Masterclass Critical Care Nutrition 2018

Introduction to Critical Care Nutrition

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- **BBraun**
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- **Fresenius Kabi**
- **Lyric**
- **Mermaid/Beacon**
- **Nestlé**
- **Novartis**
- **Nutricia-Danone**

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Member:
ESPEN guidelines committee Critical Care Nutrition for Adults
ESICM Working Group Gastrointestinal Failure
NESPEN Executive Team

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Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ESPEN Guideline

ESPEN guideline on clinical nutrition in the intensive care unit

Pierre Singer [a, *], Annika Reintam Blaser [b, c], Mette M. Berger [d], Waleed Alhazzani [e], Philip C. Calder [f], Michael P. Casaer [g], Michael Hiesmayr [h], Konstantin Mayer [i], Juan Carlos Montejo [j], Claude Pichard [k], Jean-Charles Preiser [l], Arthur R.H. van Zanten [m], Simon Oczkowski [e], Wojciech Szczeklik [n], Stephan C. Bischoff [o]

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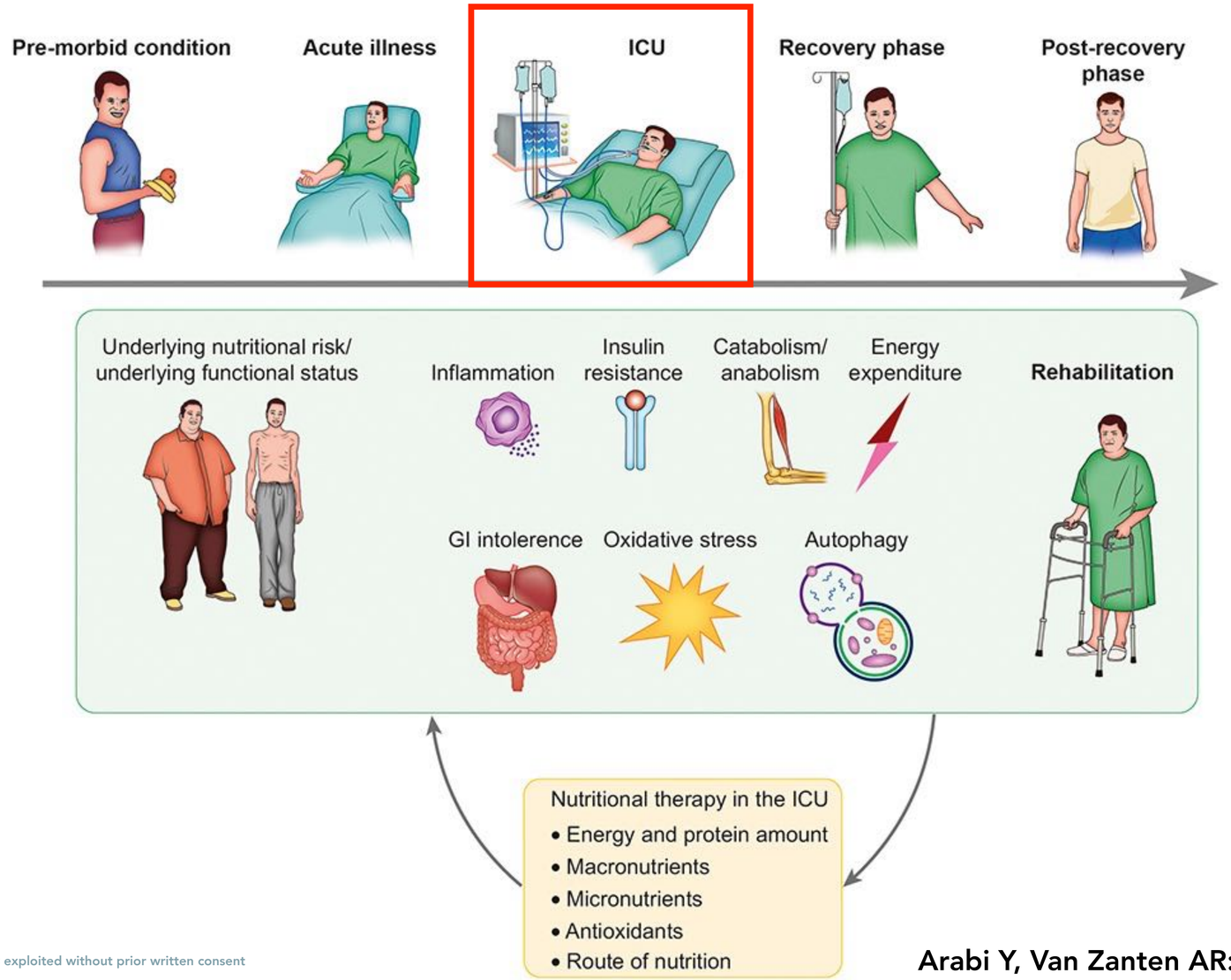
Nutritional support throughout the critically ill patient journey



Arabi Y, Van Zanten AR: Intensive Care Med 2017

Ziekenhuis Gelderse Vallei

Prediction of ICU stay

- In patients in ICU 1-2 days probably not necessary
- To predict ICU length of stay is extremely difficult
- To predict oral intake by patient is even more difficult
- So, in most cases you are unsure of ICU LOS

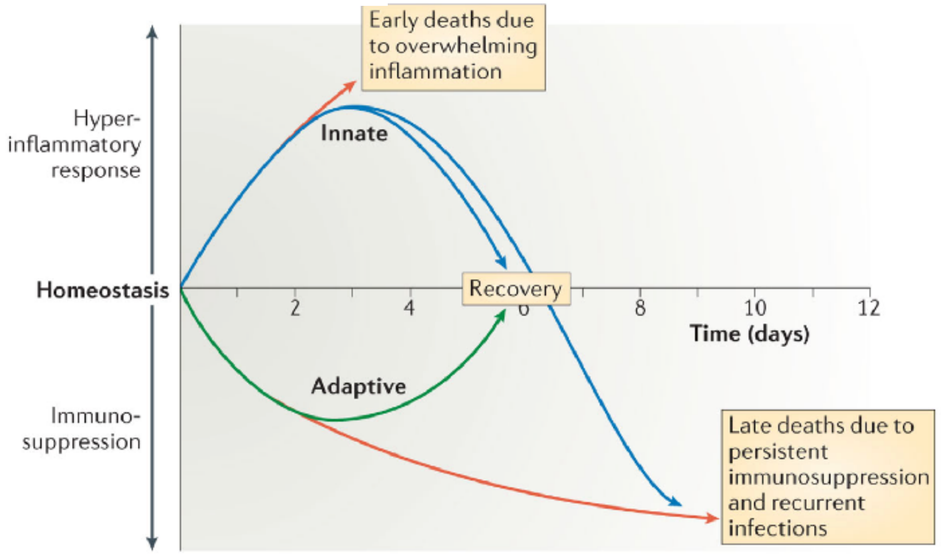
Try to start early enteral nutrition in all ICU patients

Content

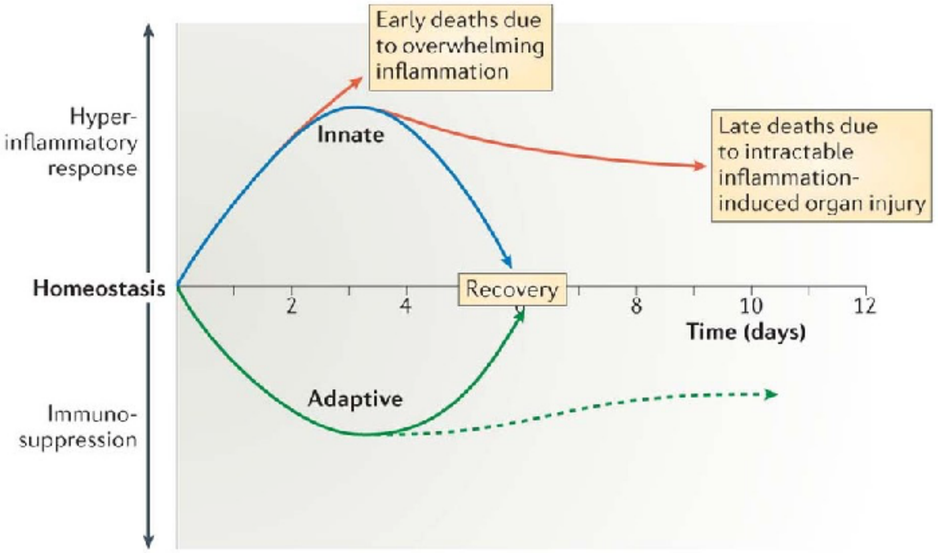
- Inflammation: Consequences
- Catabolism
- Mitochondrial dysfunction
- Risk of overfeeding
- Autophagy deficiency
- Refeeding syndrome (later topic)

Persistent inflammatory, immunosuppressed, catabolic syndrome (PICS)

Theory 1



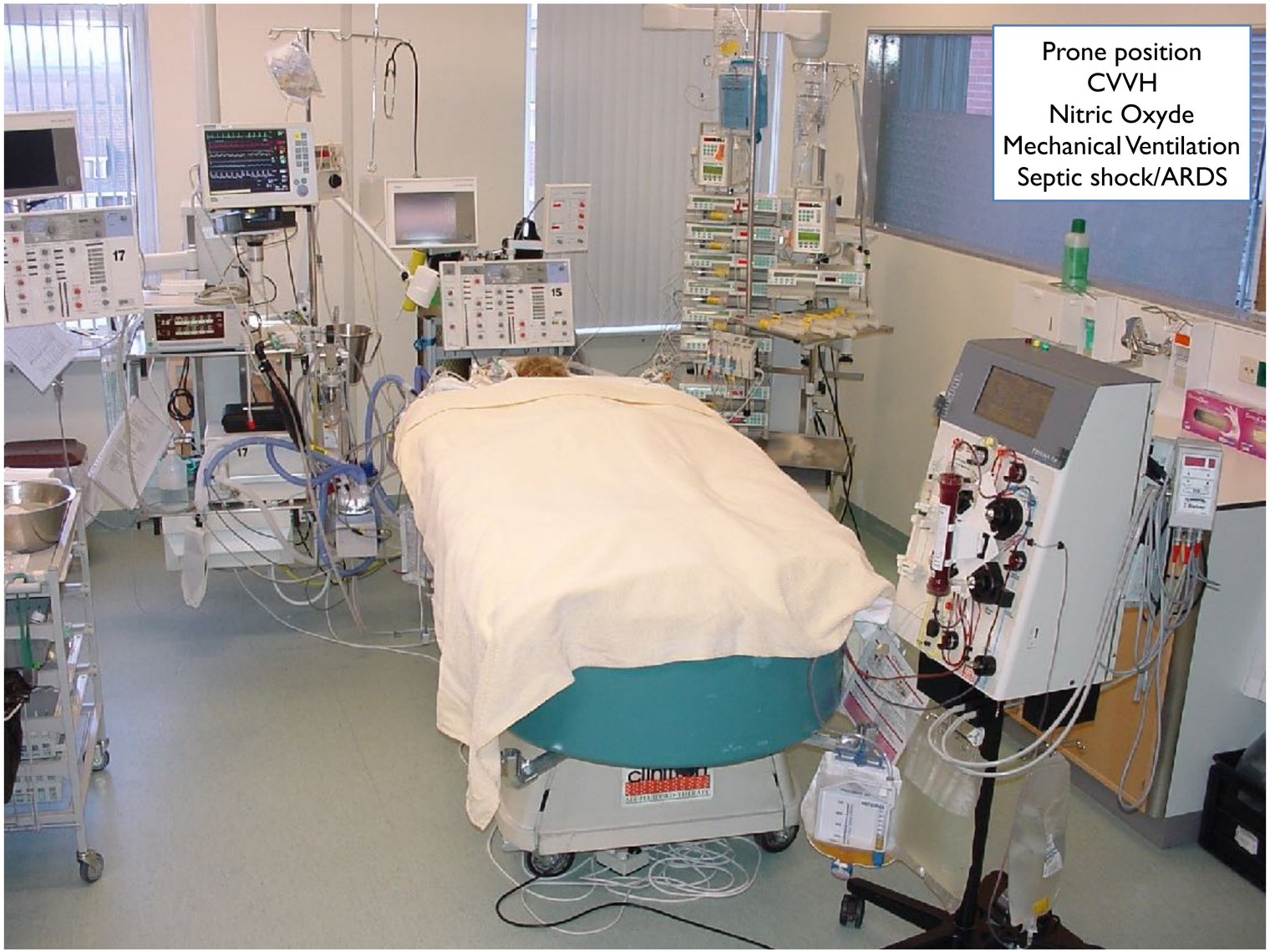
Theory 2



A new phenotype of multiple organ failure

Rosenthal MD, et al. J Adv Nutr Hum Metab 2015; 2: e784.
Hotchkiss R. Nature Reviews Immunology 13, 862–874 (2013)

Should we feed this patient with abdominal sepsis and MODS?



Ziekenhuis Gelderse Vallei

How many patients die in the ICU?

A. 75.3%

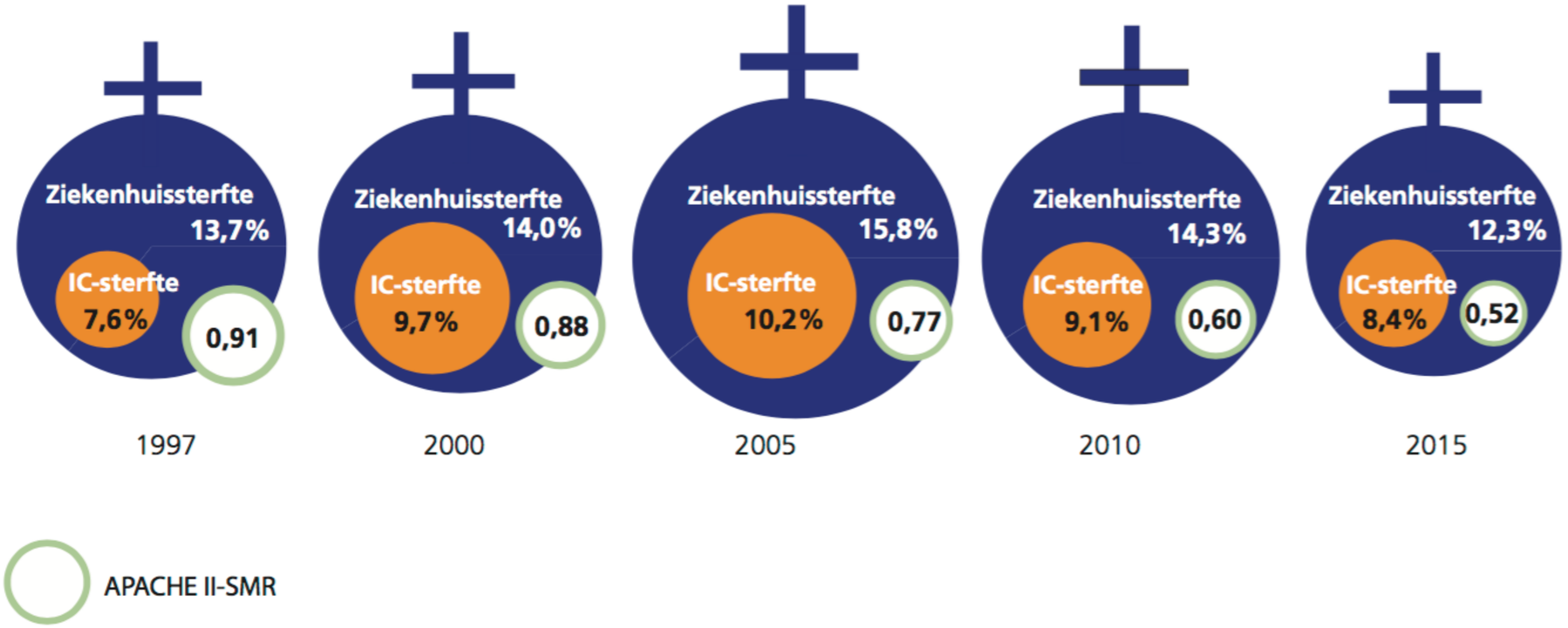
B. 51.7%

C. 32.1%

D. 8.4%

X

Hospital mortality, ICU mortality and SMR



Standardized mortality = actual mortality/predicted mortality

Which answer is true concerning ICU patients?

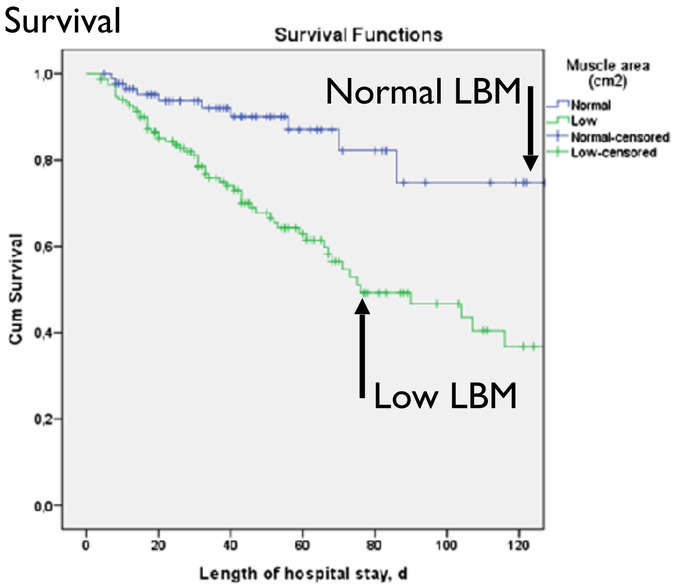
A. Obese patients have a lower survival chance

B. Loss of muscle mass is 1 kilogram per day during the first week

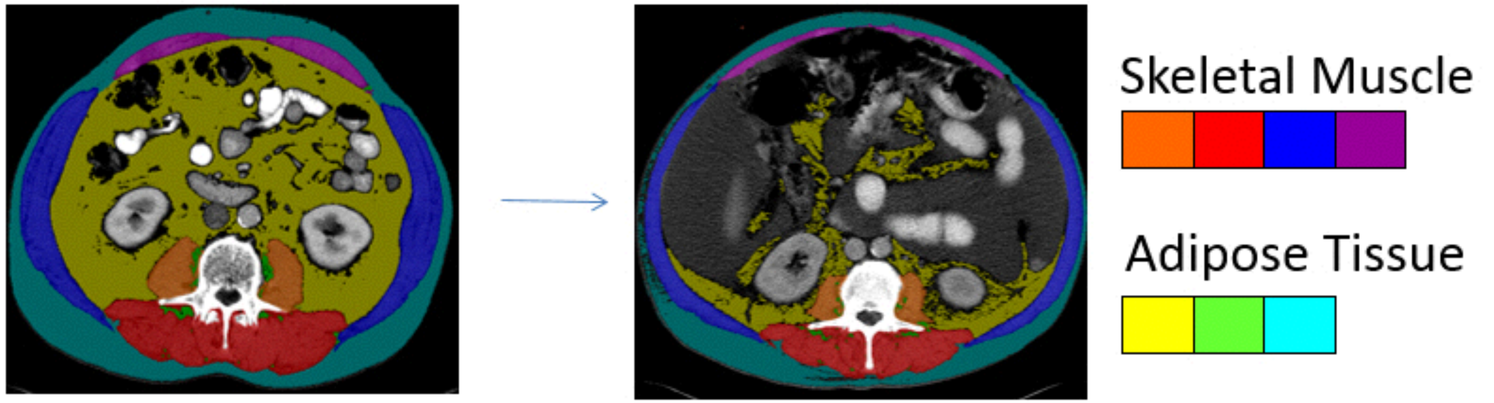
C. Three months after ICU discharge patients function as before

D. Physical therapy and cycling is dangerous for ICU patients

LBM: CT-scan and mortality

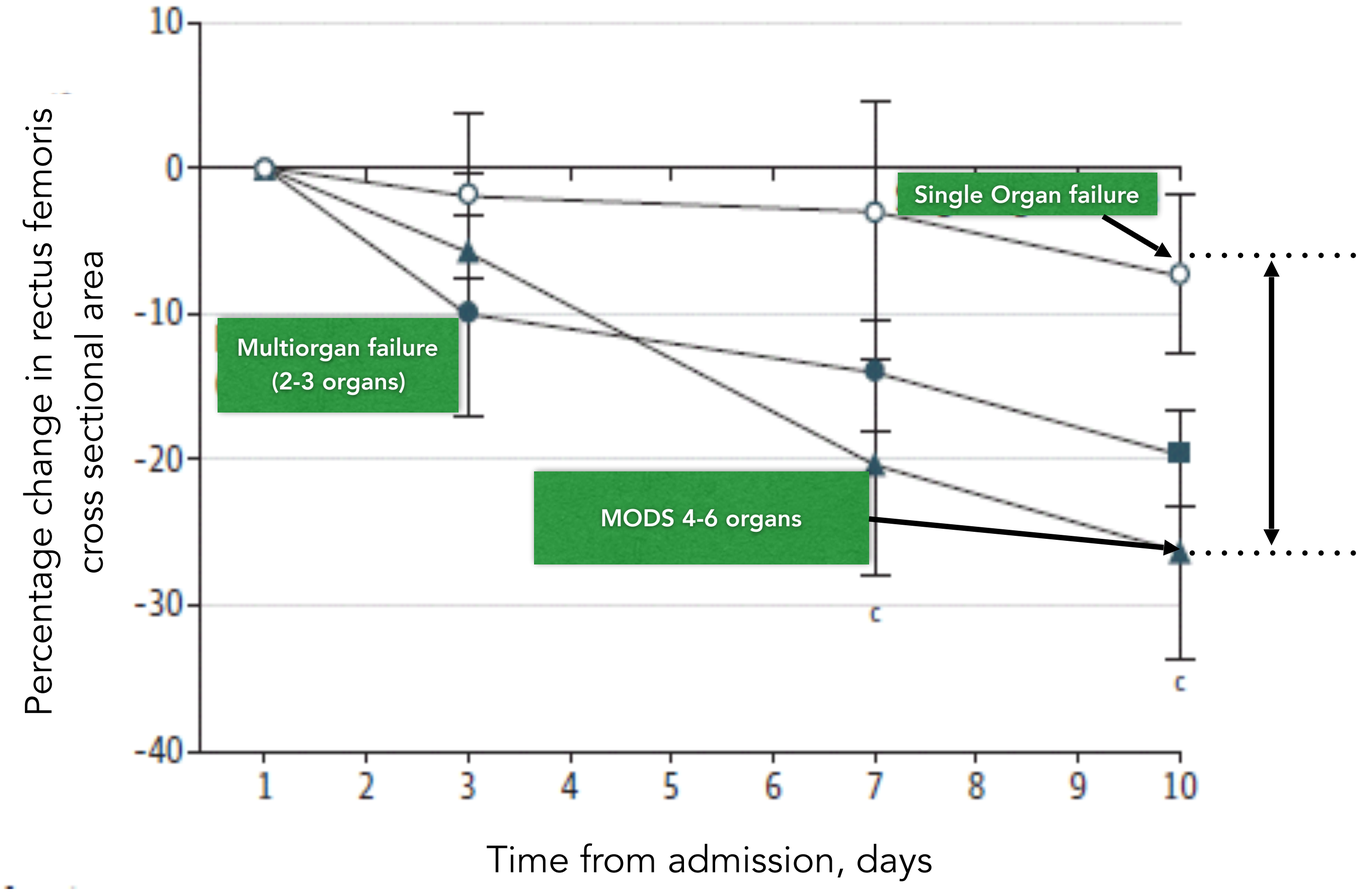


- Low skeletal muscle area, as assessed by CT scan during the early stage of critical illness, is a risk factor for mortality in mechanically ventilated critically ill patients, independent of sex and APACHE II score.
- Muscle mass is primary predictor.
- BMI is not an independent predictor of mortality when muscle area is accounted for.



Weijs et al. Critical Care 2014 18:R12

Muscle mass loss 1 kg per day



Puthucheary ZA et al., JAMA 2013

10 kilograms of muscle mass

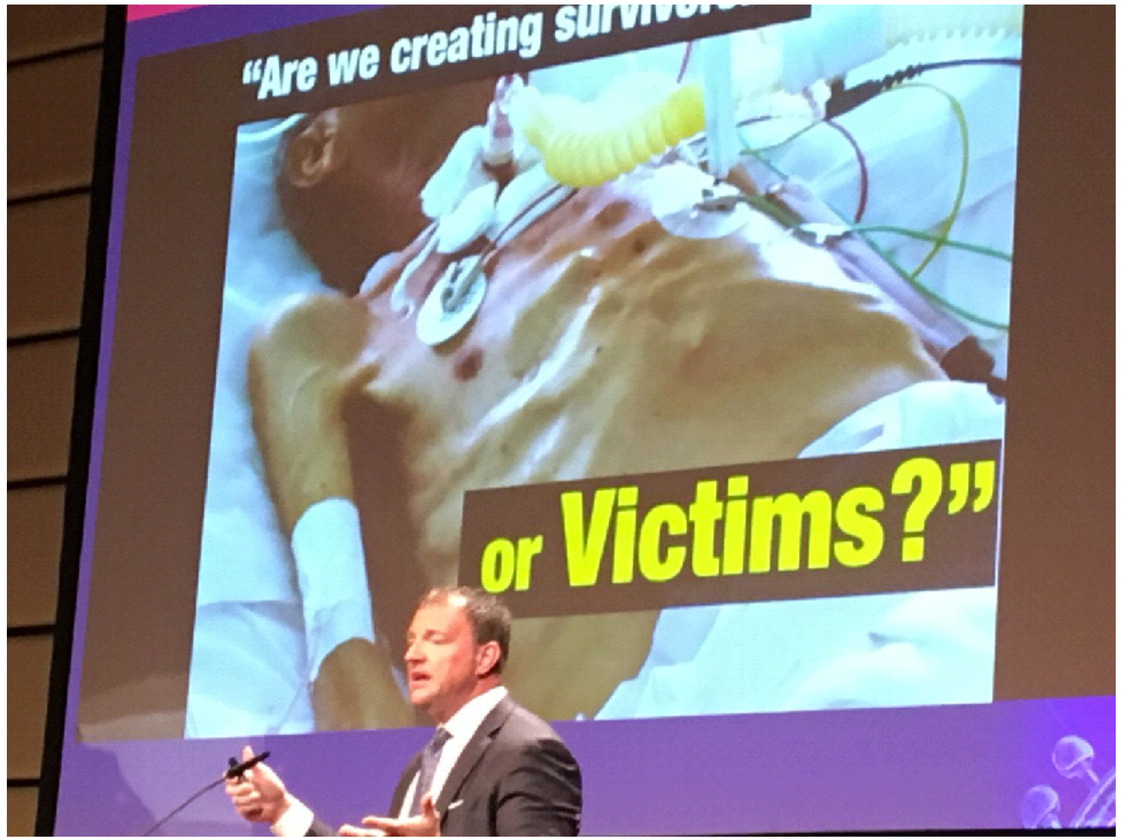
Sepsis: Survivors or Victims

33% die during first year

50% recover

17% persistent impairments

1 to 2 new functional limitations
(eg, inability to bathe or dress independently)



Prescott HC, Angus DC. JAMA. 2018;319(1):62–75.

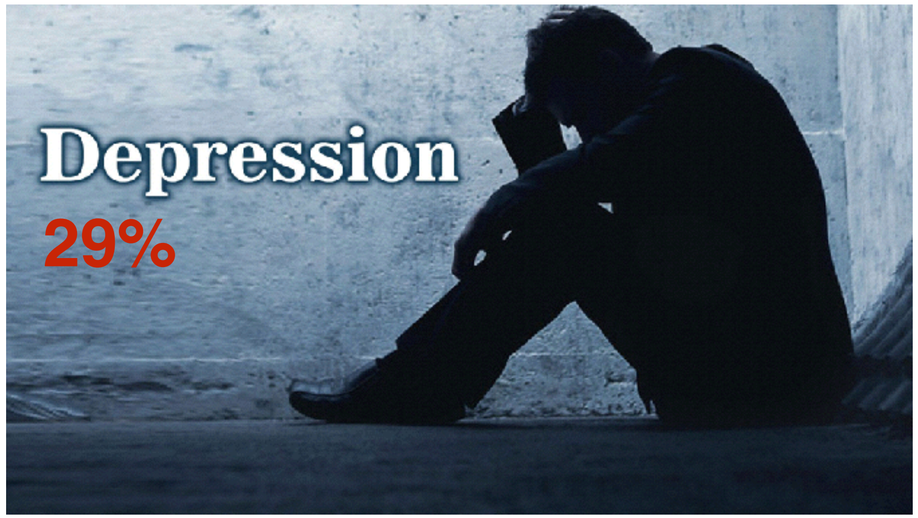
Sepsis: long-term consequences

40% of patients are rehospitalized within 90 days of discharge.

Prescott HC, Angus DC. JAMA. 2018;319(1):62–75.

Sepsis: long-term consequences

a 3-fold increase in prevalence of moderate to severe cognitive impairment (from 6.1% before hospitalization to 16.7% after hospitalization)



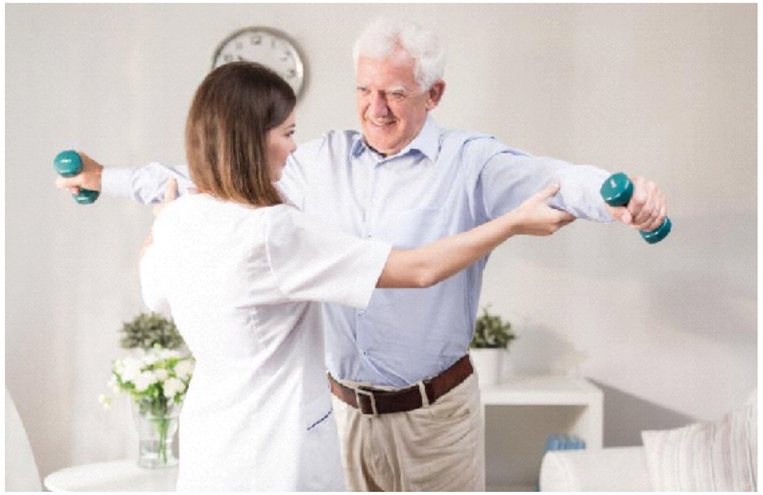
44%

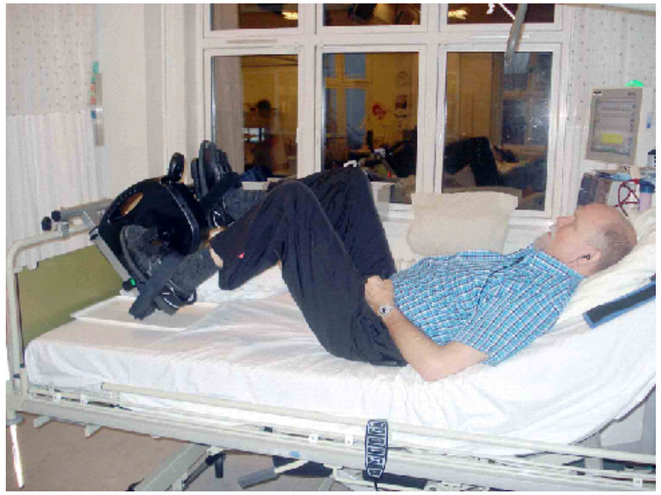
Prescott HC, Angus DC. JAMA. 2018;319(1):62–75.

Sepsis: long-term consequences

Experts recommend referral to **physical therapy** to improve exercise capacity, strength, and independent completion of activities of daily living.

Observational study involving 30,000 sepsis survivors **referral to rehabilitation within 90 days** was associated with **lower risk of 10-year mortality** compared with propensity-matched controls (adjHR, 0.94; 95% CI, 0.92-0.97, P < .001).

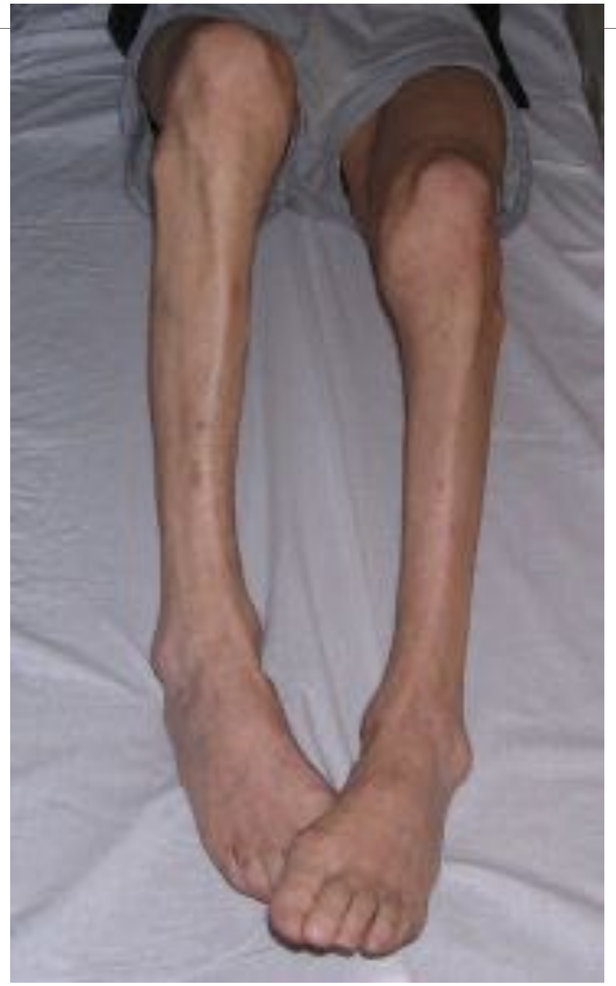




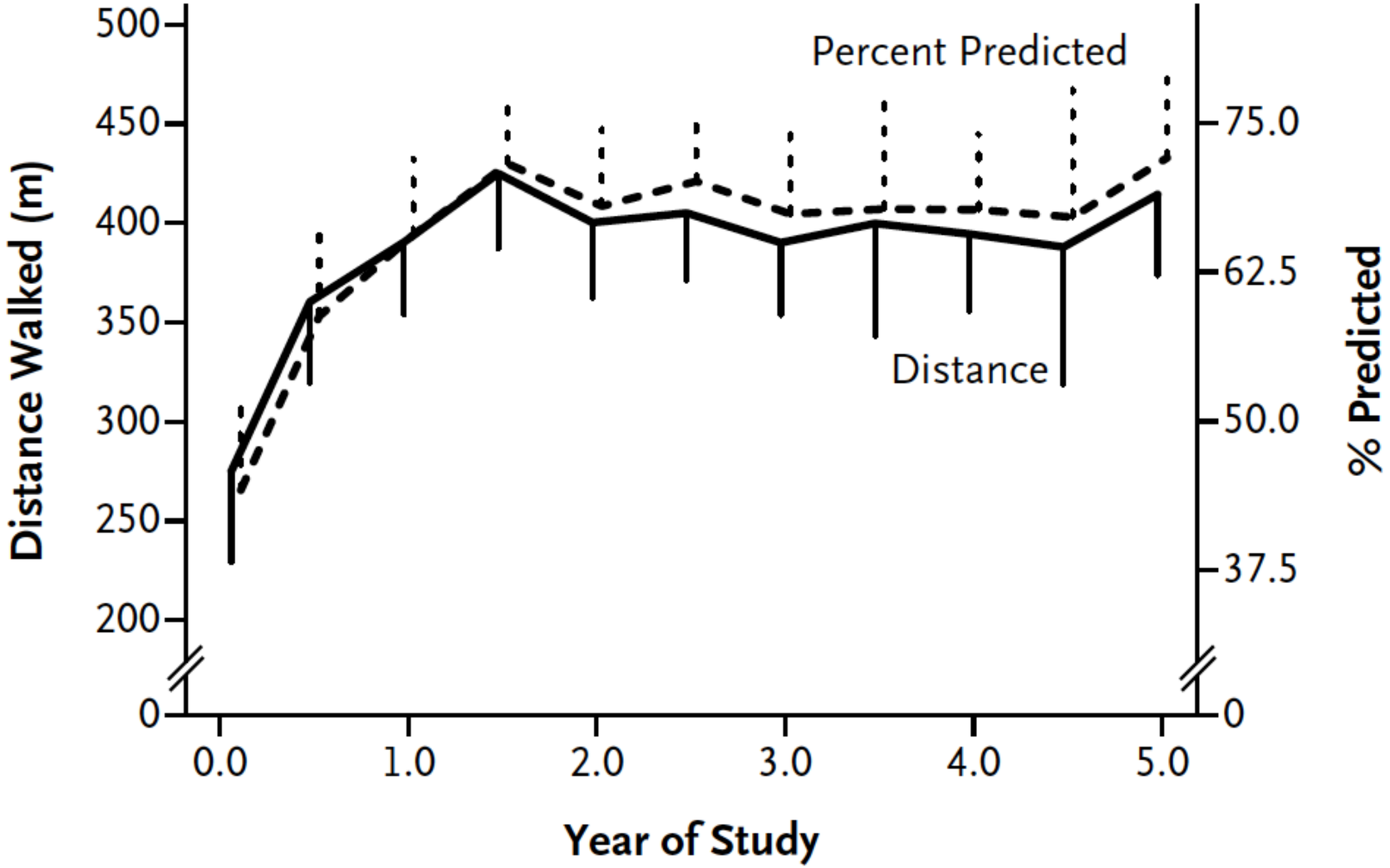
Prescott HC, Angus DC. JAMA. 2018;319(1):62–75.

Long-term effects

- Muscle wasting
- Vitamin deficiency
- Micronutrient deficiency
- Fatigue
- Psychological effects
- Infection



5 years after ARDS ICU treatment: ICU acquired weakness persists for years…..



Herridge MS et al NEJM 2011

Which answer is true concerning ICU patients?

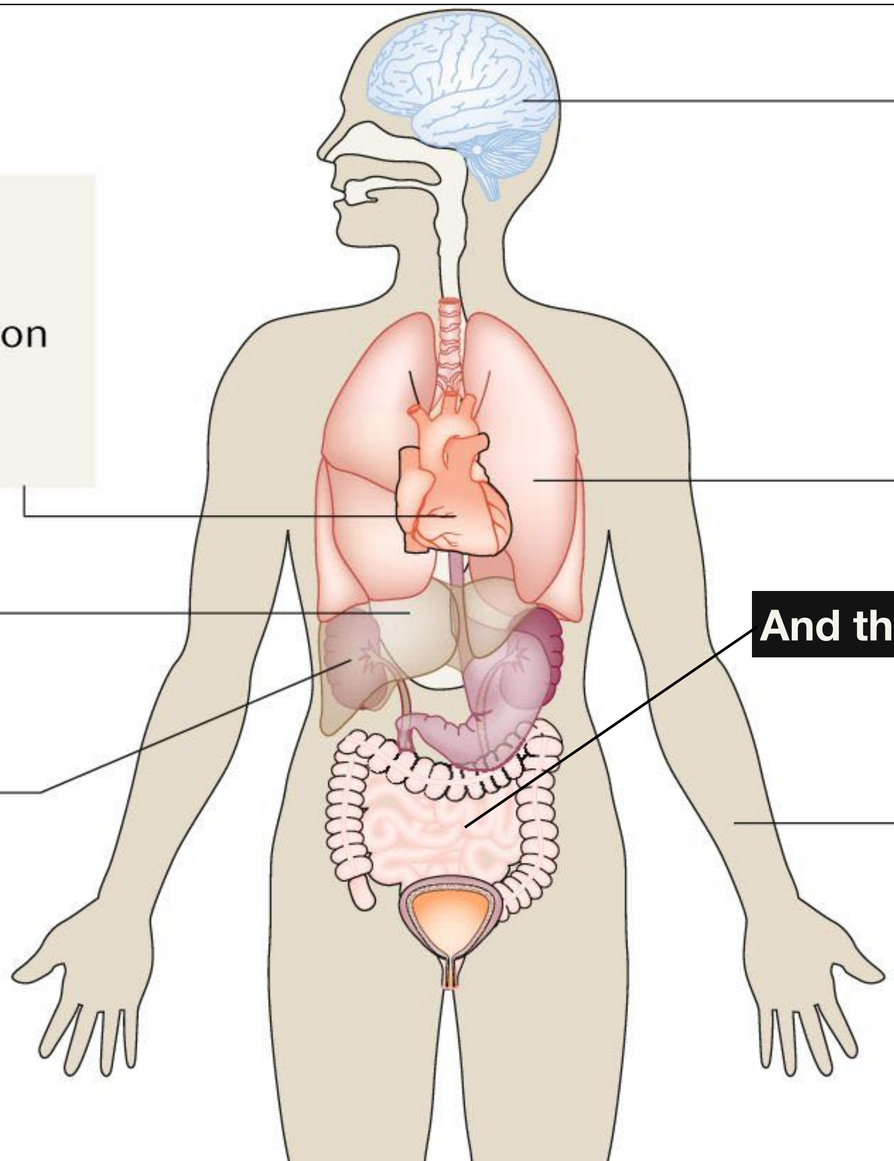
A. Only 32% of patients need insulin therapy (diabetes patients)

B. When plasma insulin levels are high glucagon levels are low

C. Mitochondria are dysfunctional during and after critical illness

D. Micronutrients have no effect on antioxidant status

Failing organ systems in sepsis



Neurological system
- Altered mentation
- Confusion
- Disorientation

Cardiovascular system
- Hypotension
- Mottled skin and altered microcirculation
- ↑ Lactate levels (in septic shock)
- Altered echocardiography variables

Respiratory system
- Hypoxaemia
- ↓ PaO_2:FiO_2 ratio

Hepatic system
- ↑ Bilirubin levels
- ↑ Liver enzymes

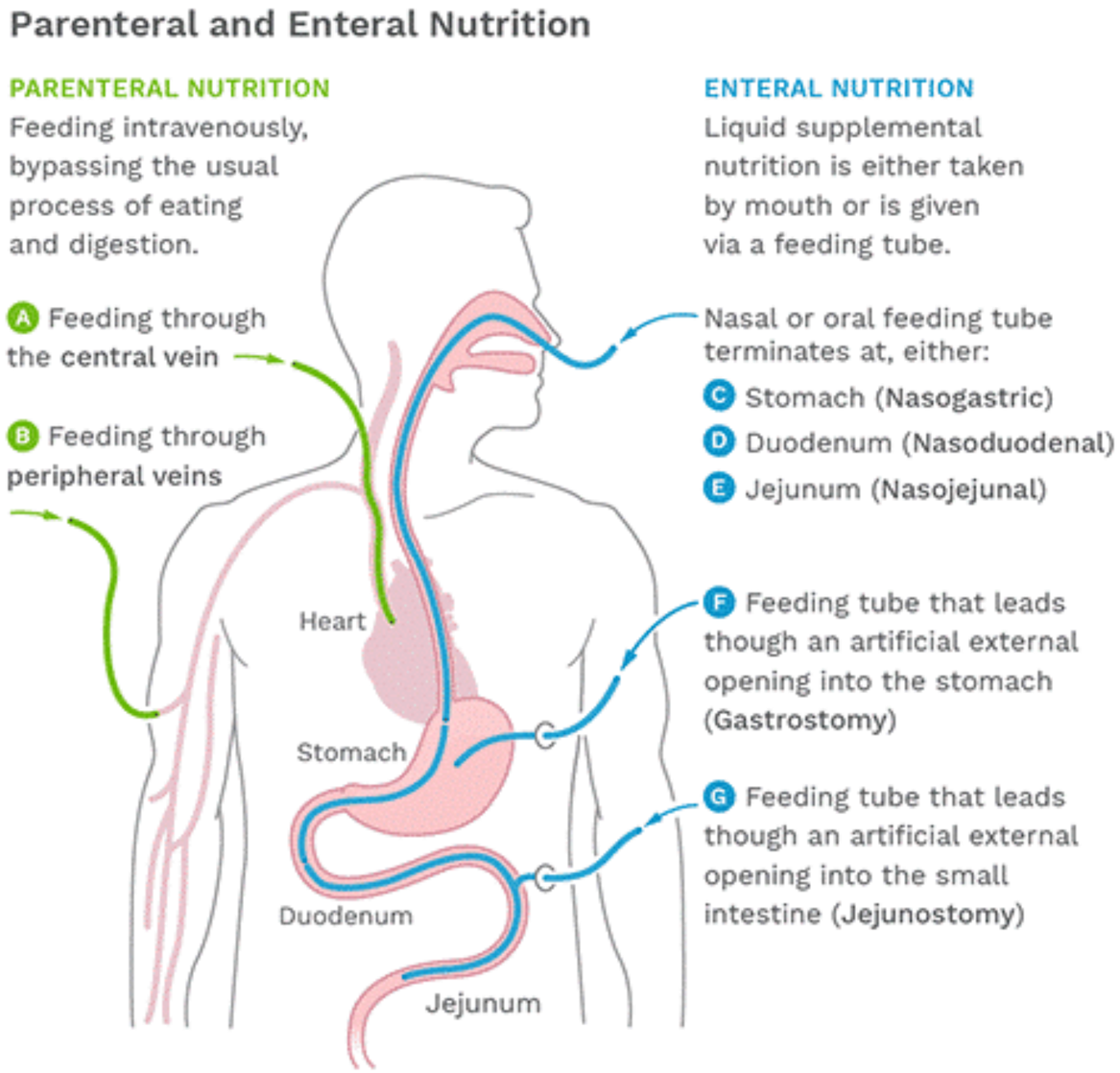
And the GI tract?

Renal system
- Oliguria
- ↑ Serum creatinine
- ↑ Blood urea nitrogen
- ↑ Biomarkers

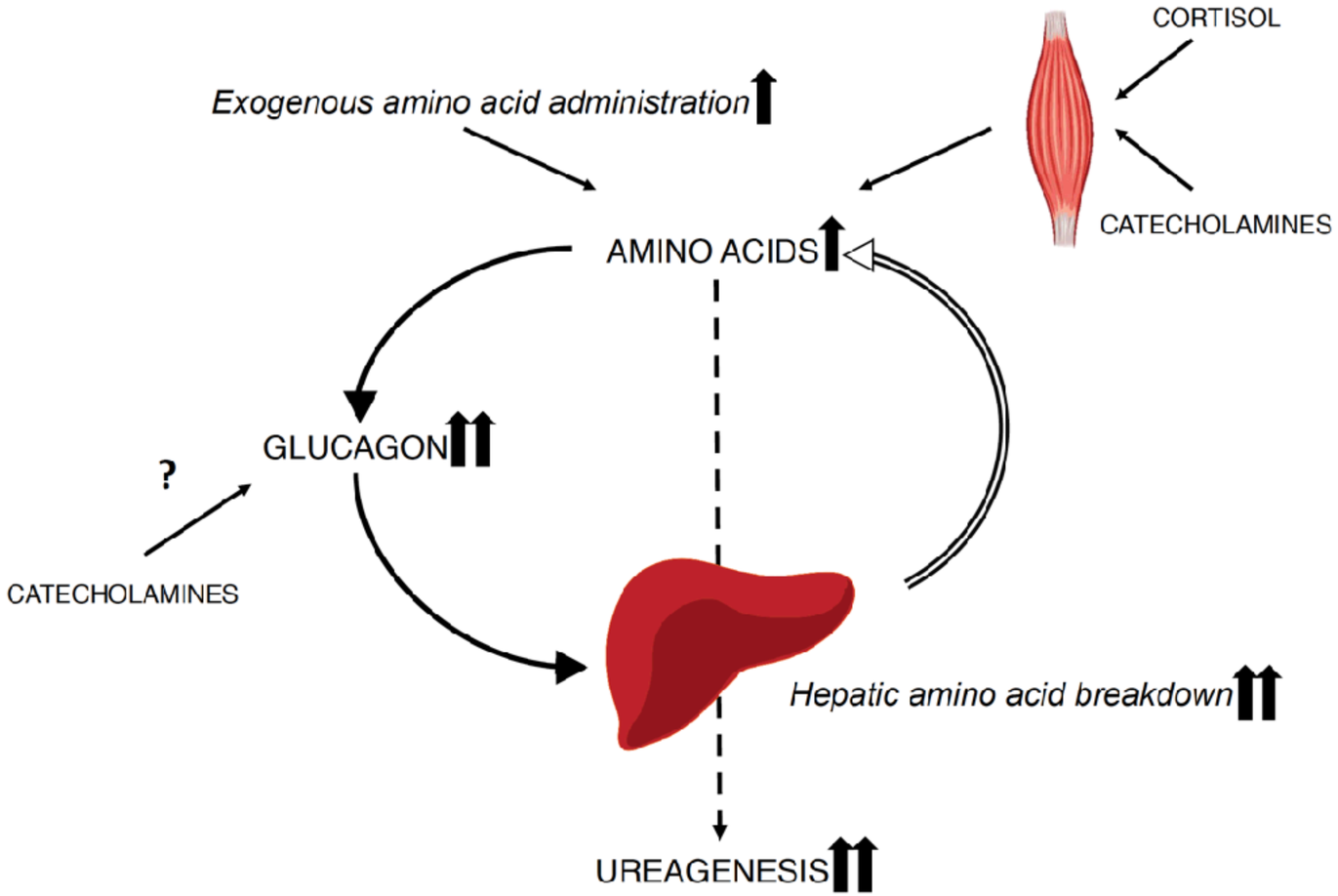
Haematological system
- Low platelet count
- Disseminated intravascular coagulation
- Petechiae (in some severe cases)

Nutrition challenges in critical illness

- Anorexia
- Immobilization
- Swallowing disorders (sedation)
- GI-tract: high GRV, digestion, absorption, and peristalsis abnormalities
- Alterations microbiome
- Catabolic state
- Insulin resistance
- All metabolic processes in the context of inflammation and acute metabolic stress
- Nutrition therapy is different during critical illness

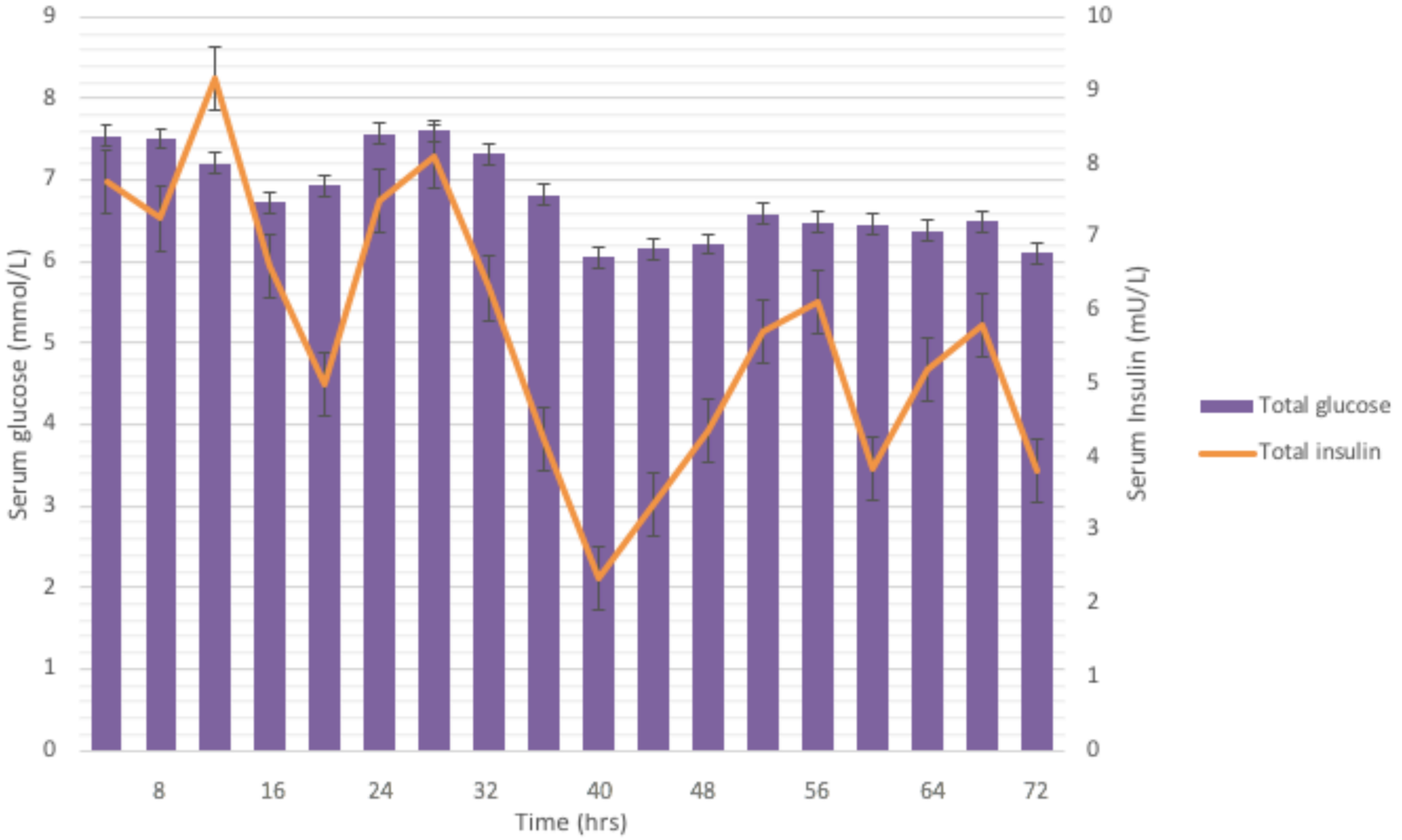


Glucagon and amino acid supplementation interaction



Thiese SE, Gunst J, Vd Berghe G, Cure Opinion Crit Care 2018

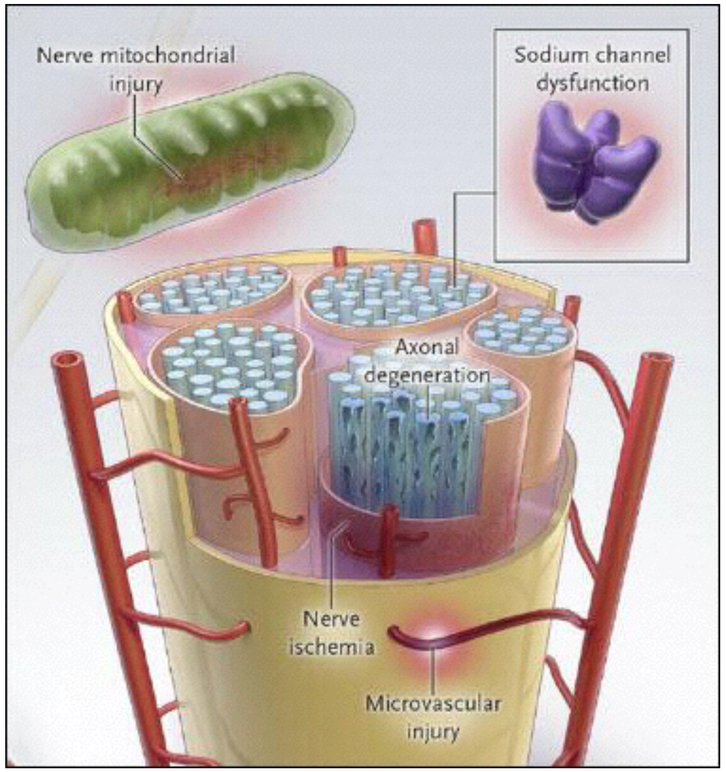
Insulin and glucose in sepsis patients



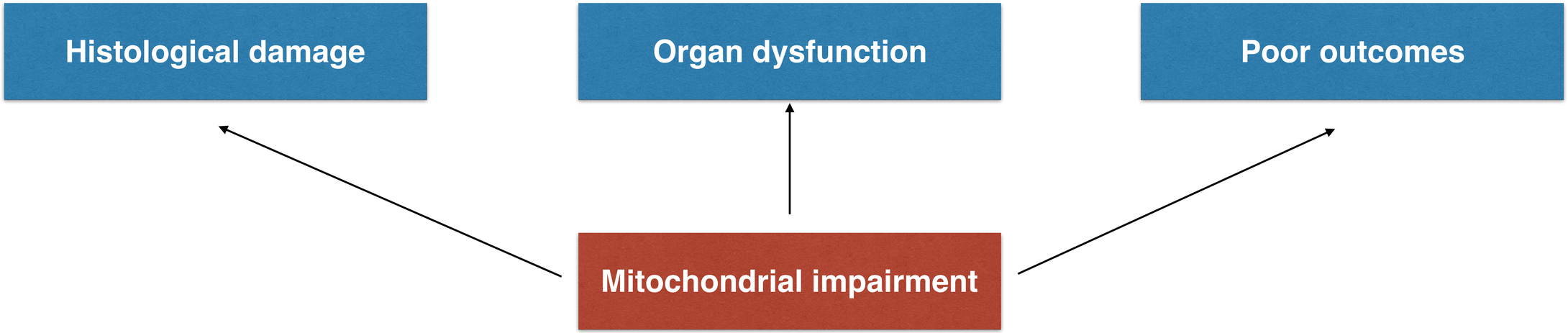
Treske N, Koekkoek K.. Van Zanten AR, submitted

Long-term consequences of ICU treatment

1. Loss of body weight
2. Loss of muscle mass
3. Loss of muscle quality
4. Loss of muscle function
5. Fat infiltration in muscles
6. VO_2 max reduced
7. Altered lactate threshold
8. Altered mitochondrial function
9. Reduced fat oxidation capacity
10. Lower age-matched survival



Mitochondrial dysfunction and outcome



Low skeletal muscle Complex I levels in critically ill patients were associated with higher organ failure scores while higher levels of ATP were seen in survivors compared with non-survivors.

Brealey D, .. Singer M. Lancet. 2002;360:219–23

Impact of the inflammatory response on mitochondria

- Insufficient oxygen to drive oxidative phosphorylation of ADP to ATP.
- Excess NO, carbon monoxide, hydrogen sulfide, and other ROS inhibit mitochondrial respiration, cause damage to mitochondrial protein and lipid membrane.
- Hormonal alterations affect mitochondrial function and efficiency, e.g.“low T3” syndrome.
- Genes transcribing mitochondrial proteins are downregulated early in the inflammatory response.

Singer M. Virulence. 2014 Jan 1; 5(1): 66–72.

What is wrong with the mitochondria?

Jiroutková *et al. Critical Care* (2015) 19:448
DOI 10.1186/s13054-015-1160-x

Critical Care

RESEARCH Open Access

Mitochondrial function in skeletal muscle of patients with protracted critical illness and ICU-acquired weakness

Kateřina Jiroutková[1*], Adéla Krajčová[1,2], Jakub Ziak[1], Michal Fric[4], Petr Waldauf[4], Valér Džupa[3], Jan Gojda[2], Vlasta Němcova-Fürstová[5], Jan Kovář[5], Moustafa Elkalaf[1], Jan Trnka[1] and František Duška[1,6]

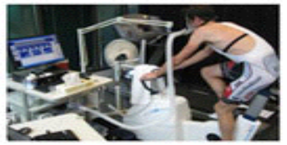
- **Compared to healthy controls, in ICU patients this group demonstrated a ~50 % reduction of the ability of skeletal muscle to synthetize ATP in mitochondria and found a depletion of complex III and IV concentrations**

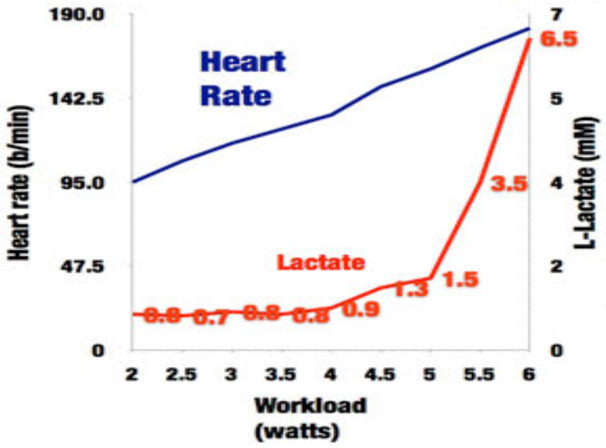
High Mitochondrial Density
High Fat and Lactate Oxidation

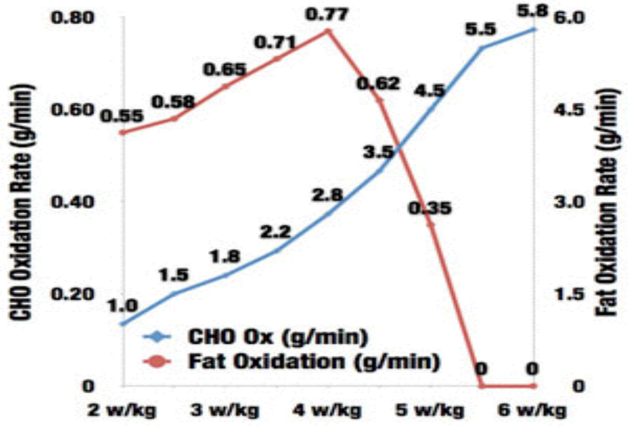
Type I muscle cells

Exercise Physiology Testing

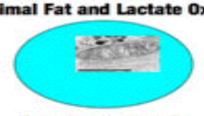
World Class Athlete







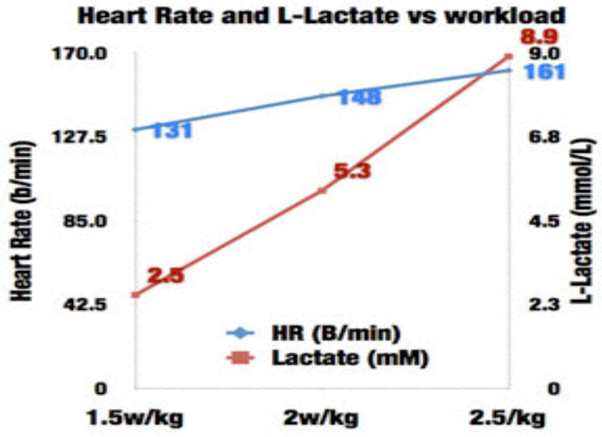
Low Mitochondrial Density
Minimal Fat and Lactate Oxidation

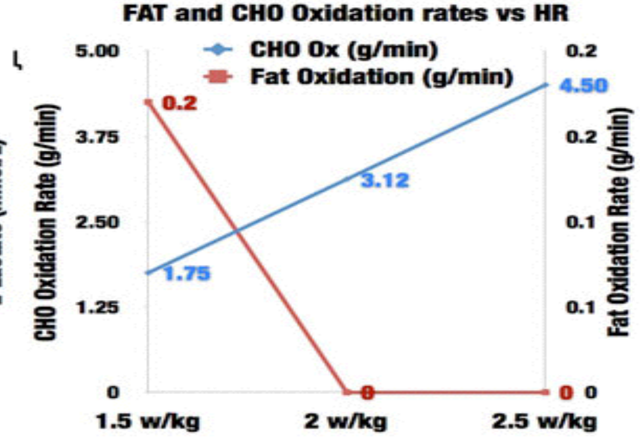


Type I muscle cells
(Mitochondrial Dysfunction)

Exercise Physiology Testing

Obese/Type II Diabetic



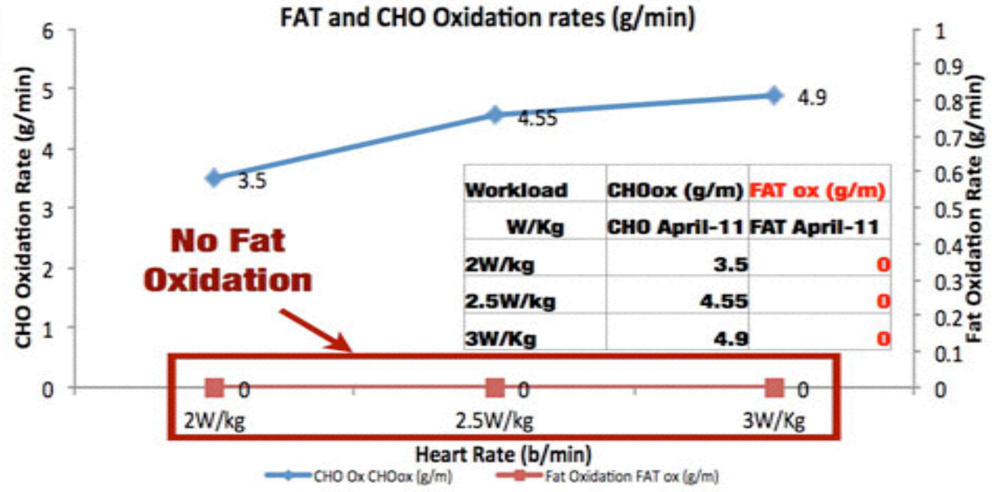


Post-Burn Patient Testing

No Mitochondrial Fxn
No Fat Oxidation

EXERCISE TESTING RESULTS

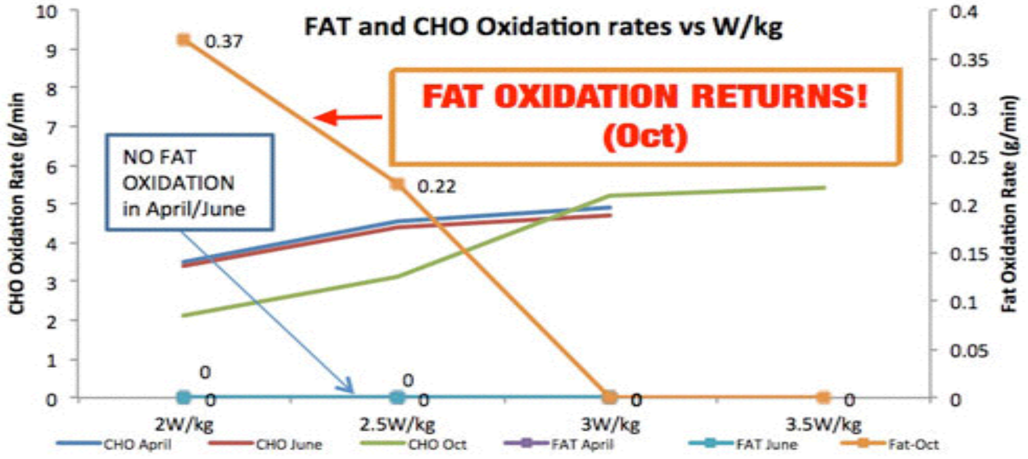
Type I muscle cells



Workload	CHOox (g/m)	FAT ox (g/m)
W/Kg	CHO April-11	FAT April-11
2W/kg	3.5	0
2.5W/kg	4.55	0
3W/Kg	4.9	0

Post-Burn Patient Testing

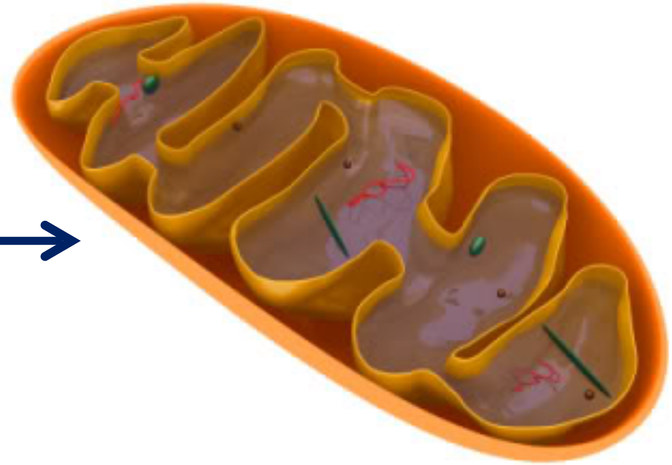
Post-Targeted Exercise Program



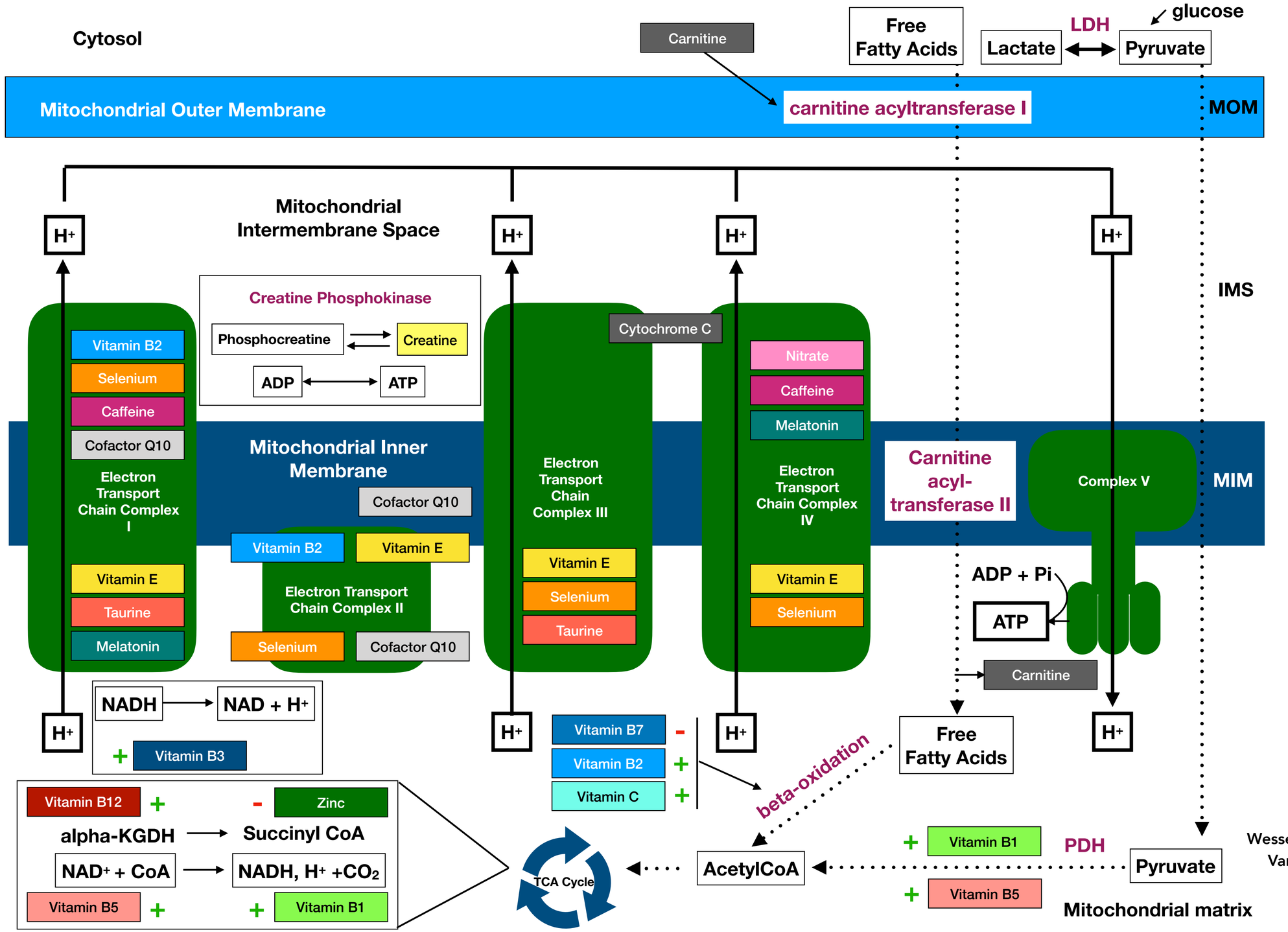
Wischmeyer PE. Crit Care. 2015; 19(Suppl 3): S6.

Propofol and mitochondrial function

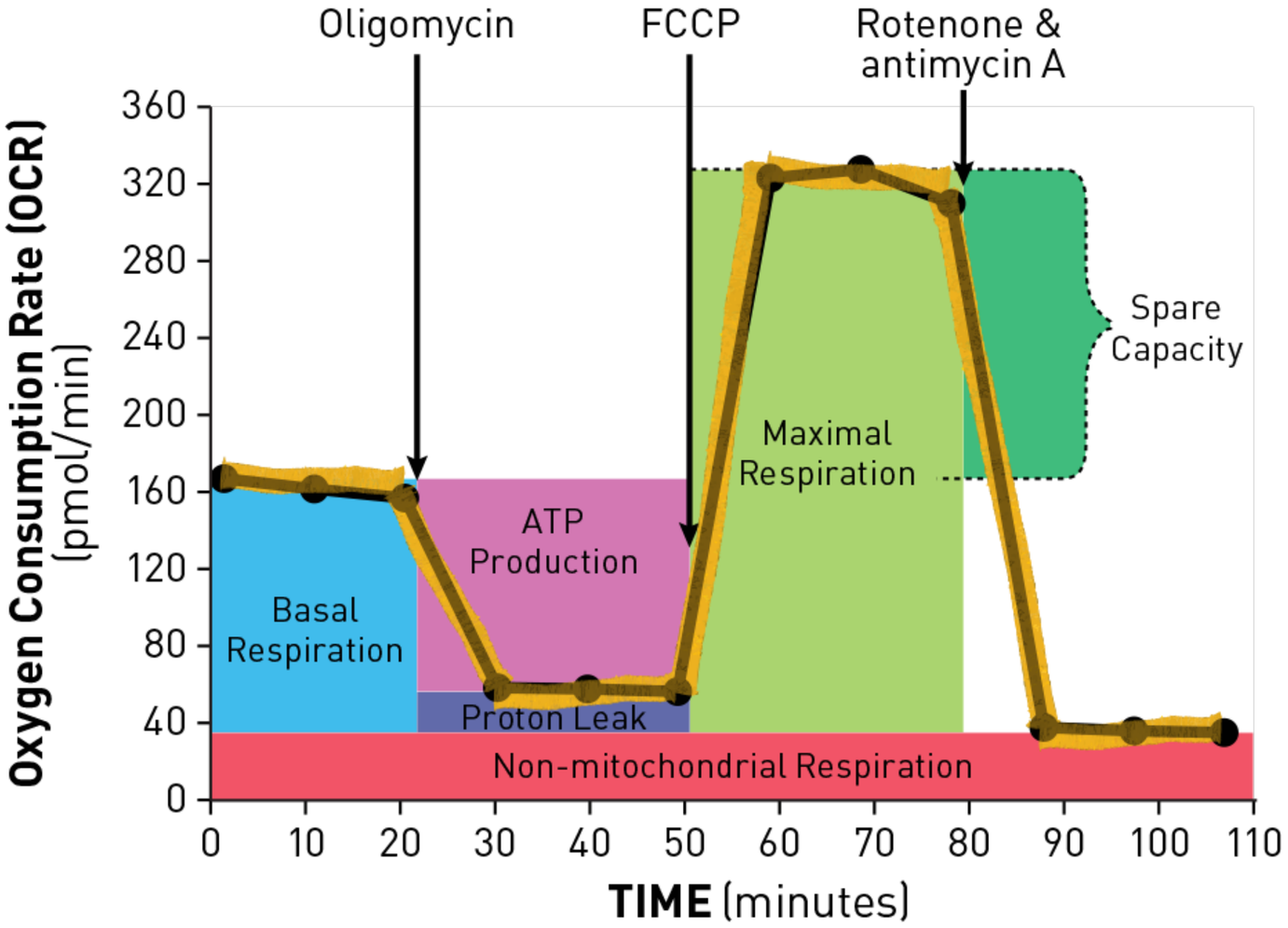
- **Concentrations of propofol seen in plasma of sedated patients in ICU cause a significant inhibition of fatty acid oxidation in human skeletal muscle cells and reduce spare capacity of electron transfer chain in mitochondria.**



Krajčová A et al. Crit Care Med 2017

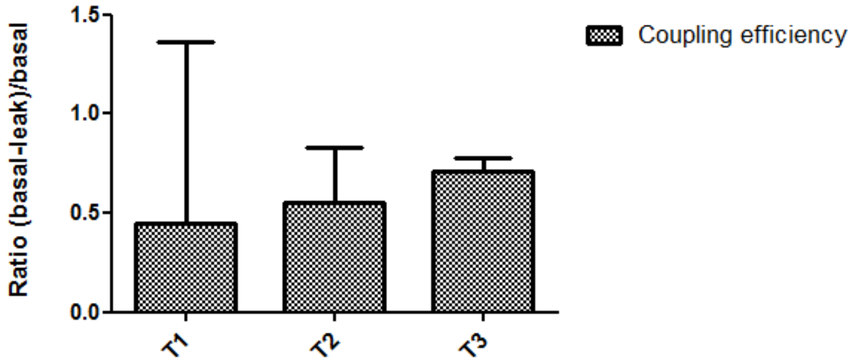

Cytosol
Carnitine
Free Fatty Acids
Lactate
LDH
glucose
Pyruvate
Mitochondrial Outer Membrane
carnitine acyltransferase I
MOM
Mitochondrial Intermembrane Space
IMS
H+
Creatine Phosphokinase
Phosphocreatine
Creatine
ADP
ATP
Vitamin B2
Selenium
Caffeine
Cofactor Q10
Electron Transport Chain Complex I
Mitochondrial Inner Membrane
MIM
Cofactor Q10
Vitamin B2
Vitamin E
Electron Transport Chain Complex II
Selenium
Cofactor Q10
Cytochrome C
Electron Transport Chain Complex III
Vitamin E
Selenium
Taurine
Nitrate
Caffeine
Melatonin
Electron Transport Chain Complex IV
Vitamin E
Selenium
Carnitine acyl-transferase II
Complex V
ADP + Pi
ATP
Carnitine
NADH
NAD + H+
Vitamin B3
Vitamin B7
Vitamin B2
Vitamin C
beta-oxidation
Free Fatty Acids
Vitamin B12
Zinc
alpha-KGDH
Succinyl CoA
NAD+ + CoA
NADH, H+ +CO2
Vitamin B5
Vitamin B1
TCA Cycle
AcetylCoA
Vitamin B1
PDH
Pyruvate
Vitamin B5
Mitochondrial matrix
Wesselink E, Koekkoek K, ... Van Zanten AR, Clin Nutr 2018

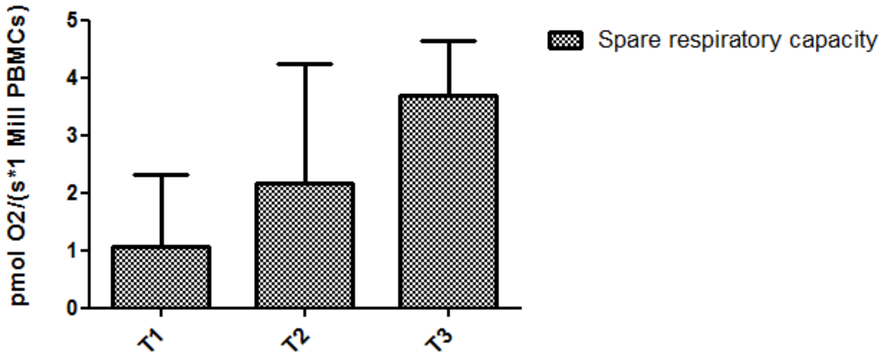
How to evaluate mitochondrial function?



Ongoing MIC study, mitochondrial function in leucocytes in sepsis patients

MIC-study winner Gelderse Vallei Hospital Research Grant in 2018





Jelle de Jong, investigator WUR
Rianne Boot, AAIC

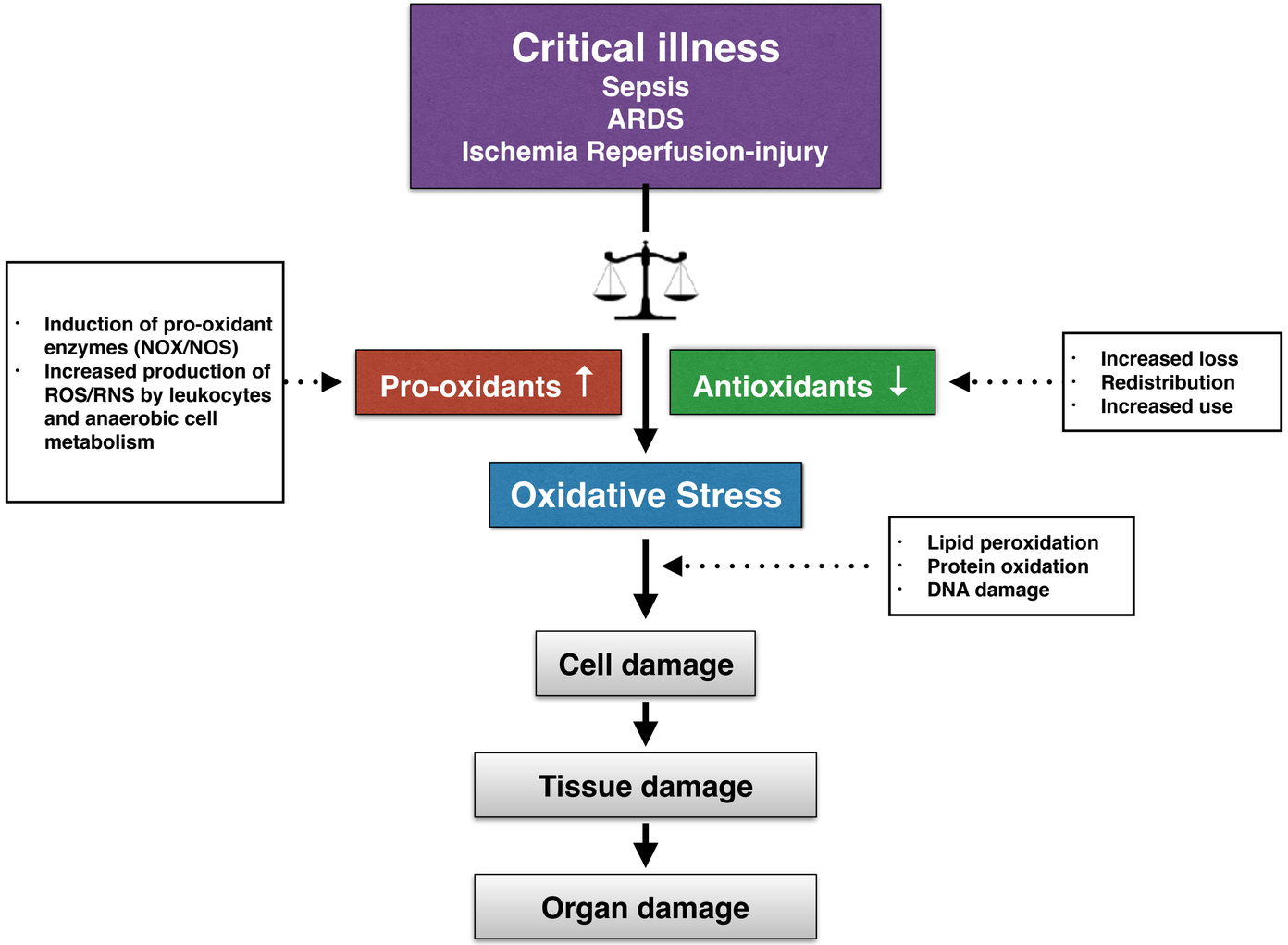
Research nurses:
Margreet, Marianne, Thera en Elly

Physical therapists:
Bert, Fraukje, Jacquelien,

Prof. Jaap Keijer, Dr. Grefte, Dr. Nieuwenhuizen (Wageningen University)

Supervisor: Dr. Arthur van Zanten

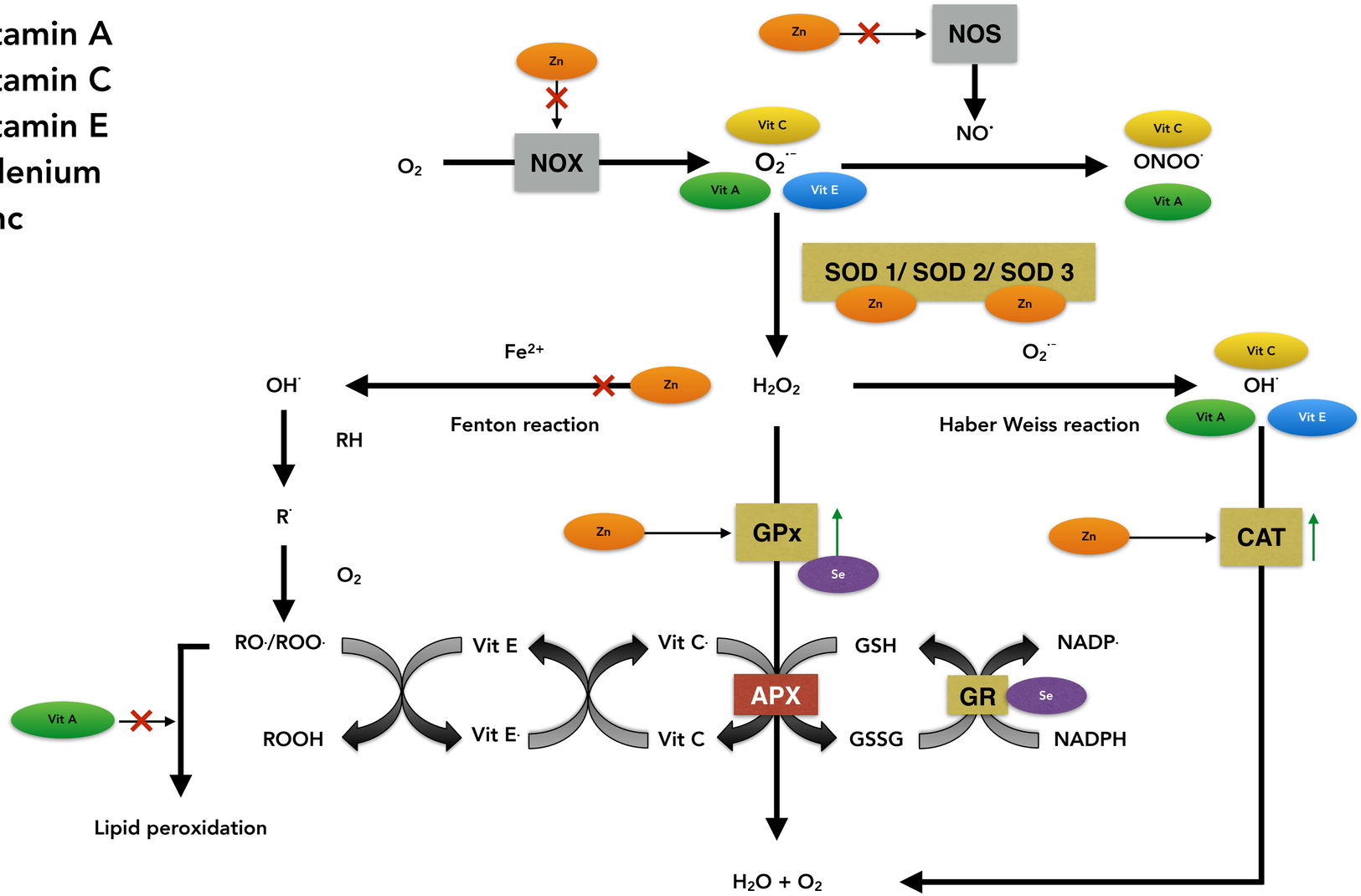
Oxidative stress: Essential for bacterial killing



Koekkoek WA, van Zanten AR. Nutr Clin Pract. 2016;31(4):457-74.

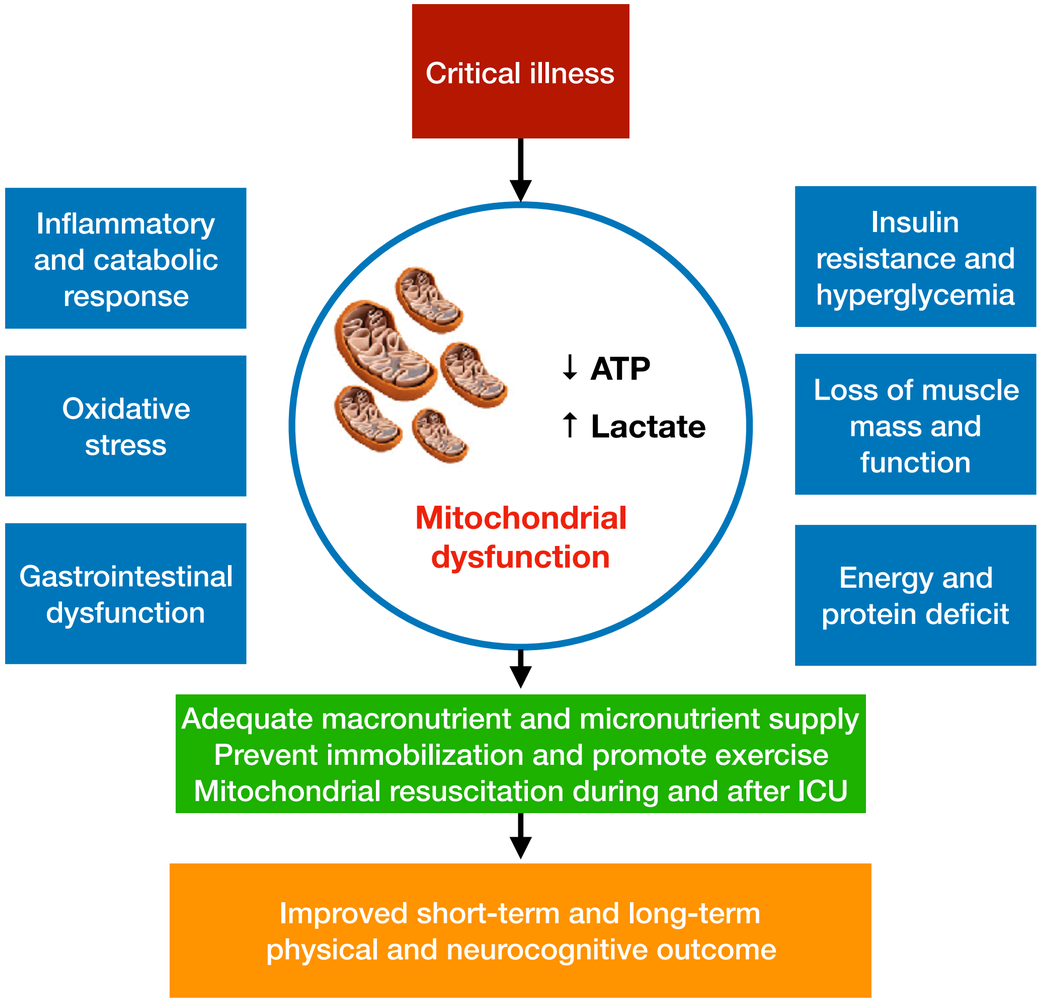
Antioxidant Network: Vitamins and trace elements

- Vit A Vitamin A
- Vit C Vitamin C
- Vit E Vitamin E
- Se Selenium
- Zn Zinc



Koekkoek WA, van Zanten AR. Nutr Clin Pract. 2016;31(4):457-74.

Deficiencies may affect mitochondrial function before, during and after critical illness



Wesselink E, Koekkoek K, …Van Zanten AR, submitted for publication

Food for mitochondria: potential candidates

Mitochondrial function	Tricarboxylic acid (TCA) cycle	Boost the electron transport chain function	Boost the electron transport chain function	Mitochondrial biogenesis
• B vitamins • ascorbic acid • α-tocopherol • Selenium • Zinc • Coenzyme Q10 • Caffeine • Melatonin • Carnitine • Nitrate • Lipoic acid • Taurine • Resveratrol	• Vitamin B1 • Vitamin B5 • Vitamin B12 • Lipoic acid • Zinc	• Vitamin B1 • selenium • α-tocopherol • Coenzyme Q10 • Caffeine • Melatonin	• Carnitine	• Resveratrol • Selenium

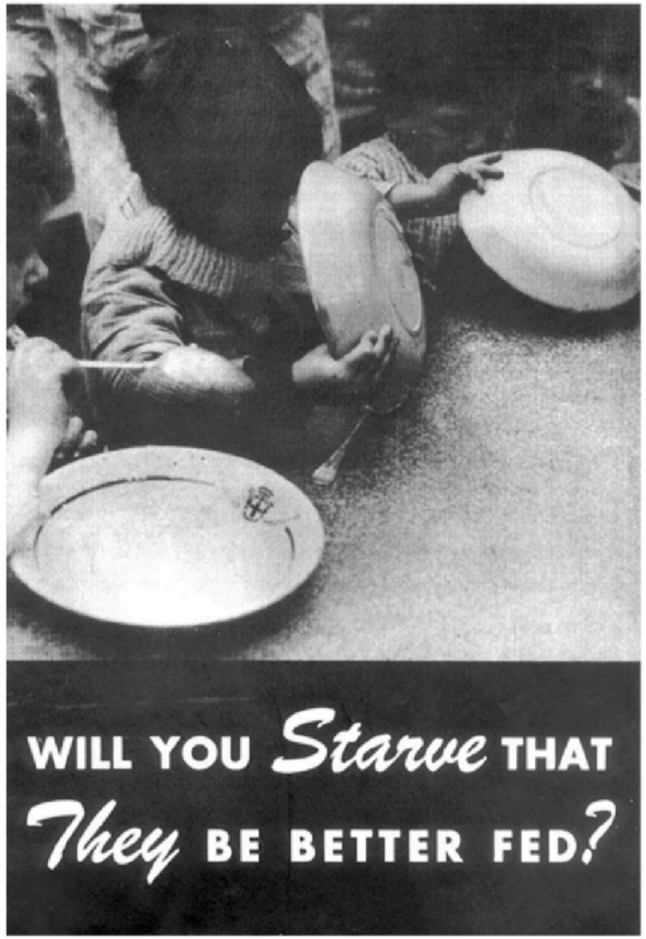
Wesselink E, Koekkoek K, …Van Zanten AR, Clin Nutrition 2018

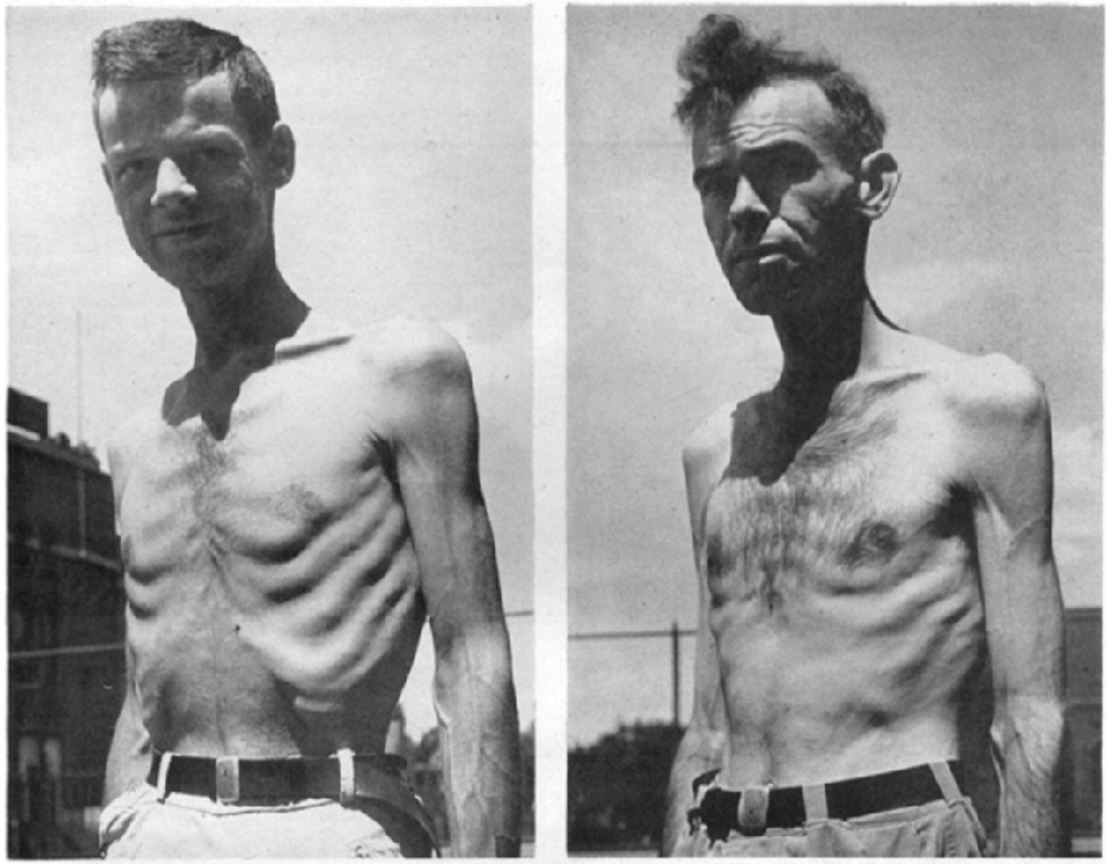
Prevention of Protein & Energy deficit essential for (functional) outcomes

Ziekenhuis Gelderse Vallei

Average ICU intake (not in Ede):	Should be (80 kg pat):
1000 kcal/day	2000 kcal/day
0.7 g proteins/kg per day	1.5 g proteins/kg per day

Tailoring nutrition therapy to illness and recovery





AFTER FIVE MONTHS OF STARVATION DIET CONSCIENTIOUS OBJECTORS SAMUEL LEGG (LEFT) AND EDWARD COWLES HAVE LOST 35 AND 30 POUNDS RESPECTIVELY

MEN STARVE IN MINNESOTA

CONSCIENTIOUS OBJECTORS VOLUNTEER FOR STRICT HUNGER TESTS TO STUDY EUROPE'S FOOD PROBLEM

Wischmeyer Critical Care 2017, 21(Suppl 3):316

Tailoring nutrition therapy to illness and recovery

Table 1 Summary of caloric needs of critically ill and healthy individuals in the context of the Minnesota Starvation Study and actual current ICU calorie delivery

		TEE/weight (kcal/kg/day)
Uehara et al., ICU study [12]		
Sepsis patients (mean age 67)		
Week 1		25 ± 5
Week 2		47 ± 6
Trauma patients (mean age 34)		
Week 1		31 ± 6
Week 2		59 ± 7
WHO calorie requirements, healthy subjects[a]		
Men		44 (range 35–53)
Women		36 (range 29–44)
Minnesota Starvation Study calorie delivery	Delivered energy (kcal/day)	Delivered energy/weight (kcal/kg/day)
Baseline period	3200	~ 50
Starvation period	~ 1800	23–30
Recovery period delivery (for recovery to occur)	~ 4000	~ 60

Starvation period:

1800 kcal/day

Recovery period:

4000 kcal/day

Actual average 1034 kcal/day delivered in critically ill patients over first 12 days of ICU stay [15]
REE resting energy expenditure, *TEE* total energy expenditure, *WHO* World Health Organization
[a]Data for a healthy 70-kg person with intermediate physical activity (1.75 physical activity level factor).
Reference: http://www.fao.org/docrep/007/y5686e/y5686e00.htm#Contents

Wischmeyer Critical Care 2017, 21(Suppl 3):316

Masterclass Critical Care Nutrition 2018

Calories in Critically ill Patients with and without Sepsis

Cumulative Energy Depletion Hypothesis

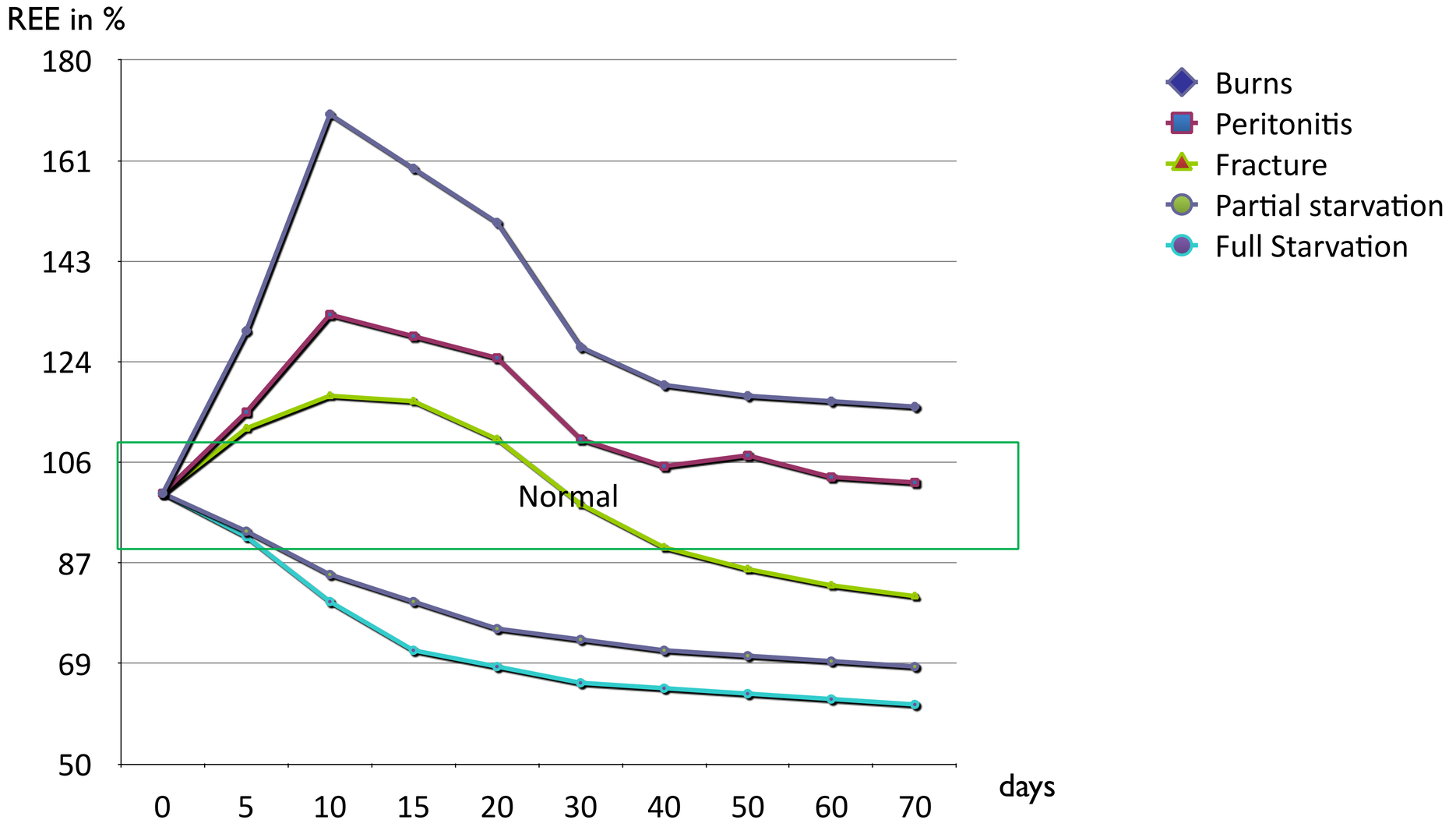
- 48 patients, mean daily intake 1090 kcal
- Combined enteral & parenteral highest energy intake
- Mean cumulative energy balance:

-12.600 kcal after 1 week

- More complications (P<0.001) mainly infections.

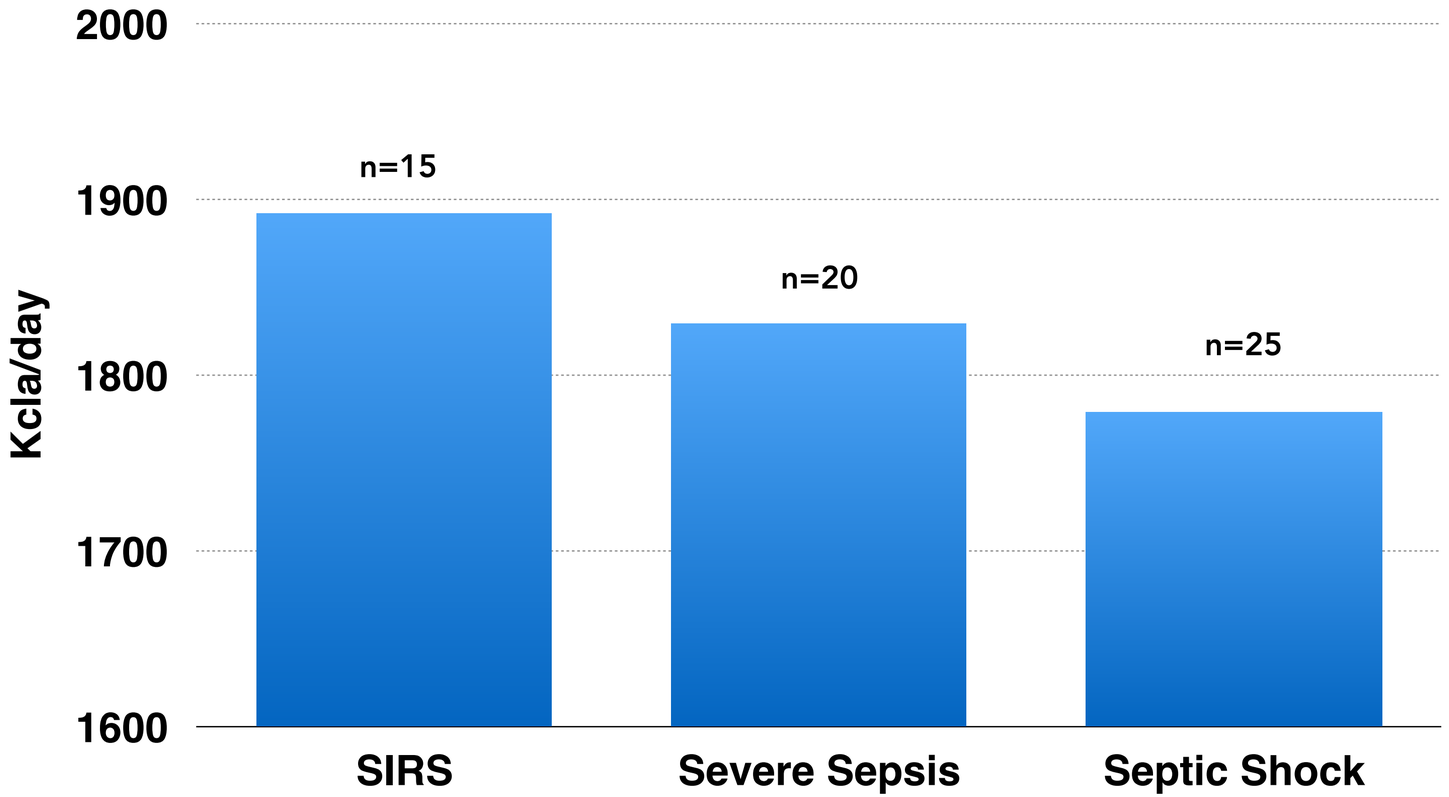
Villet S et al. Clin Nutr. 2005; 24(4):502-9

Resting Energy Metabolism



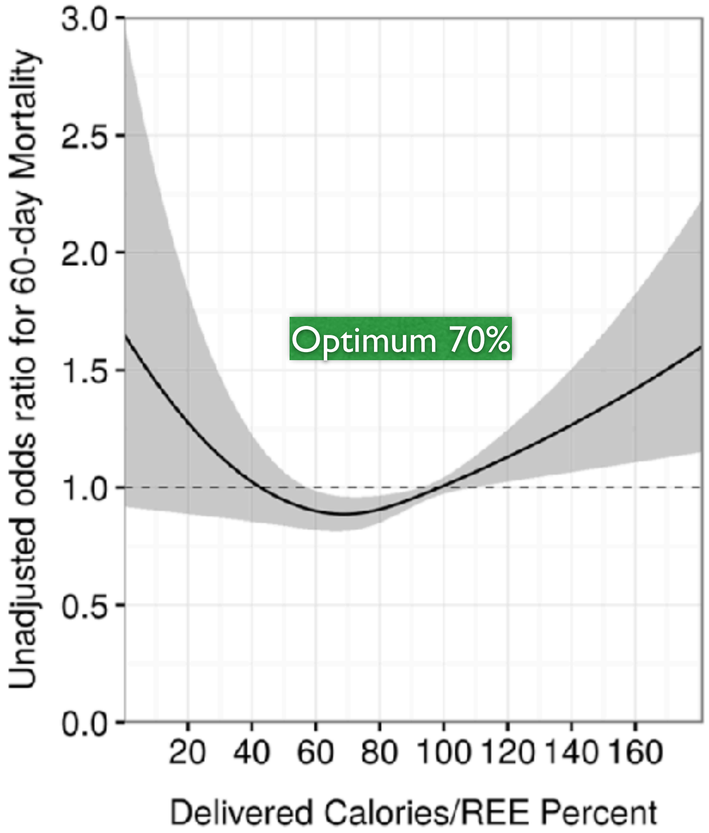
Energy Expenditure: SIRS, Severe Sepsis & Septic Shock

Bioenergetic failure, hibernation?

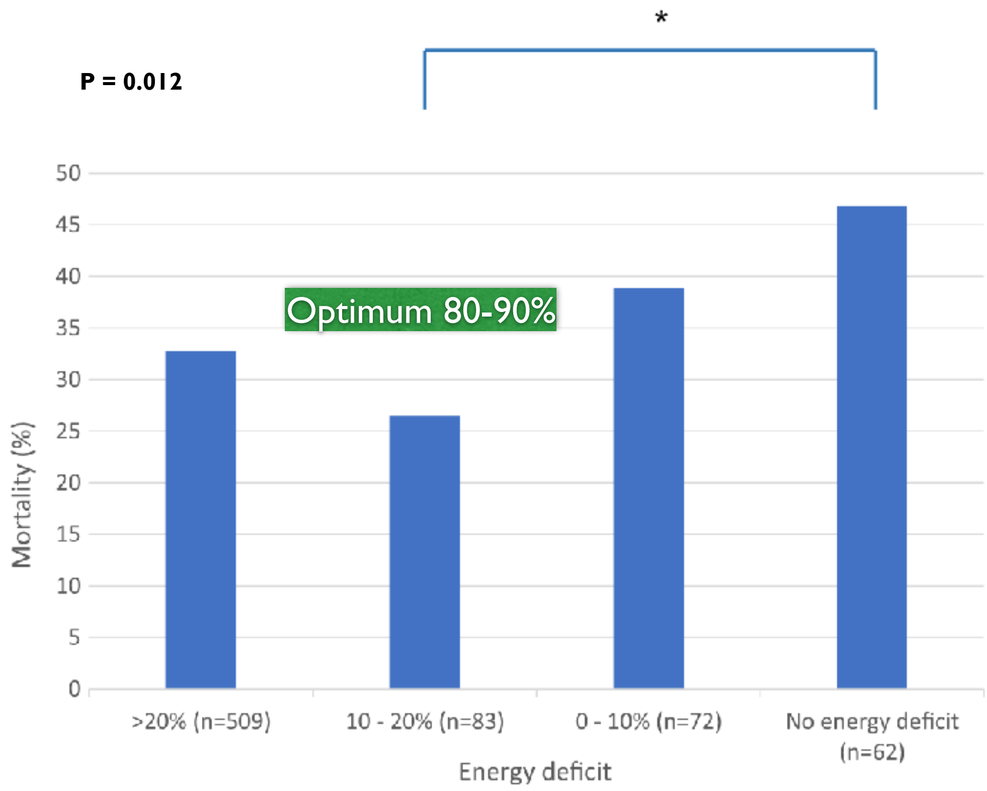


Subramaniam A et al. Crit Care Resusc 2012; 14: 202–210

Hospital mortality and cumulative energy deficit in ICU patients based on measured energy expenditure



during first 4 days of ICU stay for 726 non-septic ICU patients



During EN with 100% target, target achieved is typically 80-85% due to feeding interruptions

Zusman et al. Crit Care 2016;20:367, Weijs P. Crit Care 2014;18:701

Overfeeding in ICU patients

- Uremia
- Hypertonic dehydration
- Metabolic acidosis
- Hyperglycemia
- Hypertriglyceridemia
- Hepatic steatosis
- Fat-overload syndrome
- Hypercapnia
- Refeeding syndrome

Using parenteral nutrition the risk of overfeeding is more common than using enteral nutrition

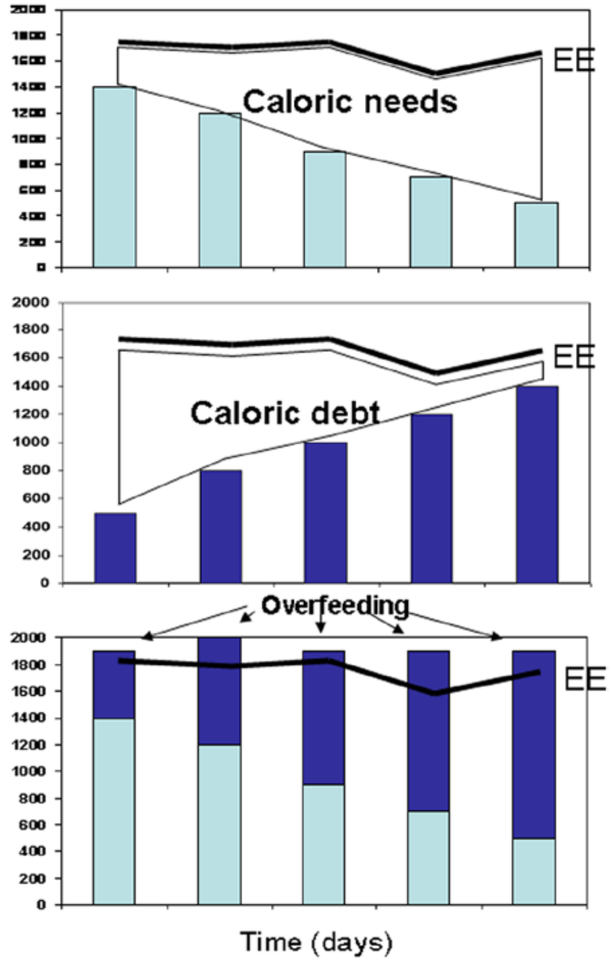
Klein C. J Am Dietetic Ass 1998;98:795-806

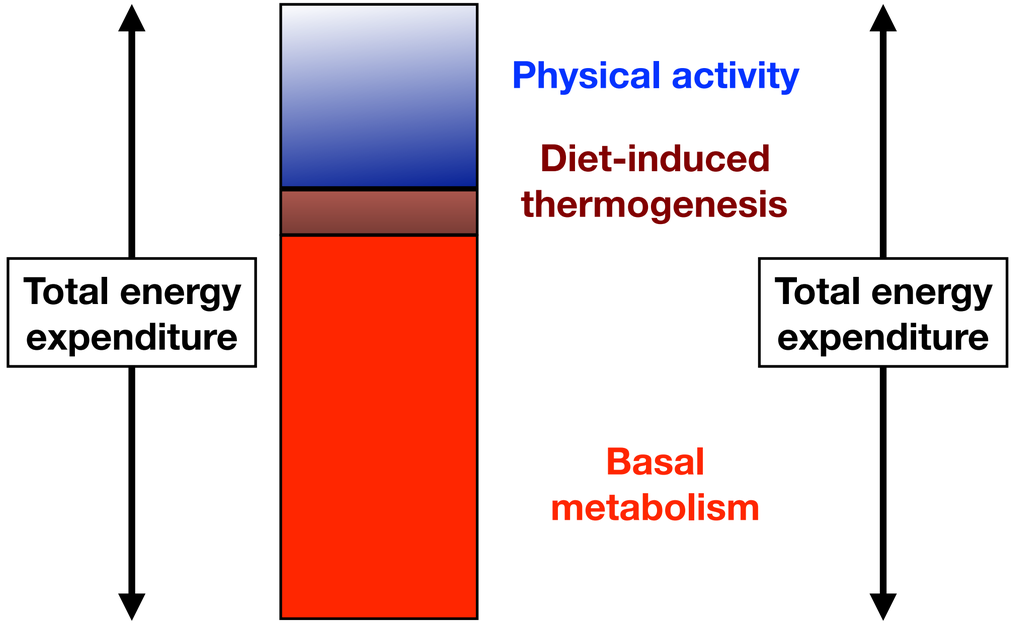
Consequences of early non-inhibitable endogenous energy production and overfeeding risk in critical illness

endogenous production

nutritional intake

total intake





Fraipont V, Preiser JC. JPEN J Parenter Enteral Nutr. 2013;37(6):705-13.

How to prevent underfeeding in ICU patients?

artificial nutrition enterally

PRO

- more physiological
- no need for central venous catheter
- less risk for contamination
- costs low

CON

- not always tolerated
- complications such as vomiting, aspiration, diarrhea, and ischemia
- not always achieve the caloric goals
- absorption unclear

artificial nutrition parenterally

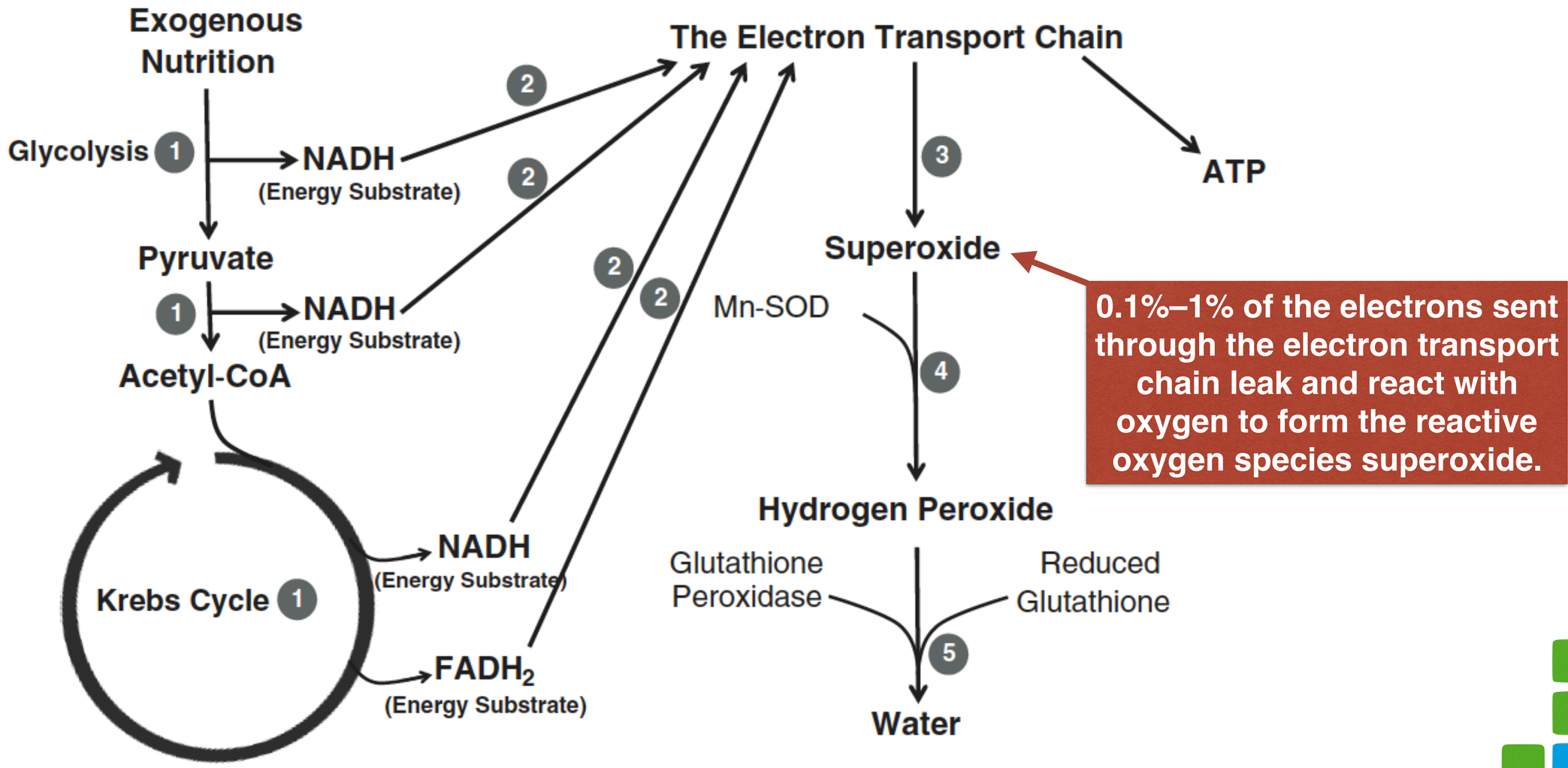
PRO

- maximal bioavailability of nutrients
- easy to reach caloric goals
- feasible in all patients

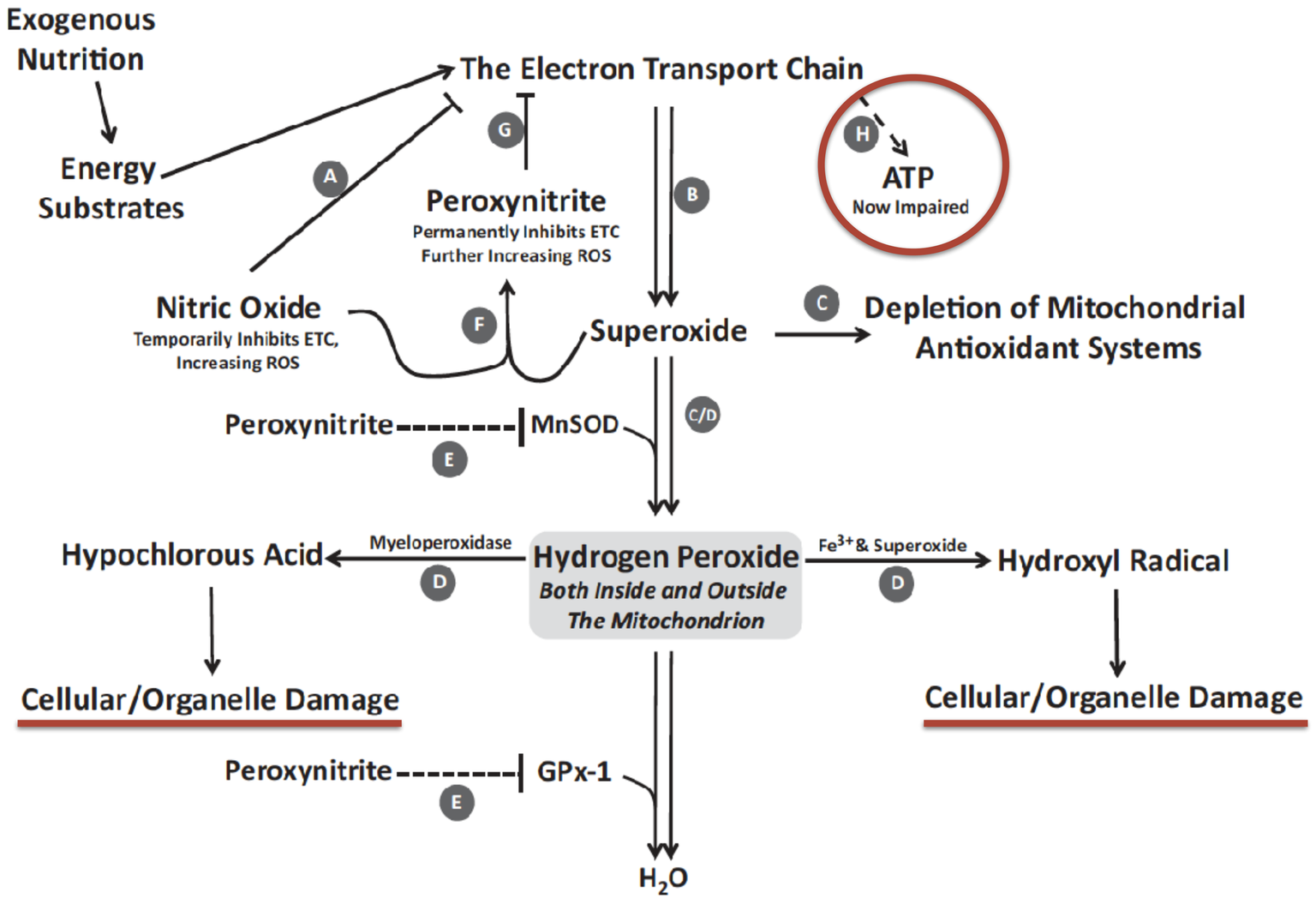
CON

- need for central venous catheter
- complications such as hyperglycemia, hypertriglyceridemia, and uremia
- risk of overfeeding – associated with complications
- costs high

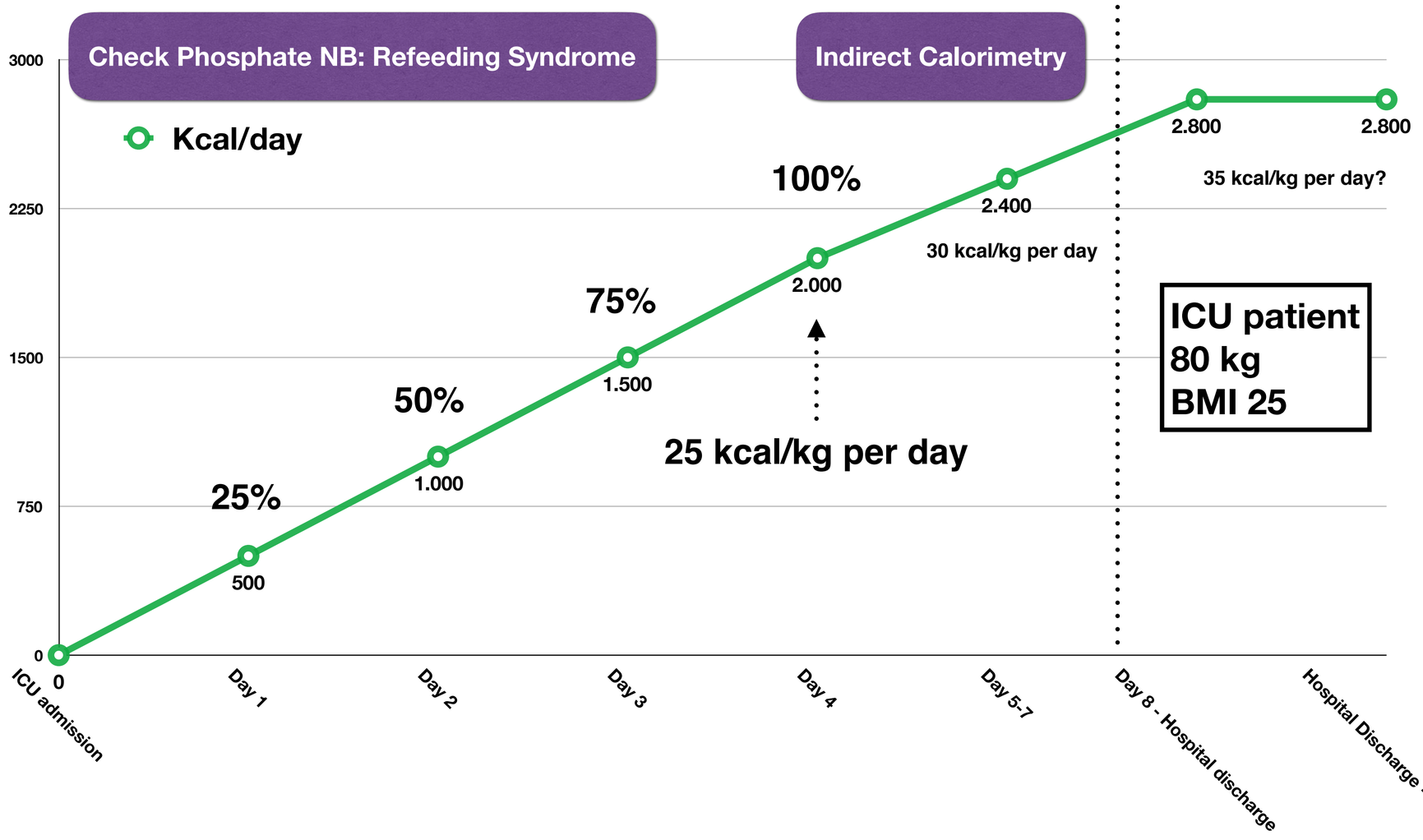
Nutrition in health



Excess exogenous nutrition may hamper mitochondrial function



Energy targets in ICU patients



Koekkoek KWAC, van Zanten ARH. Curr Opin Anaesthesiol. 2018

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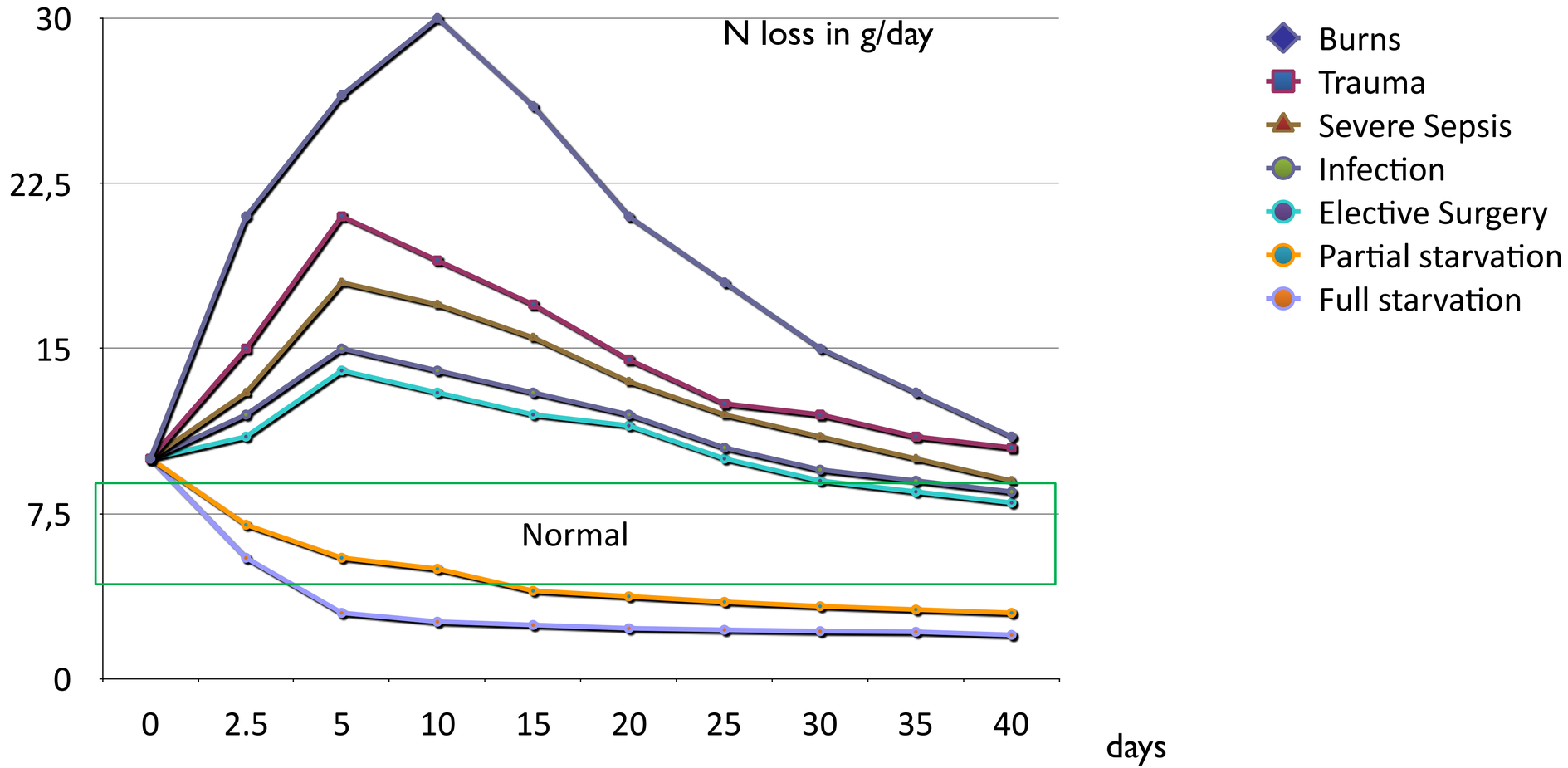
Proteins in Critically ill Patients with and without Sepsis

Nitrogen loss



Protein Balance

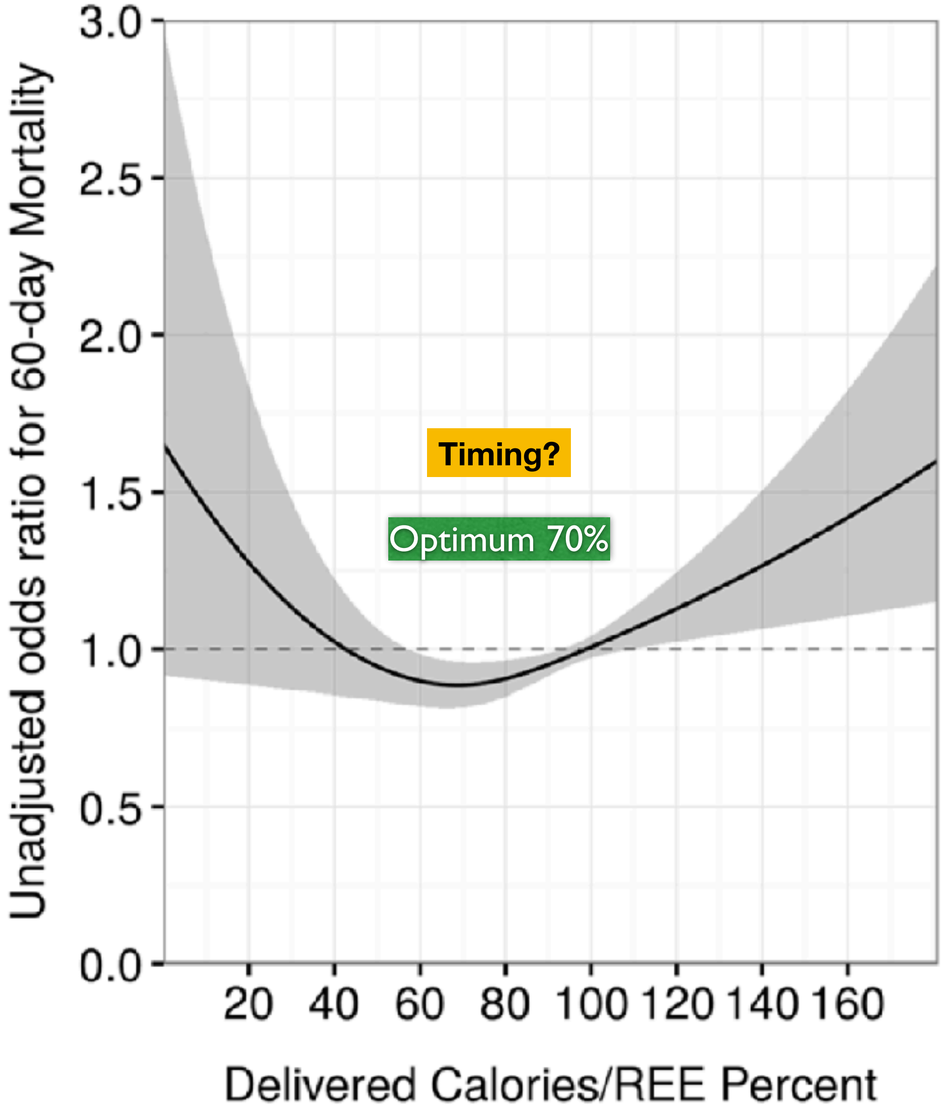
Catabolism

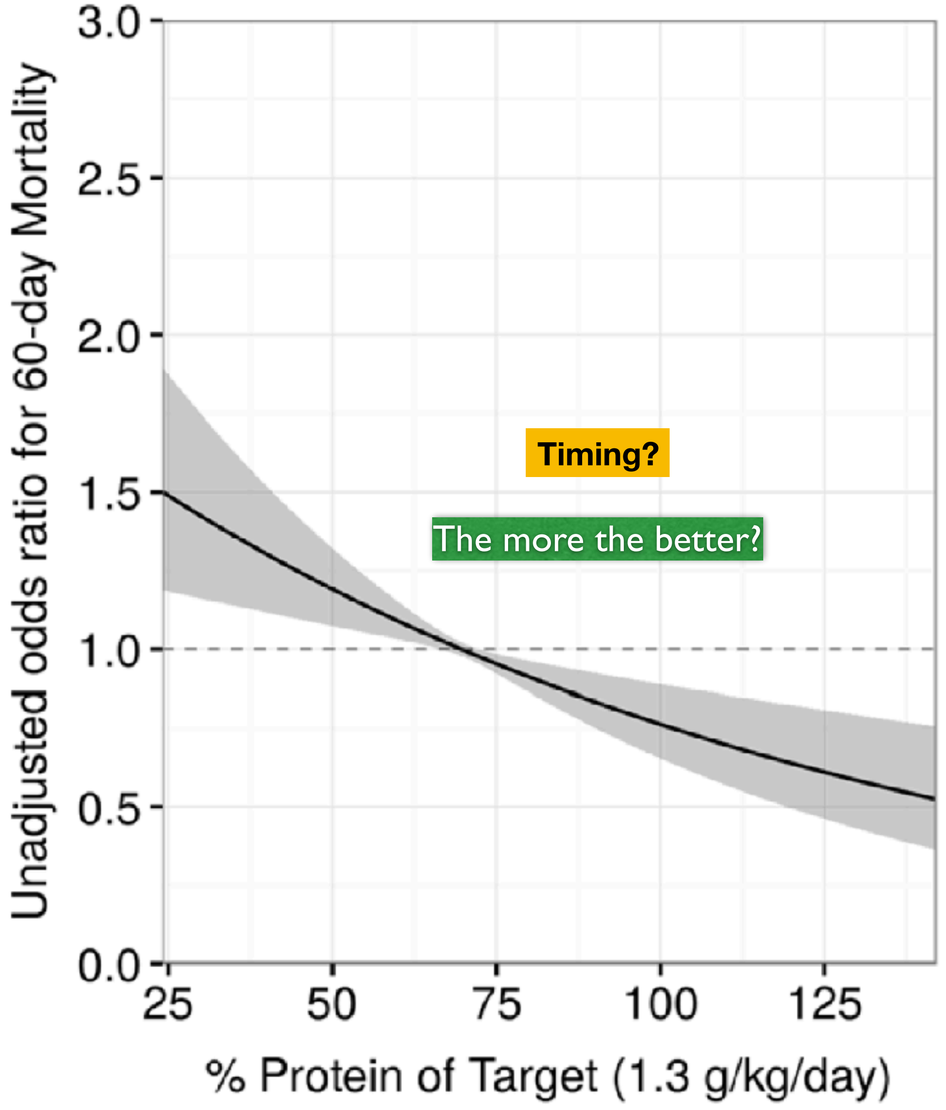
Protein-degradation in sepsis
2,2 g protein.kg^{-1}.day^{-1}
(1,4 for starving healthy persons)

Anabolism

Maximum protein synthesis
(septic) patients: 1,5-1,7 g
Protein.kg^{-1}.day^{-1} cBWT

Feeding the critically ill is different

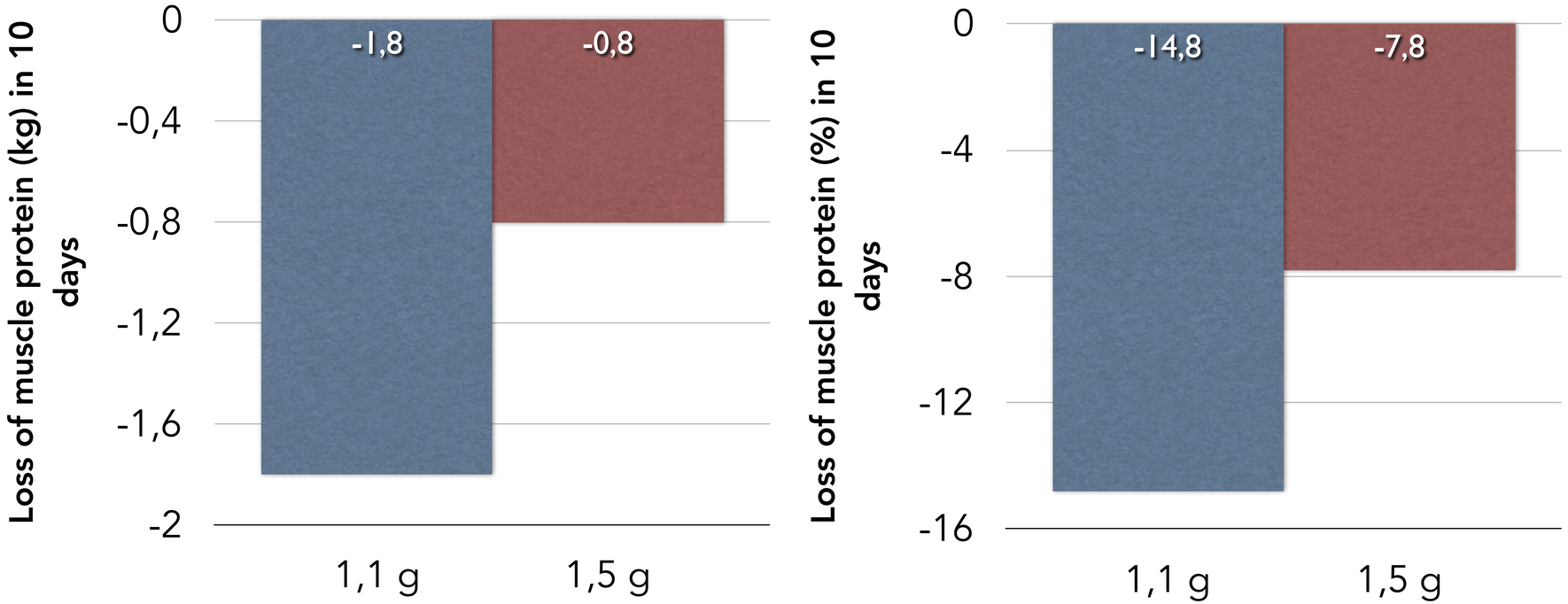




Zusman et al. Crit Care 2016;20:367

Effect of high protein intake on lean body mass (LBM)

in vivo neutron activation

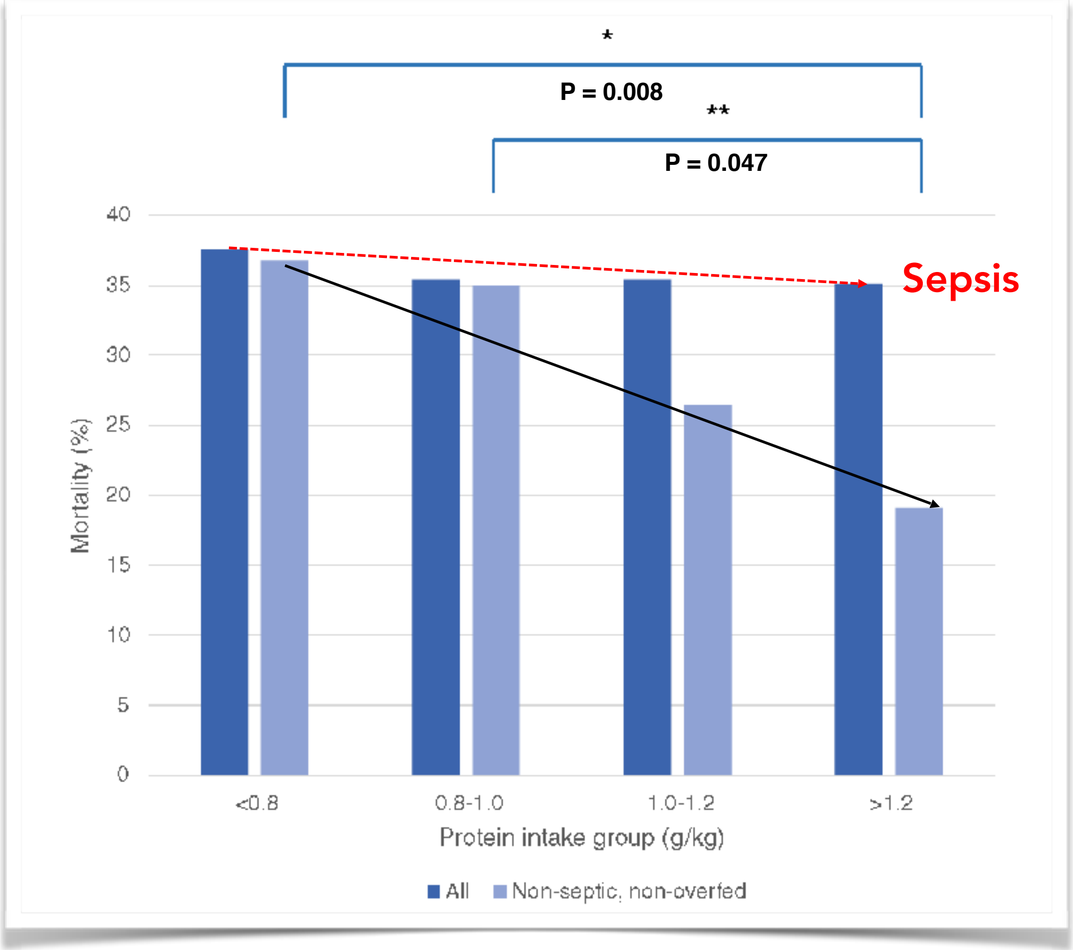


-1.8 kg of proteins reflects 9 kg of muscle mass

Ishibashi N et al. Crit Care Med 1998

Hospital mortality per protein intake group

More protein intake is associated with lower in-hospital mortality

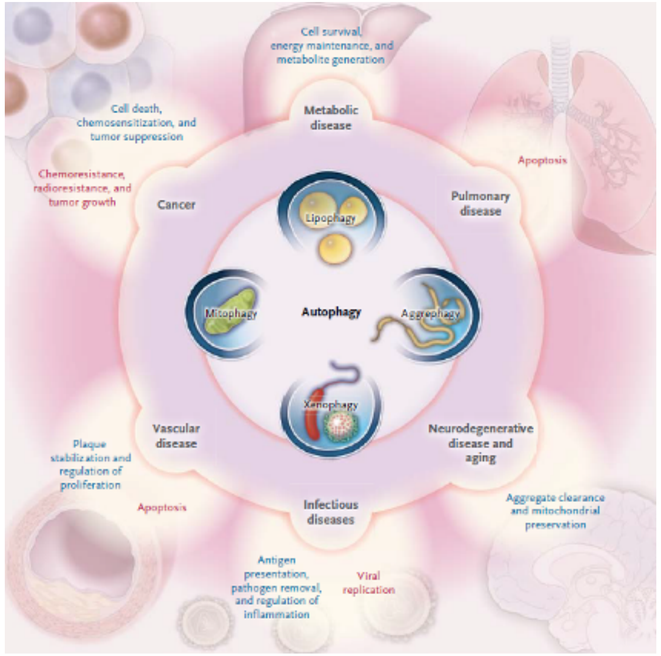


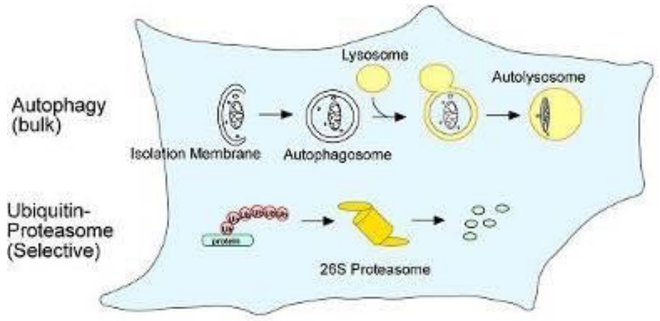
0.8 g/kg per day

1.2 g/kg per day

Weijs P. Crit Care 2014;18:701

Proteins and Autophagy



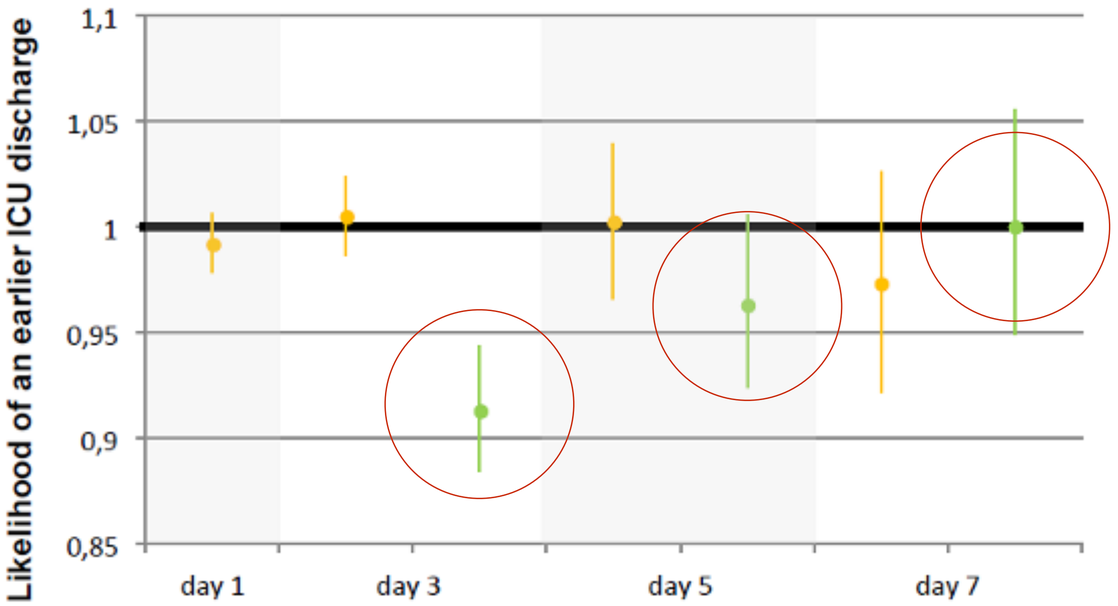


- **Method eukaryotic cells dispose damaged organelles or protein aggregates too large for proteasome ubiquitin system**
- **Involves lysosomal system for removing unfolded proteins, virus, bacteria, fat/carb, organelles**
- **Autophagy role in immunity, inflammation, infection, cancer, aging, pulmonary diseases (COPD), metabolic and neurodegenerative diseases**

AMK Choi et al NEJM 2013;368:651

Epanic trial Suggests that early Protein administration induced Deleterious Effects, Not Glucose

Epanic trial 4600 patients randomized to early or late SPN



Glucose

HR (CI) per 10% of target increase in glucose intake (± 28 g / day)

Protein

HR (CI) per 10% of target increase in protein intake (± 7 g / day)

Implication: Nutrition Rx (not IV glucose load) caused adverse outcome

Casaer MP. Am J Respir Crit Care Med 2013;187:247-55.

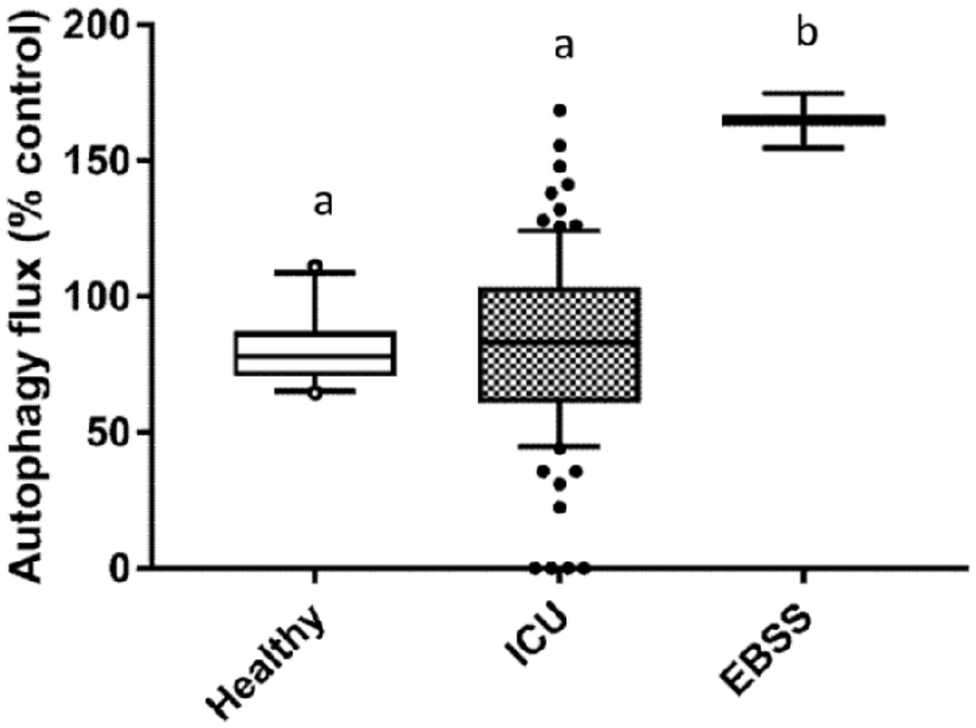
Divergent autophagy response in critical illness

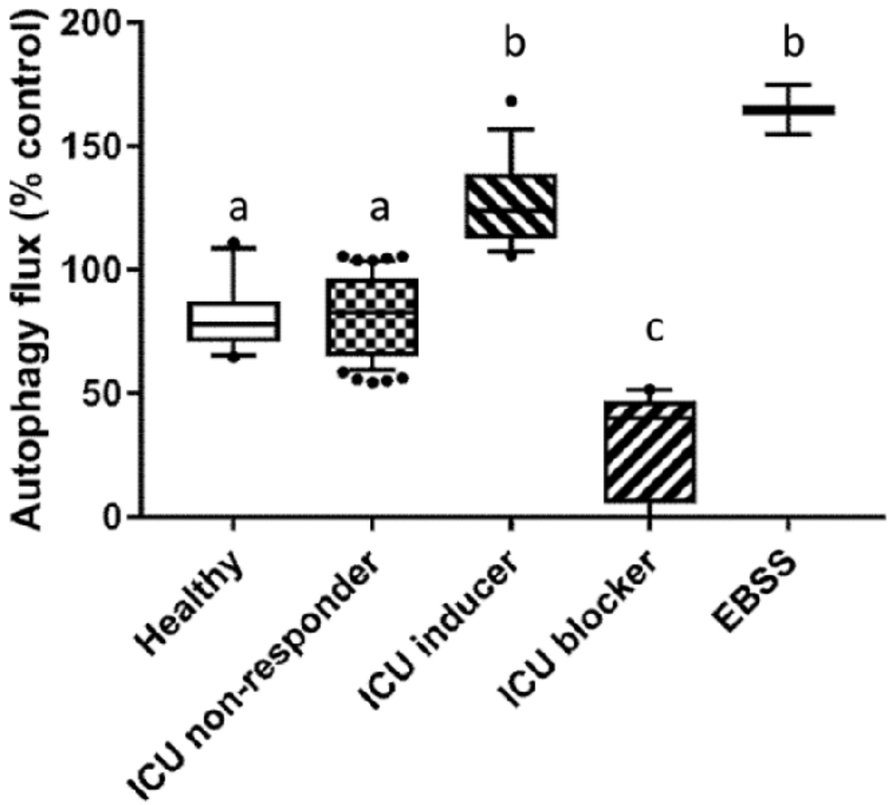
	Healthy (n = 10)	ICU non-responder (n = 59)	ICU inducer (n = 18)	ICU blocker (n = 16)	*p*
Age (years)	49 [44–53]	57 [52–63]	59 [50–69]	56 [46–67]	0.55
Sex (F/M)	(5/5)	(21/38)	(7/11)	(8/8)	0.66
BMI (kg/m^2)	—	26.8 [25.3–28.2]	27.4 [24.3–30.5]	27.0 [23.3–30.8]	0.95
Length of Stay (days)	—	4.5 [3.2–5.9]	5.2 [2.0–8.3]	5.3 [2.3–8.2]	0.94
SOFA	—	6.3 [5.4–7.2]	5.9 [3.8–8.1]	7.9 [5.6–10.1]	0.26
APACHE	—	17.5 [15.4–19.7]	18.3 [14.6–22.1]	19.5 [16.7–22.3]	0.31
Number of organ failing	—	2.8 [2.5–3.1]	2.9 [2.2–3.7]	3.4 [2.6–4.2]	0.23

No clinical indicators of autophagy response

Tardif N, Rooijackers O et al. Nature Science Report 2019 45:1283–1287

Divergent autophagy response in critical illness

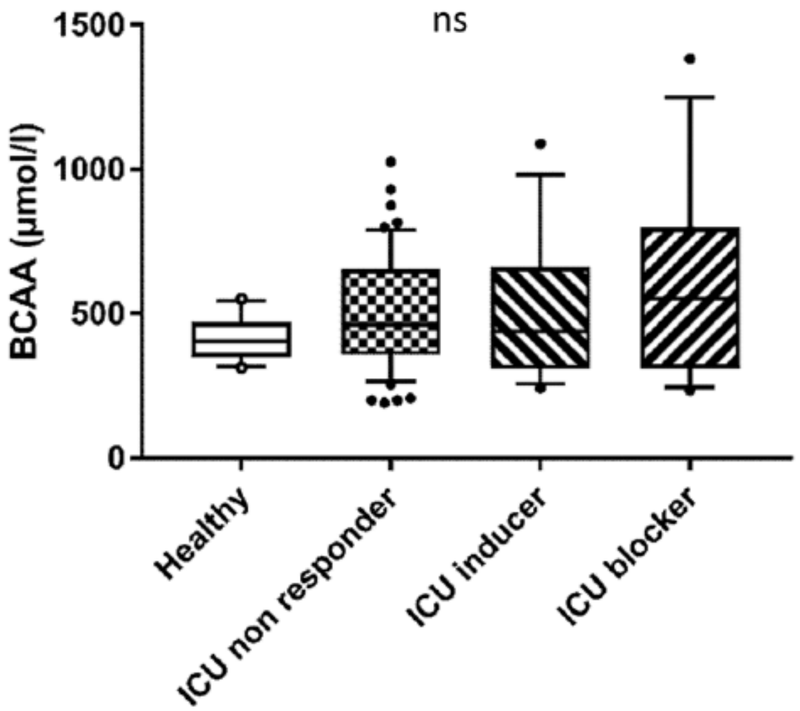


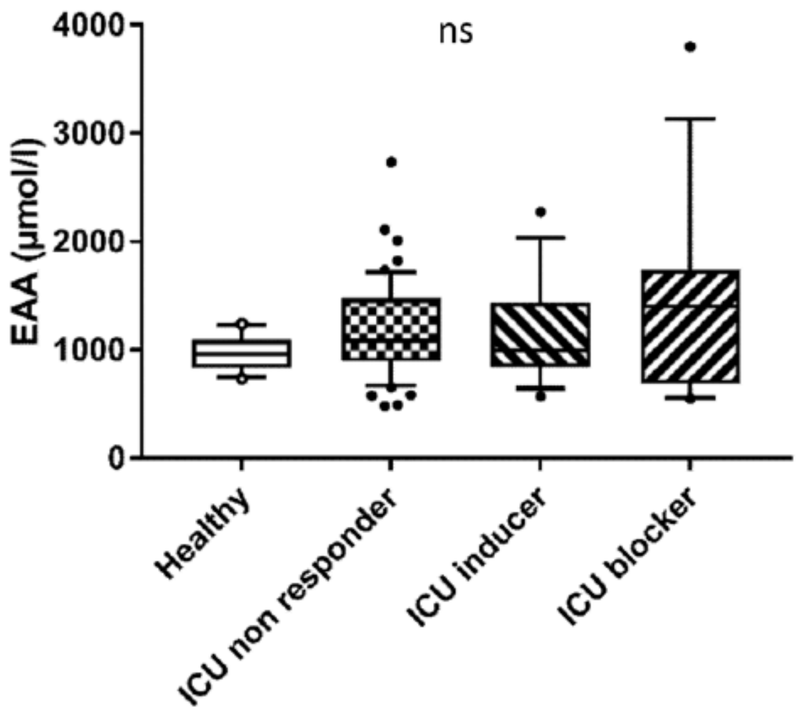


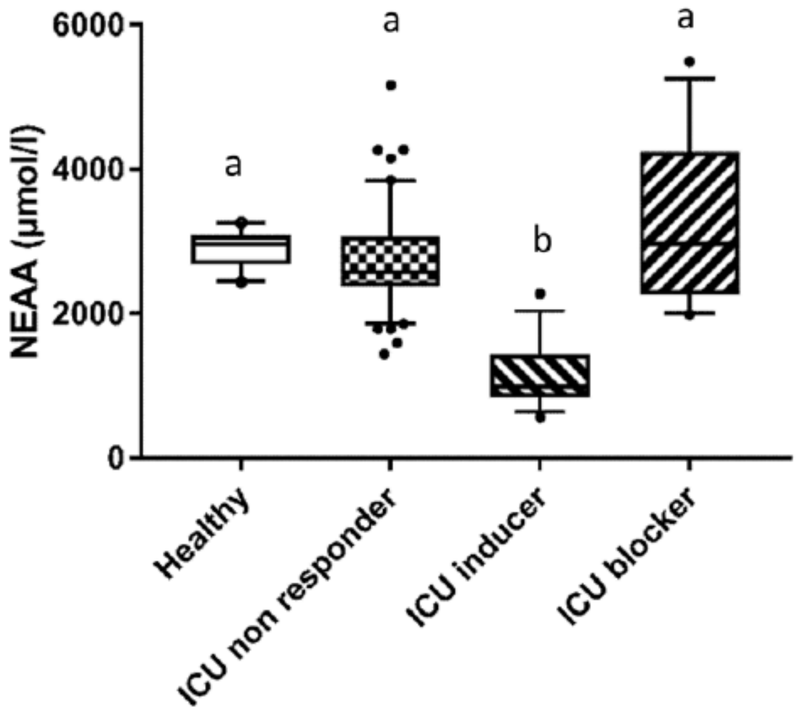
block was related to an accumulation of autophagosomes/autolysosomes, which indicates an impairment in the last steps of the autophagy process.

Tardif N, Rooijackers O et al. Nature Science Report 2019 45:1283–1287

AA do not block autophagy in critical illness, low levels of non-essential AA induce autophagy







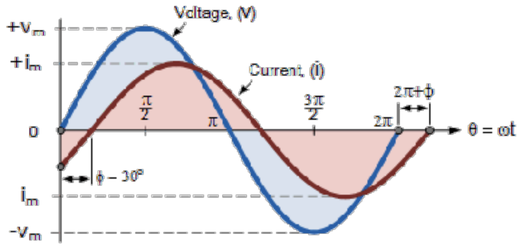
Branched chain amino acids: phenylalanine, threonine, tryptophan, methionine, lysine and histidine

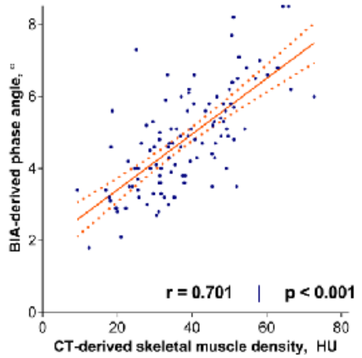
Essential amino acids: phenylalanine, valine, threonine, tryptophan, methionine, leucine, isoleucine, lysine, and histidine

Non-Essential amino acids: arginine, cysteine, glycine, glutamine, proline, and tyrosine. alanine, aspartic acid, asparagine, glutamic acid, serine, and selenocysteine

Tardif N, Rooijackers O et al. Nature Science Report 2019 45:1283–1287

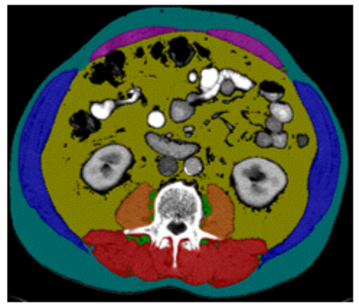
How to monitor the effect of proteins and AA in critical illness?

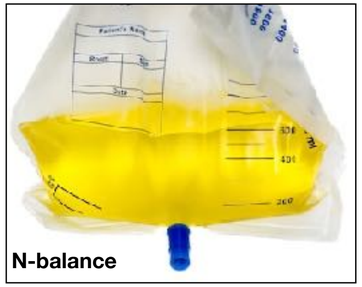




BIA
Phase angle

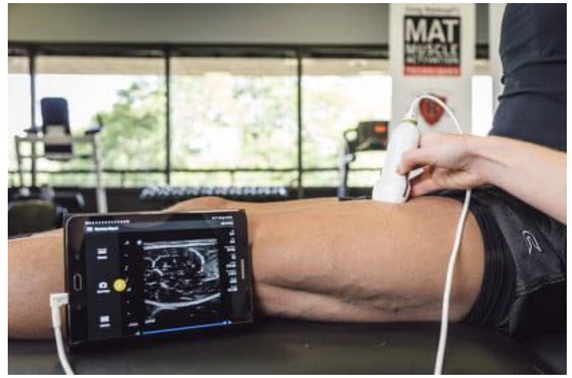
CT scan



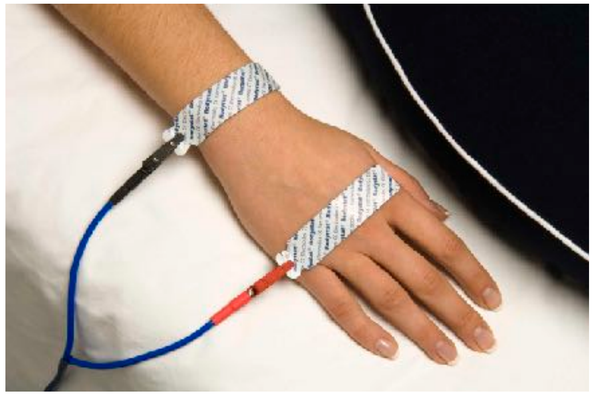


N-balance

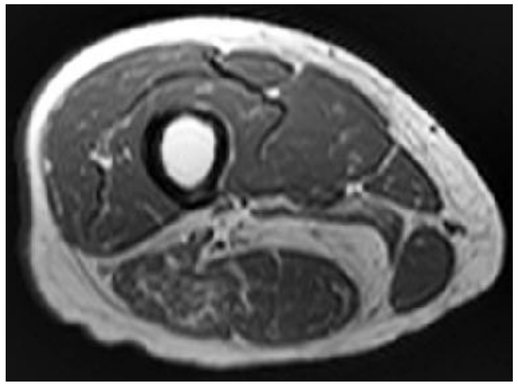
hand grip strength



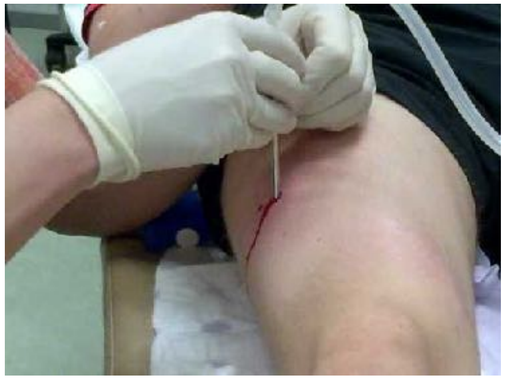
muscle ultrasound



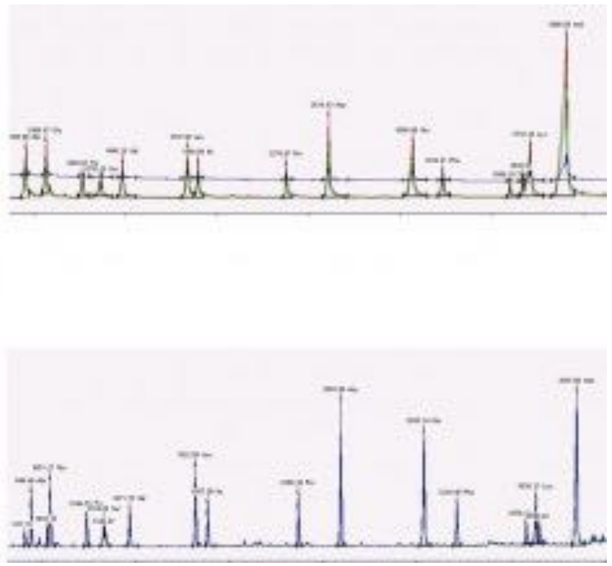
MRI



muscle biopsy



Protein turnover studies using stable isotopes



Conclusions

- Energy expenditure is variable during sepsis and ICU stay
- Catabolism is extreme during critical illness
- Insulin resistance is common
- Early overfeeding through endogenous energy production should be prevented
- Mitochondrial dysfunction plays a role in critical illness, and nutrients can have beneficial but also negative effects
- Long-term consequences are an important new focus