Thermal Control of Brown Adipose Tissue in ^{18}F-FDG PET

Annah Skillen[1,2], Geoffrey M. Currie[1,3] and Janelle M. Wheat[1,3]

[1]Faculty of Science, Charles Sturt University, Wagga Wagga, Australia; [2]Nuclear Medicine and PET, Hunter New England Imaging, John Hunter Hospital, Newcastle, Australia; and [3]Australian School of Advanced Medicine, Macquarie University, Sydney, Australia

The visualization of hypermetabolic brown adipose tissue (BAT) on ^{18}F FDG PET lowers the efficacy of PET and has been linked with the environmental temperature of the patient before presentation. The objective of this paper is to investigate the effectiveness of thermal control on BAT and ^{18}F-FDG PET. **Methods:** Three hundred patients undergoing ^{18}F-FDG PET were defined by 1 of 2 groups. Group A consisted of 150 consecutive patients from August to October 2009 (spring). Group B consisted of 150 consecutive patients from December to February 2010 (summer). In addition to normal preparation, group B received instructions to dress warmly and was warmed during the uptake period of their scan. Images were assessed for the presence of BAT. Standardized uptake value data were collected and compared. **Results:** BAT was present in 9.3% of patients; 15.3% of patients that were not warmed (group A) demonstrated BAT, and this was reduced to 3.3% in the group that underwent warming (group B) ($P = 0.0005$). BAT was more common in men (10.9%) than women (6.8%), and women responded better to warming. Younger patients were more likely to demonstrate BAT ($P < 0.001$). No significant relationship between BAT and height, weight, or body mass index was found. The most common site for BAT visualization was the cervical region (89%), followed by supraclavicular (75%), paravertebral (50%), suprarenal (21%) and paraaortic (7%) regions. **Conclusion:** Thermal control for the reduction of BAT can achieve reductions in the incidence of BAT by as much as 78%. The reduction of BAT on PET images can reduce false-positive and false-negative results and minimize the need for rescanning.

Key Words: hypermetabolic brown adipose tissue; BAT, ^{18}F-FDG PET; temperature control

J Nucl Med Technol 2012; 40:99–103
DOI: 10.2967/jnmt.111.098780

Brown adipose tissue (BAT) has been shown to exist in both pediatric and adult humans (*1*) and is responsible for nonshivering thermogenesis. In response to cold conditions, nonshivering thermogenesis may be initiated, and heat is produced within the fat cells to maintain core body temperature (*2*). BAT is characterized by a higher degree of vascularity and mitochondrial density over white adipose tissue, and it is these characteristics that define both coloration and function (*3*). Metabolically, BAT is designed simply to generate heat through a process initiated by the sympathetic nervous system (*3*). These characteristics explain the use of both metaiodobenzylguanidine and sestamibi (and tetrofosmin) for imaging BAT (*3*). BAT uses glucose as a source of adenosine triphosphate to generate the heat, providing a pathway by which ^{18}F-FDG can localize within the brown adipocyte (*4*).

BAT is reported to be present on approximately 2%–4% of ^{18}F-FDG PET scans (*2,5,6*) predominantly in 5 locations: the cervical, supraclavicular, paraaortic, paravertebral, and suprarenal areas (*7*). During the winter, it is more commonly noted in women and in the pediatric population, where it plays a major role in thermal control (*2*). Nonetheless, BAT is not limited to these cohorts of patients and has been shown to exist in both sexes, across varying age groups, climates, and patient body mass indexes (BMIs) (*8*).

The emergence of PET/CT prompted more careful evaluation of lesions in the neck and chest, resulting in a recognition that nonmalignant accumulation of ^{18}F-FDG occurred in areas of fat. When present, BAT can reduce the efficacy of ^{18}F-FDG PET in a variety of cancers because of the difficulties, even with CT coregistration, in differentiating disease from BAT accumulation. As a result, false-positive and false-negative results may arise, and this is particularly concerning in staging of nodal disease (*9*). Consequently, several methods have been explored to reduce or eliminate BAT accumulation on ^{18}F-FDG PET scans.

Several pharmaceutical methods have been used to reduce the appearance of BAT on ^{18}F-FDG PET scans. Despite reports of some success, there are clearly risks associated with prescription medications that, combined with potential side effects, contraindications, and adverse reactions, may make a universal protocol less than optimal. To date, the administration of propranolol (a nonselective β-blocker) has proven the most effective pharmaceutical, reducing the appearance in approximately 90% of patients (*10–12*). It works by blocking epinephrine and norepinephrine on both β-receptors and, thus, prevents the stimulation of BAT to produce heat. Diazepam has been used previously in ^{18}F-FDG PET to reduce neck muscle accumulation associated with stress, anxiety, and muscle tension. It is both an anxiolytic and a muscle relaxant that, due to its lipid solubility, is largely stored in adipose tissue. Reserpine is an antipsychotic that

Received Sep. 28, 2011; revision accepted Dec. 12, 2011.
For correspondence or reprints contact: Geoff Currie, Faculty of Science, Locked Bag 588, Charles Sturt University, Wagga Wagga 2678, Australia.
E-mail: gcurrie@csu.edu.au
Published online May 2, 2012.

blocks norepinephrine, and thus it is not surprising that its impact on BAT accumulation is similar to that of propranolol, with reports of reductions in uptake down to 30% (*13*).

The limitations in applying a universal pre–^{18}F-FDG medication protocol, the relatively small proportion of patients who would benefit from preventative measures, and the prevalence of BAT accumulation in pediatric and female populations demand an alternative noninterventional approach. Rescanning the 2.5%–30% (*6,14*) of patients with BAT accumulation is neither time- nor cost-effective and includes additional radiation exposure. Given the predilection of BAT toward winter months (*9,15*) and reports of BAT visualization in patients exposed to colder temperatures over shorter periods (2 h) (*8*), more careful management of the patients' environmental temperature may provide an effective, low-cost, noninvasive method of BAT control suitable universally across patient cohorts.

Several small studies have reported that warming the patient before ^{18}F-FDG injection and during the uptake phase may reduce BAT in up to 90% of patients (*16–18*). Conclusions are largely constrained by small numbers of recruits, and thus, there is a pressing need for investigation of the impact of warming on BAT accumulation in a larger cohort of patients in a variety of environmental conditions (indigenous climates). This investigation examines incident cases of and characterization of BAT in a relatively temperate climate.

MATERIALS AND METHODS

Patients

Three hundred patients undergoing ^{18}F-FDG oncology–based PET/CT at the Nuclear Medicine Department at Calvary Mater Hospital in Newcastle (Australia) were split into 2 groups. Group A consisted of 150 consecutive patients from August to October 2009 (spring). Group B consisted of 150 consecutive patients from December to February 2010 (summer). Both groups of patients fasted for approximately 6 h and were well hydrated before their scan. Group B patients received additional verbal instruction to dress warmly before their presentation to the PET department and were warmed before their ^{18}F-FDG injection and PET scan. The investigation was sanctioned by the Charles Sturt University Ethics in Human Research Committee.

Uptake Phase

The temperature of the uptake rooms remained at 21°C for the duration of the study. Patients received an intravenous injection of 270 MBq of ^{18}F-FDG. For those patients defined as pediatric (<18 y old), dose was calculated using a weight-based dose adjustment system. Patients were scanned after a 60-min uptake phase. During the uptake phase, group A patients received 1 or 2 standard hospital blankets for comfort. Group B patients received 2 blankets, 1 of which had been warmed in a blanket oven at 50°C. Additionally, group B patients were covered with an emergency "space" blanket (such as those used to prevent hypothermia) for insulation of the warm blanket.

Imaging

PET/CT images were acquired using the Discovery 690 PET/CT system (GE Healthcare) from the patient's eyes to the midthigh region at 2 min per bed position for patients less than 100 kg and 2.5 min for those greater than 100 kg. Images underwent attenuation correction with CT data and were reconstructed using the time-of-flight method.

Analysis

PET/CT images were interpreted by 1 of 4 nuclear medicine staff specialists for the presence of BAT using the Advance Workstation (GE Healthcare). BAT, when identified, was placed into one or more categories based on location: cervical, supraclavicular, paravertebral, paraaortic, or suprarenal. Where supraclavicular BAT was identified, a standardized uptake value (SUV) ratio was obtained between the supraclavicular area and an area of the liver defined as having a normal appearance. This ratio was also compared with other variables of the study. Temperature data were obtained from the Bureau of Meteorology for the location of the PET center. Where data were unavailable for this site, the nearest available location was used.

The statistical significance was calculated using χ^2 analysis for nominal data and Student *t* test for continuous data. The Pearson χ^2 test was used for categoric data with a normal distribution, and the likelihood ratio χ^2 test was used for categoric data without a normal distribution. The *F* test ANOVA was used to determine statistically significant differences within grouped data. A *P* value of less than 0.05 was considered significant. The differences between independent means and proportions were calculated with a 95% confidence interval (CI). CIs without an overlap or those that did not include zero were considered to support a statistically significant difference, whereas CIs with an overlap or those that included zero represented differences for which chance could not be excluded as the cause.

RESULTS

Of the 300 patients, 183 (61%, with a 95% CI of 55.4%–66.3%) were male and 117 (39%, with a 95% CI of 33.7%–44.6%) were female. There was a statistically significant increase in the number of male patients referred for oncology-based PET ($P < 0.001$), and this is supported by an absence in overlap between the 2 cited CIs. The mean patient age was 59.3 y (95% CI, 57.3–61.4 y), with a range of 1–89 y and a median of 63 y. Only 12 patients were less than 18 y old (2%). The mean patient height was 173.3 cm (95% CI, 171.0–173.6 cm), the mean weight was 79.3 kg (95% CI, 77.1–81.6), and the mean BMI was 26.6 (95% CI, 25.9–27.2). The mean maximum daily temperature throughout the duration of the study was 25.7°C, with a range of 18.9°C–40.3°C. The mean minimum daily temperature was 14.2°C, with a range of 3.8°C–23.4°C.

There was a degree of heterogeneity between the 2 cohorts. Group A (not warmed) consisted of 150 patients (88 male, 62 female), and group B consisted of 150 patients (95 male, 55 female), although there was no statistically significant difference in the sex distributions between cohorts ($P = 0.407$). Table 1 summarizes the patient demographics within the 2 groups. The differences in demographics were not deemed statistically significant ($P > 0.05$). The mean age for group B was 61.0 y (95% CI, 58.1–63.9), and the mean age for group A was 57.7 (95% CI, 54.8–60.6). No statistically significant difference was

TABLE 1
Summary of Respective Patient Demographics for the 2 Cohorts

Demographic	Group A (not warmed)	Group B (warmed)	*P*
Male	88 (58.7%)	95 (63.3%)	0.407
Female	62 (41.3%)	55 (36.7%)	0.407
Mean age (y)	57.7 (95% CI, 54.8–60.6)	61.0 (95% CI, 58.1–63.9)	0.117
Mean weight (kg)	80.5 (95% CI, 77.3–83.6)	78.2 (95% CI, 75.1–81.4)	0.325
Mean height (cm)	171.7 (95% CI, 170.0–173.5)	172.9 (95% CI, 171.1–174.6)	0.381
Mean BMI	27.1 (95% CI, 26.2–28.0)	26.0 (95% CI, 25.1–26.9)	0.098
Daily maximum temperature (°C)	22.3 (95% CI, 21.7–22.9)	29.2 (95% CI, 28.6–29.7)	<0.0001
Daily minimum temperature (°C)	9.5 (95% CI, 8.9–10.0)	19.0 (95% CI, 18.5–19.6)	<0.0001

noted between groups for age ($P = 0.117$), and this is supported by the overlap of the 95% CI. Similarly, no statistically significant differences were noted between the groups for height ($P = 0.381$), weight ($P = 0.325$), or BMI ($P = 0.098$). The mean maximum daily temperature experienced by patients was 22.3°C for group A and 29.2°C for group B ($P < 0.0001$). The mean minimum daily temperature was 9.5°C for group A and 19.0°C for group B ($P < 0.0001$). The differences in the mean maximum and minimum daily temperatures experienced by both groups were deemed statistically significant, and there was no overlap between 95% CIs (Table 1).

BAT was present in 28 patients (9.3%) (95% CI, 6.5%–13.2%), with the remaining 272 patients (90.7%) having no evidence of BAT (95% CI, 86.8%–93.5%). Of the 150 warmed patients (group B), 3.3% (5 male) were found to have BAT present, whereas 15.3% (15 male, 8 female) of the 150 patients who were not warmed (group A) were found to have BAT ($P = 0.0005$) (Fig. 1; Table 2).

Generally, a greater proportion of men (10.9%) than women (6.8%) were found to have BAT present (Table 2); however, the difference was not deemed statistically significant ($P = 0.310$). The mean age of patients with BAT was 45.4 y (95% CI, 38.9–51.9)—a statistically significant decrease ($P < 0.001$) compared with the mean age (60.8 y) of those without BAT (95% CI, 58.7–62.9). The lack of overlap between the 95% CIs supports this observation. No statistically significant differences were noted between the patients with BAT and those without BAT with respect to height ($P = 0.426$), weight ($P = 0.580$), or BMI ($P = 0.330$).

Of the 12 pediatric patients (<18 y of age) included in this study, 3 (25%) were identified as having BAT. These patients were all male and did not undergo warming (group A). As pediatric patients are known for their predisposition to BAT, a subanalysis was performed on the adult population, with no alteration to the outcomes outlined above being noted.

The distribution of BAT among patients predominantly demonstrated cervical uptake (89%). The supraclavicular area was seen in 75% of patients, the paravertebral in 50%, the suprarenal in 21%, and the paraaortic in 7%. The SUV data were limited by an inadequate population size in the warmed cohort ($n = 2$) who presented with BAT appearance. Nonetheless, no statistically significant differences were noted between the BAT SUV–to–liver SUV with respect to sex ($P = 0.9157$), patient age ($P = 0.5059$), height ($P = 0.2940$), weight ($P = 0.3314$), or BMI ($P = 0.6756$). There was no statistically significant difference in the liver SUV based on either daily maximum temperature ($P = 0.5152$) or daily minimum temperature ($P = 0.4375$) supporting its use as a reference.

DISCUSSION

BAT activation is a sympathetic response of the nervous system as a consequence of cold exposure (*2*). Its appearance on ^{18}F-FDG PET has been linked to lower temperatures on the days and weeks preceding the PET scan and has been described to be more common in the months succeeding the onset of winter (*19*). This evidence supports the theory that BAT activation occurs in response to prolonged cold exposure. Nonetheless, BAT has also been visualized on ^{18}F-FDG PET after cold exposure over a shorter time frame, ranging from 1 or 2 d to several hours before a PET scan (*8,15*). Whether the activation of BAT occurs as a consequence of acute cold exposure, prolonged cold exposure, or a combination of both remains debatable. Nevertheless, for the potential reduction of BAT on ^{18}F-FDG PET through the use of warming techniques, it is the acute effects of cold exposure that are the most manageable.

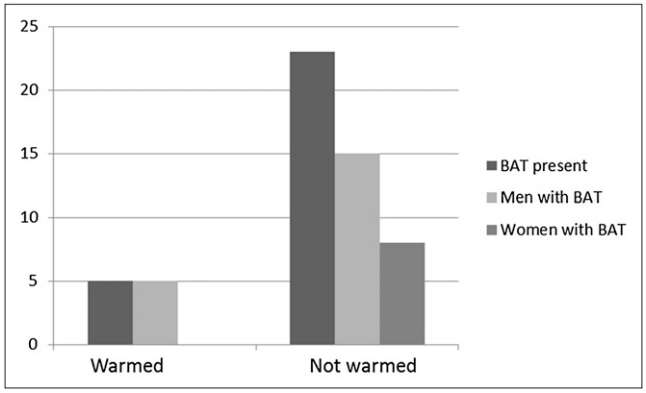

FIGURE 1. Numbers of patients with BAT between warmed and not-warmed cohorts, highlighting impact of warming overall and on men and women, respectively.

TABLE 2
Summary of BAT Statistics

Parameter	BAT present	No BAT present	*P*
Overall	9.3% (95% CI, 6.5%–13.2%)	90.7% (95% CI, 86.8%–93.5%)	—
Male	10.9%	89.1%	0.310
Female	6.8%	93.2%	
Mean age (y)	45.4 (95% CI, 38.9–51.9)	60.8 (95% CI, 58.7–62.9)	<0.001

Several methods have been evaluated as a means to prevent the acute effects of cold exposure causing BAT appearance on ^{18}F-FDG PET. Warming techniques have been included in the patient instructions, such as keeping warm for 48 h before the scan using winter-type clothing, warming the interior of the car before travel to the PET center, and using prewarmed blankets and temperature-controlled rooms for up to 2 h before ^{18}F-FDG injection (*16,17*). The warming techniques described have demonstrated effectiveness in reducing the appearance of BAT in controlled research environments. In the clinical setting, it may be difficult to control the patients' environmental temperature for an extended time. Universal compliance is more likely to be achieved through shortened, simplified preparation instructions. That is, for thermal control to offer a marginal benefit over other reduction methods, such as pharmaceutical approaches, the technique needs to be readily applied in a universal manner with minimal intrusion or demands that might undermine compliance.

The approach adopted in this investigation relied on the use of 2 minimally intrusive techniques: instructing the patient to dress warmly ("in winter-type clothing") before presenting to the department on the day of the PET scan, and providing warmed blankets and an emergency "space" blanket for insulation during the postinjection uptake phase. These approaches caused minimal interruption to department workflow. Adopting this approach, a 78% reduction in the incidence of BAT on PET scans was observed (15.3% incidence reduced to 3.3%) (Fig. 2). By sex, a 100% reduction in BAT presentation was observed for female patients and 67% for male patients.

The predominance of BAT in women is widely reported, and this is evident in the results of previous investigations into the use of thermal control (*16,18*). Within this study, a higher number of male patients was observed to have BAT. The difference was not deemed significant and was attributed to a male dominance in the random selection process. We also noted that female patients were more likely to respond to thermal control. It is possible that due to the higher percentage of BAT in women than in men, in women the response to intervention occurs over a shorter time.

Study Limitations

Because of the contiguous recruitment of the study and the clinical nature of the PET department, a degree of variability in the 60-min uptake period after radiopharmaceutical administration was encountered. Consequently, the SUV data, despite being concordant with observer data, may lack precision. Furthermore, there are known inaccuracies when SUV is calculated from time-of-flight reconstructions. These limitations were addressed using the BAT-to-liver ratios.

The cohorts were deliberately sampled during seasonally variant periods. Group A (not warmed) was studied during the cooler period of winter and early spring, whereas group B (warmed) was studied during the warmer summer period. From the data collected, there is no way to eliminate seasonal change as the only reason for the change in incidence of BAT. Indeed, it is possible, although unlikely, that the presence of BAT simply represents the chronic thermal environment previously discussed. The specific aim of this investigation was to determine whether the acute thermal environment could be managed. The lack of correlation between incidence of BAT and SUV ratio with daily maximum temperatures in the presence of a statistically significant correlation with the daily minimum temperature suggests that acute thermal regulation played

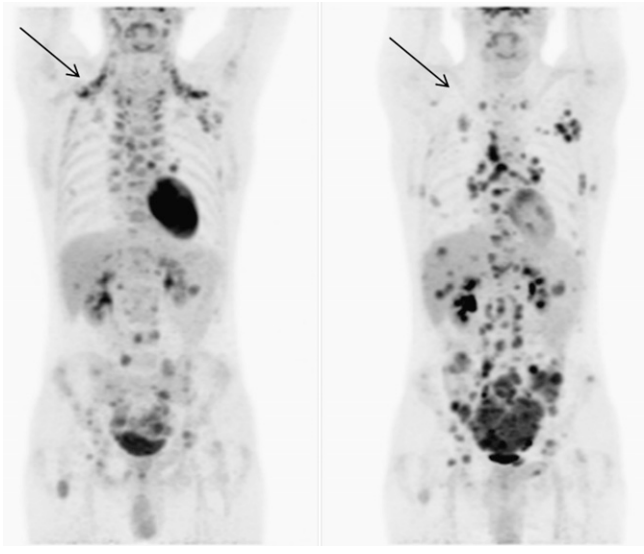

FIGURE 2. A 28-y-old man with desmoplastic small-round-cell tumor presented in October 2009 for initial ^{18}F-FDG PET study (left) and subsequently in January 2010 (right). Both studies used approximately 270 MBq of ^{18}F-FDG and were obtained after 60-min uptake phase. Initial image was obtained without warming techniques. Follow-up image was obtained with warming intervention. Apart from disease progression, presence and absence of significant BAT accumulation is noted.

a role in the observed results. Furthermore, in colder periods (group A), patients are more inclined to dress warmly; increase home, office, and car environmental temperatures; and present for the procedure in a warm state. This again supports the role of in-department thermal control in minimizing BAT. The cited temperatures themselves are unlikely to represent the actual temperature of the environment that the patient predominantly occupied during the chronic or acute phases of the study.

Recommendations

Further evaluation is required in a larger population with matching of seasonal variation as a variable between the 2 cohorts. Recording and correlation of patient medications (e.g., β-blockers) should also be included in future studies. Although lacking clinical practicality, there would be value in undertaking a repeated-measures design for more rigorous control.

CONCLUSION

Managing the patients' thermal environment in the hours preceding ^{18}F-FDG administration and during the uptake phase offers a cost-effective technique to reduce BAT that can be applied safely and universally with minimal intrusion on patient or departmental resources. Improved efficacy through elimination of false-positive and false-negative studies might be expected without the burden of repeated imaging after intervention (e.g., pharmaceutical). Further investigation into the clinical application of warming techniques is recommended.

ACKNOWLEDGMENT

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Virtanen KA, Lidell ME, Orava J, et al. Functional brown adipose tissue in healthy adults. *N Engl J Med.* 2009;360:1518–1525.
2. Cypess AM, Lehman S, Williams G, et al. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med.* 2009;360:1509–1517.
3. Fukuchi K, Ono Y, Nakahata Y, Okada Y, Hayashida K, Ishida Y. Visualization of intrascapular brown adipose tissue using ^{99m}Tc-tetrofosmin in pediatric patients. *J Nucl Med.* 2003;44:1582–1585.
4. Weber WA. Brown adipose tissue and nuclear medicine imaging. *J Nucl Med.* 2004;45:1101–1103.
5. Yeung HW, Grewal RK, Gonen M, Schöder H, Larson SM. Patterns of ^{18}F-FDG uptake in adipose tissue and muscle: a potential source of false-positives for PET. *J Nucl Med.* 2003;44:1789–1796.
6. Hany TF, Gharehpapagh E, Kamel EM, Buck A, Himms-Hagen J, von Schulthess GK. Brown adipose tissue: a factor to consider in symmetrical tracer uptake in the neck and upper chest region. *Eur J Nucl Med.* 2002;29:1393–1398.
7. Nedergaard J, Bengtsson T, Cannon B. Unexpected evidence for active brown adipose tissue in adult humans. *Am J Physiol Endocrinol Metab.* 2007;293:E444–E452.
8. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, et al. Cold-activated brown adipose tissue in healthy men. *N Engl J Med.* 2009;360:1500–1508.
9. Cohade C, Vanhommerig JW, Smulders NM. Uptake in supraclavicular area fat ("USA-Fat"): description on ^{18}F-FDG PET/CT. *J Nucl Med.* 2003;44:170–176.
10. Söderlund V, Larsson SA, Jacobsson H. Reduction of FDG uptake in brown adipose tissue in clinical patients by a single dose of propranolol. *Eur J Nucl Med Mol Imaging.* 2007;34:1018–1022.
11. Agrawal A, Nair N, Baghel NS. A novel approach for reduction of brown fat uptake on FDG PET. *Br J Radiol.* 2009;82:626–631.
12. Parysow O, et al. Low-dose oral propranolol could reduce brown adipose tissue F-18 FDG uptake in patients undergoing PET scans. *Clin Nucl Med.* 2007;32:351–357.
13. Tatsumi M, Engles JM, Ishimori T, Nicely O, Cohade C, Wahl RL. Intense ^{18}F-FDG uptake in brown fat can be reduced pharmacologically. *J Nucl Med.* 2004;45:1189–1193.
14. Zukotynski KA, Fahey FH, Laffin S, et al. Constant ambient temperature of 24 degrees C significantly reduces uptake by brown adipose tissue in children scanned during the winter. *Eur J Nucl Med Mol Imaging.* 2009;36:602–606.
15. Kim S, et al. Temporal relation between temperature change and FDG uptake in brown adipose tissue. *Eur J Nucl Med Mol Imaging.* 2008;35:984–989.
16. Garcia CA, Van Nostrand D, Atkins F, et al. Reduction of brown fat 2-deoxy-2-[F-18] fluoro-D-glucose uptake by controlling environmental temperature prior to positron emission tomography scan. *Mol Imaging Biol.* 2006;8:24–29.
17. Christensen CR, Clark PB, Morton KA. Reversal of hypermetabolic brown adipose tissue in F-18 FDG PET imaging. *Clin Nucl Med.* 2006;31:193–196.
18. Garcia CA, Bandaru V, Van Nostrand D, et al. Effective reduction of brown fat FDG uptake by controlling environmental temperature prior to PET scan: an expanded case series. *Mol Imaging Biol.* 2010;12:652–656.
19. Cohade C, Mourtzikos KA, Wahl RL. "USA-Fat": prevalence is related to ambient outdoor temperature—evaluation with ^{18}F-FDG PET/CT. *J Nucl Med.* 2003;44:1267–1270.