PET/MRI in Infection and Inflammation

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PET/MRI in Infection and Inflammation

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Hybrid positron emission tomography/magnetic resonance imaging (PET/MR) systems are now more and more available for clinical use. PET/MR combines the unique features of MR including excellent soft tissue contrast, diffusion-weighted imaging, dynamic contrast-enhanced imaging, fMRI and other specialized sequences as well as MR spectroscopy with the quantitative physiologic information that is provided by PET. Most of the evidence of the potential clinical utility of PET/MRI is available for neuroimaging. Other areas, where PET/MR can play a larger role include head and neck, upper abdominal, and pelvic tumours. Although the role of PET/MR in infection and inflammation of the cardiovascular system and in musculoskeletal applications are promising, these areas of clinical investigation are still in the early phase and it may be a little longer before these areas reach their full potential in clinical practice. In this review, we outline the potential of hybrid PET/MR for imaging infection and inflammation. A background to the main radiopharmaceuticals and some technical considerations are also included.
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Introduction

Positron emission tomography (PET) developed in the 1970s, was implemented in clinical practice in the late 1980s and early 1990s.[1,2] Hybrid PET/computed tomography (PET/CT) imaging systems were developed with the aim of utilizing high-resolution CT for attenuation correction purposes as well as for anatomical localization of the molecular information provided by PET. The development of hybrid PET/magnetic resonance imaging (PET/MR) systems has been far slower than the development of PET/CT. This has been mainly due to technical issues related to electromagnetic interference, leading to artifacts and signal-to-noise reduction in the PET or MR images.[3] Therefore, MR-compatible PET scanners were developed based on fiberoptic coupling of the scintillator and the photodetectors[4] or the replacement of photomultiplier technology with magnetic field Y-insensitive avalanche photodiodes or silicon photomultipliers.[5-7] A PET/MR system capable of concurrent dynamic PET and MR scanning allowing the use of MR information for dynamic motion correction during PET data acquisition has been introduced recently.[3,7] In addition to the technical consideration, equipment costs, operational costs and related logistics probably also account for the slow adoption of the method; from 2010, only about 70 systems have been installed worldwide.[2,8] In addition to a lack of ionizing radiation which makes PET/MR very appealing for application in the paediatric population, MR offers superior soft tissue contrast compared to CT even without the use of contrast agents, particularly in tissues such as in cartilage, and bone marrow.

MR can also provide measurement of other factors that can characterize disease and their patient-specific biological properties, including blood vessels generated by a tumour, perfusion properties through dynamic contrast enhancement imaging and[9] cellular membrane integrity using diffusion weighted imaging.[10] Real-time image acquisition enables temporal co-registration of dynamic PET data acquisition and anatomical/functional MR data, providing a range of functional information, e.g. perfusion (micro vessel density, vessel leakage, etc.), diffusion (cell density, microstructure, etc.), and metabolism (cell death, proliferation, etc.)[11] to study the complex pathogenesis in infectious and inflammatory disorders.

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In this review, we summarize PET imaging of molecular processes in inflammatory and infectious diseases and outline the potential of PET/MR for these applications. A background to the main radiopharmaceuticals and some technical considerations also are included.

Focus on Radiopharmaceuticals: Old and New Probes

Radiopharmaceuticals used in inflammation and infection imaging have been developed to target specific phase of the pathophysiology of each process. Therefore, knowledge of the specific pathophysiology pathways will facilitate an understanding of their applications as well as their advantages and limitations.

PET Radiopharmaceuticals

Commercially available PET tracers have been used for imaging infection and inflammation. The two most widely applied radiotracers for infection and inflammation imaging are ^{18}F-fluorodeoxyglucose ([^{18}F]FDG) and ^{18}F-sodium fluoride ([^{18}F]NaF). [^{18}F]FDG PET is a widely used marker for glucose metabolism and is sensitive to areas of acute phase cellular response (neutrophils or PMNs),[12] but it's not limited to these cells subtypes, as monocyte-macrophages,[13] and CD4$^+$ T-lymphocytes[14] also are [^{18}F]FDG-avid. The molecular mechanism of [^{18}F]FDG uptake into cells relies on the presence of membrane glucose transporters, GLUT. Once internalized into the cells, [^{18}F]FDG is phosphorylated by hexokinase under kinetics similar to those of glucose. However, after the chemistry of the FDG prevents any further the metabolism or catabolism of the phosphorylated [^{18}F]FDG, which remains effectively trapped in the cell cytoplasm. Due to the variety of conditions that present high glucose metabolism and, consequent high [^{18}F]FDG uptake the differential diagnosis may be difficult and false-positive results should be always considered.

[^{18}F]NaF is a long recognized bone-seeking agent that is able to probe bony remodelling. [^{18}F]NaF was first recognized as a bone-seeking agent in 1962[15] and approved for PET imaging by the United States Food and Drug Administration (FDA) in 1972. The mechanism of skeletal uptake of [^{18}F]NaF is based on ion exchange.[16] Bone tissue is continuously renewing itself through remodelling at the bone surface. ^{18}F ions exchange with hydroxyl ions on the surface of the hydroxyapatite to form fluoroapatite.[17] This exchange occurs at a rapid rate; however, the actual incorporation of ^{18}F ions into the crystalline matrix of bone may take days or weeks. Uptake of [^{18}F]NaF is a function of osseous blood flow and bone remodelling. [^{18}F]NaF uptake on PET images are interpreted as processes that increase exposure of the surface of bone and provide a higher availability of binding sites, such as osteolytic and osteoblastic processes.[18] ^{8}F-sodium fluoride has been also used to identify areas of microcalcification in atherosclerotic plaque in vivo. Fluoride was shown to colocalize closely and preferentially bind to pathological mineralization, and the increased surface area of microcalcification relative to macrocalcification resulted in increased tracer uptake.[19] [^{18}F]NaF uptake may occur at sites of macrocalcification, but distinct areas of [^{18}F]NaF uptake and macrocalcification occurring in isolation demonstrated that [^{18}F]NaF uptake reflects the active mineralization process in microcalcification rather than simply the burden of macrocalcification.[20] Plaque imaging is very promising and challenging application of PET/MR systems for the potential of identifying characteristics for the vulnerability of a plaque such as degree of stenosis, presence of thin cap with a large lipid core, endothelial denudation with superficial platelet aggregation, fissured/injured plaque and active inflammation.[21,22] In addition to [^{18}F]FDG and [^{18}F]NaF there are several other potential radiopharmaceuticals for the identification of plaque inflammation/vulnerability such as those targeting macrophage-driven inflammation (somatostatin receptor analogues, ^{18}F-fluoromethylcholine/^{11}C-choline, ^{68}Ga-pentixafor, ^{11}C-PK11195) and inflammation and neoangiogenesis (integrin $\alpha_V\beta_3$)[23,24]

While radiolabelled granulocytes (WBC, Fig. 1) are a common clinical practice with SPECT applications, tracking WBC *in vivo* with PET using the positron emitting in still in the research phase. The short physical half-life of ^{18}F, which has been used in the very first studies, is not suitable for late time imaging acquisition. In addition, non-specific uptake was observed when [^{18}F]FDG is used to label activated WBC mainly as a consequence of high efflux rate of [^{18}F]FDG shortly after the radiolabelling.[25] Different approaches have been developed for tracking radiolabelled leukocytes *in vivo* with PET using longer half-life isotopes such as copper-64 (^{64}Cu, $t_{1/2}$ = 12.7 h) and zirconium-89 (^{89}Zr, $t_{1/2}$ = 78.4 h). Cationic [^{64}Cu]$^{2+}$ requires a chelate to transport it into cells; [^{64}Cu]-pyruvaldehyde-bis(N^4-methylthiosemi-carbazone), [^{64}Cu]-polyethylenimine and [^{64}Cu]-loaded magnetic nanoparticles have been reported for WBC labelling.[26-28] [^{64}Cu]-PTSM proved to be superior to [^{18}F]FDG-labelled leukocytes with a higher and more reproducible labelling efficiency.[29] ^{89}Zr-labelled nanoparticles have been used for *in vivo* macrophage imaging (dextran nanoparticles)[30] for *in vivo* cell trafficking with PET ([^{89}Zr]-oxinate$_4$)[31] and for radiolabelling mixed human leukocytes ([^{89}Zr]-loaded chitosan nanoparticles.[32] The highest labelling efficiency with ^{89}Zr was observed with nanoparticles built from 190 to 310 kDa, and after a fast initial adhesion of the [^{89}Zr]- chitosan nanoparticles to the cell membrane a partial release was observed, leading to only a fraction of nanoparticles being internalised into the cell.[32]

Many other radiopharmaceuticals have been investigated for PET infection and inflammation imaging (Fig. 1) whereas for some of them only preliminary clinical data are currently available. For example, synovial angiogenesis in patients with rheumatoid arthritis (RA) was accomplished using [^{68}Ga]Ga-PRGD$_2$.[33] The elevated agent uptake was detected in the sites of active inflammation, rich neovasculaturization, and physiological integrin receptor expression, while no tracer accumulation was detected in axillary lymph nodes with reactive hyperplasia and

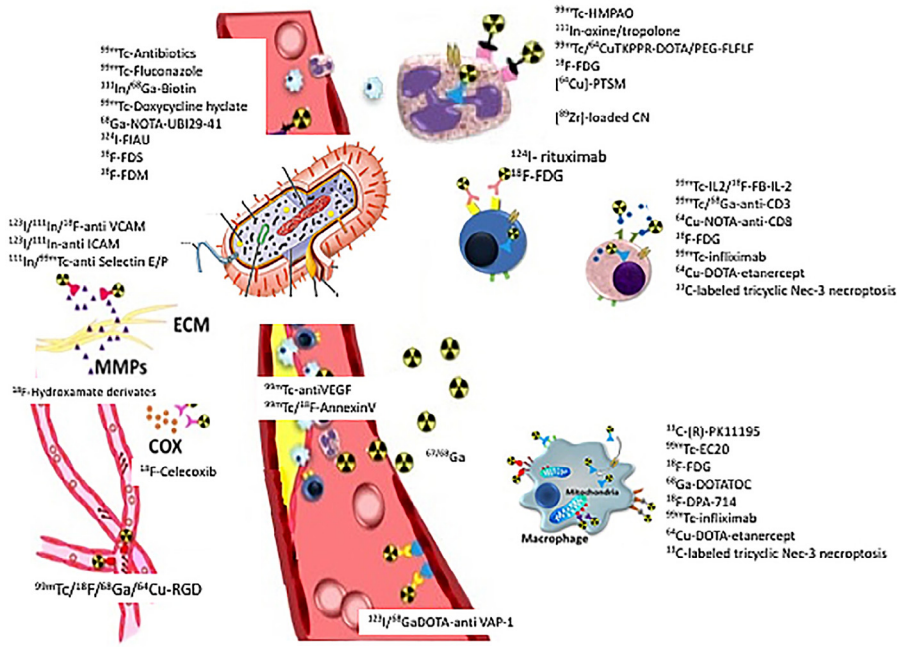

Figure 1 Schematic representation of possible target of inflammation (Adapted from Theranostics 2013;3(7):448466).

strenuous skeletal muscles. [^{68}Ga]Ga-pentixafor for detection and quantification of CXCR4 receptor density has been used for imaging chronic infection of the bone, such as osteitis/osteomyelitis of peripheral bone, osteomyelitis of the maxilla and infected endoprostheses.[34] [^{18}F]fluoro-PEG-folate was investigated in patients with clinically active RA[35] providing the same positive results of the Tc-labelled folate moiety who showed accumulation in inflamed hand and foot joints of rheumatoid arthritis as compared to nonarthritis patient's hands and feet [36]. Iodine-124 1-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-iodouracil (^{124}I-FIAU) is an example of a PET probe for bacterial infections, being a substrate for the native thymidine kinase from a wide variety of bacteria. A pilot study on musculoskeletal bacterial infections showed increased uptake of the radiopharmaceuticals in septic native joints, in prosthetic joints and in soft tissues.[37] However, further experience with [^{124}I]FIAU PET/CT imaging argues against its potential as a robust imaging tool for PJI diagnosis. The specificity for bacterial infection was suboptimal. Metal artefacts in CT images resulted in pronounced PET signal localized to the prosthetic joint attributable to attenuation correction artefact, making the unequivocal detection of bacteria-specific uptake very challenging, particularly in cases where only a unilateral prosthesis was present.[38]

PK11195, a target agent that binds to the peripheral benzodiazepine receptor (PBR), a protein highly expressed in activated cells of the mononuclear phagocyte lineage, has been used for their clinical evaluation.[39] Indeed, since the early 1980s, [^{11}C]PK11195 has been used for PET imaging of inflammatory diseases in the human brain on the basis of the low expression of PBRs in normal brain tissue and high expression in activated microglia, the resident phagocytes in brain tissue, during neuroinflammation.[40]

A very interesting novel approach based on the development of selective metabolic probes that are substrate for specific strains have recently renewed the interest in pathogen-specific imaging agents. In fact, while traditional approaches have been based on radiolabelling existing antibiotics (i.e. ciprofloxacin) or antimicrobial peptides (i.e. ubiquicidin)[41] designed to kill or disable bacteria at very minimal concentrations, thus potentially limiting their effectiveness as a radiotracer due to lack of signal amplification, researchers tested almost 1,000 radiolabelled small molecules as substrates for essential metabolic pathways in bacteria. Out of that, they identified 3 novel, nontoxic analogues of U.S. Food and Drug Administration (FDA)–approved compounds, PABA, D-mannitol and D-sorbitol and synthesized ^{3}H-2-F-PABA, ^{3}H-2-F-mannitol, and [^{18}F]fluorodeoxysorbitol ([^{18}F]FDS).[42] *In vitro* and *in vivo* studies demonstrated that [^{18}F]FDS avidly accumulates in *Enterobacteriaceae* infection foci, with little uptake in mammalian cells, sterile inflammation foci, or infection due to other bacteria species.[43] [^{18}F]FDS holds tremendous potential for identifying and monitoring known or suspected infection caused by *Enterobacteriaceae*. In the first biodistribution study in healthy human volunteers,[44] after [^{18}F]FDS administration, radioactivity was initially visualized in the vascular compartment and then rapidly distributed to the liver and kidneys. The radiotracer was mainly excreted through the urinary system. Radioactivity could be visualized in the urinary bladder as early as 5 min after [^{18}F]FDS injection was eliminated through the kidneys mainly within 3 hrs. A small portion of the radiotracer was cleared into the gut through the hepatobiliary system. Segmental accumulation of [^{18}F]FDS was observed in the small intestine. The gut radioactivity gradually moved towards the terminal ileum and finally into the ascending colon by the end of acquisition. The liver, spleen, and breasts demonstrated moderate

uptake, while the brain, lungs, thyroid, bone marrow, adrenal glands, and pancreas revealed only mild uptake.

Bimodal Imaging Agent

Nowadays, even though there are many radiopharmaceuticals and contrast media available there is not the possibility of using a single probe for the simultaneous acquisition of PET/MRI. Therefore, the only way to exploit this interesting possibility is the administration of a cocktail of tracers (i.e. [^{18}F]FDG for PET and Gd-DTPA for MRI at the same time). The basic idea of having a bimodal imaging agent is that by having two imaging reporters, the properties of both modalities can be synergistically combined. However, the obvious limitation is the different sensitivities of the two imaging techniques. In fact, whereas nuclear medicine techniques (i.e. PET and SPECT) have very high sensitivities (i.e. nanomolar or lower concentrations of imaging agent required), MRI has very low sensitivity (i.e. millimolar concentrations required). This enormous difference makes the addition of MRI reporters to radiotracers unrealistic. On the other hand, the addition of radionuclides to a MRI contrast agent is feasible. In this case, the different concentrations necessary for detecting both imaging signals require radiolabelling with very low specific activities. Adding a radionuclide to a MR contrast agent results in several advantages such as improved detection of low-contrast agent areas, as a consequence of the high sensitivity, and a better signal-to-noise ratio. In addition, the radionuclide signal of bimodal agents would allow more accurate and sensitive measurements of the biodistribution of the MR contrast agents, providing methods for the attenuation correction comparable to that which is performed with PET/CT scanners today. Using a bimodal PET/MR probe, it has proven suitable to use the PET for estimating the overall concentration of an agent and the MR signal to determine its molar relaxivity, giving an accurate estimation of the specific biochemical and physiologic target. In this perspective, efforts have been made to develop multimodal probes for PET/MR. Most of them are based on the bioconjugation of a tracer to a carrier, inducing the chemical modification of existing molecules or entrapping the diagnostic compound using not completely biocompatible materials. Examples of these dual probes include arginine-glycine-aspartic (RGD) conjugated to iron oxide nanoparticles,[45] ^{124}I serum albumin conjugated with Mn-doped Fe_2O_4,[46] ^{64}Cu and Gd to evaluate fibrin imaging effect,[47] ^{64}Cu associated with doxorubicin conjugated with SPIONs,[48] [^{18}F]FDG adsorbed on core shell nanoparticles encapsuled with DTPA-Gd[49] and many others. As reviewed by Lahooti et al., the best targeting results are generally obtained with peptides or engineered mAb (with lower molecular weights) with an approximate hydrodynamic size of 40 nm, PEGylated radiolabelled with ^{64}Cu or ^{68}Ga. However, there are some exceptions and some good results have also been obtained with nanoprobes with a different composition.[50] At this stage, *in vitro* research has demonstrated the nanovector ability to improve the relaxometric proprieties and preserve the radioactivity without any chemical modification of the molecules. Future developments will clarify their stability and biodistribution profile.

Central Nervous System

PET is a noninvasive imaging procedure with a wide range of clinical and research applications in the evaluation of the pathophysiology of brain disorders, such as neurodegenerative diseases, infection, epilepsy, psychiatric disorders, and brain tumors, as well as in the study of neurophysiology of the normal brain. PET is referred to as a functional or molecular imaging tool that enables the study of biologic function in both health and disease, while MR provides morphologic information and can also evaluate some brain functions such as tissue perfusion and brain activation after performing a task, and connectivity.[51] Acquiring both PET and MR in a single session on a hybrid system is feasible, minimizing patient discomfort while maximizing clinical information, however some MRI attenuation correction-related PET errors may occur in neurodegenerative disease quantification.[52]

Although PET/MR potentially has great clinical utility in the evaluation of **encephalitis** and **brain infection**, few data are currently available, related to the relatively low incidence of these conditions and the relative scares diffusion of the PET/MRI system. Case reports on voltage-gated potassium channel antibody-associated limbic encephalitis, neurocysticercosis, necrotizing granulomatous inflammation and neurosarcoidosis, have been reported, highlighting the value of PET/MR in the diagnostic and treatment monitoring setting.[53-56] Figure 2 shows an example of necrotizing granulomatous inflammation detected by ^{68}Ga-DOTATATE PET/MR.[55] **Multiple sclerosis** (MS) is characterized by chronic inflammatory demyelination. PET/MR helps to obtain more specific information on the pathological mechanism of the disease. Translocator protein (TSPO)-targeted PET imaging has the ability to quantify neuroinflammation, to monitor disease progression, to predict prognosis, and to evaluate effects of treatment in MS.[7,57] [^{18}F]FDG and [^{18}F]fluoromethylcholine PET/MR have been used to assess the metabolic features of different variants of MS.[58] ^{11}C-PIB, a PET tracer, originally developed for amyloid imaging, has been recently reproposed to quantify demyelination and remyelination in MS. The use of myelin PET imaging, is limited due to its low resolution that deteriorates the quantification accuracy of white matter lesions. A multimodal partial volume correction approach by using PET/MR, allowing a better signal characterization of ^{11}C-PIB uptake in lesions in both phantom and patients, has been recently proposed.[59] Immune and inflammatory mechanisms may play a fundamental role in the development of some forms of epilepsy.[60] Several lines of evidence support this assumption like the activation of the immune system in some patients with seizure disorders or the high incidence of seizures in some forms of autoimmune encephalitis. It has also been reported that various injuries lead to microglial activation, including status epilepticus in rats.[61] A hallmark in the neuropathology of temporal lobe epilepsy is brain

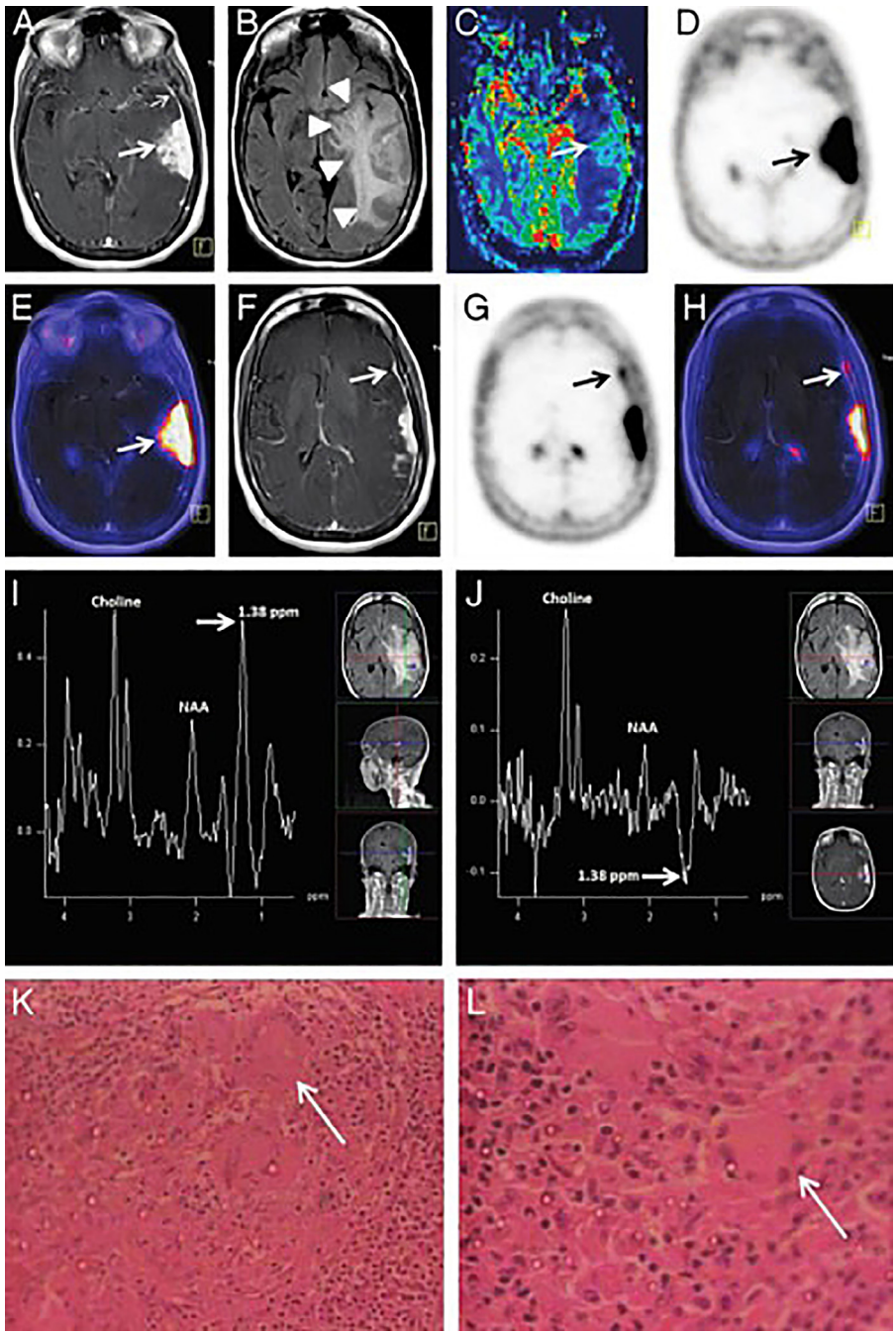

Figure 2 Example of necrotizing granulomatous inflammation detected by ^{68}Ga-DOTATATE PET/MRI. Contrast-enhanced axial T1 weighted MRI (T1W) images show an enhancing extra-axial, dural-based, space-occupying lesion in the left temporal region (arrow in A) with enhancement of the dura tail (small arrow in A) and associated white matter edema (arrowheads in B). MRI perfusion relative cerebral blood volume map shows increased regional perfusion (arrow in C). PET and PET/MRI images show ^{68}Ga DOTATATE uptake in the enhancing lesion (arrows in D and E). Post-contrast T1W images reveal a subcentimeter-enhancing satellite lesion anteriorly (arrow in F) characterized by ^{68}Ga DOTATATE uptake (arrow in G and H). Proton magnetic resonance spectroscopy identifies a lactate peak (arrow in I and J). Histopathologic examination of the specimen revealed well-formed noncaseating epitheloid granulomas (arrow in K and L). From Taneja S, Jena A, Kaul S, Jha A, Sogani SK. Somatostatin receptor-positive granulomatous inflammation mimicking as meningioma on simultaneous PET/MRI. Clin Nucl Med. 2015;40(1):e71-2. *Reprint permission requested*

inflammation which has been suggested as both a biomarker and a new mechanistic target for treatments. Non-invasive imaging of microglia activation biomarkers could be a relevant tool for detection, and especially for monitoring disease progression, therefore of great support to the evaluation of novel therapies[62] especially for epileptogenesis. Recently, inflammation has been demonstrated to be involved in neurodegenerative diseases. Immune cells, such as microglia and astrocytes, mediate the release of pro- and anti-inflammatory molecules. Their over- and underexpression, respectively, may result in neuroinflammation and thus disease onset and progression.[63-66] *In vivo*, microglial activation can be detected using PET ligands for the TSPO[67,68] and the reversible antagonist at TSPO [^{11}C]-(*R*)-PK11195 is often used for studying diseases that involve microglial activation or the recruitment of macrophages as in multiple sclerosis,[69] stroke,[70] Alzheimer disease,[71] traumatic brain injury.[72]

Future investigations are foreseen to elucidate central nervous system diseases, taking advantage of new specific PET tracers targeting neuroinflammation and MRI advancement. The combination of the information provided by the two techniques may advance the knowledge and hopefully, contribute to the development of new therapeutic targets.

Bone & Soft Tissue Infection

Imaging plays a major role in the diagnosis and management of musculoskeletal disease. MRI is able to provide multiple different structural and functional contrasts in soft tissue that are unavailable with any other imaging modality. In the clinical setting, MRI is the primary imaging system used to diagnose injuries in soft tissues such as intervertebral disc injuries; tears in the menisci, ligaments and tendons; as well as occult bone injuries. In addition, MRI is also widely used to study pathogenesis of many musculoskeletal disorders using advanced MRI techniques that provide unique functional information.[73,74] T2 and T1 rho relaxometry as well as magnetization transfer techniques provide information about cartilage biochemistry and have been shown to have significant prognostic value.[75,76] Further, arterial spin labelling[77] and chemical exchange saturation transfer[78,79] techniques are able to assess muscle perfusion and energetics, respectively. Although MRI is not typically associated with bone imaging, tissue diffusion[80] and ultra-short echo time[81,82] methods are able to provide important information about bone strength and fracture risk. Because MRI can offer novel functional contrasts, its combination with PET offers powerful observations of distinct physiological processes occurring in bone and cartilage at the same time.

Both [^{18}F]FDG and [^{18}F]NaF are very commonly used for PET imaging of musculoskeletal disorders.[83] As already discussed there are several interesting radiopharmaceuticals that are currently in the research setting and that hold promised in this specific field.[33-35] The introduction of PET/MR imaging adds a major dimension to research and clinical applications of PET in a variety of musculoskeletal disorders including infection, diabetic foot, painful arthroplasty, metabolic bone marrow/bone disease, back pain, nonmalignant bone marrow disorders, and arthritis.

Osteoarthritis (OA) is a chronic, degenerative disease of the joint. Its pathogenesis is poorly understood. Inflammatory processes have been cited as a possible mechanism of OA tissue degeneration.[84] [^{18}F]NaF-PET/MRI systems allow for comprehensive imaging of the whole joint in OA, including soft tissues and bone, offering the opportunity to simultaneously assess the role of metabolic activity, and relate it to qualitative MRI metrics of bone pathologies.[84] One of the biggest benefits of hybrid PET/MR imaging of OA is the ability to simultaneously evaluate molecular and morphologic spatial relationships across multiple tissues (metabolic bony activity in subchondral bone pathology and cartilage morphology) and by using [^{18}F]FDG, it may also provide complementary information linking changes in the soft tissues with bone remodeling and inflammation. **Ankylosing spondylitis** (AS) is a fairly common autoimmune-mediated chronic inflammatory disease that predominantly affects the spine and the sacroiliac joints. The simultaneous acquisition of high-resolution anatomical and functional MR images and metabolic information by [^{18}F]NaF-PET provides new insights into the link between inflammatory cascades, local metabolic changes, and the development of structural manifest inflammation in AS.[85] **Rheumatoid arthritis** is an autoimmune disease, associated with systemic and chronic inflammation of the joints, resulting in synovitis and pannus formation. For many years, the evaluation of RA has been restricted to conventional radiography, even though this technique lacks sensitivity for detecting the inflammatory process that occurs in the initial stages. Additionally, the introduction of biological treatments claims for other imaging modalities able to achieve an early diagnosis and an adequate follow-up.[86] Conventional nuclear medicine provides a great contribution to RA imaging. The introduction of [^{18}F]FDG-PET technology, sensitive to inflammatory changes within the synovial tissue, presenting some advantages than conventional imaging such as a higher spatial resolution and quantification, increases the use of molecular imaging in RA. In particular, [^{18}F]FDG-PET/MR provides metabolic information which has the potential to assess different aspects of arthritis such as bony disintegration and inflammatory activity, together with the precise anatomical and morphological data and the excellent soft tissue contrast, maximizes the strengths of both imaging approaches in RA imaging[87] and treatment monitoring.[88] In addition to [^{18}F]FDG, other tracers may be used to image RA. The relationship between synovial hypoxia and synovial inflammation has been evaluated. Hypoxia-inducible factors play a major role in RA disease progression, acting as key regulators of inflammation.[89] Preclinical data have shown that noninvasive imaging of inflammation-induced hypoxia in arthritic joint inflammation with PET/MR and hypoxia-specific radiotracer (^{18}F-fluoromisonidazole and ^{18}F-fluoroazomycinarabinoside) might be a promising clinical tool for uncovering affected, but clinically silent, joints at an early stage.[90] The diagnosis of **spondylodiscitis**

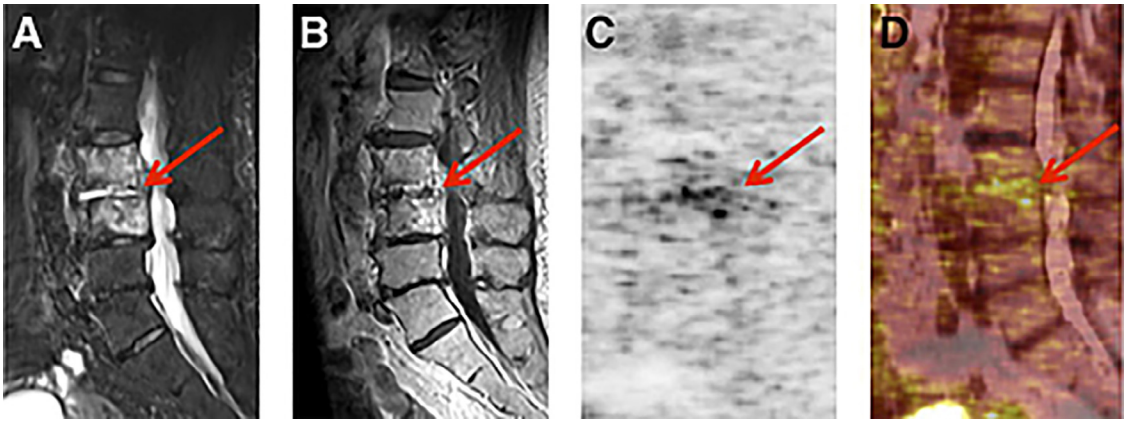

Figure 3 Simultaneous [^{18}F]FDG PET/MRI in 71-y-old female patient with final diagnosis of spondylodiscitis. MRI alone was inconclusive. (A) TIRM with typical hyperintense signal alterations at intervertebral disk level L4–L5 (arrow). (B) Moderate postcontrast signal (arrow) on T1-weighted MRI. (C and D) [^{18}F]FDG PET (C) and combined [^{18}F]FDG PET/MRI (D) show focally elevated uptake in affected disk (arrow; SUV_{max}, 8.14; SUV_{mean}, 3.99) as sign of active inflammation. This research was originally published in *JNM*. Simultaneous [^{18}F]FDG PET/MRI in 71-y-old female patient with final diagnosis of spondylodiskitis. Jeanette Fahnert et al. J Nucl Med 2016;57:1396-1401 © by the Society of Nuclear Medicine and Molecular Imaging, Inc.

(SD) is often challenging. MRI is sensitive (up to 96%) but lacks specificity in the presence of fractures or spinal implants, and distinction from erosive osteochondritis is often difficult. [^{18}F]FDG-PET/MR improves diagnostic certainty for the detection of SD (sensitivity = 100% and specificity = 88%) compared to MRI assessment, especially in patients with inconclusive clinical or MRI findings.[91] Figure 3 shows an example of [^{18}F]FDG PET/MRI in a patient with SD.

In **diabetic foot infections** imaging has a pivotal role in clinical decision making since it helps to diagnose soft tissue infection and osteomyelitis, to differentiate Charcot arthropathy from osteomyelitis, and to evaluate ischemia/atherogenesis component in some cases.[92] PET/MR could improve accuracy in detecting soft tissue lesions in osteomyelitis [65]. Additionally, it would be useful to quantify PET detectable functional changes and spectroscopy measurable metabolites simultaneously in diabetic neuropathy.[93] Because of the

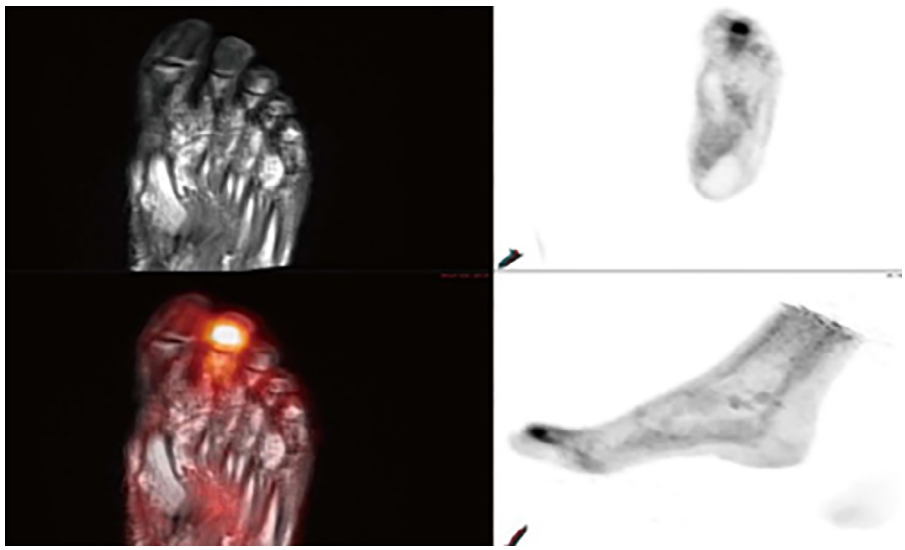

Figure 4 A 71-year-old male with poorly controlled diabetes and end-stage renal disease presents with worsening right foot pain. Bone scan revealed diffuse radiotracer uptake within the right foot without focal abnormality. MRI of the right foot demonstrates diffuse abnormal T1 and T2 signal within the right foot digits. Multiplanar PET/MRI images reveal focal [^{18}F]FDG uptake within the distal right second digit with corresponding heterogeneous T1 hypointense, T2 hyperintense signal compatible with osteomyelitis. PET: Positron emission tomography; MRI: Magnetic resonance imaging; FDG: [^{18}F]fluorodeoxyglucose. From Chaudhry AA, Gul M, Gould E, Teng M, Baker K, Matthews R. Utility of positron emission tomography-magnetic resonance imaging in musculoskeletal imaging. *World J Radiol* 2016; 8(3): 268-274. *Reprint Permission Requested*

limited availability of this hybrid scanner as of today, PET/MR cannot be considered an established modality for clinical practice in diabetic foot [65]. Figure 4 shows an example of PET/MR in Charcot disease.[94] In patients with **prostheses**, PET/MR has been used for technical purpose (i.e. artefacts due to metal implants and images reconstruction) rather than clinical ones (i.e. loosening/infection).[85]

Cardiovascular System

Specific requirements have to be fulfilled when PET/MR is used to image the cardiovascular system. Therefore before reviewing the most important applications of PET/MR in cardiovascular infection and inflammation, we will discuss some of the details of these requirements, including proper patient preparation and motion correction algorithms.

Patient Preparation

[^{18}F]FDG is often used for the evaluation of inflammatory processes since these conditions are characterized by increased glucose uptake by macrophages and other inflammatory cells. Therefore, suppression of physiological myocardial [^{18}F]FDG uptake is mandatory and usually obtained with dietary restriction.[95,96] A recent study showed that a high fat, low carbohydrate diet without fasting is successful in suppressing [^{18}F]FDG uptake in 84% of patients.[97] A recent procedural joint statement on myocardial [^{18}F]FDG imaging in inflammation is available.[98] The main goal of adequate patient preparation imaging large vessel vasculitis (LVV) is to reduce physiologic tracer uptake in normal tissues (myocardium, skeletal muscle, urinary tract and brown adipose tissue) while maintaining uptake in diseased tissues and organs. Glucocorticoids (GC) may reduce vascular wall uptake of [^{18}F]FDG: few data are available on the effect of GC withdrawal on [^{18}F]FDG uptake. It is confirmed recently that the diagnostic accuracy of LVV with [^{18}F]FDG PET remains for up to 3 days after initiation of GC, thereafter the upatke decreases significantly.[99,100] Therefore, there may be a diagnostic window of opportunity within 3 days of initiation of GC.

Motion Correction Algorithms and Attenuation Correction

Cardiac and respiratory motion can degrade image quality leading to a reduced diagnostic accuracy of PET/MR scans. In particular, the presence of motion artefacts can negatively affect myocardial attenuation maps resulting into false positive perfusion defects. Therefore, motion correction is mandatory to obtain diagnostic images and to improve the co-registration between PET and MR images.[101] Motion compensation due to cardiac contraction is usually obtained synchronizing PET image acquisition to the ECG allowing the reconstruction of images in the same, near "motion-free", phase of the cardiac cycle. A similar approach can be applied also for respiratory motion correction combining data obtained at analogous respiratory positions from multiple breathing cycles.[102] While these gating approaches have been widely used in several static PET acquisitions, they are not so efficient for four-dimensional (dynamic) PET studies due to the insufficient number of detected counts available for each reconstruction.[102] In order to obviate this problem, using more sophisticated approaches, motion information can be derived directly from PET data[103,104] for first from high-resolution anatomical MR images and then applied to PET images.[105]

Traditionally, cardiovascular imaging has been performed in PET-only and PET/CT systems by relying on attenuation correction (AC) maps obtained from a rotating transmission source or CT measurement, respectively. In hybrid PET/MR systems, these options are not available and alternative solutions have to be found. In general, segmented MR-based AC (DIXON MR-AC) maps are currently chosen as AC method-of-choice for integrated PET/MR imaging. Transformation from MR-images into AC maps are based on segmentation algorithms, which segment the images into four tissue types, with each tissue classification assigned to a vendor-specific attenuation (ATN) value.[106] In general, myocardial FDG imaging obtained from MR-based attenuation corrected [^{18}F]FDG PET is comparable to standard CT-based attenuation corrected FDG PET, suggesting interchangeability of both AC techniques.[107] In MRI, non-magnetic metals cause a signal void that exceeds the actual size of the object, which in turn might result in an underestimation of the attenuation. More importantly, however, these devices may interact with the radiofrequency and cause malfunction or sometimes heating of the leads of electronic heart devices. As a consequence, some patients cannot be examined using MR (and thus by PET/MRI).

Cardiovascular Applications of PET/MR Imaging

Cardiac MR and cardiac [^{18}F]FDG PET are both well-established techniques in the evaluation of inflammatory myocardial diseases. With a multi-parametric approach MR provides anatomical information regarding myocardial oedema (T2 sequences), focal or diffuse myocardial fibrosis (late gadolinium enhancement, LGE, and T1 mapping) and myocardial contractility. On the other hand, [^{18}F]FDG PET imaging can assess the status of the disease allowing the functional evaluation of the extension and the degree of the inflammatory process. Despite this potential complementary role, the additional value of this hybrid approach over the use of each single modality alone, in terms of diagnosis and cardiovascular risk stratification, has still to be proven.

Heart involvement is an adverse prognostic factor in patients with **sarcoidosis** and it usually manifests as heart failure and new onset cardiac arrhythmia. Although accurate diagnosis of subclinical but active **cardiac sarcoidosis**

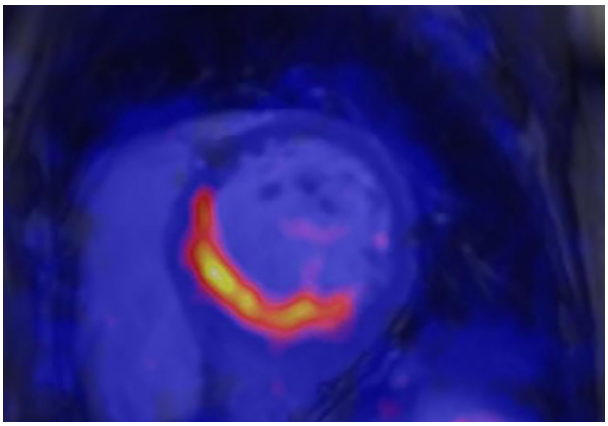

Figure 5 Example of [^{18}F]FDG PET/MR in a woman, 57 yrs old, with sarcoidosis. Images shows positive signal on MRI T1 and T2, and [^{18}F]FDG uptake in the inferoseptal wall. Reduced LVEF and wall motion disturbances were present.

is the key to guide patient therapy and to prevent long-term complications, a gold standard imaging technique is lacking. Both cardiac MR and [^{18}F]FDG PET imaging are currently used clinically for the diagnosis of cardiac sarcoidosis[108-110] with comparable diagnostic performance.[111] In this pre-simultaneous PET/MR imaging images are usually interpreted independently, losing the complementary information they provide. The feasibility of imaging cardiac sarcoidosis with hybrid PET/MR systems was initially described in a few case reports which showed accurate anatomical correlation between areas of fibrosis on MR delayed enhanced images and increased activity on PET iamging.[112,113] Recently, Dweck and colleagues demonstrated that the simultaneous acquisition of MR and PET images provides accurate localization of myocardial injury on late enhancement images and disease activity on PET allowing the differentiation of patients with active disease from patients with inactive disaese. In addition, the combination of negative LGE but positive, diffuse [^{18}F]FDG myocardial uptake on PET images allowed the identification of false positive findings due to incomplete myocardial suppression.[114] Figure 5 shows an example of PET/MR in a patient with cardiac sarcoidosis. Besides early diagnosis, other potential applications of PET/MR could be the monitoring of disease response to therapy and the estimation of individual risk assessment.[115] A multimodality imaging approach may be necessary for instance for decision making about pacemaker or ICD.[110] MR is less specific for inflammation. However, they may help in the assessment of LV remodeling, left as well as right ventricular function, pulmonary artery hypertension and in the follow-up of end stage heart failure from cardiac sarcoidosis. Observational studies suggest an important role for [^{18}F]FDG PET for monitoring efficacy of immunosuppressive therapy,[116] for accurate differentiation of residual myocardial inflammation from fibrosis.

Novel PET radiopharmaceuticals for imaging cardiac sarcoidosis are being investigated with the benefit of no background uptake, such as somatostatin receptor based hybrid imaging.[117,118] The somatostatin receptor subtype 2 (SSTR2) is highly expressed in sarcoid granulomas and several ^{68}Gallium-labeled somatostatin analogues are able to image this.

Cardiac MR is considered the reference standard in the diagnosis of **myocarditis** in patients presenting with chest pain, raised troponin and normal coronary arteries.[119,120] Few case reports demonstrate good correlation between areas of epicardial fibrosis detected on LGE, oedema and hyperemia and [^{18}F]FDG uptake on PET images (Fig. 6).[121,122] T2 mapping had the highest correlation rate with [^{18}F]FDG uptake.[121] Besides confirming the diagnosis of myocarditis, PET/MR may have a role in improving the diagnostic accuracy of cardiac MR in the detection of chronic myocarditis.[119] In addition, PET/MR can provide additional information on inflammatory activity, which is critical for monitoring therapeutic response. Novel PET tracers for the evaluation of myocarditis are currently under investigation. In a rat model of autoimmune myocarditis, ^{11}C-methionine PET imaging was able to detect foci of myocardial inflammation.[123] The advantage of using this tracer is that there is no need for dietary restriction since there is no physiological myocardial ^{11}C-methionine uptake. The combined approach of [^{18}F]FDG PET/MR may result in improved diagnosis. However, even though there is accumulating evidence for this approach, further studies are warranted.

Large vessel vasculitis (LVV) is defined as a disease affecting mainly large arteries, with two major variants, Takayasu arteritis (TA) and giant cell arteritis (GCA).[124] Vasculitis can be distributed locally in the branches of the internal and external carotid artery or the aorta and its main branches more central in the thorax. GCA and TA also show some overlap, regarding histopathology of arterial lesions reflecting shared pathways in tissue inflammation.[125] [^{18}F]FDG PET and MRI solely can identify the presence of systemic LVV in patients with GCA and TA. Morphological imaging is represented mainly by MRI. Increased vessel wall thickness (usually with a diffuse circumferential pattern), associated with vessel wall edema on T2 and fat-suppressed sequences, and mural contrast enhancement on T1 sequences are early signs of vascular inflammation. Post-contrast T1 images are superior to T2 or fat-suppressed images to detect early large vessel inflammation. Moreover, MRI angiography (MRA) provides luminal information, such as arterial stenosis, occlusion and dilatation. In active LVV, there is increased [^{18}F]FDG uptake by the vessel wall, typically with a smooth linear pattern, showing elevated uptake in inflammatory association cells, such as macrophages, monocytes and lymphocytes (chronic LV phase) . To date, there is only study, which compared the diagnostic performance of [^{18}F]FDG PET/MR and [^{18}F]FDG PET/CT. Einspieler et al., studied a total of 16 [^{18}F]FDG PET/MRI and 12 [^{18}F]-FDG PET/CT examinations were performed in 12 patients with LVV (Fig. 7).[126] MRI of the vessel wall by T1-weighted and T2-weighted sequences was used for anatomical localization of FDG uptake and identification of morphological changes associated with LVV. In addition,

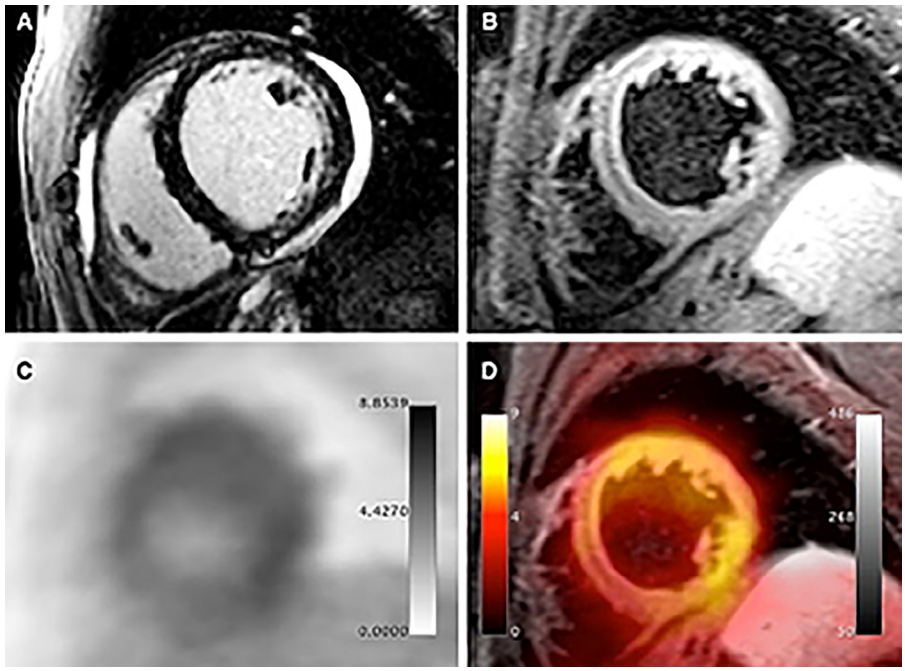

Figure 6 [^{18}F]FDG PET/MRI examination in a 32-year-old male presenting with dyspnoea, mild ventricular dysfunction (51% LFEV), and a history of recent systemic viral disease. Patchy intramyocardial late gadolinium enhancement in the lateral and inferior wall as well as pericardial effusion. B shows significantly increased T2 signal in the lateral wall representing myocardial oedema. C (PET) and D (fusion between T2-weighted MR image and PET) show diffusely increased [^{18}F]FDG uptake in the lateral, anterolateral, and inferolateral wall. Histopathological assessment after endomyocardial biopsy showed acute myocarditis with lymphocytic infiltration and moderate myocyte apoptosis. The patient demonstrated elevated levels of C-reactive protein (4.1 mg/dl) as well as elevated myocardiocytolysis serum markers (Troponin-I: 0.42 ng/ml). PCR and immunohistochemical analysis did not detect specific infectious agents such as viruses, bacteria, or fungi. From Nensa F, Kloth J, Tezgah E, Poeppel TD, Heusch P, Goebel J, et al. Feasibility of FDG-PET in myocarditis: Comparison to CMR using integrated PET/MRI. J Nucl Cardiol. 2016. *Reprint permission requested*

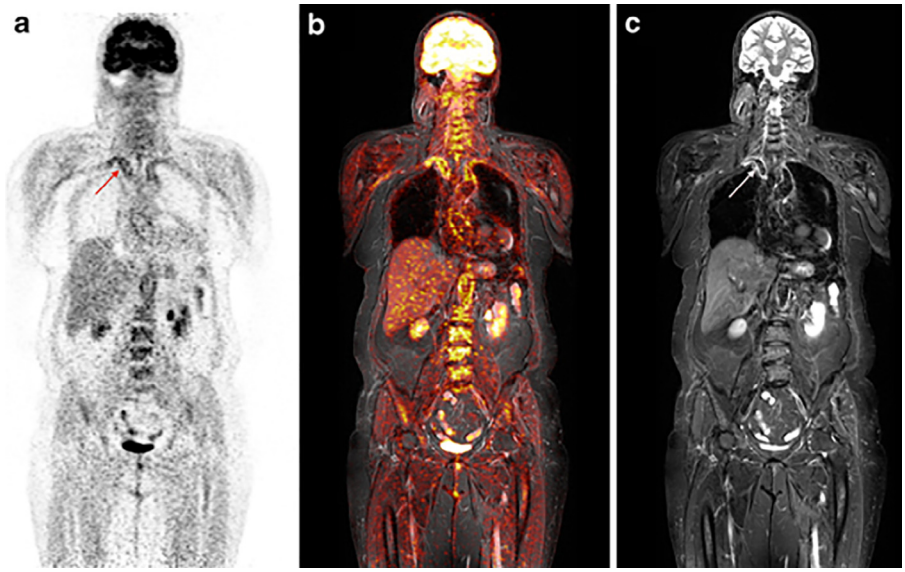

Figure 7 Signal elevation (indicating oedema) and visual wall thickening of the right subclavian artery in the coronal T2w STIR (white arrow; c) with corresponding pathological [^{18}F]FDG uptake in the coronal positron emission tomogram (red arrow; a), best seen on the fused PET/MRI images (b). Einspieler I, Thürmel K, Pyka T, Eiber M, Wolfram S, Moog P, et al. Imaging large vessel vasculitis with fully integrated PET/MRI: a pilot study. Eur J Nucl Med Mol Imaging. 2015;42(7):1012-24. *Reprint permission requested*

contrast-enhanced MRA was performed. The vascular FDG uptake in the vasculitis group was compared to a reference group of 16 patients using a four-point visual score.[127] Visual scores and quantitative parameters [maximum standardized uptake value (SUV_{max}) and target to background ratio (TBR)] were compared between PET/MR and PET/CT.In this study the authors showed that adding the anatomical information provided by MR the number of vascular segments classified as vasculitic by PET imaging increased from 86 to 95.[126] Promising, still unexplored fields of application include endocarditis and vascular prosthesis inflammation where quantification of disease activity may have an additional value, in particular for therapy monitoring.

Abdominal Diseases

PET/MR, enabling the simultaneous registration of dynamic and moving phenomena, is particularly important in the evaluation of the abdomen where the relative positions of organs may be altered due to peristaltic motion and bladder filling. Moreover, both PET and MRI images are acquired simultaneously under the same physiological conditions, which is particularly important in the evaluation of abdominal diseases.[128] Imaging plays a pivotal role in the diagnosis and management of inflammatory bowel disease (IBD).[129] In fact, monitoring subclinical inflammation is crucial, since it will affect the treatment strategy and disease outcome.[130,131] Although endoscopy is the gold standard for the evaluation of **inflammatory bowel diseases** (IBD), non-invasive imaging has been extensively used in this setting. Because of the lack of ionizing radiation, the bowel can be imaged by MR at multiple time points, providing a dynamic assessment of mural signal intensity and enhancement to assess both active and chronic inflammatory changes.[129] Many MR features (hyperintensity of the intestinal wall on diffusion-weighted imaging, rapid gadolinium enhancement, differentiation between the mucosa-submucosa complex and the muscularis propria, bowel wall thickening, parietal edema, and the presence of ulceration) have been reported to be associated to endoscopic findings in ulcerative colitis (UC).[131] MR performs better in moderate to severe UC than in mild cases[132] and its role in the differentiation of a quiescent lesion from an active lesion in UC is not defined.[131] Crohn's disease (CD). In quiescent Crohn's disease (CD) patients, the presence of restricted diffusion in the distal ileum is suggestive of an active inflammation. Therefore MR-DWI may serve as a clinical tool in the follow-up of these patients implying subclinical inflammatory flares.[133] More recently [^{18}F]FDG PET/CT has been applied in IBD. PET has been reported to be sensitive tool for detecting intestinal inflammation (pooled sensitivity of 84%, specificity of 86% on per-bowel-segment analysis[134] [75]) however, its role in quiescent UC is not established yet.[131] Few promising results have been reported on the use of PET/MR in IBD evaluation. Particularly, [^{18}F]FDG PET/MR was useful for identifying subclinical inflammation in UC[131] and PET/MR enterography biomarkers (SUV_{max}, signal intensity on T2-weighted images × SUV_{max}, and apparent diffusion coefficient × SUV_{max}) was successfully used to differentiate purely fibrotic strictures from mixed or inflammatory strictures in CD.[135] Additionally PET/MR-enterography has been reported to be highly accurate in the assessment of CD lesions including extra-luminal disease and distant localization before operation, thus contributing to clinical management of patients with small-bowel CD.[136] Figure 8 presents an example of PET/MR in a patient with cecal inflammation.

Fully integrated [^{18}F]FDG PET/MRI was also evaluated in **retroperitoneal fibrosis** showing better performance as compared to clinical and inflammatory parameters to assess disease activity as well as the ability to detect associated large-vessel vasculitis and aneurysms that may occur apart from the site of the retroperitoneal fibrosis.[137]

Recently, [^{18}F]FDG PET/MRI has been used for the management of a parasitic disease, in a patient with *Echinococcus multilocularis*. Images show peri-lesional uptake in a hepatic lesion, opening the possibility to further systematic evaluation of the technique in the routine management of alveolar echinococcosis (Fig. 9).[138]

Paediatric Population

Paediatric imaging has emerged as a key application of combined PET/MR, especially in the context of paediatric oncology.[139] Advantages of the technique in this special patient population include high imaging quality, significantly lower radiation exposure and a reduction in the total number of required imaging studies, which simplifies clinical workflows and reduced the number of necessary sedation in younger children. Specific imaging protocols for children and young adults are currently under investigational evaluation. Preliminary results show that a gadolinium-free cancer PET/MR staging of children and young adults provided superior tumor diagnosis and 74% reduction in effective dose compared to standard clinical imaging tests. In this series, PET/MR provided clinically important detail about the primary tumor and excellent detection of pulmonary nodules ≥5 mm.[140] The role of PET/MRI in non-oncologic imaging has not been this clearly defined in children yet despite numerous non-oncologic applications are conceivable such as in case of fever of unknown origin or inflammatory conditions (i.e. chronic inflammatory bowel disease, rheumatoid disorders or chronic infectious disease). Figure 10 shows an example of PET/MR in a 17-year-old girl with acute lung inflammation in cystic fibrosis.

Conclusions

PET/MR has gained momentum in the areas of oncology and neuroscience whereas research in the field of infection and inflammation are still very limited. Currently, PET/MR imaging

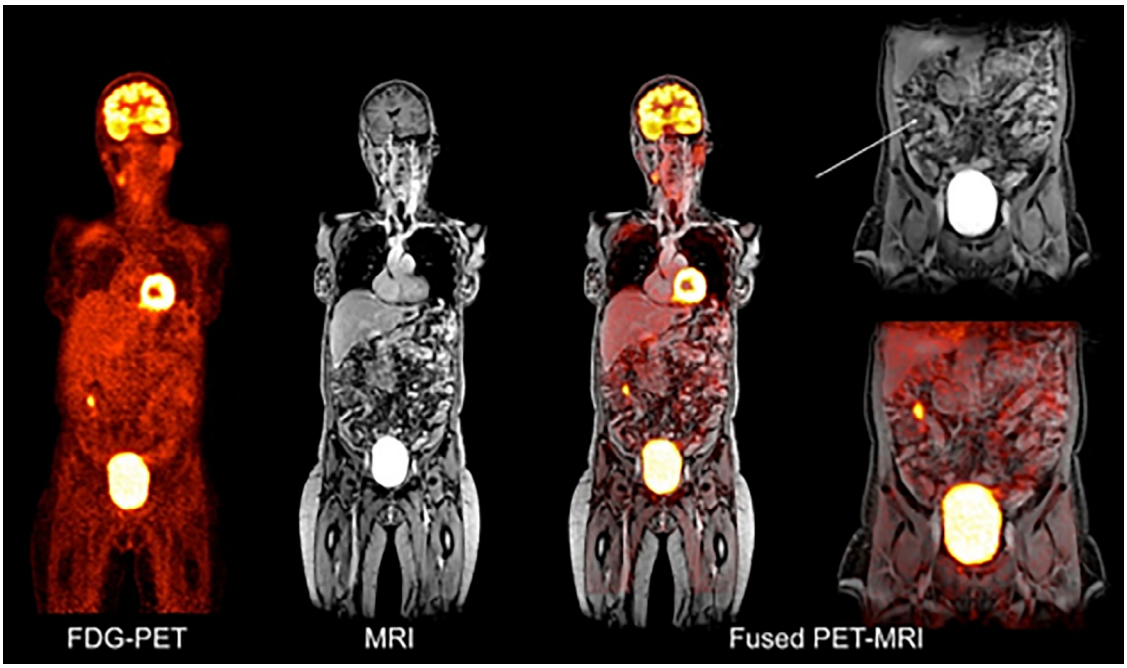

Figure 8 PET/MRI of patient with cecal inflammation. Fused imaging demonstrates small area of active inflammatory changes in the cecum that would be difficult to diagnose on either [^{18}F]FDG-PET or MR imaging independently. From Rahul A. Sheth and Michael S. Gee (2012). The Imaging of Inflammatory Bowel Disease: Current Concepts and Future Directions, Inflammatory Bowel Disease, Dr. Imre Szabo (Ed.), InTech, DOI: 10.5772/53025. Available from: https://www.intechopen.com/books/inflammatory-bowel-disease/the-imaging-of-inflammatory-bowel-disease-current-concepts-and-future-directions

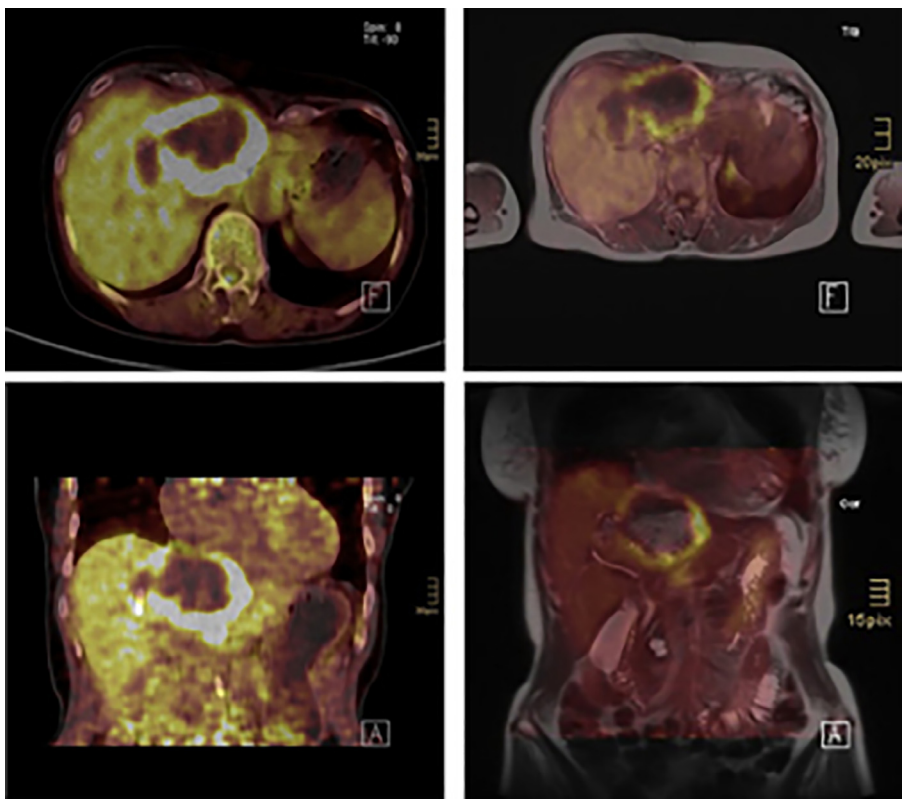

Figure 9 Axial (upper row) and frontal (lower row) sections from [^{18}F]FDG PET/CT (left) and [^{18}F]FDG PET/MRI (right), showing strong peri-lesional uptake in a patient with a hepatic lesion caused by *Echinococcus multilocularis*—the fox tape worm. *Felix Lötsch, Fredrik Waneck, Herbert Auer, Klaus Kaczirek, Georgios Karanikas, Michael Ramharter*. From *FDG-PET/MRI in alveolar echinococcosis International Journal of Infectious Diseases* Volume 64, Pages 67-68 (November 2017) DOI: 10.1016/j.ijid.2017.09.006

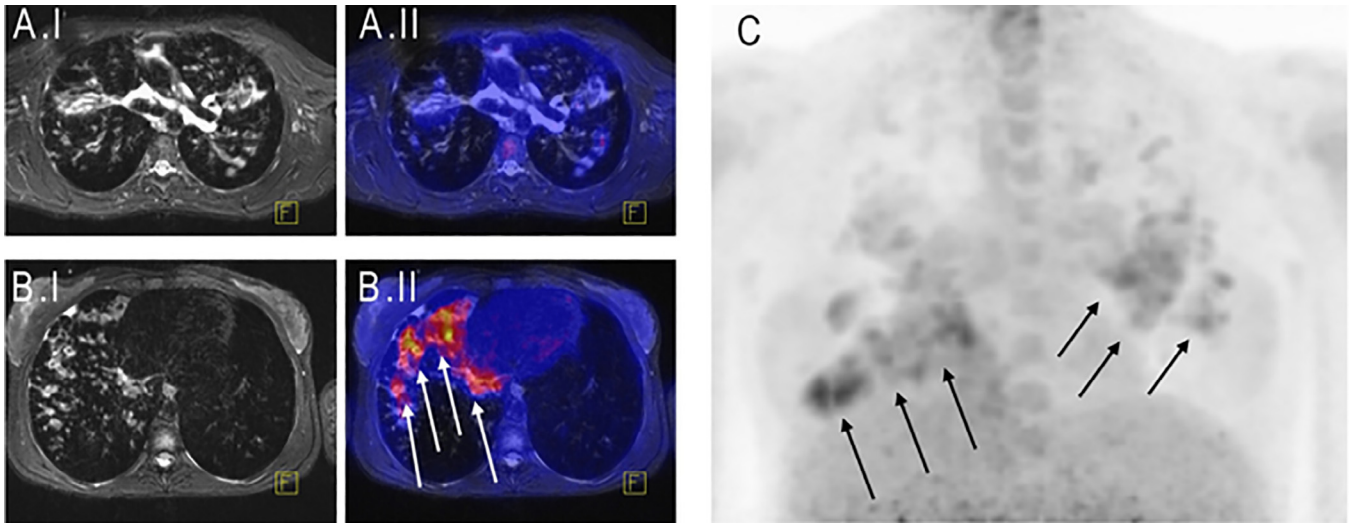

Figure 10 17-year-old girl with severe pulmonary manifestations of cystic fibrosis, referred to exclude an acute pulmonary infection before planned lung transplantation. MRI (transversal T2 w TSE sequence, A.I and B.I) shows inflammatory changes but cannot discriminate between chronic and acute inflammation. [^{18}F]FDG-PET (A.II, B.II, C) shows active inflammation of the lower lobes. Gatidis S, Bender B, Reimold M, Schäfer JF.Eur J Radiol. 2017 Sep;94:A64-A70. doi: 10.1016/j.ejrad.2017.01.018. PET/MRI in children. *Reprint permission requested*

is likely the most strongly emerging research platform in imaging science, and over the next few years, it will show its potential for providing new options in clinical diagnosis. Preclinical studies have indicated several potential new radiopharmaceuticals that warrant clinical research in this specific field of investigation. In the near future, PET/MR imaging studies in infection and inflammation should be more and more focused on the whole integration of the multiparametric functional information offered by both modalities rather than limited to the use of the MR information as a mere anatomic landmark for the functional information from PET. Accordingly, clinical studies providing the value of PET and MR imaging through the synergy arising from their combination rather than the comparison of the results with other modalities as PET/CT in terms of sensitivity and specificity are foreseen. The complexities of MR physics, MR sequence optimization, artifacts, the functional aspects of MR imaging, and a huge volume of intricate anatomy will require specific education and training, thus representing the next challenge for the nuclear medicine community to unravel the full potential of this new technology and to make it entering into daily clinical practice.

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