INVITED COMMENTARY

^{18}F-FDG in Cardiology and Oncology: The Bitter with the Sweet

In oncology and cardiology, ^{18}F-FDG has proven of great practical use. Its use is so widespread that we often forget that the physiologic interpretation of the uptake and metabolism of ^{18}F-FDG is by no means straightforward and has been the subject of argument for decades (*1*). The article by Herrero et al. (*2*) in this issue of *The Journal of Nuclear Medicine* revisits one of these fundamental interpretational problems by asking whether cardiac ^{18}F-FDG metabolism really represents glucose metabolism. In so doing, Herrero et al. remind us that our understanding of how to interpret images of this "molecule of the century" is far from complete: To what extent does ^{18}F-FDG uptake represent ^{18}F-FDG metabolism? To what extent does ^{18}F-FDG metabolism actually represent glucose metabolism? And what does measurement of glucose metabolism really tell us about energy consumption? These are just a few of the questions that come to mind. The article of Herrero et al. focuses on only the second of these questions, and only as it applies to myocardial imaging. Nonetheless, the article serves as a stimulus to reflect on how these mostly unanswered questions might affect the interpretation of ^{18}F-FDG PET imaging in both cardiology and oncology.

CAN ^{18}F-FDG METABOLISM BE USED TO INFER GLUCOSE METABOLISM?

There has been controversy (*1*) about this question ever since Sokoloff's pioneering work on ^{18}F-FDG metabolism in the brain. The 2 principal elements in this controversy involved how "constant" the so-called lumped constant (LC) really was and whether ^{18}F-FDG, once it had been phosphorylated, really was permanently trapped in the cell. ^{18}F-FDG is in some cases more easily transported across the cell membrane than is glucose, in both the brain and the heart (and presumably in tumors). Furthermore, once inside the cell, ^{18}F-FDG is in general phosphorylated less easily than is glucose. These 2 differences had to be corrected for when using measurements of ^{18}F-FDG metabolic rate to infer glucose metabolic rates. The combined effect of these differences was initially assumed to be constant and was accounted for by a constant scale factor relating ^{18}F-FDG metabolism to glucose metabolism—the LC. To some extent the brain's metabolic processes (around which the early controversy centered) are quite simple compared with those of the myocardium or perhaps even of tumors. The brain is isolated by the blood–brain barrier from most of the various substrates available in the blood. No such isolation exists for the myocardium or for tumors. Tumors are usually thought to be supplied by very "leaky" vessels, much more permeable to even large molecules than are normal capillaries. The heart is a "metabolic omnivore," and a wide variety of different substrates compete with glucose for energy production. Compared with the brain (and even the heart), less is known about the mechanisms used by tumors to satisfy their energy needs (*3*).

Problems arise in interpreting cardiac or tumor scans if the LC is not, in fact, constant. Two sorts of changes in the value of the LC might be of concern, global temporal changes (e.g., from one study to the next) and regional changes (e.g., variation in the LC at different portions of the tumor or heart during the same study). Global changes in the LC have been shown to be produced by global changes in the cardiac milieu (e.g., glucose, fatty acids, and insulin) by Herrero et al. (*2*) and others. Although such changes in LC can make physiologic measurements problematic, many clinical cardiac ^{18}F-FDG scans look only at relative ^{18}F-FDG uptake around the myocardium (e.g., viability measurements) during a single study. In such situations, global changes in the LC might not be a serious practical problem. When ^{18}F-FDG scans are used to monitor tumor therapy, however, such global changes in the LC could be problematic. In the current paradigm, one assumes that reduction in glucose use with therapy indicates tumor response. If the LC changes during treatment, changes in glucose use would not be mirrored by changes in ^{18}F-FDG.

The second potential change in the LC would be the occurrence of regional changes in the LC, in which, for example, one part of the myocardium or tumor had an LC different from that of other parts. Such regional changes could conceivably result from regional changes in the myocardial or tumor cells themselves or from regional changes in the cellular milieu, such as large differences in blood flow from one part of the tumor or heart to another. If such regional blood flow changes induced regional changes in the LC, then the ^{18}F-FDG distribution would not reflect a similar pattern of glucose use.

Changes in the LC, often very large changes, have been observed using both nuclear magnetic resonance spec-

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troscopy and PET (*4–7*) primarily in isolated heart preparations, although there have been some conflicting results in the literature. These studies have primarily involved changing the cardiac milieu through alterations in glucose and insulin, although other studies have suggested that large increases in myocardial blood flow will also alter the LC. In the current article (*2*), Herrero et al. have made in vivo measurements in dogs, examining how well both ^{18}F-FDG PET and ^{11}C-glucose PET mirrored actual glucose consumption (determined with unlabeled glucose by Fick methods). Herrero et al. varied the myocardial milieu in a variety of ways, changing substrate availability, insulin levels, and cardiac work (and therefore blood flow). Under this variety of conditions, ^{18}F-FDG uptake rate, using a single fixed value for the LC, had a significantly poorer correlation with true glucose consumption than did ^{11}C-labeled glucose. Even when an attempt was made to allow the LC to vary using a previously reported variable LC model (*8*), the agreement between ^{18}F-FDG and unlabeled glucose remained poor and a significant bias resulted.

Far less is known about whether such effects might also occur in tumors—does the LC change from one tumor type to another, does it change as the tumor grows, or with therapy? Hariharan et al. (*5*) suggest, referring to cardiac studies, that "To validate the tracer analog method, uptake of ^{18}F-FDG must be measured simultaneously with a true glucose tracer under conditions similar to those in vivo. . . . " This is what has been done in isolated heart preparations and is what Herrero et al. (*2*) do in dogs in vivo in the current article. It is an approach that also is needed for tumors. Unfortunately, the measurements that are proposed by Herrero et al. are considerably more complex to perform than are similar quantitative measurements with ^{18}F-FDG. ^{11}C-glucose has a shorter half-life and produces many metabolites that are difficult to correct for ($^{11}CO_2$ and ^{11}C-lactate). Nonetheless, Herrero et al. show that the measurements can be performed in vivo, albeit with some difficulty.

The observations of Herrero et al. (*2*) are of obvious importance for cardiac imaging (at least for measurements in which absolute glucose use rates are desired). Do any of these findings help us understand what the limitations for tumor imaging might be? Given our limited understanding of tumor metabolism (*3*) (and the wide array of very different tumors), and given the large variation of perfusion within a tumor and across tumor types, we must proceed with care. The articles questioning the constancy of the LC for hearts must make us think carefully before we accept ^{18}F-FDG use as really representing glucose metabolism in tumors. This in no way detracts from the empirically proven clinical utility of ^{18}F-FDG in both cardiac and tumor imaging. It simply means that interpretation of the physiologic significance of ^{18}F-FDG measurements is not straightforward.

DOES ^{18}F-FDG UPTAKE REPRESENT ^{18}F-FDG METABOLISM?

There are 3 principal reasons that the amount of ^{18}F-FDG taken up by a tumor or by the myocardium does not necessarily reflect the ^{18}F-FDG metabolic rate of that structure. First, ^{18}F-FDG uptake represents the total amount of ^{18}F-FDG that is present in the tissue at the particular time one acquires the image. Often, that amount will continue to increase (especially in tumors) long after the standard 1-h imaging time. Second (and related to the first), ^{18}F-FDG uptake is not equal to the total amount of ^{18}F-FDG that has been metabolized (i.e., phosphorylated). Instead, it is the sum of ^{18}F-FDG that has been metabolized and ^{18}F-FDG that is as yet unmetabolized (e.g., in the blood within the tumor, in the intercellular spaces, and within the cells themselves). This amount can be considerable, depending on the blood concentrations of ^{18}F-FDG at the time of imaging—often quite high in oncology imaging and even occasionally in glucose-loaded cardiac subjects. Third, the uptake depends on the injected dose (which is easy to correct for) and the amount of ^{18}F-FDG available to the tumor or myocardial cells. This "available dose" in turn depends on how much of the injected ^{18}F-FDG is taken up by other structures within the body. Calculations of standardized uptake value attempt to compensate for this by assuming that the amount taken up by the rest of the body depends only on total weight, or lean body mass, or body surface area. For patients who are receiving radiation or chemotherapy or have progressive metastatic disease, this assumption is unlikely to be true. Changes in ^{18}F-FDG uptake of a tumor over time may therefore not reflect changes in ^{18}F-FDG metabolism over time (*9*). More elaborate analyses of the data, such as Patlak analysis or a full 3-compartment model, avoid these problems, but only at the expense of requiring a dynamic acquisition and requiring knowledge of the arterial activity as a function of time, A(t). It is possible that other normalization schemes, such as some form of "simplified kinetic analysis" (*10,11*), might be sufficient to minimize the difficulties associated with variations in the "available dose" (i.e., variations of the input function) from one study to the next. In addition, late imaging (*12,13*) may serve to reduce the contribution of unmetabolized ^{18}F-FDG and reduce the time dependence of ^{18}F-FDG uptake. It is possible that in the future some new scheme for ^{18}F-FDG normalization may be feasible, combining the simplicity of standardized uptake value with the increased accuracy of Patlak analysis. Much work remains to be done in this arena.

DOES GLUCOSE METABOLIC RATE REFLECT ENERGY CONSUMPTION?

In the heart it is clear that, even discounting possible LC variability, ^{18}F-FDG metabolic rate does not tell one much concerning energy consumption. Too many other substrates can compete with glucose (including both fatty acids and lactate). More important, the amount of energy produced per glucose molecule depends

crucially on oxygen supply. In tumors, it is not even completely clear what the primary sources of energy production are. In vitro studies indicate that glutamine and glutamate might contribute as much as 65%–80% of total energy production under aerobic conditions (*3*). In vivo studies have shown differing results. Even if glucose were the only substrate in tumors, the energy produced per molecule of glucose consumed can of course vary by a factor of 19 depending on whether only glycolysis occurs or whether oxidative phosphorylation also proceeds. Obviously then, the glucose (and ^{18}F-FDG) use will vary greatly depending on the type of metabolism taking place, for the same rate of energy consumption. This will depend presumably on flow-related oxygen supply and even on the state of differentiation of the cells, since it is thought that the degree to which tumor cells depend on glycolysis is related to how poorly differentiated the cells are.

The bottom line is that we must not let the proven clinical utility of ^{18}F-FDG in cardiology and oncology make us complacent. There still is an immense amount to learn about even the most basic aspects of metabolism and ^{18}F-FDG. Many more studies such as that of Herrero et al. (*2*) and the in vitro work that preceded it will be required before we fully understand what ^{18}F-FDG uptake really means. In the meantime, we must consider ourselves fortunate that despite our limited understanding of the physiology, ^{18}F-FDG PET has come to play a dominant role in medical imaging.

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