Letters to the Editor

The Potential for Low-Dose Functional Studies in Maternal–Fetal Medicine Using PET/MR Imaging

TO THE EDITOR: We wish to draw attention to the potential for a novel application of PET/MR imaging for studies of the human fetus in vivo. This application fills the unmet need for modern preventive medicine at the beginning of life. We believe that administering low levels of imaging biomarkers labeled with short-lived positron emitters such as ^{15}O and ^{11}C to the pregnant mother, in conjunction with high-sensitivity PET, will allow sufficient data acquisition to examine tracer kinetics in the fetus at acceptable absorbed doses of radiation. This application might open a new investigative area for molecular imaging that has the potential to substantially affect clinical care and lifelong health. Conceptual studies might include measuring oxygen uptake in the fetal brain using the 2.1-min half-life tracer ^{15}O. Nutrient delivery or metabolism investigations might be undertaken using, for example, ^{11}C-labeled amino acids, as shown in pioneering research performed on nonhuman primates (*1*). Studies to detect inflammation in the fetus might be enabled using biomarkers of the 18-kDa translocator protein. Important placenta transport functions might be investigated using markers such as a substrate for system A transporters: for example, [*N*-methyl-^{11}C]α-methylaminoisobutyric acid (*2*).

The importance and need to study aspects of fetus function in vivo are based on some compelling facts:

- Three million stillborn deaths occur every year worldwide (*3*).
- Fifteen million premature births occur every year worldwide. Of these, 1.1 million babies die of preterm complications, and many surviving babies are disabled. The United States ranks third in the world, with 12% preterm births (*4*).
- Intrauterine growth restriction is the cause of many neonatal deaths and premature births. It is believed to be caused by an abnormal placenta and altered transporter expression and function (*2*). It is associated with raised neonatal mortality and morbidity and with an increased incidence of diabetes, hypertension, ischemic heart disease, and metabolic syndrome in adulthood (*2*).
- Fetal inflammation is associated with increased schizophrenia, autism, cognitive impairment, and neurologic diseases in later life (*5,6*).

Applying the sensitivity and specificity of PET to the challenges of fetal medicine might have a prospective lifelong impact on health, compared with the current emphasis on retrospective late-in-life imaging studies of established diseases such as cancer and dementia. PET has unique sensitivity for detecting low levels of radioactivity, enhanced through time-of-flight (TOF) acquisition of 3-dimensional data and extended axial field-of-view tomographs (*7*). Because the levels of administered radioactivity are likely to be below that needed to reconstruct images with contemporary spatial resolution, a key advantage of combined PET/MR imaging is that volumes of interest for the maternal aortic arterial blood pool, the placenta, and the whole body or brain of the fetus could be derived

from MR imaging and placed into PET sinogram space. This would permit reconstructions for predetermined volumes with minimal statistical noise (*8*), thus enabling accurate kinetic and tissue concentration data. In addition, MR imaging–based attenuation correction obviates the CT dose, and MR imaging enables motion compensation for dynamic datasets. PET imaging of the large pregnant abdomen would capitalize on the value of TOF in reducing noise within the reconstructed data. Because the fetus is surrounded by the amniotic fluid cavity, which would exchange tracer slowly with the maternal blood, it is enclosed in a space devoid of tracer. Hence, spillover of signal from surrounding maternal tissue would be minimal, and MR imaging–guided volume-of-interest reconstructions within the cavity would provide accurate measures of the scatter background. The resulting reconstructed datasets would then provide the tissue concentration time-course data from which functional measurements of delivery and exchange to the placenta and fetus could be derived. There is also the opportunity to avoid reconstructions by deriving, with more statistical certainty, the tissue concentrations and time–activity data for the fetus and placenta directly from counts that fall within the TOF-defined volume. These would amount to a diameter of some 15 cm, which is equivalent to 2×7.5 cm in full width at half maximum, as is achievable with currently practiced 500-ps timing.

Mother–fetus body kinetic studies using an ^{11}C-labeled compound should be possible with activity as low as 18.5 MBq. This is estimated to result in an absorbed radiation dose to the fetus of 0.2–0.5 mSv based on our calculations using the MIRD schema (*9*) that depend on fetal age and accumulated activity, and estimates made by others for ^{18}F-FDG (*10*). This dose is a fifteenth of the annual dose, including radon, of 3 mSv in the United States. Such estimates are in line with reports about fetuses accidentally irradiated in pregnant patients undergoing ^{18}F-FDG imaging for cancer (*10*). Notably, the fetus is less sensitive to radiation when near term (when one would propose imaging evaluations) than earlier in gestation. Furthermore, operating PET at low counting rates with minimal registration of dead time and random coincidences, together with accurate measures of the scatter contribution, would result in maximum noise-equivalent counts per unit of administered radioactivity and hence optimum signal per unit of absorbed dose. If the methodology of TOF windowing were to be developed to record tracer concentrations in the fetus directly and thereby avoid reconstruction, it is expected that the needed radioactivity would be an order of magnitude lower.

The potential ability of PET to trace the passage of a chemical compound from mother to fetus epitomizes the fundamental strength of the tracer principle. When PET is combined with the range of molecules that can be labeled with ^{11}C, a broad and important area for investigation could be uniquely empowered to uncover new information on the relationship of intrauterine health to the lifelong health of an individual. If this field were to develop, it could also stimulate the advance of generic PET methodology by increasing the PET axial field of view (*7*) and introducing faster detectors for TOF imaging; together, sensitivity is foreseen to be more than one order of magnitude greater than that of current practice. We propose that the molecular imaging community consider fostering this application of PET/MR imaging, initially by engagement with fetal health experts and

obstetricians. Undertaking preclinical studies on large pregnant animals, such as sheep, would then be appropriate to consolidate the combined methodologies and establish firm radiation dose facts to enable future studies on humans.

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Prognostic Implications of Imaging-Based Bone Marrow Assessment in Lymphoma: ¹⁸F-FDG PET, MR Imaging, or ¹⁸F-FDG PET/MR Imaging?

TO THE EDITOR: We read with interest the recent article by Berthet et al. (*1*), who investigated the prognostic implications of ¹⁸F-FDG PET–based bone marrow assessment in diffuse large B-cell lymphoma (DLBCL). Their well-designed retrospective study included 133 patients with newly diagnosed DLBCL, of whom 32 were positive for bone marrow involvement according to ¹⁸F-FDG PET whereas only 8 were positive according to bone marrow biopsy. In a multivariate analysis, Berthet et al. showed that only the International Prognostic Index (IPI) and the ¹⁸F-FDG PET bone marrow status were independent predictors of progression-free survival ($P = 0.005$ and $P = 0.02$, respectively), whereas only the IPI remained an independent predictor of overall survival ($P = 0.004$). Almost simultaneously, another study on the same subject

was published by Khan et al. (*2*). In their retrospective study that included 130 patients with newly diagnosed DLBCL, 35 were judged to have marrow involvement; of these, 33 were identified by ¹⁸F-FDG PET and 14 by bone marrow biopsy. Cases with bone marrow deposits identified by ¹⁸F-FDG PET but not by biopsy had progression-free and overall survival similar to Ann Arbor stage IV disease without involved bone marrow (*2*). Both studies suggest that ¹⁸F-FDG PET–based bone marrow assessment in newly diagnosed DLBCL may have prognostic implications and that the importance of ¹⁸F-FDG PET bone marrow status may overshadow that of the bone marrow biopsy result in this context (*1,2*).

Although ¹⁸F-FDG PET is a powerful method for evaluation of the bone marrow, it is a pity that neither Berthet et al. (*1*) nor Khan et al. (*2*) make any mention of the role of MR imaging in this setting. Back in 1997, Tsunoda et al. (*3*) had already reported on the prognostic value of bone marrow MR imaging in lymphoma. In their study, Tsunoda et al. retrospectively investigated a mixed population consisting of 56 patients with newly diagnosed low-, intermediate-, and high-grade non-Hodgkin lymphoma ($n = 48$) and Hodgkin lymphoma ($n = 8$). At the time of diagnosis, all patients underwent masked bone marrow biopsy of the posterior iliac crest and MR imaging of the femoral bone marrow at 1.5 T. The findings of the biopsy were negative in 39 patients, of whom 12 had positive results on MR imaging. Patients were followed for 1–58 mo after the MR imaging examination, with a median of 17 mo. Interestingly, patients with a positive MR imaging result but a negative biopsy result had a significantly shorter overall survival than did those for whom both MR imaging and biopsy were negative ($P = 0.016$). Tsunoda et al. concluded that abnormal MR imaging findings for the femoral bone marrow are associated with a significantly poorer survival in patients with lymphoma, regardless of histologic findings in the bone marrow. Since 1997, MR imaging has made a giant leap forward; nowadays, a high-quality MR imaging examination of the bone marrow in the entire body (i.e., from cranial vertex to toes) can be routinely obtained in less than half an hour. Recent data have shown that the sensitivity of whole-body MR imaging for the detection of lymphomatous bone marrow involvement equals that of ¹⁸F-FDG PET (*4*). Even more interestingly, preliminary data from our ongoing prospective study on the value of whole-body MR imaging in DLBCL patients with a negative masked bone marrow biopsy show that disease relapse or progression and death occur more frequently if whole-body bone marrow MR imaging findings are positive. Thus, although more prospective research is warranted and a comparison with established prognostic stratification models such as the IPI should be done, both older and more recent data indicate that bone marrow MR imaging findings may have prognostic implications in lymphoma, independently of (masked) bone marrow biopsy results.

In conclusion, both ¹⁸F-FDG PET and MR imaging play a major clinical role in the evaluation of bone marrow diseases, including lymphomatous bone marrow involvement. Given this background information, one may wonder which of the two should be used as a noninvasive bone marrow biomarker of prognosis in lymphoma. ¹⁸F-FDG PET/MR imaging will both answer this question and relieve us from the difficult decision of choosing between them.

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