Increased myocardial [¹²³I]-metaiodobenzylguanidine uptake after enalapril treatment in patients with chronic heart failure

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Abstract

Objective—To assess non-invasively the effect of enalapril on cardiac sympathetic neuronal uptake function in patients with congestive heart failure, by using [¹²³I]-metaiodobenzylguanidine (MIBG), which is a noradrenaline analogue. Cardiac MIBG uptake was visualised by single photon emission tomography (SPET). In addition, plasma noradrenaline concentration, indicating systemic sympathetic activity, was measured to see whether it was related to cardiac MIBG uptake.

Design—Consecutive patients were treated with enalapril and served as their own controls.

Setting—Cardiac unit of a tertiary care centre.

Patients—23 Patients with chronic, mild to moderate, stable congestive heart failure, and a left ventricular ejection fraction less than 40%. Heart failure was caused by ischaemic heart disease or was idiopathic.

Interventions—Cardiac MIBG SPET was performed and plasma noradrenaline concentration was measured before and after 6 weeks treatment with enalapril.

Main outcome measures—Cardiac uptake of MIBG was measured by using the left ventricular cavity and a venous blood sample as a reference.

Results—Cardiac uptake of MIBG increased significantly after enalapril treatment, indicating improved cardiac neuronal uptake function. Plasma noradrenaline concentration did not decrease significantly. Cardiac MIBG uptake was not related to plasma noradrenaline concentration.

Conclusions—Cardiac MIBG SPET can be used to assess changes in cardiac sympathetic neuronal uptake function caused by pharmacological intervention. Enalapril seemed to improve cardiac sympathetic neuronal uptake function but did not significantly affect plasma noradrenaline concentrations in a group of patients with predominantly moderate heart failure. These results accord with the hypothesis that restoration of cardiac neuronal uptake of noradrenaline is one of the beneficial effects of enalapril in such patients.

Keywords: [¹²³I]-metaiodobenzylguanidine SPET, heart failure, enalapril

In patients with congestive heart failure, angiotensin converting enzyme (ACE) inhibitors are known to reduce mortality and morbidity,¹⁻³ to improve haemodynamics,⁴ and to inhibit the process of remodelling.⁵ The suppression of neurohormonal systems by ACE inhibitors may contribute to some of these beneficial effects.⁶

In congestive heart failure the sympathetic nervous system is activated, as is reflected by the increase in the concentration of plasma noradrenaline. In addition, in the failing myocardium an impairment of neuronal uptake of noradrenaline has been shown.^{7,8} Both the enhanced release of noradrenaline and the altered cardiac neuronal uptake may be responsible for the observed downregulation of β adrenoceptors in patients with heart failure.⁹

The neuronal uptake mechanism can non-invasively be assessed by [¹²³I]-metaiodobenzylguanidine (MIBG).^{10,11} MIBG shares similar uptake and storage mechanisms in the sympathetic nerve endings as noradrenaline.^{11,12} In contrast with noradrenaline, MIBG is not metabolised.¹³ Cardiac neuronal uptake of MIBG can be measured non-invasively by single photon emission tomography (SPET).

ACE inhibitors are known to increase cardiac β adrenoceptor density and to reduce cardiac sympathetic activity in patients with heart failure.¹⁴ It can be assumed that an improvement in cardiac neuronal uptake, which has been demonstrated to be the predominant mechanism for terminating the action of noradrenaline on the β adrenoceptors, may contribute to these findings.¹⁵

The aim of this study was non-invasively to measure the effect of short term treatment with enalapril on cardiac neuronal uptake in patients with congestive heart failure, using a new method to quantify myocardial MIBG uptake.¹⁶

Patients and methods

STUDY DESIGN

We prospectively studied cardiac MIBG activity and hormonal variables in 26 patients who were treated with enalapril and served as their own controls. The protocol was approved by the Ethics Committee and the Investigational Review Board of the Academic Medical

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Accepted for publication
19 February 1996

(Heart 1996;76:218-222)

Figure 1 Short axis reconstruction of a cardiac [¹²³I]-metaiodobenzylguanidine SPET acquisition in a patient with congestive heart failure. Myocardial uptake (A) before (20.9 Bq/ml/MBq dose) and (B) after six weeks treatment with enalapril (35.0 Bq/ml/MBq dose). C, Left ventricular cavity; M, myocardium; L, liver. The yellow and white areas represent high and very high MIBG uptake respectively, whereas the red areas represent low MIBG uptake.

Center. Written informed consent was obtained from each patient by one of the investigators.

PATIENT SELECTION

Patients with stable chronic heart failure (NYHA class II–IV) for at least two months, left ventricular ejection fraction < 0.40, and fixed medication for at least two weeks were included. We excluded patients who were treated with ACE inhibitors or other drugs that can influence neuronal MIBG uptake (β adrenoceptor agonists/antagonists and tricyclic antidepressants). All other medications were allowed provided that the dose was not changed during the study. Patients with insulin dependent diabetes mellitus, hyperthyroidism, recent myocardial infarction (within the past two months), neurological diseases, prior valve replacement, and myectomy of the left ventricle were also excluded.

TREATMENT

Patients were initially treated with 2.5 mg enalapril twice a day. The dose was increased to 10 mg enalapril twice a day in two weeks and adjusted if symptomatic hypotension occurred. Enalapril was stopped when there was an allergic reaction or deterioration of renal function (30% increase in plasma creatinine concentration). After the titration phase of two weeks the highest tolerated dose was continued for four weeks. Efficacy variables were assessed before and after six weeks treatment.

MYOCARDIAL MIBG SPET ACQUISITION
PROTOCOL

All patients received 100 mg potassium iodide orally to block thyroid uptake an hour before intravenous injection of 185 MBq [¹²³I]-MIBG

(specific activity > 0.2 TBq/mmol; Cygne BV Technical University Eindhoven, The Netherlands). To minimise non-neuronal uptake of MIBG, SPET images were obtained after four hours bedrest (Siemens MultiSPECT3, medium energy collimators). A 20% energy window centered on the 159 keV photopeak of [¹²³I] was used. Data were collected using 60 frames over 360 degrees, for 60 seconds per frame, a 64 × 64 pixel matrix, zoomfactor of 1.23, and the camera auto-contour facility. No attenuation correction was applied. Figure 1 shows an example of the effect of enalapril on myocardial MIBG uptake in a patient with chronic heart failure.

QUANTIFICATION OF MYOCARDIAL MIBG UPTAKE

Myocardial MIBG uptake was measured by a previously described method.^{16 17} Briefly, cardiac short axis slices were reconstructed. In each short axis slice elliptic regions of interest were semi-automatically drawn over the left ventricular myocardium and left ventricular

Table 1 Baseline characteristics (mean (SD))

Characteristic	
Number of patients (male/female)	23 (16/7)
Age (years)	60.0 (10.6)
Heart failure history (mnth)	20.1 (28)
Heart rate (beats/min)	81.6 (13.3)
Functional class (NYHA):	
II	12 (52%)
III	9 (39%)
IV	2 (9%)
Aetiology of heart failure:	
Ischaemic	15 (65%)
Idiopathic	8 (35%)
Coronary bypass grafting	4 (17%)
History of hypertension	5 (22%)
Concomitant medications:	
Digitalis	6 (26%)
Diuretics	13 (56%)
Nitrates	2 (9%)
Plasma renin activity (ng/ml/h)	1.35 (0.71)

Figure 2 Percentage changes of hormonal variables after treatment with enalapril, *P < 0.02. ANP, plasma atrial natriuretic peptide concentration; MIBG, myocardial [¹²³I]-metaiodobenzylguanidine uptake; NA, plasma noradrenaline concentration.

Figure 3 Plot of changes in myocardial [¹²³I]-metaiodobenzylguanidine uptake after treatment with enalapril. Individual data for each patient as well as the mean (SD) for the averaged results are shown.

cavity. Volumes of interest were constructed and quantified using the Cardiac SPECT Analysis-tool package (CASPAR Version 1.1). At the time of SPET acquisition, a venous blood sample was drawn and [¹²³I] activity was measured in duplicate using a gamma counter (Auto-gamma 5000, Packard Instruments Company, Downers Grove, Illinois, USA). Myocardial MIBG uptake was calculated from the ratio of average activity per voxel in the myocardium (M) and the ventricular cavity (C) times the [¹²³I] activity measured in a venous blood sample (A) according to the following equation:

Myocardial MIBG uptake = $\frac{M}{C} \times A$ (Bq/ml)

All data were corrected for injected radioactivity and radioactive decay. All studies were blindly analysed.

HORMONE ANALYSIS

Patients fasted from 0000 on the day of investigation although medication was continued. Patients were not allowed to take products containing caffeine the day before study. At 0800 an intravenous indwelling catheter was inserted in the median cubital vein. After the patient had rested in a supine position for 30 minutes, blood pressure was measured non-invasively (Dinamap 845, Critikon, Tampa, USA) and venous blood samples were drawn from the catheter. Blood samples were stored on ice for up to 10 minutes before they were processed. Plasma was stored at -30°C. Plasma noradrenaline concentration was determined by high performance liquid chromatography and electrochemical detection, after purification on Biorex 70 and concentration by solvent extraction. Atrial natriuretic peptide (ANP) was determined by radioimmunoassay (Nichols Institute Diagnostics, Wijchen, The Netherlands). Plasma renin activity (PRA) was determined by radioimmunoassay for angiotensin I.¹⁸

STATISTICAL ANALYSIS

Student's *t* test for paired data was used where appropriate, otherwise the Wilcoxon signed ranks test was used. Differences were regarded as being significant at a two-tailed probability of 0.05 or less. Correlations were expressed as the Pearson correlation coefficient.

Results

Twenty six patients were enrolled into the study. Two patients did not complete the full study period; one died because of progressive heart failure and one stopped enalapril treatment because of exanthema. SPET data for one patient could not be analysed owing to technical problems. Data from the remaining 23 patients were used for analysis. These patients remained clinically stable during the course of the study.

Fifteen patients (65%) were known to have coronary artery disease as shown by either coronary angiography or well documented myocardial infarction. Eight patients (35%) were classified as having idiopathic cardiomyopathy. Baseline characteristics are shown in table 1.

The average daily dose of enalapril was 13.5

Table 2 Changes after 6 weeks enalapril treatment

Variable	Before Mean (SD)	After Mean (SD)	Difference	
			95% CI	P
MIBG (Bq/ml/MBq)	16 (8.45)	20 (9.67)	-6.52 to -8.70	0.013
NA (ng/L)	361 (177)	300 (146)	-22.62 to 146.02	0.14
ANP (ng/L)	283 (239)	170 (141)	20.51 to 205.84	0.019
Creatinine (mmol/L)	75.6 (17.3)	75.2 (15.7)	-3.07 to 3.76	0.83
BP _{syst} (mm Hg)	130 (12.8)	119 (12.4)	5.66 to 17.60	0.001
BP _{diast} (mm Hg)	81 (9.6)	73 (10.6)	4.30 to 13.39	0.001

ANP, plasma atrial natriuretic peptide concentration; MIBG, cardiac [¹²³I]-metaiodobenzylguanidine uptake; NA, plasma noradrenaline concentration; PRA, plasma renin activity; BP_{syst}, systolic blood pressure; BP_{diast}, diastolic blood pressure.

(6) mg, ranging from 5 to 20 mg. The mean PRA at baseline was 1.35 (0.71) ng/ml/h (normal value < 3.2 ng/ml/h).

Changes of variables from baseline to six weeks treatment are shown in table 2. Plasma creatinine concentration did not change significantly. Systolic and diastolic blood pressure decreased significantly from 130 (12.8) to 119 (12.4) mm Hg ($P = 0.001$) and from 81 (9.6) to 73 (10.6 mm Hg ($P < 0.001$) respectively.

Myocardial MIBG uptake increased significantly from 16 (8) to 20 (10) Bq/ml/MBq injected dose; $P < 0.02$ (fig 2). Individual data points are shown in fig 3.

The mean plasma noradrenaline decreased from 361 (177) to 300 (146) ng/l, which was not significant. Plasma ANP decreased significantly from 283 (239) ng/l to 170 (141) ng/l; $P < 0.02$ (fig 2).

Discussion

In the failing human myocardium, increased concentrations of circulating noradrenaline, an increased neuronal release, and a reduced neuronal uptake of noradrenaline have been reported.^{7,8,19} These alterations result in an increased noradrenaline concentration in the synaptic cleft and are responsible for the myocardial β adrenoceptor downregulation. To measure the effect of enalapril on the cardiac neuronal uptake of noradrenaline, we used a quantitative cardiac MIBG SPET method.¹⁶

The present study is, as far as we know, the first to show an increase in myocardial MIBG uptake after pharmacological intervention in patients with heart failure. This suggests an improvement of cardiac neuronal uptake function caused by enalapril treatment. This accords with the *in vitro* experiments of Takatsu *et al* who showed that cardiac MIBG uptake was increased in cardiomyopathic Syrian hamsters after treatment with cilazapril.²⁰

Improved neuronal uptake results in a more adequate termination of the action of noradrenaline on the myocardial β adrenoceptors. Therefore, our findings are consistent with those of Gilbert *et al* who showed increased myocardial β adrenoceptor density in endomyocardial biopsy specimens and decreased coronary sinus noradrenaline concentration after 12 weeks lisinopril treatment of patients with heart failure.¹⁴

The improvement in neuronal function by enalapril can be explained by two mechanisms. First, ACE inhibitors may improve directly cardiac neuronal uptake of noradrenaline by reducing angiotensin II concentrations. It has been shown that angiotensin II prevents the neuronal uptake of noradrenaline.²¹ This local effect may result in an increased exposure of the myocytes to noradrenaline and a subsequent downregulation of the myocardial β adrenoceptors in patients with heart failure.

Second, ACE inhibitors are known to improve haemodynamics.²² This systemic effect may indirectly result in a reduced cardiac neuronal release and a restoration of neu-

ronal uptake of noradrenaline. In the present study, haemodynamic improvement is supported by the decreased blood pressure and plasma ANP concentration, indicating a diminished afterload and preload respectively.²³ However, this systemic effect of ACE inhibitors seems to be of less importance because plasma noradrenaline concentration did not change significantly, reflecting unchanged systemic sympathetic activity.²⁴

The predominance of moderate heart failure in our group of patients probably accounts for the unchanged plasma noradrenaline concentration. It has been reported that ACE inhibitors reduce plasma noradrenaline concentrations in patients with moderate heart failure to a lesser extent than in those with severe heart failure.^{16,14} The absence of a significant correlation between plasma noradrenaline concentrations and myocardial MIBG uptake is explained by the fact that plasma noradrenaline does not reflect cardiac sympathetic activity because cardiac noradrenaline spillover accounts for less than 3% of total body noradrenaline release.²⁵

A possible limitation of the study is the small number of patients studied. Since each patient served as their own reference, a placebo treated control group was not studied. This was considered appropriate because no subjective end points were used. All variables were assessed automatically and were analysed blindly.

Myocardial MIBG uptake was measured within a short period of time without any change in the clinical situation and treatment of each patient. Therefore, it can be assumed that the condition under which MIBG uptake was measured remained the same during the course of the study.

It might be anticipated that myocardial MIBG uptake in infarcted areas would be lower than in viable myocardium because of sympathetic denervation, and therefore the inclusion of patients with ischaemic cardiomyopathy may have influenced our results. With the present method it is not possible to assess segmental MIBG uptake. Therefore, MIBG uptake of the entire myocardium was determined. Furthermore, the inclusion of denervated myocardium in the measurement should have led to an underestimation of the effect of enalapril on myocardial MIBG uptake because reinnervation is unlikely to occur in this relatively short period of study.

These data suggest that cardiac MIBG SPET can be used as a non-invasive method to assess changes in cardiac sympathetic neuronal function caused by pharmacological intervention. Short term treatment with enalapril primarily improves cardiac sympathetic neuronal uptake function rather than reducing systemic sympathetic activity in subjects with predominantly moderate heart failure.

This finding suggests that in these patients the beneficial effects of enalapril are at least partly due to improvement in cardiac sympathetic neuronal uptake function as non-invasively measured by MIBG SPET. Because

decreased cardiac MIBG uptake has been associated with unfavourable prognosis,²⁶ future studies must determine the relation between cardiac MIBG uptake and the beneficial effects of ACE inhibitors on mortality and morbidity.

This research was supported by grants from the Netherlands Heart Foundation (grant 92-342) and Merck Sharp & Dohme.

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