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EDITORIAL

The precise physiological definition of tissue perfusion and clearance measured from imaging

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Blood flow can be expressed in several forms: (a) fraction of cardiac output, (b) absolute blood flow (millilitres per minute), or (c) perfusion, which is blood flow per unit tissue volume or mass (millilitres per minute per millilitre or gram). With respect to perfusion, however, what constitutes 'per millilitre or gram' is often not clear and depends on the technique used to measure it, and more specifically whether or not the tissue extracellular volume is taken into account. Perfusion is often measured using indicators or radioactive tracers (markers), so the same dependency also applies to blood clearance of markers into tissue, which is tissue perfusion multiplied by marker extraction fraction. The aim of this article is to identify what precisely constitutes 'per millilitre or gram' for techniques used to measure perfusion and clearance in clinical practice and research, with emphasis on techniques based on imaging, which are as follows:

1. The *Kety-Schmidt technique* is based on the tissue uptake and 'washout' of diffusible markers such as nitrous oxide [1], radioactive inert gases [2] and positron-labelled water [3] that are taken up and released in a perfusion-dependent manner. This classical technique essentially measures the residence time of marker within the tissue [3]. For example, the reciprocal of the rate constant (k) of washout of radioactive inert gas from tissue following bolus arterial injection is the mean transit time of tracer through the tissue, including extracellular volume; k is therefore equal to perfusion in units of millilitres per minute per millilitre or gram of tissue, including blood and interstitial space.
2. *Indicator dilution* records the venous outflow concentration of a marker following injection into a vessel (usually an artery) supplying the tissue [4]. Blood flow is derived in absolute units of millilitres per minute by dividing the administered amount of marker by the area under the outflow time–concentration curve. Imaging, however, gives the marker concentration within the tissue itself, so perfusion is obtained in units of millilitres per minute per millilitre of total tissue volume. An example of this latter approach is dynamic perfusion CT, which records the contrast-enhanced CT density in blood and tissue following bolus intravenous injection of iodinated contrast agent [5]. The maximum gradient of the first-pass enhanced tissue Hounsfield unit–time curve is divided by the peak Hounsfield unit value in a region of interest (ROI) over a ventricular cavity or artery. No allowance is made for extracellular volume within the tissue so the perfusion units are millilitres per minute per millilitre of total tissue. Perfusion can be obtained, without the injectate volume limitations of contrast agent [6], using the same theoretical approach to the first-pass kinetics of any PET tracer, with identical units.
3. *Nonlinear least squares computerized compartmental modelling*, as used in positron emission tomography (PET), gives the transport constants governing tracer distribution among compartments in an appropriate compartmental model, most often a three-compartment model with input constant K_1 and forward and reverse rate constants, k_3 and k_2, as typically displayed by ^{18}F-fluorodeoxyglucose (FDG) in most tissues. Tracer input is obtained from sampled arterial blood or a ROI over a major artery or ventricular cavity. The values of the transport constants that between them generate the curve that most closely resembles the measured tissue curve are computed using the least squares approach. The blood volume of the organ, as a proportion of total organ volume (vascular fraction, V_b), is generally included as a model parameter in the computation [7]. The interstitial space, however, increases modelling complexity so is usually ignored. V_b therefore also includes a contribution from

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the interstitial space, depending on how freely the tracer exchanges across the endothelium. K_1, the input constant, is then the blood clearance of tracer into the tissue with units of millilitres per minute per millilitre where 'per millilitre' refers to a virtual volume that excludes the blood volume plus an element of interstitial volume of magnitude that depends on tissue vascularity and capillary permeability (i.e. on K_1 and k_2). With respect to FDG, that undergoes phosphorylation in the tissue, the principal interest is usually the blood clearance of phosphorylated FDG, called the uptake constant (Ki). Ki is equal to $K_1 \times k_3/(k_2 + k_3)$ and has the same units as K_1. If vascular fraction is not included as a model parameter then the nature of the model is fundamentally changed in that the input constant now refers to tracer transfer from the central blood to the tissue as a whole rather than from tissue capillary blood to the intracellular space, and K_1 becomes tissue blood flow in units of millilitres per minute per millilitre of total tissue volume.

In the context of perfusion measurement in a clinical setting, least squares computer modelling is well illustrated by the use of ^{82}Rb for measurement of myocardial blood flow. In this context, vascular fraction is taken into account, so K_1 has units that exclude the extracellular volume. In general, the tissue extraction fraction of a tracer with uptake that is partly diffusion-dependent, such as ^{82}Rb in the myocardium, decreases nonlinearly as perfusion increases. The ensuing relationship between clearance and perfusion is defined by the Crone-Renkin equation, which is used to convert K_1 to myocardial perfusion in millilitres per minute per millilitre of myocyte volume [8]. Omitting the vascular fraction as a model parameter would, as explained above, give K_1 as myocardial tissue perfusion in units of millilitres per minute per millilitre of total tissue volume, including the extracellular space. In practice, however, the vascular fraction has to be taken into account because of 'spillover' of activity into the myocardial ROI from ventricular blood pool activity, which 'adds on' to the myocardial blood volume. The magnitude of spillover can be appreciated from the high values of V_b reported by Coxson et al. that reached about 0.45 after dipyridamole administration [9], which is clearly much higher than myocardial extracellular volume.

4. In *Gjedde-Patlak-Rutland graphical analysis* the tissue-to-blood tracer concentration ratio is plotted against 'normalized time' (integral of arterial concentration divided by instantaneous arterial concentration) to generate a graph with gradient equal to blood clearance of tracer into the tissue (uptake constant, Ki). Like indicator dilution, the signal detected from the ROI over the tissue includes tracer in all elements of the tissue, so the units of Ki are millilitres per minute per millilitre of total tissue volume including the extracellular space. Fat, which is important with respect to the liver because of its highly variable fat content, is also included, but its physical influence on the interpretation of hepatic Ki, especially in obese individuals [10], has generally not been discussed. Graphical analysis has previously been compared with nonlinear least squares computerized compartmental modelling in which vascular fraction was included as a model parameter, especially in studies of tissue glucose uptake based on FDG, but the anticipated lower values of Ki from graphical analysis compared with Ki from modelling (by $[1 - V_b]$-fold) were not acknowledged [11–14].

Other techniques for measuring perfusion that are not based on imaging are relevant to this discussion since they may be used as gold standards for an imaging method. They include the following:

1. The *microsphere technique* is applicable only to animals. In this technique, radiolabelled microspheres are injected into the left side of the heart at the same time as blood is continuously withdrawn from a peripheral artery at a known constant rate. The microsphere concentration in the arterial blood is then compared ex vivo with the concentration in a sample of the tissue of interest. If the two concentrations happened to be the same, for example, then the original blood flow to the sampled tissue in millilitres per minute would be the same as the arterial blood withdrawal rate. Before counting, however, the tissue sample is usually washed, which removes its contained blood, dried and weighed, so that the perfusion units are millilitres per minute per gram of bloodless tissue.
2. *Dividing organ blood flow rate (millilitres per minute) by an estimate of organ weight* is an indirect method for measuring perfusion. Blood clearance of markers that are highly extracted in a single organ, such as organic anions by the liver, is almost equal to organ blood flow in millilitres per minute, and can be divided by an estimate of organ weight as a fraction of body weight to derive the perfusion rate [15]. Such weight estimates are bloodless, so the perfusion rate has units of millilitres per minute per gram of bloodless tissue. By dividing Ki obtained from graphical analysis by indocyanine green clearance, this approach has been used to calculate the hepatic extraction fraction of FDG that is phosphorylated [10]; however, the units of the numerator but not those of the denominator include blood volume.
3. *Plethysmography* is not based on measurement of blood or tissue marker concentration, but instead measures volume expansion of a limb following transient abolition of venous return and divides this by limb volume to give perfusion in units that include total limb volume [16].

So the precise definition of perfusion depends on the technique used to measure it. The extent to which this matters

depends on the magnitude of the vascular fraction. Tissue blood volume as a proportion of total volume varies from ~0.05 for the brain [7], to ~0.1 for the myocardium [17] and to ~0.25 for the liver [12]. For the liver, however, the vascular fraction includes a large interstitial space, termed 'extended blood volume' by Munk et al. [12], who found a mean value of 0.4 in pigs. In some tissues, for example the spleen, which functions essentially as an 'open' blood cell sorter, the concept of vascular fraction is largely lost. The definition of perfusion also matters when one technique is used as a gold standard for another that gives perfusion in different units, such as microspheres compared with the Kety-Schmidt technique [18] and Gjedde-Patlak-Rutland graphical analysis [13], or graphical analysis compared with computerized compartmental modelling [11–14].

In conclusion, it is strongly suggested that publications on tissue perfusion and clearance specify exactly what their 'per millilitre' or 'per gram' refers to, especially for tissues with large extended blood volumes, such as the liver and spleen.

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