# ORIGINAL ARTICLE

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# Pre-medication to block [18F]FDG uptake in the brown adipose tissue of pediatric and adolescent patients

**Abstract** *Background*: Radiopharmaceutical uptake of [18F]2-deoxy-2-glucose (FDG) in brown adipose tissue is noted on 15–20% of positron emission tomography (PET) scans in children and adolescents. One report suggests that moderate-dose oral diazepam can partly or completely block FDG uptake in brown adipose tissue. *Objective*: To determine whether [18F]FDG uptake in brown adipose tissue can be adequately blocked by pre-medication other than moderate-dose oral diazepam. *Materials and methods*: One hundred and eighteen [18F]FDG PET body imaging studies were performed in 69 pediatric patients with a variety of solid tumors. The mean age at the time of imaging was 12.9 years (range 1.2–22.6 years), and 33 studies were performed in patients younger than 10 years old. Seventy-six were performed in boys and 42 in girls. Patients were imaged using a dedicated PET camera. Pre-medication was given in 88 studies: 45 received intravenous fentanyl (0.75–1.0 μg/kg), 34 received low-dose oral diazepam (0.06 mg/kg) and 9 received moderate-dose oral diazepam (0.10 mg/kg). Thirty patients received no pre-medication, 7 of whom were known to have received opiates for pain during the 12 h before the study. Six body regions in the neck and chest were reviewed for [18F]FDG uptake in brown adipose tissue. Uptake of FDG in brown fat was visually graded: 0 for no FDG uptake, 1 for low-grade uptake, 2 for moderate uptake, and 3 for intense uptake. Visual grades 2 and 3 were considered to interfere potentially with image interpretation in the neck and chest. Data were analyzed by multivariate regression using a Poisson distribution. *Results*: [18F]FDG uptake in brown adipose tissue was most often seen in the lateral neck region and superior and lateral to the lungs (in 36 and 39 studies, respectively). Uptake was also seen near the costovertebral junctions (15 studies), in the superior and central neck in 7 studies and in the anterior mediastinum in 2. Brown adipose tissue uptake was thought to interfere potentially with image interpretation (visual grades 2 and 3) in 19 studies—in 6 of 23 (26.1%) studies after no pre-medication and no opiates for pain, in 10 of 34 (29.4%) after low-dose oral diazepam, in 0 of 9 (0%) after moderate-dose oral diazepam, in 3 of 45 (6.7%) after intravenous fentanyl, and in 0 of 7 (0%) after opiates prescribed for pain. Intravenous fentanyl reduced the grade of brown adipose tissue compared to no drug ($P = 0.0039$) and low-dose diazepam ($P = 0.0024$). Low-dose diazepam had no effect when compared to no drug ($P = 0.984$). There were inadequate data for statistical testing of moderate-dose valium and opiates prescribed for pain. Children younger than 10 years had lower uptake grades ($P = 0.019$) than those older than 10 years. *Summary*: The frequency of interfering [18F]FDG uptake in brown adipose tissue is reduced by intravenous fentanyl pre-medication, which appears to be an effective alternative to the existing standard pre-medication, moderate-dose oral diazepam.

**Keywords** Brown adipose tissue · Neoplasm · FDG · PET

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## Introduction

Until recently, there was no explanation for the uptake of several tumor-imaging radiopharmaceuticals in the supraclavicular and thoracic costovertebral regions of young patients. Costovertebral uptake of [18F]2-fluoro-2-deoxyglucose (FDG) was attributed to anxiety and muscle tension by Barrington and Maisey [1], who demonstrated that it could be partly or completely blocked by pre-medication with oral diazepam. In 2002, Okuyama et al. [2] demonstrated that 125I-meta-iodob-enzylguanidine (MIBG) accumulated in brown adipose

tissue of experimental animals. They also demonstrated that ^{123}I-MIBG uptake in children in these regions occurred more often in cold weather than in warm weather, consistent with the hypothesis that the increased ^{123}I-MIBG uptake was related to non-shivering thermogenesis [2]. Also in 2002, Hany et al. [3] demonstrated that [18F]FDG uptake in the supraclavicular and costovertebral regions occurred in areas of fat tissue density on co-registered CT images obtained with a positron emission tomography (PET)/CT scanner. Cohade et al. [4] and Yeung et al. [5] have further described [18F]FDG uptake in brown adipose tissue. Unfortunately, brown adipose tissue uptake occurs in regions that are frequently sites of nodal involvement with malignancy, particularly lymphoma [4, 5], and brown adipose tissue uptake could obscure uptake in tumor-bearing nodes or be confused with sites of tumor involvement.

The suppression of brown adipose tissue uptake of [18F]FDG by oral diazepam in the Barrington and Maisey [1] study demonstrated that pharmacological suppression of brown adipose tissue [18F]FDG uptake is possible. However, a number of other drugs, including opiates, are known to block cold-induced physiological responses. There is extensive medical literature on the pharmacological blockade of post-operative shivering, and it shows that intravenous meperidine is most often used in adults [6]. We searched for a drug with a more rapid onset and shorter duration of action than oral diazepam that would suppress brown adipose tissue uptake of [18F]FDG. That led us to pre-medicate with intravenous fentanyl, an opiate that is also rapidly cleared from the blood.

## Materials and methods

One hundred and eighteen [18F]FDG PET imaging studies were performed in 69 pediatric patients with a variety of non-central nervous system solid tumors. Twenty-two patients had two studies, 5 had three studies, 3 had four studies, and 2 had five studies. Imaging was performed in a mobile PET unit (Siemens Exact or Accel, provided by Shared PET LLC, Canton, Ohio, USA) during a period of 17 months from mid-December 2002 to April 2004. The mean age of the patients at the time of imaging was 12.9 years of age; 33 studies were performed in patients between 1.2 and 9.9 years of age, and 85 were performed in patients between 10.0 and

22.6 years. Seventy-six studies were performed in boys and 42 in girls. The administered activity was 0.140 mCi/kg (5.2 MBq/kg). Imaging was started at various times from 30 to 90 min post-injection of [18F]FDG, usually at $45 \pm 10$ min.

The study was retrospective. There was no randomization. Pre-medication included no pre-medication and no opiates for pain within 12 h in 23 imaging studies, low-dose oral diazepam in 34 studies, moderate-dose oral diazepam in 9, and intravenous fentanyl in 45. In 7 other studies, the patients were known to have received various opiates for pain during the 12 h before the [18F]FDG imaging study and no pre-medication was given. Doses of pre-medication are summarized in Table 1. For intravenous fentanyl, patients who weighed less than 25 kg received 1.0 μg/kg and patients who weighed more than 25 kg received smaller doses on a per-kilogram basis, usually 0.75 μg/kg, with a maximum dose of 50 μg. When oral diazepam was given as pre-medication, [18F]FDG was injected 30–60 min after oral diazepam was given. When intravenous fentanyl was given as pre-medication, fentanyl preceded the [18F]FDG injection by 10 min. A nurse trained to administer sedation administered all drugs, and a trained nurse monitored the patient, including pulse oximetry, after sedation with intravenous fentanyl and a moderate dose of oral diazepam. Patients who received intravenous fentanyl were monitored by the nurse for 30 min after the drug was administered and by other personnel trained to use pulse oximetry until the end of the imaging study.

To assure patient safety, all drugs, including fentanyl, were administered according to an existing pediatric sedation program with a proven record of safety [7], and after consultation with an established Sedation Committee that included radiology, nursing, and anesthesiology representatives. Institutional Review Board approval was obtained for retrospective review of patient data and images.

Six body regions were reviewed for [18F]FDG uptake in brown adipose tissue. The body regions and grades of [18F]FDG uptake in brown adipose tissue are shown in Figs. 1 and 2. The regions were: (1) along the lateral edge of the trapezius muscle (labeled tr in Fig. 2), (2) in the more central and superior portions of the neck (cn), (3) adjacent to the pleura superior and lateral to the lungs (lu), (4) at the costovertebral junctions sometimes extending to the suprarenal region (cv), (5) in the anterior mediastium (am), and (6) in the sternocleidomastoid

**Table 1** Pre-medication used to block brown adipose tissue uptake of [18F]FDG

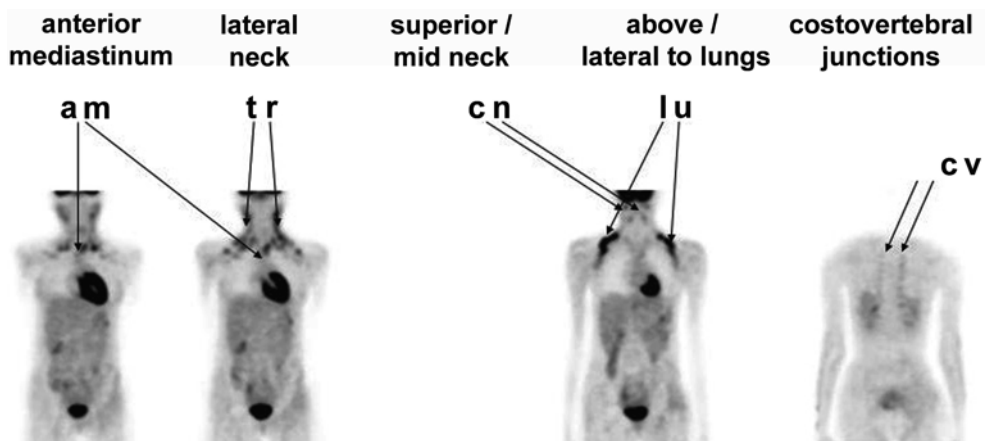| N | Drug and route | Dosage | Mean dose | Maximum dose |
|---|---|---|---|---|
| 34 | Diazepam, p.o. (low dose) | < 0.8 g/kg | 0.58 mg/kg | |
| 9 | Diazepam, p.o. (moderate dose) | ≥0.8 mg/kg | 0.96 mg/kg | 7.5 mg |
| 45 | Fentanyl, i.v. | ≤ 1.0 μg/kg | 0.75 μg/kg | 50 μg |
| 23 | No pre-medication | | | |
| 7 | On opiates for pain, by any route of administration | | | |

**Fig. 1** Examples of grades 1–3 uptake of [¹⁸F]FDG are shown. Grade 1 uptake was thought to be too low to interfere with image interpretation for the presence of lymphadenopathy caused by tumor infiltration
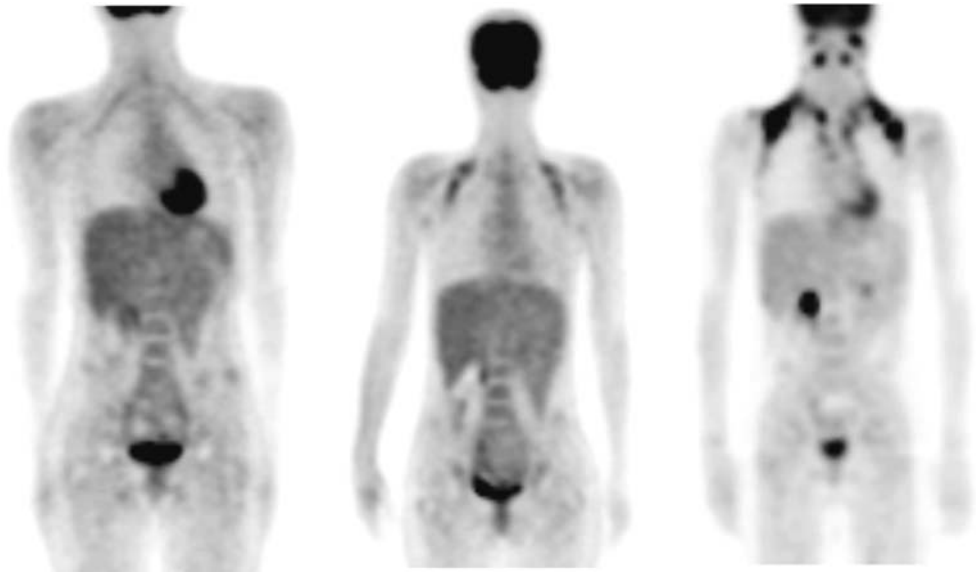


muscle region. Uptake of FDG in brown adipose tissue was visually graded 0 for no FDG uptake, 1 for low-grade uptake, 2 for moderate uptake, and 3 for intense uptake. Visual grades 2 and 3 were considered to interfere potentially with interpretation of the [¹⁸F]FDG images. Data for region 6, the sternocleidomastoid muscle region, were analyzed separately. Images were reviewed without knowledge of type and quantity of any pre-medication administered prior to the study.

The mean outside temperature on the day of the imaging study was recorded for each patient study. Data were analyzed by multivariate regression using a Poisson distribution. Independent variables were drug, age, sex, and mean outside temperature for day of the study. The dependent variable was visual uptake grade. The maximum standardized uptake value (SUV) in brown adipose tissue for each study was recorded for each patient. Visual uptake grade in the analysis of data was used instead of SUV, because the time of imaging after radiopharmaceutical injections varied during the study, and because the SUV values in a few patient studies were lower than expected.

## Results

[¹⁸F]FDG uptake in brown adipose tissue was found in 55 of 118 studies (46.6%). The highest visual uptake (grade 3) was seen in 9 studies (7.6%), while grade 2 uptake was seen in 10 studies (8.5%) and grade 1 in 36 studies (30.5%). [¹⁸F]FDG uptake was often found in more than one region.

Uptake in brown adipose tissue was found in region 1 (lateral edge of trapezius muscle) in 36 studies, in region 2 (central and superior neck) in 7, in region 3 (superior and lateral to the lungs) in 39, in region 4 (costovertebral) in 15 and region 5 (anterior mediastinum) in 2. Of the 15 studies where there was uptake in region 4 (costovertebral), 7 had maximum brown adipose tissue uptake in another region that was grade 2 in intensity and 7 had grade 3 uptake. Of the 8 studies where there was uptake in region 2 (central and superior neck) and/or region 5 (anterior mediastinum), 6 had maximum brown adipose tissue uptake in another region that was grade 3 in intensity. Visual uptake grade, highest SUV at

**Fig. 2** Regions evaluated for the presence of brown adipose tissue uptake of [¹⁸F]FDG: anterior mediastinum (*am*), lateral edge of trapezius muscle (*tr*), central superior neck (*cn*), along pleura superior and lateral to the lungs (*lu*) and costovertebral (*cv*) junction regions extending to the suprarenal regions. See Fig. 3 for an example of stenocleidomastoid muscle region uptake

any site, and number of positive regions were closely correlated (Pearson correlation coefficients 0.83–1.00).

In nine studies, there was [18F]FDG uptake in the sternocleidomastoid regions. In eight of the nine studies, there was greater uptake of [18F]FDG in the right sternocleidomastoid region than in the left (Fig. 3). During the period from injection of [18F]FDG until the start of imaging, all patients were supine in a room with an accompanying parent seated on their left and a blank wall on the right.

Table 2 summarizes the effect of pre-medication, in particular intravenous fentanyl, on brown adipose tissue uptake of [18F]FDG. Figure 4 shows absence of brown adipose uptake of [18F]FDG in a 5-year-old child, only after pre-medication.

In the entire group of 118 studies, the number of studies with visual grade 2 or 3 uptake of [18F]FDG in brown adipose tissue was similar in boys and girls, occurring in 12 of 76 studies (15.8%) of boys and 7 of 42 (16.7%) of girls. In the entire group, the uptake grade of

[18F]FDG was not related to the mean outside temperature or the gender of patient. However, studies in patients who were 10 years and older more often demonstrated visual grade 2 or 3 brown adipose tissue uptake, 17 of 85 (20.0%), than studies performed in patients younger than 10 years, 2 of 33 (6.1%) (P < 0.0039). The difference in the grade of brown adipose tissue uptake between age groups was driven by differences in the incidence of brown adipose tissue uptake in girls.

All medications were well tolerated by the patients. After the doses of intravenous fentanyl, a few patients fell asleep for 10–20 min, but most remained awake and felt sleepy for a short period of time.

## Discussion

In this study, pre-medication with low-dose diazepam did not suppress uptake of [18F]FDG in brown adipose



Fig. 3 [18F]FDG uptake is seen in the right sternocleidomastoid muscle region (arrow), but not in the corresponding location on the left on coronal and sagittal sections. During the period from injection of [18F]FDG until the start of imaging, all patients were supine in a small room with a parent seated to the left and a wall to the right
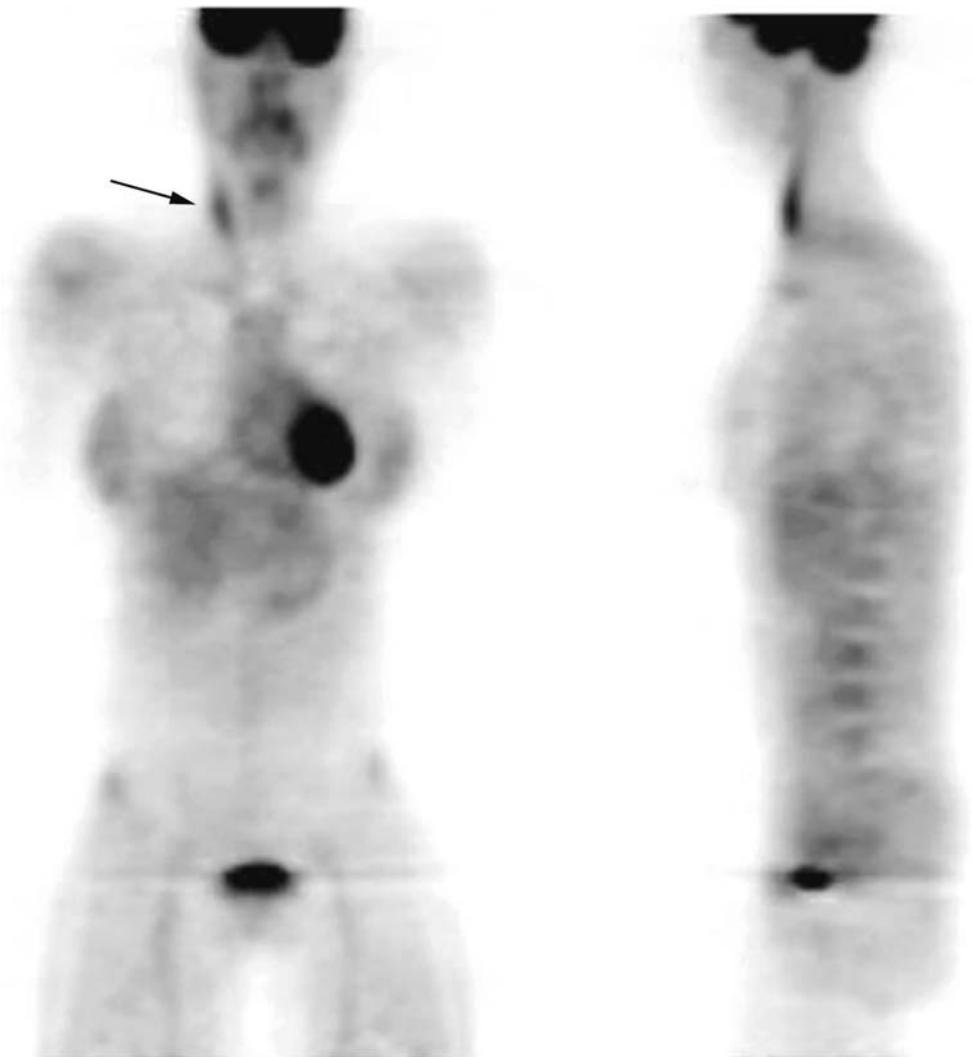
**Table 2** Effect of pre-medication to block brown adipose tissue uptake of [18F]FDG

| Drug and route | Number with grade 2 or 3 [18F]FDG uptake (%) |
| --- | --- |
| Diazepam, p.o. (low dose) | 10/34 (29.4%)[a] |
| Diazepam, p.o. (moderate dose) | 0/9 (0%) |
| Fentanyl, i.v. | 3/45 (6.7%)[b] |
| No pre-medication | 6/23 (26.1%)[c] |
| Received opiates for pain within 12 h of imaging | 0/7 (0%)*** |

[a]Low-dose diazepam had no effect when compared to no drug ($P = 0.984$)
[b]Fentanyl reduced the grade of brown adipose tissue uptake compared to no drug ($P = 0.0039$) or low-dose diazepam ($P = 0.0024$)
[c]Data were inadequate for statistical testing of moderate-dose diazepam and opiates prescribed for pain

tissue, but intravenous fentanyl was usually successful. Only 6.7% of studies in patients who received fentanyl had grade 2 or grade 3 [18F]FDG uptake in brown adipose tissue, compared to 26.1% after no pre-medication and 29.4% after low-dose oral diazepam ($P = 0.0039$ and 0.0024, respectively, compared to intravenous fentanyl). Although no grade 2 or 3 [18F]FDG uptake was noted in brown adipose tissue after moderate-dose oral diazepam or in studies performed after patients received opiates for pain, there were too few patient studies in these groups to achieve statistical significance.

[18F]FDG uptake in brown adipose tissue was most often seen in regions 1 and 3 (along the lateral edge of the trapezius muscle and adjacent to the pleura superior and lateral to the lungs). Uptake near the costovertebral junctions (region 5) was a less common finding, and uptake in regions 2 and 4 was even less common. In fact, uptake in regions 2, 4 and 5 was almost always associated with grade 2 or 3 uptake in another region, particularly in regions 1 and 3, the lateral neck and adjacent to the pleura superior and lateral to the lungs. It would appear that only with the highest grades (2 and 3) of [18F]FDG uptake in brown adipose tissue is uptake



**Fig. 4** Brown adipose tissue uptake of [18F]FDG (*arrows*) in a 5-year-old child after no pre-medication on a day with a mean outside temperature of 2°C (*left*). A study performed in the same child on a different date (mean outside temperature 4°C) after intravenous fentanyl pre-medication (*right*)
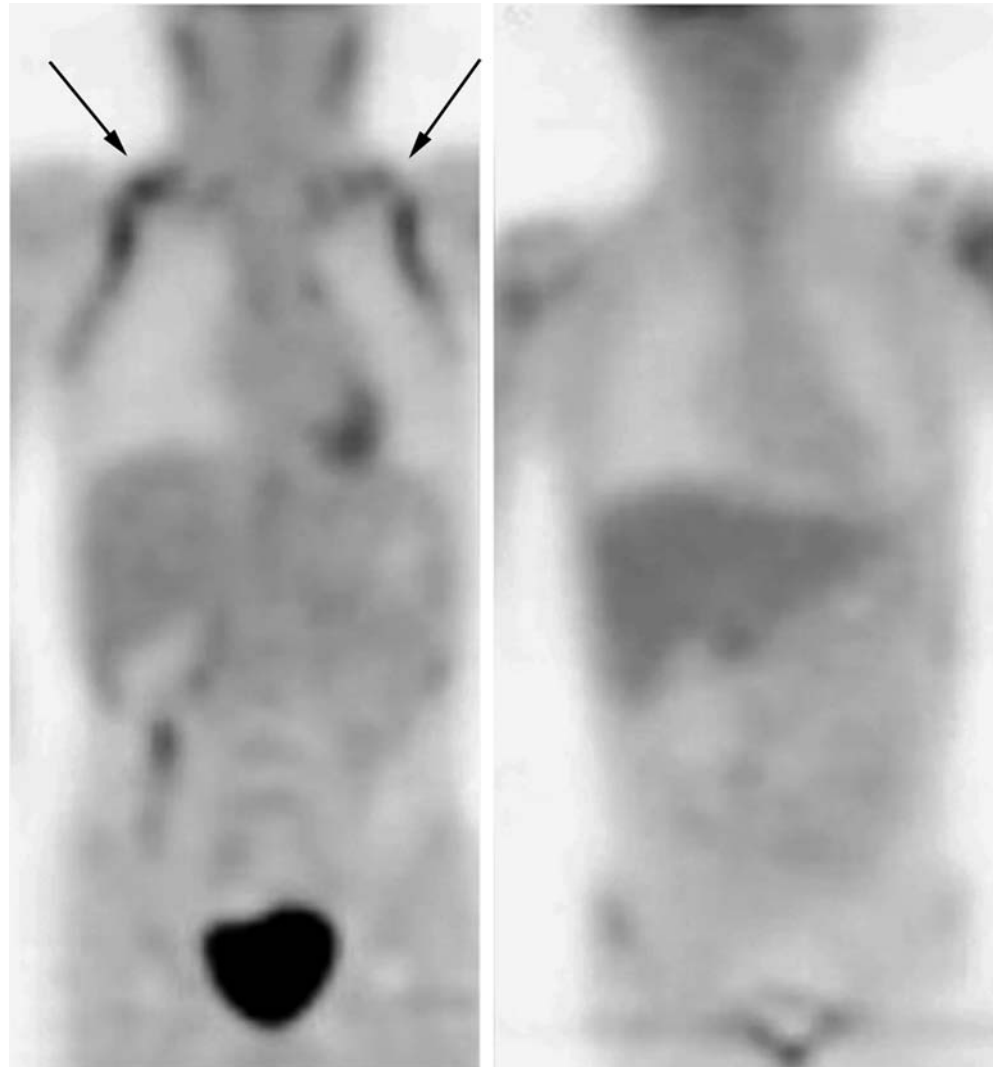
seen in the other, less frequently visualized regions, namely, the costovertebral regions, central and superior neck, and anterior mediastinum. In the study of Yeung et al. [5], there were six patients younger than 20 years. In that study, the two patients who had the most intense uptake of [$^{18}$F]FDG in brown adipose tissue in the neck also had paravertebral and/or mediastinal uptake in brown adipose tissue [5]. Additional sites of brown adipose tissue uptake are sometimes seen along the diaphragm and in the perirenal regions [5, 8].

In this study, uptake of [$^{18}$F]FDG in region 6, the sternocleidomastoid region, appears to represent uptake in the sternocleidomastoid muscle. In eight of nine studies, there was greater uptake in the right sterno-cleidomastoid muscle than in the left. In every study, the patients were injected and absorbed the [$^{18}$F]FDG in a room where they could look only to the left at an accompanying parent or upward at the ceiling. Turning the head to the left involves contraction of the right sternocleidomastoid muscle.

Others have stated that uptake of [$^{18}$F]FDG in brown adipose tissue-containing regions, such as the neck and the costovertebral region, is more common in young and/or girl patients [1, 5, 8]. In this study, when data were analyzed only in pediatric patients, this did not hold true. We observed that [$^{18}$F]FDG uptake in brown adipose tissue occurred with the same frequency in boys and girls and occurred more frequently in pediatric patients older than 10 years than in those younger than 10 years. However, uptake in girls was the reason for the greater incidence of brown fat uptake in patients older than 10 years when compared to children younger than 10 years.

The high incidence of [$^{18}$F]FDG uptake in brown adipose tissue in the school-age and teenage populations suggests that there is a need to address the problem of [$^{18}$F]FDG uptake in brown adipose tissue. In the combined no pre-medication and low-dose diazepam groups, we observed grade 2 or 3 (potentially interfering) [$^{18}$F]FDG uptake in brown adipose tissue in 16 of 57 (28.0%) studies. In a recent report by Bar-Sever et al. [9], who studied 123 pediatric patients at two hospitals in a region that has year-round warm temperatures, 14.5% of 130 sites that were thought to be equivocal on PET alone were labeled as brown adipose tissue on PET/CT. The concern was raised that hospital air-conditioning alone might provide enough cold stimulation to cause brown adipose tissue uptake of [$^{18}$F]FDG. In another study by Nanni et al. [10], 9 of 48 pediatric patients (18.8%) had uptake in brown adipose tissue that also required PET/CT clarification. Unlike Cohade et al. [11], we did not observe a relationship between outside temperature and brown adipose tissue uptake of [$^{18}$F]FDG, but successful use of pre-medication to block brown adipose tissue uptake might have obscured this relationship.

Our observations and those of Barrington and Maisey [1] suggest that pre-medication with either moderate-dose oral diazepam or intravenous fentanyl can be used to block potentially confounding [$^{18}$F]FDG uptake in brown adipose tissue. However, it is possible that neither fentanyl nor diazepam will be the drug of choice. Brown adipose tissue metabolism is stimulated by sympathetic nervous system outflow, and a recent report also demonstrated that, in mice, propranolol prevented [$^{18}$F]FDG uptake in brown adipose tissue [12, 13]. In the literature, many drugs have been used with some success in the treatment of post-operative shivering [6, 14–16], interrupting another thermoregulatory mechanism that is stimulated by cold. Ideally, a drug used to prevent [$^{18}$F]FDG uptake in brown adipose tissue will have the following characteristics: (1) suppression of [$^{18}$F]FDG uptake in brown adipose tissue in 100% of patients, (2) no requirement for patient monitoring, (3) if given orally, a rapid onset of action, and (4) if the drug is sedating, a duration of action of no more than 60 min.

An alternative to pre-medication that has been suggested is maintenance of a warm environment at higher temperatures than the ambient hospital temperature for a period of 1 h prior to injection of [$^{18}$F]FDG [17]. If prolonged warming of the patient prior to [$^{18}$F]FDG injection works as well as pre-medication, a pre-warming, non-pharmacological approach should also be considered. Physicians who perform PET in children and adolescents should closely follow the literature as it is determined which preparative regimen maintains patient safety and gives the best results.

It has also been suggested that PET/CT is the solution to the problem of [$^{18}$F]FDG uptake in brown adipose tissue. The co-registered CT image can be used to determine whether the uptake is in an area of fat density or in a lymph node. This might be a shortsighted approach. Lymph nodes containing tumor and brown adipose tissue might be present in the same regions closely adjacent to each other. As shown in Fig. 1, brown fat uptake might appear to be confluent. With PET/CT it might be possible to determine whether [$^{18}$F]FDG uptake is located in an area of fat density, but if there are a few nodes in an area of confluent intense [$^{18}$F]FDG uptake, can one determine with certainty whether there is pathological uptake of [$^{18}$F]FDG in the nodes? Also, because [$^{18}$F]FDG uptake will sometimes concentrate in tumor sites that are not identified on CT, if reliance is placed solely on PET/CT and there is no suppression of brown adipose tissue uptake, a few tumor sites might not be recognized because of confusing [$^{18}$F]FDG uptake in brown adipose tissue. With either PET or PET/CT, suppression of brown adipose tissue uptake should simplify image interpretation and possibly prevent some errors in interpretation.

Pre-medication offers the promise of avoiding unnecessarily degraded PET and PET/CT images in pediatric and adolescent patients who are more likely to have [$^{18}$F]FDG uptake in brown adipose tissue.

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