Ischemic Preconditioning Effect of Prodromal Angina Is Attenuated in Acute Myocardial Infarction Patients With Hypertensive Left Ventricular Hypertrophy

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Background: Several animal experiments on acute myocardial infarction (AMI) have shown that the cardioprotective effects of ischemic preconditioning are more significant in hypertensive subjects. However, because there are no clinical data on the impact of hypertension on ischemic preconditioning in patients with AMI, whether clinical ischemic preconditioning of prodromal angina was beneficial in AMI patients with hypertension was investigated in the present study.

Methods and Results: 125 patients with a first anterior AMI who had undergone successful reperfusion therapy were divided into 2 groups, with or without hypertension, and into 2 further subgroups based on the presence or absence of prodromal angina. Dual-isotope (thallium-201(Tl)/Tc-99m pyrophosphate) single-photon emission computed tomography (SPECT) was performed within 1 week of reperfusion therapy. Left ventricular (LV) function and LV mass index (LVMI) were measured by left ventriculography and echocardiography, respectively. In patients without hypertension, prodromal angina resulted in significantly less myocardial damage on TL-SPECT, better LV ejection fraction and a greater myocardial blush grade compared to patients without prodromal angina. However, these cardioprotective effects of prodromal angina were significantly diminished in hypertensive patients. Importantly, the myocardial salvage effects of prodromal angina showed a significant negative correlation with LVMI, which was significantly greater in hypertensive patients.

Conclusions: The cardioprotective effects of prodromal angina were attenuated in patients with hypertension. Hypertensive LV hypertrophy may crucially limit the effects of ischemic preconditioning in AMI. (Circ J 2011; 75: 1192–1199)

Key Words: Acute myocardial infarction; Hypertension; Left ventricular hypertrophy; Reperfusion

Brief ischemic episodes educe endogenous cardioprotective mechanisms, known as ischemic preconditioning. It has been demonstrated that angina attacks occurring shortly before the onset of acute myocardial infarction (AMI) are associated with favorable outcomes such as smaller infarct size, improved left ventricular (LV) function and increased survival ratio after reperfusion therapy. However, recent experimental observations have suggested that the beneficial effects of ischemic preconditioning are blunted in pathological conditions such as the aged heart or those with diabetes mellitus or hypercholesterolemia. Prodromal angina in elderly AMI patients and patients with diabetes mellitus has been reported to have fewer cardioprotective effects and a worse prognosis.

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Hypertension is a significant risk factor not only for the development of AMI but also for poor outcomes after AMI. However, in most animal experiments on AMI, the cardioprotective effects of ischemic preconditioning in hypertensive subjects have been reported to be just as, or more, beneficial than those in normotensive subjects. On the other hand, a couple of experimental studies suggest that the effects of ischemic preconditioning were lost in an animal model of longstanding hypertension. Studies of ischemic preconditioning in hypertensive hearts have yielded conflicting results, and there are no clinical data on the impact of hypertension on ischemic preconditioning in patients with AMI. Therefore, we...
investigated whether the clinical ischemic preconditioning of prodromal angina could exert beneficial effects in AMI patients with hypertension.

**Methods**

**Study Subjects**

The present study included a total of 125 patients with a first anterior AMI and a total or subtotal occlusion of the left anterior descending coronary artery on admission who underwent successful percutaneous coronary intervention (ie, achievement of Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow within 12 h of the onset of chest pain). Diagnosis of AMI was based on the following criteria: (1) chest pain suggestive of ongoing myocardial ischemia lasting more than 30 min; (2) ST-segment elevation of more than 0.1 mV in at least 2 adjacent precordial ECG leads; and (3) increases in serum creatine kinase (CK) and CK isoenzyme-myocardial band isoenzyme; IVST, intraventricular septal wall thickness; PWT, posterior wall thickness; LVDd, left ventricular internal end-diastolic diameter; LVMI, left ventricular mass index; TIMI, Thrombolysis In Myocardial Infarction.

The present study was reviewed and approved by the Ethics Committee for Clinical Studies at Asahikawa City Hospital and Asahikawa Medical College. Written informed consent for data collection and reporting was given by all patients.

**Study Protocol**

All patients underwent coronary angiography and percutaneous coronary intervention following injection of 2.5 mg isosorbide dinitrate into the coronary artery. While administration of isosorbide dinitrate was continued for 2 days, we did not use nicorandil, carperidine or high-dose catecholamine in the study patients. Patients who underwent coronary stenting were maintained on aspirin and ticlopidine.

Thallium-201 (TL)/Tc-99m pyrophosphate (PYP) dual-isotope single-photon emission computed tomography (SPECT) was performed in all patients within 1 week of the onset of AMI (acute period): 740 MBq of PYP was injected intravenously while at rest after overnight fasting and 2 h later, 111MBq of TL was injected intravenously and imaging started after 15 min. Four weeks after admission (subacute period), TL SPECT was repeated in 78 patients (62%). A gamma camera (Maxxus 4000i, General Electric) with a low-energy, high-resolution collimator was used. Energy windows were set at 140 keV±10% (PYP) and 72 keV±10% (TL). Data were obtained in a 64×64 matrix nuclear medicine computer system. Data acquisition parameters were 30 s/step in 32 steps with 180-degree rotation. All reconstructed images were obtained with Butterworth and Ramp filters.

**SPECT Imaging Analysis**

SPECT images of the LV were divided into 18 segments for semiquantitative analysis. The short-axis slices were each separated into 8 segments at the basal and mid-ventricular levels. The apical portion was evaluated in 2 segments in the vertical long-axis slices. In TL–SPECT, each segment was visually graded into scores of 0–3 (0: normal, 1: mildly reduced uptake,
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2: moderately reduced uptake, 3: severely reduced uptake or absent uptake) in a blinded manner by 3 experienced cardiologists. Differences of opinions in the grading of images were resolved by consensus. The agreement ratios of the cardiologists were 95%.

We defined the sum of each TL score as the total defect score, reflecting the severity of impaired myocardial perfusion, and the number of PYP uptake segments as the extent score, reflecting area at risk. The myocardial salvage ratio (%) was calculated as: $[1-(\text{total defect score of TL/extent score of PYP}) \times 3] \times 100$.

**Echocardiographic Analysis**

M-mode echocardiography was performed using 2-dimensional monitoring within 24 h after the revascularization procedure. M-mode measurements were performed according to the American Society of Echocardiography recommendations. Intraventricular septal wall thickness (IVST), posterior wall thickness (PWT) and LV internal end-diastolic diameter were estimated on the echocardiogram. LV mass (LVM) was calculated from Devereux and Reichek’s formula.

The LV mass index (LVMI) was obtained by dividing the LVM by the body surface area.

**Angiographic Analysis**

Coronary angiograms and left ventriculograms were analyzed by cardiologists who were unaware of the clinical variables reviewed. Left anterior descending artery flow was determined in accordance with the TIMI study classification. The extent of collateral circulation was graded according to Rentrop’s classification. Myocardial blush grade was estimated from the coronary angiogram after reperfusion, as described by van’t Hof et al, by 3 experienced cardiologists in a blinded manner (0, no myocardial blush; 1, minimal myocardial blush; 2, moderate myocardial blush; 3, normal myocardial blush).

Left ventriculography was performed in 89 patients (71%) after reperfusion therapy (acute period) and repeated 4 weeks.
Attenuated Preconditioning in AMI With LVH

later (subacute period). The LV ejection fraction (LVEF) was calculated by the area–length method in the 30-degree right anterior oblique projection, and regional LV wall motion was calculated by the centerline method.

Statistical Analysis
Continuous data are expressed as the mean±SD, and categorical data are presented as counts and percentages. In subjects with and without hypertension, the differences in each variable between the 2 study groups were evaluated using Welch’s t-test for continuous variables and the chi-square test for categorical variables. For the assessment of the differences of each variable among the 4 subgroups, 1-way analysis of variance with Scheffé’s adjustment was applied for continuous variables, and the chi-square test for categorical variables. Multiple linear regression analysis was performed to detect predictors of the myocardial salvage ratio. The relation between myocardial salvage ratios and each predictor was assessed by linear regression analysis. All analyses were conducted using SPSS software for Windows, version 11.01 (SPSS). A P-value <0.05 was considered to be statistically significant.

Results

Patents’ Characteristics
Of the 125 patients (97 men, 28 women; mean age: 65±11 years), 71 (57%) had hypertension, and 60 (48%) had episodes of prodromal angina. Patients with hypertension were significantly older and smoked more than those without hypertension (Table 1). Among the 4 groups, there were no significant differences in the baseline characteristics of the subgroups of patients with and without prodromal angina, with the exception of age; the hypertensive patients without prodromal angina were significantly older than the normotensive patients with prodromal angina (Table 2). Among the hypertensive patients, there was no significant difference between patients with and without prodromal angina in pre-admission medications (Table 2).

Table 3. Multiple Linear Regression Analysis of Predictors of Salvage Ratio on TL

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>β</th>
<th>95% CI</th>
<th>Standardized β</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.063</td>
<td>–0.207 – 0.333</td>
<td>0.041</td>
<td>0.644</td>
</tr>
<tr>
<td>Diabetes or IGT</td>
<td>5.219</td>
<td>–0.530 – 10.967</td>
<td>0.153</td>
<td>0.075</td>
</tr>
<tr>
<td>Time to reperfusion</td>
<td>–0.018</td>
<td>–0.035 – 0.001</td>
<td>–0.166</td>
<td>0.048</td>
</tr>
<tr>
<td>LVMI</td>
<td>–0.099</td>
<td>–0.193 – 0.005</td>
<td>–0.176</td>
<td>0.040</td>
</tr>
<tr>
<td>Prodromal angina</td>
<td>9.834</td>
<td>4.210 – 15.458</td>
<td>0.292</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rentrop grade ≥2</td>
<td>2.273</td>
<td>–0.810 – 5.357</td>
<td>0.122</td>
<td>0.147</td>
</tr>
</tbody>
</table>

TL, thallium-201; CI, confidence interval. Other abbreviations see in Table 1.
There were no significant differences between the normotensive and hypertensive groups for peak CK and CK-MB levels (Table 1). Among the 4 groups, normotensive patients with prodromal angina showed significantly lower peak CK and CK-MB levels compared to patients without prodromal angina (Table 2). There were no significant differences in the peak CK and CK-MB levels in hypertensive patients with or without prodromal angina.

LVMI, IVST and PWT were significantly greater in the hypertensive group (Table 1). No significant differences were observed between the normotensive and hypertensive groups in the development of collateral circulation with Rentrop grade ≥2 (Table 1). Among the 4 groups, hypertensive patients with prodromal angina showed significantly well-developed collateral circulation (Table 2).

No significant differences were observed between the normotensive and hypertensive groups for myocardial blush grade of 2 or 3 (Table 1). Normotensive patients with prodromal angina showed significantly greater myocardial blush grade than patients without prodromal angina (Table 2). There was no significant difference in myocardial blush grade in the hypertensive patients with or without prodromal angina.

Myocardial Salvage Ratios on SPECT and the LVMI

Among the 4 groups, the normotensive patients with prodromal angina showed a significantly greater myocardial salvage ratio than the other subgroups (Figure 1). Multiple linear regression analysis was performed to detect the myocardial salvage ratio predictors and it was revealed that the presence of prodromal angina, time to reperfusion and LVMI were independent predictors (Table 3).

As indicated by the multiple linear regression analysis, there was a significant negative correlation between the myocardial salvage ratio and LVMI in all patients studied (r=-0.21, P=0.02). However, it was more specific to patients with prodromal angina. No significant relations were observed between LVMI and the myocardial salvage ratio on TL/PYP SPECT in patients without prodromal angina (Figure 2A). In contrast, for patients with prodromal angina, LVMI correlated inversely with the myocardial salvage ratio (Figure 2B: hypertensive patients tended to be distributed in the lower right-hand area of the graph).

TL SPECT was repeated in some of the patients [78 (62.4%) ] in the subacute period and essentially showed similar findings to those for the acute period (data not shown in detail). Particularly, in patients with prodromal angina, LVMI correlated inversely with the myocardial salvage ratio in the subacute period (r=-0.52, P=0.001; hypertensive patients tended to be distributed in the lower right-hand area of the graph). No significant relation was observed between LVMI and the myocardial salvage ratio in patients without prodromal angina in the subacute period.

Left Ventriculographic Findings and LVMI

In the acute period, there was no significant correlation between LVEF and LVMI. In the subacute period, no significant relations were observed in patients without prodromal angina (Figure 3A), but for patients with prodromal angina, there were positive correlations between LVMI and LVEF (Figure 3B).

Discussion

In this study, the cardioprotective effects of prodromal angina...
were significantly attenuated in AMI patients with hypertension, contrary to the results of several previous experimental studies. We also found that LV hypertrophy was a crucial factor in determining the effects of ischemic preconditioning in hypertensive patients.

**Hypertension, LV Hypertrophy and Ischemic Preconditioning**

Hypertensive patients with AMI have a higher morbidity than normotensive patients, and myocardial infarct size relative to the area at risk is frequently larger in hypertensive subjects. However, it is controversial whether ischemic preconditioning, a major cardioprotective mechanism in AMI, is effective in hypertensive subjects.

Although there are no clinical studies investigating the impact of hypertension on ischemic preconditioning in patients with AMI, several experimental studies have reported that ischemic preconditioning induces better cardioprotective effects in the hypertensive heart. Speechly-Dick et al investigated the ischemic preconditioning effects in hypertensive rats models of deoxycorticosterone acetate and surprisingly, the infarct size-limiting effects of ischemic preconditioning were significantly greater in the hypertrophied groups than in the normotensive groups. Furthermore, greater ischemic preconditioning effects have been reported in the hypertrophied hearts of spontaneously hypertensive rats (SHR), and transgenic hypertensive rats with enhanced activity of the local rennin–angiotensin system. In contrast, Moolman et al reported that ischemic preconditioning effects were blunted in SHR, and their findings are consistent with our human data. Although the exact reason for these discrepancies in animal experiments remains unknown, a plausible explanation is the development of hypertensive hearts in the 1-year-old rats used by Moolman et al. Younger hypertensive hearts may not represent clinical conditions in human hypertensive hearts. Recently, Ebrahim et al reported that ischemic preconditioning induced cardioprotection effects in hypertrophied myocardium from both juvenile and mature SHR, whereas this was not seen in aging SHR at 12–13 months, independent of the duration of systemic hypertension or the degree of LV hypertrophy. Such conflicting results on the effect of ischemic preconditioning in the hypertensive state led us to conduct the present study in humans.

We demonstrated that the cardioprotective effects of prodromal angina were significantly attenuated in hypertensive patients. Although there was considerable variation, chronic pressure overload due to hypertension tended to induce hypertrophy, resulting in significantly greater LVMI in the hypertensive patients. LV hypertrophy is an independent risk factor for cardiovascular events, and enhanced susceptibility of the hypertrophied heart to myocardial ischemia has been demonstrated in several experimental studies. In the present study, there were no significant differences in LVMI between hypertensive patients with or without prodromal angina, suggesting that LV hypertrophy did not determine the induction of prodromal angina in hypertensive patients. Important, however, was the fact that LVMI significantly inversely correlated with the myocardial salvage ratios in patients with prodromal angina, suggesting that LV hypertrophy was a crucial determinant of the cardioprotective effects of ischemic preconditioning.

**Microvascular Circulation and Ischemic Preconditioning**

Coronary flow reserve is known to be reduced in hypertensive patients with LV hypertrophy, and it is likely that microvascular damage influences the cardioprotective effects of ischemic preconditioning. It has been reported that AMI patients with prodromal angina show greater microvascular reflow and coronary flow reserve after reperfusion therapy compared to those without prodromal angina. Preservation of the microvascular circulation is an important mechanism of lessening the myocardial damage after reperfusion therapy. Myocardial blush grade evaluated by the contrast density in the infarcted myocardium is a useful technique for estimating the integrity of residual myocardial microcirculation. Tamura et al demonstrated that the myocardial blush grade was significantly greater in patients with prodromal angina than in those without. Our study results are consistent with their findings. However, the blush grade was significantly smaller in hypertensive patients, suggesting that microcirculatory dysfunction after reperfusion was more evident in patients with hypertension, even those with prodromal angina. Coronary endothelial function and vasomotor responsiveness are frequently impaired in patients with severe hypertension and hypertrophy. Impaired nitric oxide production is known to enhance posts ischemic myocardial dysfunction. Vulnerable myocardial microcirculation potentially attenuates the cardioprotective effects of ischemic preconditioning in hypertensive AMI patients after reperfusion therapy.

**Collateral Circulation and Ischemic Preconditioning**

Collateral circulation works independently from, but additively to, prodromal angina for improving LV function in patients with AMI. Hypertensive patients with coronary artery disease are also known to have a well-developed coronary collateral circulation that corresponds to the degree of LV hypertrophy. We found that the collateral circulation was well developed in hypertensive patients with prodromal angina, but not in those without prodromal angina. These differences in the development of collateral circulation depending on prodromal angina were not observed in the normotensive patients, in whom ischemic preconditioning effects of prodromal angina were activated independent of collateral circulation. However, despite having developed collateral circulation, the ischemic preconditioning effects were significantly blunted in hypertensive patients. Importantly, multiple regression analysis revealed that collateral flow and Rentrop grade ≥2 were not significant determinant factors for the effects of prodromal angina. These results suggest that other detrimental factors, such as LV hypertrophy and coronary microcirculation disturbance, are powerful enough to eliminate the beneficial effects of collateral circulation in hypertensive patients.

**Hypertrophied Heart and Ischemic Preconditioning**

Recently, Butler et al reported that activation of signal transducers and activators of transcription (STAT)-3 signaling is essential for ischemic preconditioning in hypertrophied hearts induced by transverse aortic constriction. The efficacy of ischemic preconditioning was attenuated when STAT-3 activation was limited by treatment with the janus activated kinase (JAK)-2 inhibitor. An intrinsic inhibitor of JAK, suppressor of cytokine signaling 3 is known as the key molecule for switching on the negative feedback circuit of cardiac hypertrophy. The intriguing balance between the JAK–STAT pathway and it is likely that...
Study Limitations
By including patients with prodromal angina, the possibility remains that patients with silent myocardial ischemia might have been included in the group without prodromal angina. However, it is an inevitable limitation of a clinical study on the effects of prodromal angina in AMI.

The group of normotensive patients may have included patients who were potentially hypertensive but had no apparent history of hypertension, and their blood pressure had been externally normalized by LV dysfunction, salt-restriction therapy and the use of cardioprotective drugs, such as angiotensin-converting enzyme inhibitors and β-blockers for AMI. On the other hand, the group of hypertensive patients may have included patients who had an apparent history of hypertension, but their blood pressure had been normalized by long-term antihypertensive medication. Therefore, the absolute values of blood pressure level seemed difficult to compare in this particular study of AMI, whereas the extent of LV hypertrophy, which would be closely associated with the severity of hypertension, seemed worth comparing, and we studied the correlations between LVM and the myocardial salvage ratio or LVEF.

As we expected, the age of the hypertensive group was greater than that of the normotensive group, because hypertension is a typical age-related disease. Importantly, there were no significant age differences among the hypertensive patients with or without prodromal angina. Multiple regression analysis revealed that age was not the crucial determinant for the effects of prodromal angina in the present study (Table 3). Thus, we believe age did not significantly affect our conclusion.

We used peak CK and CK-MB levels to estimate infarct size. Although the accumulated release of CK and CK-MB is more accurate for estimating infarct size than peak CK and CK-MB levels,36 we were restrained from using the former because of the lack of some measurement data after 24 h. Although large epidemiological studies have extensively used M-mode echocardiography, technical limitations exist when calculating LVM in patients with myocardial infarction, particularly in those who have a regional wall motion abnormality. However, several studies have demonstrated a strong relationship between LV hypertrophy detected by echocardiography and necropsy.

Conclusion
The cardioprotective effects of prodromal angina were significantly attenuated in hypertensive patients, contrary to several previous experimental studies. LV hypertrophy accompanying hypertension is a crucial determinant of the effects of ischemic preconditioning.

Acknowledgments
We gratefully acknowledge Drs A. Ido, M. Okura, J. Matsumi and K. Hirasaawa for their expert advice and assistance.

Disclosure
None of the authors have any relationship with industry or any conflict of interest.

References


