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INTERNATIONAL CONSENSUS CONFERENCE

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# Hemodynamic monitoring in shock and implications for management

## International Consensus Conference, Paris, France, 27–28 April 2006

Paramètres de l'oxygénation

Pr LEVY Bruno

Nancy

# Définition

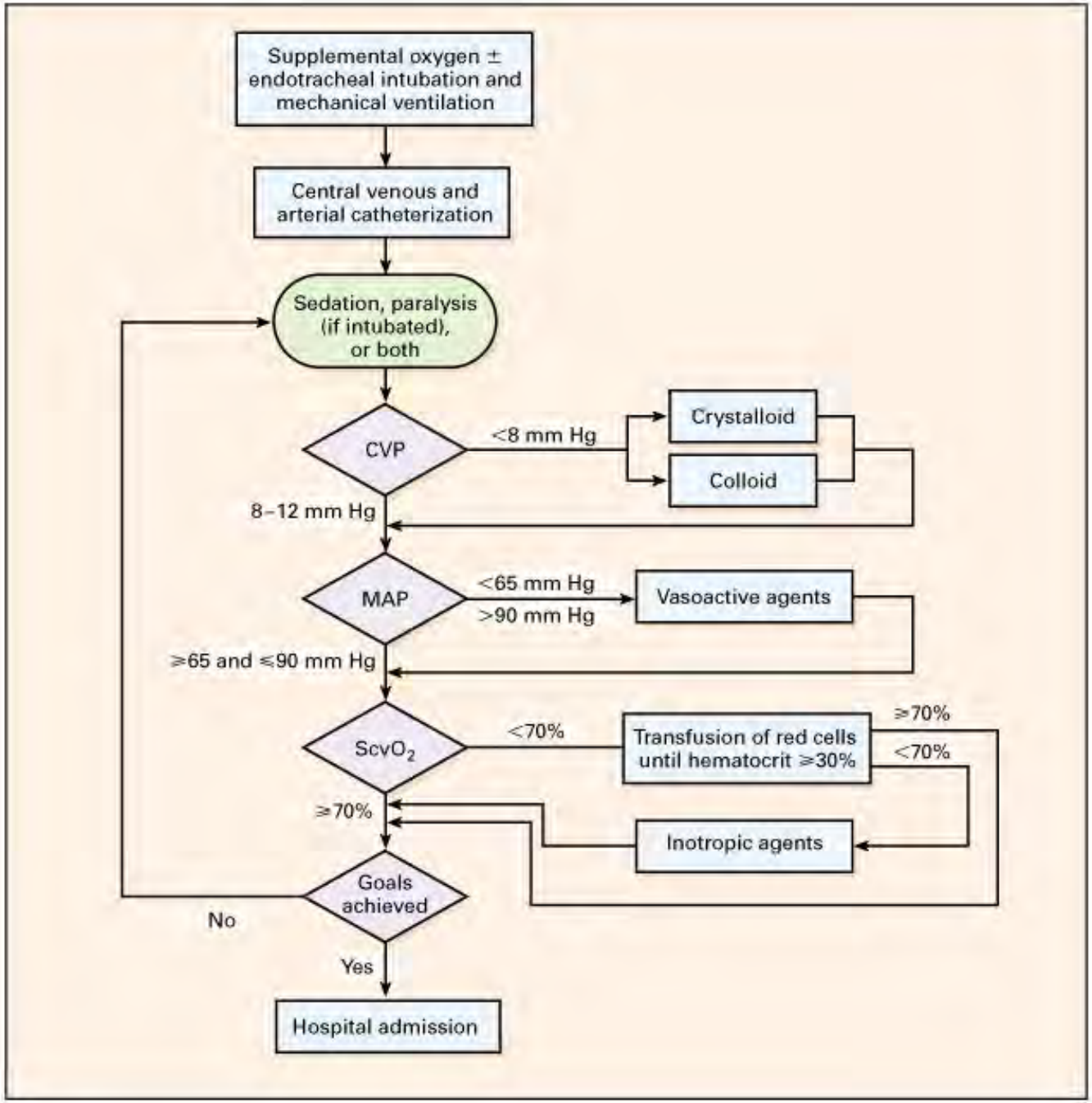
- Situation de “maldistribution” généralisée du flux sanguin induisant une incapacité à délivrer et/ou utiliser de facon adéquate l’oxygène et entrainant une dysoxie tissulaire
- En l’absence d’hypotension, le jury recommande de mesurer un marqueur de perfusion inadequate : $SCVO_2$, lactate, BE, pH .

Le choc septique non réanimé est hypokinétique.

**Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock**

*Emanuel Rivers, M.D., M.P.H., Bryant Nguyen, M.D., Suzanne Havstad, M.A., Julie Ressler, B.S., Alexandria Muzzin, B.S., Bernhard Knoblich, M.D., Edward Peterson, Ph.D., Michael Tomlanovich, M.D., for the Early Goal-Directed Therapy Collaborative Group*

N Engl J Med 2001; 345 : 1368-77.


Supplemental oxygen ± endotracheal intubation and mechanical ventilation
Central venous and arterial catheterization
Sedation, paralysis (if intubated), or both
CVP
<8 mm Hg
Crystalloid
Colloid
8–12 mm Hg
MAP
<65 mm Hg
>90 mm Hg
Vasoactive agents
≥65 and ≤90 mm Hg
ScvO2
<70%
Transfusion of red cells until hematocrit ≥30%
≥70%
<70%
≥70%
Inotropic agents
Goals achieved
No
Yes
Hospital admission

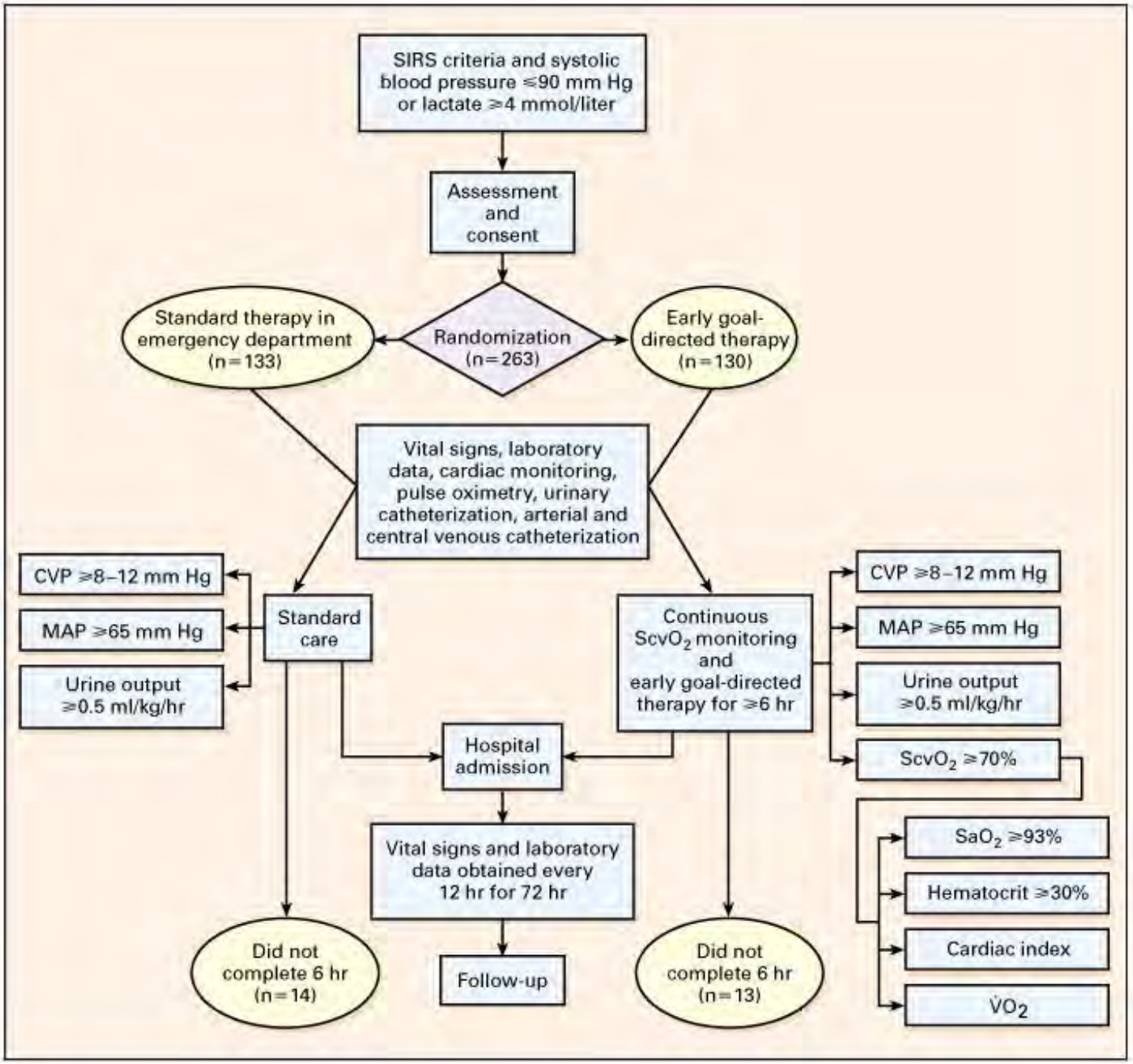

SIRS criteria and systolic blood pressure ≤90 mm Hg or lactate ≥4 mmol/liter
Assessment and consent
Randomization (n=263)
Standard therapy in emergency department (n=133)
Early goal-directed therapy (n=130)
Vital signs, laboratory data, cardiac monitoring, pulse oximetry, urinary catheterization, arterial and central venous catheterization
CVP ≥8–12 mm Hg
MAP ≥65 mm Hg
Urine output ≥0.5 ml/kg/hr
Standard care
Continuous $ScvO_2$ monitoring and early goal-directed therapy for ≥6 hr
CVP ≥8–12 mm Hg
MAP ≥65 mm Hg
Urine output ≥0.5 ml/kg/hr
$ScvO_2$ ≥70%
$SaO_2$ ≥93%
Hematocrit ≥30%
Cardiac index
$\dot{V}O_2$
Hospital admission
Vital signs and laboratory data obtained every 12 hr for 72 hr
Follow-up
Did not complete 6 hr (n=14)
Did not complete 6 hr (n=13)

**TABLE 3.** KAPLAN–MEIER ESTIMATES OF MORTALITY AND CAUSES OF IN-HOSPITAL DEATH.*

| VARIABLE | STANDARD THERAPY (N=133) | EARLY GOAL-DIRECTED THERAPY (N=130) | RELATIVE RISK (95% CI) | P VALUE |
|---|---|---|---|---|
| | no. (%) | | | |
| In-hospital mortality† | | | | |
| All patients | 59 (46.5) | 38 (30.5) | 0.58 (0.38–0.87) | 0.009 |
| Patients with severe sepsis | 19 (30.0) | 9 (14.9) | 0.46 (0.21–1.03) | 0.06 |
| Patients with septic shock | 40 (56.8) | 29 (42.3) | 0.60 (0.36–0.98) | 0.04 |
| Patients with sepsis syndrome | 44 (45.4) | 35 (35.1) | 0.66 (0.42–1.04) | 0.07 |
| 28-Day mortality† | 61 (49.2) | 40 (33.3) | 0.58 (0.39–0.87) | 0.01 |
| 60-Day mortality† | 70 (56.9) | 50 (44.3) | 0.67 (0.46–0.96) | 0.03 |
| Causes of in-hospital death‡ | | | | |
| Sudden cardiovascular collapse | 25/119 (21.0) | 12/117 (10.3) | — | 0.02 |
| Multiorgan failure | 26/119 (21.8) | 19/117 (16.2) | — | 0.27 |

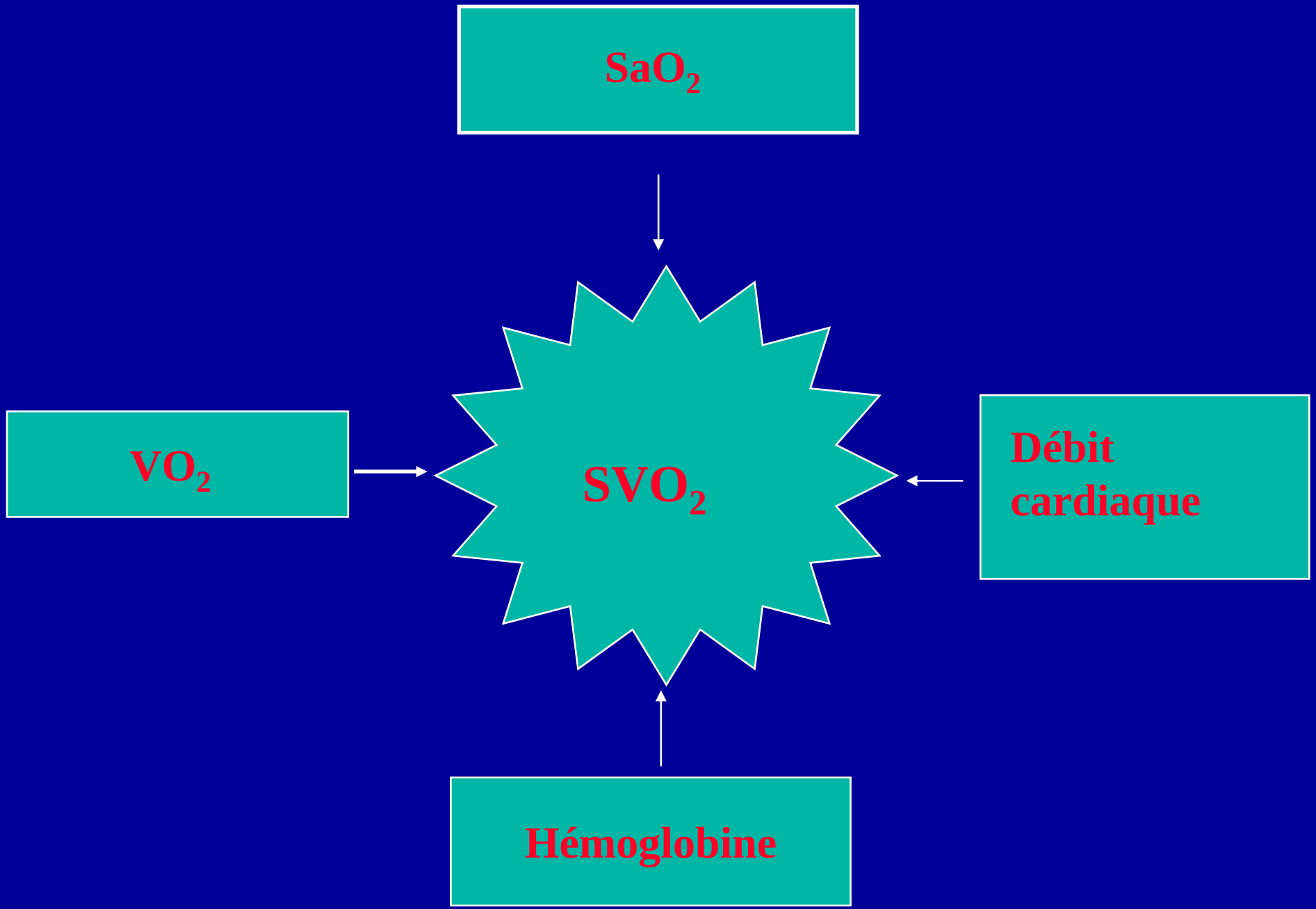
*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.

†Percentages were calculated by the Kaplan–Meier product-limit method.

‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.

**TABLE 4.** TREATMENTS ADMINISTERED.*

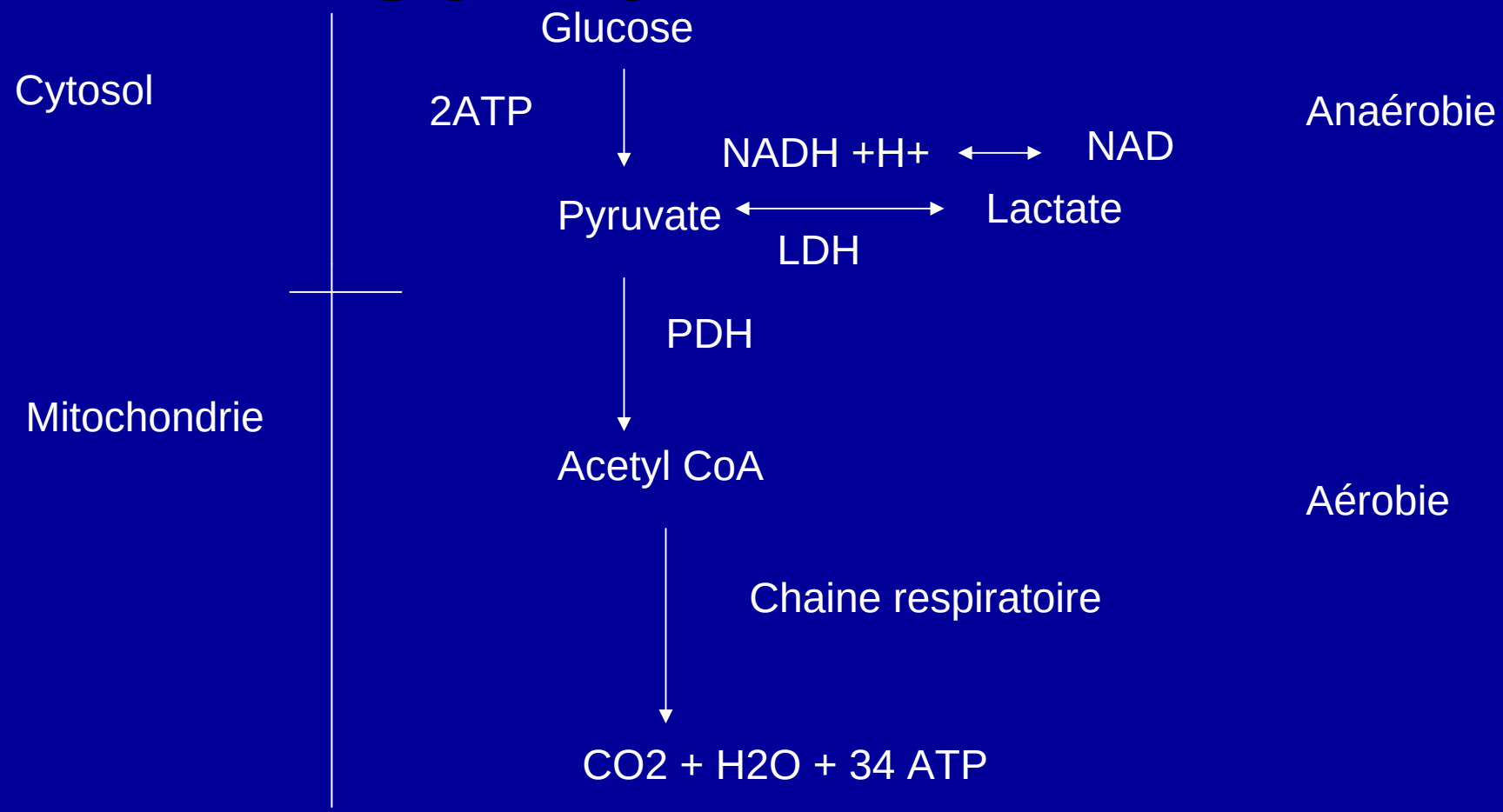
| TREATMENT | HOURS AFTER THE START OF THERAPY | | |
|---|---|---|---|
| | 0–6 | 7–72 | 0–72 |
| Total fluids (ml) | | | |
| Standard therapy | 3499±2438 | 10,602±6,216 | 13,358±7,729 |
| EGDT | 4981±2984 | 8,625±5,162 | 13,443±6,390 |
| P value | <0.001 | 0.01 | 0.73 |
| Red-cell transfusion (%) | | | |
| Standard therapy | 18.5 | 32.8 | 44.5 |
| EGDT | 64.1 | 11.1 | 68.4 |
| P value | <0.001 | <0.001 | <0.001 |
| Any vasopressor (%)† | | | |
| Standard therapy | 30.3 | 42.9 | 51.3 |
| EGDT | 27.4 | 29.1 | 36.8 |
| P value | 0.62 | 0.03 | 0.02 |
| Inotropic agent (dobutamine) (%) | | | |
| Standard therapy | 0.8 | 8.4 | 9.2 |
| EGDT | 13.7 | 14.5 | 15.4 |
| P value | <0.001 | 0.14 | 0.15 |
| Mechanical ventilation (%) | | | |
| Standard therapy | 53.8 | 16.8 | 70.6 |
| EGDT | 53.0 | 2.6 | 55.6 |
| P value | 0.90 | <0.001 | 0.02 |
| Pulmonary-artery catheterization (%)‡ | | | |
| Standard therapy | 3.4 | 28.6 | 31.9 |
| EGDT | 0 | 18.0 | 18.0 |
| P value | 0.12 | 0.04 | 0.01 |


$SaO_2$
$VO_2$
$SVO_2$
Débit cardiaque
Hémoglobine

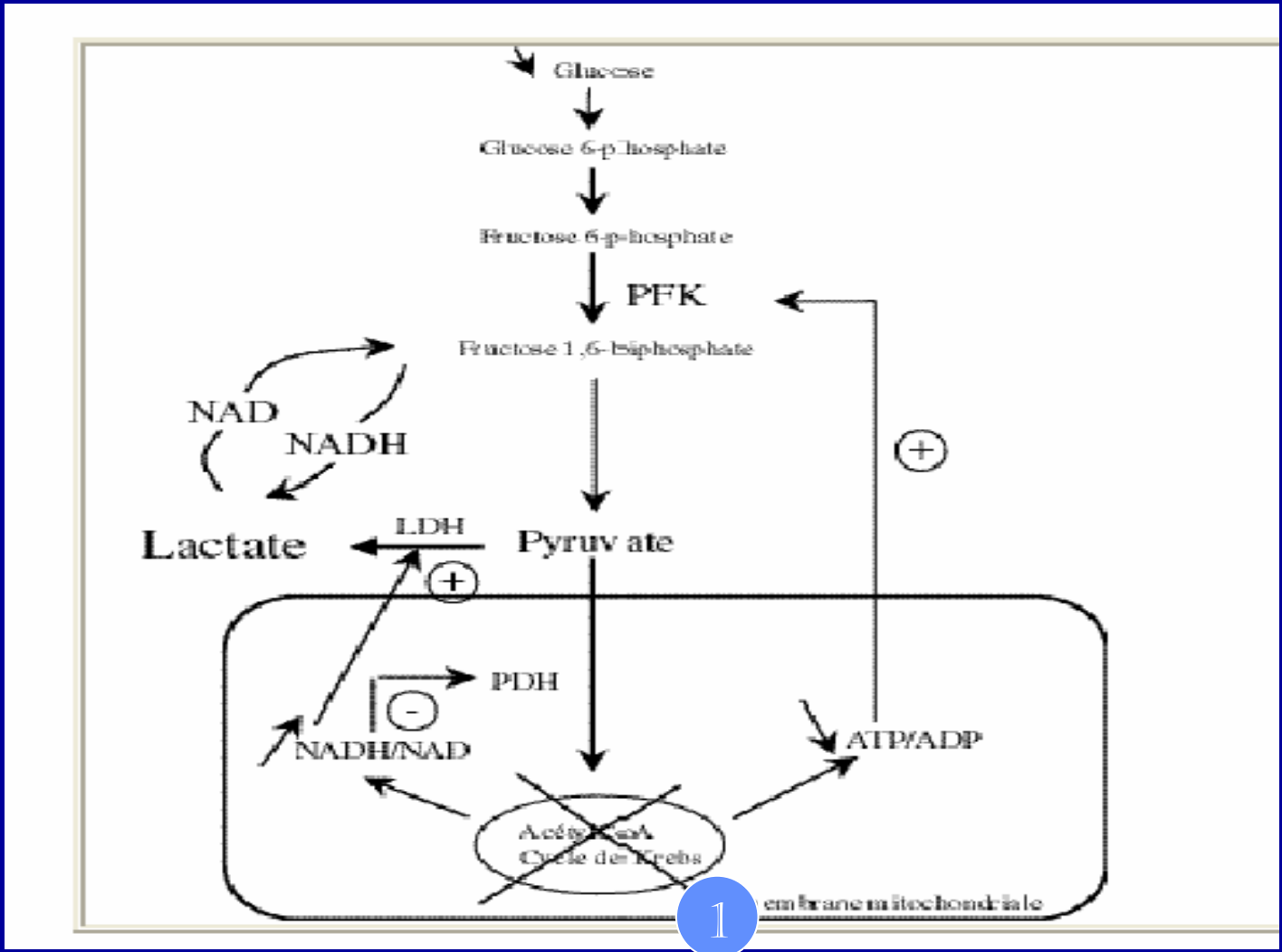
# LACTATE

**12. We suggest serial measurements of lactates and/or base deficit as a predictor of outcome.**
**Level 2; QoE moderate (B)**

# La glycolyse

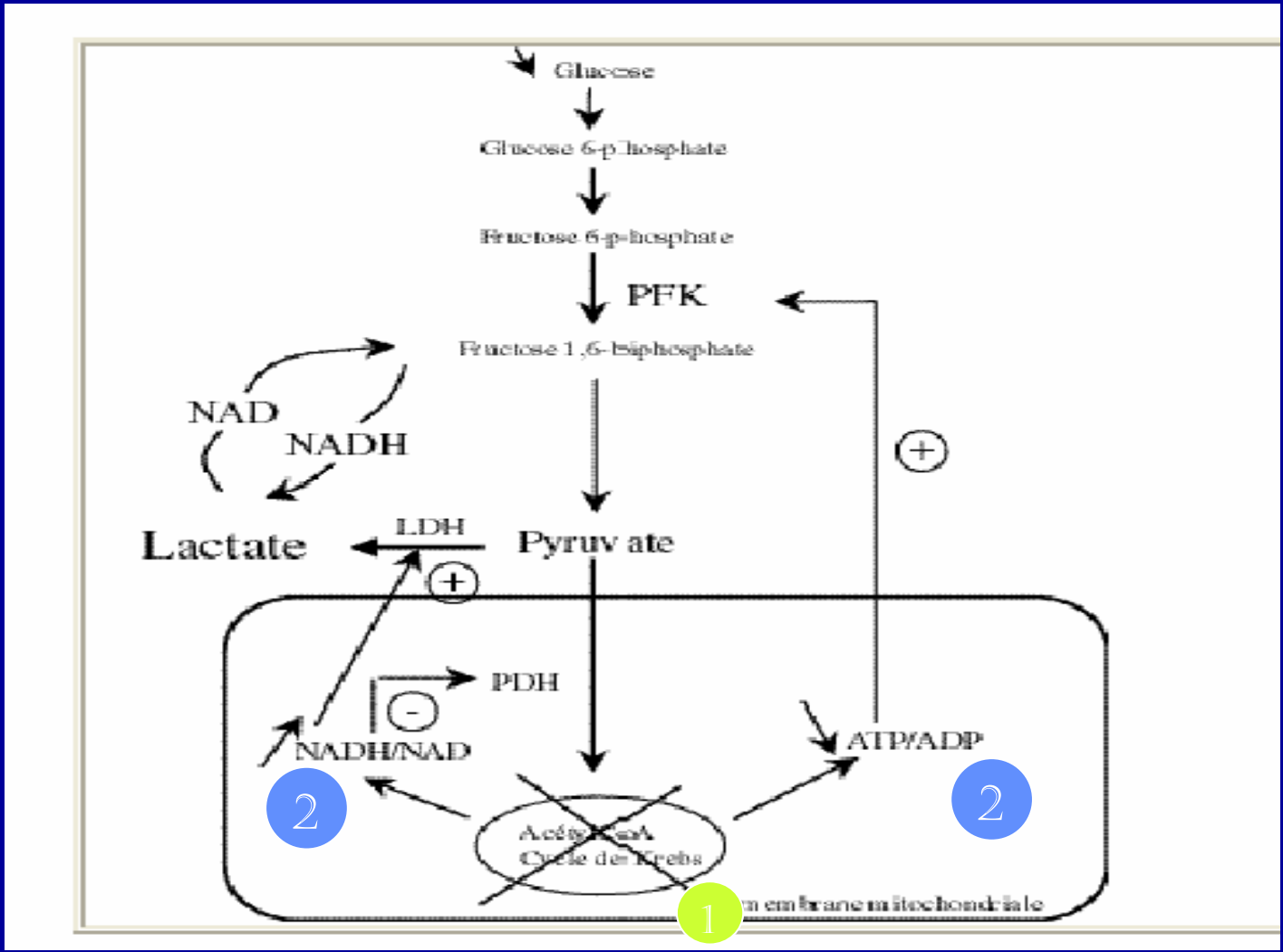


# Lactate formation during hypoxia



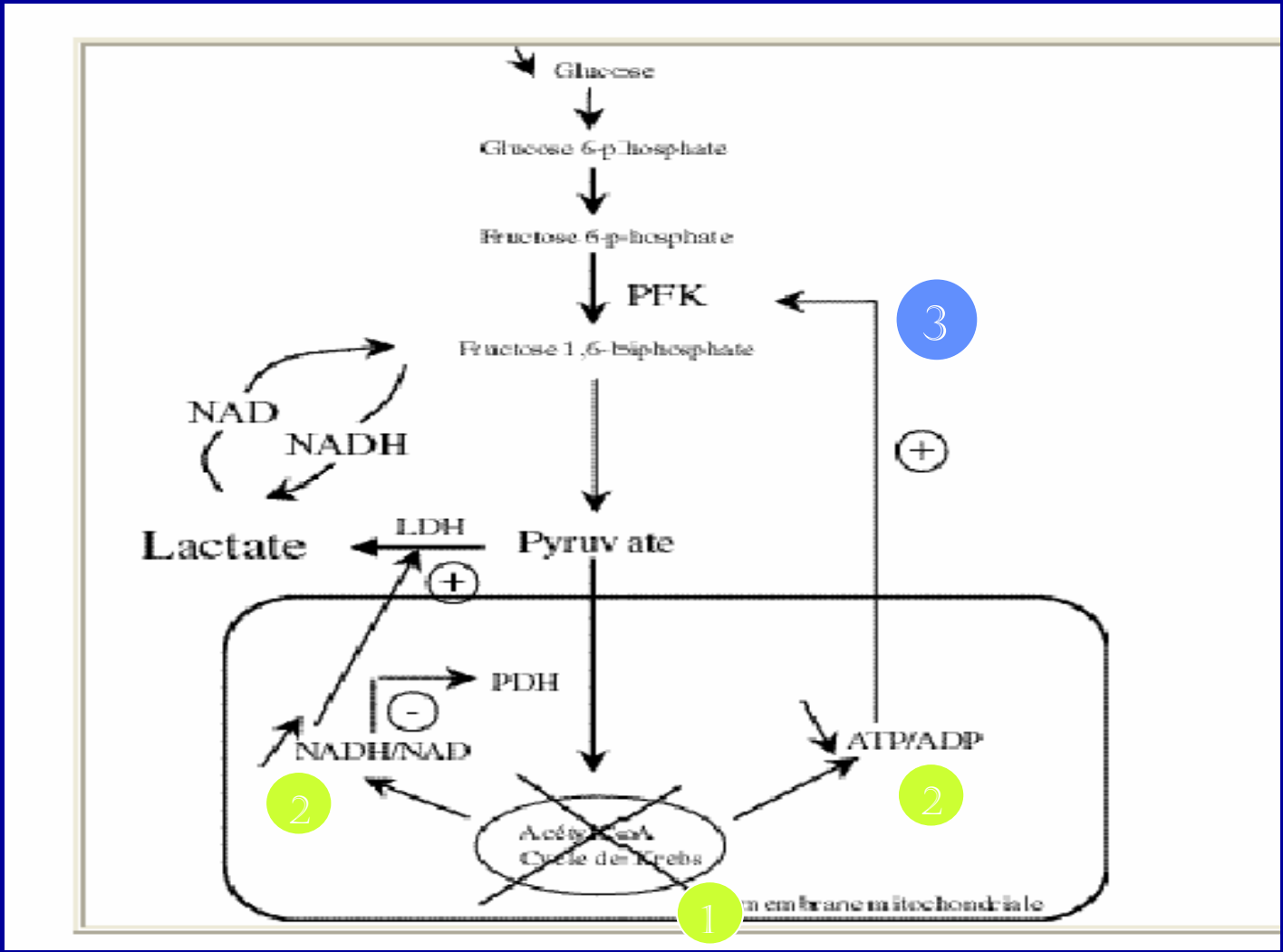

**1. Absence of $O_2$ : stoppage or decrease in ATP production by mitochondrial electron transfer**

# Lactate formation during hypoxia



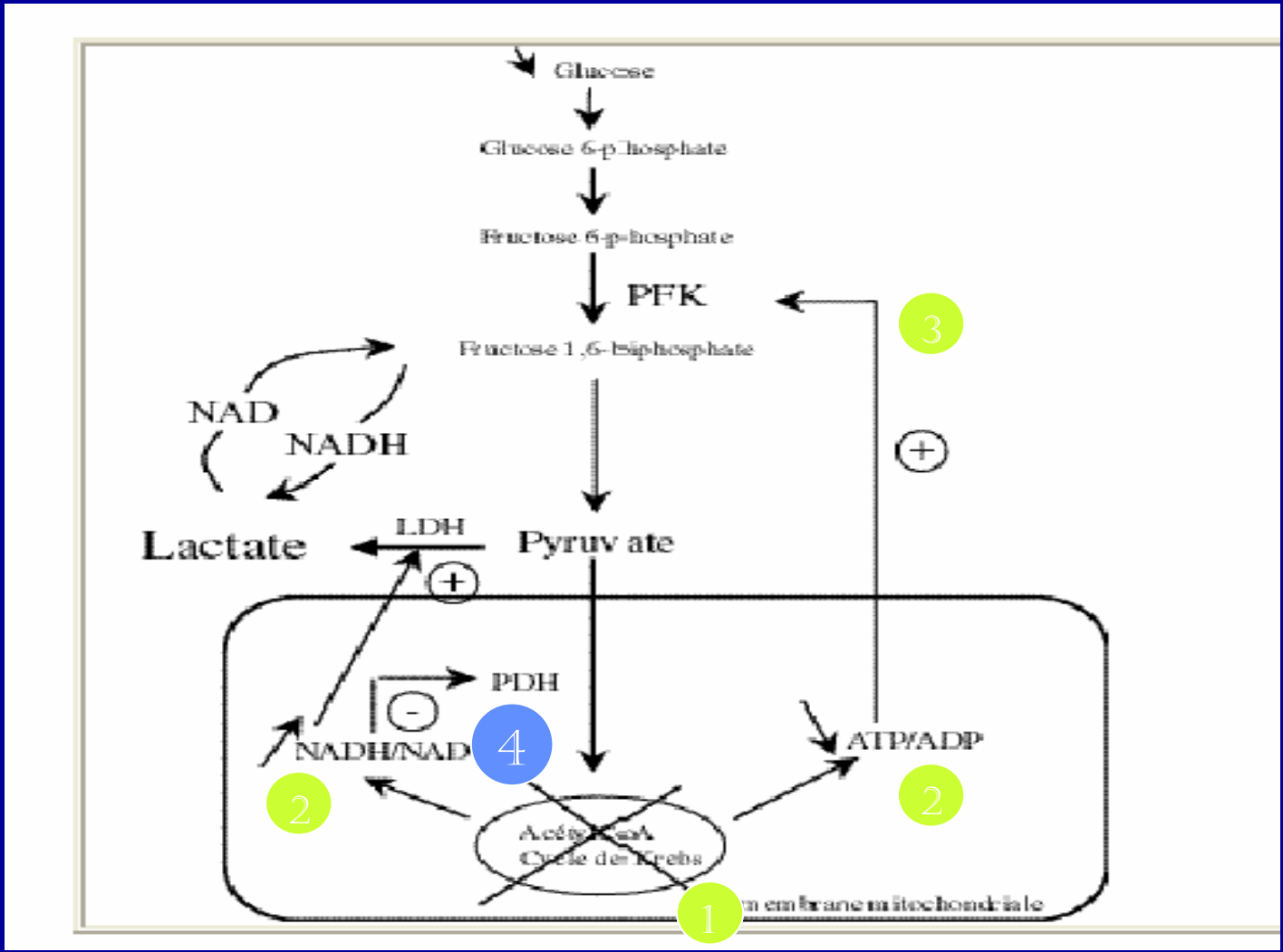

**2. Decrease in ATP/ADP ratio and increase in NADH/NAD ratio**

# Lactate formation during hypoxia



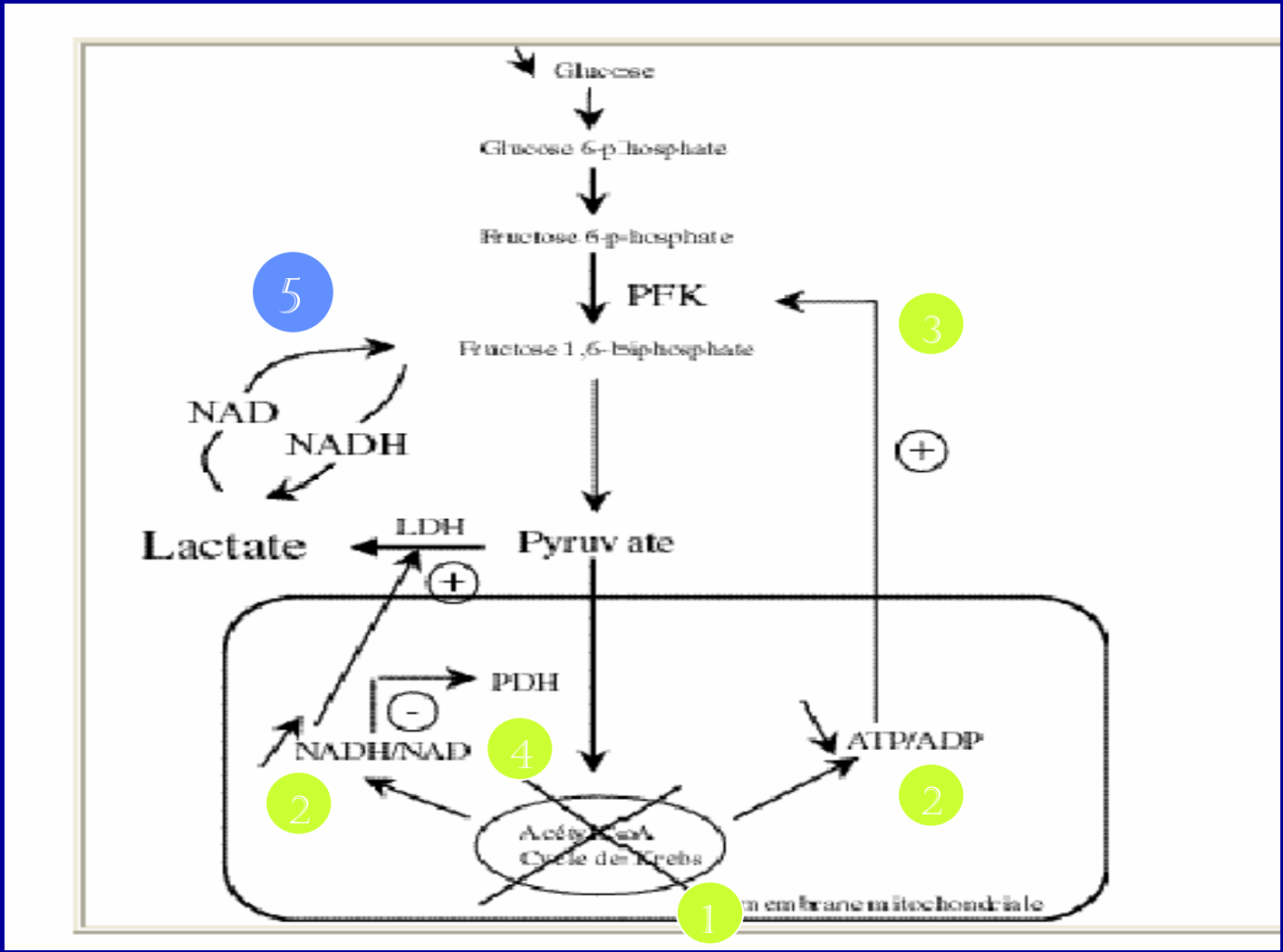

**3. The decrease in ATP/ADP ratio induces an increase in PFK activity**

# Lactate formation during hypoxia




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

# Lactate formation during hypoxia

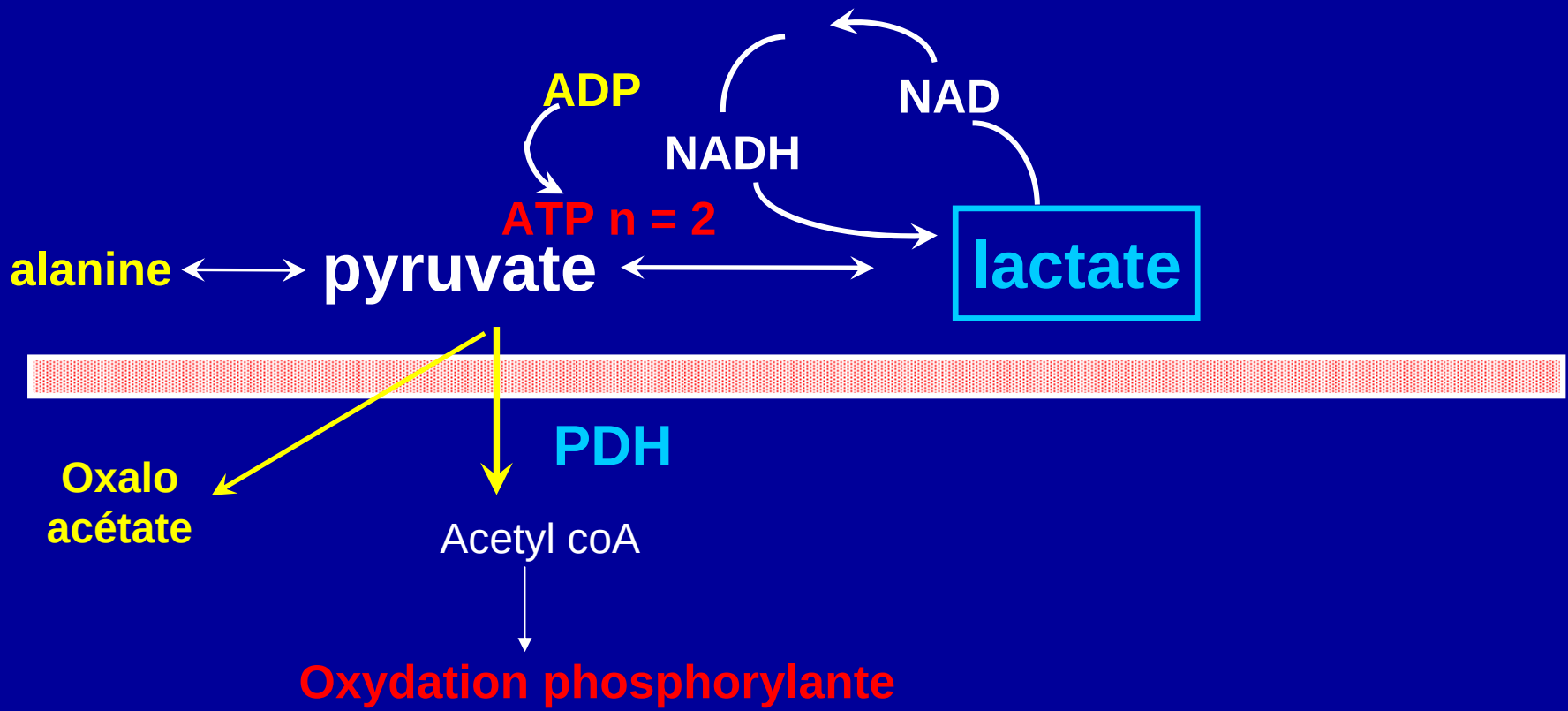



**5. The conversion allows NAD regeneration and ATP production (2 ATP for one glucose)**

Anaerobic energy metabolism is characterized by the absence of respiration, hyperlactatemia associated with an elevated lactate/pyruvate ratio, greater glucose utilization and low energy production.

# METABOLISME DU LACTATE

$$\frac{L}{P} = k \cdot \frac{NADH}{NAD} < 12$$



# Rapport lactate/pyruvate

- **Pyruvate + NADH +H+ ⇔ lactate + NAD**
- **Lactate/pyruvate = K. NADH/NAD . H+**
- Rapport dépendant du rapport NADH/NAD et du pH ($H+ = 10^{-ph}$)
- Quid du rapport cytoplasmique et mitochondrial?

→ Permet il de différencier les hyperlactatémies hypoxiques des hyperlactatémies par augmentation du flux glycolytique sans hypoxie?

# *Levy B et al. Crit Care Med 2000;28:114-9*

| Variable | Survivors (n = 25) | Nonsurvivors | |
|---|---|---|---|
| | | ISS (n = 15) | MODS (n = 20) |
| MAP, mm Hg | 70 ± 5 | 55 ± 7[b] | 68 ± 5 |
| CI, L/min/$m^2$ | 4.0 ± 0.4 | 3.3 ± 0.5[b] | 5.0 ± 0.5 |
| $\dot{D}o_2$, mL/min/$m^2$ | 700 ± 81 | 570 ± 72[b] | 839 ± 96 |
| $\dot{V}o_2$, mL/min/$m^2$ | 177 ± 23 | 130 ± 28[b] | 202 ± 27 |
| SVRI, dyne·s/$cm^5$·$m^2$ | 1800 ± 234 | 1157 ± 210[b] | 1308 ± 143[b] |
| Arterial pH | 7.31 ± 0.01 | 7.10 ± 0.02[b] | 7.30 ± 0.02 |
| OSF | 2.4 ± 0.2 | 4.0 ± 0.1[b] | 3.2 ± 0.2[b] |
| Dopamine[a] | 9 (16 ± 1) | 9 (7 ± 2) | 5 (18 ± 1) |
| Norepinephrine[a] | 14 (0.7 ± 0.1) | 15 (2.3 ± 0.3[b]) | 15 (1.2 ± 0.2) |
| APACHE II score | 19 ± 1 | 32 ± 5[b] | 22 ± 1 |

ISS, intractable septic shock; MODS, multiple organ dysfunction syndrome; MAP, mean arterial pressure; CI, cardiac index; SVRI, systemic vascular resistance index; $\dot{D}o_2$, oxygen delivery index; $\dot{V}o_2$, oxygen consumption index; OSF, number of organs in failure; APACHE II, Acute Physiology and Chronic Health Evaluation II.

[a]The number of treated patients (dose, μg/kg/min) is shown for dopamine and norepinephrine; [b]$p < .05$ vs. survivors.

# Lactate/Pyruvate and Arterial Ketone Body Ratios in Early Course of Septic Shock

*Levy et al. Crit Care Med 2000;28:114-9*

| Patients | Lactate/Pyruvate | Acetoacetate/ β-hydroxybutyrate |
|---|---|---|
| **Controls (n = 20)** | 8 ± 2 | 1.30 ± 0.15 |
| **Septic shock Died < 24 hrs (n = 15)** | 37 ± 4 | 0.41 ± 0.10 |
| **Septic shock Survived (n = 25) < 4hrs** | | |
| **Septic shock Survived (n = 25) 24hrs** | | |
| **Cardiogenic shock (n = 10)** | 40 ± 6 | 0.20 ± 0.05 |

# Lactate/Pyruvate and Arterial Ketone Body Ratios in Early Course of Septic Shock

*Levy et al. Crit Care Med 2000;28:114-9*

- [lactate]/[pyruvate] = K × [NADH] / [NAD+] × [H+]

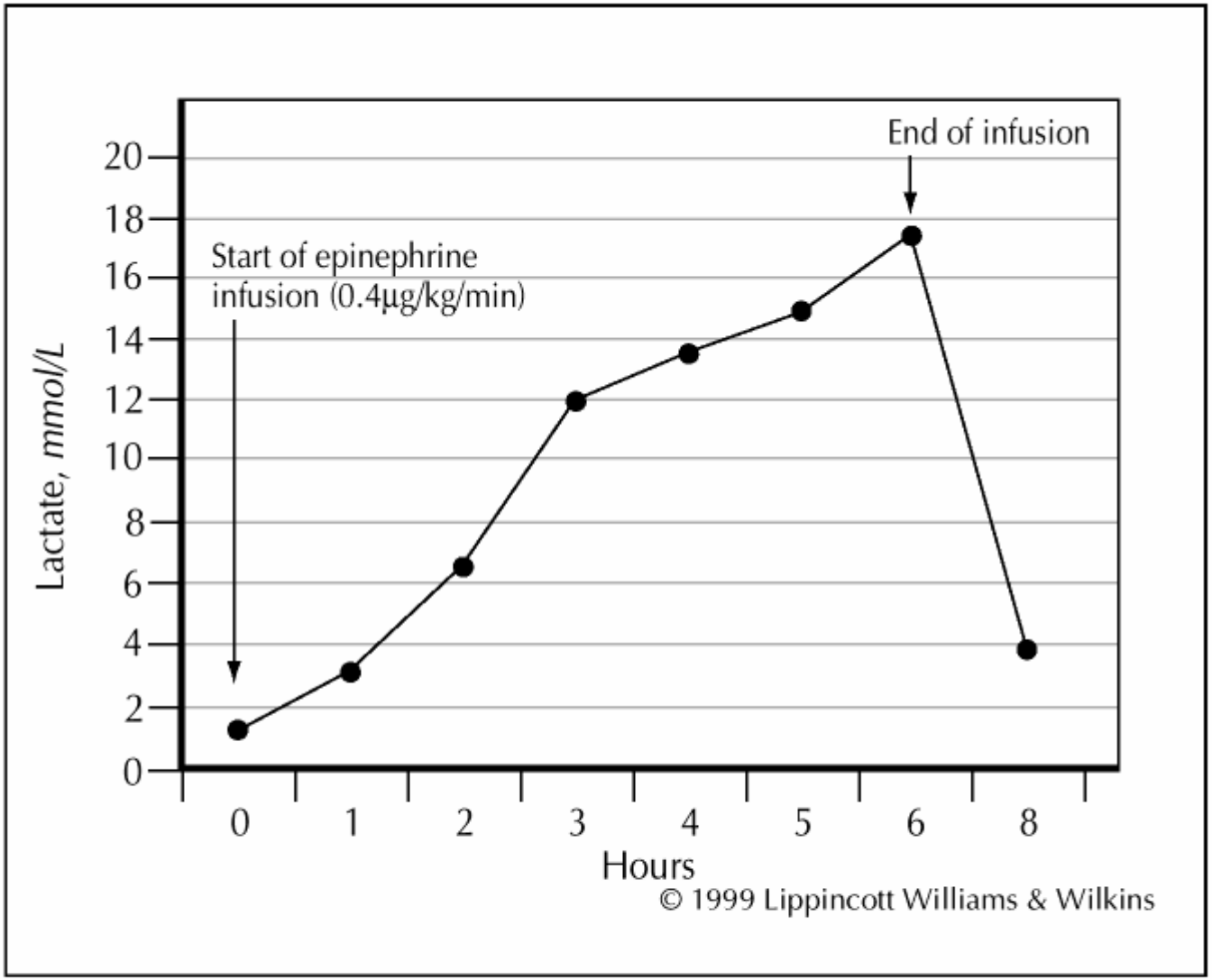
| Patients | Lactate/Pyruvate | Acetoacetate/ β-hydroxybutyrate | pH |
|---|---|---|---|
| **Controls (n = 20)** | 8 ± 2 | 1.30 ± 0.15 | 7.38 |
| **Septic shock Died < 24 hrs (n = 15)** | 37 ± 4 | 0.41 ± 0.10 | 7.10 ± 0.02 |
| **Septic shock Survived (n = 25) < 4hrs** | 19 ± 1 | 0.52 ± 0.07 | 7.31 ± 0.01 |
| **Septic shock Survived (n = 25) 24hrs** | 14 ± 1 | 1.72 ± 0.17 | 7.33 ± 0.02 |
| **Cardiogenic shock (n = 10)** | 40 ± 6 | 0.20 ± 0.05 | 7.25 ± 0.03 |

# Le cas du sepsis

- Les patients septiques lactiques devraient avoir un $TaO_2$ diminué.
  - Gilbert EM, Am Rev Respir Dis 1996
- L'augmentation du TaO2 devrait corriger cette hyperlactatémie
  - Silverman H, Chest 1991
- Les taux d'ATP devraient être diminués
  - Tresarden JC , Clin Sci 1988

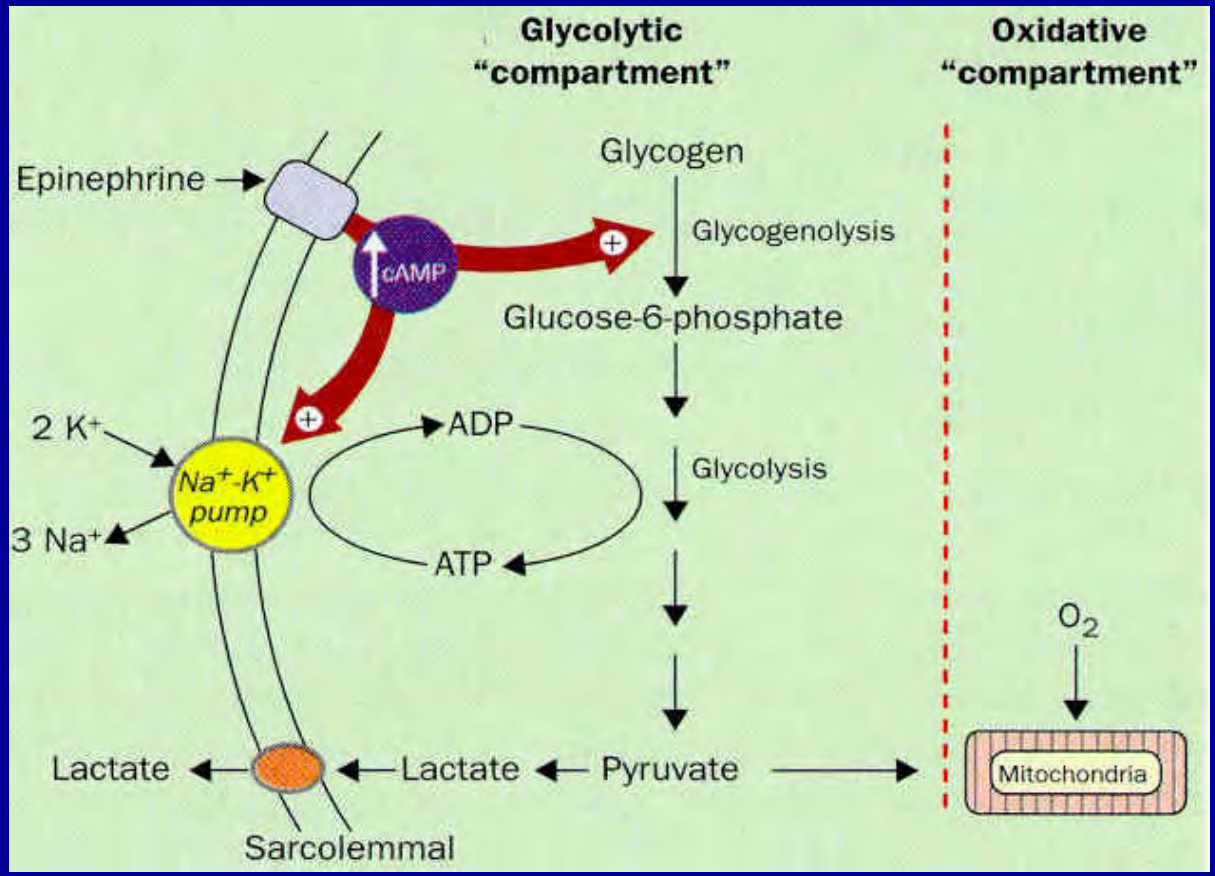
# Mais…..le cas du sepsis

- La $PO_2$ devrait être basse
  - Boekstegers P, Crit Care Med 1994
- Les médicaments sans effets sur l'oxygénation ne devraient pas avoir d'effet sur le lactate
  - Dichloroacétate Stacpoole N Engl J Med 1983
- Hyperlactatémie régionale : splanchnique?
  - De Backer D et al, Crit Care Med 2001




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.

# Production aérobique de lactate




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

Mechanisms of Disease

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

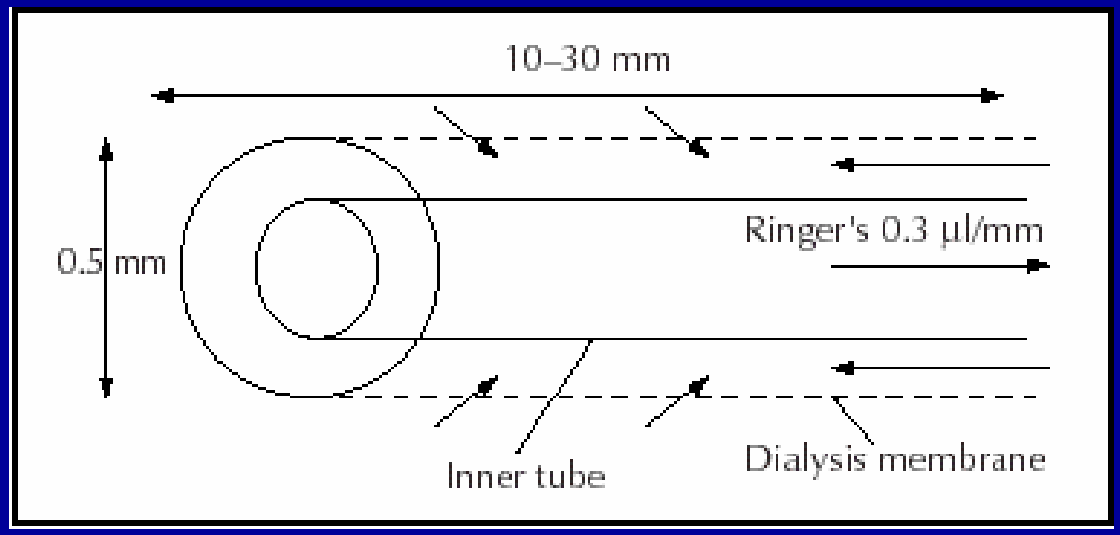
Bruno Levy, Sébastien Gibot, Patricia Franck, Aurélie Cravoisy, Pierre-Edouard Bollaert

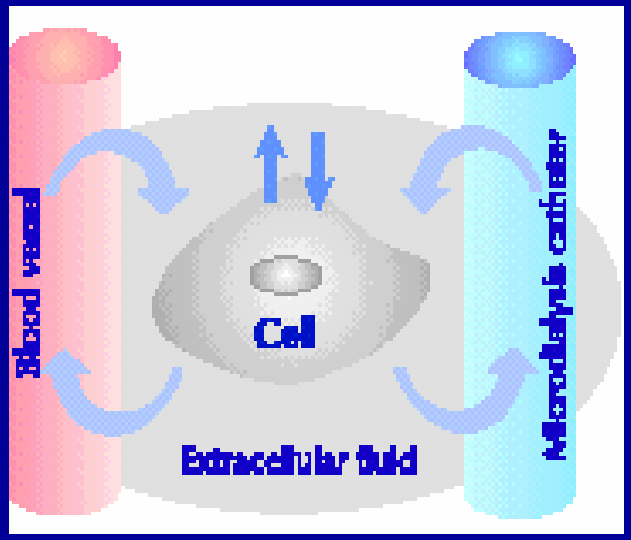
Lancet 2005; 365: 871–75

# The patients….

- 14 patients with septic shock
- 65 ±12 mean age
- CI : 4.0 ± 0.4 l/min/$m^{-2}$, SVO2 : 76 ±6%, $PCO_2$ gap : 14 ±6
- 8 Epinephrine and 6 Norepinephrine
- Lactate : 4 ± 2.1 mmol/L
- Lactate/pyruvate : 27 ± 8
- Baseline : MAP : 75 ±8 mmHg, Fc : 110 ±15 b/min

# Microdialysis



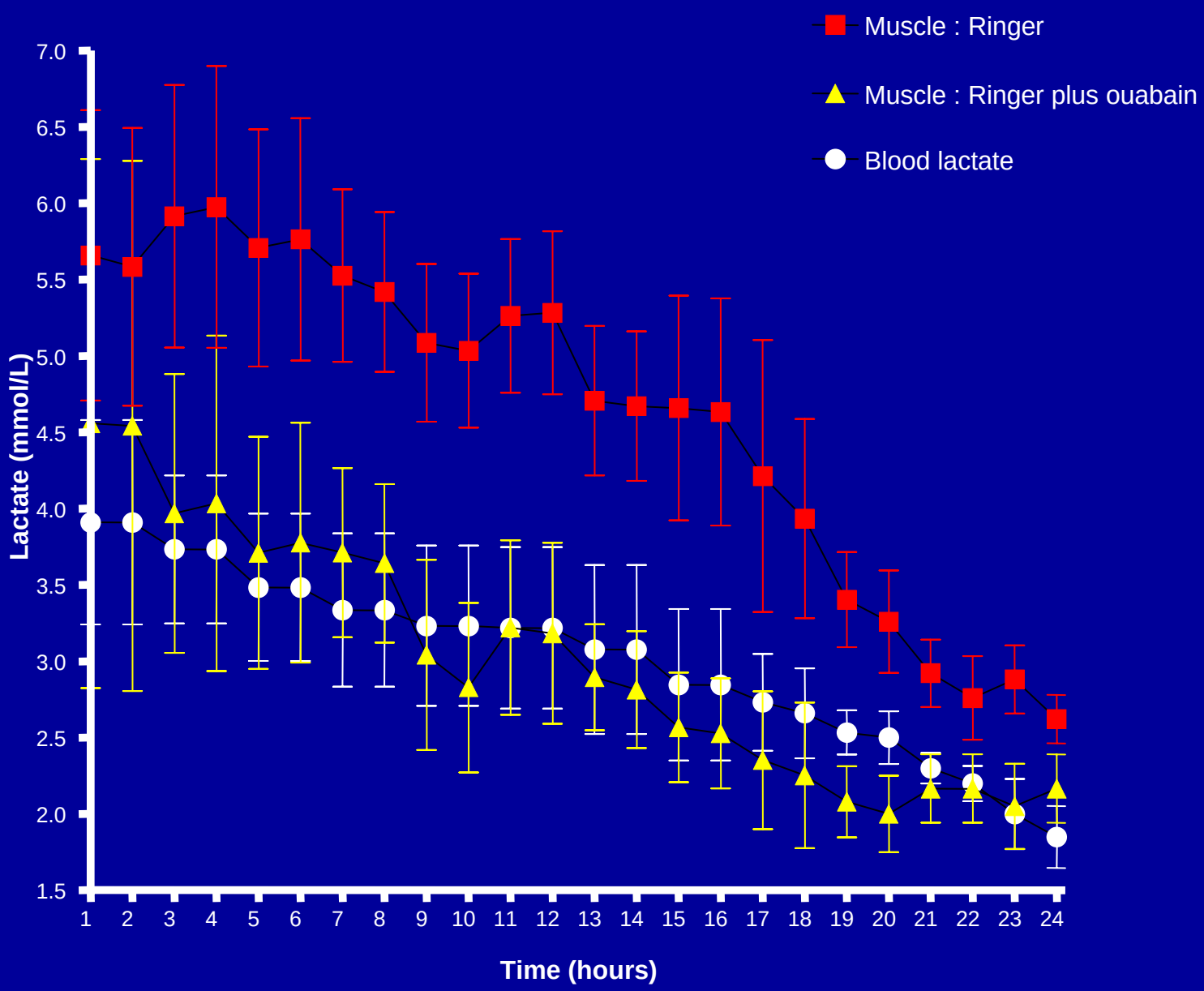




- Insertion of a semi permeable membrane infused in the muscle
  - the solutes presentes in the interstitium freely diffuse into the catheter according to their concentration gradient
- Assessment of interstitial concentration of various metabolites
- Pharmacological modulation without any systemic effects
- Measurement of tissue-arterial gradient

# Methods

- 2 microdialysis probes (CMA 60, CMA/Microdialysis, Stockholm, Sweden) were inserted into the quadriceps muscle
  - One with  Ringer free lactate
  - One with Ringer free lactate + ouabaine (10-7M) at 0.3µl/min
  - One hour equilibration
- Measurement of lactate and pyruvate in the muscle and in blood each hour during 24 hours

# LACTATE


Muscle : Ringer
Muscle : Ringer plus ouabain
Blood lactate
Lactate (mmol/L)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Time (hours)

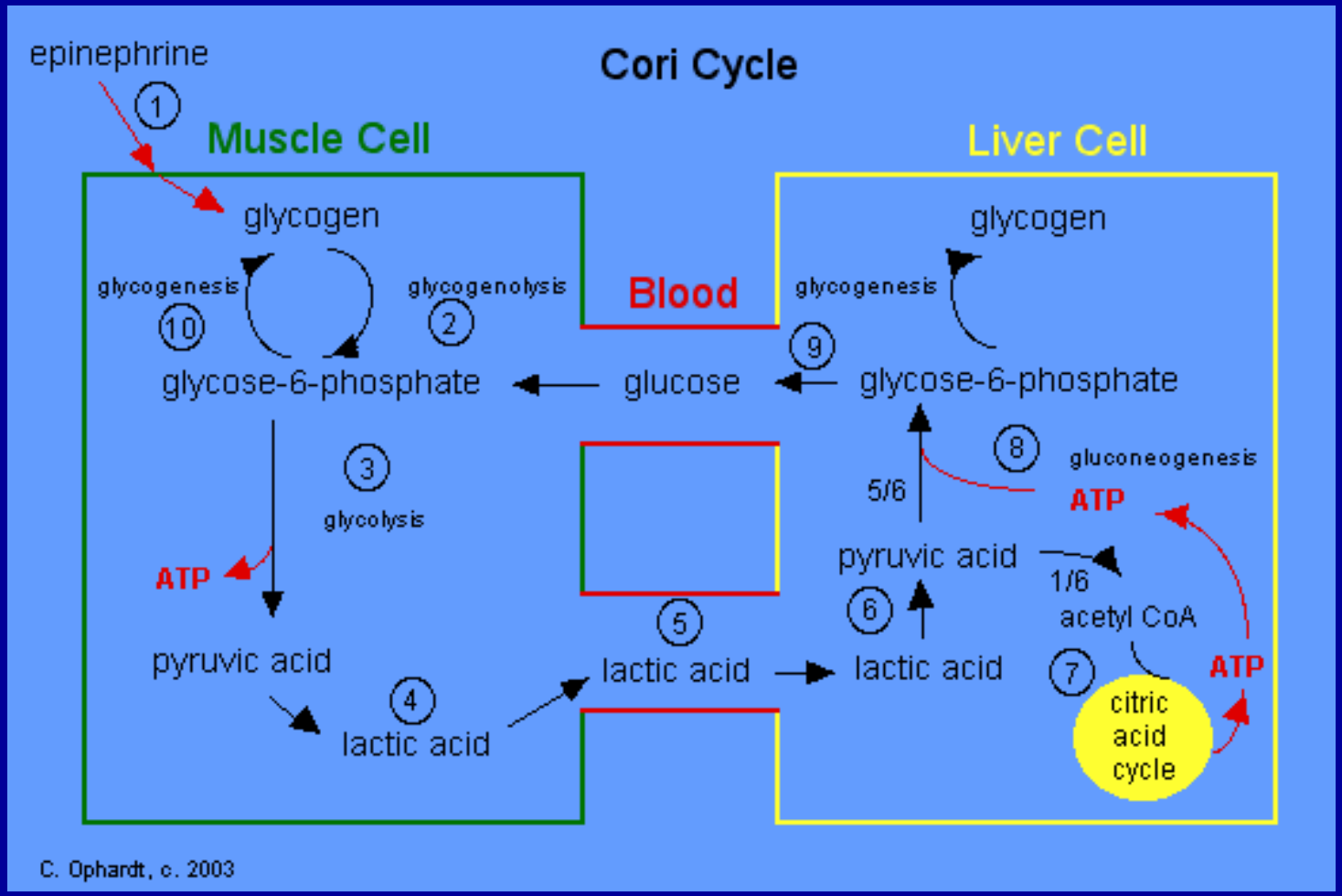
# Discussion

- Le muscle dans le choc septique réanimé produit du lactate et du pyruvate.
- Cette production est totalement abolie par l'inhibition de la pompe Na-K ATPase
- Ce mécanisme est théoriquement indépendant de la glycolyse oxydative et de l'apport en $O_2$

# Conclusions

- Reconsidération de la signification physiopathologique et du rôle du lactate dans le choc septique
  - Mécanisme adaptatif
  - Comburant préférentiel (cœur, cerveau)
  - Message métabolique
- Marqueur de gravité
- La production pulmonaire et digestive est probablement aussi d’origine inflammatoire

# Cycle de Cori



# Lactate et pronostic

- Relation bien établie entre morbidité/mortalité et intensité/durée de l'hyperlactatémie

## Serial Blood Lactate Levels Can Predict the Development of Multiple Organ Failure Following Septic Shock

Jan Bakker, MD, Philippe Gris, MD, Michel Coffernils, MD, Robert J. Kahn, MD, Jean-Louis Vincent, MD, PhD, *Brussels, Belgium*

***Am J Surg.*** **1996;171:221–226.**

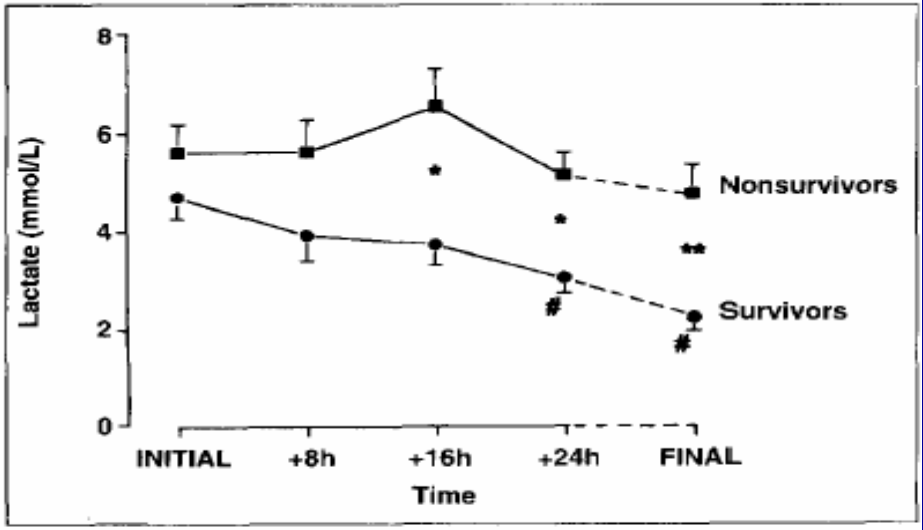
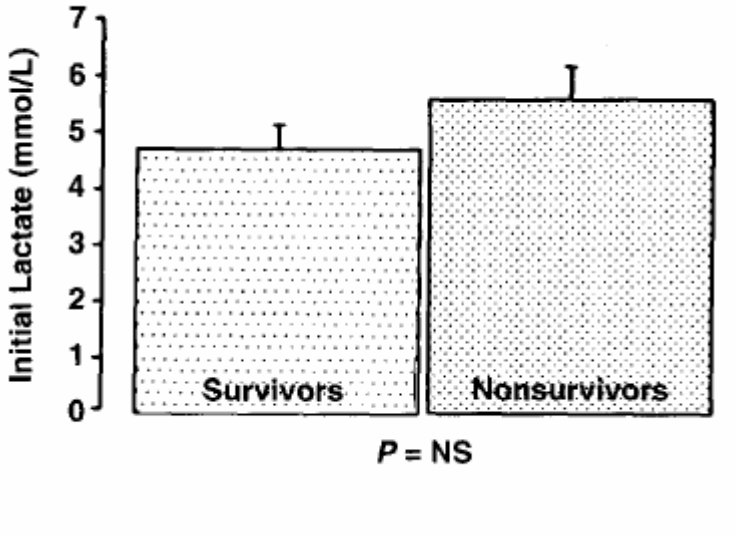


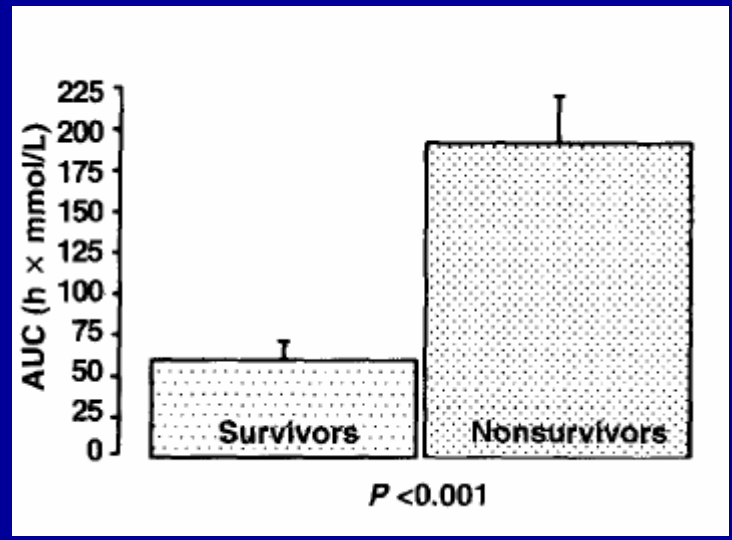

**Figure 1.** Time course of blood lactate levels for the 33 survivors and the 41 nonsurvivors. Initial values were taken at onset of shock, and the final values at time of recovery or before death (mean ± standard error of the mean). *$P$ <0.05; **$P$ <0.01 (survivors versus nonsurvivors); #$P$ <0.05 versus initial blood lactate level.

**TABLE IV**

**Discriminants of Survival by Multiple Regression Analysis of All Measurements in the 74 Patients Surviving the First 24 Hours of Septic Shock**

| Variable | $R^2$ at End of Stepwise Regression Analysis | $P$ Value of the $R^2$ Change |
|---|---|---|
| Lactime (h) | 0.266 | 0.001 |
| Age (y) | 0.384 | 0.001 |
| Heart rate (bpm) | 0.440 | 0.02 |
| Mean arterial pressure (mm Hg) | 0.485 | 0.04 |



Excerpta Medica

The American Journal of Surgery

The American Journal of Surgery 185 (2003) 485–491

Scientific paper

# Serum lactate and base deficit as predictors of mortality and morbidity

Farah A. Husain, M.D.*, Matthew J. Martin, M.D., Philip S. Mullenix, M.D., Scott R. Steele, M.D., David C. Elliott, M.D.

*Department of Surgery, Madigan Army Medical Center, Fort Lewis, WA 98431, USA*

Manuscript received January 13, 2003; revised manuscript January 23, 2003

Presented at the 89th Annual Meeting of the North Pacific Surgical Association, Seattle, Washington, November 8–9, 2002

Table 3
Independent predictors of total mortality among all patients (n = 137)

| Independent variable | Significance (*P*) |
|---|---|
| Significant independent predictor | |
| APACHE II score | 0.000 |
| Lactate clearance time | 0.007 |
| 24-Hour lactate | 0.021 |
| Not significantly predictive | |
| Initial base deficit | 0.179 |
| Age | 0.436 |
| Sex | 0.573 |
| Initial lactate | 0.872 |
| 24-Hour base deficit | 0.957 |

Clearance time : temps d’apparition du premier lactate normal

# Correlation of Serial Blood Lactate Levels to Organ Failure and Mortality After Trauma

PANAGIOTIS MANIKIS, MD,
STANISLAW JANKOWSKI, FRCA, MRCP, HAIBO ZHANG, MD,
ROBERT J. KAHN, MD, JEAN-LOUIS VINCENT, MD, PHD

AMERICAN JOURNAL OF EMERGENCY MEDICINE ■ Volume 13, Number 6 ■ November 1995

**TABLE 4.** Demographic Data, Scores, Blood Lactate Levels, and Duration of ICU Stay in Relation to Mortality and Morbidity in the 129 Patients (Mean and Range of Values)

| | Outcome | | Organ Failure | |
|---|---|---|---|---|
| | Survivors | Nonsurvivors | Absent | Present |
| Number of patients | 100 | 29 | 45 | 84 |
| Age (years) | 36 (17-88) | 43 (17-78) | 33 (18-81) | 34 (17-88) |
| ISS | 21 (1-61) | 31 (9-66)* | 21 (1-61) | 24 (4-66) |
| Glasgow coma score | 11.5 (3-15) | 5.3 (3-15)* | 12.6 (3-15) | 8.8 (3-15)* |
| RTS | 6.7 (4.1-78) | 4.0 (1.7-7.8)* | 6.7 (4.7-7.8) | 5.8 (1.7-7.8)* |
| TRISS score | 89 (22-99) | 40 (1-94)* | 90 (22-99) | 72 (1-99)* |
| Initial lactate, mEq/L | 2.8 (0.4-10.2) | 4.0 (1-12.7)† | 2.4 (0.4-7.6) | 3.4 (0.7-12.7)* |
| Highest lactate, mEq/L | 3.4 (0.4-12.3) | 4.6 (1-12.7)† | 2.8 (0.4-8.9) | 4.1 (0.7-12.7)* |
| Lactime, days | 1.6 (0-8) | 2.2 (0-8) | 1.0 (0.0-4.0) | 2.2 (0-8)* |
| ICU stay, days | 8.7 (2-31) | 7.8 (1-27) | 4.3 (2-22) | 10.8 (1-31)* |

* $P < .01$, † $P < .05$ versus preceding column.

ABBREVIATIONS: ISS, injury severity score; RTS, revised trauma score.

Excerpta Medica

The American Journal of Surgery

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Scientific paper

# Prolonged lactate clearance is associated with increased mortality in the surgical intensive care unit

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| | Group 1 (n = 12) No clearance | Group 2 (n = 16) 48–98 hours | Group 3 (n = 15) 24–48 hours | Group 4 (n = 51) <24 hours |
|---|---|---|---|---|
| Mortality | 100% | 42.5% | 13.3% | 3.9% |
| Age (years) | 68.9 ± 8.8 | 68.7 ± 13.6 | 67.6 ± 13.0 | 73.6 ± 10.2 |
| Apache II score | 23 ± 6.2 | 19.6 ± 5.7 | 17.2 ± 6.2 | 16.6 ± 4.9 |
| Apache III score | 74.4 ± 28.2 | 73.3 ± 20.7 | 62.9 ± 24.1 | 53.9 ± 15.6 |
| Predicted mortality (%) | 50.5 ± 24.6 | 32.8 ± 23.0 | 30.1 ± 13.9 | 29.6 ± 15.4 |
| Oxygen delivery (mL · min$^{-1}$ · m$^{-2}$) | 497.6 ± 134.2 | 519.4 ± 203.6 | 641.7 ± 330.9 | 557.7 ± 144.9 |
| Oxygen consumption (mL · min$^{-1}$ · m$^{-2}$) | 133.9 ± 55.7 | 137 ± 44.4 | 109 ± 12.1 | 130 ± 51.2 |
| Initial systolic blood pressure (mm Hg) | 84.7 ± 14.1 | 97.4 ± 38.3 | 105.8 ± 44.5 | 135.2 ± 50.9 |
| pH | 7.23 ± 0.15 | 7.29 ± 0.06 | 7.33 ± 0.13 | 7.38 ± 0.07 |
| Initial lactate level (mmol/L) | 9.5 ± 6.1 | 6.15 ± 2.5 | 5.26 ± 2.4 | 2.26 ± 1.09 |