^{18}F-FDG PET Imaging of Muscle Activity in Runners

Manabu Tashiro, Toshihiko Fujimoto, Masatoshi Itoh, Kazuo Kubota, Takehiko Fujiwara, Masayasu Miyake, Shoichi Watanuki, Etsuo Horikawa, Hidetada Sasaki and Tatsuo Ido

Divisions of Nuclear Medicine and Nuclear Pharmacology, Cyclotron and Radioisotope Center; Department of Medicine and Science in Sports and Exercise, School of Medicine; Division of Nuclear Medicine and Radiology, Institute of Development, Aging and Cancer; College of Medical Sciences and Department of Geriatric Medicine; Tohoku University, Sendai, Japan.

PET with three-dimensional data acquisition using ^{18}F-fluorodeoxyglucose (FDG) was applied to evaluate skeletal muscle activity in runners. **Methods:** Seven healthy adult male volunteers were studied. They ran for a total of 35 min, 15 min before and 20 min after intravenous injection of FDG. Another 7 adult male control subjects were also examined at rest. Images obtained through a set of whole-body PET scans were analyzed. Regions of interest (ROIs) were manually drawn on images of muscles of both thighs, legs and feet, and the standardized uptake ratio (SUR) and total radioactivity distribution (TRD) for each region were calculated. **Results:** The work load was below the anaerobic threshold. SUR of foot, leg and thigh were low at rest but during running increased 5.19, 4.30 and 1.74 times, respectively. The SUR of posterior-to- anterior compartment of the leg was 1.1 ± 0.1 at rest and 1.6 ± 0.5 ($P < 0.01$) during running. The laterality index of both SUR and TRD changed significantly only in the foot of the dominant side during running. TRD of the leg, less than half that of the thigh at rest, became equivalent to that of the thigh during running. TRD of the foot did not change significantly. **Conclusion:** Sole muscles showed highest metabolic activation per unit volume during running, which was higher in the dominant side. Comparison of whole muscle activity during running indicated the highest metabolic activation was in the posterior compartment of the leg, whereas thigh muscles showed relatively little changes during running. Our data indicate that whole-body FDG PET, especially three-dimensional data acquisition, is a useful tool for the investigation of muscular activity during exercise.

Key Words: fluorodeoxyglucose; PET; three-dimensional data acquisition; muscle metabolism; running; exercise

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Running consists of a series of smoothly coordinated jumps (*1*) and is usually achieved by a combination of muscle contractions in each stride. The function of each muscle involved in running is based on its anatomic location and attachment to the tendons and bones. However, the use of this static approach to understand the biomechanics of each muscle is limited. Examination of muscles during dynamic conditions (e.g., running) should provide a better understanding of the differences in muscular usage.

Skeletal muscle activity has been examined during running or walking by continuous recording of the electromyographic (EMG) activity (*2,3*). However, although EMG has a high time resolution, it is more suitable for investigating the temporal sequences of contraction of a particular group of muscles and is not suitable for the evaluation of muscles of the whole body or large groups of muscles. On the other hand, imaging of muscle activity with ^{201}Tl SPECT has been used for diagnosis and evaluation of occlusive arterial diseases; however, this method merely provides information regarding blood flow, an indirect index of muscle activity (*4–7*).

PET with ^{18}F-fluorodeoxyglucose (FDG) has been used to examine glucose metabolism in vivo. Accumulation of FDG in "resting" skeletal muscles has been used as a reference to evaluate the grade of malignancy of tumors in cancer patients (*8,9*). FDG PET has also been used to study the local metabolic rate of the lumbar musculature in patients with peripheral vascular diseases (*10*) and generalized tendomyopathy (*11*) and to study insulin sensitivity of glucose uptake in skeletal muscles of patients with diabetes (*12*) or hypertension, as well as normal subjects (*13,14*). Kostakoglu et al. (*15*) visualized speech-related muscular activity of the vocal cords in humans. However, FDG PET whole-body examination of the physiological activity of skeletal muscles during dynamic exercise has not been reported.

We recently reported the feasibility of whole-body metabolic mapping using three-dimensional FDG PET (*16*). The purpose of this study was to perform whole-body mapping of muscle activity and analyze the relative contribution of each muscle group of the lower extremities during running.

SUBJECTS AND METHODS

Seven healthy male subjects aged 19–23 y (mean ± SD 20.7 ±1.6 y) volunteered for the study. They were all amateur recreational baseball players or athletes who did not participate in national or international competitions. The study protocol was approved by the Human Ethics Review Committee of our institution, and a signed consent form was obtained from each subject. All

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For correspondence and reprints contact: Manabu Tashiro, MD, Division of Nuclear Medicine, Cyclotron and Radioisotope Center, Tohoku University, Aoba, Aramaki, Aoba, Sendai, Miyagi 980–8578, Japan.

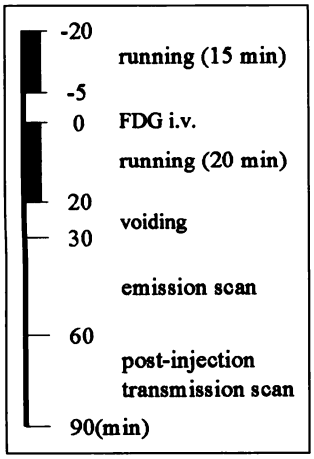

FIGURE 1. Time schedule of examination

subjects refrained from eating and drinking for at least 3 h before the test. They were requested to run around the building of our facility for a total of 35 min, including 15 min before and 20 min after intravenous injection of FDG (70.3 ± 33.3 MBq [1.9 ± 0.4 mCi]) for three-dimensional data acquisition; about 10%–20% of the usual dose used for conventional two-dimensional imaging (*17*). Intravenous blood samples were drawn before injection of FDG to measure plasma glucose concentration, which showed normal values (99.8 ± 6.0 mg/dL). Running pace was selected to keep the heart rate at 140–150 beats per minute using a heart rate monitor (VantageXL; Polar Electro, Finland) attached on the subject's wrist throughout the exercise. The running course was fixed in advance such that the number of right and left turns were equal in each study. After urination, a set of three-dimensional whole-body emission scans was obtained over 30 min, using a PET scanner (SET-2400W; Shimadzu Inc., Japan) with a transaxial spatial resolution of 3.9 mm full width at half maximum (FWHM) (Fig. 1). The axial field-of-view of the scanner is 200 mm and the whole body was scanned by performing 10 increment scans. Scanning of each position took 180 s. Transmission scans, which lasted 180 s each, using a $^{68}Ge/^{68}Ga$ external rotating line source, were obtained after the emission scans (postinjection transmission) over a period of 30 min (*17, 18*).

Seven male subjects (age 26.1 ± 3.3 y) were also examined at rest and served as controls. The amount of data obtained by three-dimensional PET is about 18 times that of two-dimensional PET. However, the time required for computation was shortened by using the SuperComputer (SX3/44R) at Tohoku University Computer Center, which allows completion of all necessary calculations in about 10 min (*17*).

We also obtained whole-body MR images of all the subjects. To evaluate the PET scans, we displayed transverse images of MRI and PET at the same level and defined the margins of muscle groups by using MR images as references. We manually defined different regions of interest (ROIs) in the lower extremities, including both feet, legs and thighs, as well as the anterior and posterior compartments of each leg in all slices. For this purpose, the legs were defined as the distance between the ankle and knee joints. The anterior compartment of the leg, including the tibialis anterior muscle, and the posterior compartment, including the gastrocnemius and soleus muscles, were recognized easily using

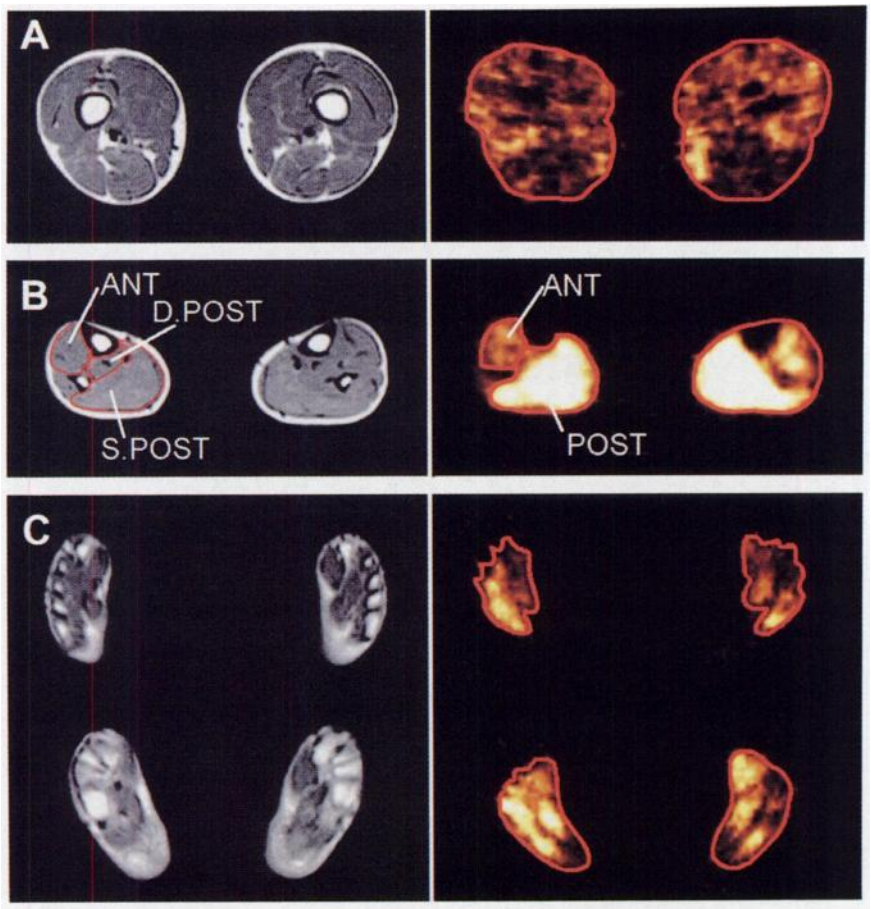

FIGURE 2. Transverse MR and PET images of thighs (A), legs (B) and feet (C). ROI for thigh was defined along surface line of thigh region as shown in A, right panel. ROIs for leg and foot were defined in similar fashion (B and C). ROI for anterior (ANT) compartment of leg was defined based on MR images. ROI for posterior compartment of leg measured FDG uptake of both superficial (S.POST) and deep (D.POST) posterior compartments. Region lateral to fibula is lateral compartment and was not measured in this study.

the individual MR images as references and using defects in PET images corresponding to the tibia and fibula as landmarks (Fig. 2). The posterior compartment included both the medial and lateral heads of gastrocnemius muscles. The standardized uptake ratio (SUR) was calculated to examine FDG uptake of muscle tissue per unit volume according to the following equation (*19*).

$$SUR = \frac{\text{mean ROI count (cps/pixel)/body weight (g)}}{\text{injected dose (mCi)} \times \text{calibration factor (cps/mCi)}}$$

The total amount of FDG uptake by each muscle group was evaluated by defining the total radioactivity distribution (TRD), based on the radioactivity concentration (*20*), which was expressed by: TRD = total organ count (hertz) / (injected dose × calibration factor). We also calculated the ratio of TRD and SUR during running to that at rest, or the exercise-to-rest (E/R) ratio, which was expressed by: E/R ratio = (running / rest) × 100.

In calculating these, the data of both lower extremities were averaged and presented as the mean of thigh, leg and foot. The laterality index (%) of SUR and TRD of each part was also calculated as follows: laterality = 100 × (dominant − opposite)/(average of both sides).

The dominant foot during exercise was checked in each subject by Tueblinger Luria Christensen Handedness test, Chapman's test (*21*) and Edinburgh Inventory (*22*).

Statistical significance of difference between the running and control groups was examined for TRD, SUR and the laterality index (%) of SUR and TRD, with Student *t* test and Welch's *t* test.

RESULTS

The selected exercise work load was about 40%–50% of VO_2max, maximum oxygen volume, which was well under the anaerobic threshold of each subject. The transaxial images of the lower extremities in a representative subject during running are shown in Figure 2. High FDG uptake was observed in the sole and other muscles of the lower legs. The coronal and sagittal images showed a high uptake and accumulation of FDG in the brain, heart, bladder and lower

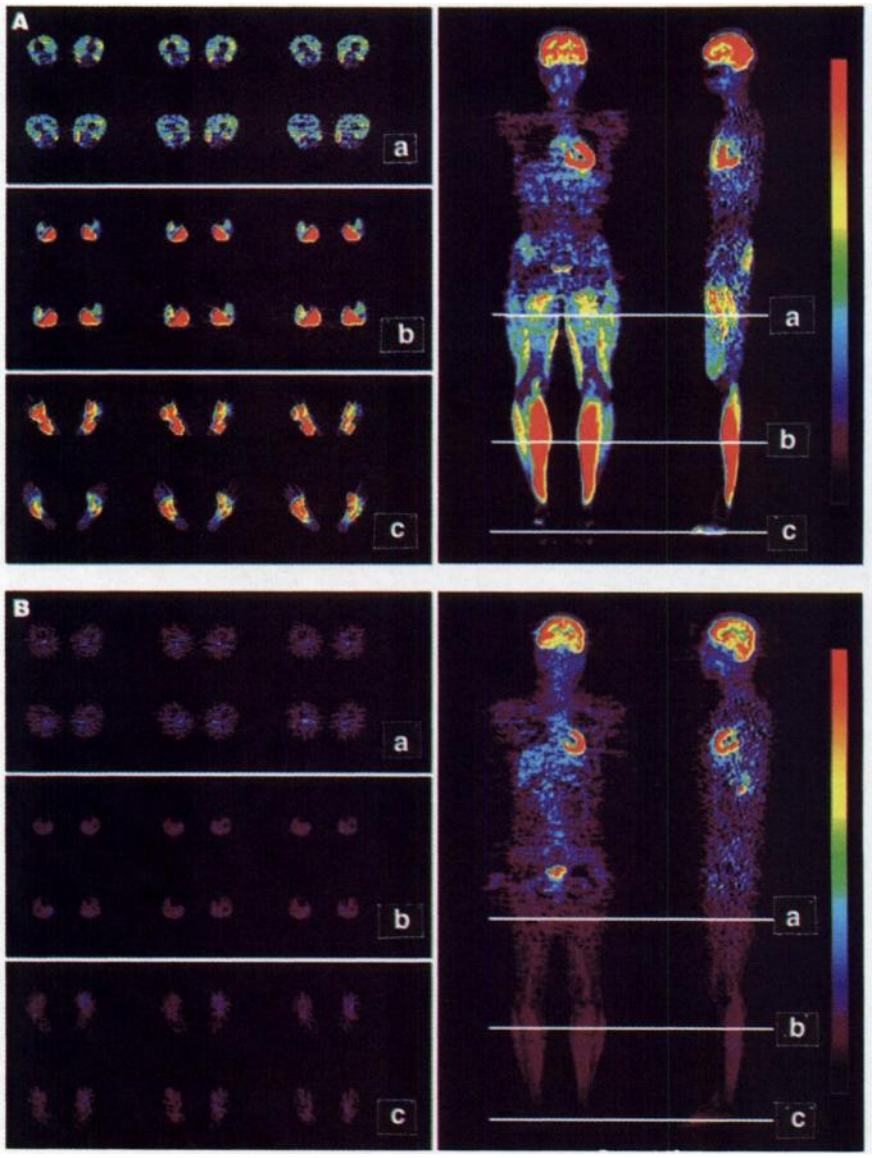

FIGURE 3. Whole-body images of runner (A) and control (B) obtained by FDG PET. Left: Transverse images of thighs (a), legs (b) and feet (c); right: coronal and sagittal sections of reconstructed whole-body image of representative subject in each group. White lines show levels of transverse scans. Note high FDG uptake per unit volume in posterior compartment of lower legs and feet of runner (A).

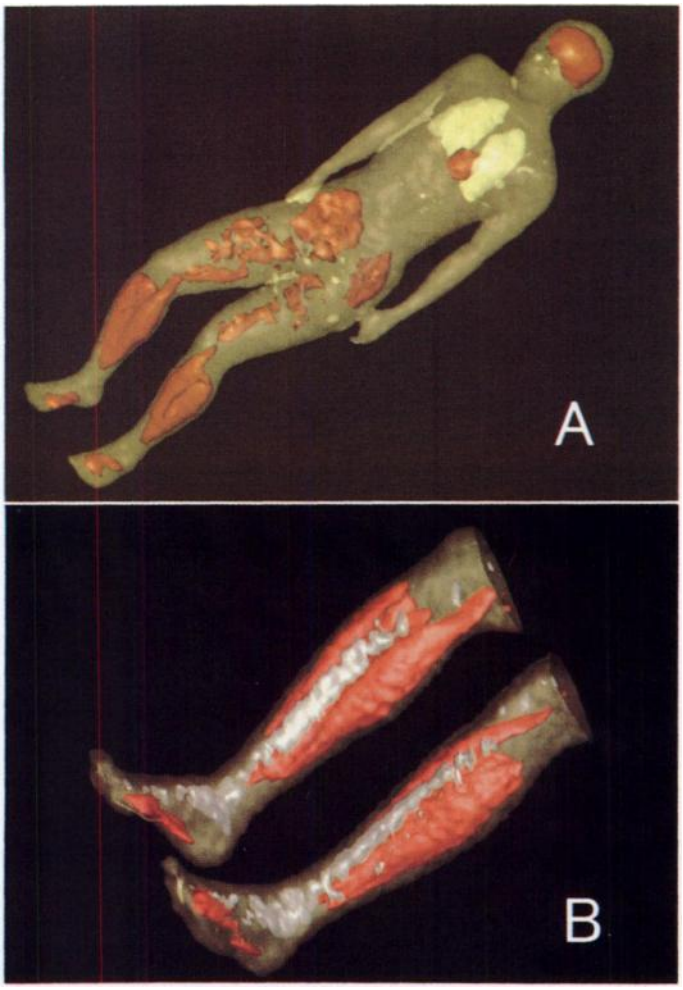

FIGURE 4. Volume-rendered images of whole body (upper) and (lower) in representative runner. Graphical data of whole-body emission and transmission scans were processed together into "volume rendered images" by AVS Medical Viewer, presented by AVS (Application Visualization System). Red color denotes high FDG uptake in brain, heart and lower extremities. White shows very low uptake areas that are compatible to tibia and bones of feet.

extremities (Fig. 3A). The volume-rendered images, reconstructed from both emission and transmission images, clearly showed high FDG uptake in the plantar extensor muscles (Fig. 4). Abnormal artifactual accumulation reported by Engel et al. (*9*) and Barrington et al. (*23*) was not found in the neck, trunk or upper and lower extremities of the control subjects (Fig. 3B).

The TRD, which represents total FDG uptake by each muscle of the lower extremities, is summarized in Table 1. The mean TRD values of feet, legs and thighs during running (0.50, 6.81 and 6.53, respectively) were generally higher than at rest (0.42, 1.99 and 4.09, respectively). TRD for the whole lower extremities was higher during running than at rest. In addition, the mean TRD at rest in the legs was less than half of that in the thighs. However, TRD values in the legs during running became similar to that in the thighs. The mean TRDs in the legs and thighs were 3.43 and 1.60 times higher during running, respectively, than at rest. The TRD in the posterior compartment of the legs was higher than in the anterior compartment with a posterior-to-anterior (P/A) ratio of 7.67, whereas a P/A ratio at rest was 3.26 ($P < 0.05$).

The SURs, which represent FDG uptake per muscle volume for each part of the lower limbs, are shown in Table 2. The SURs of the feet, legs and thighs during running (1.10, 1.40 and 0.57, respectively) were higher than at rest (0.21, 0.32 and 0.33, respectively). The SURs at rest were similar in the feet, legs and thighs. However, SURs in the legs and feet during running were greater than that in the thighs. The mean SURs in feet, legs and thighs during running were 5.19, 4.30 and 1.74 times higher, respectively, than at rest. Furthermore, the average SURs of the posterior and anterior compartments during rest were similar with a P/A ratio of 1.08. However, during running, the SUR of the posterior compartment was higher than the anterior, with a P/A value of 1.59 ($P < 0.05$).

Only 1 subject (subject 3, Table 1) among 7 runners was left-side dominant. All 7 control subjects were right-side dominant. Table 3 shows the laterality indices based on the TRD for each subject. The TRD of the sole muscles was higher in the dominant side in all subjects, and the average laterality index for feet was 23.6%. The foot laterality index based on the SUR was 21.02% (Table 4), and the value was similar when based on the TRD. Laterality was not recognized for legs, thighs or the whole lower extremities.

DISCUSSION

The outstanding advantage of FDG PET compared with EMG recording is that subjects can be examined noninva-

TABLE 1
Total Radioactivity Distribution of Muscle Groups in Lower Limbs

Subject no.	Soles	Legs	Thighs	Total	Legs		P/A ratio
					Posterior	Anterior	
Running							
1	0.10	5.02	3.94	9.07	3.89	0.25	15.56
2	0.37	5.88	11.51	17.76	4.80	0.80	6.00
3	0.97	8.88	7.17	17.01	5.67	1.09	5.20
4	0.40	5.46	3.52	9.39	3.60	0.64	5.63
5	0.51	7.60	5.43	13.54	5.17	0.38	13.61
6	0.23	3.01	3.79	7.03	2.37	0.50	4.74
7	0.95	11.85	10.36	23.17	1.55	0.53	2.92
Mean	0.50	6.81†	6.53*	13.85†	3.86†	0.60	7.67*
SD	0.34	2.91	3.28	5.79	1.50	0.28	4.86
Control							
8	0.12	0.90	1.47	2.48	0.60	0.20	3.00
9	0.55	1.78	4.94	7.27	1.09	0.48	2.27
10	0.34	1.82	3.33	5.50	1.25	0.30	4.17
11	0.39	1.77	4.57	6.73	1.32	0.36	3.67
12	0.62	3.34	6.27	10.23	1.92	0.67	2.87
13	0.56	2.52	4.26	7.35	1.71	0.52	3.29
14	0.34	1.79	3.77	5.90	1.38	0.39	3.54
Mean	0.42	1.99	4.09	6.49	1.32	0.42	3.26
SD	0.17	0.76	1.49	2.34	0.43	0.15	0.61
E/R ratio	1.21	3.43	1.60	2.13	2.92	1.43	2.35

Statistically significant at *$P < 0.05$ and †$P < 0.01$ compared with the control group.
P/A = posterior-to-anterior; E/R = exercise-to-rest.

sively after exercise as a result of metabolic trapping (*24*). In addition, the high sensitivity in the three-dimensional data acquisition mode reduces the dose of the tracer to about 10% of that used in the two-dimensional acquisition, a dose suitable for physiological experiments using normal human subjects.

Actively contracting skeletal muscles accelerate carbohydrate and fat metabolism during exercise. Previous studies have demonstrated that the contribution of plasma glucose is constant at about 10% or so of the total substrate requirement for the first 30 min of long exercise at 40%– 65% VO_2max (*25,26*). Romijin et al. (*26*) showed that plasma glucose uptake in muscles can increase proportionately with exercise intensity (*27*). Effects of other factors such as insulin sensitivity (*28,29*), local blood supply (*13,30,31*), muscle fiber types (*32–34*) and plasma glucose concentration (*28*) can be estimated as small.

The exercise work load in this study was estimated at about 40%–50% of VO_2max, which is under the anaerobic threshold. Our additional measurement of glucose and lactate concentration before and after an equivalent exercise strength in 1 of our subjects showed little change. Because the cardiovascular system and muscle metabolism have already adapted to the exercise condition at the time of FDG injection after 15-min of running, FDG uptake should be proportional to muscle activity. Therefore, in general, FDG uptake during the relatively early phase of running may reflect the regional muscle energy consumption.

In this measurement, the SUR may reflect the work strength of muscles per unit volume, whereas the TRD may reflect the total work strength of the bulk of each muscle group. Our results showed that the E/R ratios of both the leg TRD and SUR were higher than those of the thighs, and the posterior compartment of the legs showed higher E/R ratios of both TRD and SUR than those of the anterior compartment. Our results suggest that the legs, especially the posterior compartment, were more active during running than the anterior compartment. This dominance in the posterior compartment may suggest that the contraction of the posterior compartment may be the most important power source for running. The roles of the anterior compartment of the legs may be to perform dorsiflexion when a runner swings the lower limb forward and to stabilize the ankle joints at foot striking. The different roles in running may explain the difference in E/R ratios.

The basic function of the thigh muscles is to stabilize the pelvic girdle as well as to lift the lower limb forward. However, during sustained running, the latter function can be achieved by inertia only. This is perhaps the reason that the SUR of the thighs was relatively lower despite higher TRD. The relatively large volume of thigh muscles may also partly explain the relatively higher TRD.

The sole muscles are involved in action during running,

TABLE 2
Standardized Uptake Ratio

Subject no.	Soles	Legs	Thighs	Total	Legs		P/A ratio
					Posterior	Anterior	
Running							
1	1.04	1.27	0.34	0.57	1.59	1.04	1.53
2	0.83	1.56	0.70	0.86	1.48	0.90	1.64
3	0.97	1.45	0.62	0.90	1.80	1.09	1.65
4	0.88	1.00	0.36	0.60	1.64	1.01	1.62
5	2.12	1.81	0.71	1.12	2.42	0.98	2.47
6	0.38	0.54	0.31	0.38	0.63	0.52	1.21
7	1.46	2.15	0.93	1.33	2.53	2.46	1.03
Mean	1.10†	1.40†	0.57*	0.82†	1.73†	1.14†	1.59*
SD	0.55	0.53	0.24	0.33	0.64	0.61	0.46
Control							
8	0.16	0.18	0.19	0.18	0.19	0.19	1.00
9	0.20	0.32	0.30	0.29	0.36	0.35	1.03
10	0.14	0.29	0.24	0.23	0.35	0.29	1.04
11	0.31	0.38	0.38	0.32	0.45	0.43	1.19
12	0.31	0.55	0.57	0.48	0.65	0.64	1.19
13	0.19	0.29	0.26	0.26	0.34	0.30	0.99
14	0.17	0.26	0.35	0.30	0.29	0.28	1.16
Mean	0.21	0.32	0.33	0.29	0.38	0.35	1.08
SD	0.07	0.12	0.13	0.09	0.14	0.15	0.09
E/R ratio	5.19	4.30	1.74	2.79	4.60	3.23	1.47

Statistically significant at *$P < 0.05$ and †$P < 0.01$ compared with the control group.
P/A = posterior-to-anterior; E/R = exercise-to-rest.

TABLE 3
Laterality Indices for Total Radioactivity Distribution

Subject no.	Soles	Legs	Thighs	Total	Legs	
					Posterior	Anterior
Running						
1	33.08	−16.36	−5.32	−11.02	−8.36	−85.38
2	38.62	11.26	−13.14	−4.00	12.86	19.04
3	12.48	−9.90	−13.88	−10.32	−6.22	−21.38
4	24.68	−10.96	33.06	7.10	−6.56	−25.60
5	23.64	3.34	4.64	4.62	1.90	54.68
6	14.54	1.20	−6.82	−2.68	−1.34	−2.34
7	18.40	1.98	19.64	10.56	1.18	15.54
Mean	23.63*	−2.78	2.60	−0.82	−0.93	−6.49
SD	9.57	9.79	17.76	8.46	7.28	44.17
Control						
8	7.56	2.54	6.76	5.26	5.03	−9.22
9	−0.86	−0.28	3.12	1.98	5.74	−9.56
10	5.68	0.18	1.70	1.44	−4.50	2.54
11	−9.52	−4.18	0.42	−1.38	−6.80	−5.24
12	−9.10	0.16	−5.00	−3.68	0.98	−5.00
13	4.73	11.75	3.26	6.28	13.02	6.50
14	−9.10	0.16	−5.00	−3.68	0.98	−5.00
Mean	−1.52	1.48	0.75	0.89	2.06	−3.57
SD	7.67	4.95	4.38	4.01	6.66	5.96

Statistically significant at $^*P < 0.01$ compared with the control group.

too. The basic function of these muscles may be to maintain the arch structure of the foot base, which is suitable for upright standing. The ground reaction force, which the lower limbs must face while standing, will be tolerated only by tendons and bones forming the arch. However, muscular involvement will be required while walking and running, because the ground reaction force increases proportional to the running speed (*35*), and a stronger contraction of the sole muscles will be required as the running speed increases. This may explain the high SUR of the sole muscles despite the low TRD.

Most runners in this study manifested higher TRD and SUR in the dominant side of the soles, but not of the legs and thighs. Such laterality was not evident in control subjects. It is suggested that individuals tend to use the sole of the dominant side more intensively to bear the body weight during running. The body is very unstable and is always affected by forward, lateral components of ground reaction force, as well as vertical force. It may be a natural explanation that the contribution of the sole muscles to balance the body during ongoing movement is more on the skilled (dominant) side.

Absolute quantification of glucose metabolic rate during running was technically impossible because of the difficulty in arterial blood sampling during running in the field. However, manipulation of SUR and TRD seems to be satisfactory for the purpose of this study to examine the relative activity of each muscle group. Muscles are used in similar ways by subjects during running. Only a small variation in the muscle activity was observed among runners under a similar cardiovascular load. However, this variation will be the theme of further investigations related to training habits and history, and levels of achievement by professional athletes and beginners. This method can be applied to a wide range of research activities, including training science, biomechanics and rehabilitation medicine.

CONCLUSION

In conclusion, whole-body FDG PET based on three-dimensional data acquisition showed the usefulness of analysis of muscle activity during running. The advantage of metabolic trapping and obtaining whole-body information in a set of scans makes this technique unique compared with other techniques such as EMG. Metabolic mapping of muscular activity is clinically applicable in various fields of sports science and rehabilitation medicine. This technique, showing the pattern of muscle usage, can provide an index for the proper training of a particular muscle or group of muscles used in specific tasks. Three-dimensional PET may be the most suitable device for this purpose with a minimum radiation exposure.

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TABLE 4
Laterality Indices for Standardized Uptake Ratio

Subject no.	Soles	Legs	Thighs	Total	Legs	
					Posterior	Anterior
Running						
1	10.62	−5.86	−6.18	−20.10	−3.24	−49.70
2	16.76	11.20	−12.30	−3.80	10.84	23.10
3	5.40	−7.08	−15.12	−10.56	−10.94	−14.42
4	16.84	−8.96	33.04	7.54	−5.60	−30.08
5	18.78	1.44	5.02	4.12	−1.10	38.28
6	62.32	−1.60	−7.46	−4.04	−0.42	0.44
7	16.38	−2.96	11.68	3.32	−1.52	0.72
Mean	21.01*	−1.97	1.24	−3.36	−1.71	−4.52
SD	18.80	6.79	16.91	9.59	6.61	30.11
Control						
8	−1.12	−1.46	2.54	0.88	−0.90	−5.54
9	−4.72	−3.24	−0.98	−1.84	0.76	−0.12
10	1.72	−1.48	−0.16	−0.32	−5.30	7.00
11	−7.40	−3.72	−1.72	−3.80	−6.40	−0.64
12	7.76	−1.80	0.02	−2.36	−2.14	−0.54
13	1.98	9.53	0.76	3.84	11.12	9.43
14	−3.76	−7.80	−3.58	−5.08	−5.14	−8.36
Mean	−0.30	−0.36	0.08	−0.60	−0.48	1.60
SD	2.55	1.26	2.49	1.92	1.17	3.83

Statistically significant at $^*P < 0.05$ compared with the control group.

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