

# Delayed Preconditioning-Mimetic Action of Nitroglycerin in Patients Undergoing Coronary Angioplasty

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**Background**—Experimental studies suggest that the cardioprotective effects of the late phase of ischemic preconditioning (PC) can be mimicked pharmacologically. However, to date, no drug has been tested with respect to its ability to elicit a late PC effect in humans. As a consequence, clinical exploitation of the powerful anti-stunning and anti-infarct actions of late PC has been elusive thus far.

**Methods and Results**—A total of 66 patients were randomized to receive a 4-hour intravenous infusion of nitroglycerin (NTG) or normal saline; on the following day, they underwent percutaneous transluminal coronary angioplasty (three 2-minute balloon inflations 5 minutes apart). Measurements of ST-segment shifts (intracoronary and surface ECGs), regional wall motion (quantitative 2D echocardiography), and chest pain score indicated that the infusion of NTG 24 hours before angioplasty rendered the myocardium relatively resistant to ischemia and that the degree of this cardioprotective effect was comparable to that afforded by the ischemia associated with the first balloon inflation in control subjects (early phase of ischemic PC). Collateral flow (estimated from a pressure-derived index) did not differ between control and NTG-pretreated patients, indicating that the enhanced tolerance to ischemia in NTG-pretreated patients cannot be accounted for by baseline differences in collateral function.

**Conclusions**—NTG protects human myocardium against ischemia 24 hours after its administration. To the best of our knowledge, this is the first report that a late PC effect can be recruited pharmacologically in humans. The results suggest that prophylactic administration of nitrates could be a novel approach to the protection of the ischemic myocardium in patients. (*Circulation*. 2001;103:2935-2941.)

**Key Words:** ischemia ■ reperfusion ■ myocardial infarction ■ nitrates ■ collateral circulation

Ischemic preconditioning (PC) is the phenomenon whereby brief episodes of ischemia enhance the tolerance of the heart to subsequent ischemic insults.<sup>1-3</sup> Originally described as an immediate adaptation to ischemia, it is now recognized that ischemic PC consists of 2 chronologically and pathophysiologically distinct phases: an early phase, which develops immediately after the ischemic stress and lasts 1 to 2 hours, and a late phase, which begins 12 to 24 hours after the initial ischemic challenge and lasts 3 to 4 days.<sup>1-3</sup> Unlike the early phase, which protects against myocardial infarction but not against myocardial stunning, the late phase protects against both stunning and infarction.<sup>1-3</sup> Because of this and because of its prolonged duration, the phenomenon of late PC may have considerable clinical relevance.<sup>2,3</sup>

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Therapeutic exploitation of this endogenous mechanism for the protection of the ischemic myocardium in patients with coronary artery disease is conceptually attractive but is

hindered by the lack of clinically relevant interventions that can be substituted for ischemia to elicit a late PC effect. In experimental models, many pharmacological agents have been shown to induce delayed cardioprotection similar to that elicited by ischemia ("late PC mimetics"); however, most of them are associated with untoward effects that make them impractical for clinical use,<sup>4-9</sup> and none of them has been tested with respect to its ability to recapitulate late PC in patients. Clearly, the identification of pharmacological interventions capable of mimicking the protective actions of late PC in humans represents a critical step toward developing clinically applicable strategies aimed at maintaining a chronically preconditioned state in individuals at risk for myocardial infarction or other acute coronary events.

Recent experimental evidence indicates that nitric oxide (NO; either endogenous NO released during ischemic stress or exogenous NO released by pharmacological agents) plays a pivotal role in triggering the process of late PC.<sup>10</sup> Specifically, it has been demonstrated that the development of the

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Tables I and II can be found Online at <http://www.circulationaha.org>

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late phase of ischemic PC is blocked by inhibiting NO synthesis during the initial ischemic stress<sup>11,12</sup> and, conversely, that administration of NO donors in the absence of ischemia can induce a late PC effect that is indistinguishable from that elicited by ischemia (NO donor-induced late PC).<sup>13,14</sup> The concept that NO triggers late PC has important therapeutic implications because it suggests that NO-releasing agents (eg, nitrates) may be useful as a PC-mimetic therapy in humans.<sup>2</sup>

The present investigation was undertaken as an initial step to test this hypothesis. The study was conducted in patients undergoing percutaneous transluminal coronary angioplasty (PTCA), a clinical setting previously used by numerous investigators to assess cardioprotective interventions.<sup>15–18</sup> The primary objective was to determine whether an intravenous infusion of nitroglycerin (NTG) 24 hours before PTCA alleviates the severity of the myocardial ischemia associated with balloon inflations. In addition, we sought to determine whether the salutary actions of NTG are due to genuine PC of the myocardium or merely to coronary collateral recruitment. The results demonstrate, for the first time, that NTG induces a delayed cardioprotective effect in humans that is manifest many hours after discontinuation of NTG infusion and is unrelated to differences in coronary collateral function.

## Methods

### Study Population

The patient population consisted of 66 subjects referred for PTCA of an isolated obstructive lesion (internal diameter reduction >70% by visual assessment) in the proximal two thirds of a major coronary artery. Patients were prospectively selected on the basis of the following criteria: (1) no angiographically visible collateral vessels; (2) no history or electrocardiographic evidence of prior myocardial infarction in the territory supplied by the vessel undergoing PTCA; (3) no conduction defects on the ECG; (4) no evidence of left ventricular (LV) hypertrophy on the echocardiogram; and (5) no baseline ST-segment abnormalities on the surface or intracoronary ECG. Twenty-four patients were admitted with a diagnosis of unstable angina, and the remaining 42 had clinically stable angina pectoris (Table). The average interval between the last episode of angina and PTCA was 75±1 hours in controls and 67±3 hours in NTG-pretreated patients. No patient had angina pectoris in the 48 hours before PTCA. On the LV angiogram, the ejection fraction was 58±1% in control patients and 59±1% in NTG-pretreated patients (Table). This study was approved by the Institutional Review Board on August 2, 1998; informed consent, via an institutionally approved human investigation form, was obtained from all patients.

### Experimental Protocol

In this single-blind study, patients were randomly allocated to a control or an NTG-pretreated group. No patient received intravenous or intracoronary NTG on the day of PTCA or during the procedure. Antianginal medications were not discontinued before the procedure except for oral long-acting nitrates, which were discontinued in the treated group before the infusion of NTG (this was done to preclude any potential early PC effects of nitrates<sup>2</sup> from confounding the late PC effects of NTG). The rationale for not discontinuing nitrates in control patients was that we sought to determine whether NTG-induced PC provides any additional benefit compared with conventional nitrate therapy. All patients were studied after an overnight fast and were premedicated with midazolam (1 mg IV 10 minutes before the procedure).

### Clinical Features of the 2 Groups of Patients

	Control Group (n=33)	NTG-Pretreated Group (n=33)
Age, y	56±2	61±2
Sex, M/F	25/8	16/17
Hypertension	24	29
Smoking	23	21
Diabetes mellitus	14	15
Previous CABG	0	0
Previous PTCA	7	9
Previous myocardial infarction in non-PTCA territory	4	3
LV ejection fraction, %	58±1	59±1
Anginal syndrome on admission		
CCS class 1–2	22	20
CCS class 3–4	11	13
Interval between last episode of angina and PTCA, h	75±1	67±3
Antianginal medications		
Long-acting nitrates	16	15
β-Blocking agents	19	24
Calcium channel blocking agents	17	15

Data are mean±SEM or No. of patients.

CABG indicates coronary artery bypass graft surgery; CCS, Canadian Cardiovascular Society.

Twenty-four hours before PTCA, patients were randomized to normal saline or NTG infusion. NTG was infused at a rate of 10 μg/min and was gradually titrated up to 50 μg/min. During the NTG infusion, blood pressure and pulse rate were monitored and recorded every 15 minutes by an automated blood pressure device (Propaq 102 EL, Protocol Systems); the NTG infusion was titrated to a systolic blood pressure ≥100 mm Hg. NTG was infused for a total duration of 4 hours; the average total dose was 11.6±0.3 mg.

PTCA was performed by a standard technique as previously described.<sup>16,17</sup> After the balloon dilation catheter was positioned across the lesion, patients underwent 3 balloon inflations, each lasting 120 s, interspersed with 5-minute periods of reperfusion during which the balloon was deflated and withdrawn proximal to the lesion with the guidewire remaining across the lesion. The ST-segment shift on the surface, intracoronary ECGs, and the intensity of chest pain were measured as previously described.<sup>16,17</sup>

### Assessment of Coronary Collaterals

In a subset of 26 patients (10 control and 16 NTG-pretreated subjects), coronary collateral function was estimated by calculating the collateral flow index (CFI).<sup>19,20</sup> A 0.014-inch (0.036 cm) fiberoptic pressure monitoring guidewire (WaveWire, Endosonics) was set at zero, calibrated, advanced through the guiding catheter, and positioned distal to the stenosis to be dilated. A rapid-exchange balloon angioplasty catheter was then advanced over the WaveWire, positioned across the lesion, and inflated; in these patients, the intracoronary ECG was obtained from the WaveWire. The mean aortic pressure ( $P_{ao}$ ) and the simultaneous mean distal coronary artery pressure ( $P_{occl}$ ) were measured at the end of each balloon inflation. From these measurements, the CFI was calculated as  $(P_{occl}-CVP)/(P_{ao}-CVP)$ ,<sup>19,20</sup> where CVP indicates central venous pressure (estimated to be equal to 5 mm Hg<sup>20</sup>). The CFI expresses collateral flow relative to normal flow through the patent vessel, as previously reported.<sup>19,20</sup>

## Echocardiographic Studies

Two-dimensional echocardiograms were performed serially in 18 patients (9 control and 9 NTG-pretreated subjects) at baseline, at the end of each balloon inflation (ie, 110 to 120 s into the inflation), and at 5 minutes after each balloon deflation. The methods have been described in detail.<sup>16,17,21</sup> Quantitative analysis of regional wall motion was performed from the apical 4- and 2-chamber views using a centerline method that corrects for ventricular translation.<sup>21</sup> The LV ejection fraction was calculated by the biplane modified Simpson's method.<sup>22</sup> The echocardiographic studies were analyzed by an echocardiographer (M.F.S.) who had no knowledge of the treatment.

## Statistical Analysis

All data are reported as means $\pm$ SEM. Continuous variables were analyzed with a 1-way or 2-way repeated-measures ANOVA, as appropriate. Post hoc contrasts between groups at various time points or between time points within one group were performed with Student's *t* tests for unpaired or paired data, as appropriate, using the Bonferroni correction.

## Results

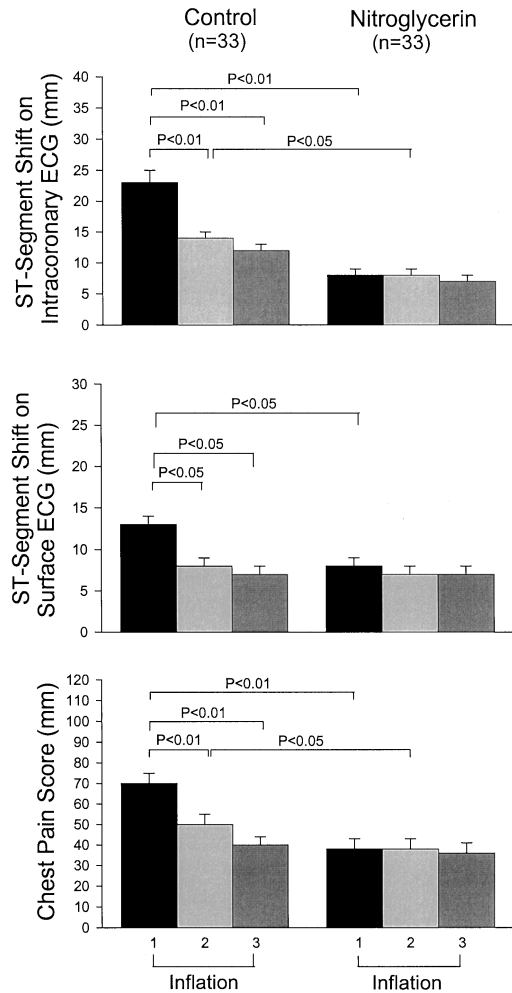
A total of 33 patients in the control group and 33 in the NTG-pretreated group met the criteria detailed under Methods and had technically adequate intracoronary and surface ECGs associated with complete resolution of ischemia between balloon inflations. Complete resolution of ischemia was defined as chest pain resolution and return of the ST-segment on the intracoronary and surface ECGs to within 1 mm of baseline during the 5 minutes that elapsed between the first, second, and third balloon inflations. The clinical features of the control and NTG-pretreated patients are summarized in the Table. There were no significant differences between the 2 groups. Administration of NTG resulted in a decrease in systolic and mean arterial blood pressures from  $137\pm 2$  and  $94\pm 2$  mm Hg, respectively, at baseline to  $115\pm 3$  and  $83\pm 2$  mm Hg at the end of the infusion ( $P<0.01$ ), which was associated with an increase in heart rate from  $65\pm 2$  beats/min at baseline to  $76\pm 2$  beats/min at the end of the infusion ( $P<0.01$ ).

## Coronary Angioplasty

The anatomic and hemodynamic features of the study population are summarized in Table I, which can be found Online at <http://www.circulationaha.org>. PTCA was successfully performed in all 66 patients. Heart rate and arterial blood pressure did not differ between the 2 groups during the 3 inflations (data not shown). The rate-pressure product was also similar (Table I). There was no electrocardiographic evidence of myocardial injury in any patient.

## Electrocardiographic Manifestations of Myocardial Ischemia

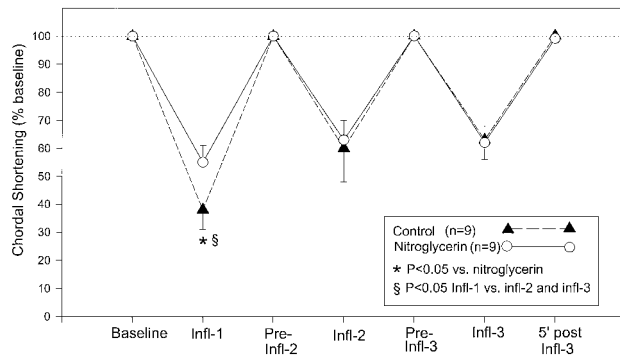
All patients exhibited ST-segment elevation during balloon inflation. In the control group, the ST-segment shift was significantly greater during the first balloon inflation than during the second and third inflations on both the intracoronary ECG ( $23\pm 2$  versus  $14\pm 1$  and  $12\pm 1$  mm, respectively) and the surface ECG ( $13\pm 1$  versus  $8\pm 1$  and  $7\pm 1$  mm, respectively; Figure 1). In contrast, in the NTG-pretreated group, there were no differences in the ST-segment shift



**Figure 1.** ST-segment shift on the intracoronary ECG (top), ST-segment shift on the surface ECG (middle), and chest pain score (bottom) at the end of the first, second, and third balloon inflations in control and NTG-pretreated patients. Values are means $\pm$ SEM.

during the first, second, and third balloon inflations on either the intracoronary ECG ( $8\pm 1$ ,  $8\pm 1$ , and  $7\pm 1$  mm, respectively) or the surface ECG ( $8\pm 1$ ,  $9\pm 2$ , and  $8\pm 1$  mm, respectively; Figure 1).

The ST-segment shift recorded on the intracoronary ECG was significantly smaller in the NTG-pretreated group than in the control group during the first and second balloon inflations ( $8\pm 1$  versus  $23\pm 2$  mm [ $-65\%$ ],  $P<0.01$ , and  $8\pm 1$  versus  $14\pm 1$  mm [ $-43\%$ ],  $P<0.05$ , respectively), but it did not differ significantly between the 2 groups during the third inflation (Figure 1). The ST-segment shift recorded on the surface ECG was significantly smaller in the NTG-pretreated group than in the control group during the first inflation ( $8\pm 1$  versus  $13\pm 1$  mm, respectively;  $P<0.05$ ), but it did not differ significantly between the 2 groups during the second and third inflations (Figure 1). The effect of NTG on the ST-segment shift was independent of the presence of a history of unstable angina. Indeed, when the analysis was restricted to the 42 patients with stable angina pectoris, the results were similar to those obtained in the entire cohort. For example,



**Figure 2.** Chordal shortening in the ischemic/reperfused LV region at baseline, at the end of the first, second, and third balloon inflations (Infl-1, Infl-2, and Infl-3), immediately before the second and third inflations (Pre-Infl-2 and Pre-Infl-3), and 5 minutes after the third inflation (5' post Infl-3) in control and NTG-pretreated patients. Chordal shortening was determined by quantitative 2D echocardiography using the centerline method (see Methods) and expressed as a percent of baseline values. Values are means  $\pm$  SEM.

during the first and second balloon inflations, the intracoronary ST-segment shift averaged  $22 \pm 2$  and  $12 \pm 2$  mm, respectively, in the 22 control patients with stable angina pectoris and  $8 \pm 2$  and  $7 \pm 1$  mm, respectively, in the 20 NTG-pretreated patients with stable angina pectoris ( $P < 0.05$  between groups at each inflation).

### Chest Pain

In the control group, the severity of chest pain was significantly greater during the first inflation than during the second and third inflations ( $70 \pm 5$  versus  $50 \pm 5$  and  $40 \pm 4$  mm, respectively; Figure 1). In contrast, in the NTG-pretreated group, the chest pain score did not differ significantly during the first, second, and third inflations ( $38 \pm 5$ ,  $38 \pm 5$ , and  $36 \pm 5$  mm, respectively; Figure 1). The chest pain score was significantly smaller in the NTG-pretreated group than in the control group during the first and second inflations (Figure 1).

Among the 42 patients with stable angina pectoris, the chest pain score was significantly ( $P < 0.05$ ) less in the NTG-pretreated group than in the control group during the first and second inflations. Thus, the effect of NTG on the severity of chest pain was independent of the presence of unstable angina.

### Regional LV Wall Motion

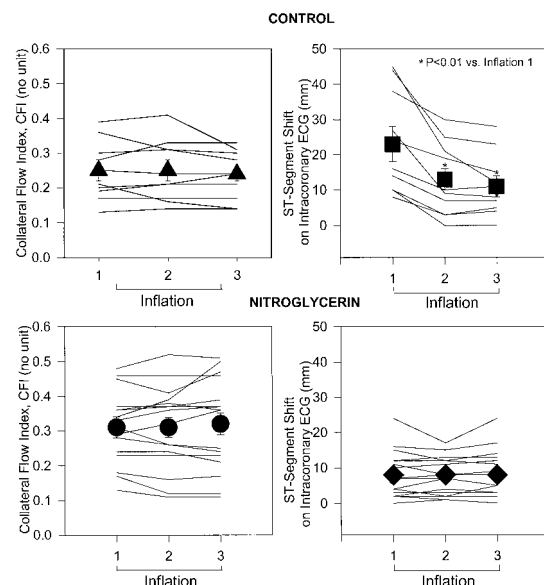
The baseline chordal shortening in the distribution of the artery undergoing PTCA averaged  $8.2 \pm 0.5$  and  $7.9 \pm 0.5$  mm in the control and NTG-pretreated groups, respectively ( $n = 9$  in each group). In the control group, chordal shortening in the territory subserved by the occluded artery decreased markedly (by  $62 \pm 7\%$ ) during the first balloon inflation and recovered 5 minutes after deflation (Figure 2). During the second and third inflations, the decrease in chordal shortening was significantly less than during the first inflation ( $-40 \pm 12\%$  and  $-37 \pm 7\%$ , respectively; each  $P < 0.05$  versus first inflation; Figure 2). In the NTG-pretreated group, the reduction in chordal shortening during the first inflation was

significantly smaller than in the control group ( $-45 \pm 6\%$  versus  $-62 \pm 7\%$ ,  $P < 0.05$ ; Figure 2). Furthermore, in contrast to the control group, in the NTG-pretreated group, there were no significant differences in chordal shortening during the first, second, and third balloon inflations ( $-45 \pm 6\%$ ,  $-37 \pm 7\%$ , and  $-38 \pm 6\%$ , respectively; Figure 2).

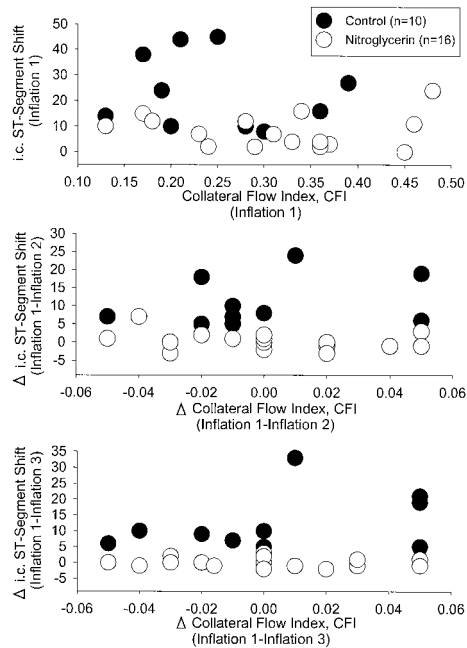
The baseline LV ejection fraction averaged  $65 \pm 2\%$  and  $63 \pm 2\%$  in the control and NTG-pretreated groups, respectively ( $P = \text{NS}$ ). In the control group, LV ejection fraction decreased to  $40 \pm 1\%$ ,  $43 \pm 1\%$ , and  $47 \pm 1\%$  during the first, second, and third inflations, respectively ( $P = \text{NS}$ ). In the NTG-pretreated group, LV ejection fraction fell to  $50 \pm 4\%$ ,  $49 \pm 3\%$ , and  $49 \pm 3\%$ , respectively, during each inflation ( $P = \text{NS}$ ).

### Collateral Flow Index

Previous studies have validated the CFI as an accurate estimate of collateral perfusion in patients.<sup>19,20</sup> In the subset of patients in whom the CFI was measured (10 controls and 16 NTG-pretreated subjects), the changes in intracoronary ST-segment shift and chest pain score paralleled those observed in the entire cohort of patients (Table II). The CFI did not differ significantly in control and NTG-pretreated patients during the first balloon inflation ( $0.25 \pm 0.03$  and  $0.31 \pm 0.03$ , respectively) and did not change appreciably during the second and third inflations (Table II), indicating that significant recruitment of coronary collaterals did not occur with subsequent occlusions in either group. Individual measurements of CFI and intracoronary ST-segment shift are illustrated in Figure 3. In the control group, all patients exhibited a marked decrease in the intracoronary ST-segment shift during the second and third inflations compared with the first, despite the fact that the CFI remained essentially constant. In the NTG-pretreated group, the intracoronary ST-segment



**Figure 3.** CFI (left) and ST-segment shift on the intracoronary ECG (right) at the end of the first, second, and third balloon inflations in control (top) and NTG-pretreated (bottom) patients. Solid symbols represent means  $\pm$  SEM.



**Figure 4.** Top, Relationship between CFI (horizontal axis) and ST-segment shift on the intracoronary ECG (vertical axis) at the end of the first balloon inflation in control (●) and NTG-pretreated (○) patients. Middle, Relationship between the changes in CFI (horizontal axis) and the changes in ST-segment shift on the intracoronary ECG (vertical axis) between the first and second balloon inflations in control and NTG-pretreated patients. Bottom, Relationship between the changes in CFI (horizontal axis) and the changes in ST-segment shift on the intracoronary ECG (vertical axis) between the first and third balloon inflations in control and NTG-pretreated patients. There was no significant relationship between the variables examined.

shifts during all 3 balloon inflations were much less than in controls, despite the fact that the CFI was similar to that measured in controls. In addition, the rate-pressure product (an index of myocardial oxygen demand) was similar in the 2 groups (Table II).

In both the control and NTG-pretreated groups, there was no discernible correlation between intracoronary ST-segment shift and CFI during the first balloon inflation or between the changes in intracoronary ST-segment shift and the changes in CFI on the second and third inflations versus the first (Figure 4). Taken together, these data indicate that (1) the differences in ST-segment shift between the 2 groups cannot be accounted for by baseline differences in collateral function and (2) the attenuation of the ST-segment shift in control patients cannot be accounted for by recruitment of coronary collaterals.

## Discussion

Although the late phase of ischemic PC provides sustained protection against both myocardial stunning and infarction,<sup>1,2</sup> its pharmacological exploitation has thus far been elusive. The major obstacle to the translation of basic knowledge into clinical therapies has been the identification of agents that can be safely used to recruit this cardioprotective mechanism in patients at risk for acute myocardial ischemia. The search for PC-mimetic drugs has been intense, and many candidates

have been evaluated in experimental models.<sup>2-9,13,14</sup> However, to date, no drug has been tested with respect to its ability to elicit a late PC effect in humans.

The present investigation indicates that the infusion of NTG 24 hours before PTCA markedly enhances the tolerance of the heart to the ischemia associated with balloon inflations and that the magnitude of this salubrious effect is similar to that observed during the early phase of ischemic PC. Specifically, pretreatment with NTG resulted in a significant attenuation of the mechanical, electrocardiographic, and symptomatic manifestations of ischemia associated with the first balloon inflation, as measured by the changes in regional LV wall motion, ST-segment shift, and chest pain score, respectively. This protective effect was observed  $19.0 \pm 0.5$  hours after the end of NTG infusion, at a time when any direct action of the drug had long subsided. The wall motion abnormalities, ST-segment shift, and chest pain score noted during the first balloon inflation in NTG-pretreated patients were similar to those observed during the third balloon inflation in untreated patients; thus, the degree of protection afforded by NTG was comparable to that afforded by the early phase of ischemic PC induced by the first 2 balloon inflations in the control group. This conclusion is further supported by the finding that the wall motion abnormalities, the ST-segment shift, and the severity of chest pain decreased significantly after the first balloon inflation in the control group but not in the NTG-pretreated group, which indicates that the superimposition of early ischemic PC did not enhance protection above and beyond that afforded by NTG; that is, the myocardium was already "maximally" preconditioned by NTG. Importantly, the augmented tolerance to ischemia in NTG-pretreated patients cannot be ascribed to differences in collateral function because the CFI was similar between control and treated groups during each of the 3 inflations.

Taken together, these results demonstrate, for the first time, that NTG protects human myocardium against ischemia 24 hours after its administration. To the best of our knowledge, this is also the first report that pretreatment with a drug can recruit a late PC effect in humans. The results suggest that the prophylactic administration of nitrates could be a novel approach to the protection of the ischemic myocardium in patients with coronary artery disease.

Among the clinically available nitrates, we selected NTG because this drug is a mainstay of the therapeutic armamentarium for acute myocardial ischemia<sup>23</sup> and because it has been shown to elicit late PC against both myocardial stunning<sup>14</sup> and infarction<sup>2</sup> in experimental models, suggesting that it could be effective in conferring delayed cardioprotection against both reversible (stunning) and irreversible (infarction) ischemic injury in patients. The potential usefulness of NTG as a PC-mimetic is further emphasized by the experimental demonstration that NTG-induced late PC lasts for 72 hours and is not affected by the presence of nitrate tolerance.<sup>2</sup> Thus, it is conceivable that a protracted or even chronic PC state could be implemented by administering appropriate doses of NTG or other nitrovasodilators on a regular basis every 2 to 3 days. As shown in the Table, approximately half of the patients were treated with long-acting nitrates in both groups (in the NTG-pretreated group, these drugs were discontinued

on the day before PTCA). It is possible that the administration of long-acting nitrates may have elicited delayed cardioprotection, in which case the late PC effect of intravenous NTG measured in this study would have been underestimated.

Whereas in experimental studies NTG-induced late PC attenuated the severity of contractile dysfunction after the resolution of ischemia but not during ischemia,<sup>14</sup> in the present study NTG pretreatment alleviated ischemic dysfunction (Figure 2). The reason for this difference is unknown but could involve species differences and/or differences in the occlusion protocol (2-minute coronary occlusions versus 4-minute occlusions in the animal studies<sup>14</sup>). It must also be stressed that the end points used herein (ST-segment changes, ischemic dysfunction, and pain) are appropriate for the setting of PTCA but differ from those used experimentally (ie, infarct size and postischemic dysfunction<sup>11–14</sup>). It remains to be seen whether NTG pretreatment is salutary in clinical situations (eg, cardiac surgery and acute infarction) that are associated with more severe ischemic injury than that incurred during PTCA.

A recent study in rabbits<sup>24</sup> indicates that changes in the ST segment do not correlate with infarct size when ATP-sensitive potassium ( $K_{ATP}$ ) channels are manipulated pharmacologically. Because the ATP-sensitive potassium channel is thought to be an end-effector of the early phase of PC,<sup>1</sup> it was suggested that ST-segment changes are not a reliable indicator of a protected state when the distal pathway of PC is interrogated.<sup>24</sup> These data were obtained in the setting of the early phase of PC, and it is unknown whether they are applicable to the late phase, which was the focus of the present investigation. Regardless of this, other studies by the same group have demonstrated that the magnitude of the ST-segment shift accurately reflects the presence and magnitude of the infarct size limitation afforded by the early phase of either ischemic<sup>25</sup> or pharmacological<sup>26</sup> PC, indicating that the ST-segment shift is a valid marker of PC when the proximal (triggering) events of the PC cascade (such as the induction of PC by NTG) are examined. Importantly, studies in patients undergoing PTCA have shown that the ST-segment shift correlates with both metabolic and contractile parameters of myocardial ischemia (that is, with the magnitude of lactate production<sup>15,18</sup> and regional wall motion abnormalities<sup>17</sup>). The present finding that NTG pretreatment alleviated the severity of mechanical dysfunction (Figure 2) provides an index of cardioprotection that is completely independent of the ST-segment voltage.

In conclusion, this study reveals a new, heretofore unappreciated action of nitrates. The notion that in addition to their immediate anti-ischemic effects, nitrates can also trigger a long-lasting adaptation that renders the heart resistant to ischemia at a distance of 24 hours suggests novel therapeutic applications of these agents. Thus far, nitrates have been used mainly for their antianginal and preload-reducing properties. The present findings support the novel idea that these drugs may also be useful for the prophylaxis of ischemic myocardial injury. Such an effect could be as important as, or possibly even more important than, their short-term effects. Most agents that elicit a late PC-like protection in experimental animals are not clinically applicable for various rea-

sons.<sup>4–9</sup> In contrast, nitrates are generally well tolerated. Accordingly, the present results provide a rationale for investigating the effectiveness of nitrates as a PC-mimetic therapy in patients with coronary artery disease. In the clinical trials that have examined the effect of nitrates in acute coronary syndromes, treatment was started either during or immediately after the index ischemic insult.<sup>27,28</sup> We suggest that it might be fruitful to re-explore the role of nitrate therapy given before the onset of ischemia.

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