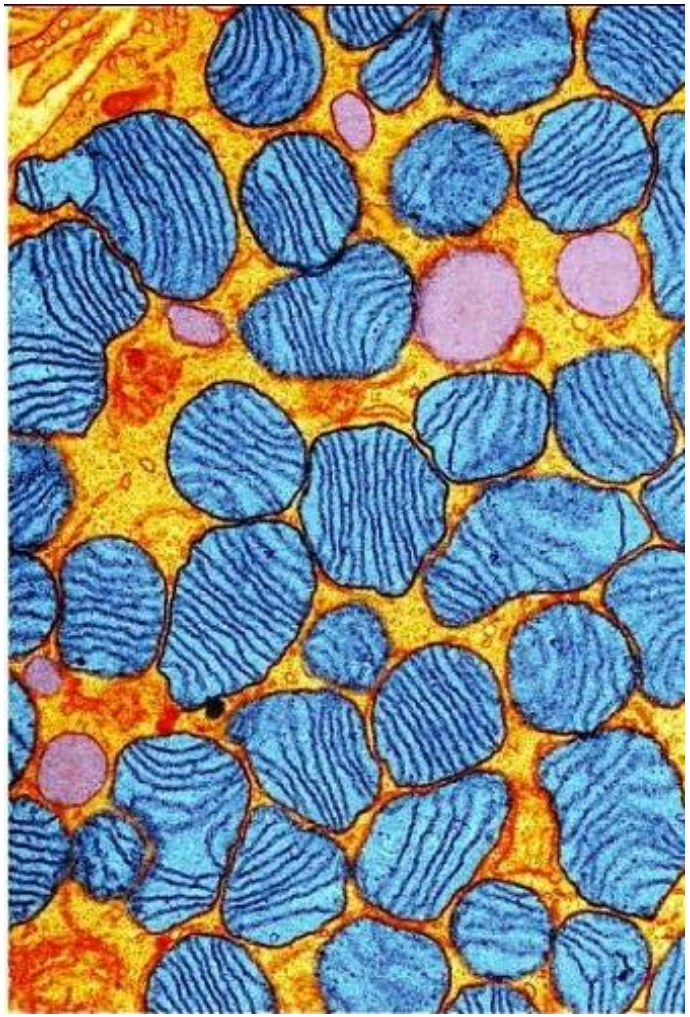
On terminology for mitochondrial respiration using different substrates



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RESPIRATORY ENZYMES IN OXIDATIVE PHOSPHORYLATION

III. THE STEADY STATE*

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Table I

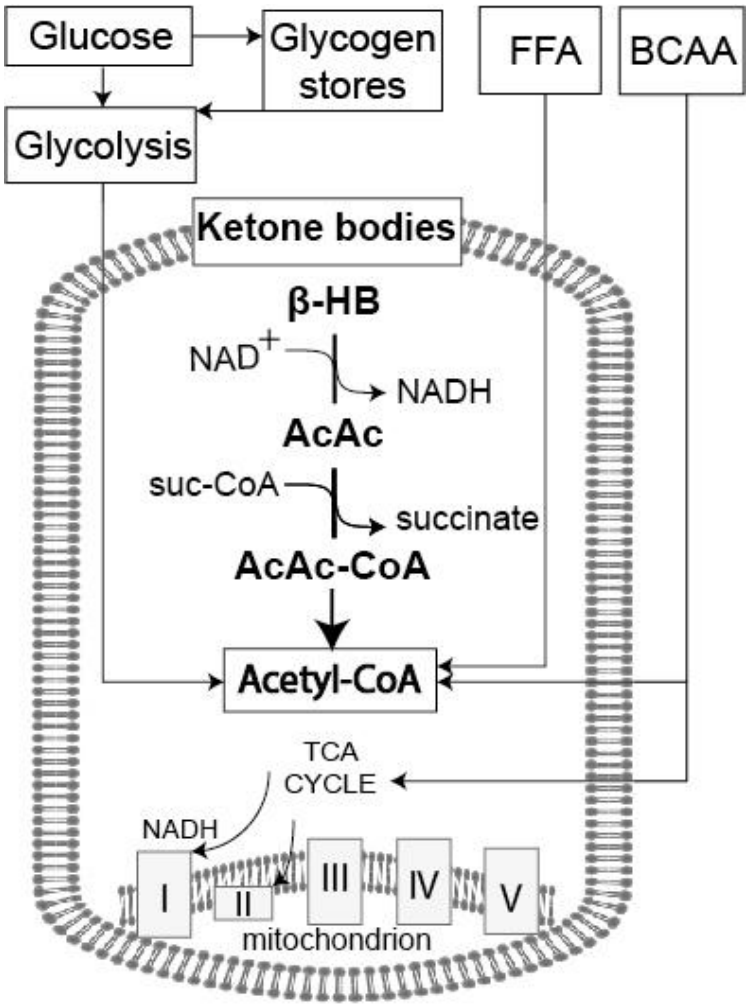
States of Respiratory Pigments in Mitochondria

	State 1	State 2	State 3	State 4	State 5
Characteristics	Aerobic	Aerobic	Aerobic	Aerobic	Anaerobic
ADP level	Low	High	High	Low	High
Substrate level	Low-endogenous	Approaching 0	"	High	"
Respiration rate	Slow	Slow	Fast	Slow	0
Rate-limiting component	Phosphate acceptor	Substrate	Respiratory chain	Phosphate acceptor	Oxygen

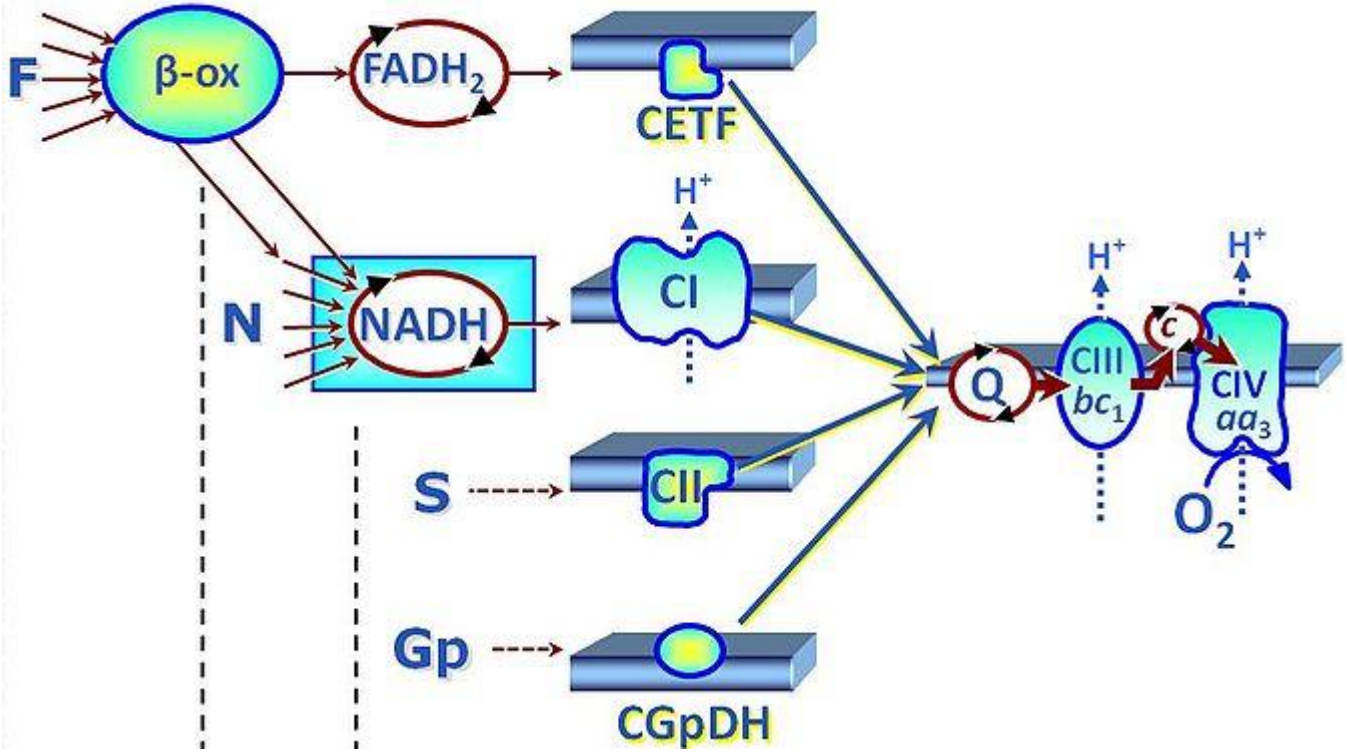
Different substrates

- Chance&Williams 1955: ‘Succinate gives greater reductions [in O_2 concentration] in state 3 and 4 than β-hydroxybutyate’

- Evolution of terminology
  - state 3u
  - state 4o

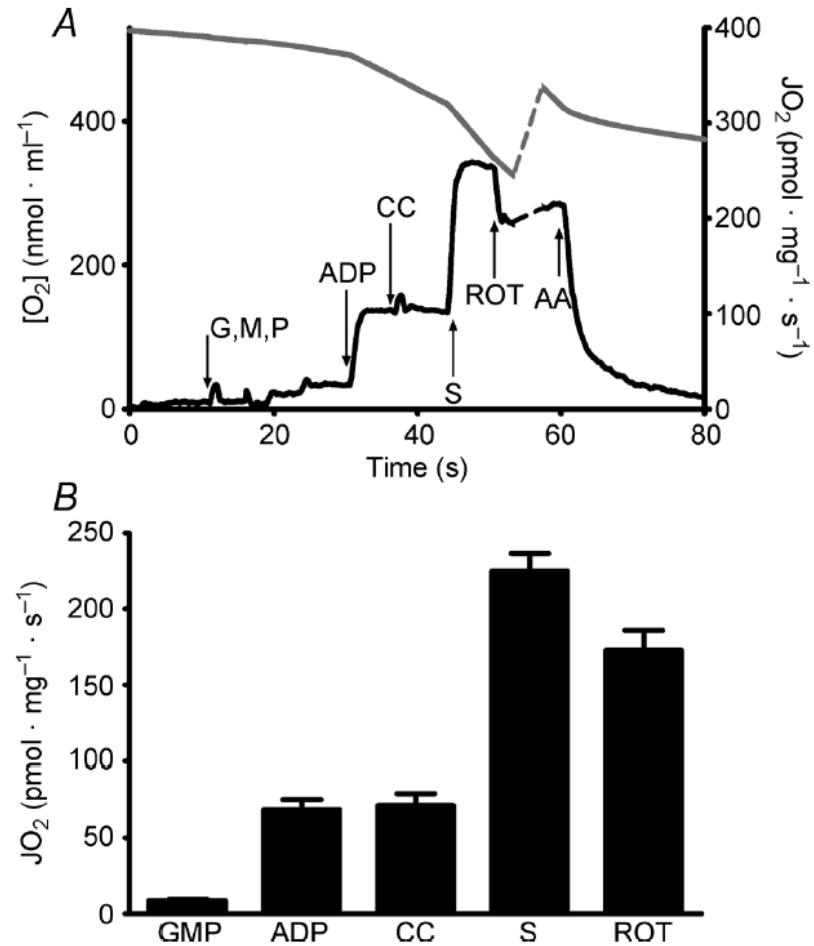


Convergent electron input



Convergent electron input: a practical respiration example

- Complex I substrates:
  - Glutamate
  - Malate
  - Pyruvate
- Complex II substrate:
  - Succinate (+Rotenone)
- FAO substrates:
  - Octanoylcarnitine (medium)
  - Palmitoylcarnitine (long)



Rat cardiac permeabilized fibers

Wüst et al., 2015 J Physiol 593:1829-

New ‘states’

- Complex I-linked substrate state
- Complex II-linked substrate state
- Complex I&II-linked substrate state
  - Or: complex I(+II) coupled respiration?

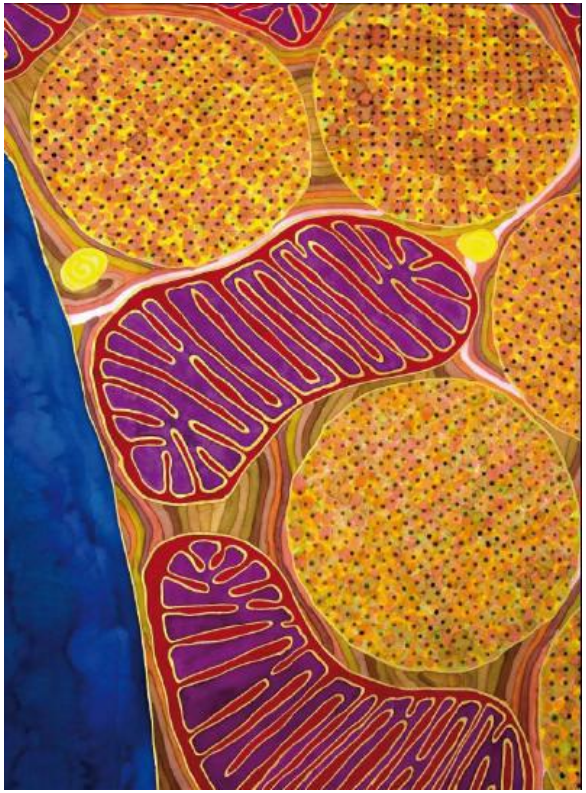
- FAO-linked substrate state?
  - BUT: malate and complex I needed!
- Ketone-linked substrate state?

- **Flux control ratios** (*FCR*), are ratios of oxygen flux in different respiratory control states, normalized for maximum flux in a common reference state
  - Or: normalized complex I/II/FAO respiration?
  - And normalize to what (OxPhos or ETS)?

http://wiki.oroboros.at/index.php/MitoPedia:_Respiratory_states

Substrate dependent differences in mitochondrial respiration: a practical example

- Qualitative *vs.* quantitative differences in mitochondrial respiration
- Complex I vs II function
- FAO vs glucose metabolism



Cardiac hypertrophy (CH) and heart failure (HF)

Single injection of monocrotaline to induce pulmonary arterial hypertension

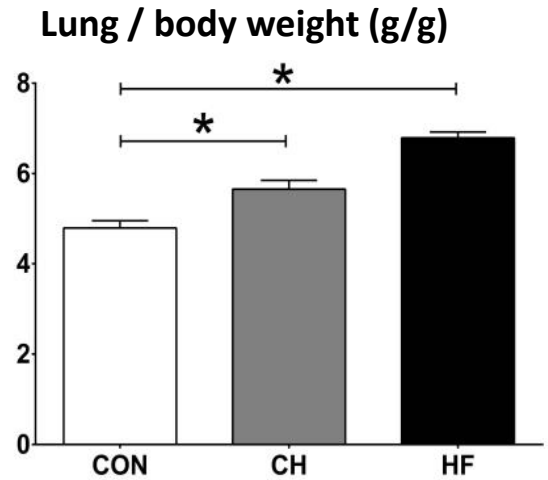
After 23 ±1 days:

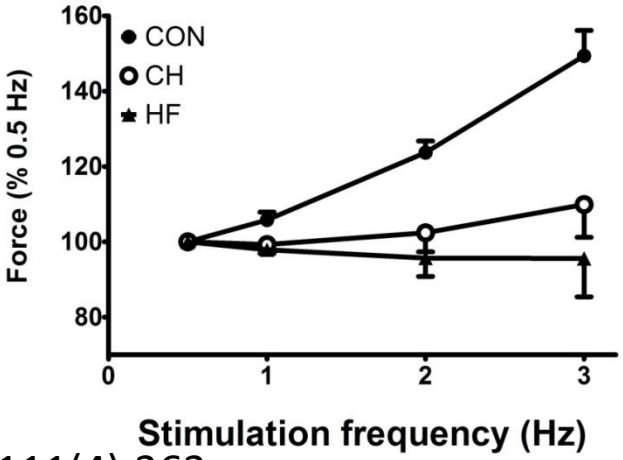
CH (40 mg/kg, n=8) and

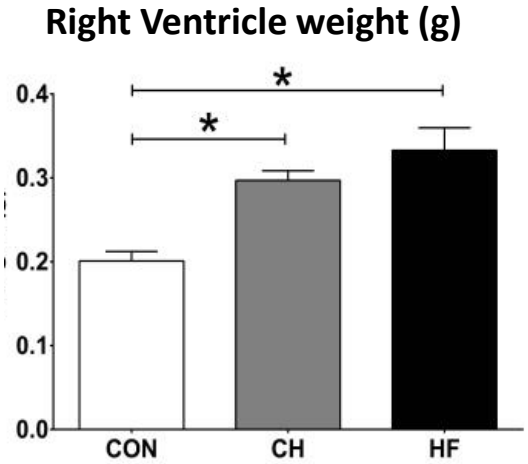
HF (60 mg/kg, n=12)

Are compared with

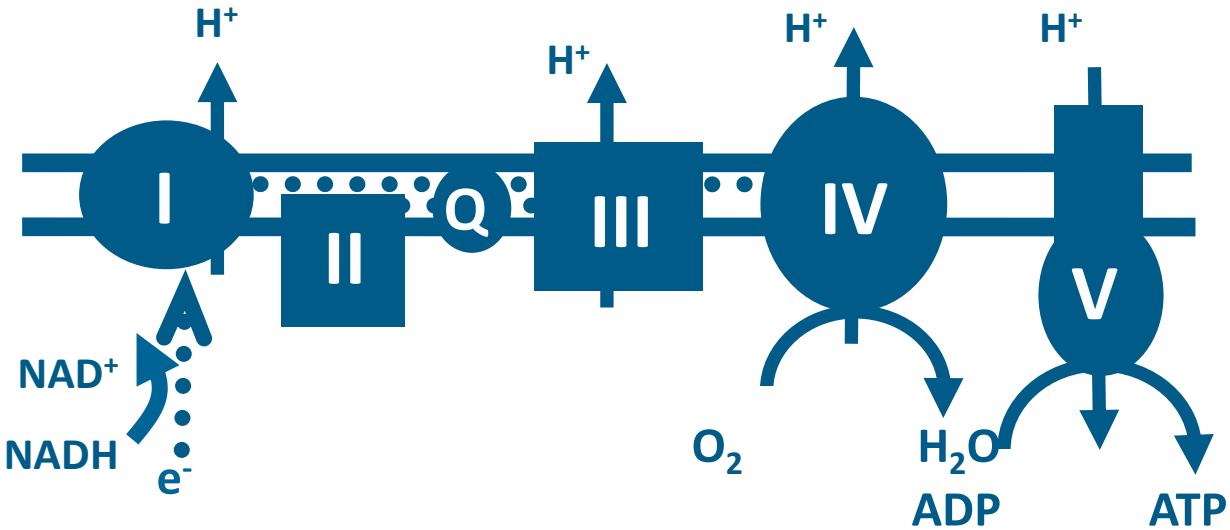
CON (saline, n=10)

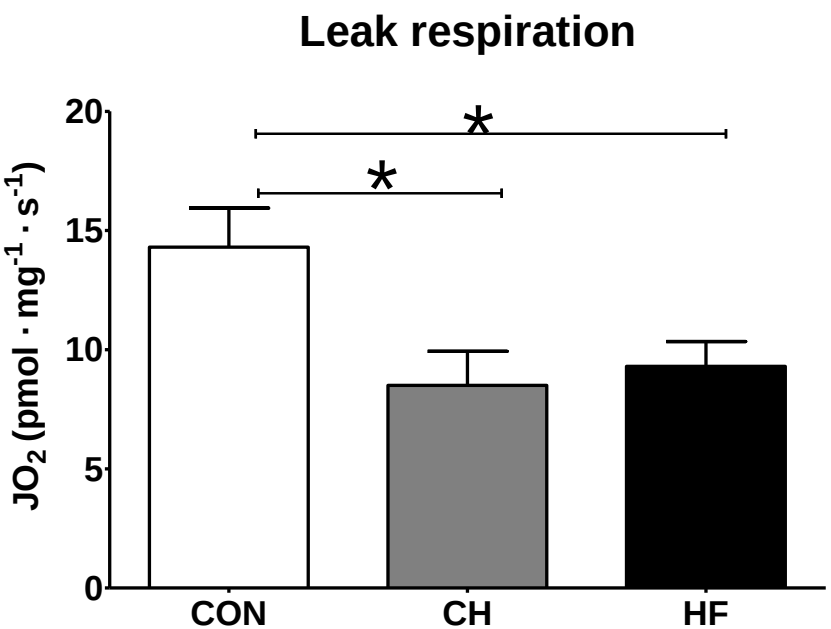


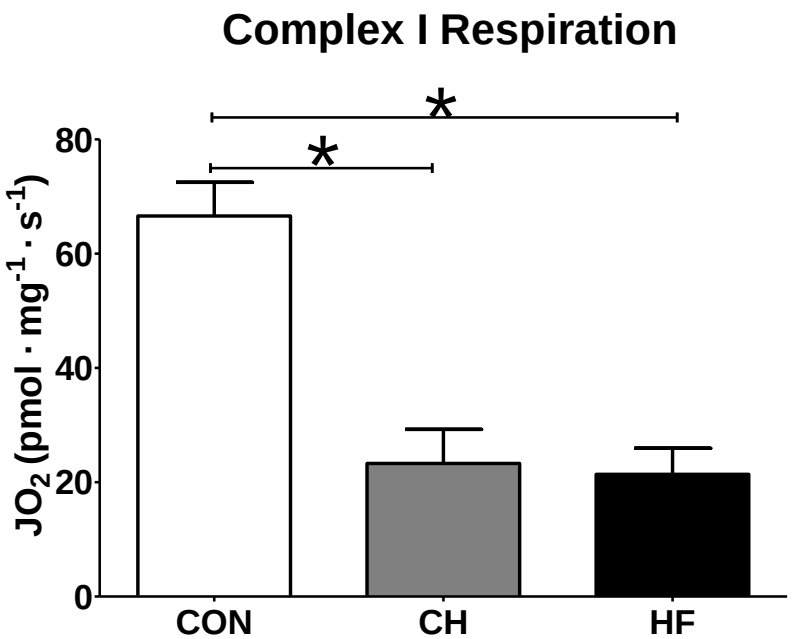




Wüst et al., 2016 Cardiovasc Res 111(4):362

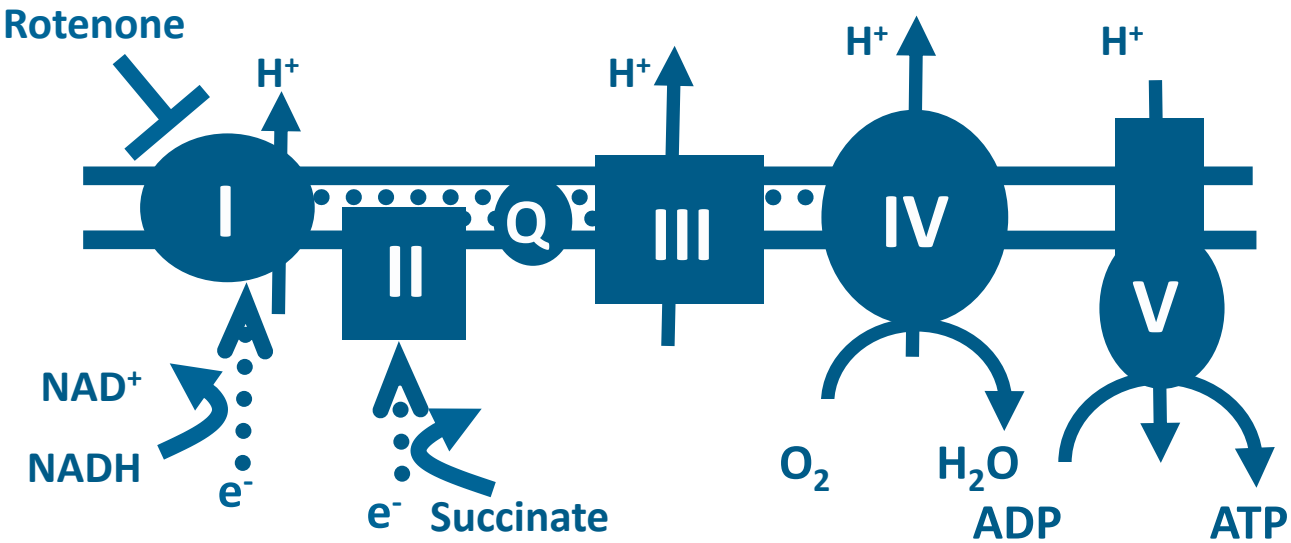


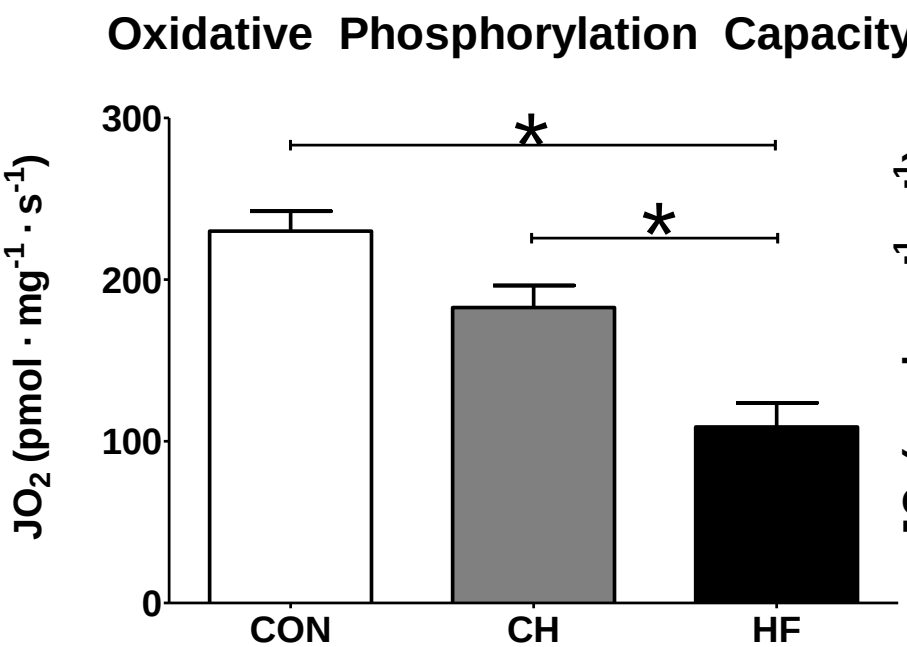


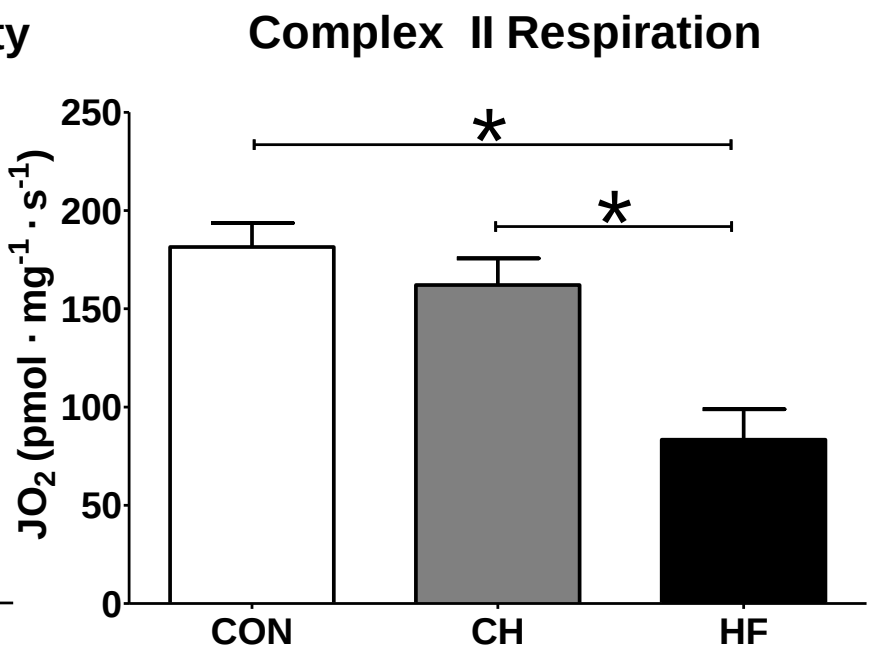


Wüst et al., 2016 Cardiovasc Res 111(4):362

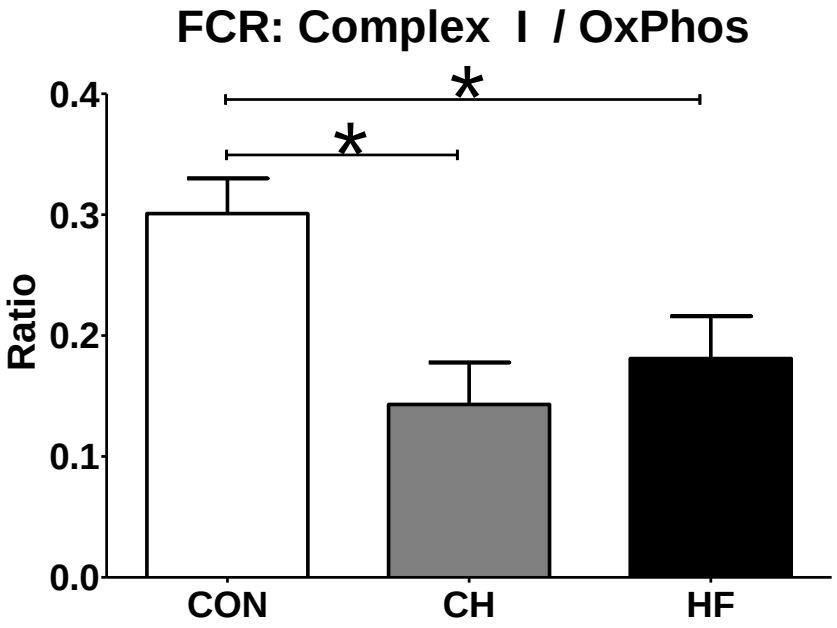
*: $p<0.05$ between conditions

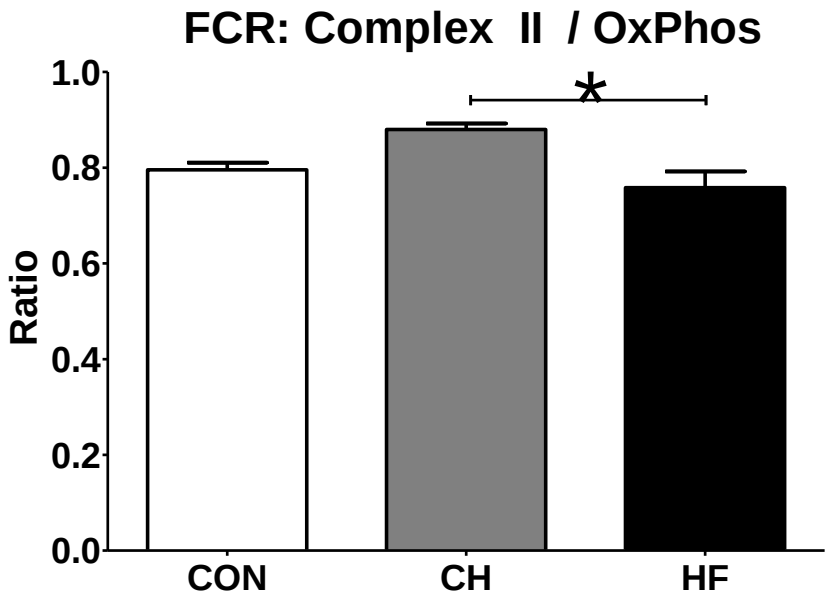


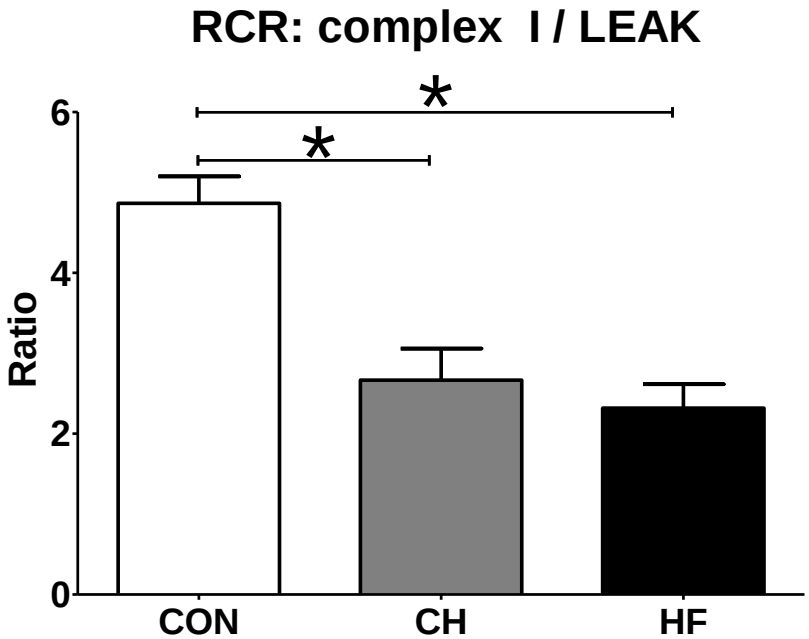


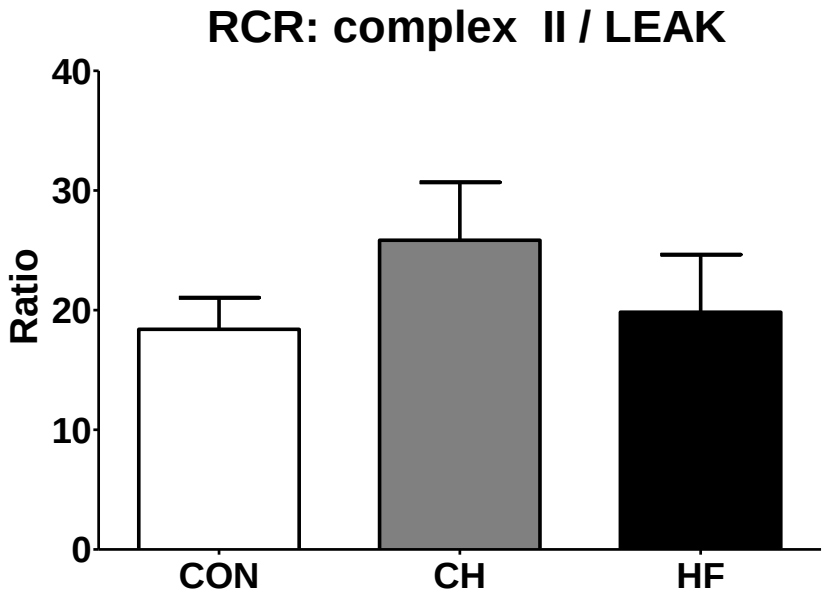


*: $p<0.05$ between conditions


FCR: Complex I / OxPhos
Ratio
0.4
0.3
0.2
0.1
0.0
*
*
CON
CH
HF


FCR: Complex II / OxPhos
Ratio
1.0
0.8
0.6
0.4
0.2
0.0
*
CON
CH
HF


RCR: complex I / LEAK
Ratio
6
4
2
0
*
*
CON
CH
HF


RCR: complex II / LEAK
Ratio
40
30
20
10
0
CON
CH
HF

Substrate terminology

- Flux control ratio *vs.* normalized respiration/flux?
  - Confusing with flux control coefficient?

    Changes in overall flux to changes in activity of one enzyme/transporter (Nicholls & Ferguson, Bioenergetics 4)
- Leak respiration?
  - Absolute values –> substrate dependent?
  - Leak/OxPhos = complex I substrates / complex I+II substrates.
- Complex I substrate-linked respiration *vs.* ETS minus Complex II?

Global terminology

- Oroboros *vs.* Seahorse users
  - Routine *vs.* Basal respiration
  - Leak respiration:
    - With substrates, without ADP?
    - With oligomycin?
  - Maximal respiration *vs.* Uncoupled ETS capacity
  - Non-mitochondrial respiration *vs.* Residual oxygen consumption
  - Spare capacity *vs.* Excess E-R capacity

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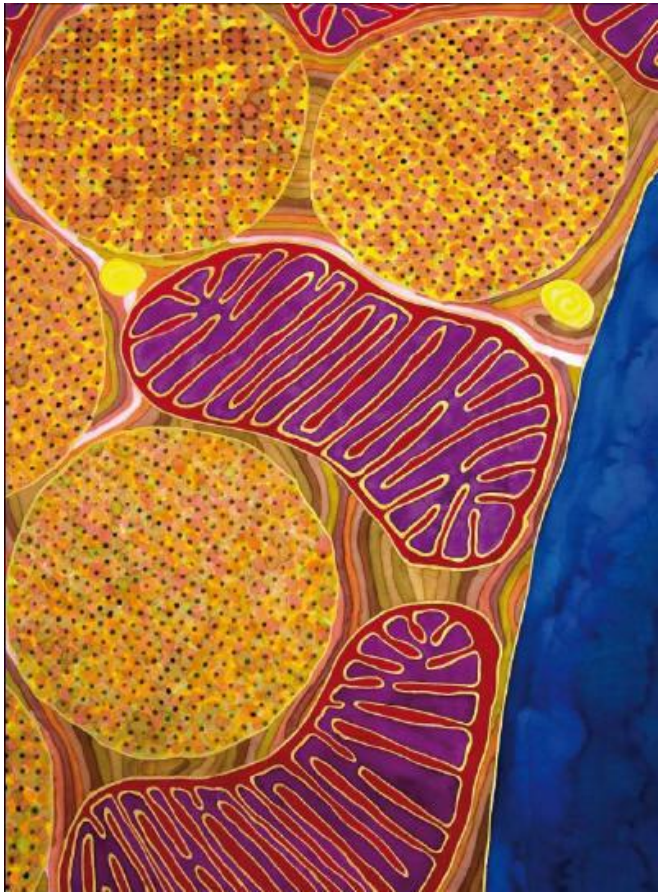

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