Evidence of a Cellular Protective Effect by Antecedent Angina Independent of Collateral Flow Recruitment During Coronary Angioplasty in Humans

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The main aim of this study was to elucidate whether the beneficial effect of antecedent angina is a cellular protective effect or the result of an increase of collateral flow. Of 42 patients with angina who underwent percutaneous transluminal coronary angioplasty (PTCA) for proximal left anterior descending artery (LAD) stenosis, 22 had experienced antecedent anginal pain (AP) within 7 days prior to PTCA. 99mTc-sestamibi was injected during balloon inflation, and quantitative analysis of ischemic severity during coronary occlusion was calculated (SS). An electrocardiogram was recorded during ballooning to calculate the sum of ST elevation (ΔST). ΔST was significantly reduced in patients with AP compared with patients without AP (1.88±0.89 mV vs 1.18±0.74 mV, p=0.0088); however, no difference was observed in defect severity. A close correlation was observed between SS and ΔST in both groups. The multivariate regression model demonstrated that both a large SS (p<0.0001) and the absence of preceding AP (p=0.001) were significantly related to the elevation of ΔST.

Recent angina can render the myocardium more resistant to subsequent ischemia during angioplasty and is true preconditioning rather than simply an increase of flow. (Circ J 2002; 66: 741–745)

Key Words: Angina pectoris; Collateral flow; Coronary angioplasty; Ischemic preconditioning; Myocardial perfusion

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Experimental animal studies suggest that repetitive brief coronary occlusions render the heart resistant to subsequent episodes of myocardial ischemia, a phenomenon known as ischemic preconditioning. Clinically, angina is the most commonly encountered manifestation of reversible myocardial ischemia and frequently occurs in patients prior to an infarction. A number of relatively small studies have suggested that antecedent angina may afford some degree of myocardial protection but whether this effect is a cellular protective response against ischemia (ischemic preconditioning) or is the result of recruiting collateral flow is still unknown. The purpose of this study was to use a human percutaneous transluminal coronary angioplasty (PTCA) model to determine whether the acute beneficial effect of preceding angina on subsequent ischemia is attributable mainly to true preconditioning or an increase in collateral flow.

Methods

Subjects

After informed consent was obtained, we studied 42 patients with angina who underwent elective coronary angioplasty to proximal left anterior descending artery (LAD) stenosis, with a normal electrocardiogram (ECG) at rest, normal left ventricular wall motion, and without severe stenosis (>75%) in either the right coronary artery or left circumflex artery. Twenty-two patients experienced prior anginal pain within 7 days of the angioplasty procedure (PAP+), and the remainder did not (PAP−). Because the diagnosis for all patients was stable effort angina, only the typical chest squeezing or burning sensation upon effort was defined as AP and atypical chest symptoms such as palpitation were excluded.

Catheterization Procedure

Coronary angioplasty was performed using 7Fr guiding catheters and an over-the-wire dilatation system according to a standard procedure. Ionic contrast medium was used in all patients who were pretreated with aspirin and ticlopidine at least 1 week before the procedure. Antianginal medications including Ca++ antagonists, nitrate and ß-blockers were not discontinued. No patients were taking...
drugs affecting potassium channel function, such as nicorandil, aminophylline, adenosine or glibenclamide. During the procedure, 7,000 U of heparin were administered to all patients to prolong the activated clotting time over 300 s. After placing the guiding catheter and guidewire, the balloon catheter was placed at the lesion immediately after the baseline ECG recording; 2 min of balloon inflation was started and 740 MBq of $^{99m}$Tc-sestamibi was injected via the femoral vein for the quantification of ischemic severity (severity score, SS) (Fig 1).

Quantification of ST Change
A 12-lead surface ECG was monitored throughout the study. Only the ST values in the leads with an ST elevation exceeding 0.1 mV at 80 ms after the J point and 1 min after ballooning were measured and summed for the calculation of $\Delta$ST (Fig 2).

Quantification of Ischemia Severity
$^{99m}$Tc-sestamibi was injected during the initial balloon inflation, and single photon emission computed tomography (SPECT) was performed when the PTCA was completed. SPECT imaging was obtained with a wide field-of-view rotating gamma camera (ZLC-7500, Siemens Co. Ltd) equipped with a low energy, high resolution parallel hole collimator on the 140 KeV photo peak with a 30% window. The camera was rotated through a 180° arc in an elliptical orbit around the patient’s thorax from 40° right anterior oblique to 40° left posterior oblique at 6° increments for 30 s at a time. Data was collected in a 64x64 array with a pixel size of 4.5 mm. Transaxial slices were reconstructed using a filtered back projection algorithm with a Butterworth–Winner filter without attenuation and scatter correction. Short axis tomograms were reconstructed from the transaxial slices. Polar maps of regional distribution of $^{99m}$Tc-sestamibi were displayed and each map was normalized for peak myocardial activity and compared with our normal limits: pixels with tracer uptake less than 2 standard deviations below mean normal values were considered abnormal. Two types of polar maps were generated (Fig 3). In the extent map, the abnormal area on each short axis slice was first multiplied by a correction factor that corrected the spatial distortion and allowed for differences in myocardial slice mass from apex to base. The corrected abnormal area was then summed to obtain the total area of ischemia, expressed as a percent of the left ventricular surface. In the severity map, the value of each pixel was computed such that if the pixel was above the normal limit, it was assigned a value of 1, and if below, it received a fractional value linearly dependent on how far it fell below the normal limit. Therefore, the SS represented the degree of abnormality, which we regarded as the severity of ischemia, and was used for the quantification of flow to the ischemic zone.

Statistical Analysis
Statistical analysis was performed using Statview Version 5.0 software (Abacus Concepts, Calabasus, CA, USA). For a comparison of the mean values, the differences in $\Delta$ST and SS between the 2 groups were analyzed using the non-paired t test. A multivariate regression model was used to test the significance of PAP independent of SS by applying following formula: $\Delta$ST=a SS+b PAP+c. In this model, the value of 1 was applied to the case without PAP, and the value of 0 was applied to the case with PAP. Correlation coefficients were calculated using Pearson’s method. Significant difference was defined at p<0.05.

Results
Characteristics of Each Patient Group
The clinical, and anatomical features of the patients in the 2 groups are summarized and presented in Table 1. The interval between the last attack of angina and PTCA in the patients with PAP and those without was 2.8±1.3 days and 10.9±2.7 days, respectively. Although the frequency of anginal pain within 1 month was not significantly different between 2 groups, only the patients in the PAP+ group experienced pain within 7 days. The frequency of anginal pain within 2 days prior to angioplasty was 1.0±0.5 times and within 7 days prior was 2.1±0.9 times in the group with PAP+ group. Of note is that stenoses of the target lesions prior to coronary angioplasty were significantly more severe in the patients with PAP than in the those without. As for the prescribed medication, only b-blockers were prescribed slightly more in the PAP+ group than the PAP- group. There were no differences in the doses of nitrate and Ca antagonist between the groups. Coronary angioplasty was successfully performed in all 42 patients and all procedures were free of complications, without ECG or enzymatic evidence of myocardial injury.
Difference in ST Elevation

ΔST ranged from 0.25 mV to 3.40 mV (mean, 1.88±0.89) in the group without PAP, and from 0 to 2.80 mV (mean, 1.18±0.74) in the group with PAP, which was statistically significant (Fig 4).

Difference in theSeverity of Ischemia

The SS of 99mTc-sestamibi imaging ranged from 16.3 to 136.5 (mean, 79.1±34.1) in the group without PAP, and from 1.06 to 181.9 (mean, 75.5±45.9) in the group with PAP, which was not statistically significant (Fig 5).

Difference in the Relationship Between ST Elevation and Severity of Ischemia

A close correlation was observed between SS and ΔST in both groups (Fig 6) and multiple linear regression analysis yielded a significant relation between ΔST and recent preceding angina, as well as the SS (ΔST=0.014×SS+0.646×PAP+0.112, standardized correlation coefficient and p value; SS: 0.649 p<0.0001, PAP: 0.371 p=0.001). These results suggest a cellular protective effect against ischemia by preceding angina.
Discussion

This study clearly demonstrates 2 important points. First, the degree of ST elevation varies widely even if the patients are stratified according to coronary anatomy such as the proximal LAD lesions. This variation results from the differences in ischemia severity, especially in patients without preceding angina. In other words, the degree of ST elevation can be used as an index of the severity of ischemia in this patient population. Second, and more importantly, the occurrence of angina within 1 week prior to angioplasty induced myocardial cellular resistance to subsequent ischemia that is not attributable to an increase of collateral flow.

Assessment of Myocardial Perfusion During Coronary Angioplasty by 99mTc-Sestamibi

99mTc-sestamibi is a well known myocardial perfusion imaging tracer that is widely used for the assessment of the extent of myocardial ischemia and infarction.9,10 99mTc-sestamibi because it remains relatively fixed in myocardial cells after initial extraction, with minimum delayed redistribution. Therefore, it can be used to delineate collateral flow relative to non-obstructed myocardium and the distribution of the occluded artery during balloon inflation. Restoration of hyperemic reperfusion flow after balloon deflation does not significantly alter the original distribution of the tracer when injected during coronary occlusion, as demonstrated by Sinuses and De Coster with open-chest dogs.11,12 The use of 99mTc-Sestamibi imaging as a measure of myocardial ischemia severity during coronary occlusion not only in the setting of acute coronary syndrome but also during controlled coronary artery occlusion as in our model, has been validated.13 Furthermore, we recently demonstrated that the extent and severity of the defect in myocardial perfusion of the territory of the occluded artery are highly correlated with collateral flow reserve, which is a theoretically and clinically well validated index of collateral circulation calculated from coronary pressure during balloon occlusion and can be used for quantitative assessment of collateral blood flow in conscious humans.14,15

Pfisterer et al.16 studied 25 patients during elective PTCA of a single LAD lesion and found perfusion defects on occlusion images obtained using 99mTc-sestamibi. They found significant differences between proximal and distal lesions, and most importantly, the only factor that related to the presence or absence of perfusion defects was the presence of collateral vessels. Haronian et al also demonstrated a discrepancy between the perfusion measurement of the myocardium at risk and the angiographical estimation of the area at risk, and this difference resulted from the degree of recruitment of the collateral channels.17 Our study is also consistent with their findings that angiographically similar coronary lesions may have different functional severities that are highly variable.

ST Segment Change as an Index of Cellular Ischemic Severity

Experimental work suggests that during acute ischemia, the magnitude of ST segment changes reflects the area of ischemia.18 Because both ST segment shift and perfusion abnormality are similarly and simultaneously affected by collateral development, these factors should correlate well with each other. In the present study, the patients without angina within 7 days prior to angioplasty did show a good correlation, but there was deterioration of this correlation in the patients with preceding angina. This finding may stem from a variable degree of preconditioning of the myocardium by the recent anginal episodes resulting in variable metabolic consequences. Steg et al also demonstrated that ST segment changes are primarily a reflection of the severity of ischemia and there is some discrepancy with the myocardium at risk as assessed by 99mTc-sestamibi.19

Comparison With Previous Studies of the Induction of a Cellular Protective Effect by Preceding Angina

Until now, no previous clinical study concerning the favorable effect of angina prior to acute myocardial infarction or adaptation of ST change during coronary angioplasty could rule out the confounding effect of collateral circulation on cellular protection against ischemia, because definitive data regarding myocardial blood flow during subsequent ischemia were not available. The opening of preformed collateral vessels as a consequence of ischemic stimulus in humans was addressed by Cribier et al.20 In their study, collateral circulation to the ischemic territory was angiographically assessed by visual grading of flow to the LAD during balloon inflation, as well as by measurement of the coronary arterial pressure distal to the inflation balloon. Their results indicated that the adaptation that occurs during PTCA can indeed be explained by increased collateral flow, although it would be premature to rule out any element of a preconditioning-mediated adaptation. That observation strongly suggests that the collateral effect should be eliminated in order to investigate the presence of an ischemic preconditioning effect. Positive21 as well as negative22 results for a favorable effect of preceding ischemia have been reported using angioplasty as the model of repeated episodes of regional ischemia in humans. Negative results of an absence of an adaptation might be caused by the myocardium already being in an adapted state because of a previous ischemic episode. The data from our present study strongly support this hypothesis.

Another major concern regarding the present study results is the difference in the drugs prescribed for each group. The dosages and distribution of anti-anginal medications did not differ and none of the patients received drugs that are associated with preconditioning, such as intravenous administration of nitroglycerin,23 nicorandil,24-26 adenosine,27 glibenclamide28 and others29

Study Limitations

The exposure of patients to ischemic stimulus was judged subjectively and the total ischemic burden prior to angioplasty was not quantified. Previous reports suggest that the majority of ischemic episodes occurring during normal activities are asymptomatic.30 Although we excluded patients who were expected to have a defective anginal warning system because of conditions such as diabetes, old myocardial infarction, and severe multi-vessel disease (only patients with LAD stenosis without significant stenosis in other vessels were studied), this methodological limitation may underestimate or overestimate the true ischemic burden. Moreover, only chest burning sensation and pain during physical activity were defined as anginal attacks in this study and therefore we can not extend this result to other types of chest symptoms such as prodrome before acute myocardial infarction.
Conclusion

Recent antecedent angina in humans can induce a cellular protective effect against subsequent ischemia during coronary angioplasty and is independent of the recruitment of collateral flow.

References