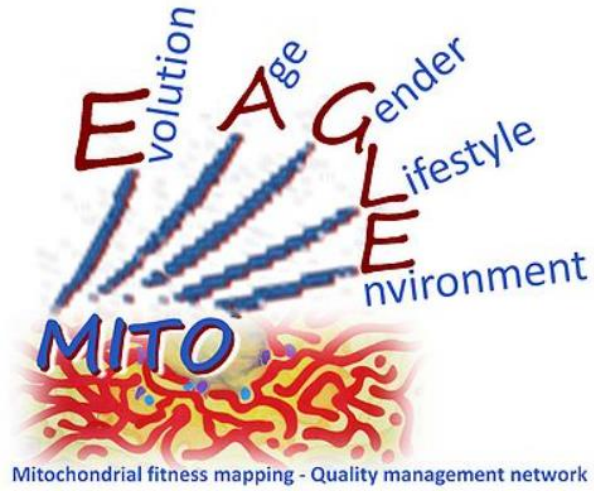


MITOEAGLE data repository in muscle

TG2.1 Skeletal

TG leaders: Garcia-Roves Pablo M ES / Votion Dominique-Marie BE / Coen Paul M US

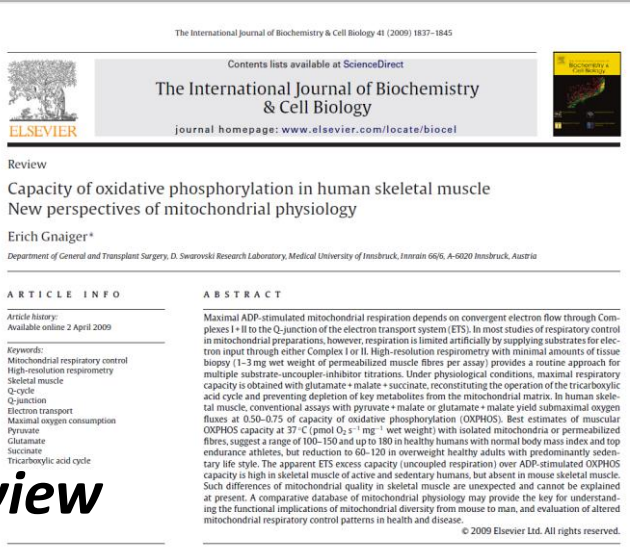
TG participants: Boyle John P UK, Chabi Beatrice FR, Garcia-Roves Pablo MES, Lehti Maarit FI, Mars Tomaz SI, Pirkmajer Sergej SI, Rustan Arild NO, Schlattner UweFR, Wuest Rob C NL and many others

TG2.2 Cardiac

TG leaders: Larsen Terje S NO / Makrecka-Kuka Marina LV

TG participants: Muntean Danina M RO , Schlattner Uwe FR, Vendelin Marko EE, Wuest Rob C NL

Mitochondrial fitness mapping - Quality management network



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Review

Capacity of oxidative phosphorylation in human skeletal muscle
New perspectives of mitochondrial physiology

Erich Gnaiger*

Department of General and Transplant Surgery, D. Swarovski Research Laboratory, Medical University of Innsbruck, Innrain 66/6, A-6020 Innsbruck, Austria

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ABSTRACT

Maximal ADP-stimulated mitochondrial respiration depends on convergent electron flow through Complexes I + II to the Q-junction of the electron transport system (ETS). In most studies of respiratory control in mitochondrial preparations, however, respiration is limited artificially by supplying substrates for electron input through either Complex I or II. High-resolution respirometry with minimal amounts of tissue biopsy (1–3 mg wet weight of permeabilized muscle fibres per assay) provides a routine approach for multiple substrate-uncoupler-inhibitor titrations. Under physiological conditions, maximal respiratory capacity is obtained with glutamate + malate + succinate, reconstituting the operation of the tricarboxylic acid cycle and preventing depletion of key metabolites from the mitochondrial matrix. In human skeletal muscle, conventional assays with pyruvate + malate or glutamate + malate yield submaximal oxygen fluxes at 0.50–0.75 of capacity of oxidative phosphorylation (OXPHOS). Best estimates of muscular OXPHOS capacity at 37 °C (pmol O_2 s^{-1} mg^{-1} wet weight) with isolated mitochondria or permeabilized fibres, suggest a range of 100–150 and up to 180 in healthy humans with normal body mass index and top endurance athletes, but reduction to 60–120 in overweight healthy adults with predominantly sedentary life style. The apparent ETS excess capacity (uncoupled respiration) over ADP-stimulated OXPHOS capacity is high in skeletal muscle of active and sedentary humans, but absent in mouse skeletal muscle. Such differences of mitochondrial quality in skeletal muscle are unexpected and cannot be explained at present. A comparative database of mitochondrial physiology may provide the key for understanding the functional implications of mitochondrial diversity from mouse to man, and evaluation of altered mitochondrial respiratory control patterns in health and disease.

Summary of the discussion about …

→ *Proposal for a state-of-the-art literature review*

- Leader of the project: Paul Coen
- Topic: human skeletal muscle mitochondrial function
- Cf. revue from Erich (2009) → extensive literature since the last ten years
- Of interest for further researchers but…
  - **Definition of "quality control criteria"** for data to be included in the review (or distinction of data according on whether the data meets these inclusion criteria or not)
- **To be included (or additional paper(s))**
  - Description of protocols (that include quality controls: Cyt *c*, O_2, T°…) according to objectives of the study
  - Cultured muscle cells (myoblast, myotubes)
    Leader of this chapter (or paper): Arild Rustan
- Targeted journal "Physiological review" (contact the editor)

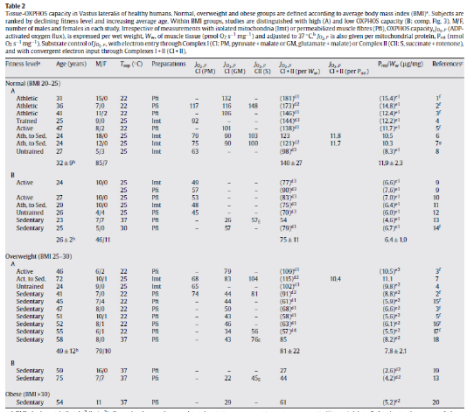

Table 2

Tissue-OXPHOS capacity in Vastus lateralis of healthy humans. Normal, overweight and obese groups are defined according to average body mass index (BMI)[a]. Subjects are ranked by declining fitness level and increasing average age. Within BMI groups, studies are distinguished with high (A) and low OXPHOS capacity (B; comp. Fig. 3). M/F, number of males and females in each study. Irrespective of measurements with isolated mitochondria (Imt) or permeabilized muscle fibres (Pm), OXPHOS capacity, $J_{O_2,p}$ (ADP-activated oxygen flux), is expressed per wet weight, W_w, of muscle tissue (pmol O_2 s^{-1} mg^{-1}) and adjusted to 37 °C. $J_{O_2,p}$ is also given per mitochondrial protein, P_{mt} (nmol O_2 s^{-1} mg^{-1}). Substrate control of $J_{O_2,p}$, with electron entry through Complex I (CI; PM, pyruvate + malate or GM, glutamate + malate) or Complex II (CII; S, succinate + rotenone), and with convergent electron input through Complexes I + II (CI + II).

Fitness level[a]	Age (years)	M/F	T_{exp} (°C)	Preparations	$J_{O_2,p}$ CI (PM)	$J_{O_2,p}$ CI (GM)	$J_{O_2,p}$ CII (S)	$J_{O_2,p}$ CI+II (per W_w)	$J_{O_2,p}$ CI+II (per P_{mt})	P_{mt}/W_w (µg/mg)	Reference
Normal (BMI 20–25)											
A											
Athletic	31	15/0	22	Pft	–	132	–	(181)[c]		(15.4)[c]	1[c]
Athletic	36	7/0	22	Pft	117	116	148	(172)[c]		(14.8)[c]	2[c]
Athletic	41	11/2	22	Pft	–	106	–	(146)[c]		(12.4)[c]	3[c]
Trained	25	9/0	25	Imt	92	–	–	(144)[c]		(12.2)[c]	4
Active	27	8/2	23	Pft	–	101	–	(138)[c]		(11.7)[c]	5[c]
Ath. to Sed.	24	18/0	25	Imt	79	90	103	123	11.8	10.5	6
Ath. to Sed.	24	12/0	25	Imt	75	90	100	(121)[c]	11.7	10.3	7[c]
Untrained	27	5/3	25	Imt	63	–	–	(98)[c]		(8.3)[c]	8
	32 ± 6[b]	85/7						140 ± 27		11.9 ± 2.3	
B											
Active	24	10/0	25	Imt	49	–	–	(77)[c]		(6.6)[c]	9
			25	Pft	57	–	–	(90)[c]		(7.6)[c]	9
Active	27	10/0	25	Pft	53	–	–	(83)[c]		(7.0)[c]	10
Ath. to Sed.	29	10/0	25	Imt	48	–	–	(75)[c]		(6.4)[c]	11
Untrained	26	6/4	25	Pft	45	–	–	(70)[c]		(6.0)[c]	12
Sedentary	23	7/7	37	Pft	–	26	57[j]	54		(4.6)[c]	13
Sedentary	25	5/0	30	Pft	–	57	–	(76)[c]		(6.7)[c]	14[c]
	26 ± 2[b]	46/11						75 ± 11		6.4 ± 1.0	
Overweight (BMI 25–30)											
A											
Active	46	6/2	22	Pft	–	79	–	(109)[c]		(10.5)[c]	3[c]
Act. to Sed.	72	10/1	25	Imt	68	83	104	(119)[c]	10.4	11.1	7
Untrained	24	9/0	25	Imt	65	–	–	(102)[c]		(9.8)[c]	4
Sedentary	41	7/0	22	Pft	74	44	81	(91)[c]		(8.8)[c]	2[c]
Sedentary	45	7/4	22	Pft	–	44	–	(61)[c]		(5.9)[c]	15[c]
Sedentary	47	8/0	22	Pft	–	50	–	(68)[c]		(6.6)[c]	3[c]
Sedentary	51	10/1	22	Pft	–	43	–	(58)[c]		(5.6)[c]	5[c]
Sedentary	52	8/1	22	Pft	–	46	–	(62)[c]		(6.1)[c]	16[c]
Sedentary	55	6/1	22	Pft	–	34	56	(57)[c]		(5.5)[c]	17[c]
Sedentary	58	8/0	37	Pft	–	43	76[k]	85		(8.2)[c]	18
	49 ± 12[b]	78/10						81 ± 22		7.8 ± 2.1	
B											
Sedentary	59	16/0	37	Pft	–	–	–	27		(2.6)[c]	19
Sedentary	75	7/7	37	Pft	–	22	45[k]	44		(4.2)[c]	13
Obese (BMI > 30)											
Sedentary	54	11	37	Pft	–	29	–	61		(5.2)[c]	20

Carolina Doerrier

Larsen Steen

Summary of the discussion about …

→ different types of media

How to get robust conclusion since other factors may influence results?

→ Proposal for two joint experiments

- 1. with experts in the field of *human skeletal muscle*
  - **In Denmark**
- 2. with experts in the field of *mouse skeletal muscle*
  - **In Innsbruck**

NB:

+ researchers from Inclusiveness Target Countries

Date: after April 2018 (2nd grant period)

Pablo Garcia-Roves

Summary of the discussion about …

→ MitoEAGLE WG2 pilot study

Aim: Implementation of a reference protocol as a tool for instrumental and technical quality control in muscle tissues

→ Collection of data (Permeabilized fibers (pfi) - soleus)

Mouse model

- Mouse strain: C57BL6 J - Age: 14-20 weeks
- Gender: male (N=4) and female (N=4), total N=8
- **SUIT protocol: 1PM;2D;2c;3G;4S;5U;6Ama**

→ Quick analysis of data

- **Variability among groups (Flux)**
- **Same *FRC***

→ How to improve the protocol to reduce the variability?

- **Additional labs**
- **Factors: Ww, mechanical permeabilisation (video, picture)**
- **Supply of chemicals to participating labs**

Summary of the discussion about …

→ cardiac muscle respirometry data in MitoEAGLE format

→ Search of the literature

- **Data according to different diseases**
- **Several studies in clinical journals:** *often lack of robust description of the methodology*
- **Probably not one paper to be written but several ones according to the condition and preparations**

→ Working team extended

Evolution Age Gender Lifestyle Environment

MITO

Mitochondrial fitness mapping - Quality management network

Thank you Zuzana for the great organisation

cost
EUROPEAN COOPERATION
IN SCIENCE & TECHNOLOGY