The cardiac sympathetic nervous system in health and disease

Anatomically the heart, particularly the left ventricular (LV) myocardium, has dense sympathetic innervation. Postganglionic neurons originate in the thoracic, stellate and cervical ganglia of the sympathetic chain, and run alongside the coronary arteries from the base to the apex of the heart, innervating myocardium and blood vessels along the way. Sympathetic nerve stimulation causes rapid release of the neurotransmitter nor-epinephrine (NE) from presynaptic terminals, which activates adrenergic receptors (adrenoceptors) on the surface of adjacent cardiac myocytes (figure 1). This leads to changes in chronotropy, inotropy and lusitropy (relaxation) via G-protein-coupled intracellular mechanisms.

Abnormal sympathetic function is an important component of the pathogenesis of heart failure. Increased sympathetic tone initially aids the failing cardiovascular system, raising cardiac output through an increase in heart rate and myocardial contractility. However, long-term overstimulation leads to increased peripheral vascular constriction and salt and water retention, increasing afterload and preload on the heart. There are also direct toxic effects on the myocardium, with increased risk of arrhythmias, desensitisation of adrenoceptors, and triggering of myocyte death by apoptosis.

Cardiac sympathetic function can also be disrupted following myocardial infarction, with damage not only to sympathetic neurons innervating the infarcted territory itself, but also to fibres running through the infarct zone on their way to innervate more apical regions of the left ventricular myocardium. This may produce an area of viable and perfused but denervated muscle, which could act as a substrate for subsequent ventricular arrhythmias. Some studies have also demonstrated abnormal cardiac sympathetic function in the setting of advanced coronary artery disease without prior infarction.

Cardiac sympathetic abnormalities have been implicated in the pathogenesis of hypertrophic cardiomyopathy. It is suggested that sympathetic overstimulation produces trophic factors that contribute to left ventricular hypertrophy, while excess NE provokes myocyte growth, fibre disarray and scarring. This theory could explain why β-blockers are beneficial in hypertrophic cardiomyopathy.

Principle of cardiac 123I-MIBG scintigraphy

Meta-iodobenzylguanidine (MIBG) is an analogue of NE with similar pharmacokinetic properties, allowing it to be used in the assessment of sympathetic function (figure 2). Following intravenous injection, MIBG is taken up into presynaptic nerve terminals via the NE transporter membrane protein, and stored in vesicles (figure 1). In contrast to NE and other endogenous catecholamines, MIBG is not metabolised by either the monoamine oxidase or catechol O-methyltransferase enzyme systems. Thus, the uptake of MIBG within the LV myocardium reflects the anatomical and physiological integrity of sympathetic nerve terminals.

When labelled with the radionuclide iodine-123, the distribution of MIBG can be imaged scintigraphically with a gamma camera. This allows non-invasive evaluation of global and regional sympathetic nerve function using planar or single photon emission computed tomography (SPECT) imaging respectively.

123I-MIBG scintigraphy was initially used in humans for the investigation of catecholamine producing tumours of the adrenal medulla, such as phaeochromocytoma and neuroblastoma. Although shown to be feasible more than 20 years ago, cardiac 123I-MIBG imaging has not been widely used in clinical practice in the UK. Recently there has been a resurgence of interest, particularly in the setting of heart

![Figure 1](image1.png)

**Figure 1**
Representation of sympathetic nerve terminal. Norepinephrine (NE) is released from storage vesicles, and acts on post-synaptic myocardial adrenoceptors, as well as on pre-synaptic adrenoceptors which regulate subsequent NE release. Excess NE is taken back up by the presynaptic terminal via the membrane NE transporter protein, and is reincorporated into storage vesicles or metabolised. MIBG is also taken up by the NE transporter, but cannot be metabolised.

![Figure 2](image2.png)

**Figure 2**
Molecular structure of MIBG (right) compared with norepinephrine (left).
Technical aspects of cardiac \(^{123}\text{I}\)-MIBG scintigraphy

Following thyroid blockade with oral potassium iodide or perchlorate approximately one hour previously, \(^{123}\text{I}\)-MIBG (185–400MBq) is injected intravenously at rest. Planar imaging is carried out 10-15 minutes after initial injection, and is then repeated 3-4 hours later. Images are acquired in an anterior projection; medium energy collimators are optimal, but low energy high resolution collimators are also acceptable. Image acquisition typically takes 15 minutes, with the main energy window for iodine-123 set at 159keV (±10%); simultaneous acquisition of a 194keV (±10%) window allows scatter correction of the \(^{123}\text{I}\)-MIBG images. SPECT acquisition can also be performed, though poor counts in the inferior LV wall are frequently seen, and uptake in extracardiac organs (liver and lungs) may limit image quality.

The two sets of planar images can be used to derive quantitative measures of global LV sympathetic function, including the early and late heart-to-mediastinum (H:M) ratio and the myocardial washout rate (Figure 3). Early H:M ratio is a measure of the density of innervation and NE transporter function, washout rate assesses sympathetic tone, and late H:M ratio is a reflection of both. H:M ratios are derived by manually drawing separate regions of interest (ROIs) around the entire heart (H) and in the upper mediastinum (M), and measuring the counts per pixel within the two regions; both values can be scatter-corrected by subtracting the counts per pixel obtained from the same ROIs on the 194keV energy window images. The H:M ratio is simply derived by dividing the corrected Heart ROI counts per pixel by the corrected Medistinal ROI counts per pixel. The upper mediastinal ROI is a suitable background region as there is little or no sympathetic innervation in that area.

Washout rate quantifies sympathetic tone by measuring the reduction in myocardial counts from early to delayed images. The calculation can be refined by subtracting background Medistinal counts from the Heart counts, and also by correcting for radioactive decay. The formula used is given below, adapted from Ogita et al:

\[
WR = \frac{[H]_e - [M]_e}{(0.5)(1/T)} - \frac{[H]_d - (M)_{ROI}(0.5)(2/T) \times 100}{[H]_e - [M]_e} / (0.5)(1/T)
\]

\([H]_e\) = mean counts per pixel, heart ROI, early acquisition; \([H]_d\) = as above, delayed acquisition; \([M]_e\) = mean counts per pixel, mediastinum ROI, early acquisition; \([M]_d\) = as above, delayed acquisition; \(t\) = time from isotope injection to early imaging; \(t'\) = time from isotope injection to delayed imaging; \(T\) = half-life of \(^{123}\text{I}\)-MIBG, 13.3 hours.

SPECT imaging may provide additional information regarding relative regional sympathetic function. \(^{123}\text{I}\)-MIBG images can also be viewed alongside those obtained from conventional myocardial perfusion SPECT in order to evaluate ‘mismatch’ between innervation and viability/perfusion, which has been hypothesised to be a substrate for arrhythmias.

Controversy remains over which of the values derived from \(^{123}\text{I}\)-MIBG scintigraphy characterises cardiac sympathetic activity most accurately. Much of the recent literature has focussed on late H:M ratio as the preferred measure. A pooled meta-analysis of \(^{123}\text{I}\)-MIBG imaging studies found that washout rate and particularly late H:M ratio appeared to be the best predictors of prognosis in patients with heart failure.\(^8\)

Cardiac \(^{123}\text{I}\)-MIBG scintigraphy and prognosis in heart failure

Abnormalities of \(^{123}\text{I}\)-MIBG uptake and washout on scintigraphy have been demonstrated in patients with ischaemic heart disease, dilated cardiomyopathy and idiopathic ventricular arrhythmias. Moreover, these abnormalities predict adverse cardiac events including death and ventricular arrhythmia: \(^{123}\text{I}\)-MIBG uptake is a stronger predictor of prognosis in heart failure than left ventricular ejection fraction (LVEF). LV volumes and several other haemodynamic parameters.\(^7,9-12\)

The recent AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) study provides the most up-to-date insight into the prognostic value of \(^{123}\text{I}\)-MIBG imaging.\(^3\) This large prospective international study recruited 961 patients with predominantly NYHA class 2 heart failure symptoms and LVEF <35%, on full pharmacological treatment. The underlying aetiology was coronary artery disease in 66%. Patients underwent \(^{123}\text{I}\)-MIBG imaging, and were followed for two years to determine the occurrence of adverse events. The composite event rate was inversely related to late H:M ratio: 15% for a value \(\geq 1.6\) (21% of the study population) and 37% for a value <1.6. The late H:M ratio separately predicted the occurrence of all-cause death, cardiac death, heart failure progression and life-threatening arrhythmia, and provided information that was complementary to LVEF and BNP level.

Other studies have demonstrated improvements in \(^{123}\text{I}\)-MIBG imaging parameters with conventional drug therapy for heart failure, including \(\beta\)-blockers, spironolactone and angiotensin-converting enzyme inhibitors.\(^3,4,13\) Non-pharmacological treatments also produce improvements, including cardiac resynchronisation therapy (CRT) devices and LV assist devices (LVADs).\(^14,15,16\, unpublished data

\(^{123}\text{I}\)-MIBG and arrhythmia risk

\(^{123}\text{I}\)-MIBG scintigraphy provides robust prognostic data in heart failure, but this may be insufficient to lead to its adoption into routine clinical practice. A relatively expensive investigation is only likely to be widely used if it can be shown to guide patient management. One promising area is the use of \(^{123}\text{I}\)-MIBG scintigraphy in the selection of patients for implantable cardioverter defibrillator (ICD) devices. ICDs can reduce mortality and prevent potentially life-threatening arrhythmias in high risk individuals. Recent trials have progressively extended the indications for ICD implantation to include not only patients who have suffered a previous arrhythmic episode (secondary prevention),\(^17,18\) but even those who simply have significantly impaired LV systolic function whether due to ischaemic heart disease or a dilated cardiomyopathy (primary prevention).\(^19,20\) However, many individuals, particularly in the primary prevention group, will never suffer an arrhythmia requiring therapy from their device.\(^21\) Moreover, there are considerable drawbacks to device therapy, including the high cost, the risk of peri-procedural complications, and the risk of inappropriate shocks that have been linked to subsequent mortality.\(^22\) There is, therefore, much interest in improving the risk stratification of patients being considered for ICD therapy, to distinguish between those most likely to benefit and those in whom device implantation could safely be avoided.
Boogers and colleagues followed 116 patients with advanced heart failure undergoing ICD implantation, and demonstrated a significant association between 123I-MIBG SPECT defect score on delayed imaging and the likelihood of appropriate ICD discharge. Surprisingly, none of the conventional planar MIBG imaging parameters was found to be predictive, which may reflect technical issues with the imaging. In our own institution, we have performed 123I-MIBG scintigraphy prospectively in 27 heart failure patients prior to ICD implantation for primary prevention. The risk of subsequent device therapy was significantly associated with both early and late H:M ratio, and 123I-MIBG SPECT defect score: a summed score threshold of 31 yielded sensitivity 78%, specificity 77%, and negative predictive value 86% for significant arrhythmia at 16 months follow-up (data submitted for publication).

Summary

The cardiac sympathetic nervous system plays an important role in the regulation of normal cardiovascular physiology, and may be disrupted in pathological states. Cardiac 123I-MIBG scintigraphy to assess sympathetic function is easy to perform, and provides robust prognostic information in heart failure. 123I-MIBG indices have been shown to improve with heart failure therapy, and there is preliminary evidence to support a possible future role for the technique in the prediction of ventricular arrhythmias in potential ICD recipients. The number of referrals for cardiac 123I-MIBG scintigraphic studies may rise significantly over the coming decade.

References

1. Inoue H, Zipes D P. Results of sympathetic denervation in the canine heart: supersensitivity that may be arrhythmogenic. Circulation 1987;75:877-887.