PET with $^{18}$F-FDG–Labeled T Lymphocytes for Diagnosis of Acute Rat Renal Allograft Rejection

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We proposed small-animal PET with $^{18}$F-FDG–labeled T lymphocytes as a new method for image-based diagnosis of acute allogeneic renal transplant rejection (AR) established in a rat model. 

**Methods:** One and 2 h after tail vein injection of $30 \times 10^6$ ex vivo $^{18}$F-FDG–labeled human T cells into male 10-wk-old uninephrectomized, allogeneically transplanted rats (aTX; Lewis–brown Norway [LBN] to Lewis), whole-body radioactivity distribution was assessed in vivo by small-animal PET (postoperative day 4), and percentage injected dose (%ID) as a parameter of T-cell infiltration was assessed and compared between graft and native kidney. In vivo results were confirmed by autoradiography and staining of human CD3 after postmortem dissection. Syngeneically transplanted rats (sTX) (LBN to LBN), rats with ischemia–reperfusion injury (IRI) (45-min warm ischemia), and rats subjected to acute cyclosporine A (CSA) toxicity (50 mg/kg for 2 d intraperitoneally) served as controls. 

**Results:** The accumulation of labeled cells was significantly elevated in allografts with AR ($0.07 \pm 0.28$ %ID), compared with native control kidneys ($0.49 \pm 0.18$ %ID) ($p < 0.0001$). No differences were found among native controls, sTX, CSA toxicity, and kidneys with IRI. In vivo uptake of $^{18}$F-FDG–labeled T cells measured in the PET scanner correlated with results obtained by autoradiography, histologic evaluation, and polymerase chain reaction. 

**Conclusion:** We proposed graft PET imaging using $^{18}$F-FDG–labeled T cells as a new option to detect rat renal AR with a low dose of $^{18}$F-FDG in a noninvasive, fast, and specific manner in rats.

**Key Words:** renal transplantation; acute rejection; radiolabeled T lymphocytes; $^{18}$F-FDG; PET


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At present, diagnosis of acute transplant rejection (AR) in humans relies on graft biopsy on renal allograft dysfunction (1,2). However, more than 50% of the rejection episodes are subclinical, without acute impairment of renal function and, interestingly, with a histologic severity score that was found to be comparable to that of patients with a decrease in glomerular filtration rate during AR (3). Therefore, one may undergo protocol biopsies at a defined time course after transplantation, irrespective of the status of graft function, to diagnose AR (2). Biopsy is an invasive procedure that is cumbersome to the patient, carries the risk of graft injury, and is not feasible in recipients taking anticoagulant medication (4,5). In addition, the sampling site is small and AR may be missed (i.e., when rejection is focal or patchy) (6). Thus, in diagnostics, entirely image-based methods visualizing the whole organ would be superior. Nuclear imaging approaches including SPECT and PET have the advantages of high intrinsic sensitivity, excellent tissue penetration, and a wide range of clinically available molecular imaging probes (7). Recently, we have established $^{18}$F-FDG PET as an entirely image-based method to assess and to monitor acute renal rejection (8,9). However, potential drawbacks in applying $^{18}$F-FDG PET to the clinical setting should be noted. First, urinary excretion of the tracer necessitates late acquisitions to reduce the amount of $^{18}$F-FDG in the urine. Further, the renal pelvis should be carefully excluded from the measurements. Second, $^{18}$F-FDG uptake is not disease-specific. Thus, a more specific method is desirable.

AR results from interactions between the recipient’s immune system and the foreign antigens serving as a target. T lymphocytes (CD4$^+$ and CD8$^+$) are central and specific to the AR process, whereas B cells and the congenital immune system (e.g., complement, monocytes and macrophages, neutrophils, and dendritic cells) participate (10,11). After recognition of donor-derived antigens, T cells migrate into the transplant and infiltrate the interstitial space (12). Because recruitment and activation of inflammatory cells, in particular lymphocytes, play decisive roles in AR, efforts have already been made to image infiltration by means of radiolabeled leukocytes (7). Because infiltration of leukocytes, especially T lymphocytes in allografts, appears before physiologic or mechanical manifestations of organ dysfunction is apparent, nuclear imaging using lymphocytes might be a promising tool for sensitive and early detection of rejection. However, PET with $^{18}$F-FDG–labeled T lymphocytes for diagnosis of AR has never been tested before. Thus, we applied PET with $^{18}$F-FDG–labeled human T lymphocytes in an established rat renal transplant model (9). $^{18}$F-FDG uptake of the renal parenchyma was assessed on postoperative day 4 (POD) in uninephrectomized, allogeneically kidney-transplanted animals (aTX) with, and additionally in native controls and syngeneically transplanted (sTX) animals without, rejection or impairment of renal function. Because acute cyclosporine A (CSA) nephrotoxicity and acute tubular necrosis (ATN) caused by ischemia–reperfusion injury (IRI) are important
differential diagnoses of AR, we have included these 2 additional groups into the study.

MATERIALS AND METHODS

Animal Models

Surgical and imaging experiments were approved by a government committee on animal welfare and performed in accordance with national animal protection guidelines. Male Lewis–Brown Norway (LBN) and Lewis (LEW) rats (200–270 g of body weight; Charles River) with free access to standard rat chow (Altromin) and tap water were used. Surgeries were performed under anesthesia with ketamine (100 mg/kg of body weight intraperitoneally) and xylazine (5 mg/kg of body weight intraperitoneally) (Xylazin and Ketamin; CEVA Tiergesundheit). Further doses of ketamine were injected as needed.

Transplantation was simultaneously performed by 2 investigators as published before (9,13,14). In short, the left kidney including ureter, renal artery, a piece of aorta, and renal vein were transferred into the recipient. Kidneys from age- and weight-matched LBN rats were transplanted into LEW rats (aTX). Transplantations were performed immediately after left nephrectomy of the recipient. Although the total operation time of the recipient did not exceed 90 min, the ischemia time of the graft was always shorter than 40 min. Grafts were studied on POD4 after transplantation. The chosen aTX model leads to histologic and functional changes typical for AR (9,13,14). As in the model cited by those studies without immunosuppression, graft necrosis starts only a few days beyond POD4; thus, we decided to investigate kidneys on POD4. Syngeneically transplanted rats (LBN to LBN, sTX) without AR served as controls. Because ATN and acute CSA toxicity are common differential diagnoses of AR, these groups have been also included. ATN (induced by IRI) and acute CSA toxicity were induced as published before (9,15). For IRI, the left renal artery was dissected as in transplant groups and ligated for 45 min using a microvascular clamp. After clamp release, the return of original surface color of the kidneys was confirmed visually. For acute CSA-induced nephrotoxicity, rats received 50 mg of CSA per kilogram (Sandimmun; Novartis) intraperitoneally for 2 d.

T-Cell Isolation and Labeling

18F-FDG was produced in a clinical routine setup on-site using an RDS 111 cyclotron (CTI). T lymphocytes were isolated from humanuffycoats (containing mainly white and red blood cells and platelets) (DRK Münster) by negative antibody selection using the RosetteSep method according to the manufacturer’s protocol (Stemcell). After cell numbers were counted in a Neubauer chamber, cells were adjusted to the desired amount, incubated with 80–120 MBq of 18F-FDG in 300 μL of 0.9% NaCl solution into a tail vein. Thereafter, the catheter was purged with an additional 700 μL of 0.9% NaCl solution. Rats remained in a restrainer under anesthesia until the start of the scan. During acquisition, rats were further anesthetized with oxygen-isoflurane inhalation (2% isoflurane, 0.7 l/min oxygen), and body temperature was maintained at physiologic values by a heating pad. Scans were obtained using a PET camera with a high-resolution multiwire chamber (quadHIDAC; Oxford Positron Systems Ltd.) (16).

PET Image Analysis and Quantitative Evaluation

A renal parenchyma volume of interest was manually traced around the kidneys on reconstructed coronal images. Mean 18F-FDG T-cell activity of the renal parenchyma was calculated by the ratio of total counts and volume.

Autoradiography

To validate the data obtained by PET, animals were sacrificed and kidneys were excised immediately after PET scanning. High-resolution autoradiography (μ-imager; Biospace Measures) was performed as published before (9). In short, kidneys were snap-frozen and sliced into 10-μm-thick cryosection, and the radioactivity was measured in a midcoronary renal slice for 3 h.

Histology

Portions of kidneys were snap-frozen and fixed in 4% formaldehyde in phosphate-buffered saline. Histologic changes (glomerulitis, tubulitis, endothelialitis, and infiltration) were examined by light microscopy in paraffin-embedded tissue with periodic acid-Schiff and hematoxylin and eosin staining. For the evaluation, only the cortex was chosen because the extent of medullary inflammation does not reflect the degree of AR (17).

Immunohistochemistry

After fixation in 4% formaldehyde in phosphate-buffered saline and embedding in paraffin, 3-μm-thick slices of kidneys were deparaffinized with Clear Rite (Microm) and rehydrated in descending ethanol series. Portions of kidneys were snap-frozen and fixed in 4% formaldehyde in phosphate-buffered saline and embedded in paraffin, 3-μm-thick cryosections, and the radioactivity was measured in a midcoronary renal slice for 3 h.

Flow Cytometry

T-lymphocyte purity of isolated cells was verified by staining with CD4−APC, CD8−PE, CD3−FITC, and CD45−PerCP-Cy5.5 (BD Biosciences) and subsequent fluorescence-activated cell sorting analysis as described previously (19).

Real-Time (RT) Polymerase Chain Reaction (PCR)

Expression profiles of selected marker genes for infiltrating cells were validated by RT PCR, which was performed using SYBR Green PCR Master Mix or TaqMan Universal PCR Master Mix on an ABI Prism 7700 Sequence Detection System. Table 1 lists the specific [Table 1]
Results and Discussion

Flow Cytometry and Labeling of Isolated T Lymphocytes

Flow cytometry analysis with CD45 as a general marker for leukocytes and CD3 as a specific marker for T cells revealed a mean T-lymphocyte purity of approximately 90% (n = 3). Supplemental Figure 1 (available online only at http://jnm.snmjournals.org) shows a representative experiment in which about 60% of the isolated cells belong to the subpopulation of CD4+ T-helper cells and about 30% are part of the group of CD8+ cytotoxic T-effector cells (CD4+/CD8+ ratio, 1.9).

The mean labeling efficiency of T lymphocytes with 18F-FDG using physiologic saline was 5.4% ± 2.1%. To elevate 18F-FDG labeling efficiency by means of stimulating insulin-dependent glucose transporters (GLUT), for example, GLUT4, T cells were coincubated with insulin and K+. However, neither the addition of insulin (6.0% ± 2.0%) or K+ (6.4% ± 2.6%) nor the combination of insulin and K+ (6.6% ± 3.0%) significantly increased the 18F-FDG uptake in T lymphocytes (Fig. 1A).

Labeling stability slowly decreased in vitro over time. Retention of the radionuclide in T cells slowly decreased from 80.7% ± 0.64% after 10 min to 71.25% ± 0.46% after 30 min to 56.42% ± 1.14% after 60 min, finally reaching 45.2% ± 0.97% after 120 min (Fig. 1B).

PET Image Analysis and Quantitative Evaluation

In allografts undergoing AR (POD4), we detected a clearly elevated T-lymphocyte signal already at 1 h after injection, which had only slightly increased further after 2 h (Fig. 2A; Supplemental Fig. 2). The quantification of 18F-FDG–labeled T-cell accumulation as percentage injected dose (%ID) within the parenchyma of the investigated kidneys revealed a significant increase in allografts only (aTX: 1.07 ± 0.28 %ID after 1 h, n = 7, and 1.18 ± 0.32 %ID after 2 h, n = 7, P < 0.0001 vs. all other controls), when compared with native control kidneys (0.49 ± 0.18 %ID, n = 17, and 0.66 ± 0.15 %ID, n = 16) and sTX (0.55 ± 0.11 %ID, n = 7, 0.61 ± 0.14 %ID, n = 5), CSA toxicity (0.34 ± 0.07 %ID, n = 10, and 0.39 ± 0.18 %ID, n = 10), and kidneys with IRI (0.37 ± 0.14 %ID, n = 6, and 0.40 ± 0.20 %ID, n = 6) (Fig. 2B).

 Autoradiography

Assessment of inflamed tissue by autoradiography confirmed that accumulation of 18F-FDG–labeled cells correlated to the degree of infiltration. Therefore, we chose autoradiography as a reference method to validate PET results with 18F-FDG–labeled T lymphocytes. As described previously, POD4 was chosen because accumulation of radiolabeled T cells reached significance at that time, whereas graft integrity was still maintained. On POD4, mainly the renal cortex but also the medulla of aTX kidneys demonstrated a significant accumulation of radiolabeled cells (Supplemental Fig. 3). Allografts exhibited a nearly 4-fold increased tracer uptake, when compared with native control kidneys, isografts, kidneys with IRI, and kidneys with acute CSA toxicity (Table 2).

Histology

To estimate renal damage and infiltration for validation of 18F-FDG data, we evaluated renal histology and quantified the number of CD3-positive infiltrating T lymphocytes. In allografts, we found distinct signs of acute rejection (marked
Infiltration of radiolabeled T lymphocytes in all used renal injury models was confirmed by the presence of CD3 and CD8b on POD4. Furthermore, 18F-FDG PET can be applied for the early evaluation of immunosuppressive treatment response and might assist in the differential diagnosis of AR, ATN, and acute CSA toxicity. However, potential drawbacks of 18F-FDG are, on the one hand, urinary excretion of 18F-FDG and drainage into the renal pelvis, aggravating assessment of parenchymal glucose metabolism, potentially inducing false-positive 18F-FDG signaling, and requiring late acquisitions to reduce urinary 18F-FDG. On the other hand, 18F-FDG uptake represents unspecific metabolic activity, thus, especially graft infection or potentially also lymphoma might generate a similar 18F-FDG accumulation pattern (24). Although clinical symptoms and additional serologic and image-based methods can assist in the differential diagnosis, a more specific tracer would be desirable. Because recruitment of T lymphocytes does not play a leading role in the development of infection, this diagnosis can usually be ruled out using PET with radiolabeled T cells. Moreover, using 18F-FDG PET for the detection of AR, we applied PET assessment 3 h after injection for several reasons, such as 18F-FDG drainage or elimination of free 18F-FDG. Although this is earlier than diagnostics by histologic means, it is not feasible in patients receiving anticoagulation therapy and might present false-negative results, if AR is focal or patchy (6).

Because activated leukocytes highly accumulate 18F-FDG, which can be assessed by PET, we recently established 18F-FDG PET for the noninvasive detection and monitoring of renal allograft rejection (9). Moreover, 18F-FDG PET can be applied for the early evaluation of immunosuppressive treatment response and might assist in the differential diagnosis of AR, ATN, and acute CSA toxicity (8).

To verify our hypothesis that graft infiltration with radiolabeled T cells is directly related to the degree of inflammation in AR, we correlated the number of CD3-positive cells per field of view of each group with their corresponding %ID. This correlation was found to be significant ($R^2 = 0.61$) (Fig. 3B).

**RT PCR Analysis**

We used RT PCR analysis ($n = 5$/group) to confirm and characterize inflammatory cell pattern in aTX. Analysis of the aTX and CD8b on POD4 (Table 3). Upregulation of CD3 and CD8b was absent in isografts (sTX), IRI, and CSA toxicity, confirming the absence of AR or T-cell accumulation. Notably, messenger RNA (mRNA) expression of CD3 and CD8b significantly correlated with the accumulation of 18F-FDG-labeled T cells ($R^2 = 0.41$ and 0.40).

**DISCUSSION**

Episodes of AR are characterized by a distinct inflammation pattern (20), where leukocytes, mainly activated T lymphocytes, are recruited into the transplant (21). The updated Banff classification categorizes infiltration and finally scores renal transplant rejection (1,22,23). At present, core needle biopsy is the gold standard in the definite diagnosis of AR. However, as an invasive method it bares the risk of severe graft injury. Moreover, it is not feasible in patients receiving anticoagulation therapy and might present false-negative results, if AR is focal or patchy (6).

To validate our data, transferred T lymphocytes were stained with a human-specific antibody against the CD3 ε-subunit. Although all kidneys were perfused for further histologic analysis, at least some CD3-positive cells were found in the cortex of renal allografts undergoing acute rejection (aTX), whereas more or less no human cells could be documented in controls (sTX, CSA toxicity, ATN) (Supplemental Fig. 4).

**Correlation of PET Data and Histology**

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and transplant models was quantitatively evaluated from PET images and calculated as %ID. Allografts developing AR exhibit a significant elevation of %ID on POD4, when compared with isografts. POD4 was chosen because signs of AR clearly occur on POD4 (9), whereas graft perfusion and function are still preserved. Consistently, injured kidneys with common differential diagnoses of AR, namely ATN and acute CSA toxicity, did not show any accumulation of radiolabeled T cells. Using 18F-FDG–labeled leukocytes, Tosso et al. tried to assess AR of pancreatic islet transplants in the liver. Their approach remained unsuccessful because of the well-known free 18F-FDG uptake in the liver (background activity) (25).

To elevate 18F-FDG-labeling efficiency, T cells were coincubated with insulin and K+). However, neither the addition of insulin or K+ nor the combination of insulin and K+ significantly increased the 18F-FDG uptake in T cells (Fig. 1). These results are concordant with those in the literature because T lymphocytes mainly express the insulin-independent GLUT1 and GLUT3 (26) and do not respond to insulin with an upregulation of GLUTs (27). Interestingly, Botti et al. were able to demonstrate much higher labeling efficiencies. However, they used lower amounts of radioactivity for cell incubation, resulting in a better ratio of radioactivity to cell number in their experiments (28).

To validate our PET data, we correlated the entirely imaged-based measurements of T-cell accumulation to results from reference methods, for example, histologic quantification of infiltration (leukocytes, CD3-positive T lymphocytes) (Fig. 3; Supplemental Fig. 4) and mRNA expression of T-cell markers within the kidneys (Table 3). We found a significant correlation between enhanced accumulation of radiolabeled T cells and histologic infiltration (Fig. 3). In contrast, native controls showed a low 18F-FDG uptake only, which also correlated with the histologic findings. In addition, stX, as well as kidneys with ATN and acute CSA toxicity, exhibited only marginal histologic signs of infiltration, again correlating well with the 18F-FDG uptake. These results were supported by RT PCR analysis of marker genes. As commonly observed during AR (10), we detected significant mRNA upregulations of activated T-lymphocyte surface antigens such as CD3 and CD8b in renal allografts on POD4. These upregulations were absent in stX, ATN, and CSA toxicity (Table 3). Notably, the expression of CD3 and CD8b significantly correlated with accumulation of 18F-FDG–labeled T lymphocytes in all measured groups.

### TABLE 2
<table>
<thead>
<tr>
<th>Kidney part</th>
<th>aTX</th>
<th>sTX</th>
<th>IRI</th>
<th>CSA toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td>3.98*</td>
<td>1.38</td>
<td>1.12</td>
<td>0.91</td>
</tr>
<tr>
<td>Medulla</td>
<td>3.76*</td>
<td>1.53</td>
<td>1.26</td>
<td>0.85</td>
</tr>
</tbody>
</table>

*P < 0.001.

Accumulation of radiolabeled T cells in renal medulla and cortex was assessed by autoradiography, expressed as radioactivity ratio of respective tissue sample and native controls. n = 5/group.

### TABLE 3
<table>
<thead>
<tr>
<th>Cell type</th>
<th>mRNA</th>
<th>aTX</th>
<th>sTX</th>
<th>IRI</th>
<th>CSA toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>T cells</td>
<td>CD3</td>
<td>100.6 ± 12.7*</td>
<td>2.4 ± 0.3</td>
<td>3.2 ± 0.3</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>Cytotoxic T cells</td>
<td>CD8b</td>
<td>115.8 ± 12.6*</td>
<td>1.4 ± 0.2</td>
<td>2.3 ± 0.2</td>
<td>1.6 ± 0.5</td>
</tr>
</tbody>
</table>

*Significantly increased relative to control (P < 0.0001).

Data are mean values (compared with control values, n = 4–6) ± SEM.
As a third reference method, autoradiography revealed a significantly higher accumulation of radiolabeled cells in allogeneic transplants than in native controls and kidneys with ATN, acute CSA toxicity, or sTX (Table 2). In detail, allografts exhibited a nearly 4-fold increased activity when compared with control kidneys (native controls, sTX, IRL, and CSA toxicity). Taken together, these results indicate that PET with radiolabeled T cells is not only able to diagnose, but also able to quantify AR and thereby represent its histologic degree of inflammation.

The use of radiolabeled cells has several advantages in comparison to conventional 18F-FDG PET imaging. First, despite the low amount of radioactivity contained within the radiolabeled T cells, a strong signal can be detected in renal allografts, mitigating in favor of a potential higher sensitivity, while simultaneously reducing the patient’s radiation dose to a minimum.

Second, less urinary excretion of free 18F-FDG was documented, which potentially could lead to false-positive results. In humans, PET imaging using 18F-FDG–labeled leukocytes leads to less than 10% leakage of free 18F-FDG in the urinary system after 6 h (29). Our in vitro labeling stability studies revealed that the amount of free 18F-FDG slowly increases over time (Fig. 1B). This increase has also been shown by Bötti et al. who assessed the liberation rate of 18F-FDG in T cells (28). However, because urine microscopy after PET scans did not reveal relevant amounts of T cells (data not shown), the activity shown in the bladder accounts at least in part to free 18F-FDG.

Most likely, the activity was released by (destructed) T cells. In cases of acute rejection, some of this 18F-FDG should be delivered by T cells to the kidney and locally released. However, we assessed the bladder activity in all groups of rats and could not find differences between the groups (∼2–3%ID). Thus, liberation of activity was equal in all groups, leading us to the conclusion that activity is probably released from destructed cells, which have been affected, for example, by the immune response. This finding is supported by data from Pellegrino et al. who analyzed the form of 18F-FDG trapped in 18F-FDG–labeled white blood cells (30). They observed that the chemical form of 18F as analyzed by thin-layer radiochromatography demonstrated that virtually all radioactivity inside the white blood cells was present as 18F-FDG-6P, a chemical form incapable of egression from the cell and minimally reconverted to 18F-FDG.

Third, using radiolabeled lymphocytes, PET can be applied as early as 1 h after injection, thereby significantly accelerating the diagnostic procedure. The T-cell 18F-FDG signal of sTX subsequently increased after injection of T cells, reaching a significant difference, compared with the native kidney, at ∼30–50 min after the injection. The time point 50–70 min was chosen because it combined a significant increase in 18F-FDG signal with a good visual delineation of the graft.

One might question the fact that xenogene cells were used for the detection of AR. However, this has been established before. Wang et al. performed in vivo PET imaging using human cells in a Parkinson disease rat model (31), and Hay et al. used human 111In-labeled leukocytes to assess inflammatory lesions in rats (32). Moreover, imaging of total-body T-cell distribution in our rats exhibited a distinct allocation, with a primary emphasis on the reticuloendothelial system and was comparable to the biodistribution of 18F-FDG–labeled leukocytes in healthy humans.

Imaging using ex vivo radiolabeled leukocytes is a well-established method that found its way into daily clinical routine particularly in the diagnosis of inflammatory and infectious disorders (e.g., scintigraphy using 111In- and 99mTc-labeled leukocytes) (33–36). Because recruitment and activation of inflammatory cells, especially T lymphocytes, play a pivotal role in AR, there have been efforts made to image graft infiltration by means of radiolabeled cells. SPECT-based imaging with 111In- and 99mTc-labeled leukocytes has already been used to assess AR in a small cohort of intestinal and kidney transplant recipients (37,38). However, PET has the advantage of a quantitative analysis (assessment of %ID or standardized uptake value), which is useful in the diagnosis of allograft rejection and for monitoring patients’ responses to therapy. Thus, PET with 18F-FDG–labeled autologous T lymphocytes might be translated to humans in the near future.

CONCLUSION

We present and validate an entirely imaging-based noninvasive method to assess AR using PET with 18F-FDG–labeled T lymphocytes. Requiring extremely low radioactive doses, this method is highly specific and can differentiate between AR and ATN. A clinical translation to investigate the kinetics of AR and the response to therapeutic intervention seems promising.

DISCLOSURE

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