PET-MRI: Challenges and new directions

It is becoming increasingly evident that combining the imaging of 'form' provided by techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) and 'function' provided by the ever-increasing tracers available with positron emission tomography (PET), have tremendous potential. This is practically reflected with the dramatic growth of PET CT, especially in oncology and to a lesser extent in cardiac and neurological applications.

Magnetic resonance imaging, which provides unmatched soft tissue details along with a reasonable array of functional information through techniques such as spectroscopy and a slowly growing number of contrast agents among others, stands at the cusp of imaging of form and function. It is clear that it will be a long time before MRI can provide the molecular detail that PET does and PET provides the anatomic information that MRI does, so a combination of the two technologies is the most reasonable option.

As with any new and expensive technology, questions are always raised. In this case, does this provide anything over the visual and mathematical methods, where we can combine the information provided by the two modalities, and will it really make a difference to patient care or our understanding of the disease? The answer I believe, as with most things medical is, "if you build it, they will come". Just as PET was initially read in isolation, then correlated with CT and now life without PET-CT seems hard to imagine, so may become the case with PET-MR; but that also will have to go through its stages and teething troubles.

In this article, we will focus on some of the challenges involved in creating a combined PET-MRI unit and strategies to overcome them followed by some potential applications and finally, what it augurs for us in the nuclear medicine community.

CHALLENGES IN IMPLEMENTATION

There are three major concerns while creating a combined PET MRI unit; the first is putting a PET system with photomultiplier tubes (PMTs), which are extremely susceptible to magnetic fields, into a high magnetic field (and having PET detector units that do not interfere with magnetic fields), second, creating attenuation maps for PET images, and third, a proper construct for the PET-MRI system.

a) PET detector element related issues

In terms of the ideal detector crystal, Lutetium oxyorthosilicate (LSO) and Bismuth germinate (BGO) have been shown to be least susceptible to MR artifacts.[1] At present, there are a few major strategies to limit the interference of the magnetic field of the MRI scanner, with the detection of the PET signal. The first involves using optical fibers that guide light away from the magnetic field, for detection,[2,3] another involves replacing the PMT with avalanche photodiode devices (APDs),[4-6] and yet another involves shielding the PMT from the surrounding magnetic field.[7]

b) Attenuation correction-related issues

Although CT and transmission scans do provide acceptable methods of attenuation correction, they are not perfect and various MR-based techniques are also being considered. Hoffmann *et al.* have created an excellent summary of various approaches to MR-based attenuation correction.[8] As expected, attenuation correction in brain imaging is less challenging than the torso. A brief overview is as follows:

One approach to MR-based attenuation correction is using segmentation.[9-12] In this, a transmission scan is used to generate an attenuation map which is co-registered to the MRI images (usually T1 weighted images, which are best for depicting the anatomy). Subsequently, the MR image is segmented into areas with different attenuation values (bone, brain tissue, fluid, air in the paranasal sinuses) and then this attenuation map is applied to the PET images.

Another approach is to use atlas-based methods, where a template brain MRI image is created from multiple subjects (atlas) and the attenuation values on it are assigned either by segmentation into multiple tissue types (air, bone, water, etc.) or continuous values, using transmission or CT scans. These template images can then be warped and co-registered with the subject image, and the attenuation values can then be assigned to the PET image, based on the attenuation values assigned to the MRI.[10,13,15]

In brain imaging, these methods have been found to have variations of between 3 and 10% from standard transmission attenuation correction techniques and most studies have involved a small number of subjects.[10,11,14,15] Data from torso imaging studies is still evolving, and there is a possibility that by using histogram matching and atlas-based approaches, it may be possible to generate MR-based attenuation maps for torso imaging.[14,15]

Although these developments are promising, further challenges exist when dealing with the accurate representation of bone,

truncation effects on structures that extend beyond the MRI field of view, and MR surface coils that would be in the PET field of view, but not the MRI. There is still much that needs to be done in this area while taking PET-MRI into the clinical arena.

c) System construction

The ideal construct for a PET-MRI system is not yet entirely clear and at present, three models are considered, sequential, insert, and integrated.

In the sequential construct, the PET and MRI scanner are placed in sequence, just as with the PET-CT systems and the currently available PET-MRI systems are of this type.[17] The advantages of this method are, minimal adjustment to existing technology, but magnetic shielding and certain front-end software changes would be required. Furthermore, the disadvantage of non-simultaneous acquisition remains.

The insert construct system involves building a removable PET detector ring that can be placed within the MR gantry or around the subject, when simultaneous acquisition is needed. In this situation, the PET ring must produce minimal disturbance to the magnetic field, the PET detector must be resistant to magnetic field fluctuations or have an external read-out and all parts must be shielded to prevent electromagnetic interference. Various options, which include using optical fibers or Avalanche photodiodes (APDs) are presently under development.[2,4,5,17-19] This system has the advantage of allowing simultaneous PET-MRI acquisition and the opportunity for it to be adapted to any center that already has an MRI system. The drawback, besides developing the technology to create excellent quality images with excessive interference, is a further decrease in the space within the bore of the MRI scanner.

Integrated systems presently rely on three major technologies; the first is a split superconducting magnet, where the PET detector ring lies in the space between a split superconducting magnet and optical fibers carry the scintillation light to an area outside the 1 mT fringe field for processing. At present, this can only be used at a low magnetic field, with a specialized gradient set, limiting its utility somewhat.[5,20] Second (field cycled acquisition), using two separate and dynamically controllable magnets (one for excitation of protons on the MR and the other for reading the MR signal), an interleaved acquisition can be created that allows a window for PET data acquisition.[21] In the third method, the crystals and photomultiplier components are located between the MRI's send and receive coils, which naturally again leads to space constraints and electromagnetic as well as heat-related issues.[22] Finally, there is some work being done on integrating some of these solutions to produce a more comprehensive solution (www.hybrid-pet-mr.eu).

CLINICAL APPLICATIONS

Of all the areas for growth on PET-MRI, neuroimaging shows the most promise. This is primarily because of the excellent tools available to us with both the modalities, to assess various aspects of the brain anatomy and function, as well as its relatively symmetric, stationary, and rigid structure, which makes it ideal for imaging. Other areas, where PET-MR can play a larger role would be head and neck, upper abdominal, and musculoskeletal applications. Although the role of MRI-PET in cardiac and other torso applications is exciting, these areas prove to be a challenge when trying to obtain semi-quantitative information with MR, and it may be a little longer before these areas reach their full potential.

A comprehensive review of potential clinical applications for PET-MRI is beyond the scope of this article, but a basic outline of potential areas for exploration is provided.

The superior soft tissue resolution and anatomy provided by MRI along with its semi-quantitative macromolecular information (in micromolar quantities through MR spectroscopy, perfusion imaging, cell migration imaging, with iron labeling and oxygen consumption imaging, with ^{17}O among others) can now be combined with the picomolar detail that metabolic imaging with PET provides. This provides us with an arsenal of information that can be used to understand various aspects of disease anatomy and physiology at a macro, microscopic, and molecular level *in vivo*. The information can then be used to identify, stage, prognosticate, and follow-up a variety of diseases from stroke and neurodegenerative disorders to cardiovascular disease and neoplasia.[6,23-26]

A prime example of this would be in stroke imaging, where MR angiography would identify the anatomic lesion, spectroscopy could assess lactate buildup, ^{18}F-MISO imaging could identify the extent of hypoxia and diffusion, and perfusion MRI could be correlated with ^{15}O and $H_2{}^{15}O$, to gain information on identifying irreversibly functionally impaired, but morphologically intact tissue. This will have significant implications on treatment options.[26]

High resolution MR information in dynamic studies such as MRI perfusion could be used to determine flow-dependent constants, which could be used for compartmental analysis of PET data and PET techniques, such as, ^{15}O water perfusion, which could be used for validation of MRI perfusion techniques such as arterial spin labeling (ASL).[6,23-26]

Magnetic image resonance techniques that target specific anatomy such as diffusion tensor imaging (DTI) or T2 mapping and T1 rho imaging of an articular cartilage could be used for a more detailed understanding of the distribution of radiotracers to specific, normal, and pathological regions.[6,23-26]

From a molecular and cellular perspective, while MRI techniques could track the distribution of cells and also the secondary effects of their activity at a macroscopic level, PET-labeled molecular markers of angiogenesis, apoptosis, and transfer of genetic information would validate and confirm their presence in these effects. Furthermore, variations in these could provide

clues to the progression or regression of these processes. This may especially have a tremendous potential in stem cell-related procedures.[6,23-26]

IMPLICATIONS FOR THE NUCLEAR MEDICINE COMMUNITY

PET-MRI is an exciting modality that will give us unprecedented simultaneous insight into form and function *in vivo*. While we are well aware and comfortable with the appearance, distribution, and implications of changes in radiotracer distribution, we will now have to deal with one of the most technically challenging imaging modalities, the MRI. The complexities of MR physics, MRI sequence optimization, artifacts, the functional aspects of MR imaging, and a huge volume of intricate anatomy, will all soon become the responsibility of the imager. Those who will deliver the best of both worlds will ultimately take the modality into the forefront of research and clinical care. If we are to make a greater impact in this field, now is the time to create the next generation of molecular imagers who will be equipped to deal with these challenges. For a start, we need to understand not just the limitations, but also the strengths of other imaging modalities and start incorporating these more regularly into our daily clinical routine and educational directives.

CONCLUSION

PET-MRI is a modality with tremendous potential for combining form and function *in vivo*. The advent of the first few human scanners is a step toward integrating this in clinical practice. Significant challenges still exist before this becomes a routine part of our imaging arsenal. Meanwhile, we should be developing an infrastructure that will equip us to cope with the challenges that lie ahead, by learning how other imaging modalities will supplement what we already know.

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