Muscle wasting in the ICU: recent insights into causes, futility of early feeding BCAA or protein and possible ways forward

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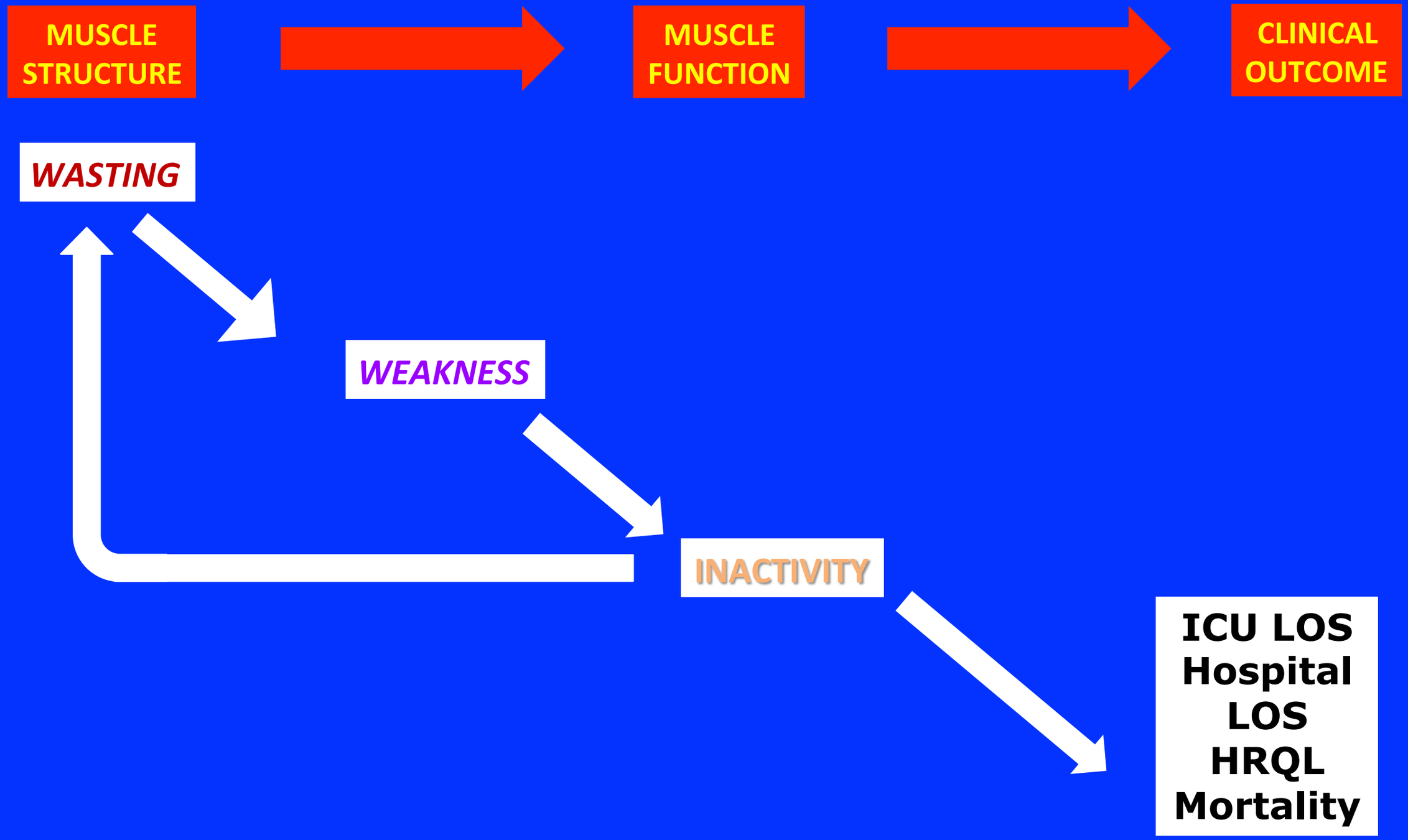
Outline of talk

- What happens to the muscle in the ICU patient
- What are the drivers of anabolism for musculoskeletal tissues?
  - Nutrition
  - Exercise
- What goes wrong during
  - Ageing
  - Disuse
  - Critical illness

COMPARATIVE INCIDENCE OF ICU-ACQUIRED WEAKNESS

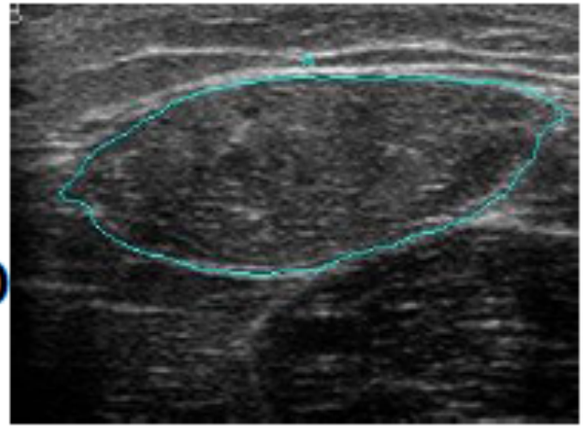
	ICU-AW	VAP	DVT	CVC infection
highest incidence	50%	25%	30%	0.058%
Lowest incidence	25%	10%	4%	0.001%

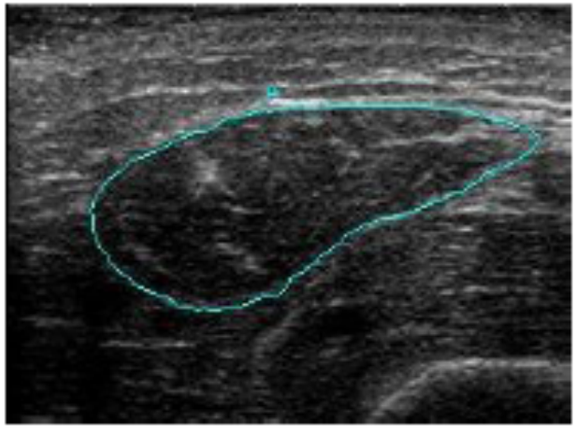

MUSCLE STRUCTURE
MUSCLE FUNCTION
CLINICAL OUTCOME
WASTING
WEAKNESS
INACTIVITY
ICU LOS
Hospital LOS
HRQL
Mortality

MUSCLE MASS AND QUALITY

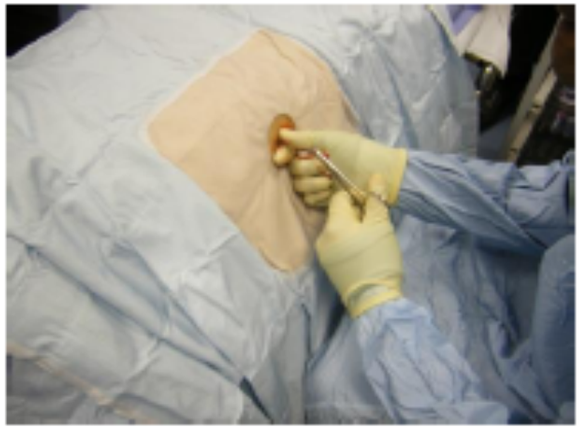
DAY 1 3 7 10

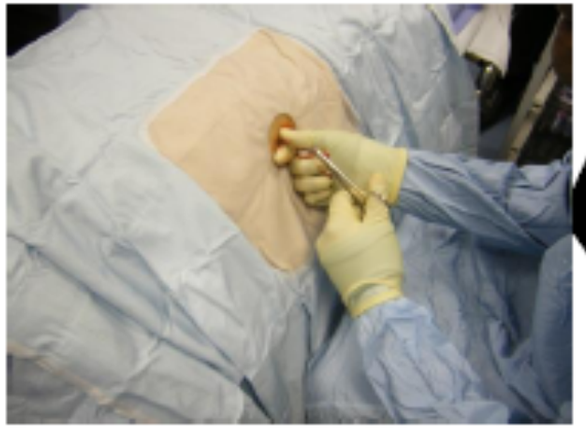
RECTUS FEMORIS ULTRASOUND

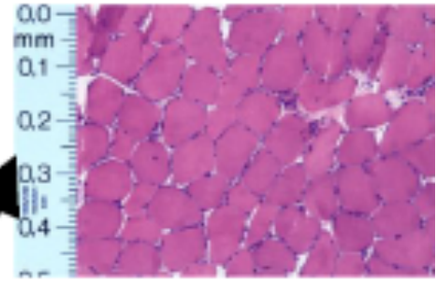




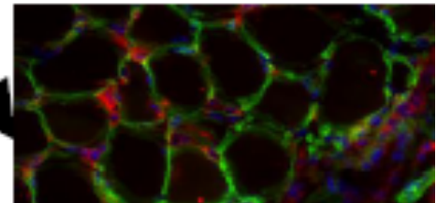
MUSCLE BIOPSY



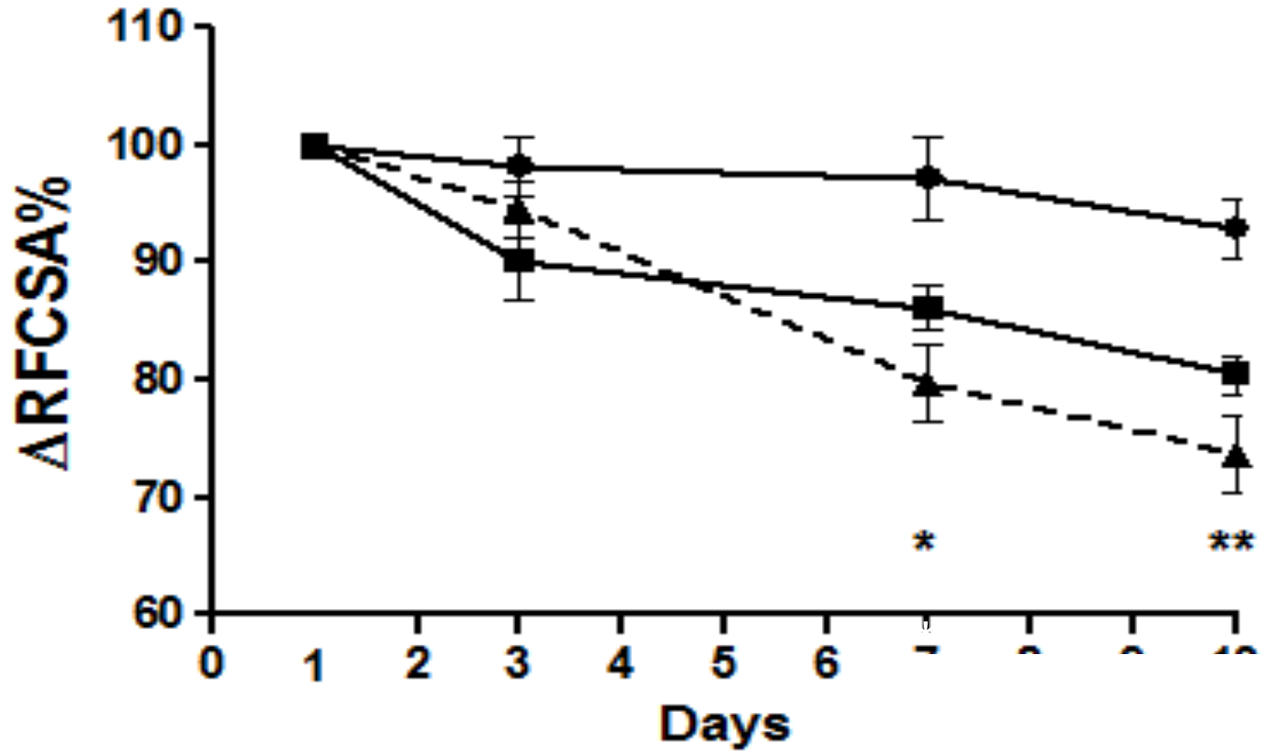




PROTEIN/DNA RATIO



Time course of acute muscle loss during ICU stay: stratification by organ failure



Single Organ Failure (n=15)

Multi-Organ Failure (2-3) (n=33)

Multi-Organ Failure (4-6) (n=14)

** p<0.01

* p<0.05

Organ Failure Stratification

- Respiratory : P/F ratio < 47kPa
- Cardiac: Use of Dobutamine >1/hr
- Liver: bilirubin 33-101 micromol/l
- Coagulation: platelets <100 $10^3/mm^3$
- Glasgow Coma Scale 10-12
- Renal: Creatinine 171-299 micromol/l or less than <500ml urine/day

VINCENT, J. L (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Medicine, 22, 707-710.*

Muscle wasting was significantly greater in the sickest patients

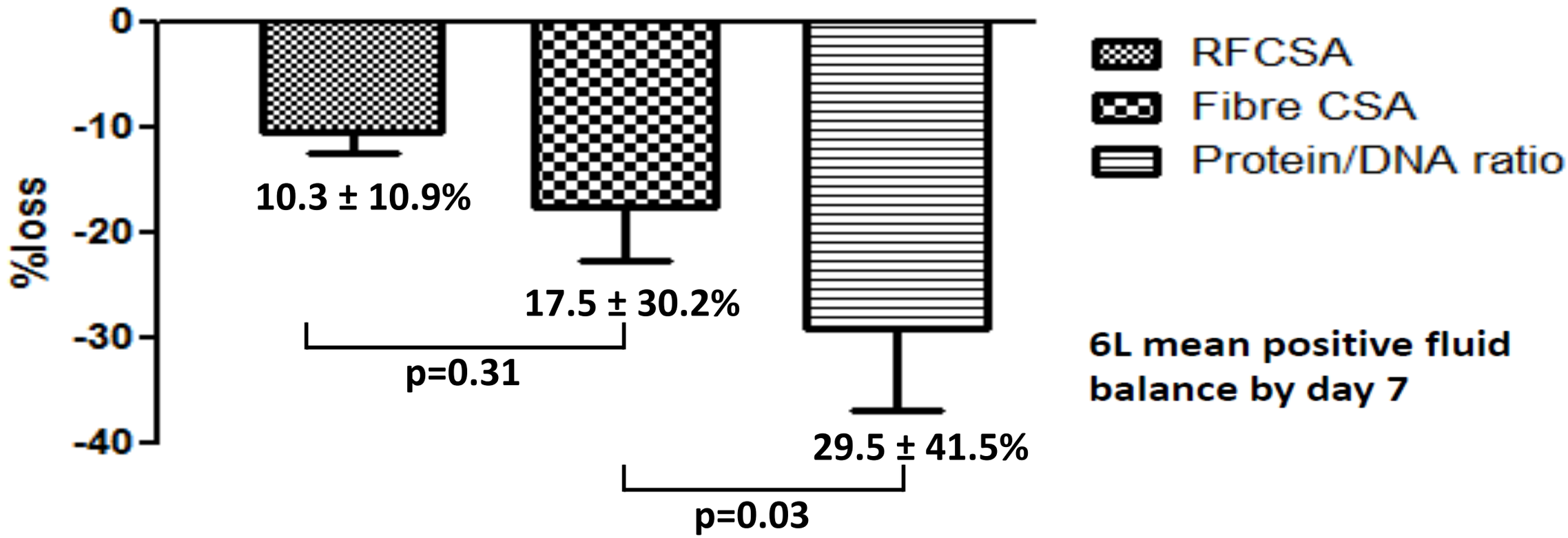
7% loss in RF_{CSA} 1 organ failure

20% loss in RF_{CSA} with >2 organ failure

26% loss in RF_{CSA} with >4 organs failure

Puthucheary et al JAMA 2013

First Week in ICU



Composition of Muscle: Fat and Fat Free Solids and Water ic and ec

	Age Group	Patients	Reference Group
Fat (kg/kg FFS)	All subjects	0.12 ± 0.11	0.09 ± 0.07
	<60 yrs[a]	0.09 ± 0.04	0.06 ± 0.04
	>60 yrs[b]	0.14 ± 0.13	0.13 ± 0.08
H_2O total (L/kg FFS)	All subjects	3.67 ± 0.49[c]	3.36 ± 0.15
	<60 yrs	3.56 ± 0.23	3.33 ± 0.18
	>60 yrs	3.74 ± 0.6	3.41 ± 0.09
H_2O ic (L/kg FFS)	All subjects	2.79 ± 0.37	2.91 ± 0.07
	<60 yrs	2.75 ± 0.35	2.91 ± 0.06
	>60 yrs	2.82 ± 0.40	2.91 ± 0.09
H_2O ec (L/kg FFS)	All subjects	0.87 ± 0.34[e]	0.46 ± 0.16
	<60 yrs	0.81 ± 0.28[d]	0.42 ± 0.17
	>60 yrs	0.96 ± 0.36[e]	0.51 ± 0.14

ic, intracellular; ec, extracellular.

Reference base is fat free solids. Reference Group refers to a third reference group from Forsberg et al (16).

[a]<60 yrs: patients (n = 8), reference group (n = 10); [b]>60 yrs: patients (n = 12), reference group (n = 11); significantly different from reference group: [c]$p < .05$; [d]$p < .01$; [e]$p < .001$.

Skeletal muscle and plasma free amino acids in critical illness (mean plus minus SD)

Gamrin, Lena; Essen, Pia; Forsberg, Ann Marie; Hultman, Eric; Wernerman, Jan
Critical Care Medicine. 24(4):575-583,
:

	Muscle (mmol/L ic water) Patients (n = 20)	Muscle (mmol/kg wet weight) Patients (n = 20)	Muscle (mmol/kg) wet weight) Reference Group (n = 17)[a]	Plasma (μmol/L) Patients (n = 20)	Plasma (μmol/L) Reference Group (n = 17)[a]
Taurine	17.2 ± 1.42	9.96 ± 3.62[b]	12.7 ± 3.11	40 ± 25	47 ± 20
Aspartate	1.46 ± 0.15	0.85 ± 0.4	1.08 ± 0.42	9 ± 5[c]	5 ± 2
Threonine	0.8 ± 0.15	0.48 ± 0.22	0.45 ± 0.14	75 ± 44[b]	110 ± 44
Serine	0.89 ± 0.08	0.53 ± 0.21	0.48 ± 0.11	70 ± 25[c]	102 ± 29
Asparagine	0.63 ± 0.06	0.38 ± 0.15	0.33 ± 0.09	43 ± 26	45 ± 8
Glutamate	2.72 ± 0.42	1.58 ± 1.06[d]	3.01 ± 0.63	46 ± 25	52 ± 26
Glutamine	5.81 ± 0.56	3.45 ± 1.47[d]	12.4 ± 2.51	365 ± 126[c]	471 ± 84
Glycine	1.90 ± 0.15	1.13 ± 0.35	1.08 ± 0.36	134 ± 58[c]	200 ± 48
Alanine	3.68 ± 0.37	2.18 ± 0.98	1.72 ± 0.41	208 ± 124	224 ± 74
Valine	0.34 ± 0.04	0.25 ± 0.11	0.19 ± 0.04	184 ± 76	164 ± 42
Homocystine	—	0.35 ± 0.46[b]	0.51 ± 0.29	89 ± 36	87 ± 15
Methionine	0.13 ± 0.01	0.08 ± 0.04[d]	0.03 ± 0.01	24 ± 21	17 ± 7
Isoleucine	0.18 ± 0.02	0.12 ± 0.06[d]	0.06 ± 0.02	47 ± 37	44 ± 10
Leucine	0.31 ± 0.04	0.20 ± 0.11[c]	0.11 ± 0.03	95 ± 42	90 ± 22
Tyrosine	0.21 ± 0.02	0.14 ± 0.06[b]	0.09 ± 0.03	70 ± 41[b]	44 ± 14
Phenylalanine	0.23 ± 0.03	0.16 ± 0.08[d]	0.07 ± 0.02	114 ± 58[d]	41 ± 12
Ornithine	0.17 ± 0.10	0.11 ± 0.06[b]	0.18 ± 0.11	56 ± 37	56 ± 18
Lysine	0.61 ± 0.08	0.39 ± 0.21[d]	0.73 ± 0.22	136 ± 61	128 ± 23
Histidine	0.24 ± 0.03	0.15 ± 0.08[d]	0.26 ± 0.08	54 ± 17[b]	67 ± 11
Carnosine	6.05 ± 0.84	3.58 ± 2.38	3.94 ± 1.44	—	—
Tryptophan	—	—	—	37 ± 17	33 ± 7
Arginine	0.52 ± 0.12	0.30 ± 0.30[b]	0.48 ± 0.16	49 ± 22[c]	67 ± 12
Total amino acids	21.5 ± 1.43	13.2 ± 3.59[d]	23.1 ± 4.3	1897 ± 157	1992 ± 94
Branch-chain amino acids	0.83 ± 0.1	0.56 ± 0.26[c]	0.34 ± 0.11	316 ± 29	263 ± 36
Essential amino acids	13.37 ± 0.31	2.16 ± 0.81[b]	2.71 ± 0.64	831 ± 70	793 ± 44
Aromatic amino acids	0.44 ± 0.23	0.30 ± 0.14[d]	0.16 ± 0.05	184 ± 221[d]	85 ± 7
Basic amino acids	1.35 ± 0.77	0.75 ± 0.42[d]	1.46 ± 0.42	238 ± 21	263 ± 10

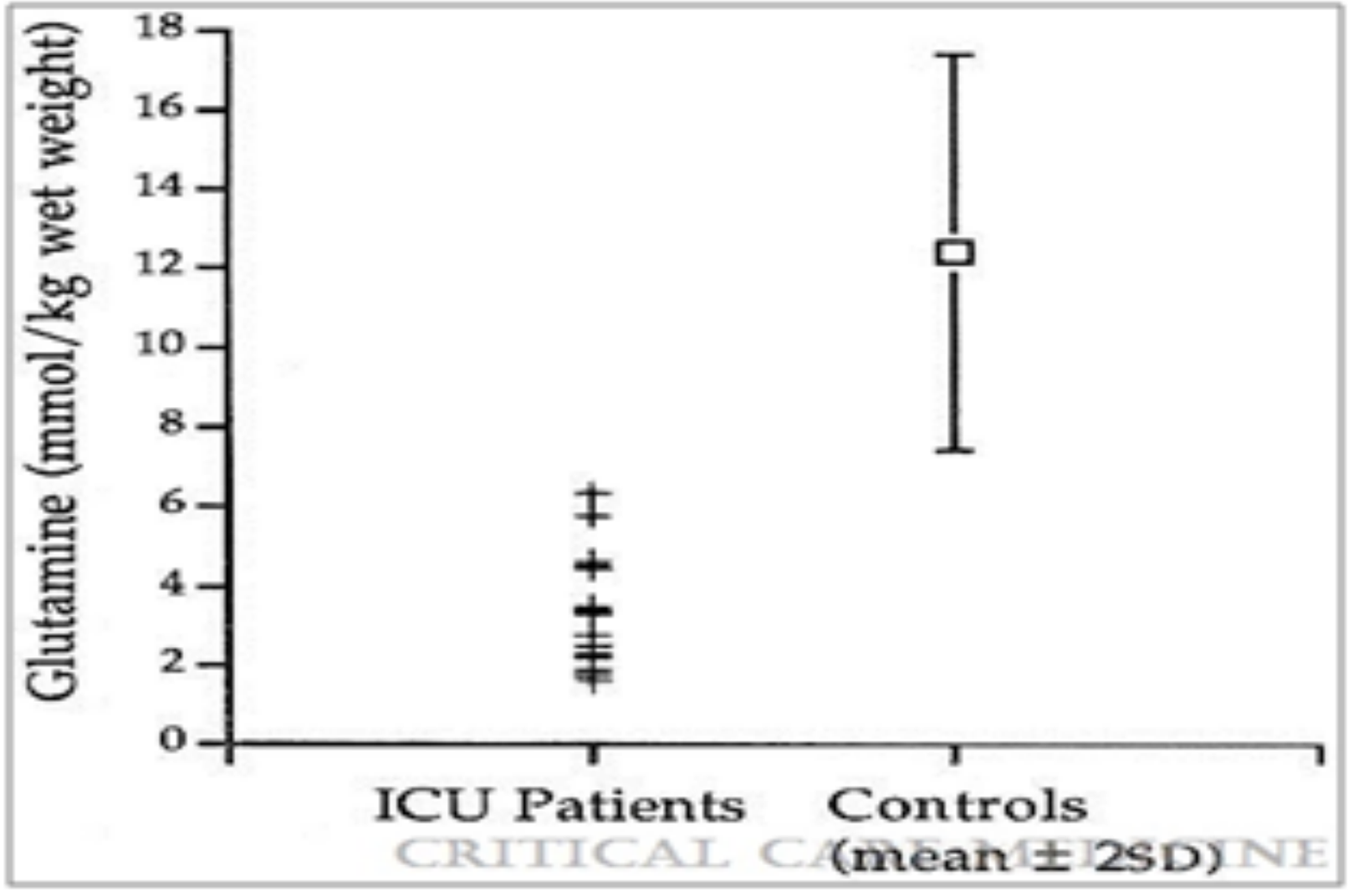
ic water, intracellular water.
[a]Reference group (values from Hammarqvist et al., 1992); [b]$p < .05$; [c]$p < .01$; [d]$p < .001$.

LOW GLN and LEU suggest low potential for Muscle Protein Synthesis

HIGH LEU and BCAA probably due to INC MPB ; increased use as fuels in muscle

HIGH AROMATIC AA suggests large net imbalace between MPS and MPB with MPS<MPB

Glutamine in ICU patients and hospital controls



Gamrin, Lena; Essen, Pia; Forsberg, Ann Maria; Hultman, Eric; Wernerman, Jan
Critical Care Medicine. 24(4):575-583, April 1996

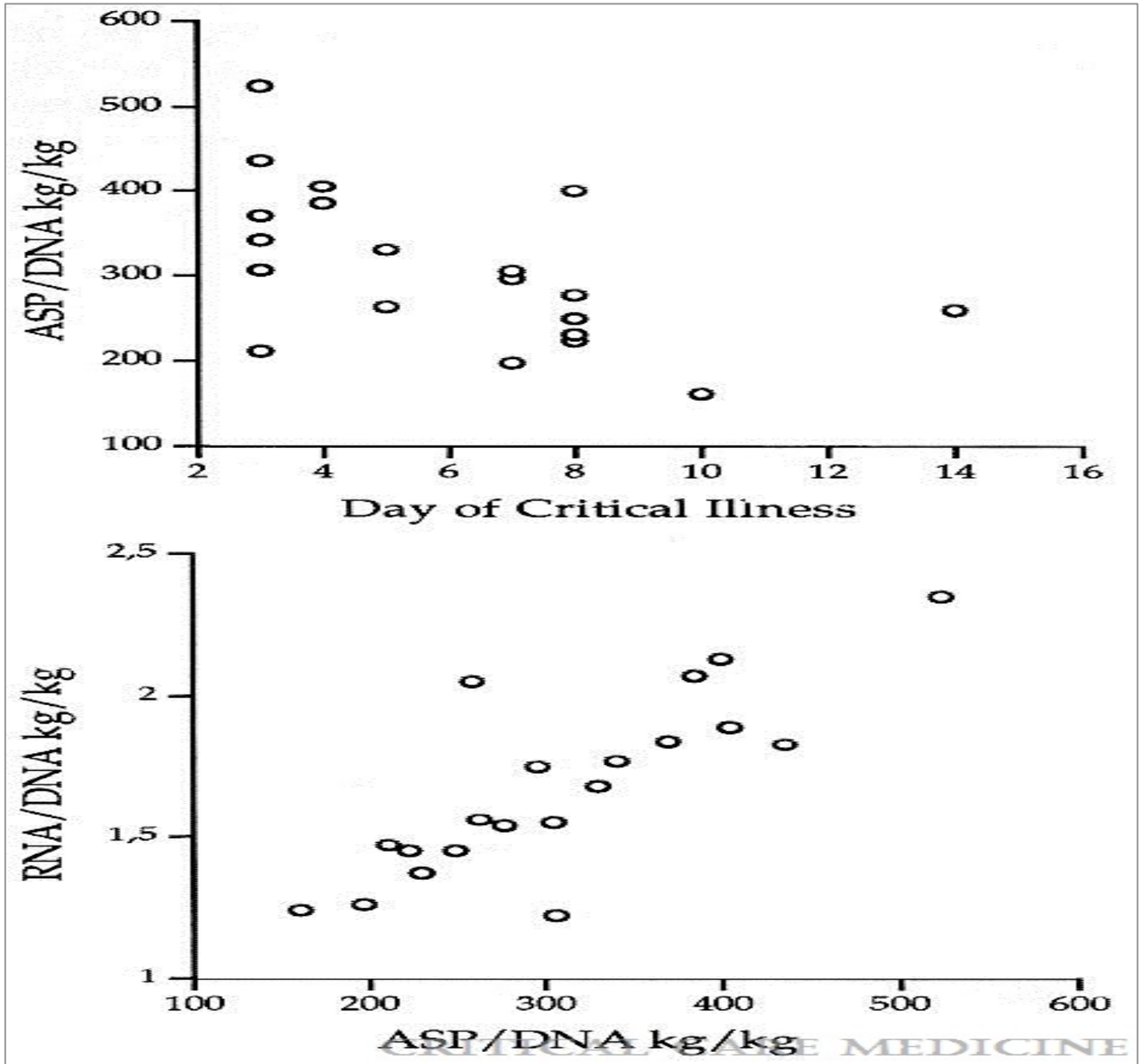
ICU Patients Muscle Composition data

	Age Group	Patients	Reference Group
DNA (g/kg FFS)	All subjects	2.46 ± 0.72	2.13 ± 0.36
	ICU day ≥5[a]	2.74 ± 0.66[b]	2.13 ± 0.36
	<60 yrs[c]	1.91 ± 0.42	1.80 ± 0.19
	>60 yrs[d]	2.82 ± 0.66	2.44 ± 0.22
RNA (g/kg FFS)	All subjects	3.95 ± 0.72	3.56 ± 0.28
	ICU day ≥5	4.22 ± 0.62[b]	3.56 ± 0.28
	<60 yrs	3.78 ± 0.77	3.79 ± 0.14
	>60 yrs	4.06 ± 0.68	3.51 ± 0.29
ASP (g/kg FFS)	All subjects	698 ± 18	700 ± 20
	ICU day ≥5	693 ± 19	700 ± 20
	<60 yrs	706 ± 12	707 ± 20
	>60 yrs	692 ± 20	694 ± 17
DNA (g/kg ASP)	All subjects	3.53 ± 1.06	3.05 ± 0.58
	ICU day ≥5	3.96 ± 0.99[b]	3.05 ± 0.58
	<60 yrs	2.72 ± 0.62	2.61 ± 0.31
	>60 yrs	4.06 ± 0.96	3.53 ± 0.36
RNA (g/kg ASP)	All subjects	5.67 ± 1.05	5.11 ± 0.34
	ICU day ≥5	6.10 ± 0.89[b]	5.11 ± 0.34
	<60 yrs	5.37 ± 1.16	5.35 ± 0.21
	>60 yrs	5.87 ± 0.97	5.07 ± 0.35
ASP (kg/kg DNA)	All subjects	308 ± 91	340 ± 65
	ICU day ≥5	266 ± 63[b]	340 ± 65
	<60 yrs	384 ± 82	389 ± 46
	>60 yrs	258 ± 56	286 ± 30
RNA (kg/kg DNA)	All subjects	1.67 ± 0.32	1.56 ± 0.36
	ICU day ≥5	1.58 ± 0.29	1.56 ± 0.36
	<60 yrs	1.98 ± 0.20	2.21 ± 0.17
	>60 yrs	1.46 ± 0.18	1.45 ± 0.18
FFS (kg/kg DNA)	All subjects	440 ± 126	484 ± 84
	ICU day ≥5	383 ± 88[b]	484 ± 84
	<60 yrs	544 ± 114	549 ± 56
	>60 yrs	371 ± 80	412 ± 34

ICU, intensive care unit.
Reference Group refers to a third reference group from Forsberg et al (16).
[a]ICU day ≥5 includes patients in whom sampling was performed on or after day 5 of ICU stay (n = 12); [b]$p < .01$, significantly different from reference group; [c]<60 yrs: patients (n = 8), reference group (n = 10); [d]>60 yrs: patients (n = 12), reference group (n = 11).

Gamrin, Lena; Essen, Pia; Forsberg, Ann Marie; Hultman, Eric; Wernerman, Jan
Critical Care Medicine. 24(4):575-583, April 1996.

Changes of muscle protein (ASP) and cell size (ASP/DNA) and ribosome content (RNA/DNA) per muscle cell with days of illness



1. [Protein]/ Muscle Cell falls
2. [RNA]/ Muscle Cell falls

Gamrin, Lena; Essen, Pia; Forsberg, Ann Marie; Hultman, Eric; Wernerman, Jan
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Outline of talk

- What happens to the muscle in the ICU patient
- What are the drivers of anabolism for musculoskeletal tissues?
  - Nutrition
  - Exercise
- What goes wrong during
  - Ageing
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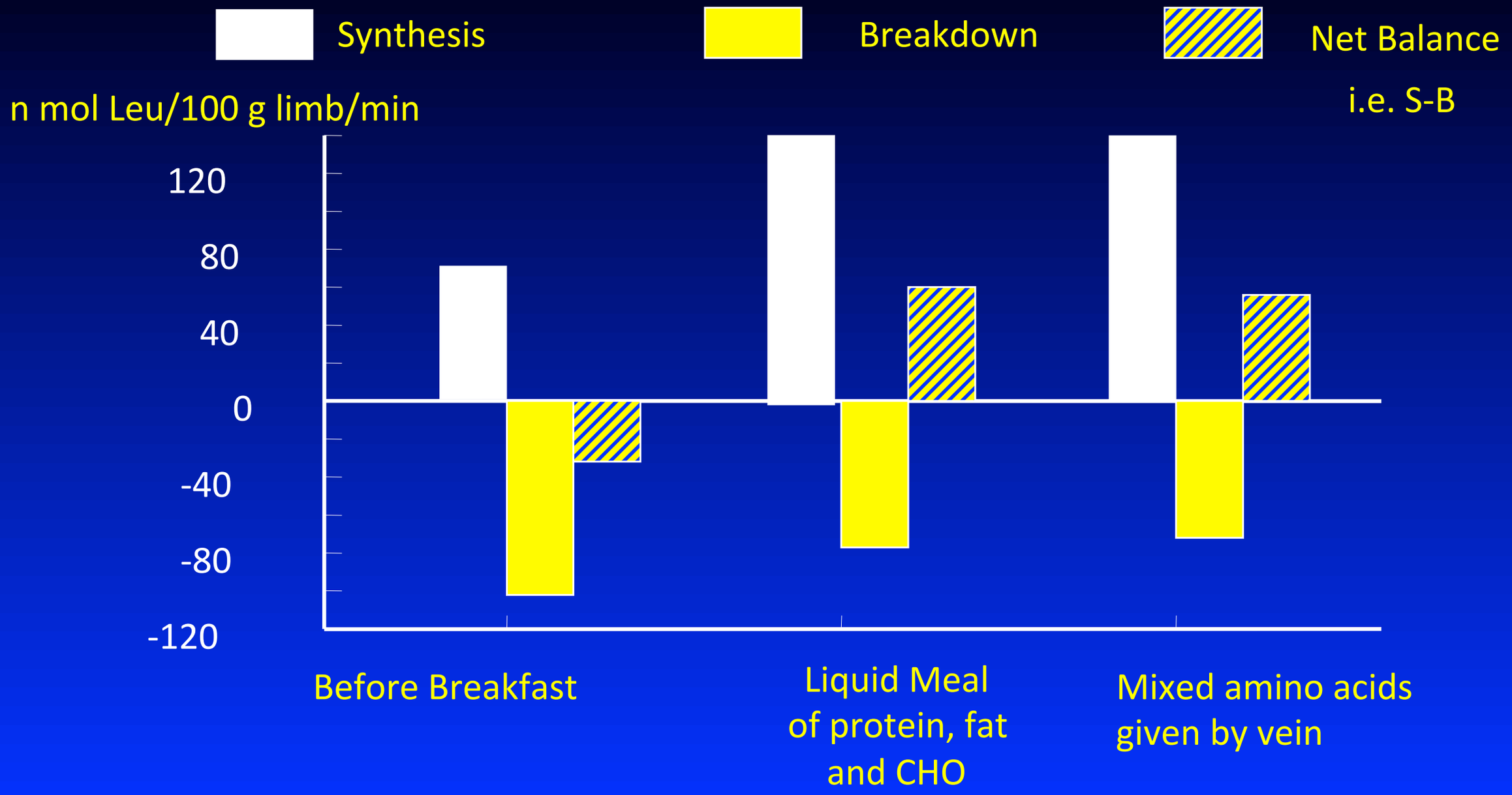
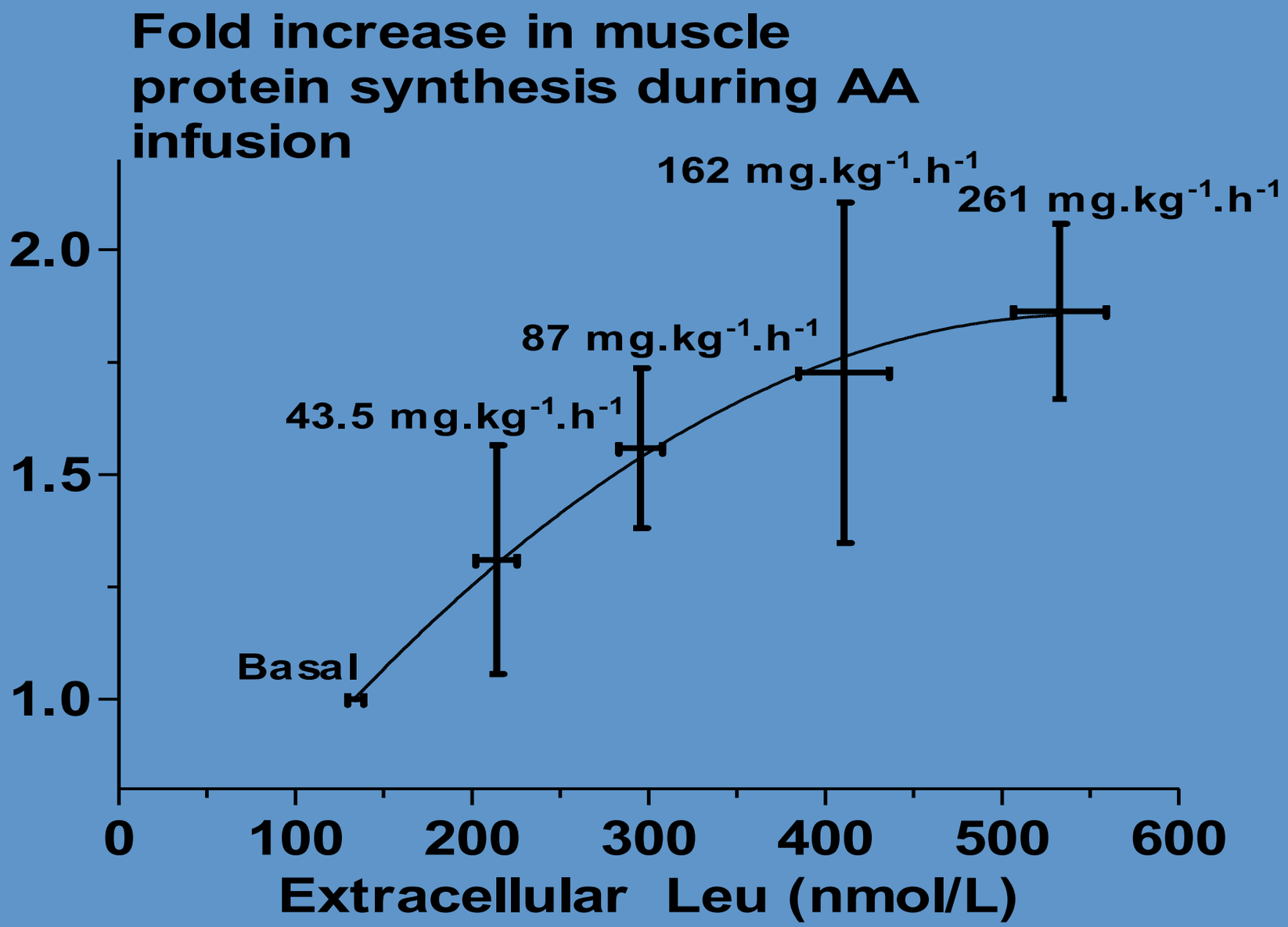

Synthesis
Breakdown
Net Balance
i.e. S-B
n mol Leu/100 g limb/min
120
80
40
0
-40
-80
-120
Before Breakfast
Liquid Meal
of protein, fat
and CHO
Mixed amino acids
given by vein

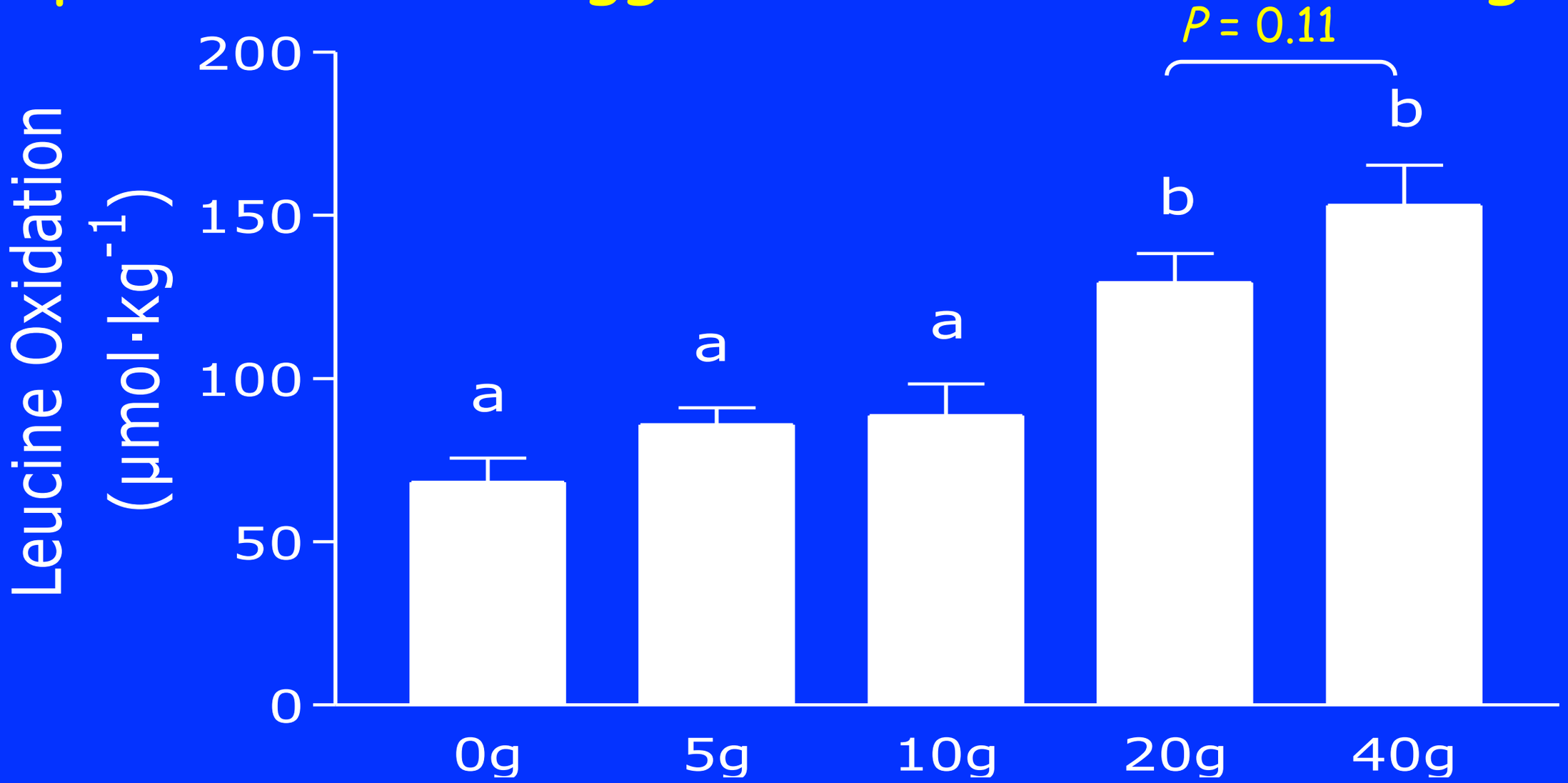

Fold increase in muscle protein synthesis during AA infusion
2.0
1.5
1.0
Basal
43.5 mg.kg-1.h-1
87 mg.kg-1.h-1
162 mg.kg-1.h-1
261 mg.kg-1.h-1
0
100
200
300
400
500
600
Extracellular Leu (nmol/L)

So, if we are supplied large amounts of protein we will build big muscles?

No - because of major limitations to increasing muscle mass on high protein diet -

1. Enzymes of AA catabolism have high K_m i.e. rate of catabolism scales with delivery of AA
2. Induction of enzymes of amino acid catabolism for BCAA, S-AA and Aromatic AA

Leucine oxidation stimulated > 10g protein dose- suggests muscle full at 10-20g

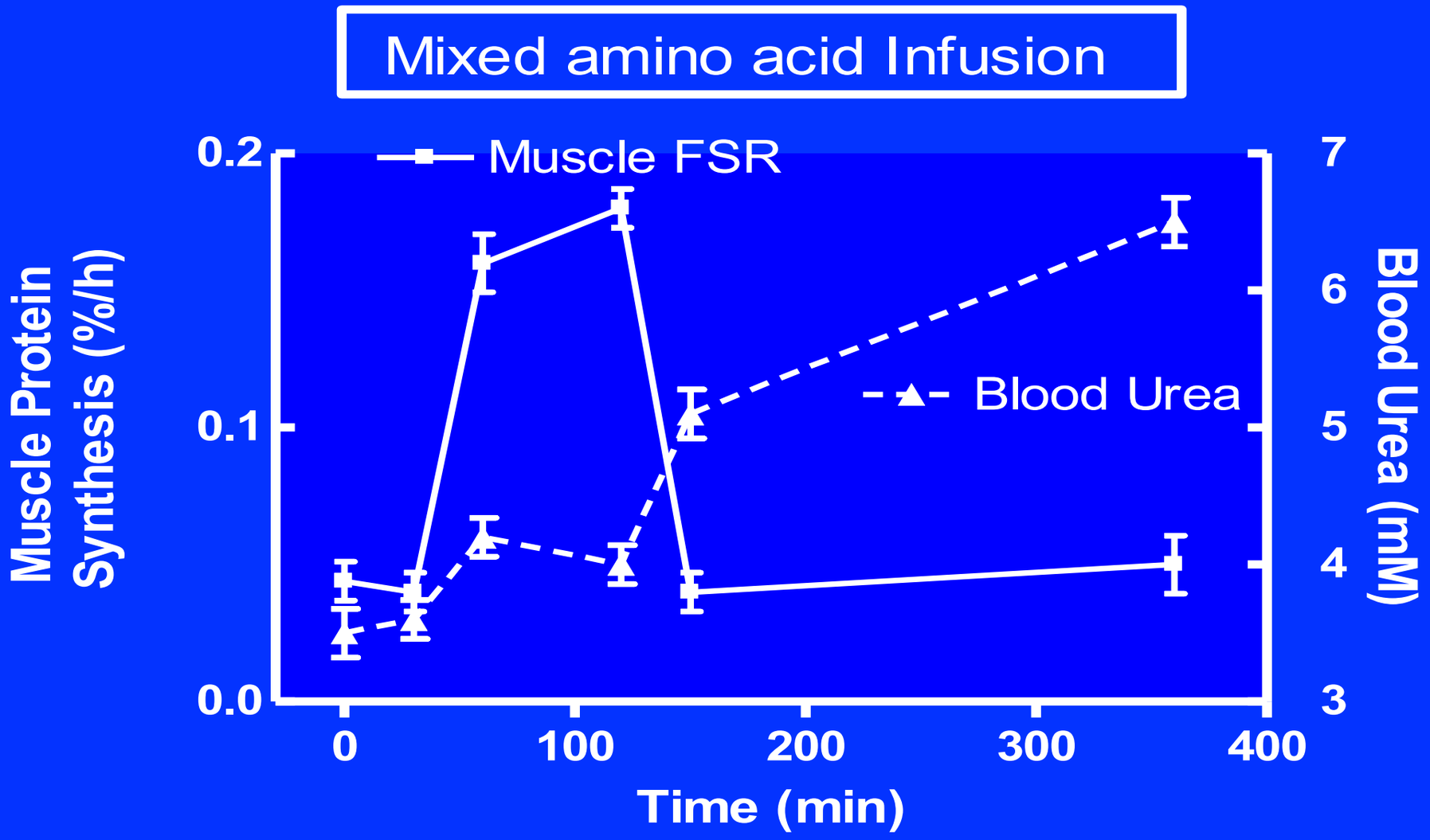


Moore and Phillips 2007 Unpub work

Another major limitation to increasing muscle mass mass on high protein diet

3. **Tachyphylaxis** of muscle anabolism - “muscle full” state

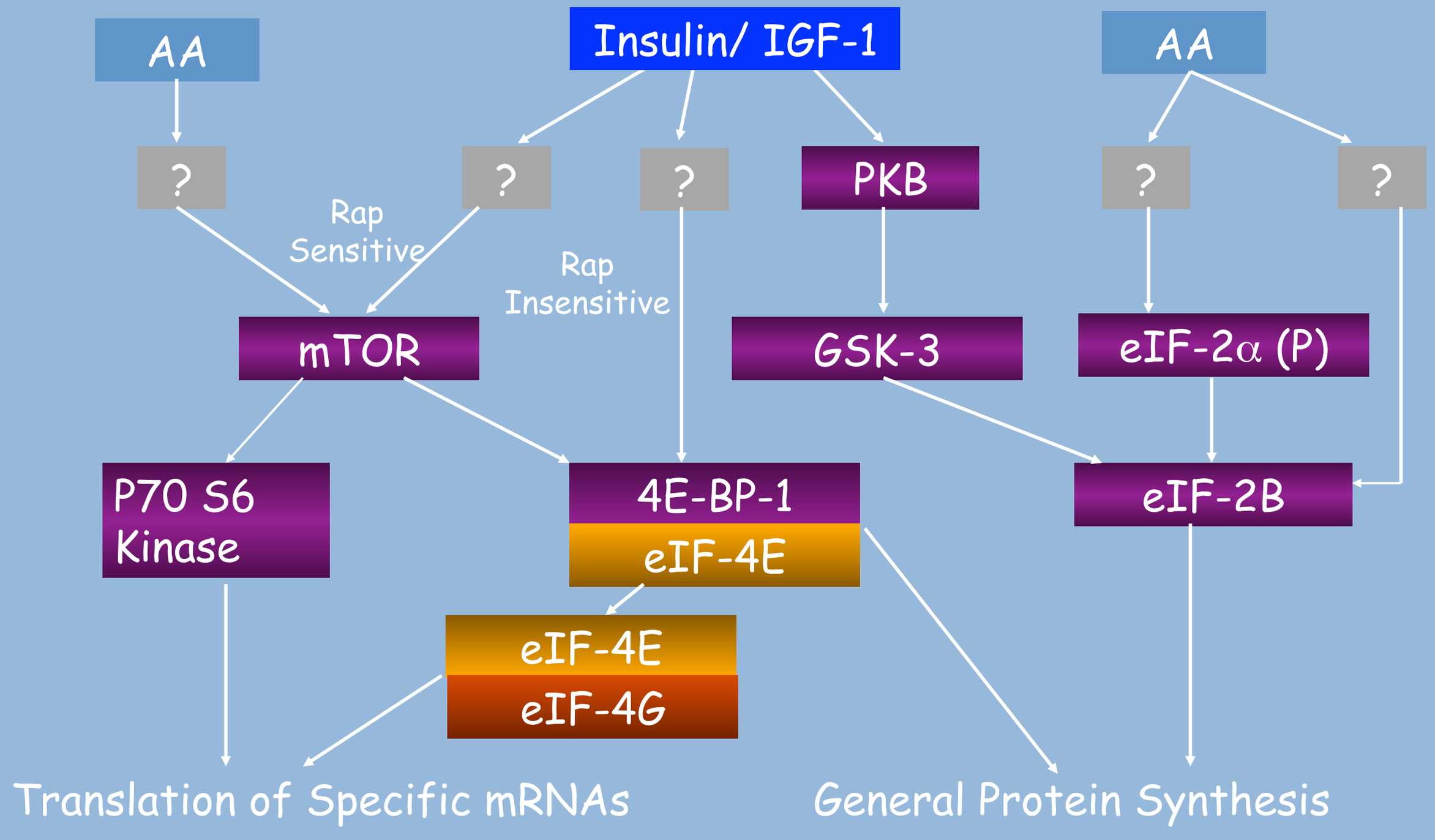
Response of muscle protein synthesis and blood urea to continuous availability of amino acids



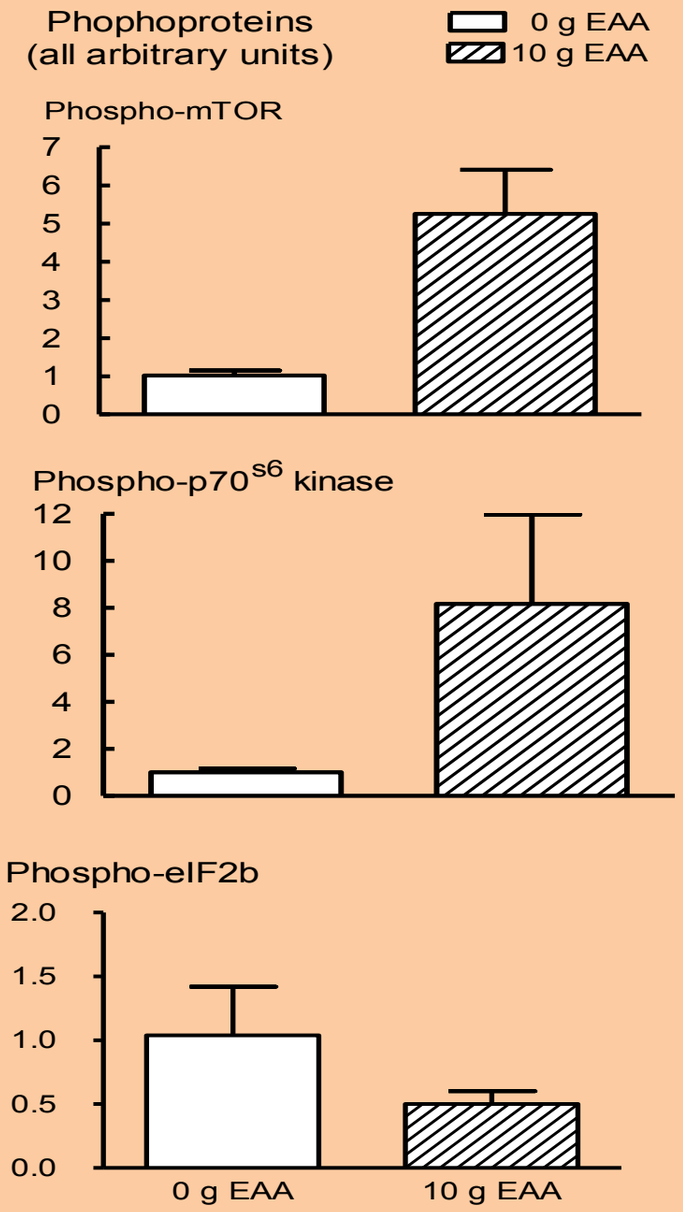
So how does muscle know to increase muscle building when amino acids are available ?

What *sensing* and *signalling mechanisms* are involved?

Regulation of mRNA translation by Amino Acids and Insulin



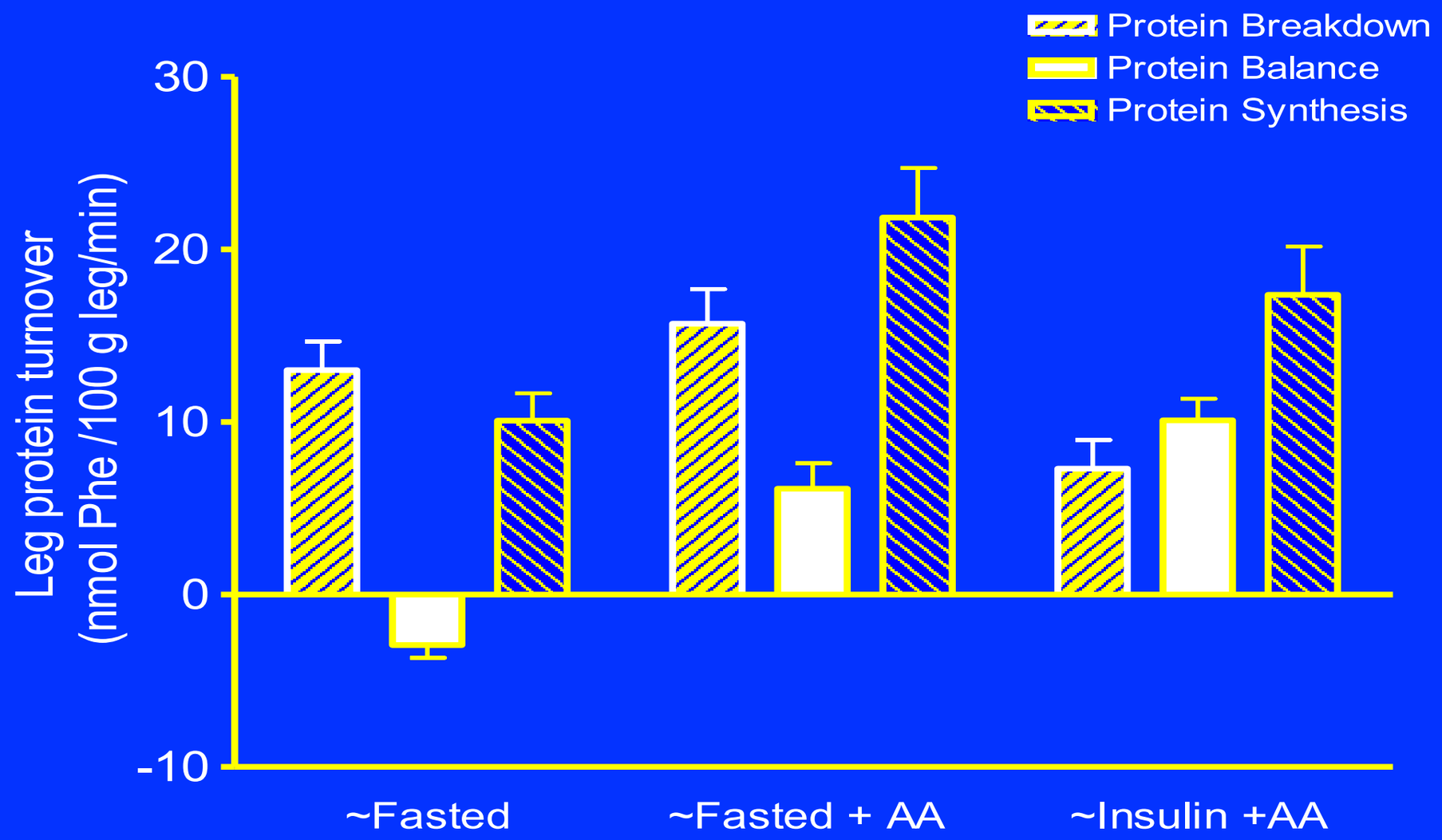
Effect of Essential AA on activation of signalling molecules by phosphorylation



Do hormones explain the effects of amino acids in stimulating muscle building?

Certainly not insulin, growth hormone or IGF-1…….

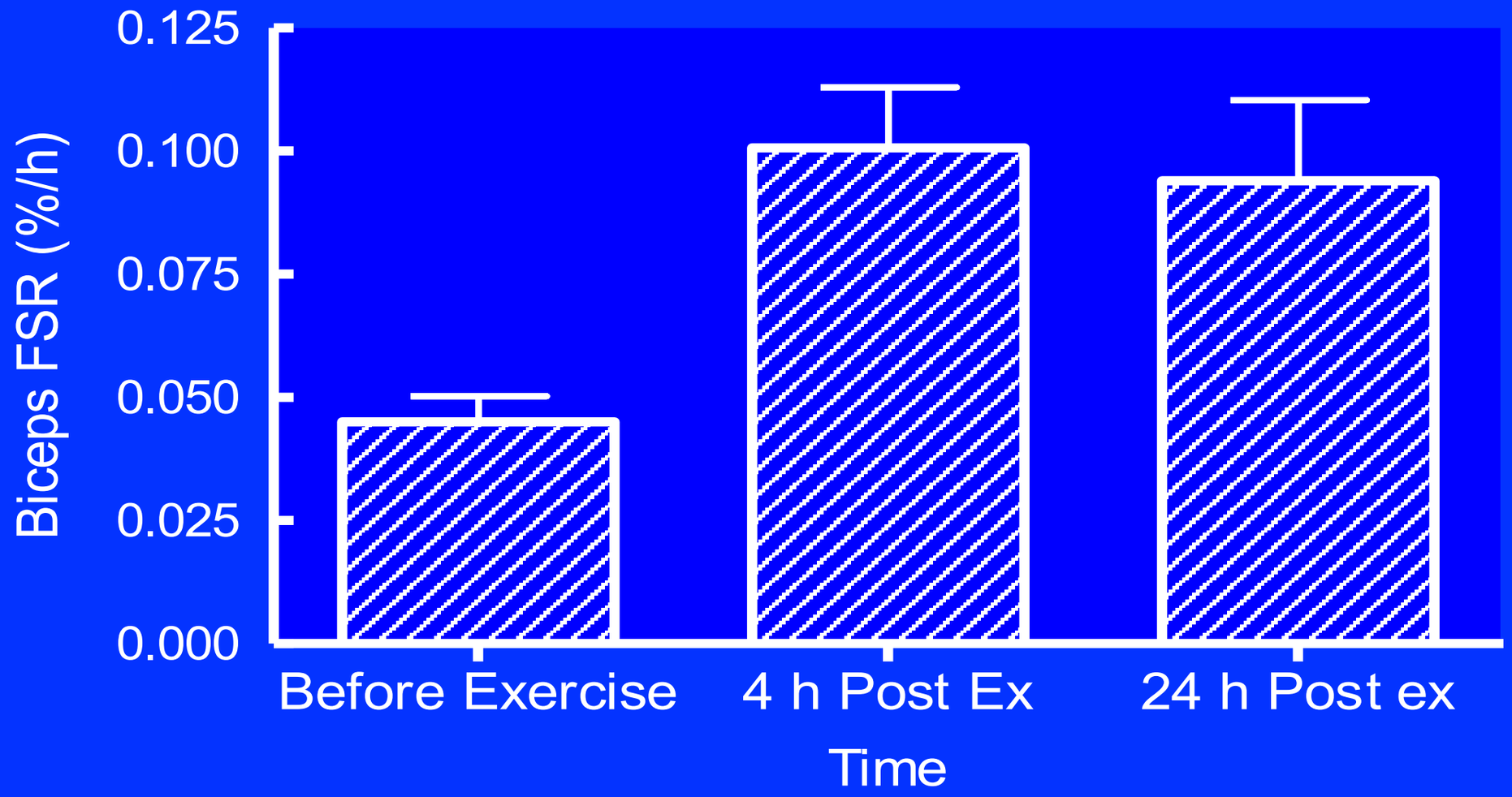
Studies carried out with insulin, GH and IGF-1 clamped



- *AA alone stimulate synthesis with no effect on breakdown*
- *Insulin decreases breakdown with no further effect on synthesis*
- *No requirement for GH or IGF-1 for anabolic effect of AA*

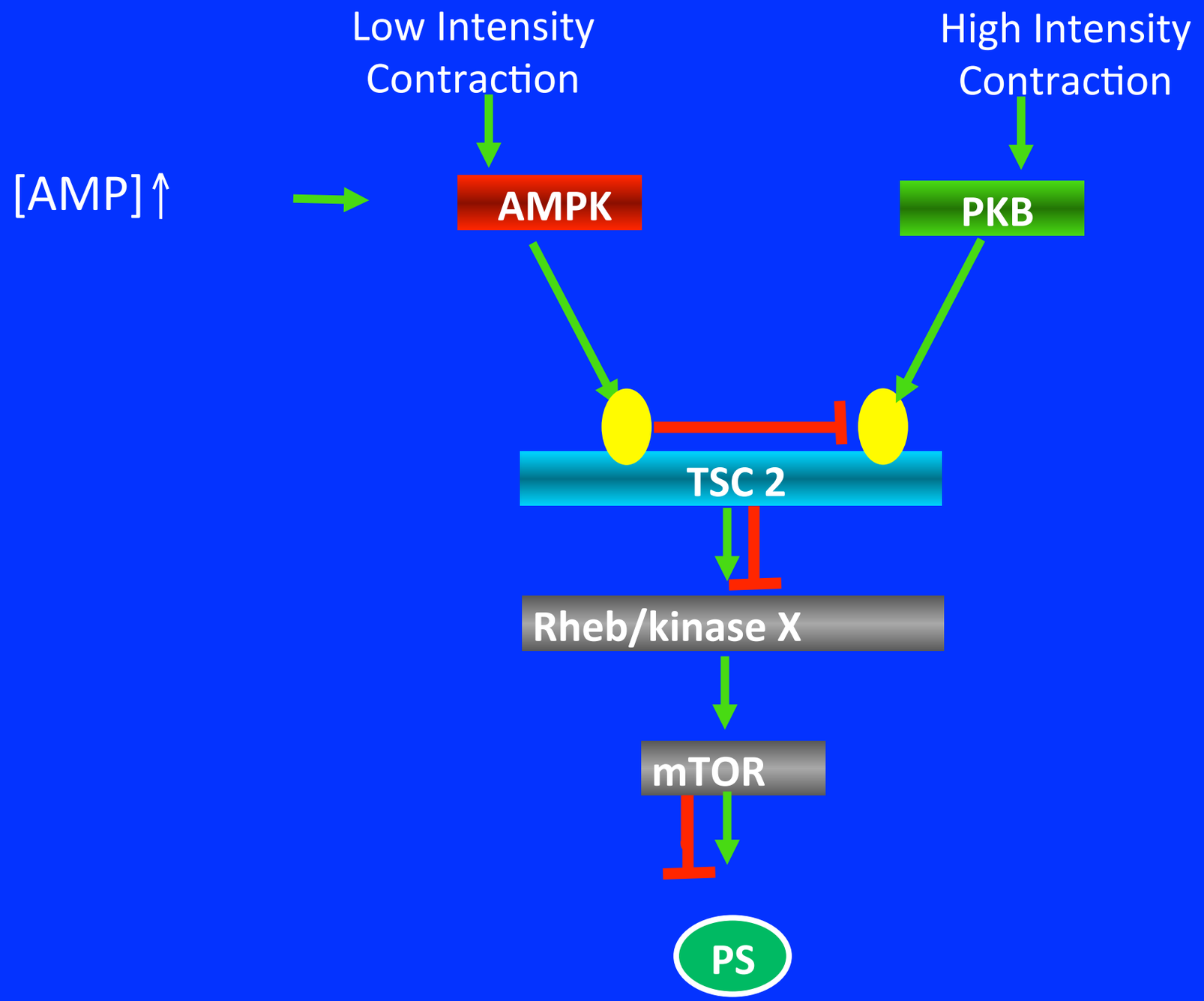
What happens with *exercise/physical* activity?

Effect of resistance exercise on muscle protein synthesis



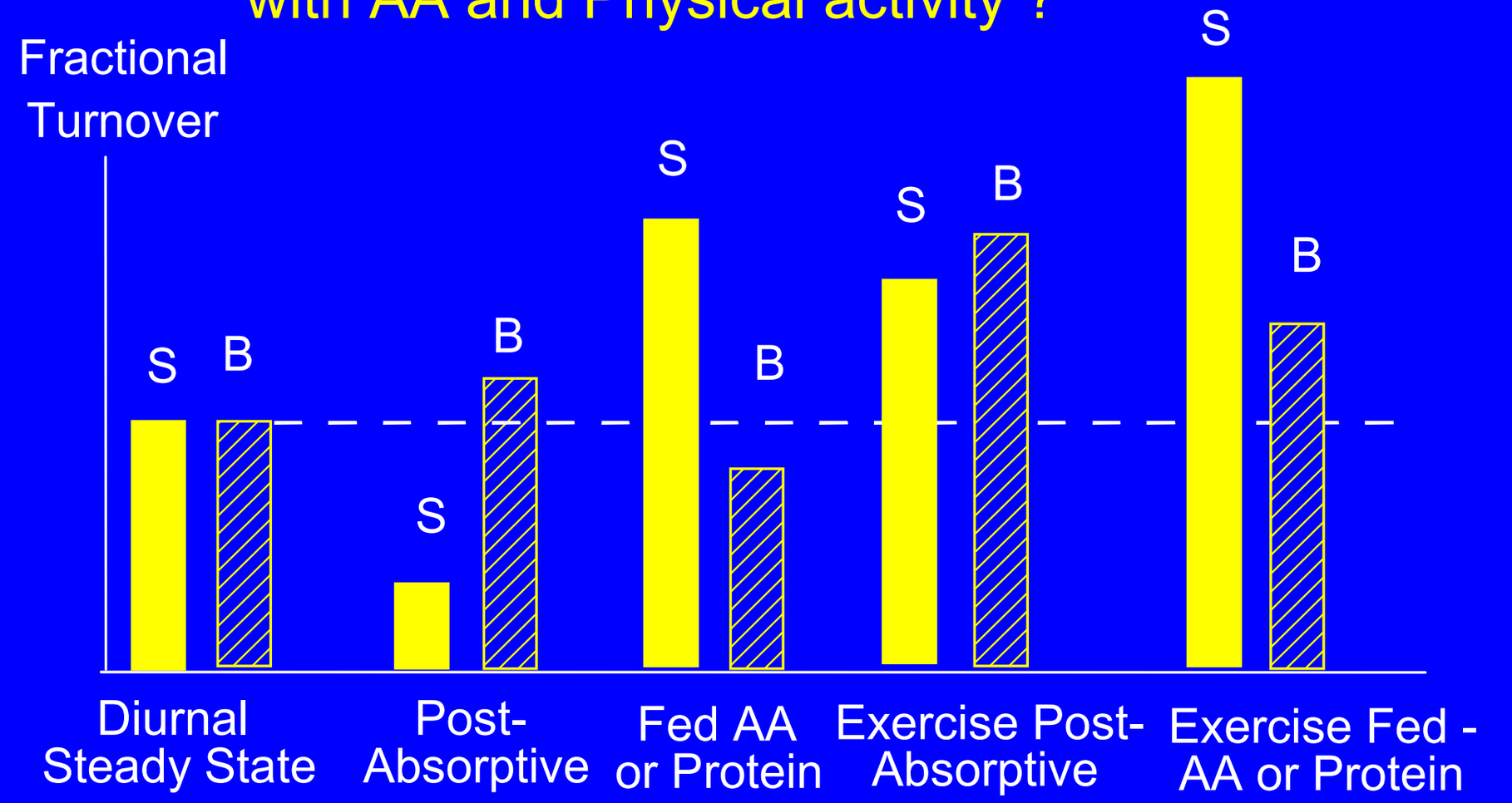
Chesley, Macdougal, Tarnopolsky Atkinson & Smith 1992

What about signalling after exercise?

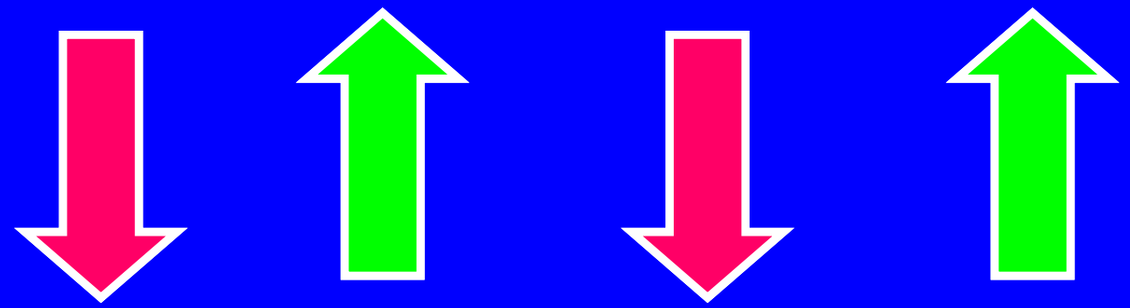

Low Intensity Contraction
High Intensity Contraction
[AMP]↑
AMPK
PKB
TSC 2
Rheb/kinase X
mTOR
PS

Synergistic effects of food and muscle activity?

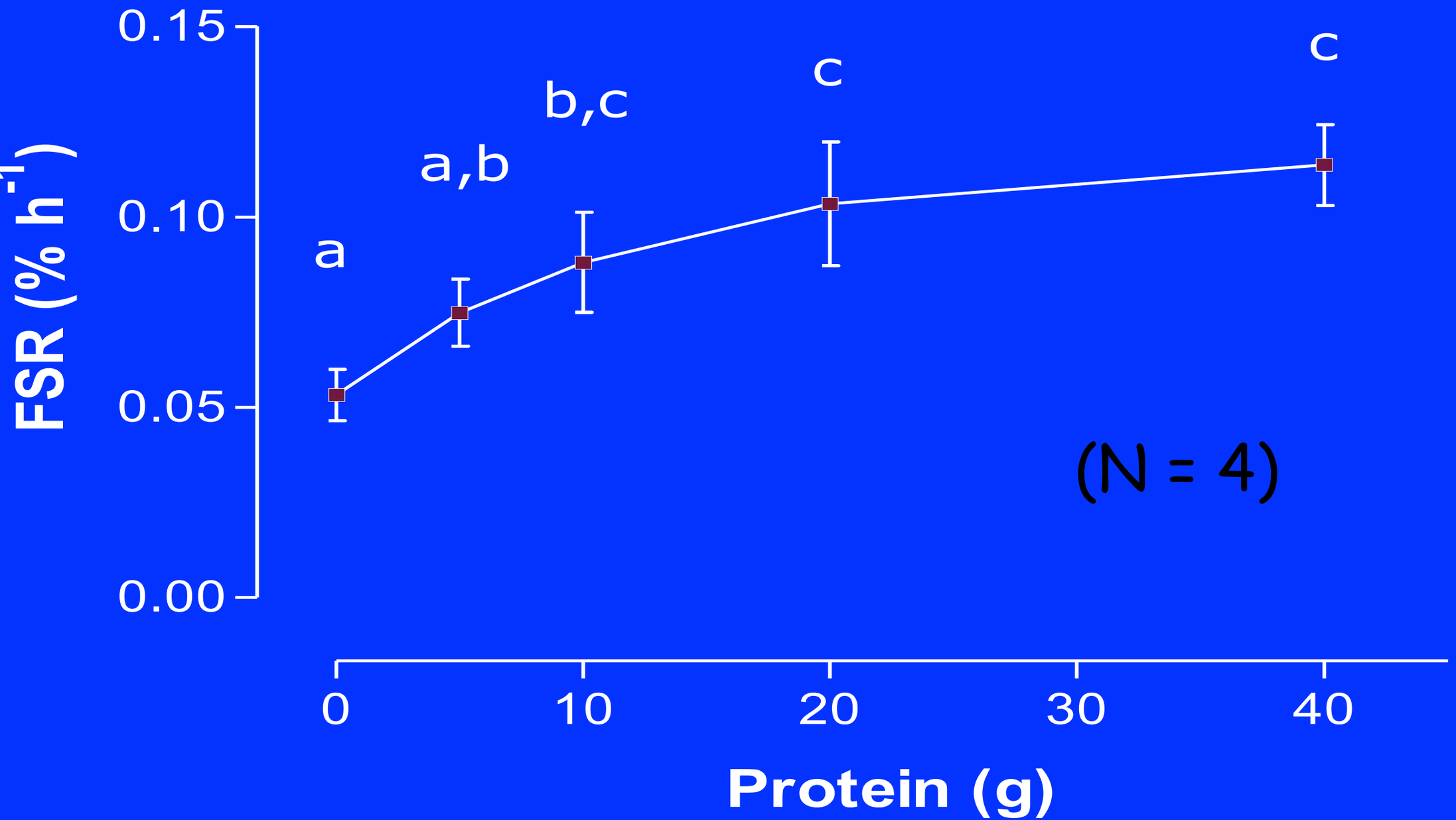
What do we know about Muscle Protein Turnover with AA and Physical activity ?



Net Effect

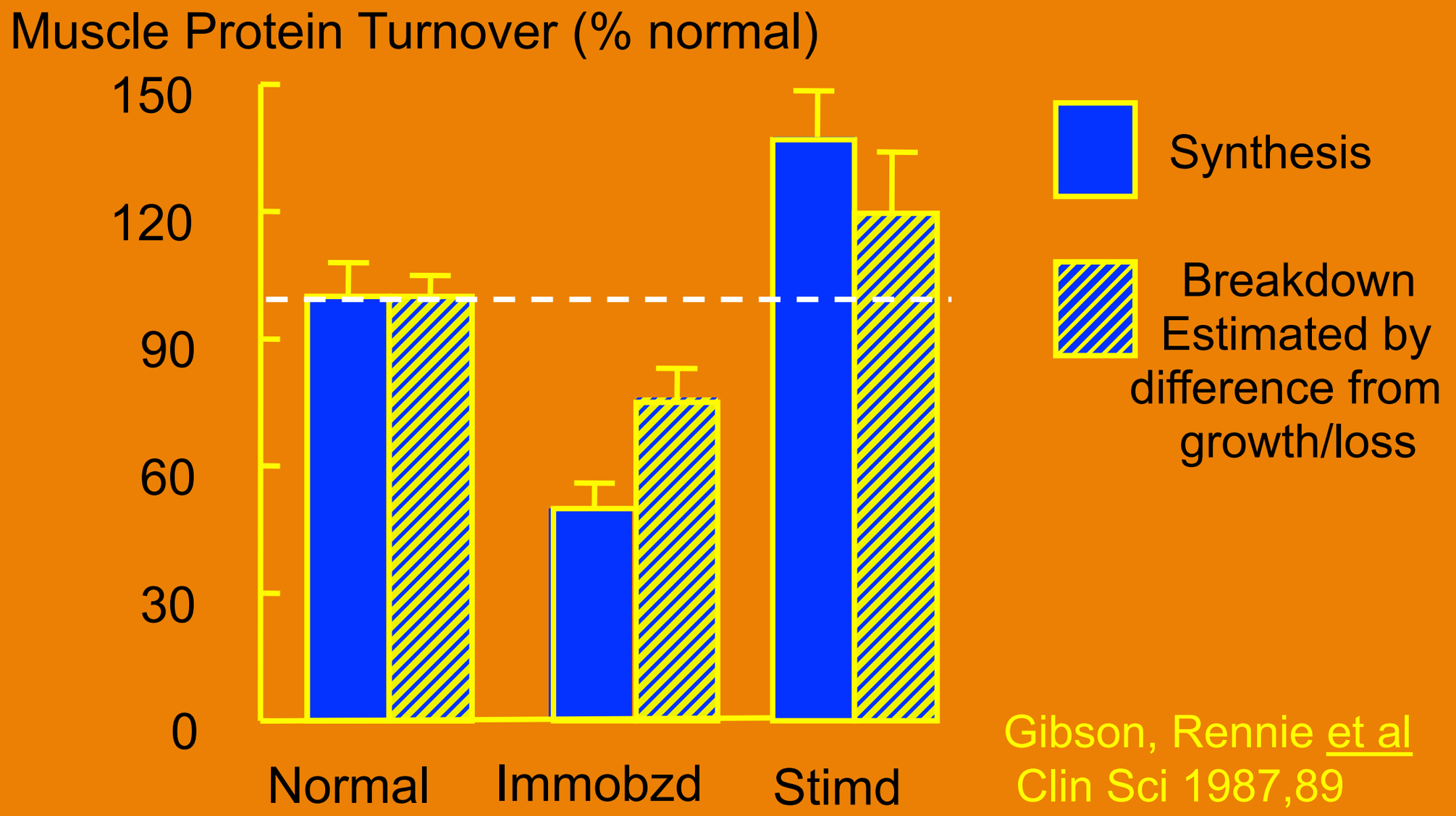


Maximal rate of protein synthesis at 20g



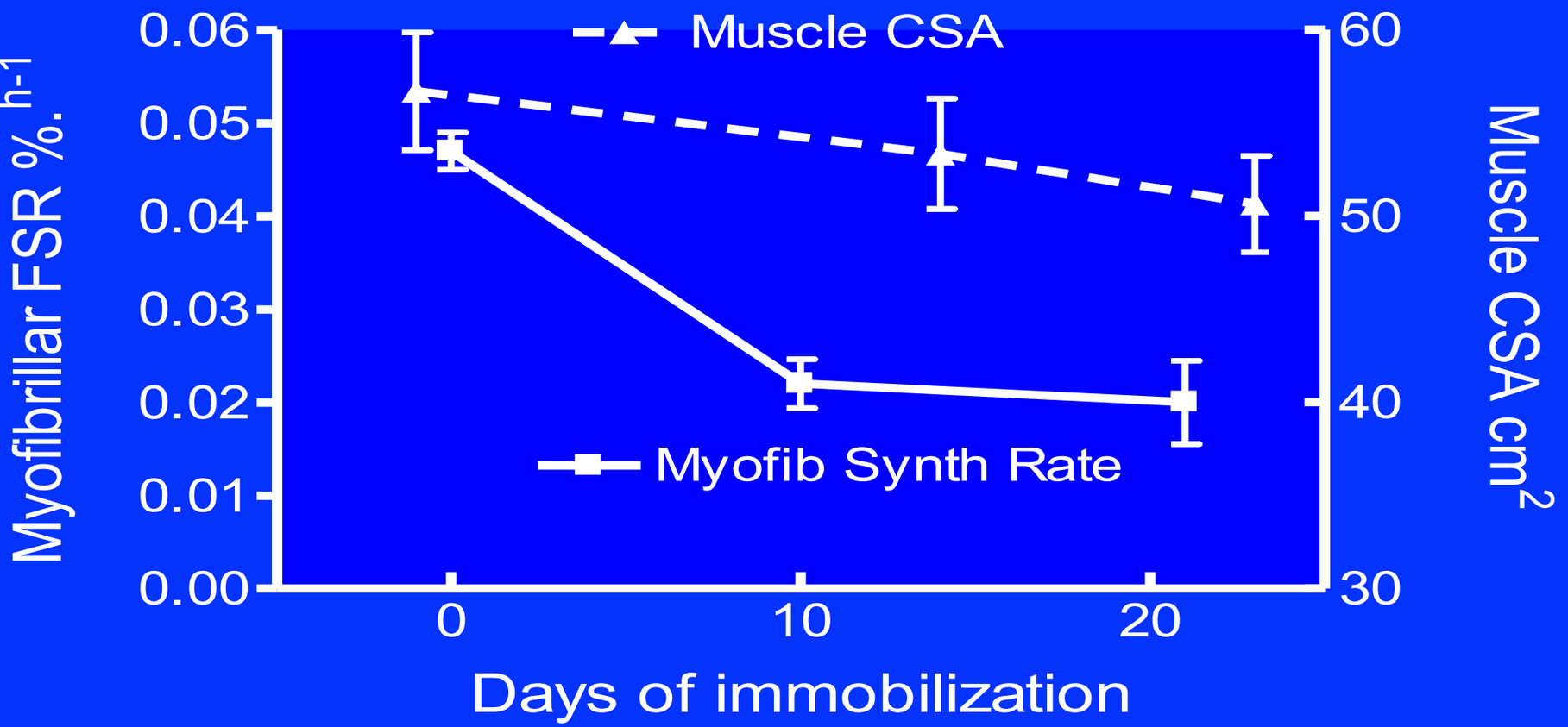
Is immobilization simply the opposite of activity ?

Effects of 7 weeks immobilization in long leg cast and plus electrical stimulation (NB in post absorptive state)



Gibson, Rennie et al
Clin Sci 1987,89

Effect of immobilisation on human quadriceps size and protein synthesis



What causes muscle wasting with inactivity, ageing, cirrhosis, cancer etc?

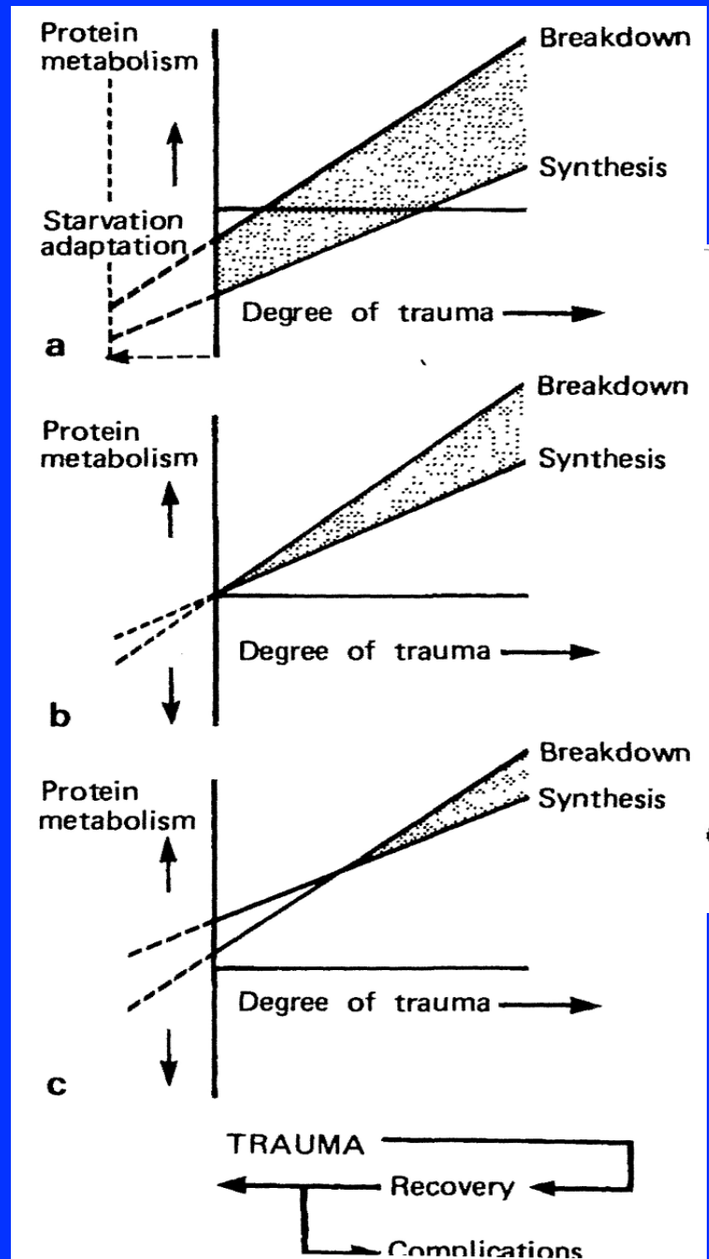
Hypothesized alterations to protein metabolism with activity, disease trauma and sepsis Rennie (Br Med Bull, 1985)

Whole Body Protein Synthesis

(a) Starved

(b) Normally nourished

(c) Enterally or parenterally fed



Muscle Protein Turnover

		Synthesis	Breakdown
Exercise	Acute	↓↓	= or ↓
	Chronic	↑↑	= or ↑
Starvation	Acute	↓↓	↓
	Chronic	↓↓	↑↑
Muscular dystrophy	Acute	?	?
	Chronic	↓↓	↓
Cancer cachexia	Acute	?	?
	Chronic	↓	↓
Trauma, *Sepsis*	Acute	?	?
	Chronic	?	?

Are effects time-dependent? A summary of what is currently known about several circumstances resulting in loss of protein or amino acids from muscle

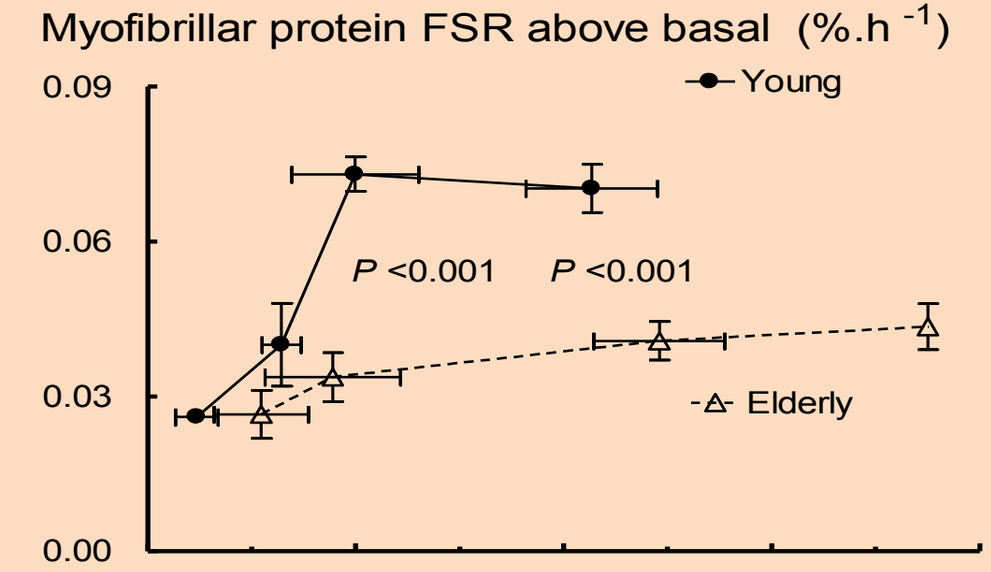
What is our current understanding of the mechanisms of muscle wasting in chronic and acute disease?

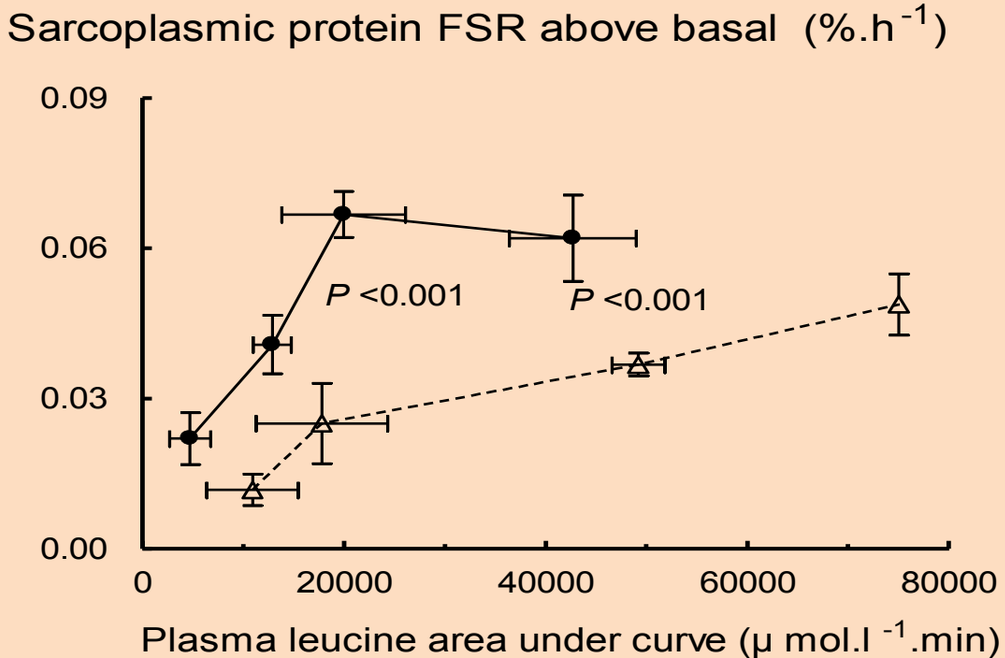
	Prot Syn	Prot Bkdn
Chronic Wasting		
P/E Malnut	↓↓	↓
Immobilization	↓↓	↓
"Slow" Cancer	↓↓	↓
Acute Wasting		
Sepsis	↑	↑↑
Burns	↑	↑↑
Trauma	↓	↑↑ = ?

Should we try to match therapy with mechanisms ?

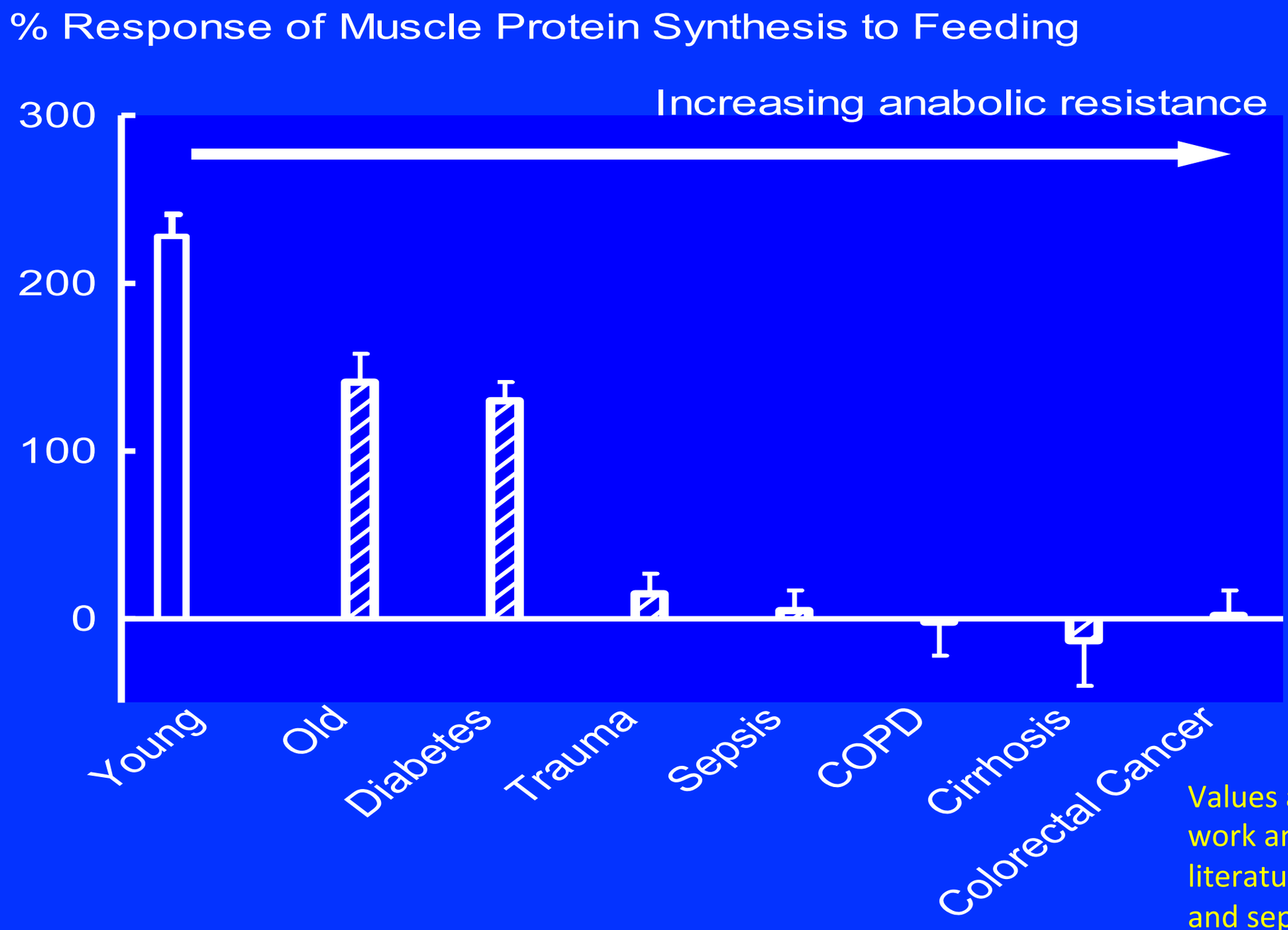
Ageing as a paradigm condition of “anabolic resistance”

Muscle protein synthesis responses during insulin clamps at 10 µU/ml





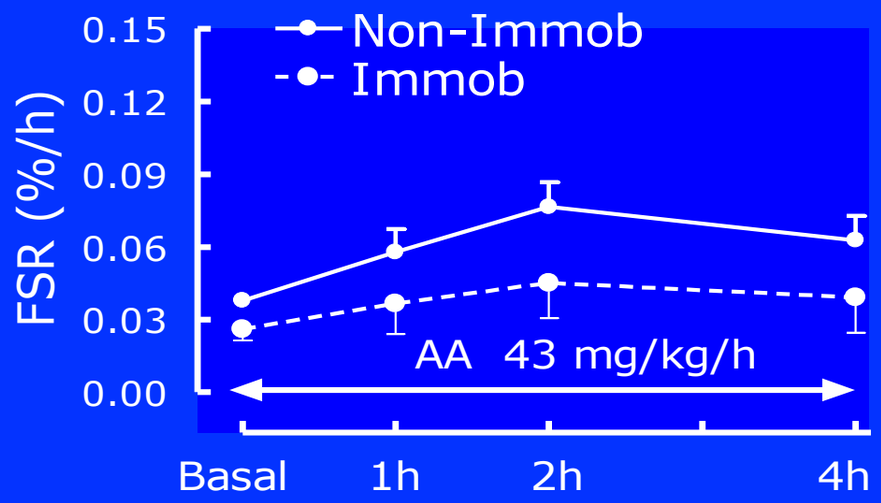
Anabolic resistance to feeding

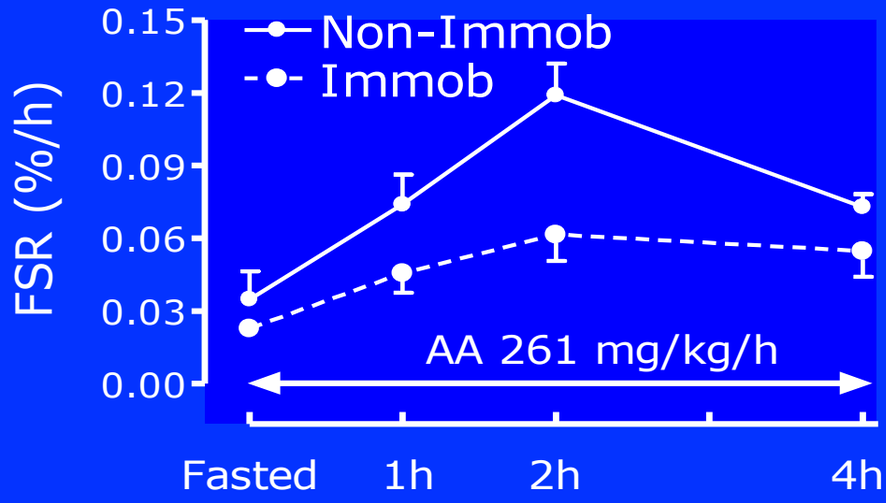


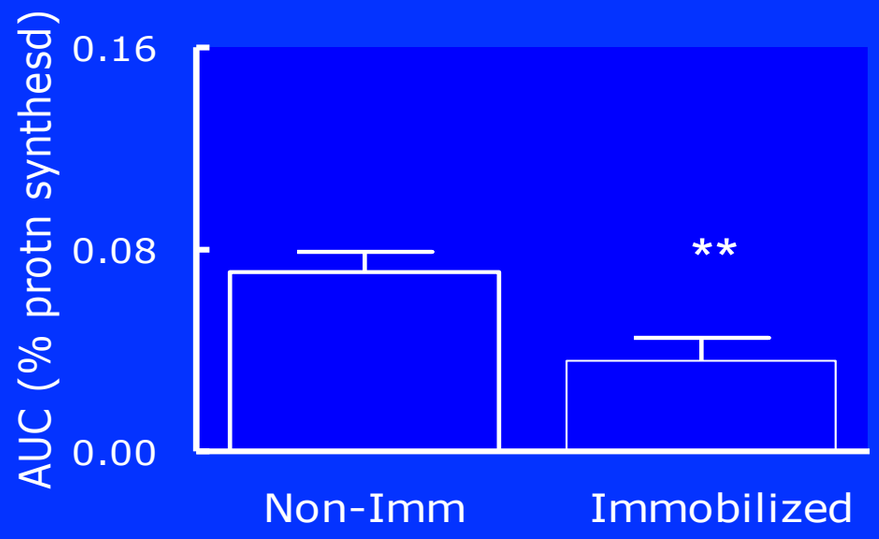
Values are from own work and from literature for trauma and sepsis

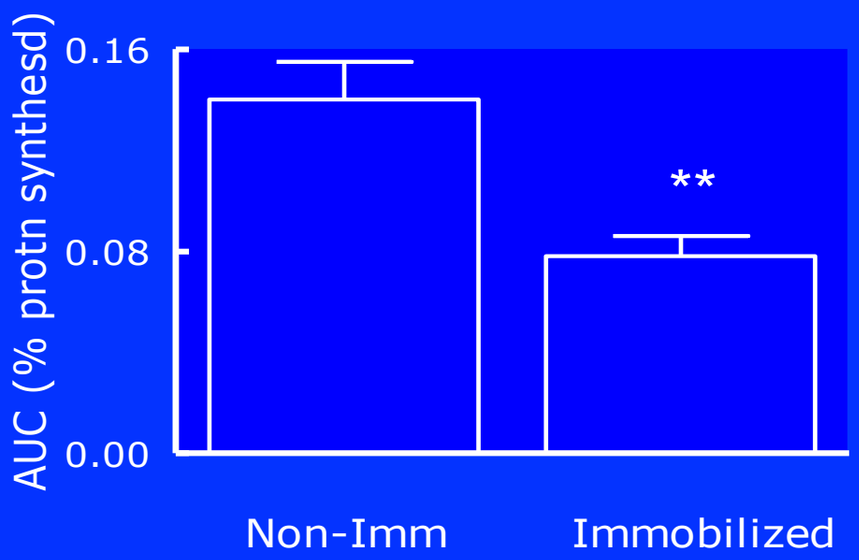
Immobilization and anabolic resistance?

Anabolic resistance after 14 d disuse



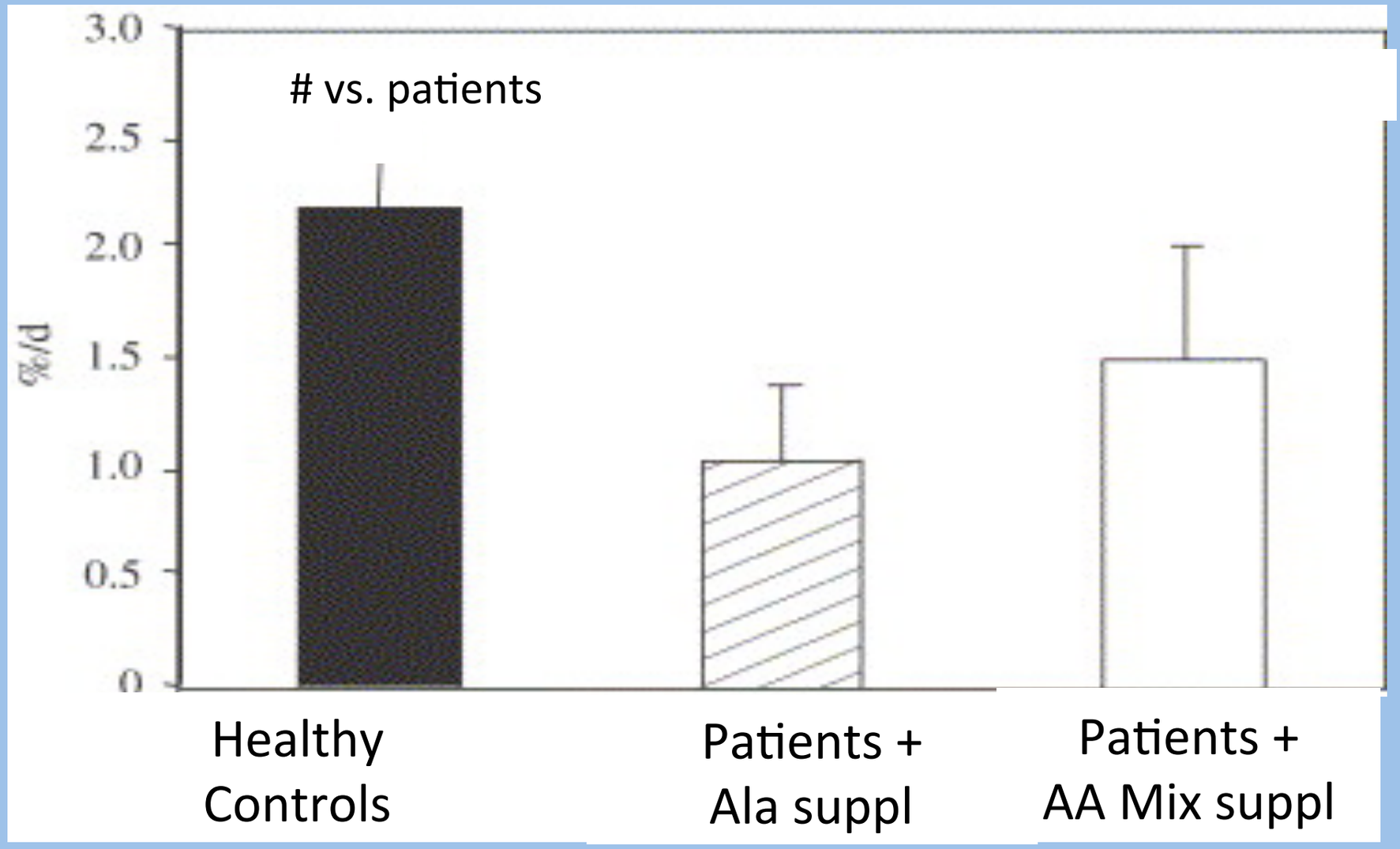






Trauma and anabolic resistance?

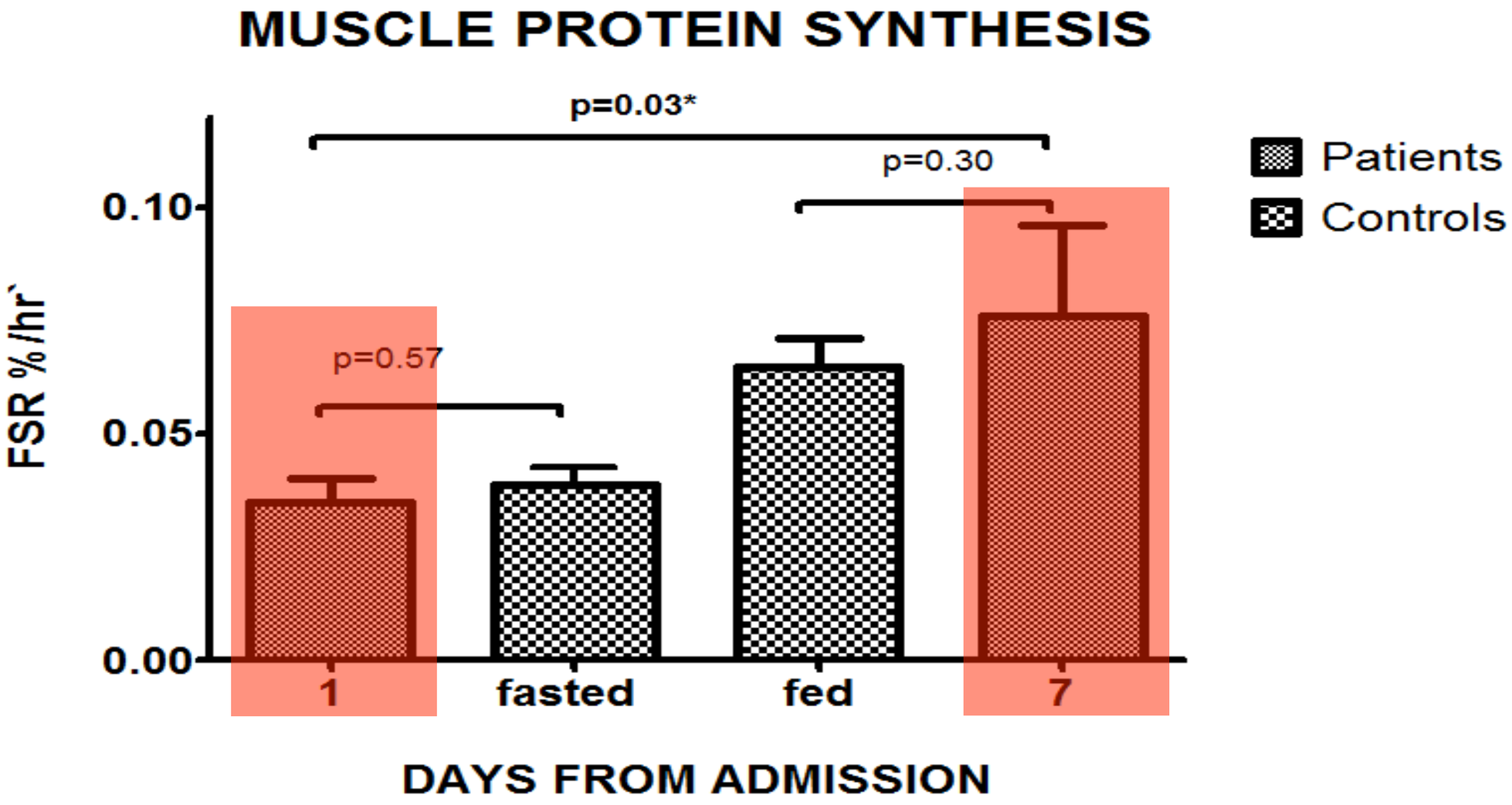
Muscle protein synthesis in ICU patients (all head trauma) fed enterally + AA parenteral supplements



Mansoor et al 2007 Clin Nutr

Work on 62 ICU patients studied by Zudin Puthucheary in UCL/KCL 2009-2012

PROTEIN HOMEOSTASIS (n=11)

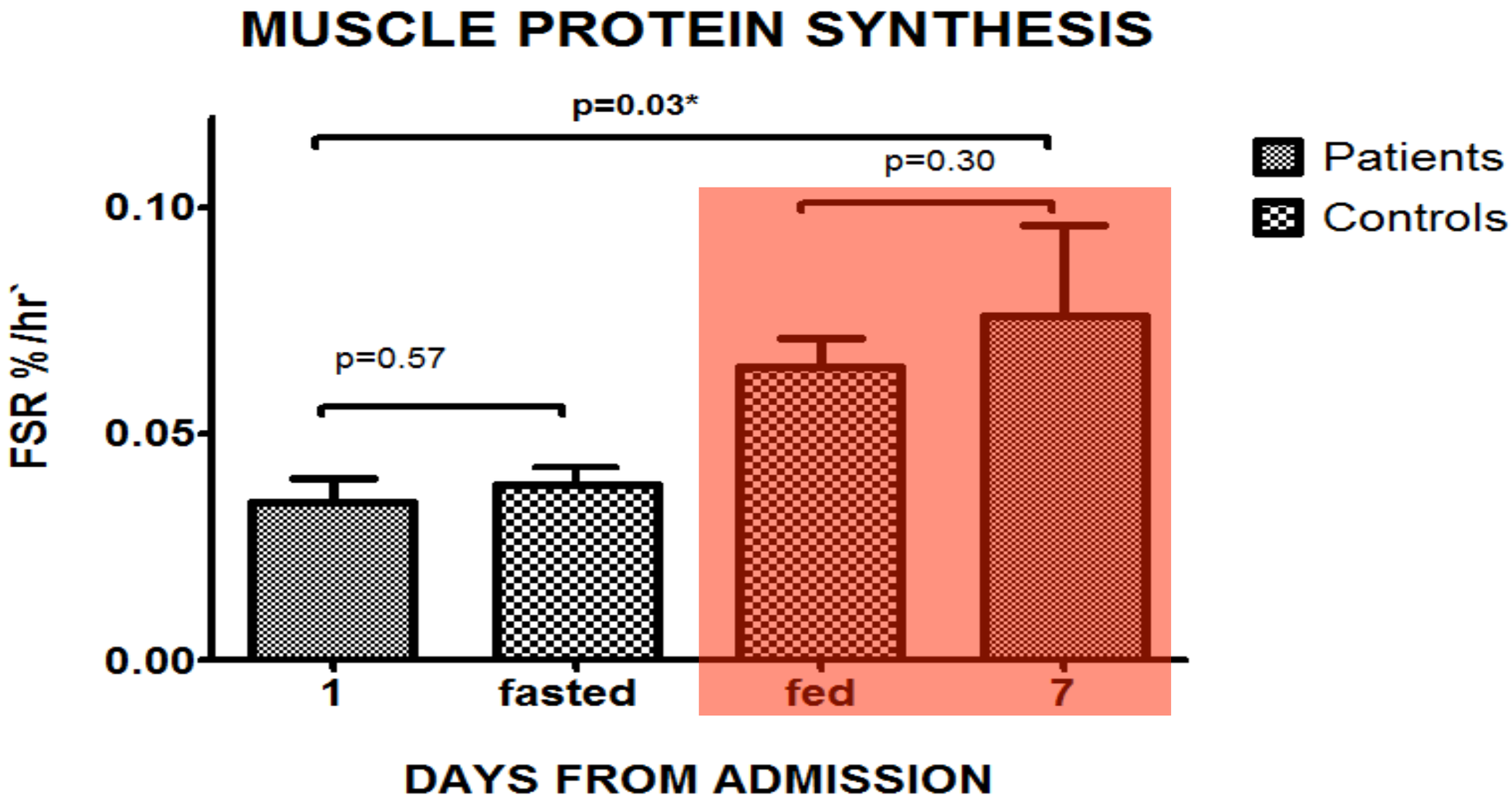


MPS rates at day 1 were depressed to levels observed in fasted healthy controls

Significant Increase in MPS from day 1 to day 7

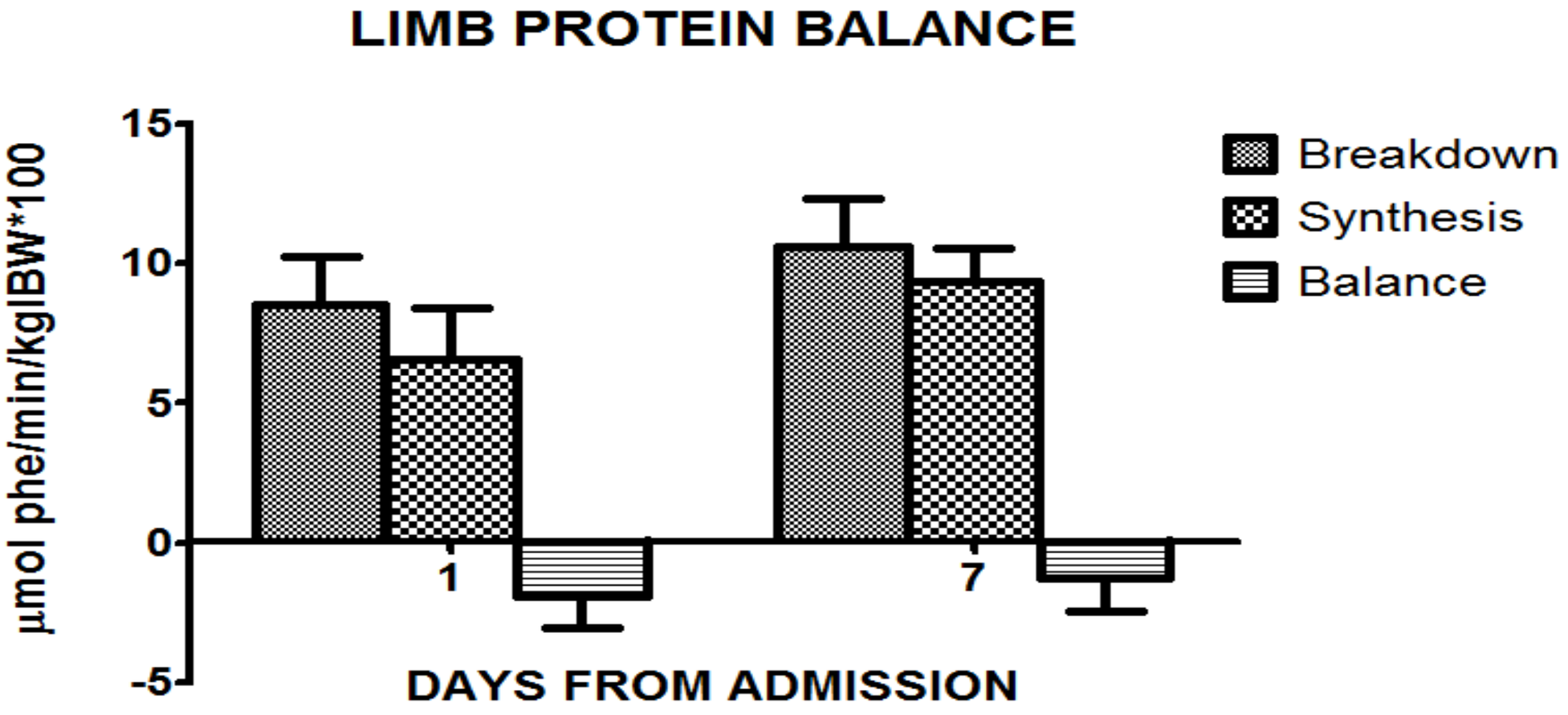
MPS rates at day 7 recovered to similar levels of healthy fed controls

PROTEIN HOMEOSTASIS (n=11)

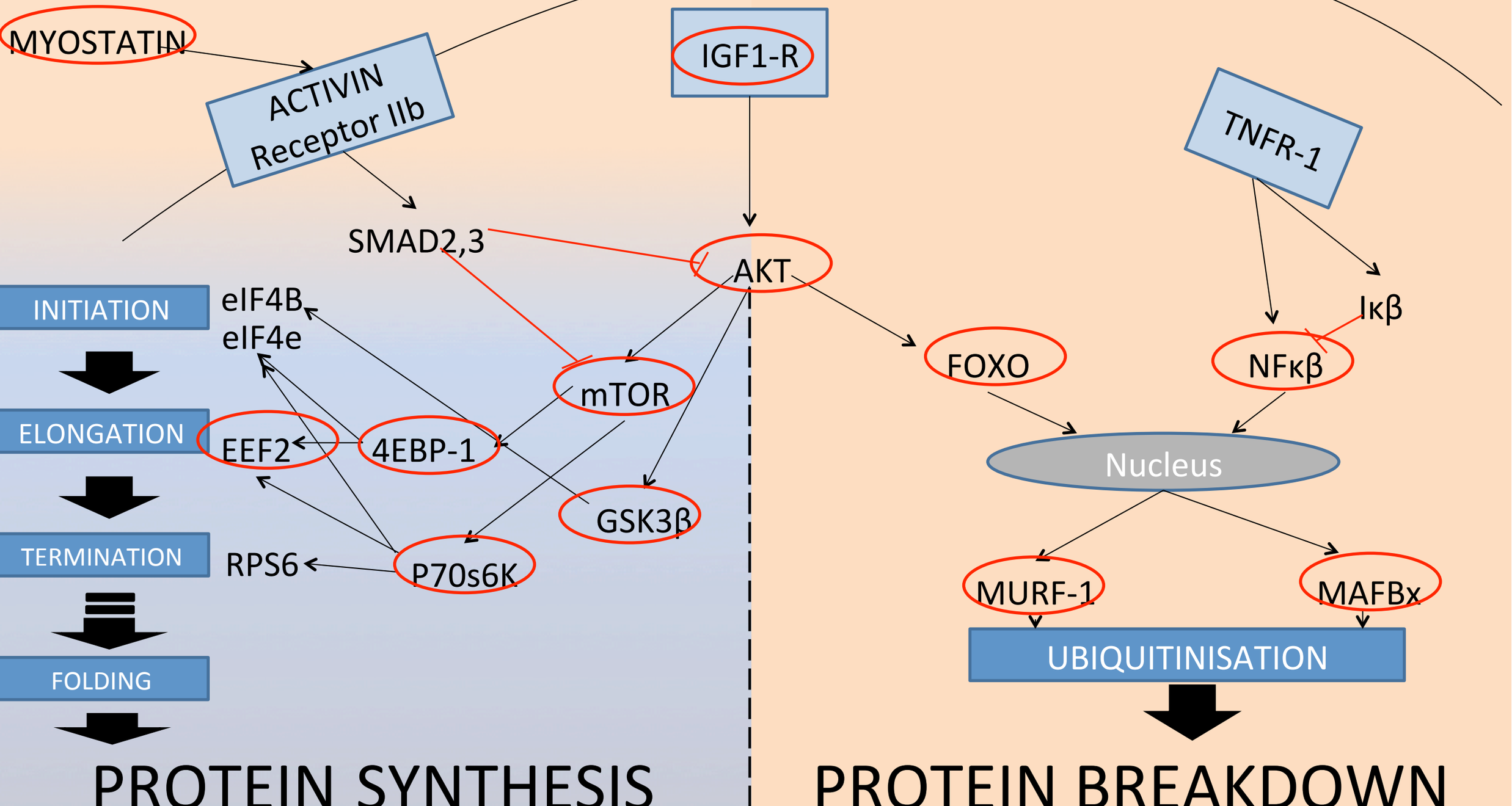


MPS rates at day 1 were depressed to levels observed in fasted healthy controls
Significant Increase in MPS from day 1 to day 7
MPS rates at day 7 recovered to similar levels of healthy fed controls

PROTEIN HOMEOSTASIS (n=11)
NB Breakdown unchanged throughout



SIGNALLING IN MUSCLE PROTEIN HOMEOSTASIS

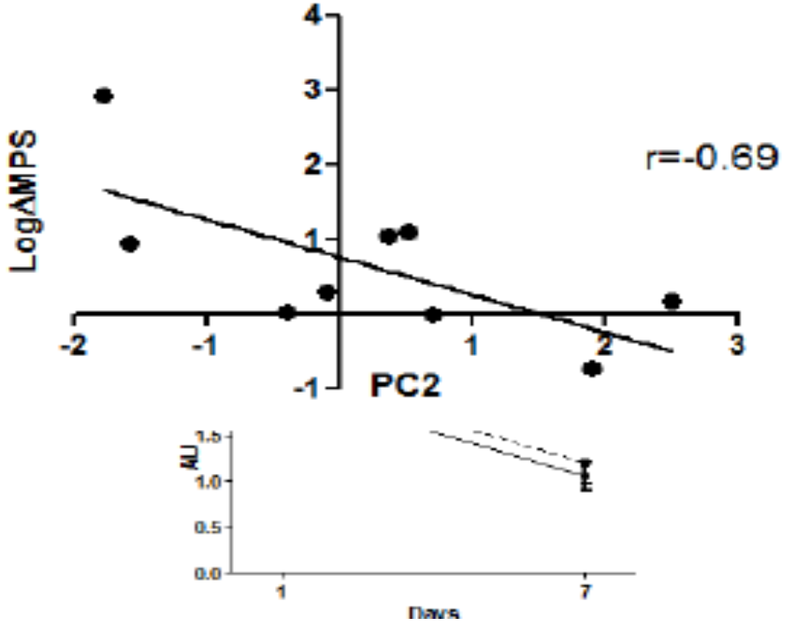


INTRACELLULAR SIGNALLING DATA

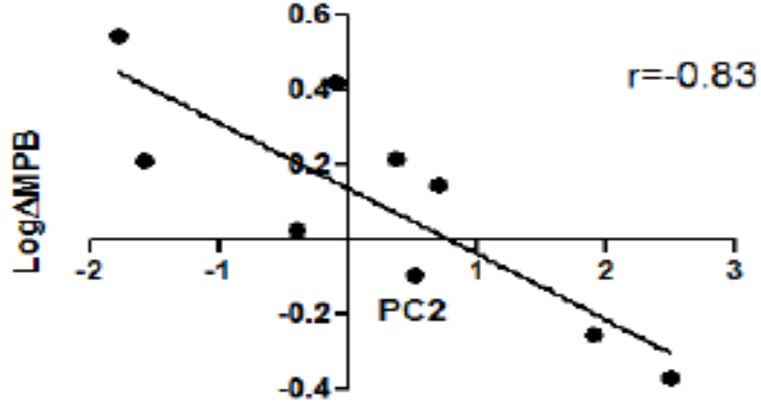
1. No clear pattern of change in expression of individual components.
2. ***Decrease*** in ubiquitin ligases, confirmed by independent mRNA quantification.
3. Principle Component analysis revealed relationships between anabolic and catabolic pathways and real-time measures of protein turnover

D1 D7 D1 D7

Intracellular signalling vs Limb Protein Synthesis



Intracellular signalling vs Limb Protein Breakdown



Principle Component Analysis demonstrated the relationship between anabolic and catabolic pathways and real time measures of protein turnover

Interim Conclusion

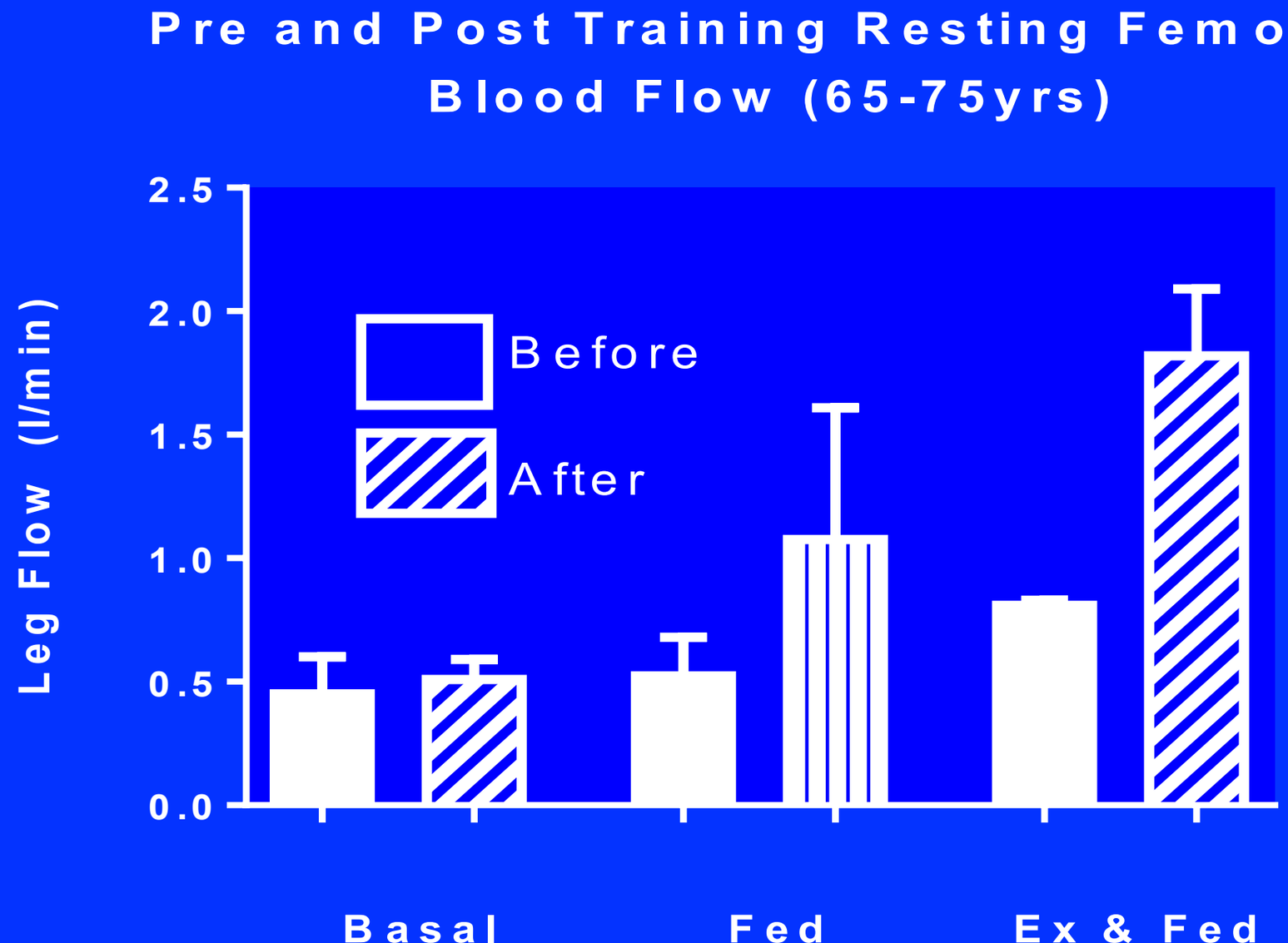
- Critical illness induced muscle wasting occurs rapidly and early - the first 7D
- Critical illness induced muscle wasting is most pronounced in multi-organ failure
- Muscle wasting is the result of a decrease in muscle protein synthesis and a net catabolic state
- Early in critical illness MPS is similar to healthy fasted ‘starved’ controls
- By the end of the first week MPS is similar to that in healthy ‘fed’ controls
- Critical illness muscle wasting correlated with hypoxaemia & protein loading (not shown today)

Summary so far

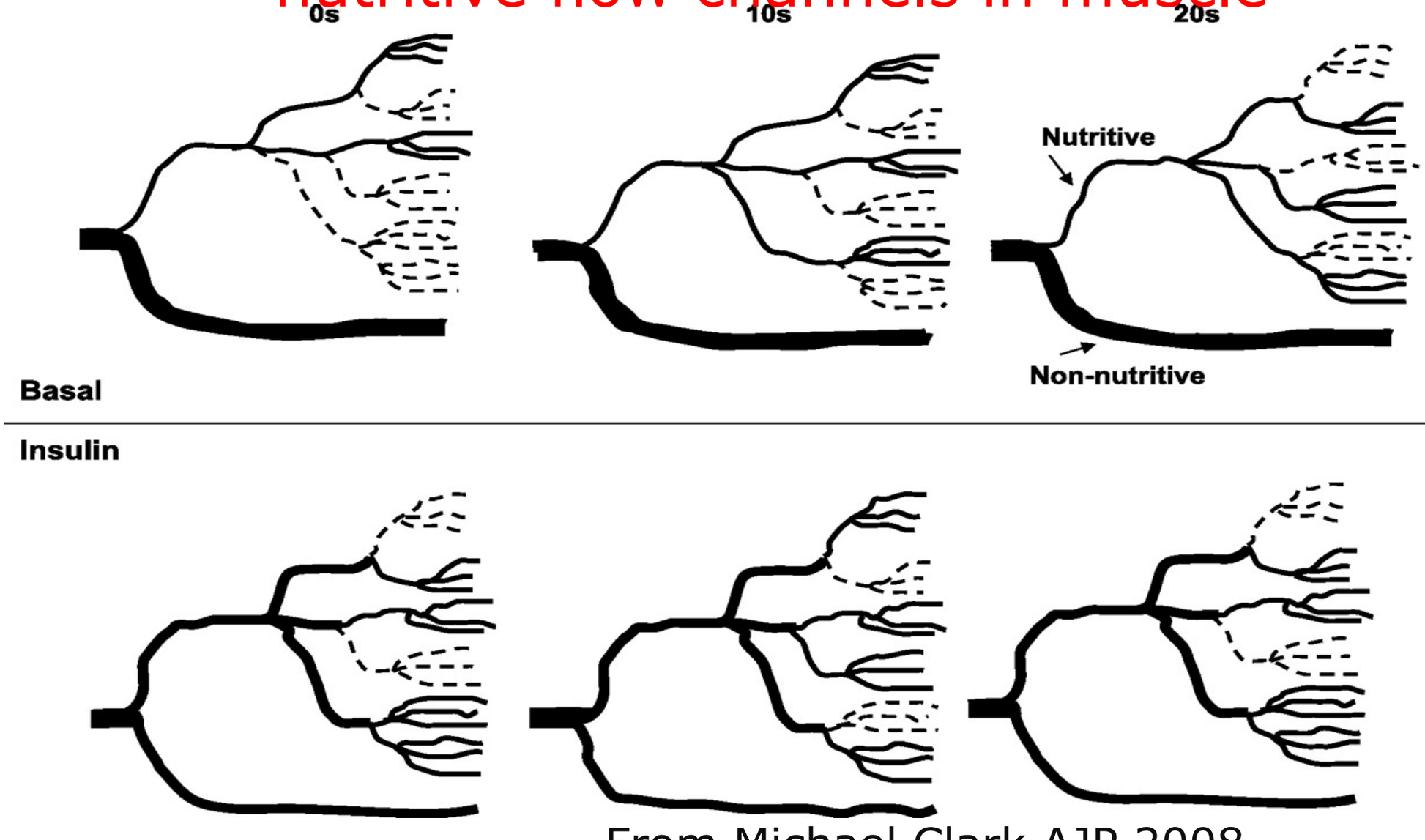
- Amino acids (esp leucine?) act as signals as well as substrates indep of hormones to inc muscle protein synthesis via PKB/mTOR/P70
- Muscle response dose and time limited
- Use and disuse modulate protein accretion – probably dependent on mode, intensity and duration of ± load"
- Age, disuse, trauma and cancer burden all cause "anabolic resistance" – which seems increasingly likely to be final common pathway for slow muscle atrophy in adults

Mechanisms of slow protein wasting?

Muscle blood flow is low and unresponsive in old people but rejuvenated by RET



Bulk vs microvascular flow:
Effect of insulin at very low doses "recruiting" nutritive flow channels in muscle-

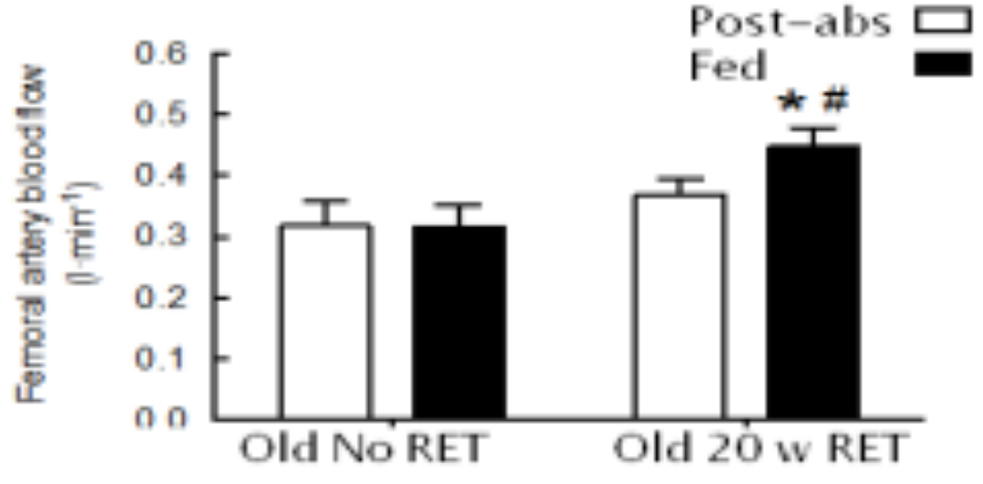


From Michael Clark AJP 2008

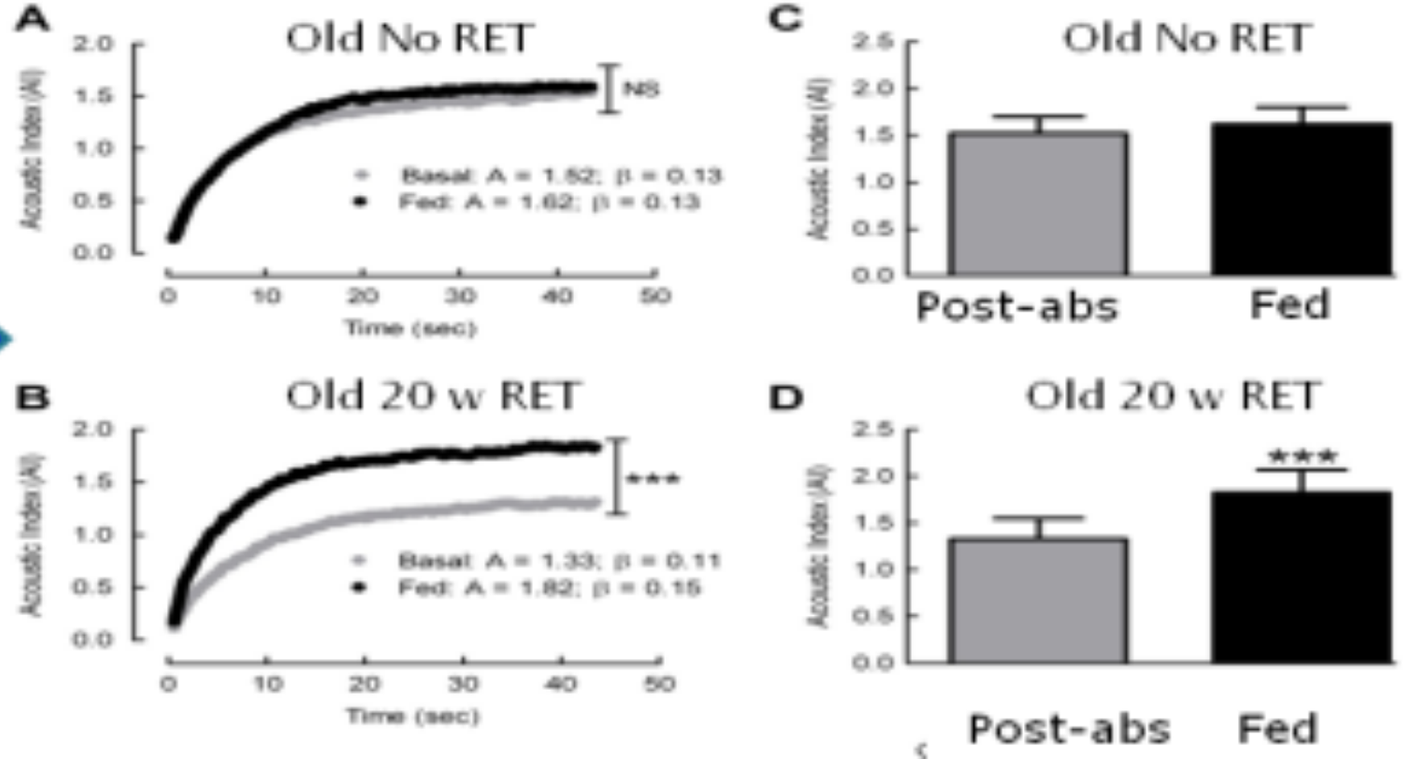
7 Most obvious way to study effect of increased mass is after RET in which strength ↑ 40% and muscle mass ↑ 2-11% in 70 y old men

Resistance Exercise Training in men ~70 y causes adaptations in muscle blood flow *promoting increased muscle mass maintenance*

***In both* Bulk Femoral Arterial Flow**

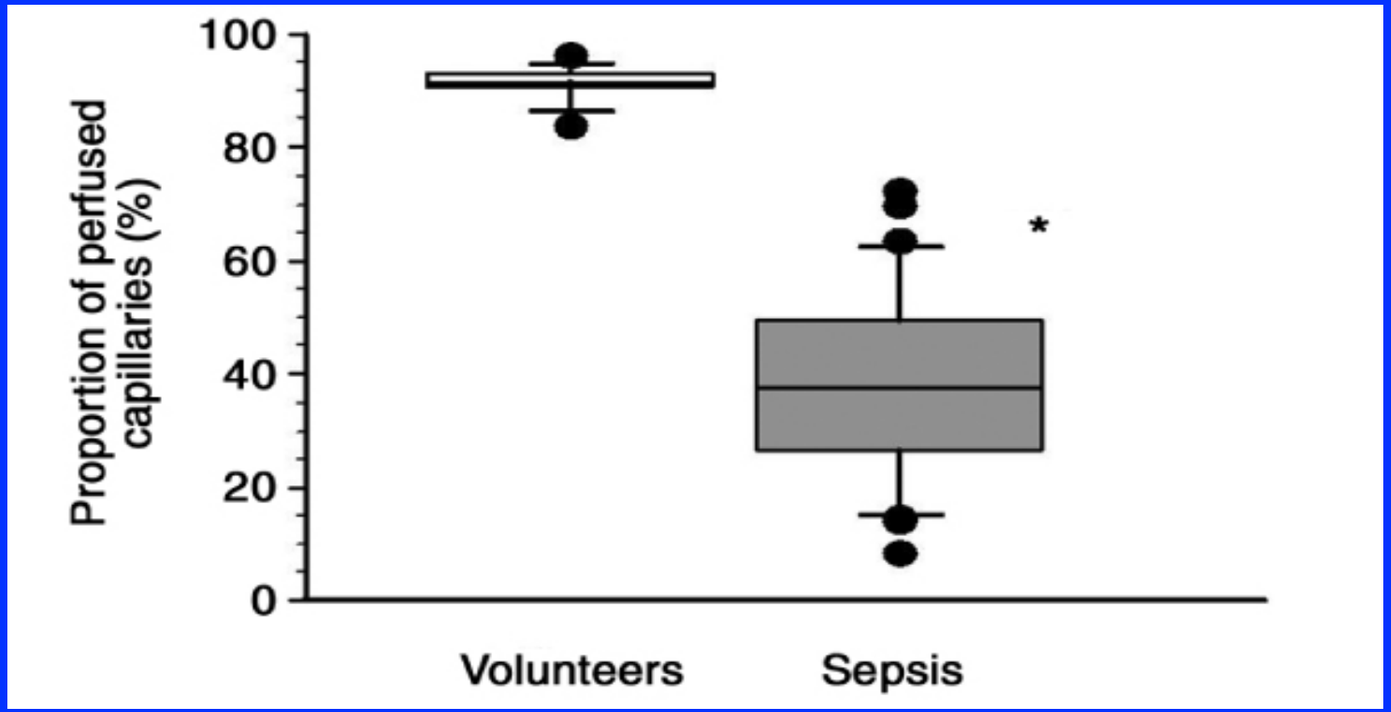


***And in* Muscle Microvascular Flow**



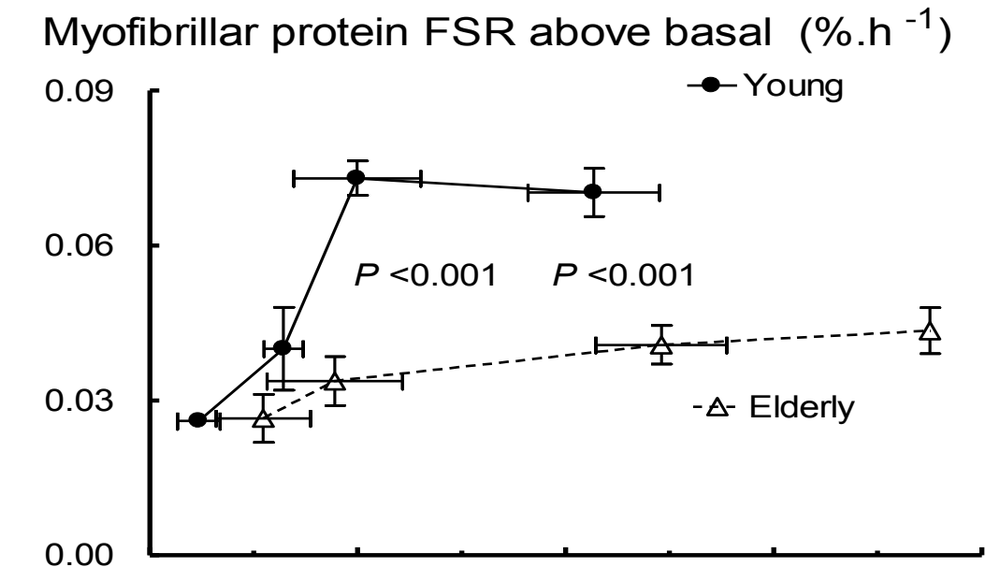
***Both* Bulk & Microvascular Blood Flow ↑ after RET**

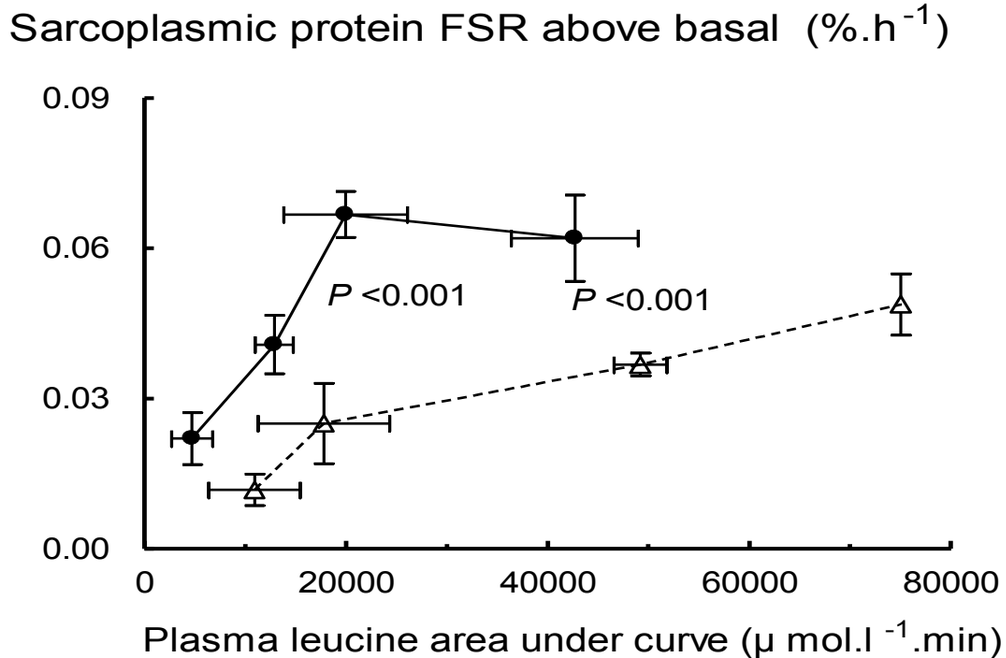
Even if leg blood flow is elevated, muscle microcirculatory flow is *compromised* in critically ill patients incl in sepsis ?

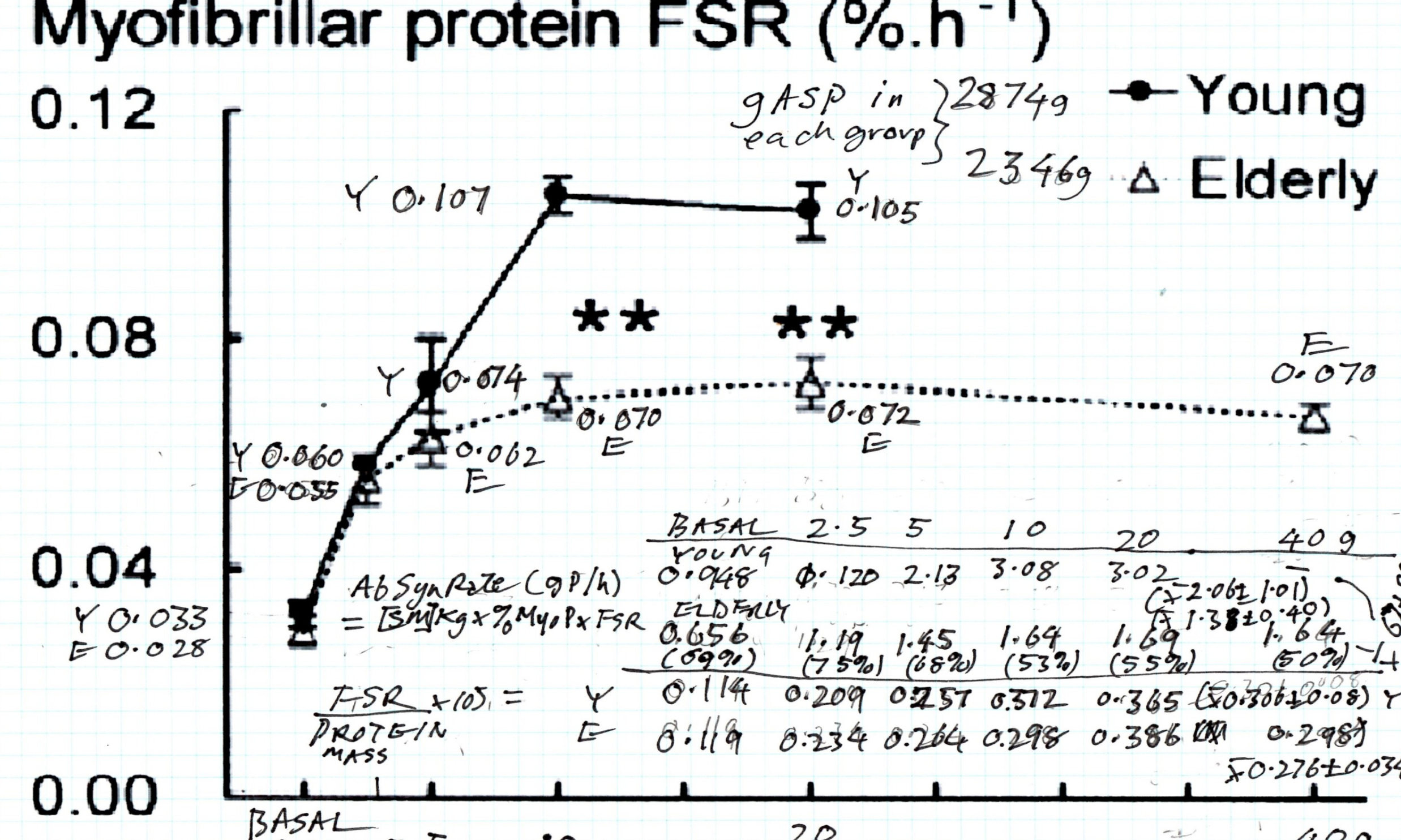


Vincent and De Backer. Crit Care, 2005, 9:S9-12. Microvascular dysfunction as a cause of organ dysfunction in severe sepsis

Muscle protein synthesis responses during insulin clamps at 10 µU/ml






Myofibrillar protein FSR (%.h-1)
0.12
0.08
0.04
0.00
gASP in each group } 2874g 2346g
Young
Elderly
Y 0.107
Y 0.105
Y 0.074
E 0.070
E 0.072
E 0.070
Y 0.060
E 0.055
E 0.062
Y 0.033
E 0.028
** **
AbSynRate (gP/h) = [BM]Kg x %MyoP x FSR
FSR x10 = PROTEIN MASS
BASAL 2·5 5 10 20 40 g
YOUNG
0·948 0·120 2·13 3·08 3·02 (±2.06 1.01)
ELDERLY
0.656 (69%) 1.19 (75%) 1.45 (68%) 1.64 (53%) 1.69 (55%) 1.38±0.40 1.64 (50%)
Y 0·114 0.209 0.257 0.312 0.365 (±0.306±0.08)
E 0·119 0·234 0.264 0.298 0.386 0.298
±0.276±0.034
BASAL

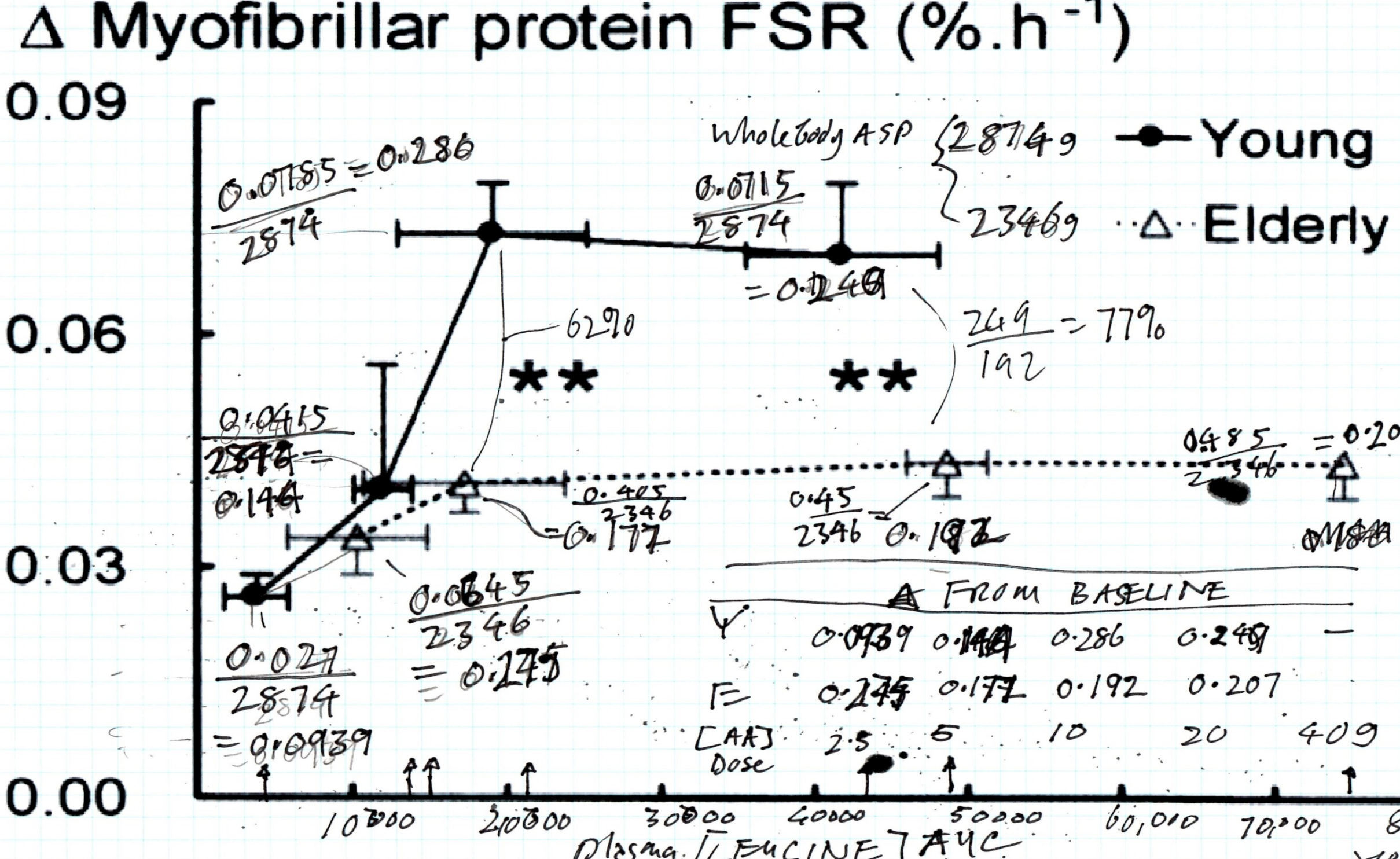

Δ Myofibrillar protein FSR (%.h⁻¹)
0.09
0.06
0.03
0.00
Young
Elderly
Whole body ASP
28749
23469
0.0715/2874 = 0.286
0.0715/2874 = 0.249
269/192 = 77%
6290
**
**
0.0485/2346 = 0.207
0.0415/2874 = 0.144
0.045/2346 = 0.192
0.0405/2346 = 0.177
0.0645/2346 = 0.275
0.027/2874 = 0.00939
Δ FROM BASELINE
Y 0.00939 0.144 0.286 0.249 —
F= 0.275 0.177 0.192 0.207
[AA] Dose 2.5 5 10 20 40g
10000 20000 30000 40000 50000 60,000 70,000
Plasma [LEUCINE] AUC

Table 1

Characteristics of the subjects[a]

Characteristic	*Young*	*Elderly*
Age (years)	28 ±6	70 ± 6
Height (m)	1.77 ± 0.06	1.75 ± 0.05
Weight (kg)	75 ± 10	79 ±13
Body mass index (BMI, kg.m^{-2})	24 ± 3	26 ± 4
Body fat (%)	18 ± 6	24 ± 5
Lean body mass (kg)	60 ± 6	55 ±8
Appendicular lean soft tissue mass (ALST, kg)	29 ± 3	24 ± 3
Appendicular muscle mass (kg)	25 ± 3	21 ± 3
Total skeletal muscle mass (kg)	33 ± 3	28 ± 4
Alkali soluble muscle protein (mg.g wet weight^{-1})	13.2 ± 1.9	12.7 ± 2.2
Protein/DNA (µg/µg)	185 ± 26	167 ± 24
RNA/Protein (µg/mg)	7.3 ± 2.0	6.2 ± 1.3[b]
RNA/DNA (µg/µg)	1.3 ± 0.3	1.0 ± 0.2[b]
Myofibrillar FSR/RNA at 10 g EAA (µg protein synthesized.µg RNA^{-1}.h^{-1})	0.020 ± 0.005	0.011 ± 0.002[c]
Basal plasma glucose (mM)	4.7 ± 0.3	4.9 ± 0.5
Basal plasma insulin (IU.l^{-1})	10 ± 5	9 ± 3
Basal insulin: glucose ratio (I U.mol^{-1})	2.3 ± 1.1	1.8 ± 0.5
Basal IGF-1 (µg.l^{-1})	96 ± 36	73 ± 21[b]
Basal IGF-1 binding protein 3 (µg.l^{-1})	2.50 ± 0.60	2.54 ± 0.91
Basal plasma leucine (µM)	118 ± 12	122 ±12
Basal plasma α-ketoisocaproate flux (µg.kg. body wt.$^{-1}$.h^{-1})	209 ± 24	180 ± 18[c]

"Physical and metabolic characteristics of 20 young and 24 elderly subjects (except values derived from DEXA, which are for 20 elderly and 11 young subjects, and values for muscle composition, which are for 12 young and 20 elderly subjects). Values are means ± SD. [b]$P < 0.05$. [c]$P < 0.01$, Student's *t* test.

Mean Absolute Syn Rate (SEM) g P/h = Y 2·062 ± 1·01, E 1·38 ± 0·40 — 67 ± 8 E/Y

FSR / PROTEIN MASS + 105 = Y 0·263 g/hr ± 0·108, g/hr ± 0·097 — E/Y = 99%

Δ FSR at ... range = 3

E/Y 10g = 62

E/Y 20g = 77%

14 Explanations?

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- Basal rate of Fractional Synthetic Rate depends on mass of [RNA]/[DNA] i.e. protein synthetic capacity – i.e. the capacity per managed" domain of cell sarcoplasm; the analogy is with the maintenance rate per building floor area
- Thus, a bigger house needs ↑ maintenance but *unit* maintenance rate is CONSTANT i.e. basal FSR is fixed but ASR *scales* with muscle mass involved and is modulated by stimulating influences e.g. acute exercise or [EAA]
- Influences that ↑[RNA] (chronic exercise, steroids, clenbuterol) and those that ↓ [RNA] e.g. (immobilization, aging) have no effect on basal FSR; rather they ↑/↓ ASR according to ability to drive "*efficiency*" of translation, i.e. FSR/[RNA]. Thus ribogenesis/ribopenia control basal FSR and *activation state* of anabolic signalling controls extent of utilization of capacity
- Anabolic resistance *follows* from inability of [EAA] to modulate *not* capacity (i.e. [RNA]/[DNA]) but only FSR/[RNA]

NB

1. Fractional Protein Syn Rate normalizes when expressed per protein mass
2. Absolute Syn Rate is FSR x Muscle Protein Mass
3. FSR/[RNA] is very low in old
4. AA have effect only within window set by [RNA]

Explanations?

- **Basal rate of Fractional Synthetic Rate depends on mass of [RNA]/[DNA] i.e. protein synthetic capacity – i.e. the capacity per managed" domain of cell sarcoplasm; the analogy is with the maintenance rate per building floor area**

- **Thus, a bigger house needs ↑ maintenance but *unit* maintenance rate is *CONSTANT* i.e. basal FSR is fixed but ASR *scales* with muscle mass involved and is modulated by stimulating influences e.g. acute exercise or [EAA]**

- **Influences that ↑[RNA] (chronic exercise, steroids, clenbuterol) and those that ↓ [RNA] e.g. (immobilization, aging) have no effect on basal FSR; rather they ↑/↓ ASR according to ability to drive "*efficiency*" of translation, i.e. FSR/[RNA]. Thus ribogenesis/ribopenia control basal FSR and *activation state* of anabolic signalling controls extent of utilization of capacity**

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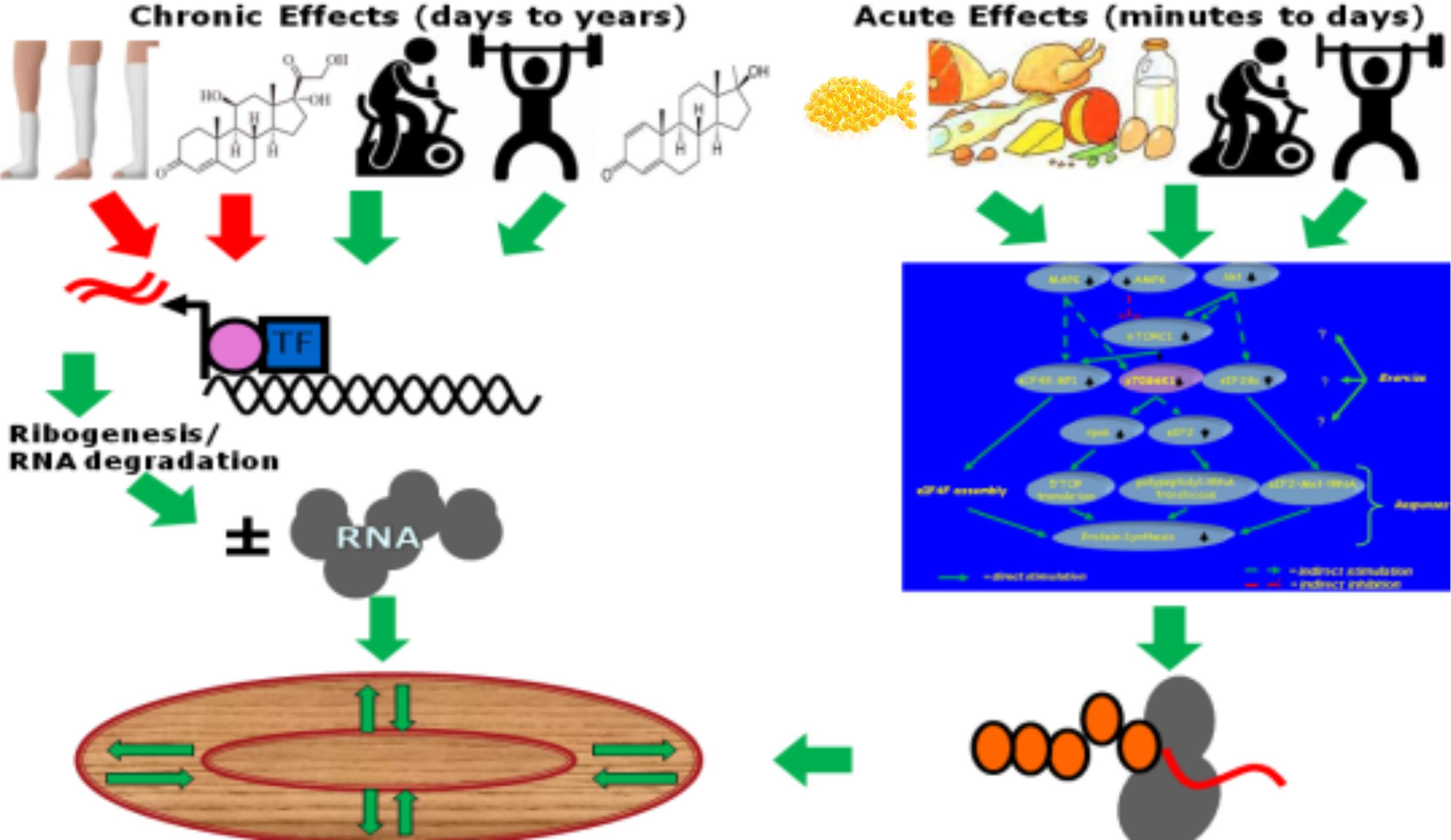
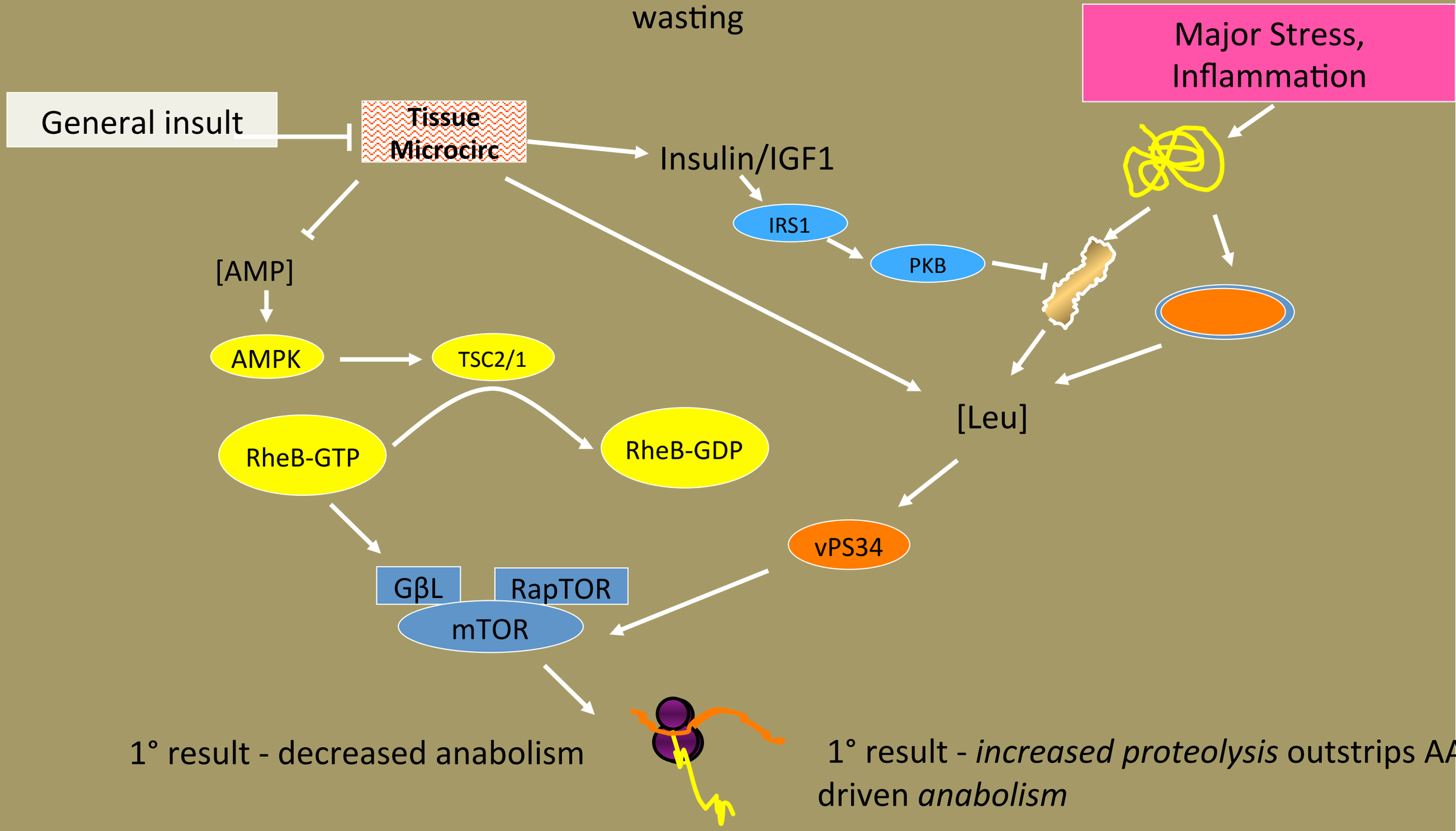
How Capacity for MPS and Translational Efficiency Influence FSR and ASR



But what about *fast* wasting?

In *sepsis and burns* muscle breakdown is *elevated* sufficiently to drive muscle synthesis to supra-normal values

Hypothesis regarding loss of muscle protein in slow and fast wasting



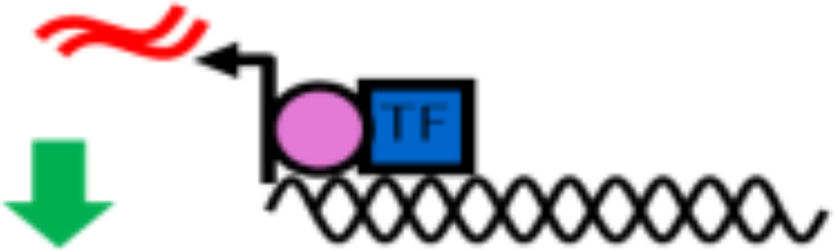
How to ameliorate muscle mass loss in ICU patients

- Increase muscle [RNA] by any means possible
- THEN , and ONLY then add EAA, protein, n-3 PUFA etc

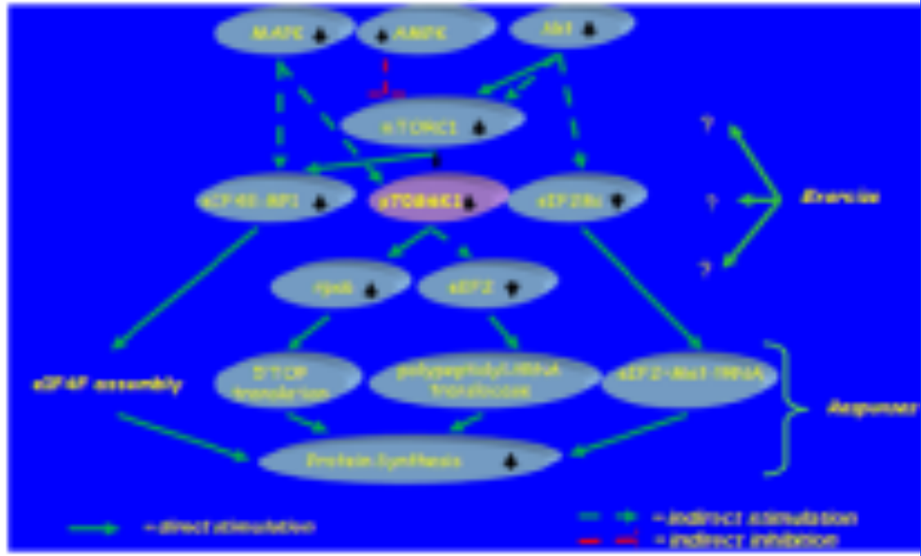
How Capacity for MPS and Translational Efficiency influence FSR and ASR

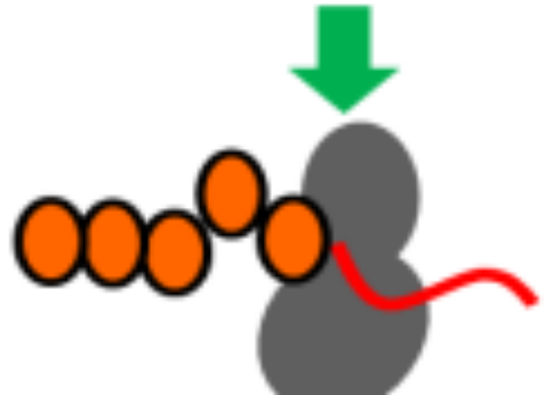
Chronic Effects (days to years)

Acute Effects (minutes to days)



Ribogenesis/
RNA degradation





We thank

- The subjects and the team

- Nick Hart and Zudin Puthucheary, Stu Phillips, Marco Narici, Paul Greenhaff, Joe Millward, the late Richard Edwards, Dave Halliday
- Unilever PLC, BBSRC, Dunhill Med Trust, MRC, Wellcome, Mason Trust and University of Nottingham for financial support