[18F]-FDG positron emission tomography—an established clinical tool opening a new window into exercise physiology

Thorsten Rudroff,1 John H. Kindred,1 and Kari K. Kalliokoski2

1Integrative Neurophysiology Laboratory, Department of Health and Exercise Science, Colorado State University, Fort Collins, Colorado; and 2Turku PET Centre, University of Turku, Turku, Finland

Rudroff T, Kindred JH, Kalliokoski KK. [18F]-FDG positron emission tomography—an established clinical tool opening a new window into exercise physiology. J Appl Physiol 118: 1181–1190, 2015. First published March 12, 2015; doi:10.1152/japplphysiol.01070.2014.—Positron emission tomography (PET) with [18F]-fluorodeoxyglucose (FDG) is an established clinical tool primarily used to diagnose and evaluate disease status in patients with cancer. PET imaging using FDG can be a highly valuable tool to investigate normal human physiology by providing a noninvasive, quantitative measure of glucose uptake into various cell types. Over the past years it has also been increasingly used in exercise physiology studies to identify changes in glucose uptake, metabolism, and muscle activity during different exercise modalities. Metabolically active cells transport FDG, an 18fluorine-labeled glucose analog tracer, from the blood into the cells where it is then phosphorylated but not further metabolized. This metabolic trapping process forms the basis of this method’s use during exercise. The tracer is given to a participant during an exercise task, and the actual PET imaging is performed immediately after the exercise. Provided the uptake period is of sufficient duration, and the imaging is performed shortly after the exercise; the captured image strongly reflects the metabolic activity of the cells used during the task. When combined with repeated blood sampling to determine tracer blood concentration over time, also known as the input function, glucose uptake rate of the tissues can be quantitatively calculated. This synthesis provides an accounting of studies using FDG-PET to measure acute exercise-induced skeletal muscle activity, describes the advantages and limitations of this imaging technique, and discusses its applications to the field of exercise physiology.

glucose uptake; exercise; noninvasive imaging; skeletal muscle; tracer

POSITRON EMISSION TOMOGRAPHY (PET) is a noninvasive imaging technique that produces high-resolution images of the physiological function of human tissues. These functions include measurements of blood perfusion and metabolic processes, as well as quantification of neurotransmitter/hormonal receptor densities. The most useful clinical tracers are usually labeled with naturally occurring isotopes of basic elements, including carbon (15C), nitrogen (13N), and oxygen (15O). Currently, the most widely used PET tracer is the fluorinated analog of glucose, 18F-2-deoxy-d-glucose (FDG).

FDG-PET is routinely used in oncology to detect malignant tumors due to the increased utilization of glucose to generate ATP in these cells. However, FDG-PET is not limited to the study of cancer and has been used in a variety of clinical applications ranging from cardiology to neurology. The appreciation that functional imaging modalities, such as PET, may offer an earlier diagnosis, and more precise staging than conventional anatomic imaging has supported PET’s increased use.

The fundamental principles of in vivo PET imaging are summarized in Fig. 1. Several steps are involved in the imaging process, beginning with the selection and production of a suitable, pharmaceutically labeled positron-emitting radionuclide tracer. Next, the tracer is administered to an individual, followed by the imaging of either the tracer’s kinetics within the tissues with dynamic imaging or the spatial distribution of the tracer with static imaging. After reconstruction, images are ready for detailed evaluation. Regions of interest (ROI) are identified through both manual and automated processes, and outcome measures, such as the standardized uptake value (SUV), are quantified.

A major challenge for the precise interpretation of PET images is the absence of anatomic structures in the images. PET images generally have a lower resolution than structural imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI). The technique of fusing a PET image with a CT or MRI image can improve the anatomical identification of tracer uptake and has been recognized in the field of oncology (5, 6, 73). Vanteenkiste et al. (72) showed that fusing PET with CT can improve interpretation accuracy over using standalone PET images. As a result, combined PET/CT and PET/MRI cameras have been developed to further improve PET image analysis.

This synthesis review provides an accounting of studies using FDG-PET to measure exercise-induced skeletal muscle activity, describes the advantages and limitations of this imagi-
FDG-PET and Exercise Physiology

FDG-PET allows researchers to investigate long-term changes associated with chronic physical activity and exercise training. A recent review by Heinonen et al. (18) addresses those areas, as well as discussion of FDG-PET being used to investigate the activity of other tissue types. The focus of this synthesis is on muscle activity during acute exercise.

FDG-PET METHOD

The widespread use of FDG is facilitated by the relatively long half-life of the $^{18}$F isotope (109 min), which allows for tracer transport and typical whole body imaging protocols. PET imaging generally lasts about 20 min after a resting uptake period ranging from 30 to 60 min.

FDG is transported from the plasma into cells in the same fashion as glucose. After transport across the cell’s membrane, FDG is phosphorylated, preventing its return to the circulation. At this point FDG is trapped within the cell and is not metabolized further. This trapping is based on the properties of the parent molecule, 2-deoxy-D-glucose (DG), which is a normal glucose molecule from which one of the OH groups has been replaced by H. DG has also been labeled with other isotopes, such as tritium ($^3$H) or radiocarbon ($^{14}$C), which are mainly used in preclinical research, because the analysis and calculation of tracer uptake requires tissue slicing and slice imaging using autoradiography. After injection, PET imaging is performed and immediately followed by CT or MR anatomical imaging to maintain coregistration. Due to the increased spatial resolution of the CT and MR images, the PET image is fused to fit the CT/MR image or vice versa. Regions of interests (ROI) are then created on MR or CT images, then applied to the PET image for FDG quantification.

FDG-PET is well suited for the exercise sciences because tracer uptake can occur while participants are moving freely. The distribution and quantity of tracer uptake can then be

Fig. 1. Basic principles and procedures for PET imaging.
visualized with a postexercise scan. FDG-PET imaging of muscle activity relies on the principle that active muscle cells exhibit increased glucose uptake (19, 20). Several studies have used FDG-PET to monitor cumulative muscle activity during different exercise modalities and to provide images of the spatial distribution of skeletal muscle metabolism (2, 10, 11, 12, 16, 27, 28, 31, 37, 39, 48, 50, 53, 54, 59, 63, 64, 69). When investigating cumulative muscle activity, FDG is the preferred tracer because of its relatively long half-life compared with other PET tracers such as $^{15}$O-water, which is used for muscle perfusion measurements and has a half-life of only 2 min. FDG uptake is also closely correlated with exercise intensity, which allows task-specific comparisons to be made (16, 31, 50) (Fig. 2). For example, Pappas et al. (50) demonstrated increased FDG uptake in elbow flexor muscles with increasing exercise intensity. Quantitative FDG uptake increases as the muscle performs against greater resistance, reflected by increased glucose uptake as the muscle becomes increasingly active. Using both functional imaging and quantitative FDG uptake measurements, task-specific muscles can also be identified, which is impossible with EMG. Furthermore, Pappas et al. (50) also showed that FDG-PET provides information about the spatial distribution of activity within a given muscle, along both the longitudinal and transverse axes. In contrast to traditional biomechanical assumptions, the level of intramuscular activity was found to vary considerably along both axes (50).

The plasma time-activity curve indicates that the plasma FDG concentration is high in the first 10 min after injection and then gradually decreases when the tracer is taken up by the tissues, and it is also partly degraded in the plasma as well. The tracer disappearance rate from the plasma directly depends on the level of the whole body metabolism and cumulative uptake by the tissues. FDG injection, typically 150-400 MBq, should occur at least 2–3 min after the start of exercise to ensure that steady-state conditions have been reached before the injection. After the tracer injection, exercise should be continued for 10–30 min, depending on the exercise task, to ensure sufficient tracer uptake into the muscles. Although a prolonged exercise task lasting up to 60 min after injection would not otherwise affect the FDG uptake, utilization of other fuel sources during prolonged exercise may result in an inaccurate representation of muscle activity. With this in mind, FDG-PET is a very suitable technique for studies on exercise physiology, separating the “task phase” (the first 10–30 min) and the “data acquisition phase” (30–90 min or so after injection) (69).

A main benefit of FDG-PET is the ability of participants to carry out any task, static or dynamic, in a free living environment. This includes activities such as running, cycling, swimming, resistance training, and even driving a car. Thus, although the temporal resolution of the FDG-PET technique is limited to monotonous tasks, it provides the opportunity to investigate a large number of muscles simultaneously, including the muscles lying deeper in the body that are inaccessible with EMG. This makes the application of this technique to the science of human movement very useful (69).

**Quantification of FDG-PET**

It is necessary to normalize FDG uptake to compare exercise tasks completed on different days. The most commonly used measure of FDG uptake is the standardized uptake value (SUV). SUV is calculated as the radioactivity concentration within a ROI corrected for time difference between time of injection and scan, injection dose, and body weight.

An important point to consider is that the SUV depends strongly on the net uptake of other bodily tissues, and in some cases may give misleading results when comparing two or more exercise conditions (e.g., between exercise intensities, before and after training, etc.). To account for this, blood samples can be taken to determine the tracer concentration in the blood during exercise. Net whole body uptake can be calculated from the plasma tracer concentration values over time, and therefore, repeated plasma sampling from the time of the tracer injection to the end of the PET scan is strongly recommended in exercise physiology settings. Traditionally, FDG-PET data have been analyzed using the graphical analysis originally described by Patlak and Blasberg (51). This method cannot be reliably used when the postexercise scan is performed. However, if blood sampling has been performed, a good approximation of the graphical analysis can be performed by calculating the fractional uptake rate of the tracer by dividing decay-corrected tissue activity counts measured from PET image by the time integral of the plasma counts from the time of the injection to the time of the PET scan.

Blood sampling during complex movements is sometimes difficult or impossible, and therefore other methods have been used to estimate FDG and glucose uptake rates. In simple tasks, where only a small amount of muscle is used, normalization can be done relative to inactive muscles, assuming that uptake in the inactive muscles remains unchanged (26, 27). Muscle FDG uptake has also been compared with bone tissue uptake.

![Fig. 2. Representative cross-sectional PET images of glucose uptake of the thigh region during steady-state cycling with 3 different exercise intensities for 1 subject. Color scale shows the glucose uptake in a relative scale. [Reprinted from Heinonen et al. (16) with permission].](image-url)
assuming that uptake in bone is largely unaffected by exercise intensity (2). It should, however, be noted that studies have shown almost fivefold difference in bone (femur) FDG uptake between resting and exercising legs during one leg knee extension exercise at moderate intensity (15). It is not known whether bone glucose uptake differs between exercise intensities, but in the same study, bone perfusion increased from rest to exercise but did not increase with increasing exercise intensity (15). This indirectly suggests that bone could be a good reference tissue for comparisons between different exercise intensities but not necessarily between rest and exercise conditions. Nevertheless, these reference tissue calculations can still be considered only semiquantitatively at best, and blood sampling for deriving input function is recommended if possible.

In some studies with complex tasks, separate resting control groups have been used for normalization (64), but that should be discouraged as there is large interpersonal variation in FDG uptake between different muscles.

**Methodological Considerations**

A current and unavoidable drawback of the FDG-PET technique for exercise studies is a limited temporal resolution. Static PET images show the culmination of activity from tracer injection to image capture. Therefore, short-lived features of neuromuscular recruitment may not be represented in these types of images. Because of the lower time resolution, changes to subject technique and, subsequently, use of different muscles during exercise are not reflected in the results. It should further be noted that some amount of the tracer remains in the blood at the end of exercise and is being taken up during the postexercise period and PET scan. However, postexercise tissue uptake of the tracer most probably correlates very well with the uptake during the actual exercise, because GLUT4 transporters remain in the cell membrane up to hours postexercise (71).

For technical reasons, it is challenging to perform PET scanning during exercise because the target tissue should be as stable as possible. There have, however, been successful attempts to overcome the problems using localized muscular exercise with continuous (29, 30, 56) and intermittent (17, 29, 31) contractions and measurements of muscle perfusion and oxygen consumption with $^{15}$O-labeled tracers and glucose uptake with FDG-PET. In addition, even dynamic one leg knee extension exercise has been successfully used during PET imaging (15, 16, 17, 35). However, more complex tasks must be performed outside the scanner. A particular strength of this approach is that the subject can be completely stabilized during the actual PET scan, which improves the accuracy of the image capture.

One consideration is that with FDG-PET one can measure only the amount of glucose taken up by muscle cells but not the proportion of glucose entering oxidative or nonoxidative metabolism. Therefore, this method needs to be combined with other methods if the entire fate of the glucose molecule from circulation to cellular oxidation needs to be determined (12).

The transport and phosphorylation of glucose and FDG in skeletal muscle is not completely similar because of the difference in affinity of glucose transporters and hexokinase between glucose and FDG. This must be corrected if quantitative glucose uptake is to be calculated from rate constants of FDG uptake obtained by fractional uptake rate or graphical analysis (51). Correction is made using a correction factor, lumped constant (LC) of 1.2 for skeletal muscle and has also been shown to be stable during different physiological conditions in experimental animal studies (23, 42).

**FDG-PET in the Assessment of Muscle Activity During Exercise**

**Activity between Muscles**

Electromyography is traditionally used to investigate muscle activity in various sports (4, 44, 66). In addition to the disadvantages of the EMG signal it is unavoidable that equipment attached to the body disturbs the sport activity level and limits the type of sports investigated. When investigating complex whole body movements, FDG-PET is a promising supplement or alternative to other methods for investigating muscle activity without limitation as to the type of exercise. The only limitation in this regard with FDG-PET is that the movements should ideally be monotonous, repetitive movements for longer periods of time, such as in endurance disciplines, although some successful attempts have been made to use FDG-PET while running sprints (47). Additionally, EMG is much more insightful when considering issues related to single motor unit favoring the use of EMG in those studies (57, 58).

FDG-PET has only been applied in a limited extent in complex sports movements such as cycling or running (10, 12, 14, 31, 48, 67). For example, Fujimoto et al. (10) and Tashiro et al. (67) investigated FDG uptake in muscles during running and found the greatest activation in the posterior lower leg. Bojesen-Møller et al. (2) investigated muscle activation strategies during double poling skiing at two different work intensities. They showed that, surprisingly, FDG uptake did not increase significantly from typical aerobic training intensity to close to competition intensity in most upper body muscles; however, an increased uptake was found for the knee flexor (27%) and extensor muscles (16%) and for abdominal muscles (21%). Their data suggest that when exercise intensity increases in skiing with double poling, the muscles that span the lumbar spine, hip, and knee joints increasingly contribute to the task. However, they did not take blood samples and therefore could not calculate absolute rate of glucose uptake, which still could have increased in the upper body muscles. Nevertheless, this does not overrule the finding that the relative muscle contribution changed from upper body muscles to the legs and abdomen with increased intensity. The previously mentioned study by Ohnuma et al. (47) was the first that investigated muscle activity during a sprint using FDG-PET. They showed greater FDG uptake in the posterior thigh muscles than in the anterior and posterior lower leg muscles of subjects during the exercise. Their study, as well as Nakase et al. (45), who investigated whole body muscle activity during a warm-up program, suggested that PET-FDG can provide useful information to further advance sports rehabilitation and injury prevention programs.

In another study (12) muscle glucose uptake response was determined when trained and untrained men performed bicycle exercise at low, moderate, and high intensity. A particular strength of that study is that blood samples were taken, and therefore, actual glucose uptake values could be calculated.
Their findings showed that glucose uptake increases linearly up to the highest intensity in endurance-trained subjects while it levels off after moderate intensity in untrained subjects. This indicates that endurance training increases the capacity of contraction-induced glucose uptake in skeletal muscle (Fig. 3). This finding also has implications for obesity and type II diabetes because exercise training is often encouraged. Identifying how this skeletal muscle glucose uptake capacity is altered with disease as well as training could lead to more individualized exercise prescriptions and training modalities. An often stated question is how well the muscle activity measured with FDG-PET and EMG are matched. As we know, sEMG comprises the sum of the electrical contributions made by the active MUs as detected by electrodes placed on the skin overlying the muscle. Therefore, sEMG reflects both peripheral and central properties of the neuromuscular system (8). Although the global sEMG is a useful measure of muscle activation, the limitations of the information that can be extracted from this signal are often not appreciated (8). Three examples of these issues are amplitude cancellation (33), influence of innervation zone (9), and crosstalk from neighboring muscles (8, 9). An overview of the nonphysiological factors and physiological properties that influence recording of sEMG can be found in Farina et al. (8).

Furthermore, sEMG quantification requires normalization of EMG amplitude to the EMG amplitude of maximal voluntary contractions (MVCs), which some individuals, e.g., older adults or diseased persons, are unable to achieve (65). Additionally, sEMG is not able to evaluate the activities of deep muscles; it is also not possible to measure MVC forces. Theoretically, activation measured with EMG during different tasks shows the percentage of the particular muscle’s activation in relation to maximal voluntary contraction of the same muscle. FDG-PET, on the other hand, shows the uptake of a tracer that closely follows the glucose uptake in the particular muscle, and if blood samples are taken, shows even the absolute glucose uptake of the particular muscle. To the best of our knowledge, no one has ever attempted to correlate the PET results to the maximal uptake of the muscles that can be achieved. Therefore, although both methods measure muscle activation from their own perspective, the results will not necessarily correlate with each other. However, some attempts to compare the methods have been done (39, 40, 41, 54), but the results have not been shown to be consistent.

**FDG Uptake Heterogeneity—Possible Measure of Muscle Fiber Activation Heterogeneity within Muscle?**

Adequate muscle force production is necessary to accomplish activities of daily living. However, this ability is often impaired in clinical populations, such as the elderly and those with neuromuscular diseases. Alterations in neuromuscular activation may contribute to the impairments; however, the underlying physiological mechanisms within the neuromuscular system are yet to be fully understood. Muscle force is regulated by the nervous system in two ways: motor unit recruitment and rate of motor unit firing. These variables are known to change with aging and clinical status.

Farina et al. (7) and Merletti et al. (43) used multichannel sEMG to estimate motor unit behavior during force production. Their findings showed that spatial activation of muscle fibers is nonuniform and that the spatial EMG pattern is altered by contraction level and fatigue. This spatial distribution, or heterogeneity, of different muscle fibers innervated by one motor neuron in a limited region of the muscle might explain this phenomenon (21, 22). However, because of the limitations of sEMG, as outlined before, FDG-PET may provide an improved measurement of heterogeneity within the skeletal muscle. This approach has been used to investigate blood flow heterogeneity and the underlying mechanisms during dynamic and isometric contractions (15, 17, 29, 56). With FDG-PET, uptake is actually measured within small three-dimensional volume elements (voxels) that makes it possible to calculate variation in FDG uptake between voxels, i.e., FDG uptake heterogeneity as the coefficient of variation (SD/mean) (16, 30). With the typical image reconstruction, each voxel is approximately the same size as a muscle biopsy sample, thus PET measurements of whole muscles provide much more information about whole muscle and muscle groups compared with the much used biopsy method. As the tracer is accumulated over a long period of time, the measure of heterogeneity solely represents spatial distribution because temporal variation within the voxels cannot be determined. Heinonen et al. (16) suggests that FDG uptake heterogeneity may provide a good estimate of muscle fiber activation within the muscles. Because more motor units, and thus more muscle fibers, are activated during exercise with increasing intensities, FDG uptake heterogeneity is decreased. A recent study by Rudroff et al. (53) found greater FDG uptake heterogeneity in knee muscles of older men than younger men during isometric contractions (Fig. 4). They suggested that FDG uptake heterogeneity is greater in old than young men and especially so for old men who exhibit greater muscle atrophy.

Because of these encouraging findings, it is suggested that FDG uptake heterogeneity might be a valuable noninvasive tool for the investigation of altered muscle fiber activation induced by aging and diseases of the neuromuscular system. However, more research is needed to confirm that the observed changes in heterogeneity actually depict changes in the activation of muscle fibers.
ASSESSING MUSCLE FUNCTION IN CLINICAL POPULATIONS

As evident even from the title of this review, PET already has a long tradition in clinical studies of different patient populations, particularly in oncology and cardiology (13, 25, 52). However, researchers are beginning to use FDG-PET as a very promising tool in clinical and therapeutic settings to evaluate impaired and/or inefficient muscle activation strategies as well as to monitor rehabilitation programs. However, only a few studies have used this technology.

Aging

Often times, older adults have reduced muscle strength and mass, which usually explains their walking impairments. Previous studies have shown that older adults use altered muscle activation strategies to accomplish activities of daily living (23, 60). Shimada et al. (60) showed greater FDG uptake in hamstring and deep layer hip muscles of older adults than young adults during 50 min of treadmill walking (Fig. 5). Greater muscle activity, as indicated by greater FDG uptake, imbalanced activation, and coactivation of the hamstring and quadriceps muscles result in increased mechanical energy cost. This is reflected by increased whole body metabolic cost, indicating inefficient muscle activation strategies (60). This supports conclusions made by Hortobágyi et al. (23) regarding coactivation and increased effort to perform activities of daily living in elderly individuals.

Another study by Rudroff et al. (54) also found that older men used greater levels of muscle activity across force and position tasks among agonist, antagonist, and accessory muscles as a strategy to accomplish isometric fatiguing contractions with the knee extensors. On the other hand, young adults were able to modulate leg muscle activities during the task (Fig. 6), indicated by greater FDG uptake during the position task than the force task. These findings were consistent with age-associated changes in motor unit activation strategies. Only one study (61) evaluated exercise intervention using FDG-PET in older adults. They used the robotic stride assistance system (SAS) to automatically control the walk ratio during walking. By using this device twice a week for 3 mo, walking speed of elderly women (72- to 85-years old) was improved and FDG uptake by the gluteus muscles, rectus femoris, and pelvic muscles was reduced. The findings indicated that subjects were able to direct the exaggerated use of the muscles in the pelvic area toward the larger thigh and leg muscles and ultimately improve their walking performance. Yet more studies are needed to identify whether exercise interventions facilitate efficient muscle activation strategies that can reduce increased glucose uptake and increase muscle fatigue resistance during walking in older adults. Furthermore,
future studies are needed to explore the associations between increased skeletal muscle FDG uptake and muscle weakness, neuromuscular dysbalances, physical activity levels of daily living, and physiological dysfunctions in older adults.

**Multiple Sclerosis**

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory disease of the central nervous system resulting in axonal demyelination and degeneration (3, 74). One of the early signs of MS is weakness in one leg, which has been determined to be a significant cause of progressive worsening of walking abilities (47, 70). To this point, only one study has been published using FDG-PET to investigate muscle activity in patients with MS. Rudroff et al. (55) compared the distribution of leg muscle activation in mildly disabled patients with MS during walking at a self-selected speed. The findings showed that FDG uptake in knee and hip flexors was higher compared with the CON group. The study also showed that the MS group exhibited asymmetrical strength of the knee flexors and that FDG uptake was significantly lower in the weaker knee flexors of patients with MS (Fig. 7). It is suggested that FDG uptake and strength asymmetries in the legs of mildly disabled patients with MS indicate greater metabolic costs during activity, which may play a major role in premature muscle fatigability and subsequent impaired walking capacity, leading to reduced physical activity and inactivity-related health problems. The findings of this study suggest that motor function may begin to deteriorate in the early stages of the disease. Furthermore, the findings highlight the importance of bilateral and whole leg musculature assessment and the need for therapies targeted at reducing such differences early in the disease process. Future, larger studies that include higher walking intensities and MS patients with a higher disability level are needed to investigate the association between asymmetrical FDG uptake in weak leg muscles and performance fatigability.

**PERSPECTIVES AND FUTURE RESEARCH DIRECTIONS**

FDG-PET is a powerful tool that can provide answers no other measurement can provide. Compared with sEMG, FDG-PET offers information about the activation of unlimited amount of muscles including deeper muscles such as multifidus, iliocostalis, and rhomboids. As outlined before, FDG-PET can show differences in muscle glucose uptake indicating which muscles are more or less compromised during activity. In addition, previous studies have shown that spatial activation in a muscle is nonuniform because of the heterogeneity of different muscle fiber locations and a clustering of muscle fibers innervated by one motoneuron in a limited region of the muscle (21, 22). FDG-PET can provide a measurement of heterogeneity within a muscle. This information is very useful for the investigation of age-associated differences in the modulation of muscle activation and may provide new insights into sarcopenia (53). For instance, morphological changes in the aging skeletal muscles include the change to a less heterogeneous type of muscle tissue, which can be explained by a
loss of type II muscle fibers or a conversion from type II to type I muscle fibers. This may result in inadequate muscle activation and force production in the aged population. Furthermore, using this technique in a clinical population, such as MS, glucose uptake heterogeneity measured by FDG-PET provides new insights of muscle fiber activation during functional tasks and may explain motor deficits and disability (34).

Another advantage of FDG-PET is that this measurement does not require normalization to a maximal voluntary contraction, which some individuals, e.g., older adults or persons with disease (e.g., patients with low back pain and with joint replacements), are unable to achieve (65). Rather, by normalizing glucose uptake to the muscle volume, FDG-PET takes into account the muscle size.

Previous studies used FDG-PET for quantifying muscle activation during running (11, 67) and walking (56, 60, 62) in younger and older subjects. Because participants can move freely during dynamic activities, no alterations or impairments due to attachments to the skin (electrodes, cables) occur. This fact also emphasizes the value of FDG-PET measurements during activities of daily living in healthy subjects and subjects with disease.

No studies have used FDG-PET to investigate muscle activation strategies in obese individuals. This is surprising because EMG is not capable of accurate measurement of muscle activity in this population because the signal is highly sensitive to the fatty tissue layer (1, 8).

FDG-PET overcomes this challenge because during task performance subcutaneous adipose tissue glucose uptake is relatively unchanged, allowing for FDG uptake into activated muscles, and thus provides more accurate information regarding alterations in muscle activation and motor patterns compared with traditional methods.

Furthermore, FDG-PET is useful for designing rehabilitative and sport science exercise prescriptions for the quantification of the efficacy of rehabilitation tools. For example, some studies (38, 49, 62) used FDG-PET to assess the function of healthy and injured rotator cuff muscles. With the use of specific exercise protocols, FDG-PET may prove useful for objective evaluation of rotator cuff muscle activity (38, 62). FDG-PET might be useful for other areas of rehabilitation, such as anterior cruciate ligament tears or muscle ruptures, and for sports medicine in general. Quantifying the spatial distribution of FDG uptake, along the vertical and horizontal axis, within the quadriceps muscles as well as tendons after ACL reconstruction may provide additional information about how muscle function is restored and the efficacy of rehabilitation.

Significant increases in chronic disease risk have been attributed to a lack of physical activity as well as prolonged periods of sedentary behavior by recent epidemiological studies. Tikkanen et al. (71) investigated EMG activity of leg muscles for 12 h during normal daily life of healthy subjects. Although wearable EMG enables measurement of details of muscle inactivity and activity during normal daily life, FDG-PET could add important information regarding activity of muscles not accessible with EMG. This knowledge is important to understand the intensity, volume, and distribution of physical activity of healthy individuals.

Because muscle fibers and motoneurons form motor units, FDG uptake in muscles may correlate with activity in corresponding brain regions. This signifies another interesting area of FDG-PET research. Tashiro et al. (67, 68) examined linear correlations between the regional brain activity and leg muscle activity of the lower extremity using the whole body PET data. Significant correlations were observed between the glucose uptake in the leg muscles and the primary sensorimotor cortex, as well as the temporoparietal association cortex, posterior parietal cortex, and premotor regions. Interestingly, the strongest correlation was observed in the primary sensorimotor cortex (especially in the leg motor area), whereas the activation in this region during running merely remained in the threshold level. The exquisite correlation between the primary sensorimotor cortex and muscular activities most likely reflects the fact that this region is most tightly functionally connected with the skeletal muscle systems. Hence, the FDG-PET technique can serve as a unique tool to examine the brain-muscle interaction at a whole body level. Furthermore, applying this technique in the study of progressive neurological diseases could provide useful information about changes in disabilities associated with autonomic nervous system and peripheral ef-
factors, allowing for new estimates and predictions of disabilities in this population. The study by Kindred et al. (33) was the first that found that FDG uptake in specific spinal cord segments was reduced during walking in patients with MS. Because sympathetic branches of the autonomic nervous system and motoneuron pools of the lower limbs are located within these regions, failure to activate central pattern generators and lower motoneuron pools during walking may contribute to the impaired walking ability of patients with MS.

CONCLUSIONS

This synthesis describes the integration of the FDG-PET technique in the study and evaluation of the human musculoskeletal system and opens the doors for clinicians and researchers to use FDG-PET. The noninvasiveness of FDG-PET provides unmatched insight into human skeletal muscle activity and energy metabolism in vivo. Performing imaging after an exercise task can be an advantage due to the fact that participants can perform the activity in a free living environment with no attached equipment. Combined with other noninvasive techniques, i.e., EMG, important in vivo data concerning human movement and clinical function can be obtained. For these reasons we believe that FDG-PET will become a useful tool in exercise physiology research.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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