Imaging Cardiac Neuronal Function and Dysfunction

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In recent years, the importance of alterations of cardiac autonomic nerve function in the pathophysiology of heart diseases including heart failure, arrhythmia, ischemic heart disease, and diabetes has been increasingly recognized. Several radiolabeled compounds have been synthesized for noninvasive imaging, including single photon emission CT and positron emission tomography (PET). The catecholamine analogue I-123 metaiodobenzylguanidine (MIBG) is the most commonly used tracer for mapping of myocardial presynaptic sympathetic innervation on a broad clinical basis. In addition, radiolabeled catecholamines and catecholamine analogues are available for PET imaging, which allows absolute quantification and tracer kinetics modeling. Postsynaptic receptor PET imaging added new insights into mechanisms of heart disease. These advanced imaging techniques provide noninvasive, repeatable in vivo information of autonomic nerve function in the human heart and are promising for providing profound insights into molecular pathophysiology, monitoring of treatment, and determination of individual outcome.

Introduction

The autonomic nervous system plays an important role for regulation of cardiac performance under various physiologic and pathophysiologic conditions. Nuclear imaging techniques provide noninvasive information about global and regional myocardial autonomic innervation at pre- and postsynaptic level. The following review summarizes currently available information on the use of nuclear medicine imaging of autonomic nervous system.

Biology of the Sympathetic Nervous System

The regulation of cardiac function is achieved, in principle, by the cardiac muscle fiber length and its tension as an consequence of ventricular volume and pressure through the operation of Starling's law of the heart [1]. However, it is well known that the autonomic nervous system is important for cardiac adaptation to the varying demands of daily life [2]. The central nervous system collects data such as blood pressure, flow, and chemical milieu via receptors located in the left ventricle, carotid sinus, aortic arch, and brainstem, which are connected via afferent neurons. Based on the collected information, the autonomic nervous system controls heart rate, speed, and pattern of ventricular contraction via efferent neurons. The autonomic nervous regulation is also determined by circulating hormonal factors such as catecholamine, angiotensin II, vasopressin, arterial natriuretic peptide, brain natriuretic peptide (BNP), and endotheline-1 [3]. These neuronal activations are usually beneficial in the early stages of heart failure. Adversely, neuronal activation plays an important role in the vicious cycle of advanced heart failure by increasing myocardial energy requirements, afterload, and arrhythmias.

The central component of the cardiac autonomic nervous system is in the medulla where sensory afferent and efferent neurons form complex network loops [4]. They consist of the sympathetic and parasympathetic nervous system, with their major neurotransmitters being norepinephrine and acetylcholine, respectively [5]. The sympathetic nervous system exerts positive inotropic effects, whereas the stimulation of the parasympathetic system results in negative inotropic and chronotropic effects [5].

Sympathetic nervous system

Sympathetic nervous fibers are well distributed throughout the entire myocardium. They travel along epicardial vascular structures and penetrate the myocardium with coronary vessels. The sympathetic neurotransmitter norepinephrine is generated from tyrosine in the presynaptic ending of sympathetic nerves, via dihydroxyphenylalanine and dopamine. Norepinephrine is stored in terminal

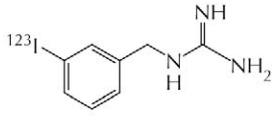
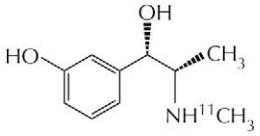
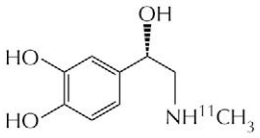
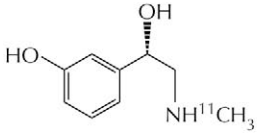
Compound	Chemical structures	Type	Main biologic target
I-123 metaiodobenzylguanidine		Catecholamine analogue	Presynaptic uptake
C-11 hydroxyepinephrine		Catecholamine analogue	Presynaptic uptake
C-11 epinephrine		Catecholamine	Presynaptic uptake and storage
C-11 phenylephrine		Catecholamine analogue	Presynaptic uptake and metabolism

Figure 1. Radiotracers for sympathetic nerve imaging of presynaptic level.

vesicles by energy requiring vesicular amine transporter (VMAT) [6]. Voltage-dependent calcium channels open as a firing impulse arrives at the synaptic ending releasing norepinephrine into the synaptic cleft via exocytosis. Only a small part of the norepinephrine in the cleft binds to adrenoreceptors including α- and β-adrenoreceptors; β1-receptors are predominant in cardiac myocytes. Most of the norepinephrine is reabsorbed into nerve ending via the presynaptic uptake-1 transporter [7]. Uptake-1 plays an important role to regulate extraneuronal catecholamine concentration protecting the heart from rapidly changing plasma catecholamine levels. There is a second re-uptake mechanism into nonneuronal tissue (cardiocyte and vascular endothelial cell) mediated by the so-called uptake-2 transporter [8]. This uptake-2 mechanism, unlike the uptake-1 mechanism, is not dependent on energy and sodium concentration and is important in ATP depletion conditions such as ischemia. A small fraction of norepinephrine released into the neural cleft spills over into vascular space and can be measured in coronary sinus vein blood [9]. In addition to neuronal stimulation, there are a number of regulatory mechanisms by presynaptic receptors, including α2-adrenergic receptor, that provide negative feedback for exocytosis [10]. Radiolabeled tracers of catecholamine and catecholamine analogues used for single-photon emission CT (SPECT) and positron emission tomography (PET) imaging share the same uptake-1 mechanism and endogenous storage characteristics as the true neurotransmitters and can provide information about the functional integrity of the nerve terminal [11].

Parasympathetic nervous system

The parasympathetic nervous system predominantly counteracts the effects of sympathetic function and is essential for maintaining homeostasis of heart function [5]. Parasympathetic neurons are distributed mainly in the atria and conduction nodules. The density of parasympathetic neurons within myocardium is low compared with sympathetic neurons rendering them a difficult target for nuclear imaging. Acetylcholine is the main neurotransmitter in parasympathetic neurons and is synthesized from choline at the nerve endings. It is transported via the vesicular acetylcholine transporter into storage vesicles. Upon nerve stimulation, acetylcholine is released from the nerve terminals to the neuronal cleft and binds to muscarinic receptors (M2-subtype) on the myocyte, activating changes in cardiac ion channel function [12,13].

Imaging of the Cardiac Autonomic Nervous System

There are several radiolabeled tracers to evaluate the sympathetic and parasympathetic nervous systems at pre- and postsynaptic levels. Commonly utilized SPECT and PET tracers for presynaptic sympathetic innervation are either true catecholamine or catecholamine analogues (Fig. 1) [14–19]. Radiolabeled true neurotransmitters follow the entire metabolic pathways, whereas analogues are resistant to specific steps of metabolisms. The specificity for the presynaptic uptake-1 transporter and vesicular storage inside the nerve terminal varies among currently available tracers [14–19].

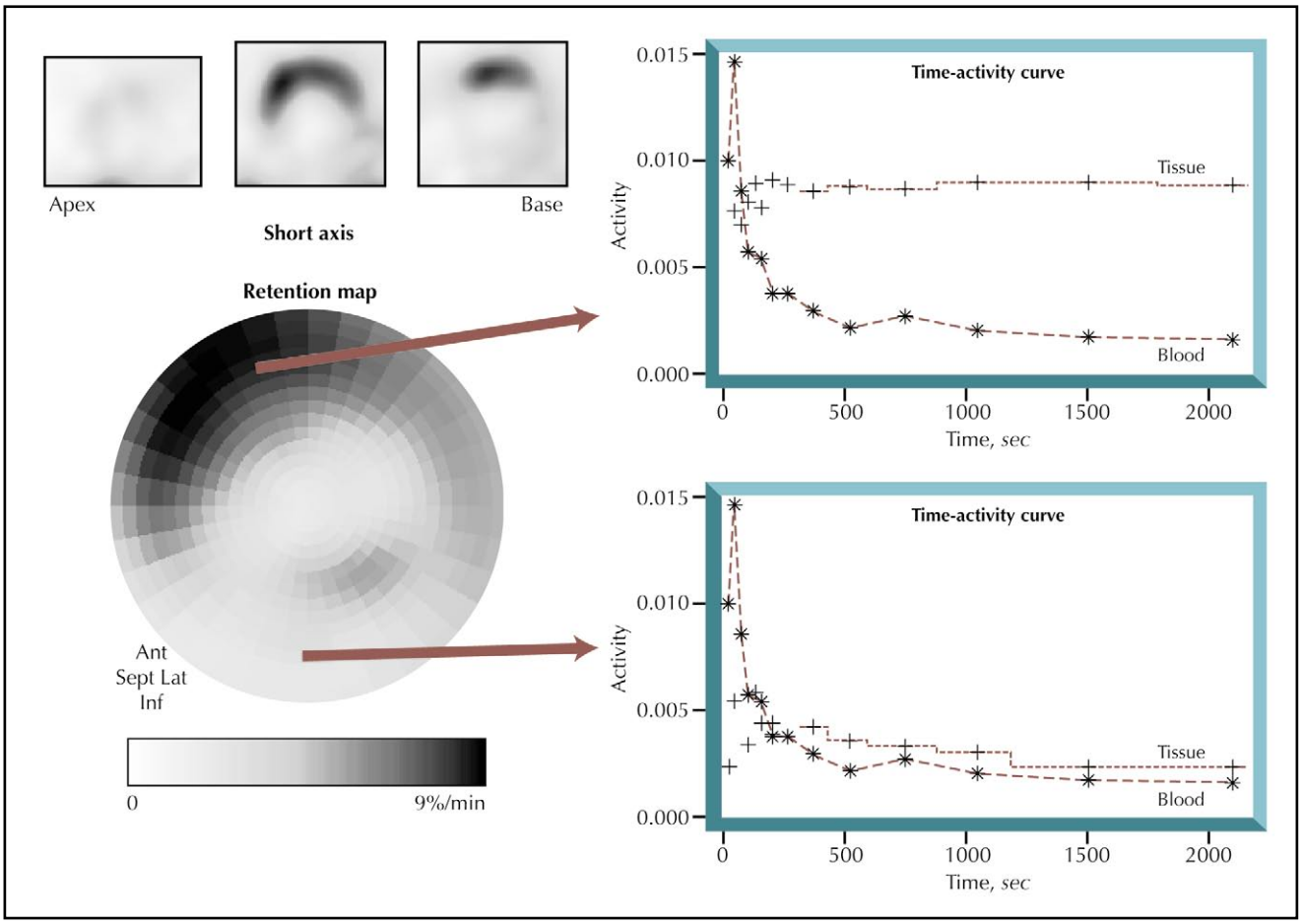


Figure 2. A tracer retention polar map of the left ventricle and time-activity curves for blood and myocardial tissue as obtained by dynamic C-11 hydroxyephedrine of a cardiac transplant recipient at 3 years after transplantation. Anteroseptum wall area shows reinnervation, but the inferolateral wall area remained denervated. Curves from a segment with normal sympathetic innervation (*top*) and from abnormal innervation (*bottom*).

I-123/I-131 metaiodobenzylguanidine

I-123/I-131 metaiodobenzylguanidine (MIBG) is a most commonly employed SPECT tracer for myocardial sympathetic innervation imaging at the presynaptic level [20,21]. This agent is an analogue of norepinephrine that is modified based on the chemistry of the potent neuron blocking agents guanethidine and bretylium. Intravenously administered plasma MIBG that travels to the neural cleft is also believed to undergo heart uptake through the two uptake mechanisms. Although approximately 30% of the heart uptake in the rat, mouse, and dog is via an unspecific uptake-2 mechanism, most of the heart uptake in humans reflects specific neuronal uptake (uptake-1) [22–24]. Additionally, MIBG is metabolically resistant to monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT) enzymes unlike the true neurotransmitter norepinephrine [20]. Thus, the MIBG stored in the vesicle of the nerve ending shows longer retention than norepinephrine without further metabolism. When a firing impulse arrives at the terminal, stored MIBG is released to the cleft again and is taken up in the neuronal tissue via uptake-1 transporter or spillover into the blood. MIBG does not show any biologic activity to the norepinephrine receptor. Consequently, possible factors for decreased MIBG uptake and retention are enhancement of norepinephrine release from nerve ending, deterioration of uptake-1 transporter (eg, ATP exhaust), decreased density of sympathetic nerve endings, competitive inhibition with norepinephrine. Generally, imaging with MIBG includes a planar and tomographic SPECT acquisition with a two-step protocol at 15 to 30 minutes (early phase) and 3 to 4 hours (delayed phase) after MIBG injection. Kinetics can be determined by comparing initial uptake and delayed retention as well as regional distribution of uptake [25].

C-11 meta-hydroxyephedrine

C-11 meta-hydroxyephedrine (HED) is a norepinephrine analogue that is the most frequently used PET tracer for sympathetic nerve imaging in human studies [19,26]. Plasma HED is transported into cardiac sympathetic nerve terminals via the uptake-1 mechanism. Highly neuronal specific uptake in the heart has been proven with

92% reduction of myocardial HED uptake by selective neuronal uptake-1 blockage using desipramine. Vesicular storage seems to occur, but binding inside vesicles is low due to a higher lipophilicity of HED compared with norepinephrine. Similar to MIBG, because HED is metabolically resistant to MAO and COMT enzymes, the retention in myocardium mainly reflects a continuing release and re-uptake of HED in the sympathetic nerve [27]. HED PET can quantify the retention fraction of HED in myocardial tissue to the arterial input function. PET tracers offer several advantages over single photon approaches in spatial resolution, sensitivity and the ability of quantification. In addition, the concentrations of the tracer in blood and in myocardial tissue and their changes over time can be quantified and, therefore, application of tracer kinetics permits modeling-sensitive measurements of biologic behavior of the tracers (Fig. 2).

Other PET tracers for sympathetic innervation

There are additional PET tracers for sympathetic innervation in the presynaptic level including C-11 epinephrine (EPI) and C-11 phenylephrine (PHEN) [28,29]. They both are vulnerable to cytosolic MAO degradation and allow assessment of neuronal uptake and vesicular storage with PET scan. These different available C-11–labeled tracers reflect different mechanisms of norepinephrine metabolism in sympathetic nerve endings and may be combined to identify more specific pathophysiology on processes of norepinephrine uptake, vesicular storage, and metabolism in presynaptic adrenergic nerve terminals [19].

PET tracers for postsynaptic receptor imaging

Several postsynaptic receptor ligands have been labeled and proposed as PET tracers for cardiac imaging [14,30]. However, the clinical use of receptor-targeted tracers has been limited to a few studies and still faces significant challenge. High specific binding, high affinity, and hydrophilicity, which avoids binding to internalized inactive receptors, lack of pharmacologic effects and, finally, a simple and reliable tracer synthesis are requirements that must be met for a widespread application of receptor ligands for cardiac PET. C-11 CGP12177, a hydrophilic nonselective β-adrenoreceptor antagonist, is still the most widely used tracer for adrenergic receptor imaging [31]. Synthesis of this tracer is not simple and requires C-11 phosgen as a precursor, which has prevented a broader clinical application until now. CGP12177 has high specific affinity and fast plasma clearance, suggesting feasibility for clinical imaging. A graphical method, which adjusts for kinetics related to metabolites, has been established for quantification in humans [32]. This approach requires a dual-injection protocol with tracer doses of high and low specific activity. β-adrenergic receptor density (Bmax) measured by C-11 CGP12177 PET correlated well with in vitro measurements of myocardial samples in both healthy volunteers and patients with congestive cardiomyopathy. C-11 CGP12388 is another recently introduced nonselective β-adrenergic receptor antagonist. C-11 CGP12388 can be labeled easier than CGP12177 via a one-step procedure using 2-C-11-acetone [33]. It is more hydrophilic than C-11 CGP12177 and the biodistribution and retention of CGP12388 is reported to be similar to CGP12177 [34,35].

PET tracers for parasympathetic nerve imaging

F-18 fluoroethoxybenzovesamicol (FEOBV) is a specific tracer that binds to the acetylecholine transporter on parasympathetic neurons [36]. Unfortunately, specific binding in the heart is low and the usefulness of the tracer for clinical cardiac PET imaging is considered low. PET imaging of cardiac parasympathetic neurons is complicated due to the low density of cholinergic neurons within the ventricular myocardium and the parasympathetic neurotransmitter mechanism, which is highly specific for acetylcholine, that is very rapidly metabolized in blood. C-11 methylquinuclidinyl benzilate (MQNB) is a tracer for parasympathetic muscarinic receptors [37]. PET studies in healthy volunteers demonstrated rapid plasma clearance and heart uptake mainly in the ventricular septum and in the left ventricular wall, whereas the atria were not visualized [38,39].

Autonomic Nerve Imaging in Heart Disease

The transplanted heart

The transplanted heart is completely denervated by transsection of nerve fibers at transplantation surgery. There is little retention of MIBG or HED in myocardium early after operation reflecting denervation of the allograft. Reinnervation of the myocardium has been observed with MIBI/SPECT and HED/PET measurements in basal anterior myocardium years after transplantation (Fig. 2). However, complete restoration of sympathetic innervation was never observed even up to 14 years after transplantation [40–44]. There studies suggest slow partial reinnervation of the transplanted human heart. Several groups studied the in reinnervation the transplanted heart as a model of regional denervation. They showed that the sympathetic innervation is associated with improvement of endothelial-dependent vascular reactivity regulation, response of heart rate, and ventricular function [45–47]. These results support the functional importance of reinnervation of transplanted hearts, and may guide further therapies employing neuronal growth factor or stem cells.

Diabetes mellitus

Neuropathy is one of the major complications of diabetes mellitus, which involves the autonomic nervous system. A pattern of regional myocardial denervation due to cardiac diabetic neuropathy has been described, which involved apical, inferior, and lateral segments of the

left ventricle using HED PET and MIBG SPECT [48,49]. This heterogeneous sympathetic dysfunction in diabetes has been considered as a pathophysiologic factor for the development of lethal arrhythmias and may be supported by the enhanced cardioprotection from β-blockade observed in these subjects [48]. Kiyono et al. [50] provided molecular insights into the mechanism of sympathetic nerve dysfunction using diabetic rat. They showed that regional myocardial sympathetic dysfunction as shown by MIBG correlates with enhanced polyol pathway which leads to an heterogeneous decrease of norepinephrine transporter expression. Further study by Di Carli et al. [51] reported that the flow response to sympathetic stimulation by cold pressor test was reduced in patients with cardiac neuropathy defined with HED imaging than in those without neuropathy. Whether imaging of the cardiac sympathetic nerve imaging can provide prognostic information requires prospective study protocol. Imaging may be useful monitoring progress and regression of autonomic dysfunction in diabetic patients with and without therapy.

Ischemic heart disease

Cardiac sympathetic nerve terminals are reported to be more sensitive to ischemia than myocardial cells [52]. Clinical studies using MIBG have shown sympathetic nerve injury in patients without myocardial infarction such as patients with unstable angina [53,54]. Minardo et al. [55] show that the defect of MIBG is larger than the region of infarction in canine model. Matsunari et al. [56] confirmed these findings in patients undergoing reperfusion therapy for acute coronary syndromes. The neuronal damage as assessed by MIBG was well correlated with the sintigraphic risk area as defined by MIBI SPECT prior to intervention. Kasama et al. [57] have recently demonstrated that nicorandil, an ATP-sensitive potassium channel opener, has beneficial effects on sympathetic nerve function evaluated with MIBG imaging and ventricular remodeling in patients with acute myocardial infarction. Whether the amount or degree of sympathetic nerve damage in ischemic heart disease is related to outcome remains to be determined.

Heart failure

Dysfunction of the autonomic nervous system is an inherent feature of heart failure. The pathophysiologic importance of alterations of the autonomic system has been increasingly emphasized. SPECT and PET imaging has contributed significantly to the understanding of the role of autonomic innervation in the failing heart.

A number of clinical studies reported abnormal MIBG findings such as impaired early and delayed uptake and enhanced washout from early to delayed uptake in patients with heart failure [21]. The synaptic nerve endings in the heart failure patients shows enhanced norepinephrine release, decreased efficacy of norepinephrine re-uptake, and decreased norepinephrine storage. Because MIBG shares the same uptake-1 mechanism as norepinephrine, but is resistant to metabolism by MAO and COMT, the abnormal findings may reflect the decrease of MIBG storage secondary to enhanced MIBG release and decreased MIBG re-uptake via the uptake-1 mechanism.

Combined evaluation of pre- and postsympathetic nerve function using PET can provide further insights into the pathophysiology of sympathetic nerve function in heart failure. Ungerer et al. [58,59] demonstrated a mismatch of the presynaptic and postsympathetic system in cardiomyopathic heart failure patients using PET before heart transplantation. They reported that presynaptic sympathetic nervous uptake-1 density did not correlate with β-adrenoreceptor density but rather correlated with expression of receptor inactivating enzyme β-adrenoceptor kinase. Regulation of levels and activity of β-adrenoreceptor kinase are considered to play an important role in the developing of heart failure.

Merlet at al. [60] reported for the first time the significance of MIBG imaging as a prognostic factor. The low heart to mediastinum uptake ratio of MIBG identified high-risk patients, and was the best predictor for survival compared with other indices such as ejection fraction. Recently, Kyuma et al. [61] assessed synergistic prognostic value of MIBG imaging and other factors in patients with heart failure. The hazard ratio of elevated BNP or delayed MIBG uptake for fatal pump failure was increased to 34 when both indicators were present.

Nakata et al. [62••] tested whether MIBG imaging can predict an improved prognosis using angiotensin-converting enzyme inhibitors or β-blockers in patients with heart failure. They showed that when MIBG uptake was maintained, the therapies reduced the risk of mortality twice as much as compared with the other group, which showed impaired MIBG uptake. These findings demonstrate an attractive approach to MIBG nerve imaging for the management of heart failure patients, but require further confirmation with larger prospective studies.

Arrhythmia

An abnormal autonomic nervous system appears to be associated with lethal arrhythmias [63,64]. The precise relationship between arrhythmia and sympathetic nerve dysfunction is not clear, but enhanced β-adrenoreceptor stimulation is thought to one of the possible mechanism for lethal arrhythmia. The enhanced stimulation of β-adrenoreceptors causes a down-regulation of adrenoreceptors, which is associated with up-regulation of G-protein and subsequent activation of adenylyl-cyclase. The activation leads to an increased level of intracellular cyclic AMP (cAMP). The cAMP will produce a rise in intracellular calcium ion levels via protein kinase A. The heterogeneity of local calcium transients in the myocardium may cause triggering of the lethal arrhythmias by dispersion of local repolarization times.

In recent trials, the implantable cardioverter defibrillator (ICD), which can convert episodes of ventricular

fibrillation and tachycardia to sinus rhythm, has been shown to improve survival of patients [65,66]. Arora et al. [67•] evaluated the possibility of autonomic nerve imaging using MIBG to select patients who would benefit from an ICD therapy. The group with at least one episode of discharge of ICD showed significantly larger MIBG defects and lower uptake in the heart than those without episode of discharge. These data indicate the possibility of MIBG imaging for predicting lethal arrhythmias. Further confirmation is required by currently performed clinical trials.

Conclusions

The important role of the autonomic nervous system in heart disease has been known for many years. Advanced PET and SPECT imaging techniques can provide noninvasive measurement of global and regional presynaptic nerve terminal integrity and receptor function. Imaging allows for a unique functional characterization of cardiac innervation, which may be especially attractive for clinical research and evaluation of new therapeutic strategies to restore neuronal function. There is increasing evidence that neuronal imaging can provide prognostic information. Quantitative parameters derived from images may add to the value of other biomarkers in defining individual risk for cardiac complication. This may be extremely useful for selecting patients for costly new therapies such as ICD implantation. Further clinical studies are needed to support the widespread clinical application of neuronal imaging.

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- •• Of major importance

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