Dynamic Imaging of Transient Metabolic Processes: PDT Is Just the Beginning

Most clinical nuclear medicine procedures, both PET and SPECT, acquire images at a single time point, usually a fixed time after injection of the radiotracer. For example, ^{18}F-FDG images generally are obtained at least an hour after injection, at which time the tracer has reached approximate equilibrium and the regional uptake represents a measure of glucose metabolism.

Dynamic imaging, in which changes in tracer uptake over time are recorded, provides much more information on the underlying physiology. In addition to the equilibrium measurement, dynamic imaging provides data during the uptake and washout phases,

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when the competing effects of blood flow, delivery, and retention can be studied. Further, fitting kinetic models to the dynamic data provides truly quantitative parameters associated with the underlying physiology, such as rates of glucose metabolism. Dynamic imaging is limited in that it generally is performed after a bolus injection of the tracer and, therefore, any changes in the system over time can be measured only by additional injections. If these changes are transient or represent rapid alterations in the underlying physiology, then the relatively slow kinetics of the tracer can mask the true behavior of the system under study. Because the metabolic changes associated with these transient effects are concurrent with the kinetics of ^{18}F-FDG uptake, it is extremely difficult to extract the true contribution to the uptake from each factor. Further, the slow kinetics of ^{18}F-FDG uptake do not allow an instantaneous measurement of glucose metabolism from a single bolus injection.

For detection of transient changes in uptake, a slow infusion of the tracer is the preferred method. In this method, the tracer is injected continuously throughout the experiment. After a certain period, the tracer reaches a sustained equilibrium in which the concentration in tissue remains constant. The kinetics of ^{18}F-FDG during an infusion are slightly different. Because of the slow dephosphorylation rate, the concentration of ^{18}F-FDG in tissue does not reach an equilibrium state. Instead, the rate of increase in ^{18}F-FDG accumulation remains constant. Alterations in the physiology of the subject will lead to transient changes in the distribution of the tracer, which eventually will settle into a new equilibrium state. It is important to note, however, that any transient alterations in uptake can occur only at a rate governed by the kinetics of the tracer; that is, a tracer with slow kinetics may not accurately follow rapid transient effects.

Infusion protocols have been used to study transient changes in physiology, particularly in neuroimaging applications. The interactions between receptors in the brain and exogenous drugs and endogenous neurotransmitters have been studied using competition with a radioligand (*1*). The slow infusion of the radioligand allowed investigators to study the interaction at the receptor binding site dynamically (*2,3*). For example, studies of the dopamine receptor system using an infusion of radiolabeled tracers such as ^{11}C-raclopride have shown competition with the endogenous neurotransmitter dopamine (*4,5*). Studies on mice have demonstrated that, using a single-scan infusion protocol, imaging can detect direct competition at the receptor with an antagonist (*6*).

Photodynamic therapy (PDT), a promising treatment for accessible tumors, is localized to the tumor tissue by using photosensitive drugs. PDT may lead to tumor regression through several mechanisms, including direct oxidative damage to the tumor cells or vascular stasis leading to indirect tumor cell death (*7,8*). Imaging tumors in mice with ^{18}F-FDG PET could provide important data on the mechanisms of action of the various PDT photosensitizers (*9*). However, previous attempts at imaging transient changes in tumor activity resulting from PDT have been limited to single scans at different time points after illumination (*10*). In these studies, the uptake pattern of ^{18}F-FDG indicated the different mechanisms of PDT. The early time point showed a reduction in ^{18}F-FDG uptake resulting from the PDT drug that targets the vascular system, whereas the later time point showed the effect of the PDT drugs that directly target tumor cells. Although this study indicated the different modes of action of the PDT drugs, it was clear that 2 time points were not sufficient to fully classify the underlying mechanisms involved in tumor cell death.

The paper presented by Bérard et al. (*11*) in this issue of *The Journal of Nuclear Medicine* takes these studies one step further. With an infusion protocol, the transient changes in glucose use resulting from PDT could be

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monitored almost in real time. ^{18}F-FDG was infused over the duration of the experiment and, within the limitations of the kinetics of ^{18}F-FDG, changes in tracer uptake were interpreted as the metabolic response in tumor cells resulting from treatment. Kinetic modeling of the dynamic data would have given more detailed measures of tumor physiology, such as those differentiating changes in blood flow from changes in metabolism, but this requires arterial blood sampling, a considerably more invasive procedure. Again, it is important to note that changes in signal intensity on the images occur because of a combination of changes in tumor metabolism coupled with the kinetics of the tracer, such that transient changes that are extremely brief may not be reflected accurately by alterations in ^{18}F-FDG uptake. As the authors' state, the PET data are not an instantaneous measurement of tumor metabolism but, rather, a time average dependent on the kinetics of the tracer. This limitation is further complicated by the time-varying nature of the PDT drugs, which continuously evolve throughout the experiment.

Despite the complex interaction between tracer uptake kinetics and the PDT-induced time-varying tumor metabolism, the results are profound. The 2 different classes of PDT drugs clearly yield different response patterns in ^{18}F-FDG uptake. The drugs that induce direct cell death, such as $ZnPcS_2$-PDT, resulted in a rapid reduction in ^{18}F-FDG uptake in the tumor, which recovered quickly to a level that was more than 80% of the initial rate after the illumination ended. This apparently reversible tumor damage contrasted with the drugs that act on tumor vasculature, such as $AlPcS_4$-PDT, for which the initial reduction in tumor uptake was delayed but the recovery also was delayed and remained significantly lower. Although ^{18}F-FDG is subject to other confounding effects, such as apoptosis and inflammatory response in the tumors, the differences in tumor metabolism revealed by dynamic imaging with a continuous infusion of tracer are strong evidence of the different modes of action of the 2 classes of PDT drugs.

Further experiments could involve the coadministration of both classes of PDT drugs and observation of the transient effects on tumor metabolism. The observed transient metabolic pattern might well reveal a possible synergistic effect of such combined therapy. Similarly, the early action mechanism and efficacy of multiple therapies, including PDT and chemotherapy, could be assessed by observing the transient metabolic effects resulting from the application of these combined treatments. Important information on the administration protocol, timing, and dosage of the multitherapy could be gathered and exploited to optimize treatment efficacy.

Another interesting feature of this experiment was the observation of a systemic response to PDT, even in tumors shielded from light. These control tumors exhibited significant variations in ^{18}F-FDG uptake, during both the illumination phase and the recovery phase. The likely cause of this remote effect is the dispersion into the circulation of vasoactive signaling factors, which then act on the vasculature of the distant tumors. This observation was possible only due to the imaging protocol, which enabled both tumors to be monitored simultaneously in the field of view of the scanner.

The dynamic imaging period was limited in this study to 2 h. However, with appropriate physiologic monitoring and life support of the animal, the imaging period could be extended to several hours, enabling indirect exploration with ^{18}F-FDG of some delayed effects of the treatment, such inflammation and apoptosis of the tumor cells. Indeed, these other processes could be observed directly using tracers specific for apoptosis (*12,13*) or inflammation or by measuring tumor proliferative state using a tracer such as ^{18}F-FLT. The same infusion protocol could be used with these other tracers, allowing the observation of transient changes in a multitude of tumor functions resulting from PDT or other therapies. Clearly, the infusion rate and imaging protocol need to be adapted individually for the kinetics of each tracer and also for the time course of the biologic processes being investigated. The amount of information that could be gathered about tumors and their response to treatment could greatly enhance our understanding of tumor physiology. Most important of all, every aspect of this work is directly translatable to humans.

In conclusion, dynamic imaging using an infusion of tracer has tremendous potential for the study of transient alterations in tumor physiology resulting from PDT and other therapies. The technique of Bérard et al. reported in this issue is a promising first step and, coupled with more detailed kinetic modeling and the use of additional tracers for specific tumor functions, could provide vital information on screening new drugs and optimizing treatment regimens.

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REFERENCES

1. Laruelle M. Imaging synaptic neurotransmission with in vivo binding competition techniques: a critical review. *J Cereb Blood Flow Metab.* 2000; 20:423–451.
2. Endres CJ, Carson RE. Assessment of dynamic neurotransmitter changes with bolus or infusion delivery of neuroreceptor ligands. *J Cereb Blood Flow Metab.* 1998;18:1196–1210.
3. Watabe H, Endres CJ, Breier A, Schmall B, Eckelman WC, Carson RE. Measurement of dopamine release with continuous infusion of [^{11}C]raclopride: optimization and signal-to-noise considerations. *J Nucl Med.* 2000;41: 522–530.
4. Martinez D, Slifstein M, Broft A, et al. Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: amphetamine-induced dopamine release in the functional subdivisions of the striatum. *J Cereb Blood Flow Metab.* 2003;23:285–300.
5. Brody AL, Olmstead RE, London ED, et al. Smoking-induced ventral striatum dopamine release. *Am J Psychiatry.* 2004;161:1211–1218.
6. Acton PD, Hou C, Kung MP, Plössl K, Keeney CL, Kung HF. Occupancy of dopamine D2 receptors in the mouse brain measured using ultra-high resolution single photon emission tomography and [^{123}I]IBF. *Eur J Nucl Med.* 2002;29:1507–1515.
7. Chan WS, Brasseur N, La Madeleine C, Ouellet R, van Lier JE. Efficacy and mechanism of aluminium phthalocyanine and its sulphonated

derivatives mediated photodynamic therapy on murine tumours. *Eur J Cancer.* 1997;33:1855–1859.
8. Oleinick NL, Evans HH. The photobiology of photodynamic therapy: cellular targets and mechanisms. *Radiat Res.* 1998;150(suppl):S146–S156.
9. Moore JV, Waller ML, Zhao S, et al. Feasibility of imaging photodynamic injury to tumours by high-resolution positron emission tomography. *Eur J Nucl Med.* 1998;25:1248–1254.
10. Lapointe D, Brasseur N, Cadorette J, et al. High resolution PET imaging for in vivo monitoring of tumor response after photodynamic therapy in mice. *J Nucl Med.* 1999;40:876–882.
11. Bérard V, Rousseau JA, Cadorette J, et al. Dynamic imaging of transient metabolic processes by small-animal PET for the evaluation of photosensitizers in photodynamic therapy of cancer. *J Nucl Med.* 2006;47:1119–1126.
12. Blankenberg FG, Katsikis PD, Tait JF, et al. Imaging of apoptosis (programmed cell death) with ^{99m}Tc annexin V. *J Nucl Med.* 1999;40:184–191.
13. Blankenberg FG. Recent advances in the imaging of programmed cell death. *Curr Pharm Des.* 2004;10:1457–1467.