I-123 metaiodobenzylguanidine innervation imaging as a tool for norepinephrine transporter research: A possible application for genetic analysis in heart failure

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Nuclear cardiology is widely used to characterize the physiologic condition of the muscles, blood vessels, and sympathetic nerves of the heart. Myocardial perfusion imaging, in combination with functional study with electrocardiographic gating, allows detection of myocardial ischemia and infarction in patients with coronary artery disease. While nuclear imaging evaluates perfusion at the myocardial cellular level, x-ray computed tomography and magnetic resonance imaging can be used to assess perfusion, and provide visualization of the coronary vascular anatomy responsible for different patterns of myocardial blood flow. However, for examining the status of myocardial sympathetic nerves, nuclear methods using the SPECT agent ^{123}I-mIBG or positron tracers such as ^{11}C-hydroxyephedrine,[1] ^{11}C-epinephrine,[2] ^{11}C-CGP12177,[3] and ^{11}C-Me@HAPTHI (preclinical)[4] provide unique information not available using anatomic imaging modalities.

^{123}I-MIBG UPTAKE MECHANISM

Norepinephrine transporter (NET) is responsible for reuptake of extra-cellular norepinephrine (NE) and dopamine, and plays an essential role for regulating sympathetic nervous transmission and function. Among the imaging agents available for studying the NET system, ^{123}I-mIBG, an analogue of NE, has been the most successfully utilized. ^{123}I-mIBG is taken up into the synaptic terminal primarily via NET-mediated reuptake (uptake 1), stored in synaptic vesicles, and released into synaptic clefts. Due to the different structure from norepinephrine, ^{123}I-mIBG does not bind to post-synaptic receptors and is not metabolized by monoamine oxidase or catechol-O-methyl transferase. However, as ^{123}I-mIBG and norepinephrine share the same uptake mechanism, the hypothesis that variation in the gene which codes for the NET system might influence ^{123}I-mIBG imaging findings, as explored in the study by Verschure et al, is understandable.[5]

^{123}I-MIBG IMAGING AS A CLINICAL TOOL

One of the major indications for ^{123}I-mIBG imaging is heart failure (HF). In Japan, after official approval of ^{123}I-mIBG (MyoMIBG, FUJIFILM RI Pharma, Co. Ltd) during 1992,[6] diagnostic and prognostic use of ^{123}I-mIBG is a class I indication, and use for examining the effect of medications is a class IIa indication.[7] In the USA, the indication for ^{123}I-mIBG (Adreview, GE Healthcare) is for risk assessment of patients with HF[8] with New York Heart Association functional classes II and III, based on the ADMIRE-HF multicenter study.[9]

Editorial for the Journal of Nuclear Cardiology on: Derk Verschure, et al. Polymorphism of SLC6A2 gene does not influence outcome of myocardial ^{123}I-mIBG scintigraphy in patients with chronic heart failure.

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Table 1. Areas of research and clinical interest regarding ^{123}I-mIBG and NET system

Physiology, pathophysiology
Development of new radiotracers for NET system
Genetics of NET
Appropriate kinetic model
Age and gender dependency of ^{123}I-mIBG
Effect of medications on ^{123}I-mIBG parameters
Clinical applications of ^{123}I-mIBG in cardiology
Coronary artery disease
Cardiomyopathies
Arrhythmogenicity
Heart failure, diagnosis, and prognosis
Treatment effects by medications
Indications of cardiac devices for lethal arrhythmia
Chemotherapy and drug-induced cardiotoxicity
Denervation/reinnervation
Clinical applications of ^{123}I-mIBG in neurology
Lewy body diseases including Parkinson disease, dementia with Lewy bodies, and pure autonomic failure

NET norepinephrine transporter

In Europe, cardiac indications for ^{123}I-mIBG vary by country and often do not specifically refer to HF patients.

Other cardiac utilizations of ^{123}I-mIBG imaging besides for HF, for both physiological and pathological conditions, are listed in Table 1. In Japan, since indications of ^{123}I-mIBG were widely approved in cardiac diseases, various applications of both clinical and pathophysiological bases have been investigated. The most effective application was cardiac diseases related to ischemia, which included acute and subacute phase of infarction,[10] coronary spastic angina, and unstable angina. Neurological application for Lewy body disease is also widely used, which included Parkinson disease, dementia with Lewy body disease (DLB) and pure autonomic failure.[11,12] Since prodromal DLB and diagnostic overlap with Alzheimer disease and DLB are also known to exist, diagnostic ability of ^{123}I-mIBG in such atypical cases has been noted.[13]

SIGNIFICANCE OF REDUCED ^{123}I-MIBG UPTAKE

As decrease in ^{123}I-mIBG uptake is observed in a wide variety of pathophysiological conditions, does ^{123}I-mIBG reflect results of secondary myocardial damage and dysfunction or any cause of diseases? Sympathetic activity suppression may be seen in spastic angina[14] and Takotsubo cardiomyopathy, but imaging defects could be the result of ischemic condition at a microcirculation level. In conditions when transmural or scattered fibrosis occurs, even in infarction and cardiomyopathies, both regional myocardial perfusion and innervation are affected. Sympathetic defect on ^{123}I-mIBG images is always larger than perfusion defect, and the regional mismatch may be related to the occurrence of ventricular tachycardia or lethal arrhythmogenicity.[15] As such, although the pathophysiological meaning of derangement of activity with respect to causal relationship remains unknown, abnormal ^{123}I-mIBG activity in the heart is a sensitive and sometimes early finding to identify NE transporter abnormality. Even when genetic influence on NET system is demonstrated in patients with HF, secondary myocardial damage unrelated to genetic abnormalities may coexist. In addition, contribution of non-specific ^{123}I-mIBG uptake (non-NET-mediated) on early and late imaging findings is not well understood. Therefore, careful differentiation between a true genetic effect and HF-related myocardial damage will be required.

^{123}I-MIBG AND RESEARCH ON NET

Verschure et al evaluated the NET (uptake-1), encoded by the solute carrier family 6 (SLC6A2),[5] in a series of HF patients undergoing ^{123}I-mIBG imaging. Although several single-nucleotide polymorphisms (SNP) were found in their study, none of the SNPs were functional. Thus, it is not surprising that no associations were found between these polymorphisms and any ^{123}I-mIBG parameters of cardiac sympathetic activity such as heart-to-mediastinum (H/M) ratio or washout rate. Functional variations in NET SNPs are known to exist in psychiatric and cardiovascular phenotypes such as idiopathic postural orthostatic intolerance, and therapeutic applications for regulating NET system have been sought in attention-deficit hyperactivity disorder, neurodegenerative disorders, depressive disorders, and other psychiatric diseases.[16,17] However, the likelihood that such variants would be found in a broad heterogeneous population of HF patients is small. The question of whether presence of functional NET SNPs might play a role in development or progression of HF, and thereby be detectable using functional imaging such as with ^{123}I-mIBG, remains unanswered. Even if there is a connection between NET SNPs and HF pathophysiologic condition, it would probably require genomic analysis of thousands of patients to characterize the association. Given the complex pathophysiological factors that influence cardiac ^{123}I-mIBG kinetics, such as storage, release, and reuptake, much more work to elucidate genetic influences on cardiac uptake of ^{123}I-mIBG is needed.

EXPECTATION FOR TECHNOLOGICAL IMPROVEMENTS IN TRACER KINETICS

The study of Verschure et al represents only a starting point for examining the relationships between NET genetics in HF and ^{123}I-mIBG kinetics. The H/M ratio is a very crude parameter to analyze whole-heart kinetics of MIBG, although it is a practical tool for clinical evaluation of risk in HF. Standardization of methodology for calculating H/M ratio improves its usefulness with different camera systems and risk model creation.[18,19] Nevertheless, more precise analysis using positron tracers allows determination of parameters such as receptor binding capacity, rate constants, and volume of reaction as in cardiac beta-adrenergic receptor study with ^{11}C-CGP 12177.[3] Analysis using ^{11}C-hydroxyephedrine uses parameters of clearance or retention parameters.[1] Improvements in ^{123}I-mIBG imaging are possible using high-resolution and high sensitivity cadmium-zinc-telluride cameras, which permit dynamic SPECT acquisitions.[20] Further, absolute quantification with a unit of Bq/cm^3 is feasible using SPECT/CT. Appropriate kinetic modeling is also indispensable for analyzing kinetics around the sympathetic terminal. New radiotracers such as ^{11}C-Me@HAPTHI offer promise for better demonstration of the NET system,[4] and these preclinical investigations may lead to development of clinically effective parameters that reflect NET activity. Finally, electrocardiographic and respiratory gating may be required for analyzing a moving heart. At present, we cannot expect such complete quantification using ^{123}I-mIBG. However, H/M ratio may be used for the initial evaluation to find the possible abnormality before proceeding to precise kinetic analysis.

^{123}I-MIBG FOR PATHOPHYSIOLOGICAL STUDIES AND PERSPECTIVES OF NET IMAGING

^{123}I-mIBG innervation imaging can be a powerful tool to supplement information provided by other imaging modalities. In clinical settings, clinical usefulness and effectiveness should be further validated for the evaluation of severe or lethal events including HF death, sudden cardiac death, and arrhythmic death. For physiological/pathophysiological indications, suitable reference standards are needed in order to understand the significance of ^{123}I-mIBG results in populations with disease. For example, age-dependent physiological decline in ^{123}I-mIBG uptake was observed in some studies.[21,22] ^{123}I-mIBG uptake was decreased after an exposure to altitude hypoxia.[23] In addition, potential influence of pre-examination medical treatments is still not confirmed systematically, except for reserpine, labetalol, and tricyclic anti-depressant.[24]

Within the next few years, it is likely that further research will show that genetic variations in NET coding can affect susceptibility to sympathetic nerve dysfunction, predispose patients with heart disease to develop HF, or affect responsiveness to HF therapeutics. When such genomic discoveries are made, molecular imaging including SPECT and/or PET of NET function should be a part of the characterization of the functional significance of the genomic results. Before going to the era of generalized NET imaging, further studies on basic characteristics of ^{123}I-mIBG are still required, even as research on new NET system radiotracers and appropriate kinetic modeling techniques continues.

Disclosure

The authors have no conflict of interest to disclose for this editorial.

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