SPECT and PET in Sympathetic Innervation

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CHAPTER 8

Summary, discussion and future perspectives

SUMMARY

This thesis provides farsighted insights in the presence of denervation in different patient groups, the outcome of patients with denervation and the value of SPECT and PET in predicting outcome. Cardiac amyloidosis is associated with denervation and therefore belonging to one of these indications. Amyloidosis in general is caused by misfolded proteins which are deposited throughout the body. Cardiac manifestation is a rare condition leading to a form of restrictive cardiomyopathy; which is mainly right-sided heart failure with restrictions in ventricular filling, resulting in liver enlargement, ascites and oedema. Echocardiography is the modality of choice for the assessment of cardiac amyloidosis. However, typical findings - focal or generalized echolucency (highly refractile echo's, or 'sparkling') and interatrial septum and left ventricular (LV) wall thickening – are usually present in more advanced stages of the disease. Imaging of cardiac sympathetic innervation is of interest in patients with cardiac amyloidosis, since these amyloid depositions can also be present along the sympathetic nerves, and thus leading to electromechanical dissociation.

Chapter 2 investigates the use of iodine-123 labelled meta-iodobenzylguanidine ([^{123}I]-MIBG) in three subgroups of patients with systemic amyloidosis: AL, ATTR, and AA type amyloidosis. Cardiac sympathetic innervation of the entire cohort of patients is disrupted compared to healthy control subjects. Amyloidosis patients who show typical features of cardiac involvement on echocardiography also show more severely impaired cardiac sympathetic innervation. In this study we demonstrate that in patients with ATTR type amyloidosis [^{123}I]-MIBG scintigraphy can detect cardiac manifestation even before typical echocardiographic features are present.

In **chapter 3** the clinical use of different nuclear medicine modalities for the assessment of ATTR amyloidosis are discussed. In addition to [^{123}I]-MIBG scanning, conventional bone scintigraphy can also detect cardiac involvement in patients with ATTR amyloidosis. Myocardial accumulation of bone scan tracers also detects cardiac amyloidosis before typical echocardiography features are present. Therefore, nuclear medicine modalities are useful to provide an overview of the extent and severity of cardiac involvement in this group of patients.

Chronic kidney disease (CKD) is another indication in which cardiac sympathetic innervation imaging is of interest. CKD can be a result of different underlying mechanisms, for example diabetes mellitus, hypertension, and atherosclerosis. Especially patients with end-stage kidney failure and those on renal replacement therapy (haemodialysis, HD) are at risk for cardiovascular morbidity and mortality, such as myocardial ischemia, myocardial infarction, ventricular arrhythmias, and sudden cardiac death. However, the traditional risk factors for cardiovascular events do not fully explain the higher prevalence of these events. Autonomic dysfunction is considered as a novel independent risk factor for cardiovascular morbidity. Uraemia is considered to contribute to an increase in sympathetic activity and thus impaired cardiac sympathetic innervation.

Chapter 4 focuses on the use of [^{123}I]-MIBG for denervation imaging in patients with CKD stage 5 who make the transition from the pre-dialysis phase to maintenance HD. Cardiac sympathetic innervation is already disrupted before the start of maintenance HD. The impaired cardiac sympathetic innervation does not seem to worsen during the first months of HD. However, cardiac sympathetic denervation before the start of HD precedes the development of myocardial perfusion abnormalities. This may further support the idea that the cardiomyocyte is more vulnerable to innervation changes than to perfusion alterations.

A third group of interest for cardiac sympathetic innervation imaging is patients with (non-) ischemic heart failure. In both ischemic and non-ischemic cardiomyopathy, myocytes surviving structural changes suffer from maladaptation to myocardial injury, resulting in pathological remodelling, consisting of dilation and reduced contractility. One of the mechanisms leading to progression of heart failure is neurohumoral activation of the sympathetic nervous system. This may already occur in early stages of the disease. Continuous stimulation of the sympathetic nervous system results not only in systemic effects, but also in myocardial electrical instability, and thus a higher risk on development of ventricular arrhythmias.

Chapter 5 describes the use of carbon-11 labelled meta-hydroxy-ephedrine ([^{11}C]-mHED) in patients with ischemic cardiomyopathy, treated with prophylactic implantable cardioverter defibrillator. This study evaluates the role of cardiac sympathetic denervation in patients with a low and high risk of ventricular arrhythmias. As expected, a history of ventricular arrhythmia leads to a higher prevalence of these arrhythmias during follow up. In addition, larger areas of denervation are associated with higher mortality.

Chapter 6 investigates the use of [^{11}C]-mHED in patients with non-ischemic cardiomyopathy treated with cardiac resynchronization therapy (CRT). We were not able to find a difference in mean [^{11}C]-mHED retention as a reflection of cardiac sympathetic innervation abnormalities from baseline to six months after the start of CRT. This lack of improvement is partially in line with earlier research. However, patients with an improvement of LV ejection fraction after the start of CRT did show an improvement in presynaptic cardiac sympathetic innervation. This may support the literature based idea that CRT not only restores postsynaptic β-adrenoceptor density and balance, but also may improve presynaptic norepinephrine retention.

Finally, patients with metastasized neuroendocrine tumours are studied. These tumours frequently produce serotonin, and in lesser extent also catecholamines. In case of metastatic disease, especially in the liver, serotonin is released in large amounts into the circulatory system. Due to the circulating serotonin, patients may suffer from carcinoid syndrome, such as flushing, diarrhoea and - in case of long-standing disease - carcinoid heart disease (CHD). Echocardiography is the modality of choice for the evaluation of CHD, which is characterized by right-sided valve thickening, and thus tricuspid valve insufficiency and pulmonary valve stenosis.

Furthermore some reports state that cardiac metastases can be considered as a feature of CHD.

In **Chapter 7** the value of L-3,4-dihydroxy-6-[^{18}F]fluoro-phenylalanine ([^{18}F]-FDOPA) in detecting cardiac metastases and the relationship of these metastases to the presence of typical characteristics of carcinoid heart disease on echocardiography is evaluated. The prevalence of these myocardial metastases, detected using [^{18}F]-FDOPA PET, is higher than previously assumed. There was no relationship between the presence of cardiac metastases and the development of cardiac arrhythmias or typical echocardiographic features of CHD. This further supports that both CHD and myocardial metastases are two different entities within the same disease.

DISCUSSION AND FUTURE PERSPECTIVES

Functional imaging using SPECT or PET based modalities will continue to play a pivotal role in diagnosis and response evaluation of treatment strategies. As a consequence of the rapid evolvements within this field, nuclear medicine is continuously improving its acquisition methods, searching for new indications for diagnosis and treatment, and establishing its additional value to existing anatomical imaging modalities. Also within nuclear cardiology there is a continuously need for non-invasive imaging techniques as reliable alternatives to, for example, biopsy procedures. This section focuses on new clinical indications and novel radiopharmaceuticals for evaluating the role of nuclear cardiac sympathetic innervation imaging within nuclear cardiology.

Further exploration of existing indications

In cardiac amyloidosis, the relationship between cardiac sympathetic innervation and autonomic function testing has not yet been fully investigated. At present, only one large trial investigated this relationship in 143 patients with ATTR type amyloidosis (1). Survival of patients with autonomic failure (apart from cardiac sympathetic innervation) was significantly reduced compared to patients with negative autonomic function tests. However, multivariate analysis identified cardiac sympathetic denervation as assessed by iodine-123 labelled meta-iodobenzylguanidine ([^{123}I]-MIBG) as the only independent prognostic predictor. Concerning AL type patients, large clinical trials on this topic are still lacking. Future studies should focus on the added value of cardiac sympathetic innervation imaging to autonomic function tests for blood pressure variability, skin autofluorescence, dynamic electrocardiography for heart rate variability (especially the standard deviation of normal beats, SDNN), and 12-lead electrocardiography.

Imaging of cardiac sympathetic innervation is not the only application of nuclear medicine modalities in the area of cardiac amyloidosis. There is an increasing need for (consensus-based) guidelines for image acquisition and images-based clinical decision-making in patients with cardiac amyloidosis, especially in those patients with normal findings on echocardiography. Several nuclear medicine imaging techniques apart from [^{123}I]-MIBG have become available for the diagnosis and prognostic stratification of cardiac amyloidosis during the last two decades. The different classes of radiopharmaceuticals are potentially able to bind different constituents of the amyloidotic infiltrates, with some relevant differences among the various etiologic types of amyloidosis and the different organs and tissues involved.

For example, bone seeking tracers (in particular diphosphonates) visualize cardiac amyloid of the ATTR type very specifically, at an early stage of the disease, and can be used to differentiate between the amyloid types, since AL amyloid shows only weak or no imaging at all (2). The nature of this specific binding to ATTR amyloid has not been clarified yet. The understanding of this phenomenon should be a challenge for the near future. Furthermore, it is important to further explore

the diagnostic value of serial bone scintigraphy in quantification, and to determine its role in disease progression and response to treatment in ATTR patients.

The introduction of hybrid camera systems makes superposition of physiological and anatomical information possible. The simultaneous acquisition of PET and MRI using hybrid PET/MRI systems is the most recent development in medical imaging. In MRI, gadolinium can be used as a contrast enhancement agent, which is an extracellular fluid tracer that accumulates in expanded interstitial place. Usually, in the intact myocardium, the distribution of gadolinium is very low and therefore gadolinium enhancement is absent. However, in case of myocardial interstitial space expansion, such as in amyloidosis due to extracellular amyloid infiltration, gadolinium concentration may increase within myocardial tissue. Therefore, evaluation of cardiac amyloidosis has the potential to become a unique application for PET/MRI, in which either modality provides complementary information, especially since the introduction of novel MRI sequences as non-contrast T1 mapping (3). Pittsburgh compound-B labelled with the positron emitter carbon-11 ([^{11}C]-PiB), derived from the amyloid stain thioflavin, as well as fluorine-18 ([^{18}F]) labelled florbetapir have been recently used as tracers for cardiac amyloid (4,5) with still inconclusive clinical results. However, PET tracer retention at the location of subendocardial delayed gadolinium enhancement or noncontrast T1 mapping may increase the positive predictive value of the presence of cardiac amyloidosis on either PET or MRI.

Finally, the combination of nuclear medicine modalities with proteomics may be a field worthwhile for exploration. In the subtypes of amyloidosis different proteins are both up- and down-regulated. The background of this alteration is yet not entirely clear and could either be reactive due to the disease or related to amyloid deposits in the microenvironment of the extracellular space. Proteomics may teach us about the specific composition of amyloid and surrounding tissue in order to develop new tracers that specifically target cardiac amyloid (6,7). Realizing unambiguous imaging of cardiac amyloid may fill two great clinical needs: early disease detection and reliable monitoring of a treatment effect. Targeting these proteins and visualizing their distribution in the body may lead to new insights within amyloidosis in general.

So, in conclusion, the future of nuclear medicine modalities for cardiac amyloidosis is not only limited to imaging cardiac sympathetic innervation abnormalities. The combination of different radiopharmaceuticals for functional information, and the addition to anatomical information from MRI, has the potential to further reduce the use of potential high-risk invasive procedures.

New indications

Nuclear medicine techniques can play an important role in rapidly evolving new areas within medicine. Sports medicine is one of these rapidly evolving areas. Apart from the obvious indications for bone scintigraphy to visualize or exclude osseous injuries, imaging of cardiac sympathetic innervation may be of special interest. For example, sympathetic innervation may play an important role in the development of (unexplained) sudden cardiac deaths in athletes. Actually, athletes with high sympathetic tone in the recovery phase after exercise appeared to have an increased cardiac vagal activity (8). This autonomic imbalance is probably the 'conditio sine qua non' for the induction of arrhythmias in the recovery phase.

Early exploratory studies in this field showed that [^{123}I]-MIBG uptake is decreased in athletes compared to normal control subjects, and that prolonged exercise further decreases this uptake (9-11). Furthermore, athletes with sinus bradycardia appeared to have a defect of [^{123}I]-MIBG uptake in the inferior wall, suggesting selective inferior wall denervation as a consequence of the increased vagal tone (12).

For better understanding the mechanism of cardiac sympathetic innervation abnormalities in athletes, future studies should focus on the development of dysinnervation in young athletes. For example, in rowers who are starting an intensive training programme to eventually deliver high-level maximum exercise. Sympathetic innervation in these athletes should be investigated in a prospective setting, in which [^{123}I]-MIBG is combined with electro- and echocardiography, for electrical and structural alterations. These investigations should be performed at baseline (before the start of the training programme) and at follow-up (immediately after the last matches), to evaluate whether the onset of intensive physical exercise is accompanied by the development of cardiac sympathetic denervation.

New radiopharmaceuticals

Presynaptic innervation

Although the value of [^{123}I]-MIBG for imaging cardiac sympathetic innervation abnormalities is well established, this tracer has some limitations. For example, image quality is relatively poor (in terms of spatial resolution) and the capabilities of quantitative analysis (modelling) are lacking. The introduction of the positron emitting radiopharmaceutical [^{11}C]-mHED has overcome these limitations. However its application is limited to those PET centres with an on-site cyclotron, due to the short half-life of the radionuclide [^{11}C] (approximately 20 minutes). Fluorine-18 [^{18}F] has a longer half-life (approximately 110 minutes), making it suitable for application on a prolonged distance from its production site: PET centres without an own on-site cyclotron. Therefore, radiopharmaceuticals containing [^{18}F] could be an attractive alternative for both [^{123}I]-MIBG and [^{11}C]-mHED.

One of the introduced [^{18}F]-labelled alternatives to [^{123}I]-MIBG and [^{11}C]-mHED may be meta-[^{18}F]fluorobenzylguanidine ([^{18}F]-MFBG). This fluoro analogue of [^{123}I]-MIBG is of special interest due to the placement of fluorine at the same position as that of iodine in MIBG, and should result in minimal structural alterations. However, in early reports about the production of [^{18}F]-MFBG, fluorodenitration with the activating group in the meta position resulted in a five-fold lower yield than its isomer para-[^{18}F]fluorobenzylguanidine ([^{18}F]-PFBG) (13). A major disadvantage of [^{18}F]-PFBG found in early preclinical studies is the strong affinity for uptake-2 mechanism in the cardiomyocyte, which acts as a confounder when the images are analyzed (14). Nonetheless, based on in vitro and in vivo analyses, [^{18}F]-MFBG showed great similarities to [^{123}I]-MIBG, especially regarding the presynaptic sympathetic nerve terminal uptake.

Recently, the yield of [^{18}F]-MFBG was slightly increased by reducing the reaction time and lowering the reaction temperatures during the synthesis, compared to the previous mentioned studies (15). Despite these improvements, the overall radiochemical yield of [^{18}F]-MFBG was merely 11 ± 2%. Nonetheless, the use of [^{18}F]-MFBG in the setting of neuroendocrine tumour cells in mice appeared to result in higher image quality than [^{18}F]-PFBG and [^{123}I]-MIBG. Furthermore, [^{18}F]-MFBG has an additional advantage of lower radiation burden due to the more rapid clearance of this more hydrophilic analogue (15,16). At present, the use of [^{18}F]-MFBG for cardiac sympathetic innervation imaging in humans has not been reported.

Another [^{18}F]-labelled radiopharmaceutical which has the potential to be an alternative to [^{123}I]-MIBG and [^{11}C]-mHED is the ligand for the norepinephrine transporter (*N*-[3-bromo-4-(3-1^{8}F- fluoro-propoxy)-benzyl]-guanidine ([^{18}F]-LMI1195) (17). Preclinical studies in rats showed that the heart-to-liver ratios of [^{18}F]-LMI1195 were high, even significantly higher than those of [^{123}I]-MIBG (17,18). This makes [^{18}F]-LMI1195 an attractive alternative for planar scintigraphy and SPECT.

Very recently, the first application of [^{18}F]-LMI1195 in twelve healthy volunteers has been reported (19). The data from this phase-1 clinical trial suggest that [^{18}F]-LMI1195 is a well-tolerated PET tracer for cardiac sympathetic innervation imaging with acceptable radiation dose. Its diagnostic accuracy in determining innervation abnormalities in humans is yet to be established.

Postsynaptic innervation

In addition to presynaptic sympathetic innervation imaging using norepinephrine analogues, it is also possible to measure postsynaptic β-adrenoceptor density on the cardiomyocyte. Changes in β-adrenoceptor density are of importance in the development of heart failure: β-adrenoceptor density is down-regulated as a consequence of enhanced sympathetic drive in heart failure (20,21). The PET tracer S-4-(3-([^{11}C]-isopropylamino)-2-hydroxypropoxy)-2H-benzimidazol-2-one ([^{11}C]-CGP12388) has the potential to monitor β-adrenoceptor remodelling induced by

therapeutic regimen (22). However, this has not yet been visualized. In a preclinical setting, [^{11}C]-CGP12388 seems to outperform [^{18}F] labelled tracers for (selective) β-adrenoceptor imaging (23,24).

Since cardiac resynchronization therapy is able to restore the β-adrenoceptor balance in patients with severe heart failure, this group of patients would be of great value for the proof of principle of this restoration visualized by [^{11}C]-CGP12388.

In conclusion, sympathetic innervation imaging is a continuously evolving field of interest within nuclear cardiology. Future studies using radiopharmaceuticals for both pre- and postsynaptic imaging should focus on absolute quantification of regional denervation and therapy induced changes in the β-adrenoceptor density, respectively, and to determine its value in the prediction for sudden cardiac death. Finally, the aim for the future should also concern inclusion of sympathetic innervation imaging into guidelines for clinical decision making.

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