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Nicorandil administration shows cardioprotective effects in patients with poor TIMI and collateral flow as well as good flow after AMI

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Background: Nicorandil (NCR) has been reported to have cardioprotective effects in patients with AMI. And collateral flow and TIMI flow are also important determinants of final salvaged myocardium in patients with AMI. There is no evidence as to whether TIMI or collateral flow modifies the cardioprotective effects of NCR in patients with AMI. ***Methods and Results:*** We studied 68 initial AMI patients without restenosis which was defined as 50% diameter reduction of the intervention site in the chronic period. On initial CAG, 41 patients with poor flow (collateral: Rentrop 0 or 1 and TIMI 0 or 1) were NCR/Non-NCR = 20/21. Twenty-seven patients with good flow (collateral: Rentrop 2 or 3 or TIMI 2 or 3) were NCR/Non-NCR = 13/14. NCR was administered intravenously (4 mg) via intracoronary injection (2 mg) or continuously (4 mg/h). ^{99m}Tc-tetrofosmin (TF) and ^{123}I-BMIPP SPECT were performed in the subacute and chronic (6 Mo) periods. In 20 SPECT segments, summed defect scores (TDS) and regional wall motion (WMS: −1 = dyskinesis〜4 = normal) of AMI segments using TF-QGS were estimated. In poor flow patients, the following values for NCR patients were higher ($p < 0.05$) than for Non-NCR patients in the improvement degree of TDS (BMIPP) (NCR: 6.5 ± 3.9 vs. Non-NCR: 4.0 ± 3.4), the improvement degree of TDS (TF) (NCR: 5.7 ± 4.6 vs. Non-NCR: 2.2 ± 4.6), and delta WMS (NCR: 1.4 ± 1.1 vs. Non-NCR: 0.9 ± 1.0). In good flow patients, the following values for NCR patients were better ($p < 0.05$) than for Non-NCR patients in TDS (BMIPP) (subacute) (NCR: 9.9 ± 5.2 vs. Non-NCR: 16.5 ± 10.4) and (chronic) (NCR: 5.1 ± 5.2 vs. Non-NCR: 12.4 ± 8.5), WMS (subacute) (NCR: 1.7 ± 1.3 vs. Non-NCR: 1.0 ± 1.0), and WMS (chronic) (NCR: 3.0 ± 1.5 vs. Non-NCR: 2.1 ± 1.3). ***Conclusion:*** We conclude that the cardioprotective effects of nicorandil administration are observable in both AMI patients with poor collateral and TIMI flow and good flow before reperfusion therapy.

Key words: nicorandil, cardioprotective effect, AMI

INTRODUCTION

CORONARY REPERFUSION by thrombolysis and/or angioplasty is an established core therapy for cases of acute myocardial infarction (AMI).[1,2] Recently, certain investigators have demonstrated that pharmacologic treatment, such as intracoronary verapamil or nicorandil and adenosine, in conjunction with coronary reperfusion, may enhance functional improvements in the left ventricle of patients with AMI.[3–6] Several of these experimental studies have stressed that nicorandil may enhance the recovery of postischemic contractile dysfunction and reduce infarct size.[3,7–9]

Nicorandil is a nicotinamide ester with a dual mechanism of action. Its distinctive pharmacological effect is to open ATP-sensitive potassium channels (K_{ATP}), thereby dilating peripheral and coronary resistance arterioles. It also possesses a nitrate moiety that dilates systemic veins and epicardial coronary arteries. Thus, it increases

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coronary blood flow, reduces preload and after-load,[10–12] and offers an antianginal efficacy and safety profile similar to that of oral nitrates, beta-blockers, and calcium antagonists.[13–15] In addition to relieving symptoms of ischemia, nicorandil also has potential cardioprotective effects. These effects are likely due to its ability to mimic the powerful ischemic preconditioning phenomenon by opening K_{ATP} channels, as shown in clinical and preclinical studies.[16–19]

Spontaneous anterograde flow to infarcted areas assessed before reperfusion therapy is reported to be associated not only with greater improvements in LVEF after reperfusion, but also with higher LVEF during the acute phase of AMI.[20–24] Moreover, good collateral flow is reported to be effective in decreasing infarct size and in improving LVEF.[25,26] On the other hand, nicorandil has cardioprotective effects that decrease infarct size and improve LV function and prognosis in patients with AMI[3,27,28] and unstable angina pectoris.[29] However, whether nicorandil's effectiveness is influenced by collateral flow grade and TIMI flow grade before reperfusion remains controversial. This study was designed to clarify whether TIMI or collateral flow modifies the cardioprotective effects of nicorandil in patients with AMI.

METHODS

Patients. Ninety patients with AMI who had undergone successful percutaneous coronary intervention (PCI) with or without stenting within 24 h of the onset of symptoms were recruited for this study. Subsequently, patients were randomly assigned to either of two patient groups: those receiving and not receiving nicorandil administration. A diagnosis of AMI was based on the following criteria: acute chest pain lasting ≥30 min; serum creatine kinase activity over ≥500 IU; and development of abnormal electrocardiographic Q waves.

Patients who fulfilled the following criteria were included in the statistical analysis: successful PCI with or without coronary stenting with angiographic confirmation of ≤25% residual stenosis; no significant stenosis in other vessels; good image quality for all radiotracer studies during the subacute and chronic period. Twenty-two patients had restenosis which was defined as 50% diameter stenosis of the intervention site on coronary angiography (CAG) 6 months after admission. The final study population consisted of 68 patients (46 men and 22 women; 46 to 75 years of age, mean age: 64 ± 12 years). The infarct-related vessel was the left anterior descending coronary artery in 41 patients, the left circumflex artery in 9 patients, and the right coronary artery in 18 patients.

Study Protocol. In the group receiving nicorandil administration, we injected nicorandil (4 mg) (Sigmart, Chugai, Tokyo) intravenously, and kept a continuous infusion at 4 mg/h over a 24-hour period, which was started before PCI. Then we injected nicorandil (2 mg) into the coronary artery just after reperfusion. Other treatments were the same for patients receiving and not receiving nicorandil administration. All patients underwent cardiac catheterization through a femoral approach following injection of 5,000 units heparin. Following injection of 2.5 mg of isosorbirate into the coronary artery, we performed coronary angiography (CAG) and PCI. Heparin administration was continued for 1 or 2 days. At the same time, nitroglycerin was continuously infused at 3 m*l*/h over a period of 1 or 2 days. All patients were maintained on a regimen of aspirin and ticlopidine. Patients were divided into two groups based on collateral flow using the Rentrop grading scale (0 = none; 1 = filling of side branches of the artery to be dilated via collateral channels without visualization of the epicardial segment; 2 = partial filling of the epicardial segment via collateral channels; 3 = complete filling of the epicardial segment of the artery dilated via collateral channels) and TIMI flow on CAG just before PCI. The group with poor flow was defined as the group of patients for whom collateral flow Rentrop grade 0 or 1 and TIMI flow grade 0 or 1, including 21 patients not receiving nicorandil administration who were defined as group A (poor flow without NCR) and 20 patients receiving nicorandil administration who were defined as group B (poor flow with NCR). The group with good flow was defined as the group of patients with collateral flow Rentrop grade 2 or 3, or TIMI flow grade 2 or 3, including 14 patients not receiving nicorandil administration who were defined as group C (good flow without NCR) and 13 patients receiving nicorandil administration who were defined as group D (good flow with NCR).

The scintigraphic studies used were resting ^{99m}Tc-pyrophosphate (PYP) single photon emission computed tomographic (SPECT) images on the third day; rest ^{99m}Tc-tetrofosmin gated SPECT on the sixth day, and ^{123}I-methyl-iodophenyl pentadecanoic acid (BMIPP) SPECT on the ninth day after admission. On follow-up (6 months later), rest ^{99m}Tc-tetrofosmin SPECT using QGS software, ^{123}I-BMIPP SPECT, and CAG were also performed. All scintigraphic studies were performed after a 12-h overnight fast in the absence of antianginal medication.

All patients provided informed consent in accordance with the guidelines set by our hospital's Human Clinical Study Committee.

^{99m}Tc-PYP SPECT. Each patient received 740 MBq of ^{99m}Tc-pyrophosphate intravenously, 2 hours after which all patients underwent myocardial imaging.

^{99m}Tc-tetrofosmin gated SPECT. The ^{99m}Tc-tetrofosmin was obtained commercially (Nihon Medi-Physics, Chiba, Japan). The patients received intravenous injections of 740 MBq of ^{99m}Tc-tetrofosmin while sitting upright. Gated SPECT images were acquired 30 min after injection. The RR interval was divided into 16 subintervals for gated SPECT.

^{123}I-BMIPP SPECT. The ^{123}I-BMIPP was obtained

commercially (Nihon Medi-Physics, Chiba, Japan). The patients received intravenous injections of 111 MBq of ^{123}I-BMIPP while sitting upright. SPECT images were acquired 15 min after injection.

Myocardial SPECT Imaging. Myocardial SPECT imaging was performed using a PRISM3000 (PICKER, Cleveland, OH) three-headed SPECT system with low-energy, all-purpose resolution, parallel-hole collimators. The detector system was linked to a dedicated nuclear medicine computer. A total of 72 projection images were obtained over a 360° arc in 5° increments, with 55 sec/view acquisitions for ^{99m}Tc-PYP and ^{123}I-BMIPP, and with 40 sec/view acquisitions for ^{99m}Tc-tetrofosmin. The energy discriminator was centered on 140 keV for ^{99m}Tc-PYP and ^{99m}Tc-tetrofosmin with a 15% window, and 159 keV for ^{123}I-BMIPP with a 20% window. Data were recorded in 64 × 64 matrices to a magnetic disk. Butterworth (order: 8, cutoff frequency: 0.25 cycle/pixel) and ramp filters were used to reconstruct transaxial tomographic images from each acquisition. Short- and long-axis slices (5.4 mm thick) were generated.

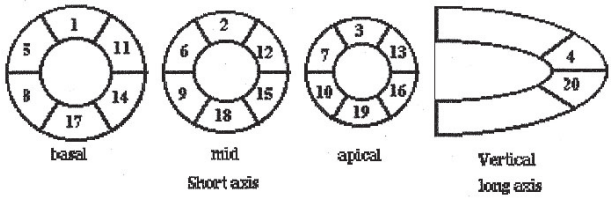

Fig. 1 Myocardial SPECT imaging.

Analysis of SPECT. For each study, SPECT analysis was based on one vertical long-axis slice and three short-axis slices. In each patient, the corresponding vertical long- and short-axis tomograms from the ^{99m}Tc-PYP, ^{99m}Tc-tetrofosmin, and ^{123}I-BMIPP SPECT image sets were aligned. Additionally, one vertical long-axis slice and three short-axis views from the apical, middle, and basal ventricular levels were chosen for comparison. The vertical long-axis slice was used to evaluate the apical region, which was divided into two segments, while each short-axis slice was divided into six segments (Fig. 1). All SPECT images were analyzed by two experienced observers with no knowledge of the patients' clinical history. Semiquantitative visual analysis was performed by assigning regional tracer uptake activity by a four-point scoring system (defect score): 3 = absent; 2 = significantly reduced uptake; 1 = mildly reduced uptake; and 0 = normal uptake. Disagreements in interpretation were resolved by consensus. We defined the number of segments in which the ^{99m}Tc-PYP accumulated as the extent score (ES). We defined the sum of defect scores in the infarcted area in which the ^{99m}Tc-PYP accumulated as the total defect score (TDS). Delta TDS was calculated as TDS in the subacute period minus TDS in the chronic period.

Table 1 Characteristics of all groups

	Group A (Poor flow without NCR) (n = 21)	Group B (Poor flow with NCR) (n = 20)	Group C (Good flow without NCR) (n = 14)	Group D (Good flow with NCR) (n = 13)
Age (yrs)	63 ± 12	63 ± 10	63 ± 14	67 ± 11
Number of men	15 (71%)	15 (75%)	6 (43%)	8 (62%)
Peak CK (U/*l*)	4069 ± 2882	4422 ± 2915	2630 ± 1444$^{\#}$	1592 ± 770$^{*,\#\#}$
Time to reperfusion (h)	5.2 ± 4.4	4.8 ± 3.6	4.7 ± 3.2	5.2 ± 3.6
Risk factors				
Diabetes mellitus	7 (33%)	5 (25%)	5 (36%)	3 (23%)
Hypertension	8 (38%)	8 (40%)	5 (36%)	4 (31%)
Hyperlipidemia	5 (24%)	8 (40%)	3 (21%)	4 (31%)
Smoking	16 (76%)	14 (70%)	11 (79%)	9 (69%)
Infarcted artery				
LAD	14 (67%)	13 (65%)	7 (50%)	5 (56%)
LCX	3 (14%)	2 (10%)	2 (14%)	1 (11%)
RCA	4 (19%)	5 (25%)	5 (36%)	3 (33%)
History of angina pectoris	11 (52%)	8 (40%)	8 (57%)	7 (54%)
History of preinfarction angina	7 (33%)	6 (30%)	4 (29%)	5 (38%)
Medicines				
Beta-blocker	4 (19%)	2 (14%)	2 (14%)	2 (15%)
Ca-antagonist	4 (19%)	5 (36%)	5 (36%)	2 (15%)
ACE inhibitor or ARB	13 (65%)	7 (50%)	7 (50%)	8 (62%)
Nitrate	12 (60%)	9 (64%)	9 (64%)	6 (46%)

Data are presented as number of patients (in percent) or mean value ± SD. *: $p < 0.05$ vs. group A, $^{\#}$: $p < 0.05$ vs. group B, $^{\#\#}$: $p < 0.01$ vs. group B. Abbreviations: CK = creatine kinase; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

Table 2 Outcomes of all groups

	Group A (Poor flow without NCR) (n = 21)	Group B (Poor flow with NCR) (n = 20)	Group C (Good flow without NCR) (n = 14)	Group D (Good flow with NCR) (n = 13)
Extent score	8.8 ± 4.2	8.8 ± 3.4	7.6 ± 4.1	6.7 ± 4.1
TDS (TF)				
Subacute	14.5 ± 9.5	12.4 ± 9.4	8.1 ± 6.1*	4.1 ± 4.3*,#
Chronic	12.3 ± 9.7	6.7 ± 6.7*	5.4 ± 5.7**	2.0 ± 3.0**
Delta TDS	2.2 ± 4.6	5.7 ± 4.6**	2.6 ± 1.8#	2.1 ± 4.1#
TDS (BMIPP)				
Subacute	20.3 ± 11.1	19.7 ± 8.6	16.5 ± 10.4	9.9 ± 5.2**,#
Chronic	16.4 ± 9.7	13.2 ± 9.2	12.4 ± 8.5	5.1 ± 5.2**,#,$
Delta TDS	4.0 ± 3.4	6.5 ± 3.9*	2.6 ± 1.8	2.1 ± 4.1
LVEF (%)				
Subacute	48 ± 10	50 ± 14	56 ± 12*	61 ± 7**,#
Chronic	52 ± 9	54 ± 12	58 ± 11	64 ± 8**,#
Delta LVEF	4 ± 6	5 ± 7	3 ± 6	4 ± 5
WMS				
Subacute	0.6 ± 0.9	0.6 ± 1.0	1.0 ± 1.0**,##	1.7 ± 1.3**,##,$$
Chronic	1.5 ± 1.3	2.0 ± 1.4**	2.1 ± 1.3**	3.0 ± 1.5**,##,$$
Delta WMS	0.9 ± 1.0	1.4 ± 1.1**	1.1 ± 0.9#	1.3 ± 1.0

Data are presented as number of patients (percent) or mean value ± SD. *: $p < 0.05$ vs. group A, **: $p < 0.01$ vs. group A, #: $p < 0.05$ vs. group B, ##: $p < 0.01$ vs. group B, $: $p < 0.05$ vs. group C, $$: $p < 0.01$ vs. group C. Abbreviations: TDS = total defect score, Delta TDS = subacute TDS − chronic TDS, TF = ^{99m}Tc-tetrofosmin, BMIPP = methyl-iodophenyl pentadecanoic acid, LVEF = left ventricular ejection fraction, Delta LVEF = chronic LVEF − subacute LVEF, WMS = wall motion score, Delta WMS = chronic WMS − subacute WMS.

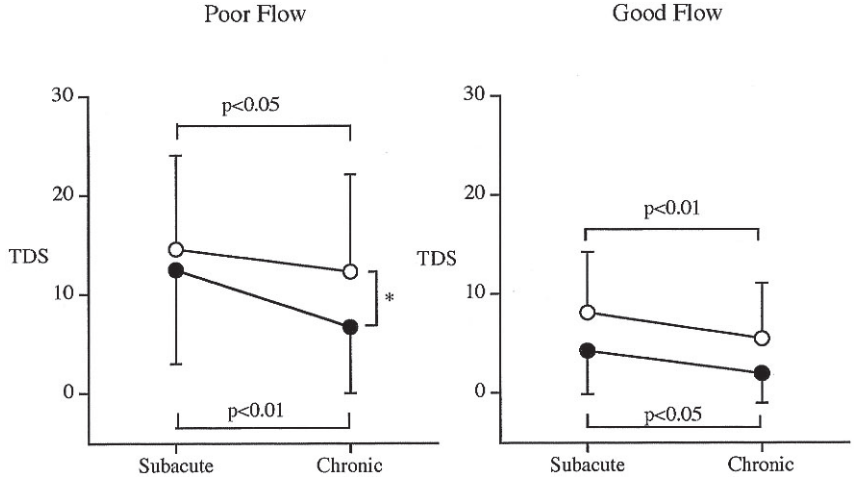

Fig. 2 Changes in total defect score of ^{99m}Tc-tetrofosmin of poor flow groups (*left*) and good flow groups (*right*). *: $p < 0.05$. TDS = total defect score. Open circles indicate groups without nicorandil administration. Closed circles indicate groups with nicorandil administration.

Analysis of LV function. The Quantitative Gated SPECT (QGS) program (Cedas-Sinai Medical Center, Los Angeles, CA) was used for gated SPECT analysis.[30] Calculations of left ventricular ejection fraction (LVEF) values, and wall motion analysis were performed by means of automatic determination of endocardial and epicardial surfaces for all gating intervals in the cardiac cycle. Regional wall motion was estimated visually using the cine-mode display of the data in 20 segments corresponding to SPECT segments. Semiquantitative visual analysis was performed by assigning scores to wall motion observations using a six-point scale (WMS: wall motion score): −1 = dyskinesis; 0 = akinesis; 1 = severe hypokinesis; 2 = moderate hypokinesis; 3 = mild hypokinesis; and 4 = normokinesis. Delta LVEF and delta WMS were calculated as those in the subacute period minus those in the chronic period.

Statistical Analysis. All data were presented as mean ± SD. ANOVA was used to determine differences between values. Chi-square analysis or Fisher's exact test

was used to determine the distribution of categoric variables. A p value <0.05 was considered statistically significant.

Furthermore, regulation factors of the improvement of regional wall motion in the infarcted area were estimated by multivariate analysis. Administration of nicorandil, age, gender, CK, reperfusion time, 4 risk factors, infarcted artery, history of angina pectoris, history of preinfarction angina, good or poor flow and 4 medicines. Preinfarction angina was defined as anginal attack within 24 hours before the onset of acute myocardial infarction.

RESULTS

Baseline Characteristics

Table 1 gives the baseline characteristics. There were no significant differences in age, gender, time to reperfusion, incidence of coronary risk factors, infarct-related arteries, history of angina pectoris, history of preinfarction angina or medicines. There were also no significant differences in peak serum creatine kinase level between those receiving and not receiving nicorandil administration in the poor or good flow groups. However, peak CK in group C was significantly lower than that in group B, and peak CK in group D was significantly lower than that in groups A and B.

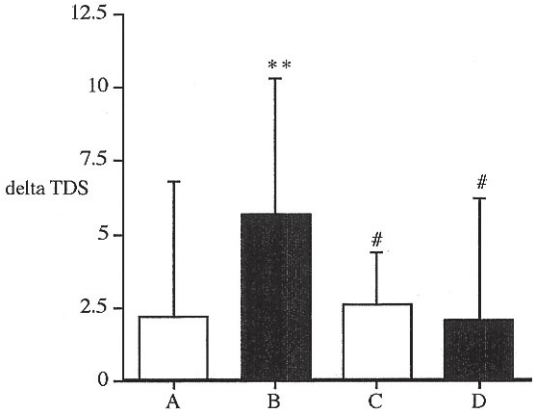

Fig. 3 Delta TDSs of ^{99m}Tc-tetrofosmin in all groups. **: $p < 0.01$ vs. group A, #: $p < 0.05$ vs. group B. TDS = total defect score, Delta TDS = subacute TDS − chronic TDS.

Extent Score and Changes in Perfusion and Fatty Acid Metabolism

There were no significant differences in extent scores (Table 2). TDS of ^{99m}Tc-tetrofosmin improved in all groups (Table 2 and Fig. 2). TDSs of ^{99m}Tc-tetrofosmin in groups of good flow were lower than that of group A in both periods. Moreover, TDS of ^{99m}Tc-tetrofosmin in group B was lower than that of group A in the chronic period (Table 2). Delta TDS of ^{99m}Tc-tetrofosmin in group B was higher than those in groups A, C and D (Table 2 and Fig. 3). TDS of ^{123}I-BMIPP SPECT also improved in all groups (Table 2 and Fig. 4). TDS of ^{123}I-BMIPP in group D was lower than that of group A in both periods (Table 2). Moreover, TDS of ^{123}I-BMIPP in group D was lower than that of group C in the chronic period (Table 2). Delta TDS of ^{123}I-BMIPP SPECT in group B was higher than that of group A (Table 2 and Fig. 5).

Changes in LVEF and Regional Wall Motion

LVEF improved in two groups with poor flow, and in group D with good flow. LVEF of group C was higher than that of group A in the subacute period. LVEF of group D was higher than those of two groups with poor flow in both periods (Table 2 and Fig. 6). There was no difference in delta LVEF among the 4 groups (Table 2). WMS in the infarcted area improved during the chronic

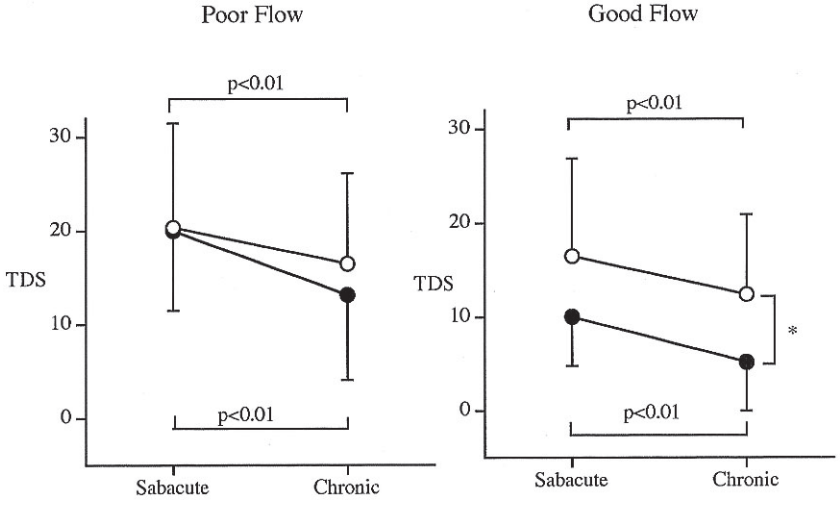

Fig. 4 Change of total defect score of ^{123}I-BMIPP of poor flow groups (*left*) and good flow groups (*right*). *: $p < 0.05$. TDS = total defect score. Open circles indicate groups without nicorandil administration. Closed circles indicate groups with nicorandil administration.

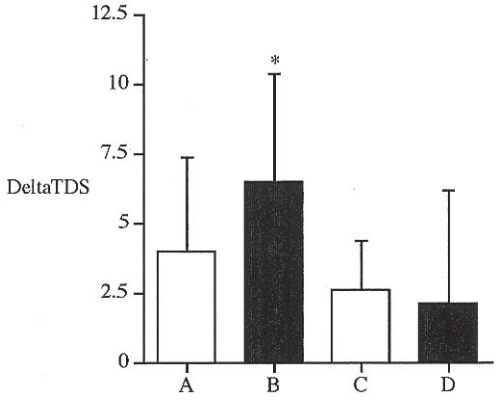

Fig. 5 Delta TDSs of ^{123}I-BMIPP in all groups. *: $p < 0.05$ vs. group A. TDS = total defect score, Delta TDS = subacute TDS − chronic TDS.

period in all groups (Table 2 and Fig. 7). In the group with poor flow, WMS in group B was significantly higher than that in group A in the chronic period (Table 2 and Fig. 7). In the group with good flow, WMS in group D was significantly higher than that in group C in both periods (Table 2 and Fig. 7). Delta WMS in group B was higher than those in groups A and C (Table 2 and Fig. 8).

Multivariate Analysis

Only the administration of nicorandil ($p = 0.037$) was left. The other factors were not significant.

DISCUSSION

In this study, we divided all patients into four groups based on administration of nicorandil, and collateral flow

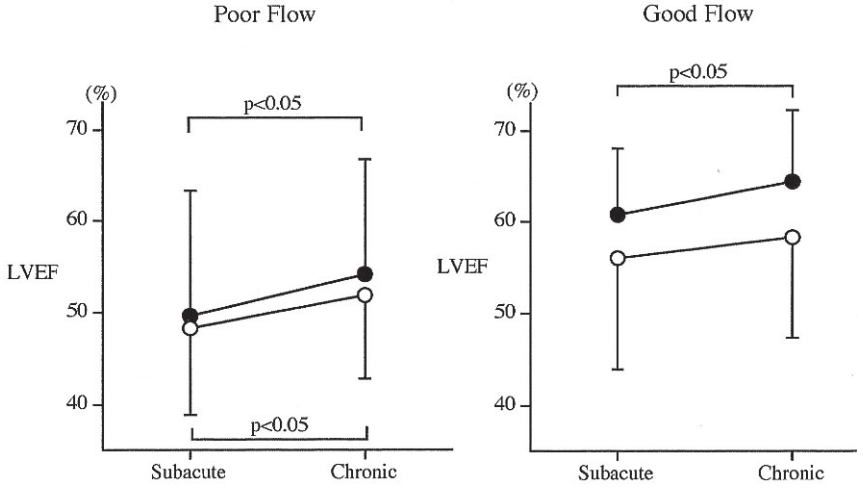

Fig. 6 Changes in LVEF. Open circles indicate groups without nicorandil administration. Closed circles indicate groups with nicorandil administration. LVEF = left ventricular ejection fraction.

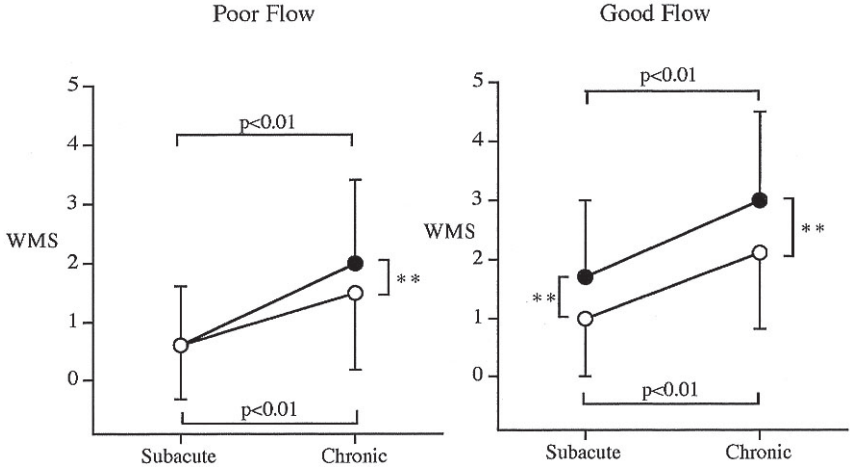

Fig. 7 Change of mean wall motion score of poor flow groups (*left*) and good flow groups (*right*). Open circles indicate groups without nicorandil administration. Closed circles indicate groups with nicorandil administration. **: $p < 0.01$. WMS = wall motion score.

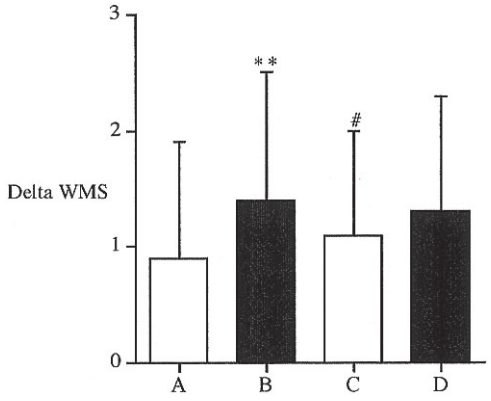

Fig. 8 Delta wall motion score in all groups. **: $p < 0.01$ vs. group A, #: $p < 0.05$ vs. group B. WMS = wall motion score, Delta WMS = chronic WMS – subacute WMS.

and TIMI flow on CAG just before PCI. We defined the group with poor flow as the group of patients having collateral flow grade Rentrop 0 or 1 and TIMI flow grade 0 or 1. We defined the group with good flow as the group of patients with collateral flow grade Rentrop 2 or 3, or TIMI flow grade 2 or 3. From our study, peak CK in the acute period, TDSs of TF and BMIPP, LVEF and regional wall motion in the subacute period of the groups with good flow were better than those for the groups with poor flow, despite nicorandil administration. These results are consistent with previous reports. Thus, we examined the effectiveness of nicorandil with regard to differences in coronary flow grade supplied by antegrade flow (TIMI flow) and collateral flow just before PCI.

Both groups of poor or good flow in our study evinced the cardioprotective effects of nicorandil during either the subacute or chronic period. Nicorandil produced some excellent results in both the poor flow group and the good flow group, compared to no nicorandil. Nicorandil demonstrated cardioprotective effects unaffected by TIMI flow or collateral flow. These results seemed to be induced by the preconditioning effect of nicorandil operating as a K_{ATP} channel opener, which was not influenced by collateral flow or TIMI flow before reperfusion.

However, there were some differences in the cardioprotective effect of nicorandil. Nicorandil took different forms in the poor and good flow groups. The effect of nicorandil in the poor flow group appeared during the chronic period on myocardial perfusion, myocardial fatty acid metabolism, and regional wall motion. The effects of nicorandil in the good flow group were already visible in the subacute period. Myocardial infarction in the poor flow group was of greater magnitude than in the good flow group. For this reason, several months were required for recovery of myocardial perfusion, myocardial fatty acid metabolism, and regional wall motion of the stunned myocardium salvaged by nicorandil. Since myocardial infarctions in the good flow group were slight, the recovery of stunned myocardium salvaged by nicorandil appears during the subacute stage.

In patients with good flow, nicorandil can easily arrive at the ischemic area because of preadministration of nicorandil, and easily shows its effect. That effect is already apparent in the subacute period. On the other hand, in patients with poor flow, the effect of preadministration of nicorandil is unclear, but nicorandil in blood can arrive at the ischemic area, and then the effect of nicorandil would be shown. Furthermore, intracoronary injection of nicorandil could work to relieve reperfusion injury just after reperfusion. For these reasons, the cardioprotective effect of nicorandil seems to be shown without depending on myocardial flow in the ischemic area.

Furthermore, the only significant factor to predict the improvement of regional wall motion in the infarcted area was the administration of nicorandil which by use multivariate analysis. This result shows that nicorandil is the most important factor to protect myocardium and improve the regional function in the infarcted area.

Nicorandil acts as both a nitrate and a potassium channel opener,[31] and several mechanisms have been postulated to explain its direct cardioprotective effects. First, nicorandil acts as a pharmacological mimetic of ischemic preconditioning, a phenomenon well described in the experimental literature and representing a potential endogenous cardioprotective mechanism. This process is responsible for the amelioration of subsequent effects of ischemia after an initial ischemic event, and the role of K_{ATP} channels in this mode of protection has been experimentally demonstrated.[32,33] Originally, the pharmacological basis for ischemic preconditioning was believed to be activation of the sarcolemmal K_{ATP} channels by a reduction in cytosolic ATP concentrations by ischemia, resulting in action potential abbreviation, reduced calcium influx, and decreased contractility.[7,34] An alternative, and perhaps more scientifically plausible, explanation for ischemic preconditioning arises from the recent demonstration of the preservation of mitochondrial integrity through the activation of specific mitochondrial K_{ATP} channels. In the current absence of any published molecular characterization, these mito-K_{ATP} channels remain only hypothetical. Nevertheless, pharmacological evidence suggests their existence, and suggests that nicorandil exerts its preconditioning effects through their activation.[35]

K_{ATP} channel openers may shorten the action potential duration, thereby reducing cellular calcium overload and preserving viability in the ischemic myocardium. This was initially proposed as the mechanism of protection of the ischemic myocardium. Nevertheless, this hypothesis cannot account for the mechanism of cardioprotection, because the abbreviation of action potentials is not required for protection.[36,37] Alternatively, recent pharmacologic evidence hints that mito-K_{ATP} channels are the primary factors. In contrast, the mito-K_{ATP} channel blocker

5HD completely negated nicorandil-induced cardioprotection, indicating that mito-K_{ATP} rather than surface K_{ATP} channels are involved in the cardioprotection provided by nicorandil.[38]

Second, nicorandil reduces neutrophil infiltration into the ischemic myocardium.[8] It also attenuates neutrophil activity in a concentration-dependent manner.[39] This reduction may attenuate microvascular injury caused by neutrophils, increasing myocardial blood flow. Vessels <100 μm are more sensitive to nicorandil than vessels either smaller or larger.[40] These factors improve coronary microvascular function.

Study Limitations. Our study has several limitations. First, our estimates were based on concurrent TIMI flow and collateral flow, factors that need to be examined in isolation. We were compelled to estimate the effects of each factor on nicorandil's cardioprotective effects. Moreover, we regarded TIMI 2 flow grade and Rentrop 2 collateral flow grade as the same flow grade, although it is unclear whether these flow grades are indeed identical. Second, the doses of nicorandil may not have been optimal in all cases. Third, regional wall motion was estimated by visual analysis. On this account it is lacking in the precision. This will be evaluated by quantitative evaluation in future if quantitative evaluation is enabled in QGS software. Fourth, we could not evaluate patients with the same culprit lesions because of the limited number of patients. Finally, the size of the study population was insufficient to permit firm conclusions concerning the beneficial effects of nicorandil. For these reasons, a large-scale, randomized study is needed to confirm the results of this study.

Conclusion. Nicorandil administration shows the cardioprotective effects in patients with poor TIMI and collateral flow as well as good flow after AMI.

REFERENCES

1. Hillis LD, Former S, Braunwald E. Risk stratification before thrombolytic therapy in patients with acute myocardial infarction. *J Am Coll Cardiol* 1990; 16: 313–315.
2. Gruppo Italiano per lo Studio Della Streptokinesi Nell' Infarcto Micardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; I: 397–401.
3. Ito H, Taniyama T, Iwakura K, Nishikawa N, Masuyama T, Kuzuya T, et al. Intravenous nicorandil can preserve microvascular integrity and myocardial viability in patients with reperfused anterior wall myocardial infarction. *J Am Coll Cardiol* 1999; 33: 654–660.
4. Ishii H, Ichimiya S, Kanashiro M, Amano T, Imai K, Murohara T, et al. Impact of a single intravenous administration of nicorandil before reperfusion in patients with ST-segment-elevation myocardial infarction. *Circulation* 2005; 112: 1284–1288.
5. Taniyama Y, Ito H, Iwakura K, Masuyama T, Hori M, Takiuchi S, et al. Beneficial effect of intracoronary verapamil on microvascular and myocardial salvage in patients with acute myocardial infarction. *J Am Coll Cardiol* 1997; 30: 1193–1199.
6. Mahaffey KW, Puma JA, Barbagelata A, et al. Does adenosine in conjunction with thrombolysis reduce infarct size? Results from the controlled, randomized AMISTAD trial. *Circulation* 1997; 96 Suppl I: I-206.
7. Auchampach JA, Cavero I, Gross GJ. Nicorandil attenuates myocardial dysfunction associated with transient ischemia by opening ATP-dependent potassium channels. *J Cardiovasc Pharmacol* 1992; 20: 765–771.
8. Mizunuma T, Nithipatikom K, Gross GJ. Effects of nicorandil and glyveryl trinitrate on infarct size, adenosine release, and neutrophil infiltration in the dog. *Cardiovasc Res* 1995; 29: 482–489.
9. Klein HH, Pich S, Lindert-Heimberg S, Shade-Brittinger C, Maisch B, Nebendahl K. Comparative study on the effects of intracoronary nicorandil and nitroglycerin in ischaemic, reperfused porcine hearts. *Eur Heart J* 1995; 16: 603–609.
10. Chibana T, Nagamine F, Sunagawa R, Oshiro K, Nakada Y, Shimabukuro M, et al. Comparison of acute hemodynamic and coronary vasodilating effects between nicorandil and glyceryl trinitrate. *Arzneim-Forsh/Drug Res* 1991; 41: 591–594.
11. Treese N, Erbel R, Meyer J. Acute hemodynamic effects of nicorandil in coronary artery disease. *J Cardiovasc Pharm* 1992; 20: 52–56.
12. Taira N. Nicorandil as a hybrid between nitrates and potassium channel activators. *J Cardiol* 1989; 63: 18J–24J.
13. Doring G. Antianginal and anti-ischemic efficacy of nicorandil in comparison with isosorbide-5-mononitrate and isosorbide dinitrate: results from two multicenter, double-blind, randomized studies with stable coronary heart disease patients. *J Cardiovasc Pharm* 1992; 20 suppl 3: S74–S81.
14. Di Somma S, Liguori V, Petitto M, Carotenuto A, Bokor D, de Divitiis O, et al. A double-blind comparison of nicorandil and metoprolol in stable effort angina pectoris. *Cardiovasc Drugs Ther* 1993; 7: 119–123.
15. Swan Study Group. Comparison of the antiischaemic and antianginal effect of nicorandil and amlodipine in patients with symptomatic stable angina pectoris: the SWAN study. *J Clin Basic Cardiol* 1999; 2: 213–217.
16. Ce M, Jennings RB, Reimer KA. Preconditioning with ischaemia: a delay of lethal cell injury in ischaemic myocardium. *Circulation* 1986; 74: 1124–1136.
17. Patel DJ, Purcell J, Fox KM. Cardioprotection by opening of the KATP channel in unstable angina. *Eur Heart J* 1999; 20: 51–57.
18. Tomai F, Crea F, Gaspardone A, Versaci F, Esposito C, Chiariello L, et al. Mechanisms of cardiac pain during coronary angioplasty. *J Am Coll Cardiol* 1993; 22: 1892–1896.
19. Yellon DF, Alkulaifi AM, Pugsley WB. Preconditioning the human myocardium. *Lancet* 1993; 342: 276–277.
20. Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Kurisu S, Nishioka K, et al. Impact of spontaneous anterograde flow of the infarct artery on left ventricular function in patients with a first anterior wall acute myocardial infarction. *Am J Cardiol* 2002; 90: 5–9.
21. Brodie BR, Stuckey TD, Hansen C, Muncy D. Benefit of coronary reperfusion before intervention on outcomes after

primary angioplasty for acute myocardial infarction. *Am J Cardiol* 2000; 85: 13–18.
22. Blanke H, Cohen M, Karsch KR, Fagerstrom R, Rentrop KP. Prevalence and significance of residual flow to the infarct zone during the acute phase of myocardial infarction. *J Am Coll Cardiol* 1985; 5: 827–831.
23. Stone GW, Cox D, Garcia E, Brodie BR, Morice MC, Griffin J, et al. Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction: analysis from the primary angioplasty in myocardial infarction trials. *Circulation* 2001; 104: 636–641.
24. Lee CW, Hong MK, Yang HS, Choi SW, Kim JJ, Park SW, et al. Determinants and prognostic implications of terminal QRS complex distortion in patients treated with primary angioplasty for acute myocardial infarction. *Am J Cardiol* 2001; 88: 210–213.
25. Bruce CJ, Christian TF, Schaer GL, Spaccavento LJ, Jolly MK, O'Connor MK, et al. Determinants of infarct size after thrombolytic treatment in acute myocardial infarction. *Am J Cardiol* 1999; 83: 1600–1605.
26. Rentrop KP, Feit F, Sherman W, Stecy P, Hosat S, Cohen M, et al. Late thrombolytic therapy preserves left ventricular function in patients with collateralized total coronary occlusion: primary end point findings of the Second Mount Sinai-New York University Reperfusion Trial. *J Am Coll Cardiol* 1989; 14: 58–64.
27. Fukuzawa S, Ozawa S, Inagaki M, Shimada K, Sugioka J, Tateno K, et al. Nicorandil affords cardioprotection in patients with acute myocardial infarction treated with primary percutaneous transluminal coronary angioplasty: assessment with thallium-201/iodine-123 BMIPP dual SPECT. *J Nucl Cardiol* 2000; 7: 447–453.
28. Lim SY, Bae EH, Jeong MH, Kang DG, Lee YS, Kim KH, et al. Effect of combined intracoronary adenosine and nicorandil on no-reflow phenomenon during percutaneous coronary intervention. *Circ J* 2004; 68: 928–932.
29. Kim JH, Jeong MH, Yun KH, Kim KH, Kang DK, Hong SN, et al. Myocardial protective effects of nicorandil during percutaneous coronary intervention in patients with unstable angina. *Circ J* 2005; 69: 306–310.
30. Germano G, Kiat H, Kavanagh PB, Moriel M, Mazzanti M, Su HT, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med* 1995; 36: 2138–2147.
31. Schwaiger M, Schelbert HR, Ellison D, Hansen H, Yeatman L, Vinten-Johansen J, et al. Sustained regional abnormalities in cardiac metabolism after transient ischemia in the chronic dog model. *J Am Coll Cardiol* 1985; 6: 336–347.
32. Saito S, Mizumura T, Takayama T, Marb E. Antiischemic effects of nicorandil during coronary angioplasty in humans. *Cardiovasc Pharmacol* 1998; 31: 74–79.
33. Matsubara T, Minatoguchi S, Matsuo H, Hayakawa K, Segawa T, Matsuno Y, et al. Three minute, but not one minute, ischemia and nicorandil have a preconditioning effect in patients with coronary artery disease. *J Am Coll Cardiol* 2000; 35: 345–351.
34. Gross JG, Auchampach JA. Role of ATP dependent potassium channels in myocardial ischaemia. *Cardiovasc Res* 1992; 26: 1011–1016.
35. Sato T, Sasaki N, O'Rourke B, Marban E. Nicorandil, a potent cardioprotective agent, acts by opening mitochondrial ATP-dependent potassium channels. *J Am Coll Cardiol* 2000; 35: 514–518.
36. Yao Z, Gross GJ. Effects of the K_{ATP} channel opener bimakalim on coronary blood flow, monophasic action potential duration, and infarct size in dogs. *Circulation* 1994; 89: 1769–1775.
37. Grover GJ, Dalonzo AJ, Dzwonczyk S, Parham CS, Darbenzio RB. Preconditioning is not abolished by the delayed rectifier K^+ blocker dofetilide. *Am J Physiol* 1996; 40: H1207–H1214.
38. Sato T, Sasaki N, O'Rourke B, Marban E. Nicorandil, a potent cardioprotective agent, acts by opening mitochondrial ATP-dependent potassium channels. *J Am Coll Cardiol* 2000; 35: 514–518.
39. Pieper GM, Gross GJ. Anti-free-radical and neutrophil-modulating properties of the nitrovasodilator, nicorandil. *Cardiovasc Drugs Ther* 1992; 2: 225–232.
40. Akai K, Wang Y, Sato K, Sekiguchi N, Sugimura A, Kumagai T, et al. Vasodilatory effect of nicorandil on coronary arterial microvessels: its dependency on vessel size and the involvement of the ATP-sensitive potassium channels. *J Cardiovasc Pharmacol* 1995; 26: 541–547.