Phase changes caused by hyperventilation stress in spastic angina pectoris analyzed by first-pass radionuclide ventriculography

Jin Wu,* Tohoru Takeda,* Hinako Toyama**, Ryuichi Ajisaka,* Takeshi Masuoka,* Sigeyuki Watanabe,* Motohiro Sato,* Nobuyoshi Ishikawa*** and Yuji Itai*

*Institute of Clinical Medicine, University of Tsukuba
**Positron Medical Center, Tokyo Metropolitan Institute of Gerontology
***Department of Radiological Sciences, Ibaraki Prefectural University

To understand the effect of hyperventilation (HV) stress in patients with spastic angina, left ventricular (LV) contraction was analyzed by quantitative phase analysis.

The study was performed on 36 patients with spastic angina pectoris, including vasospastic angina pectoris (VspAP: 16 patients) and variant angina pectoris (VAP: 20 patients). First-pass radionuclide ventriculography (first-pass RNV) was performed at rest and after HV stress, and standard deviation of the LV phase distribution (SD) was analyzed.

The SD was lower in patients with VspAP than in VAP (12.8 ± 1.4 degrees vs. 14.6 ± 2.2 degrees, p < 0.005) at rest. After HV stress, the SD (HVSD) tended to increase in VspAP patients (62.5%), whereas the SD decreased in VAP patients (70%). Due to HV stress, the percentage change in SD (%SD) in VspAP patients was 8.9 ± 23.7% whereas that in VAP patients was −9.1 ± 17.3% (p < 0.01). Moreover, phase histograms were divided into HVSD increase and HVSD decrease groups. The HVSD increase group had a decrease of HVEF, but the HVSD decrease group tended to have more decreased HVEF than the HVSD increase group.

These results indicate that spastic angina pectoris patients show various responses to HV stress. The HVSD increase group might have additional myocardial ischemia due to regional coronary spasm. In contrast, in the HVSD decrease group severe LV dysfunction or diffuse wall motion abnormality might have been generated, and this caused a reduction in the SD value. Phase analysis would therefore add new information regarding electrocardiographically silent myocardial ischemia due to coronary spasm, and HV stress might increase sensitivity for the detection of abnormalities in quantitative phase analysis, especially in VspAP patients.

Key words: variant angina pectoris, vasospastic angina pectoris, phase analysis, radionuclide ventriculography and blood pool scintigraphy, hyperventilation stress test

INTRODUCTION

Coronary artery spasm plays a role in a wide spectrum of ischemic coronary events, associated with typical effort angina pectoris, acute myocardial infarction and sudden cardiac death. The accurate detection of coronary artery spasm is very important in clinical practice, but the transience of coronary artery spasm makes it difficult to diagnose. Coronary angiography combined with ergonovine or acetylcholine provocation has been used as the standard diagnostic method to detect coronary spasm and to determine its severity. Diagnostic sensitivity to these drugs is reported to be 94%2 and 90%3 in spastic angina pectoris, but coronary catheterization is invasive, and occasionally produces catheter-induced spasm.4 Reliable noninvasive methods for diagnosing coronary artery spasm are needed.

In electrocardiographical studies, numerous stresses such as ergonovine, hyperventilation, histamine, exercise and cold pressor, have been reported to improve the

Received July 14, 1998, revision accepted November 10, 1998.
For reprint contact: Tohoru Takeda, M.D., Institute of Clinical Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, JAPAN.
diagnostic sensitivity of variant angina. The ratio of provoked coronary spasm in these tests is reported to be 96%, 54%, 47%, 46% and 11%, respectively in spastic angina pectoris. The ergonovine stress test has the highest sensitivity, but this drug is usually used in a catheterization laboratory because of the potentially fatal risk. Currently, hyperventilation (HV) stress is receiving considerable attention.

Recently, radionuclide ventriculography (RNV) combined with HV stress has been attempted to evaluate the myocardial ischemia in stable exertional AP and spastic AP. The response of left ventricular (LV) ejection fraction (EF) to HV stress has been reported to be sensitive for identifying coronary spasm and its sensitivity ranged from 66.7% to 74% in patients with spastic angina.

Phase analysis which can demonstrate LV contraction sequence, is used to detect various abnormalities in interventricular electrical conduction and ischemic heart diseases. One of the sensitive parameters is a standard deviation of the LV phase distribution to reveal myocardial ischemia. The results of our previous study suggested that the SD was very sensitive in detecting asynchronous contraction abnormality induced by spastic angina pectoris even at rest, but there are no reports demonstrating the kinds of phase changes that will be produced by HV stress in patients with spastic angina. This study investigated changes in LV contraction before and after HV stress in patients with spastic angina by means of quantitative phase analysis.

METHODS

Patient selection
The study population consisted of 36 spastic angina patients. The spastic angina patients were subdivided into vasospastic angina (VspAP) and variant angina pectoris (VAP) based on the results of CAG and ECG as follows:

1) VspAP group: 16 patients with 50–75% coronary spasm and transient ST segment depression.

2) VAP group: 20 patients with more than 75% coronary spasm and transient ST segment elevation.

Twenty-five of the 36 patients with spastic angina were males and 11 were females, and their ages ranged from 37 to 71 years (mean: 57.3 ± 8.5 years). None of these patients had a history of previous myocardial infarction, congestive heart failure, or valvular heart disease.

Hyperventilation stress test
The hyperventilation (HV) stress test was performed by breathing deeply and rapidly (at least 40 inspirations per min) for 5 min, following a metronome. A 12-lead electrocardiogram as well as blood pressure were recorded at 1-min intervals during the examination. A positive stress test was signified by characteristic electrocardiographic changes (ST segment elevation or depression 1 mm at 0.08 sec after the J point) with or without chest pain during the examination. With the first-pass RNV, imaging of the left ventricle was performed before HV stress and at 3 min after the end of the HV stress. If angina or ST segment changes appeared, stress images were obtained soon. The percentage change in heart rate (HR) after hyperventilation stress (HR) was calculated as follows:

\[ \text{%HR} = \frac{\text{HV HR} - \text{resting HR}}{\text{resting HR}} \times 100\% \]

Radionuclide technique
First-pass radionuclide ventriculography (first-pass RNV) was used to evaluate the LV dysfunction produced by HV stress-induced spasm. Multigated equilibrium radionuclide ventriculography (multigated equilibrium RNV) which has a relatively high signal noise ratio was also performed to assess the reliability of first-pass RNV at rest. Six mg of stannous chloride pyrophosphate dissolved in 3 ml of saline was intravenously (IV) injected for premedication. The first-pass RNV images were obtained after a bolus IV injection of 555–740 MBq (15–20 mCi) of technetium (Tc)-99m pertechnetate at rest. Soon after the resting first-pass RNV examination, multigated equilibrium RNV was performed by in-vivo labeling of red blood cells. Then HV stress examination of first-pass RNV was performed after a bolus IV injection of 555 MBq (15 mCi) of Tc-99m pertechnetate. Background subtraction was performed in HV stress first-pass RNV.

Images were obtained with a gamma camera (ZLC-7500, Siemens Co., Ltd.) in which a slant-hole, low-energy collimator was used to increase the precision of measurement. First-pass RNV images were obtained in the right anterior oblique at 30 degree (RAO) position, and multigated equilibrium RNV images were obtained in the modified left anterior oblique (LAO) position with a 15-degree caudal tilt to diminish the overlap of cardiac structures. The following acquisition parameters were used: an energy window of 20%, a peak at 140 keV, a 40-msec interval after the R wave, and 10% rejection of abnormal beats (corresponding to about 600 beats). Data were processed in a ScintiPAC-700 computer (Shimadzu Co. Ltd., Japan) and 64 × 64 matrix images were obtained. The resting and HV stress ejection fraction (EF) based on the first-pass RNV method (resting EF and HV EF) and the resting EF based on the equilibrium method were calculated from time-activity curves. In our laboratory, a study is defined as abnormal when the EF decreases more than 5% after the HV stress. The percentage change in EF after hyperventilation stress (%EF) was calculated as follows:

\[ \text{%EF} = \frac{\text{HV EF} - \text{resting EF}}{\text{resting EF}} \times 100\% \]
Table 1  Comparison of the various parameters of the left ventricle between the VspAP and VAP groups by the first-pass method

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>HR</th>
<th>%HR</th>
<th>EF</th>
<th>%EF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>rest</td>
<td></td>
<td>rest</td>
<td></td>
</tr>
<tr>
<td>VspAP</td>
<td>16</td>
<td>66.7 ± 10.5</td>
<td>62.5 ± 9.2</td>
<td>−6.6 ± 5.5</td>
<td>62.5 ± 7.9</td>
</tr>
<tr>
<td>VAP</td>
<td>20</td>
<td>62.6 ± 8.6</td>
<td>60.6 ± 7.7</td>
<td>−1.3 ± 6.9</td>
<td>60.6 ± 7.1</td>
</tr>
</tbody>
</table>

for the LV were calculated from these histograms as absolute values in msec. The SD in degrees and the percentage change in SD after hyperventilation stress (%SD) were calculated as follows:

\[
SD (\text{degrees}) = \frac{SD (\text{msec}) \times 360}{\text{mean R-R interval (msec)}}
\]

\[
%SD = \frac{HVSD - \text{resting SD}}{\text{resting SD}} \times 100\%
\]

Coronary arteriography
CAG was performed with the Judkins or Sones technique. Increasing doses of methylergonovine was injected as 1, 5 and 10 µg into the right coronary artery, and 1, 5, 10 and 30 µg into the left coronary artery at 5 min intervals. The severity of coronary spasm was determined by the methylergonovine provocation.

Statistical analysis
All data were expressed as the mean value ± s.d. Student’s t-test (two-tailed, unpaired) was used for comparison of the results. A linear regression analysis by the least squares method was performed to assess the relationship between the parameters. A p value less than 0.05 was considered significant.

RESULTS
HV stress was performed in 36 patients with spastic angina pectoris. There was no significant ischemic electrocardiographic (ECG) change observed after HV stress. HR was slightly slower after HV stress, and %HR became −6.6 ± 5.5% in the VspAP group and −1.3 ± 6.9% in the VAP group, respectively, whereas EF decreased significantly in both VspAP (from 62.5 ± 7.9% to 54.0 ± 9.6%, p < 0.01) and VAP (from 60.6 ± 7.1% to 50.1 ± 9.5%, p < 0.01) groups after HV stress. The %EF in the VAP group tended to decrease significantly compared to that in the VspAP group, but the difference was not statistically significant (−19.2 ± 9.1% vs. −12.8 ± 10.3%, p = n.s.) (Table 1).

The SD was obtained from RAO and LAO images by first-pass RNV and multigated equilibrium RNV, respectively. A linear correlation was found between the SD obtained by first-pass RNV and that by multigated equilibrium RNV in the patients with spastic angina pectoris.

Phase analysis
Phase analysis of multigated equilibrium RNV and of first-pass RNV were performed with the first component of Fourier harmonics to fit a cosine curve to the time-activity curve on each pixel. Phase histograms of the LV were constructed from the phase images.

The borders of the LV were manually determined with an amplitude image and the left atrium was eliminated. Then the mean phase value and standard deviation (SD)
at rest ($r = 0.71, p < 0.0001$) (Fig. 1).

The changes in SD at rest and after HV stress test are shown in Figure 2. At rest, the SD in the VspAP group was lower than that in the VAP group (12.8 ± 1.4 degrees vs. 14.6 ± 2.2 degrees, $p < 0.005$), whereas after HV stress test, the SD in both the VspAP and VAP groups became almost the same (13.8 ± 3.1 degrees vs. 13.1 ± 2.4 degrees, $p = n.s.$). Thus, after HV stress, SD tended to increase in the VspAP group, but decrease in the VAP group. The %SD was 8.9 ± 23.7% in the VspAP group and -9.1 ± 17.3% in the VAP group ($p < 0.01$) (Fig. 3).

Phase histograms were divided into 2 groups due to the increase and decrease in the SD value. In the VspAP group, an increase in SD was observed in 62.5%, but in the VAP group, a decrease in the SD value was observed in 70% (Fig. 4).

Figure 5 shows the relationship among the %SD, %EF and %HR of two patterns in both VspAP and VAP groups.

1) In the HVSD increase group, the decreases of %EF and %HR, and an increase of %SD were found (Fig. 5 left). The %EF significantly decreased in the VAP group, but the %SD increased in the VspAP group.

2) In the HVSD decrease group, a decrease in both %EF and %SD was observed (Fig. 5 right), but %HR showed a higher value, and %EF and %SD tended to decrease in the VAP group.

Table 2 shows various parameters such as HR, EF and SD in both the HVSD increase and HVSD decrease groups.

**Table 2** Comparison of various parameters of the left ventricle between the HVSD increase and HVSD decrease groups by the first-pass method

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>%HR</th>
<th>EF</th>
<th>%EF</th>
<th>SD</th>
<th>%SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rest</td>
<td>HV</td>
<td></td>
<td>rest</td>
<td>HV</td>
<td></td>
</tr>
<tr>
<td>SD inc.</td>
<td>16</td>
<td>65.4 ± 9.4</td>
<td>61.4 ± 9.7</td>
<td>-6.8 ± 7.0</td>
<td>63.2 ± 7.8</td>
<td>54.2 ± 11.1</td>
</tr>
<tr>
<td>SD dec.</td>
<td>20</td>
<td>63.5 ± 9.7</td>
<td>62.9 ± 9.1</td>
<td>-1.1 ± 6.5</td>
<td>60.6 ± 6.5</td>
<td>49.7 ± 7.6</td>
</tr>
</tbody>
</table>

Correlation between SD increase and decrease groups: *: $p < 0.05$, **: $p < 0.0001$

16 Jin Wu, Tohoru Takeda, Hinako Toyama, et al

*Annals of Nuclear Medicine*
groups. Resting EF was slightly lower in the HVSD decrease group than in the HVSD increase group, but the statistical difference was not significant (60.6 ± 6.5% vs. 63.2 ± 7.8%, respectively, p = n.s.). Nevertheless, resting SD was higher in the HVSD decrease group than in the HVSD increase group (14.2 ± 2.2 degrees vs. 12.9 ± 1.5 degrees, p < 0.05). After HV stress, EF decreased in the VspAP and VAP groups. There was no statistical difference, however, HVEF tended to lower value in VAP than that in VspAP group (49.7 ± 7.6% vs. 54.2 ± 11.1%, p = n.s.).

DISCUSSION

In the present study, a linear correlation was observed between SD in the multigated equilibrium RNV and that in the first-pass RNV at rest (r = 0.71). An excellent LV global EF relationship between the resting multigated equilibrium RNV and the resting first-pass RNV (r = 0.91) has been reported, but the LVSD relationship between the two methods has not yet been examined. Our data showed that the correlation coefficient r was equal to 0.71. This relatively low correlation might be caused by: 1) a relatively poor signal-to-noise ratio of first-pass images in method, 2) the geometrical difference due to RAO and LAO projection generated different segment values. This segment difference was also reported in regional LVEF studies by Papapietro et al.10

After HV stress test, EF decreased in 69% of patients with vasospastic angina. This result supports the finding of reduced LV wall motion after HV stress reported in previous studies.9

In CAD patients a relationship between EF decrease and SD increase in stress tests has been reported.10-12 Regional change in the mechanical performance caused by ischemia first affects the synchronicity of wall motion and causes a phase shift in the ischemic segments. We therefore assumed that, after HV stress, increased SD of LV phase distribution would occur in both VspAP and VAP groups, and the diagnostic sensitivity would be greatly improved by phase analysis. In the VspAP group, SD increased 8.9% after HV stress, resembling the findings of previous investigations in CAD patients, but a different response of SD after HV stress was observed in the VAP group. In the VAP group, SD was decreased 9.1%. This finding was quite unexpected.

Then the pattern of the phase histogram was examined to see if HVSD increase or not. As a result, we found that HVSD was increased in 62.5% of patients with VspAP. In contrast, HVSD was decreased in 70% of VAP patients.

In the HVSD increase group, myocardial dysfunction as shown by the decrease in EF and increase in SD became more severe after HV stress. This suggested that a new myocardial ischemic region was produced in these patients. In the usual type of myocardial ischemia induced by organic coronary stenosis, regional myocardial contraction was decreased by stress, and a decrease in %EF and an increase in %SD were observed10-12 so that the patients with an SD increase caused by HV stress were thought to have a similar response to CAD patients.

In the HVSD decrease group, %EF decreased similarly to the HVSD increase group. In contrast, resting LVEF was within normal limits, but tended to be lower than in the HVSD increase group. After HV stress, LVEF tended to be lower in the HVSD decrease group than in the HVSD increase group. These phenomena suggested that residual myocardial dysfunction such as myocardial stunning existed at rest (mainly detected as asynchronicity), and additional, more severe LV dysfunction might be produced by HV stress in the HVSD decrease group. It has reported that HV stress-induced multivessel coronary spasm (one or more major coronary arteries) was generated in VAP patients,19 and regional wall motion was significantly impaired by only 10–20% blood flow reduction.20 Therefore, diffuse LV wall motion reduction in the HVSD decrease group might be generated after HV stress. In CAD patients, the decrease in SD after bicycle exercise stress had been described by Ratib et al.,12 when diffuse LV enlargement and greatly reduced EF were induced by the stress, and the SD value decreased like that in a resting study due to obscure regional myocardial ischemia. In the HVSD decrease group, the change in SD might not be helpful in assessing the severity of LV dysfunction, but the change in EF is thought to be a better parameter.

Although the signal-to-noise ratio of the LV image in the first pass RNV was smaller than that in the multigated equilibrium RNV, reduction in EF and asynchronous contraction were noted. Further investigation will be needed to determine the precise reasons for this phenomenon, but our study demonstrated that phase analysis would add new information regarding electrocardiographically silent myocardial ischemia due to coronary spasm, and HV stress might increase sensitivity in the detection of abnormalities in quantitative phase analysis, especially in VspAP patients.

ACKNOWLEDGMENTS

We sincerely thank Mr. Yuuichi Inaoka and Mr. Ryuichi Ban (Shimadzu Co. Ltd.) for programming the quantitative phase analysis, and to Rokuo Hatakeyama RT, Masashi Seki RT, Hiroshi Yokota RT and Toshihiro Kusumoto RT for technical assistance.

REFERENCES


