EDITORIAL

Labeled Carbon Dioxide: How Transient a Metabolite?

In this issue of the *Journal*, Dr. Shields' study raises the question common to many tracer studies: How rapidly does a labeled gas such as carbon dioxide clear from the circulation? The question is important because the inherent great diffusibility of the gases themselves is tempered by binding or "fixation," (e.g., in the case of oxygen or carbon monoxide). Dr. Shields' and his associates' answer to this question is deceptively simple: Only 58% of an intravenous bolus of carbon dioxide/bicarbonate (total CO_2) leaves the body of a dog within an hour of administration, indicating that 42% remains trapped as total CO_2 or nonvolatile CO_2 metabolites.

Papers on PET dealing with labeled carbon dioxide have appeared regularly but infrequently since 1979 (*1*), mostly reporting the methods developed for measuring tissue pH. However, in their paper, the authors consider CO_2 to be a contaminant. Carbon-labeled-CO_2 must of course be distinguished from oxygen-labeled CO_2. The latter is used as a blood flow indicator because the label is transferred to water. The former transfers its label to bicarbonate. Both lose the label in the rapid equilibrium catalyzed by carbonic anhydrase.

Because of the position of the equilibrium, total CO_2 is trapped largely (i.e., 80%–90%, depending on the pH) as bicarbonate and therefore occupies a considerable volume of distribution in blood and tissues. The distribution impedes clearance of CO_2 by a factor of at least ten in the lungs and favors the incorporation into nonvolatile compounds, of which urea, glucose, and lactate predominate as a result of the action of the arginine-ornithine-citrulline cycle. Of the CO_2 metabolites, urea readily diffuses across cell membranes to distribute in the entire water phase of the body. Glucose and lactate have somewhat lower degrees of permeability.

The initial distribution of a bolus of the carbon dioxide/bicarbonate mixture delivered by the circulation follows regional blood flow (*2*), but the bolus redistributes according to pH with a half-time of less than 10 min. Although the duration of initial inhomogeneity is shortened by bolus injection, slower rising blood curves deliver less radioactivity to the tissue in the beginning when the distribution is uneven.

In this paper, the accumulation of nonvolatile metabolites (i.e., CO_2 'fixation') is slow, amounting to about 10% in 1 hr. This is somewhat less than that in the study of Buxton et al. (*2*) in which CO_2 fixation in the brain reached 25% in 20–30 min, although the half-time of fixation was reported to be 2.5 hr.

The different rates of appearance and clearance of total CO_2 after injection of glucose, acetate, and thymidine reflect the different rates of labeled CO_2 generation from the three different molecules and therefore are not directly relevant to the issue of the relative rate of clearance of total CO_2, except to suggest that if the rate of generation is very slow, as in the case of 1-carbon-labeled glucose, total CO_2 will immediately distribute according to pH and the metabolites of CO_2 will remain negligible (i.e., less than 0.5% at 60 min). With acetate and thymidine, CO_2 metabolites may account for much more of the blood radioactivity (i.e., 6%–8% at 60 min) and thus allow only cautious interpretation of studies that extend beyond 30 min.

For all tracers that generate CO_2, potentially three or more, different labeled compounds coexist in the circulation, all seeding radioactivity to the tissues. Although they depend on each other in a determinate manner, in the sense that the total CO_2 levels will determine the levels and specific kinds of metabolites, the CO_2 metabolites found in the tissue may have been generated in situ as well as having entered from the circulation. Hence, some tissue CO_2 metabolites may differ between tissues. The question is whether the CO_2 metabolites and their distribution to tissues can be predicted with reasonable certainty once the total CO_2 level in the circulation is known. An intravenous bolus of $^{11}CO_2$ can be used to describe the impulse response functions for the sum of total CO_2 and CO_2 metabolites in the tissue. In addition, the study should be constrained so as to minimize the problem of CO_2 fixation in urea and other compounds. How generalized is it possible to make this impulse response function? This question raises the issue of the rate-limiting step in the CO_2 transit.

In Dr. Shield's study, the times of transit of the carbon label through the pre-CO_2 pools were approximately 6 min for acetate and thymidine, but greater than 60 min for glucose. In the latter case, pulmonary clearance probably keeps pace with the rate of generation and blood level is entirely a function of the rate of generation (rate-limiting step). With acetate and thymidine, the rate-limiting step in the transit of total CO_2 remains the rate of pulmonary clearance (hence the difference in total blood CO_2 levels generated by the two tracers). The slow generation of CO_2 in the case of 1-carbon-labeled glucose may argue in favor of little loss of tissue radioactivity as CO_2. Quantitatively, such an argument may not be entirely valid, however, since the loss of CO_2 from the tissue precedes the loss of CO_2 from the circulation.

The total CO_2 in the circulation represents 50% or more of the total

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blood radioactivity for acetate and thymidine, and tissue radioactivity due to total CO_2 will reach approximately half of that because of the lower pH of the tissues. Thus, tissue background radioactivity is close to one-quarter of the total blood radioactivity in these cases.

The approach to the problem of CO_2 distribution and fixation must be the solution of a general model, as also suggested by the authors. Such models can be established for many tracers of which labeled metabolites enter tissues in a predictable manner. One such model describes the generation of labeled methyl-fluorodopa after fluorodopa administration (*3,4*). The tracer and its metabolites both belong to the group of large neutral amino acids transported across cell membranes by the L-type (leucine-type) facilitated diffusion transporter. The contribution of the tracer and its metabolite to tissue radioactivity can be assessed separately, using the assumption that the rate of transport of the two labeled compounds has some fixed ratio, e.g. 1:2 (*3*) or 1:1 (*4*). A different assumption is required for CO_2, relative to its parent compounds, since total CO_2 is a gas (largely bound as bicarbonate) and the parent compounds are water-soluble tracers. If the distribution of total CO_2 initially follows blood flow, reflecting rapid transfer into the tissue, it may be sufficient simply to calculate tissue curves that assume instant steady-state with the circulation, at half the blood level. This may be the most general solution to the problem of separately assessing and subtracting the total CO_2 background when the blood level does not rise too rapidly. The total CO_2 level should be determined by means of the method described in Shield et al's article.

Unfortunately, this article does not give a complete set of blood and tissue curves for any organ for either dogs or humans. Such curves help the reader determine the relation between total CO_2 in the circulation and the tissue. Curves representing the brain of dog were given by Buxton et al. (*1*) and they generally confirm the imposition of a 1:2 ratio between tissue and circulation. Whether such a simplification is always valid must be tested specifically.

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