Effects of Intravenous Nicorandil Before Reperfusion for Acute Myocardial Infarction in Patients With Stress Hyperglycemia

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OBJECTIVE — Stress hyperglycemia increases the risk of mortality and poor outcomes in patients with acute myocardial infarction (AMI). We aimed to assess effects of intravenous nicorandil administered before reperfusion on AMI patients with stress hyperglycemia.

RESEARCH DESIGN AND METHODS — This study consisted of 158 consecutive first AMI patients with stress hyperglycemia who underwent percutaneous coronary intervention (PCI) within 24 h from the onset. They were randomly assigned to receive 12 mg of nicorandil ($n = 81$) or a placebo ($n = 77$) intravenously just before reperfusion. Stress hyperglycemia was defined as a blood glucose level ≥10 mmol/l (180 mg/dl). We examined various aspects of epicardial flow and microvascular function as immediate data and major adverse cardiac events (MACEs) (coronary heart disease death or unplanned readmission due to congestive heart failure) as late-phase data.

RESULTS — The incidence of slow flow after PCI was lower in the nicorandil group (13.6 vs. 27.3%, $P < 0.04$). ST segment resolution >50% was observed in 70.4 and 53.2% on nicorandil and placebo, respectively ($P < 0.03$). Patients treated with nicorandil had a lower peak creatine kinase level ($3,137 \pm 2,577$ vs. $4,333 \pm 3,608$, $P < 0.02$). Upon Kaplan-Meier analysis, 5 years' freedom from MACEs was 86.4% in the nicorandil group and 74.0% in the placebo ($P < 0.05$).

CONCLUSIONS — Adjunctive therapy with administration of intravenous nicorandil before reperfusion on AMI patients with stress hyperglycemia significantly improves epicardial flow and prevents the occurrence of severe microvascular reperfusion injury, resulting in better outcomes in these patients.

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A n association between admission plasma glucose levels and an increased risk of mortality and poor prognosis after acute myocardial infarction (AMI) was well noted (1–4). In patients with AMI, glucose metabolism is modified and stress hyperglycemia can be observed. These phenomena are observed not only in patients with diabetes but also in patients without diabetes. Some mechanism for the association between stress hyperglycemia and adverse outcomes after AMI are possible (5–8) but are not well understood. Furthermore, there are limited data about pharmacological intervention, which has beneficial effects for AMI patients with stress hyperglycemia.

On the other hand, nicorandil, a hybrid compound of ATP-sensitive K$^+$ channel (K_{ATP} channel) opener and nitric oxide donor, has a pharmacological preconditioning effect in the human heart (9). In some reports, intravenous nicorandil has been reported to ameliorate early functional and clinical problems in patients with AMI (10–12). In the present study, we assessed the cardioprotective effects of single intravenous nicorandil before reperfusion with percutaneous coronary intervention (PCI) for AMI with stress hyperglycemia.

RESEARCH DESIGN AND METHODS — Between November 1998 and October 2003, we did a randomized study of single intravenous administration of nicorandil before reperfusion in 368 patients with ST-segment elevation AMI (12). Of those patients, 158 (81 in the nicorandil group and 77 in the placebo group) had stress hyperglycemia at admission and they were enrolled in the study.

AMI was diagnosed by chest pain, persisting between 30 min and 24 h and proving unresponsive to nitrates, electrocardiogram (ECG) ST-segment elevation with at least two contiguous ECG leads, and more than double creatine kinase elevation above the normal upper limit. Stress hyperglycemia was defined as a blood glucose level ≥10 mmol/l (180 mg/dl) at admission to the hospital as stated by previous studies (13,14). Patients were diagnosed with diabetes if they had a previous or current diagnosis of diabetes at hospital admission or if an abnormal oral glucose tolerance test or HbA$_{1c}$ ≥6.5% was found after admission.

The physicians obtained written informed consent from each patient, and the study was approved by the hospital ethics committee.

The details of the study design, methods, patient characteristics, and inclusion and exclusion criteria have been previously described (12). In brief, the patients were randomized by the concealed-envelope method. They were divided into

Table 1—Baseline patient characteristics

Characteristics	Placebo	Nicorandil	P
n	77	81	
Age (years)	64 ± 9.3	63 ± 9.3	0.60
Male	62 (80.5)	61 (75.3)	0.43
Hours to reperusion from onset	4.4 ± 2.5	5.0 ± 3.0	0.16
Blood glucose level at admission (mmol/l)	14.9 ± 5.4	14.3 ± 3.9	0.43
Heart rate (bpm)	82 ± 16	81 ± 16	0.98
Systolic blood pressure (mmHg)	135 ± 23	125 ± 29	0.17
Pulmonary capillary wedge pressure (mmHg)	15 ± 7.0	15 ± 7.8	0.82
Cardiac output (l/min)	5.1 ± 1.3	5.4 ± 1.2	0.31
Creatine kinase (IU/ml)	165 (96–316)	171 (99–385)	0.76
Diabetes	45 (58.4)	48 (59.3)	0.92
Antidiabetic treatment			
Diet (n)	21	20	0.53
Sulfonylureas (n)	12	14	0.79
Insulin (n)	9	9	0.88
Other (n)	3	5	0.52
Hyperlipidemia	20 (26.0)	26 (32.1)	0.35
Hypertension	27 (35.1)	27 (33.3)	0.71
Smoking	26 (33.8)	27 (33.3)	0.88

Data are means ± SD, median (interquartile range), or n (%), unless otherwise indicated.

two groups: those who received intravenous nicorandil before reperfusion with PCI and those who received placebo. In the nicorandil group, 12 mg dissolved in 100 ml of 0.9% saline was administered by intravenous injection over a 20- to 30-min period before the procedure. In the placebo group, 100 ml of 0.9% saline was administered intravenously. Other protocols were the same for the two groups.

Oral medications were also similar in both groups. For all patients, aspirin (162 mg/day) was administered orally, and ticlopidine or cilostazol was applied when the stent was implanted. In the absence of contraindications such as hyperkalemia, ACE inhibitors, or angiotensin II receptor blockers were administered.

The following immediate data were assessed after reperfusion: *1*) thrombolysis in myocardial infarction (TIMI) trial grade after PCI, *2*) resolution of ST-segment elevation on ECG after PCI, *3*) corrected TIMI frame count after PCI, and *4*) maximum serum creatine kinase.

The first ECG was done just before coronary angiography and the second was done 15 min after PCI. The amount of ST-segment elevation was measured 20 ms after the end of QRS complex in leads I, aV_L and V_1 through V_6 for anterior, and leads II, III, aVf, and V_5 through V_6 for nonanterior myocardial infarction. The corrected TIMI frame count was measured as the number of cine frames required for contrast to first reach standardized distal coronary landmarks in the culprit coronary artery (15). The filming speed was 30 frames/s in the present study. In the case of occluded vessels, a frame count of 100 was used. Samples for serum creatine kinase were obtained at admission and every 3–48 h, and from these data, maximum creatine kinase level was checked. All measurements were performed by an experienced observer who was blinded to randomization.

We also analyzed follow-up data for major adverse cardiac events (MACEs) (coronary heart disease death or unplanned readmission due to congestive heart failure) and the composite end point of all-cause mortality or all-cause admission. Data were obtained from hospital charts and telephone interviews with the patients.

All measurements were performed by an experienced observer who was blinded to randomization.

Statistical analysis
All values are expressed as means ± SD or incidences (%). Univariate analysis of differences between the two groups was performed by the two-tailed unpaired *t* test for continuous outcome variables and by χ^2 or Fisher's exact tests for discrete outcome variables. Differences in long-term cardiac event-free survival between the two groups was examined with the Kaplan-Meier method and compared using the log-rank test. We also used Cox proportional hazards models for long-term follow-up. Differences were considered significant at $P < 0.05$.

RESULTS — Intravenous nicorandil was assigned to 81 patients and placebo was given to 77 patients. In Table 1 and Table 2, the baseline characteristics of the nicorandil and placebo groups are presented. There were no significant differences in age, sex, time to reperfusion, incidence of coronary risk factors, blood pressure, heart rate, pulmonary capillary wedge pressure, or culprit lesions between the two groups.

Table 3 provides a summary of detailed information for the angiographic results and ECG observations. Good myocardial reperfusion on ECG after PCI (ST-segment elevations <50% of initial value) was seen in 70.4% of the nicorandil group and 53.2% of the placebo (P = 0.027). Slow flow phenomena after PCI (TIMI flow grade ≤2 after PCI) occurred statistically less frequently in the nicorandil group (13.6 vs. 27.3%, P = 0.032). Cor-

Table 2—Angiographic and ECG findings

Characteristics	Placebo	Nicorandil	P
n	77	81	
Culprit lesion			0.92
Left anterior descending artery	36 (46.8)	40 (49.4)	
Right coronary artery	33 (42.9)	35 (43.2)	
Left circumflex artery	7 (9.1)	5 (6.2)	
Left main trunk artery	1 (1.3)	1 (1.2)	
TIMI grade before PCI (0/1/2/3) (n)	56/10/8/3	60/10/9/2	0.96
Multivessel disease	25 (32.5)	25 (30.9)	0.83
Collateral flow (Rentrop grade 2 or 3)	8 (10.4)	9 (11.1)	0.88
Corrected TIMI frame count before PCI	91.9 ± 20.3	90.3 ± 22.2	0.64
ST-segment score before PCI (mm)	9.3 ± 6.8	9.5 ± 8.0	0.89

Data are means ± SD or n (%), unless otherwise indicated.

Table 3—Angiographic results and ECG observations

	Placebo	Nicorandil	*P*
n	77	81	
Slow flow after PCI (TIMI ≤2)	21 (27.3)	11 (13.6)	0.032
Good myocardial reperfusion after PCI*	41 (53.2)	57 (70.4)	0.027
ST-segment score after PCI (mm)	5.2 ± 3.6	3.6 ± 4.6	0.039
ST post (%)	60.3	34.2	0.032
Corrected TIMI frame count after PCI	28.0 ± 17.8	22.2 ± 8.9	0.01

Data are means ± SD or *n* (%), unless otherwise indicated. *ST-segment elevation <50% of initial value was defined as a marker of good myocardial reperfusion.

rected TIMI frame count was furthermore lower in the nicorandil group (22.2 ± 8.9 vs. 28.0 ± 17.8, *P* = 0.01). From samples for serum creatine kinase, the maximum serum level of creatine kinase was much lower in the nicorandil group than in the placebo group (3,137 ± 2,577 vs. 4,333 ± 3,608 IU, *P* = 0.018) (Fig. 1). These data show that intravenous nicorandil improved epicardial flow and accelerated ST-segment resolution in patients with AMI and furthermore infarct size measured by enzyme release was lower in the group on treatment with nicorandil.

Figure 2 shows Kaplan-Meier curves of follow-up data for freedom from MACEs. Over a 5-year period, the rate at which subjects avoided MACEs was 86.4% in the nicorandil group and 74.0% in the placebo group (hazard ratio 0.48 [95% CI 0.23–0.99], *P* = 0.048). A total of 5 (6.2%) patients in the nicorandil group and 11 (14.3%) in the placebo group experienced unplanned hospital admission for congestive heart failure. The rate of cardiovascular death was 7.4% (six patients) in the nicorandil group and 11.7% (nine patients) in the placebo group, respectively.

Intravenous nicorandil was also of significance for the composite end point of all-cause mortality or all-cause admission (hazard ratio 0.60 [95% CI 0.36–1.01], *P* = 0.052).

CONCLUSIONS — Several studies have reported that stress hyperglycemia with AMI is an important risk factor for the development of cardiovascular events. For both patients with and without diabetes, acute stress hyperglycemia at the time of AMI is a common phenomenon. To our knowledge, this is the first reported study that demonstrates that intravenous nicorandil just before reperfusion has beneficial effects in AMI patients with stress hyperglycemia. Our study shows not only early but also long-term effects after administration of nicorandil, with improvements in prognosis after AMI with stress hyperglycemia.

Several mechanisms can be postulated to explain the effectiveness of nicorandil. First, nicorandil may prevent diminution of cardioprotective effects such as preconditioning phenomenon, which contributes to cardioprotection (16–18). Recent experimental studies have reported that the mitochondrial K_{ATP} channel is recognized as an end factor of ischemic preconditioning and K_{ATP} channel openers act like ischemic preconditioning effect (19), but some studies demonstrated that stress hyperglycemia abolishes the protective effects of ischemic preconditioning and attenuates reductions of myocardial infarct size because stress hyperglycemia impairs activation of mitochondrial K_{ATP} channels and exacerbates myocardial ischemic injury (8,19–21). By contrast, nicorandil directly opens the K_{ATP} channels on the mitcondrial membrane at a much lower concentration than is required to open the same channels on the cell membrane (22). In addition, K_{ATP} channels opening activation results in a reduction in calcium overload during ischemia secondary to action potential shortening and prevention or attenuation of membrane depolarization. These actions would be also expected to protect cardiac function because calcium overload in cardiac muscle causes cellular damage. Through their activation, nicorandil might exert salutary effects and decrease in infarct size (23).

The second possible examination is that nicorandil acts on antioxidant stress. Hyperglycemia is related to oxidant stress. In the heart, elevated oxidative stress is associated with severely compro-
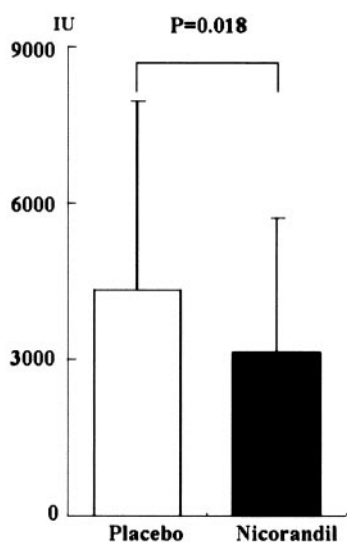

Figure 1—*The maximum serum creatine kinase: The maximum serum level of creatine kinase was much lower in the nicorandil group than in the placebo group (3,137 ± 2,577 vs. 4,333 ± 3,608 IU,* P *= 0.018)*
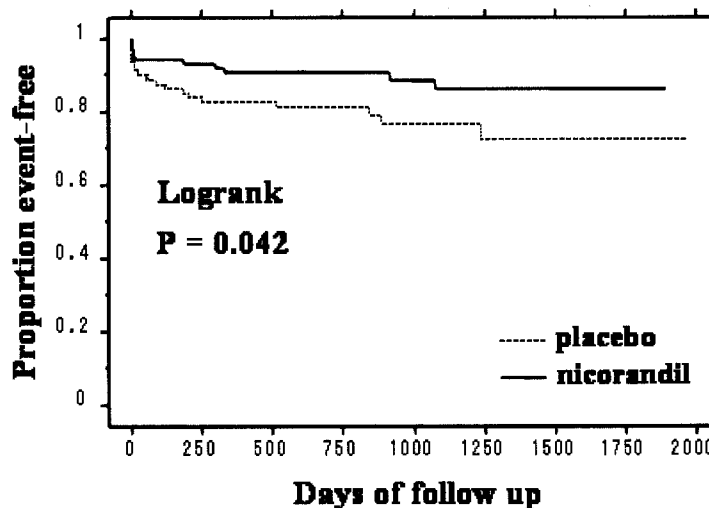

Figure 2—*Kaplan-Meier estimates: freedom from MACE defined as coronary heart disease death or unplanned hospital admission for congestive heart failure.*

mised mitochondrial functions and poor prognosis (24). Patients with hyperglycemia are prone to have elevated tumor necrosis factor (TNF)-α (25). TNF-α levels and its negative effects are increased in patients with AMI (26). It is reported that potassium channel openers protect cardiac mitochondria by attenuating oxidant stress at reoxygenation, mimicking the protective efficacy of conventional free radical scavengers (27). Furthermore, nicorandil inhibits the release of TNF-α from lymphocytes (28).

The third possible examination is that nicorandil has vasodilatory effect on coronary blood flow (29). Acute hyperglycemia impairs endothelium-dependent vasodilation (7), and collateral circulation to the risk area might be less frequently observed in patients with stress hyperglycemia (30). Therefore, this action might be associated with lower incidence of slow flow and might increase collateral blood flow in the nicorandil group.

Some studies show that intravenous glucose-insulin-potassium may have a positive metabolic influence in patients with AMI (31,32). However, another study (33) shows that glucose-insulin-potassium infusion as adjunctive therapy to PCI or thrombolysis in AMI may not result in enhanced myocardial salvage or a significant mortality reduction. Until now, there are limited reports as to whether other pharmacological intervention in the treatment for AMI with stress hyperglycemia has beneficial effects on microcirculatory impairment and clinical prognosis. Our findings are of great significance in this context.

Several issues need to be considered with respect to our study. The first study limitation is that we did not analyze serum insulin, catecholamine levels, or free fatty acids, which may have provided important additional information. Second, the present trial was of single-center design.

Our findings suggest that AMI patients with stress hyperglycemia receiving nicorandil continue to have markedly lower major complications in both early and late phase with much better outcomes. We conclude that adjunctive therapy with administration of intravenous nicorandil before reperfusion on AMI patients with stress hyperglycemia significantly improves epicardial flow and prevents the occurrence of severe microvascular reperfusion injury, resulting in better outcome in these patients.

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