Preconditioning Effect during Coronary Angioplasty in Patients with Stable Angina Pectoris

Kenya Sakai, Togo Yamagata, Hiroki Teragawa, Hideo Matsuura and Kazuaki Chayama

Abstract

Objective To determine whether collateral recruitment is involved in the preconditioning effect on the electrocardiogram, chest symptoms, and lactate metabolism during coronary angioplasty in patients with stable angina pectoris.

Methods and Patients Sixteen patients with stable angina pectoris underwent three consecutive 2-min balloon inflations 5-min apart. The greatest ST elevation (ASTmax), the sum of ST elevations in all leads (ΣST), and QT dispersion (QTd) were measured at the end of each balloon inflation. Chest pain score was evaluated on a scale ranging from no pain (0) to the most severe pain (10). Lactate extraction ratio (LER) was determined by simultaneous blood sampling from the aorta and the coronary sinus. Collateral flow index (CFI) was derived from simultaneous measurements of mean aortic pressure and coronary wedge pressure obtained from a pressure guidewire during balloon inflation.

Results Significant decreases were noted in ASTmax (3.3±2.1 vs. 3.0±1.9 vs. 2.6±1.8 mm, p<0.01), ΣST (9.7±7.2 vs. 8.5±6.1 vs. 6.9±5.3 mm, p<0.01), QTd (55.3±13.8 vs. 46.9±9.0 vs. 42.5±10.0 ms, p<0.01), and chest pain score (4.3±3.1 vs. 2.8±2.6 vs. 1.4±1.5, p<0.01) during the three sequential balloon inflations. LER significantly increased (-55.5±47.8 vs. -36.7±34.3 vs. -19.6±26.2%, p<0.01), indicating decreased lactate production. No significant difference was observed in CFI (0.16±0.10 vs. 0.15±0.10 vs. 0.15±0.10).

Conclusion Repeated balloon inflations during coronary angioplasty elicited a preconditioning effect on ST-segment shift, QT dispersion, chest pain, and lactate production that does not involve collateral recruitment.

(International Medicine 41: 509–515, 2002)

Key words: collateral recruitment, ST-segment, QT dispersion, lactate

Introduction

Under optimal conditions, repeated brief ischemia and reperfusion induce a powerful endogenous protective effect on the myocardium against the subsequent prolonged ischemia. Since the introduction of this phenomenon known as ischemic preconditioning by Murry et al in 1986 (1), its mechanisms and clinical implications have been investigated in great detail. Changes in the electrocardiogram (ECG) and chest symptoms observed during coronary angioplasty in patients with stable angina pectoris are considered to be models of clinical manifestations of ischemic preconditioning. That is, many studies have shown that ST-segment shift and chest pain occurring during initial balloon inflation tend to diminish with subsequent balloon inflations. Lactate production during coronary angioplasty was reported to decrease with repeated balloon inflations (2), reflecting metabolic changes related to the preconditioned state. QT dispersion was also reported to decrease with repeated balloon inflations (3) as an electrophysiologic manifestation of preconditioning. However, these various adaptations to ischemia associated with repeated balloon inflations could conceivably result from progressive collateral recruitment as well as ischemic preconditioning.

Although we have revealed that both balloon-induced preconditioning and nicorandil-induced preconditioning during coronary angioplasty are independent of collateral recruitment (4), we have evaluated only ST-segment shift and chest pain as an index of the preconditioning effect.

In the present study, we examined the preconditioning effect on lactate metabolism and QT dispersion during coronary angioplasty in addition to assessment of collateral recruitment using a pressure guidewire.

Methods

Study population

The study population consisted of 16 patients (14 men and 2 women; age range, 39 to 76 years; mean age, 66±10 years) with clinically stable angina pectoris undergoing elective coronary angioplasty because of symptoms related to coronary ar-

From the First Department of Internal Medicine, Hiroshima University School of Medicine, Hiroshima
Received for publication September 3, 2001; Accepted for publication January 22, 2002
Reprint requests should be addressed to Dr. Kenya Sakai, the First Department of Internal Medicine, Hiroshima University School of Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551

Internal Medicine Vol. 41, No. 7 (July 2002) 509
Coronary angioplasty was performed using the standard technique. A Goodale-Lubin catheter was used to sample blood for the measurement of lactate. Collateral blood flow index was assessed during balloon inflation. At the end of each inflation, the intensity of chest pain was assessed using a visual analog scale. Patients were informed that they might develop chest pain during balloon inflation. The greatest ST elevation (ASTmax) and the sum of ST elevations in all leads (ΣST) were determined, with both of these expressed in millimeters (1 mm=0.1 mV). The QT interval was manually measured from ECG recordings before angioplasty and could not be measured accurately were excluded from analysis. The mean QT interval of three consecutive cycles in each ECG lead was taken as the QT interval. QT dispersion was defined as the difference between maximal and minimal QT interval measurements occurring in any of the ECG leads. All ECG measurements were performed by a cardiologist who had no knowledge of the study protocol.

**Assessment of chest pain**

At the beginning of the coronary angioplasty procedure, patients were informed that they might develop chest pain during balloon inflation. The intensity of anginal pain was assessed using a visual analog scale. 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).

**Blood sampling**

A Goodale-Lubin catheter was used to sample blood for the measurement of lactate. The balloon catheter was then placed across the lesion. Balloon size was selected according to the 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 the first, second, and third inflations was identical with nominal pressure. During each interval between inflations, the balloon was withdrawn into the guiding catheter with the pressure guidewire remaining across the lesion. 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 further inflations or stent implantation were based on coronary angiographic findings after the third inflation.

**Study protocol**

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 hours 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 or right coronary artery, coronary angiograms were obtained using nonionic contrast medium. In case of a stenotic lesion within the left coronary artery, a 6Fr coronary sinus catheter (Goodale-Lubin; Medtronic, Danvers, MA) was advanced through the right internal jugular vein to the coronary sinus before angioplasty. Coronary angioplasty was performed using the standard technique via the 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; RAJI Medical Systems, Uppsala, Sweden) was positioned distal to the stenosis to be dilated. The balloon catheter was then placed across the lesion. Balloon size was selected according to the 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 the first, second, and third inflations was identical with nominal pressure. During each interval between inflations, the balloon was withdrawn into the guiding catheter with the pressure guidewire remaining across the lesion. 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 further 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, Texas). 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 greatest ST elevation (ASTmax) and the sum of ST elevations in all leads (ΣST) were determined, with both of these expressed in millimeters (1 mm=0.1 mV). The QT interval was measured from ECG recordings before angioplasty and at the end of each balloon inflation. QT interval was manually measured from the onset of the QRS complex to the end of the T wave, defined as its return to baseline. If a U wave was present, the QT interval was measured at the nadir of the curve between the T and U waves. ECG leads in which the QT interval could not be measured accurately were excluded from analysis. The mean QT interval of three consecutive cycles in each ECG lead was taken as the QT interval. QT dispersion was defined as the difference between maximal and minimal QT interval measurements occurring in any of the ECG leads. All ECG measurements were performed by a cardiologist who had no knowledge of the study protocol.

**Figure 1. Flow chart detailing study protocol.**
ostium of the middle cardiac vein where lactate production caused by balloon occlusion of the right coronary artery is reflected. The catheter tip was carefully observed to maintain the same position throughout the study. Simultaneous blood sampling from the aorta and the coronary sinus were performed 30 seconds after each balloon deflation. Lactate extraction ratio (LER) was calculated according to the following formula: LER (%) = [(arterial lactate concentration (in the sample obtained via the guiding catheter) – coronary venous lactate concentration (in the sample obtained via the coronary sinus catheter)] / arterial lactate concentration × 100.

**Assessment of collateral recruitment**

To assess the influence of invisible collateral recruitment during balloon inflation, a pressure monitoring guidewire was used. Collateral flow index (CFI) was calculated as the ratio of mean coronary wedge pressure to mean aortic pressure (10). Higher ratios indicate more fully developed collateral recruitment in the ischemic myocardium. 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 the Fisher’s test was used for comparison between the three inflations. A p value<0.05 was considered statistically significant.

**Results**

**Patient characteristics**

The clinical characteristics of patients in the study are summarized in Table 1. The stenotic lesion was located within the left anterior descending coronary artery in 9 patients, the left circumflex coronary artery in 3 patients, and the right coronary artery in 4 patients. Stenosis severity before angioplasty was 80±6%, based on the use of quantitative coronary angiography.

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) 66±10</td>
</tr>
<tr>
<td>Male/female (n) 14/2</td>
</tr>
<tr>
<td>Coronary artery lesion (n)</td>
</tr>
<tr>
<td>LAD 9</td>
</tr>
<tr>
<td>LCx 3</td>
</tr>
<tr>
<td>RCA 4</td>
</tr>
<tr>
<td>Stenosis severity (%) 80±6</td>
</tr>
<tr>
<td>Hypertension (n) 10</td>
</tr>
<tr>
<td>Hypercholesterolemia (n) 8</td>
</tr>
<tr>
<td>Diabetes mellitus (n) 4</td>
</tr>
<tr>
<td>Smoking (n) 4</td>
</tr>
<tr>
<td>LAD: left anterior descending coronary artery, LCx: left circumflex coronary artery, RCA: right coronary artery.</td>
</tr>
</tbody>
</table>

**Coronary angioplasty**

Three 2-min balloon inflations separated by a 5-min interval were performed successfully in all 16 patients (residual stenosis<50%). The average balloon size was 2.6±0.3 mm in diameter. Heart rate and arterial blood pressure did not differ during the three inflations (data not shown). Stent implantation was performed in 6 patients.

**ST-segment shift**

ST-segment elevation during balloon inflation was exhibited in 14 of the 16 patients. ST-segment depression during balloon inflation was not exhibited in any patient. Elevation was similar during the three sequential inflations in 1 of the 14 patients, but did not increase in any of the patients. Both ΔSTmax and ΣST showed the highest values at the end of balloon inflation during each of the three inflations. The ΔSTmax was 3.3±2.1, 3.0±1.9, and 2.6±1.8 mm at the first, second and third inflations, respectively, representing a significant decrease with the repeated balloon inflations (p<0.01, Fig. 2). The ΣST was 9.7±7.2, 8.5±6.1, and 6.9±5.3 mm at the first, second, and third inflations, respectively, again showing a significant decrease with the repeated balloon inflations (p<0.01, Fig. 2).

**QT dispersion**

The average maximal QT interval was 475.2±38.1, 478.3±37.3, 476.5±35.4, and 475.5±36.6 ms before angioplasty, at the first, second, and third inflations, respectively. The average minimal QT interval was 438.4±33.5, 423.0±34.5, 429.7±33.0, and 433.0±34.2 ms at the same four time points. And average QT dispersion was 36.8±12.3, 55.3±13.8, 46.9±9.0, and 42.5±10.0 ms at the same four time points, representing a significant decrease with the repeated balloon inflations (p<0.01, Fig. 2). The gradual decrease in QT dispersion during the three inflations resulted mainly from gradual lengthening of the shortened minimal QT interval induced by balloon inflation.

**Chest pain score**

Chest pain during balloon inflation was observed in 14 of the 16 patients. Pain was similar during the three sequential inflations in 3 of the 14 patients, but did not worsen in any patients. Chest pain score representing the intensity of anginal pain was 4.3±3.1, 2.8±2.6, and 1.4±1.5 at the first, second, and third inflations, respectively, showing a significant decrease with the repeated balloon inflations (p<0.01, Fig. 2).

**Lactate extraction ratio**

Lactate extraction ratio (LER) was calculated 30 seconds after each balloon deflation since lactate concentrations in the coronary sinus showed a slight rise during balloon inflation and a large rise immediately after balloon deflation (data not shown). Blood sampling for measurement of lactate was performed in 12 of the 16 patients. LER was −55.5±47.8, −36.7±34.3, and −19.6±26.2% at 30 seconds after the first, second, and third deflations, respectively, representing a significant increase with the repeated balloon inflations (p<0.01,
Figure 2. Changes in ΔSTmax (upper left), ΣST (upper right), QT dispersion (lower left), and chest pain score (lower right) associated with balloon inflation during coronary angioplasty.

Figure 3. Change in lactate extraction ratio associated with balloon inflation during coronary angioplasty.

Figure 4. Change in collateral flow index associated with balloon inflation during coronary angioplasty.
Preconditioning during Angioplasty

Fig. 3). These data, in turn, showed a decrease in lactate production during the three inflations.

**Collateral flow index**

The pressure guidewire was kept across the lesion in all patients and intracoronary pressure measurements were completed successfully. Collateral flow index (CFI) was 0.16±0.10, 0.15±0.10, and 0.15±0.10 at the first, second, and third inflations, respectively. No significant differences in CFI were evident between the three inflations (Fig. 4), indicating that collateral recruitment did not develop during the series of balloon inflations. In addition, individual values of CFI were insufficient for collateral recruitment during balloon inflation to contribute to myocardial tolerance of ischemia.

**Discussion**

The present results indicate that electrocardiographic, clinical, and metabolic responses to repeated balloon inflations during coronary angioplasty in patients with stable angina pectoris result from ischemic preconditioning not involving collateral recruitment.

Billinger et al (11) showed the relation of collateral recruitment to preconditioning using a pressure guidewire in an angioplasty protocol similar to that in the present study. Collateral flow indexes in their study were 0.13±0.11, 0.15±0.10, and 0.19±0.10 at the first, second, and third inflations, respectively. They concluded that myocardial tolerance to repetitive ischemia was closely related to collateral recruitment. Their data differ from ours, possibly because some patients with angiographically visible collaterals were included in that study. The degree of preinterventional angiographic collateral, according to the classification of Rentrop et al (12), was 0 (no filling of collateral vessels) in our study, while it was 1.0±0.7 in their study. Although the conflicting results may be due to the difference in baseline collateral circulation, they showed that further collateral recruitment does occur during repeated balloon inflations.

Coronary angiography for collateral assessment during balloon inflation was not performed in the present investigation. van Liebergen et al (13) reported a relationship between angiographic presence of collateral vessels during balloon inflation and the coronary wedge/aortic pressure ratio (Pw/Pao). 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 Pw/Pao is a better marker of functional significance of collateral vessels than findings by coronary angiography. Accordingly, the use of a pressure guidewire is a valid method for evaluating collateral recruitment during balloon inflation. We found that collateral recruitment is functionally insignificant according to the values of collateral flow index that we obtained.

Birincioglu et al (14) showed that the mitochondrial K_{ATP} channel protects the myocardium, while the sarcolemmal channel is responsible for changes in ST elevation. These investigators concluded that changes in ST segment elevation therefore do not necessarily reflect the state of myocardial protection. However, a discrepancy between ST-segment shift and other indexes such as chest pain response or lactate production during the three balloon inflations was not recognized in the present study. It has been shown that the change in the ST-segment correlates with metabolic and contractile parameters of myocardial ischemia during coronary angioplasty (2, 15). Matsubara et al (8) reported that nicorandil, a K_{ATP} channel opener, suppresses ST-segment elevation during coronary angioplasty, suggesting a pharmacological preconditioning effect. Therefore, some degree of caution may be necessary in interpreting ST-segment changes.

Increased QT dispersion has been reported to be associated with the incidence of ventricular arrhythmias (16–18). We measured QT dispersion as an index of antiarrhythmic effects of ischemic preconditioning. Okishige et al (3) reported that QT dispersion is increased by balloon inflation during coronary angioplasty while repeated balloon inflations cause reduction in QT dispersion. They suggested a relationship between QT dispersion and ischemic preconditioning. While our results are similar to theirs, they measured the QT interval during reperfusion after balloon deflation. We measured the QT interval immediately at the end of balloon inflation, representing the most ischemic time point with maximal QT dispersion. In fact, QT dispersion increased at the end of balloon inflation more than at any other time point during the subsequent 5-min interval in the present study (data not shown). Okishige et al (3) reported that the decrease in QT dispersion with repeated balloon inflations was mainly due to shortening of the maximal QT interval rather than to lengthening of the minimal QT interval, while the latter change was responsible for the decrease in our study. Previous studies showed that the minimal QT interval was reduced by acute ischemia during coronary angioplasty (19–22). Therefore, the reduced minimal QT interval immediately following balloon inflation would be expected to lengthen during the subsequent 5-min interval. These differing results may be due to the different time points in measuring the QT interval.

Our study design included several limitations. The stenotic lesion was located in one of the three major coronary arteries, so some possible differences in ST-segment shift and lactate production related to the specific lesion site were not considered. The patients with the stenotic lesion located within the proximal left anterior descending coronary artery may have to be enrolled as entry criteria. However, recent studies concerning the angioplasty model of preconditioning do not necessarily follow such selection criteria (11, 15, 23, 24). The ischemic area associated with balloon occlusion of the left anterior descending coronary artery also may vary. Since coronary angiography was not performed during the first or second 5-min interval, whether or not similar dilation was achieved during the three intervals is unknown. A slight difference in stenosis severity may influence the preconditioning effect. ST-segment shift and QT interval were measured manually, so the amount of error may have been relatively large. Particular difficulty...
occurs in accurately determining the QT interval in every lead. Automatic measurement with high precision would be desirable. The precise intracoronary pressure-derived collateral flow index is calculated as the ratio between the coronary wedge minus central venous pressure divided by the mean aortic minus central venous pressure. The central venous pressure is low and can be omitted (10). Some investigators estimate the central venous pressure to be equal to 0 mm Hg (13, 24), while others use an estimated value of 5 mm Hg (11, 25). Direct measurement of central venous pressure might be preferable. Finally, the present patients had various coronary risk factors such as hypertension or diabetes mellitus, and their medical therapy was not uniform. These additional factors may have influenced our results (26–29).

The mechanisms of preconditioning are complex and were not elucidated in the present study. Recent reports have demonstrated that activation of protein kinase C and the opening of $K_{ATP}$ channels are important in ischemic preconditioning (30–35). In particular, mitochondrial $K_{ATP}$ channels appear to be the end-effectors of signal transduction pathways in preconditioning. Studies are needed to further explore the detailed mechanisms and their clinical implications.

In conclusion, repeated balloon inflations during coronary angioplasty in patients with stable angina pectoris elicited a preconditioning effect on ST-segment shift, QT dispersion, chest pain, and lactate production. These changes were not accompanied by enhanced collateral recruitment.

Acknowledgements: We are grateful to Drs. Hidekazu Hirao, Yukihiro Fukuda, Keiji Matsuda, and Fumiharu Miura of the First Department of Internal Medicine at Hiroshima University for their technical assistance. We also thank Miss Yuko Omura for secretarial assistance.

References

30) Gross GJ, Fryer RM. Mitochondrial $K_{ATP}$ channels: Triggers or distal
Preconditioning during Angioplasty


