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Electrophysiologic Effects of Ischemic Preconditioning on QT Dispersion During Coronary Angioplasty

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Objectives. **The aim of this study was to examine the effect of ischemic preconditioning on the manner of ventricular repolarization by assessing the change in QT dispersion during coronary angioplasty.**

Background. **QT interval dispersion reflects regional variations in ventricular repolarization and cardiac electrical instability. Previous studies have suggested that increased QT dispersion is associated with an increased incidence of malignant ventricular arrhythmias, whereas brief episodes of myocardial ischemia can render the heart more resistant to subsequent ischemic episodes, a phenomenon called ischemic preconditioning.**

Methods. **To assess the effects of ischemic preconditioning on myocardial repolarization by examining the change in QT dispersion during coronary angioplasty, we studied 47 consecutive patients (39 men and 8 women; mean age 57 ± 16 years). QT dispersion was measured after each balloon inflation during coronary angioplasty. Statistical analysis was performed by using repeated measurement of analysis of variance.**

Results. **There were significant differences in QT dispersion as the number of balloon inflations increased (mean ± SD 52 ± 14, 42 ± 11, 36 ± 9, 31 ± 10 and 29 ± 11 ms, respectively [$p < 0.01$], for the first, second, third, fourth and fifth balloon inflations). The magnitude of decrease in QT dispersion was significant in the first and second balloon inflations, then became insignificant with later inflations.**

Conclusions. **These data indicate that the gradual decrease in QT dispersion provoked by coronary artery occlusion and reperfusion during coronary angioplasty may be associated with electrophysiologic effects of ischemic preconditioning on myocardium in the human heart.**

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Previous studies (1–6) have demonstrated that several brief episodes of myocardial ischemia separated by brief episodes of reflow can render the heart more resistant to subsequent ischemic episodes, a phenomenon that has been called ischemic preconditioning. The mechanism mediating ischemic preconditioning is not known, however, a variety of explanations for its beneficial effects have been proposed. These include the slowing of energy metabolism during ischemia (7), formation of "heat shock" messenger ribonucleic acids that result in rapid transcription to heat shock proteins (8,9), prostaglandin metabolism (10), stimulation of A1 adenosine receptor (11) and an increase in collateral blood flow and development of new collateral channels (12).

Electrophysiologic studies suggest that QT interval prolongation is associated with increased regional heterogeneity of repolarization. Dispersion of repolarization has been proposed (13) as a measure of repolarization heterogeneity, and increased dispersion has been found (14–16) to be associated with an increased incidence of malignant ventricular arrhythmias.

In the present study, we examined whether dispersion of ventricular repolarization may be affected by the effects of ischemic preconditioning provoked during coronary angioplasty.

Methods

Study patients. The study group consisted of 47 patients referred for elective angioplasty of isolated stenotic disease in the relatively large left or right coronary arteries. All patients had clinically stable angina pectoris. Table 1 outlines the demographic features and anatomic details demonstrated at the time of diagnostic angiography. The severity of stenosis was visually assessed by three experienced angiographers. No patients had unstable angina when they underwent coronary angioplasty. Patients with previous myocardial infarction underwent angioplasty ≥1 month after infarction. No patients were taking antiarrhythmic agents other than beta-adrenergic blocking agents at the time of angioplasty.

Study protocol. Percutaneous transluminal coronary angioplasty was performed after written informed consent had

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Table 1. Patient Characteristics of 47 Patients at Time of Diagnostic Coronary Angiography

Age (yr)	57 ± 16
Male/female	39/8
Heart disease	
Prior MI	14
Angina pectoris	33
Coronary artery lesion	
LAD	27
LCx	9
RCA	11

Data presented are mean value ± SD or number of patients. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; RCA = right coronary artery.

been obtained, with use of the Judkins technique and a movable guide wire system. All procedures were performed with nonionic contrast medium (iopamidol, Eisai, Tokyo). Cardioactive medications were not discontinued for the angioplasty procedure. The baseline 12-lead electrocardiogram (ECG) was recorded before the arterial puncture. Standard limb and precordial ECG electrodes were applied and recorded.

With the standard coronary angioplasty procedure, the balloon catheter was placed within the stenosis, and the balloon was inflated for 1 to 2 min. After balloon deflation, an equilibration period of ≥5 min (mean ± SD 11 ± 3.4) was allowed to reestablish the baseline hemodynamic condition. A 12-lead ECG was recorded at each point after balloon deflation during this interval. Subsequent balloon inflations of 2 min were then performed, and 12-lead ECG recording was repeated at each interval ~3 to 5 min after the balloon deflation when the elevated ST segment returned to its baseline. This series of maneuvers was then repeated up to a maximum of five times to attain the clinical end point. Standard 12-lead ECGs were recorded at a paper speed of 25 mm/s. ECG tracings were enlarged by a factor of 2 for accurate measurement of the QT interval of each lead, and were shown in random order to investigators who did not know the angioplasty stage or the clinical data. The point of T wave offset was defined by the return of the T wave to baseline. If a U wave was present, the T wave offset was defined as the nadir between the T and U waves (17). The QT interval was defined as the average of the QT intervals of three consecutive beats in each of the ECG leads. Dispersion of the QT interval was defined as the difference between the maximal and minimal QT interval measurements occurring in any of the 12 leads on a standard ECG. Balloon pressure during inflation was almost identical in each patient. After the last inflation, coronary angiography was completed on the basis of the specific needs of individual patients. Coronary angioplasty was then concluded in accordance with standard clinical criteria. All procedures were carried out successfully (final stenosis <50%), and no complications were encountered.

Statistical analysis. All data are reported as mean value ± SD. The changes in QT dispersion at each inflation and deflation were examined by using a repeated measurement analysis of variance (ANOVA) to assess the correlation between QT dispersion and the number of balloon inflations and deflations. A p value < 0.01 was considered significant.

Results

Study patients. Of the 54 patients enrolled in this study, 7 were excluded because of a poor-quality ECG (n = 5), the presence of bundle branch block (n = 1) or the presence of atrial fibrillation (n = 1). The remaining 47 patients satisfied the entry criteria for this study.

Coronary angioplasty. All 47 patients had coronary angiograms. The coronary lesion was identified within the right coronary artery in 11 patients (23%) and the left coronary artery in 36 (77%). Coronary angioplasty was carried out in 15 patients (32%) with previous myocardial infarction and in 32 patients (68%) with angina pectoris. Total occlusion of the coronary artery was not identified in any case. The procedure was performed in all patients without complications.

ECG analysis. ECG recording was performed approximately a few minutes after deflation of the balloon, at a paper speed of 25 mm/s. The mean QT interval averaged over 12 leads for all patients was 422 ± 39 ms (range 305 to 575). The maximal QT interval, 439 ± 38 ms (range 365 to 575), occurred in a precordial lead in 37 patients (79%) and in a limb lead in 10 (21%). The minimal QT interval, 392 ± 31 ms (range 305 to 505), occurred in a precordial lead in 21 patients (47%) and in a limb lead in 26 (53%). The average QT dispersion for all study patients was 41 ± 18 ms (range 25 to 85).

QT dispersion by angioplasty status. There were significant differences in QT dispersion according to the coronary artery status after each of the five balloon inflations. The average QT dispersion was 25 ± 11 ms in the control state (before angioplasty), whereas it was 52 ± 14, 42 ± 11, 36 ± 9, 31 ± 10 and 29 ± 11 ms, respectively, at the first, second, third, fourth and fifth balloon inflations and deflations, ($p < 0.01$). These differences were manifested as a stepwise decrease in QT dispersion with increasing numbers of balloon inflations and deflations (Fig. 1). There was no significant difference between QT dispersion in the control state and that after the fifth balloon deflation. The average maximal QT interval was 448 ± 82.1, 440 ± 56.2, 428.6 ± 62.1, 422.3 ± 46.7 and 423 ± 81.4 ms and the minimal QT interval was 398.1 ± 93.8, 397.2 ± 58.2, 391.9 ± 68.3 and 398 ± 98.3 ms at the first, second, third, fourth and fifth balloon inflations and deflations, respectively. Therefore, the decrease in QT dispersion was mainly due to shortening of the maximal QT interval rather than to lengthening of the minimal QT interval in almost all cases.

Discussion

Comparison with previous studies. Previous reports (18) demonstrated that the significant effects of ischemic preconditioning could be invoked during coronary angioplasty. Our

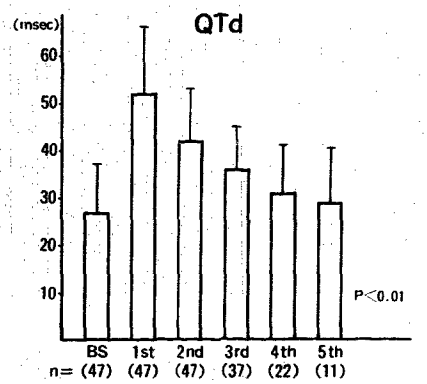

Figure 1. Change in QT dispersion (QTd) from baseline (BS) among patients in the five balloon inflation and deflation groups. The number of patients undergoing each coronary angioplasty procedure is given in parentheses.

interest has been in the possibility that short periods of ischemic stress might have a beneficial influence on the electrophysiologic excitability of the myocardium and a protective effect against the life-threatening ventricular arrhythmias that result from a more prolonged period of coronary artery occlusion, and which are responsible for a large proportion of clinical sudden cardiac deaths.

QT interval dispersion, which approximates the time from the earliest depolarization of the ventricular myocardium to its latest repolarization, and which is measured as interlead variability in the QT interval, has been proposed (13–15) as a marker of heterogeneous repolarization and electrical instability. Heterogeneity in the recovery of ventricular excitability is presumed to increase the propensity for ventricular fibrillation (16). Zareba et al. (19) reported that increased dispersion of ventricular repolarization is associated with a greater likelihood of arrhythmic cardiac death and contributes independently to the risk of arrhythmic cardiac death in patients with coronary artery disease. QT dispersion increases reversibly during ischemia in patients with coronary artery disease (20,21). This increase in dispersion is presumed to result from a combination of a local repolarization abnormality and altered conduction within ischemic areas (17). Moreno et al. (22), examining the effects of successful thrombolytic therapy on QT dispersion in patients after acute myocardial infarction, demonstrated that the therapy significantly reduced QT and JT dispersion in such patients. When the effects of ischemic preconditioning on reperfusion-induced arrhythmias were experimentally examined, the vulnerability to arrhythmias during the second period of reperfusion was found to correlate inversely with the incidence of arrhythmias elicited during the first period (23). This resistance to reperfusion-induced arrhythmias was acquired in a short time but persisted for a relatively long time (≥2 h), and recovery frequently took several days. Taken together, these observations suggest that the electrophysiologic activity of the ventricular myocardium might be modified in the short term by the effects of ischemic preconditioning.

In the present study, we demonstrated that the changes in dispersion of the QT interval observed during the clinical coronary angioplasty procedure might be regarded as the manifestation of electrophysiologic effects of ischemic preconditioning of ventricular myocardium. With increasing numbers of preconditioning occlusions of the coronary artery, the additive effects of ischemic preconditioning became smaller, a finding previously demonstrated in the rat heart (23,24). The effect of preconditioning was most pronounced at the first or second inflation and then gradually attenuated as the number of balloon inflations increased. Hoffmeister et al. (25) speculated that this finding could be explained by a progressive reduction in adenosine triphosphate turnover as a consequence of a progressive reduction in oxygen demand.

Mechanism of antiarrhythmic effects. Regarding the antiarrhythmic effects of ischemic preconditioning, prostacyclin (10), bradykinin (26), and nitric oxide (27) have been proposed experimentally as endogenous myocardial protective substances (28). Shiki and Hearse (23) suggested that a large loss of intracellular potassium may be another possible mechanism of the antiarrhythmic effects of ischemic preconditioning, because this potassium loss combined with extracellular accumulation is suspected (29) to be an important factor in the genesis of ischemia-induced arrhythmias. Other investigators have demonstrated that ischemic preconditioning lessened the degree of acidosis and anaerobic glycolysis during sustained ischemia (30), lessened the increase in intracellular calcium ion during ischemia in the globally ischemic heart (31) and decreased the rate of acidosis during sustained regional ischemia (32). These actions may also contribute to the electrophysiologic effect of ischemic preconditioning. In the present study, the decrease in QT dispersion was due mainly to shortening of the maximal QT interval rather than to lengthening of the minimal QT interval, thus indicating the beneficial effects of ischemic preconditioning on the myocardium in preventing arrhythmias during ischemia. The effect of ischemic preconditioning on subsequent ischemic stress is a complex phenomenon that presumably results from an interplay of multiple factors (33). Further investigation is necessary to clarify the interaction of these factors in exerting the electrophysiologic effect of ischemic preconditioning.

Study limitations. One limitation of this study is the short duration (2 min) of balloon inflation. Several clinical and experimental studies (2,4,34) have demonstrated that 2 min of coronary occlusion is sufficient to obtain significant ischemic preconditioning effects. However, it is not clear whether 2 min of balloon inflation is sufficient to exert the beneficial electrophysiologic effects of ischemic preconditioning.

Second, we did not examine change in the ST segment shift during consecutive balloon inflations as the variable that indicates the occurrence of ischemic preconditioning. However, several previous studies (2,18) have demonstrated that ischemic preconditioning occurs during coronary angioplasty. Our study was based on the premise that ischemic precondi-

tioning must occur during the coronary angioplasty procedure used in this study.

Third, none of our patients had the arrhythmic events usually observed in patients with pathologically increased QT dispersion (15); therefore, it might be difficult to adopt all the results of this study in considering the effects of ischemic preconditioning on electrophysiologic activity, such as QT dispersion in terms of prophylaxis of arrhythmias. Finally, QT interval assessment is not always measurable in every lead, and it may be difficult to determine the various portions necessary for accurate measurement of the QT intervals in certain leads. In this study, QT intervals were evaluable in all except 1 or 2 leads (average 11). Measurement of these intervals with use of an automatic measurement technique is recommended.

Conclusions. Myocardial preconditioning with brief episodes of ischemia and reperfusion exerts electrophysiologic protective effects, as demonstrated by the gradual significant attenuation of QT dispersion during coronary angioplasty.

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