The Origins of Equine PET

Positron emission tomography (PET) and horses? The question was first brought up in 2013, when technological evolution introduced compact PET scanners, which would potentially allow equine limb imaging. PET is a cross-sectional nuclear medicine imaging modality; this means that similar to scintigraphy, the patient is injected with a radiotracer, but instead of obtaining 2-dimensional images, data are acquired in 3 dimensions, allowing for multiplanar reformat and volume rendering. The tracer most commonly used in human PET imaging is a radioactive glucose, 18F-fluorodeoxyglucose (18F-FDG), but other tracers are also available. PET provides information on changes occurring at the molecular level that might precede structural changes. For this reason, PET is considered “functional imaging,” sometimes also referred to as “molecular imaging.” As PET is primarily known for its oncological applications, its use in equine imaging was surely not obvious, with neoplasia being extremely uncommon in the equine distal limb. However, anecdotal human reports suggested application of 18F-FDG for tendinopathy imaging. Also, laminitis was recognized as a condition where assessment of local glucose metabolism could be pertinent. With these potential applications in mind, the first equine PET scans were performed at University of California (UC)-Davis in April 2015, with 3 research horses imaged with 18F-FDG for an exploratory study. As the first 3 horses were just imaged with 18F-FDG, a manuscript entitled “Evaluation of 18F-fluoride PET/MR and PET/CT in patients with foot pain of unclear cause” was published. 18F-fluoride (18F-NaF) is an excellent osseous tracer, accumulating at sites of bone turnover, where the hydroxyapatite matrix is exposed. The reported study was on human patients, but “foot pain of unclear cause” sure sounds very close to home, for any veterinarian working on equine lameness! In a heartbeat, it was decided that an equine 18F-NaF PET exploratory study was needed. The feet of 3 research horses with associated lameness were imaged with 18F-NaF PET by July 2015. The findings in these 3 cases suggested a wide range of applications for 18F-NaF PET from distal phalanx and navicular bone assessment to evaluation of subchondral bone and enthesis. The development of a dedicated PET scanner to image the distal limb of horses with standing sedation led to new applications, where PET is used as a first-line advanced imaging tool, in particular for foot, fetlock, and tarsal imaging. A complimentary clinical review of when to seek advanced imaging in equine athletes can be found in the companion Currents in One Health by Garrett in the July 2022 issue of the Journal of American Veterinary Medical Association. The clinical use of PET in human medicine remains mainly focused on oncological imaging; however, numerous small-scale clinical studies have demonstrated valuable applications for musculoskeletal imaging. These include assessment of foot and ankle pain, osteoarthritis of the knee and hip, osteoporosis, response to bisphosphonates, and chronic osteomyelitis. The use of musculoskeletal PET in dogs remains quite limited, but a few studies have recently been published and clinical interest is growing. The available research data and clinical applications between horses, humans, and dogs are currently quite disparate, but all suggest great promises for earlier and more accurate clinical diagnosis, as well as better understanding of pathophysiology and response to treatment. Translating knowledge from a species to another will undoubtedly help further growth of musculoskeletal PET.
of subchondral bone, enthesis, or dystrophic mineralization. One of the most striking images was the presence of focal $^{18}$F-NaF uptake at the sagittal ridge of the flexor surface of the navicular bone of an older Quarter-Horse mare (Figure 1). Computed tomography (CT), standing low-field (0.3 T) magnetic resonance imaging (sMRI), and bone scintigraphy were also performed on the same foot, but none of these modalities identified any abnormalities. The opposite foot of this horse had a large resorptive lesion of the navicular bone flexor surface appreciated on all modalities. It was concluded that PET had detected early findings of a bilateral condition that other imaging modalities were not able to detect.

The results of this exploratory study led to the establishment of a clinical equine PET program at UC-Davis in August 2016. In addition to the early use for distal limb imaging for lameness assessment, a comparative imaging study of the Thoroughbred racehorse fetlock was undertaken. This study confirmed the promising results from the exploratory study and demonstrated that $^{18}$F-NaF PET was particularly well suited for assessment of stress remodeling of the racehorse fetlock. $^{18}$F-NaF PET detected sites of increased uptake where abnormalities were not recognized with CT, sMRI, or scintigraphy.

The major limitation at this stage was that all scans had been performed under general anesthesia. For proper signal acquisition, the PET detectors need to be arranged in a full ring, circling the area to be imaged. With funding support from the horse racing industry, an equine-dedicated PET scanner (LONGMILE Veterinary Imaging, BrainBiosciences Inc) was designed with a horizontal, freely openable detector ring. This scanner was first validated at UC-Davis in October 2019, prior to being installed at Santa Anita Park (Arcadia, CA) in December 2019. Two similar scanners were later installed at the University of Pennsylvania and UC-Davis in 2020 and 2021, respectively. The ability to perform PET scans on horses without the need for general anesthesia has exponentially increased the use of the modality. In 5 years of performing PET in horses that were under general anesthesia at UC-Davis, 150 studies were performed. Currently, each of the 3 sites with the ability to perform PET in standing horses images over 150 cases per year. In addition to these 3 scanners, at least 4 other equine clinics will be equipped with equine PET in the United States by the end of 2022. In an era where advanced imaging through scintigraphy, CT, and MRI is increasingly available, what will be the role for equine PET? How does this

Figure 1—Images of the right front foot of a Quarter Horse mare with a resorptive lesion of the navicular flexor surface on the opposite foot. The $^{18}$F-sodium fluoride ($^{18}$F-NaF) positron emission tomography (PET) (A) showed focal increased uptake, confirmed to be at the flexor surface of the navicular bone with fusion with computed tomography (CT) (B). The CT (C), magnetic resonance imaging (MRI) (D and E), and scintigraphic (F) images did not identify any abnormality of the navicular bone.
newcomer compete with the other protagonists in the equine musculoskeletal imaging race? The strength of PET is its complementarity with the other imaging techniques. PET provides functional information that complements structural information provided by other modalities. The fairly simple logistics compared with scintigraphy and the ability to quantify changes further add values to this modality.

**Equine PET in 2022**

There are currently 3 main applications of PET in horses: an enhanced alternative to scintigraphy, an addition to CT or MRI, or a first-line advanced imaging to complement the routine imaging obtained thorough radiography and ultrasound.

**18F-NaF PET as enhanced bone scintigraphy**

18F-NaF PET relies on similar principles as bone scintigraphy with uptake of radioactive tracer at sites of exposed apatite matrix but benefits from providing cross-sectional information and a higher spatial resolution than scintigraphy. For these reasons, the racehorse fetlock, commonly imaged with scintigraphy, was identified as a pertinent application to assess 18F-NaF PET in horses. An exploratory study in 9 Thoroughbred racehorses demonstrated that 18F-NaF PET identified more abnormalities than scintigraphy and was able to further characterize lesions. These findings were further confirmed in a larger scale study including 33 horses for a total of 72 fetlocks imaged with both 18F-NaF PET and bone scintigraphy. This was the first PET study performed on standing horses. 18F-NaF PET again identified more sites of increased radiopharmaceutical uptake than scintigraphy. This was particularly true in the proximal sesamoid bones. 18F-NaF PET was also able to better characterize the sites of increased uptake (Figure 2). Of particular interest was the identification of focal increased uptake at the dorsal abaxial aspect of the medial proximal sesamoid bone, a site where remodeling has been associated with fracture of the sesamoid bone leading to catastrophic breakdowns in racehorses.

Another advantage of PET over scintigraphy is the ability to quantify the severity of a lesion, using standardized uptake values (SUV). SUV is a measurement of the amount of radioactivity in a region of interest, normalized to the administered dose corrected for the decay, and the weight of the patient. A grading system to assess the severity of lesions in racehorses has been validated in a longitudinal study where 25 racehorses were scanned for follow-up at 6 and 12 weeks after a fetlock lesion was diagnosed with 18F-NaF PET. The ratio between the maximal SUV (SUVmax) of a lesion and the bone background was used: grade 1 was attributed when Lesion SUVmax < 2 X background SUVmax; grade 2 when Lesion SUVmax was > 2 X but < 3 X background SUVmax; and grade 3 when Lesion SUVmax > 3 X background SUVmax. It was found that grade 3 lesions took longer to resolve and were less likely to resolve than lower grade lesions. This grading system is now used to help decide the amount of time-off training needed. Several horses have been imaged multiple times not only for following up healing during layup but also for monitoring possible recurrence when back in training.

The racehorse fetlock has definitely been the area most commonly imaged with 18F-NaF PET, with over 300 horses imaged in California in the last 2 years, but carpus and suspensory origin are also regularly imaged in the racehorse population. 18F-NaF PET has also been used in the sport horse population to further characterization of bone scintigraphy findings (Figure 3).

**18F-NaF PET fused with CT or MRI**

Outside of the racehorse population described above, PET has been most commonly combined with CT or sMRI. When PET was performed under general anesthesia, horses were systematically also imaged with CT. Although image acquisition for each modality was performed with a different scanner, coregistration of the 2 data sets for fusion can be performed with a dedicated software (Galatea, BrainBiosciences Inc.). 18F-NaF PET has been particularly helpful at...
identifying active enthesopathy that was not necessarily identified on CT or MRI. This was for example the case with enthesopathy of the collateral ligament of the distal interphalangeal joint, but it also helped identify active remodeling at the site of attachment of the chondrosesamoidean ligament on the distal phalanx. This condition had not been commonly recognized before. The PET findings suggest it is commonly associated with other lesions of the navicular apparatus, but in some cases the chondrosesamoidean enthesopathy was the primary lesion. PET is also commonly used for imaging proximal suspensory enthesopathy. Combined with CT, PET helped determine active from inactive lesions as illustrated in Figure 4.

The functional characteristics of PET imaging are also a great resource for assessment of subchondral remodeling. 18F-NaF PET detects changes in the compact subchondral bone plate prior to changes being apparent on CT or MRI. A PET/CT study in the sport horse fetlock demonstrated that PET recognized abnormality in the subchondral bone more commonly than CT and that these changes were associated with the clinical status of the patient. The ability of PET to distinguish between active and inactive lesions is also very pertinent for subchondral imaging. For example, in the fetlock of an off-the-track thoroughbred, use of PET was able to distinguish chronic inactive injuries from current active subchondral remodeling (Figure 5).

18F-FDG PET fused with CT or MRI

Although 18F-NaF is by far the most commonly used tracer in equine PET, 18F-FDG has a very interesting role to play in the assessment of the activity of soft tissue lesions. The value of 18F-FDG PET for assessment of the deep digital flexor tendon first recognized in the initial PET exploratory study has been confirmed in a comparative imaging study involving 8 horses with deep digital flexor tendon injuries. The comparison with arterial contrast enhanced CT images and MRI T2-weighted images confirmed the ability of 18F-FDG PET to detect active deep digital flexor tendon lesions. The ability to quantify the 18F-FDG uptake using SUV.
suggesting a chronic inactive lesion. Of imaging on standing horses, now PET can be used. Advanced imaging, such as CT or MRI. With the ease of imaging on standing horses, now PET can be used. In addition to other advanced imaging, such as CT or MRI. With the ease of imaging, PET can be used. Anesthesia was required, PET was used as an advanced imaging technique, in order to help decide whether or not CT or MRI is indicated. The most common example would relate to imaging for distal limb lameness. As diagnostic analgesia may have limitations in localizing the source of pain, imaging of the fetlock might be indicated even for lameness improved with a palmar digital or sesamoid abaxial nerve block. As both feet and both fetlocks can be imaged within 20 minutes with PET, this provides valuable information on deciding whether both feet and fetlocks should be imaged with MRI and whether unilateral or bilateral MRI study is indicated. Tarsal imaging has also become one of the most common PET studies performed in the standing horse. As radiographs of the tarsus have limited correlation with clinical signs and as standing MRI or CT imaging of the tarsus is quite challenging, PET has been used as the first advanced imaging modality. Depending on the findings as illustrated in Figure 7, a decision to potentially anesthetize the horse for further advanced imaging can be made.

**Musculoskeletal PET across Species**

**Musculoskeletal PET in human medicine**

The use of PET in human medicine remains largely dominated by oncological imaging. The majority of the 18F-NaF studies\footnote{6,20,21} relate to assessment of bone metastasis; however, in the last 10 years, there has been an increasing number of small-scale clinical studies\footnote{22–25} looking at use of 18F-NaF PET for nonmalignant osseous lesions. Early work\footnote{26,27} looked at postoperative assessment of implants used in knee and hip surgery. The value of 18F-NaF PET was further confirmed more recently in a larger scale study\footnote{28} with 41 patients, where PET was found helpful for early adjustment of surgical fixation devices in order to improve healing of complex fractures. The use of both 18F-NaF and 18F-FDG was found helpful for surgical planning in cases with chronic osteomyelitis.\footnote{29} 18F-FDG was considered superior to 18F-NaF for assessment of sepsis associated with femoral prostheses.\footnote{30}

Back pain has been assessed with 18F-NaF PET through several studies\footnote{31–34} and was found helpful in a variety of conditions including spondylosis, fractures, osteitis pubis, and sacroilitis. 18F-NaF PET of the foot and ankle is another topic that was evaluated through several studies. In addition to the case series of feet with “pain of unclear cause,”\footnote{35} a comparative bone scintigraphy and 18F-NaF PET study of the foot and ankle demonstrated that PET provided clinically relevant information on cases where bone scintigraphy was inconclusive. More recently, SUVmax, SUVmean, and total lesion activity, a product of

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**Figure 5** — Images of the left hind fetlock of a 14-year-old off the track Thoroughbred, used for eventing and presenting with left hind lameness. On the fused 18F-NaF PET CT images (top row), increased uptake was appreciated at the medial aspect of the subchondral bone of the proximal phalanx (long arrows), the dorsomedial metatarsal condyle (arrowhead), and the dorsal aspect of the medial proximal sesamoid bone (short arrow) (medial is to the left). There was no CT abnormality appreciated at these sites of increased uptake. A focal subchondral defect (bottom row) was appreciated in the lateral aspect of the subchondral bone of the proximal phalanx (black arrows), but no uptake was appreciated on 18F-NaF PET, suggesting a chronic inactive lesion.
metabolic target volume and SUVmean, were found to provide considerable information in the assessment of impairment of traumatized ankles.\textsuperscript{36}

Osteoarthritis research is another area where PET appears promising. Body mass index was found to have an effect on \textsuperscript{18}F-FDG and \textsuperscript{18}F-NaF uptake in the knee and hip, likely due to increased joint inflammation and degeneration.\textsuperscript{37,38} Association between subchondral and cartilage changes in early knee osteoarthritis was confirmed with PET, as increased \textsuperscript{18}F-NaF subchondral bone uptake was associated with degenerative articular cartilage changes.\textsuperscript{39} \textsuperscript{18}F-NaF PET may detect abnormalities in the subchondral bone that are not recognized with MRI.\textsuperscript{40} Higher SUVmax values were found to be associated with pain in patients with hip osteoarthritis.\textsuperscript{41} SUVmax was also found as the best predictor of pain worsening in hip osteoarthritis.\textsuperscript{42} A high-resolution PET scanner has been used with \textsuperscript{18}F-FDG to assess disease activity in rheumatoid arthritis. This appeared as a promising tool for understanding the pathogenesis of the disease and help with therapy selection.\textsuperscript{43,44}

\textsuperscript{18}F-NaF PET has been used for assessment of osteoporosis\textsuperscript{45–47} and response to treatment with bisphosphonates.\textsuperscript{48–50} Decrease in SUV after treatment with bisphosphonates was confirmed in several studies.\textsuperscript{48–50} There is limited information regarding use of \textsuperscript{18}F-NaF for assessment of physiological bone remodeling associated with athletic activities, but an increased \textsuperscript{18}F-NaF uptake was identified in all bone tissues of the knees immediately after exercise.\textsuperscript{51} The authors\textsuperscript{51} concluded that PET was a promising diagnostic tool in imaging of biomechanics.

\textsuperscript{18}F-FDG is less commonly used than \textsuperscript{18}F-NaF for musculoskeletal imaging, but a few case reports\textsuperscript{52–54} have shown potential applications of \textsuperscript{18}F-FDG for assessment of neuropathic pain.\textsuperscript{55}

**Musculoskeletal PET in dogs**

The majority of PET publications in dogs relate to oncology, but a few musculoskeletal studies\textsuperscript{55} were recently published. Kinetics of \textsuperscript{18}F-NaF uptake was assessed in 4 normal dogs. A clinical study\textsuperscript{56} in 12 dogs with elbow pain demonstrated that PET could identify uptake in areas where no abnormalities

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**Figure 6**—Images of the left hind suspensory origin (A–I) and proximal aspect of the body of the suspensory (J–R) of a 12-year-old Warmblood. A dual tracer \textsuperscript{18}F-NaF and \textsuperscript{18}F-fluorodeoxyglucose (\textsuperscript{18}F-FDG) PET scan was performed. \textsuperscript{18}F-NaF images (C and L) were obtained first. \textsuperscript{18}F-FDG was then injected during the same anesthesia and combined tracer images (F and O) were obtained. The \textsuperscript{18}F-NaF images were subtracted from the combined tracer images to obtain \textsuperscript{18}F-FDG-like images (I and R). A, D, G, J, M, and P—CT images (bone window [A and J] and soft tissue window [D, G, M, and P]). B, E, H, K, N, and O—PET/CT fused images. Lateral is to the left. There was marked focal increased \textsuperscript{18}F-NaF uptake (long arrow) at the lateral planlar proximal aspect of the third metatarsal bone, visible in both \textsuperscript{18}F-NaF (B and C) and combined \textsuperscript{18}F-NaF/\textsuperscript{18}F-FDG (E and F) images, at the attachment of the suspensory ligament, with associated contour irregularity on the CT, indicative of active enthesopathy. There was no abnormal \textsuperscript{18}F-FDG uptake at the suspensory origin. The focal uptake adjacent to the second metatarsal bone (arrowhead) was vascular uptake. The bone uptake was not apparent on the subtracted images (H and I). There was moderate increased \textsuperscript{18}F-FDG uptake at the lateral aspect of the body of the suspensory ligament (short arrow), associated with loss of normal architecture of the suspensory ligament on CT (M and P) appreciated on both the combined \textsuperscript{18}F-NaF/\textsuperscript{18}F-FDG (N and O) and the subtracted (Q and R) images. This indicated an active suspensory body desmitis. The arrowheads indicate incidental vascular uptake.
were recognized on CT. PET scores had a higher correlation with clinical score than CT scores. An example of $^{18}$F-NaF PET/CT in a dog elbow is presented in Figure 8. $^{18}$F-FDG has also been used in clinical patients with lameness. In a study with 25 patients, $^{18}$F-FDG PET detected soft tissue lesions not appreciated on contrast CT; these included flexor carpi ulnaris muscle tear, psoas major myopathy, and tarsal desmopathy.

A few university centers have started offering musculoskeletal PET in dogs as a clinical service. The indications include providing further information when CT or MRI is inconclusive, assessing activity of findings found on other imaging modality, or providing functional information to help localize the site responsible for the lameness (Figure 9).

The Future of Musculoskeletal PET

Over 15 years ago, it was questioned whether molecular imaging was "the latest fad or the new frontier?" The amount of literature
published since then suggest it was not a fad, but there are still a lot of opportunities for further growth.

The comparison between the work done in humans, horses, and dogs brings some interesting perspectives. The racehorses represent the first large population of athletes of any species, animal or human, that have benefited from longitudinal monitoring of stress-related injuries through PET. The clinical use in horses is quickly expanding for a range of indications, involving both bone and soft tissues. Veterinary medicine has the advantage to be able to localize on physical examination. There was marked focal increased uptake of the right caudal humeral head (arrows). The left shoulder and both elbows (arrows) were within normal limits. The CT images (not provided) confirmed an osteochondrosis lesion of the right humeral head.

One of these areas of interest would be the work done with bisphosphonates. Although the applications for use of bisphosphonates in horses are fairly different from the applications in human medicine, $^{18}$F-NaF could be an interesting tool for assessment of the effect of bisphosphonates in osseous resorptive lesions in horses.

The work on assessment of chronic osteomyelitis could be very pertinent to apply to horses, to assist in patient management and surgical planning in various cases of sepsis.

Canine musculoskeletal PET is surprisingly trailing the field, behind humans and horses both in term of numbers of publications and clinical use. The opportunities are however many. $^{18}$F-NaF PET appears very promising for elbow imaging and would likely apply to other joints such as the hip and the knee. The potential reported in human studies for assessment of healing of complex fractures or monitoring for sepsis of implants would definitely apply to small animal orthopedic surgery. Also, coupling both $^{18}$F-NaF and $^{18}$F-FDG PET to MRI in dogs for assessment of neck and back pain could considerably improve the clinical management of these cases.

The question now is where does PET fit in the competition with other advanced imaging modalities? PET is ultimately more a team player than a foe. The only true competition would be with bone scintigraphy. $^{18}$F-NaF PET ultimately replacing bone scintigraphy in humans has been suggested. The same will likely apply in dogs. In horses for distal limb imaging, $^{18}$F-NaF PET outperforms scintigraphy, but for equine proximal limb and axial skeleton imaging, bone scintigraphy remains the only contender. PET definitely shines in combination with CT and MRI, where it helps in interpreting clinical meaning of findings or provides additional information. A novel use of PET seen in equine imaging is the role as a screening modality, as a first-line advanced imaging tool, to help decide on further imaging steps. In these regards, the arrival of PET in the musculoskeletal imaging field is exciting news; more than taking down other contenders, PET strengthens them and provides additional strategies. Ultimately, improved patient care will be the winner of this competition.

In summary, musculoskeletal PET imaging is an actively growing field that will have a major role in the future of health care, both in human and veterinary medicine. As different applications have been developed in different species, translating knowledge from a species to another will undoubtedly contribute to further rise of musculoskeletal PET.

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