Nicorandil Enhances Myocardial Tolerance to Ischemia Without Progressive Collateral Recruitment During Coronary Angioplasty

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Nicorandil, a hybrid nitrate and ATP-sensitive potassium channel opener, has had a preconditioning effect in some coronary angioplasty studies. The present study investigated whether the cardioprotective effects of nicorandil involve coronary collateral function. Thirty-two patients with stable angina pectoris were randomized to receive a 1-min intravenous infusion of nicorandil (100 µg/kg) or normal saline. Five minutes later they underwent three 2-min balloon inflations 5-min apart. The maximum ST-segment elevation (Δ STmax), the sum of ST-segment elevations in all leads (Σ ST), and the chest pain score were determined at the end of each balloon inflation. The collateral flow index (CFI) was derived from simultaneous measurement of the mean aortic pressure and the coronary wedge pressure obtained from a pressure guidewire during balloon inflation. The Δ STmax, Σ ST, and chest pain score decreased progressively during the 3 sequential balloon inflations in both groups, and the Δ STmax and Σ ST were less in the nicorandil group than in the control group during each inflation. The CFI did not change during the 3 inflations in either group and was similar in the 2 groups during each inflation. In conclusion, pretreatment with intravenous nicorandil enhances myocardial tolerance to ischemia without progressive collateral recruitment during coronary angioplasty. (*Circ J* 2002; 66: 317–322)

Key Words: Collateral recruitment; Coronary angioplasty; Nicorandil; Preconditioning

Repeated brief ischemia and reperfusion induce a powerful endogenous protective effect against subsequent prolonged myocardial ischemia,^{1,2} and the mechanisms and clinical implications of this phenomenon, known as ischemic preconditioning and initially reported by Murry et al in 1986³ have been investigated in great detail. There have been many studies, involving a variety of agents that mimic or prevent preconditioning, carried out in the clinical setting of coronary angioplasty producing ischemia.^{4–14} Nicorandil is a hybrid nitrate and ATP-sensitive potassium channel opener¹⁵ and it is the ATP-sensitive potassium channel that is thought to be an end-effector of preconditioning.¹⁶ Previous studies have found that intravenous administration of nicorandil attenuates ST-segment elevation¹² and improves lactate metabolism¹³ during coronary angioplasty, suggesting that pharmacological preconditioning is induced by nicorandil. However, it has not been established whether these cardioprotective effects involve coronary collateral function.

The aim of the present study was to examine the effects of intravenous administration of nicorandil on myocardial ischemia and collateral recruitment during coronary angioplasty in patients with stable angina pectoris (AP).

Methods

Study Population

The study population comprised 32 patients (27 men, 5 women; age range, 39–84 years; mean age, 66±9 years) with clinically stable AP who underwent elective coronary angioplasty. Patients were prospectively selected according to the following criteria: (1) single-vessel disease with an isolated obstructive lesion of a major coronary artery; (2) stenosis severity ranging from 75% to 90% by visual assessment; (3) lesion length less than 20 mm; (4) no angiographically visible collateral vessels; (5) no wall-motion abnormalities on the echocardiogram or evidence of prior myocardial infarction on the electrocardiogram (ECG) in the myocardial territory of the vessel undergoing angioplasty; and (6) no baseline ST-segment abnormalities or conduction defects on the ECG. For example, patients with atrial fibrillation, bundle branch block, or left ventricular hypertrophy were excluded. Additionally the following exclusion criteria were used: (1) stenosis severity exceeding 90%, because preconditioning might have been induced when the guidewire was passed across the lesion; (2) anginal pain in the 48 h preceding angioplasty, which may have induced a delayed preconditioning effect, the so-called ‘second window of protection’;¹⁷ (3) medication with sulfonylurea or theophylline compounds, which may attenuate the preconditioning effect;^{4,5} and (4) medication with oral nicorandil. All patients gave written informed consent to participate in the study and the protocol was approved by the Ethics Committee of Hiroshima University.

Study Protocol

Patients were randomly allocated to a control or a nico-

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Fig 1. Flow chart of study protocol.

Table 1 Clinical Features of the 2 Groups of Patients

	Control (n=16)	Nicorandil (n=16)	p value
Age (years)	66±10	67±8	NS
M/F (n)	14/2	13/3	NS
Dilated artery (n)			NS
LAD	9	9	
LCx	3	4	
RCA	4	3	
Stenosis severity (%)	80±6	78±8	NS
Hypertension (n)	10	12	NS
Hypercholesterolemia (n)	8	9	NS
Diabetes mellitus (n)	4	6	NS
Smoking (n)	4	5	NS

LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; NS, not significant.

randil treatment group. The control group consisted of 16 patients (14 men, 2 women; age range, 39–76 years; mean age, 66±10 years), and the nicorandil group consisted of 16 patients (13 men, 3 women; age range, 50–84 years; mean age, 67±8 years). All drugs, including antianginal medications, were continued until coronary angioplasty. Aspirin (100 mg/day) and ticlopidine (200 mg/day) were administered to all patients for at least 24 h before angioplasty. All patients underwent diagnostic coronary angiography, including angiographic collateral assessment using a right radial approach. After injection of 2.5 mg of isosorbide dinitrate into the left and right coronary arteries, coronary angiograms were obtained using nonionic contrast medium. Coronary angioplasty was performed by a standard technique using a right radial approach. After placement of a 6Fr guiding catheter and injection of 10,000 IU of heparin, the 0.014-inch pressure monitoring guidewire (Pressure Wire; RADI Medical Systems, Uppsala, Sweden) was positioned distal to the stenosis to be dilated. The nicorandil group then received an intravenous infusion of 100 µg/kg of nicorandil dissolved in 20 ml of 0.9% saline over 1 min. The control group received an equivalent volume of 0.9% saline. Five minutes after the infusion of either nicorandil or saline, the balloon catheter was placed across the lesion and inflated. Balloon size was selected based on diameters of normal regions of the coronary artery adjacent to the stenosis. All patients underwent three 2-min balloon inflations separated by a 5-min interval (Fig 1). Balloon pressure during 3 inflations was identical with nominal pressure.

During each interval between inflations, the balloon was withdrawn into the guiding catheter, leaving the pressure guidewire in place across the lesion. The aortic pressure measured via the guiding catheter, distal coronary artery pressure, including coronary wedge pressure during balloon inflation, heart rate, and the surface ECG were monitored continuously throughout the procedure. Decisions regarding additional inflations or stent implantation were based on coronary angiographic findings after the third inflation.

ECG Analysis

The standard surface 12-lead ECG was continuously monitored and simultaneously recorded throughout the procedure (Cardio Lab System; Prucka Engineering Inc, Sugar Land, TX, USA). All recorded data were stored on an optical disk. ST-segment elevation from baseline was measured from ECG recordings 80 ms after the J point at the end of each balloon inflation. The maximum ST-segment elevation (Δ STmax) and the sum of ST-segment elevations in all leads (Σ ST) were determined and expressed in millimeters (1 mm=0.1 mV). All ECG measurements were performed by a cardiologist who was blind to the study protocol.

Assessment of Chest Pain

At the beginning of coronary angioplasty, patients were informed that chest pain might worsen during balloon inflation. At the end of each balloon inflation, the intensity of anginal pain was assessed using a visual analog scale.¹⁸ Patients were asked to place a mark on a scale of 10 ranging from no pain (0) to the most severe pain ever experienced (10).

Assessment of Coronary Collaterals

A pressure monitoring guidewire was used to assess the effect of angiographically invisible collateral recruitment during balloon inflation. The collateral flow index (CFI) was calculated as the ratio of the mean coronary wedge pressure to the mean aortic pressure.¹⁹ Higher ratios indicate more fully developed collateral recruitment in the ischemic myocardium. The CFI was determined at the end of each balloon inflation.

Statistical Analysis

All data were reported as mean value±SD. One-factor repeated measures analysis of variance (ANOVA) followed by Fisher's test was used for intragroup comparison of the 3 inflations. Student's unpaired t-test was used to compare the 2 groups at various time points. A p value <0.05 was considered statistically significant.

Table 2 Electrocardiographic Data During Coronary Angioplasty in the Control Group

Case no.	Dilated artery	ΔST_{max} (mm)			ΣST (mm)		
		1st inflation	2nd inflation	3rd inflation	1st inflation	2nd inflation	3rd inflation
1	LAD	2.4	2.2	2.0	8.2	6.8	5.5
2	LAD	6.1	5.8	5.6	10.8	10.0	9.3
3	LCx	2.4	2.1	1.8	4.2	4.0	2.9
4	LAD	7.0	5.9	5.7	26.3	21.9	20.5
5	LCx	5.7	5.4	4.8	16.5	15.8	13.0
6	LAD	4.1	3.8	3.2	13.6	11.2	8.7
7	LAD	5.1	4.9	3.5	14.7	12.8	8.5
8	RCA	1.5	1.4	1.0	5.0	4.6	3.1
9	RCA	1.1	1.1	0.8	4.0	4.0	3.5
10	LAD	3.6	3.0	2.2	12.7	10.8	7.9
11	LCx	0.0	0.0	0.0	0.0	0.0	0.0
12	RCA	2.0	2.0	2.0	4.0	4.0	4.0
13	LAD	4.8	4.5	3.7	19.0	16.5	12.4
14	LAD	3.3	2.9	2.8	7.6	6.8	6.1
15	RCA	0.0	0.0	0.0	0.0	0.0	0.0
16	LAD	3.9	3.3	2.5	8.3	6.9	4.9
Mean		3.3	3.0	2.6	9.7	8.5	6.9
$\pm SD$		2.1	1.9	1.8	7.2	6.1	5.3

LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; NS, not significant.

Table 3 Electrocardiographic Data During Coronary Angioplasty in the Nicorandil Group

Case no.	Dilated artery	ΔST_{max} (mm)			ΣST (mm)		
		1st inflation	2nd inflation	3rd inflation	1st inflation	2nd inflation	3rd inflation
1	LCx	2.4	2.1	1.9	8.9	6.1	4.1
2	LAD	1.1	0.9	0.7	1.5	1.2	1.0
3	LAD	1.8	1.8	1.6	5.5	4.6	4.4
4	LAD	3.7	3.6	3.5	11.3	11.1	10.8
5	LCx	1.0	0.7	0.3	1.2	1.0	0.3
6	RCA	1.0	0.8	0.4	2.9	2.5	1.5
7	LAD	0.0	0.0	0.0	0.0	0.0	0.0
8	LCx	0.0	0.0	0.0	0.0	0.0	0.0
9	LCx	1.9	0.9	0.6	7.9	3.4	3.2
10	LAD	0.0	0.0	0.0	0.0	0.0	0.0
11	LAD	3.8	3.8	3.8	8.0	7.7	7.2
12	LAD	2.3	2.2	2.1	3.8	2.9	2.7
13	RCA	3.2	3.2	2.9	8.1	7.9	7.7
14	RCA	1.6	0.9	0.7	3.0	1.4	1.3
15	LAD	1.9	1.7	1.5	3.3	2.7	2.3
16	LAD	4.1	3.7	3.6	10.7	8.3	7.2
Mean		1.9	1.6	1.5	4.8	3.8	3.4
$\pm SD$		1.3	1.3	1.4	3.9	3.5	3.3

LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; NS, not significant.

Results

There were no significant differences in clinical features between the control and nicorandil-treated patients (Table 1). Mean blood pressure decreased and heart rate increased immediately after the intravenous infusion of nicorandil, but returned to baseline before the first inflation (data not shown). Intravenous infusion of 100 μ g/kg of nicorandil for 1 min did not cause other adverse effects.

Coronary Angioplasty

Three 2-min balloon inflations separated by a 5-min interval were performed successfully in all 32 patients (residual stenosis <50%). The average balloon size was 2.6 ± 0.3 mm in the control group and 2.8 ± 0.6 mm in the nicorandil group ($p=NS$). Heart rate and arterial blood pressure were similar in the 2 groups during the 3 inflations (data not shown). Stent implantation was performed in 6 patients of the

control group and in 8 patients of the nicorandil group.

ST-Segment Shift

Electrocardiographic data are shown in Tables 2 and 3. ST-segment elevation during balloon inflation was exhibited in 14 patients of the control group and in 13 patients of the nicorandil group. Elevation was similar during the 3 sequential inflations in 1 patient of the control group and in 1 patient of the nicorandil group, but did not increase in any patient of either group. The ΔST_{max} and ΣST were highest at the end of balloon inflation during each of the 3 inflations in both groups. The ΔST_{max} was greater during the first inflation than during the second and third inflations in both the control (3.3 ± 2.1 vs 3.0 ± 1.9 and 2.6 ± 1.8 mm, respectively) and nicorandil groups (1.9 ± 1.3 vs 1.6 ± 1.3 and 1.5 ± 1.4 mm, respectively) (Fig 2). The ΣST was also greater during the first inflation than during the second and third inflations in both the control (9.7 ± 7.2 vs 8.5 ± 6.1 and 6.9 ± 5.3

Fig2. Change in Δ STmax at the end of balloon inflation during coronary angioplasty. * $p < 0.01$, ** $p < 0.05$.

Fig3. Change in Σ ST at the end of balloon inflation during coronary angioplasty. * $p < 0.01$, ** $p < 0.05$.

Fig4. Change in chest pain score associated with balloon inflation during coronary angioplasty. * $p < 0.01$, ** $p < 0.05$.

mm, respectively) and nicorandil groups (4.8 ± 3.9 vs 3.8 ± 3.5 and 3.4 ± 3.3 mm, respectively) (Fig 3). Both the Δ STmax and Σ ST were smaller in the nicorandil group than in the control group during each inflation (Figs 2, 3).

Chest Pain Score

Chest pain during balloon inflation was observed in 14 patients of the control group and in 12 patients of the nicorandil group. Pain was similar during the 3 sequential inflations in 3 patients of the control group and in 2 patients of the nicorandil group, but did not worsen in any patient of either group. The chest pain score was higher during the first inflation than during the second and third inflations in both the control (4.3 ± 3.1 vs 2.8 ± 2.6 and 1.4 ± 1.5 , respectively) and nicorandil groups (2.2 ± 2.1 vs 1.2 ± 2.1 and 0.8 ± 1.4 , respectively) (Fig 4). The chest pain score was lower in the nicorandil group than in the control group during the first inflation (Fig 4).

Collateral Flow Index

The pressure guidewire remained across the lesion in all patients and intracoronary pressure measurements were completed successfully. In the control group, the CFI was 0.16 ± 0.10 , 0.15 ± 0.10 , and 0.15 ± 0.10 during the first, second, and third inflations, respectively. In the nicorandil group, it was 0.17 ± 0.10 , 0.18 ± 0.13 , and 0.17 ± 0.10 during the first, second, and third inflations, respectively. The CFI did not change during the 3 sequential inflations in either group and was similar in the 2 groups during each inflation

Fig5. Change in collateral flow index at the end of balloon inflation during coronary angioplasty.

(Fig 5), indicating that collateral recruitment did not develop during the series of balloon inflations in either group. In addition, the individual values of CFI were insufficient for collateral recruitment during balloon inflation to contribute to myocardial tolerance to ischemia.

Discussion

This is the first report to demonstrate the relationship between nicorandil-induced preconditioning during coronary angioplasty and coronary collateral function. The present results indicate that electrocardiographic and clinical responses to repeated balloon inflations during coronary angioplasty in patients who were pretreated with intravenous nicorandil resulted from pharmacological preconditioning not involving collateral recruitment.

Ischemic preconditioning initially referred to the ability of short periods of ischemia to limit infarct size in animal experimental models.³ In humans, it is difficult to design the strict conditions of experimental studies on preconditioning in which infarct size is the end-point. Coronary angioplasty in patients with stable AP represents an opportunity for clinically investigating the mechanisms and manifestations of preconditioning. Two or 3 cycles of a 90- to 120-s balloon ischemia followed by a 3- to 5-min interval have been used for this purpose in a number of previous studies^{4-6,8-11,13,14,20,21} Accordingly, we adopted a preconditioning protocol of 3 sequential 2-min balloon inflations separated by a 5-min interval.

The cardioprotective effects of nicorandil have been the subject of several clinical studies.^{12,13,22-26} The administra-

tion of nicorandil suppresses ST-segment elevation,¹² an index of myocardial ischemia, lactate production,¹³ reflecting the metabolic changes of preconditioning, and the increase in QT dispersion²² reflecting the electrophysiological changes of preconditioning, during coronary angioplasty in patients with stable AP. Anti-ischemic effects of nicorandil in patients with unstable AP²³ and improvement in the functional and clinical outcomes of patients with acute myocardial infarction undergoing reperfusion therapy with adjunctive nicorandil therapy^{24–26} also have been reported. Moreover, a recent report from an animal model demonstrated that nicorandil suppresses norepinephrine release from the cardiac sympathetic nerve terminals during myocardial ischemia, suggesting that nicorandil-induced preconditioning attenuates sympathetic nerve injury.²⁷ These cardioprotective effects of nicorandil are believed to be attributable to its ATP-sensitive potassium channel opening action rather than its nitrate effect. Matsubara et al reported that the administration of isosorbide dinitrate does not suppress ST-segment elevation during coronary angioplasty.¹² Therefore, intracoronary administration of isosorbide dinitrate before angioplasty was not thought to influence the preconditioning effect of nicorandil in this study. However, a recent study reported that nitroglycerin, an NO-releasing agent, elicits a late preconditioning effect clinically.¹⁴

Because collateral recruitment can occur during coronary angioplasty,^{28,29} the adaptation to ischemia during repeated balloon inflations may result from progressive collateral recruitment, as well as the preconditioning response. Van Liebergen et al reported the relationship between the presence of angiographically identifiable collateral vessels during balloon inflation and the coronary wedge/aortic pressure ratio (Pw/Pao)³⁰ The Pw/Pao in their study was 0.24 ± 0.08 in patients without collateral vessels, 0.33 ± 0.12 in patients with recruitable collateral vessels, and 0.45 ± 0.11 in patients with spontaneously visible collateral vessels. They concluded that the Pw/Pao is a better marker of the functional significance of collateral vessels than the angiographic findings. Seiler et al also reported that intracoronary pressure measurements using a pressure guidewire during angioplasty can detect well-developed collaterals more accurately than traditional methods, such as ST-segment changes, chest pain, and angiographic findings.³¹ Thus, the use of a pressure guidewire is a valid method for detecting collateral recruitment during balloon inflation. Recent studies concerning the preconditioning effect during coronary angioplasty have also used a pressure guidewire to assess coronary collateral function.^{14,20} The absence of a change in the CFI in either group in the present study shows that collateral recruitment was functionally insignificant during 3 sequential balloon inflations. That is, both ischemic preconditioning and pharmacological preconditioning were independent of collateral recruitment.

Birincioglu et al found that the mitochondrial ATP-sensitive potassium channel protects the myocardium, whereas the sarcolemmal channel is responsible for changes in ST-segment elevation, and they concluded that changes in ST-segment elevation therefore do not necessarily reflect the state of myocardial protection.³² However, the magnitude of the change in the ST-segment has been frequently used as an index of myocardial ischemia in studies of preconditioning during angioplasty.^{4–6,8–14,20–22} In addition, it has been shown that the change in the ST-segment correlates with metabolic and contractile parameters of myocardial

ischemia during coronary angioplasty.^{11,21} Two conflicting results have been reported in studies of patients treated with nicorandil. Matsubara et al reported that intravenous nicorandil suppresses ST-segment elevation during coronary angioplasty, suggesting a pharmacological preconditioning effect,¹² but Yasuda et al reported that nicorandil improves lactate metabolism during angioplasty without significantly affecting ST-segment elevation.¹³ Our data are consistent with the former. In any event, some degree of caution may be needed in interpreting the ST-segment changes.

Quantification of subjective chest pain presents difficulties and is affected by a number of biases. Nevertheless, many studies of the preconditioning effect during angioplasty have assessed the intensity of chest pain using a visual analog scale (0–10 or 0–100).^{4,6,8–11,14,20,21} Accordingly, we also used a visual analog scale to assess chest pain. The chest pain score decreased progressively with the repeated balloon inflations in both groups, suggesting that ischemic preconditioning had occurred. However, the chest pain score during the first inflation was lower in the nicorandil group than in the control group, suggesting that the suppression of chest pain was the result of pharmacological preconditioning.

The Δ STmax and Σ ST during the first inflation in the nicorandil group were smaller than during the third inflation in the control group, and the chest pain score during the first inflation in the nicorandil group was lower than during the second inflation in the control group. These data suggest that nicorandil-induced preconditioning may be superior to ischemic preconditioning.

The Δ STmax, Σ ST, and chest pain score in the nicorandil group decreased progressively during the 3 sequential balloon inflations, suggesting the superimposition of ischemic preconditioning. That is, the myocardium had not been maximally preconditioned by nicorandil alone. Matsubara et al administered 80 μ g/kg of nicorandil intravenously, and ST-segment elevation was suppressed only during the first half of the subsequent 2-min balloon inflation.¹² The present study used 100 μ g/kg of intravenous nicorandil, which suppressed ST-segment elevation throughout each of the 3 inflations. Yasuda et al administered an intravenous bolus injection of 2 mg nicorandil followed by at least 1 h of continuous infusion (6 mg/h) prior to coronary angioplasty, suggesting a preconditioning effect of nicorandil.¹³ Although it is unknown whether the myocardium can be maximally preconditioned by nicorandil alone, there still appears to be room for consideration about the amount or mode of administration of nicorandil to elicit pharmacological preconditioning.

Study Limitations

First, the stenotic lesion was located in one of the 3 major coronary arteries, so potential differences in ST-segment changes and chest pain related to the specific site were not considered. A study limited to patients whose stenotic lesion is located within the proximal left anterior descending coronary artery may be preferable. However, recent studies concerning the angioplasty model of preconditioning do not necessarily follow such selection criteria.^{10,11,14,20} The ischemic area associated with balloon occlusion of the left anterior descending coronary artery also may vary. Second, because coronary angiography was not performed during the first and second 5-min intervals, whether similar dilatation was achieved during the 3 intervals is unknown. A slight difference in stenosis severity may influence the

preconditioning effect. Third, study patients had a variety of coronary risk factors, such as hypertension and diabetes mellitus, and their medical therapy was not uniform, so these variables may have affected our results.^{33–37}

In conclusion, pretreatment with intravenous nicorandil enhances myocardial tolerance to ischemia during coronary angioplasty in patients with stable AP. This pharmacological preconditioning is comparable to ischemic preconditioning and is not accompanied by progressive collateral recruitment.

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References

- Tomai F, Crea F, Chiariello L, Giffone PA. Ischemic preconditioning in humans: Models, mediators, and clinical relevance. *Circulation* 1999; **100**: 559–563.
- Yellon DM, Dana A. The preconditioning phenomenon: A tool for the scientist or a clinical reality? *Circ Res* 2000; **87**: 543–550.
- Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; **74**: 1124–1136.
- Tomai F, Crea F, Gaspardone A, Versaci F, De Paulis R, Penta de Peppo A, et al. Ischemic preconditioning during coronary angioplasty is prevented by glibenclamide, a selective ATP-sensitive K⁺ channel blocker. *Circulation* 1994; **90**: 700–705.
- Claeys MJ, Vrints CJ, Bosmans JM, Conraads VM, Snoeck JP. Aminophylline inhibits adaptation to ischaemia during angioplasty: Role of adenosine in ischaemic preconditioning. *Eur Heart J* 1996; **17**: 539–544.
- Tomai F, Crea F, Gaspardone A, Versaci F, De Paulis R, Polisca P, et al. Effects of A₁ adenosine receptor blockade by bamiphylline on ischaemic preconditioning during coronary angioplasty. *Eur Heart J* 1996; **17**: 846–853.
- Strauer BE, Heidland UE, Heintzen MP, Schwartzkopff B. Pharmacologic myocardial protection during percutaneous transluminal coronary angioplasty by intracoronary application of dipyridamole: Impact on hemodynamic function and left ventricular performance. *J Am Coll Cardiol* 1996; **28**: 1119–1126.
- Leesar MA, Stoddard M, Ahmed M, Broadbent J, Bolli R. Preconditioning of human myocardium with adenosine during coronary angioplasty. *Circulation* 1997; **95**: 2500–2507.
- Tomai F, Crea F, Gaspardone A, Versaci F, Ghini AS, De Paulis R, et al. Phentolamine prevents adaptation to ischemia during coronary angioplasty: Role of α -adrenergic receptors in ischemic preconditioning. *Circulation* 1997; **96**: 2171–2177.
- Tomai F, Crea F, Gaspardone A, Versaci F, Ghini AS, Ferri C, et al. Effects of naloxone on myocardial ischemic preconditioning in humans. *J Am Coll Cardiol* 1999; **33**: 1863–1869.
- Leesar MA, Stoddard MF, Manchikalapudi S, Bolli R. Bradykinin-induced preconditioning in patients undergoing coronary angioplasty. *J Am Coll Cardiol* 1999; **34**: 639–650.
- 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.
- Yasuda T, Hashimura K, Matsuura Y, Kato Y, Ueda T, Mori I, et al. Nicorandil, a hybrid between nitrate and ATP-sensitive potassium channel opener, preconditions human heart to ischemia during percutaneous transluminal coronary angioplasty. *Jpn Circ J* 2001; **65**: 526–530.
- Leesar MA, Stoddard MF, Dawn B, Jasti VG, Masden R, Bolli R. Delayed preconditioning-mimetic action of nitroglycerin in patients undergoing coronary angioplasty. *Circulation* 2001; **103**: 2935–2941.
- Taira N. Nicorandil as a hybrid between nitrates and potassium channel activators. *Am J Cardiol* 1989; **63**: 18J–24J.
- Ghosh S, Standen N, Galinanes M. Evidence for mitochondrial KATP channels as effectors of human myocardial preconditioning. *Cardiovasc Res* 2000; **45**: 934–940.
- Yellon DM, Baxter GF. A 'second window of protection' or delayed preconditioning phenomenon: Future horizons for myocardial protection. *J Mol Cell Cardiol* 1995; **27**: 1023–1034.
- Huskinson EC. Measurement of pain. *Lancet* 1974; **2**: 1127–1131.
- Pijls NHJ, DeBruyne B. Validation of fractional flow reserve in animals. In: Pijls NHJ, DeBruyne B, editors. Coronary pressure. Boston, Mass: Kluwer Academic Publishers; 1997: 121–141.
- Kyriakides ZS, Kremastinos DT, Kolettis TM, Tasouli A, Antoniadis A, Webb DJ. Acute endothelin-A receptor antagonism prevents normal reduction of myocardial ischemia on repeated balloon inflations during angioplasty. *Circulation* 2000; **102**: 1937–1943.
- Deutsch E, Berger M, Kussmaul WG, Hirschfeld JW, Herrmann HC, Laskey WK. Adaptation to ischemia during percutaneous transluminal coronary angioplasty: Clinical, hemodynamic, and metabolic features. *Circulation* 1990; **82**: 2044–2051.
- Kato T, Kamiyama T, Maruyama Y, Tanaka S, Yoshimoto N. Nicorandil, a potent cardioprotective agent, reduces QT dispersion during coronary angioplasty. *Am Heart J* 2001; **141**: 940–943.
- Patel DJ, Purcell HJ, Fox KM. Cardioprotection by opening of the KATP channel in unstable angina: Is this a clinical manifestation of myocardial preconditioning? Results of a randomized study with nicorandil (CESAR 2 investigation: Clinical European studies in angina and revascularization). *Eur Heart J* 1999; **20**: 51–57.
- Sakata Y, Kodama K, Komamura K, Lim YJ, Ishikura F, Hirayama A, et al. Salutory effect of adjunctive intracoronary nicorandil administration on retraction of myocardial blood flow and functional improvement in patients with acute myocardial infarction. *Am Heart J* 1997; **133**: 616–621.
- Kobayashi Y, Goto Y, Daikoku S, Itoh A, Miyazaki S, Ohshima S, et al. Cardioprotective effect of intravenous nicorandil in patients with successful reperfusion for acute myocardial infarction. *Jpn Circ J* 1998; **62**: 183–189.
- Ito H, Taniyama Y, Iwakura K, Nishikawa N, Masuyama T, Kazuya 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.
- Miura T, Kawamura S, Tatsuno H, Ikeda Y, Mikami S, Iwamoto H, et al. Ischemic preconditioning attenuates cardiac sympathetic nerve injury via ATP-sensitive potassium channels during myocardial ischemia. *Circulation* 2001; **104**: 1053–1058.
- Rentrop KP, Cohen M, Blanke H, Phillips R. Changes in collateral filling immediately following controlled coronary artery occlusion by an angioplasty balloon in man. *J Am Coll Cardiol* 1985; **5**: 587–592.
- Tomai F, Crea F, Gaspardone A, Versaci F, De Paulis R, Penta de Peppo A, et al. Determinants of myocardial ischemia during percutaneous transluminal coronary angioplasty in patients with significant narrowing of a single coronary artery and stable or unstable angina pectoris. *Am J Cardiol* 1994; **74**: 1089–1094.
- van Liebergen RAM, Piek JJ, Koch KT, de Winter RJ, Schotborgh CE, Lie KI. Quantification of collateral flow in humans: A comparison of angiographic, electrocardiographic and hemodynamic variables. *J Am Coll Cardiol* 1999; **33**: 670–677.
- Seiler C, Fleisch M, Garachemani A, Meier B. Coronary collateral quantitation in patients with coronary artery disease using intravascular flow velocity or pressure measurements. *J Am Coll Cardiol* 1998; **32**: 1272–1279.
- Birincioglu M, Yang XM, Critz SD, Cohen MV, Downey JM. S-T segment voltage during sequential coronary occlusions is an unreliable marker of preconditioning. *Am J Physiol* 1999; **277**: H2435–H2441.
- Ueda Y, Kitakaze M, Komamura K, Minamino T, Asanuma H, Sato H, et al. Pravastatin restored the infarct size-limiting effect of ischemic preconditioning blunted by hypercholesterolemia in the rabbit model of myocardial infarction. *J Am Coll Cardiol* 1999; **34**: 2120–2125.
- Kersten JR, Toller WG, Gross ER, Pagel PS, Warltier DC. Diabetes abolishes ischemic preconditioning: Role of glucose, insulin, and osmolality. *Am J Physiol Heart Circ Physiol* 2000; **278**: H1218–H1224.
- Kitakaze M, Asanuma H, Takashima S, Minamino T, Ueda Y, Sakata Y, et al. Nifedipine-induced coronary vasodilation in ischemic hearts is attributable to bradykinin- and NO-dependent mechanisms in dogs. *Circulation* 2000; **101**: 311–317.
- Sato M, Engelman RM, Otani H, Maulik N, Rousou JA, Flack JE, et al. Myocardial protection by preconditioning of heart with losartan, an angiotensin II type1-receptor blocker: Implication of bradykinin-dependent and bradykinin-independent mechanisms. *Circulation* 2000; **102**: III-346–III-351.
- Miki T, Miura T, Tsuchida A, Nakano A, Hasegawa T, Fukuma T, et al. Cardioprotective mechanism of ischemic preconditioning is impaired by postinfarct ventricular remodeling through angiotensin II type 1-receptor activation. *Circulation* 2000; **102**: 458–463.