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Nutrients, insulin and muscle wasting during critical illness

Sarah Derde

Introduction

- Critical illness: feeding-resistant hypercatabolism
  - Imbalance between protein synthesis and breakdown

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  - Skeletal muscle = main protein source

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Severe muscle weakness

- rehabilitation: delayed
- mortality risk ↗
- after hospital discharge: quality of life ↘

Muscle weakness

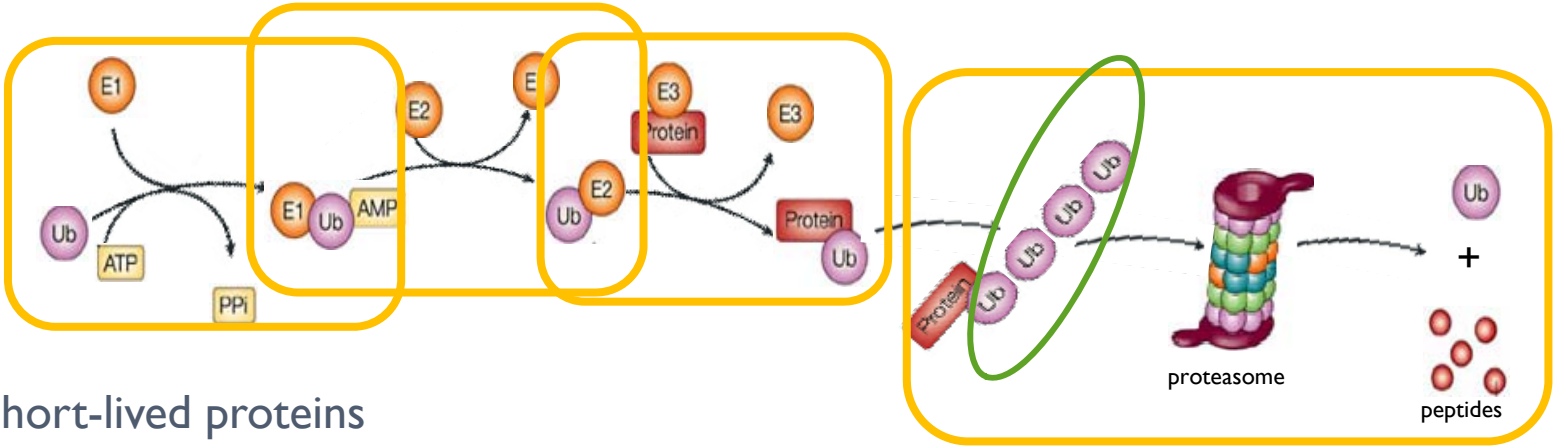
Myofibrillar protein

↓ **synthesis**

breakdown ↑

- Ubiquitin proteasome system
- Autophagy

Protein degradation pathways:
Ubiquitin-proteasome system



Short-lived proteins
myofibrils

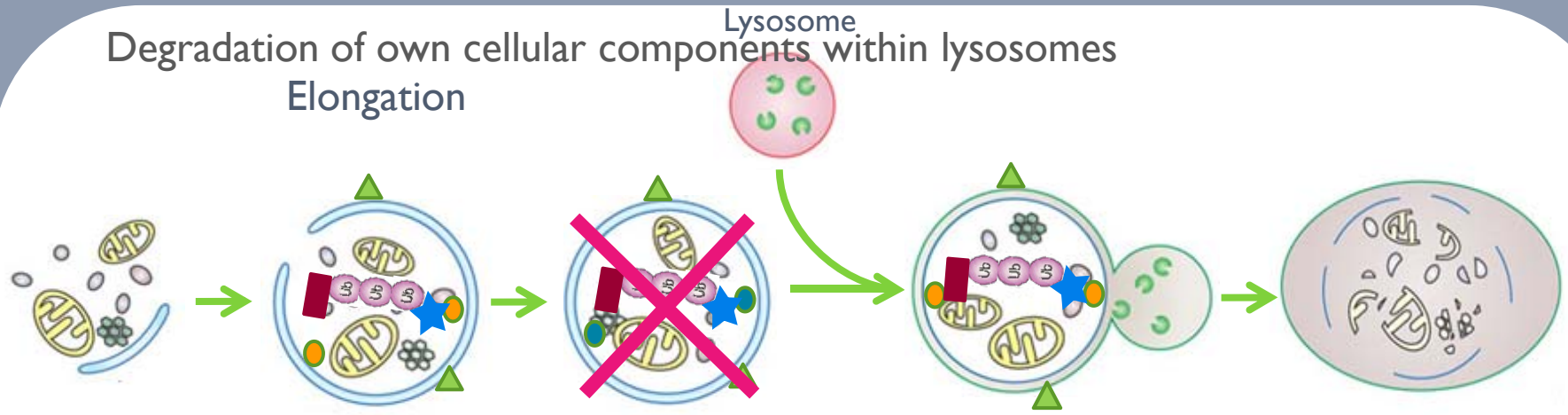
Muscle wasting

↑ MuRF-1
↑ Atrogin-1

↑ Lysosomal system

Protein degradation pathways:
Autophagy

Degradation of own cellular components within lysosomes



removing damaged proteins
energy supply

+ accumulation toxic protein aggregates

Role of autophagy in muscle wasting?

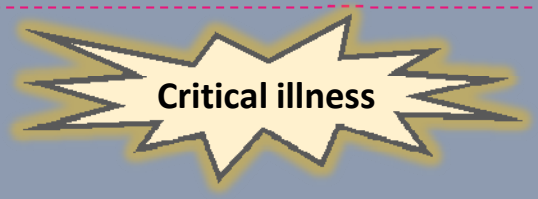
- Excessive activation → could aggravate muscle wasting
- Impairment/inhibition → could evoke atrophy and myopathy

  ⇨ muscle fiber degeneration

  ⇨ muscle weakness

- Effect of autophagy during prolonged critical illness **?**

Inhibitors of catabolism



- Insulin
- Nutrients

- Insulin resistance
- Dysfunctional gastro-intestinal tract
- Intravenous nutrition:

ineffective to safely counteract hypercatabolism

promotes catabolism

General hypothesis

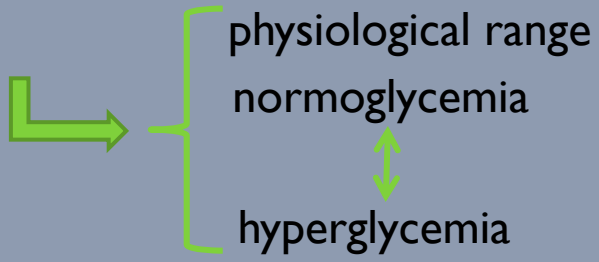
Intravenous nutrition, while maintaining normoglycemia, safely counteracts muscle wasting during prolonged critical illness

Objectives

- 1. Effect of strict blood glucose control with intensive insulin therapy on muscle wasting in fed critically ill patients

- 2. Efficacy in counteracting protein degradation and safety of intravenous nutritional interventions in an animal model

  - Effect of fasting versus ↗ intravenous glucose load



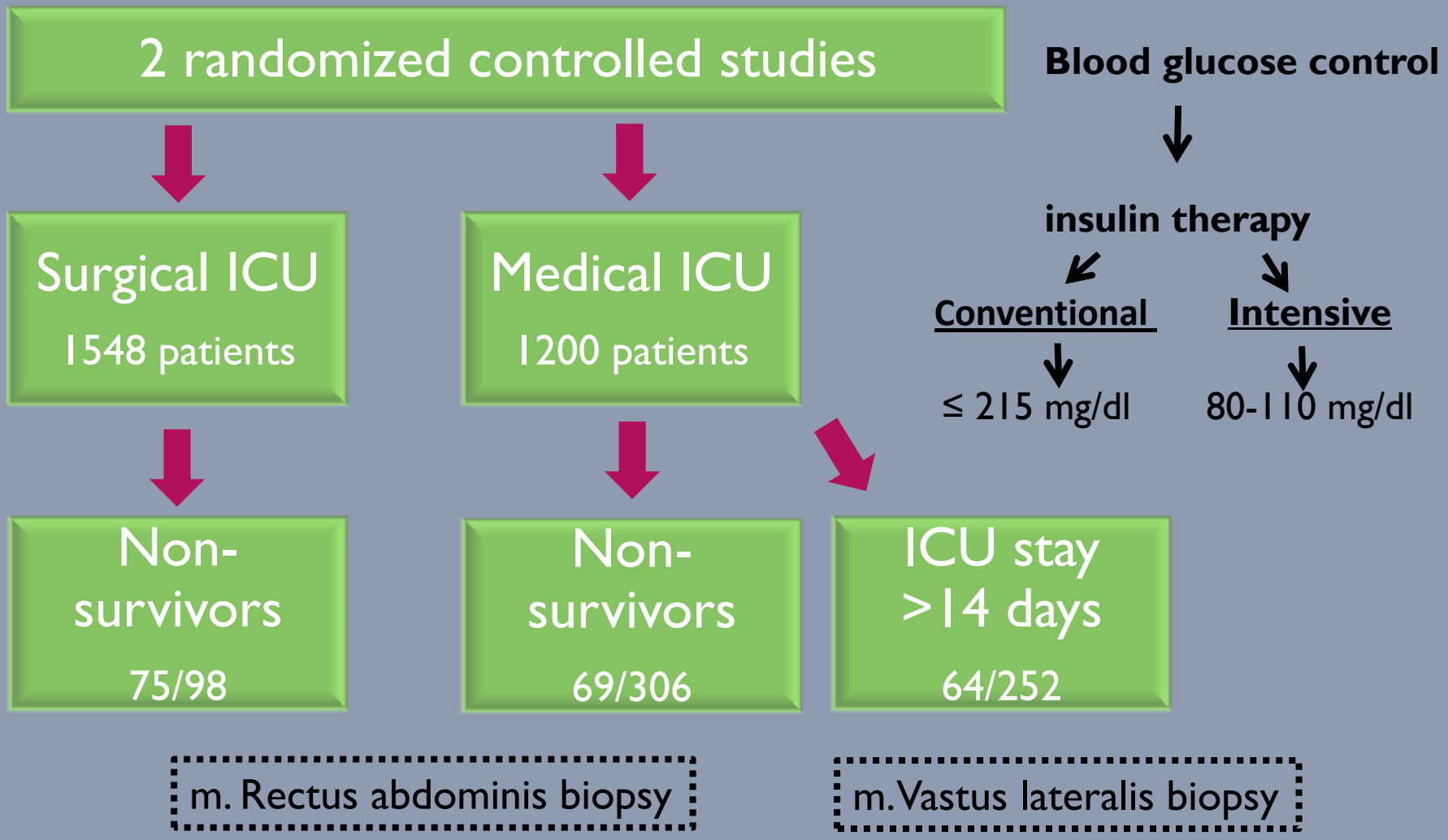
  - Impact of altering nutritional substrate composition

Hypothesis I

Muscle atrophy in fed critically ill patients
can be attenuated by intensive insulin therapy

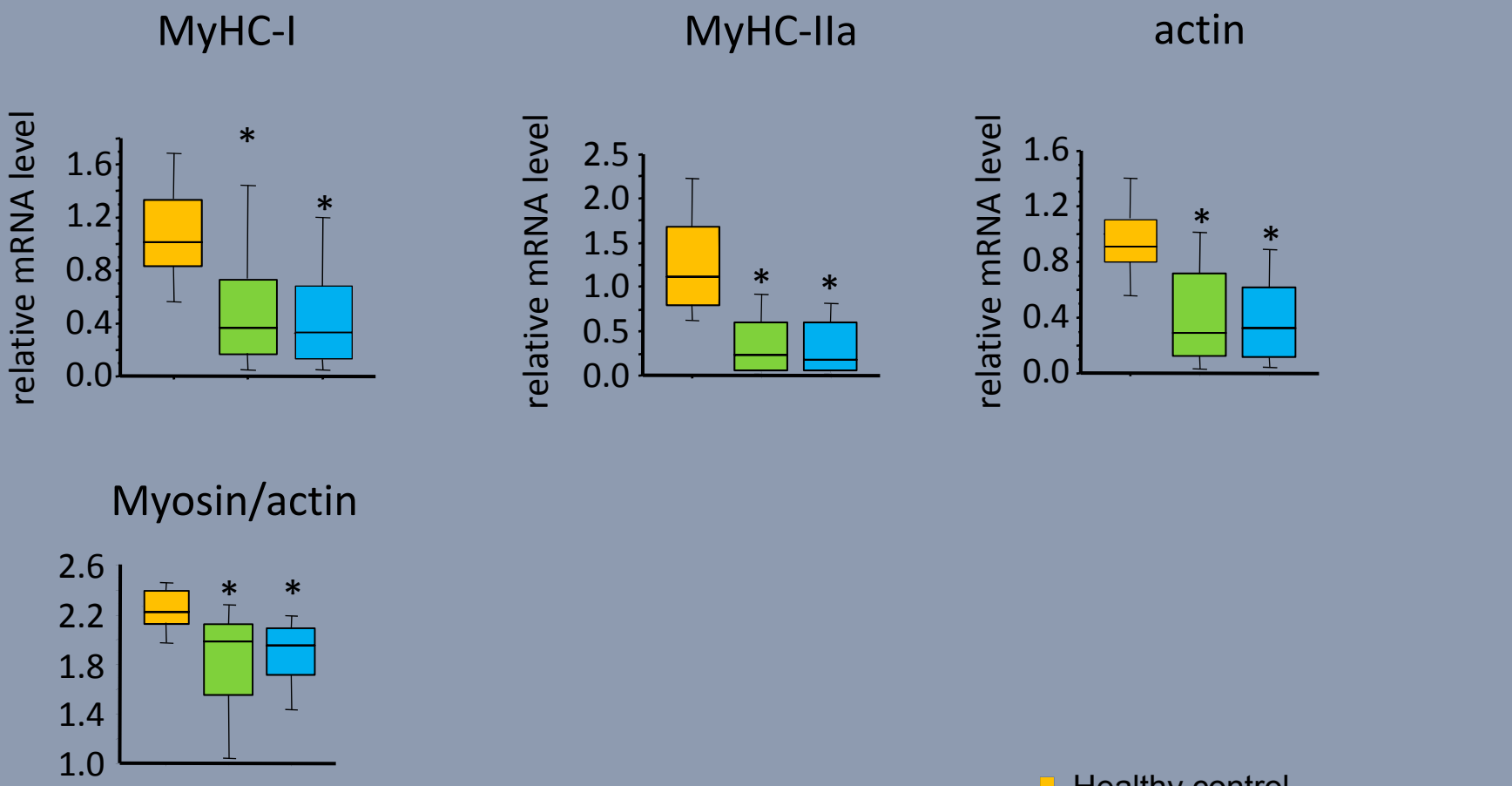
Derde et al, Crit Care Med 2012, 40:79-89
Vanhorebeek et al, J Clin Endocrinol Metab 2011, 96:E633-E645

Patient population



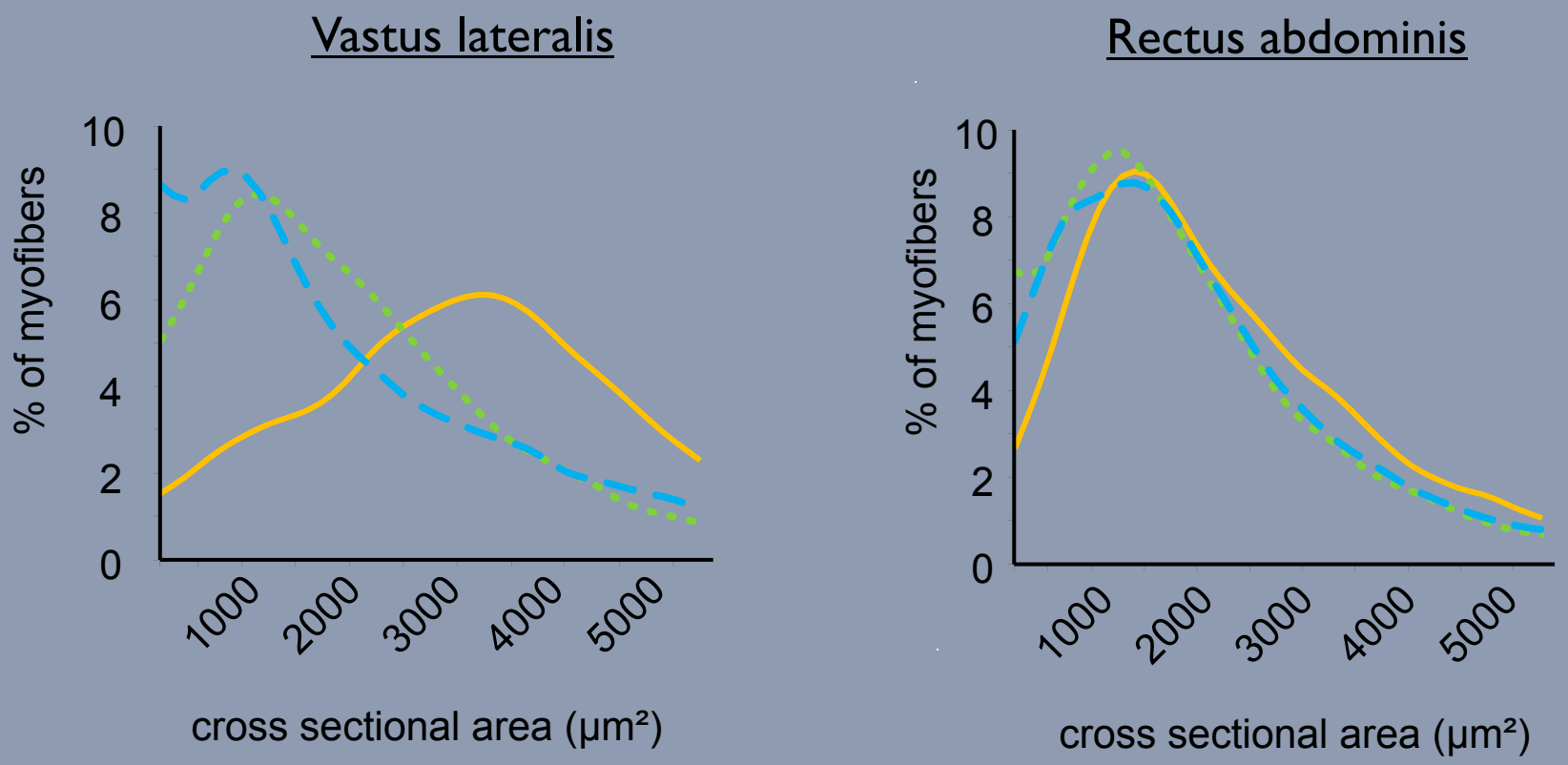
- Muscle protein synthesis
- Myofiber size and morphology
- Muscle protein degradation

Synthesis of myofibrillary proteins



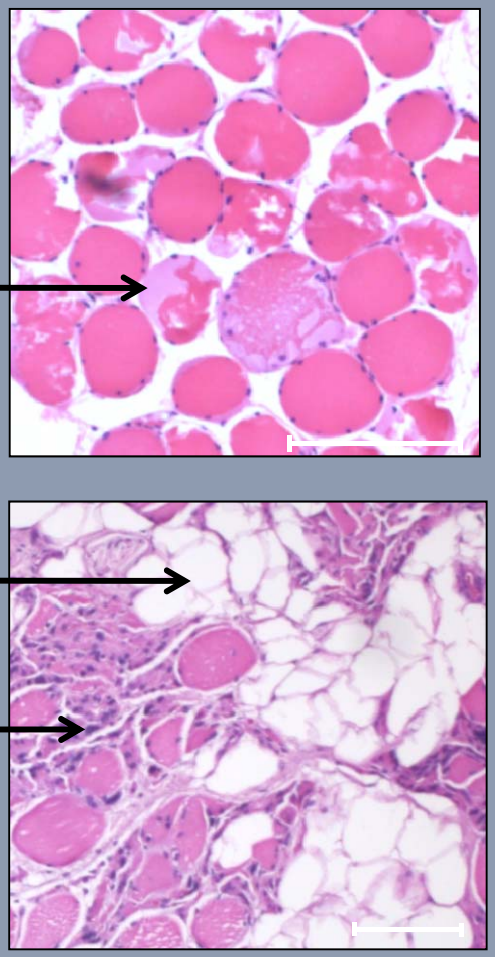
* : P ≤ 0.05 versus control

Myofiber size: fiber cross-sectional area



Study 1: Insulin therapy and muscle wasting

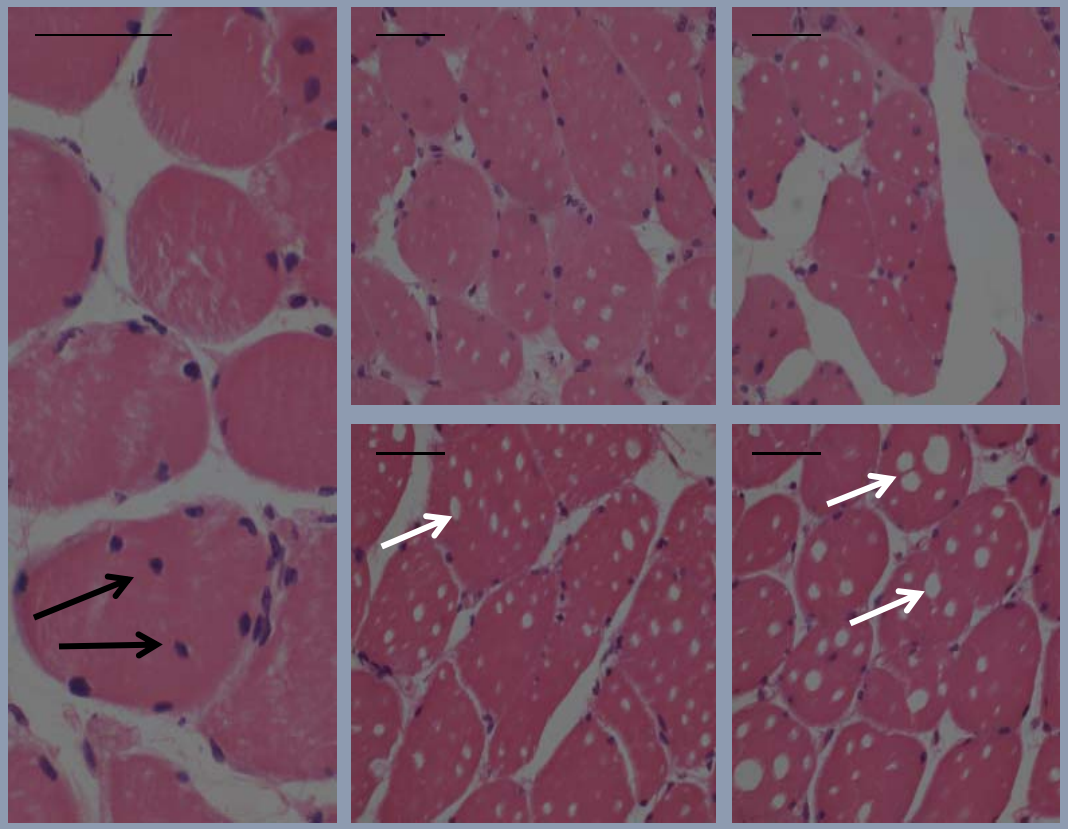
Morphological analysis of skeletal muscle:

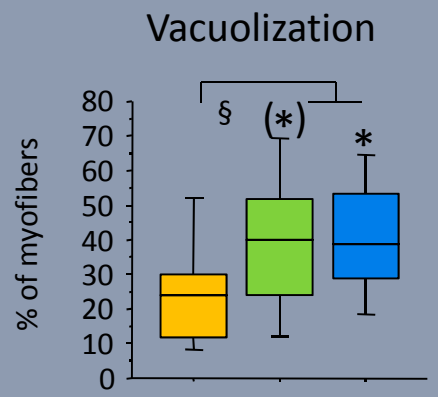


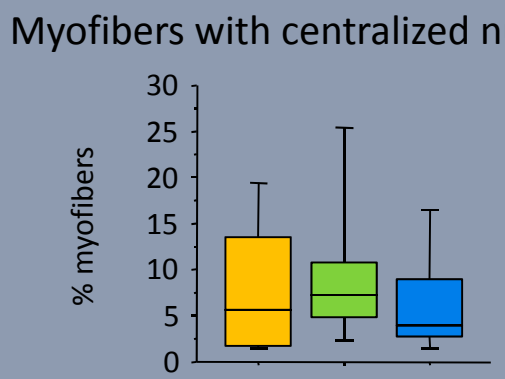
Rectus abdominis

Inflammation and/or necrosis (n, %)	Present	P-value
		0.09
Control	0 (0)	
CIT	20 (28)	
IIT	16 (32)	
Presence of adipocytes (n, %)		
		0.01
Control	4 (36)	
CIT	55 (76)	
IIT	30 (60)	

Myofiber degeneration







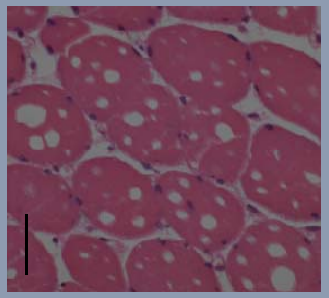
Control
Conventional insulin therapy
Intensive insulin therapy

* : p ≤ 0.05 versus control// (*) : p ≤ 0.1 versus control// §: p ≤ 0.05 sick versus control

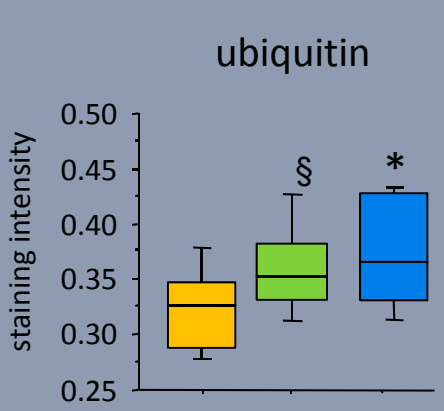
Study 1: Insulin therapy and muscle wasting

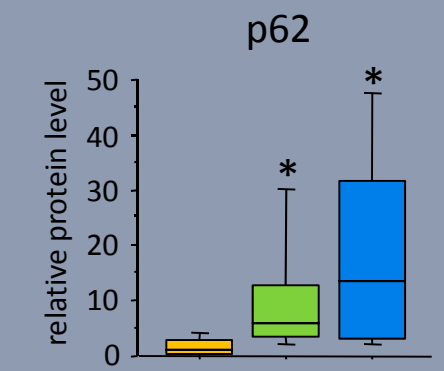
Protein degradation: autophagy

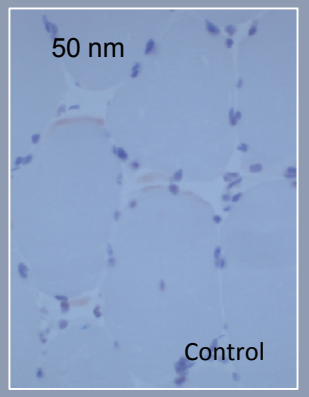
Vacuolization ↑

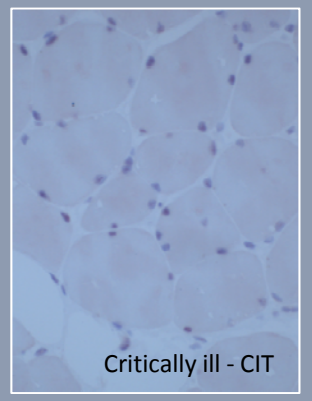


Impaired autophagy





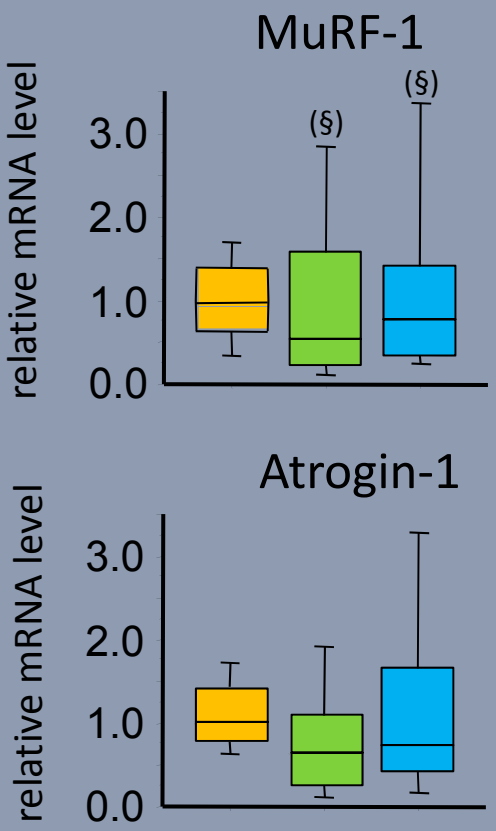


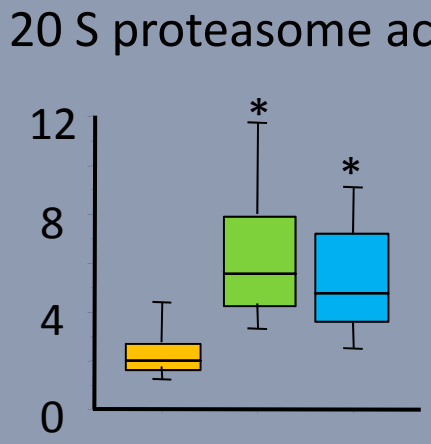


* : $p \leq 0.05$ versus control
(§): $p \leq 0.1$ sick versus control

Control
Conventional insulin therapy
Intensive insulin therapy

Protein degradation : Ubiquitin-proteasome system





- Healthy control
- Conventional insulin therapy
- Intensive insulin therapy

* : p ≤ 0.05 versus control// (§): P ≤ 0.1 sick versus control

Protein degradation: results

Conclusions

	Prolonged cri… illne…
gene expression myofibrillary proteins	
myosin/actin ratio	↘
Myofiber size	↘
autopha…	↘
2… …easome	↗

No effect of intensive insulin therapy

2. Efficacy to attenuate protein degradation and safety of intravenous nutrition in an animal model of prolonged critical illness

Hypothesis 1

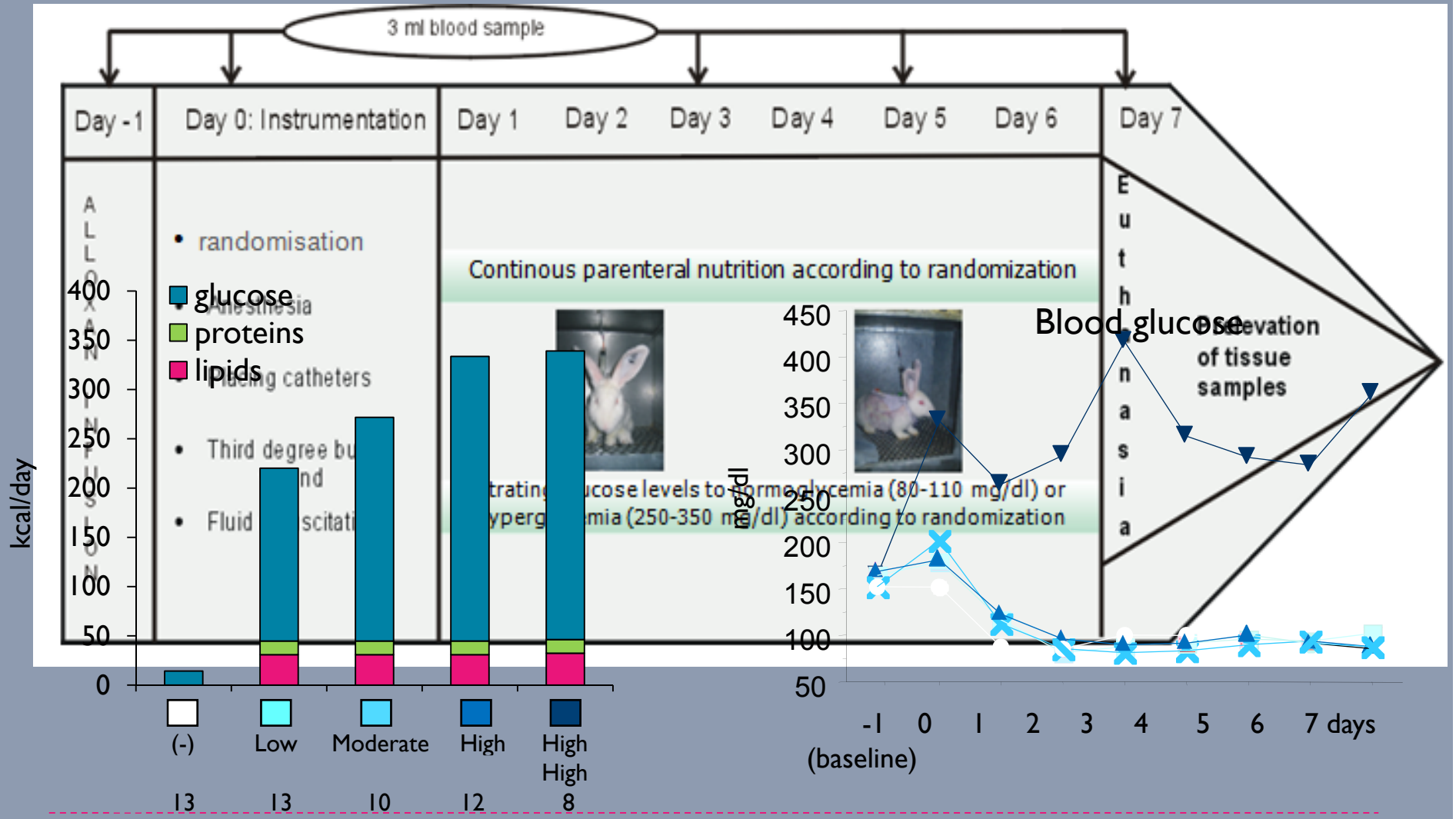
Increasing the intravenous glucose load,

within the physiological range and while maintaining

normoglycemia, safely counteracts muscle catabolism

Derde et al, Crit Care Med 2010, 38:602-611

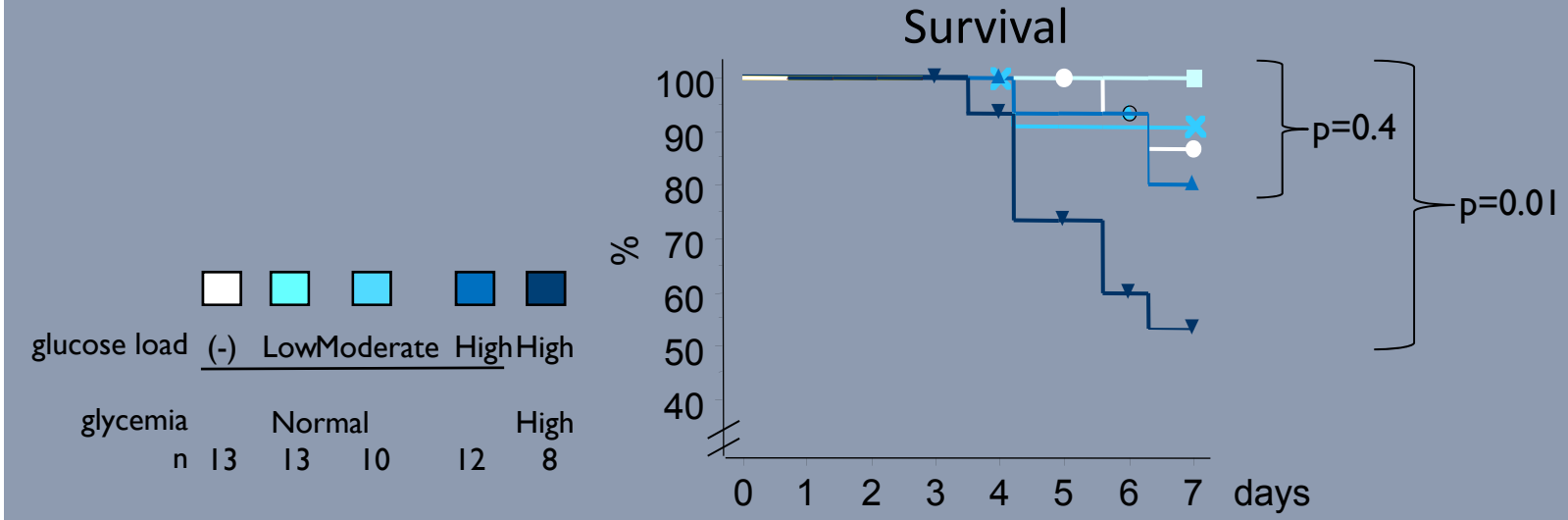
Experimental setup 1

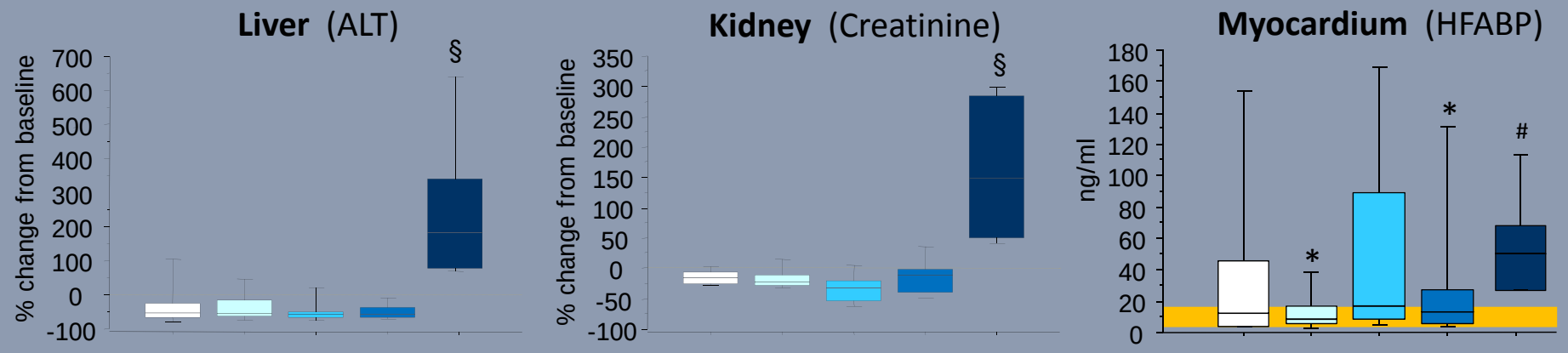


Study 2: increasing the intravenous glucose load

- Safety evaluation: survival & organ function
  - Muscle protein degradation

Safety:Survival and organ function



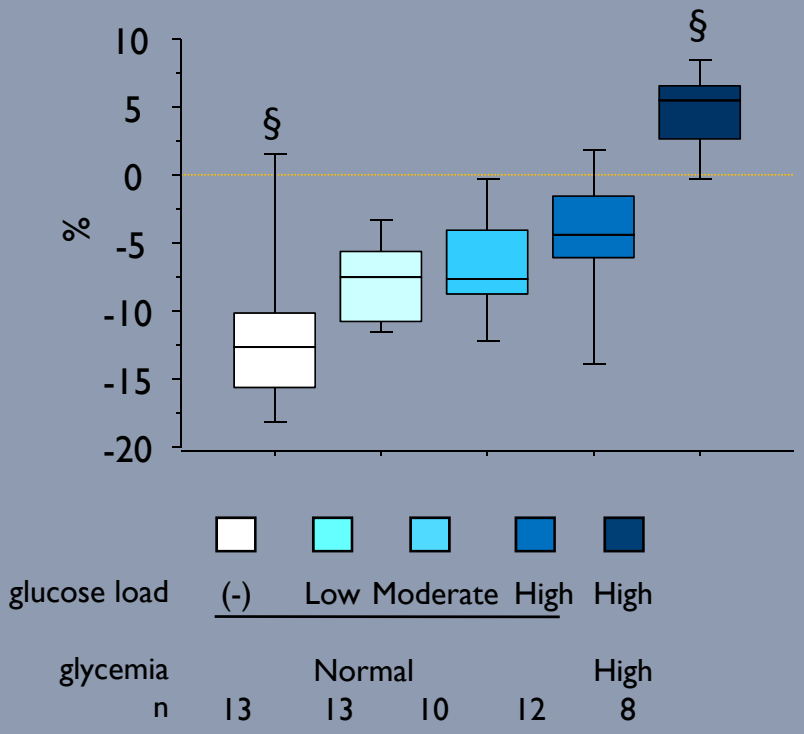


§: p < 0.05 versus all other groups// * : p < 0.05 versus high/hg rabbits// #: p < 0.05 versus healthy control rabbits// : healthy reference range

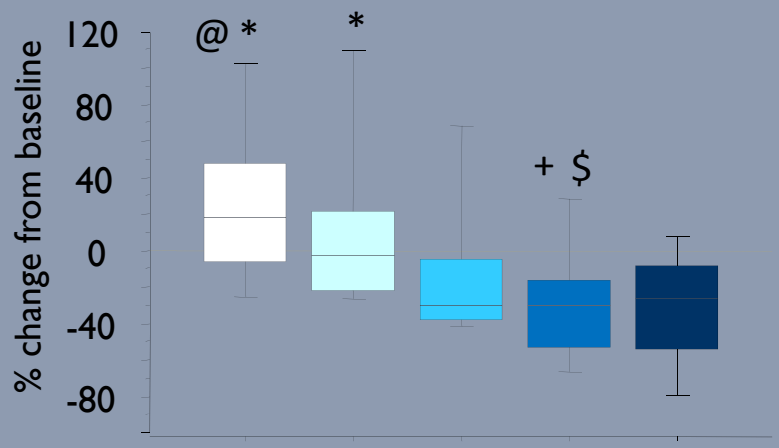
- Study 2: increasing the intravenous glucose load

Muscle proteolysis

Weight loss



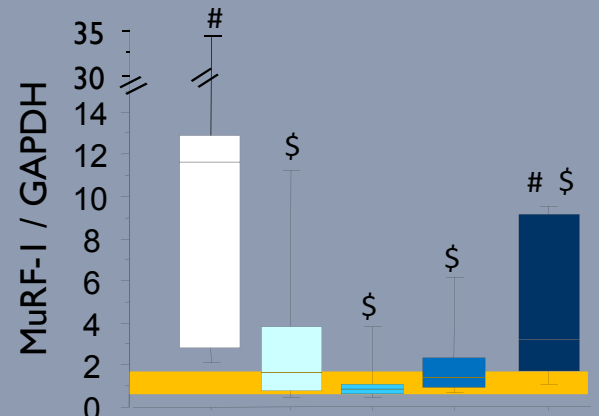
Urea

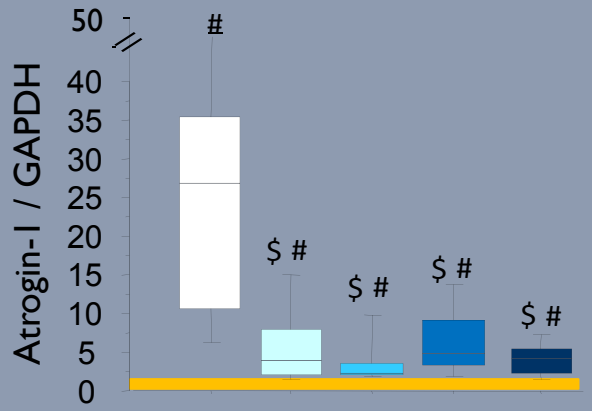


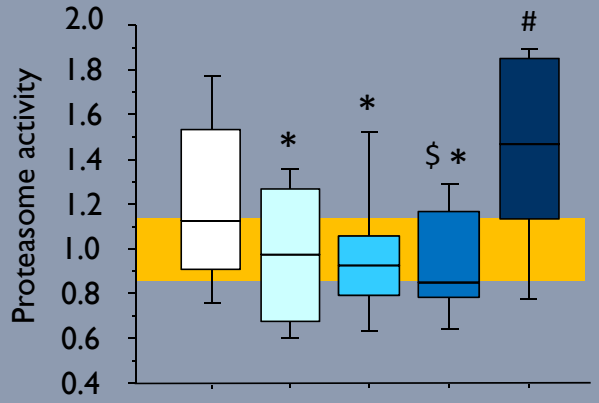
*: p < 0.05 versus high/hg rabbits // @: p < 0.05 versus moderate/ng rabbits//:$: p < 0.05 versus no/ng rabbits// #: p < 0.05 versus healthy control rabbits // +:p <0.05 versus low/ng rabbits //▬: healthy reference range// §: p < 0.05 versus all other groups

- Study 2: increasing the intravenous glucose load

Muscle proteolysis: Ub-proteasome







glucose load	(-)	Low	Moderate	High	High
glycemia	Normal				High
n	13	13	10	12	8

*: p < 0.05 versus high/hg rabbits // @: p < 0.05 versus moderate/ng rabbits//:$: p < 0.05 versus no/ng rabbits// #: p < 0.05 versus healthy control rabbits // +:p <0.05 versus low/ng rabbits // : healthy reference range

- Study 2: increasing the intravenous glucose load

Conclusion

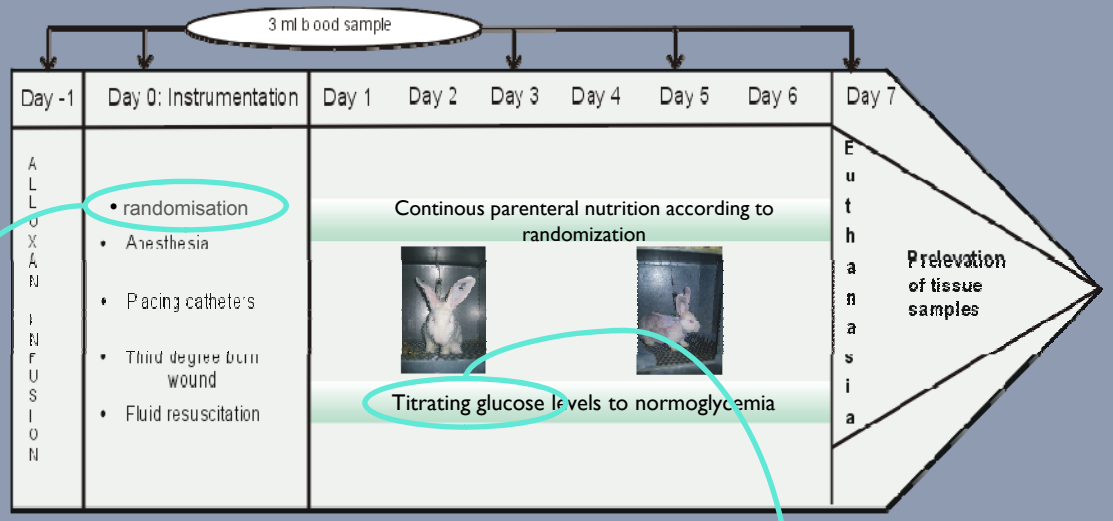
- Increasing intravenous glucose load within physiological range while normoglycemia is maintained
  - Safe with regard to organ function and survival
  - Reduces biochemical markers of catabolism as compared with fasting
  - Optimum may be reached with moderate glucose intake
- High glucose load / hyperglycemia: ↘ protective effect nutrition

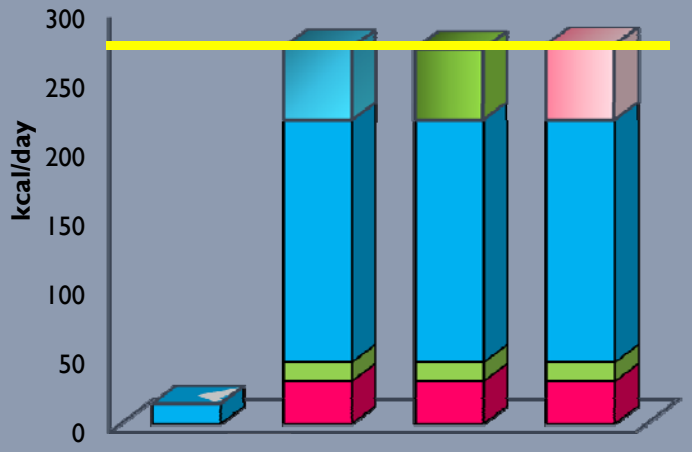
Hypothesis 3

Impact of feeding on the catabolic pathways may be nutrient-specific

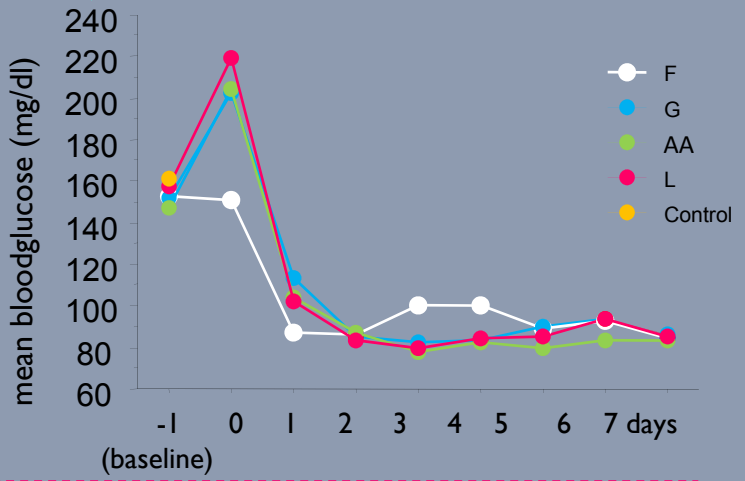
Derde et al, Endocrinology. 2012 May;153(5):2267-76

Experimental setup 2





Glucose
Amino acids
Lipids



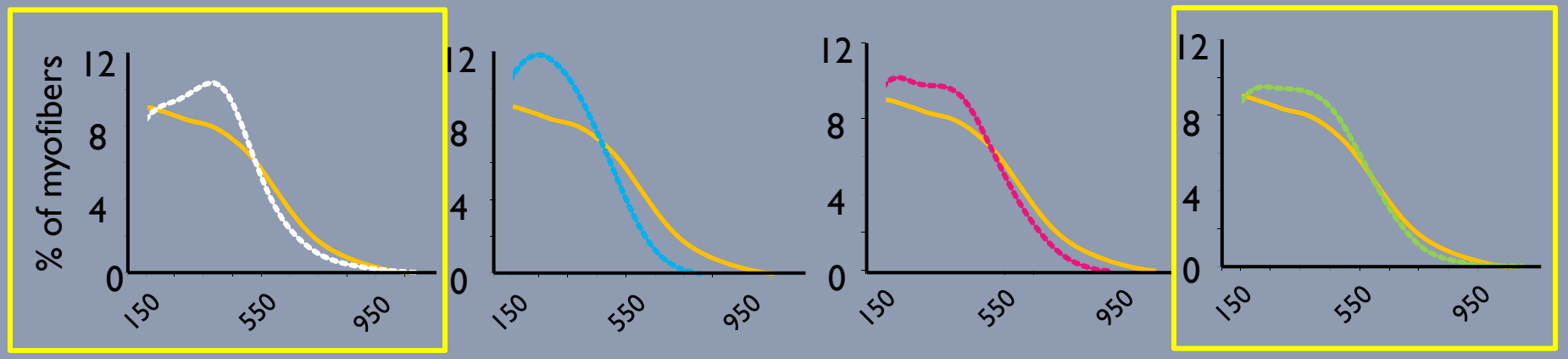
Study 3: altering substrate composition

- Safety evaluation: survival & weight loss
- Muscle fiber size: cross-sectional area
- Muscle protein degradation
  - Ubiquitin proteasome pathway
  - autophagy

Safety: Survival and weight loss

- Survival: no mortality difference among groups
- Feeding attenuated weight loss observed in fasted critically ill rabbits

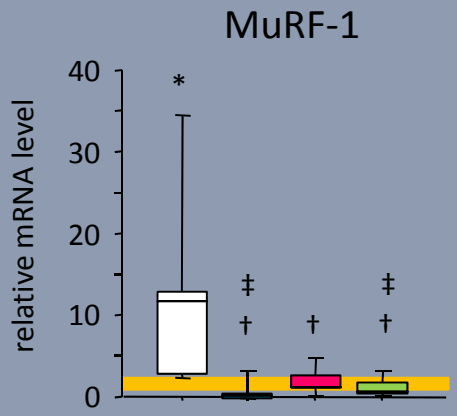
Muscle fiber size: cross-sectional area

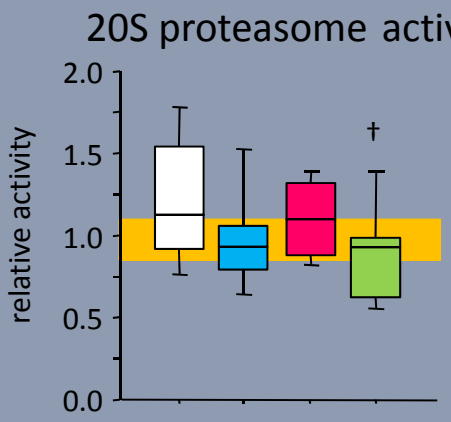


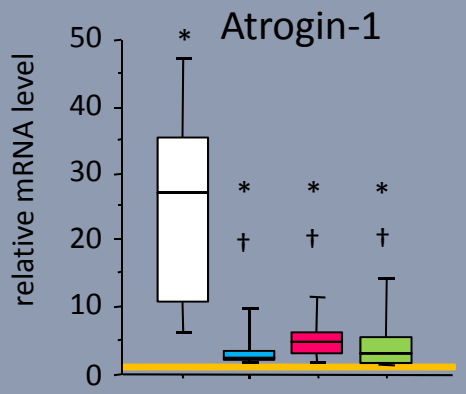
- fasted critically ill
- fed critically ill, extra glucose
- fed critically ill, extra lipids
- fed critically ill ,extra amino acids
- healthy reference range

Study 3: altering substrate composition

Muscle proteolysis: Ub-proteasome







fasted critically ill

fed critically ill, extra glucose

fed critically ill, extra lipids

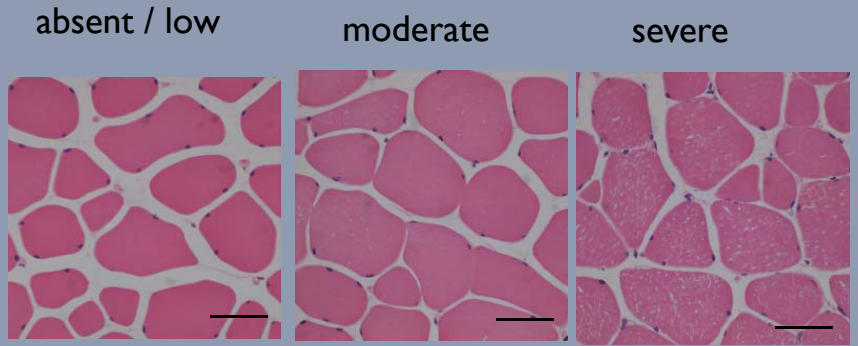
fed critically ill ,extra amino acids

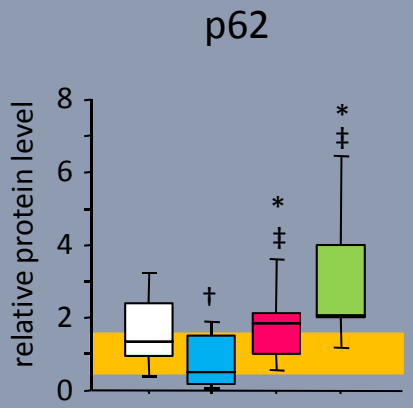
healthy reference range

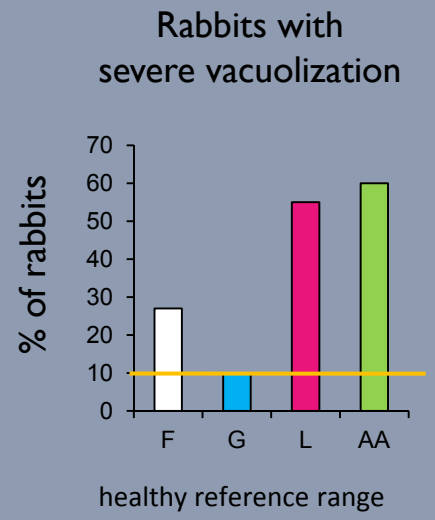
*: $p \leq 0.05$ versus healthy control rabbits ; † $p \leq 0.05$ versus fasted critically ill rabbits; ‡ $p \leq 0.05$ versus critically ill rabbits from the glucose group

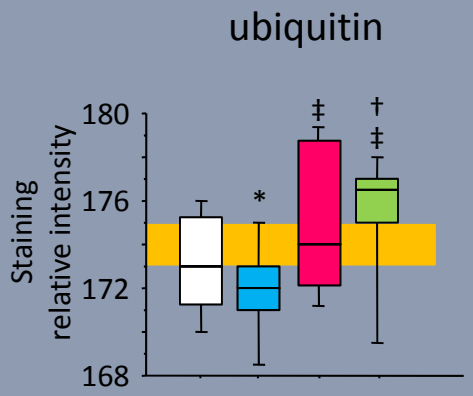
Study 3: altering substrate composition

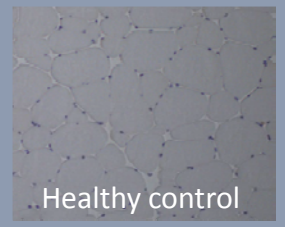
Muscle proteolyis: autophagy

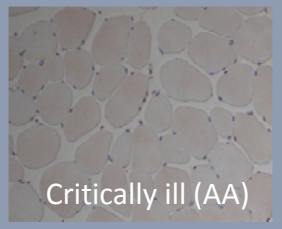












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Conclusions

- Moderate amount of intravenous nutrition
  - Suppression atrophy at level of gene expression and activity
    - minor effect of nutrient composition: AA most effective?
    - reduced fiber size most preserved with extra AA
  - Suppression of autophagy
    - accumulation toxic protein aggregates /damaged organelles
      in skeletal muscle most pronounced with AA
  - Most anti-catabolic intervention (AA) may have been most toxic

Study 3: altering substrate composition

General conclusion and perspectives

- Prevention of hyperglycemia in the fed condition is crucial to prevent ↗ mortality

- Intravenous nutrition while maintaining normoglycemia ↘ catabolism

  BUT possible toxic side effects by inhibition autophagy!!

  clinical setting ?

- Pharmacological intervention to stimulate autophagy

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