Effect of Prodromal Angina Pectoris on the Infarct Progression in Patients With First ST-Elevation Acute Myocardial Infarction

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Background: Prodromal angina pectoris (AP) has a cardioprotective effect by the mechanism of ischemic preconditioning, and the QRS score on the admission electrocardiogram (ECG) reflects myocardial damage at presentation. This study was undertaken to investigate the effect of prodromal AP on infarct progression after the onset of acute myocardial infarction (AMI).

Methods and Results: The study group comprised 291 patients with a first ST-elevation AMI who underwent coronary angiography within 24 h of symptom onset. QRS score was calculated from the admission ECG. Patients were divided into 3 groups according to elapsed time from onset of AMI to angiography: early group (<2 h), intermediate group (2–6 h) and late group (6–24 h). Prodromal AP was defined as angina occurring 24 h before the onset of AMI. Patients with prodromal AP (n=101; 35%) had a significantly lower QRS score than those without (2.4±2.4 vs 3.2±3.0, P=0.02). In patients without prodromal AP, the QRS score linearly increased as elapsed time increased: 2.6±2.8, 3.0±3.0 and 5.5±2.9 in the early, intermediate and late groups, respectively. In patients with prodromal AP, the QRS score remained low until 6 h after onset and then increased: 2.0±1.8, 2.0±2.1, and 4.1±3.3, respectively.

Conclusions: The findings suggested that prodromal AP might delay infarct progression during the early hours after the onset of AMI and extend the window of time for reperfusion therapy. (Circ J 2010; 74: 1651–1657)

Key Words: Ischemic preconditioning; Prodromal angina pectoris; QRS score; Wavefront phenomenon

The time elapsed from coronary occlusion to reperfusion is 1 of the most important factors that determine the extent of myocardial necrosis.1,2 After coronary occlusion, myocardial necrosis first occurs in the subendocardial region but with increasing duration of the occlusion, irreversible injury progresses as a wavefront toward the subepicardium.3,4 This infarct progression is modified by several factors, including the presence of functioning collateral coronary arteries to the area at risk, myocardial oxygen demands, and ischemic preconditioning. Episodes of transient ischemia protect the myocardium against subsequent prolonged ischemia. Prodromal angina pectoris (AP) has a cardioprotective effect by the mechanism of ischemic preconditioning.5 Experimental studies have demonstrated that ischemic preconditioning delays the progression of myocardial infarction (MI).6,7 However, there are no clinical data on the effect of prodromal AP on progression of MI in humans, because of the difficulty in measuring the extent of myocardial necrosis before reperfusion. Development of Q wave and R-wave regression of the electrocardiogram (ECG) reflects the progression of the infarction process, and the QRS score has been used to estimate the size of myocardial necrosis.8–12 QRS score at presentation is a measure of myocardial damage before reperfusion and predict myocardial salvage and major adverse cardiac events.13,14 This study was undertaken to investigate the effect of prodromal AP on the relationship between time to reperfusion and myocardial necrosis assessed by QRS score before reperfusion in patients with ST-elevation acute MI (AMI).
Methods

Study Patients
This study investigated 291 patients with a first ST-elevation AMI who underwent coronary angiography within 24 h of symptom onset. ST-elevation AMI was diagnosed as chest pain consistent with ongoing myocardial ischemia persisting >30 min and ≥2 mm ST elevation in ≥2 adjacent precordial ECG leads. ECG was recorded after admission and coronary angiography was performed immediately (approximately 30 min in most cases). Patients with ECG signs of left or right ventricular hypertrophy, or left or right bundle branch block, or left anterior or posterior fascicular block, which precluded QRS scoring, were excluded. Serum creatine kinase (CK) was measured every 3 h for ≥24 h and the peak value had to be more than twice the normal upper limit. We divided patients into 3 groups according to time to angiography: the early group was <2 h (n=77), intermediate group 2–6 h (n=170), and late group 6–24 h (n=44).

Angiographic Analysis
The perfusion status of the infarct-related artery was determined in accordance with the Thrombolysis In Myocardial Infarction (TIMI) study classification. An occluded artery was defined as initial TIMI grade 0 or 1 flow. The initial TIMI flow grade was assessed before the initiation of reperfusion therapy. Patients with initial TIMI flow grade 2 or 3 were excluded. Multivessel coronary disease was defined as ≥75% stenosis in 1 or more vessels remote from the infarcted artery. Collateral circulation was considered to be present if partial or complete filling of the infarcted artery distal to the infarct was present. After angiography, 289 patients (99%) underwent primary coronary intervention.

Definition of Prodromal AP
Data were collected on the study form regarding whether patients had ever experienced AP before AMI. Prodromal AP was defined as typical chest pain episode(s) persisting <30 min either at rest or during effort ≤24 h before the onset of AMI. Patients with stable AP were also included if they had chest pain episode(s) ≤24 h before AMI.

QRS Score Analysis
The Selvester QRS-scoring system was used to estimate the extent of myocardial necrosis. We adopted a modified QRS-scoring system described as a 37-criteria and 29-point system. QRS score was calculated as the sum of the points of each lead from the ECG recorded at presentation. High
QRS score means advanced myocardial necrosis and we defined it as a QRS score $\geq 6$ and low QRS score as $<6$ on the admission ECG.

Data Analysis
Clinical data were collected at the time of hospital admission. Statistical analysis was performed with the chi-square test for categorical variables. Analysis of variance and t-test were used to compare continuous variables. Differences were considered significant if the P value was $<0.05$. All data are expressed as mean±SD.

Results
There were 101 patients (35%) with prodromal AP. Table 1 lists the baseline clinical and angiographic characteristics of patients with and without prodromal AP. The baseline characteristics of the early, intermediate and late groups are listed in Table 2. The QRS score at presentation was significantly lower in patients with prodromal AP compared with those without (2.4±2.4 vs 3.2±3.0, $P=0.02$), and prodromal AP was associated with a significantly lower incidence of high QRS score (8.0% vs 18.4%, $P=0.01$) (Figures 1,2). High QRS score was associated with a significantly higher peak CK com-
pared with low QRS score (4,795±2,697 IU/L vs 3,088±2,077 IU/L, P<0.001). A significant difference in peak CK between patients with high and low QRS scores was observed in the early group (5,886±2,512 IU/L vs 2,735±2,021 IU/L, P<0.001), intermediate group (5,114±3,105 IU/L vs 3,415±2,140 IU/L, P=0.003) and late group (4,054±2,162 IU/L vs 2,201±1,404 IU/L, P=0.002). QRS score and the incidence of a high QRS score depend on the time to angiography. QRS score at presentation was 2.4±0.3, 2.6±0.2, and 4.8±0.4 in the early, intermediate, and late groups, respectively (P<0.001) (Figure 3a). The incidence of a high QRS score was 8%, 12% and 39% in each group (P<0.001) (Figure 4a). Figure 3b shows the QRS scores in patients with and without prodromal AP in each group. In the early group, there was no significant difference in the QRS score between patients with and without prodromal AP (2.0±1.8 vs 2.6±2.8, P=0.35). QRS score was significantly lower in patients with prodromal AP in the intermediate group (2.0±2.1 vs 3.0±3.0, P=0.03). In the late group, the QRS score was high regardless of the presence or absence of prodromal AP (4.1±3.3 vs 5.5±2.9, P=0.13). Figure 4b shows incidence of high QRS score in patients with and without prodromal AP in each group. There was no significant difference in the incidence of a high QRS score between patients with or without prodromal AP in the early group (5% vs 9%, P=0.50). The incidence of a high QRS score was significantly lower in patients with prodromal
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AP in the intermediate group (2% vs 17%, P=0.002), and in the late group, both patients with and without prodromal AP showed a high incidence of a high QRS score (30% vs 46%, P=0.28).

Discussion

This study showed that the extent of myocardial necrosis assessed by QRS score before reperfusion was smaller in patients with prodromal AP compared with those without. In patients without prodromal AP, myocardial necrosis assessed by QRS score depended on the time elapsed from symptom onset to angiography. In patients with prodromal AP, however, the QRS score remained low in the early and intermediate groups, and increased only 6h after the onset of AMI (late group). These findings suggested that prodromal AP might delay the progression of myocardial necrosis before reperfusion.

Before the reperfusion era, the Selvester QRS scoring system was developed for estimating myocardial infarct size.\(^8\) The original criteria were later validated by postmortem anatomic studies and modified so that every criterion achieved at least 95% specificity for the presence of MI.\(^9-12\) The modified QRS score has been shown to correlate well with the postmortem anatomically measured size of a single MI. Recently, several studies in AMI patients who underwent re-

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**Figure 4.** Incidence of high QRS score in (a) each time-to-angiography group and (b) patients with and without prodromal angina pectoris in each group.
perfusion therapy have shown significant correlation between the QRS score and imaging modalities, such as radionuclide imaging, echocardiography, and contrast-enhanced cardiac magnetic resonance (ceCMR). A good correlation between ceCMR and the Selvester QRS score estimation of infarct size has been reported in patients 1 week following reperfused AMI. Although there is not a clinical study that has evaluated the relationship between QRS score on admission ECG and imaging modalities for estimating myocardial necrosis before reperfusion therapy in AMI patients, the QRS score on admission has been reported to provide important information for predicting myocardial salvage and 30-day mortality with reperfusion therapy. We adopted a modified QRS scoring system as a measure of the extent of myocardial necrosis at presentation. In this study, a high QRS score was associated with higher peak CK and reflected progression of myocardial necrosis.

The progression of myocardial necrosis depends on the time from onset of AMI and extends from the subendocardium toward the epicardium in a “wavefront of ischemic cell death”. The time frame for this process is thought to be short and the benefit of reperfusion of the infarct-related artery is greatest in the early period as a consequence of myocardial salvage. After this early period, myocardial necrosis rapidly progresses and the extent of myocardial salvage is reduced. Infarct progression, however, is modified by several factors, including the presence of functional collateral coronary arteries to the area at risk, myocardial oxygen demands, and ischemic preconditioning. Several clinical studies have demonstrated that prodromal AP occurring shortly before the onset of AMI has a cardioprotective effect. In the thrombolytic and PCI era, prodromal AP has been reported to be associated with smaller infarct size, improved left ventricular function, and favorable short- and long-term prognoses after AMI. Murry et al described the phenomenon of ischemic preconditioning, by which brief, intermittent periods of coronary artery ischemia separated by periods of reperfusion precede the more prolonged myocardial ischemia, resulting in highly significant cardioprotection. Experimental studies have reported that preconditioned myocytes tolerate ischemia by reducing energy demand, preserving ATP and slowing the development of the osmotic load and acidosis. By the mechanism of preconditioning, prodromal AP delays cardiac myocyte death and has a cardioprotective effect against ischemic injury before reperfusion.

Restoration of blood flow to the ischemic myocardium limits infarct progression, but, at the same time, can induce reperfusion injury. The final size of the myocardial infarct may be determined by ischemic injury before reperfusion and reperfusion injury. Ischemic preconditioning has been reported to have a cardioprotective effect against both ischemic injury and reperfusion injury. However, it remains unclear whether prodromal AP could delay infarct progression in patients with AMI.

In this study, the incidence of a high QRS score was low in the early group, regardless of the presence or absence of prodromal AP. After the early period had elapsed, the QRS score increased in patients without prodromal AP, but remained low until 6 h after the onset of AMI. In the intermediate group, the incidence of a high QRS score at presentation was significantly lower in patient with prodromal AP compared with those without. These findings suggested that prodromal AP might delay the progression of myocardial necrosis before reperfusion in patients with AMI.

The concept of preconditioning is that it delays but does not prevent myocyte death during ischemia. Thus, if the duration of ischemia is excessive or reperfusion is not eventually instituted, preconditioning will not work. In this study, QRS score and the incidence of a high QRS score were high in late group, regardless of the presence or absence of prodromal AP. We considered that the effect of prodromal AP faded and myocytes eventually underwent irreversible cell death after a long duration of ischemia.

**Study Limitations**

This study has the limitations common to all retrospective investigations. However, all consecutive patients with AMI who underwent coronary angiography were prospectively included in a single-center registry. Small sample size is another limitation. Because of the inclusion criteria, the influence of prodromal AP on the abortion of AMI, which was most likely to occur in patients in the very early group, was not assessed. The QRS scoring system cannot be used for patients with left or right ventricular hypertrophy, or left or right bundle branch block, or left anterior or posterior fascicular block, so they were excluded from this study. The study form that was obtained during hospitalization did not include detailed information about medication use before AMI, which potentially had an effect on the progression of MI. We measured peak CK to estimate the extent of myocardial damage after reperfusion. The area under the curve of CK (CKt) is more accurate for estimating infarct size than peak CK, which is influenced by several factors, including reperfusion. However, final TIMI grade 3 flow was achieved in more than 90% patients and there was no significant difference in the rate of achieving final TIMI grade 3 flow between patients with a high or low QRS score. We also did not assess left ventricular function.

**Conclusion**

The extent of myocardial necrosis as assessed by QRS score was smaller in patients with prodromal AP compared with those without. Prodromal AP might delay infarct progression during the early hours after the onset of AMI and extend the window of time for reperfusion therapy.

**References**

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