ANTIOXIDANT AND NUTRITION

André Van Gosssum, MD, PhD &
Jean-Charles Preiser, MD, PhD

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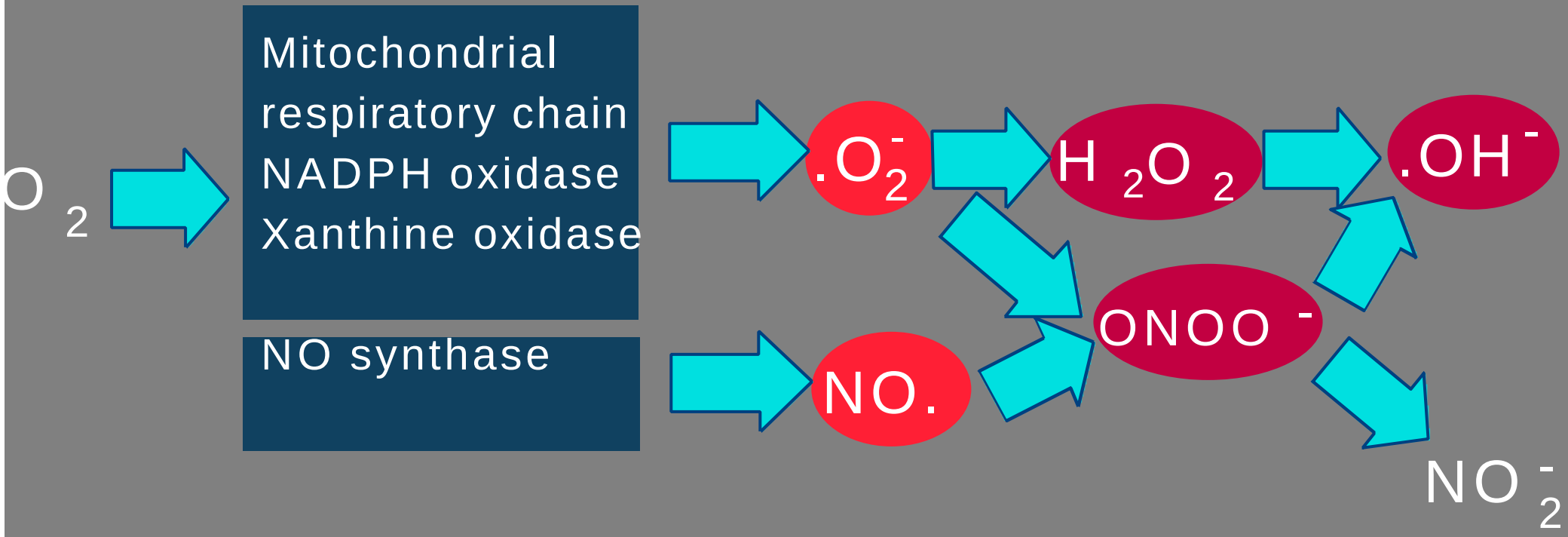
- 3 - Adding antioxidant compounds to nutrition support is physiological.

REACTIVE OXYGEN SPECIES

Adapted from Favier and Leverve



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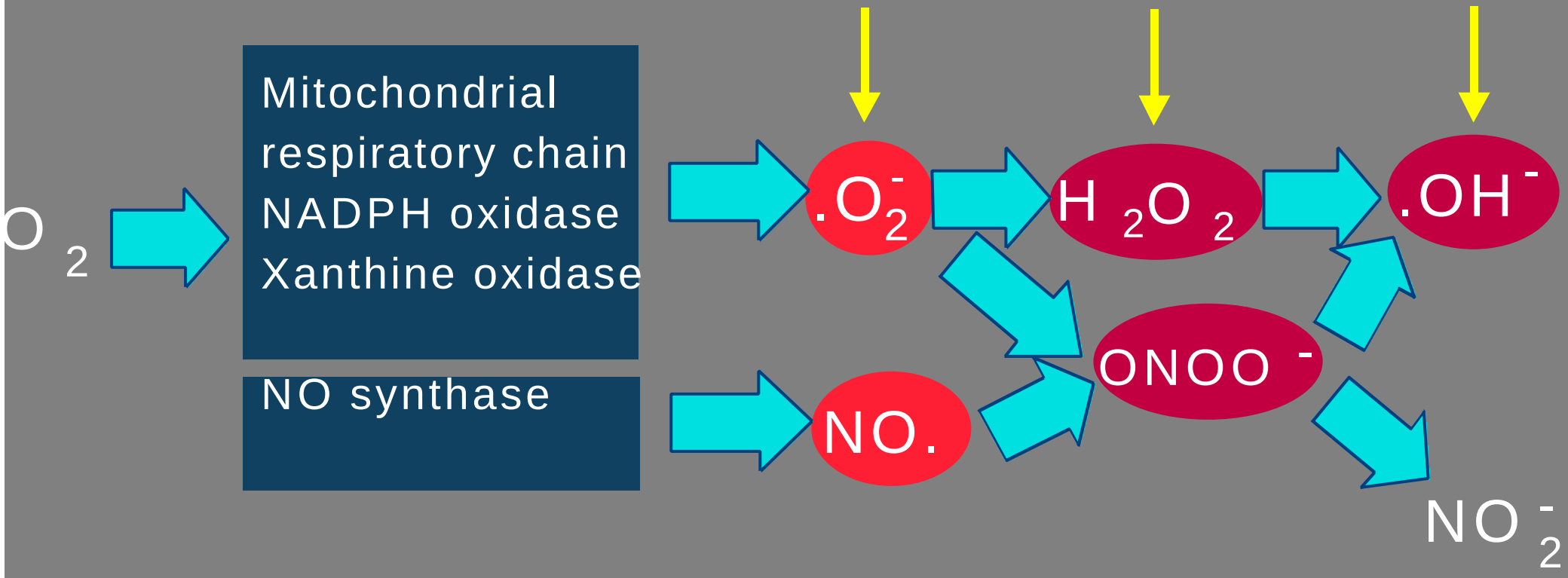

ANTIOXIDANT MECHANISMS

- **Free electron scavengers**
  - **Exogenous : Vitamins A, C and E, ubiquinone**
  - **Endogenous : Glutathione**

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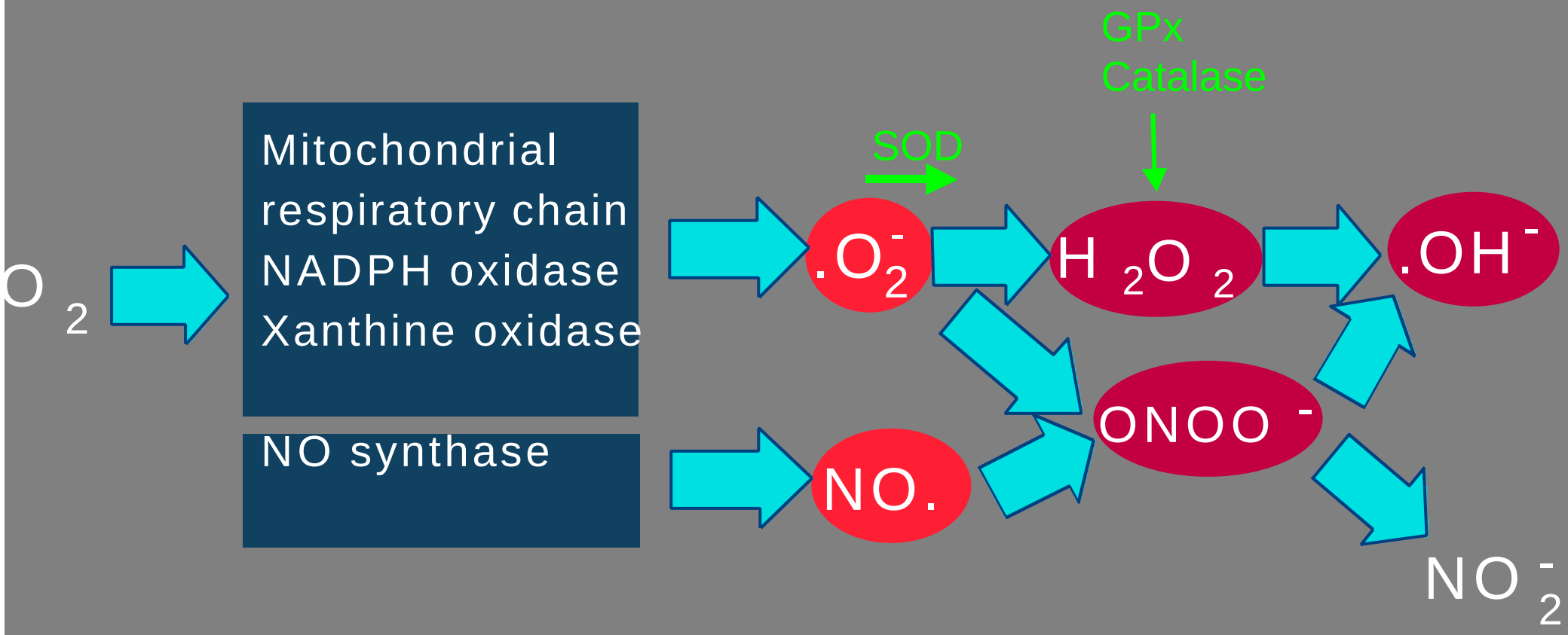

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  - Glutathione peroxydase (Se)

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- **Uric acid, bilirubin, albumin**

BIOMARKERS OF OXIDATIVE STRESS

- ↗Total antioxidant capacity
- ↗Antioxidant enzyme activity
- ↗SOD, GPx, Catalase
- ↗Nonenzymatic antioxidant concentration (plasma or tissue)
- ↗GSH, vitamins A, C, E, ubiquinol
- ↗Oxidative damage
- ↗proteins, lipids, DNA
- ↗Resistance to oxidative stress

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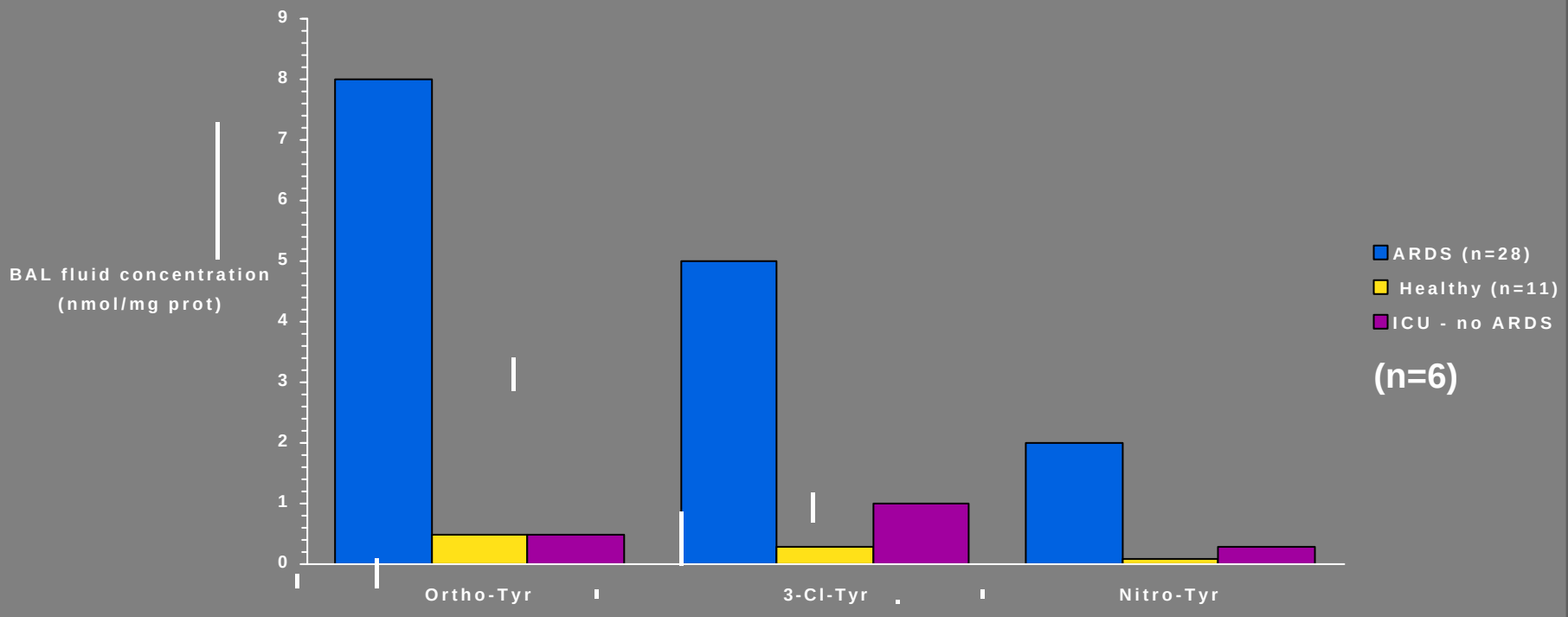
OXIDATIVE DAMAGE IN ARDS

- **Patients:** 26 patients with ARDS
  6 ventilated patients without ARDS
  11 normal healthy controls
- **Methods:** Bronchoalveolar lavage fluid samples
  - ® Orthotyrosine (aromatic hydroxylation of phenylalanine by $OH^{\bullet}$)
  - ® Chlorotyrosine (hypochlorous acid production by activated inflammatory cells)
  - ® Nitrotyrosine (reaction between NO and superoxide)
  - ® Myeloperoxydase (neutrophil recruitement and activation)

Lamb N., Crit Care Med 1999;27:1738

OXIDATIVE DAMAGE IN ARDS

Lamb et al Crit Care Med 2000;27:1738



PLASMA REDOX STATUS IN CRITICALLY ILL PATIENTS

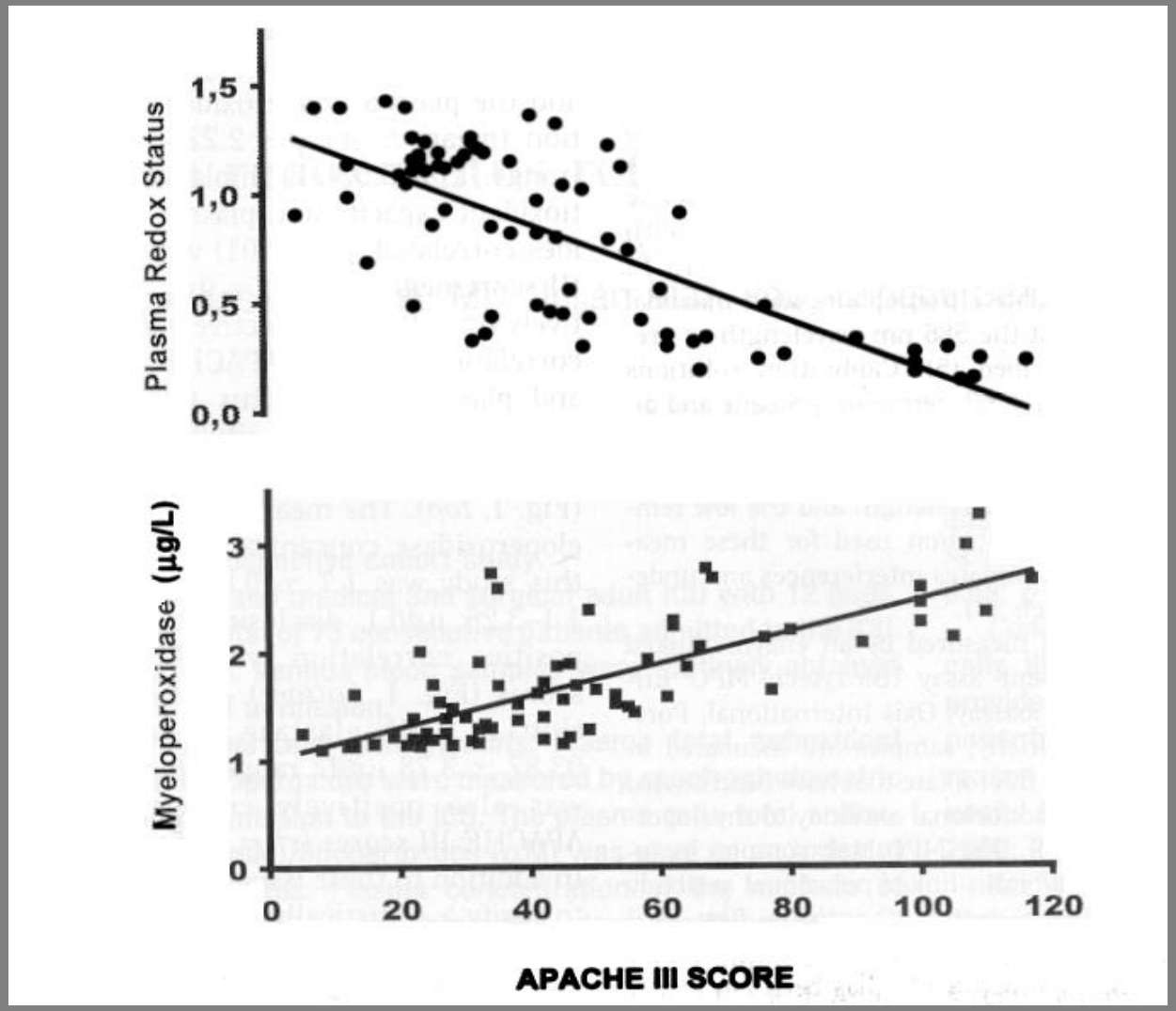
- **Patients:** 73 consecutive patients admitted to the ICU
- **Methods:** Venous blood samples with 24 hours
  - ® index of plasma redox status

    $$\frac{\text{total anti-oxydant capacity (mM)}}{\text{lipoperoxides (µM)}}$$

  - ® marker of leukocyte activation (myeloperoxidase/elastase)
  - ® severity index Apache III score

Alonso De Vega J., Crit Care Med 2000;28:1812

ANTIOXIDANT CAPACITY INVERSELY CORRELATES WITH DISEASE SEVERITY



Alonso de Vega et al Crit Care Med 2000;28:1813

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ANTIOXIDANT STORES ARE DEPLETED

- **Schorah et al Am J Clin Nutr 1996; 63: 760**
  - ***...median concentrations of total vitamin C and ascorbic acid in critically ill patients were < 25 % of the values found in healthy control and in subjects in which reactive oxygen species are reported to be increased***
- **Dasgupta et al Life Sci 1997;60:335**
  - ***..antioxidant capacity of serum was significantly reduced in MICU patients***
- **Nguyen et al J Burn Care Rehabil 1993;14:602**
  - ***... patients with burns reduced levels of vitamin E***

ANTIOXIDANT STORES ARE DEPLETED *(continued)*

- **Forceville et al Crit Care Med 1998;26:1536**
  - ***134 medicosurgical ICU pts… low plasma selenium values. inversely correlated with Apache II, SAPS II, presence of SIRS.***
- **Curran et al Br J Surg 2000;87:301**
  - ***…13 consecutive patients…compared with 26 matched controls. Pts had significantly lower levels of antioxidants (retinol, alpha-tocopherol, beta-carotene) than controls. In patients with mild acute pancreatitis (AP), the concentrations were higher than those in patients with severe AP. This coincided with a reduction in CRP level.***

THERAPEUTIC INTERVENTIONS

- Glutathione precursor (N-acetylcysteine, procysteine)

N-ACETYLCYSTEINE

N-acetylcysteine ® Cysteine ® Gluthatione

- ® Antioxidant
- ® Cardiovascular function (vasodilatation, regional blood flow)
- ® Immune function (suppression of nuclear factor-k B activation)

EFFECTS OF GLUTATHIONE PRECURSORS

Walsh and Lee Intensive Care Med 1999;25:432

...despite positive experimental evidence, clinical trials of N-acetylcysteine in humans have equivocal results.... patients with established ARDS found no benefit (Jepsen Crit Care Med 1992) whereas another observed a trend towards decreased lung injury scores ventilatory requirements (Bernard Chest 1997, Suter Chest 1994) ... similar results in patients with sepsis-associated lung injury (Spapen Chest 1998).

...multicenter trial in ALI of procysteine, which was stopped because of *concern regarding mortality in the intervention group.*

THERAPEUTIC INTERVENTIONS

- Glutathione precursor (N-acetylcysteine, procysteine)
- Trace elements

SELENIUM REPLACEMENT IN PATIENTS WITH SEVERE SIRS

↗**Patients:** 42 patients

↗**Methods:** Se+ 535 ® 155 µg sodium selenite (IV)

Se- 35 µg sodium selenite (IV)

↗ **Results:** - Apache III score lower in Se+ (p. 045)

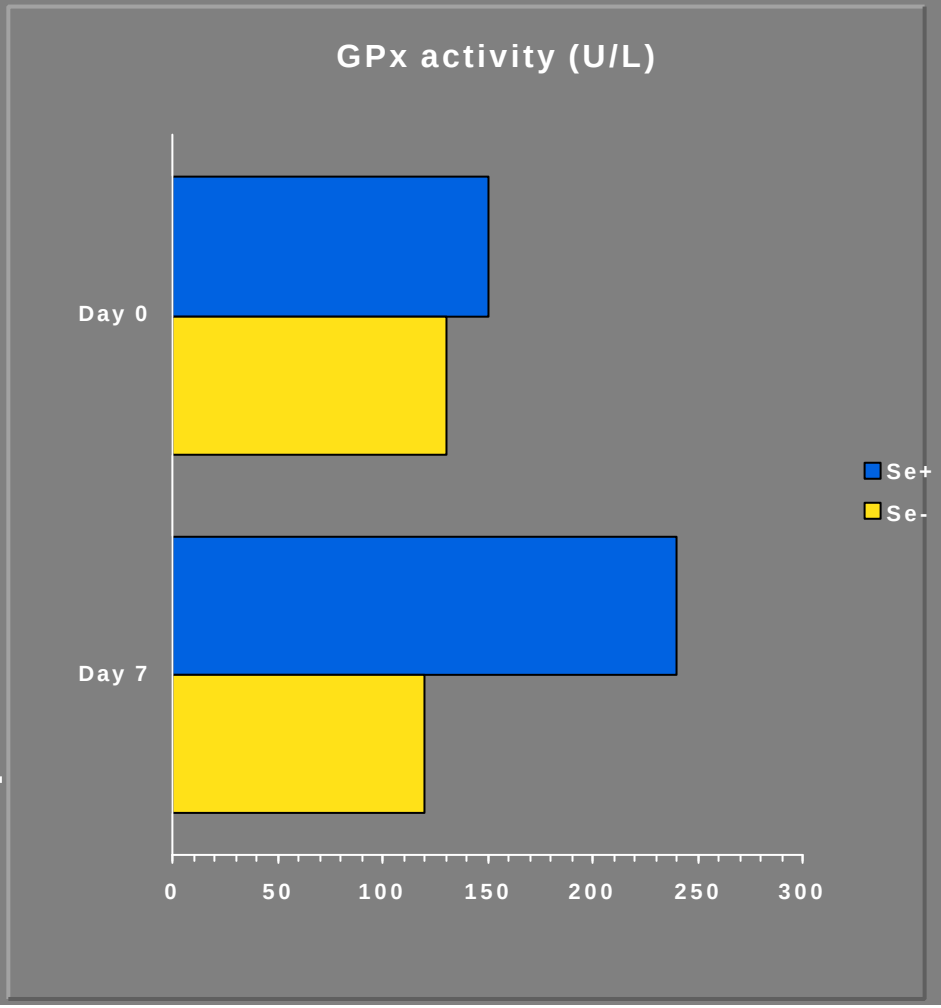
- Lower incidence of hemodialysis in Se+

Angstwurm M., Crit Care Med 1999;27:1607

EFFECTS OF SELENIUM

Angstwurm Crit Care Med 1999;27:1807

- 42 pts with SIRS, Apache II > 15
- Randomized for 9d to
  - Se 535, 285, 155 µg/d (Se+)
  - Se 35 µg/d (Se-)
- CVVH in 9/21 (Se-) vs 3/21 (Se+)



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NUTRITIONAL INTERVENTIONS

- Physiological

OXIDATIVE STRESS AND NUTRITION

- Good side
  - Nutrition brings
    - anti-oxidant molecules
- Bad side
  - Nutrition brings
    - pro-oxidant molecules (iron)
    - substrate for peroxidation (polyunsatrated fatty acids)

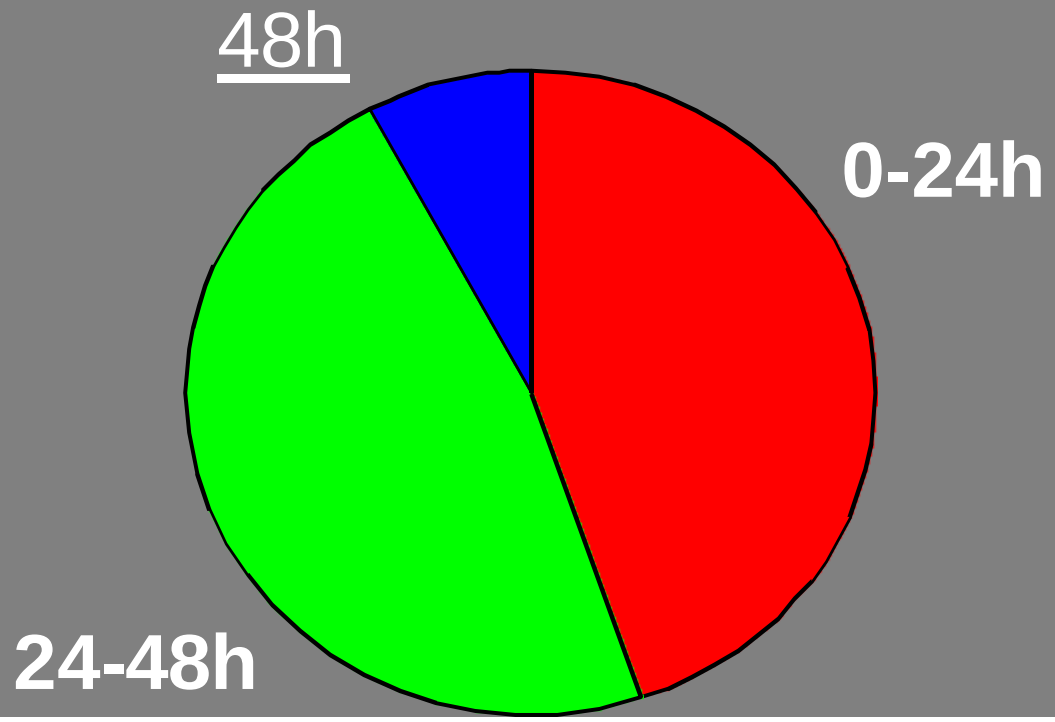
NUTRITIONAL INTERVENTIONS

- Physiological
- Early - prior to oxidant-induced damage

CURRENT PRACTICE OF ENTERAL NUTRITION

How soon after admission do you start enteral feeding?

Preiser et al Intens Care Med 1999;25:95-101



END POINTS OF THE STUDY

- Preiser et al Crit Care Med 2000; 28: 3828
- Absorption and fate of beta-carotene and alpha-tocopherol added to enteral nutrition formula.
- Effects on lipid peroxidation and resistance to an oxidative stress on erythrocytes and low-density lipoproteins.

PATIENTS' ELIGIBILITY

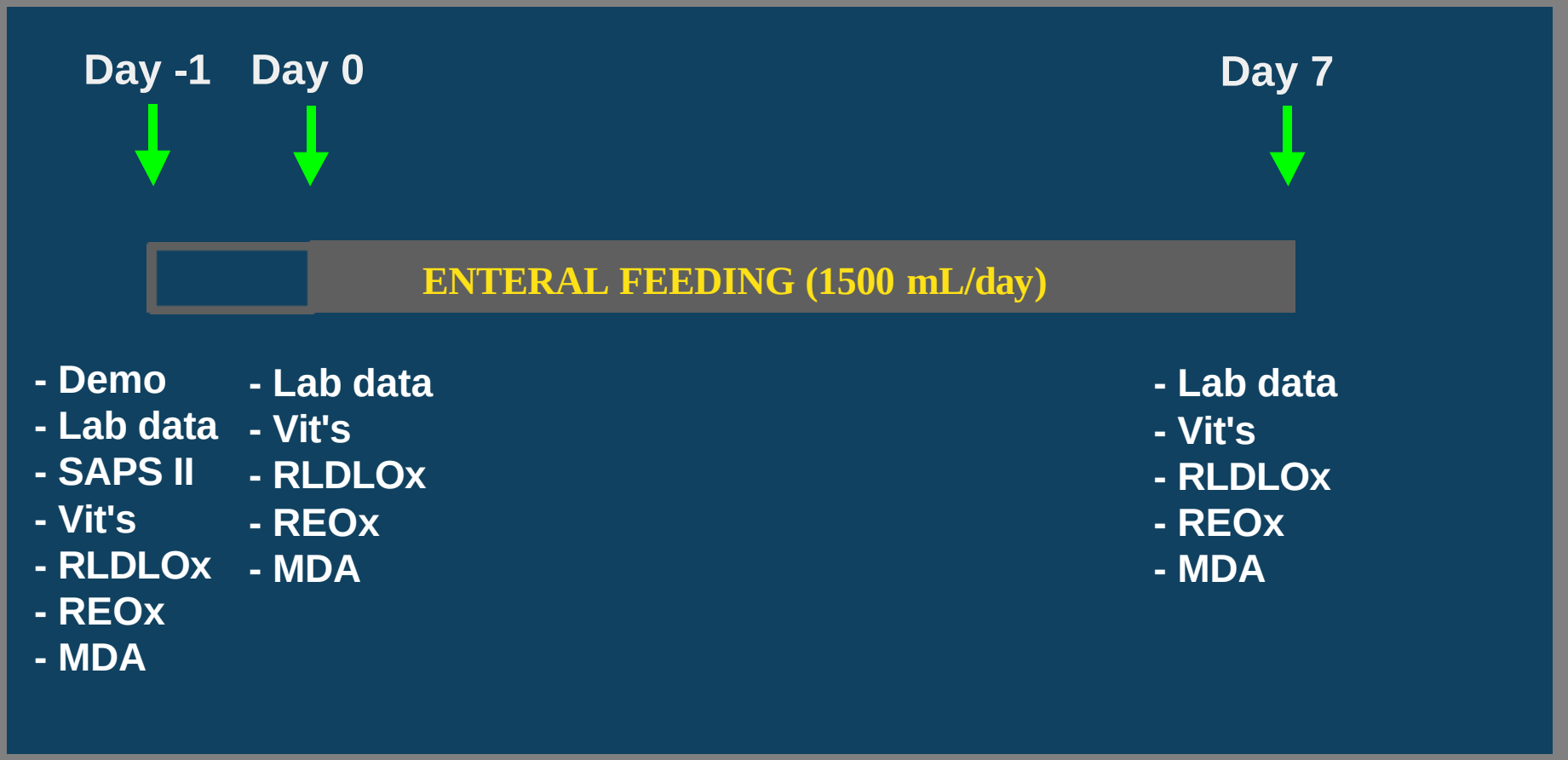
INCLUSION CRITERIA :

- Age > 18 years.
- Admitted in the Intensive Care Department and expected to stay for at least one week.
- Eligible for exclusive enteral nutrition for > 7 days with a polymeric solution.

EXCLUSION CRITERIA :

- Parenteral nutrition.
- Contra-indication to naso-gastric tube or gastrostomy.

STUDY PROTOCOL



RESISTANCE TO OXIDATIVE STRESS : METHODS

- Separation of erythrocytes (Dextran extraction method) and lipoproteins (Sequential ultracentrifugation).
- Erythrocyte resistance by haemolysis after AAPH challenge.
- LDL resistance to oxidation with copper sulfate.

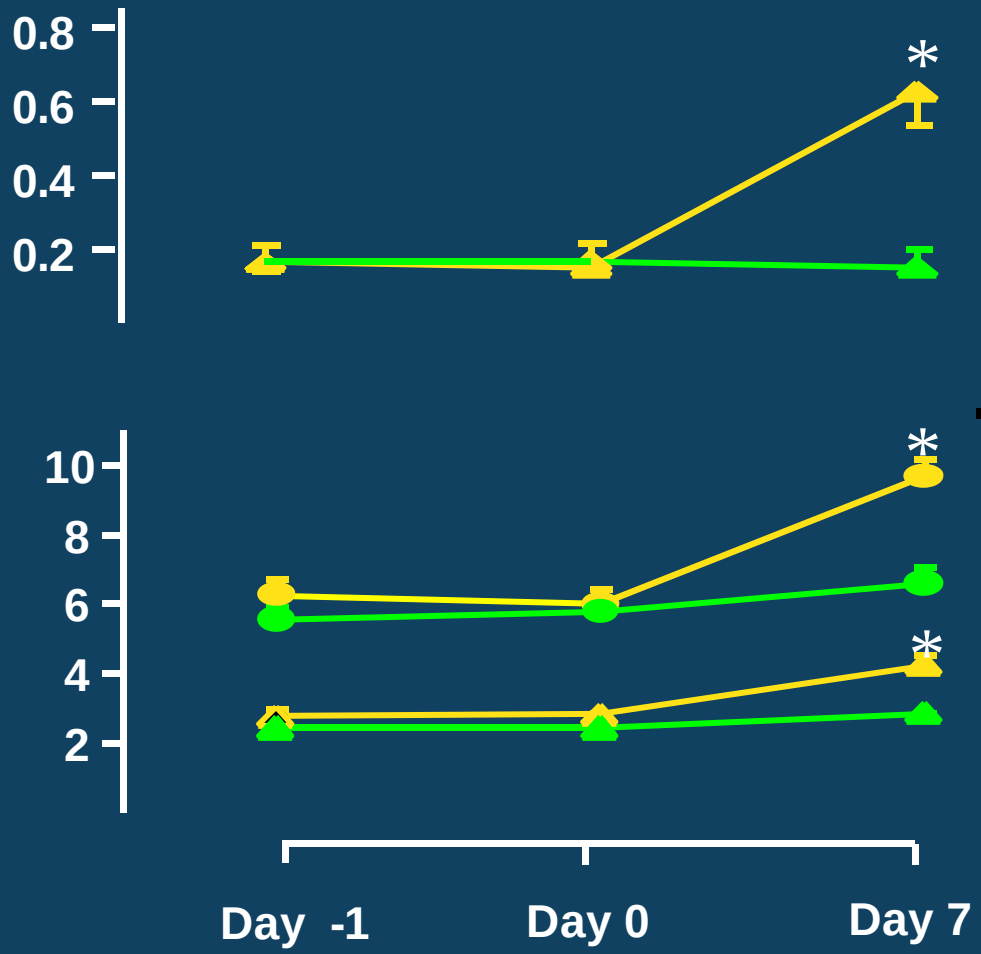
COMPOSITION OF THE FORMULAS

	PLACEBO	EXPERIMENTAL
Caloric content	125 kcal/dl	125 kcal/dl
Proteins	6.85 g/dl	6.85 g/dl
Free Arginine	0 g/dl	0.87 g/dl
Lipids	4.9 g/dl	4.9 g/dl
Carbohydrates	13.6 g/dl	13.6 g/dl
Vitamin A	66.7 µg/dl	133 µg/dl
B-carotene	0	67 µg/dl
Vitamin C	5 mg/dl	13.3 mg/dl
Vitamin E	0.81 mg/dl	4.94 mg/dl

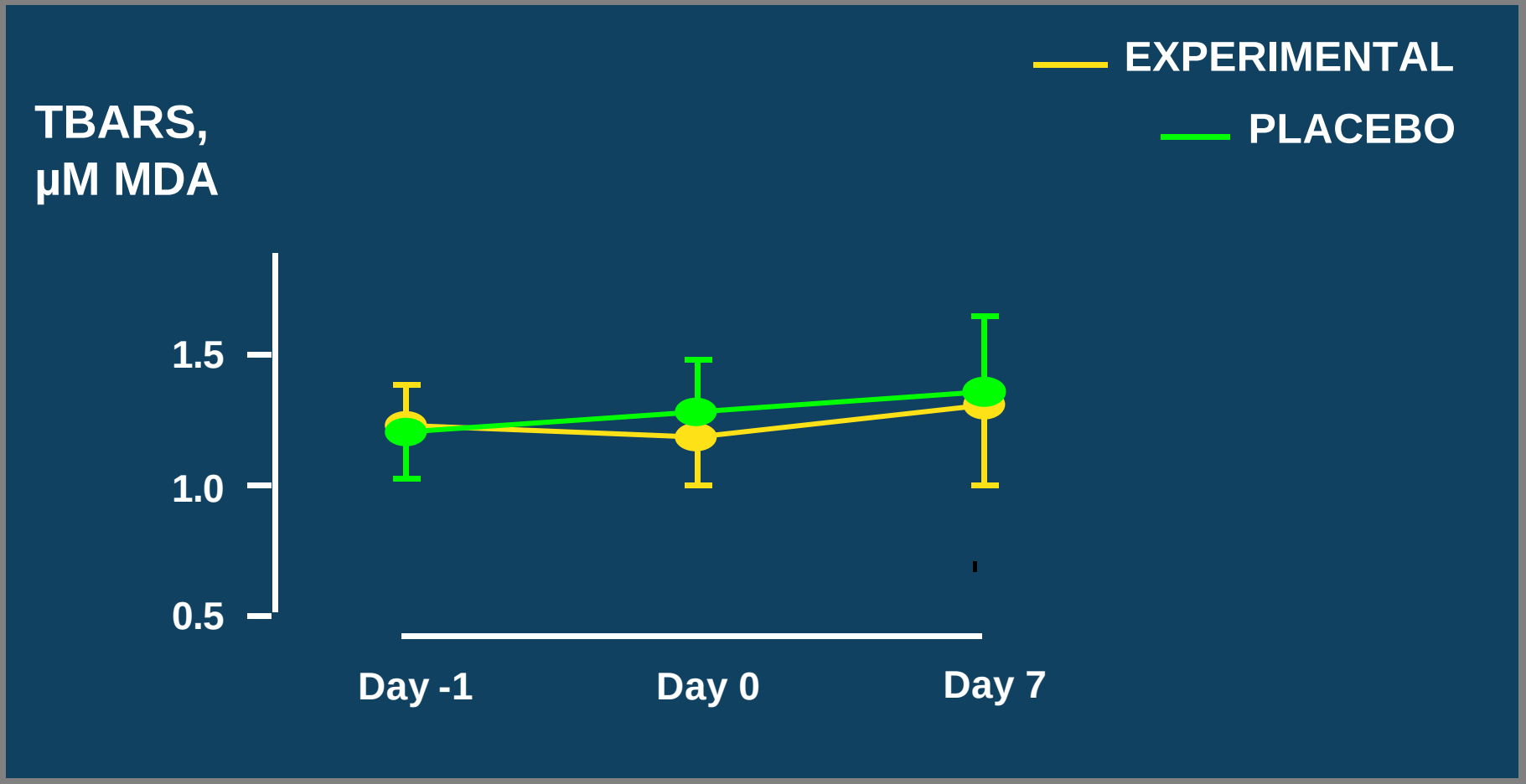
PATIENTS' CHARACTERISTICS

	PLACEBO	EXPERIMENTAL
# patients	17	20
Age	57 + 4	57 + 3
Sex (M/F ratio)	12/5	12/8
SAPS II	34 + 3	33 + 3
Resp failure	5	5
Neurological pts	11	15
Sepsis	1	0
Total volume	7049+299	7870+246
Daily volume	943+42	1074+33

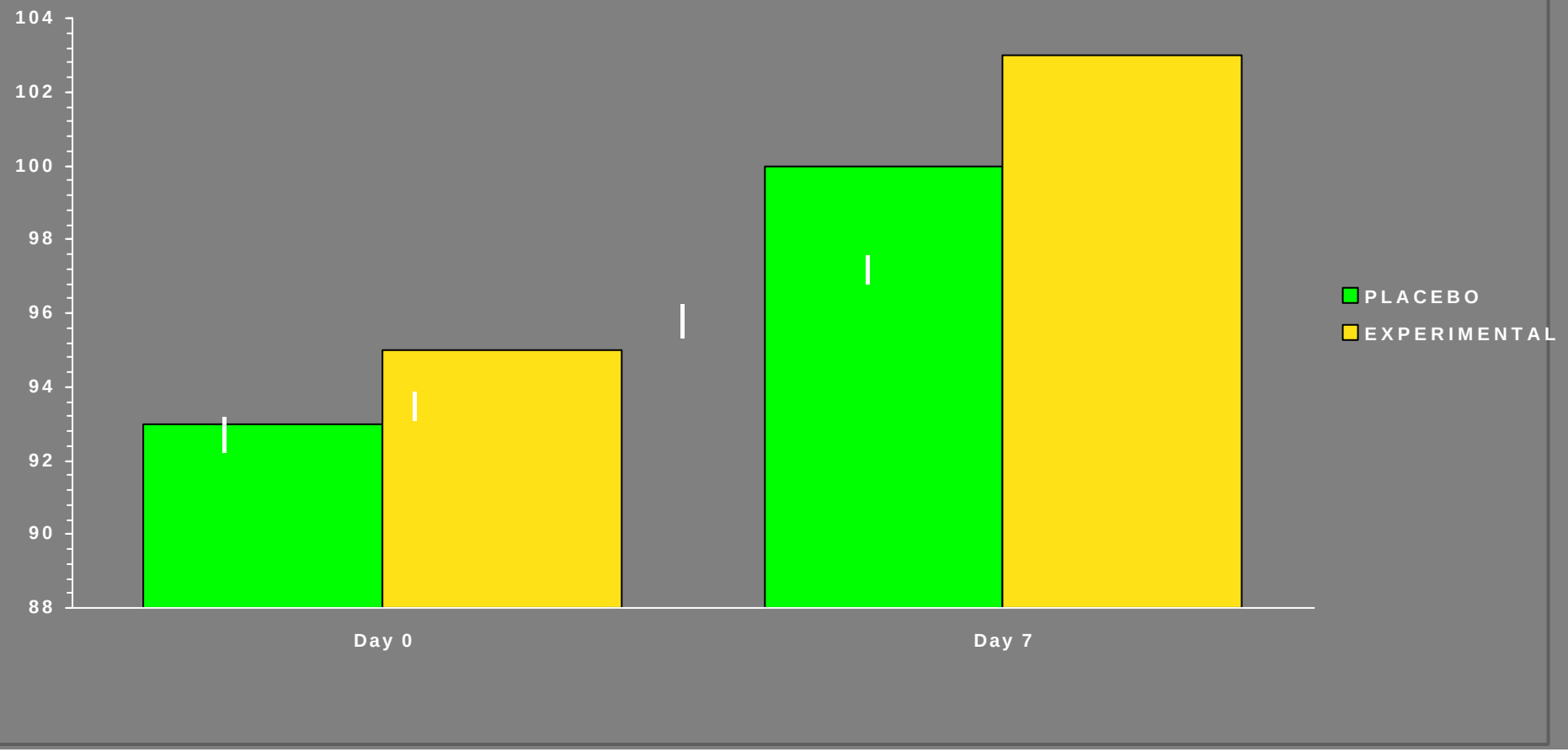
RESULTS : VITAMINS



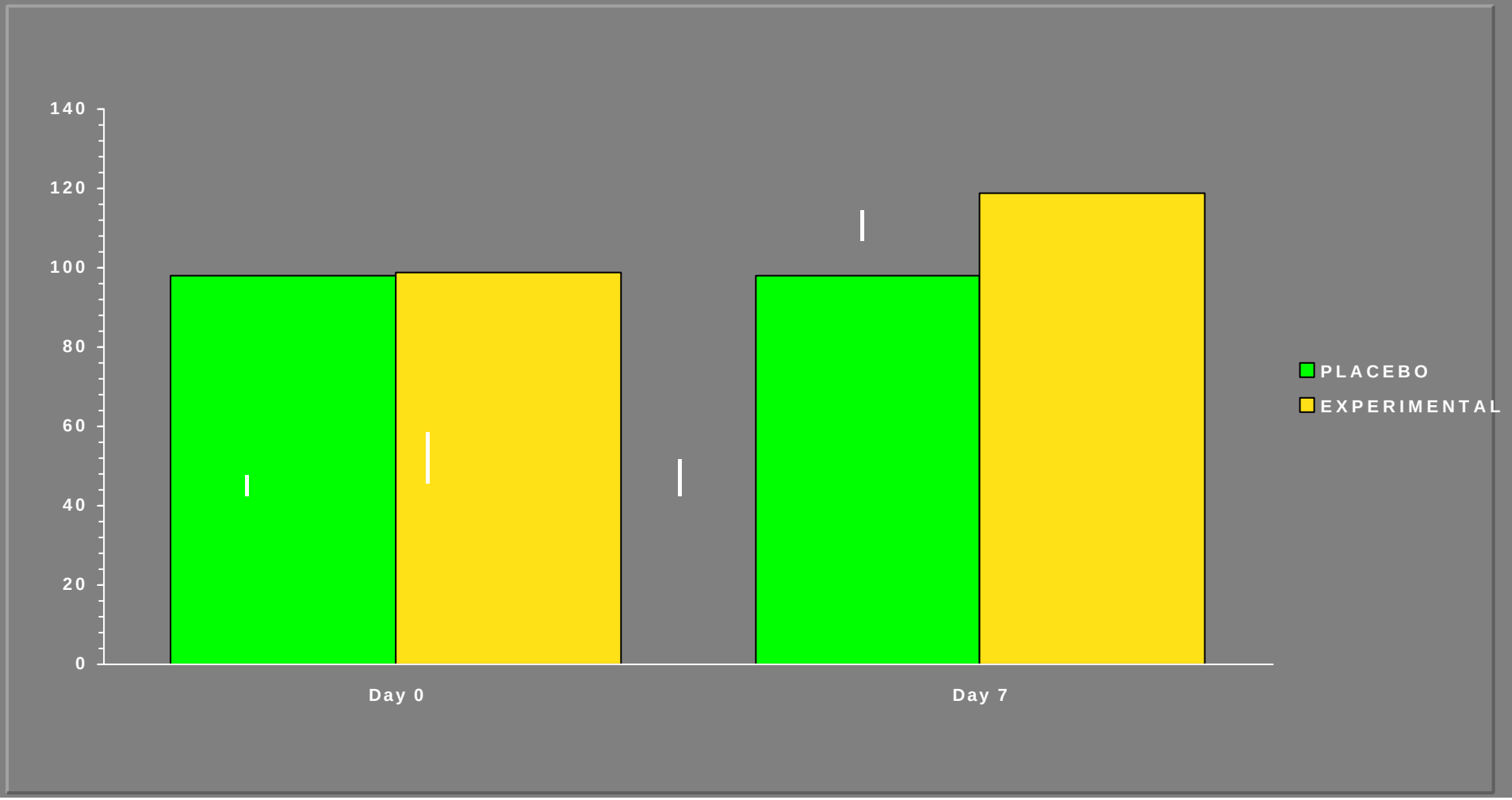
RESULTS : LIPID PEROXIDATION



ERYTHROCYTE RESISTANCE TO OXIDATIVE STRESS



LDL RESISTANCE TO OXIDATIVE STRESS



ANTI-INFLAMMATORY EFFECTS OF VITAMIN E

- **Experimentally :**
  - **Enteral vitamin E (100 mg/kg for 5d) inhibits the LPS-induced TNF production by rat peritoneal macrophages (Bulger Arch Surg 1997; 132:1337).**
  - **Pretreatment of young pigs with vitamin E (600 mg 3d) attenuate the elevation in plasma IL-6 - cortisol caused by ip LPS (Webel J Nutr 1998;128:1657).**

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↗ **Clinically :**

- **alpha-tocopherol (400 mg/d 6 wks) decreases production of O2- by PMNs, TNF, IL-1, IL-8 by PBMC (van Tits Am J Clin Nutr 2000;71:458)**
- **Vitamin E (600 mg - 30d) reduces monocyte tissue factor expression in cirhotic patients (Ferro Blood 1999;93:2945)**

FOOD AND ANTI-OXIDANT

COCOA POWDER and dark chocolate

↓

Rich in flavonoids (procyanidins)

↓

Reduce LDL oxidation susceptibility

Increase serum total antioxidant capacity

Wan Y. et al, Am J Clin Nutrition 2001;74:596-602

CONCLUSIONS

- 1 - Oxidative stress is increased in critically ill patients a contributes to organ damage / malignant inflammation.
- 2 - As the increase in oxidative stress is associated with depletion of the stores of antioxidants, the administratio of antioxidants can be beneficial
- 3 - Adding antioxidant compounds to nutrition support is logical and efficient.
- 4 - **Clinical effects of the addition of antioxidants to nutritional support of ICU patients need to be studied.**