]	11.4	18.5	−16.1	−6.0	15.9	7.0

Lactate reference range: 0.5–1.6 mmol l^{-1} (10).

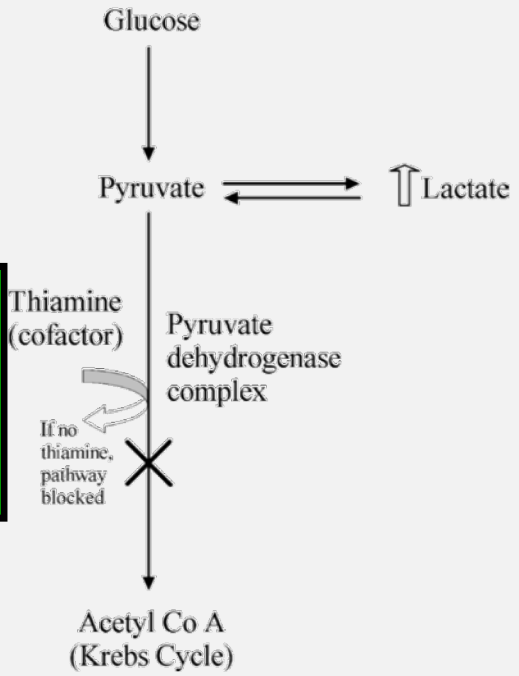
Hyperlactatémie très élevée, clairance en 60 min

Lipka et al. Acta Anaesthesiol Scand 2003

LACTATE ET CANCER

Age (yr)/ Sex	Diagnosis	Onset	Hepatomegaly	Chemo/ Thiamine Given?	LA Resolved?
3/M	Acute monocytic leukemia	R	Yes	Thiamine	Yes
3/M	Acute lymphoblastic leukemia	R	Yes	Thiamine	Yes
26/M	Burkitt Lymphoma	D	No	Chemo	No
70/M	Diffuse large B-cell lymphoma	D	Yes	Chemo	Yes
64/F	Large B-cell lymphoma	D	No	Chemo	No
11 mo/F	B-cell leukemia/ lymphoma	D	No	Thiamine	Yes
60/F	T-cell lymphoma	D	Yes	Chemo	No
48/M	Diffuse large cell lymphoma	D	Yes	Chemo	No
21/M	Undifferentiated lymphoma	D	Yes	Chemo	No
53/F	Anaplastic large cell lymphoma	D	Yes	Chemo	No
7/M	Acute lymphoblastic leukemia	D	Yes	Chemo	Yes
29/M	T-cell acute lymphoblastic leukemia	R	No	Chemo	Yes
74/M	Burkitt lymphoma	D	No	Chemo	No
24/M	B-cell immunoblastic lymphoma –> AML	D	No	Chemo	No

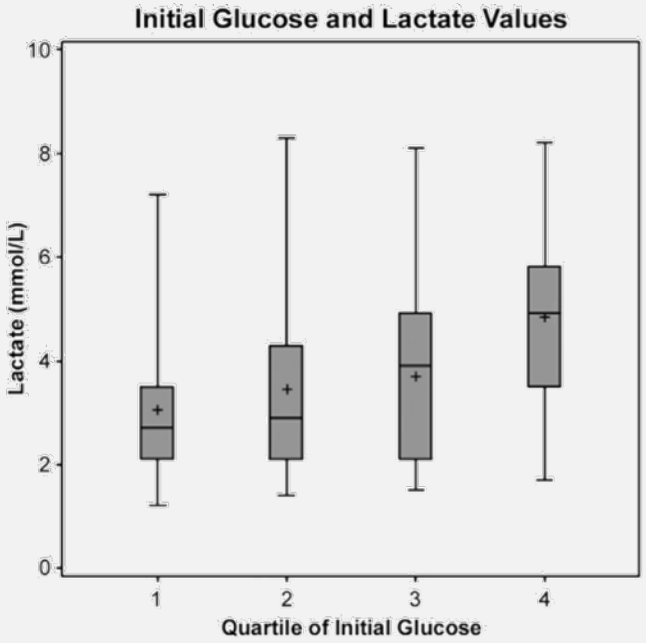
Lymphome
Au diagnostic
Grosse masse tumorale
Atteinte hépatique

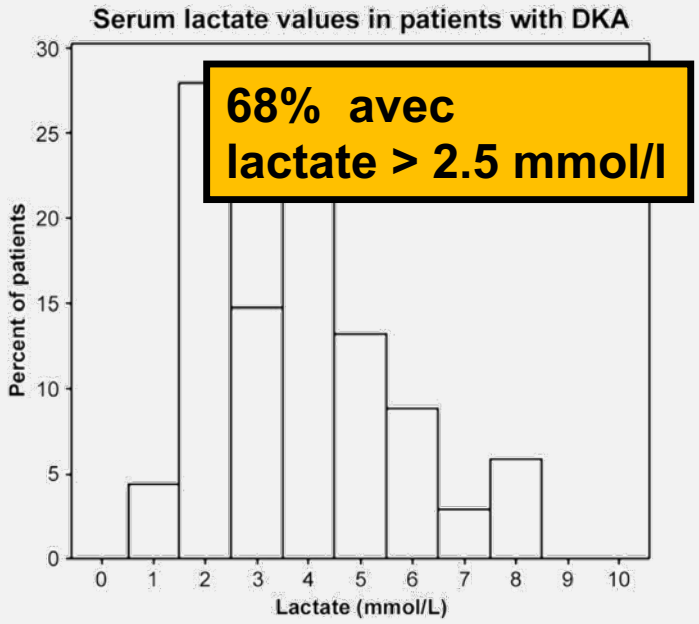


Friedenberg et al. Medicine 2007

LACTATE ET ACIDOCÉTOSE

Rétrospective, monocentrique, 68 acidocétose diabétique, prévalence acidose lactique





Cox et al. J Crit Care. 201

Mécanisme inconnu, facteur non pronostic

HYPERLACTATÉMIE D'ORIGINE MÉDICAMENTEUSE OU TOXIQUE

TABLE 2. Common Drugs and Toxins Associated With Elevated Lactate Levels[a]

Drug/toxin	Risk factors	Proposed mechanism	Suggested treatment in addition to cessation of the offending agent
Metformin[104,105b]	Congestive heart failure, kidney failure, liver failure, or overdose	Inhibition of gluconeogenesis and mitochondrial impairment, inhibition of lactate elimination	Consider hemodialysis
Acetaminophen[131]	Overdose	Impairment of the mitochondrial electron transport chain; later hepatotoxicity and systemic effects	Enteral activated charcoal and *N*-acetylcysteine
NRTI[106-108]	Female sex	Direct mitochondrial toxicity	No specific treatment
Linezolid[109-111]	Possibly prolonged use in elderly patients	Direct mitochondrial toxicity	No specific treatment
β_2-Agonists[61,112,113]	Not applicable	β_2-Adrenergic stimulation causing increased glycogenolysis, glycolysis, and lipolysis; free fatty acids released by lipolysis may inhibit PDH	Depending on the clinical situation, the β_2-agonist may/should be continued
Propofol[114-117]	Prolonged high-dose use (propofol infusion syndrome[c])	Impairment of the mitochondrial electron transport chain and fatty acid oxidation	Supportive treatment and potentially hemodialysis should be considered
Epinephrine[118,119]	Not applicable	Likely due to β_2-adrenergic stimulation (see β_2-agonists)	Depending on the clinical situation, epinephrine may be continued
Theophylline[120,121]	Overdose, although reported in standard doses	Increased levels of catecholamines (see β_2-agonists)	Enteral activated charcoal; hemodialysis in severe cases
Alcohols (ethanol, methanol, propylene glycol)[122-124bd]	Clinical relevance controversial and may be confounded by comorbidities (thiamine deficiency, seizures, sepsis, and other toxins)	Increased NADH levels due to ethanol metabolism may inhibit PDH and the use of lactate; contributions from underlying comorbidities or possibly ketoacidosis may play a role	Identification and treatment of underlying disorders, including administration of thiamine
Cocaine[125,126]	Not applicable	β_2-Adrenergic stimulation (see β_2-agonists); vasoconstriction causing ischemia	Supportive care and benzodiazepine
Carbon monoxide[127,128]	Not applicable	Decreased oxygen-carrying capacity of the blood	High-flow/hyperbaric oxygen; consider co-exposure to cyanide
Cyanide[129,130]	Not applicable	Noncompetitive inhibition of cytochrome c oxidase causing mitochondrial dysfunction and inability to use oxygen	Hydroxocobalamin or other cyanide antidote kit (sodium nitrite, amyl nitrite, sodium thiosulfate); consider co-exposure to carbon monoxide

Metformine	Inhibition néoglucogenèse
Paracétamol	Toxicité mitochondriale
Linézolide	Toxicité mitochondriale
β2-agoniste	Stimulation β adrénergique
Propofol	Toxicité mitochondriale
Adrénaline	Stimulation β adrénergique
Théophyline	
Alcool	Inhibition PDH
Cocaïne	Stimulation β adrénergique
CO	↘ portage O_2
Cyanure	Inhibition cytochrome C oxydase

Andersen et al. Mayo Clin Proc. 2013

TAKE HOME MESSAGE: LACTATE WITH OR WITHOUT HYPOPERFUSION VERSUS TISSUE HYPOXIA

- **Hyperlactatemia**

- **Anaerobic glycolysis in hypoperfused territories**
- **Stress-related adrenergic-induced aerobic glycolysis**
- **Impaired hepatic lactate clearance**
- **Mitochondrial dysfunction limiting pyruvate metabolism**

- **Eliminate or integrate the potential confounders**
  - **Epinephrine, other drugs, liver dysfunction, cells proliferation..**
  - **Presence of shock?**
- **Metabolic acidosis or not?**
- **Adequation of cardiac output (echo, Picco, Swann-Ganz) and/or adequation of volemia (dynamic test) : flow dependant**
  - **Lactate clearance plus $ScVO_2$ plus PCO_2 gap plus CFT**
- **Research of local ischemia (mesenteric +++)**

WHAT'S NEW IN INTENSIVE CARE

The ten pitfalls of lactate clearance in sepsis

Glenn Hernandez[1], Rinaldo Bellomo[2,3,4,5] and Jan Bakker[1,6,7,8*]

Intensive Care Med. 2019 Jan;45(1):82-85.

Stress hyperlactataemia: present understanding and controversy

Mercedes Garcia-Alvarez, Paul Marik, Rinaldo Bellomo

Lancet Diabetes Endocrinol. 2014 Apr;2(4):339-47

Current Trends in Lactate Metabolism: Introduction

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