COMPARISON OF THE EFFECTS OF EXERCISE AND ISOPROTERENOL ON THE ANTEGRADE REFRACTORY PERIOD OF THE ACCESSORY PATHWAY IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME

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The effects of exercise and isoproterenol infusion on the antegrade effective refractory period of the accessory pathway (ERP-AP) were compared in 10 patients with Wolff-Parkinson-White (WPW) syndrome. During an electrophysiologic study, the ERP-AP (paced cycle length: 400 msec) was measured before and during isoproterenol infusion at a rate of 1 μg/min. On the next day, a symptom-limited ergometer exercise test was performed and the ERP-AP (paced cycle length: 400 msec) was measured before and during the test using an indwelling atrial electrode catheter. Isoproterenol infusion and the exercise test increased the heart rate from 84 ± 24 to 122 ± 17 beats/min and from 85 ± 25 to 128 ± 25 beats/min, respectively (p = NS isoproterenol versus exercise). The ERP-AP was shortened from 268 ± 34 to 230 ± 19 msec with isoproterenol infusion (p < 0.001) and from 273 ± 42 to 237 ± 31 msec with the exercise test (p < 0.001). There was no significant difference between the effects of isoproterenol and exercise. The percent change in the ERP-AP with exercise (Y) was significantly correlated to that with isoproterenol infusion (X) (Y = -3.04 + 0.70X, r = 0.92, p < 0.001). In conclusion, isoproterenol infusion at the present dose shortens the ERP-AP to the same degree as exercise, and thus is useful for predicting the exercise-induced shortening of the ERP of the accessory pathway in patients with WPW syndrome. (Jpn Circ J 1994; 58: 22–28)

Atrial fibrillation with a rapid ventricular response is a life-threatening event in patients with Wolff-Parkinson-White (WPW) syndrome. This is especially true for patients with a short antegrade effective refractory period of the accessory pathway (ERP-AP). To evaluate the degree of risk for such a life-threatening event, the ERP-AP or the shortest R-R interval during induced atrial fibrillation is generally measured with an electrophysiologic study. However, an electrophysiologic study at rest may be insufficient for evaluating the risk faced by a patient with WPW syndrome. Changes in autonomic tone that occur during exercise or due to anxiety or hypotension associated with the arrhythmia may influence the functional properties of the accessory pathway.

Key words:
Effective refractory period of the accessory pathway
Exercise
Isoproterenol
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and affect the ventricular response during atrial fibrillation. However, it is not always easy to perform an exercise test during an invasive electrophysiologic study in every patient.

Isoproterenol infusion is widely used to predict exercise-induced changes in properties of the accessory pathway, but the correlation between the effects of exercise and isoproterenol on the ERP-AP has not been examined sufficiently. To determine whether isoproterenol infusion could be used as a substitute for exercise, we compared the effects of exercise and isoproterenol infusion on the ERP-AP in patients with WPW syndrome.

### TABLE I  PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex/Age</th>
<th>Location of AP</th>
<th>Documented arrhythmias</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/23</td>
<td>right paraseptal</td>
<td>CMT, af</td>
</tr>
<tr>
<td>2</td>
<td>M/51</td>
<td>left lateral</td>
<td>CMT, af</td>
</tr>
<tr>
<td>3</td>
<td>M/27</td>
<td>right posterior</td>
<td>CMT</td>
</tr>
<tr>
<td>4</td>
<td>F/29</td>
<td>right posterior</td>
<td>CMT</td>
</tr>
<tr>
<td>5</td>
<td>M/13</td>
<td>left lateral</td>
<td>CMT, af</td>
</tr>
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<td>left lateral</td>
<td>CMT, af</td>
</tr>
<tr>
<td>7</td>
<td>M/66</td>
<td>right paraseptal</td>
<td>CMT</td>
</tr>
<tr>
<td>8</td>
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<td>right paraseptal</td>
<td>CMT, af</td>
</tr>
<tr>
<td>9</td>
<td>F/50</td>
<td>right paraseptal</td>
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</tr>
<tr>
<td>10</td>
<td>M/44</td>
<td>right paraseptal</td>
<td></td>
</tr>
</tbody>
</table>

$af=$ atrial fibrillation, $AP=$ accessory pathway, $CMT=$ circus movement tachycardia utilizing an accessory pathway.

Electrophysiologic study

Using standard techniques, 3 electrode catheters (USCI) were introduced percutaneously into the femoral vein and advanced to cardiac chambers under a fluoroscopic control: one quadrupolar Josephson catheter was positioned at the high right atrium, one tripolar catheter was positioned at the His bundle site and one quadrupolar Josephson catheter was positioned at the right ventricular apex. Another quadrupolar Josephson catheter was introduced percutaneously into the right subclavian vein and advanced into the coronary sinus. Atrial and ventricular pacing were accomplished with a use of a programmable stimulator (Nihon Kohden SEC3102, Japan) that delivered rectangular pulses with a 2 msec duration at an output of twice the diastolic threshold. The location of the accessory pathway was determined by catheter mapping along the atrioventricular groove during circus movement tachycardia and ventricular rapid pacing. The site which showed the shortest ventriculo-atrial conduction interval was defined as the accessory pathway site. The antegrade ERP-AP was measured with a standard extrastimulus technique from the high right atrium during atrial pacing at a
### TABLE II  THE ELECTROPHYSIOLOGIC PARAMETERS BEFORE AND DURING ISOPROTERENOL INFUSION AND BEFORE DURING THE ERGOMETER EXERCISE TEST

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Isoproterenol</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ERP-AP</td>
<td>HR</td>
</tr>
<tr>
<td></td>
<td>Baseline (msec)</td>
<td>ISP (msec)</td>
</tr>
<tr>
<td>1</td>
<td>240</td>
<td>210</td>
</tr>
<tr>
<td>2</td>
<td>220</td>
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<td>3</td>
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<td>260</td>
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<td>9</td>
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<td>250</td>
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<td>10</td>
<td>250</td>
<td>210</td>
</tr>
</tbody>
</table>

*Mean ± SD = 268 ± 34, 230 ± 19*, -14 ± 7, 84 ± 24, 122 ± 17*, +50 ± 23, 273 ± 42, 237 ± 31*, -13 ± 5, 85 ± 25, 128 ± 25*, +60 ± 32

bpm = beats/min, ΔERP = % change in ERP-AP from the baseline, ERP-AP = effective refractory period of the accessory pathway, Ex = exercise, HR = heart rate, ΔHR = % change in heart rate from the baseline, ISP = isoproterenol, SD = standard deviation, *p < 0.001 vs baseline value.
cycle length of 400 msec. After the baseline ERP-AP was determined, isoproterenol was administered intravenously at a rate of 1.0 μg/min. Measurement of the antegrade ERP-AP was repeated during isoproterenol infusion after the heart rate stabilized. The study was terminated after a 5 French-size bipolar electrode catheter with a helical tip (Cordis) was inserted through the right subclavian vein and left in the right atrial appendage. During the electrophysiologic study, 3 leads of the electrocardiogram (I, II and V1) and bipolar electrograms (filtered with a bandpass between 50 and 1000 Hz) at the high right atrium, proximal and distal coronary sinus. His bundle position and right ventricular apex, were continuously monitored on an oscilloscope using a polygraph (Sen-ei 361, Japan) and recorded at a paper speed of 100 mm/sec. All data were also recorded on a Sony NFR-3000 tape recorder for subsequent playback and analysis.

Exercise Test

On the next day, all of the patients performed an exercise test using a bicycle ergometer (Siemens S-002) in an upright position. Three leads of the electrocardiograms in which the delta wave was most clearly depicted were monitored continuously and atrial extrastimulation using an indwelling bipolar electrode catheter was performed by the same method used during the electrophysiologic study. After the baseline ERP-AP was determined, the exercise was started at a workload of 50 W and increased by 25 W every 2 min. When the patient complained of fatigue, the workload was decreased by 25 W and maintained. The antegrade ERP-AP was measured again at this exercise load.
Fig. 2. Left Panel: Correlation between the percent change in the effective refractory period of the accessory pathway (ERP-AP) during isoproterenol infusion and the baseline ERP-AP determined before isoproterenol infusion. Right Panel: Correlation between the percent change in the ERP-AP during the exercise test and the baseline ERP-AP determined before exercise.

Fig. 3. Correlation between the percent change in the effective refractory period of the accessory pathway (ERP-AP) during isoproterenol infusion and that during the exercise test.

Statistical Analysis
All values are expressed as the mean ± one standard deviation. Statistical analysis was performed using the paired and unpaired t-tests. Correlation coefficients were obtained by the least square method. A p value <0.05 was considered statistically significant.

RESULTS
Effect of Isoproterenol on the Effective Refractory Period of the Accessory Pathway
The heart rate increased from 84 ± 24 beats/min to 122 ± 17 beats/min (p < 0.001) with isoproterenol infusion (Table II, Fig. 1: left panel). The ERP-AP was shortened from 268 ± 34 msec to 230 ± 19 msec with isoproterenol infusion (p < 0.001) and the percent change from the control was −14 ± 7% (Table II, Fig. 1: right panel). The number of high risk patients, i.e., those with an effective refractory period of less than 220 msec, increased from 1 to 5 after isoproterenol infusion. The percent change in the ERP-AP correlated with the baseline ERP-AP that was determined before isoproterenol infusion (p < 0.01) (Fig. 2: left panel). In other words, patients who had a longer ERP-AP showed a greater change in the ERP-AP with isoproterenol infusion.

Effect of Exercise on the Effective Refractory Period of the Accessory Pathway
The maximum workload during exercise ranged from 75 to 100 W and the antegrade conduction over the accessory pathway persisted during exercise testing in all of the pa-

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tients. The heart rate increased from $85 \pm 25$ beats/min to $128 \pm 25$ beats/min with exercise ($p<0.001$) and this change was not significantly different from that induced by isoproterenol infusion (Table II, Fig. 1: left panel). In all of the patients, the ERP-AP decreased with exercise from $273 \pm 42$ msec to $237 \pm 31$ msec ($p<0.001$) with a percent change from baseline of $-13 \pm 5\%$ (Table II, Fig. 1: right panel). The number of high risk patients increased from 1 to 5 after exercise.

There was no significant difference between the changes in the ERP-AP induced by isoproterenol infusion and those induced by exercise testing (Fig. 1: right panel). The percent change in the ERP-AP correlated with the baseline ERP-AP that was determined before the exercise ($p<0.05$) (Fig. 2: right panel). In other words, patients who had a long ERP-AP showed a greater change in the ERP-AP with exercise. There was a significant correlation between the percent change in the ERP-AP induced by exercise and that induced by isoproterenol ($p<0.001$) (Fig. 3).

**DISCUSSION**

The antegrade ERP-AP is a major determinant of ventricular response during atrial fibrillation in patients with WPW syndrome. A short ERP-AP leads to a rapid ventricular response during atrial fibrillation and may lead to ventricular fibrillation. In patients with WPW syndrome, therefore, the antegrade ERP-AP is used to assess the risk of sudden cardiac death during atrial fibrillation. Although the effective refractory period can be measured during an invasive electrophysiologic study, it is generally assessed in the supine, resting position. Since exercise changes the tone of the autonomic nervous system, it may influence the functional properties of the accessory pathway and thus affect the ventricular response during atrial fibrillation. Assessment of the properties of the accessory pathway at rest is not sufficient for predicting the potential for the development of life-threatening arrhythmia in patients with WPW syndrome. In the present study, to assess the changes in the functional properties of the accessory pathway during exercise, the ERP-AP was measured before and during an upright ergometer exercise test using an indwelling bipolar electrode catheter with a helical tip left in the atrial appendage. Furthermore, this result was compared to that obtained from an isoproterenol infusion test during an electrophysiologic study. This study clearly showed that the antegrade ERP-AP was significantly shortened by the ergometer exercise test, as well as by isoproterenol infusion. Furthermore, the percent change in the ERP-AP induced by exercise significantly correlated with that induced by isoproterenol infusion. Frank et al. measured the ERP-AP in 14 patients at rest and during a submaximal exercise test and found a 26% reduction in the mean ERP-AP with exercise. Crick et al. induced atrial fibrillation at rest and during a maximal exercise test in 10 patients with WPW syndrome and found an average reduction of 28% in the minimal R-R interval between 2 preexcited cycles recorded during exercise. Our data from the exercise test are consistent with these previous results. An obvious improvement of the conduction over the accessory pathway during exercise was demonstrated, especially in patients with a relatively long refractory period. Thus, assessment of the accessory pathway at rest seems to be insufficient for identifying patients who have a high risk of developing life-threatening arrhythmia.

Infusion of isoproterenol during the electrophysiologic study showed similar results. Wellens et al. found an average reduction of 18% in the ERP-AP with isoproterenol infusion. Cosio et al. found that isoproterenol infusion caused a shortening of the minimal R-R interval between 2 preexcited cycles (from 270 to 180 msec) during atrial fibrillation. Although a significant shortening of the ERP-AP with both isoproterenol and exercise has been previously reported, the correlation between the changes induced by isoproterenol and exercise has not been examined sufficiently. According to a recent report in which isoproterenol infusion and a supine ergometer exercise test were performed successively during one electrophysiologic study, isoproterenol and the exercise test induced a similar decrease in the ERP-AP. In the present study, isoproterenol infusion at a rate of 1 μg/min caused a significant improvement of the conduction over the accessory pathway and the change.
in the ERP-AP significantly correlated with that induced by the upright ergometer exercise test that was performed in a symptom-limited manner on the next day. Thus, the results of the present study are consistent with those reported recently\(^{14}\) and they suggest that isoproterenol infusion at the present rate during an electrophysiologic study is quite useful for predicting the change in the ERP-AP caused by exercise in patients with WPW syndrome. The effects of isoproterenol and exercise on the shortest R-R interval during atrial fibrillation were not evaluated in this study. Chimienti et al\(^{14}\) reported that exercise induced a smaller reduction of the mean and the shortest R-R interval during atrial fibrillation than isoproterenol, despite a similar increase in heart rate and a similar shortening of the ERP-AP.

**Limitation**

The antegrade ERP-AP was measured by atrial pacing from the high right atrium during isoproterenol infusion, but by atrial pacing from the right atrial appendage during the ergometer exercise test. Measurement of the refractory period of the accessory pathway can be affected by the intervening tissue between the pacing and accessory pathway sites. Thus, overestimation of the accessory pathway refractory period may occur due to conduction delay in this intervening tissue, especially in cases with a left-sided accessory pathway. In this study, since the relationship between the pacing site and the accessory pathway site was the same in both the isoproterenol infusion test and the exercise test, the influence of the intervening tissue on the effects of isoproterenol and exercise on the accessory pathway refractory period is believed to be minimal.

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