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POSITRON-EMISSION TOMOGRAPHY – THE MOST ADVANCED IMAGING DIAGNOSTIC METHOD IN MEDICINE

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ABSTRACT

Positron emission tomography (PET) is a state-of-the-art imaging technique that has an extremely high potential for evaluating metabolic processes in the body. The mechanism of action is based on the introduction into the body of a radioactive isotope of glucose (most often *18F-fluorodeoxyglucose, 18F-FDG*), after which its accumulation in various organs and tissues is measured. Unlike other imaging methods, PET does not provide structural information about the patient's anatomy, but provides functional information based on the interaction of the radioisotope at the molecular level in relation to physiological processes. In order to facilitate the localization of areas with increased accumulation of the respective radiotracer, PET is usually combined with computed tomography (CT).

This type of research is most widely used in neoplastic diseases (especially for the detection of metastases), diseases of the thyroid gland, kidneys, and other internal organs. Its use in the field of veterinary medicine is limited due to its high cost, which is why it is an insufficiently studied imaging-diagnostic method, characterized by huge diagnostic potential.

Key words: nuclear tomography, positron, radioisotope, glucose, 18F-FDG

INTRODUCTION

Positron Emission Tomography (PET) is a nuclear medicine imaging technique, developed in the mid-1970s that has the ability to visualize the metabolic activity of cells (Cherry, 2006). It is a technique that provides functional information, in addition to structural information obtained with computed tomography (CT). *Positron emission tomography* is the first imaging diagnostic method that provides information about the functional state of the brain (Kitson et al., 2009).

The most common application of this technique is cancer diagnostics and staging, using 18F-fluorodeoxyglucose (*18F-FDG*), which is a radioactive isotope of glucose. The mechanism of action is based on the introduction into the body of the isotope, after which its accumulation in various organs and tissues is reported, thus being an indicator of their metabolic activity (Hsu PP et al., 2008). The available data in the field of veterinary medicine is limited, nevertheless human

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studies have shown benefit with the addition of PET both for assessment of the primary tumor and detection of metastatic diseases (Grant et al., 2008).

18F-FDG is an excellent marker of metabolic activity and is particularly useful for the detection of neoplasia, as tumor cells often preferentially utilize glucose for glycolysis and subsequently display increased numbers of glucose transporters (Hsu PP et al., 2008). However, 18F-FDG uptake is not only found in neoplastic tissue but also in areas of inflammation (Love et al., 2005).

Other type of commonly used tracer is the *18F-fluoride* (*18F-NaF*). This radiotracer has the characteristics of an excellent marker of bone remodeling since it gets integrated into the hydroxyapatite matrix of the bone in the sites of a bone turnover. 18F-NaF is commonly used in oncology for detection of primary osseous neoplasias or metastases, but it is also successfully applied for non-oncologic imaging (Yoshikawa et al., 2013).

MECHANISM OF ACTION

Positron emission tomography (PET) is a nuclear imaging method that provides functional data based on the three-dimensional localization of positrons emitted by radiotracers (Bushberg et al., 2012). *PET* data reflect the degree of radiation from the applied radioactive isotope, but do not provide structural information related to the patient's anatomy. Functional information based on the interaction of radiotracers at the molecular level concerning physiological processes is obtained. To facilitate the anatomical and structural localization of certain areas, *PET* is usually combined with computed tomography (CT).

In positron emission tomography we have a wide choice of transport substances, as *18 fluoride (18F)* is the most commonly used positron-emitting radionuclide. It is characterized by a two-hour half-life, making it convenient for clinical activity and easily integrating into various organic molecules in place of a hydroxyl group, most commonly included in *18F-fluorodeoxyglucose* (18F-FDG). Like glucose, *18F-FDG* is actively transported in cells from a group of structurally related transport proteins. For this reason, *18F-FDG* is an excellent marker of metabolic activity and is indispensable for the detection of neoplastic processes (Hsu PP et al., 2008). Cancer staging is the most common application of PET using *18F-FDG*. However, there is evidence to show that the concentration of *18F-FDG* increases not only in neoplastic tissue but also in areas of active inflammation, which could complicate diagnosis (Love et al., 2005).

The different colors and degrees of brightness in the CT image show the difference in glucose consumption for the respective tissue. Healthy tissue also consumes glucose, and in one study it would accumulate *18F-FDG*, but neoplastic tissue uses much more glucose, respectively *18F-FDG* will be in much higher concentrations and the corresponding area appears brighter than normal tissue (Kitson et al., 2009). PET application and availiability is still limited in the veterinary field, but there is a growing interest in this nuclear method so it will likely have a growing role in veterinary medicine not only for oncologic imaging but also for assessment of inflammation and pain.

APPLICATION

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In humans, *fluorine-18 fluorodeoxyglucose positron emission tomography* (**18F-FDG PET**) is an accurate diagnostic tool for the detection of cerebral necrosis, paraneoplastic limbic encephalitis, and various neoplasms. (Weber et al., 1999; Small et al., 2008; Meller et al., 2003; Scheid et al., 2004; Weaver et al., 2007; Czernin et al., 2002). *FDG-PET* can assess brain glucose metabolism (Fiorella et al., 2001; Lee et al., 2004), and it has a role in the detection of functional abnormalities before anatomic changes occur (Scheid et al., 2004; Weaver et al., 2007).

In human medicine, this diagnostic method is widely used in the early diagnosis of Alzheimer's disease (**Fig. 1**).

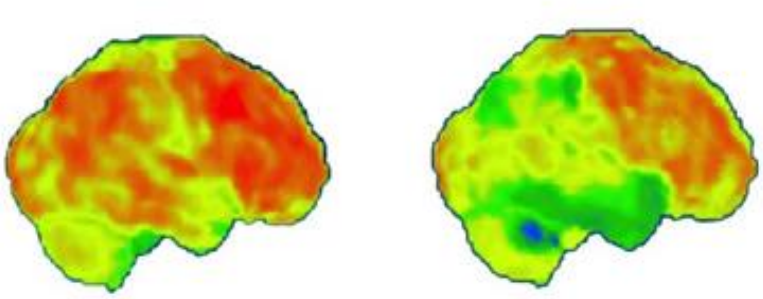

Fig. 1 - left – PET image in normal brain; **right** - image in Alzheimer's disease - an increase in green and blue colors indicates decreased brain activity (Mayo Foundation for medical education and research)

The significance of PET in dental patients using *18F-FDG* for oral cancers has become very clear (Bogsrud et al., 2006; Fischbein et al., 1998; Kubota et al., 2004; Farber et al., 1999). It has been reported that the accumulation of *18F-FDG* in the oral cavity could be caused by periodontal diseases, apical periodontitis or post-extraction wounds, but not dental caries (Kubota et al., 1992; Shimamoto et al., 2008). Nevertheless, recent studies have shown that there is a correlation between the size of bone resorption caused by periapical or periodontal inflammation and the amount of *18F-FDG* accumulation within the resorption area. These results show that, in reality, the *18F-FDG* accumulation could reflect the extent of dental inflammation and resorption (Kito et al., 2012).

Despite it is widely used in many medicine fields, the application for functional imaging to examine dental implants has not been reported in the literature. Imaging is of fundamental relevance, not only for the planning and realization of dental implant projects, but also for implant monitoring (Greenberg, 2015; Rios et al., 2017). In a study from 2018, three patients (from a total of 31) and 4 implants (of a total 121) showed localized peri-implant hypermetabolism. In all the patients presenting abnormal peri-implant activity, the implants with normal activity were clinicaly and radiogicaly normal, whereas those with hypermetabolism presented peri-implantitis. This concludes that there is a link between peri-implant hypermetabolism and peri-implantitis. Therefore, FDG PET CT could become a new tool for the assessment of peri-implant diseases (Benouaich et al., 2018).

PET CT is useful in the evaluation of patients with carcinoma of unknown primary origin before panendoscopy and biopsy, detection of synchronous second primary tumor, staging of cervical lymph node metastasis and assessing for distant metastases. In the post-treatment phase, it is clear that PET CT is recommended to assess treatment response, detect residual/recurrent tumor and rule out distant metastases (Tantiwongkosi et al., 2014).

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Several recent publications in the human literature have showed the benefits of *18F- NaF* PET imaging for non-oncological skeletal lesions (Even- Sapir et al., 2007; Fischer, 2013; Frost et al., 2013; Jadvar et al., 2015; Kobayashi et al., 2015). *18F- NaF* PET led to changes in the management of patients with obscure foot pain when compared with MRI (Fischer et al., 2010; Rauscher et al. 2015), identification of subchondral lesions of the knee not observed with MRI (Draper et al., 2012), early detection of osteoarthritis of the hip joint (Kobayashi et al., 2013) and demonstrating the efficacy of pharmacological agents targeting bone metabolism, such as biphosphonates (Frost et al., 2013). These examples suggest that *18F- NaF* PET has important clinical applications in the diagnosis and monitoring of orthopedic lesions.

POSITRON EMISSION TOMOGRAPHY IN VETERINARY MEDICINE

Positron emission tomography is a rarely used diagnostic method in veterinary medicine due to the high financial value of equipment and research. However, it has been used increasingly over the past few years, but the applications have all been limited to small animals, mostly dogs and cats (Gutte et al., 2015; Hansen et al., 2011; Guillot et al., 2015). Until recently, PET had not been performed in the horse, mainly due to poor compatibility between the physical design of conventional PET systems and horse anatomy (Selberg and Ross, 2012). Conventional clinical PET scanners are coupled to a CT gantry with the PET component located behind the CT component. The distance between the entry of the CT gantry and the PET field of view is typically too long even for imaging the distal limb of a horse. A second impediment to the development of equine PET is the large radiotracer dose necessary to achieve sufficient signal- to- noise (SNR) performance in a clinical scanner and the concern over resultant radiation exposure for imaging staff. However, in the last decade, PET technology has evolved considerably and has resulted in high resolution scanners designed for organ- specific imaging, for example breast, brain and limbs. Due to their smaller size, and in some instances portability, these systems offer much more versatility for imaging. Moreover, the higher detection efficiency of geometrically compact high-resolution scanners enables reduced injected doses for equivalent SNR performance. Using a highly sensitive portable PET system, imaging of the equine distal limb using *18F- FDG* was recently shown to be feasible (Spriet et al., 2016). Comparing the radiation exposure rate in a PET examination and scintigraphy no significant differences are observed (Spriet et al., 2018).

It is extremely important that the PET results are interpreted together with the clinical signs and combined with other diagnostic methods in order to optimize the accuracy and reduce the false-positive results (Spriet et al., 2019).

A 2013 study diagnosed oral squamous cell carcinoma in 12 cats, with the authors noting that tumors were many times more noticeable in PET scans than contrast computed tomography (CT) scans. In the same study, PET was also successfully used to identify hypermetabolic tissue suspected of being neoplastic but located outside the tumor area. In this study, there was only limited cytological confirmation of metastases, but of the three cytologically confirmed lymph node metastases, two were identified based on PET findings but were not visible on contrast computed tomography (Randall et al., 2016). There is a general tendency for PET to be more susceptible to detecting metastases than CT and MRI, but some studies have found a lack of specificity (Ng et al., 2005).

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Feline oral squamous cell carcinoma is one of the most refractory feline malignancies. Most patients die due to failure in local tumor control. Yoshikawa et al. compare gross tumor volume using *18F-FDG* vs. computed tomography (CT) for stereotactic radiation therapy planning in cats with oral squamous cell carcinoma. It was discovered that when measuring a neoplastic lesion by PET and contrast computed tomography (CT), the tumor volume was smaller in PET than it was in the CT examination, suggesting that *18F-FDG* PET is an important supplemental imaging modality in cats with oral squamous cell carcinoma due to the fact that it detects regions of possible primary tumor that were not detected on CT images (Yoshikawa et al., 2013). This statement is also confirmed by a human study, showing a lower volume of pharyngolaryngeal squamous cell carcinoma measured with *18F- FDG* PET, compared to CT and MRI, with a difference in volume ranging from 28 to 37%. Surgical correlation proves that all imaging methods overestimate the size of the tumor, but PET is characterized by the most accurate modality. High accuracy in defining the boundaries of neoplastic tissue is of particular importance for treatment planning, both surgically and in radiation therapy (Daisne et al., 2004).

There are limited reports in the veterinary literature evaluating the use of PET in non-oncological cases. However, there is evidence of successful application of this imaging method in the diagnosis of necrotizing meningoencephalitis in dogs (Eom et al., 2008). Idiopathic necrotizing encephalitis has been reported in small breed dogs, especially the Maltese, Yorkshire terrier, and pug (Kuwamura et al., 2002). Eom et al. provided evidence of glucose hypometabolism in areas of necrosis and cavitation associated with necrotizing meningoencephalitis using 18F-FDG PET on two dogs showing that this method has the potential to provide valuable diagnostic information in dogs with suspected necrotizing encephalitis (Eom et al., 2008). (**Fig. 2**)

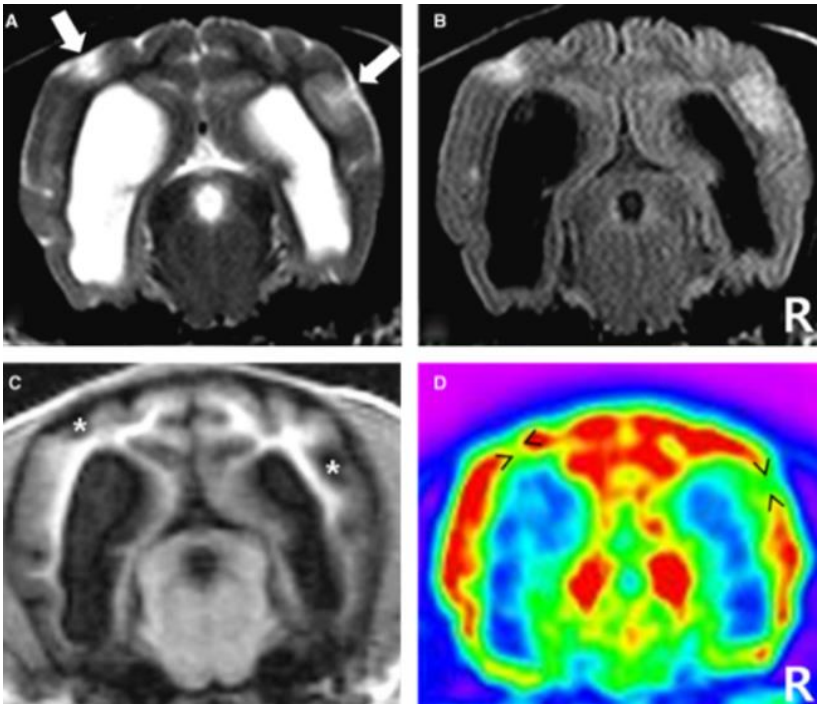

Fig. 2. (A) Transverse T2-weighted image. There are enlarged lateral ventricles. Multifocal hyperintensities in the left and right cerebral hemispheres (arrows). **(B)** Transverse fluid attenuated inversion recovery (FLAIR) image. There are multifocal hyperintensities in the cerebral hemispheres. **(C)** Transverse T1-weighted image. There are multifocal hypointensities in the cerebral hemispheres. **(D)** On transverse fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) imaging, normal metabolism of gray matter has a reddish color, but abnormal hypometabolic lesions caused by decreased glucose uptake are shown with a greenish color. (Eom et al., 2008)

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The use of 18F-FDG PET has also been described in cases of dermatitis, such as Matwichuk et al. found blastomycotic lesions in the eyes and lungs as well as in the tracheobronchial lymph nodes. Increased absorption of 18F-FDG PET has been observed in these areas without previous clinical evidence of disease. All sites of 18F-FDG PET uptake have been confirmed histologically with blastomycotic granulomas, and PET testing may be useful to determine the extent of fungal disease and detect resistant foci of infection (Matwichuk et al., 1999).

Concerning orthopedic patients, in recent years PET has been of increasing interest as a diagnostic method. This method has been proposed to assess lameness in dogs, and the PET-CT test protocol can be used successfully as a routine pelvic limb test to identify areas of congestion (or excessive glucose consumption) in muscles, tendons, and joints (Mann et al., 2016).

In 2015 veterinarians from the University of Davis, California, were the first to ever use PET to examine a horse using a prototype scanner. This represents a major breakthrough in imaging in horses, as PET scanning in horses has not been possible due to limitations in the positioning of equidae in a conventional apparatus. With the new portable design, the test can now be routinely applied as an image-diagnostic method for lameness in horses. The scanner weighs only 50 kilograms and is specially designed for veterinary use. (Fig. 3)

Fig. 3 - Left – the portable PET scanner, right - the left limb of the horse is scanned (University of Davis, California, School of Veterinary Medicine)

Over the next two years, many studies have been done on PET diagnostics in diseases of the musculoskeletal system in horses. One of the greatest achievements is the discovery of double scanning. This allows the assessment of both bone and soft tissue damage and has already been used successfully to assess complex lesions in the foot and *lig. suspensorium.* (Fig. 4)

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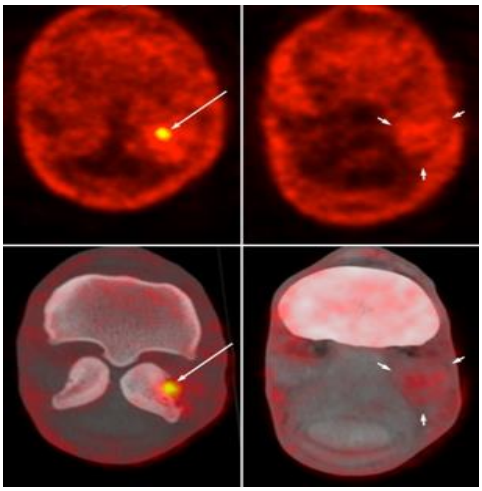

Fig. 4 – Left - there is a pronounced increased absorption of the radioisotope in the lateral proximal sesamoid bone (long arrow) and diffuse moderate absorption in the lateral branch of the lig. suspensorium (short arrows) (Rob Warren, University of Davis, School of Veterinary Medicine, California)

This preliminary data for equine PET is extremely promising and suggest several clinical applications. The first application would be cases for which radiographs, CT, MRI and/or scintigraphy have failed to identify the cause of lameness. In these cases, PET may reveal early or subtle subchondral lesions not identified with these other modalities. The second potential application would be to assess the metabolic activity of multiple lesions identified with CT or MRI, determine which are most active as the cause of lameness and institute a targeted treatment or rehabilitation plan. Finally, the functional information provided by PET could be extremely valuable for follow- up of lesions and the assessment of treatments (Spriet et al., 2018).

In another study from the University of Davis, California, the patient was a 1-year-old Labrador dog that clinically demonstrated pain and lameness in his right chest. PET examination revealed an increased accumulation of the radioisotope in the area of the right proc. coronoideus. (Fig. 5). Since the radioactive isotope accumulates in places with increased glucose consumption, the accumulation in the respective zone shows that there are active processes of bone resorption and bone remodeling (increased activity of osteoclasts and osteoblasts), which correlates with clinical signs and confirms the pathological finding.

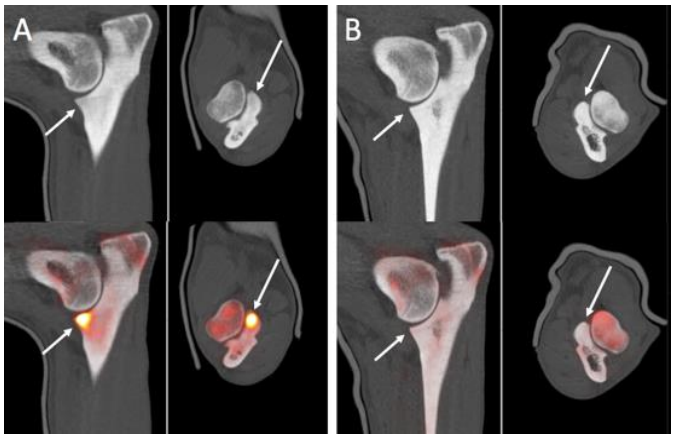

Fig. 5 (A) – right elbow area, we observe increased isotope accumulation in the area of proc. coronoideus (arrows); **(B)** – left elbow area, no increased isotope accumulation is observed (University of Davis, School of Veterinary Medicine, California)

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Despite its high accuracy and specificity, diagnosis by PET should always be accompanied by confirmatory clinical signs, paraclinical examinations, and additional imaging methods.

CONCLUSION

Positron emission tomography is an extremely sensitive and modern imaging method with very high possibilities for early detection of various pathological processes. The functional properties of the technique are applied not only for the diagnosis of the metabolic activity of tumors but also for the assessment of bone remodeling, the presence of inflammation, pain, and others. With the advancement of technology, lowering the cost, and increasing the availability of high-resolution PET scanners, this method has the potential to become the gold standard in diagnostic imaging not only in humans but also in veterinary medicine.

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