The Cause-Effect Relationship of Sympathovagal Activity and the Outcome of Percutaneous Transluminal Coronary Angioplasty

Chuen-Den Tseng, MD, Tzong-Luen Wang, MD,
Jiunn-Lee Lin, MD, Kawn-Lih Hsu, MD,
Fu-Tien Chiang, MD,
and Yung-Zu Tseng, MD

SUMMARY

We studied 25 patients who underwent percutaneous transluminal coronary angioplasty (PTCA) to determine the association of sympathovagal imbalance and the outcome of coronary angioplasty. We examined the profiles of heart rate variability (HRV) using echocardiography, stress thallium scanning and radionuclide angiography before, immediately after and 1 month after the procedure. Coronary angiography was followed up at 6 months or if restenosis was suspected, to determine whether restenosis had occurred. Frequency domain (LF/HF) and time domain (SDNN, SDANN-ind, and r-MSSD) parameters were analyzed. According to the evolution of each parameter, we classified the patients into Group A* (improved in HRV profile) and Group B* (deteriorated in HRV profile) [x = 1 for LF/HF, 2 for SDNN, 3 for SDANN-ind, and 4 for r-MSSD]. We found that there was no definite association between Gensini score and HRV profiles at the baseline for each group. No significant changes existed between the HRV profiles before and immediately after PTCA. For the LF/HF ratio, 5 of 11 in Group B* had restenosis while 0 of 14 in Group B* and 1 of 19 in Group A* had restenosis (p<0.01). There were no significant predictive values for SDANN-ind and r-MSSD (p = 0.12 and 0.07, respectively). We conclude that the sympathovagal imbalance did not reflect the severity in coronary artery disease but was associated with restenosis after successful PTCA. (Jpn Heart J 1996; 37: 455–462)

Key words: Heart rate variability  Coronary artery disease  Percutaneous transluminal coronary angioplasty (PTCA)  Restenosis

Sympathovagal imbalance has been reported after acute myocardial infarction (AMI) and chronic stable angina. Heart rate variability,
which is one of the most popular methods with which to study sympathovagal activity, has therefore been used for evaluating these conditions\textsuperscript{1-4,8-10} and for risk stratification of post-infarct complications.\textsuperscript{5-7} Moreover, sympathovagal imbalance was involved in the prognosis of AMI, coronary artery disease (CAD) and congestive heart failure (CHF). However, there have only been a few reports of sympathovagal alteration after PTCA.\textsuperscript{9-11} Our previous study showed that in patients with significant CAD, diastolic and systolic wall stress indices and segmental left ventricular dysfunction were synergistically involved in determining their sympathovagal imbalance.\textsuperscript{12} Since an alternation in the cardiac geometry that influences the discharge of afferent sympathetic mechanoreceptors is thought to be the mechanism of the derangement in autonomic control of heart rate in patients with one-vessel coronary artery disease,\textsuperscript{13} it is possible that the simple mechanism can account for sympathovagal imbalance in ischemic heart disease and thus for the development of restenosis after PTCA. The purpose of this study was to investigate the relationship between autonomic nervous function and the possible outcome (restenosis or not) after PTCA using serial Holter monitoring for assessing the evolution of frequency and time domain measures of heart rate variability. Various parameters of concomitant echocardiograms, stress thallium scan, radionuclide angiography and catheterizations were also evaluated in patients who underwent successful PTCA.

**METHODS**

**Patients and study protocol:** We considered for entry in the study 100 patients with significant coronary artery disease who underwent successful coronary angioplasty between June 1993 and July 1994. Patients were excluded if they had a history of 1) myocardial infarction within 1 year; 2) moderate to severe hypertension; 3) diabetes; 4) congestive heart failure; or 5) significant valvular heart disease. Finally 25 patients (22 men, 3 women; mean [± SD] age 64 ± 12 years) were enrolled. Each patient signed a written informed consent form approved by the Ethical Committee of our institution.

Holter monitoring for heart rate variability analysis was performed in hospital 24 hours before coronary angioplasty and was repeated 1 month after the procedure.

**Drug administration:** All patients were treated with a calcium blocking agent, usually diltiazem, 30 to 60 mg three times a day, and with long-acting nitrates and aspirin at the time of first evaluation and during follow-up. Any other medicine which could potentially affect sympathovagal activities was avoided as much as possible.

**Processing of 24-hour Holter monitoring:** All 24-hour Holter recordings
were analyzed at the Electrophysiology Laboratory of our institution using an analyzer around a microprocessor provided by Marquette Electronics (Orange County, USA). The two ECG analog channels, read by a Delmar Avionics electroscanner at 60 times the recording speed, were sampled at 10 kHz. In addition to evaluation of the usual ECG variables, including identification of QRS widths and shapes and RR interval abnormalities, the sequences of all RR intervals were stored, and each RR interval was labeled with a code number identifying its normality or class of abnormality. The computer program automatically detects and labels each QRS complex and filters out the RR intervals that differ in duration by > 30% from the previously accepted intervals. A physician would make a final check to detect the falsely labeled RR intervals and artifacts. Patients with persistent rhythm anomalies and tapes with excessive artifacts were excluded. The sequence of normal RR intervals (NN), after exclusion of each abnormal interval and of the two before and after it, used only for timekeeping purposes, was analyzed to compute frequency domain measures of heart rate variability.

The following time domain indices of heart rate variability were determined: (1) r-MSSD = root-mean-square of successive differences in normal RR (NN) intervals among consecutive normal beats; (2) SDNN index = the mean of the standard deviations of all NN intervals for all 5-minute segments; (3) SDANN index = the standard deviations of the average NN intervals of all 5-minute segments. In the frequency domain, we determined: (1) total frequency power = the total power from 0.00066 to 0.40 Hz expressed in milliseconds squared; (2) high-frequency power = the total power from 0.15 to 0.40 Hz; (3) low-frequency power = the total power from 0.04 to 0.15 Hz; (4) very-low frequency power = the total power from 0.0033 to 0.04 Hz; (5) ultra-low frequency power = the total power from 0.00066 to 0.0033 Hz. The power spectra were calculated (after correction for ectopy and noise by deletion and substitution of the subsequent NN interval) as the average of all nonoverlapping 2-minute power spectra using a 256-point fast Fourier transform with software provided by Marquette Electronics. Power spectral analysis of heart rate variability refers to the determination of the specific frequencies at which variations in heart rate occur. The technique yields a curve describing the amplitudes of the individual frequency components of a patient’s heart rate variability. The amplitudes of the oscillation, or “power”, which is amplitude squared, at any given frequency and the total contribution to heart rate variability contained within a range of frequencies can then be analyzed.

Because the distribution of the frequency domain measures of heart period variability are extremely skewed, the log transformation (Ln) of each measure (which produces nearly normal distribution) was applied before statistical analysis.
was performed.

**Cardiac catheterization, coronary angiography and angioplasty:** Right-sided catheterization values including pressure tracings and oxygen saturation at each cardiac chamber were recorded according to well-established methods. Coronary angiography was performed before the angioplasty in ≥3 projections, with cranial and/or caudal angulated views. The view with the best visualization of the lesion was selected and the severity of the stenosis diameter program included in the Phillips DCI S system (Rotterdam, the Netherlands). Severity of all coronary lesions was determined by visual assessment with the consensus of two experienced angiographers. The presence of collateral flow was graded as proposed by Cohen and Rentrop: 0 = no visible collaterals; 1 = visible intraseptal collateral channels; 2 = partial filling of a segment of the left anterior descending artery or the main side branches; and 3 = complete filling of the artery and its side branches. Left ventricular ejection fraction was calculated in the 30° right anterior oblique projection using the area-length method. All coronary lesions with >70% narrowing or stenosis of the left main coronary artery >50% were considered significant. Gensini scores and coronary artery disease prognosis indices were also calculated according to the established method to assess the severity of the coronary artery disease. Restenosis after PTCA was defined angiographically as luminal narrowing greater than 50% at the site of a previously successful PTCA.

**Statistical analysis:** Categoric variables are expressed as percent and were compared using the chi-square test. Continuous data are expressed as the mean value ± SD and were analyzed using one-way analysis of variance; if a significant ($p < 0.05$) F test was found, Student’s $t$ test for unpaired observations with the Bonferroni correction was used for multiple comparison. A paired $t$ test was performed to evaluate data obtained in the same group. A simple linear regression model was also used for evaluating the correlation coefficient between different clinical data and parameters of heart rate variability. If a $p < 0.05$ could be reached in the univariate analysis, the related variable would be enrolled into the multivariate analysis. Statistical significance was defined as $p < 0.05$.

**Results**

**Relationship between heart rate variability and coronary angioplasty:** Among the 25 consecutive patients who accomplished the complete work-up, we found that the baseline HRV profile had poor correlation with the Gensini score ($r = 0.31, p > 0.05$) by the linear regression model. The frequency domain (LF/HF) and time domain (SDNN, SDANN-ind and r-MSSD) parameters evolved after angioplasty. Comparing each parameter before and 1 month after PTCA,
HEART RATE VARIABILITY AND RESTENOSIS OF PTCA

Table I. HRV Profiles between Group Ax (Improved) and Group Bx (Deteriorated) among 25 CAD Patients before and 1 Month after PTCA

<table>
<thead>
<tr>
<th>Group</th>
<th>LF/HF</th>
<th>SDNN (ms)</th>
<th>SDANN-ind (ms)</th>
<th>r-MSSD (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A1</td>
<td>B1</td>
<td>A2</td>
<td>B2</td>
</tr>
<tr>
<td>Before</td>
<td>3.50±2.29*</td>
<td>1.98±0.79</td>
<td>107±28</td>
<td>132±20</td>
</tr>
<tr>
<td></td>
<td>90±25*</td>
<td>115±22</td>
<td>23.8±6.7*</td>
<td>34.7±11.5</td>
</tr>
<tr>
<td>1 month</td>
<td>2.02±0.95</td>
<td>2.65±0.86</td>
<td>131±35</td>
<td>106±27</td>
</tr>
<tr>
<td></td>
<td>118±35</td>
<td>88±26</td>
<td>32.2±8.8</td>
<td>27.1±8.6</td>
</tr>
<tr>
<td>p value**</td>
<td>0.013</td>
<td>&lt;0.0001</td>
<td>0.023</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*p < 0.05 compared with the corresponding Group B for the same parameter at the same time period; **p value means the significance of the changes in profile determined using the paired t-test.

Table II. Comparison of the Frequency in Group Ax or Group Bx vs Those with or without Restenosis among the 25 PTCA Patients

<table>
<thead>
<tr>
<th>LF/HF</th>
<th>Restenosis</th>
<th>No restenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A1</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Group B1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>p = 0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A2</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Group B2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>p &lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDANN-ind.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A3</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Group B3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>p = NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>r-MSSD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>group A4</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>group B4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>p = NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

we classified the patients into group Ax and group Bx, in which group A had HRV parameters which improved while group B had HRV parameters which deteriorated; x = 1 for LF/HF, 2 for SDNN, 3 for SDANN-ind and 4 for r-MSSD. Table I tabulates the comparisons between the two groups for various parameters. In addition to significant changes in each parameter between baseline and 1 month after PTCA, there were also significant differences between all of the group Ax and group Bx pairs.

Relationship between heart rate variability and restenosis: Of the 25 patients, 5 (20%) developed restenosis in the subsequent 2–6 months. Comparing the HRV and the possibility of restenosis, we found that the difference in the frequencies between the groups with restenosis and without restenosis were significant in LF/HF and SDNN but not significant in SDANN-ind and r-MSSD (Table II). This indicates that the HRV profiles at 1 month after PTCA have a predictive value for a subsequent restenosis.
DISCUSSION

Our data have shown that the HRV profile had a poor correlation with the Gensini score in CAD patients needing PTCA, indicating that sympathovagal imbalance did not reflect the severity of the CAD score. The HRV showed a significant change 1 month after PTCA, indicating that sympathovagal influence could play some role in the recovery of myocardial ischemia after PTCA. This is consistent with the findings of our previous study. According to the literature, high frequency power represents a measure of the modulation of vagal tone by respiratory frequency and depth. Thus, the increase in high frequency power after coronary angioplasty reflects the recovery of parasympathetic nervous activity. Lower frequency power, measured under strictly controlled circumstances using autoregressive analysis, has been considered an indicator of sympathetic nervous system activity. However, during 24-hour recording it reflects predominantly parasympathetic activity. Therefore, the increase in low frequency power we observed after coronary angioplasty also indicates a recovery of parasympathetic activity. Most likely, regional left ventricular dysfunction may increase afferent sympathetic activity from the heart, which in turn inhibits efferent vagal nerve activity (other than inducing an increase in efferent sympathetic activity.) Thus, after coronary angioplasty the improvement in regional left ventricular dysfunction could have reduced afferent sympathetic activity, which results in an improvement in Holter measures of vagal activity. The existence in the left ventricle of receptors subserved by vagal afferent fibers must also be considered; the activation of these receptors elicits cardioinhibitory vasodepressor and sympathoinhibitory responses. In particular, the discharge pattern of ventricular receptors with unmyelinated afferents is influenced by increases in preload and afterload and by a change in cardiac contractility. Therefore, the recovery of regional left ventricular function may conceivably increase the firing of these vagal afferent fibers and, as a consequence, increase the activity of vagal fibers directed to the sinus node. In addition, evolution of the SDANN index which evaluates long-term RR variations can furthermore support the hypothesis that the improvement in heart rate variability after successful coronary angioplasty depends mainly upon the modification of parasympathetic activity instead of sympathetic tone.

Our data furthermore show that HRV profiles at 1 month after PTCA play some part in predicting the possibility of restenosis occurring later on (Table II). The underlying mechanism was uncertain. It probably means that hemodynamic changes and regional wall motion abnormalities due to myocardial ischemia may precede restenosis. In conclusion, the sympathovagal imbalance from the HRV profile in these patients did not reflect the severity of CAD but was associated with
the restenosis after PTCA. Whether sympathovagal imbalance indicated by the HRV data causes abnormal vascular responses and possibly an atherosclerotic effect need further investigation.

REFERENCES


