Imaging of myocardial receptors: applications in the evaluation of cardiac disease

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Abstract

Several positron labelled radiopharmaceuticals have been used to assess cardiac neurotransmission both at presynaptic and postsynaptic level. Some tracers compete with endogenous noradrenaline for the transport into the presynaptic nerve terminal mainly via the neuronal uptake-1 transport system. Several beta-blocking drugs have been labelled with 11C to act as radioligands for imaging the study of postsynaptic receptors by PET. The most extensively used is 11C-(S)-CGP 12177. This is a non-selective β-adrenoceptor antagonist with high affinity and low lipophilicity. Studies in patients have demonstrated diffuse down-regulation of β-adrenoceptor density in hypertrophic cardiomyopathy and in congestive heart cardiac failure, two disorders where there is evidence of elevated levels of sympathetic activation.

Keywords: alpha adrenergic receptor, beta adrenergic receptor, cardiomyopathy, heart failure, PET

Positron emission tomography (PET) is commonly used to study cardiac metabolism by means of fluorine-18-labeled ([18F]) 2-fluoro-2-deoxyglucose (FDG). Left ventricular dysfunction is the endpoint of a progressive disorder that can be initiated by events damaging the myocytes or disrupting the ability to generate force, such as myocardial infarction, hemodynamic pressure, volume overload, or genetic cardiomyopathies. The common pathways, independent of the initiating event, are the compensatory mechanisms activated to preserve cardiac functional capacity. The most powerful compensatory mechanism is perhaps the activation of the sympathetic nervous system, resulting in an increase in adrenergic drive to the left ventricle.

Several positron-labeled radiopharmaceutical agents have been used to assess cardiac neurotransmission, at both presynaptic and postsynaptic levels. Four tracers have been used to study presynaptic sympathetic terminals: [18F]fluorometaraminol [1,2], carbon-11-labeled ([11C]) hydroxyephedrine (HED) [3] and [11C]epinephrine [4]. These tracers compete with endogenous norepinephrine for transport into the presynaptic nerve terminal, mainly via the neuronal uptake-1 transport system (Figure 1). Once within the neuron, these compounds are metabolized and trapped, and hence serve as markers of sympathetic innervation.

To date, [11C]HED has been the tracer of choice in the clinical setting to study and quantify alterations in autonomic innervation. In the early stage after myocardial infarction, the area of reduced retention of [11C]HED was found to exceed the perfusion defect [5], indicating a greater sensitivity of sympathetic neurons to ischemia that was confirmed by the finding of reduced retention of [11C]HED in patients with advanced coronary artery disease but without a detectable myocardial infarction [6]. Denervation
of the heart has been demonstrated by decreased retention of \[^{11}C\]HED in patients after cardiac transplantation [7] or diabetes [8]. Using the same technique, it has been possible to demonstrate the occurrence of sympathetic re-inervation in the anteroseptal regions of the heart [9]. This has been correlated with recovery both of the sensation of angina pectoris and of contractile function in these patients [10,11]. As illustrated in Figure 2, both pre- and postsynaptic myocardial autonomic function can be assessed non invasively by combining different tracers [12,13], for example \[^{11}C\]HED and \[^{11}C\](S)-CGP 1217.

Several \(\beta\)-blocker drugs have been labeled with carbon-11 to act as radioligands for imaging the status of postsynaptic receptors by PET [14]. Of these, the most extensively used is \[^{11}C\](S)-CGP 1217. This is a non selective \(\beta\)-adrenoceptor antagonist that is particularly suited for PET studies because of its high affinity and low lipophilicity, thus enabling the functional receptor pool on the cell surface to be studied [15]. A graphical method has been developed for the quantification of \(\beta\)-adrenoceptor density \(B_{\text{max}}\) (pmol/g of myocardium) from the PET data [16], providing parametric images of receptor concentration obtained without having to measure the input function.

Figure 1. Diagram illustrating the \[^{11}C\] labelled hydroxyephedrine (HED) transport model. NE, neuroeffector; U-1, uptake-1.

Figure 2. (a) Measurement of pre- and postsynaptic sympathetic innervation of the heart. Cardiac images in a patient suffering from hypertrophic obstructive cardiomyopathy. Left: Presynaptic sympathetic innervation measured with \[^{11}C\] labeled hydroxyephedrine (\[^{11}C\]HED). Right: \(\beta\)-Adrenoceptor density measured with \[^{11}C\] labeled (S)-CGP 1217 (\[^{11}C\]CGP). (b) Left: Catecholamine re-uptake in patients with hypertrophic cardiomyopathy (HCM) and control individuals, measured as volume of distribution (\(V_{\text{d}}\) mL/g) of \[^{11}C\]HED (means are indicated by the horizontal lines). Right: Maximum number of available binding sites \(B_{\text{max}}\) (pmol/g) for \(\beta\)-adrenoceptors in patients with HCM and control individuals, measured using \[^{11}C\]CGP (means are indicated by the horizontal lines). (Modified from [12], with permission.)
metabolites, and protein binding [17]. Studies in our institution [18] in a group of healthy individuals over a broad range of ages have yielded Bmax values of 8.4 ± 2.0 pmol/g of myocardium, a figure that is comparable to the values measured using in-vitro binding (Figure 2) [19].

Adrenergic neuroeffector axis abnormalities [20–22] are the hallmark of progressive myocardial dysfunction, and the salutary effects of β-blocking agents point to the detrimental effect of chronically increased β-adrenoceptor signaling. Both the norepinephrine uptake-1 mechanism and β-adrenoceptor density are reduced in the myocardium of patients with chronic left ventricular dysfunction, and have been demonstrated non invasively in hibernating myocardium [23] and in congestive cardiac failure [24]. The increased sympathetic activity to the heart in these patients is a generalized phenomenon that is likely to contribute to the remodeling process of the entire left ventricle. In keeping with this, downregulation of myocardial β-adrenoceptor density has been demonstrated in patients with coronary artery disease in the subacute phase of myocardial infarct, in the absence of symptoms or signs of congestive heart failure. Furthermore, the degree of myocardial β-adrenoceptor downregulation was directly related to the degree of left ventricular remodeling, 6 months after infarction [25]. As in ischemic cardiomyopathy, in dilated cardiomyopathy also, β-adrenoceptor density is downregulated and is correlated to left ventricular ejection fraction and symptoms of heart failure (judged by New York Heart Association class) [26].

Adrenergic stimuli trigger life-threatening arrhythmias that are difficult to treat. Two disorders in which there is a broad range of evidence for chronically increased levels of sympathetic nervous system activation and diffuse downregulation of β-adrenoceptor density are hypertrophic cardiomyopathy (HCM) [12,27] and arrhythmogenic right ventricular cardiomyopathy [28]. To investigate further the relationship between left ventricular function and changes in neural control of the heart in patients with HCM, we assessed [18] left ventricular function by echocardiography and myocardial β-adrenoceptor density by PET in a group of patients with HCM – one subgroup with, and another without, heart failure. Myocardial β-adrenoceptor density was directly proportional to ventricular function in patients with HCM, whether or not there were signs of heart failure.

Investigation of the α-adrenergic receptors is the next step in the characterization of myocardial autonomic trafficking. α1-Adrenoceptor density has been found to alter as a result of myocardial ischemia [29], and the receptors have also been implicated in the development of ventricular hypertrophy [30,31]. Preclinical data are available for α1-adrenoceptors in rats [32,33] and large animals [34] (Figure 3); to date, only pilot studies have been performed in man [32].

In addition to studies of the sympathetic nervous system, the density and affinity constants of myocardial muscarinic receptors have been evaluated non invasively with PET and [11C]methylquinulinyl benzilate (MQNB), a specific hydrophilic antagonist, both in experimental animals [35] and in man [36,37]. In patients with congestive heart failure resulting from idiopathic dilated cardiomyopathy, the mean receptor concentration (Bmax) was significantly greater (34.5 ± 8.9 pmol/g) than that in normal individuals (25 ± 7.7 pmol/g), with no changes in affinity constants [37] – a clear indication that congestive heart failure is associated with an upregulation of myocardial muscarinic receptors paralleling the downregulation of β-adrenoceptors. A number of new ligands for different receptors in the heart are being developed and await further confirmation of their potential to provide a better insight into cardiac pathophysiology in the clinical arena. Preliminary studies in man have been carried out to image the distribution and uptake in the heart of two highly selective ligands for μ and δ opioid receptors:

![Figure 3. Positron emission tomography images (20–90 min) after injection of 5.29 MBq/kg [11C]GB67 (left panel) and after pre-dosing with unlabeled GB67 given 20 min prior to [11C]GB67 (right) in an animal model. The bed of the scanner is drawn for clarity.](image-url)

Data obtained in experimental studies in dogs have shown the feasibility of the use of PET for non invasive quantification of dihydropyridine L-type Ca2+ channels with the antagonist 3-ethyl-5-methyl-(+)-(2-(2-aminoethoxy)ethoxy)methyl-4-(2,3-dichlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (S12968) labeled with carbon-11 [39].

The technical development of new hybrid PET–computed tomography scanners with the possibility of dual respiratory and cardiac gating could, in the near future, allow the imaging of active plaques in the epicardial coronary arteries. To date, active, inflamed plaque imaging has been performed with [18F]FDG in the carotid, iliac, and femoral arteries, with good reproducibility [40]. [11C]PK11195 is a selective ligand for the peripheral benzodiazepine receptor (PBR) which is expressed in various tissue and organs, including macrophages [41]. Inflammation is characterized by macrophage infiltration [42] and can be detected by PBR binding. At present, tracers such as [11C]PK11195 are under study to monitor either systemic arterial therapies or local, plaque-based, therapy.

REFERENCES


