

Physiological basis of exercise performance



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Prof. Arno Schmidt-Trucksäss, MD, MA, FESC
Arno.Schmidt-Trucksass@Unibas.ch

Department of Sport, Exercise and Health,
Division Sports and Exercise Medicine,
University of Basel, Switzerland



Disclosures

Nothing to declare regarding the presentation.

The physiological basis of exercise performance

Brian J. Whipp (1937–2011)

A lecture with this title was given by Brian Whipp at the 2008 Practicum in Oporto.

PhD Stanford 1967, under Karlman Wasserman (1927–2020).

Together they built the framework this course still teaches: the coupling of internal (cellular) to external (pulmonary) respiration.

Whipp BJ, Wasserman K. Efficiency of muscular work. J Appl Physiol 1969;26:644–648

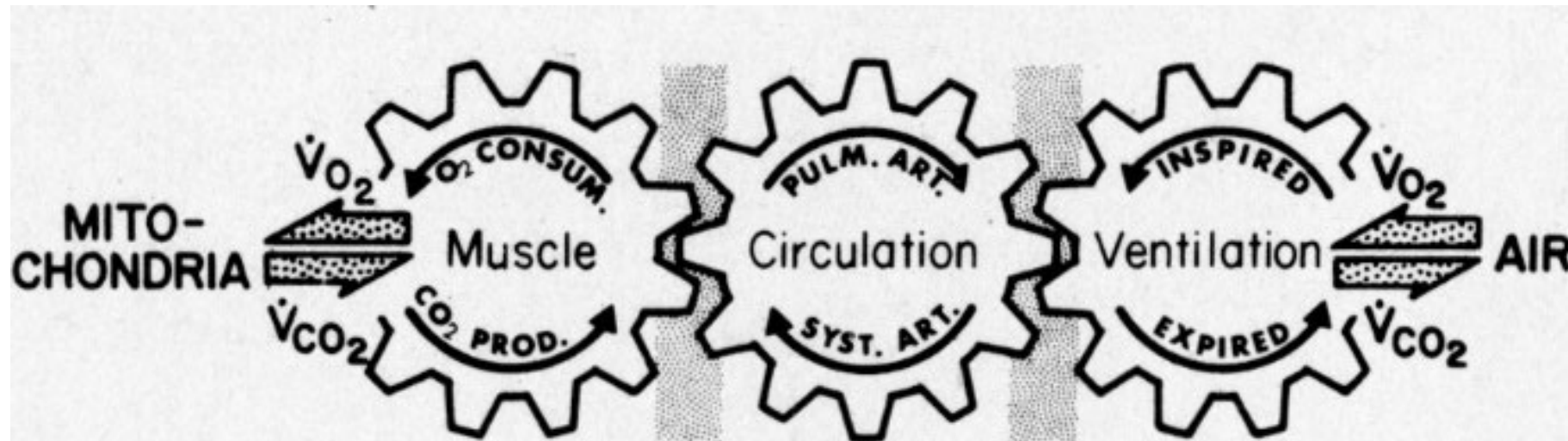
Whipp BJ, Ward SA, Lamarra N. Parameters of ventilatory and gas exchange dynamics during exercise. J Appl Physiol 1982;52:1506–1513

Beaver WL, Wasserman K, Whipp BJ. A new method for detecting the anaerobic threshold by gas exchange. J Appl Physiol 1986;60:2020–2027

His closest collaborator wrote his obituary, and takes the next lecture.

09:40 – Susan A. Ward: The Anaerobic Threshold: what it is and how to find it

Schematic Representation of the Essential Elements in Gas Exchange between the Cell Mitochondria and External Environment.



During exercise, the quantity of O_2 consumed ($\dot{V}O_2$) and CO_2 produced ($\dot{V}CO_2$) is determined by the amount of muscle activity. The interconnecting gears connote the coupling of the physiologic responses of blood flow and ventilation to metabolism.

Connecting muscle with lung function

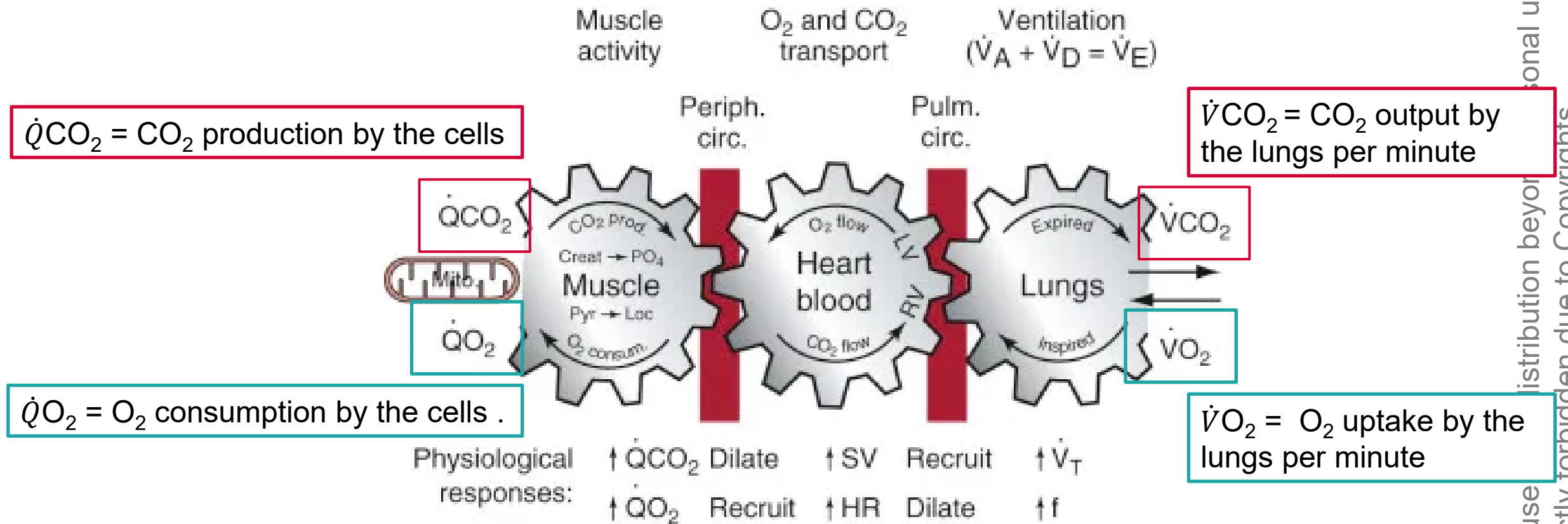
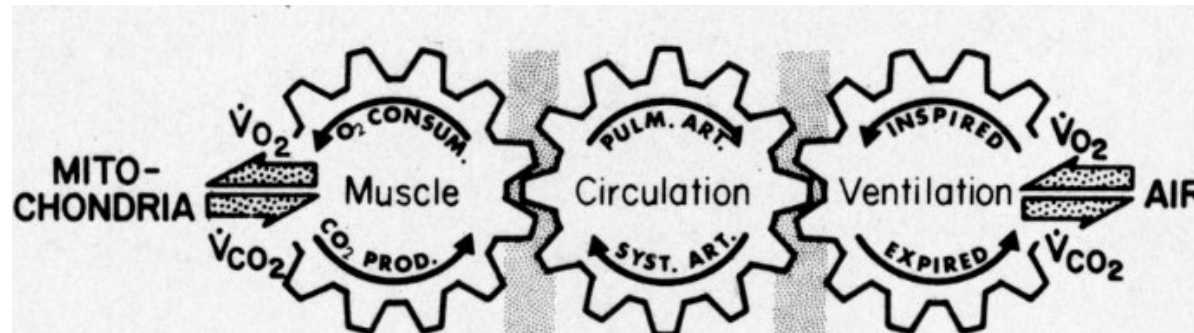


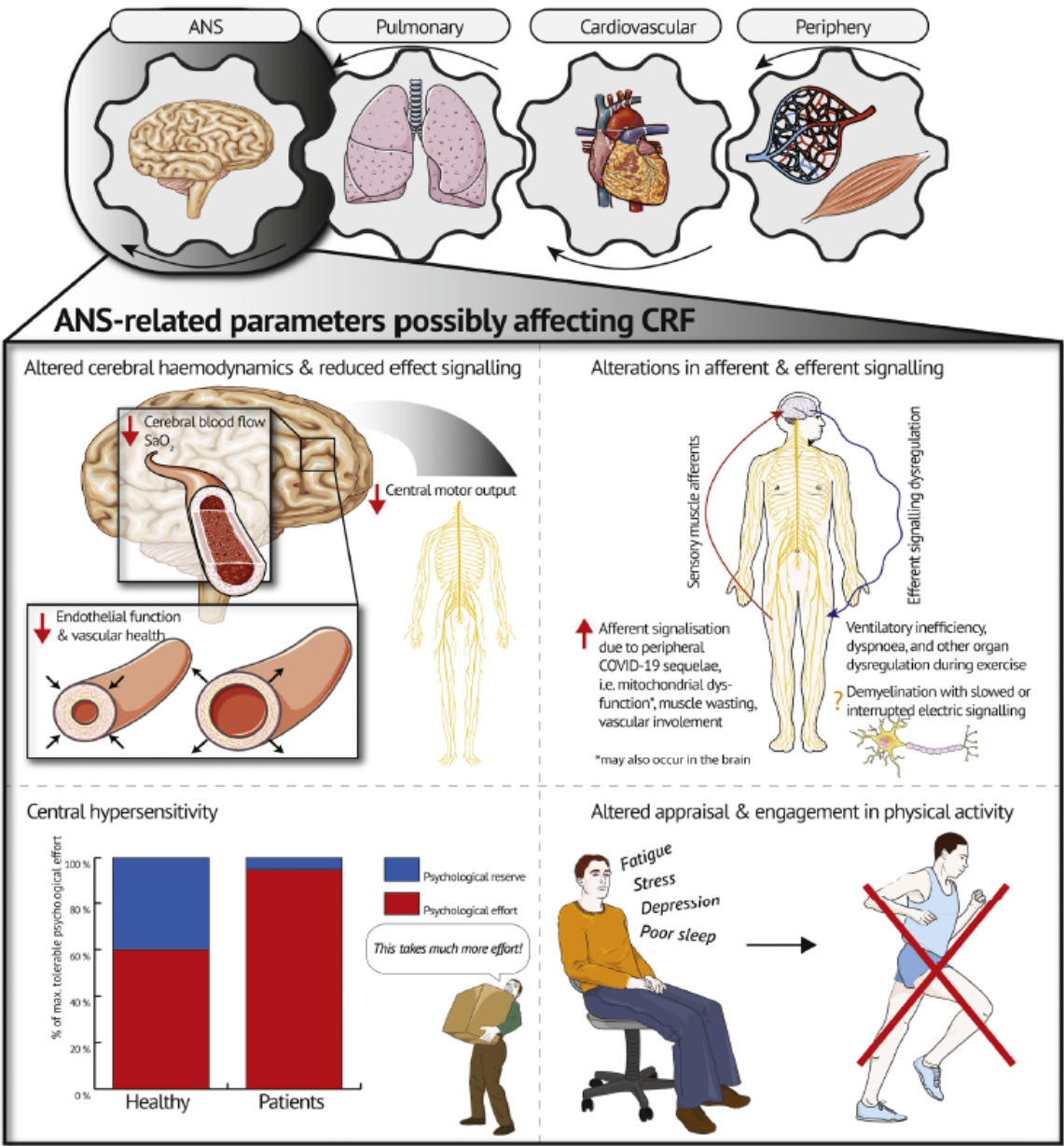
FIGURE 1. Gas transport mechanisms coupling cellular (internal) respiration to pulmonary (external) respiration. Circ = circulation; CO₂ = carbon dioxide; Consum = consumption; Creat = creatine; Lac = lactate; HR = heart rate; Mito = mitochondria; PO₄ = phosphate; O₂ = oxygen; Periph = peripheral; Prod = production; Pulm = pulmonary; Pyr = pyruvate; $\dot{Q}CO_2$ = carbon dioxide production; $\dot{Q}O_2$ = oxygen utilization; SV = stroke volume; $\dot{V}_A$ = minute alveolar ventilation; $\dot{V}_D$ = minute dead space ventilation; $\dot{V}_E$ = minute ventilation; $\dot{V}_T$ = tidal volume; $\dot{V}CO_2$ = carbon dioxide output; $\dot{V}O_2$ = oxygen uptake.

Efficient gas exchange between the cells and the environment requires ...

- Appropriate intracellular structure, energy substrate and enzyme concentrations
- A heart capable of pumping the quantity of oxygenated blood needed to sustain the energy transformations
- An effective system of blood vessels that can selectively distribute blood flow to match local tissue gas exchange requirements
- Blood with normal haemoglobin of adequate concentration
- An effective pulmonary circulation through which the regional blood flow is matched to its ventilation
- Normal lung mechanics and chest bellows
- Ventilatory control mechanisms capable of regulating arterial blood gas tensions and hydrogen ion concentration



Cardiorespiratory fitness is a vital sign

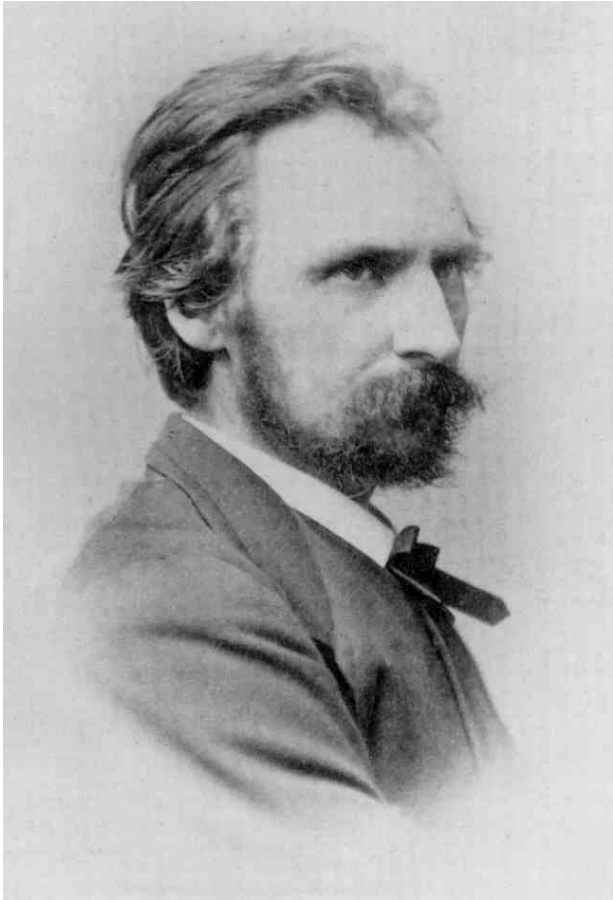


$\dot{V}O_2\text{max}$ and $\dot{V}O_2\text{peak}$ – not the same thing

- $\dot{V}O_2\text{max}$ – the highest O_2 uptake attainable; classically requires a plateau in $\dot{V}O_2$ despite a further increase in work rate
- $\dot{V}O_2\text{peak}$ – the highest $\dot{V}O_2$ observed in a test in which no plateau was demonstrated
- A plateau is reached in only a minority of clinical incremental tests
- Secondary criteria (RER, heart rate, RPE, blood lactate) support a maximal effort – they do not establish one
- Values depend on modality and protocol: cycle ergometry gives roughly 5–11 % lower values than treadmill

State which term you mean, and by which criterion.

Adolf Fick (1829–1901), Physiologist A Heritage for Anesthesiology and Critical Care Medicine



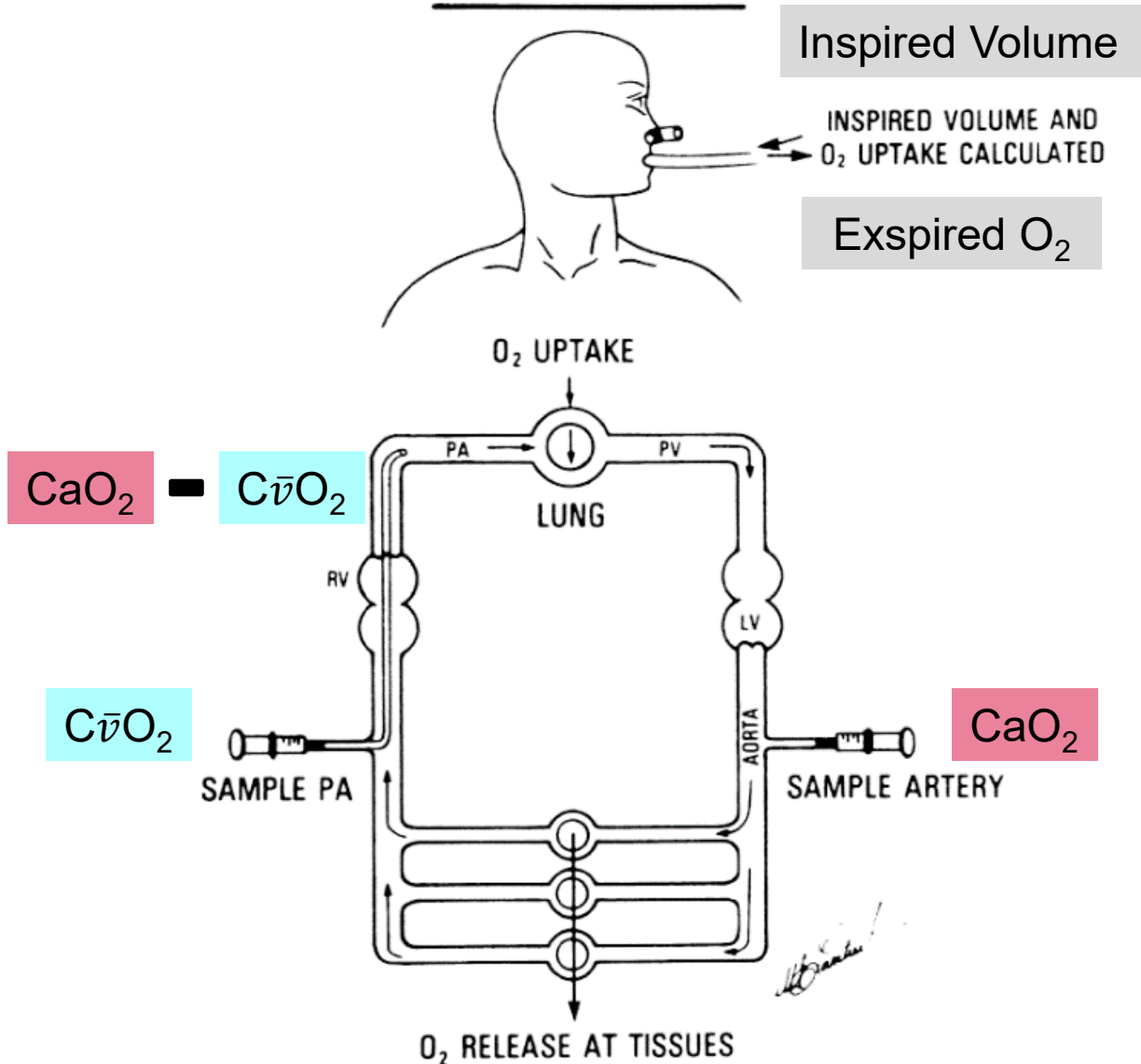
Adolf Fick in the early Zurich years.



Adolf Fick in the late Würzburg years.

Diagram of the Fick method for measurement of cardiac output.

THE FICK METHOD



$$\dot{V}O_2 = \dot{Q}(CaO_2 - C\bar{v}O_2)$$

The catheter is positioned in the pulmonary artery (PA), and blood samples are withdrawn simultaneously from a peripheral artery and the PA as room air is inspired.

The volume of expired air is measured, the inspired volume is calculated, and the difference between the oxygen content of inspired air and that measured in the expired air can then be used to calculate oxygen uptake at the lungs per minute.

From West JB: Best and Taylor's Physiological Basis of Medical Practice. 12th edition. Baltimore, Williams and Wilkins, 1990, Figure 2, 140 Section 2, Chapter 13, p 245. in: Vandam LD, Fox JA Anesthesiology. 1998;88(2):514-518.

Fick Equation

$$\dot{V}O_2 = \dot{Q}(CaO_2 - C\bar{v}O_2)$$

Heart rate * stroke volume

$$\dot{V}O_2 = HR * SV (CaO_2 - C\bar{v}O_2)$$

$$\dot{V}O_2 / (CaO_2 - C\bar{v}O_2) = HR * SV = \dot{Q} = \text{Cardiac output}$$

Fick Equation

$$\dot{V}O_2 = \dot{Q}(CaO_2 - C\bar{v}O_2)$$

Heart rate * stroke volume

$$\dot{V}O_2 = HR * SV (CaO_2 - C\bar{v}O_2)$$

Oxygen pulse

$$\dot{V}O_2 / HR = SV (CaO_2 - C\bar{v}O_2)$$

Stroke volume

$$SV = \dot{V}O_2 / HR / (CaO_2 - C\bar{v}O_2)$$
$$SV = O_2 - \text{pulse} / (CaO_2 - C\bar{v}O_2)$$

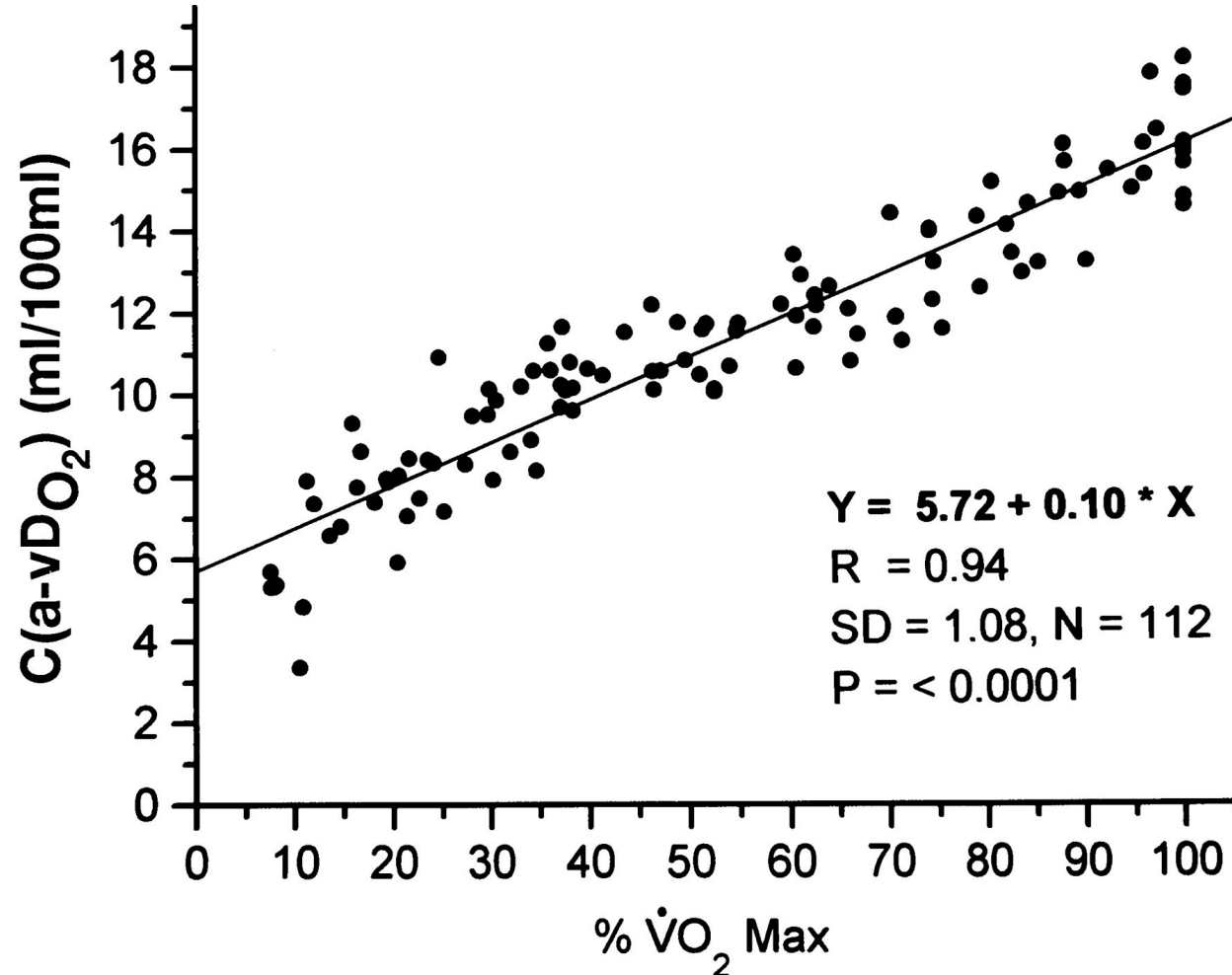
Fick Equation

$$\dot{V}O_2 = \dot{Q}(CaO_2 - C\bar{v}O_2)$$

$$\dot{V}O_{2\max} = \dot{Q}_{\max}(CaO_{2\max} - C\bar{v}O_{2\min})$$

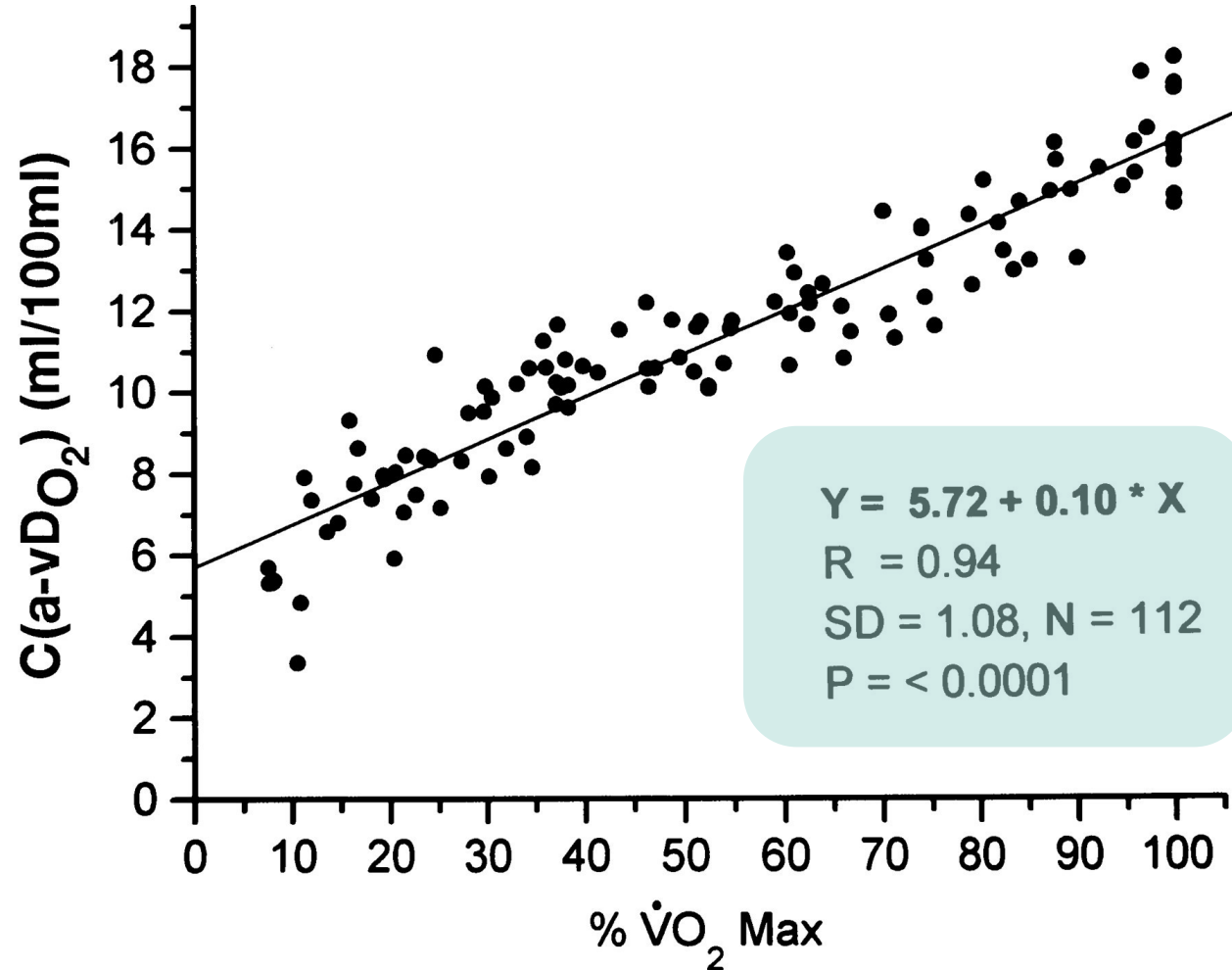
$$\dot{V}O_{2\max} = HR_{\max} * SV_{\max}(CaO_{2\max} - C\bar{v}O_{2\min})$$

Arteriovenous O₂ content difference [C(a-vDO₂)] as a function of % $\dot{V}O_2$ max.



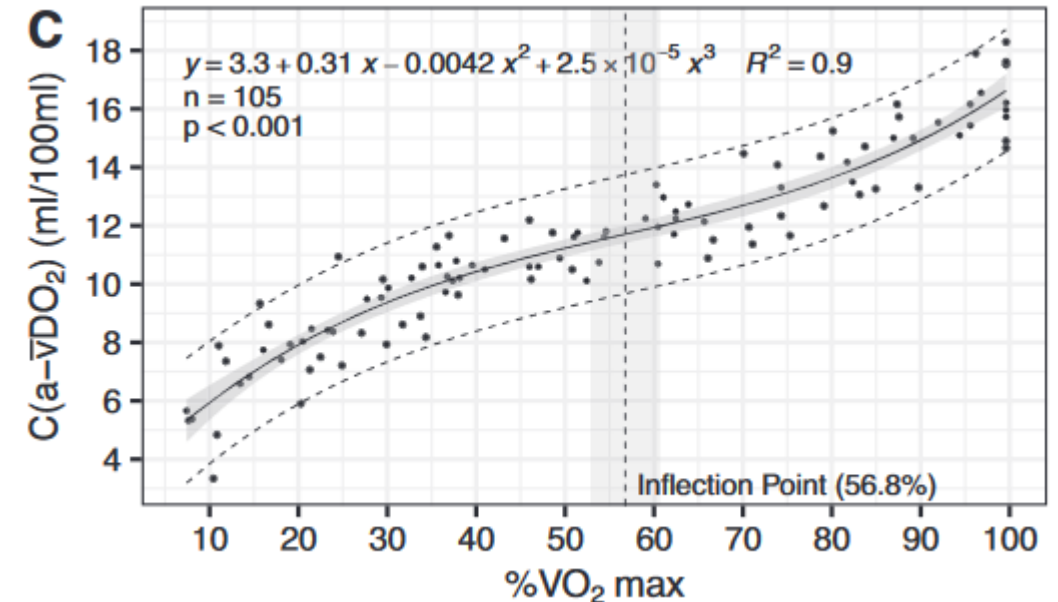
Data were determined from systemic arterial and pulmonary arterial blood that was simultaneously sampled each minute during 10 progressively increasing work rate exercise tests in 5 subjects.

Arteriovenous O₂ content difference [C(a-vDO₂)] as a function of % $\dot{V}O_2$ max.



Stringer WW, et al. J Appl Physiol (1985). 1997. 908-912

Still small miracles happen !

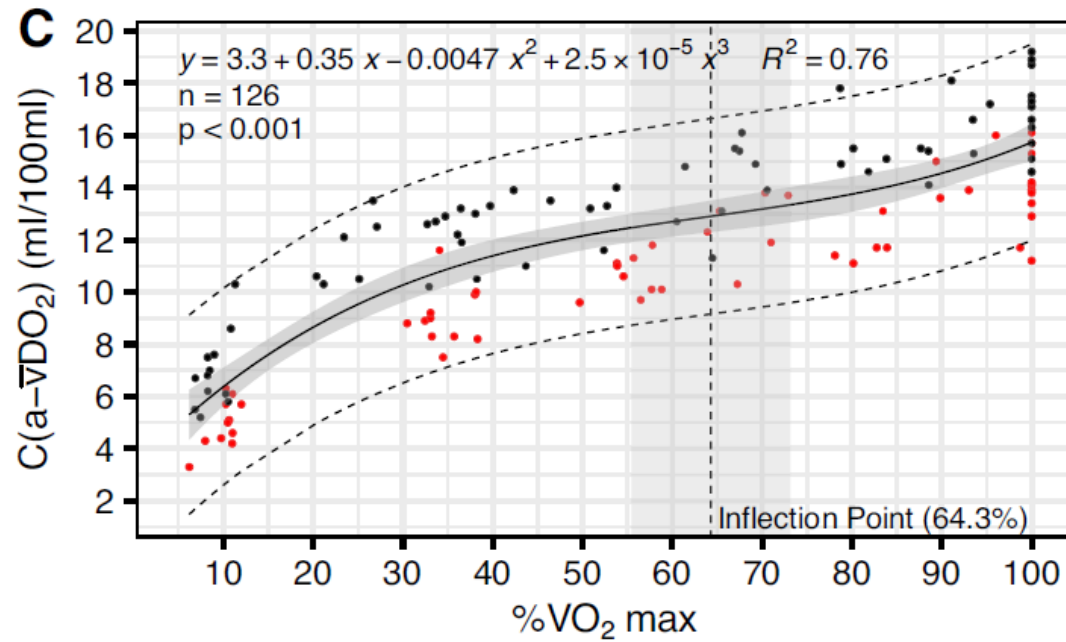


Burchert H Am J Physiol Heart Circ Physiol. 2023 Oct 1;325(4)-H656-H664

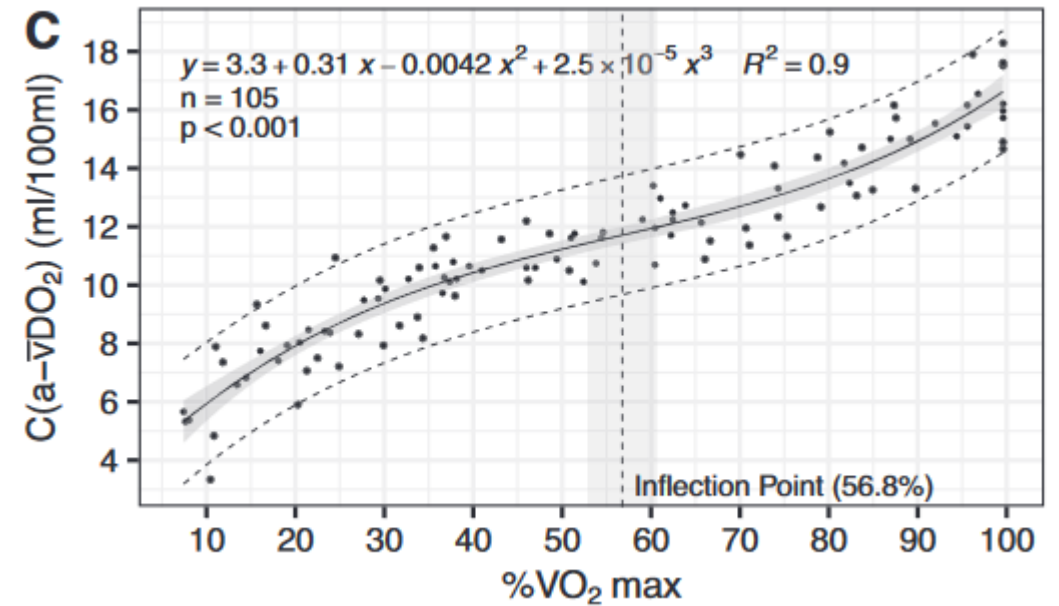
Data were determined from systemic arterial and pulmonary arterial blood that was simultaneously sampled each minute during 10 progressively increasing work rate exercise tests in 5 subjects.

Polynomial function grade 3

Stringer

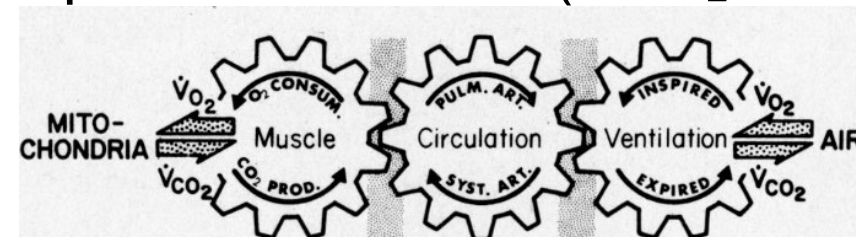


Astrand



$\dot{V}O_2\text{max}$: central and peripheral determinants

- **Central – O_2 delivery:**
 - heart rate, stroke volume, haemoglobin concentration, arterial O_2 saturation
- **Peripheral – O_2 extraction:**
 - capillary density and transit time, mitochondrial volume density, diffusive conductance
- In healthy people $\dot{V}O_2\text{max}$ is limited predominantly by convective O_2 delivery, not by mitochondrial capacity
- O_2 pulse ($\dot{V}O_2/\text{HR}$) is the gas-exchange expression of $SV \times (CaO_2 - CvO_2)$



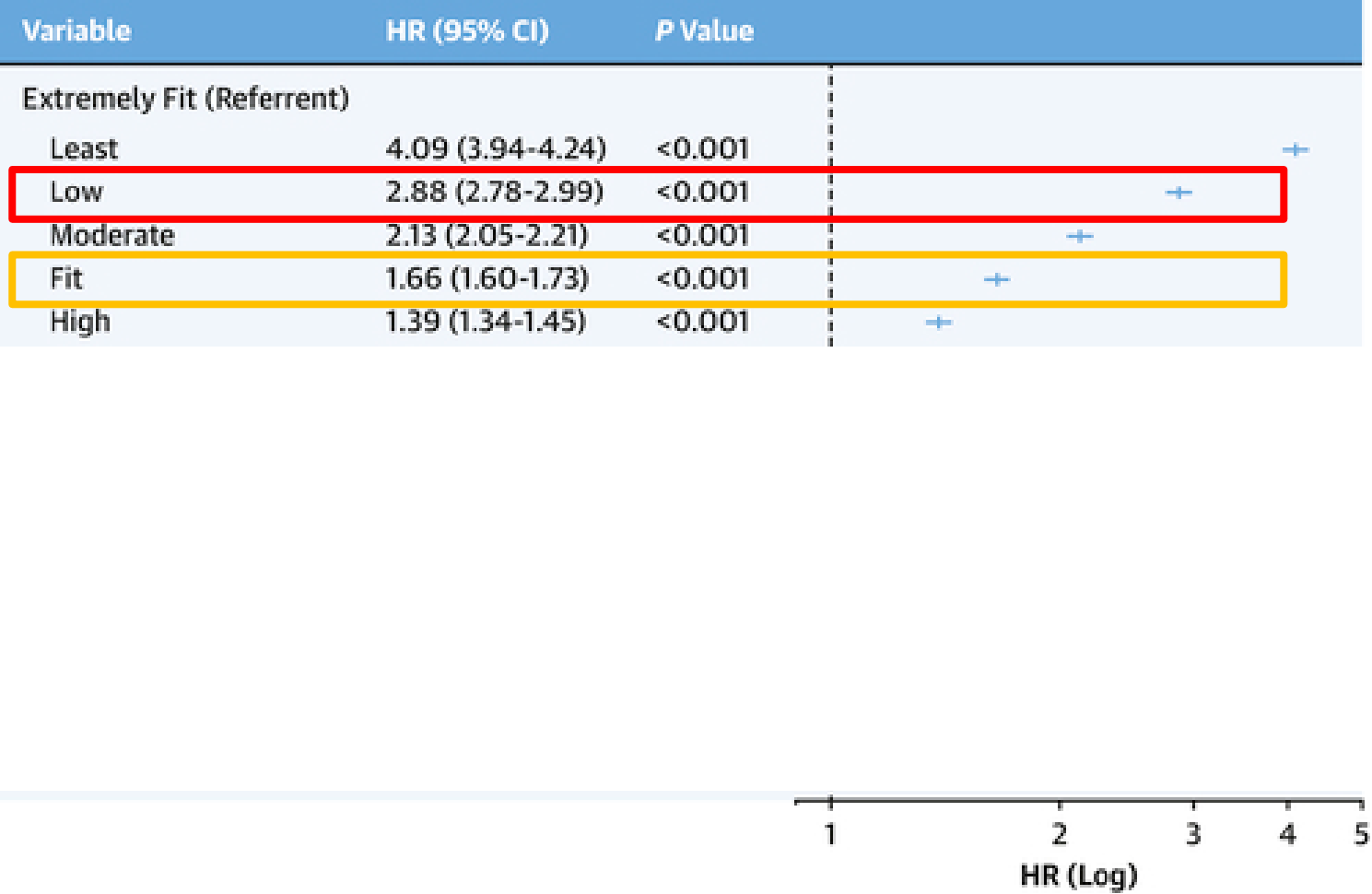
$\dot{V}O_{2\text{max}}$ /peak is a vital sign

Mortality risk of cardiorespiratory fitness compared to other diseases or risk factors

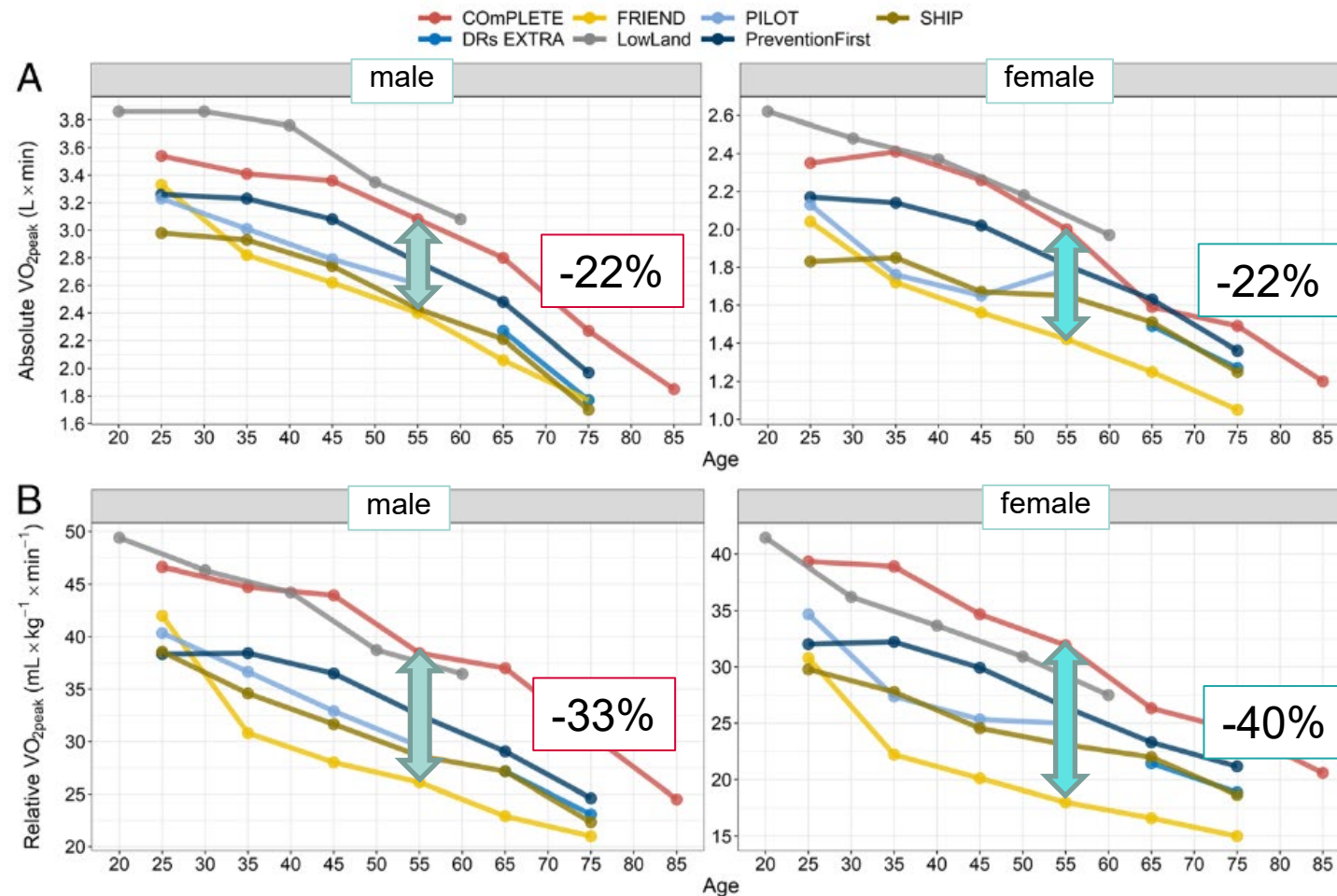
cardiorespiratory
fitness

750302 men and women
10.2 years follow-up

No increased risk for the
fittest
No risk factor or existing
disease is as dangerous
as low fitness

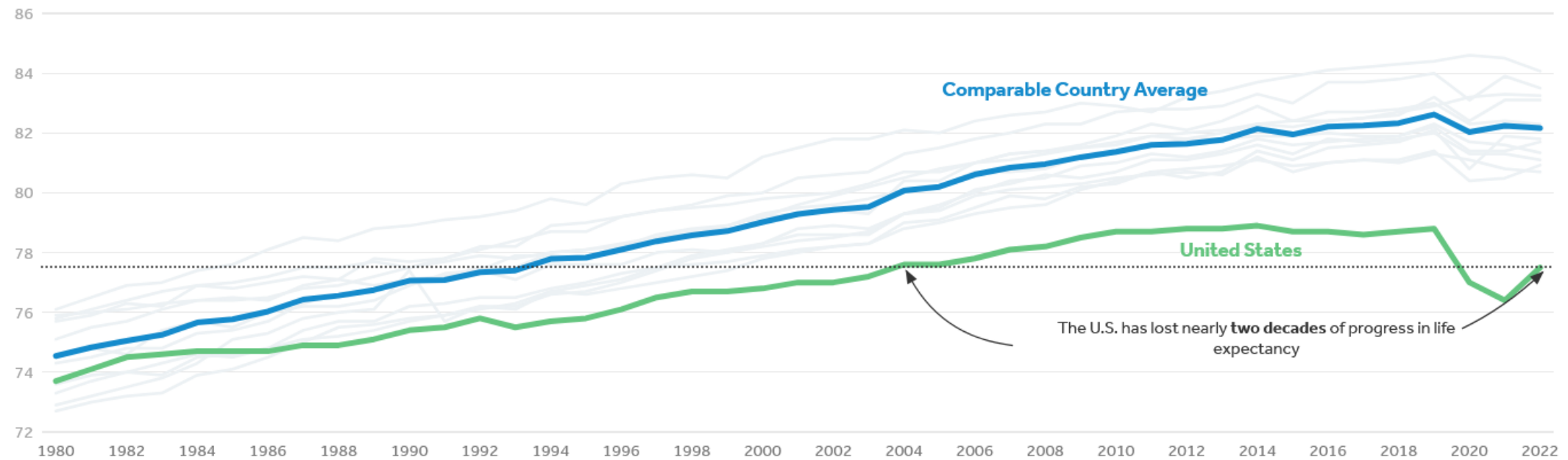


Relative and absolute $\dot{V}O_{2peak}$ reference data sets of all major studies performing cycle ergometer tests



Life expectancy at birth

Life expectancy at birth, in years, 1980-2022



Notes: Comparable countries include Australia, Austria, Belgium, Canada, France, Germany, Japan, the Netherlands, Sweden, Switzerland, and the U.K. See [Methods section](#) of "How does U.S. life expectancy compare to other countries?"

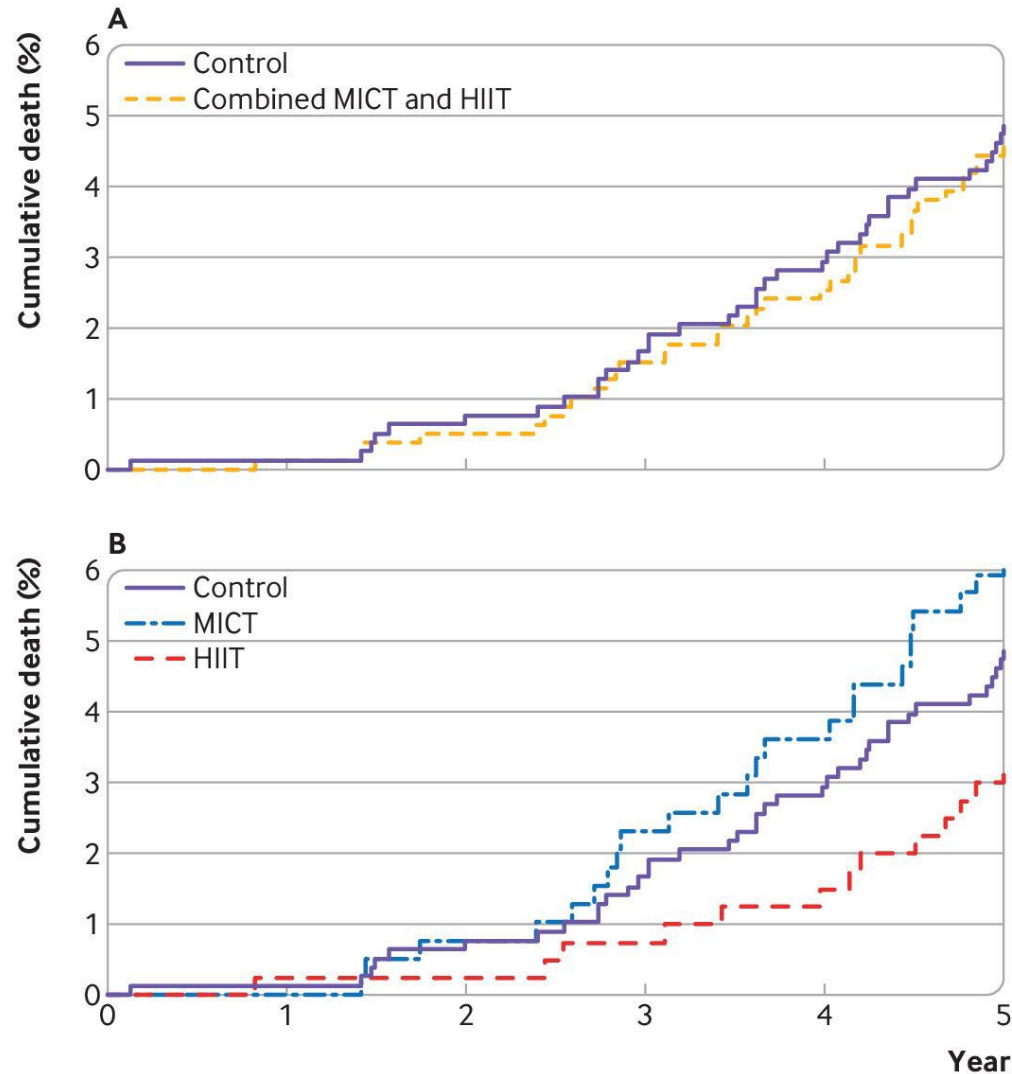
Source: KFF analysis of [CDC](#), [OECD](#), [Australian Bureau of Statistics](#), [Japanese Ministry of Health, Labour, and Welfare](#), [Statistics Canada](#), and [U.K. Office for National Statistics](#) data • [Get the data](#) • [PNG](#)

Peterson-KFF
Health System Tracker

Generation 100 – the trial website



Effect of exercise training for five years on all cause mortality in older adults-the Generation 100 study



Stensvold D et al BMJ. 2020 Oct 7;371:m3485



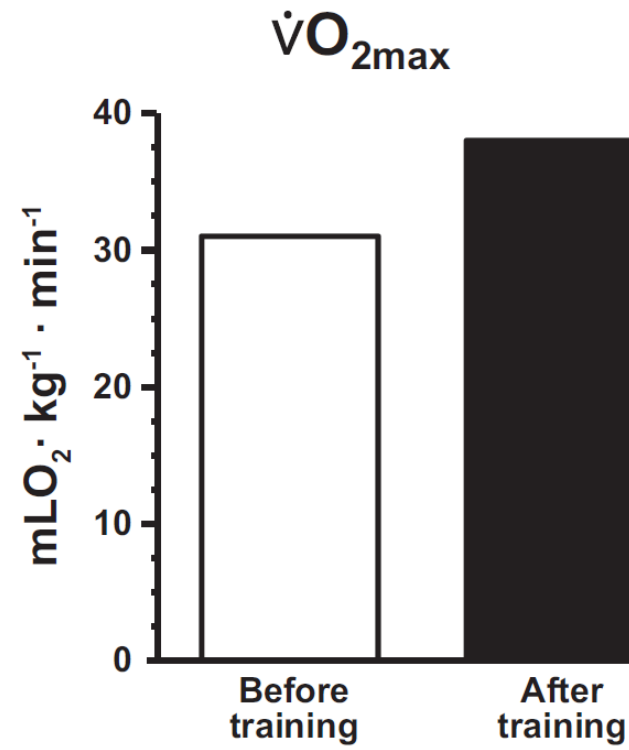
Participants 1567 older adults (70-77 years).

Design Randomised controlled trial.

Setting General population of older adults in Trondheim, Norway.

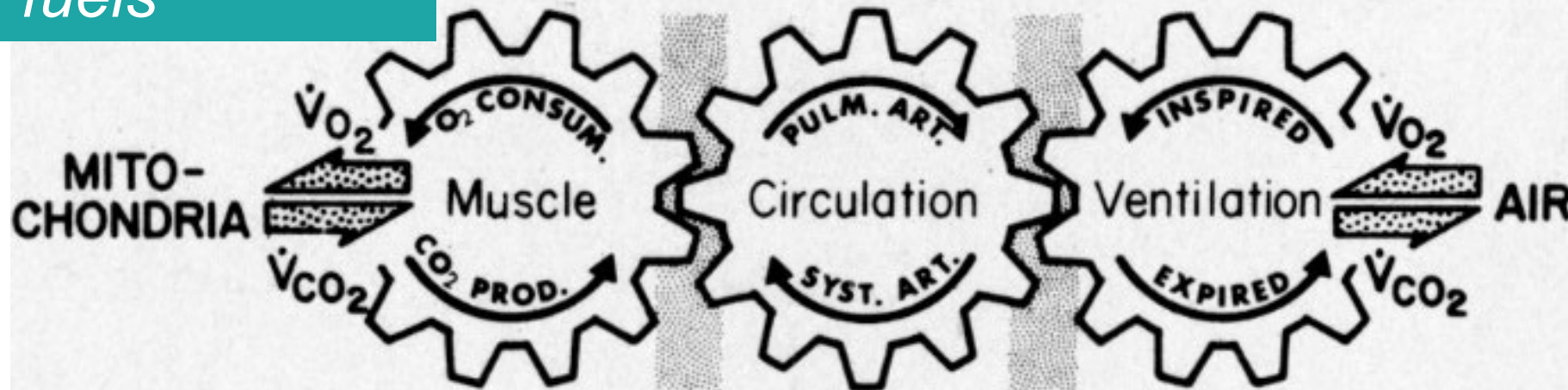
Outcome Peak oxygen uptake +0.7 mL/kg/min higher in the HIIT group compared to C and MCT

Robert Marchand *26. 11. 1911



Schematic Representation of the Essential Elements in Gas Exchange between the Cell Mitochondria and External Environment.

Energy production:
ATP, fuels



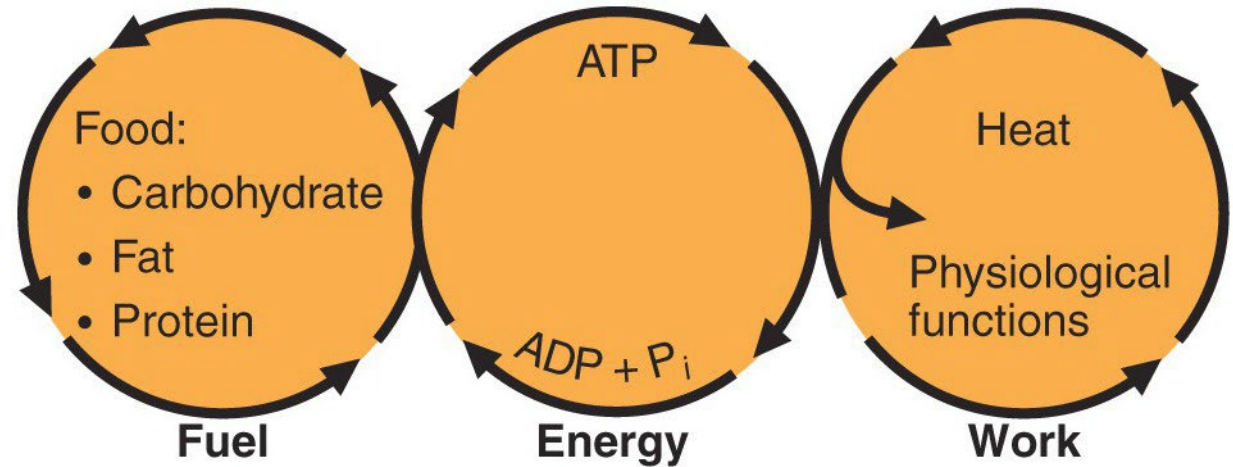
During exercise, the quantity of O_2 consumed ($\dot{V}O_2$) and CO_2 produced ($\dot{V}CO_2$) is determined by the amount of muscle activity. The interconnecting gears connote the coupling of the physiologic responses of blood flow and ventilation to metabolism.

ATP – it is all about energy

Energy-requiring reaction



Energy-yielding reaction

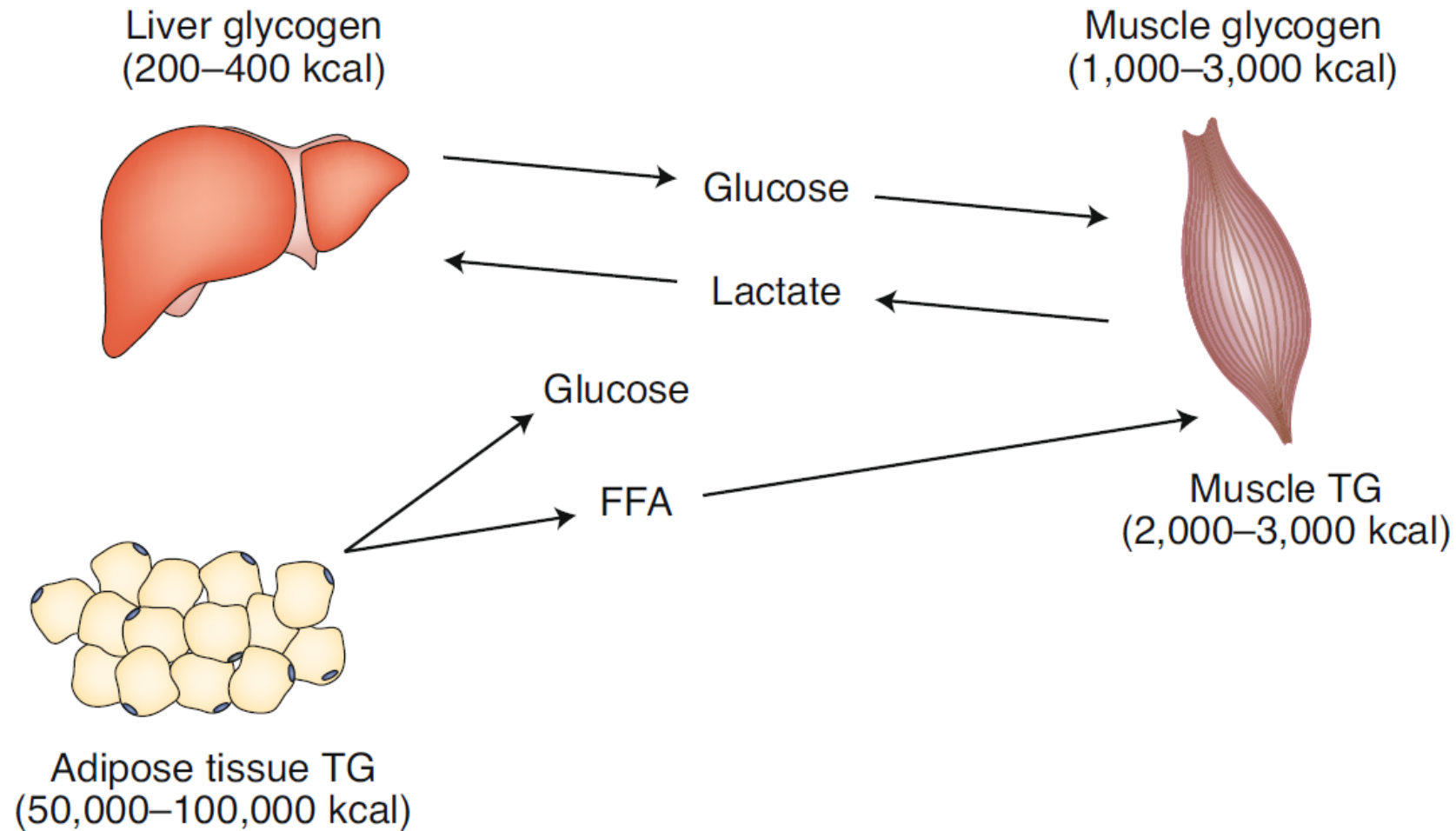


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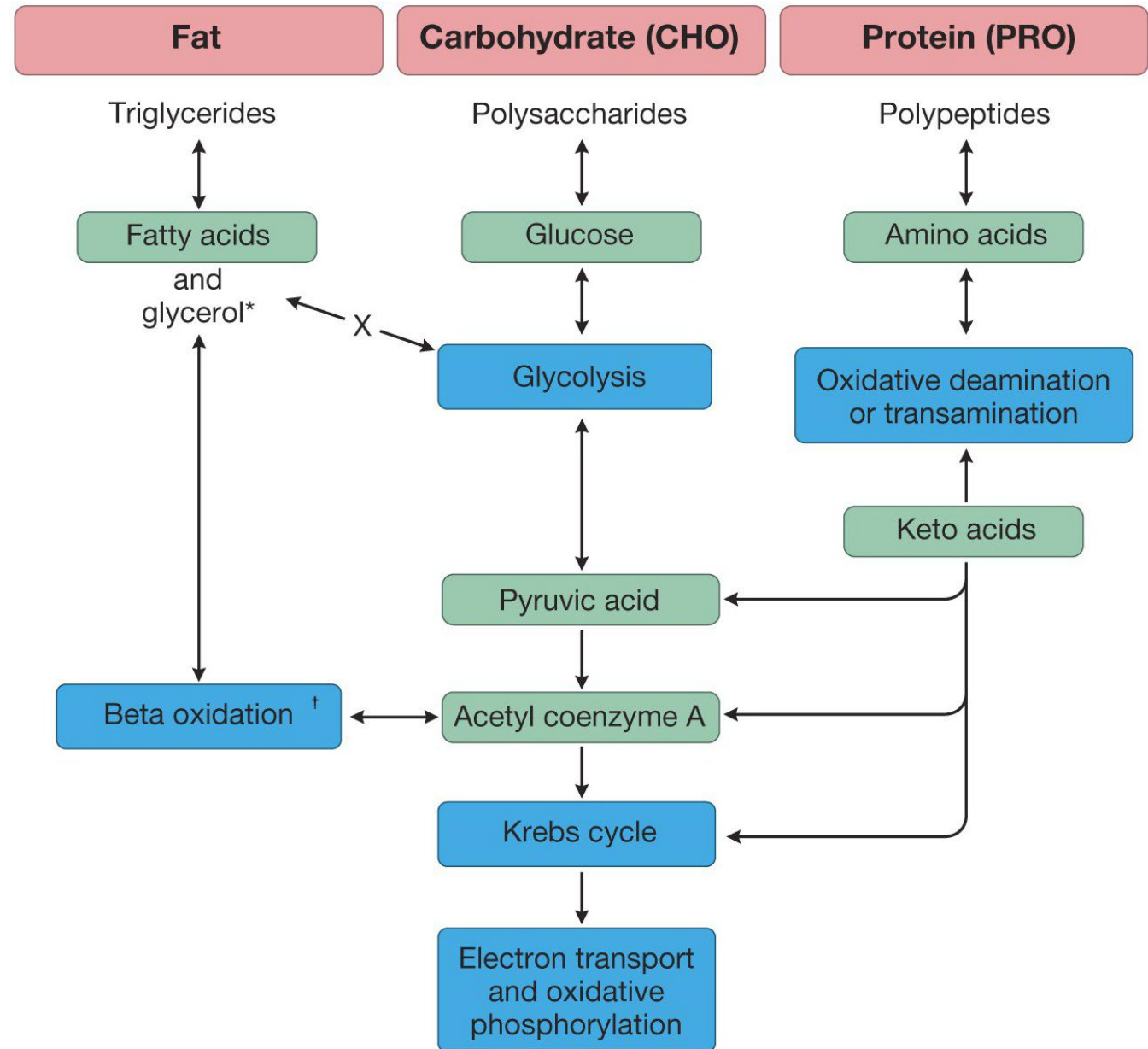
Hargreaves M, Spriet LL. Nat Metab. 2020 Sep;2(9):817-828

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Sources of energy



Energy production

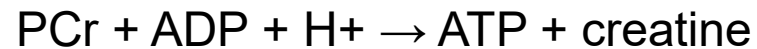


ATP generation by three processes

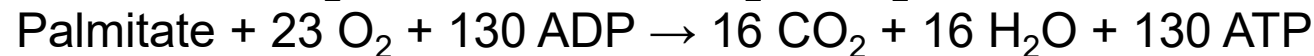
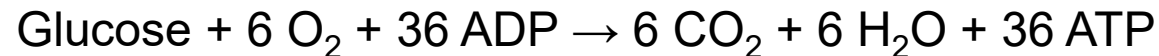
1. ADP + creatine phosphate $\rightarrow$ creatine + ATP
2. Anaerobic respiration: glycolysis
3. Aerobic respiration: Krebs cycle, electron transport/ oxidative phosphorylation

Energy metabolism in skeletal muscle - ATP resynthesis

Substrate-level phosphorylation

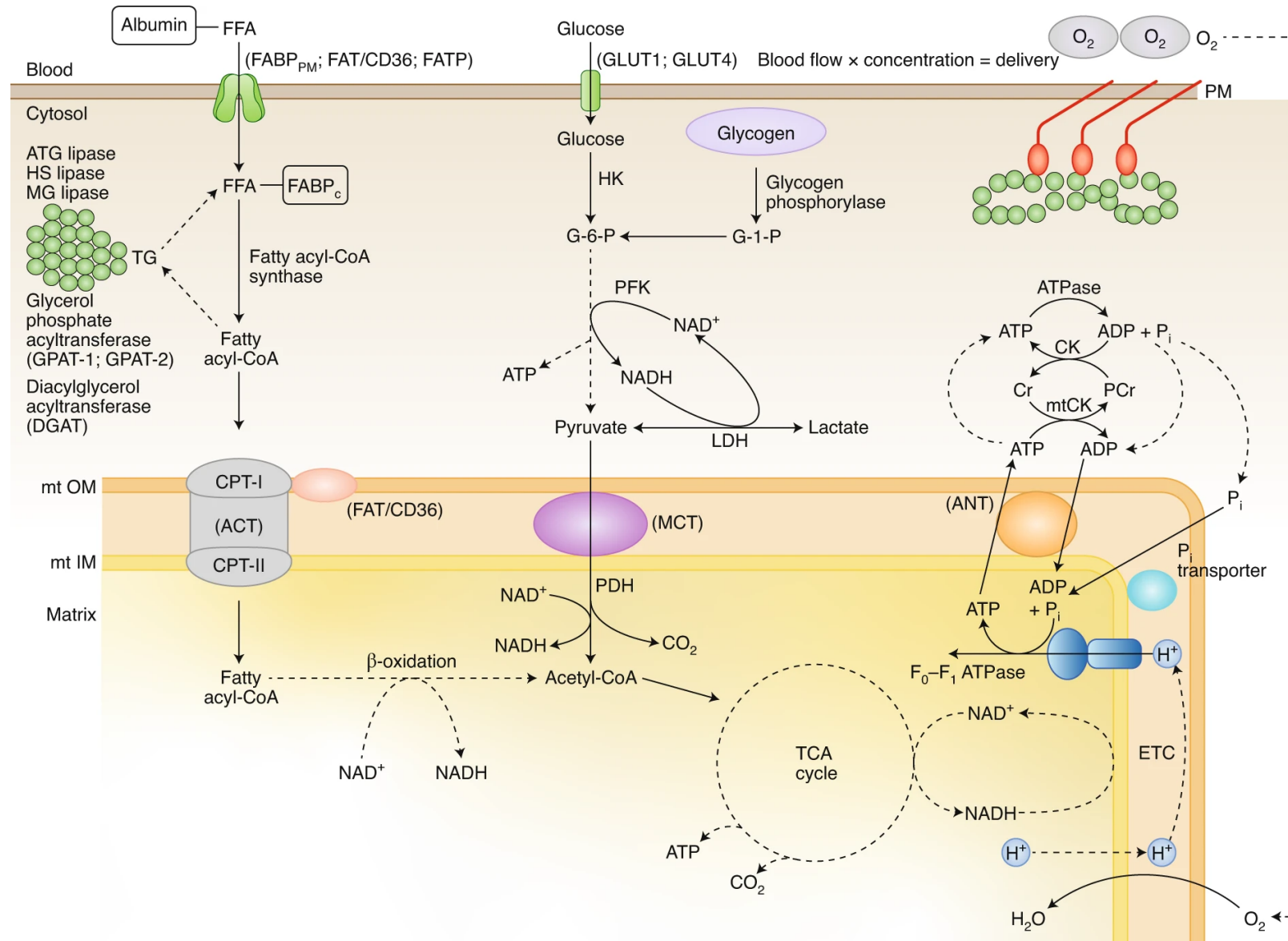


Oxidative phosphorylation

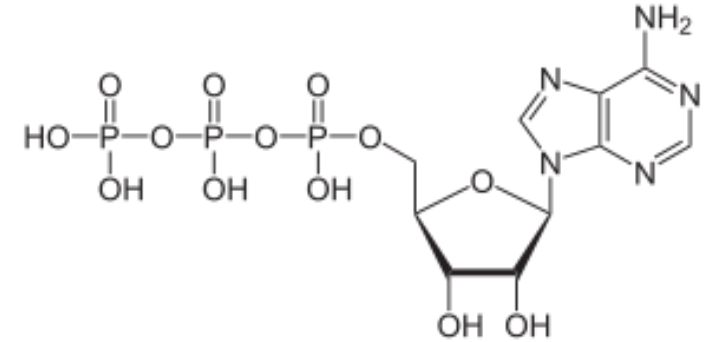


6% to 8% more ATP per mole of O_2 while metabolizing glucose compared to fatty acid

Key metabolic pathways in contracting skeletal muscle during exercise



ATP as stored energy source



Intramuscular stores of ATP are small ($\sim 5 \text{ mmol} \cdot \text{kg}^{-1}$ wet muscle)

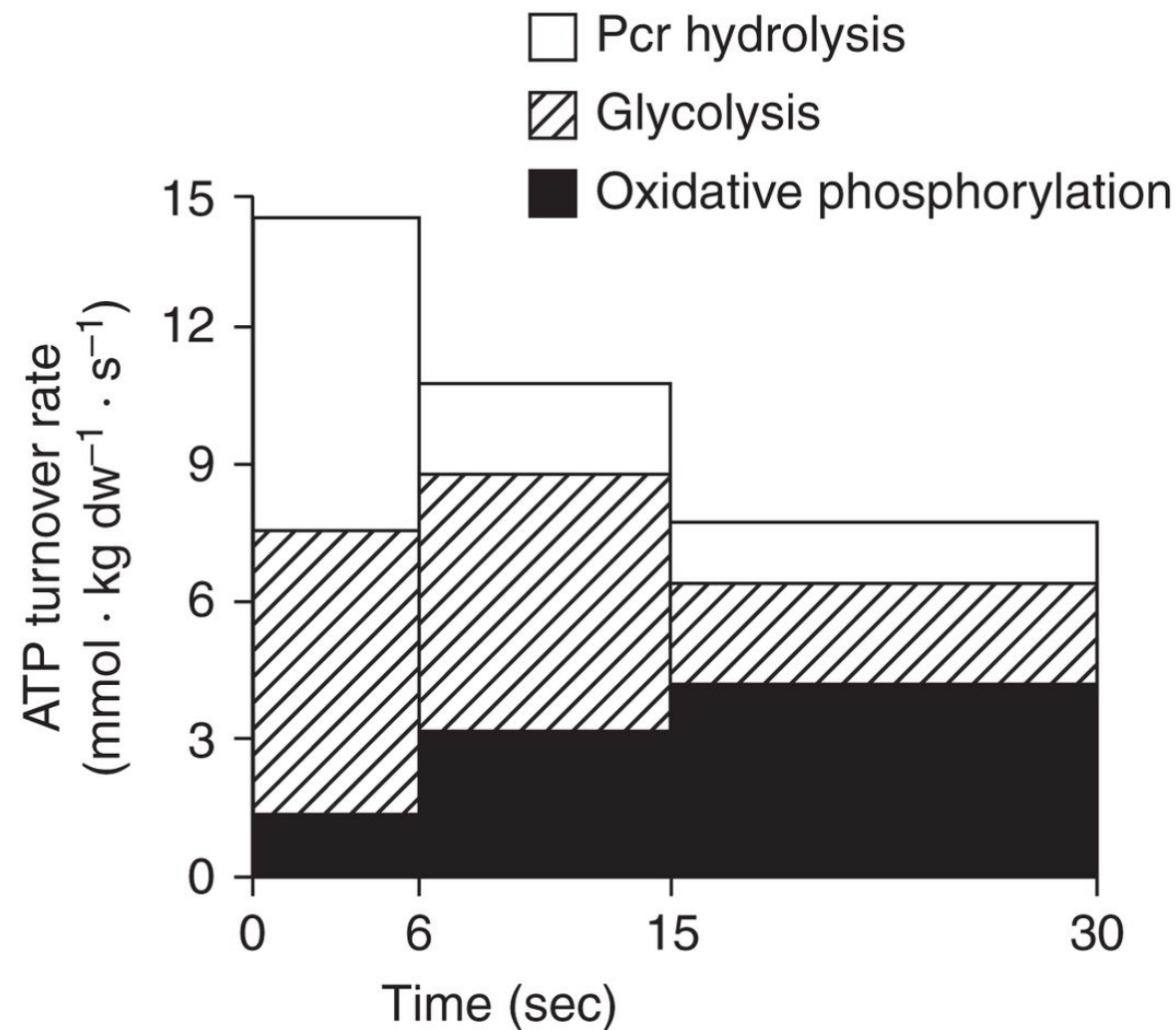
submaximal exercise at 200 Watts and $\sim 75\%$ maximal oxygen uptake ($\text{VO}_{2\text{max}}$), estimated ATP utilization rate of $0.4 \text{ mmol ATP} \cdot \text{kg}^{-1} \text{ sec}^{-1}$,

→ exercise duration 15 sec.

“All-out” maximal exercise at ~ 900 Watts and $\sim 300\%$ $\text{VO}_{2\text{max}}$, estimated $3.7 \text{ mmol ATP} \cdot \text{kg}^{-1} \text{ sec}^{-1}$

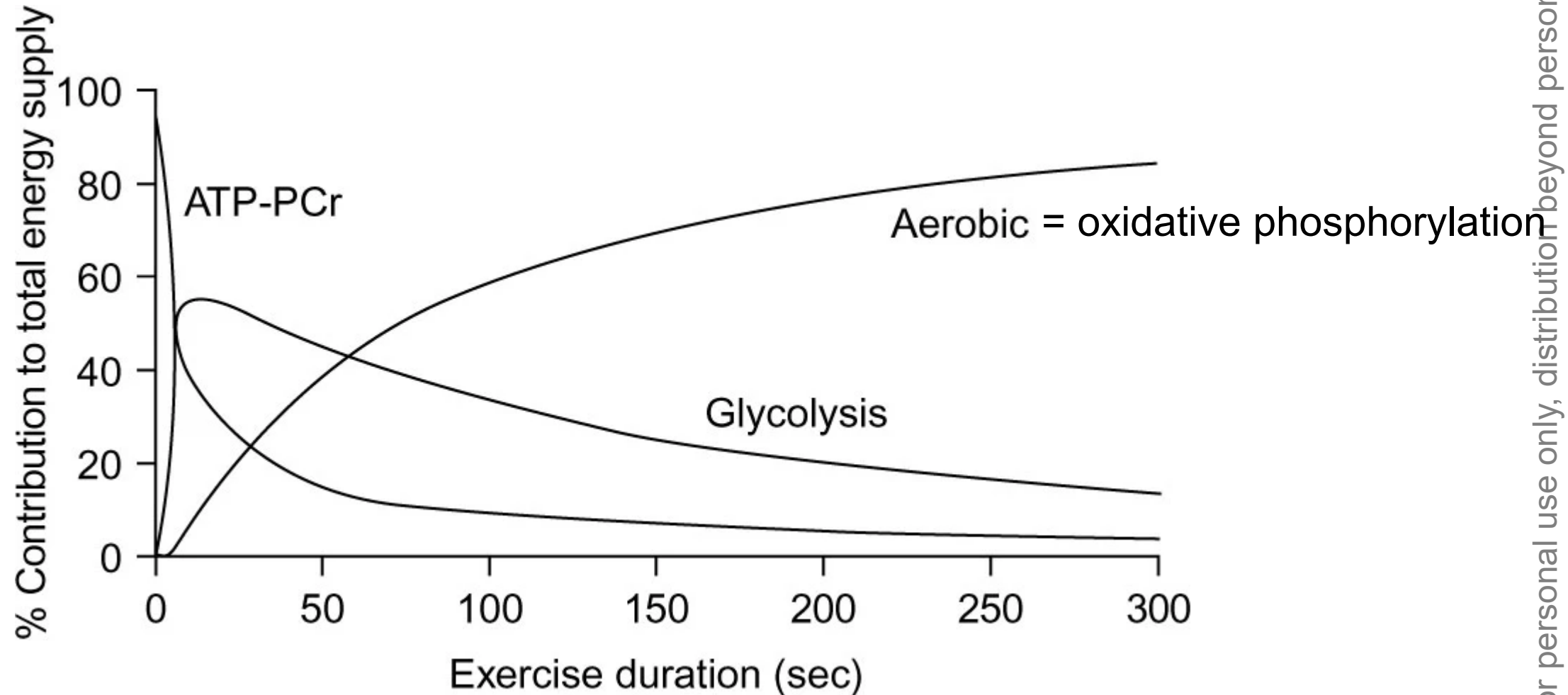
→ < 2 seconds

Contributions of phosphocreatine (PCr), glycolysis, and oxidative phosphorylation to adenosine triphosphate (ATP) turnover during 30 sec of maximal isokinetic cycling exercise.



Mark Hargreaves, and Lawrence L. Spriet Cold Spring Harb Perspect Med 2018;8:a029744 (From Parolin et al. 1999; reprinted, with permission, from the authors)

Relative energy system contribution to the total energy supply for any given duration of maximal exercise



Speed and Capacity of Energy Production

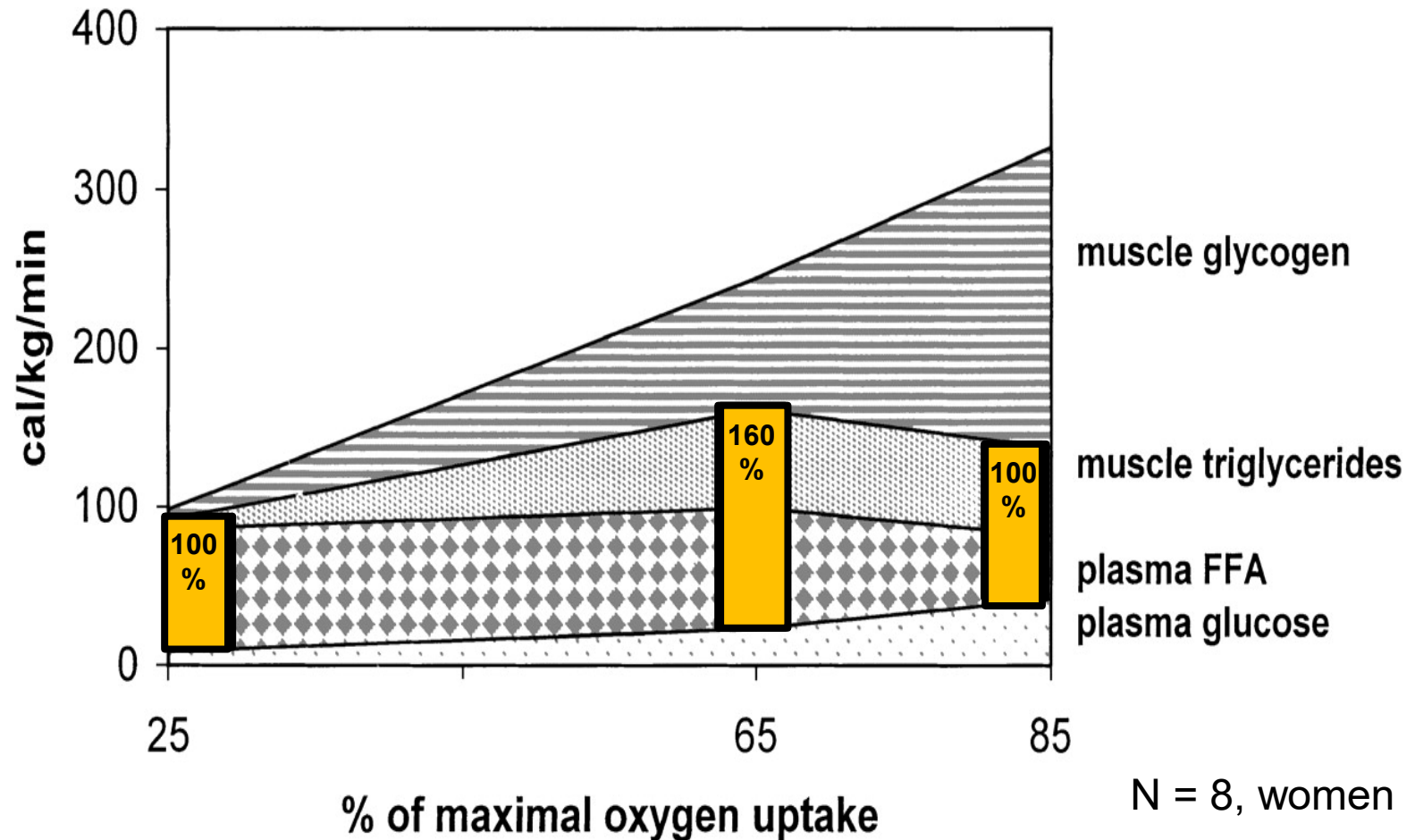
Fuel source	Maximal rate of <u>ATP</u> production (mmol/s)	Total ~P available (mmol)
Muscle <u>ATP</u>		223
Creatine phosphate	73.3	446
Conversion of muscle glycogen into lactate	39.1	6,700
Conversion of muscle glycogen into CO ₂	16.7	84,000
Conversion of liver glycogen into CO ₂	6.2	19,000
Conversion of adipose-tissue fatty acids into CO ₂	6.7	4,000,000

Substrate metabolism during exercise with different intensities

Fat relative contribution (%) of calories consumed

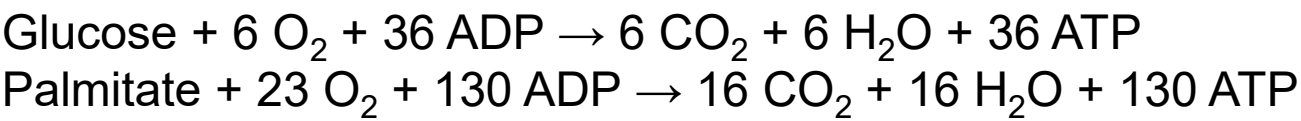


Fat contribution relative to value @25% VO_2

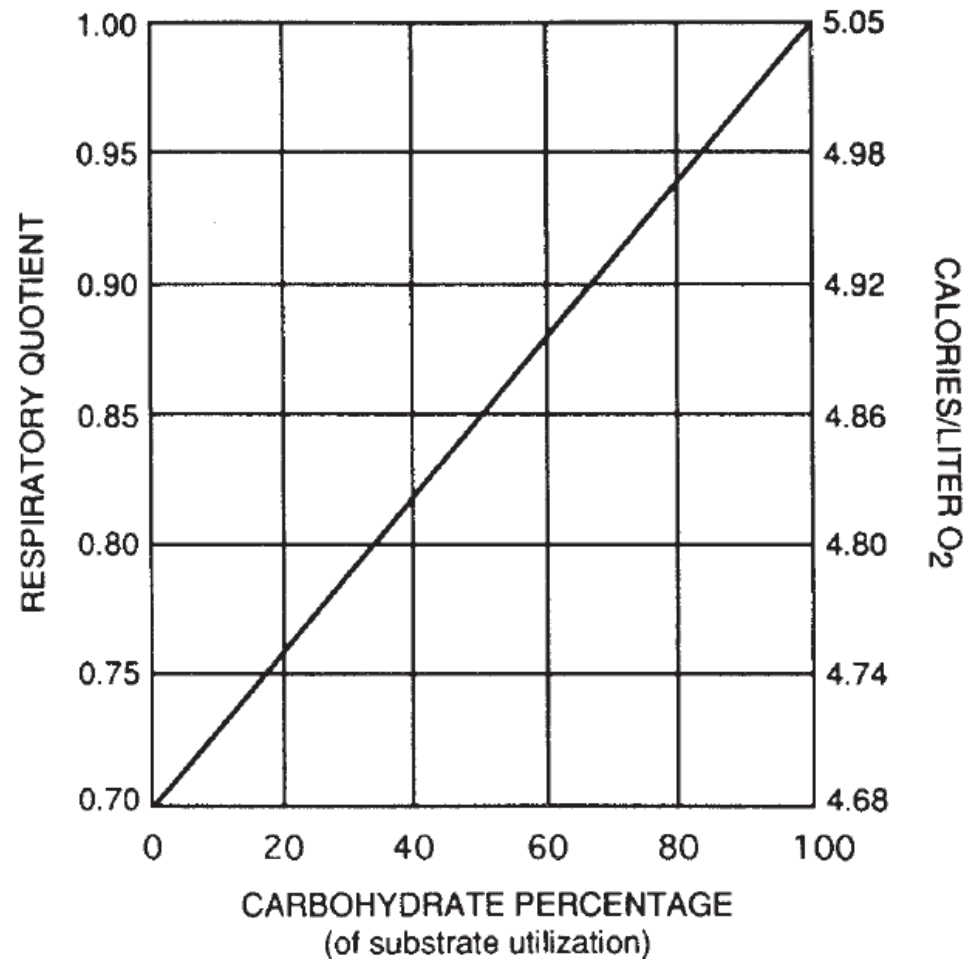


Theoretical Gas Exchange and High-Energy Phosphate Yield from Carbohydrate and Free Fatty Acid Oxidation for a Standardized Exercise Bout Requiring an O₂ Uptake of 1 L/min

	RQ	$\dot{V}O_2$ (L/min)	$\dot{V}CO_2$ (L/min)	$\sim P:O_2$ (max)	$\sim P:CO_2$ (max)
Carbohydrate (glucose)	1.0	1.0	1.0	6.00	6.00
Free fatty acid (palmitate)	0.7	1.0	0.7	5.65	8.13



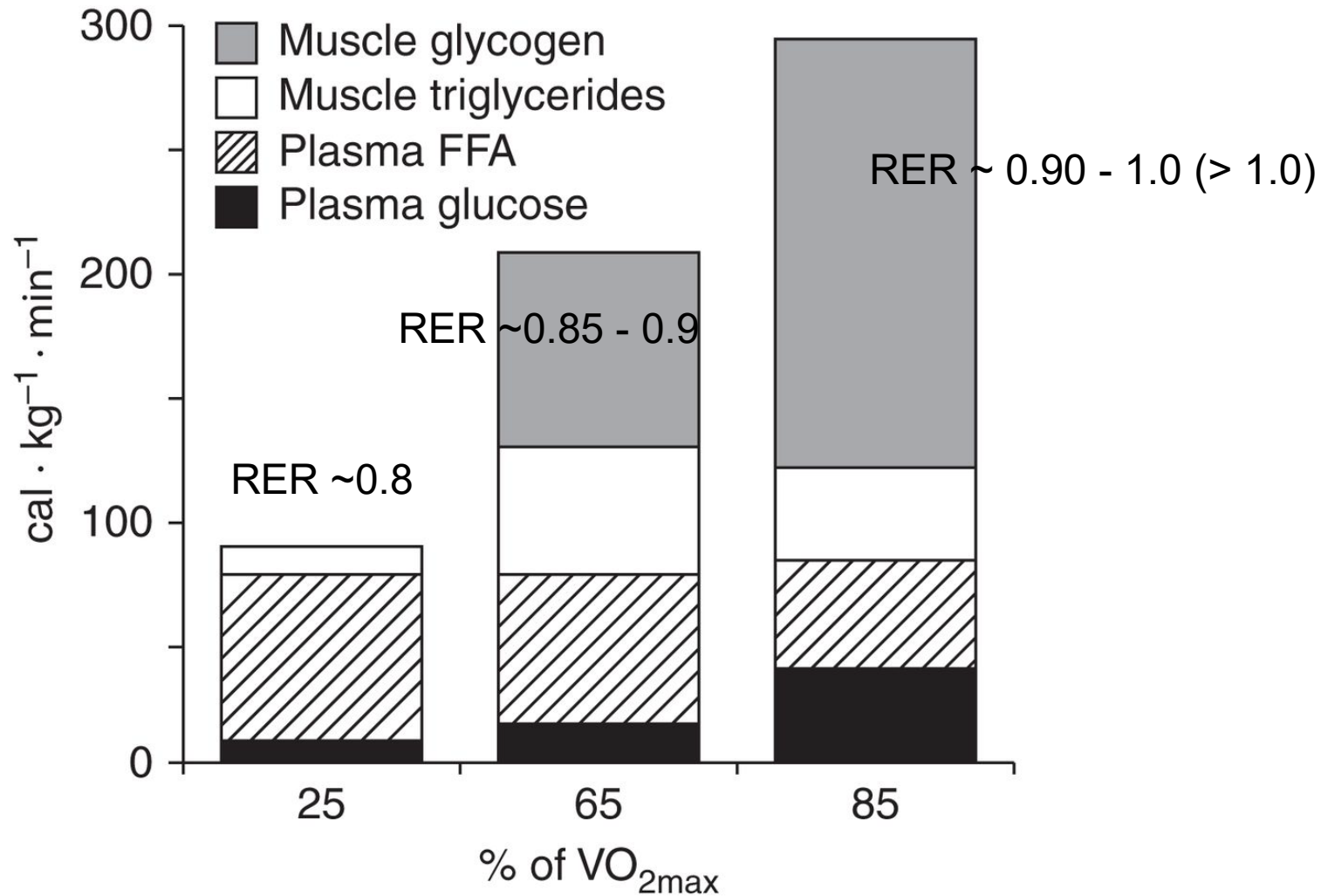
The percentage of carbohydrate substrate in the diet estimated from the respiratory quotient measurement.



Moderate intensity exercise: RQ 0.90 or 65% CHO

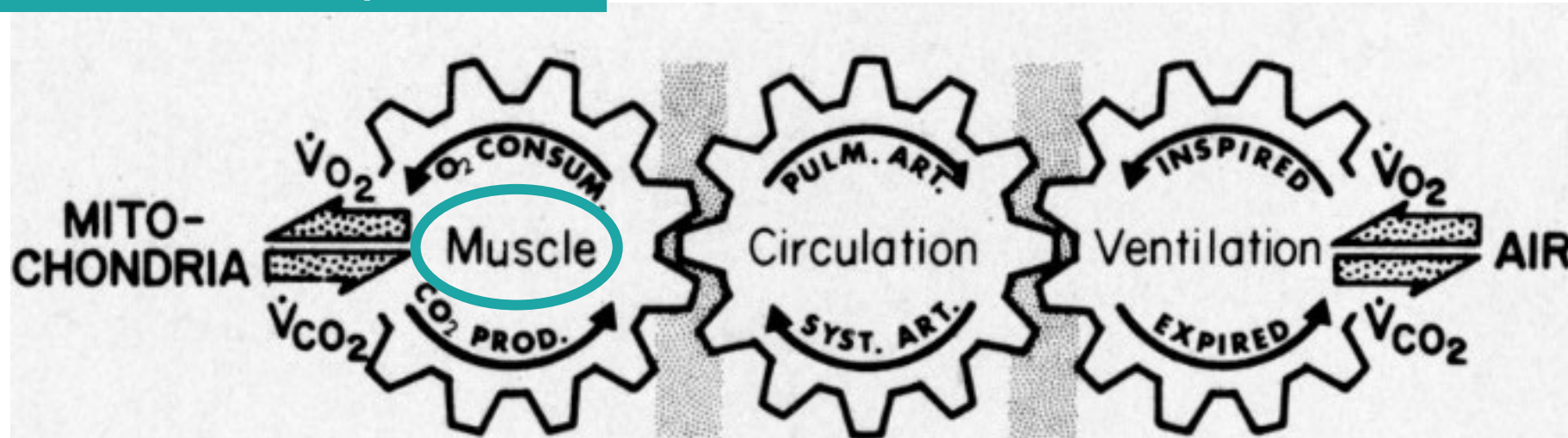
The calories of energy obtained per liter of oxygen consumed for each combination is given on the right ordinate.

Relative contribution of carbohydrate and fat fuel sources to energy metabolism during exercise of increasing intensity.



Muscle

Muscle fiber composition



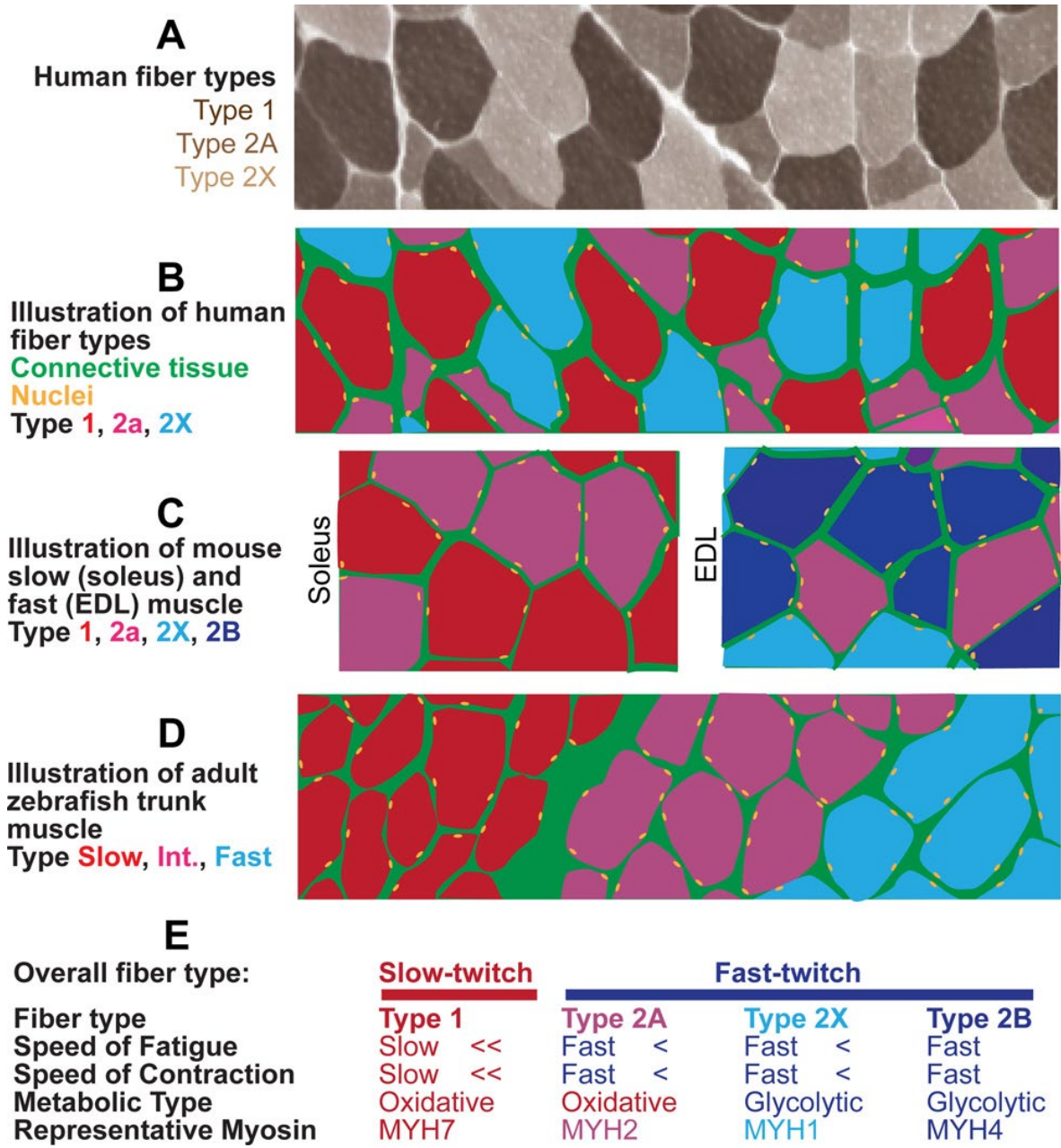
Skeletal muscle fiber types

(A) Section of human muscle, where fiber types have been differentiated using ATPase staining after pre-incubation at pH 4.6.

(B) Illustration showing healthy muscle fibers.

(C) Particular muscle groups can also be enriched for slow (Soleus) or fast (extensor digitorus longus [EDL]) muscle.

(D) In zebrafish trunk musculature, different fiber types are segregated, with the slowest fibers situated laterally, and fast fibers situated medially.



Characteristics of Muscle Fiber Types

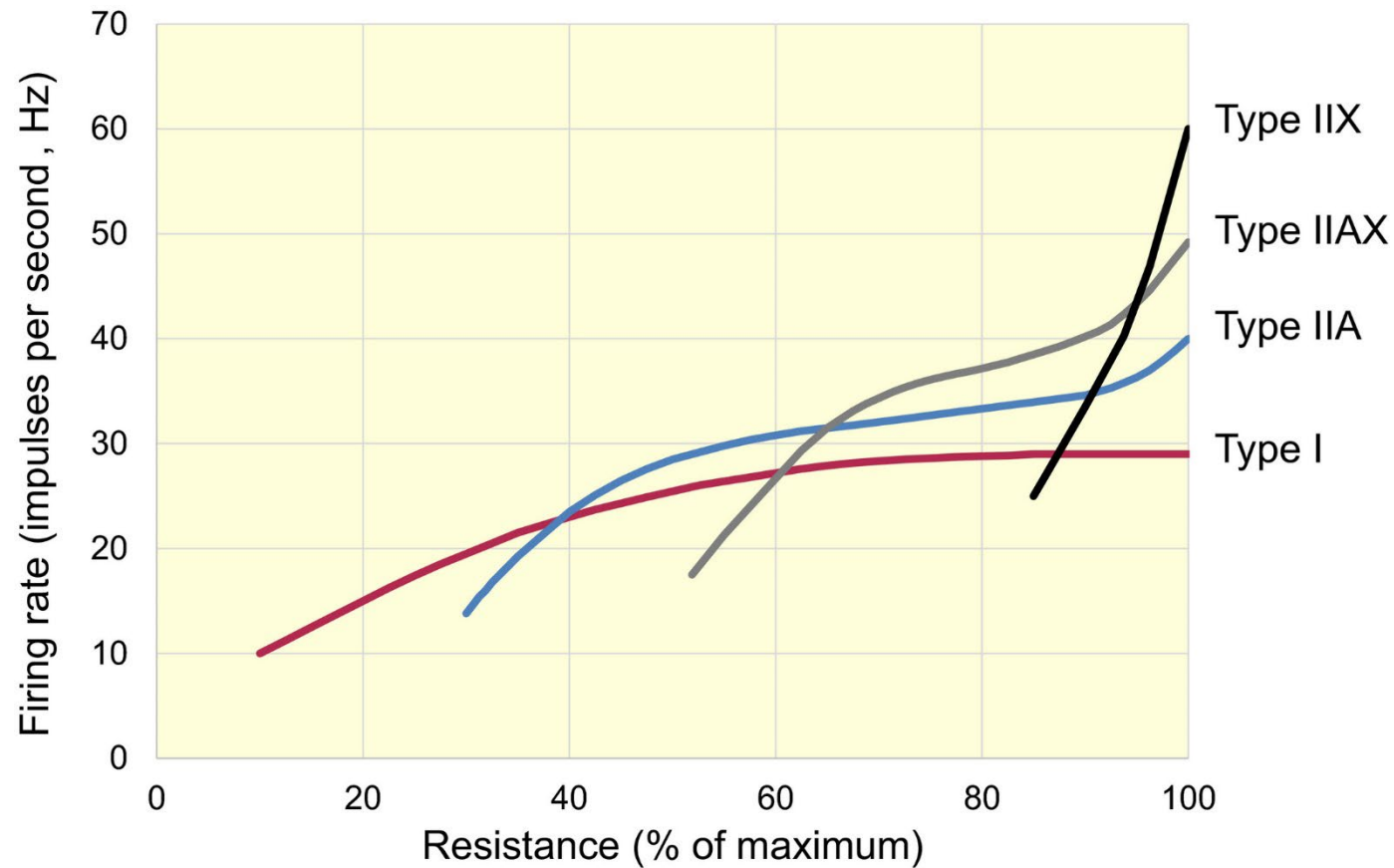
	Slow oxidative (type I)	Fast oxidative (type IIa)	Fast glycolytic (type IIx)
Contraction Velocity ($\mu\text{m/s}$)	50 (slow twitch)	100 (fast twitch)	160 (very fast twitch)
Color	Red	Red	White
Myoglobin concentration	High	High	Low
Mitochondrial content	High	High	Low
Intensity	< 70-80% $\text{VO}_{2\text{max}}$	> 70-80% $\text{VO}_{2\text{max}}$	near-maximal, brief efforts

Talbot J Wiley Interdiscip Rev Dev Biol. 2016 July ; 5(4): 518–534

Wasserman & Whipp's Principles of Exercise Testing and Interpretation. 6th Ed. 2012 Sietsema et al

Hargreaves M, Spriet LL. Nat Metab. 2020 Sep;2(9):817-828

Suggested scheme of the interplay between the recruitment of motor units innervating type I, IIA, IIX and IIX muscle fibres and the accompanying increases in firing rates with increases in contractile force production.



Fiber type distribution within human skeletal muscle varies from muscle to muscle

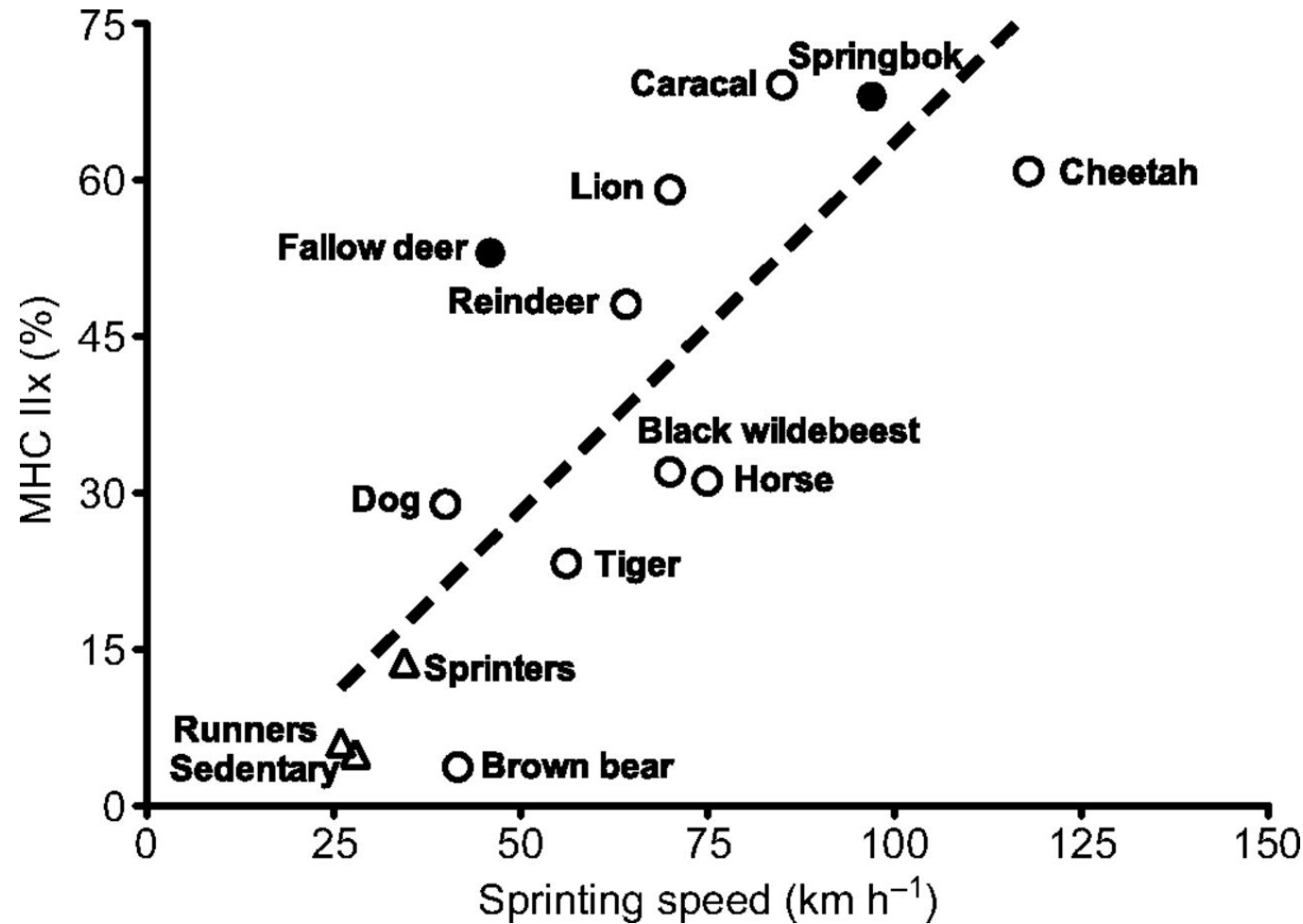
***Inter muscle* distribution differences of slow-twitch fibers**

- soleus muscle > 80%
- gastrocnemius muscle ~50%
- triceps brachii ~20% to 50%.

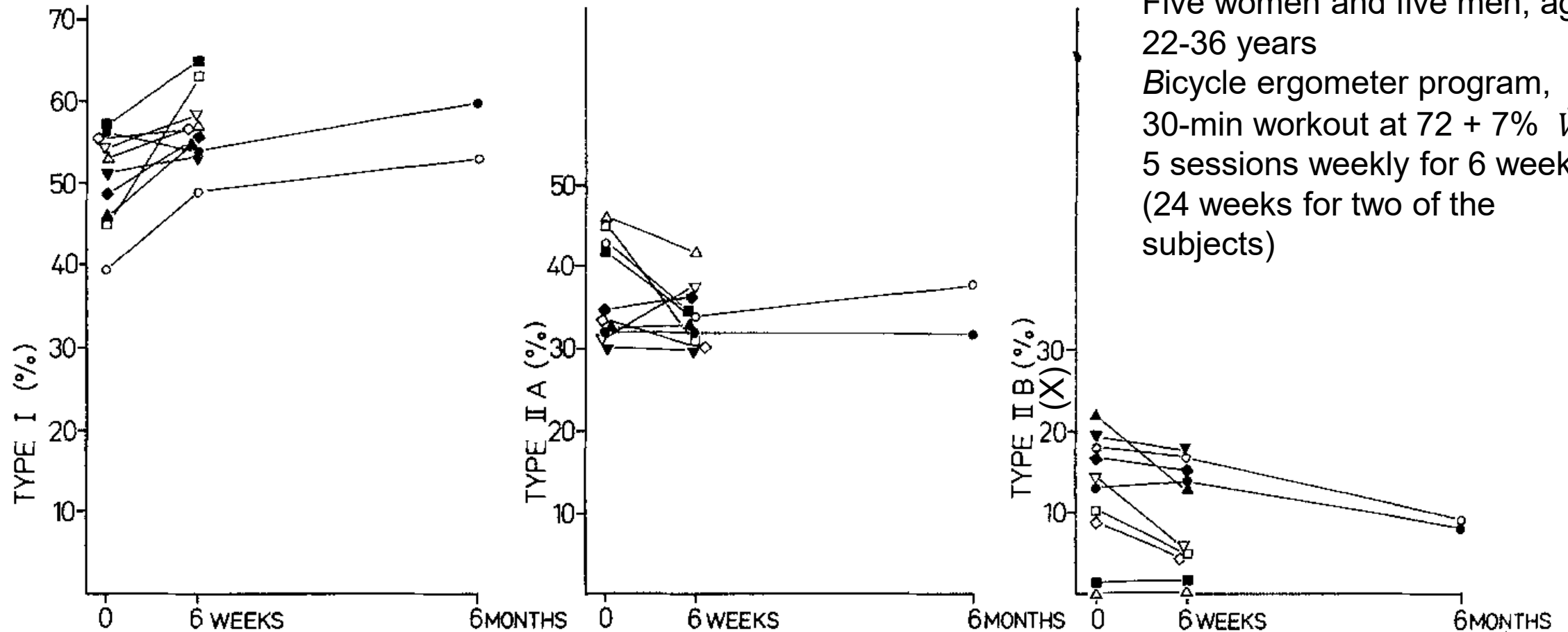
***Inter individual* differences of slow-twitch fiber content of vastus lateralis muscle**

- elite sprinters 20% to 30%.
- untrained controls ~ 50%
- elite endurance athletes > 90%

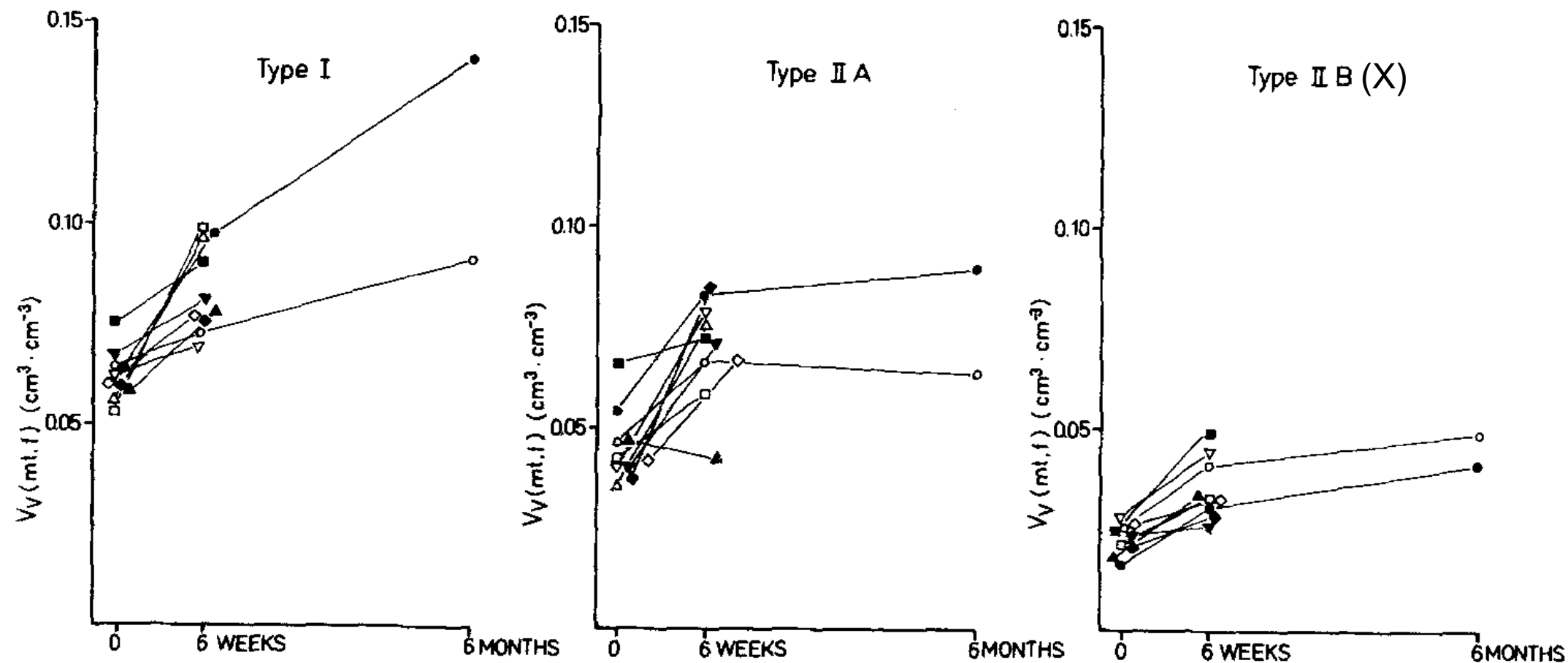
The relationship between MHC IIx isoform content in muscle and reported maximal sprinting speeds.



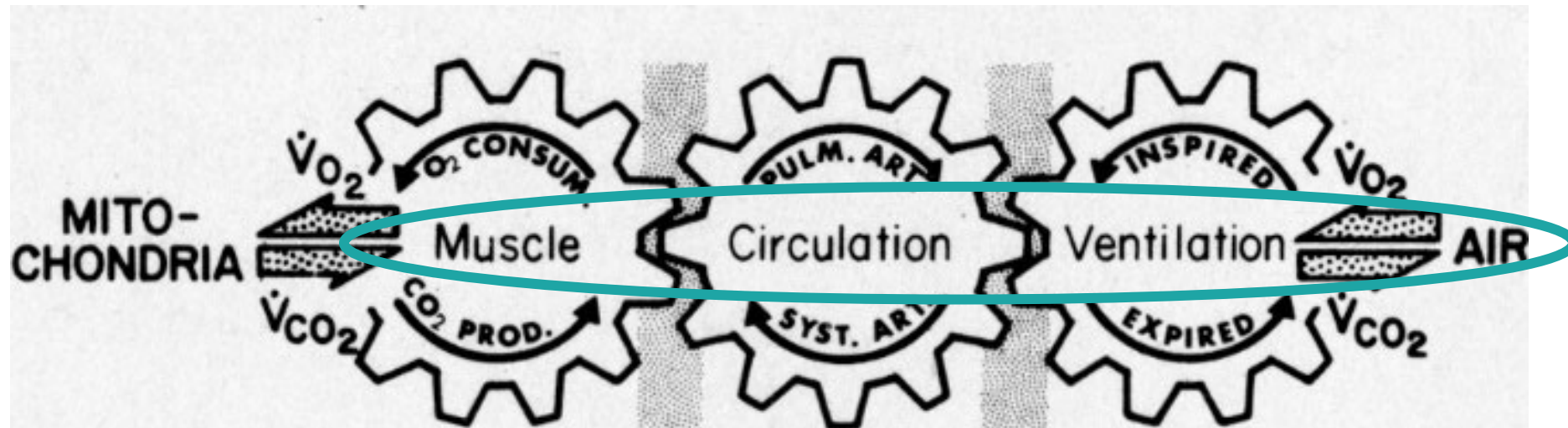
Changes in the *fiber type distribution pattern* after 6 weeks (ten subjects) and 6 months (two subjects) of endurance training. Open symbols are female, closed symbols are male subjects



Volume density of *total mitochondria* (V_v mt, f) in the different muscle fiber types before and after 6 weeks (ten subjects) and 6 months (two subjects) of endurance training.



From the muscle to the mouth



The muscle sets the demand. Circulation and ventilation have to meet it – and gas exchange at the mouth is where you read whether they do.

Susan A. Ward: The Anaerobic Threshold: what it is and how to find it

Beaver WL, Wasserman K, Whipp BJ. A new method for detecting the anaerobic threshold by gas exchange. J Appl Physiol 1986;60:2020–2027

Key points

- ATP production is a key element in exercise
- ATP generation is divided in aerobic and anaerobic processes
- ATP generation depends on intensity and duration of exercise
- Muscle has type I, IIa and type IIx fibers
- Fiber types are differing regarding their aerobic capacity
- $\dot{V}O_2\text{max}$ is set by O_2 delivery and O_2 extraction – the Fick principle
- Fractional utilisation of $\dot{V}O_2\text{max}$ – the thresholds → comes next

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Prof. Arno Schmidt-Trucksäss, MD, MA, FESC
Arno.Schmidt-Trucksass@Unibas.ch

Department of Sport, Exercise and Health,
Division Sports and Exercise Medicine,
University of Basel, Switzerland



Thank you for your attention !