Eur J Nucl Med Mol Imaging (2014) 41:144–154
DOI 10.1007/s00259-013-2538-0

ORIGINAL ARTICLE

Effects of oral nicorandil therapy on sympathetic nerve activity and cardiac events in patients with chronic heart failure: subanalysis of our previous report using propensity score matching

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Received: 1 April 2013 / Accepted: 6 August 2013 / Published online: 28 August 2013

Abstract
Purpose Nicorandil, an adenosine triphosphate-sensitive potassium channel opener, improves cardiac sympathetic nerve activity (CSNA) in patients with ischaemic heart disease. However, the long-term effects on both CSNA, as evaluated by ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy, and prognosis have not been determined in patients with chronic heart failure (CHF).
Methods This study was a subanalysis of our previous results that serial ^{123}I-MIBG scintigraphic studies are the most useful prognostic indicator in CHF patients. The study group comprised 208 patients with CHF (left ventricular ejection fraction <45 %) but no cardiac events for at least 5 months identified on the basis of a history of decompensated acute heart failure requiring hospitalization. These patients underwent ^{123}I-MIBG scintigraphy and echocardiography just before leaving the hospital and again 6 months later. We selected 170 patients and used propensity propensity score matching to compare patients who received oral nicorandil (85 patients) and those who did not (85 patients). The patients were followed up for a median of 5.03 years, with the primary and secondary study end-points defined as the occurrence of a fatal cardiac event and a major adverse cardiac event (MACE), respectively.
Results After treatment, the extent of changes in ^{123}I-MIBG scintigraphic and echocardiographic parameters in the nicorandil group were more favourable than in those not receiving nicorandil. Of the 170 patients, a fatal cardiac event occurred in 42, and a MACE in 68 during the study. Multivariate Cox regression analyses revealed that no nicorandil treatment was a significant predictor of both cardiac death and MACE in our patients with CHF. On Kaplan-Meier analysis, the rates of freedom from cardiac death or from MACE in the nicorandil group were significantly higher than in those not receiving nicorandil (all p <0.05).
Conclusion Long-term nicorandil treatment improves CSNA and left ventricular parameters in patients with CHF. Furthermore, this agent is potentially effective for reducing the incidence of cardiac events in patients with CHF.

Keywords Nicorandil · Heart failure · Prognosis · Sympathetic nervous system

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Introduction

The activation of the sympathetic nervous system is one of the cardinal pathophysiological abnormalities associated with human heart failure [1]. Therefore, plasma norepinephrine concentrations affect the prognosis of patients with chronic heart failure (CHF) [2]. Myocardial imaging with ^{123}I-metaiodobenzylguanidine (MIBG), an analogue of norepinephrine, is useful for

detecting abnormalities of cardiac sympathetic nerve activity (CSNA) in patients with CHF [3, 4]. Furthermore, previous studies have evaluated stable-period CSNA by one-time ^{123}I-MIBG scintigraphy, and shown prognostic value in patients with CHF [4–6]. We have also previously reported that a change in washout rate (delta-WR = 6-month follow-up WR − baseline WR) determined from serial ^{123}I-MIBG scintigraphic studies is the best currently available prognostic indicator in CHF [7].

Nicorandil (*N*-(2-hydroxyethyl)-nicotinamide nitrate; Chugai, Tokyo, Japan), a drug with both nitrate-like and ATP-sensitive potassium channel-activating properties [8], has been reported to reduce cardiac events in patients with stable angina [9, 10] or acute myocardial infarction (AMI) [11, 12]. Moreover, it has been reported that CSNA is modulated by activation of ATP-sensitive potassium channels [13], and thus nicorandil may improve CSNA by activating ATP-sensitive potassium channels in patients with ischaemic heart disease. We have previously reported that long-term nicorandil treatment improves CSNA in patients with AMI [14]. We therefore hypothesized that nicorandil treatment may be effective for the treatment of nonischaemic heart failure by the same mechanism (i.e. activating ATP-sensitive potassium channels). On the other hand, it is well known that the treatments for acute and chronic phases of heart failure are different. We also hypothesized that long-term nicorandil treatment may improve CSNA by activating ATP-sensitive potassium channels throughout acute and chronic phases of heart failure, and this treatment may be effective for prognosis in patients with CHF, as evaluated by serial ^{123}I-MIBG scintigraphic findings.

Accordingly, this study was performed, using our previously reported data [7], to determine whether nicorandil treatment improves CSNA as evaluated by ^{123}I-MIBG scintigraphy, and affects prognosis in patients with CHF.

Materials and methods

Patient population and protocol

From February 2000 to August 2005, 459 patients were admitted to our institution with their first episode of decompensated acute heart failure with a left ventricular ejection fraction (LVEF) of less than 45 %, according to the inclusion criteria described in our previous study [7]. This study was a subanalysis using our previous database [7]. Chest radiography, standard electrocardiography and echocardiography were performed in all patients. In the acute phase, all patients were treated with standard heart failure treatment including intravenous diuretics, vasodilators (carperitide, nicorandil, nitroglycerin), and if necessary, dopamine or dobutamine was added to maintain the blood pressure. Patients were excluded from the study if they had unstable angina or had recently had AMI, and had undergone any coronary revascularization procedure within 3 months (42 patients were excluded), or if they had primary hepatic failure, renal failure or active cancer (29 patients). Moreover, patients with severe heart failure requiring mechanical support (intraaortic balloon pumping, left ventricular assist device, or cardiac resynchronization therapy) and patients requiring heart transplantation were also excluded (38 patients) (Fig. 1).

During the stable period, the patients were treated with oral medication for heart failure, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-adrenergic blocking agents, and diuretics. None of the patients was treated with tricyclic antidepressants or other serotonin reuptake inhibitors. If necessary, oral nicorandil treatment was added instead of intravenous vasodilators on the basis of the judgement of the doctors, not by the study protocol. Because the recommended dose of nicorandil for angina pectoris is 15 mg/day, the same dose was used in our patients with CHF. We performed ^{123}I-MIBG scintigraphy and echocardiography just before hospital discharge. However, 52 patients were excluded from this study because scintigraphy or echocardiography had not been performed during hospitalization. The medical management of the patients was directed by an internist or cardiologist from our institution, and ^{123}I-MIBG scintigraphic and echocardiographic parameters were available to them. In this study, 18 patients were excluded because they experienced a hard event (cardiac event in 10, cerebral event in 5, and other events in 3) during the 5 months after enrolment.

The ^{123}I-MIBG scintigraphy and echocardiography were repeated about 6 months after hospital discharge (mean 6.4 months), and the date was defined as day 0 of observation. Patients were excluded from the study if the second evaluation had not been performed (30 patients), or if their medication changed between the first and second evaluation (26 patients). The study was approved by the ethics review board of our institution, and informed written consent was obtained from all patients. Nine patients were excluded because informed consent was not obtained. Seven patients were lost to follow-up after the second evaluation and were therefore excluded.

We followed up 208 patients who had highly reliable information on prognosis, which was obtained from the patients themselves, family members, and/or affiliated hospitals (Fig. 1). The 208 study patients consisted of 130 men and 78 women with a mean age of 68.6 years (range 35 to 87 years). In the present study, the primary end-point was the occurrence of a fatal cardiac event (i.e. cardiac death, including sudden death) and the secondary end-point was the occurrence of a major adverse cardiac event (MACE), as defined by the composite of fatal cardiac event, nonfatal myocardial infarction, and hospitalization because of heart failure.

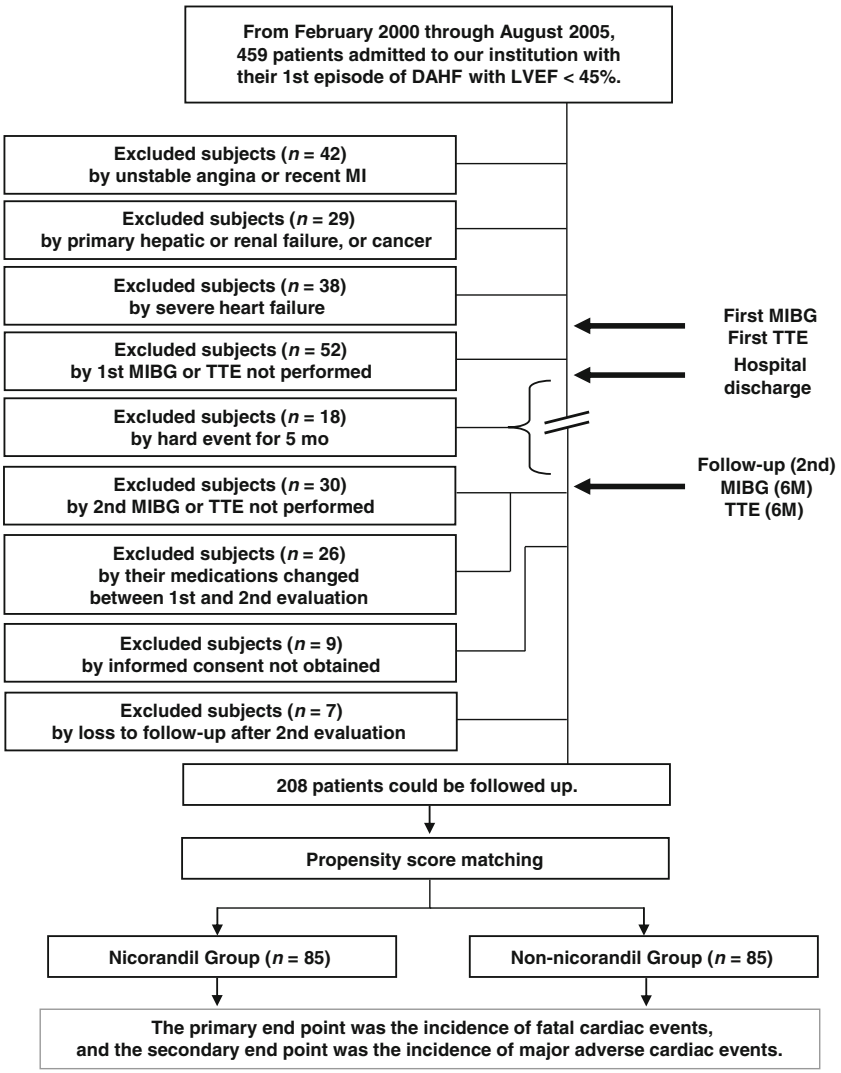

Fig. 1 Flow diagram of participants in the current study (*DAHF* decompensated acute heart failure, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *MIBG* metaiodobenzylguanidine scintigraphy, *TTE* transthoracic echocardiography, *6M* 6 months after hospital discharge)

To evaluate whether nicorandil treatment affected CSNA and prognosis in our patients with CHF, they were divided into those receiving nicorandil (85 patients) and those not receiving nicorandil (85 patients) using propensity score matching (Fig. 1). In our study protocol [7] nicorandil was started during hospitalization and was continued until the event date or censoring date. We defined the censoring date as that at the end of follow-up or the date a patient's medication (including nicorandil) was changed. Therefore, in other words, in the nicorandil group, oral administration of nicorandil was continued during the study period.

^{123}I-MIBG imaging

The method of ^{123}I-MIBG imaging has already been described [7, 15, 16]. In brief, the ^{123}I-MIBG was obtained from a commercial source (FUJIFILM RI Pharma Co Ltd, Tokyo, Japan). At 15 min and 4 h after injection, anterior planar and single photon emission computed tomographic (SPECT) images were obtained with a single-head gamma camera (Millennium MPR; GE Medical Systems, Waukesha, WI).

The heart/mediastinum count (H/M) ratio was determined from the anterior planar delayed ^{123}I-MIBG image using the method reported by Merlet et al. [4]. The WR was calculated from early and delayed planar images. Regional tracer uptake was semiquantitatively assessed using a five-point scoring system (0 normal to 4 no uptake) in 17 segments on the delayed SPECT image as recommended by the American Heart Association [17]. The total defect score (TDS) was calculated as the sum of all defect scores. The TDS was converted to a percentage of the total denervated myocardium (percentage denervation). The percentage denervation was calculated using the formula: TDS/68×100, where 68 is the maximum TDS (4×17). In our laboratory, the normal range for percentage denervation is 6 to 18, the delayed H/M ratio is 2.18 to 2.70, and the normal WR range is 20 % to 30 %, as previously reported [7].

Echocardiography

Echocardiography was performed using standard methods in a blinded manner. Two experienced, independent echocardiographers who had no knowledge about the study performed all the measurements. The LV end-diastolic volume (EDV), LV end-systolic volume (ESV) and LVEF were calculated using the modified method of Simpson [18].

Serial changes in parameters between the first and second scintigraphic and echocardiographic studies

Changes in parameters between the first and second ^{123}I-MIBG scintigraphic (percentage denervation, H/M ratio and WR) and echocardiographic (EDV, ESV and LVEF) studies were calculated using the formula: delta-X=(X after 6 months) – (X at baseline), where X is the ^{123}I-MIBG scintigraphic or echocardiographic parameter value.

Statistical analysis

Analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL) or SAS version 9.1 (SAS Institute Inc., Cary, NC). Numerical results are expressed as means ± SD. In all analyses, $p<0.05$ was considered statistically significant. A propensity-matched analysis was conducted to minimize the selection bias for nicorandil administration [19]. To obtain the propensity score for the probability that nicorandil would be administered, multivariate logistic regression analyses were performed. The propensity score was based on the following variables: age, sex, ischaemic aetiology, tobacco use, New York Heart Association (NYHA) functional class, acute phase treatments, ^{123}I-MIBG scintigraphic and echocardiographic parameters, and the presence of diabetes, hypertension and dyslipidaemia. Patients receiving those not receiving nicorandil were matched 1:1 to two digits based on the estimated propensity score for treatment with oral nicorandil.

Categorical data were compared between the two groups using two-sided chi-squared tests and differences between continuous variables were evaluated using the unpaired t-test. NYHA functional classes were compared using the Wilcoxon matched pairs signed ranks test. In patients who underwent repeat assessment, changes from baseline were evaluated within each treatment group using a paired t-test and between the two groups using two-way ANOVA. Linear regression analysis was used to determine the relationship between continuous variables.

The event date was the date of a cardiac event, and the censoring date was that at the end of follow-up or the date a patient's medication (including nicorandil) was changed after a second evaluation. A Cox proportional hazards regression analysis was performed to identify independent predictors of cardiac death or MACE using variables including clinical characteristics, risk factors, and each pharmacotherapeutic agent. These analyses did not include ^{123}I-MIBG scintigraphic parameters because the study results (including scintigraphic parameters) have been previously reported [7, 20]. The forward stepwise method was used for the multivariate analyses, with entry and removal p values set at 0.05. Kaplan-Meier survival curves were used for comparisons between patient groups, and these comparisons were made using the log-rank test. Furthermore, to evaluate the contribution of the degree of change in WR (i.e. delta-WR), univariate and stepwise multivariate analyses were used to examine the variable of interest.

Results

Follow-up periods and prognosis of patients

The median follow-up period was 5.03 years (0.78 to 7.48 years) for all study patients, and cardiac death including sudden death occurred in 42 of the 170 patients (24.7 %). Sudden death accounted for 9 deaths (5.3 %), pump failure accounted for 29 deaths (17.1 %), and the remaining 4 deaths were due to myocardial infarction (2.4 %). The fatal cardiac events occurred an average of 2.05 years (0.78 to 6.85 years) after the second evaluation. The incidence of cardiac death was 17.6 % (15/85) in patients receiving nicorandil and 31.8 % (27/85) in those not receiving nicorandil. Nonfatal myocardial infarction occurred in 7 patients (4.1 %), and 19 patients required hospitalization because of heart failure (11.2 %). Therefore, MACE occurred in 68 of the 170 patients (40.0 %) at an average of 2.72 years (0.78 to 6.85 years) after the second evaluation. The incidences of MACE were 31.8 % (27/85) in patients receiving nicorandil and 48.2 % (41/85) in those not receiving nicorandil.

Clinical characteristics, and ^{123}I-MIBG scintigraphic and echocardiographic findings in patients with and without cardiac death

Clinical characteristics, and scintigraphic and echocardiographic parameters in the patients who had and did not have a cardiac death are shown in Table 1. Gender, ischaemic aetiology and NYHA functional class were similar in both groups. Age in the patients without cardiac death was significantly lower than in those with cardiac death. With respect to pharmacotherapy in the two groups, the use of both beta-blockers and nicorandil in those without cardiac death was significantly higher than in those with cardiac death.

Among the baseline ^{123}I-MIBG scintigraphic parameters, the H/M ratio in the patients without cardiac death was significantly higher than in those with cardiac death. The WR in patients without cardiac death was significantly lower than in

Table 1 Clinical characteristics of the patients with and without cardiac death

	Without cardiac death (n = 128)	With cardiac death (n = 42)	p value
Age (years)	67 ± 12	71 ± 9	0.027
Gender (male)	76 (59 %)	26 (62 %)	0.857
Ischaemic aetiology	56 (44 %)	18 (41 %)	0.724
NYHA (I/II/III/IV)			
Baseline	0/40/69/19	0/15/22/5	0.813
Follow-up	30/52/45/1	4/20/18/0	0.147
^{123}I-MIBG scintigraphy (baseline)			
Percentage denervation	57.9 ± 10.8	59.3 ± 9.7	0.382
H/M ratio	1.68 ± 0.18	1.57 ± 0.23	0.002
WR (%)	46.6 ± 10.3	52.5 ± 11.0	0.001
^{123}I-MIBG scintigraphy (second)			
Percentage denervation	46.8 ± 13.4	59.0 ± 14.0	<0.001
H/M ratio	1.84 ± 0.22	1.59 ± 0.24	<0.001
WR (%)	39.4 ± 10.0	56.7 ± 12.9	<0.001
^{123}I-MIBG scintigraphy (changes from baseline)			
Delta-percentage denervation	−11.1 ± 11.0	−0.3 ± 11.4	<0.001
Delta-H/M ratio	0.16 ± 0.15	0.02 ± 0.17	<0.001
Delta-WR (%)	−7.2 ± 10.0	4.2 ± 10.5	<0.001
Echocardiography (baseline)			
EDV (ml)	181 ± 44	184 ± 34	0.677
ESV (ml)	122 ± 40	127 ± 34	0.434
LVEF (%)	33 ± 7	31 ± 8	0.192
Echocardiography (second)			
EDV (ml)	157 ± 41	178 ± 52	0.008
ESV (ml)	94 ± 35	117 ± 50	0.001
LVEF (%)	41 ± 9	36 ± 10	0.002
Echocardiography (changes from baseline)			
Delta-EDV (ml)	−24 ± 30	−6 ± 25	0.001
Delta-ESV (ml)	−28 ± 26	−10 ± 24	<0.001
Delta-LVEF (%)	8 ± 7	5 ± 5	0.005
Pharmacotherapy			
ACE inhibitor	86 (67 %)	28 (67 %)	0.950
Angiotensin receptor blocker	85 (66 %)	23 (55 %)	0.198
Beta-blocker	67 (52 %)	14 (33 %)	0.024
MR antagonist	58 (45 %)	12 (29 %)	0.071
Loop diuretics	128 (100 %)	42 (100 %)	1.000
Nicorandil	70 (55 %)	15 (36 %)	0.025

Values are mean ± SD or number (%)

those with cardiac death. Among the follow-up ^{123}I-MIBG scintigraphic parameters, the second percentage denervation and second WR in the patients without cardiac death were significantly lower than in those with cardiac death. The second H/M ratio in the non-cardiac-death group was significantly higher than that in the cardiac death group. With respect to the changes in imaging parameters between the first and second ^{123}I-MIBG scintigraphy, delta-percentage denervation and delta-WR in patients without cardiac death were significantly lower than in those with cardiac death. The delta-H/M ratio in patients without cardiac death was significantly higher than in those with cardiac death.

Among the baseline echocardiographic parameters, EDV, ESV and LVEF were all similar in both groups. In the follow-up echocardiographic parameters, the second EDV and ESV in patients without cardiac death were significantly lower than in those with cardiac death. The second LVEF in patients without cardiac death group was significantly higher than in those with cardiac death. With respect to the changes in the echocardiographic parameters, delta-EDV and delta-ESV in patients

Table 2 Clinical characteristics of the patients with and without nicorandil

	Nicorandil (n=85)	No nicorandil (n=85)	p value
Age (years)	68 ± 11	68 ± 12	0.834
Gender (male)	53 (62 %)	49 (58 %)	0.639
Ischaemic aetiology	40 (47 %)	34 (40 %)	0.439
Diabetes mellitus	26 (31 %)	34 (40 %)	0.610
Hypertension	46 (54 %)	45 (53 %)	0.878
Dyslipidaemia	35 (41 %)	30 (35 %)	0.528
Current smoker	29 (34 %)	25 (29 %)	0.621
NYHA functional class			
(I/II/III/IV)	0/30/41/14	0/25/50/10	0.501
^{123}I-MIBG scintigraphy			
Percentage denervation	59.5 ± 10.7	58.6 ± 10.3	0.580
H/M ratio	1.65 ± 0.21	1.65 ± 0.20	0.904
WR	48.7 ± 11.0	48.9 ± 10.4	0.932
Echocardiography			
LVEDV (ml)	182 ± 44	180 ± 39	0.755
LVESV (ml)	123 ± 37	123 ± 39	0.965
LVEF (%)	33 ± 7	33 ± 9	0.824
Medical treatment			
ACE inhibitor	56 (66 %)	58 (68 %)	0.870
Angiotensin receptor blocker	53 (62 %)	55 (65 %)	0.873
Beta-blocker	43 (51 %)	38 (45 %)	0.539
Mineralocorticoid receptor antagonist	34 (40 %)	36 (42 %)	0.876
Loop diuretics	85 (100 %)	85 (100 %)	1.000
Nicorandil	85 (100 %)	–	–
Nicorandil dose (mg/day)	15 ± 3	–	–

Values are mean ± SD or number (%)

without cardiac death were significantly lower than in those with cardiac death. Finally, the delta-LVEF in patients without cardiac death was significantly higher than in those with cardiac death.

Clinical characteristics, and ^{123}I-MIBG scintigraphic and echocardiographic findings in patients with and without nicorandil treatment

There were no significant differences in the clinical characteristics or cardiac medication between the two groups. At baseline, the percentage denervation, H/M ratio, WR, left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), LVEF and NYHA functional class were similar between patients receiving and not receiving nicorandil (Table 2). The mean dose of oral nicorandil was 15 ± 3 mg/day.

Cardiac ^{123}I-MIBG scintigraphic and echocardiographic findings before and 6 months after treatment

Table 3 shows percentage denervation, H/M ratios and WR values. In both groups, percentage denervation was significantly decreased after 6 months relative to the baseline values. However, the delta-percentage denervation in those receiving nicorandil was significantly lower than in those not receiving nicorandil. In both groups, H/M ratios were significantly increased after 6 months. However, delta-H/M ratios in the those receiving nicorandil were significantly higher than in those not receiving nicorandil. Finally, WR in both groups was significantly decreased after 6 months. However, the delta-WR in those receiving nicorandil was significantly lower than in those not receiving nicorandil.

Table 3 also shows LVEDV, LVESV, and LVEF values. In both groups, LVEDV and LVESV were significantly decreased and LVEF was significantly increased after 6 months relative to baseline values. The extent of the changes in LVEDV and LVESV in the patients receiving nicorandil were significantly greater than in those not receiving nicorandil. The extent of the change in LVEF in patients receiving

Table 3 Changes in ^{123}I-MIBG scintigraphic and echocardiographic parameters in patients receiving and those not receiving nicorandil

	Nicorandil			No nicorandil		
	Baseline	6 months	Delta	Baseline	6 months	Delta
^{123}I-MIBG scintigraphy						
Percentage denervation	59.5 ± 10.7	48.4 ± 13.3*	−11.1 ± 11.4	58.6 ± 10.3	51.1 ± 14.4**	−7.4 ± 12.1***
H/M ratio	1.65 ± 0.21	1.81 ± 0.26*	0.16 ± 0.16	1.65 ± 0.20	1.75 ± 0.24**	0.09 ± 0.16***
WR	48.7 ± 11.0	41.5 ± 12.5*	−7.3 ± 10.0	48.9 ± 10.4	45.9 ± 13.3**	−2.9 ± 12.3***
Echocardiography						
LVEDV (ml)	182 ± 44	157 ± 43*	−26 ± 25	180 ± 39	163 ± 42**	−17 ± 29***
LVESV (ml)	123 ± 37	93 ± 38*	−30 ± 26	123 ± 39	101 ± 38**	−22 ± 24***
LVEF (%)	33 ± 7	42 ± 9*	9 ± 9	33 ± 9	39 ± 9**	6 ± 5

Values are means ± SD

*p <0.001 vs. baseline, **p <0.005 vs. baseline, ***p <0.05 vs. nicorandil

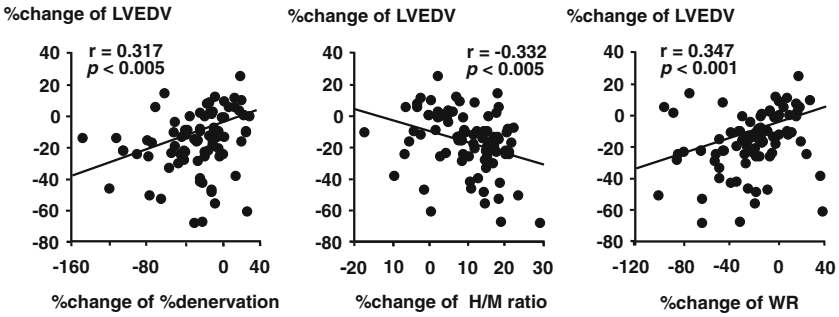

Fig. 2 Correlations between the percentage changes in ^{123}I-MIBG scintigraphic findings and left ventricular end-diastolic volume after nicorandil treatment in 85 patients with chronic heart failure (*LVEDV* left ventricular end-diastolic volume, *H/M ratio* heart/mediastinum count ratio, *WR* washout rate)

nicorandil tended to be more favourable than those not receiving nicorandil, but these changes were not statistically significant.

Relationship between percentage change in left ventricular volume and ^{123}I-MIBG scintigraphic findings before and 6 months after treatment

There were significant correlations between percentage changes in the ^{123}I-MIBG scintigraphic findings and those in LVEDV (percentage denervation, $r=0.317$, $p<0.005$; H/M ratio, $r=-0.332$, $p<0.005$; WR, $r=0.347$, $p<0.001$; Fig. 2) and LVESV in the patients receiving nicorandil (percentage denervation, $r=0.304$, $p<0.005$; H/M ratio, $r=-0.307$, $p<0.005$; WR, $r=0.313$, $p<0.005$; Fig. 3). In contrast, there was no relationship between these parameters in patients not receiving nicorandil.

Multivariate predictors of cardiac death or MACE

Table 4 shows the results of the stepwise multivariate Cox proportional hazards model analyses of cardiac death or MACE. In the multivariate analysis, no beta-blocker and no nicorandil treatments were significant predictors of fatal cardiac events. Furthermore, age, no beta-blocker treatment and no nicorandil treatment were significant predictors of MACE. The hazard ratios for no nicorandil treatment were stronger than those for age and no beta-blocker treatment for predicting MACE.

Kaplan-Meier survival analysis

As shown in Fig. 4, the cardiac death-free rate was significantly higher in patients receiving nicorandil than in those not receiving nicorandil ($p<0.05$). Figure 5 shows that the MACE-free rate was significantly higher in patients receiving nicorandil ($p<0.05$).

Evaluation of factors predicting decreased delta-WR

Table 5 shows the results of the univariate and multivariate analyses assessing factors predicting an increase in delta-WR. In the univariate analysis, age, LVESV, no beta-blocker treatment and no nicorandil treatment were predictive factors. The stepwise multivariate analysis also identified age, LVESV, no beta-blocker treatment and no nicorandil treatment as significant independent predictors of increasing delta-WR in the CHF patients, among which no nicorandil treatment had the strongest beta coefficient.

Discussion

The patients were divided into a group receiving nicorandil and a group not receiving nicorandil using propensity score matching. The ^{123}I-MIBG scintigraphic and echocardiographic parameters showed improvement in both groups, but the extent of the changes in these parameters were more favourable in the nicorandil than in the no nicorandil group. There were significant correlations between percentage

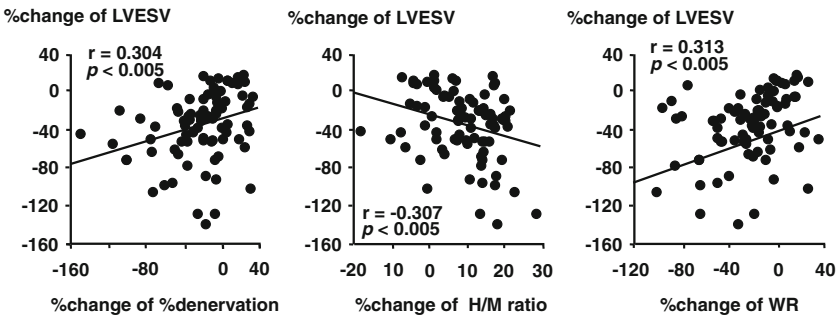

Fig. 3 Correlations between the percentage changes in ^{123}I-MIBG scintigraphic findings and left ventricular end-systolic volume after nicorandil treatment in 85 patients with chronic heart failure (*LVESV* left ventricular end-systolic volume, *H/M ratio* heart/mediastinum count ratio, *WR* washout rate)

Table 4 Multivariate predictors of cardiac death or major adverse cardiac events (MACE)

	Hazard ratio	95 % CI	*p* value
Primary end-point (cardiac death)			
Age	1.023	0.996-1.052	0.099
LVEF	0.971	0.936-1.007	0.115
Beta blocker	0.471	0.250-0.887	0.020
Nicorandil	0.502	0.268-0.940	0.031
Secondary end-point (MACE)			
Age	1.027	1.005-1.050	0.016
LVEF	0.981	0.953-1.010	0.191
Beta blocker	0.526	0.324-0.853	0.011
Nicorandil	0.436	0.266-0.715	0.009

changes in the ^{123}I-MIBG scintigraphic findings and those in LVEDV and LVESV in the nicorandil group, whereas there were no significant relationships in the no nicorandil group. During the follow-up period, cardiac death occurred in 42 of the 170 patients and MACE in 68 patients. The multivariate Cox proportional hazards analysis showed that no nicorandil treatment was a significant predictor of both cardiac death and MACE. In the Kaplan-Meier analysis, rates of freedom from cardiac death and from MACE were significantly higher in the nicorandil than in the no nicorandil group. The stepwise multivariate analyses showed that no nicorandil treatment was independently and significantly related to increasing delta-WR.

Nicorandil exerts a vasodilatory effect mainly on the systemic veins, as do conventional nitrates, but it also dilates

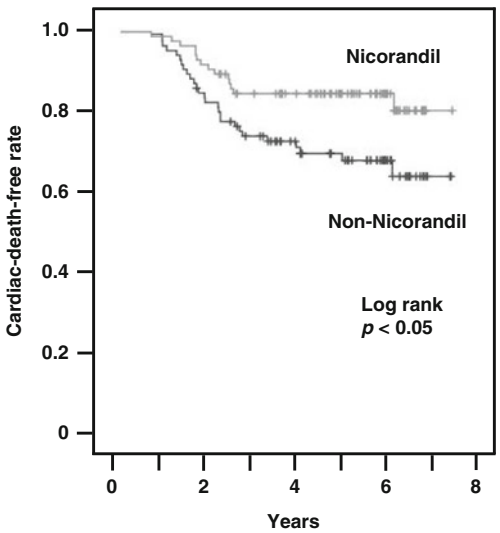

Fig. 4 Kaplan-Meier survival curves for cardiac death-free rates in patients with chronic heart failure divided into two groups, with and without nicorandil treatment. Patients receiving nicorandil had significantly lower cardiac death rates than those not receiving nicorandil ($p<0.05$)

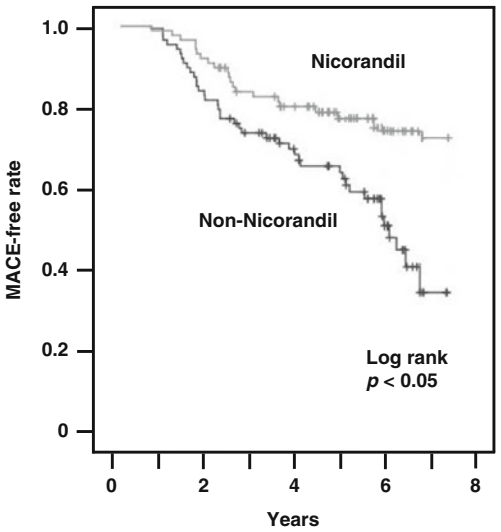

Fig. 5 Kaplan-Meier survival curves for major adverse cardiac event-free (MACE-free) rates in patients with chronic heart failure divided into two groups, with and without nicorandil treatment. Patients receiving nicorandil had significantly lower MACE rates than those not receiving nicorandil ($p<0.05$)

arteries, including peripheral arteries, by opening ATP-sensitive potassium channels [8]. Previous studies have indicated that intravenous administration of nicorandil in the acute phase improves cardiac output, reduces pulmonary pressure, and modulates haemodynamic parameters in patients with acute heart failure including nonischaemic cardiomyopathy [21]. Several potential mechanisms have been proposed for nicorandil's cardioprotective effects: (a) reduction in preload and afterload [22], (b) improved myocardial perfusion [23], (c) prevention of Ca^{2+} overload by opening ATP-sensitive potassium channels [24], and (d) free radical scavenging and neutrophil modulation [25]. Moreover, nicorandil has a pharmacological preconditioning effect [26], and this effect has

Table 5 Univariate and multivariate linear model of delta-WR

	Univariate		Multivariate	
	Correlation coefficient	*p* value	Beta coefficient	*p* value
Age	0.237	0.006	0.209	0.005
Gender, male	0.149	0.053		
Ischaemic aetiology	0.053	0.495		
NYHA functional class	0.058	0.456		
LVESV	0.168	0.029	0.160	0.023
LVEF	−0.083	0.284		
ACE inhibitor	−0.127	0.098		
Beta-blocker	−0.314	<0.001	−0.278	0.004
Nicorandil	−0.321	<0.001	−0.285	0.004

been reported to protect the heart from ischaemia. On the other hand, in nonischaemic heart failure patients, the exact mechanisms of the cardioprotective effect of nicorandil remain unknown. Neglia et al. [27] found that myocardial blood flow is severely depressed in the whole heart in heart failure patients with nonischaemic cardiomyopathy. Therefore, it seems plausible that nicorandil may have an ischaemic preconditioning-like effect during both acute and chronic phases of heart failure, as myocardial flow is depressed in these periods; and this assumption may account for a better outcome, as was the case in the previous study [21].

^{123}I-MIBG is an analogue of the adrenergic neuron-blocking agent guanethidine, which is thought to utilize the same myocardial uptake and release mechanisms as norepinephrine [28]. Therefore, cardiac ^{123}I-MIBG imaging is a useful tool for detecting abnormalities of the myocardial adrenergic nervous system in CHF patients [3, 4]. These scintigraphic findings are well known to have prognostic value in patients with CHF [4–6]. In this study, ^{123}I-MIBG scintigraphic parameters in the patients without cardiac death were all more favourable than in those with cardiac death. Furthermore, many reports have suggested that the treatment of CHF with ACE inhibitors [29–31], angiotensin receptor blockers [32, 33], beta-blockers [30, 34–36], or spironolactone [37, 38] can improve CSNA, based on cardiac ^{123}I-MIBG scintigraphic findings. However, there have been no reports of the effects of long-term nicorandil treatment on CSNA in CHF patients. In this study, we examined whether nicorandil improves CSNA in patients with CHF using ^{123}I-MIBG scintigraphy, and the patients receiving nicorandil showed greater improvement than those not receiving nicorandil. Moreover, stepwise multivariate analyses revealed that nicorandil treatment led to a significant reduction in the likelihood of both cardiac death and MACE. Furthermore, in the stepwise multivariate analyses no nicorandil treatment was independently and significantly related to increasing delta-WR in the CHF patients. Given our previously reported observation that delta-WR is the best currently available prognostic indicator for CHF [7], our findings demonstrate for the first time that nicorandil may be able to improve CSNA and prognosis in patients with CHF.

In the failing heart, as the activation of the sympathetic nervous system increases plasma norepinephrine concentrations [2] and reduces ^{123}I-MIBG uptake [28], these findings (i.e. both increasing norepinephrine concentrations and reduced scintigraphic uptake) correlate with prognosis in patients with CHF [2, 4–7]. The release of norepinephrine from presynapses has been reported to be enhanced and the uptake of norepinephrine to presynapses to be prevented in the failing heart [39]. On the other hand, Lee et al. [13] have demonstrated that the release and uptake of norepinephrine are modulated by activation of ATP-sensitive potassium channels in rats. Since nicorandil is known to activate ATP-sensitive potassium channels and also to have cardioprotective properties [8], this agent may attenuate cardiac sympathetic nerve injury. Our findings demonstrate for the first time that long-term nicorandil treatment improves CSNA in patients with CHF. However, further study is required to confirm this hypothesis.

In this study, there were significant correlations between LV volume and ^{123}I-MIBG scintigraphic parameters after treatment with nicorandil in patients with CHF. However, no significant correlations were found in patients not receiving nicorandil. With respect to the influence of nicorandil, it is still unclear whether attenuation of LV volume, i.e. due to the antiremodelling effect of nicorandil [14], increases myocardial uptake of norepinephrine or whether increased myocardial uptake of norepinephrine leads to attenuation of LV volume. Therefore, further studies are necessary to clarify the relationship between the attenuation of LV volume and the increased myocardial uptake of norepinephrine.

Conclusion

The patients with CHF were divided into those receiving and those not receiving nicorandil using propensity score matching. The ^{123}I-MIBG scintigraphic and echocardiographic parameters were improved in both the nicorandil and the no nicorandil groups, but the extent of the changes in these parameters were more favourable in the nicorandil than in the no nicorandil group. Nicorandil treatment reduced the likelihood of both cardiac deaths and MACE, and these findings were confirmed by multivariate Cox proportional hazards analysis and Kaplan-Meier survival analysis. These findings indicate that nicorandil improves CSNA and prevents LV remodelling in patients with CHF, and this agent is also potentially effective for reducing the incidence of cardiac events in these patients.

Conflicts of interest None.

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