Use of iodine-123 metaiodobenzylguanidine myocardial imaging to predict the effectiveness of \( \beta \)-blocker therapy in patients with dilated cardiomyopathy

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Abstract. It is crucial to predict drug effectiveness in chronic disease, such as dilated cardiomyopathy (DCM), in which the left ventricular (LV) function might be improved by \( \beta \)-blocker therapy. As the functional improvement effect by \( \beta \)-blocker therapy takes more than 2 months, we investigated whether iodine-123 metaiodobenzylguanidine (\(^{123}\)I-MIBG) imaging could be used to predict drug effectiveness. We studied 13 patients (11 men and two women; mean age, 43±13 years) with DCM and seven normal subjects (six men and one woman; mean age, 48±16 years). We obtained myocardial single-photon emission tomography (SPET) images 15 min and 4 h after administration of \(^{123}\)I-MIBG (111 MBq). Studies were performed in the patients with DCM before and 1 and 3 months after the administration of metoprolol and in the normal subjects. We calculated the regional \(^{123}\)I-MIBG washout rate (r-WR) in the SPET image, and the global \(^{123}\)I-MIBG washout rate (g-WR) and heart-mediastinum activity ratio (H/M) using the anterior planar image. We classified patients into those showing a \( \geq \)5% increase in LV ejection fraction (LVEF) at 3 months compared with LVEF values before the treatment (group I, \( n=7 \)) and those showing a <5% increase in LVEF (group II, \( n=6 \)). In group I, the r-WR values at pretreatment and at 1 and 3 months of treatment, respectively, were 36\(\pm\)19%, 29\(\pm\)14%*, and 25\(\pm\)13%* in the anterior segment, 39\(\pm\)17%, 33\(\pm\)17%**, and 28\(\pm\)17%* in the lateral segment, 36\(\pm\)16%, 31\(\pm\)14%* and 22\(\pm\)12%** in the septal segment and 40\(\pm\)11%, 37\(\pm\)19% and 31\(\pm\)18%* in the inferior segment; the g-WR was 45\(\pm\)11%, 43\(\pm\)10% and 34\(\pm\)9%, respectively (*\( P<0.05 \), **\( P<0.01 \) vs pretreatment). In group II, there were no significant changes in regional or global parameters during the 3-month period. In normal subjects, the r-WR values in each of the anterior, lateral, septal and inferior segments were significantly lower than those in groups I and II. These values were 18\(\pm\)9%, 18\(\pm\)15%, 20\(\pm\)12% and 21\(\pm\)15%, respectively. This study demonstrated that with regional assessment \(^{123}\)I-MIBG SPET imaging can be used to predict the functional improvement of LVEF at 1 month of \( \beta \)-blocker therapy in patients with DCM.

Key words: \( \beta \)-blocker therapy – Drug effectiveness – Iodine-123 metaiodobenzylguanidine – Bull’s eye map – Dilated cardiomyopathy


Introduction

There is no universally effective therapy for the improvement of left ventricular (LV) function in patients with dilated cardiomyopathy (DCM) and there are both medical and economic benefits to the prediction of drug effectiveness. In 1975, Waagstein et al. reported that several patients with heart failure showed clinical improvement after the administration of \( \beta \)-blockers [1]. This report left open to question the effectiveness of \( \beta \)-blocker therapy due to its negative inotropic and chronotropic effects on the myocardium. In 1991, Hjalmarson and Waagstein reported the variable effectiveness of \( \beta \)-blocker therapy for the treatment of heart failure, with 66%, 19% and 15% of patients showing improvement, no change and deterioration, respectively, following treatment [2]. No differences were noted between responders and nonresponders to \( \beta \)-blockers with regard to entry variable such as resting or exercise ejection fraction, heart rate, cardiac index, filling pressure, blood pressure or exercise capacity [3]. It is still difficult to predict whether patients will respond favourably to \( \beta \)-blocker treatment for heart failure.
Iodine-123 metaiodobenzylguanidine (123I-MIBG), an analogue of norepinephrine (NE), concentrates in adrenergic neurons [4] in various regions including the heart. Previous studies have demonstrated its potential clinical utility for the detection of the origin of ventricular tachycardia in patients with arrhythmia [5, 6] and for evaluation of pathophysiology and severity in those with congestive heart failure [7, 8]. The myocardial 123I-MIBG images in patients with DCM differ markedly from those of normal subjects, and might be expected to provide information on the severity of altered adrenergic innervation in the heart [9]. A recent report suggested that there is insignificant extraneuronal uptake in the human heart [10], and that the enhanced washout of 123I-MIBG would be most consistent with increased sympathetic nervous activity [9]. Both the regional uptake and the washout of 123I-MIBG in the canine heart were blocked by either left or right stellectomy, expressing regional sympathetic innervation [11]. We considered that the washout of 123I-MIBG from the myocardium might reflect cardiac sympathetic activity and that the washout rate of 123I-MIBG might be useful for predicting the effectiveness of β-blocker therapy in patients with DCM.

We analysed the regional and global washout rate of 123I-MIBG before and 1 and 3 months after the administration of a β-blocker to predict functional improvement in patients with DCM.

**Materials and methods**

**Protocol and subjects.** Metoprolol (β,-selective blockade) was administered orally at a dose of 5 mg and titrated weekly up to 40 mg. We performed 123I-MIBG scintigraphy and echocardiography before treatment, and after 1 month and 3 months of treatment, on the assumption that the drug effect would be manifest after more than 2 months [2, 12, 13]. We classified the patients into two groups, group I, with a 5% or more increase in LVEF [14], and group II, with a less than 5% increase in LVEF at 3 months compared with before the treatment. Seven normal subjects underwent 123I-MIBG myocardial imaging for comparison with the patient group.

Informed consent was obtained from each normal volunteer. Thirteen patients with LV dysfunction (11 men and two women with New York Heart Association class II–III; age range, 23–69 years; mean age, 43±13 years) were studied and two other patients were excluded because their symptoms deteriorated soon after the initiation of β-blocker therapy. Ten out of 13 patients had undergone cardiac catheterization and were found to have normal coronary arteriogram with reduced LV function. The remaining three patients had no clinical history to suggest coronary artery disease and did not show any ischaemic change on the exercise electrocardiogram. Four patients had concomitant hypertension and one patient concomitant impaired glucose tolerance, but both conditions were controlled to values within the normal range. All hypertensive patients underwent endomyocardial biopsy and showed no characteristic findings. All patients had been receiving diuretics, digitalis and angiotensin-converting enzyme inhibitors. Exclusion criteria were diseases known to influence the autonomic nervous system, such as diabetes mellitus and Parkinson's disease. No patients were administered reserpine or tricyclic antidepressants, which are known to affect myocardial 123I-MIBG uptake. Seven age-matched healthy volunteers (six men and one woman; age range, 30–68 years; mean age, 48±16 years) who had no cardiac disorders or other significant medical problems were studied as normal subjects.

**Myocardial 123I-MIBG imaging.** Myocardial 123I-MIBG images were obtained using a single-head gamma camera equipped with a low-energy general-purpose collimator (Model GCA901A/HG digital gamma camera and GMS-550U system, Toshiba, Japan). Energy discrimination was provided by a 20% window centered on a 160-keV photpeak for 123I-MIBG. After preprocessing of the projection images with a Butterworth filter, reconstructed processing was performed by using a Ramp filtered back-projection algorithm. Fifteen minutes and 4 h after 111 MBq of 123I-MIBG (Daiichi Radioisotope Laboratory Ltd., Tokyo, Japan) was inject-

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**Fig. 1.** The scheme of the bull’s-eye polar map display (above) and the anterior planar image (below). The g-WR was calculated from the planar image using ROIs positioned over the heart and the upper mediastinum. The r-WR in four quadrants was calculated from the bull’s eye polar map. WR, washout rate; ROI, region of interest; H, heart; M, mediastinum; 15 min, 15 min after injection of 123I-MIBG; 4 hrs; 4 h after injection of 123I-MIBG.