Cardiac involvement in various systemic conditions, such as inflammatory diseases (sarcoidosis and transplant rejection), storage diseases (amyloidosis, Fabry disease, and haemochromatosis), or cancer chemotherapy, is increasingly recognized as a key factor limiting patient survival. To guide preventive measures and therapy, early and accurate diagnosis of cardiac involvement is desired. This, however, often remains a challenge:

Endomyocardial biopsy is specific, but limited by its invasive nature which precludes its use as an early screening tool; and by sampling errors which may cause false-negative results in the case of biopsies from unaffected regions. Non-invasive functional imaging such as echocardiography, radionuclide ventriculography, or cine magnetic resonance imaging can be used to identify cardiomyopathy, but the detection of left ventricular dysfunction may be non-specific with regard to the underlying cause. Accordingly, there is a trend towards more specific techniques for non-invasive myocardial tissue characterization: advanced magnetic resonance techniques such as delayed gadolinium enhancement, fibrosis, or oedema imaging can be used to identify cardiomyopathy, but the detection of left ventricular dysfunction may be non-specific with regard to the underlying cause. Accordingly, there is a trend towards more specific techniques for non-invasive myocardial tissue characterization: advanced magnetic resonance techniques such as delayed gadolinium enhancement, fibrosis, or oedema imaging can be used to identify patterns of tissue alteration that are more specific to the underlying origin of cardiomyopathy. Also, radiotracer techniques are increasingly employed for targeting of molecular mechanisms involved in the systemic disease condition. Nuclear imaging with single-photon emission computed tomography (SPECT) or positron emission tomography (PET) can then be used for the detection of disease involvement throughout the whole body and in specific organs, including the heart. Owing to the specific nature of the tissue signal, these techniques may provide a non-invasive biopsy approach for the myocardium, which can be employed in earlier disease stages and for serial monitoring in response to therapy.

Sarcoidosis, a systemic granulomatous disease, is a prime example for the increasing role of molecular imaging. In this disease, there is a strong need for early detection of cardiac involvement, because it is considered as a major cause of death and because it can be treated with aggressive anti-inflammatory medication and preventive measures such as implantable cardioverter defibrillators can be employed. Owing to this clinical need, the use of the radiolabeled glucose analogue, F-18 fluoro-18-deoxyglucose (FDG), for PET imaging is increasingly penetrating the clinical arena in this setting, although supporting evidence is still relatively scarce.

Amyloidosis is another systemic disease where cardiac involvement is clinically relevant. Accordingly, various molecular imaging agents and techniques have been tested with regard to their feasibility. Those include FDG-PET of glucose utilization, I-123 meta-iodobenzylguanidine SPECT of cardiac innervation, and other non-specific SPECT markers of myocardial damage. Notably, they also include specific markers of amyloid deposit, which have been originally developed for brain amyloid PET imaging in dementia. These agents, for example C-11 Pittsburgh compound B, specifically bind to amyloid fibrils, but they do not allow for the separation between different types of amyloid pathologies.

In this issue of the European Heart Journal – Cardiovascular Imaging, Hutt et al. report about their experience with nuclear imaging in a large group of 300 patients with suspected amyloidosis, using a Tc-99m-labelled bone-seeking diphosphonate (DPD), which also binds to amyloid. They confirm prior work of other groups by showing an increased myocardial phosphonate uptake mostly in the transthyretin variant of amyloidosis (ATTR). Furthermore, they show a high accuracy when compared with biopsy and clinical criteria in their preselected population. Elegantly, they also show strength of nuclear imaging, namely the option for whole-body imaging, which provides information not only about cardiac involvement but also about other organs. Specifically, the authors noted varying degrees of soft-tissue uptake which masked the usual biodistribution of DPD to bone in a large fraction of cases. Finally, the authors propose an algorithm for the use of DPD imaging in suspected amyloid, where a scan pattern confirmative of ATTR amyloidosis can be used to establish the diagnosis and obviate the need for invasive
biopsy in the respective patients. Biopsy would then be restricted to uncertain cases or cases suspicious of other forms of amyloidosis.

What are the next steps? The authors clearly state that further mechanistic insights are needed to clarify the binding mechanism of DPD to amyloid. They state that such in vitro work is underway. Beyond this basic aspect, additional prospective clinical work seems warranted in order to further establish the value of molecular imaging in suspected and confirmed amyloidosis beyond its potential role in the initial diagnosis. A link between DPD scan-defined cardiac involvement and prognosis in ATTR amyloidosis has already been suggested in a small study of 63 patients and should be confirmed in larger registries. As a next step, algorithms by which imaging guides therapy may be explored, in order to define their value for improved survival. And finally, serial studies may be useful to obtain further insights into disease progression with and without a respective therapy.

In summary, the armamentarium for a non-invasive, biopsy-like characterization of myocardial tissue characteristics is steadily growing. In systemic diseases such as amyloidosis, this holds great promise for an earlier identification of cardiac involvement and, hence, for improved risk stratification and therapy management. Studies such as the one by Hutt et al. in this issue of the European Heart Journal – Cardiovascular Imaging provide a rationale for further exploration in prospective clinical projects.

References

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