EDITORIAL

Imaging of cardiac adrenergic innervation

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Development of radioactive tracers to probe both pre- and postsynaptic sympathetic function has made possible a more widespread non-invasive assessment of the sympathetic nervous system

Cardiac myocytes and the coronary circulation are innervated by both sympathetic and parasympathetic fibres which constitute the autonomic nervous system.[1 2] The autonomic outflow is controlled by regulatory centres in the midbrain, hypothalamus, pons, and medulla which integrate inputs from other brain areas as well as afferent stimuli from the periphery. The efferent signals follow descending pathways in the lateral funiculus of the spinal cord that terminate on cell bodies in the intermediolateral and intermediomedial columns. Sympathetic fibres leave the spinal cord at T1–L2-3. These myelinated preganglionic fibres synapse in the paravertebral ganglia while small unmyelinated postganglionic fibres connect with body organs.[3] Sympathetic innervation to the heart is provided by fibres originating from a series of ganglia which constitute the cardiac plexus. These fibres branch and terminate as sympathetic nerve endings in atrial and ventricular tissue. The main neurotransmitter of the sympathetic system is noradrenaline (norepinephrine) that, after its release by sympathetic nerve terminals, can bind to a series of different postsynaptic receptors (α and β) whose activation determine the stimulatory and inhibitory effects of the system.

Under normal circumstances sympathetic activation results in an increased heart rate (chronotropic effect), a more forceful contraction (inotropic effect), and enhanced atrioventricular conduction (dromotropic effect). Dysfunction of the sympathetic nervous system is thought to play a pathogenetic role in a number of cardiac diseases, including arrhythmias,[4] dilated and hypertrophic cardiomyopathies,[5 6] postinfarction remodelling, and congestive heart failure.[7]

STUDYING THE SYMPATHETIC NERVOUS SYSTEM

For many years the in vivo study of the sympathetic nervous system in patients was confined to the catheter laboratory (for example, spillover of noradrenaline in the coronary sinus) or was limited to the measurement of circulating catecholamines. Development of radioactive tracers to probe both pre- and postsynaptic sympathetic function with single photon (SPET) or positron emission tomography (PET) (table 1) has made possible a more widespread non-invasive assessment of the sympathetic system in a number of conditions.[8]

In this issue of *Heart*, Marketou and colleagues[9] studied ventricular sympathetic innervation and perfusion in 22 patients with sick sinus syndrome and indications for permanent dual chamber pacing. All patients underwent planar and SPET myocardial imaging after intravenous infusion of ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) and ^{201}thallium, respectively, before and after pacemaker implantation. Twenty healthy age matched individuals served as a control group and underwent both ^{123}I-MIBG and ^{201}thallium scanning.

The main finding of the study was that the heart to mediastinum activity ratio for ^{123}I-MIBG was significantly reduced in patients compared to controls ($p < 0.001$). Furthermore, the patients had regional ^{123}I-MIBG defects, mostly in the inferior and apical ventricular walls, which deteriorated after three months of pacing while no changes in the ^{201}thallium scan could be detected.

This study offers the unique opportunity to assess the effect of chronic ventricular pacing on myocardial adrenergic function. ^{123}I-MIBG has been obtained through a modification of the potent neuron blocking agent guanethidine that acts selectively on sympathetic nerve endings. Uptake of ^{123}I-MIBG into neurons is achieved mainly through the uptake-1 mechanism, a homeostatic system responsible for the reuptake of noradrenaline. The uptake-1 mechanism is therefore one of the main noradrenaline disposal systems and its malfunction may lead to abnormal catecholamine concentration in the synaptic cleft. For instance, a reduction in ^{123}I-MIBG retention, as reported by Marketou and colleagues,[9] may be caused by a reduced uptake-1 mechanism that, in turn, may be the indicator of an abnormal noradrenaline concentration in the synaptic cleft. Accordingly, we have recently demonstrated, using ^{11}C- hydroxyephedrine (a tracer similar to ^{123}I-MIBG) with PET, a reduced uptake of this tracer in patients with hypertropic cardiomyopathy.[10] In the same patients a simultaneous downregulation of myocardial β adrenoceptors was demonstrated using ^{11}C-CGP-12177 with PET (fig 1). From a pathophysiological point of view, a chronic reduction in catecholamine reuptake should lead to increased local neurotransmitter concentration in the synaptic cleft which can be responsible for the downregulation of myocardial β adrenoceptors.

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Abbreviations: ^{123}I-MIBG, ^{123}I-metaiodobenzylguanidine; PET, position emission tomography; SPET, single photon emission tomography

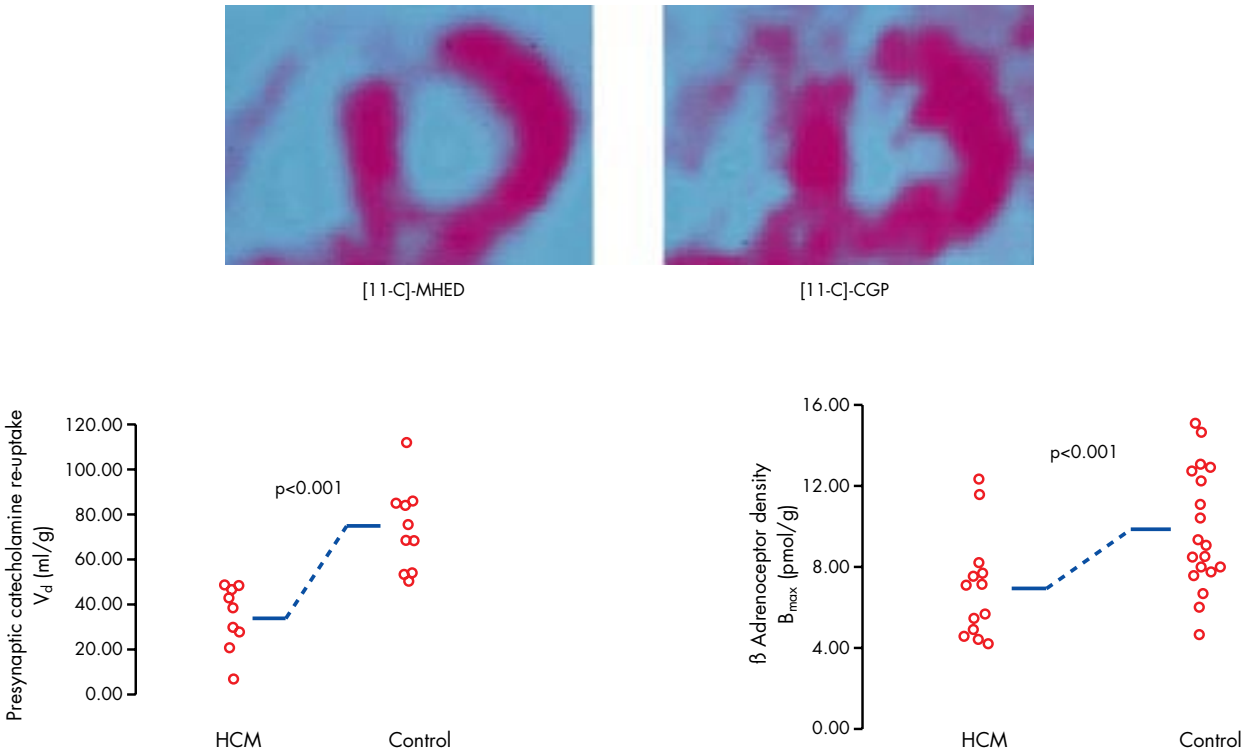

Figure 1 Top panels: Left—short axis PET image of the heart obtained after injection of [^{11}C]-hydroxyephedrine ([^{11}C]-MHED). Right—short axis PET image of the heart obtained after injection of [^{11}C]-CGP 12177 ([^{11}C]-CGP). The images were obtained in the same patient with hypertrophic cardiomyopathy (HCM). Bottom panels: Left—presynaptic catecholamine reuptake in HCM patients and controls measured by the volume of distribution (V_d, ml/g) for [^{11}C]-hydroxyephedrine. Right—maximum number of available binding sites (B_{max}, pmol/g) for β adrenoceptors in HCM patients and controls measured using [^{11}C]-CGP 12177. Note that receptor downregulation in patients is parallelled by a reduced presynaptic catecholamine reuptake. Adapted from Schafers and colleagues.[10]

β ADRENOCEPTOR DOWNREGULATION

Unlike patients with congestive heart failure, we could not find any significant increase in circulating catecholamines in our patients with hypertropic cardiomyopathy, despite the demonstration of myocardial β adrenoceptor downregulation. These data support the pathophysiological model proposed by Bristow and colleagues[11] and suggest that increases in local neurotransmitter concentrations rather than in circulating catecholamines are responsible for myocardial β adrenoceptor downregulation in hypertropic cardiomyopathy.

The mechanisms responsible for the regional abnormalities in ^{123}I-MIBG retention in the patients studied by Marketou and colleagues[9] remain to be elucidated. In particular, the effects of chronic ventricular pacing on myocardial adrenergic function deserve further investigation in view of the increased number of indications for chronic pacemaker implantation—for example, in the treatment of congestive heart failure. Non-invasive imaging of cardiac adrenergic innervation with SPET and PET can provide further insight into this interesting and clinically relevant issue.

Table 1 Three most commonly used tracers for cardiac sympathetic imaging

Targeted process	Radiopharmaceutical	Imaging modality
Presynaptic uptake-1 and storage of noradrenaline	^{123}I-MIBG	SPET
Presynaptic uptake-1 and storage of noradrenaline	^{11}C- hydroxyephedrine	PET
Postsynaptic β adrenoceptors	^{11}C-CGP-12177	PET

^{123}I-MIBG, ^{123}I-metaiodobenzylguanidine; PET, position emission tomography; SPET, single photon emission tomography

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