High Intraindividual Variability of Global Myocardial ^{18}F-FDG Uptake over Time

TO THE EDITOR: Recently, Inglese et al. documented an extreme variability in the spatial and temporal heterogeneity of regional myocardial uptake on repeated whole-body ^{18}F-FDG PET/CT in fasting oncologic patients without heart disease (*1*). The authors cautiously attributed uptake defects on myocardial ^{18}F-FDG imaging to scar tissue, unless the defects are associated with severe hypoperfusion on ^{18}F-FDG imaging used alone to evaluate myocardial viability. Furthermore, there are suggestions that ^{18}F-FDG PET can detect radiation-induced myocardial damage early (e.g., in patients with esophageal cancer), but high myocardial ^{18}F-FDG uptake corresponded to irradiated fields in only 20% of patients (*2*). In a case report, ^{18}F-FDG PET/CT demonstrated an excellent concordance between increased myocardial ^{18}F-FDG uptake and irradiated fields (*3*).

On the other hand, physiologic myocardial ^{18}F-FDG uptake in fasting individuals free of any heart disease is controversial. Khandani et al. reported that a subjective visual determination of cardiac ^{18}F-FDG uptake did not change significantly over time in 47 oncologic patients who underwent 4 to 9 serial PET scans (*4*). In contrast, de Groot et al. found that visual grading of myocardial ^{18}F-FDG uptake changed significantly in nearly two thirds of 25 oncologic patients who underwent at least 3 serial PET scans (*5*).

We would like to report a 29-y-old man without evidence or a history of heart disease who showed an extremely high variability of global myocardial ^{18}F-FDG uptake on 3 PET/CT scans. The patient was diagnosed with rhabdomyosarcoma of the right testis and underwent ablative surgery but still had multiple pulmonary and several lymphogenic metastases. The first ^{18}F-FDG PET/CT scan was performed in October 2007 after 4 cycles of palliative chemotherapy and showed metastatic disease in the right and left lungs and inguinal lymph node involvement, but myocardial ^{18}F-FDG uptake (maximal standardized uptake value [SUV_{max}], 2.7; mean [±SD] standardized uptake value [SUV_{mean}], 1.6 ± 0.2) was comparable to the mediastinal background level. A second scan in January 2008 showed partial metabolic remission of these lung metastases after high-dose chemotherapy with carboplatin and etoposide followed by autologous stem cell transplantation in November 2007 but high global myocardial ^{18}F-FDG uptake (SUV_{max}, 7.1; SUV_{mean}, 4.5 ± 0.8). The patient had never received radiation treatment. Therefore, we did not observe radiation-related myocardial damage in the second PET/CT scan. Seven weeks later, in February 2008, the patient underwent the third PET/CT scan, which was performed because of suspected progressive disease under ongoing chemotherapy for consolidation but found metabolically (and morphologically) stable disease. The image showed myocardial ^{18}F-FDG uptake comparable to the mediastinal background level of the first scan (SUV_{max}, 2.5; SUV_{mean}, 1.5 ± 0.2). All routinely measured external parameters during the 3 scans were almost identical. The patient fasted at least 12 h before each examination. The blood glucose levels at the times of the first, second, and third scans were 6.0, 4.7, and 5.2 mmol/L, respectively, and the levels of creatinine (58 μmol/L at scan 1 and 54 μmol/L at scan 3) and TSH (1.85 mIU/L at scan 1 and 1.91 mIU/L at scan 3) were always within the reference range. The administered activities were 332, 313, and 317 MBq of ^{18}F-FDG, and the scans started at 1 h 4 min, 59 min, and 59 min after injection. Of course, the reconstruction parameters for all images were identical. A 300% (!) increase in global myocardial ^{18}F-FDG uptake occurred during the second scan.

It is still unclear to us why such an extremely high intraindividual variability in global myocardial ^{18}F-FDG uptake can occur, but this variability underlines the necessity for further studies in this field. In this context, the set-up of Inglese et al. is only one side of the coin (*1*). The other side is to study modulation of glucose metabolism in myocytes for a better understanding of myocardial glucose metabolism (*6*), in particular after radiation treatment or stem cell transplantation (*7*).

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REPLY: The clinical case presented by Zöphel and Kotzerke emphasizes the complexity of ^{18}F-FDG myocardial uptake, whose variability remains a controversial issue in the literature. The case is also an added demonstration of the marked, consistent variability in global myocardial ^{18}F-FDG uptake, for which the mutual influence of systemic mediators of cell membrane glucose transporters (GLUTs) can easily be argued as the main reason. During routine ^{18}F-FDG PET examinations of fasting patients, we have also observed an individual variability in global glucose uptake related to the interval after ^{18}F-FDG administration and the delay in the timing of data acquisition. In some patients in whom

the myocardium on PET reconstruction was only faintly appreciable at 1 h, myocardial uptake was sharply improved when the PET acquisition was repeated 2 h after tracer injection.

In addition to the influence of biologic mediators on the systemic synchronization of glucose uptake by cells, a regional glucose uptake mechanism may sometime emerge and dominate myocyte glucose internalization independently of insulin, adrenalin, and several other mediators of global myocardial uptake. It is well known that in chronic regional left ventricular dysfunction, this mechanism aims at the survival of myocardium. Hibernation and chronic ischemia are not the only examples of microsystem autoregulation of the regional metabolism of the myocardium; several "nearby normal" physiologic situations probably can induce the same regional phenomenon. When blood flow or substrate supply declines, production of high-energy phosphate becomes oxygen-limited, and glucose can be considered more oxygen-efficient than free fatty acid. Translocation of GLUTs, especially of the relatively insulin-independent GLUT-1, from cytosol to the cell membrane and increased expression of GLUTs are the metabolic pathways used for energy production within this independently operating and functioning microsystem (*1–4*).

In conclusion, we believe that the major contribution of our observational study was to document changes at the local level and that these changes were independent of the global myocardial integrated system. In fact, an extremely large variability in regional myocardial uptake was demonstrated on repeated whole-body ^{18}F-FDG PET/CT in fasting oncologic patients without heart disease. Thus, an unpredictable opposite change in glucose uptake can be documented over time, comparing the ^{18}F-FDG segmental uptake in 2 contiguous myocardial regions (*5*).

Therefore, as a cautious guideline, if the clinical question is myocardial viability and the ^{18}F-FDG study is performed under fasting conditions, when regional myocardial glucose uptake is evident and exceeds perfusion tracer uptake, residual myocardial viability can reliably be confirmed. In contrast, if regional ^{18}F-FDG uptake cannot be visually and quantitatively documented, scarred tissue can be suspected but not confirmed.

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