Evaluation of Repeated Balloon Inflation in Angioplasty as a Clinical Model of Ischemic Preconditioning

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SUMMARY

Reevaluation of repeated balloon angioplasty as a model of ischemic preconditioning and of the role of collateral circulation and high-frequency electrocardiograms in repeated inflations was carried out. There have been few studies using angioplasty as a model of ischemic preconditioning of the collateral circulation during repeated inflations or of the use of high-frequency electrocardiograms during angioplasty. Twenty patients underwent 3 repeated balloon inflations, each with a duration of more than 138 seconds. During inflation, ipsilateral and contralateral coronary angiography and signal-averaged electrocardiography were performed.

At the 1st inflation, the ST segment gradually increased as the inflation time elapsed. During the 2nd and 3rd inflations, in which ST elevation was nearly equal, the ST segment gradually increased, but it was not as prominent as that at the 1st inflation; thus, the concept that ischemia is gradually ameliorated (adaptation to ischemia) was not documented. Comparison of the maximal ST elevation and ipsilateral and contralateral circulation at each inflation revealed that the ST segment became elevated and the contralateral collateral circulation increased significantly at the 1st inflation compared with those in the control. ST elevation, however decreased significantly and collateral circulation remained unchanged at the 2nd inflation; thus, collateral circulation did not cause the ST elevation decrease. The total root mean square voltage detected by signal averaging decreased significantly only at the 1st inflation. Balloon angioplasty is not always suitable as a model of ischemic preconditioning and collateral circulation is not the cause of ischemic preconditioning. (Jpn Heart J 36: 719–728, 1995)

Key words: Ischemic preconditioning Repeated angioplasty Collateral circulation High-frequency electrocardiograms

The concept of ischemic preconditioning was first articulated experimentally by Murry et al.1) Although it is not possible to observe final sustained ischemia followed by repeated brief ischemia as in experimental procedures during percutaneous transluminal coronary angioplasty in the clinical setting, coro-
nary angioplasty which provokes controlled transient repeated ischemia has been used as a model for production of ischemic preconditioning. Some clinical studies of ischemic preconditioning using percutaneous transluminal coronary angioplasty have been reported. Deutsch et al.\(^2\) reported a clinical, hemodynamic, and metabolic study of 19 patients, including 7 with single vessel anterior descending coronary artery disease who twice underwent 90-second balloon inflation. They found that the severity of ischemia in the 2nd inflation as assessed by body surface ECG and lactate extraction ratio was mild, i.e., adaptation to myocardial ischemia (ischemic preconditioning). Cribier et al.\(^3\) reported a study of intracoronary ECG and collateral circulation detected by contralateral coronary angiography during balloon inflation in 17 patients with isolated left anterior descending coronary artery disease who underwent 180-second balloon inflation 5 times. The serial ST elevation at each repeated inflation showed a significant decrease. The collateral filling at the 1st inflation was markedly less than that at the 4th inflation. Thus, their conclusions were that progressive adaptation to myocardial ischemia (ischemic preconditioning) is present in humans, that sequential episodes of myocardial ischemia are a stimulating factor for the recruitment of collateral channels, and finally, that enhanced collateral circulation might be a mechanism of ischemic preconditioning. Tomai et al.\(^4\) examined whether ischemic preconditioning was prevented by the preadministration of glibenclamide, a selective ATP-sensitive K\(^+\) (K\(_{\text{ATP}}\)) channel blocker, before percutaneous transluminal coronary angioplasty in 20 patients with isolated coronary artery disease. They concluded that ischemic preconditioning was completely abolished by glibenclamide, thus suggesting that ischemic preconditioning was mainly mediated by K\(_{\text{ATP}}\) channels in humans.

Considering this background, we prospectively studied serial changes in ST elevation, collateral circulation, and high-frequency components detected by signal-averaged electrocardiography in patients who underwent consecutive balloon inflation, to clarify whether or not ischemic preconditioning occurs and if the collateral circulation was the genesis of preconditioning in a clinical PTCA model.

**Subjects and Methods**

**Subjects:** The indication for angioplasty was determined by the presence of viable myocardium detected by stress thallium\(^{201}\) myocardial scintigraphy and by positive exercise stress testing. Of 62 patients who underwent contralateral and ipsilateral coronary angiography during balloon inflation, 20 who fulfilled the inclusion criteria given below were included in this study: 1) Presence of proximal segment stenosis with single vessel coronary artery disease with successful
angioplasty leading to less than 25% residual stenosis. 2) Absence of bundle
branch block and intraventricular conduction disturbance was documented by
ECG. 3) The noise level in signal-averaged electrocardiogram during angioplasty
under 0.5 $\mu$V. The 20 patients were classified into two groups, those with and
those without ST elevation (Table). The ST elevation group (Group A) consisted
of 7 patients with a mean age of 50 ± 4.8 years, and the nonelevation group
(Group B) consisted of 13 patients with a mean age of 58.6 ± 9.8 years. The
target site for angioplasty was the left anterior descending coronary artery in 6
patients in Group A and 9 in Group B, whereas the right coronary artery was the
target site in one patient in Group A and 4 in Group B. The mean percent
stenosis was 87.1 ± 7.8% in Group A and 93.6 ± 6.3% in Group B.

**Methods:** After written informed consent was obtained, contralateral and ipsi-
lateral coronary angiography during balloon inflation and angioplasty was per-
formed (Figure 1). Balloon angioplasty was carried out by the usual femoral
approach, using two catheters, one a guiding catheter and the other used for the
contralateral coronary angiography. Body surface 12-lead ECG, signal-averaged
electrocardiography, and contralateral and ipsilateral coronary angiography were
performed to obtain control measurements before balloon inflation. Body surface
12-lead ECG was recorded every 15 seconds throughout the procedure and ST
segment measurement was done 60 ms after the J point. During the balloon
inflation, the ST segment in each inflation was measured from the beginning of
inflation until 60 seconds after the inflation, because the coronary angiography
performed at 60 seconds after inflation would have influenced ST segment analy-
sis. The maximal ST elevation was extracted for comparison among the repeated
inflations. Signal-averaged electrocardiography was recorded by a signal-averag-
The signal averaging recording was begun 30 seconds after the 1st balloon inflation and continued until deflation of the balloon. The signal-averaged electrocardiogram was measured using a 150–250 Hz forward filter, and the filtered QRS duration and root mean square voltage of the total QRS complex were analyzed. Ipsilateral collateral filling from the contralateral artery was graded according to Rentrop’s classification. Ipsilateral collateral circulation was classified into 4 grades according to Rentrop’s classification, when the distal coronary artery of the occluded site was retrogradely perfused. On the other hand, when it was antegrade perfused, the TIMI classification was applied. In cases with both antegrade and retrograde perfusion of ipsilateral collateral filling, the sum of the antegrade and retrograde collaterals was defined as the representation of the ipsilateral collateral flow. Coronary angiography was carried out using 2 to 3 ml of contrast material, at the same rate of injection throughout the study and with the same operator. The degree of chest pain during inflation was assessed using a 10 grade classification. After subjective symptoms had subsided and ECG changes had returned to the preinflation level during the balloon deflation, control signal-averaged electrocardiogram recording was performed again. Thereafter, the same procedures as in the 1st inflation and control sequence were repeated twice.

**Statistics:** The values are expressed as mean ± standard deviation. The significance of difference was evaluated by the analysis of Bonferroni, and significant statistical difference was accepted at $p < 0.05$.

**Results**

**Clinical parameters at angioplasty (Table):** The respective mean inflation
times for Groups A and B were 107 ± 43 and 137 ± 25 seconds at the 1st inflation, 120 ± 49 and 138 ± 23 at the 2nd inflation, and 105 ± 42 and 121 ± 45 at the 3rd inflation; there were no significant differences between the groups or among the inflations. The mean intervals between the 1st and 2nd inflations were 430 ± 325 and 405 ± 244 seconds for Groups A and B, and those between the 2nd and 3rd inflations were 660 ± 396 and 660 ± 390 seconds, respectively, also without significant difference. The chest pain at the 1st inflation in Group A was significantly \( p < 0.01 \) more severe than that in Group B, and in both groups the chest pain was diminished at the 2nd and 3rd inflations. The degree of chest pain gradually decreased with repeated inflation, but the difference was not significant.

The time course of ST elevation in each repeated inflation: The time course of ST changes in Group A in each inflation are shown in Figure 2. During the 1st inflation, the ST segment gradually elevated as the elapsed inflation time increased up to 60 seconds. During the 2nd inflation, the elevation of the ST segment was not as prominent compared with that at the same elapsed time in the 1st inflation. At the 3rd inflation, the ST elevation remained at the same level as that seen in the 2nd inflation.

The collateral recruitment by serial inflation and body surface ECG ST changes (Figure 3): Compared to the control value, the ST segment showed significant \( p < 0.05 \) elevation at the 1st inflation in Group A. This group also showed a significant \( p < 0.05 \) decrease in ST elevation at the 2nd inflation compared with that at the 1st, but no further decrease was found at the 3rd inflation. On the other hand, the ST segment in Group B did not show significant changes at any time throughout the serial inflation. In Group A patients, the collateral circulation from the contralateral artery was significantly \( p < 0.01 \) increased at the 1st inflation compared to the control value, but it remained at
Figure 3. Serial changes in ST segment in body surface ECG and in ipsilateral and contralateral collateral circulation at each repeated inflation.

the same level at the 2nd inflation when the ST elevation was decreased. The collateral circulation from the contralateral artery in Group B patients remained significantly ($p < 0.05$) higher compared with that in Group A patients at all times from the control measurement to the 3rd inflation. The collateral circulation from the ipsilateral artery did not show any prominent changes similar to those seen for the contralateral artery, and the ipsilateral collateral circulation remained almost negligible throughout the study.

Changes in high-frequency component detected by signal-averaged electrocardiography (Figure 4): In both groups, filtered QRS duration did not
change significantly at any time throughout the procedure. The root mean square voltage in Group A was significantly \((p < 0.01)\) decreased at the 1st inflation compared with the control value, but no other significant change was observed either after the 1st inflation in Group A or at any time in Group B.

**DISCUSSION**

In the patients with ST elevation in this study, the ST elevation was decreased significantly only at the 2nd inflation, and thereafter no further decrease was found. The collateral circulation was increased only at the 1st inflation and no additional increase was documented during subsequent inflations, even though the ST elevation showed a significant decrease at the 2nd inflation. Thus, no gradual progressive decrease in ST elevation such as that which Cribier observed and named ischemic preconditioning was seen in this study. Furthermore, collateral circulation was not the cause of ischemic preconditioning.

**Percutaneous transluminal coronary angioplasty as a clinical model of ischemic preconditioning and the role of collateral circulation:** In an ex-
Experimental model of ischemic preconditioning, serial short ischemic episodes lasting 5 minutes were applied before sustained ischemia lasting as long as 60 minutes. During the sustained ischemia, the severity of ischemia was mild, and the area of infarction demonstrated by pathological examination was also slight compared with that in the nonpreconditioned group. In clinical percutaneous transluminal coronary angioplasty, the last balloon inflation is considered to be analogous to the sustained ischemia induced in the animal model of ischemic preconditioning, although long-lasting ischemia like that produced experimentally is not produced in this procedure.

The reports which were published prior to the advent of the concept of ischemic preconditioning indicated no progressive decrease in ischemia as assessed by body surface ECG and lactate metabolism, though the balloon inflation time was short. Zalewski et al performed 3 balloon inflations, each as long as 60 seconds, and found similar degrees of ST elevation in all 3. Serruys et al applied 4 to 6 balloon inflations (mean duration, 51 ± 12 seconds) and found that the arteriovenous lactate difference was not ameliorated but rather was constant from the 1st to 5th inflation. Hill et al reported a study of collateral circulation from contralateral and ipsilateral arteries during 10 repeated inflations, although the inflation times were short, each lasting 20 to 30 seconds. They concluded that there was neither a decrease in ST elevation nor augmentation of collateral filling. In none of the 3 studies was a progressive decrease in ischemia found, although the inflation time was short.

In contrast, there are 3 reports, which were published after the concept of ischemic preconditioning had been introduced, concerning studies in which percutaneous transluminal coronary angioplasty was used to effect ischemic preconditioning. Of the 3 studies, only in that by Cribier was inflation applied more than twice; in the other two inflation was applied twice. Cribier carried out 5 inflations, each lasting 3 minutes, and documented a progressive decrease in intracoronary ST elevation and augmentation of collateral circulation from the 1st to the 4th inflation.

In this study, neither a progressive decrease in ST elevation on body surface ECG nor an increase in collateral circulation at each repeated inflation lasting from 105 to 138 seconds was detected; thus, the phenomenon of ischemic preconditioning which has been observed experimentally was not found. However, when the analysis is limited only to the 1st and 2nd procedures, ST elevation was decreased; thus a phenomenon somewhat comparable to ischemic preconditioning might be postulated. Even if we consider this concept a possibility, collateral circulation was not the cause of the decrease in ST elevation and therefore not the cause of ischemic preconditioning.

**The changes in high-frequency components:** Abboud et al, who recorded
signal-averaged electrocardiograms and analyzed the total QRS complex of averaged electrocardiograms during balloon inflation, found that high-frequency components measured by a 150–250 Hz filter decreased and a reduced amplitude zone developed. They speculated that the decrease was caused by shifting of high-frequency potentials to low-frequency components. In our study, the root mean square voltage in Group A significantly decreased in parallel with ST segment elevation only at the 1st inflation; however, the root mean square voltage at the 2nd inflation did not increase in parallel with the decrease in ST elevation. In addition, neither the root mean square voltage in Group B nor the filtered QRS duration in either group changed significantly. Although Abboud asserted that the high-frequency components were a sensitive marker for detecting transient ischemia, our data do not support this concept. This discrepancy may be due to the influence of coronary angiography, which was performed during recording of signal-averaged electrocardiography, the patients selected, and the device used for signal-averaging.

**Study limitations:** Patients with myocardial infarction were included in our study groups. However, all of the patients with infarction had postinfarction angina and showed slight wall motion abnormalities visualized by left ventriculography, which revealed normal to hypokinetic wall motion at the infarcted ischemic region. In addition, thallium stress myocardial scintigraphy disclosed the presence of viable myocardium. Furthermore, baseline ECG in patients with postinfarction angina did not reveal ST elevation, but Q wave or poor R wave progression was seen in all patients. Accordingly, patients with postinfarction angina in this study were nearly equivalent to those with ordinary effort angina. Moreover, the relation between infarct-related target coronary artery and collateral circulation in patients with postinfarction was similar to that in those with effort angina. Considering all the above reasons, the patients selected for participation in this study should not have led to a biased result and we therefore consider the validity of the conclusion derived from this study to be comparable to that in a study of patients without myocardial infarction.

**REFERENCES**


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