# Metabolic Resuscitation: a new approach to sepsis?

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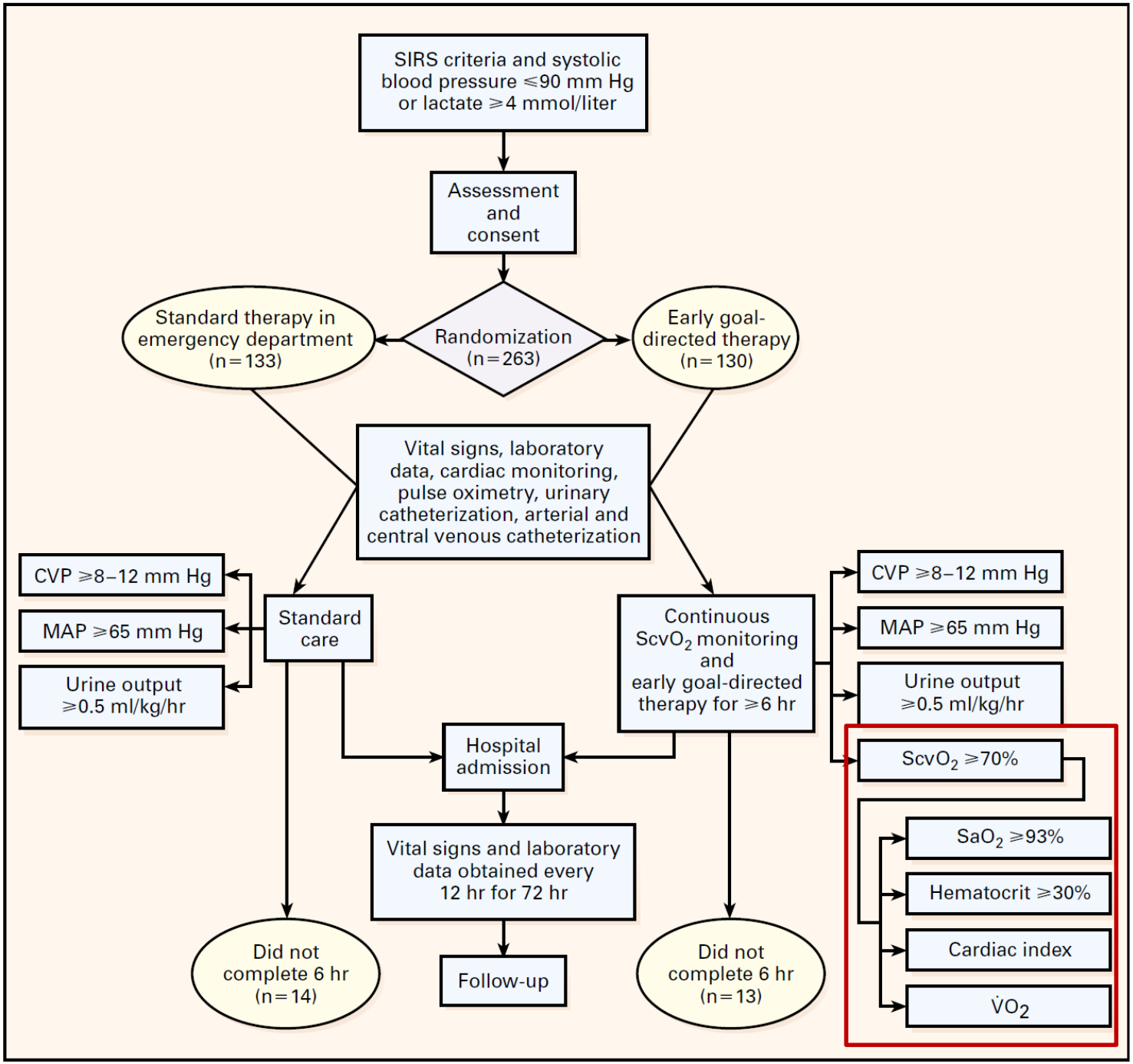
# Research Support/Disclosures

- NIH K23 HL128814-01A1 (PI)
- American Heart Association grants (co-investigator)


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)

ORIGINAL ARTICLE

# Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*

ORIGINAL ARTICLE

# Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

The NEW ENGLAND JOURNAL of MEDICINE

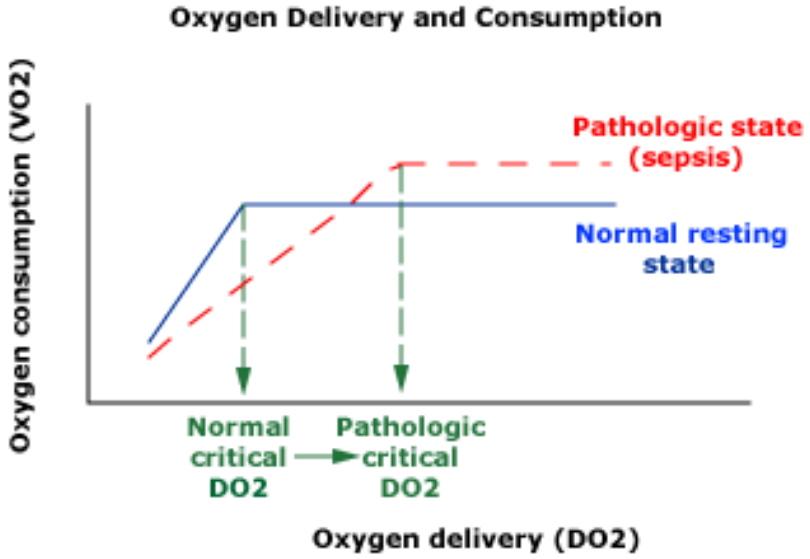
ESTABLISHED IN 1812 MAY 1, 2014 VOL. 370 NO. 18

# A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

# Why isn't it working?

## Oxygen delivery (DO2) and consumption (VO2)




In the normal state (blue line), oxygen consumption is constant over a range of DO2, and decreases only when DO2 falls below a critical level (critical DO2). Pathologic changes caused by sepsis or systemic inflammatory responses (red line) cause increased VO2 and impaired peripheral oxygen utilization, resulting in an elevation in critical DO2.

UpToDate®

**Oxygen transport patterns in patients with sepsis syndrome or septic shock: Influence of treatment and relationship to outcome.**

Hayes, Michelle; MD, FRCA; Timmins, Andrew; Yau, Ernest; Palazzo, Mark; MD, FRCP; Watson, David; Hinds, Charles

Critical Care Medicine. 25(6):926-936, June 1997.

| | Survivors | | | Nonsurvivors | | |
|---|---|---|---|---|---|---|
| | T0 | T1 | Tmax | T0 | T1 | Tmax |
| MAP (mm Hg) | 82 ± 73, 95 | 91 ± 80, 106 | 93 ± 86, 101[a] | 69 ± 64, 76[b] | 69 ± 65, 82[b] | 84 ± 80, 91[c, d] |
| PAOP (mm Hg) | 9 ± 6, 11 | 16 ± 15, 17[c] | 12 ± 10, 14[e] | 6 ± 10, 13 | 16 ± 15, 17[e] | 15 ± 13, 16[d, e] |
| SVRI (dyne·sec/cm$^5$·m$^2$) | 1622 ± 1417, 1924 | 1480 ± 1113, 1773[a] | 1120 ± 956, 1399[c] | 1379 ± 1110, 1859 | 1271 ± 1052, 1843 | 1174 ± 1082, 1281[a] |
| LVSWI (g·m$^2$) | 36 ± 32, 52 | 40 ± 33, 66[a] | 60 ± 49, 67[c] | 23 ± 18, 33[f] | 24 ± 17, 34[f] | 40 ± 33, 46[c, f] |
| C(a-$\bar{v}$)$o_2$ (mL/dL) | 3 ± 2.92, 3.98 | 2.9 ± 2.41, 3.64 | 2.6 ± 2.13, 3[a] | 3.23 ± 2.9, 3.72 | 3.33 ± 2.59, 3.87 | 2.43 ± 2.25, 2.77[c] |
| $O_2$ extr (%) | 0.23 ± 0.21, 0.28 | 0.21 ± 0.16, 0.28 | 0.17 ± 0.15, 0.22[e] | 0.25 ± 0.23, 0.3 | 0.24 ± 0.2, 0.29[a] | 0.15 ± 0.14, 0.17[c] |
| CI (L/min/m$^2$) | 3.99 ± 2.87, 4.23 | 4.17 ± 3.9, 5.18[e] | 6.22 ± 5.1, 6.68[c] | 3.38 ± 2.79, 3.97 | 3.55 ± 2.935, 4.03[b] | 5 ± 4.28, 5.77[b, c] |
| $\dot{D}o_2$ (mL/min/m$^2$) | 454 ± 382, 579 | 642 ± 460, 739[a] | 997 ± 739, 1081[c] | 435 ± 363, 577 | 489 ± 402, 606 | 800 ± 691, 865[c, d] |
| $\dot{V}o_2$ (mL/min/m$^2$) | 120 ± 95, 133 | 121 ± 112, 133 | 170 ± 136, 172[e] | 108 ± 101, 124 | 109 ± 97, 131 | 120 ± 106, 139[f] |

MAP, mean arterial pressure; PAOP, pulmonary artery occlusion pressure; SVRI, systemic vascular resistance index; LVSWI, left ventricular stroke work index; C(a-$\bar{v}$)$o_2$, arterial-venous oxygen content difference; $O_2$ extr, oxygen extraction ratio; CI, cardiac index; $\dot{D}o_2$, oxygen delivery; $\dot{V}o_2$, oxygen consumption.

[a] $p < .05$ within group statistics, when compared with baseline; [b] $p < .01$ between group statistics; [c] $p < .001$ within group statistics, when compared with baseline; [d] $p < .05$ between group statistics; [e] $p < .01$ within group statistics, when compared with baseline; [f] $p < .001$ between group statistics.

Data are expressed as median ± 25th, 75th percentiles.

# Cytopathic Hypoxia

- The breakdown of aerobic metabolism in the presence of adequate oxygen delivery
- Failure of oxygen extraction
- No known way to improve extraction

59 year-old man, found on the street, confused

T 98.6 P 110 BP 84/60 RR 32 Sat 98%

Gen: Tachyapneic, dry mucous membranes

Chest: CTA bilaterally Heart: S1 S2 reg

Abd: Soft, mild diffuse tenderness

Neuro: A & O x 2, no focal neuro findings

Extrem: Cool, clammy

Arterial Blood Gas:

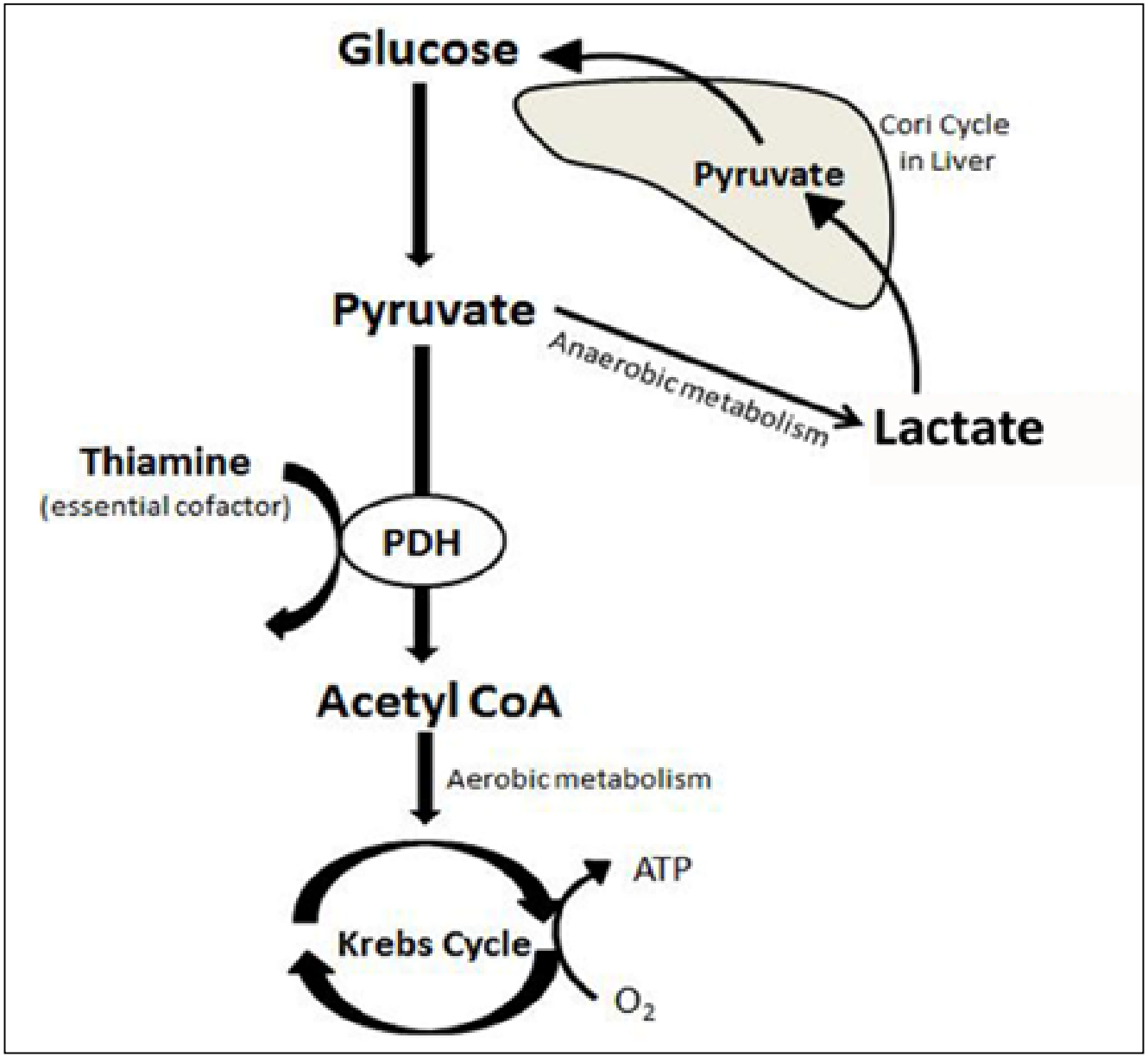
pH: 6.9 $pCO_2$: 10 $HCO_2$: 3

$pO_2$: 80 Sat: 96% Lactate: 27.2 mmol/dl

Complete Blood Count:

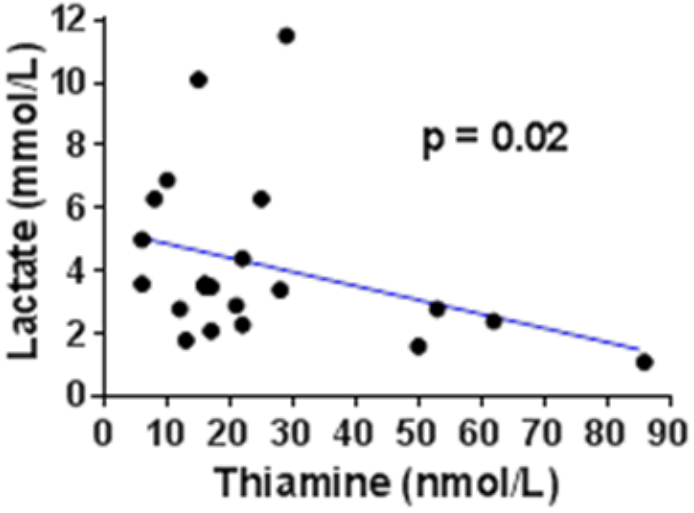
White Cell Count: 3.4 Hemoglobin: 8.1

Platelets: 230

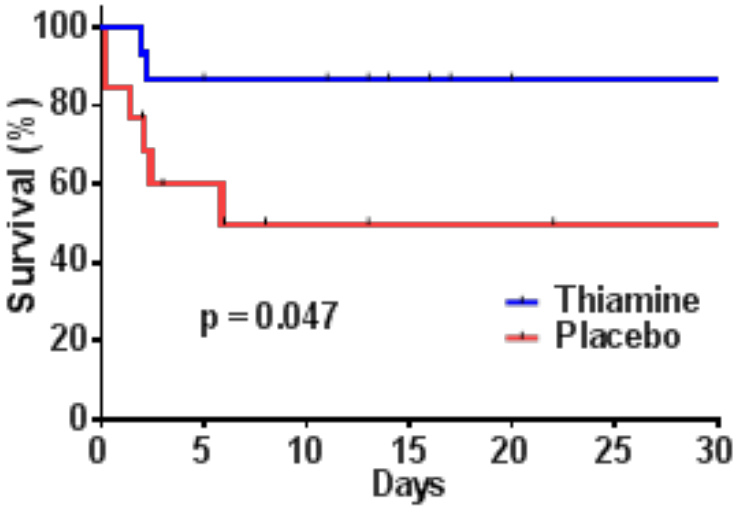

Glucose
Cori Cycle
in Liver
Pyruvate
Pyruvate
Anaerobic metabolism
Lactate
Thiamine
(essential cofactor)
PDH
Acetyl CoA
Aerobic metabolism
ATP
Krebs Cycle
O2

# Thiamine Deficiency in Critical Illness

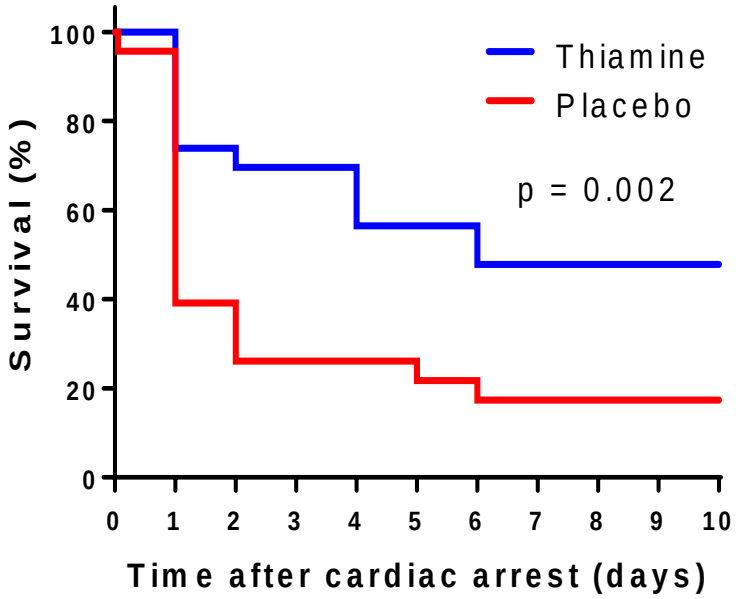
- 35% (28/80) of septic shock patients with elevated lactate
- 45% (7/16) of post-arrest patients
- Inverse correlation between thiamine and lactate in:
  - Sepsis
  - Post-arrest
  - DKA



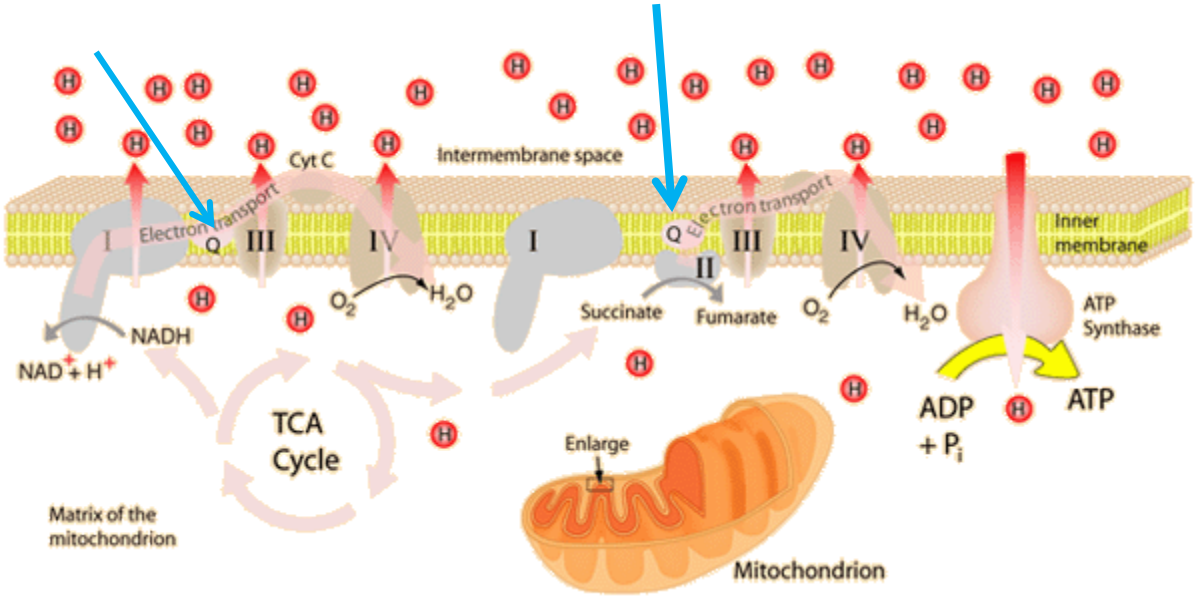
Thiamine decreased lactate and improved survival in septic shock patients with thiamine deficiency

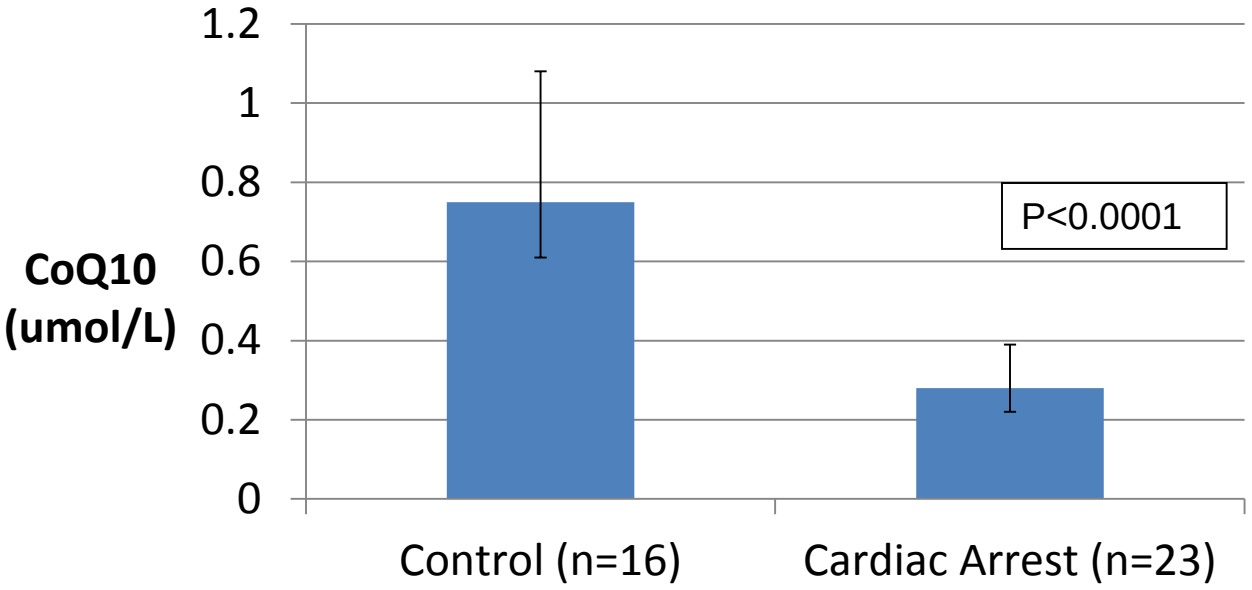



Thiamine improved survival in mouse model of cardiac arrest

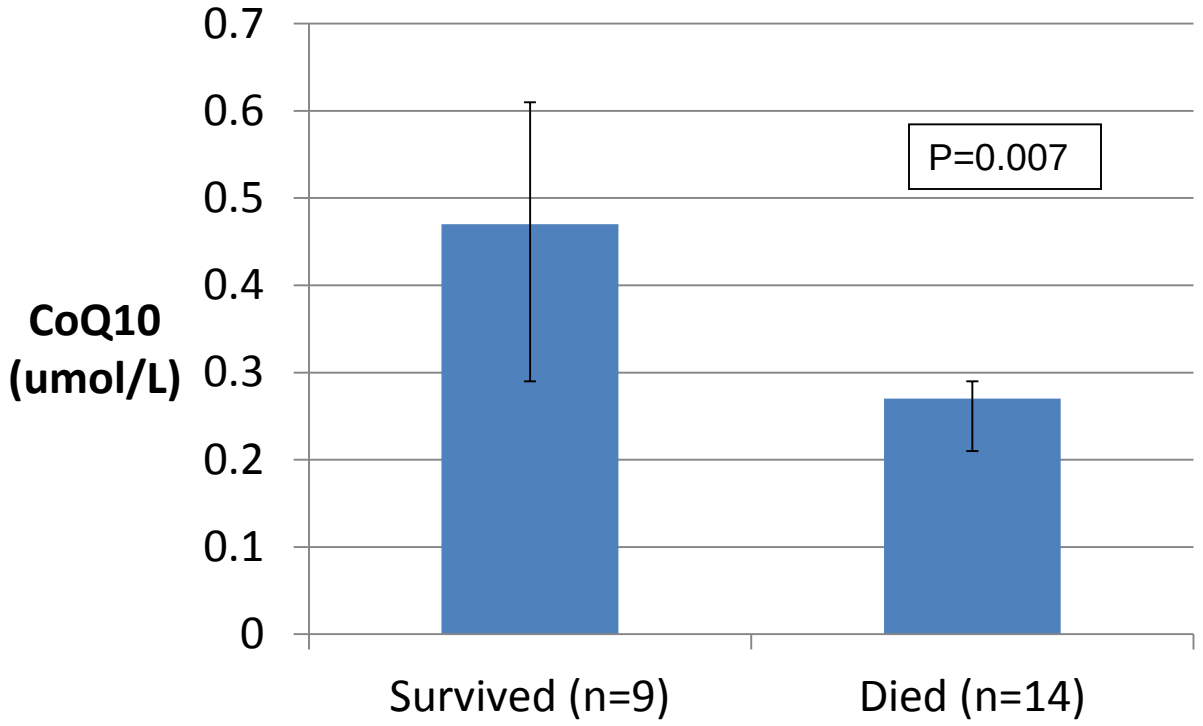


# What about Coenzyme Q10?

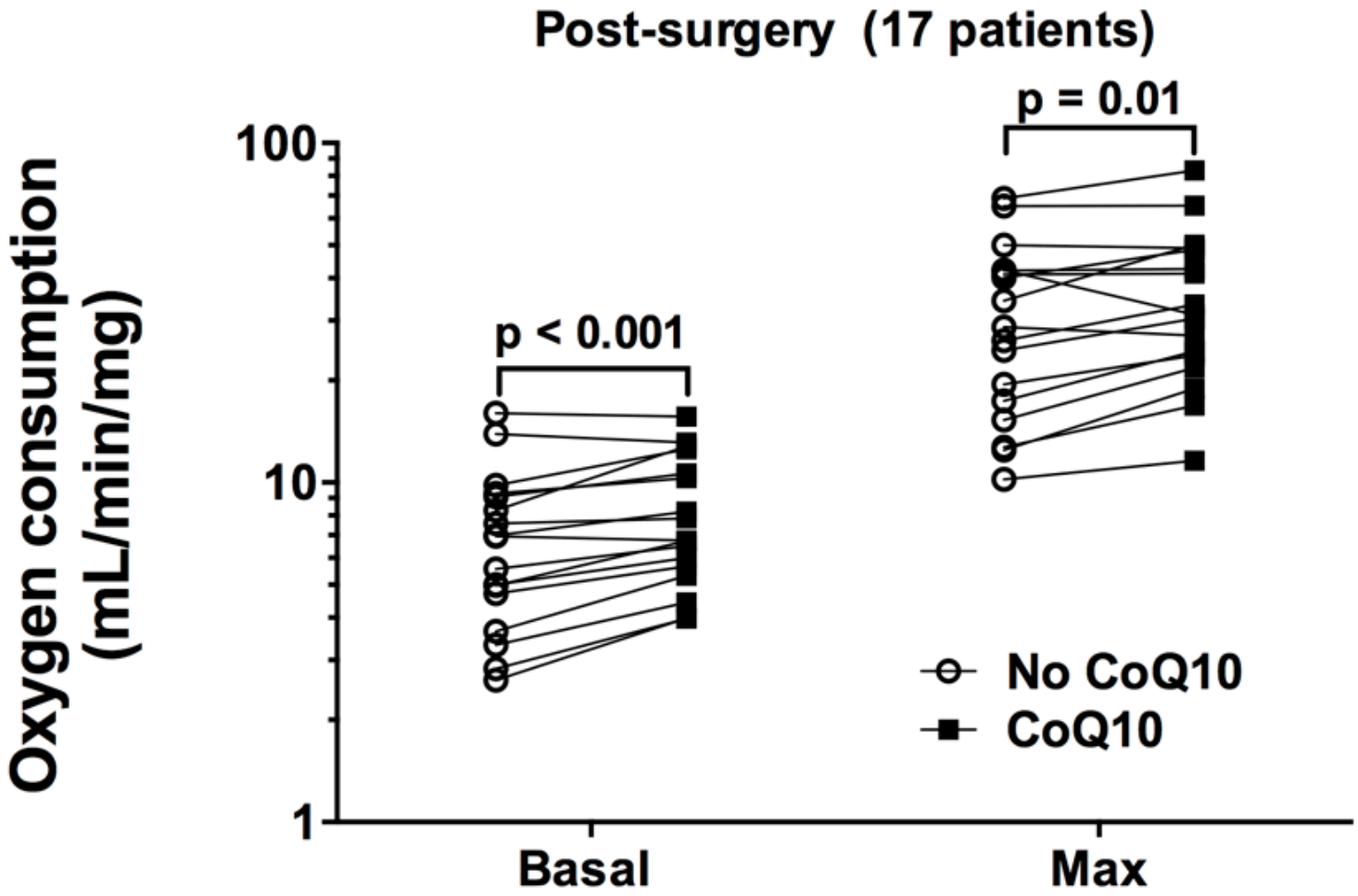





CoQ10 is low after cardiac arrest, and associated with survival



# CoQ10 increases in vitro oxygen consumption after cardiac surgery



EVMS MAGAZINE 2016-2017 | ISSUE 9.4

# A cure for sepsis?

A critical-care physician at Eastern Virginia Medical School has found what he believes is a cure for sepsis. The discovery came by accident as Paul Marik, MBBCh, was treating a patient who was dying of sepsis.

# Where do we go from here?

- Research, research, research
- Think about possible nutritional deficiencies in refractory shock
- Better understanding of mitochondrial function and how to support it may redefine “supportive care” of the critically ill patient

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