Indirect calorimetry

What is it, how does it work and how should we use it in the ICU?

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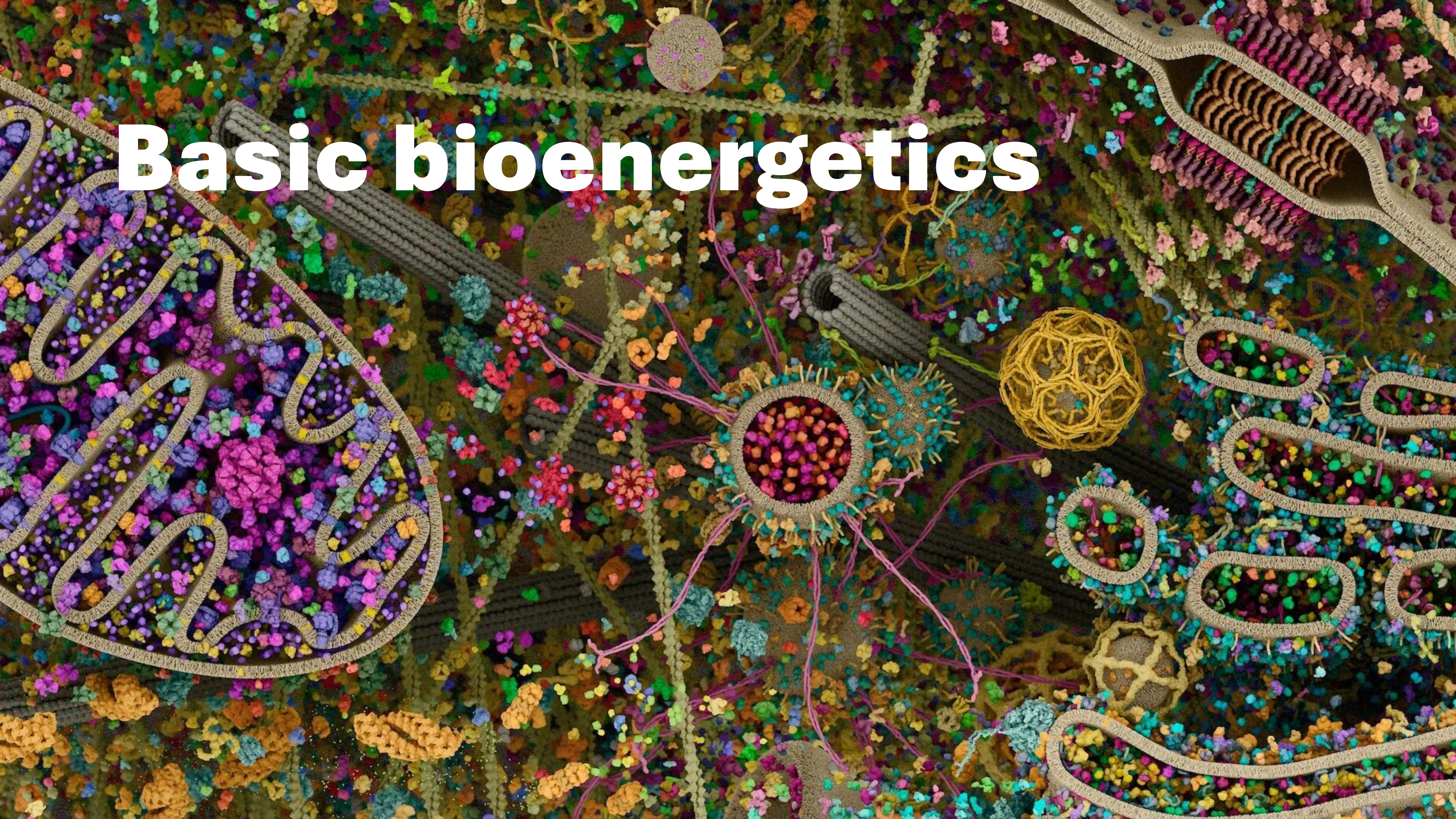
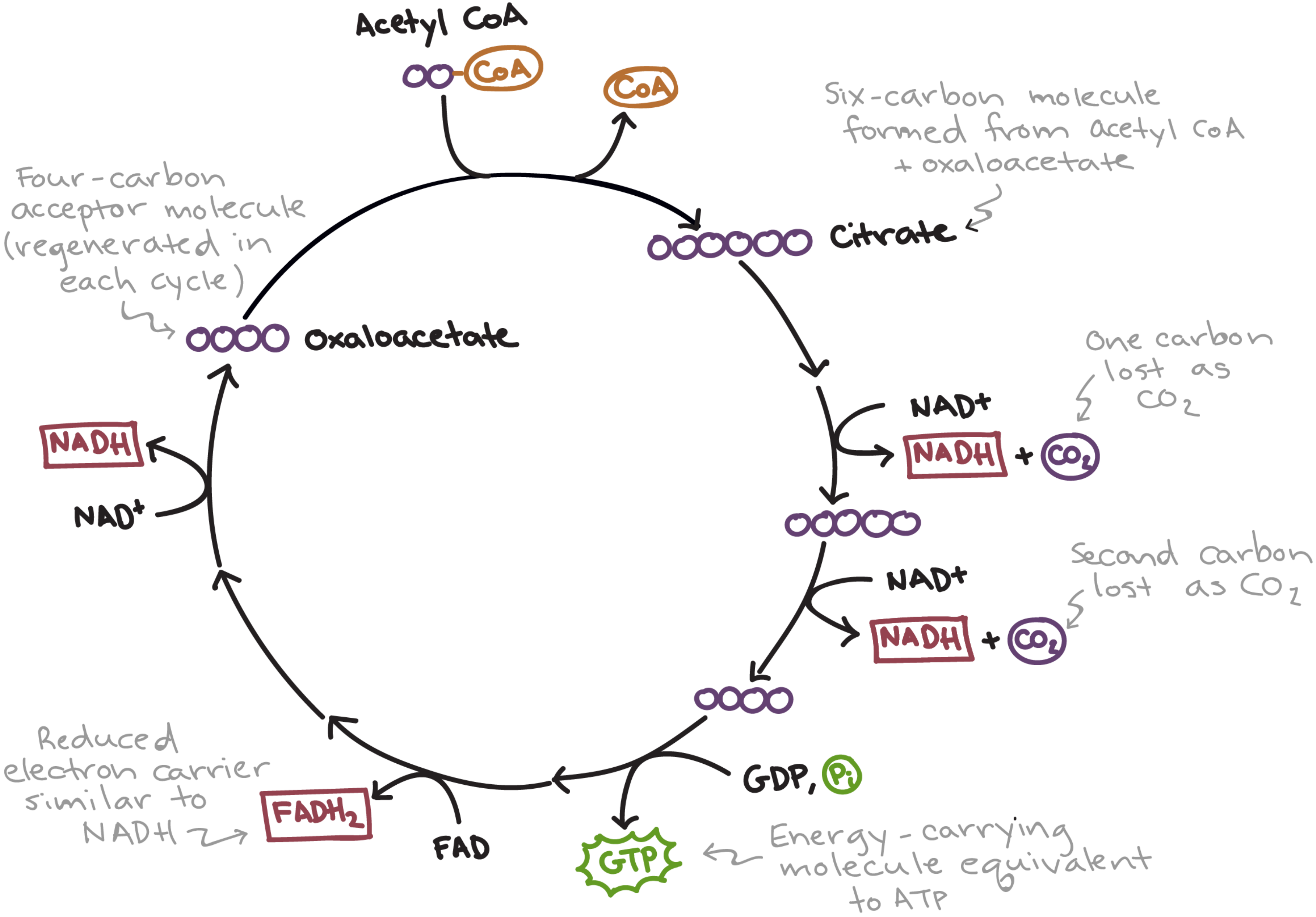
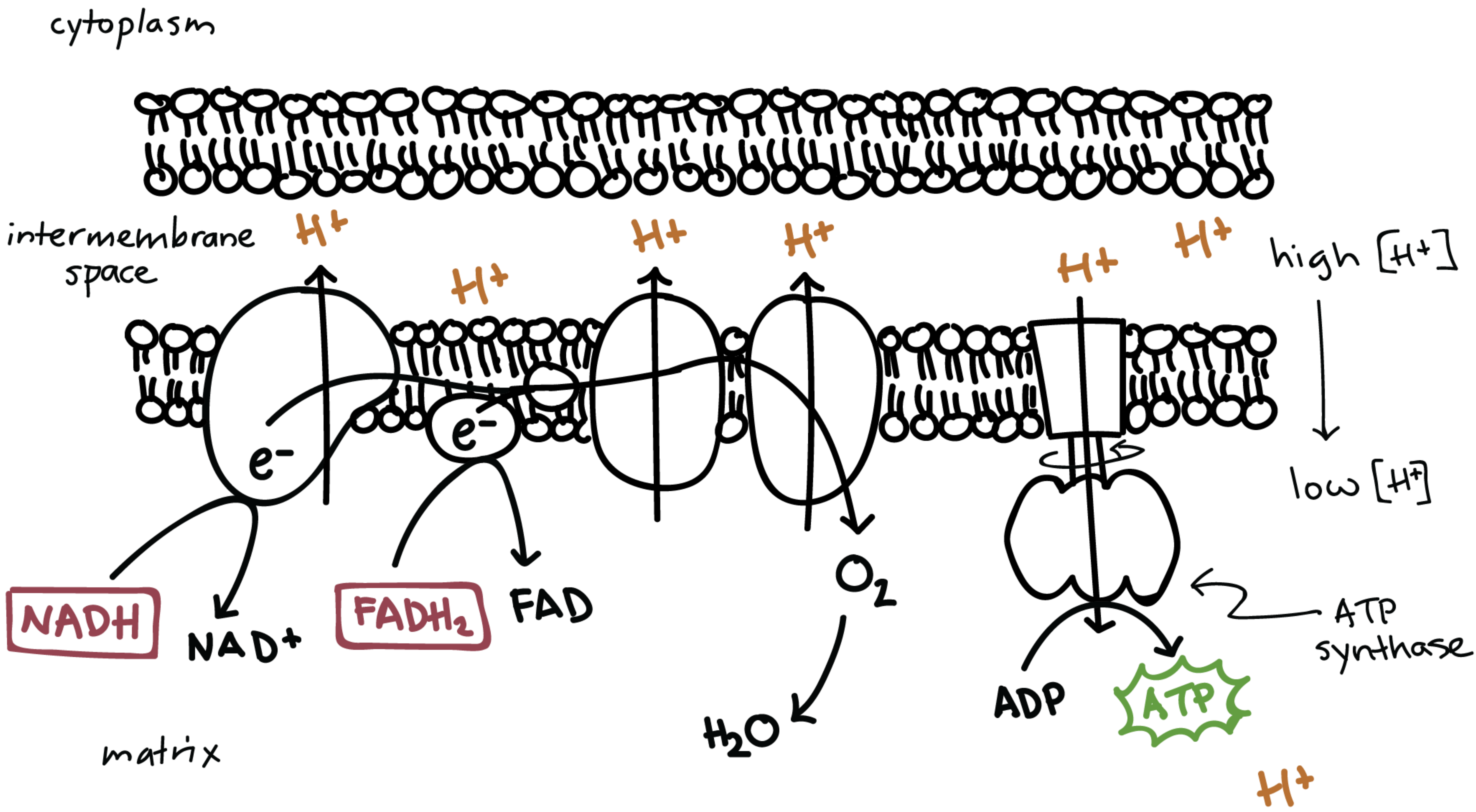
COI: None

Basic bioenergetics





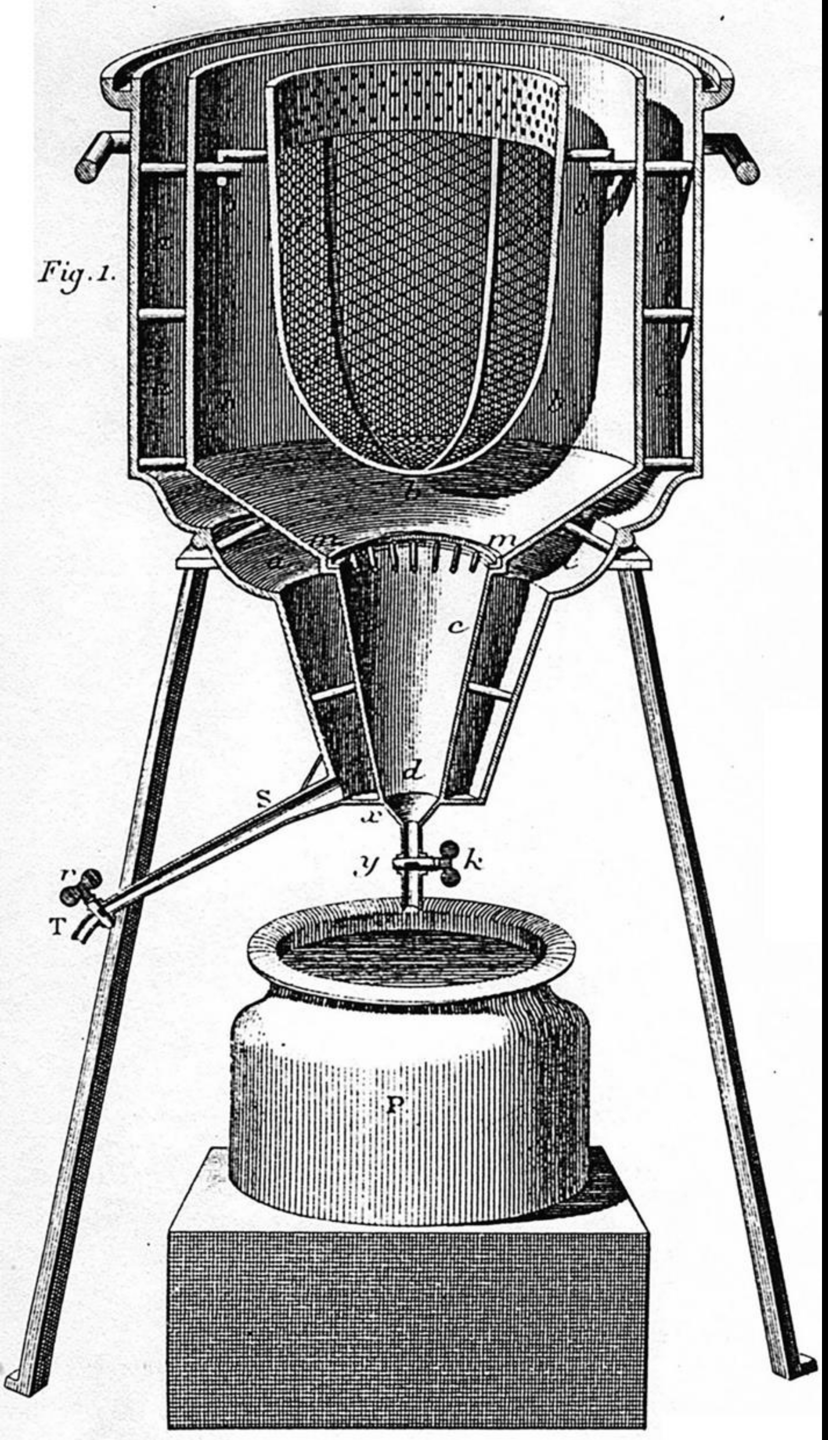
Acetyl CoA
CoA
CoA
Six-carbon molecule formed from acetyl CoA + oxaloacetate
Citrate
Four-carbon acceptor molecule (regenerated in each cycle)
Oxaloacetate
NAD+
NADH
CO_2
One carbon lost as CO_2
NADH
NAD+
NAD+
NADH
CO_2
Second carbon lost as CO_2
GDP, P_i
GTP
Energy-carrying molecule equivalent to ATP
$FADH_2$
FAD
Reduced electron carrier similar to NADH


cytoplasm
intermembrane space
H+
H+
H+
H+
H+
H+
high [H+]
low [H+]
e-
e-
NADH
NAD+
FADH2
FAD
O2
H2O
ATP synthase
ADP
ATP
matrix
H+

Thermodynamics:

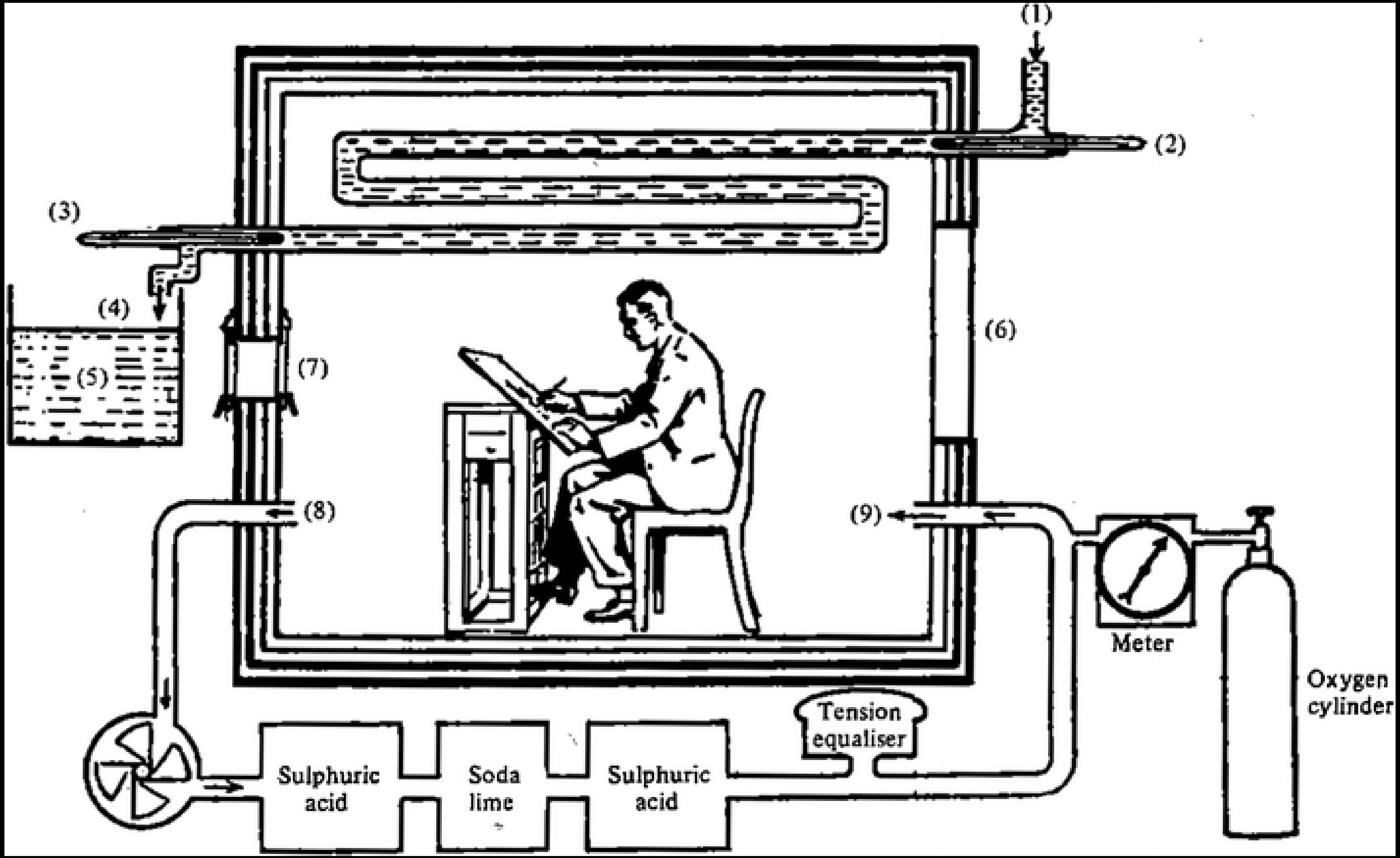
- Conservation of energy (1st law)
- Entropy will increase (2nd law)
- Thermal equilibrium (0th law)

Calorimetry = "measuring heat"



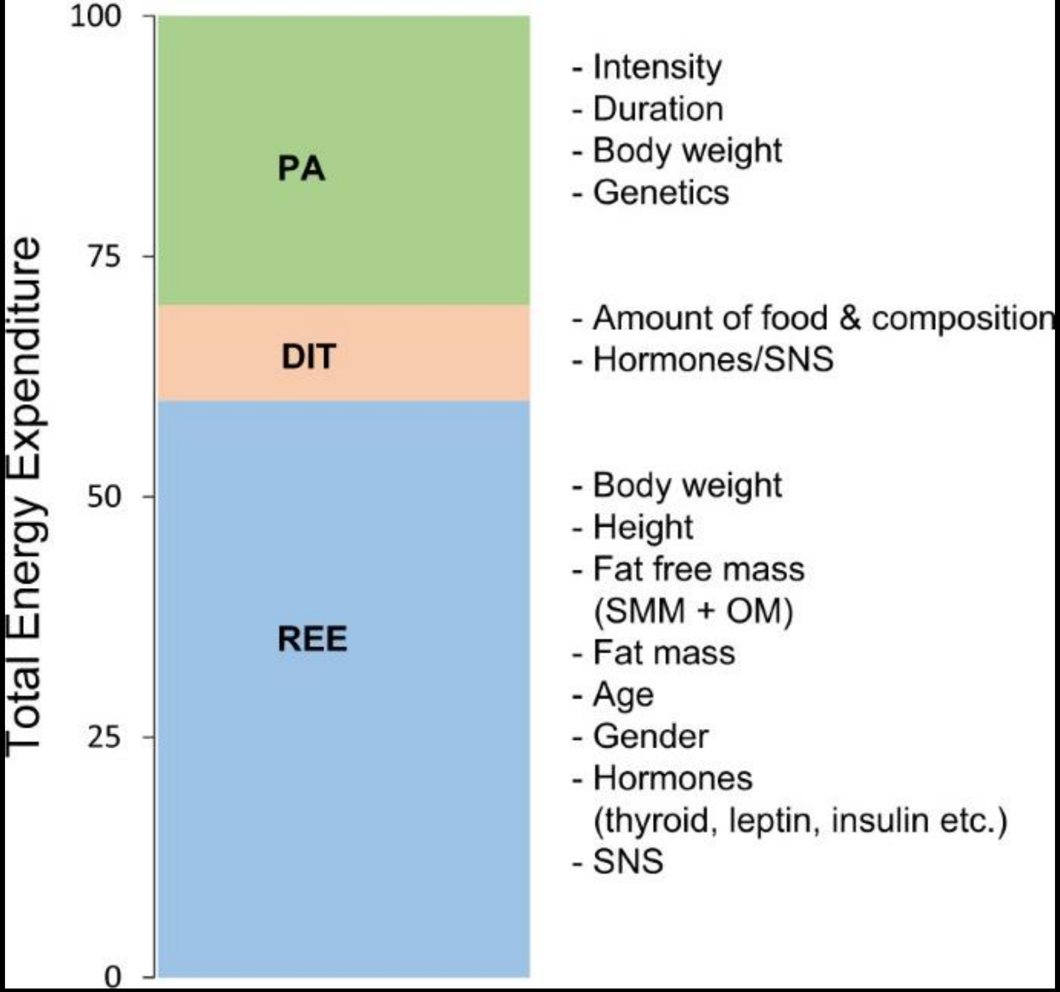
Lavoisier’s ice calorimeter, anno 1782(?)

- Heat and CO_2 production from animal respiration
- Similar heat and CO_2 production from combustion



Atwater and Benedict respiration chamber, late 19th century

Components of EE



Soares, European J Clin Nutr 2018

The theory of IC

- DC is measuring heat (energy).
- All energy comes from redox reactions.
- The conversion of O_2 to CO_2 is fundamental to all redox reactions in humans.
- Measuring VO_2 + VCO_2 production + assumptions can estimate energy liberated in redox reactions.

Gas exchange for combustion of COH, fat and protein

1 g substrate	O2 consumed (L)	CO2 produced	Urinary nitrogen (g)
Glucose	0.83	0.83	
Fat	2.02	1.43	
Protein	0.97	0.78	0.16

$$VO_2 = 0.83*COH + 2.02*Fat + 6.04*U_N$$
$$VCO_2 = 0.83*COH + 1.43*Fat + 4.89*U_N$$

These equations can be solved for COH and fat…

$$CHO_{ox} = 4.12\ VCO2 – 2.91\ VO2 – 2.54\ UN$$
$$F_{ox} = 1.69\ VO2 – 1.69\ VCO2 – 1.94\ UN$$

$EE = 4.18*COH + 9.46*Fat + 27*U_N$

Replacing COH and Fat with equations from last slide…

$EE = 3.94\ VO2 + 1.11\ VCO2 – 2.17\ UN$

Multiply by 1.44 to convert L/day → ml/min

$EE = 5.5\ VO2 + 1.76\ VCO2 – 2.17\ UN$

The ratio of VCO_2/VO_2 (RQ) will also give an indication of what's being oxidized:

- Pure COH oxidation = RQ of 1.0
- Pure fat oxidation = RQ of 0.7
- Anything in-between = mixed substrate oxidation

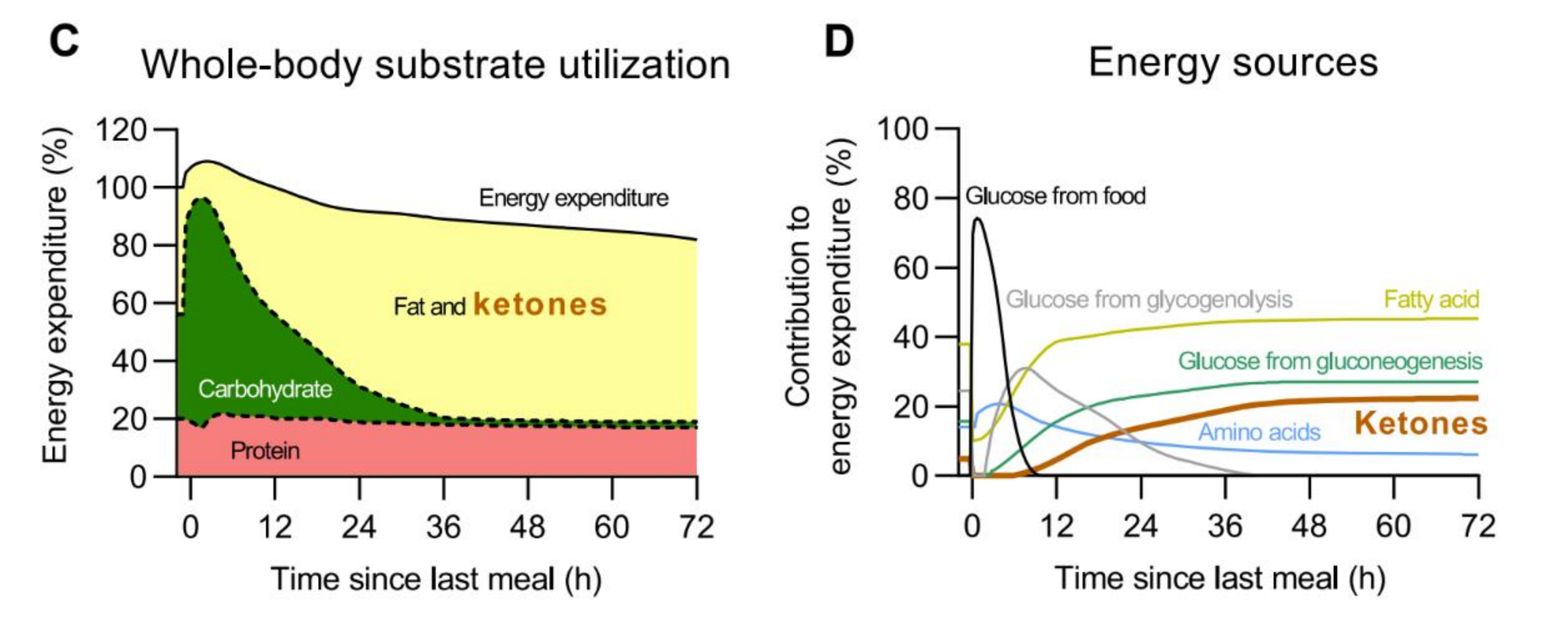
The non-protein RQ can be calculated when UN is known, but is not very reliable in non-steady state urea pool (i.e., in ICU).

Theoretical limitations

1. What’s being oxidized?
2. Steady-state pool size?

1. What's being oxidized?

- Weir (EE) equation assumes all O2 disappearance and CO2 appearance is from COH, Fat and Prot oxidation. True?



Fernandez-Verdejo, J Lipid Res 2023

1. What’s being oxidized?

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- Probably not true in ICU patients. Other metabolic pathways at play…
    - Gluconeogenesis (RQ 0.13 if powered by beta-ox)
    - Ketogenesis (RQ 0)
    - Ketone body oxidation (RQ 0.9-1)
    - Lipogenesis (RQ 5.6)
    - Ethanol oxidation (RQ 0.67)

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- Indirect calorimetry tells you nothing about the ratio of endogenous/exogenous substrates being oxidized!

Is this a problem?

- Intermediate steps don't matter if the metabolic fate is the same.
    - For example, lipolysis → ketogenesis → ketone oxidation will have same net VO_2/VCO_2, RQ and energy yield as complete lipid oxidation.

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- This may be a problem if net production exceeds oxidation or non-oxidative disposal at play, ex
  - Net lipogenesis (overfeeding → high RQ)
  - Ketones retained or excreted in urine (low RQ)
  - Net gluconeogenesis with non-oxidative glucose disposal (low RQ)
  - Ethanol oxidation (low RQ)

2. Steady state conditions

- Body O2 pool is very small (~ 1000 ml), 3-4 x VO2.
  - Changes in respiration have negligible effect on oxygen transport and thus measured VO2.
  - Increased metabolic activity will quickly be reflected in measured VO2

2. Steady state conditions

- Body O_2 pool is very small (~ 1000 ml), 3-4 x VO_2.
  - Changes in respiration have negligible effect on measured VO_2.
  - Increased metabolic activity will quickly be reflected in measured VO_2
- Body CO_2 pool is very large (~ 20 L), 100 x VCO_2.
  - Measured VCO_2 is extremely dependent on steady state respiration

Is this a problem?

- Perturbations in CO_2 pool can take hours to stabilize
  - Hyperventilation → false elevation of VCO_2, high RQ
  - Hypoventilation → false depression of VCO_2, low RQ
  - Elevation in true VCO_2 in fixed MV → measured VCO_2 will lag behind

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- This matters when IC is used in research and for interpretation of RQ (~substrate oxidation)
- Clinically the consequence for variable of interest is small, as VO2 has a much greater impact on EE.

Troubleshooting

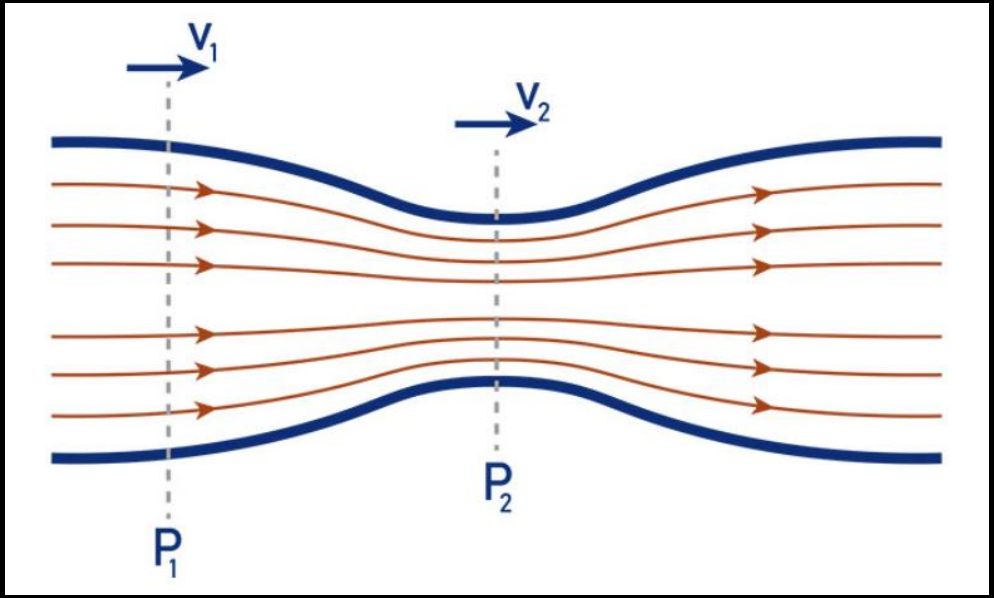
1. Is VO2 and VCO2 fairly constant during measurement?
2. Does RQ reflect mixed substrate oxidation (0.8-0.9)?
3. If not…
   - Was MV stable 1-2 h prior/during measurement? If yes…
   - High RQ → is the patient overfed?
   - Low RQ → is the patient catabolic/in ketosis/drunk?
4. Be skeptical regarding measurements with a very high (≥ 1) or very low (≤ 0.7) RQ. Unlikely that patient is only using glucose or lipids as fuel…

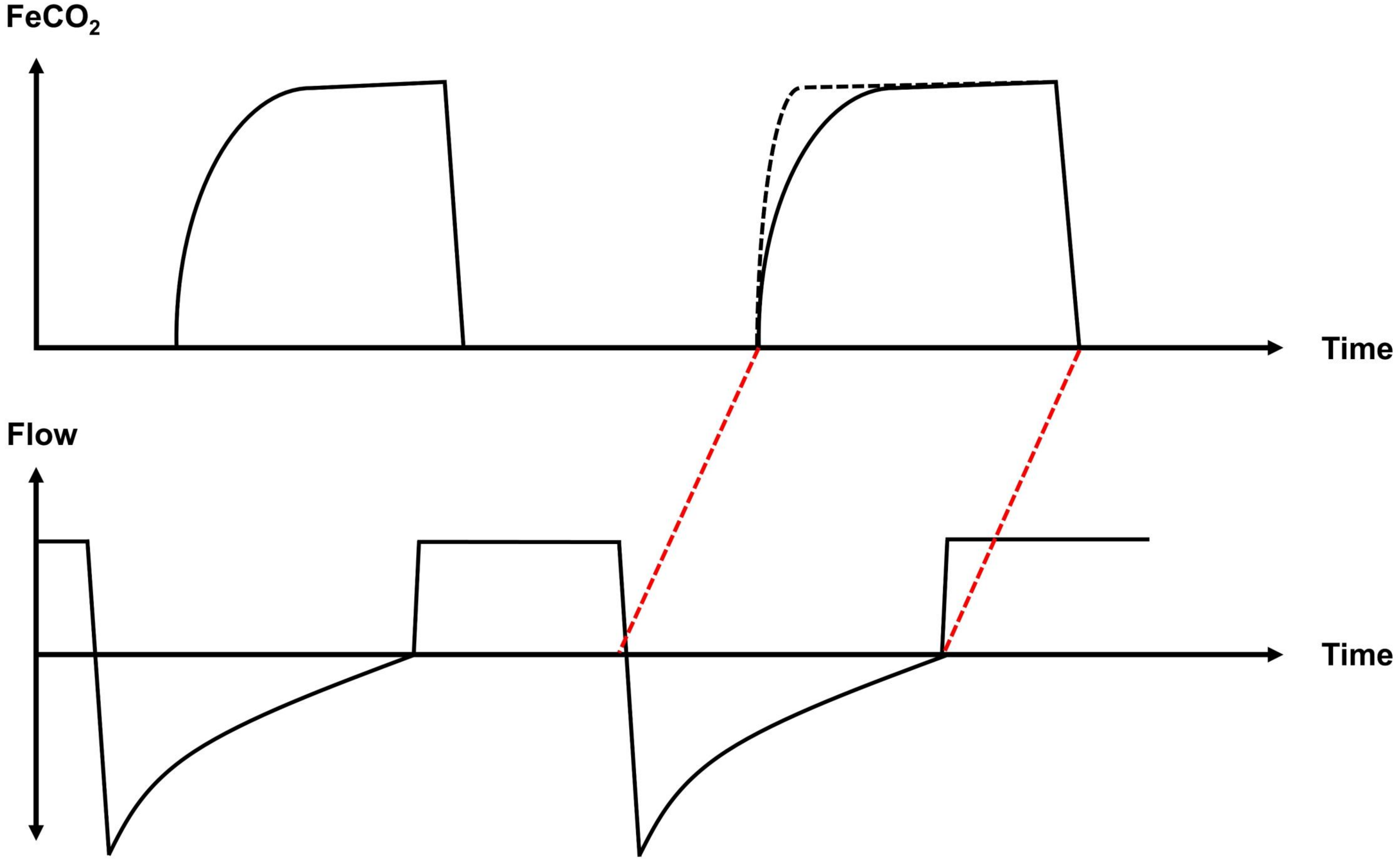
Practical limitations

1. How is gas exchange measured?
2. Potential sources of error?
3. Patient-specific factors

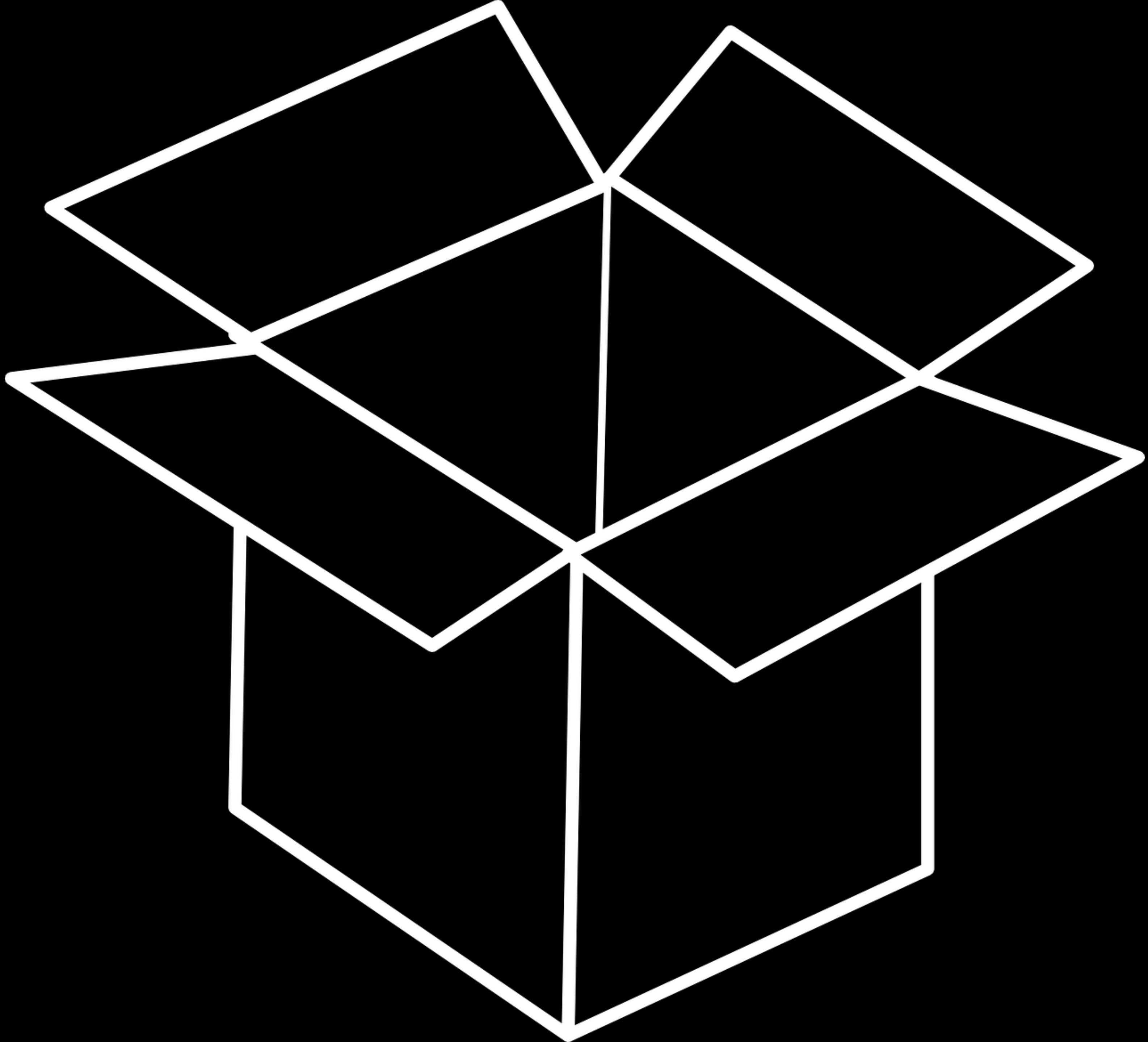
1. How is gas exchange measured?

- Nearly all modern instruments use a breath-by-breath technique
  - Gas is sampled in inspiratory limb and in proximity of ETT
  - Tidal volume is measured by differential pressure flow meter





$FeCO_2$
Time
Flow
Time



2. Pitfalls (pt 1)

- Synchronizing gas concentrations with volumes is complex at/when…
  - High airway pressures
  - High respiratory rates
  - Increased dead space introduced in circuit

- Humidity can interfere with sensors and calculations of gas volumes

2. Pitfalls (pt 2)

- VO_2 is ideally calculated as insp and exp conc*volume
  - Often just one volume is used, assuming no N_2 exchange in lungs
  - Equation to calculate VO_2 can be derived from just Ve, but behaves non-linearly at high FiO_2 (>0.7)
- Most manufacturers don’t recommend performing measurements above this threshold

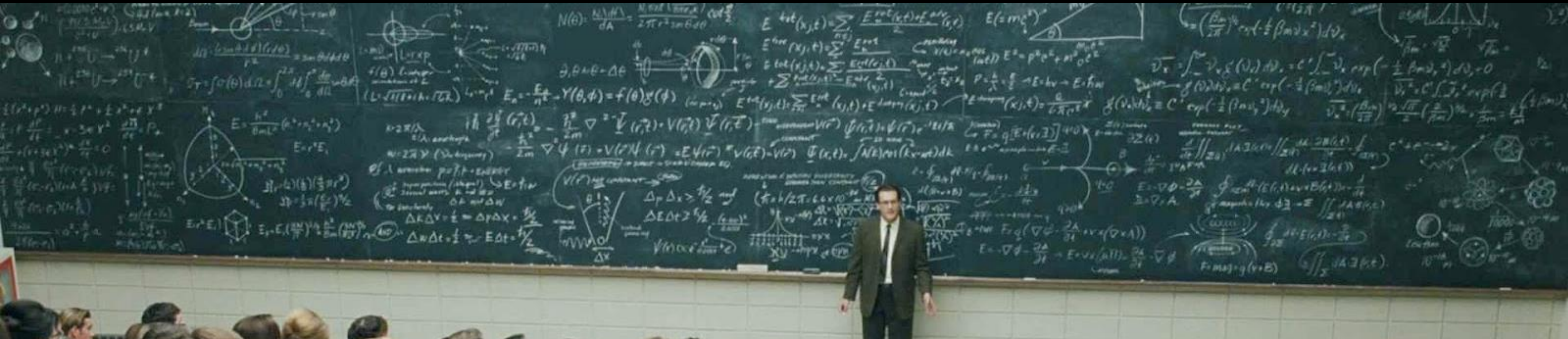
3. Patient-specific factors

- Is the measurement representative?
  - Resting conditions?
  - Fever, shivering, cooling?
- Presence of gas leak in ventilator tubing or patient?
- Extracorporeal CO_2 removal?
  - CO_2 removal during CRRT insignificant

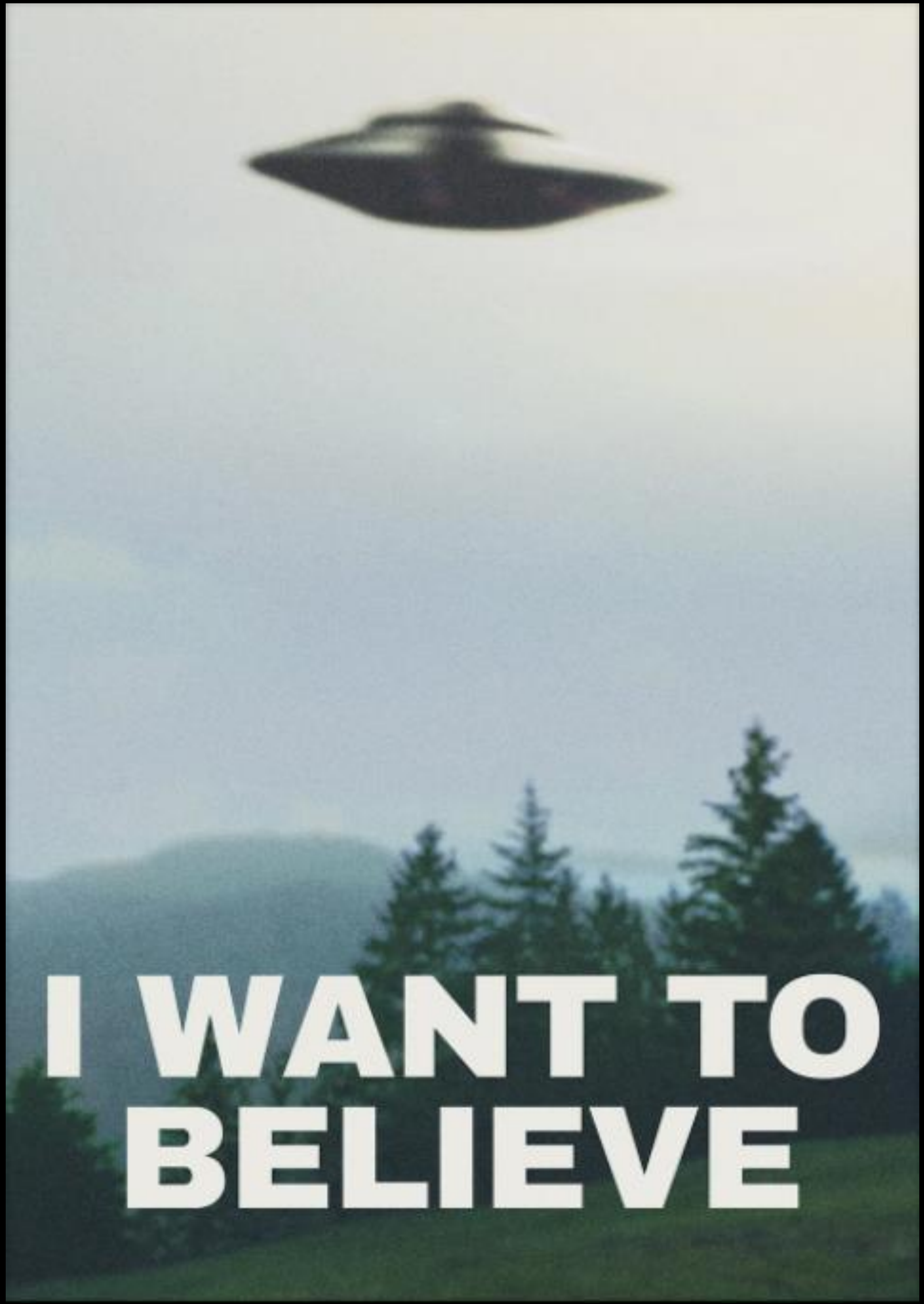
Jonckheer et al, Clinical Nutr 2020

Take-home messages

- Indirect calorimetry is a monitor that measures VO_2 and VCO_2
- Understanding the theoretical, practical and patient-specific limitations is essential to correctly interpret derived variables
- With attention to detail, reliable in majority of patients



The IC in ICU: should we be routinely using it?


I WANT TO
BELIEVE

The case against

RCT:s >100 pts…

- TICACOS (2011)
- EAT-ICU (2018)
- Azevedo et al (2019)
- TICACOS International (2020)

Singer et al, ICM 2011; Singer et al, Clin Nutr 2020; Allingstrup, Intensive Care Medicine 2018; Azevedo et al, Rev Brasiliera de Terapia Intensiva 2019

Duan *et al. Crit Care* (2021) 25:88
https://doi.org/10.1186/s13054-021-03508-6

Critical Care

RESEARCH **Open Access**

Check for updates

Energy delivery guided by indirect calorimetry in critically ill patients: a systematic review and meta-analysis

Jing-Yi Duan[1], Wen-He Zheng[2], Hua Zhou[1], Yuan Xu[1] and Hui-Bin Huang[1*]

Lower short-term mortality, RR 0.77 ($p = 0.03$). ?

Study or Subgroup	IC Events	IC Total	Predictive equation Events	Predictive equation Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Singer 2011	21	65	31	65	28.4%	0.68 [0.44, 1.05]	2011
Yang 2016	1	30	7	30	6.4%	0.14 [0.02, 1.09]	2016
Allingstrup 2017	30	100	32	99	29.5%	0.93 [0.61, 1.40]	2017
Gonzalez-Granda 2018	5	20	3	20	2.7%	1.67 [0.46, 6.06]	2018
Zhao 2019	5	29	7	29	6.4%	0.71 [0.26, 1.99]	2019
Singer 2020	22	200	29	200	26.6%	0.76 [0.45, 1.27]	2020
Total (95% CI)		**444**		**443**	**100.0%**	**0.77 [0.60, 0.98]**	
Total events	84		109				

Heterogeneity: Chi² = 5.16, df = 5 (P = 0.40); I² = 3%
Test for overall effect: Z = 2.11 (P = 0.03)

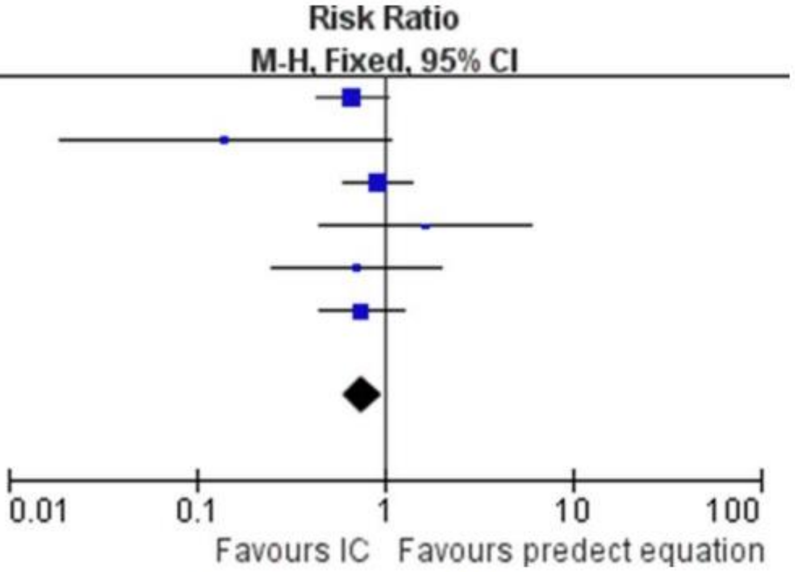


Fig. 2 Forest plot showing the effects of energy delivery guided by indirect calorimetry on short-term mortality rate in critically ill patients

Days in ICU	12.2 ± 8.9	13.1 ± 12.5
Extubation: yes/no	114/85	116/87
Reintubation Yes/no	30/169	29/174
Tracheostomy Yes/no	76/123	65/137
Days in Hospital	25.0 ± 16.0	26.8 ± 28.9
Discharged	197	159
To ward	118	131
To rehabilitation	24	20
To other hospital	8	4
Mortality ICU	46/207	45/199
Mortality 3 months	29/200	22/200
Mortality 180 days	7/198	8/199

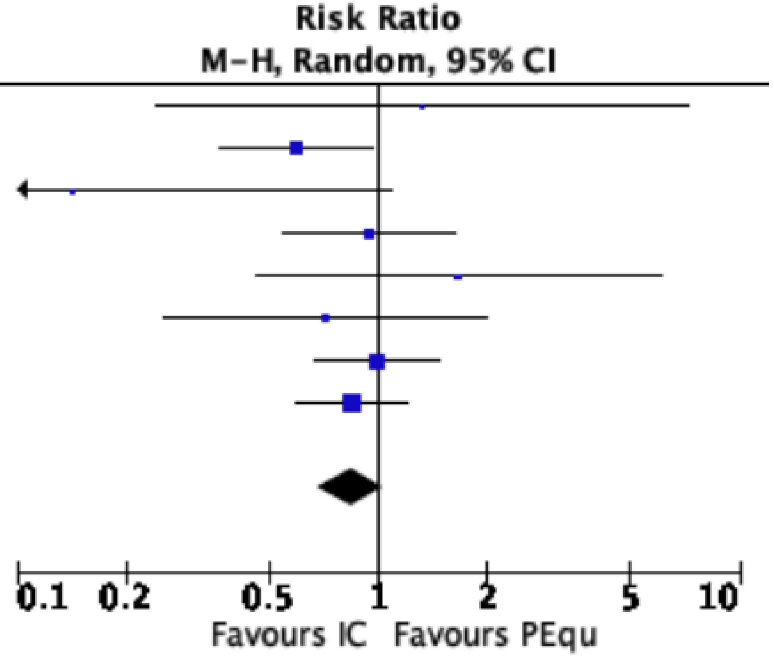
No consistent estimate in different meta-analyses

Figure 1. Overall Mortality

	Indirect calorimetry		Predictive equations			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Saffle	3	26	2	23	1.5%	1.33 [0.24, 7.26]	1990
Singer 2011	16	56	27	56	17.0%	0.59 [0.36, 0.97]	2011
Yang	1	30	7	30	1.0%	0.14 [0.02, 1.09]	2016
Allingstrup	20	100	21	99	14.1%	0.94 [0.55, 1.63]	2017
Gonzales-Granda	5	20	3	20	2.6%	1.67 [0.46, 6.06]	2018
Zhao	5	29	7	29	4.1%	0.71 [0.26, 1.99]	2019
Azevedo	26	57	29	63	26.7%	0.99 [0.67, 1.46]	2019
Singer 2020	45	209	53	208	33.0%	0.84 [0.60, 1.20]	2020
Total (95% CI)		527		528	100.0%	0.84 [0.68, 1.04]	
Total events	121		149				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.19$, df = 7 (P = 0.41); $I^2 = 3\%$

Test for overall effect: Z = 1.62 (P = 0.11)

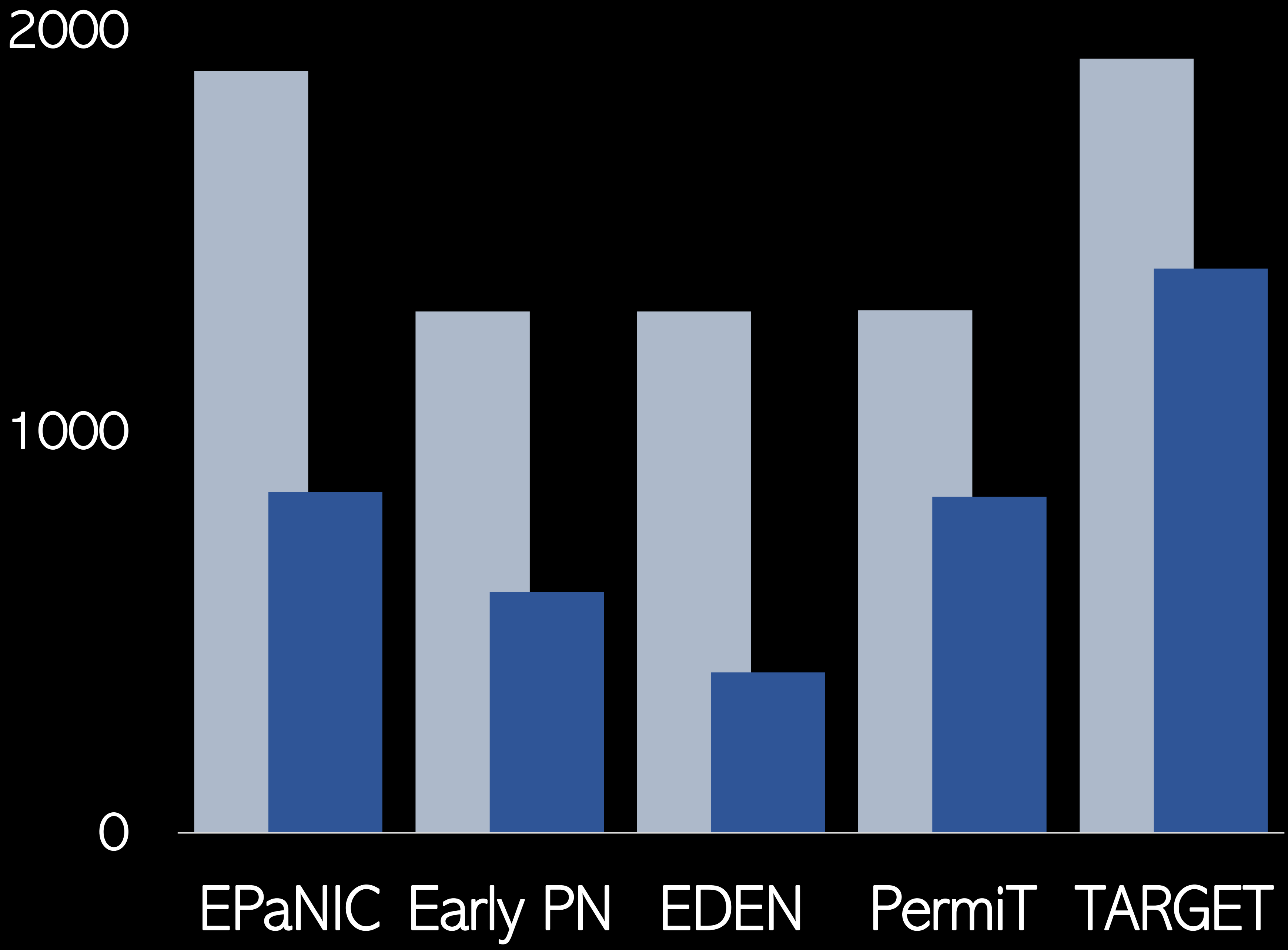


Heyland et al, criticalcarenutrition.com 2021 Watanabe et al, Nutrients 2024

Study/year	Mean energy delivered/day, kcal/day, mean ± SD	
	IC	PE
Singer 2011 [7]	2086 ± 460	1480 ± 356
Landes 2016 [22]	NR	NR
Allingstrup 2017 [20]	1877 ± 509	1061 ± 537
Gonzalez-Granda 2018 [21]	20 ± 6[a]	20 ± 8[a]
Shi 2019 [13]	NR	NR
Zhao 2019 [15]	NR	NR
Singer 2020 [14]	1746 ± 755	1301 ± 535
Yang 2016 [23]	NR	NR

IC results in higher energy delivery…

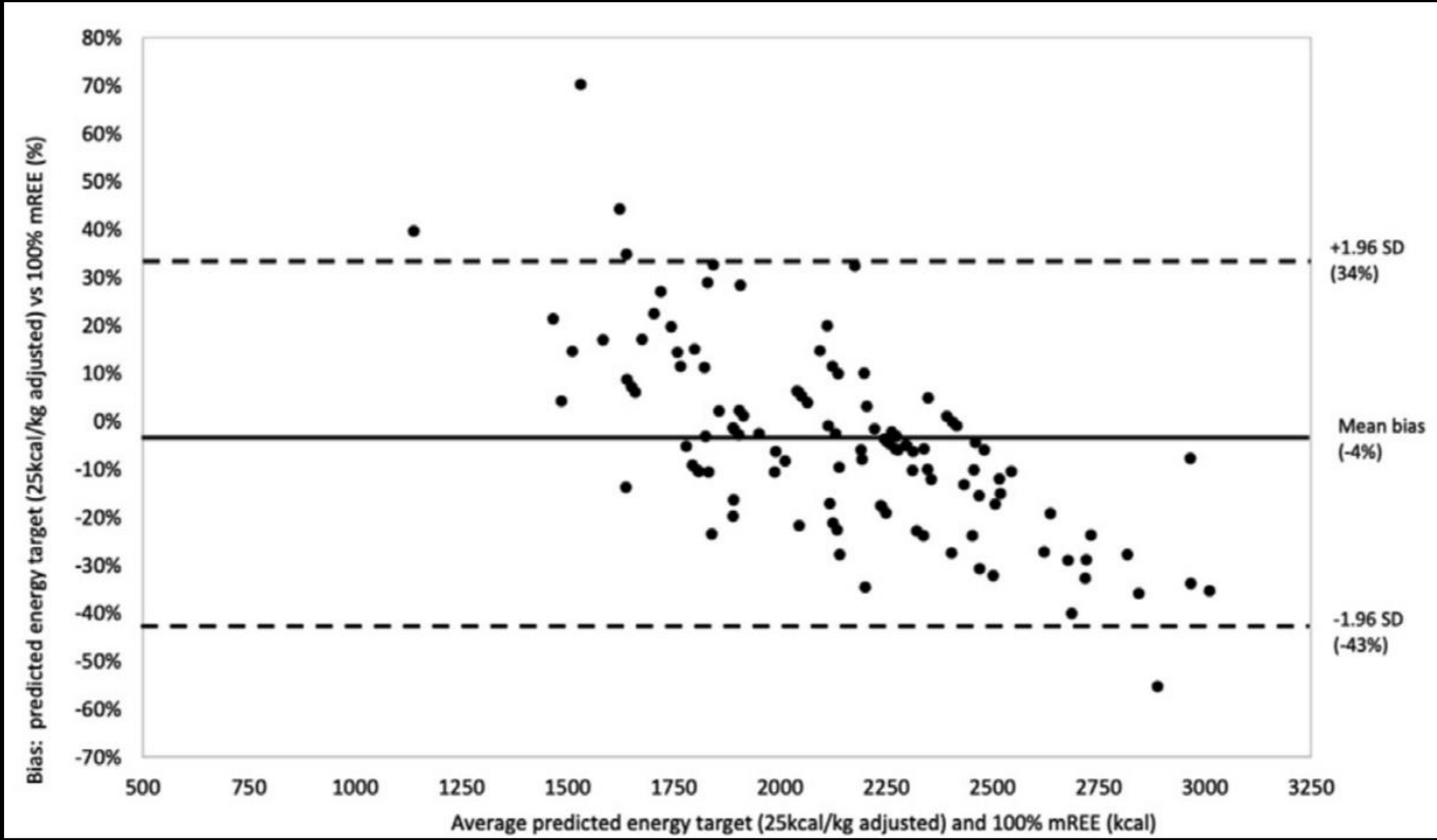
Frequently no more than 25-30% difference.


2000
1000
0
EPaNIC
Early PN
EDEN
PermiT
TARGET

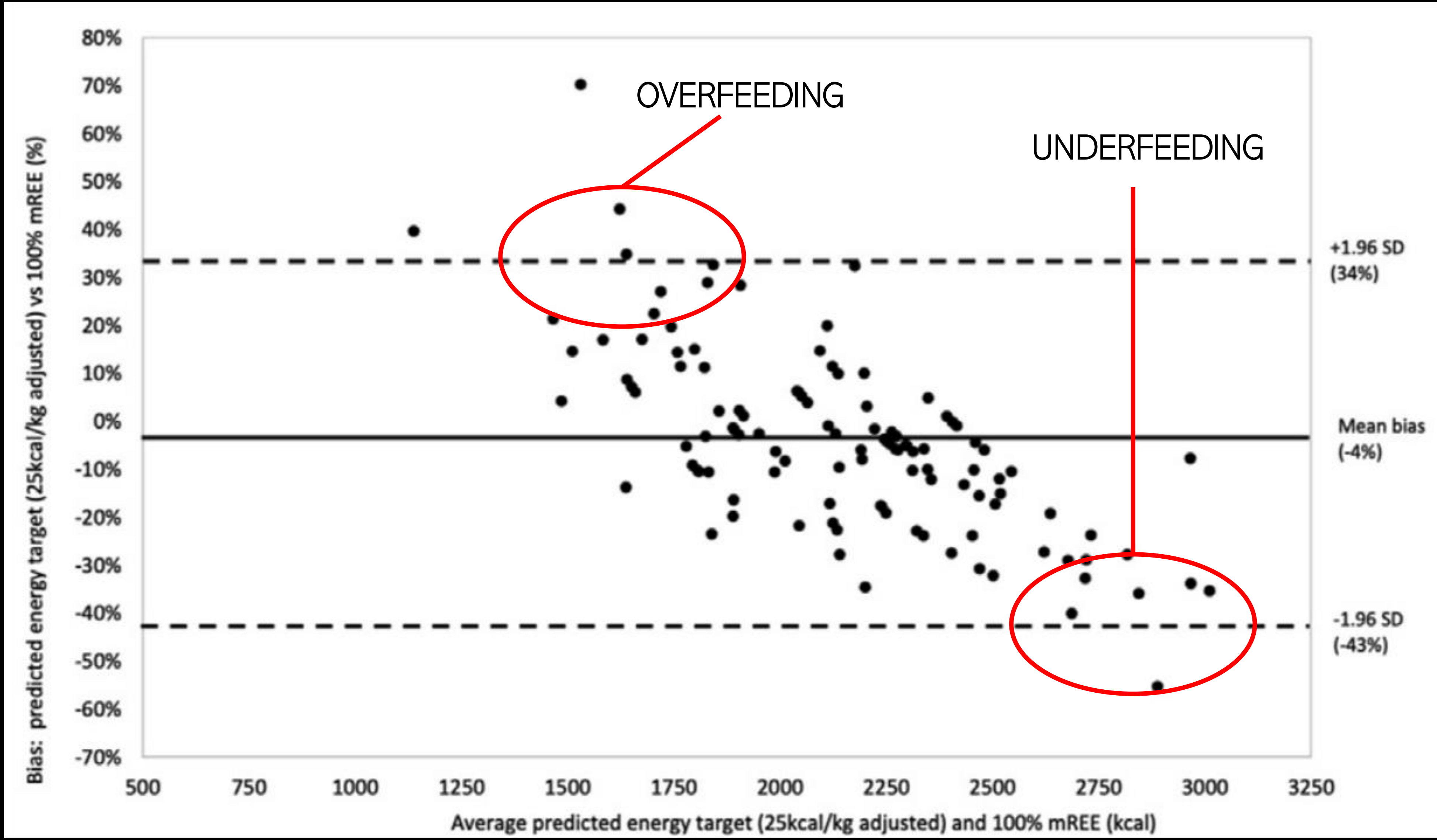
The (non-evidence based) case in favor

We know that predictive equations to estimate metabolic rate perform poorly in individual ICU patients.

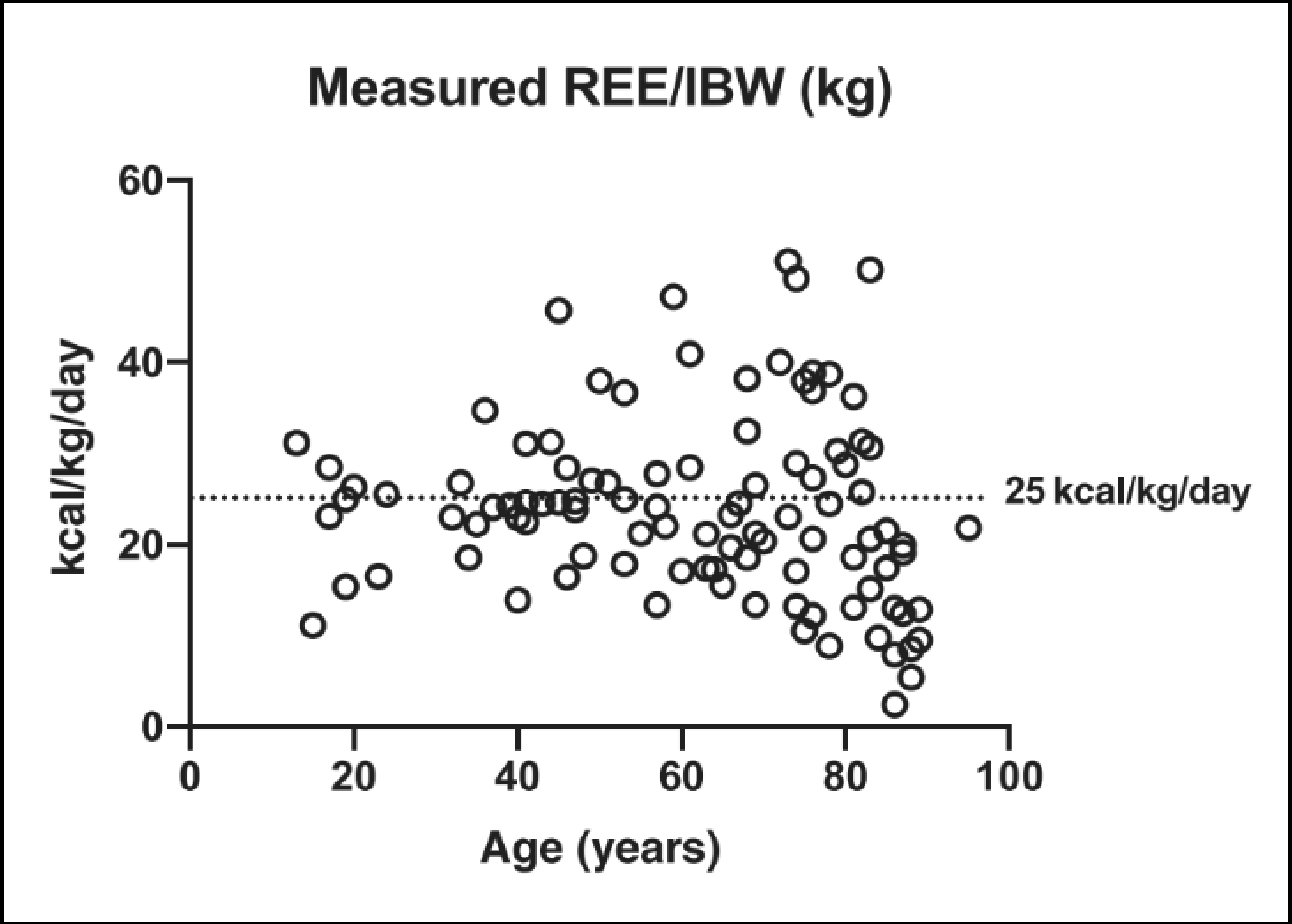
Is there any clinical relevance to getting it wrong?



Lambell et al, Clin Nutrition 2023



Lambell et al, Clin Nutrition 2023



Ebihara et al, JPEN 2022

Large RCT:s on energy delivery either short intervention (1-2 weeks) or small # of patients with prolonged ICU stay.

Signal of harm from prolonged underfeeding very difficult to detect in RCT:s of general ICU patients.

Large cumulative errors (+/-) are probably bad.

My opinions

- During first week in ICU, probably no benefit to IC over conservative energy delivery
- Early IC may avoid overfeeding in patients with very low metabolic rate
- In patients with IMV >7-10 days, IC should be used repeatedly to avoid significant over/underfeeding

My opinions

NUTRITION AND THE INTENSIVE CARE UNIT: EDITED BY MICHAEL P CASAER AND ADAM M DEANE

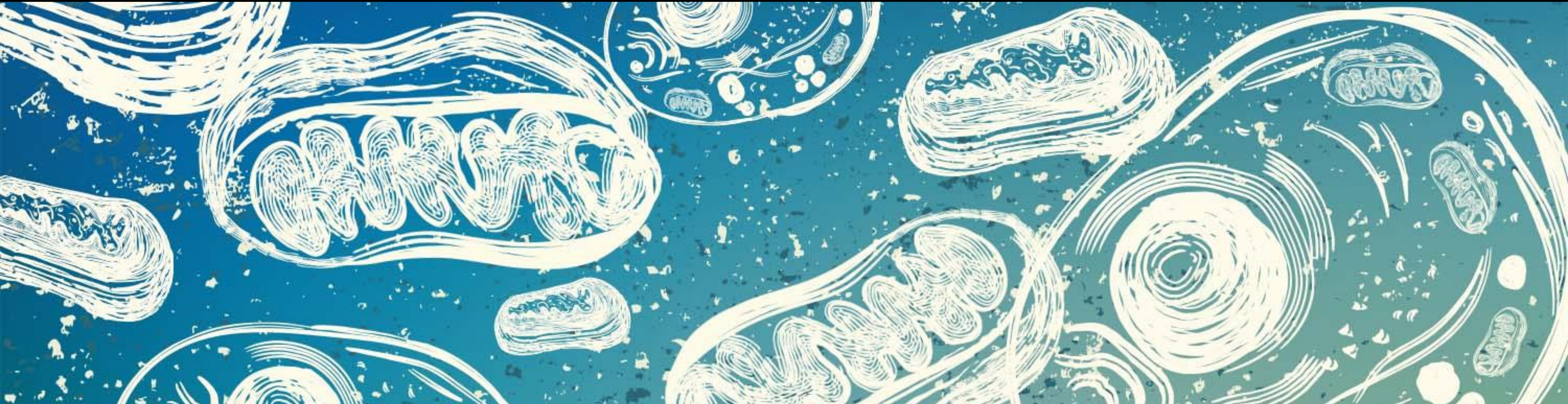
Indirect calorimetry: should it be part of routine care or only used in specific situations?

Sundström Rehal, Martin[a,b]; Tatucu-Babet, Oana A.[c]; Oosterveld, Timo[b]

Author Information

Current Opinion in Clinical Nutrition and Metabolic Care 26(2):p 154-159, March 2023. | ***DOI:*** 10.1097/MCO.0000000000000895

Tack (thanks)!



Further reading

- “Handbook of gas exchange and indirect calorimetry”, Jukka Takala & Pekka Meriläinen
- Ferrannini E: “The theoretical bases of indirect calorimetry: a review, Metabolism, Vol 37, No 3(March),1988:pp287-30
- Simonson DC, DeFronzo RA. Indirect calorimetry: methodological and interpretative problems. Am J Physiol. 1990 Mar;258(3 Pt 1):E399-412.