Monitoring of therapeutic effect in heart failure patients: a clinical application of $^{123}$I MIBG imaging?

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This editorial refers to 'Evaluation of cardiac sympathetic nerve activity and left ventricular remodelling in patients with dilated cardiomyopathy on the treatment containing carvedilol'¹ by S. Kasama et al., on page 989

Labelling of metaiodobenzylguanidine (MIBG) with $^{123}$I allows scintigraphic visualization of the cardiac sympathetic nervous system and $^{123}$I MIBG was the first radiopharmaceutical that allowed imaging of cardiac neurotransmission by single photon emission computed tomography. Norepinephrine (NE) is the major neurotransmitter of the sympathetic nervous system. $^{123}$I MIBG, an analogue of NE, and NE have similar molecular structures, and use the same uptake and storage mechanisms in the pre-synaptic sympathetic nerve ending. Uptake-1 is the most important uptake mechanism of MIBG in human, and is sodium- and energy-dependent. Other uptake mechanisms are the non-neuronal uptake-2 mechanism, which is sodium- and energy-independent, and diffusion.

The cardiac sympathetic nervous system is mainly involved in preserving circulatory homeostasis during environmental stress. Increase of sympathetic nervous activity or a rise in catecholamine levels result in cardiac adrenergic stimulation and has subsequent chronotropic (increase in heart rate), inotropic (increase in contractility), and dromotropic (enhanced atrioventricular conduction) effects. For the cardiovascular system in general, an increase in sympathetic nervous activity leads to an increase in peripheral vascular resistance, sodium and water retention, and activation of other neurohormonal systems. Although, in acute heart failure, these effects of enhanced sympathetic nervous activity are at first compensatory, prolonged hyperactivity of the sympathetic nervous system is supposed to be harmful in chronic heart failure. Vascular constriction and increased sodium and water retention will take its toll on energy demands of the myocardium.

Furthermore, altered sympathetic cardiac adrenergic function may cause arrhythmias, desensitization of post-synaptic $\beta$-adrenoceptors, and activation of the renin–angiotensin system. Prolonged exposure to NE may contribute to disease progression by acting directly on the myocardium and causing cell death. Accordingly, reduction of this hyperactivity is seen as one of the important therapeutic goals in the treatment of heart failure and this concept is supported by findings of clinical improvement after $\beta$-blockade therapy and after initiation of treatment with angiotensin converting enzyme inhibitors (ACE-inhibitors). It has been shown that patients with heart failure due to dilated cardiomyopathy (DCM) have reduced MIBG uptake and increased washout rates as compared with healthy individuals. The use of MIBG imaging to predict outcome in heart failure has been examined extensively, and it was shown that an abnormal heart-to-mediastinum ratio (HMR) is an independent predictor of death and for this purpose even a better predictor than left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, LV size, and NE content.

Merlet et al.¹ showed that, in DCM and heart failure, reduced MIBG uptake and LVEF were the best predictors of cardiac death over a follow-up period of 27 ± 20 months. Furthermore, MIBG imaging can also be applied to assess the therapeutic effect of reduction of sympathetic nervous hyperactivity. Suwa et al.² have prospectively investigated the usefulness of MIBG imaging in predicting response to bisoprolol, a selective $\beta_1$-blocker, in 45 patients with DCM. The HMR on the delayed planar images was shown to be a good predictor, with a cutoff value of 1.7, of the response to bisoprolol with a sensitivity of 91% and a specificity of 92%. An improvement in MIBG uptake, as well as an improvement in LVEF and NYHA functional class was demonstrated by Agostini et al.³ in 22 patients with DCM after 6 months of treatment with carvedilol. In this study, there was no relation between the severity of baseline MIBG uptake and the improvement in adrenergic function after $\beta$-blocker treatment. A possible explanation for this finding could be that a $\beta_1$-specific adrenergic blocker may be less effective in patients with severe heart failure compared with a non-selective $\beta$-blocker as carvedilol. In addition, ACE inhibition therapy has also been shown to enhance MIBG uptake. Somsen et al.⁴ demonstrated an improvement in cardiac MIBG uptake in heart failure patients treated with enalapril, although plasma NE levels were not affected. This suggests that the benefit of enalapril in heart failure lies in the restoration of cardiac neuronal uptake of NE. The influence of aldosterone receptor blocker spironolactone was studied previously by Kasama et al.⁵ In two groups of patients with heart failure, the aldosterone receptor blocker spironolactone increased MIBG uptake compared with placebo.

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patients with DCM and treated with ACE-inhibition and a loop diuretic, one group received also spironolactone, whereas the other group did not. It is known that aldosterone reduces NE uptake and improves structural remodelling of the heart. After 6 months of treatment with spironolactone, significant improvement was seen for delayed MIBG uptake and LVEF. Furthermore, a significant decrease was seen in the washout rate and total defect score of MIBG, whereas no significant changes for all these parameters were shown in the control group. Moreover, significant correlations between MIBG kinetics and decrease in LV end-diastolic volume (LVEDV) were found in the spironolactone group and this group showed more improvement in NYHA functional class than the control group.

Kasama et al. report on the effects of treatment with carvedilol in patients with DCM on adrenergic function. Carvedilol is a third generation β-blocker, which not only blocks β1 and β2 adrenoceptors but also α1 adrenoceptors. In 30 patients, the delayed HMR, the delayed total defect score, washout rate, regional defect score, and regional washout rate index were assessed with \textsuperscript{123}I MIBG scintigraphy. In addition, patients were evaluated with 2D echocardiography (LVEDV and LVESV, LVEF, and wall motion score index). These examinations were repeated in all patients after 1 year of treatment with 10–20 mg carvedilol per day. The authors not only reported a significant improvement of all parameters in all patients, but they also found a significant correlation between the changes in MIBG scintigraphic findings and changes in LVEDV and LVESV after 1 year of treatment with carvedilol.

As the authors state, it is difficult to determine whether the improvement in LV function, caused by remodelling of carvedilol, leads to an increase in NE uptake, or whether the improvement in NE uptake causes an improvement in LV function. Nevertheless, this study provides an important contribution to the search for an evaluation tool for monitoring therapy in heart failure. Heart failure is an important healthcare problem in the Western world today with a 5-year mortality rate up to 50%. Moreover, the number of patients living with heart failure is increasing because of the higher survival rate following myocardial infarction and more effective therapeutic strategies. In addition, it poses a considerable financial burden on healthcare economics since approximately 40% of the patients are readmitted within 1 year following their first hospital admission for heart failure. It has been demonstrated that treatment with β-blocking agents, ACE-inhibitors, and angiotensin receptor blocking agents is beneficial in patients with heart failure. Subjective endpoints as improvement in quality of life, NYHA functional class, and the 6-min hall walk test can be used to assess therapeutic effect, in addition to, for instance, clinical echocardiographic endpoints as a reduction in LVEDV and a rise in LVEF. Kasama et al. use MIBG imaging to evaluate therapeutic effect of carvedilol on the cardiac adrenergic activity in patients with DCM. Hyperactivity of the sympathetic nervous system is thought to play a major role in chronic heart failure and in the occurrence of ventricular arrhythmias. It is estimated that approximately 40% of the patients with severe heart failure die suddenly, probably as a result of arrhythmia. Several studies have used \textsuperscript{123}I MIBG scintigraphy in an attempt to predict the occurrence of ventricular arrhythmias in patients with heart failure. Although the results are promising, further studies in larger patient populations are warranted to assess the specific role of MIBG imaging in identifying high-risk patients.

Conflict of interest: none declared.

References


