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Monitor Me!

MONITOR ME! *T. RASSAF*
CONSUMER TECH PROMOTES PATIENT ENGAGEMENT, *A. CHERRINGTON*
PATIENT TRUST NEEDED FOR HEALTHCARE DATA SUCCESS, *J. GUANYABENS*
CARDIOLOGY AND MHEALTH - RETHINK ABOUT MONITORING, *R. VIDAL-PEREZ*
SENSORS IN EVERYDAY OBJECTS FOR DEMENTIA CARE, *T.G. STAVROPOULOUS ET AL.*
IMPROVING PATIENT COMPLIANCE WITH FUTURE MHEALTH, *I. DAVALUR*
IN DATA WE TRUST, *J. SINIPURO ET AL.*

INNOVATION AND A UNIQUE EXPERIENCE AT EAHM 2019, *D. HAVENITH*

THE FUTURE OF CARDIOVASCULAR DISEASE TREATMENT AND MANAGEMENT, *A. M. FELDMAN*

EDUCATING PHYSICIANS TO BE LEADERS, *E. E. SULLIVAN*

FINANCE, SKILLS GAP, GOVERNANCE: ADDRESSING CIO CHALLENGES, *S. MOORHEAD*

NURSES AND CUTTING EDGE TECHNOLOGY, *I. MEYENBURG-ALTWARG*

THE HOSPITAL AS A BRAND, *M.C.VON EIFF & W. VON EIFF*

CARDIOVASCULAR DISEASE PREVENTION 2019: QUO VARDIS? *A. A. MAHABADI*

SEX AND GENDER IMPACTS IN CARDIOVASCULAR DISEASE: A TYPICAL PRESENTATION OF CARDIOVASCULAR DISEASE? *K. LINDSTROM & T. ROHR-KIRCH-GRABER*

INOTROPIC AGENTS FOR HEART FAILURE - WISHFUL THINKING? *J. W. HERZIG*

NUCLEAR CARDIOLOGY: MOLECULAR INSIGHTS INTO THE HEART, *C. RISCHPLER ET AL.*

PUTTING MEDICAL RADIATION PROTECTION FIRST, *G. FRIJA*

CLOSING THE LOOP: THE ROAD TO ZERO MEDICATION ERRORS, *N. M. SIMS*

THE DEATH OF CANCER, THE PATIENT PERSPECTIVE, *P. KAPITEIN*

#PINKSOCKS: CHANGING THE WORLD WITH HEART SPEAK, HUGS AND GIFTING, *N. ADKINS*

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Nuclear Cardiology: **Molecular Insights into the Heart**

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Summary: Nuclear cardiology is a promising field located between research, imaging, and patient care. Through close interdisciplinary cooperation, a variety of cardiovascular diseases (eg coronary artery, inflammatory and infiltrative cardiac diseases) can not only be investigated, but also efficiently treated in daily clinical routine.

What is Nuclear Cardiology?

In nuclear medicine, molecular probes are administered to patients at nano- or picomolar concentrations in order to visualise processes non-invasively in the body. This principle is applicable in different medical fields such as oncology (eg glucose metabolism of tumour cells), neurology (eg amyloid plaques in dementia) or cardiology (eg myocardial perfusion). In general, only low amounts of weak radioactivity are given, which result in low radiation to the patient. In addition, the administered radiotracer do not usually cause pharmacological effects. Single-photon-emission-computed-tomography (SPECT) and positron-emission-tomography (PET) are scintillation cameras which detect the emitted radiation from the patient. The functional images generated by those cameras are usually combined with computed tomography (CT) or magnetic resonance imaging (MRI) for morphological correlation. Nuclear medicine also offers therapeutic interventions such as Peptide Receptor Radionuclide Therapy (PRRT) for neuroendocrine tumours; however, this is not the subject of this manuscript.

Nuclear cardiology represents a dynamic subspecialty which is dedicated to develop approaches in a variety of cardiac diseases including atherosclerosis (eg coronary artery disease, ischaemic heart failure), infectious diseases (eg myocarditis, endocarditis, cardiac implantable electronic device (CIED) - infection) and infiltrative cardiac conditions (eg amyloidosis, sarcoidosis, Morbus Fabry). Since these are complex disease entities, it is of high importance in nuclear cardiology to set up an interdisciplinary team of experts. As an example at the University Hospital Essen, a close collaboration between the Clinic for Nuclear Medicine/Institute of Radiology at the University Hospital Essen and the West German Heart and Vascular Center has been established. Patients are examined by state-of-the-art molecular imaging approaches using SPECT/CT, PET/CT, and PET/MRI. In addition, a preclinical imaging facility including micro-PET/CT was set up to pursue new, promising research approaches and translate them from basic research into clinical application. Last but not least, a professorship for nuclear cardiology has been implemented to promote this promising field. The aim is for all these approaches to lead to the promotion of cutting-edge research and patient care.

What Heart Diseases Can We Image?

Using nuclear cardiology, a variety of cardiovascular diseases can be non-invasively assessed. The most important ones include imaging of ischaemia due to coronary artery disease, viability testing in ischaemic cardiomyopathy, and imaging of infective and infiltrative cardiac diseases such as endocarditis and sarcoidosis.

Coronary Artery Disease

Coronary heart disease remains the leading cause of death in the Western world despite improvements in acute care for myocardial infarction through rapid revascularisation and optimal drug therapy. In coronary heart disease, an increasing narrowing of the coronary arteries leads to a reduced perfusion of the dependent myocardium. As the disease progresses, the probability of a sudden blockage of a coronary artery due to thrombus formation increases, leading to myocardial infarction. Stenoses of the coronary arteries can be treated with percutaneous transluminal angioplasty and stenting, but numer-

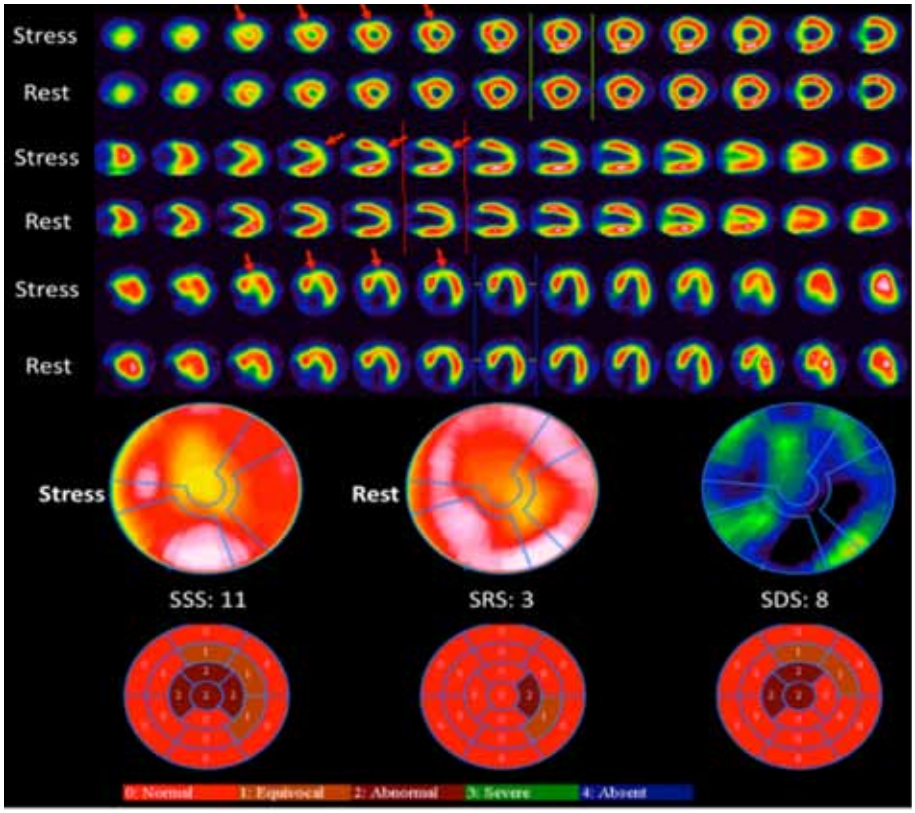

Figure 1. Myocardial perfusion scintigraphy demonstrating ischaemia.

This patient was examined using Tc-99m sestamibi SPECT/CT to rule out perfusion abnormalities. A reversible perfusion defect in the anterior wall and the apex (red arrows) was found, indicating ischaemia due to haemodynamic stenosis in the left anterior descending (LAD) territory. As the extent of ischaemia is more than 10%, revascularisation should be considered.
SSS = summed stress score, SRS = summed rest score, SDS = summed difference score

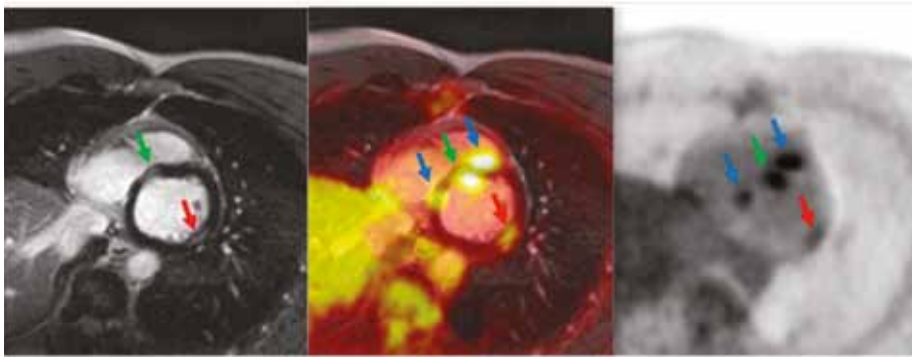

Figure 2. FDG PET/MRI of a patient with active cardiac sarcoidosis.

The examination was performed in case of suspected cardiac involvement in known systemic sarcoidosis. The MRI images show a midmyocardial LGE of the basal lateral wall with corresponding FDG uptake in PET (red arrow), which can be interpreted as an active myocardial sarcoidosis with beginning fibrosis. In addition, myocardial areas with intensive FDG accumulation without correlate in the LGE MRT can be detected (blue arrows), which are to be evaluated as active cardiac sarcoidosis without initiated fibrotic transformation of the myocardium. The green arrow also indicates active myocardial sarcoidosis of the basal septum, while the contrast enhancement in this area is most likely not due to myocardial damage, but rather fibrotic fibers of the upper part of the interventricular septum.

ous studies have shown that stenoses are the most likely to benefit from an intervention that impedes myocardial blood flow and causes ischaemia. With the help of myocardial perfusion scintigraphy as a non-invasive ischaemia test of the myocardium, the necessity of a cardiac catheter examination can be determined. In other words, myocardial perfusion scintigraphy has a gatekeeper function in the diagnosis of patients with coronary heart disease. A perfusion tracer is injected once under hyperaemic and once under resting conditions. Hyperaemia can be caused by physical stress (treadmill or bicycle ergometer) or pharmacological stress (adenosine, regadenoson, or dobutamine). After tracer injection, the stress or rest images are acquired using PET or SPECT. Based on the images obtained, a distinction can be made between normal findings, myocardial scar tissue, ischaemia, and mixed findings (Figure 1). Depending on the result, a decision must be made together with the cardiologist as to whether revascularisation is necessary or whether drug therapy and lifestyle changes with optimisation of the risk factors are sufficient.

> “NUCLEAR CARDIOLOGY REPRESENTS A DYNAMIC SUBSPECIALTY WHICH IS DEDICATED TO DEVELOP APPROACHES IN A VARIETY OF CARDIAC DISEASES”

Viability Imaging of the Heart

Coronary artery disease may result in ischaemia or myocardial infarction of the heart. Chronic or repetitive hypoperfusion of the heart may cause the heart muscle to stop contracting properly and lead to a syndrome called ischaemic cardiomyopathy. This typically manifests itself in symptoms such as shortness of breath, leg oedema, or pleural effusions. If the heart is hypoperfused but still vital, this is called 'hibernating myocardium.' Hibernating myocardium is characterised by a wall motion abnormality that is reversible after revascularisation. A typical characteristic of hibernating myocardial areas is also that they prefer the metabolisation of glucose instead of free fatty acids. It is also known that the presence and extent of hibernating myocardium is associated with cardiac events and poor prognosis, if no revascularisation is performed.

There are several approaches to non-invasively visualise myocardial vitality, which include stress echocardiography and stress MRI, myocardial perfusion

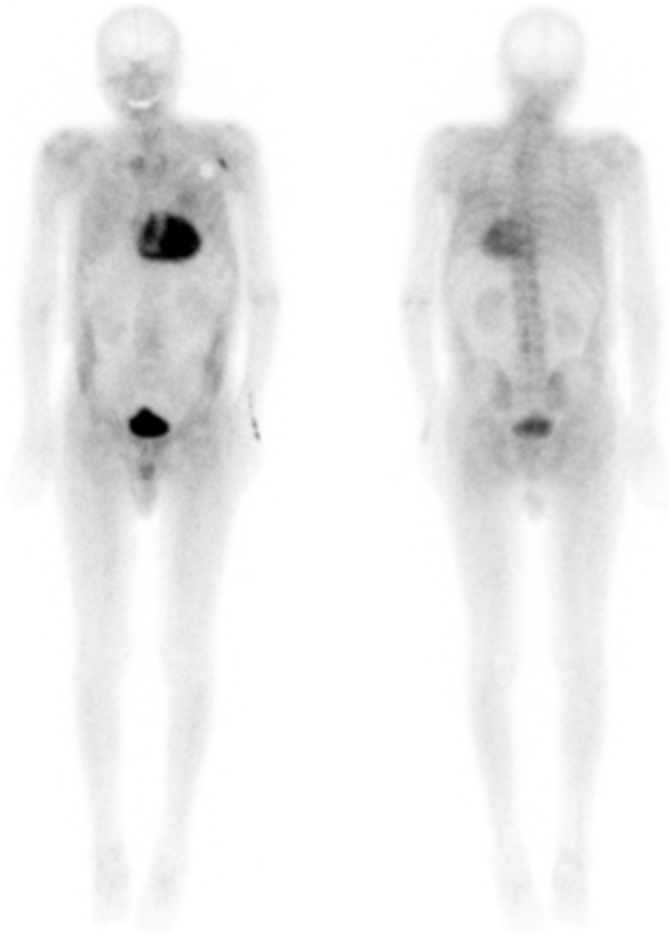

Figure 3. Tc-99m DPD scintigraphy of an 83-year old male patient with ATTR amyloidosis.

The delayed phase images of the skeletal scintigraphy show an intensive tracer accumulation of the heart (Perugini score 3), which allows the diagnosis of cardiac involvement of ATTR amyloidosis. Consequently, an endomyocardial biopsy is not required in this case

scintigraphy by SPECT using perfusion tracers, glucose metabolism imaging by F-18 fluorodeoxyglucose (FDG, a glucose analogue) PET, and late-gadolinium enhancement (LGE) MRI, which is ultimately imaging of myocardial scar tissue. In order to create ideal examination conditions, the patient must be specially prepared for FDG PET. Among the various methods used to achieve the best possible FDG uptake of the heart are oral glucose administration and simultaneous intravenous administration of glucose and insulin. If the FDG PET is combined with a perfusion study, the proportion of hibernating myocardium, ie the proportion of myocardium that is hypoperfused but has a normal or increased glucose metabolism, can be determined. LGE MRI, on the other hand, allows myocardial scar tissue to be visualised with contrast medium, since MRI contrast medium is washed out of scar tissue more slowly than from healthy myocardial tissue. FDG-PET is considered to have the highest sensitivity for the detection of vital myocardial tissue, while the MRI has a higher specificity. Therefore, it is expected that a combined PET/MRI will provide a very high diagnostic value and accuracy.

Infection and Inflammation

Both PET and MRI allow visualising inflammatory processes that play an important role in a variety of cardiac diseases such as myocarditis, cardiac sarcoidosis, or infectious endocarditis. With the help of MRI, myocardial fibrosis or oedema, pericardial effusions, and wall motion abnormalities can be detected with high sensitivity. In recent years, FDG PET has also been used with increasing frequency to visualise inflammatory processes in the heart. In particular, FDG PET allows to determine the extent of inflammatory processes and to distinguish between highly active, low-grad, or no longer active myocardial inflammation. As described in the previous section, cardiomyocytes also metabolise glucose and may therefore also show an intense FDG uptake. For this reason, it is necessary to minimise myocardial glucose metabolism prior to FDG PET if inflammatory processes are to be visualised. This is achieved by different methods to reduce the blood glucose level and to increase the free fatty acid level. These include an 'Atkins diet' (high-fat/low carb diet) the day before the examination, a longer fasting period (usually longer than 12 hours) immediately prior to the examination and the injection of unfractionated heparin prior to FDG. If the FDG is injected after such preparation, it is almost exclusively taken up by inflammation cells, and an FDG accumulation in the area of the heart thus represents inflammatory processes.

Myocarditis is an inflammatory, potentially life-threatening disease that can have several causes, the most common being a (viral) infection. The symptoms are often non-specific and of limited help in diagnosing the disease. While endomyocardial biopsy as an invasive procedure with a relatively high complication rate but only limited accuracy remains the reference procedure for the diagnosis of myocarditis, non-invasive imaging procedures are increasingly used. In a study at our institution, 65 patients with suspected myocarditis were examined by FDG PET/MRT, and a very high accuracy of the procedure was found. For this reason, FDG PET/MRT is regularly used in patients with suspected myocarditis at the University Hospital Essen.

Another inflammatory disease of the heart in which FDG PET/MRT is regularly used is cardiac sarcoidosis. Sarcoidosis is a multisystemic disease whose cause is unknown. Cardiac involvement is one of the most common causes of death in patients suffering from sarcoidosis and must, therefore, be excluded with a high degree of certainty. An increasing number of articles proves the value of the combined examination of LGE MRI and FDG PET. FDG PET can not only represent inflammatory processes of myocardial sections that are not yet scarred, but may also be used to graduate the acuteness of the disease.

> "BY APPLYING COMBINED FUNCTIONAL AND MORPHOLOGICAL IMAGING MODALITIES, PATHOPHYSIOLOGICAL PROCESSES OF CARDIAC DISEASES CAN BE VISUALISED"

The LGE MRI reflects already scarred myocardium - information that may be helpful in the context of implantation of a possibly required ICD due to cardiac arrhythmias. An example of a patient with active cardiac sarcoidosis is shown in Figure 2.

Cardiac Amyloidosis

Cardiac amyloidosis is another disease that has recently become increasingly important in cardiology and nuclear cardiology. Amyloidosis is a systemic disease that can ultimately involve any organ, with the heart, kidneys, liver, and autonomic nervous system most commonly affected. The vast majority of cardiac involvement in amyloidosis is monoclonal light chain (AL) or transthyretin (ATTR) amyloidosis. In patients with heart failure but preserved ejection fraction (HFpEF), cardiac amyloidosis is a common and often unrecognised cause, and the disease must, therefore, be safely excluded. Scintigraphy using osteotropic tracers (eg Tc-99m dicarboxypropane diphosphonate [DPD]) shows very high sensitivity, specificity, and positive predictive value for the diagnosis of cardiac ATTR amyloidosis. Cardiac AL amyloidosis, on the other hand, is usually negative in this examination and is therefore often diagnosed by endomyocardial biopsy. Using amyloid-specific PET tracers such as F-18 florbetaben or F-18 florbetapir, both AL and ATTR amyloidosis can be diagnosed and differentiated by the intensity of tracer accumulation. PET/MRI, therefore, has the potential to reliably diagnose cardiac amyloidosis: the extent of cardiac impairment can be quantified by MRI (eg impairment of left ventricular pump function, wall movement abnormalities, myocardial fibrosis) and the different amyloidosis subtypes can be differentiated by PET. An example of skeletal scintigraphy of a patient with ATTR amyloidosis and cardiac involvement is shown in Figure 3.

Conclusion

Nuclear cardiology has proven to be an important subspecialty of nuclear medicine. The main fields of application using imaging techniques such as SPECT/CT, PET/CT, and PET/MRT are coronary heart disease, heart failure, and inflammatory/infiltrative cardiac diseases. By applying combined functional and morphological imaging modalities, pathophysiological processes of cardiac diseases can be visualised, resulting in improved diagnostics with high accuracy and confidence. ■

KEY POINTS

- Nuclear cardiology is a dynamic subspecialty in nuclear medicine which allows non-invasive assessment of a variety of cardiac diseases
- Established methods include myocardial perfusion scintigraphy using Single-Photon Emission Computed Tomography (SPECT) and viability imaging of the heart using F-18 fluorodeoxyglucose (FDG) Positron-Emission Tomography (PET)
- Imaging of inflammation and infection (eg in cardiac sarcoidosis or myocarditis) or non-invasive diagnosis of cardiac amyloidosis are additional fields of application and the subject of current research

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