Determination of glucose consumption, deoxyglucose method

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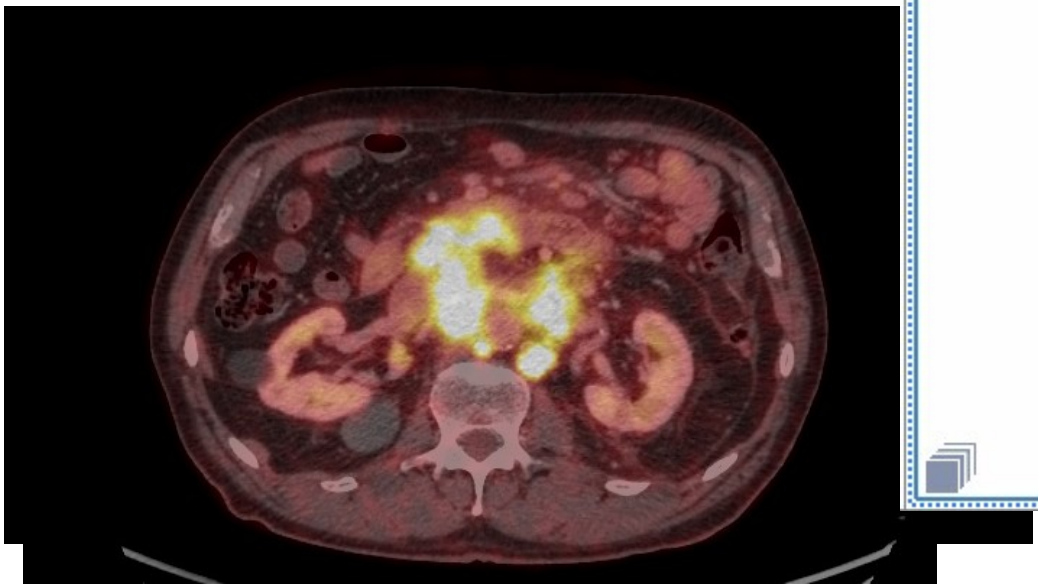
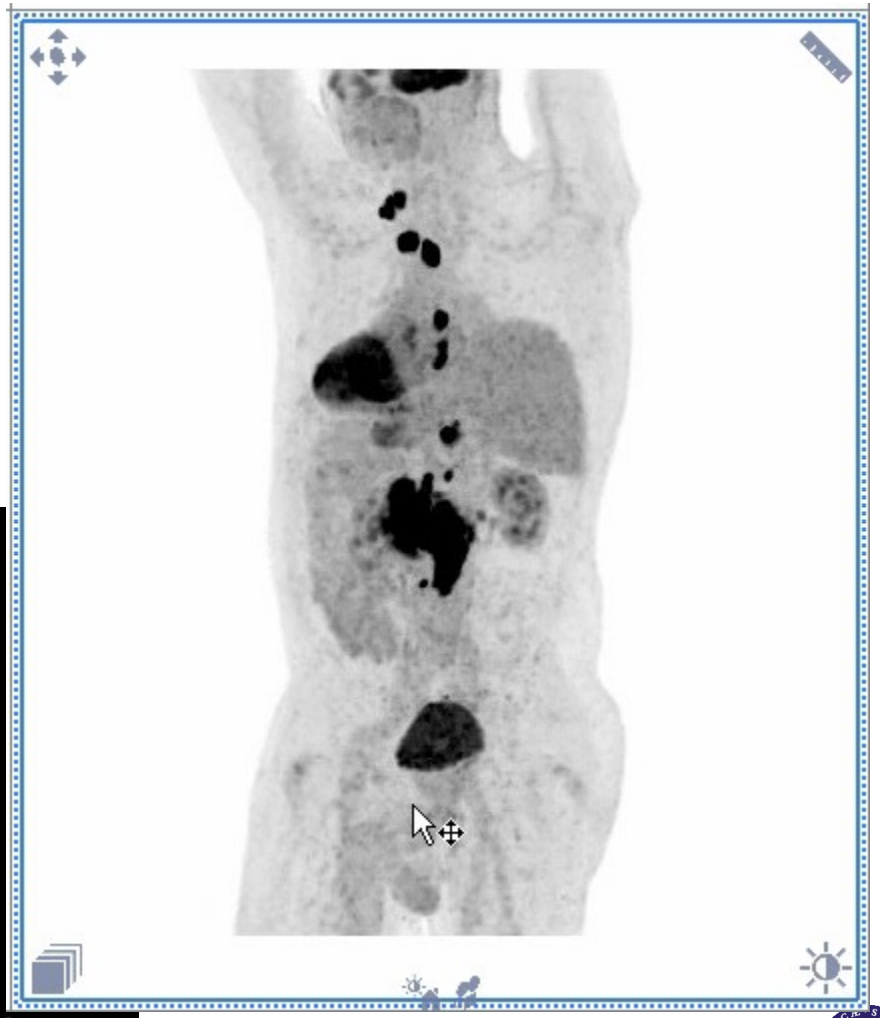
[^{18}F]FDG PET

55 year-old-man with night sweats, and weight loss of 5 kg

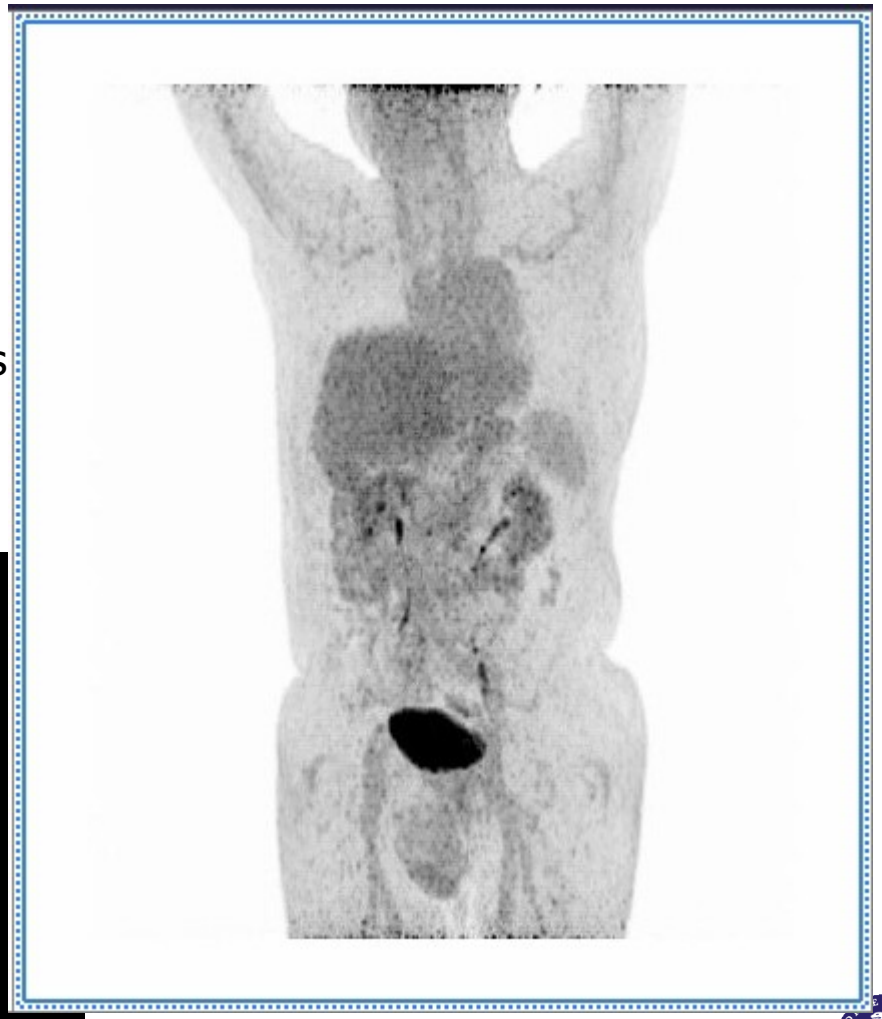


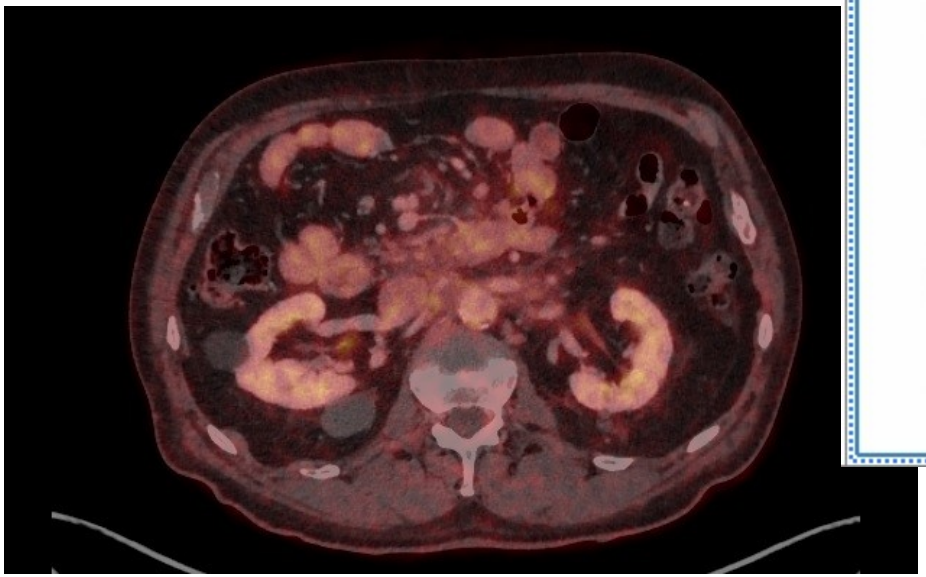


[^{18}F]FDG PET

55 year-old-man with night sweats, and weight loss of 5 kg

Biopsy show lymphoma. After 6 cycles of chemotherapy this is his PET/CT scan:





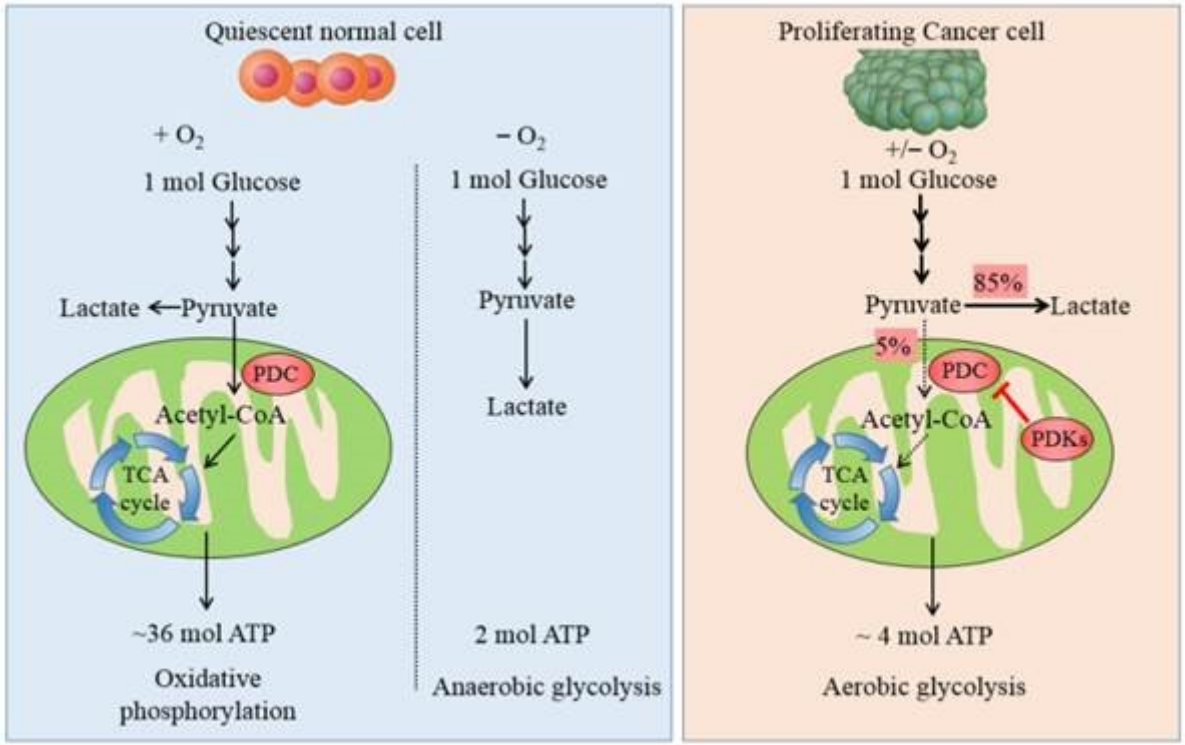
[^{18}F]FDG PET

The introduction of [^{18}F]FDG PET/CT has been a game changer in cancer diagnostics the last 25 years

But why is it so good?

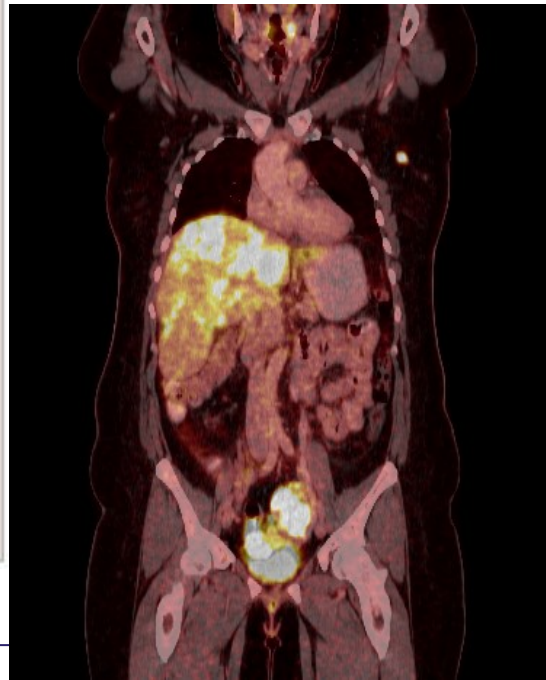
The Warburg Effect

Cancer cells can change from oxidative phosphorylation to lactate production. Thereby glycolysis can be increased up to 200 times even at normal oxygen levels



Int J Biol Sci 2015; 11(12):1390-1400.

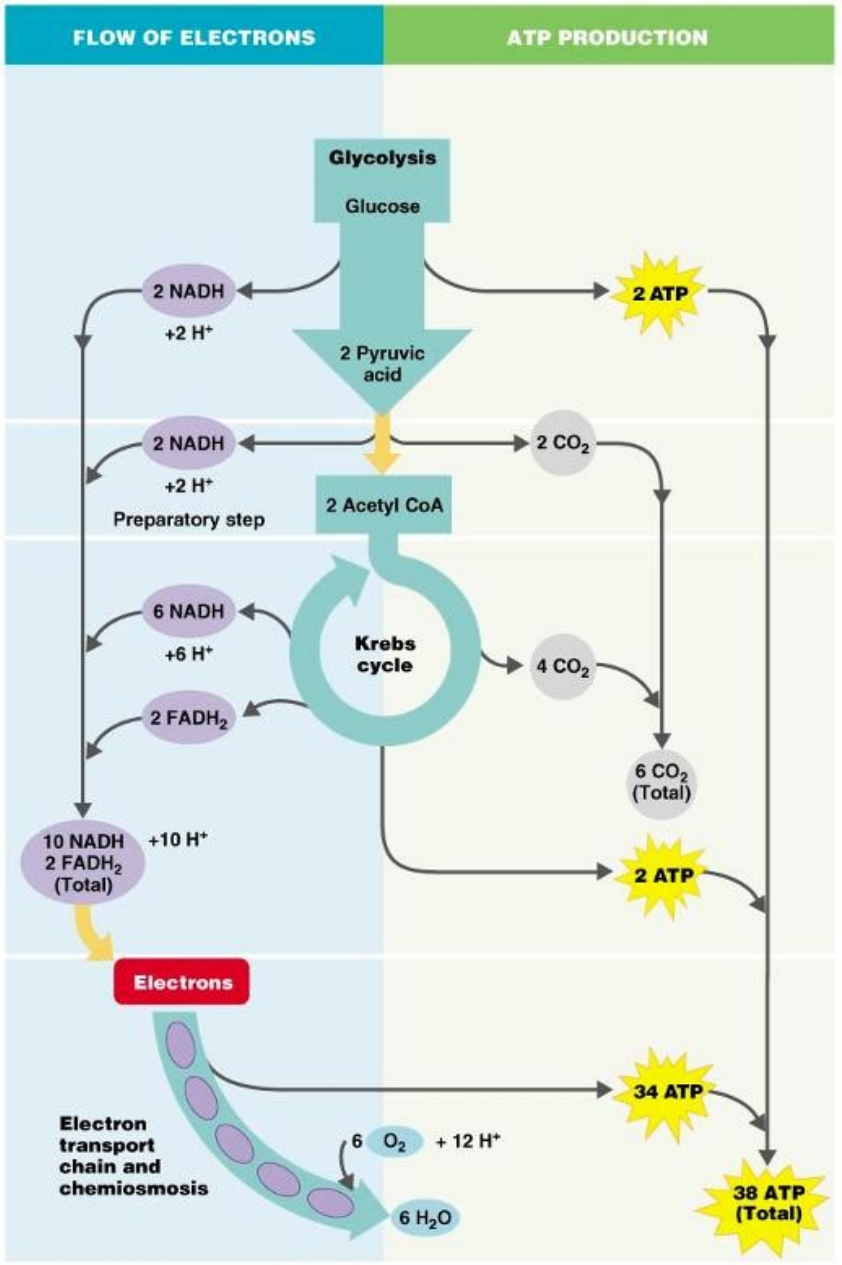
Otto H. Warburg
1883 - 1970
Nobel prize in physiology



Glucose metabolism

- Glycolysis requires no oxygen
- Only little energy production
- Oxygen consuming breakdown of glucose through Krebs cycle and electron chain reactions leads to high energy production

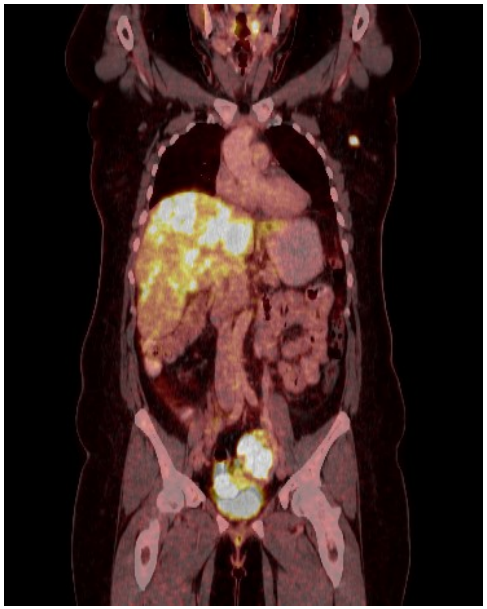
- Pyruvate can be transformed into lactate, which keeps NADH levels stable



[^{18}F]FDG PET

The introduction of [^{18}F]FDG PET/CT has been a game changer in cancer diagnostics the last 25 years

Actually, [^{18}F]FDG PET/CT is so good that you don't need to do quantification



Blobologi:
FDG PET/CT - whole body imaging – hot spots correlate to quantitative K_i measures

Thoracic Radiology

Heikki Minn, MD[2] • Kenneth R. Zasadny, PhD • Leslie E. Quint, MD • Richard L. Wahl, MD

Lung Cancer: Reprod
Quantitative Measure
2-[F-18]-Fluoro-2-dec

PURPOSE: To study the precision of repeated 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) uptake measurements at positron emission tomography (PET) in patients with primary lung cancer.

MATERIALS AND METHODS: Ten patients with untreated lung cancer

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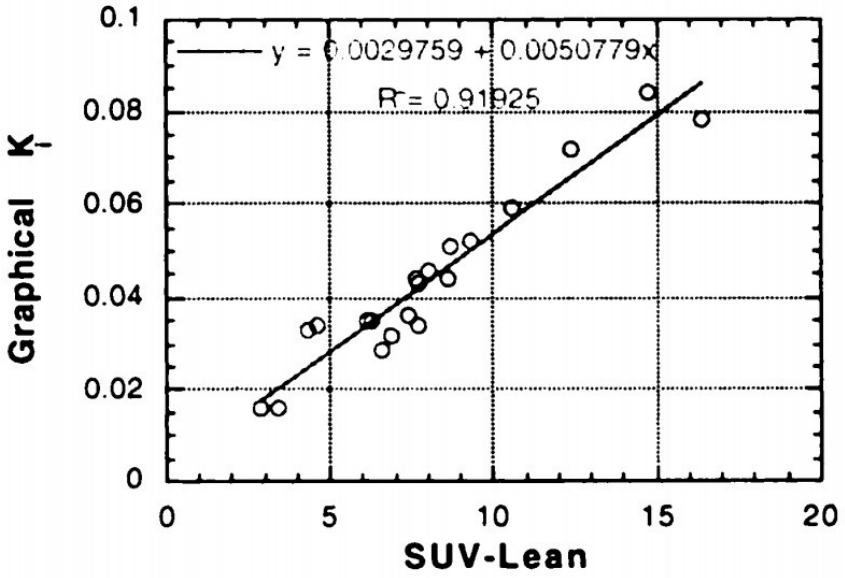

Figure 5. Relationship between SUV-lean and K_i in 20 FDG PET scans obtained in 10 patients with lung cancer.

Minn et al. 1995. Radiology 196(1):167-73

[^{18}F]FDG PET

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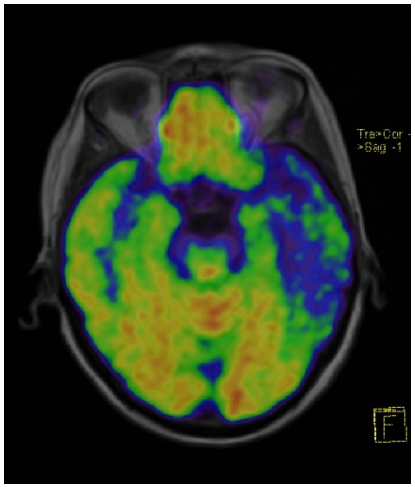
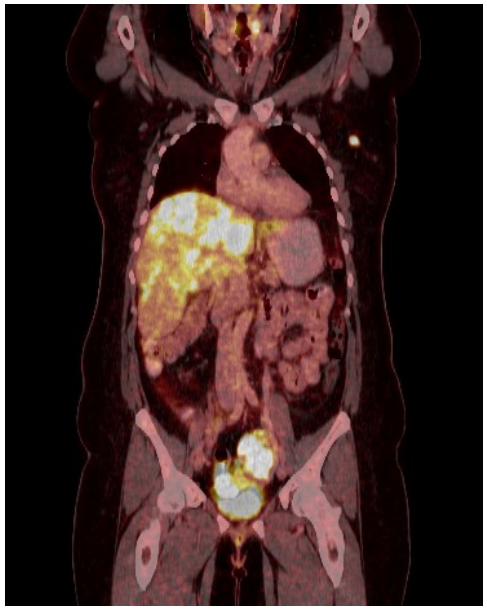
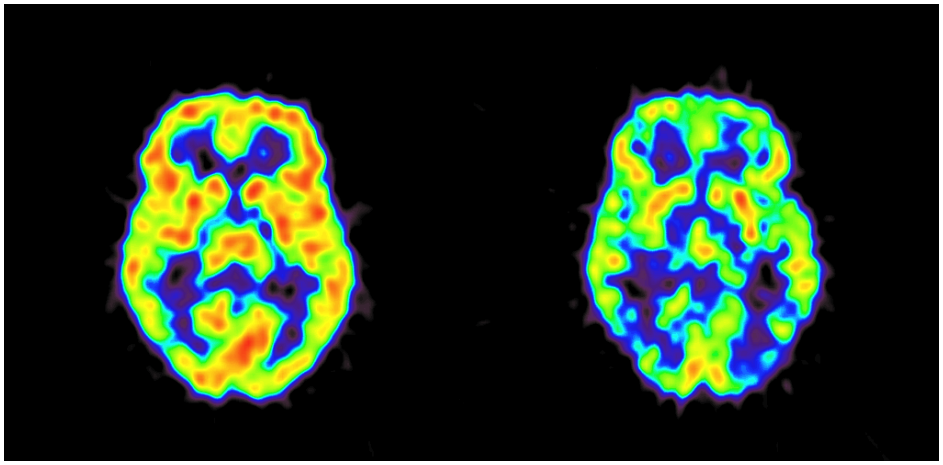


Temporal reduction in frontotemporal dementia (semantic dementia)



No need for quantification when looking for regional differences or hotspots

Quantitation of regional metabolic rate of glucose - rMRglc



33% reduction in CMRglc
during ketone infusion
– global changes

Glucose measurements methods

1. Global measurements
   - Using global blood flow measurements and Fick´s principle

2. Regional measurements using imaging
   - Deoxyglucose method in animals
   - Fluoro-deoxyglucose method in humans

THE FICK PRINCIPLE

"Everything that goes in and doesn't come out again has been taken up by the organ"

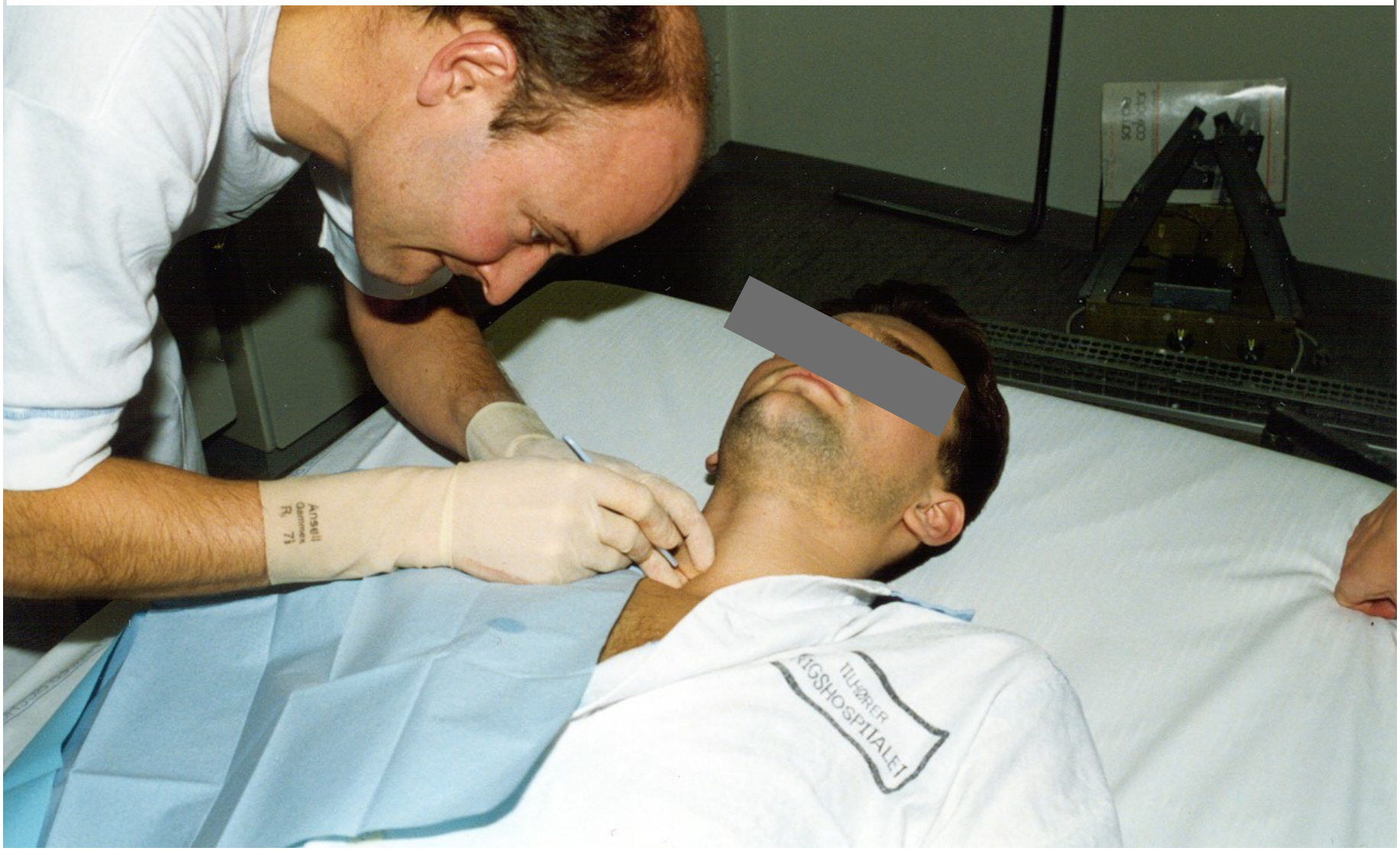
$$\text{Uptake} = F(C_a - C_v)$$

F= blood flow
C_a and C_v= substrate concentrations in arterial and cerebral venous blood

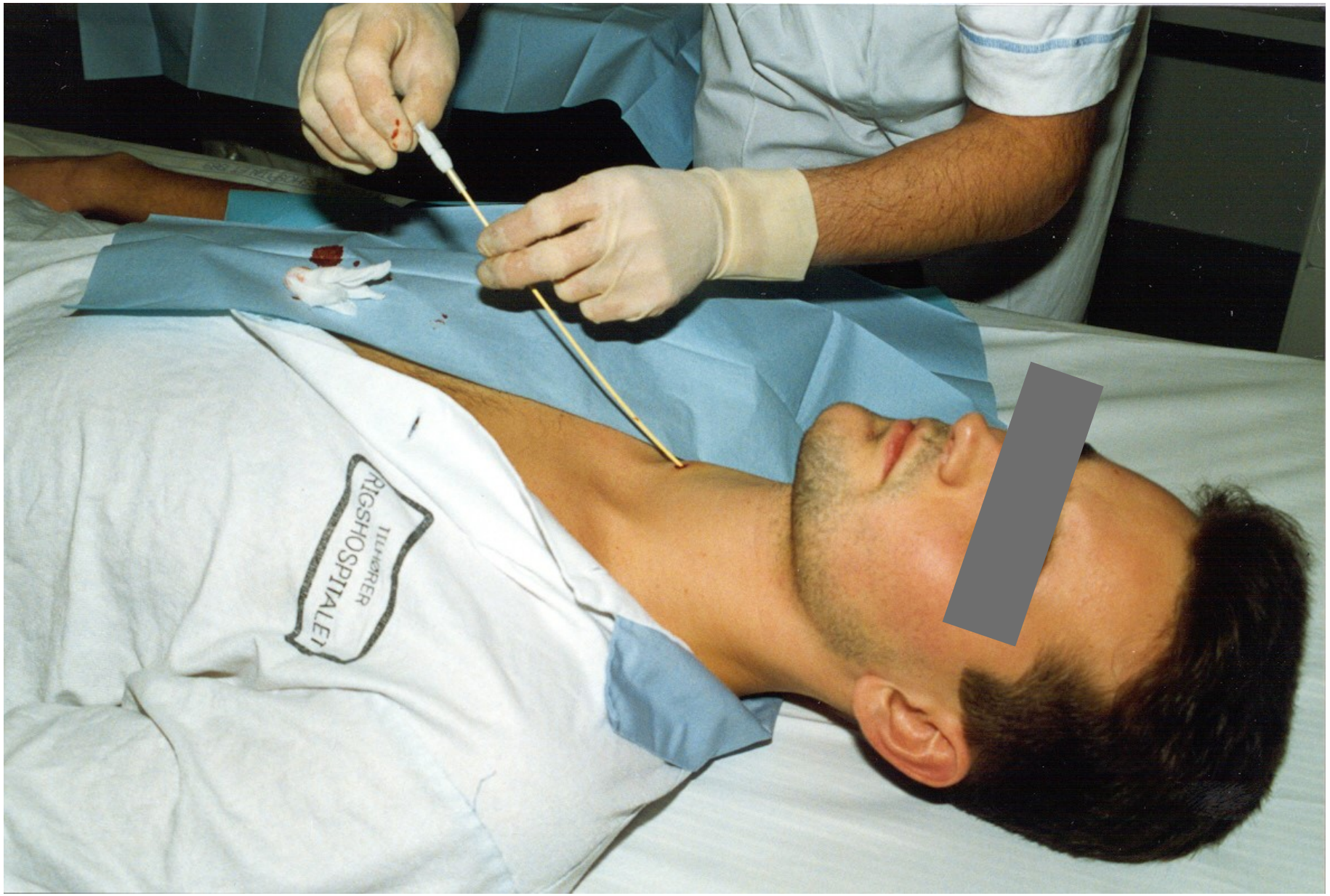
F can be measured by the Fick Principle by using an inert gas (Xenon)

Disadvantages: Very invasive!

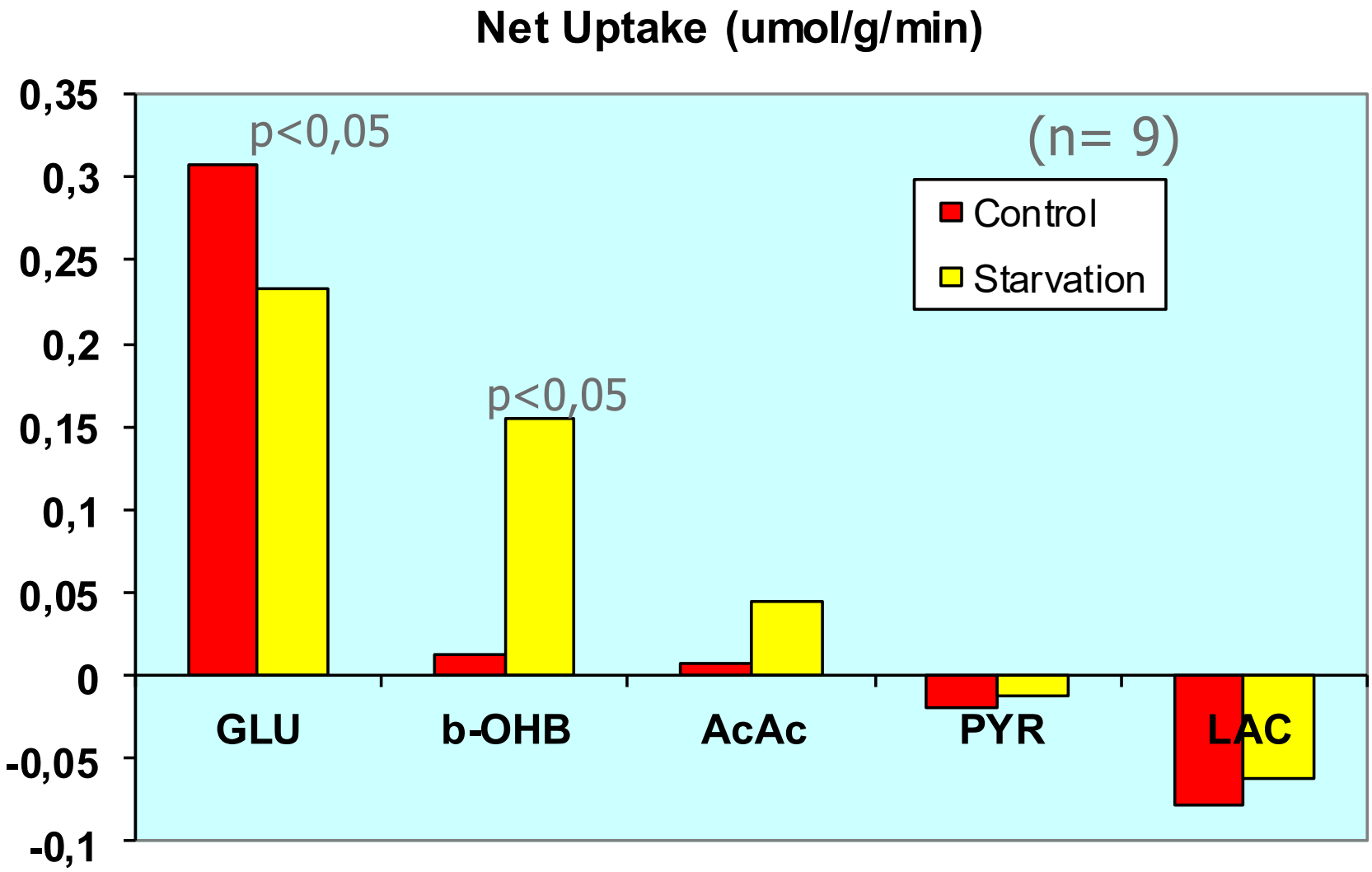
Catheter in the internal jugular vein is necessary to measure cerebral venous blood



Catheter in the internal jugular vein



Advantages: Almost everything can be measured
Ex: Brain Carbohydrate Metabolism after 3.5 Days of Starvation



Hasselbalch et al., JCBF, 1994

The deoxyglucose method

Journal of Neurochemistry, 1977, Vol. 28, pp. 897–916. Pergamon Press. Printed in Great Britain.

THE [^{14}C]DEOXYGLUCOSE METHOD FOR THE MEASUREMENT OF LOCAL CEREBRAL GLUCOSE UTILIZATION: THEORY, PROCEDURE, AND NORMAL VALUES IN THE CONSCIOUS AND ANESTHETIZED ALBINO RAT[1]

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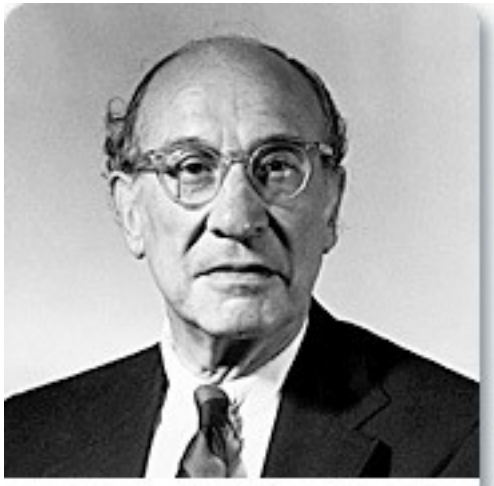
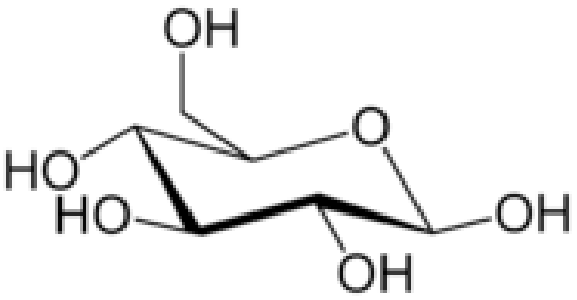
(*Received* 3 *November* 1976. *Accepted* 12 *January* 1977)

Abstract—A method has been developed for the simultaneous measurement of the rates of glucose consumption in the various structural and functional components of the brain *in vivo*. The method can be applied to most laboratory animals in the conscious state. It is based on the use of 2-deoxy-D-[^{14}C]glucose ([^{14}C]DG) as a tracer for the exchange of glucose between plasma and brain and its phosphorylation by hexokinase in the tissues. [^{14}C]DG is used because the label in its product,

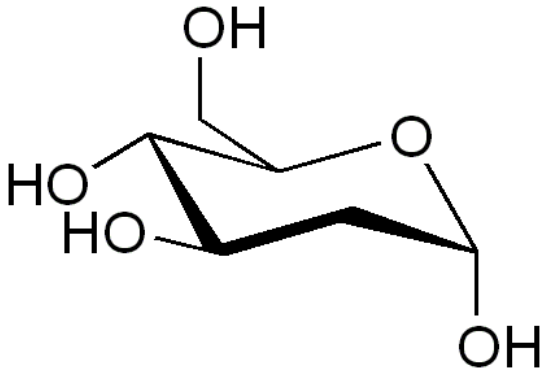


Louis Sokoloff
National Institute of Mental Health, NIH

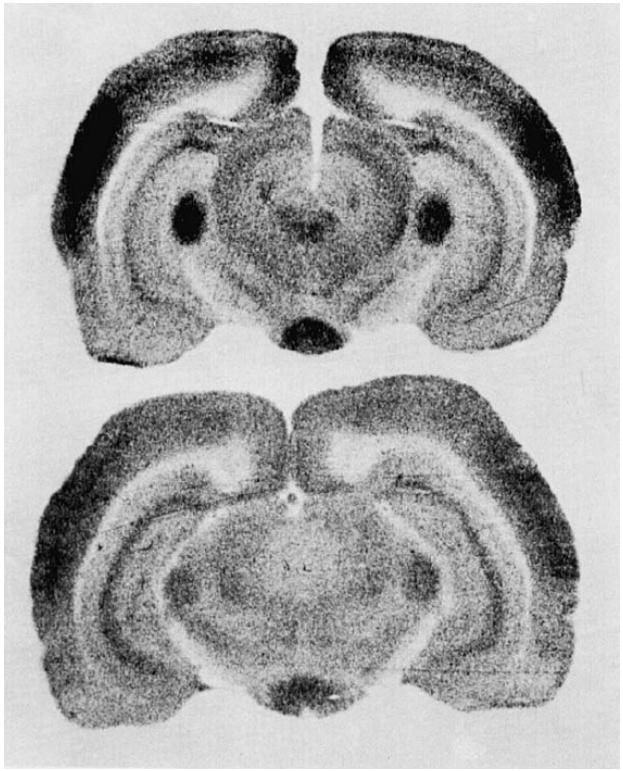
The deoxyglucose method

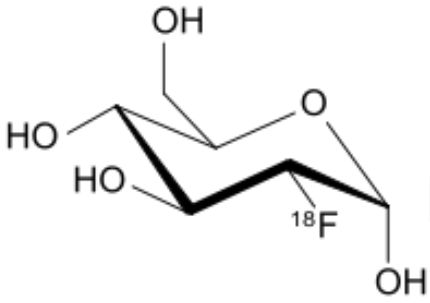


D-glucose

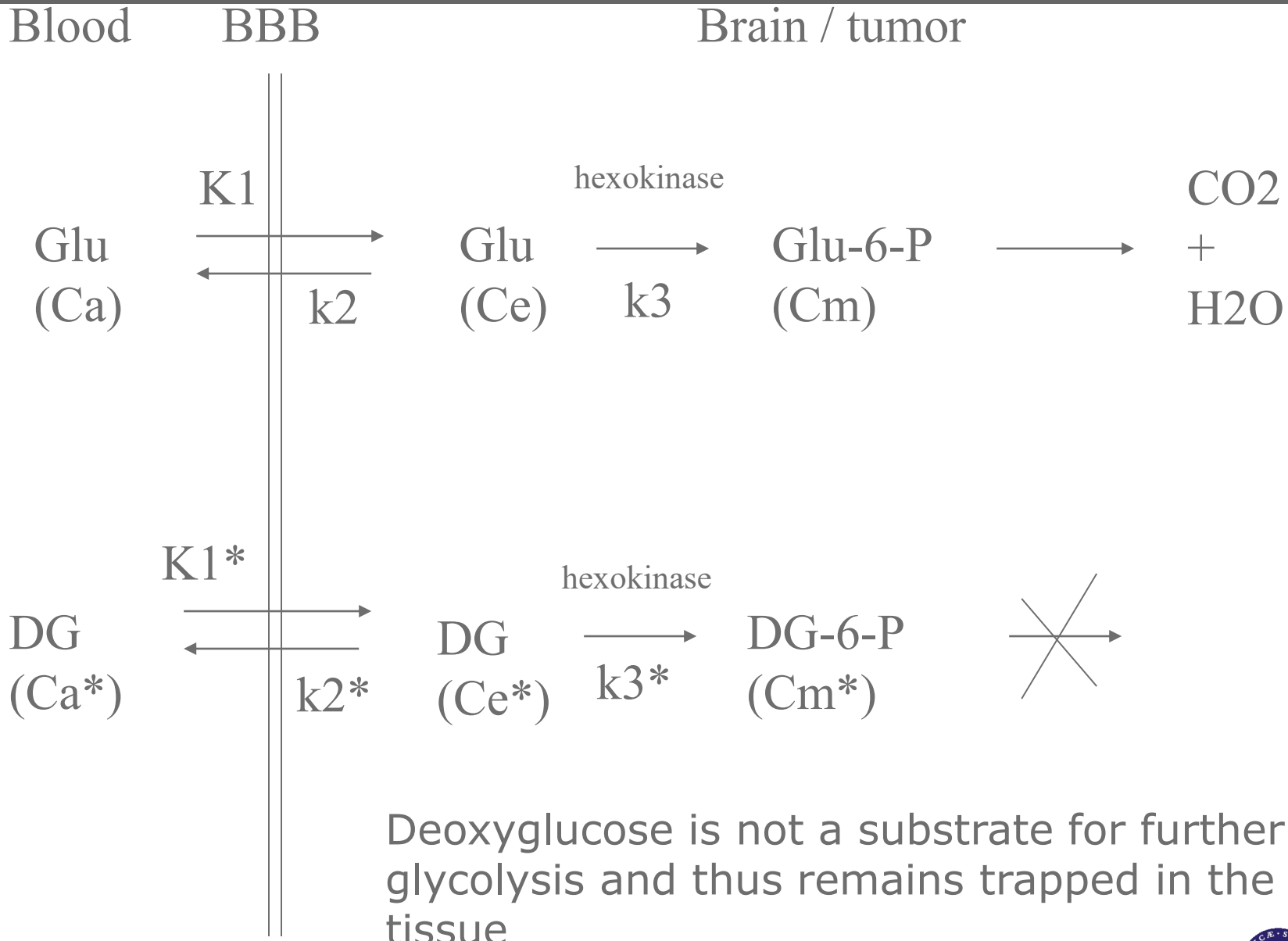


[^{14}C]2-deoxy-D-glucose



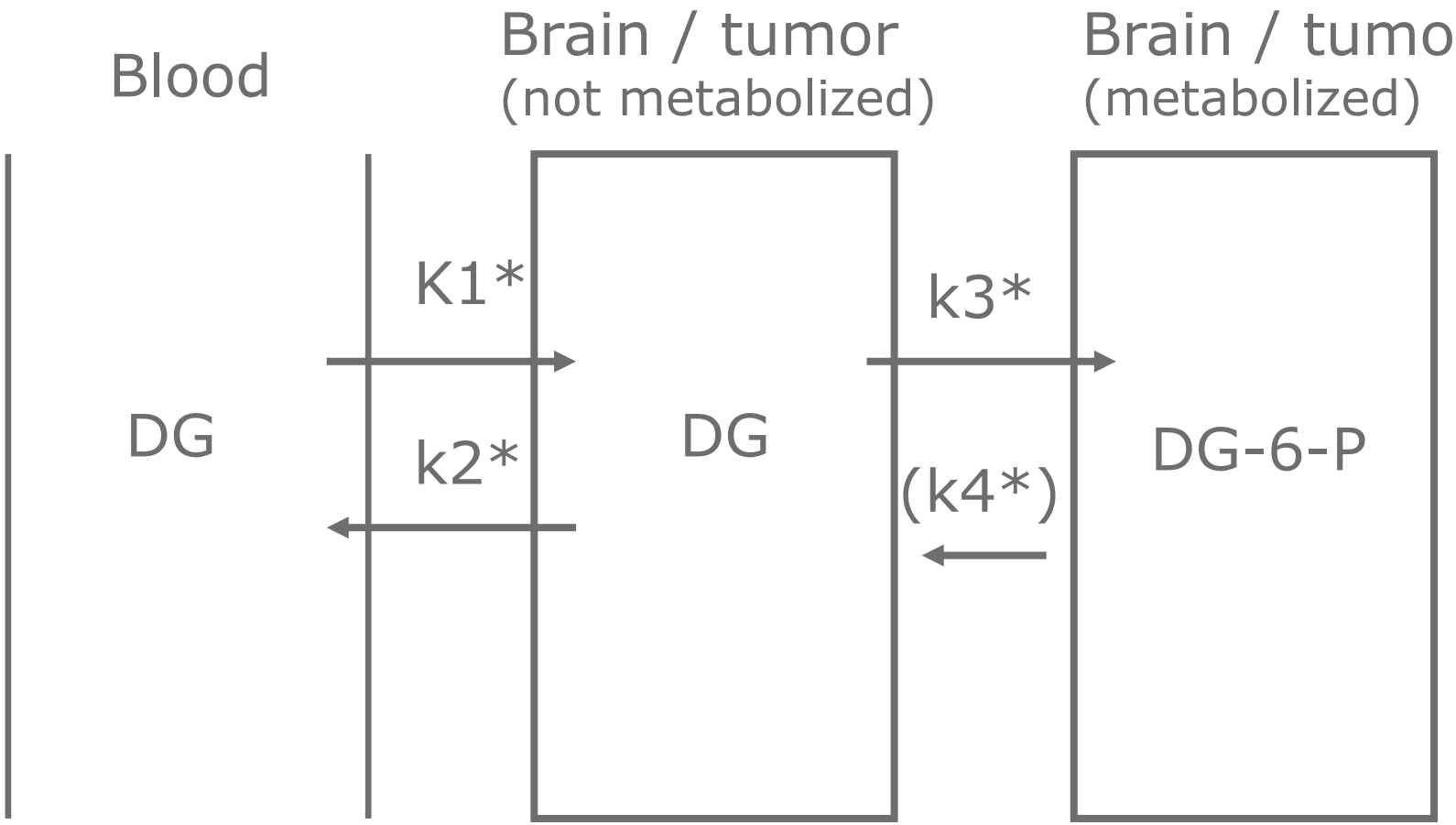


[^{18}F]2-deoxy-D-glucose = [^{18}F]FDG

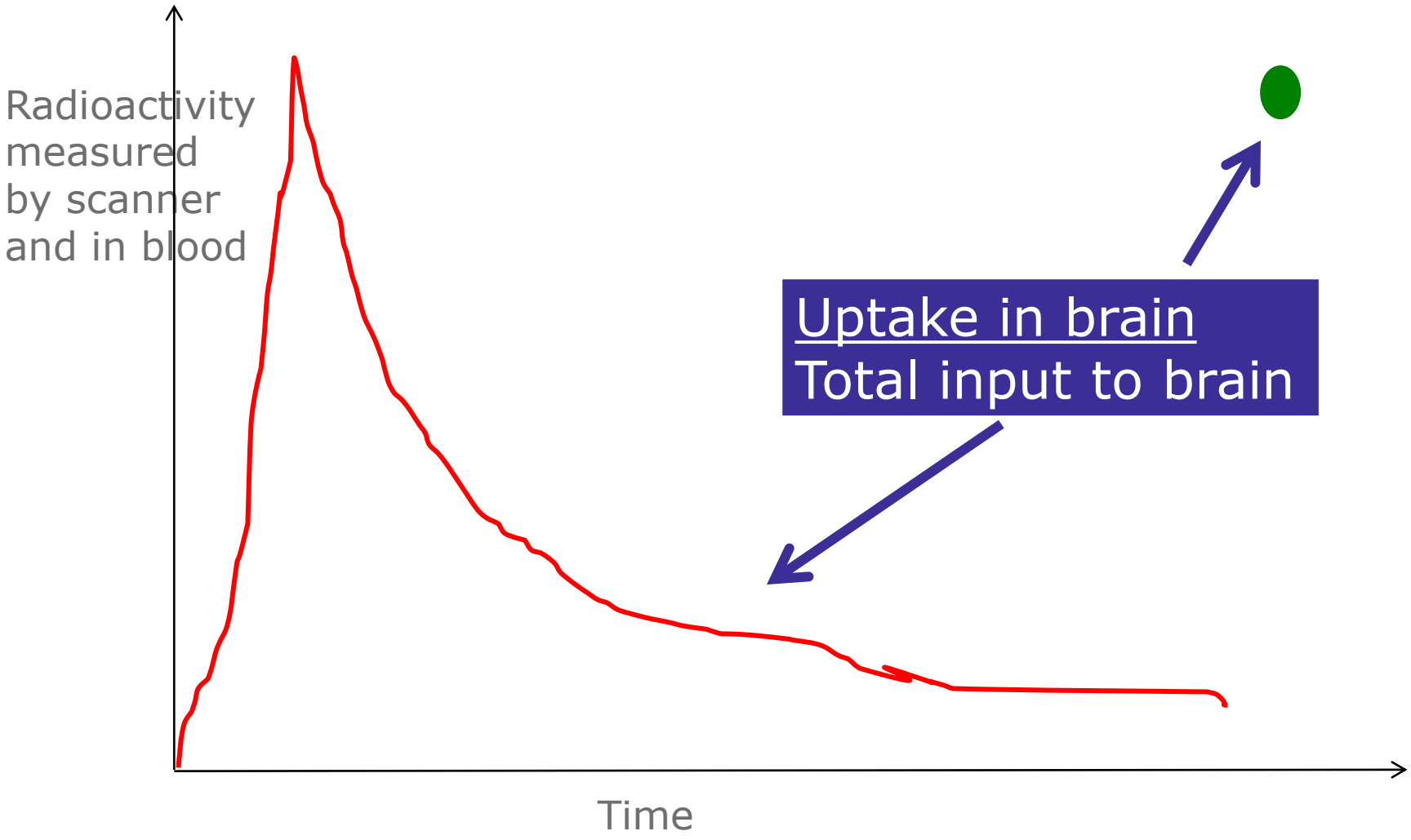


Deoxyglucose is not a substrate for further glycolysis and thus remains trapped in the tissue

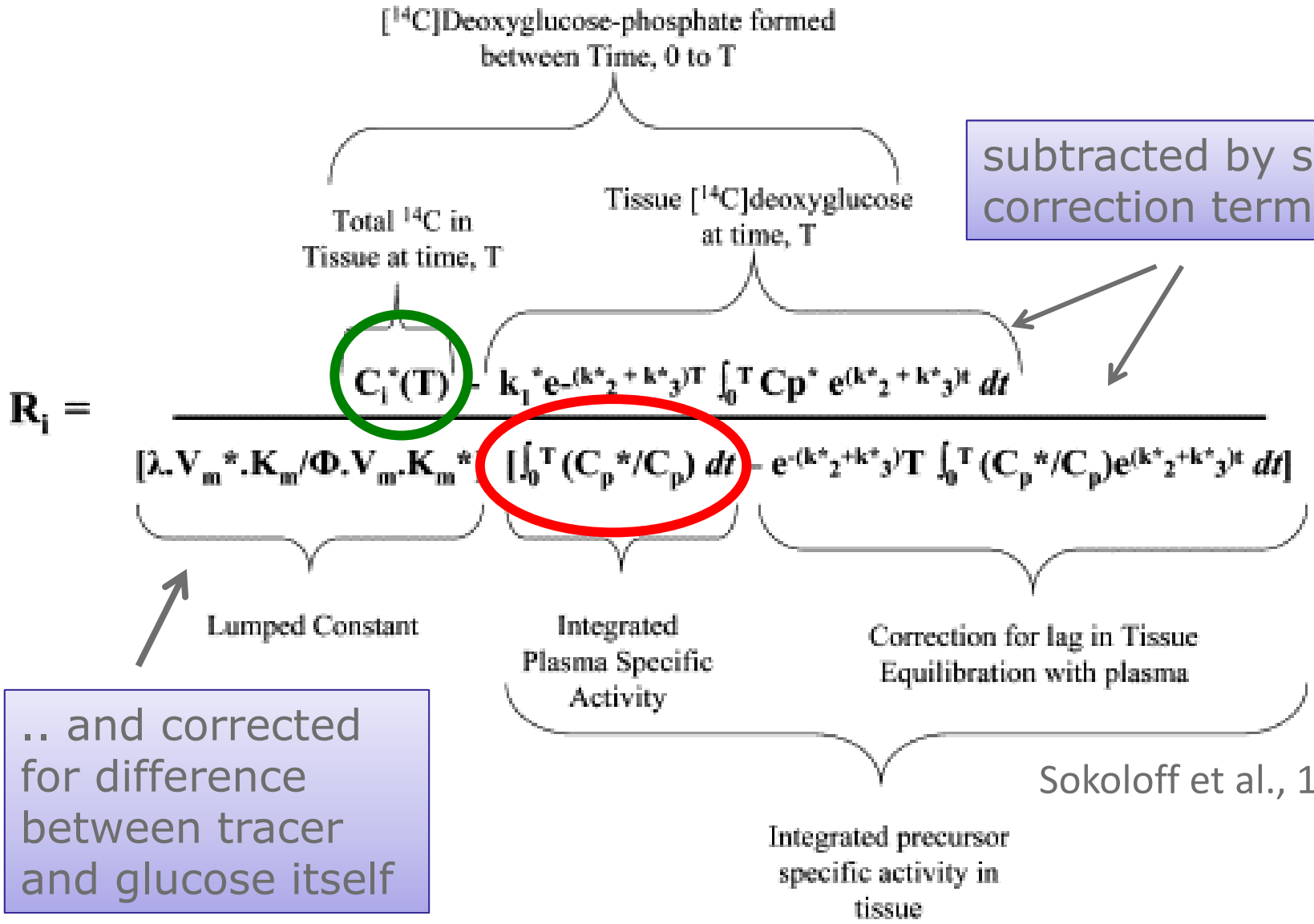
Compartment model of Deoxy-Glucose metabolism



CMRglc measured by 1 time point = "the autoradiographic method"



The autoradiographic method
- the Sokoloff equation

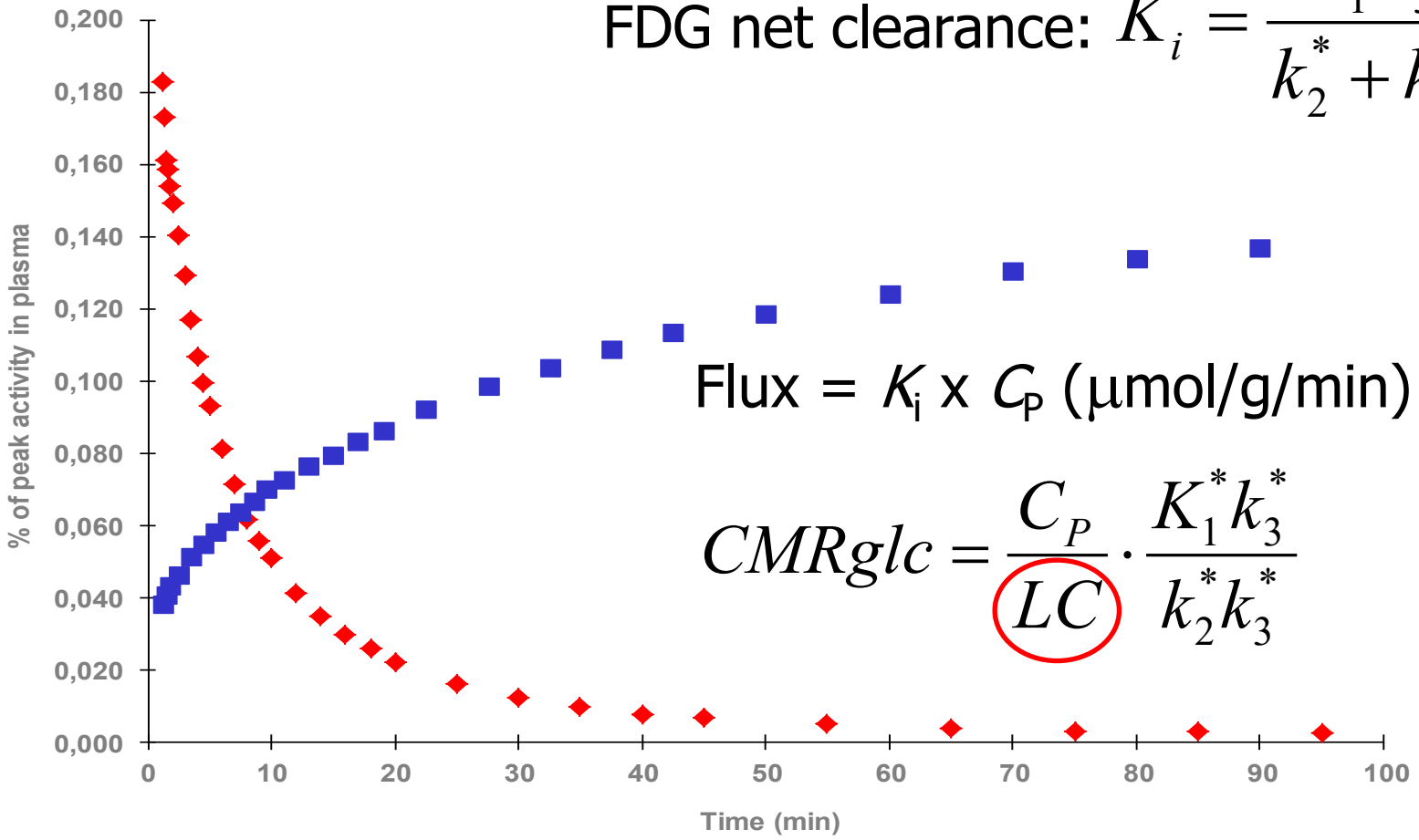


subtracted by small correction terms

.. and corrected for difference between tracer and glucose itself

Sokoloff et al., 1977

FDG uptake determined from compartment modeling (K_1*-k_3*) - "the dynamic method"



FDG net clearance: $$K_i = \frac{K_1^* k_3^*}{k_2^* + k_3^*}$$

Flux = K_i x C_P (µmol/g/min)

$$CMRglc = \frac{C_P}{LC} \cdot \frac{K_1^* k_3^*}{k_2^* k_3^*}$$

Lumped Constant - LC

LC = Net Clearance of FDG / Net Clearance of Glucose

$$LC = \frac{K_i^*}{K_i} = \frac{\frac{K_1^* k_3^*}{k_2^* + k_3^*}}{\frac{K_1 k_3}{k_2 + k_3}}$$

K_i = net clearance (mL/g/min)

Hexokinase favors glucose over FDG, and transport favors FDG over glucose

Litterature values for LC for FDG in human brains: 0.65-0.81 Can change during hypoglycemia

In tumours the LC is highly variable and [^{18}F]FDG PET may not allow accurate assessment of glucose utilization

Barrio et al. (2020) JNM :61(6)931-937

Lumped Constant

The FDG Lumped Constant in Normal Huma

Michael M. C
Thomas K. L

[1]Division of Nu
Department of
University of V

The lumped c
glucose metab
Methods: LC
male, 6 female
pendently usi
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gion-of-interes
compartmenta
mal brain was
was slightly lo
Conclusion: T
siderably high
because of methodologic differences, but agree with a recent study by Hasselbalch.

Key Words: FDG; ^{11}C-glucose; lumped constant; glucose metabolism

J Nucl Med 2002; 43:1157–1166

6 constants. The formula for the LC, defined by Sokoloff et al., is:

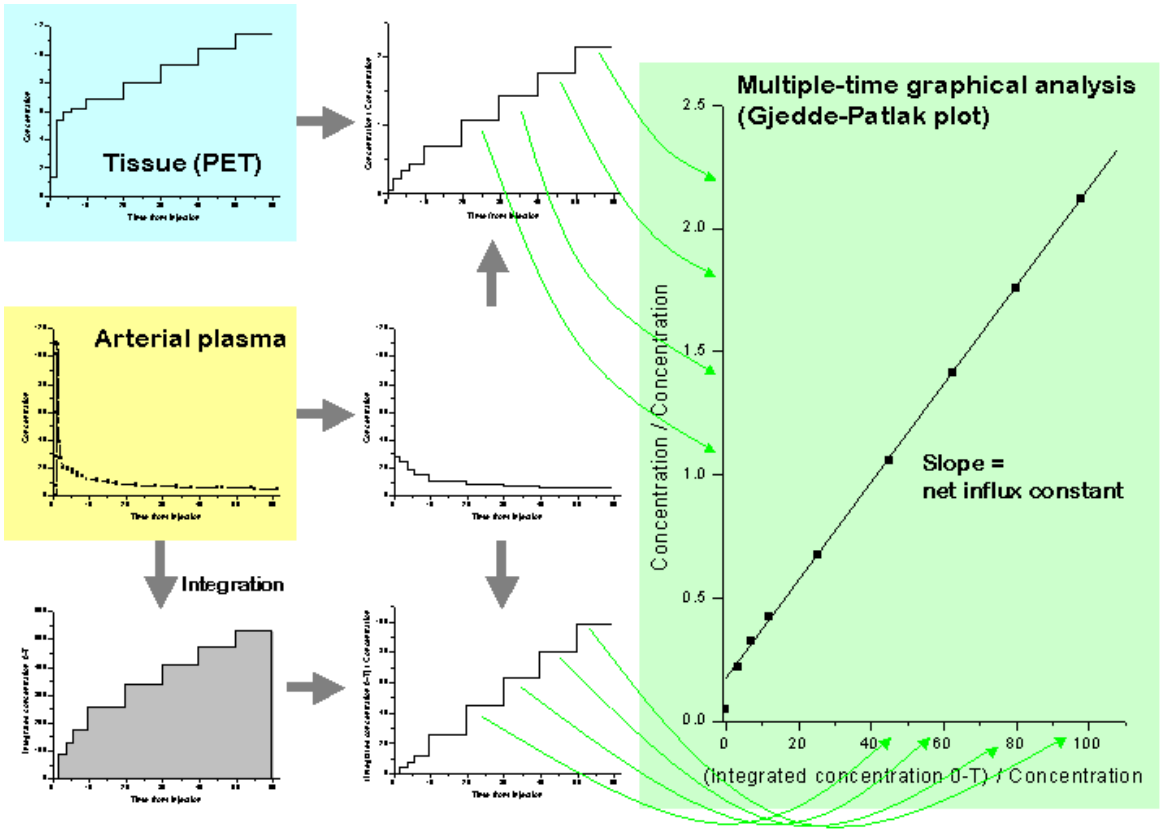
$$LC = \frac{\lambda \cdot K_m \cdot V^*_{max}}{\phi \cdot V_{max} \cdot K^*_m} \qquad \text{Eq. 1}$$

where λ is the ratio of the distribution volume of FDG to that of glucose, ϕ is the fraction of glucose that continues down the Embden–Meyerhof pathway after being phosphorylated, K_m is the Michaelis–Menten constant for phosphorylation of glucose (* indicates FDG), and V_{max} is the maximum velocity for phosphorylation of glucose (* indicates FDG). The LC is used to convert MR_{FDG} to MR_{glc} by dividing MR_{FDG} by the LC. Clearly, the value of the LC is critical in quantitative calculation of regional cerebral glucose metabolic rates when FDG is used as the tracer.

Determination of the value of the LC requires either

Linearization methods are very often used to calculate MRglc from [^{18}F]FDG PET

1. Based on compartment models with *irreversible binding*
2. *Clearance* (the amount of accumulated tracer in relation to the amount of tracer that has been available in plasma) is measured at *equilibrium* as the slope of the plot



Gjedde-Patlak plot

The solution to a two-tissue compartment model (k_4=0) is:

$$C_{\mathrm{T}} = \frac{K_1}{k_2 + k_3}\left(k_2 e^{-(k_2+k_3)t} + k_3\right) \otimes C_{\mathrm{P}}$$

This was rearranged by Gjedde and Patlak:

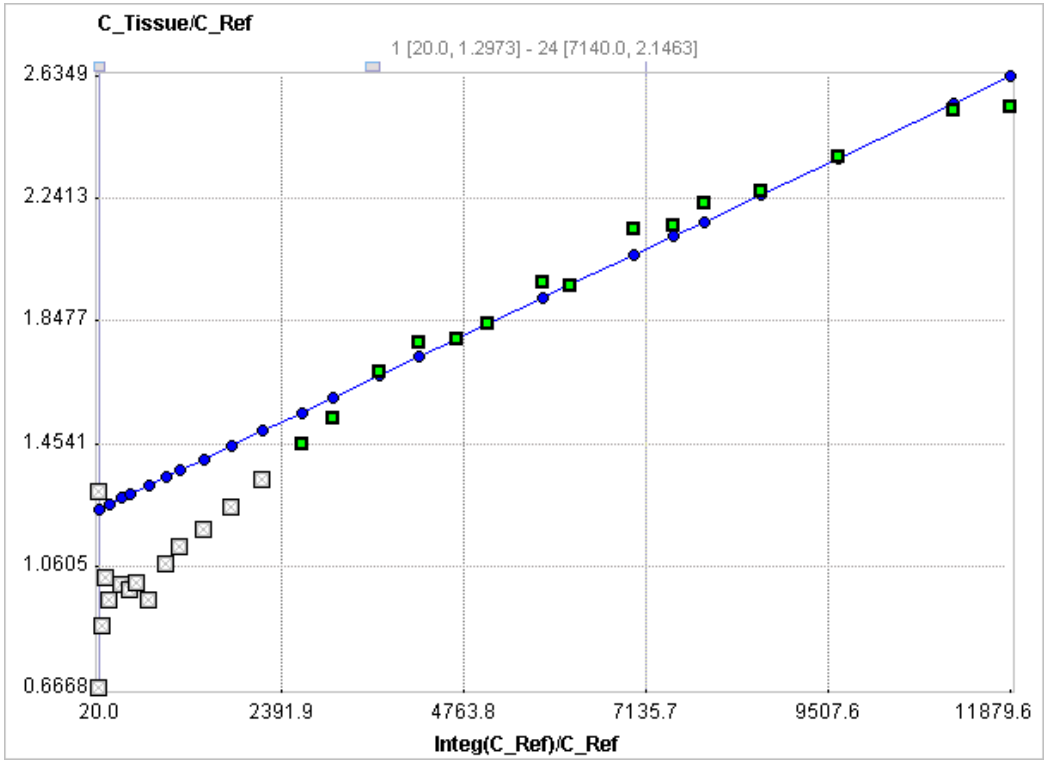
$$C_T = V_{\mathrm{ND}} C_{\mathrm{P}} + K_{\mathrm{i}} \int_0^t C_{\mathrm{P}}\, d\tau$$

Which after dividing by C_{P} is a straight line when t=t*:

$$\frac{C_{\mathrm{T}}}{C_{\mathrm{P}}} = V_{\mathrm{ND}} + K_{\mathrm{i}} \frac{\int_0^t C_{\mathrm{P}}\, d\tau}{C_{\mathrm{P}}}$$

Patlak plot

$$\frac{C_T}{C_P} = V_{ND} + K_i \frac{\int_0^t C_P \, d\tau}{C_P}$$



From the fitted line we therefore have:

- The metabolic rate $K_i = \frac{K_1 k_3}{k_2 + k_3}$ is the slope
- The distribution volume $V_{ND} = \frac{K_1 k_2}{(k_2 + k_3)^2}$ is the intercept

Graphical Linearization (Gjedde-Patlak Plot)

K_i varies with segment used for determining the slope

- why?

k_4* > zero
= tracer escapes from the brain, not true irreversible binding

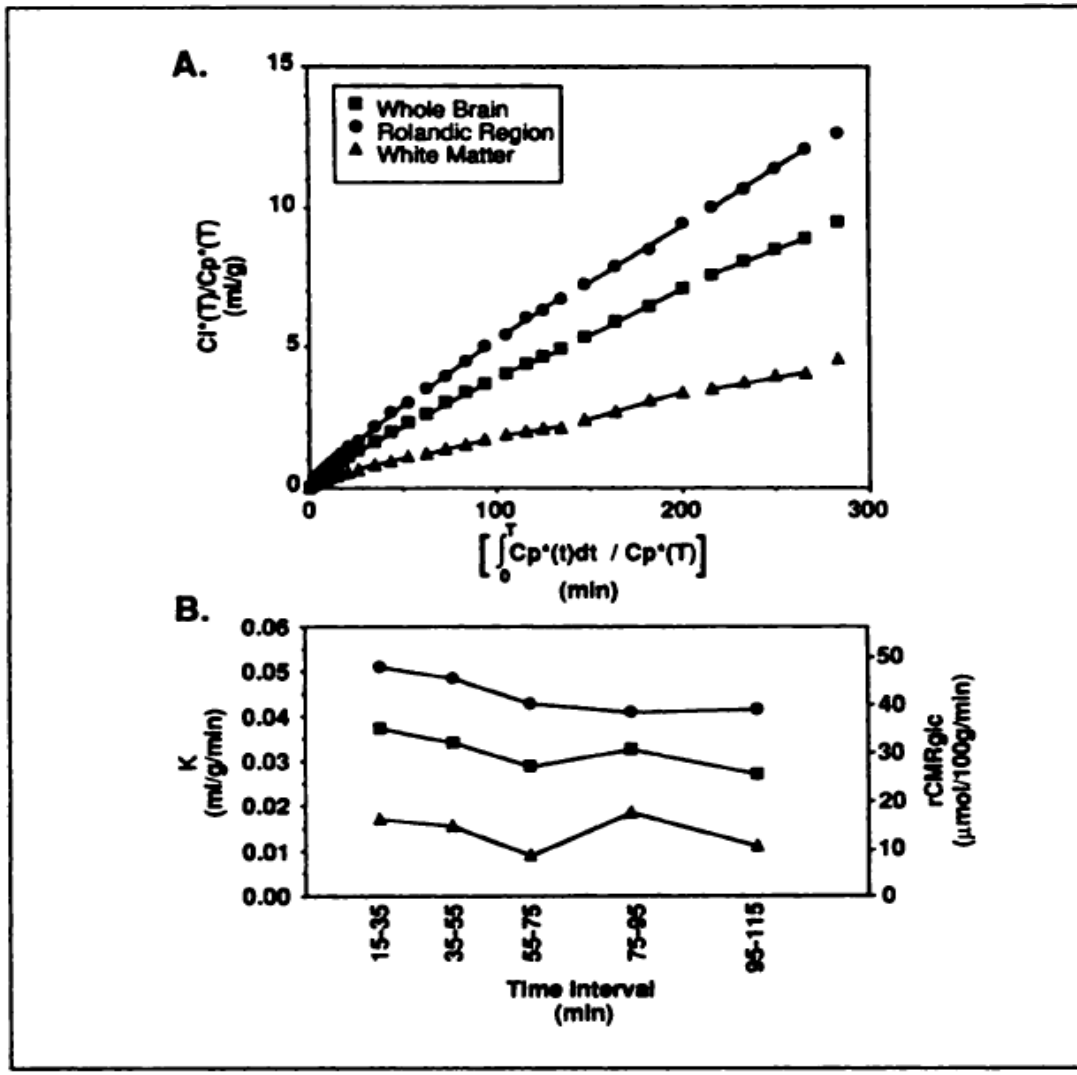
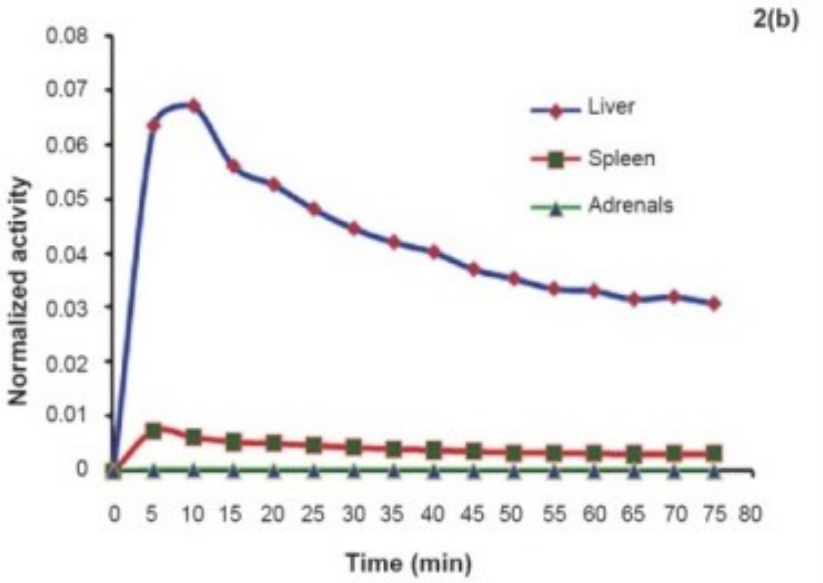
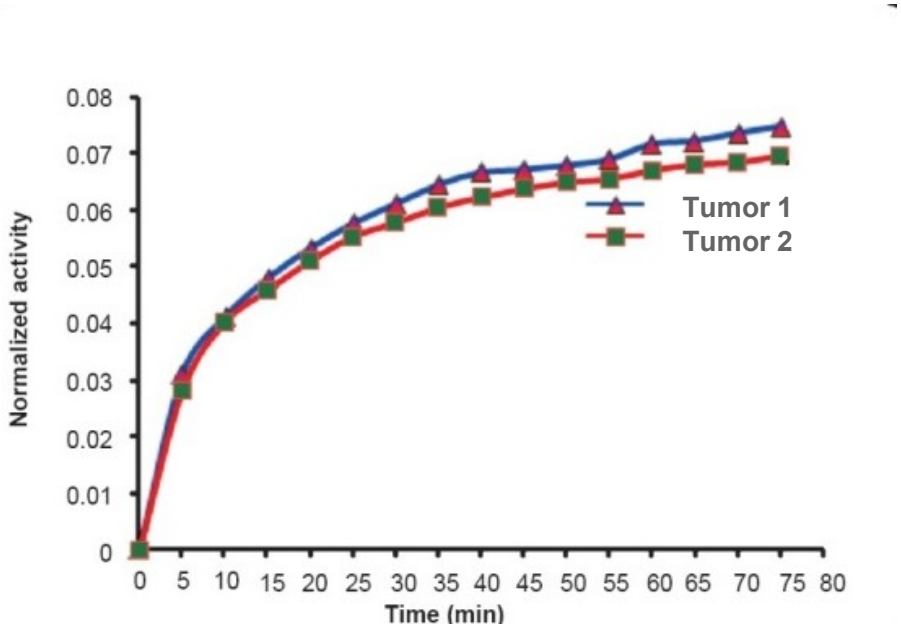


FIGURE 5. "Patlak plots" of data obtained during scanr from 0 to 120 min following a pulse of [^{18}F]FDG for the wh brain, one gray matter structure and one white structure i representative subject. (A) The graph shows five 20-min disc linear segments for each of the three ROIs. Each segment v fitted to four consecutive points, starting and ending, resp

[^{18}F]FDG PET

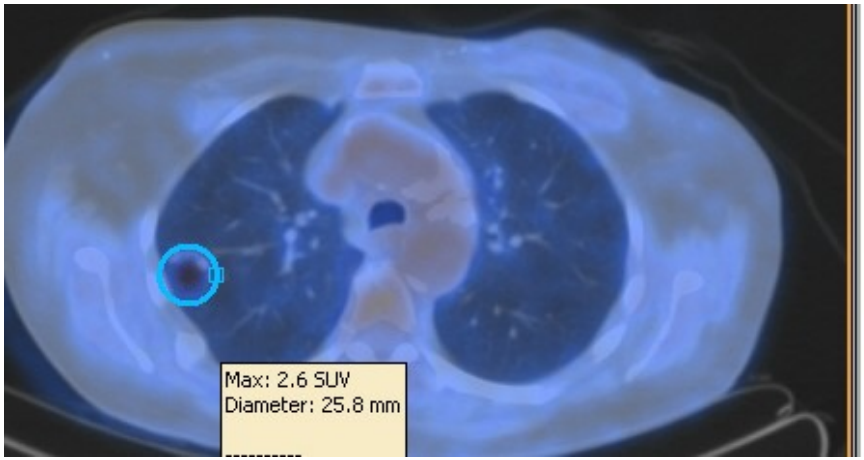


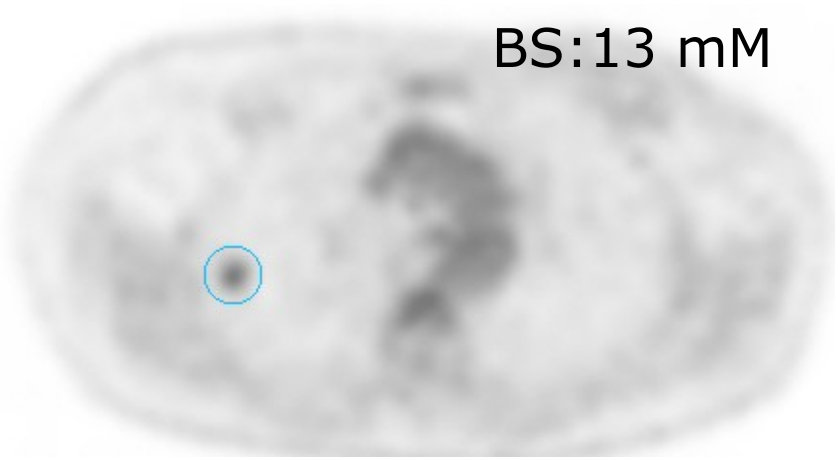


Q1: What is the difference between the liver curve on the left and the tumor curves on the right? What is the physiological difference?

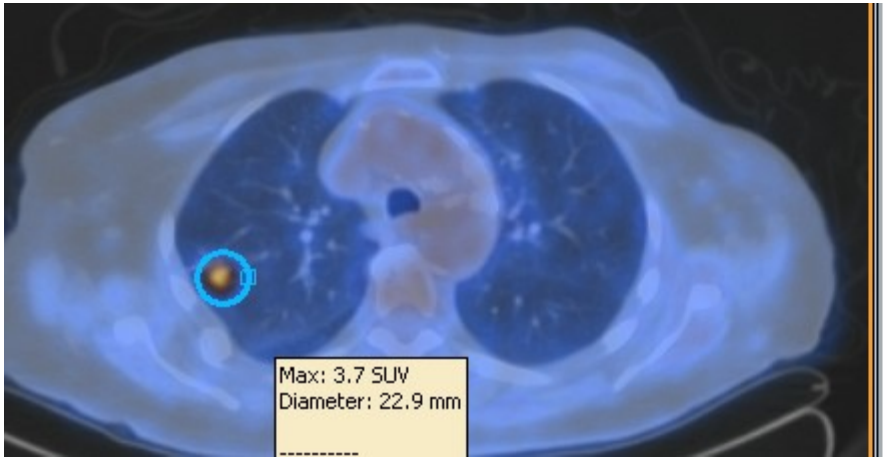
Q2: Is FDG a reversible or irreversible tracer?

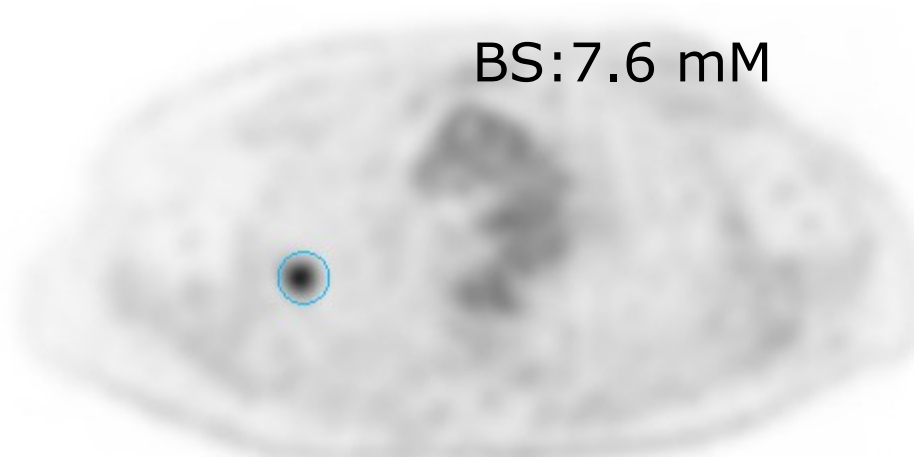
FDG PET





What is the difference between the upper scan and the lower scan that was repeated a few days later?





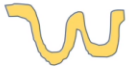
Blood glucose level

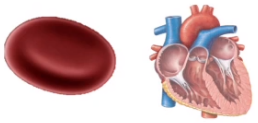
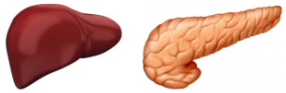
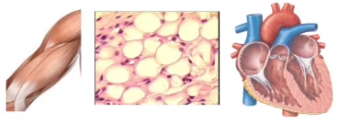
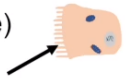
- High blood glucose levels (fasting? Diabetes?) interfere with FDG uptake
- When serum glucose > 8mM
  - SUV in tumor drops from 5.1 to 2.8, $p<0.02$
  - SUV in skeletal muscles increase
- K_i can decrease 25% with higher serum glucose
- Infusing insulin increase the translocation of GLUT 4 shunting FDG to organs with a high density of receptors (skeletal and cardiac muscles)
- Metformin strongly increase the SUV of the small and large intestines

Glucose transporters

Glucose is hydrophilic and need a transporter

Sodium-Dependent Glucose Transporters

SGLT1	• Enterocytes of Intestinal Epithelium (Luminal side) 	• Insulin-Independent • ATP- and Na-dependent • *Glucose Absorption*
SGLT2	• Proximal tubule of nephron (Kidney) 	• Insulin-Independent • ATP- and Na-dependent • *Glucose Retention*

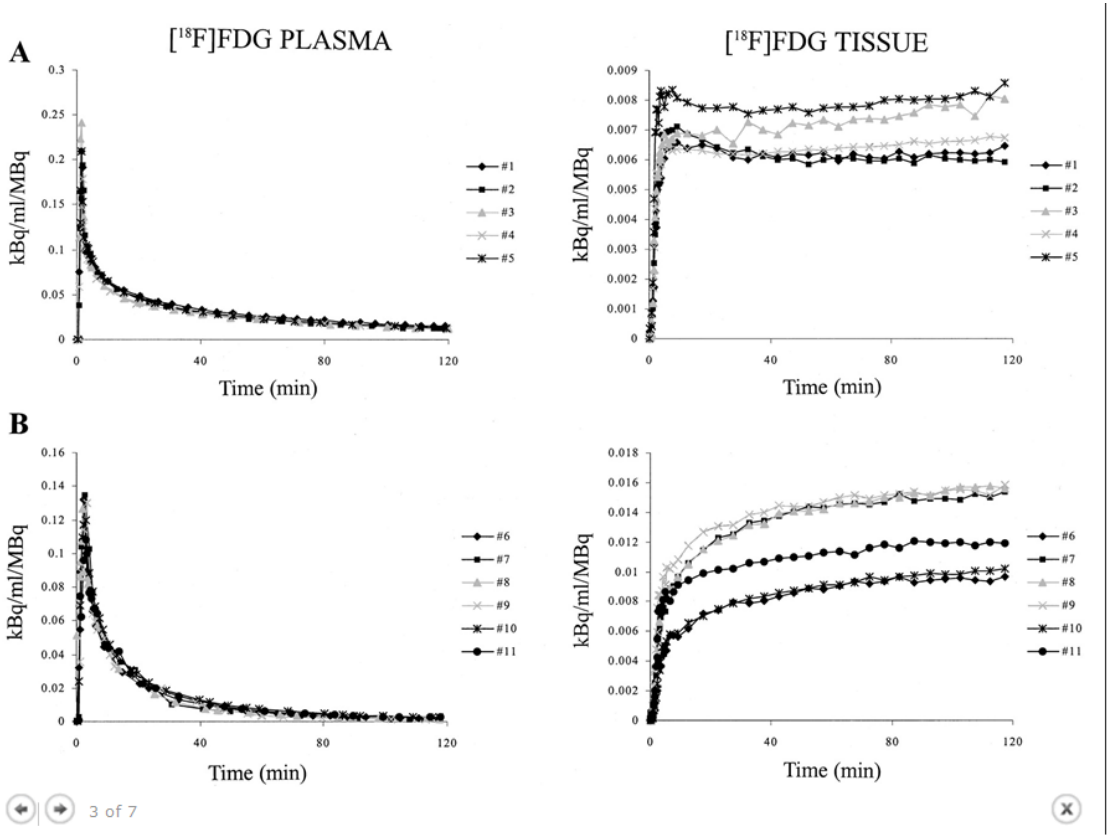
GLUT1	• Blood • Blood-Brain Barrier • Heart (lesser extent) 	• Insulin-Independent
GLUT2	• Liver • Pancreas • Small Intestine 	• Insulin-Independent • High K_m • Low Affinity
GLUT3	• Brain • Neurons • Sperm 	• Insulin-Independent • Low K_m • High Affinity
GLUT4	• Skeletal Muscle • Adipose Tissue • Heart 	• **Insulin-Dependent***** • Moderate K_m • Moderate Affinity
GLUT5	• Enterocyte of Intestinal Epithelium (Luminal Side) 	• Insulin-Independent • *Fructose Transporter*

[^{18}F]FDG is not a good substrate for SGLT

Insulin level should be low to avoid GLUT4 that transport FDG into the muscles
-> fasting!

Youtube: Glucose Transporters (GLUTs and SGLTs) - Biochemistry Lesson

Tissue activity curves



Individual [18F]FDG plasma and tissue time-activity (normalized to dose) curves in basal state (A, subjects 1–5) and during insulin stimulation (B, subjects 6–11).
Bertoldo et al. 2001 Am J Physiol Endocrinol Metab 281: E524-36

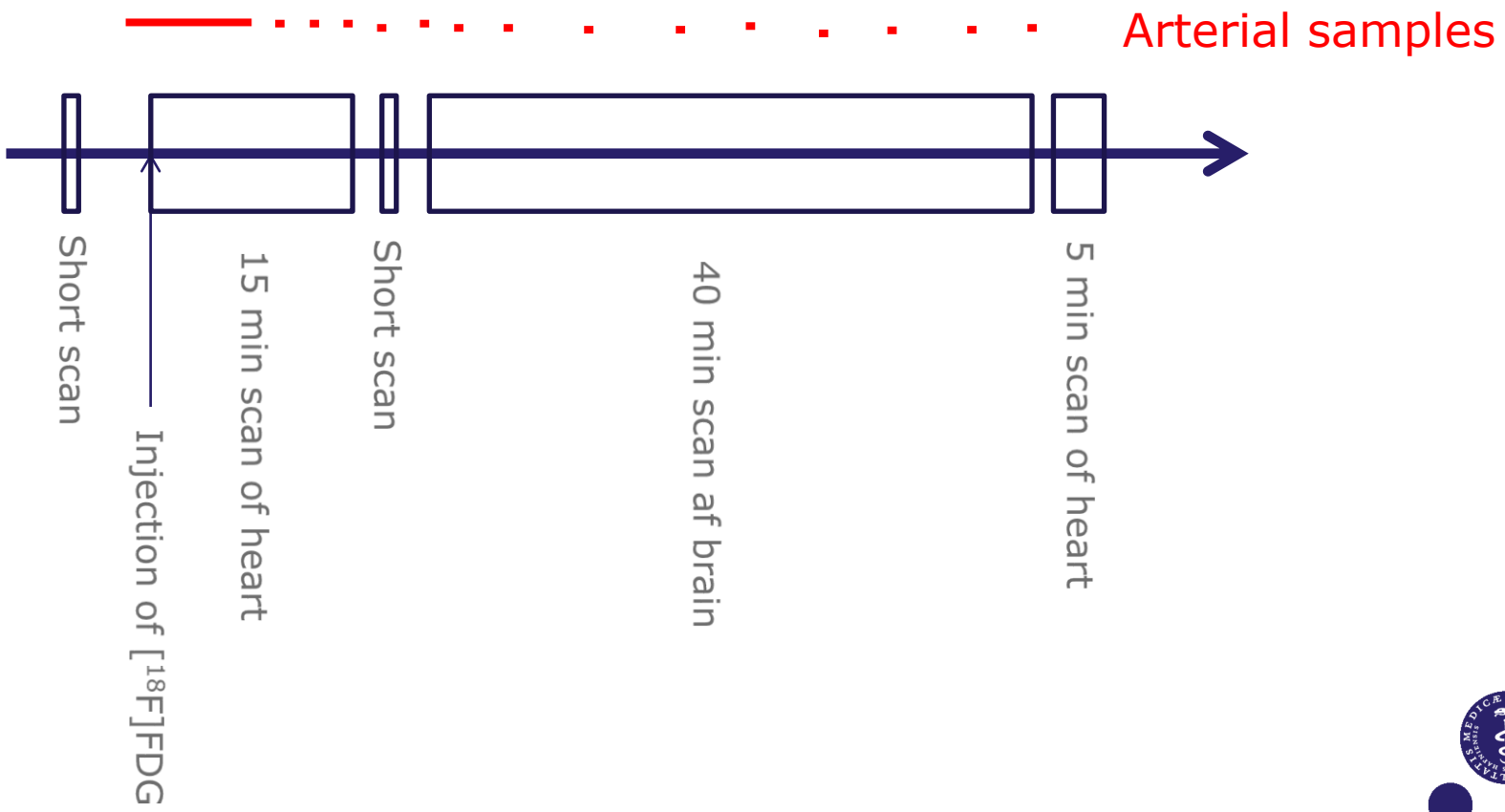
Fasting

Insulin stimulation

What happens during insulin stimulation?

How to avoid arterial cannulation for rCMglc measurements

Scan procedure



How to avoid arterial cannulation for rCMglc measurements

A.C. Henriksen, M.N. Lonsdale, D. Fuglø et al. *NeuroImage 253 (2022) 119079*

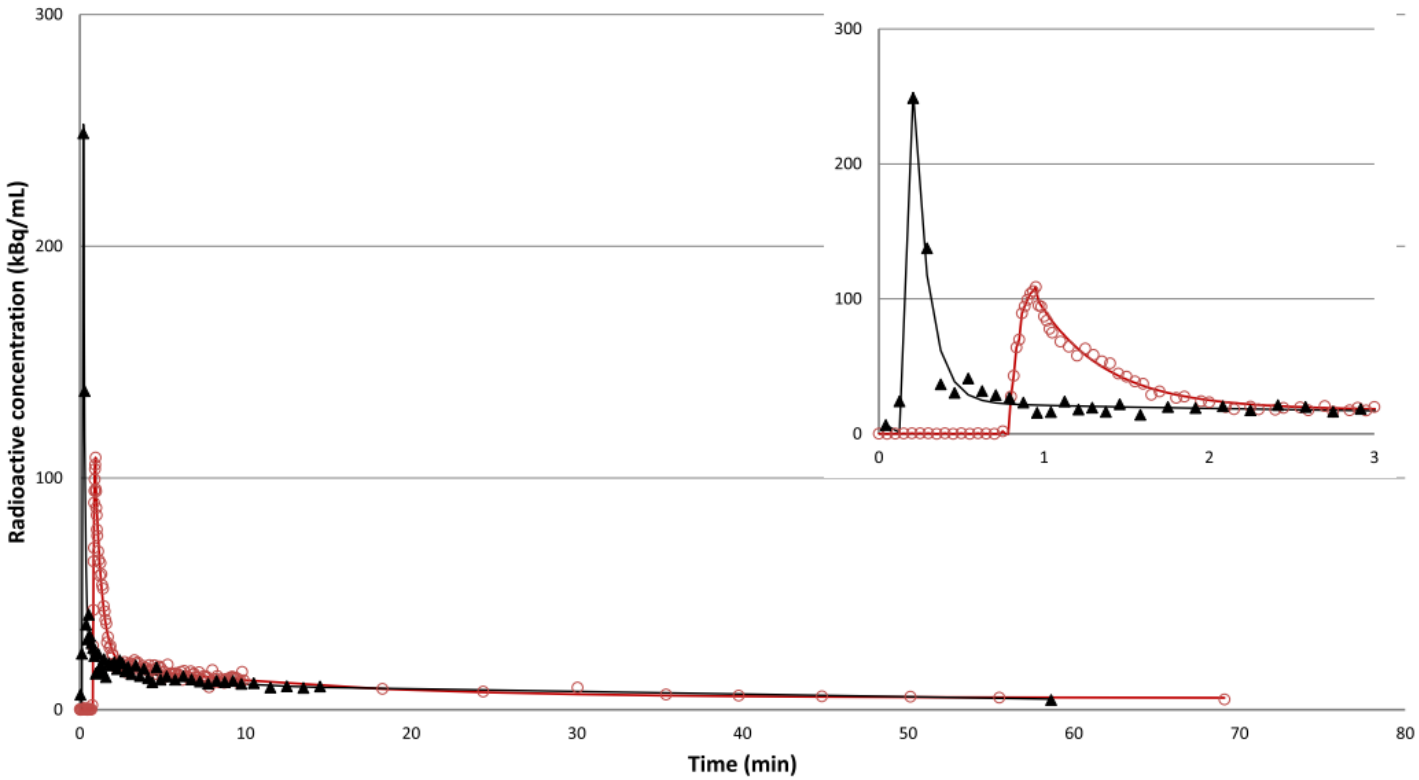
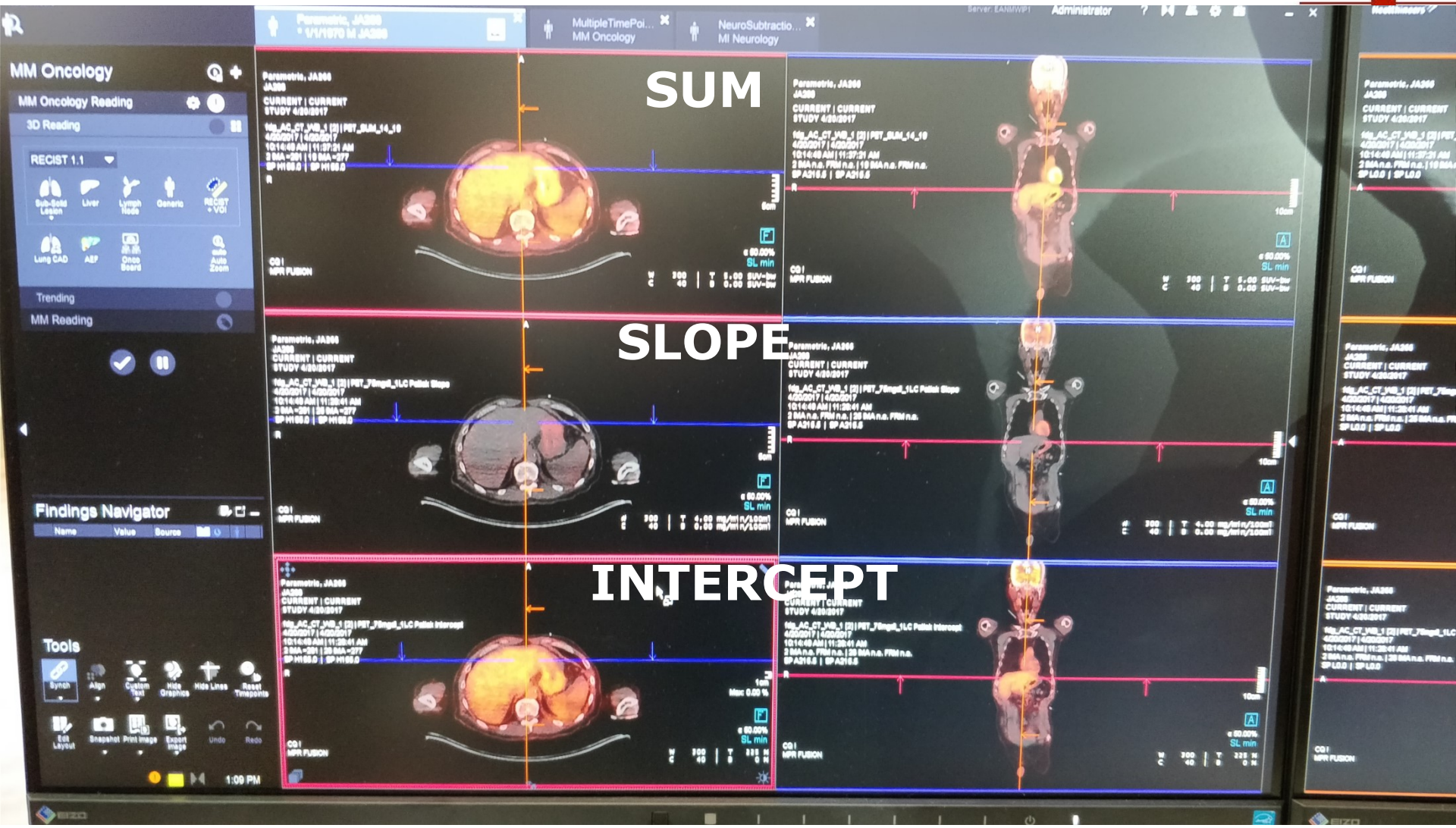


Fig. 1. Plot of the fitted arterial (AIF, red hollow circles) and image derived (IDIF, filled triangles) inputfunction. Top right the first 3 min. Note the earlier and narrower IDIF peak.

Scanners with build-in Gjedde-Patlak plot reconstruction



Siemens, Knoxville, USA

Methods to avoid the arterial cannulation

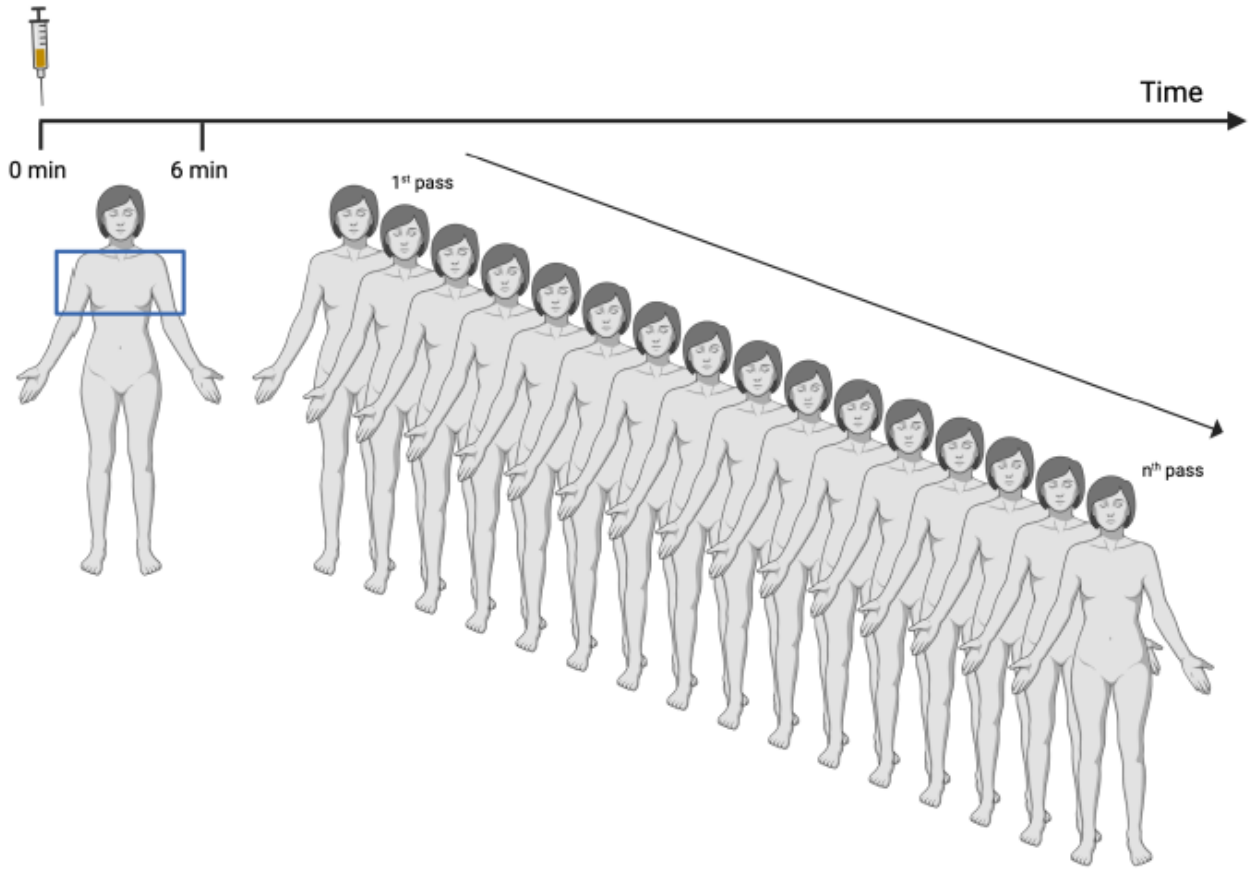
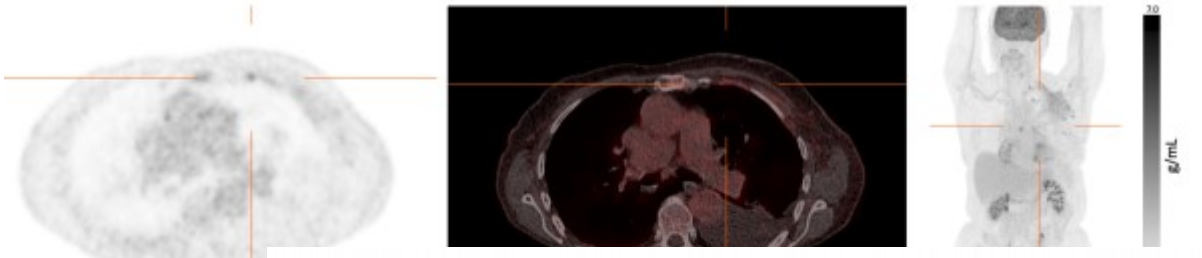


Figure 2: Example of a dynamic whole-body (D-WB) PET acquisition protocol including an initial 6-minute dynamic scan over the chest region, followed by a D-WB scan with multiple continuous bed motion passes

How to avoid arterial cannulation for rCMglc measurements



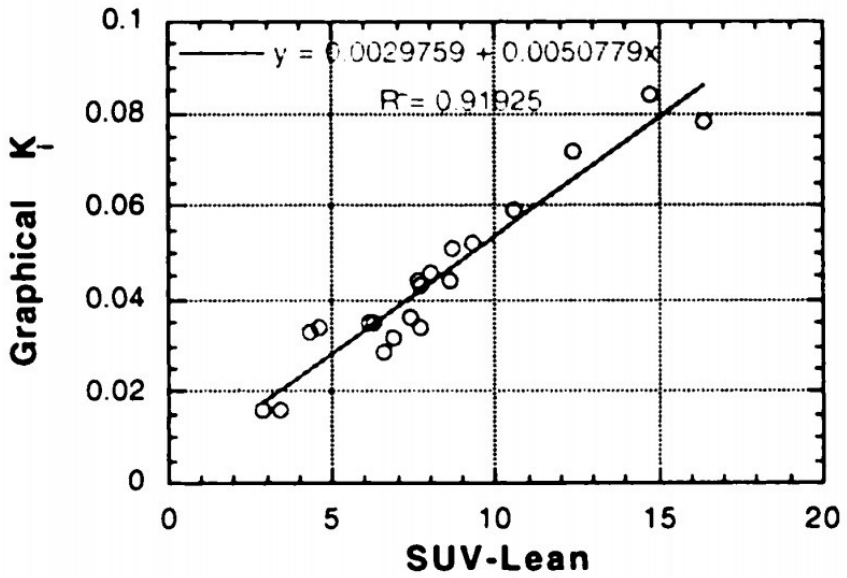
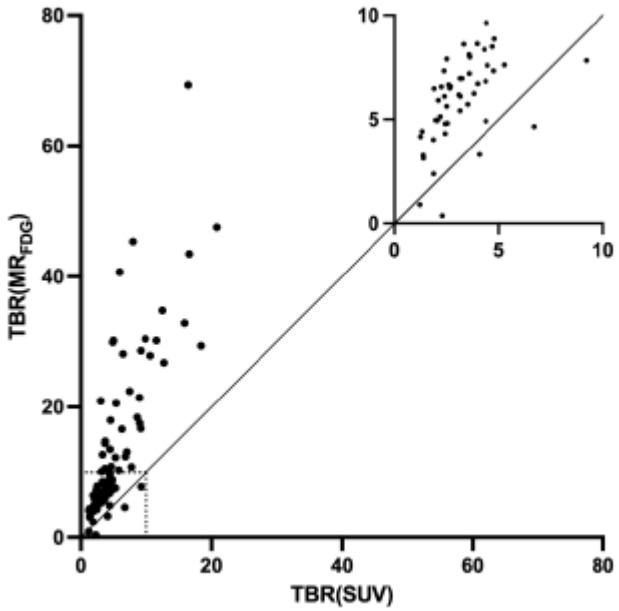


Figure 5. Relationship between SUV-lean and K_i in 20 FDG PET scans obtained in 10 patients with lung cancer.



Pe

Whole-Body [^{18}F]FDG Patlak Imaging Using LAFOV PET

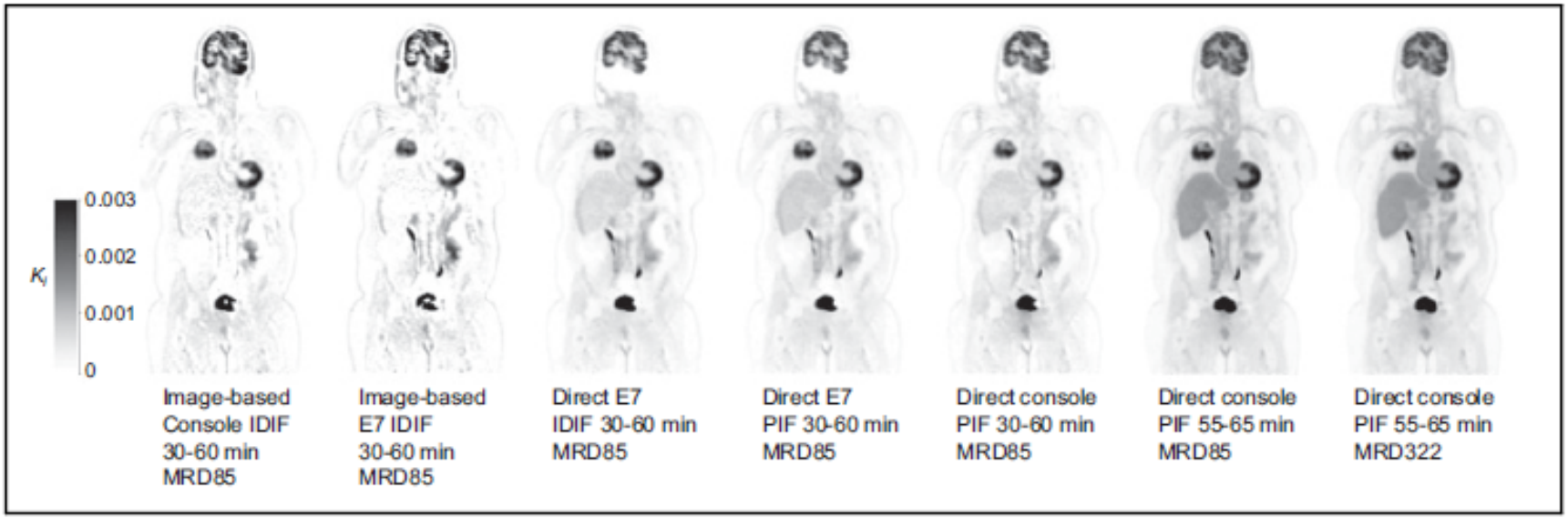


FIGURE 1. Example coronal parametric K_i images of 65-y-old man with non–small cell lung cancer. Images were obtained with different approaches using IDIF or scaled PIF at different intervals after injection.

J Nucl Med 2024; 65:1652–1657
DOI: 10.2967/jnumed.124.267784