The relationship between baroreceptor sensitivity (BRS) and cardiac sympathetic nerve function after acute myocardial infarction (AMI) was investigated in 34 patients. BRS was measured during the Valsalva maneuver and cardiac sympathetic function was assessed by the washout rate (WR) of I-123 meta-iodo-benzyl guanidine (I-123-MIBG), a tracer of myocardial sympathetic nerve function. BRS correlated with global WR (r=−0.43, p<0.0001) and regional WR of normal area (r=−0.72, p<0.0001). After AMI, baroreceptor function is linked to sympathetic activation, as elucidated by the WR of normal area, which suggests that separation of the infarcted area from the non-infarcted myocardium is necessary for evaluating sympathetic activation after AMI and that the regional kinetics of I-123-MIBG in the normal area are a more suitable marker of activated cardiac nerve function than global I-123-MIBG kinetics.

Key Words: Baroreceptor sensitivity (BRS); I-123-MIBG; Regional washout rate; Valsalva maneuver

Methods

Subjects

The study group consisted of 34 consecutive patients (25 men, 9 women; mean age 64±11 years) who had experienced an AMI (Table 1). Thirty of the patients underwent emergency percutaneous transluminal coronary angioplasty (PTCA) and the remaining 4 patients received medical treatment or underwent elective PTCA. The culprit branch was the left anterior descending artery in 21, the right coronary artery in 10 and the left circumflex artery in 3 patients. Of the 34 patients, 28 had 1-vessel disease and 6 had 2-vessel disease diagnosed at primary coronary angiography. The left ventricular ejection fraction (LVEF) measured by left ventriculography (LVG EF) at approximately 4 weeks after AMI was 45.5±9.5% in 29 of the 34 patients. Abnormal Q-waves were observed in all patients. Patients with a history of prior MI, diabetes mellitus, atrial fibrillation, frequent premature beats, coexistent significant valvular heart disease, chronic renal failure, pulmonary disease, other severe chronic disease or who had been taking ß-adrenergic blocking agents were not enrolled. The purpose of the study was fully explained to the patients, and informed consent was obtained.

In entry to the study, patients were taking medications, such as diuretics (n=11), angiotensin-converting enzyme inhibitors (n=19), angiotensin II antagonists (n=9), nitrates (n=26) or Ca antagonists (n=11), but none had been prescribed digitalis preparations or catecholamines.

Study Protocol

All patients underwent I-123-MIBG imaging and measurement of BRS within 4 weeks (average 17 days) of the onset of MI and both examinations were carried out on the same day. Electrocardiogram (ECG) gated Tc-99m (99mTc) perfusion imaging was performed within a few days of I-123-MIBG imaging.
Table 1 Clinical Characteristics of the Study Group

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Total (n=34)</th>
<th>Mild dysfunction (n=22)</th>
<th>Severe dysfunction (n=12)</th>
<th>p value (mild vs severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64±11</td>
<td>62±12</td>
<td>67±7</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male %)</td>
<td>25 (73.5%)</td>
<td>16 (72.7%)</td>
<td>9 (75.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>110±19.8</td>
<td>110±16.9</td>
<td>110±25.7</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>62±12.2</td>
<td>61±10.5</td>
<td>64±15.4</td>
<td>NS</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>75±12.9</td>
<td>73±11.8</td>
<td>80±14.2</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus (*)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (44.1%)</td>
<td>9 (40.9%)</td>
<td>6 (50.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>13 (38.2%)</td>
<td>9 (40.9%)</td>
<td>4 (30.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>20 (58.8%)</td>
<td>14 (63.6%)</td>
<td>6 (50.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>11 (32.4%)</td>
<td>5 (22.7%)</td>
<td>6 (50.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>ACE-I</td>
<td>19 (55.9%)</td>
<td>14 (63.6%)</td>
<td>6 (50.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>All antagonists</td>
<td>9 (26.5%)</td>
<td>7 (31.8%)</td>
<td>3 (25.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Nitrate</td>
<td>26 (76.5%)</td>
<td>18 (81.8%)</td>
<td>8 (66.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Ca-antagonists</td>
<td>11 (32.4%)</td>
<td>1 ( 4.5%)</td>
<td>10 (83.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Digitalis preparations</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>⊥ blocker (*)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Infarct-related artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-vessel disease</td>
<td>28 (82.4%)</td>
<td>19 (86.4%)</td>
<td>9 (75.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>6 (17.6%)</td>
<td>3 (13.6%)</td>
<td>3 (25.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>LAD</td>
<td>21 (61.8%)</td>
<td>12 (54.5%)</td>
<td>9 (75.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>LCx</td>
<td>3 ( 8.8%)</td>
<td>2 ( 9.1%)</td>
<td>1 ( 8.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>RCA</td>
<td>10 (29.4%)</td>
<td>8 (36.4%)</td>
<td>2 (16.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>LVG EF (n=9)</td>
<td>45.5±9.5</td>
<td>50.1±8.0 (n=20)</td>
<td>35.3±7.7 (n=9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gated LVEF</td>
<td>46.2±12.8</td>
<td>53.5±7.5</td>
<td>33.0±9.6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ACE-I, angiotensin converting enzyme inhibitor; AII, angiotensin II; LAD, left anterior descending artery; LCx, Left circumflex artery; RCA, right coronary artery; LVG EF, ejection fraction derived from left ventriculography; Gated EF, ejection fraction derived from Gated SPECT. *Patients with diabetes mellitus or taking ⊥ blocker were excluded.

123I-MIBG Imaging

While the patient was fasting, 123I-MIBG imaging was performed with planar acquisition and single photon emission tomography (SPECT). First, an anterior planar image was obtained (early planar image) 15 min after intravenous injection of 123I-MIBG (111 MBq) and immediately after the planar image, the SPECT image was obtained (early SPECT image). After 3.5 h, another anterior planar image (delayed planar image) and SPECT image (delayed SPECT image) were obtained. Data were acquired using 2-heads equipment (VERTEX, ADAC Co Ltd, USA) with a general-purpose parallel-hole collimator. Data acquisition for the SPECT image was performed from a 45-degree right anterior oblique to 45-degree left posterior oblique view for a 180-degree arc in 32 present sampling angles for 30 s per angle. Data were stored in a 64×64 matrix using a 20% center of 159 keV. An image processing ramp back projection filter (10 orders, 0.36 cycle/cm cutoff) was used.

Analysis of the 123I-MIBG Images

The global WR of the 123I-MIBG was calculated from the planar images. In brief, a region of interest (ROI) was manually drawn over the left ventricle according to the outline of a reference heart image obtained by the 99mTc perfusion. A rectangular ROI over the upper mediastinum (M) was used as a reference background. Mean counts per pixel were obtained both in the heart (H) and M from each ROI. The WR formula was

\[
\text{WR} = \frac{(\text{early H} - \text{early M}) - (\text{delayed H} - \text{delayed M})}{(\text{early H} - \text{early M}) \times 100} \%
\]

The regional WR of myocardial 123I-MIBG was derived from the SPECT images. A polar map was constructed from the short-axis image of the apical portion through to the basal portion on the early and delayed SPECT images and divided into 49 segments, which were classified into 3 categories: normal area, infarcted but viable area and infarcted area. Normal area was defined as the region with more than 70% counts of %uptake on both 99mTc and 123I-MIBG images on the polar map; infarcted but viable area was defined as more than 50% counts of %uptake on 99mTc and 40–70% counts of %uptake of 123I-MIBG; infarcted area was defined as a region with less than 50% of %uptake on 99mTc or less than 40% of %uptake on 123I-MIBG. Several typical regions of each area were selected automatically and thereafter, the regional WR of 123I-MIBG was calculated in each area in the same manner as for the planar image.

ECG Gated 99mTc Perfusion Imaging

Resting ECG gated 99mTc perfusion imaging was obtained 1 h after injection of 592 MBq of 99mTc perfusion tracer (99mTc SPECT image). Images were gated at 8 frames per cycle. LVEF was automatically calculated using previously validated and commercially available automated software (QGS, Cedars-Sinai Medical Center, Los Angeles, CA, USA) on a SUN workstation. The LVEF derived from the resting ECG gated 99mTc perfusion imaging was used as a parameter of ventricular function (Gated LVEF). Automatic determination of left ventricular volumes by QGS was successful in all but one patient for whom there was an operator disagreement with the software, which was subsequently resolved by manual correction.
Measurement of BRS

Measurement of BRS was performed after obtaining 123I-MIBG images in the morning. In preparation, subjects lay quietly on the bed for 20 min to adjust to the environment. An ECG and the continuous arterial pressure signal from the radial portion of the wrist (BP-508, COLIN, Japan) were recorded using a computerized data acquisition and analysis package (ANS-508, COLIN). Both signals were converted to digital format with a sampling frequency of 200 Hz.

The patients performed the Valsalva maneuver while supine. After deep inspiration, subjects exhaled forcefully into a mouthpiece connected to a digital mercury manometer (VITALPOWER KH-101, CHEST CORPORATION, Japan), maintaining a pressure of 40 mmHg over 15 s. A small air leak was placed in the mouthpiece to prevent subjects from maintaining expiratory pressure by occluding the glottis. As soon as they had finished expiration into mouthpiece, each subject resumed normal tidal breathing. All subjects had a brief practice before data collection. The Valsalva maneuver was repeated 3 times, with a 5-min rest period between maneuvers. A tachogram of the beat-to-beat RR intervals and simultaneous blood pressure tracings were displayed on the computer screen. An operator selected the phase IV period of the Valsalva maneuver for computation of arterial BRS, which comprised the interval from the first beat when actual systolic blood pressure exceeded its mean pretest value to the peak value of systolic blood pressure. Regression analysis was performed by means of the ANS-508 software between the RR interval and systolic pressure for corresponding heart beats (phase 0) as well as for subsequent beats delayed by 1 (phase 1), 2 (phase 2), 3 (phase 3), 4 (phase 4) beats. The phase with the highest correlation coefficient was regarded as the true reflex sensitivity, indicating reflex latency. Only regression slopes with a correlation coefficient exceeding 0.80 were accepted for analysis, and the average of the 3 maneuvers for each subject was used as the BRS.

Statistical Analysis

All data are presented as mean value±SD. Linear regression analysis was used to determine the significance of correlation between the parameters. Differences were considered statistically significant when p<0.05. The difference of average values of the parameters were analyzed by the ANOVA test and Bonferoni’s correction.

Results

Gated LVEF

The mean gated LVEF was 46.2±12.8% (range, 19–72%) in all cases. There was a significant correlation between gated LVEF and LVG EF (r=0.74, p<0.0001), and no difference in the value was found between the 2 methods.

WR of 123I-MIBG

The average global WR was 43.6±10.5% (range, 24.4–69.2%) in all cases. Fig 1 shows the regional kinetics of 123I-MIBG, which was lowest in the normal area, intermediate in the infarcted but viable area, and highest in the infarcted area. There were significant differences between the 3 areas.

For further analysis patients were divided into 2 subgroups according to their ventricular function. The mild dysfunction group (n=22) included patients with a gated LVEF above 45%, which was the mean value for these subjects. The severe dysfunction group (n=12) included patients with a gated LVEF below 45%. There was no significant difference in the value of the parameters was found between the 2 methods.
Relationship Between WR, BRS and Gated LVEF

The global WR of 123I-MIBG significantly correlated with gated LVEF (r = 0.36, p = 0.034) and BRS (r = 0.43, p = 0.015), but the correlation between gated LVEF and BRS was not significant. On the other hand, the regional WR of the normal area was significantly correlated with BRS (r = 0.72, p < 0.0001) (Fig 4). There was a significant correlation between the regional WR of the normal area and gated LVEF (r = 0.46, p = 0.006), and there was a good correlation between global WR and regional WR of the normal area (r = 0.63, p < 0.0001).

Discussion

The present study has shown that BRS is decreased and the global WR of 123I-MIBG is increased after MI, and if we analyze the regional WR, BRS has a more significant correlation with the regional WR of the normal area than with the global WR.

WR of 123I-MIBG After Acute Myocardial Infarction

The global WR of 123I-MIBG was increased in patients with AMI when compared with the reported normal value. The augmented regional WR of both the infarcted area and the infarcted but viable area was a predominant factor in the abnormal kinetics of 123I-MIBG in the mild dysfunction group. However, the augmented WR of the normal area also contributed to the fastened WR in the severe dysfunction group. These results suggest that the WR of 123I-MIBG is increased not only by myocardial ischemia but also by left ventricular dysfunction. The WR of 123I-MIBG is considered to reflect sympathetic activity, but our results suggest that in AMI the WR of 123I-MIBG is a function of both ischemic damage and left ventricular dysfunction. Bengel et al. reported that WR of 123I-MIBG was similarly enhanced in the infarcted and normal areas, which was similar to the finding in the patients in the severe dysfunction group. However, our results for the mild dysfunction group did not concur. Bengel et al. measured WR from the planar image whereas we determined it from a polar map derived from the SPECT images, which more effectively separates the infarcted and non-infarcted areas because the planar image cannot avoid an overlap between these 2 areas. Our study strongly suggests that 123I-MIBG WR after AMI should be evaluated by the SPECT images and the regional WR.

Measurement of BRS Using the Valsalva Maneuver

Pharmacological stimulation with intravenous phenylephrine has been a popular method of measuring BRS and the value obtained reportedly corresponds to the severity of chronic heart failure and is an independent predictor of total cardiac mortality after AMI. Recently, the Valsalva maneuver, which is a less invasive and more physiological approach, has been evaluated as a technique for BRS measurement. Previous studies have demonstrated the high reproducibility and close relation between the Valsalva method and the phenylephrine method. Rostango et al. reported that the BRS obtained by the Valsalva method could predict worsening outcomes in patients with ventricular dysfunction and the BRS value obtained in the present study is similar to theirs, which suggests that BRS is reduced in patients who have experienced an AMI.

We could not obtain the BRS in 3 patients, but there were no significant differences in the patients' characteristics other than gender.

Correlation Between 123I-MIBG, BRS and Gated LVEF

There are a few reports of the relation between baroreflex and left ventricular function. Grassi et al. reported a significant correlation between baroreceptor reflex and ventricular dysfunction, but Sopher et al. did not find any relationship. Our results agreed with the latter, so the interaction between baroreflex and left ventricular function is controversial.

On the other hand, there are several studies that have revealed a significant correlation between 123I-MIBG imaging and left ventricular function. Bengel et al. found a significant correlation between the global WR of 123I-MIBG and LVEF and other studies have reported a significant correlation between the global WR of 123I-MIBG and diastolic ventricular function or cardiac index in congestive heart failure. The present data are in accordance with those reports and, in addition, we divided the subjects into 2 subgroups according to their ventricular function. Both global and regional WRs of 123I-MIBG were higher for the group with a lower gated LVEF, which may be a reflection of greater activity of the sympathetic nerves. The cut-off level of the gated LVEF that separated the 2 subgroups was set as 45% in our study because it was the mean value of our subjects. When we analyzed the effect of the cut-off level, 35% or 40% of gated LVEF produced the same results.

A link between BRS and sympathetic nerve activity has been suspected, because impaired baroreceptor function
causes sustained activation of the sympathetic nerve system. Therefore, the increased WR of 123I-MIBG from the heart caused by a depressed BRS was considered to be a result of activated cardiac sympathetic nerve function. In our results, a significant but modest correlation was found between BRS and the global WR of 123I-MIBG, but the regional WR of 123I-MIBG in the normal area was more distinctly correlated with BRS, which suggests again that separation of the infarcted and non-infarcted areas is necessary for evaluation of sympathetic activation after AMI and that the regional kinetics of 123I-MIBG in the normal area is a more suitable marker of activated cardiac sympathetic nerve function than the global kinetics.

**Study Limitations**

Autonomic regulation may not be stable after MI and baroreflex function can improve soon after the event. Therefore, the best time to measure the autonomic function most efficiently after MI is not clear. Other reports that dealt with heart rate variability or BRS after AMI used a relatively wide time period, from 1 week to several weeks and we also set the timing for measurement of BRS from 1 to 4 weeks. Rovere et al reported that the BRS during the first month after MI was useful for predicting the patient’s outcome, so our result is acceptable.

In the present study, several typical regions were selected automatically into 3 categories according to the %uptake of the 99mTc and 123I-MIBG images; however, we cannot prove that the value of each borderline was appropriate for selection of the typical regions. Nevertheless, we consider that our method of classification is more objective than visual interpretation. The present study did not have normal control subjects. Some studies have reported that the baroreceptor function was more depressed and washout of 123I-MIBG from the heart was more increased in the patients with coronary artery disease and congestive heart failure than in the normal control subjects. Therefore, the lower value of the normal range needs to be determined in order to show the degree of autonomic nerve disorder.

In the present study, arterial tonometry was used to measure arterial blood pressure noninvasively during the Valsalva maneuver. Sato et al reported that the discrepancy between arterial tonometry and intra-arterial blood pressure values during Valsalva maneuver was small but statistically significant (<5 mmHg), although they could not demonstrate whether or not it influenced the value of BRS. However, the arterial tonometric method has more advantages than the other noninvasive method that is currently widely used to evaluate the value of BRS.

The present study did not measure hemodynamic or hormonal parameters and that may be necessary to reveal the exact relationship between the cardiovascular and autonomic systems. Therefore, further detailed studies are needed.

**Conclusion**

After AMI, the WR of 123I-MIBG was impaired in accordance with the severity of left ventricular dysfunction and myocardial ischemia. A suppressed BRS was related to a higher WR from the heart. There is a link between baroreceptor function and sympathetic activation, which can be evaluated by analyzing the regional WR of 123I-MIBG from the SPECT images.

**References**

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