Inflammatory thinking

A revolutionary new approach aims to use molecular imaging to diagnose and manage vascular disease based on its inflammatory components. Here, co-investigators Dr Søren Hess, Björn Blomberg and Professors Abass Alavi and Poul Flemming Høilund-Carlsen discuss their individual passions for the technique and their goal to increase its widespread use.

Could you provide an insight into molecular imaging?

In its broadest sense it is the imaging of molecules, specifically their movements and handling in a dynamic system, usually a living organism. In medicine it comprises imaging in cells, animals, patients and control subjects. Through the study of specific molecules’ handling in the body over time, as seen by a positron emission tomography (PET) scanner, molecular imaging enables the assessment of disease processes at the cellular level without the use of invasive procedures and without interfering with these processes.

To carry out this procedure, an infinitely small amount of radiopharmaceutical (tracer) is ingested or injected into the patient. The most widely used compound is a modified glucose molecule called fluorodeoxyglucose (FDG) – a marker of glucose metabolism, which may be increased in malignant and inflammatory cells. This is done with sensitivity and quantification far beyond that of computed tomography (CT) or magnetic resonance imaging (MRI) scans.

What are your professional backgrounds and what led you to working in this area?

SH: I am a physician, consultant and specialist in nuclear medicine. I came across the specialty as a medical student and was attracted by its diversity – virtually every medical specialty uses nuclear medicine techniques. In particular, use for inflammatory diseases holds great promise because they are often treatable if diagnosed correctly.

BB: I am a PhD researcher with a special interest in the functional and molecular imaging of cardiovascular diseases.

AA: I am Professor of Radiology and Neurology, Director of Research Education in Radiology, and Associate Director of the Center for the Study of Aging at the University of Pennsylvania. I discovered nuclear medicine in 1971 at the University, where I had the opportunity to work with some of the pioneers of tomographic emission imaging: our group was the first to introduce FDG-PET in humans. My prime objective is still to promote the use of molecular imaging with FDG-PET to minimise pain and suffering. PET and PET/CT has had a substantial impact on medicine, and inflammatory disease is an important research area for this technique.

PFHC: I was about to become a cardiologist and then a thoracic surgeon when I realised that understanding of many basic principles was lacking; so I shifted to clinical physiology, where things are measured, debated and improved in an ongoing process. Today I work in nuclear medicine, focusing on isotopes and engineered molecular compounds as vehicles for dynamic imaging and targeted therapy in cancer, atherosclerosis and inflammation.

Which diseases have these techniques been used to assess so far?

PET imaging with FDG was initially employed for brain studies, but mainly as a research tool, with the results proving slow to translate into clinical use. A more direct impact on patient management has been seen in malignancies, which have been the main focus of FDG-PET/CT for the past decade. The benefits to cancer patients have been revolutionary, especially with regards to disease staging, and in the future when it comes to therapy monitoring. The literature reports a change in management in as many as one in three patients when PET/CT scans are used.

Can you explain the pathology of atheromatosis and how molecular imaging techniques can help to tackle it?

It appears that vessel damage results in inflammation of the vessel wall and triggers the formation of atheromatosis (lipid-filled, non-calcified plaques) and, years or decades later, atherosclerosis (calcified plaques that are visible by CT imaging).

PET can directly assess the inflammatory activity in atheromatosis/atherosclerosis by utilising FDG. Using other tracers, it can detect and quantify molecular vascular calcification long before this has given rise to overt calcifications that are visible by CT. PET/CT could therefore evaluate the effect of interventions at a very early stage, when the disease process may still be reversible, and serve as a good basis for personalised treatment options.

What is preventing molecular imaging from being used more frequently, and how is your group working to overcome this challenge?

Many of the possibilities are novel, potential applications with little or no scientific evidence. Although we firmly believe in the revolution of these technologies, there is a need for more substantial research to provide the data needed to facilitate such paradigm shifts. This requires a change in the attitudes of the medical community from the conventional, structural 20th Century imaging towards the innovative, molecular imaging of the 21st Century. We endeavour to provide such evidence for a multitude of inflammatory disorders.
A new imaging paradigm

Research led by Odense University Hospital in Denmark is investigating the use of molecular imaging techniques for inflammation. This work could enable earlier diagnosis with a view towards curing instead of suppressing disease, and could also measure the effectiveness of existing treatments.

AS BIOLOGICAL PROCESSES are dynamic, the majority of diseases have changing and progressive activity that cannot be monitored sufficiently by conventional structural techniques such as X-rays, which can only provide a static snapshot in time. Molecular imaging – based on positron emission tomography (PET) scans – can provide a more fluid, in-depth picture. Using radio-labelled, disease-targeted biomolecules, it provides an unsurpassed insight into the processes of disease and can facilitate early diagnosis, staging and monitoring.

Dr Søren Hess, a physician-scientist in the Department of Nuclear Medicine at Odense University Hospital, Denmark, believes molecular imaging holds particular potential for inflammation. Along with a team of researchers from across Europe and the US, he is using these techniques to image vascular disease.

The team is applying a PET/computed tomography (CT) technique, combining the benefits of traditional structural approaches with those of newer, nuclear medicine methods. This hybrid technology brings together molecular and structural imaging capabilities in a single scanner to detect biomolecules labelled by the glucose-analogue fluorodeoxyglucose (FDG), which accumulates in cells with unusually accelerated metabolism. Using FDG-PET/CT, it is possible to study the entire body in a single examination and detect overactive cells with an unprecedented level of precision.

APPROACHING INFLAMMATION

Hypermetabolism is a hallmark of tumours, and as such FDG-PET/CT has traditionally focused on positron emission tomography (PET) scans – can provide a more fluid, in-depth picture. Using radio-labelled, disease-targeted biomolecules, it provides an unsurpassed insight into the processes of disease and can facilitate early diagnosis, staging and monitoring.

Immune cells called macrophages have a vital role in plaque initiation, progression and instability. FDG accumulates in these plaque macrophages, thereby acting as a marker of plaque activity. This could be harnessed to detect atheromatosis, quantify disease severity and even predict future risk of cardiovascular events. Indeed, research conducted by the Odense team has generated some promising initial findings: sophisticated quantitative imaging of arterial inflammation suggested a link between arterial FDG binding and cardiovascular risk factors, with a perspective for earlier medical intervention. Moreover, other groups have shown reduced arterial FDG activity over time in patients taking lipid-lowering medication showed, demonstrating that FDG-PET is an indicator of treatment efficacy. These findings pave the way to proving the feasibility and clinical benefit of FDG-PET imaging of atheromatosis.

THROMBUS DIFFERENTIATION

Hess and his colleagues are not limited to the study of arterial diseases; however; blood clots in veins cause VTE – beginning in the deep veins of the legs (deep vein thrombosis) and travelling up to block the vessel that carries blood from the heart to the lungs (pulmonary embolism), a potentially fatal condition.

Efficacious anticoagulants are available, but they can cause harmful side-effects and may be administered too late or unnecessarily. Accurate imaging is therefore vital in order to diagnose the condition early enough to prevent adverse consequences and to administer the appropriate treatment. Current diagnosis is based on changes to the structure of veins, which may remain the same for years after the clot, preventing discrimination between old and new clots; something which is vital when investigating a suspected recurrence. "There is a pressing need to differentiate between old,
Molecular imaging
The process:

1. A small amount of radiopharmaceutical tracer is ingested by, or injected into, the patient

2. The tracer comprises a substance that targets the disease, attached to a radioisotope, which makes the tracer detectable by a PET scanner

3. The information obtained by a PET scan is combined with structural images obtained by CT or MRI. This all takes place in a single ‘sandwich-like’ scanner

4. The images are fused using elaborate software

A dynamic alternative
Unlike conventional imaging techniques, molecular imaging is capable of:

- Providing information on the dynamics of the disease process, including the movements of molecules and their interplay
- Detecting diseases in the early stages when they are more amenable to therapy, can guide disease management and even help elucidate cause and effect

It is also:

- Non-invasive
- Safe and without side-effects
- Able to identify co-morbidities that may be overlooked by localised techniques

inactive clots that remain but do not require treatment and novel, active thrombi, which should be treated immediately with blood thinning agents,” Hess explains.

Like atheromatosis, inflammation is a key factor in VTE. Active inflammatory cells are found inside the clot itself and in the vessel wall. Recently, Hess and colleagues have shown that FDG accumulates in these new clots, enabling them – for the first time in consecutive patients – to accurately determine which patients require treatment. But this work could also have implications outside of VTE. A blood clot is often the first sign of an underlying cancer, and their detection could thus facilitate the early treatment that is so important for malignancies.

FUTURE PROGRESSION

Soon, these techniques could be used to assign a number, termed the global disease score, indicating the total burden of disease in the body and used to guide management and therapies. This could enable treatment of diseases while they are still curable, preventing them from becoming chronic and potentially protecting millions from disability.

Through atheromatosis and VTE, Hess’ team has provided two strong examples of how FDG-PET/CT can improve understanding of disease and transform its management for the benefit of patients. Hess argues that in the coming decade, FDG-PET/CT could initiate a paradigm shift in the approach to these diseases: “Our insights may lead to a more profound understanding of the intricate interplay between inflammatory cells, inflammation-promoting signal molecules and risk of disease. This could facilitate changes in the management of patients through much more personalised and preventive approaches,” he concludes.

72-year-old male immobilised due to pneumonia with sudden onset swelling and pain in the right leg. PET/CT shows high metabolic activity in the right lung (dotted arrow, pneumonia) and in the veins of the right leg (arrow heads) consistent with new deep venous thrombosis.

INTELLIGENCE

MOLECULAR IMAGING OF VASCULAR DISEASES

OBJECTIVES
To apply molecular imaging techniques based on positron emission tomography (PET) scans to diagnose and monitor vascular diseases.

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