Cardioprotective Effect of Intravenous Nicorandil in Patients With Successful Reperfusion for Acute Myocardial Infarction

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This study was designed to assess the cardioprotective effect of intravenous nicorandil, a potassium channel opener, in preventing reperfusion injury in acute myocardial infarction. Seventy patients were treated with placebo or nicorandil concomitant with reperfusion therapy in a prospective, randomized, double-blind fashion within 6 h after the onset of acute myocardial infarction. Nicorandil was administered before reperfusion as a 2-mg bolus iv injection followed by continuous infusion of 2–6 mg/h for the next 3 h. Thirty-six patients (17 in the placebo group, 19 in the nicorandil group) who demonstrated both complete occlusion of an infarct-related vessel before treatment and successful reperfusion were included in the final analysis. No significant changes in left ventricular ejection fraction were observed between the immediate and chronic phases in each group. In the analysis of regional ventricular function, the placebo group did not show any significant change in regional chord shortening (26.8 ± 8.2 vs $24.3 \pm 7.3\%$, NS) or hypocontractile perimeter ($36.4 \pm 28.2\%$ vs $28.3 \pm 24.8\%$, NS) between immediate and chronic phase left ventriculograms. In contrast, in the nicorandil group, a significant increase in regional chord shortening ($21.5 \pm 11.0\%$ vs $25.8 \pm 11.3\%$, $p < 0.05$) and a significant decrease in hypocontractile perimeter ($33.3 \pm 19.6\%$ vs $25.6 \pm 24.3\%$, $p < 0.05$) were observed in the chronic phase left ventriculogram. Thus, nicorandil may be a useful adjunctive therapy for preserving myocardial contractile function in patients with acute myocardial infarction undergoing reperfusion therapy. (*Jpn Circ J* 1998; 62: 183–189)

Key Words: Potassium channel opener; Acute myocardial infarction; Reperfusion therapy; Myocardial contraction

Coronary reperfusion therapy using pharmacologic and/or mechanical means has been established as part of the early management of patients with acute myocardial infarction. Recent large-scale clinical trials have shown that reduction in infarct size, recovery of left ventricular function¹ and a decrease in the cardiac mortality rate² result from early reperfusion of an occluded coronary artery. However, some patients do not experience these benefits even when early reperfusion is established, perhaps as a result of so-called reperfusion injury. Restoration of blood flow to ischemic but reversibly injured cardiac cells may result in irreversible injury to these cells. This reperfusion injury is a new problem in the current reperfusion era³

Nicorandil [N-(2-hydroxyethyl)-nicotinamide nitrate, Chugai, Tokyo, Japan] is a vasodilator used in the treatment of angina pectoris and has dual mechanisms of action. Because of its nitrate moiety, nicorandil causes vasodilation by increasing the intracellular level of cyclic guanosine monophosphate (cGMP) in a similar manner

to organic nitrate⁴. In addition, nicorandil exhibits vasodilatory activity by hyperpolarizing the smooth muscle membrane by opening ATP-sensitive membrane K^+ channels⁵. Previous studies have shown that nicorandil causes a striking enhancement of myocardial salvage and an improvement in ventricular function in experimental models of coronary occlusion and reperfusion^{6–11}. Thus, the purpose of this study was to evaluate the cardioprotective effect of nicorandil in patients with acute myocardial infarction undergoing coronary reperfusion in a prospective, randomized, placebo-controlled, double-blind manner.

Methods

Patient Selection

Seventy patients admitted to the coronary care unit of the National Cardiovascular Center because of acute myocardial infarction between July 1990 and June 1993 were enrolled in the study. Entry criteria included chest pain or oppression unresponsive to nitroglycerin lasting ≥ 20 min but < 6 h before the start of therapy, electrocardiographic (ECG) ST-segment elevation ≥ 1 mm in 2 or more contiguous leads, age ≤ 75 years, and no previous myocardial infarction in the same territory. Predetermined exclusion criteria included: persistent hypotension (systolic blood pressure < 90 mmHg unresponsive to volume expansion), angiographic evidence of spontaneous reperfusion [Thrombolysis in Myocardial Infarction

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(TIMI) Trial¹ grade ≥ 1], significant valvular disease, and history of hepatic or renal diseases.

Protocol

Immediately after the patients were transferred to the coronary care unit and diagnosed as having acute myocardial infarction, informed written consent was obtained from the patient or the family and placebo or nicorandil was given intravenously in a prospective, randomized, double-blind fashion before emergent coronary angiography was carried out. Nicorandil was given by 2-mg bolus iv followed by continuous infusion of 2–6 mg/h for the next 3 h. These doses were chosen taking the effect of nicorandil on hemodynamics into account.¹² After the initiation of the infusion, patients were transferred to the cardiac catheterization laboratory for angiographic determination of the patency of an infarct-related vessel and baseline left ventricular function. After arterial access was obtained, 5,000 U of heparin was administered intravenously. Coronary angiography was performed with standard and orthogonal views. If the infarct-related coronary artery was found to be completely occluded (TIMI grade 0), intracoronary thrombolysis or coronary angioplasty (PTCA) was performed. The method of reperfusion was decided by the operator according to the status of the patient. The time from the initiation of infusion of placebo or nicorandil to reperfusion therapy was approximately 15–30 min. Intracoronary thrombolysis was carried out with intracoronary administration of tissue-type plasminogen activator (Tisokinase; Kowa, Tokyo, Japan) in saline at a rate of 320,000 IU/min to a total dose of 6,400,000 IU. Coronary angiography was repeated every 10 min until the vessel became patent (TIMI grade 3). If the infarct-related vessel was not patent by intracoronary thrombolysis in 20–30 min, “rescue” PTCA was carried out. Primary PTCA was performed in 9 of the 70 patients. After reperfusion was achieved, left ventriculography was performed in the 30° right anterior oblique projection. Because we intended to assess the pure effect of nicorandil on reperfusion injury after myocardial infarction, we included in the final analysis only patients who had a completely occluded infarct-related artery (TIMI grade 0) and successful reperfusion (TIMI grade 3).

The following data were collected at the time of reperfusion: (1) presence or absence of exacerbation of chest pain intensity; (2) additional electrocardiographic ST-segment elevation; and (3) reperfusion arrhythmias. The following arrhythmias that had not been observed before reperfusion and appeared immediately after reperfusion were considered as reperfusion arrhythmias: accelerated idioventricular or atrioventricular junctional rhythm, ventricular tachycardia (at least 3 consecutive beats), and ventricular fibrillation.

After cardiac catheterization, patients were maintained on 10,000–20,000 U/day of intravenous heparin for 24–36 h and, if necessary, therapeutic doses of lidocaine in the coronary care unit. Aspirin (81 mg/day) was given orally during hospitalization. Calcium channel blockers and nitrates were given, if necessary, for the treatment of myocardial ischemia or hypertension. Beta-adrenergic blocking agents were withheld until chronic phase cardiac catheterization.

Four weeks later, patients were returned to the cardiac catheterization laboratory for follow-up coronary angiography and left ventriculography.

Fig 1. Flow chart of study patients. Of the 36 patients in the final entry, left ventriculograms were analyzed in 12 patients in the placebo group and in 18 patients in the nicorandil group. Vf, ventricular fibrillation. No CK elevation indicates peak creatine kinase value <3 times the upper limit of normal.

raphy and left ventriculography.

Data Analysis

Seventy patients met the entry criteria and were enrolled in this study (Fig 1). Four patients were excluded because of no drug administration by mistake ($n=2$) and ventricular fibrillation before administration of the drug ($n=2$). Fourteen patients were excluded because it emerged that they had a patent infarct-related vessel (TIMI grade ≥ 1) at the time of the acute phase coronary angiography after randomization. An additional 16 patients were excluded because of unsuccessful reperfusion (TIMI grade ≤ 2) ($n=9$) and no elevation of serum creatine kinase (<3 times the upper limit of normal) after successful very early reperfusion ($n=7$). There were no significant differences between the 2 groups in the reasons for which patients were excluded. Consequently, 36 patients (17 in the placebo group, 19 in the nicorandil group) were included in the final analysis.

All immediate and follow-up coronary angiograms and ventriculograms were reviewed by an experienced angiographer who was unaware of the treatment group. The severity of coronary stenosis was measured using a caliper method on the view that demonstrated the most severe lesion. Patients were categorized as having single-, double- or triple-vessel disease when significant stenoses (defined as $\geq 75\%$ reduction of luminal diameter) were present in one or more major epicardial coronary arteries. Collateral blood flow to the infarct-related vessel was graded on a scale of 0 to 3, depending on the degree of distal opacification of the occluded vessel.¹³

Global and regional ventricular function were determined from end-diastolic and end-systolic left ventricular endocardial contours during a well-opacified normal sinus beat of the 2 left ventriculograms obtained in the acute and chronic phases. Global ejection fraction was determined as (end-diastolic volume – end-systolic volume)/end-diastolic volume $\times 100$ by the area-length method.

Regional ventricular function was analyzed by 2 differ-

Fig 2. Schemes showing analysis of regional chord shortening from the left ventriculogram. (A) The midpoint of the aortic valve was the starting point for the radial sweep around the ventricle, and the line connecting the center of gravity and the midpoint of the aortic valve represented the radial length at 0°. Because the sweep continued in a clockwise direction in 4° increments, the whole ventricle included 90 radial lengths from the center of gravity in both end-systolic and end-diastolic contours. (B) The 90 radial lengths were divided into 8 fractions (segment 1 to segment 8) from 0 to 360° in a clockwise direction. CG, center of gravity.

ent computerized radial shortening methods. First, wall motion in infarct and non-infarct zones was assessed quantitatively by the chord-shortening method described by Rickards et al.¹⁴ The midpoint of the aortic valve was the starting point for the radial sweep around the ventricle, and the line connecting the center of gravity of the left ventricle and the midpoint of the aortic valve represented the radial length at 0° (Fig 2A). As the sweep completed a rotation in a clockwise direction in 4° increments, the whole ventricle contained 90 radial chords originating from the center of gravity in both end-systolic and end-diastolic contours. These 90 radial chords were divided into 8 fractions of the same angle (segment 1 to segment 8) in a clockwise direction (Fig 2B). Chord shortening of each radial length was calculated as (end-diastolic length – end-systolic length)/end-diastolic length × 100. Regional chord shortening of the infarct zone was obtained by averaging chord-shortening values in segments 3 and 4 in patients with anterior wall infarction and in segments 6 and 7 in patients with inferior wall infarction. In patients with lateral wall infarction (n=3), regional chord shortening of the infarct zone was obtained from the data in the most severely involved segment of the 8 segments, which turned out to be segment 4 in those 3 patients in this study. Regional chord shortening of the non-infarct zone was obtained by averaging regional chord shortening in the remaining segments not involved in infarction.

The second method of regional wall motion analysis was another radial method developed at Stanford University Medical Center.¹⁵ This model assumes that any point on the ventricular wall moves from diastole to systole toward a single point that is empirically placed at 69% of the distance from the anterior edge of the aortic valve to the apex in the end-systolic contour. The left ventricular contour was divided equally into 72 radial segments, and regional wall motion was assessed as a percentage of hypocontractile ventricular perimeter, which was defined as reduced radial shortening by >2 standard deviations (SD) from the normal mean values.¹⁵ We consider that the regional chord-shortening method quantifies the severity (or depth) of contractile dysfunction, whereas

Table 1 Baseline Characteristics

	Placebo (n=17)	Nicorandil (n=19)	p Value
Age (years)	66 ± 11	65 ± 8	NS
Number of men	15 (88)	17 (89)	NS
History			
Hypertension	12 (71)	13 (68)	NS
Diabetes mellitus	9 (53)	7 (37)	NS
Hypercholesterolemia	8 (47)	7 (37)	NS
Current smoker	8 (47)	12 (63)	NS
Angina pectoris	12 (71)	16 (84)	NS
Prior myocardial infarction	2 (12)	2 (11)	NS
Anterior myocardial infarction	9 (53)	10 (53)	NS
Pump failure	2 (12)	4 (21)	NS
Peak CK (U/L)	4001 ± 496	4042 ± 770	NS
Medication			
Ca ²⁺ blocker	9 (53)	12 (63)	NS
ISDN	14 (82)	12 (63)	NS
ACEI	1 (6)	2 (11)	NS
Time to reperfusion (h)	5.2 ± 0.4	4.4 ± 0.4	NS
No of vessels ≥ 75% stenosis	1.7 ± 0.7	1.7 ± 0.8	NS
Collateral score	0.8 ± 1.0	1.1 ± 0.9	NS
No reflow phenomenon	1 (6)	1 (5)	NS
Reperfusion methods			
Thrombolysis	9 (53)	10 (53)	NS
Primary PTCA	4 (24)	5 (26)	NS
Rescue PTCA	4 (24)	4 (21)	NS
Reocclusion after 4 weeks	2 (12)	4 (21)	NS

Abbreviations: CK, creatine kinase; ISDN, isosorbide dinitrate; ACEI, angiotensin converting enzyme inhibitor; PTCA, percutaneous transluminal coronary angioplasty.

the hypocontractile perimeter method quantifies the extent of contractile dysfunction.

Statistical Analysis

All values are expressed as mean values ± SD or incidences (%). The differences of mean values between groups were compared by the 2-tailed unpaired t test. The occurrences of reperfusion phenomena were compared by the chi-square test between groups. Serial changes in global and regional ventricular function were compared by the 2-tailed paired t test within a group. A p value < 0.05 was considered statistically significant.

Results

Table 1 summarizes baseline characteristics of the placebo and nicorandil groups. There were no significant differences between the 2 groups in clinical background, severity of the coronary artery disease, the grade of collateral development, the incidence of angiographic “no reflow phenomenon”, or time and modality of reperfusion. Also, there were no significant differences between the 2 groups in the use of nitrates, Ca²⁺ blockers, and angiotensin-converting enzyme inhibitors. The infarct-related vessel was completely occluded (TIMI grade 0) in all patients at the time of emergent catheterization as defined by the inclusion criteria. Heart rate, systolic blood pressure, and rate-pressure product were similar between the 2 groups before and during the administration of the drug (Table 2). In addition, there were no significant differences in cardiac index, pulmonary capillary wedge pressure, pulmonary artery pressure, or right atrial pressure between the 2 groups during drug infusion (Table 3). No adverse effects of nicorandil such as hypotension or serious arrhythmias were observed. There was

Table 2 Changes in Blood Pressure and Heart Rate

	Placebo (n=17)		Nicorandil (n=19)	
	Before infusion	After infusion	Before infusion	After infusion
Heart rate (beat/min)	74.1±15.6	75.7±16.6	74.1±11.8	79.8±14.3
Systolic BP (mmHg)	127±23	140±21	132±22	139±20
RPP (×10 ³)	9.6±3.1	10.7±3.5	9.7±2.3	11.1±2.8

No significant differences were observed between the two groups. BP, blood pressure; RPP, rete-pressure product.

Table 3 Hemodynamic Data

	Placebo (n=17)	Nicorandil (n=19)	p Value
Cardiac index (L/min per m ²)	3.21±0.91	3.31±0.89	NS
PCWP (mmHg)	11.7±5.9	9.3±4.2	NS
Systolic PAP (mmHg)	28.7±11.8	25.2±6.5	NS
Diastolic PAP (mmHg)	13.0±5.1	10.9±3.3	NS
RAP (mmHg)	5.8±2.0	5.0±2.3	NS

PCWP, pulmonary capillary wedge pressure; PAP, pulmonary artery pressure; RAP, right atrial pressure.

Fig 3. Bar charts showing incidences of reperfusion phenomena in the placebo and nicorandil groups.

Fig 4. Graphs showing comparisons of left ventricular global ejection fraction (EF) between immediate and chronic phases in the 2 groups.

no in-hospital death.

Reperfusion Phenomenon

Fig 3 compares the incidences of exacerbation of chest pain intensity, additional electrocardiographic ST-segment elevation, and reperfusion arrhythmias that occurred concomitantly with reperfusion. None of the incidences of those reperfusion phenomena was significantly different between the 2 groups.

Ventriculographic Data

Both left ventriculograms immediately after reperfusion and 4 weeks later were available in 12 patients in the placebo group and 18 patients in the nicorandil group. In 1 patient in the nicorandil group and 2 patients in the placebo group, left ventriculography was not performed immediately after reperfusion because of highly elevated left ventricular end-diastolic pressure (≥ 30 mmHg). In 3 patients in the placebo group, ventriculogram on the chronic phase was not available. PTCA was performed for post-infarction angina in 2 patients, and the remaining patient had a transient cerebral ischemic attack during catheterization on the chronic phase.

Data for global left ventricular function immediately

after reperfusion and 4 weeks later are shown in Fig 4. There were no significant changes in left ventricular ejection fraction between immediate and chronic phases in either the placebo or nicorandil group (placebo $51.0 \pm 11.6\%$ vs $50.8 \pm 12.1\%$, NS; nicorandil $53.4 \pm 9.0\%$ vs $55.8 \pm 10.7\%$, NS). Also, left ventricular ejection fraction between the 2 groups was not significantly different in immediate or chronic phase.

Regional chord shortening in the infarct zone was similar between the 2 groups immediately after reperfusion ($26.8 \pm 8.2\%$ vs $21.5 \pm 11.0\%$, NS). There was no significant change in regional chord shortening between immediate and chronic phases in the placebo group ($26.8 \pm 8.2\%$ to $24.3 \pm 7.3\%$, NS, Fig 5A). In contrast, a significant improvement in regional chord shortening was observed in the nicorandil group (21.5 ± 11.0 to $25.8 \pm 11.3\%$, $p < 0.05$, Fig 5A). In addition, the change in regional chord shortening in the infarct zone from immediate phase to chronic phase was significantly greater in the nicorandil group than in the placebo group ($4.3 \pm 7.5\%$ vs $-2.5 \pm 5.3\%$, $p < 0.01$, Fig 5B). Regional chord shortening in the non-infarct zone was not significantly different between immediate and chronic phases in either group (placebo $28.3 \pm 7.5\%$ vs $28.7 \pm 8.8\%$, NS; nicorandil $29.2 \pm 7.0\%$ vs $31.1 \pm 7.7\%$, NS).

To exclude the potential effect of reocclusion of the infarct-related artery, regional chord shortening was also analyzed in patients who had no reocclusion of the infarct-related artery in the chronic phase. A significant improvement in regional chord shortening was again observed in the nicorandil group (21.5 ± 12.2 to $27.1 \pm 12.2\%$, $p < 0.05$), whereas there was no significant improvement in regional chord shortening in the placebo group (27.7 ± 7.9 to $25.0 \pm 7.2\%$, NS).

Fig 6 depicts changes in regional myocardial function assessed by the hypocontractile perimeter method. There was no significant difference in percentage of hypocontractile perimeter immediately after reperfusion between the 2 groups ($36.4 \pm 28.2\%$ vs $33.3 \pm 19.6\%$, NS). No significant reduction in hypocontractile perimeter between

Fig 6. Graphs showing comparisons of percentage of hypocontractile perimeter between immediate and chronic phases in the 2 groups.

immediate and chronic phases was observed in the placebo group ($36.4 \pm 28.2\%$ to $28.3 \pm 24.8\%$, NS). In contrast, a significant reduction in hypocontractile perimeter occurred in the nicorandil group 4 weeks after reperfusion ($33.3 \pm 19.6\%$ to $25.6 \pm 24.3\%$, $p < 0.05$), indicating that the extent of regional myocardial dysfunction decreased 4 weeks after reperfusion only in the nicorandil group.

Discussion

Present Study

The present study has demonstrated in a prospective, randomized, double-blind fashion that intravenous nicorandil administered before reperfusion therapy improves both left ventricular regional chord shortening and hypocontractile perimeter in the infarct zone in the chronic phase to a greater extent than placebo in patients with acute myocardial infarction with no adverse effects. This implies that nicorandil improves both the severity (or depth) and the extent of regional myocardial dysfunction after coronary reperfusion. In addition, the fact that the 2 independent methods of assessment of regional myocardial function consistently showed significant improvement in regional function in the nicorandil group would further strengthen the reliability of the results.

Previous Studies

Despite the growing evidence that early reperfusion improves ventricular function and survival in patients with acute myocardial infarction, there remains a concern that reperfusion per se may also produce deleterious effects on viable myocardium so-called reperfusion injury.³ As the

Fig 5. (A) Graphs showing comparisons of regional chord shortening in the infarct zone between immediate and chronic phases. (B) Bar chart showing comparison of changes in chord shortening in the infarct zone from immediate phase to chronic phase between the 2 groups.

pathogenesis of this reperfusion injury, the roles of Ca^{2+} overload, free radicals, cytokines, and microcirculatory disturbances with neutrophil and platelet stagnation have been studied extensively.^{16,17} However, the precise mechanism of the development of reperfusion injury has not yet been clarified. To prevent this reperfusion injury, various therapeutic methods and agents have been tested experimentally and clinically. In experimental ischemia/reperfusion models, gradual reperfusion,¹⁸ reperfusion with acidic solution,⁹ superoxide dismutase,¹⁶ angiotensin-converting enzyme inhibitor,²⁰ a prostacyclin analog (iloprost),²¹ adenosine,²² and perfluorochemical (Fluosol)¹⁷ have been shown to attenuate reperfusion injury. However, in clinical trials, captopril,²³ iloprost,²⁴ and superoxide dismutase²⁵ failed to show beneficial effects on recovery of ventricular function in patients with acute myocardial infarction with successful reperfusion. Forman et al²⁶ showed that Fluosol in conjunction with emergency coronary angioplasty in patients with acute myocardial infarction improved regional ventricular function. However, the Thrombolysis in Acute Myocardial Infarction (TAMI) study group reported that Fluosol concomitant with intravenous thrombolytic therapy did not improve regional left ventricular function.²⁷

Effect of Nicorandil

Nicorandil acts as both a nitrate and a potassium channel opener.⁵ In experimental ischemia/reperfusion models, nicorandil administered before reperfusion has been reported to improve regional left ventricular function to a greater extent than nifedipine, nitroglycerin, and isosorbide dinitrate.⁶⁻⁸ This has been explained by a lower rate-pressure product^{6,7} and fewer increases in myocardial free fatty acid and myocardial oxygen extraction during the occlusion period,⁷ and more homogeneous blood flow distribution after reperfusion⁸ in the nicorandil-treated heart. In the present study, several potential mechanisms can be considered as reasons for the beneficial effect of nicorandil. First of all, postischemic myocardial dysfunction in the peripheral border zone of the infarct region might be attenuated because myocardial oxygen consumption might have been decreased as a result of reductions in preload and afterload with nicorandil. However, neither heart rate, systolic blood pressure, or rate-pressure product changed significantly after infusion of nicorandil, suggesting that this possibility is remote.

Secondly, although enhanced collateral blood flow with nicorandil²⁸ might be the mechanism of the better functional recovery in the nicorandil group, there was no significant difference in collateral development on the acute phase coronary angiography between the 2 groups.

Therefore, this mechanism may not play a major role.

Thirdly, improvement in coronary microvascular circulation with nicorandil^{29,30} might be a possible mechanism. Sakata et al³¹ recently reported a significant improvement in chronic phase regional wall motion with a single bolus intracoronary administration of 2 mg of nicorandil in patients with acute myocardial infarction, possibly through amelioration of no-reflow phenomenon. Although their results are of interest, the study was not carried out in a prospective, double-blind fashion. In the present study, there was no significant difference in angiographically determined no-reflow phenomenon between the 2 groups. Therefore, this possibility remains to be determined.

Finally, there is also a possibility of direct attenuation of reperfusion injury because nicorandil has been reported to have anti-free-radical and neutrophil-modulating properties¹¹. In addition, a cardioprotective effect of nicorandil via an interaction between the ATP-dependent potassium channel¹¹ and the adenosine A₁ receptor³² could be another possible mechanism for reducing reperfusion injury, as adenosine has been reported to play an important role in ischemic preconditioning³² and to reduce infarct size and improve regional ventricular function in canine ischemia/reperfusion models²².

Although in most experimental ischemia/reperfusion models^{6-8,11} drugs were started before occlusion of a coronary artery, we started the infusion of nicorandil after the onset of myocardial infarction. In this situation, how nicorandil reached the infarct region to prevent reperfusion injury is unknown. However, 2 experimental ischemia/reperfusion models^{9,10} showed that nicorandil prevented reperfusion injury even though nicorandil was started after occlusion of coronary artery without increasing collateral blood flow.

The fact that nicorandil did not reduce the incidences of reperfusion phenomena in the present study suggests that the mechanisms of reperfusion phenomena and myocardial damage may differ from each other. In fact, previous experimental evidence suggests that reperfusion arrhythmia is mediated by excess recycling of cytosolic calcium with delayed afterdepolarizations and ventricular automaticity, whereas myocardial dysfunction is mediated by free radicals, relative calcium insensitivity, and/or microvascular damage¹⁶. However, determining the pathogenesis of reperfusion injury and the exact mechanism of the beneficial effect of nicorandil is beyond the scope of the present study. Further studies are needed to clarify the precise mechanisms of the effect of nicorandil on successfully reperfused hearts.

Study Limitations

The present study has several potential limitations. First, the sample size was not large enough to draw a final conclusion on the beneficial effect of nicorandil. Therefore, a larger scale randomized study will be needed to confirm the results of the present study. Second, many patients were excluded from the final analysis because of a patent infarct-related coronary artery, unsuccessful reperfusion, and no elevation of creatine kinase. This could be a potential confounding factor in the present study. However, this exclusion was inevitable because randomization and administration of the drug after the confirmation of a total occlusion of an infarct-related coronary artery would cause an unnecessary delay in

starting coronary reperfusion therapy, resulting in a greater infarct size. This would not be allowed from the ethical viewpoint. Also, if we included the patients with unsuccessful reperfusion in the final analysis, the beneficial effect of nicorandil would be attributed to an anti-ischemic effect of the drug rather than the effect on reperfusion. Thus, because we intended to assess the pure effect of the drug on reperfusion injury after myocardial infarction, a certain number of patients were inevitably excluded. Third, we administered nicorandil by intravenous infusion starting 15–30 min before reperfusion therapy. From the viewpoint of the study design on reperfusion injury, it may be ideal to administer the drug intracoronarily at the time of reperfusion. However, to avoid the potential risk of ventricular fibrillation induced by intracoronary administration of nicorandil³³ we chose intravenous administration before reperfusion. Fourth, in the present study, regional wall motion in the placebo group had not improved 4 weeks later despite successful reperfusion. However, some of the previous studies investigating the effect of reperfusion therapy on regional wall motion failed to show an improvement in regional wall motion^{34,35}. Fifth, the long-term clinical significance of the present findings is still unclear. Although left ventricular global contractile function (ie, ejection fraction) has been established as an important determinant of long-term mortality and morbidity in patients after acute myocardial infarction, the impact of regional myocardial function on the long-term clinical course has not been established. Therefore, further studies are required to determine the prognostic importance of the improvement in regional myocardial function obtained with nicorandil in the present study.

Conclusions

We have demonstrated in a prospective, randomized, double-blind fashion that intravenous nicorandil administered before reperfusion therapy improves the chronic phase regional myocardial function to a greater extent than placebo without noticeable adverse effects in patients with acute myocardial infarction. Therefore, nicorandil may be a useful adjunctive therapy for preserving myocardial contractile function in patients with acute myocardial infarction undergoing reperfusion therapy.

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