Long-term Follow-up of the Reproducibility of Carotid Sinus Hypersensitivity in Patients with Carotid Sinus Syndrome

Mitsuhiro Nishizaki, M.D., Masataka Arita, M.D., Harumizu Sakurada, M.D.* Takahiro Ohta, M.D., Noriyoshi Yamawake, M.D., Fujio Numano, M.D.** and Masayasu Hiraoka, M.D.***

The reproducibility of carotid sinus hypersensitivity to carotid sinus massage was studied in the long-term follow-up of 8 patients with carotid sinus syndrome. A cardioinhibitory response was induced in 7 patients, while a vasodepressor response was found in the remaining patient. The 7 patients were treated with dual-chamber pacemaker implantation and the remaining patient was treated with propranolol. All of the patients remained asymptomatic during a follow-up period of 48 ± 11 months.

Carotid sinus massage during the follow-up period in patients with a cardioinhibitory response revealed asystolic intervals of 3 s or longer in 4 patients and in 3 patients at the second and third follow-up examinations, respectively, although there were no significant differences in the ventricular asystolic intervals between before, and 34 ± 11 months and 48 ± 11 months after treatment. However, each patient showed a wide variation in asystolic intervals. The differences in asystolic intervals between prior to treatment (first) and the third test were significantly greater than those between the first and the second test (2.4 ± 1.2 s vs 0.7 ± 0.6 s; p < 0.05). The one patient with a vasodepressor response had a decreased systolic blood pressure greater than 50 mmHg by carotid sinus massage at all three occasions.

In conclusion, most patients with carotid sinus syndrome showed abnormal and variable responses to carotid sinus massage during long-term follow-up period although there was no recurrence of symptoms after treatments. The lack of symptoms in these patients was believed to have been due to effective treatment with dual-chamber pacing and β-blocker, rather than to spontaneous remission. (Jpn Circ J 1995; 59: 33–39)

Carotid sinus syndrome is characterized by carotid sinus hypersensitivity and the presence of symptoms, including dizziness, presyncope or syncope!−6 Although patients with carotid sinus syndrome who receive cardiac pacing and other treatments often become asymptomatic during the follow-up period7–12 it is unclear whether the disappearance of symptoms following treatment is due to effective treatment or spontaneous remission of symptoms. Furthermore, it is also unclear whether or not the abnormal findings observed in carotid

---

Key words:
Carotid sinus syndrome
Carotid sinus hypersensitivity
Carotid sinus massage
Long-term follow-up
Unexplained syncope

(Received March 9, 1994; accepted July 4, 1994)
Department of Cardiology Yokohama Minami Kyosai Hospital
*Department of Cardiology Tokyo Metropolitan Hiroo Hospital
**Third Department of Internal Medicine, School of Medicine
***Department of Cardiovascular Diseases, Medical Research Institute, Tokyo Medical and Dental University
Mailing address: Mitsuhiro Nishizaki, M.D., Department of Cardiology Yokohama Minami Kyosai Hospital 500 Mutsuura, Kanazawaku, Yokohama Kanagawa, 236, Japan
sinus massage persist for long periods of time. In this study, we examined the reproducibility of carotid sinus hypersensitivity by carotid sinus massage during long-term follow-up in patients with carotid sinus syndrome.

METHODS

Patient Population
The study population consisted of 8 patients with carotid sinus syndrome (8 men, mean age: 63 ± 7 years). All of the patients had experienced at least one episode of sudden and unexplained loss of consciousness followed by rapid, complete recovery. No other cause for syncope could be identified despite a thorough medical history and examination in each patient, including 24-h ambulatory ECG monitoring, electroencephalography and computed tomography of the brain.

Carotid Sinus Massage
Carotid sinus massage was performed in all of the patients for approximately 5 s in the morning, first on one side of the neck and then on the other, in the supine position. The area of the carotid sinus was compressed with longitudinal massage or static pressure with the neck extended. The direction of the compression on the carotid artery was usually against the vertebral spine at the upper neck level. Carotid occlusion was avoided. An electrocardiogram and blood pressure monitoring by an intraarterial line were performed during testing. Cardioinhibitory carotid sinus syndrome was defined as symptomatic ventricular asystole lasting at least 3 s induced by carotid sinus massage. Vasodepressor carotid sinus syndrome was defined as a decrease in systolic blood pressure of at least 50 mmHg or more in association with symptoms and asystole of less than 3 s during carotid sinus massage. Mixed carotid sinus syndrome was defined as a combination of the cardioinhibitory and vasodepressor types. In this type, a drop in systolic blood pressure was observed while heart rate was kept constant by administration of atropine or ventricular pacing. Maximum ventricular asystolic interval and a decrease in systolic blood pressure were measured during carotid sinus massage, and the procedures were repeated bilaterally at least three times in each patient.

Electrophysiologic Study
After obtaining informed consent, electrophysiologic testing was performed in all of the patients in a fasting and non-sedate state. Multipolar catheters were positioned in the high right atrium, His bundle electrogram recording site and the right ventricular apex. Surface lead ECGs were recorded simultaneously with intracardiac electrograms (RM-600 recorder; Nihon Kohden Co., Tokyo). All intracardiac electrograms were filtered at 50 to 500 Hz and recorded at a paper speed of 100 mm/s. Electrical stimuli were delivered through a cardiac stimulator (BCO2: Fukuda Denshi, Tokyo) at twice the strength of the diastolic threshold.

Measurements were made of the maximal sinus node recovery time, corrected sinus recovery time, and the pacing rate which demonstrated Wenckebach atrioventricular block during incremental rapid atrial pacing. The sinoatrial conduction time was determined by Narula’s method. The effective refractory period of the atrioventricular node was obtained by premature extrastimuli from the high right atrium at a basic cycle length of 600 ms. Atropine sulfate was then administered intravenously at a dose of 0.04 mg/kg and carotid sinus massage was repeated. The intrinsic heart rate was measured after intravenous administration of 0.2 mg/kg of propranolol with atropine.

Follow-up Examination
All of the patients were examined in our clinic every 1 to 2 months during a mean follow-up period of 48 ± 11 months (range 31 to 61 months) after discharge from the hospital. Relief from symptoms was checked at each visit to the clinic in each patient during this follow-up period. Carotid sinus massage was repeated during the follow-up period with a temporary cessation of cardiac pacing or oral administration of drugs in treated patients.

Data Analysis
Values are expressed as mean ± SD. Continuous variables were compared using an analysis of variance and a paired t-test. A p value of < 0.05 was considered significant.
TABLE I CLINICAL FINDINGS AND RESPONSE TO CAROTID SINUS MASSAGE IN PATIENTS WITH CAROTID SINUS SYNDROME

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/Sex</th>
<th>Symptoms</th>
<th>Associated Diseases</th>
<th>Type of CSS</th>
<th>CSM Site of CSS</th>
<th>Site of Block</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55/M</td>
<td>Syncope</td>
<td>Arteriosclerosis</td>
<td>CI</td>
<td>Lt</td>
<td>Sinus Node</td>
<td>DDD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>obliterans</td>
<td></td>
<td>Lt, Rt</td>
<td>Sinus node, AV node</td>
<td>DDD</td>
</tr>
<tr>
<td>2</td>
<td>58/M</td>
<td>Syncope</td>
<td>(-)</td>
<td>CI</td>
<td>Lt</td>
<td>Sinus node</td>
<td>DDD</td>
</tr>
<tr>
<td>3</td>
<td>58/M</td>
<td>Syncope</td>
<td>(-)</td>
<td>CI</td>
<td>Lt, Rt</td>
<td>Sinus node, AV node</td>
<td>DDD</td>
</tr>
<tr>
<td>4</td>
<td>61/M</td>
<td>Syncope</td>
<td>Hypertension</td>
<td>CI</td>
<td>Lt</td>
<td>Sinus node</td>
<td>DDD</td>
</tr>
<tr>
<td>5</td>
<td>62/M</td>
<td>Syncope</td>
<td>CAD</td>
<td>CI</td>
<td>Lt, Rt</td>
<td>Decreased BP</td>
<td>β-blocker</td>
</tr>
<tr>
<td>6</td>
<td>65/M</td>
<td>Syncope</td>
<td>(-)</td>
<td>CI</td>
<td>Lt, Rt</td>
<td>Sinus node, AV node</td>
<td>DDD</td>
</tr>
<tr>
<td>7</td>
<td>70/M</td>
<td>Syncope</td>
<td>CAD</td>
<td>CI</td>
<td>Lt, Rt</td>
<td>Sinus node, AV node</td>
<td>DDD</td>
</tr>
<tr>
<td>8</td>
<td>78/M</td>
<td>Syncope</td>
<td>CAD</td>
<td>CI</td>
<td>Lt, Rt</td>
<td>Sinus node, AV node</td>
<td>DDD</td>
</tr>
</tbody>
</table>

CSS = carotid sinus syndrome; CSM = carotid sinus massage; CI = cardioinhibitory; VD = vasodepressor; CAD = coronary artery disease; DDD = dual-chamber pacemaker; AV = atrioventricular; BP = blood pressure

TABLE II ELECTROPHYSIOLOGIC FINDINGS IN PATIENTS WITH CAROTID SINUS SYNDROME

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Rate of AV Wenckebach conduction (ms)</th>
<th>AVN ERP (msec)</th>
<th>SACT (msec)</th>
<th>Maximal SRT (msec)</th>
<th>Corrected SRT (msec)</th>
<th>HR before and after atropine (beat/min)</th>
<th>IHR (beat/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>180</td>
<td>&lt;300</td>
<td>125</td>
<td>1480</td>
<td>380</td>
<td>54 → 75</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>140</td>
<td>320</td>
<td>50</td>
<td>910</td>
<td>230</td>
<td>—</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>140</td>
<td>360</td>
<td>94</td>
<td>1120</td>
<td>320</td>
<td>74 → 117</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>160</td>
<td>360</td>
<td>135</td>
<td>1300</td>
<td>350</td>
<td>63 → 98</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>190</td>
<td>&lt;260</td>
<td>50</td>
<td>910</td>
<td>270</td>
<td>92 → 115</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>180</td>
<td>&lt;320</td>
<td>127</td>
<td>1580</td>
<td>440</td>
<td>54 → 90</td>
<td>62</td>
</tr>
<tr>
<td>7</td>
<td>130</td>
<td>370</td>
<td>125</td>
<td>1860</td>
<td>440</td>
<td>42 → 75</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>130</td>
<td>410</td>
<td>98</td>
<td>1140</td>
<td>390</td>
<td>69 → 122</td>
<td>79</td>
</tr>
</tbody>
</table>

AV = atrioventricular; ERP = effective refractory period; AVN = atrioventricular node; SACT = sinoatrial conduction time; SRT = sinus recovery time; HR = heart rate; IHR = intrinsic heart rate

RESULTS

Carotid sinus syndrome was demonstrated by carotid sinus massage in all 8 patients. A cardioinhibitory response to carotid sinus massage was induced in seven patients, while a vasodepressor response was induced in the remaining patient (Table I).

All of the patients with carotid sinus syndrome underwent electrophysiologic testing (Tables I, II). The rate of atrial pacing which demonstrated Wenckebach atrioventricular block, the effective refractory period of the atrioventricular node, the sinoatrial conduction time, and the corrected sinus recovery time were nearly normal in all patients. The heart rate after the administration of atropine sulfate and the intrinsic heart rate were abnormal in 3 patients (patients 1, 6, and 7), and were within normal limits in the remaining patients. Among the 7 patients with a cardioinhibitory response, 3 had sinus arrest and 4 had both sinus arrest and atrio-Hisian block. However, a prolonged ventricular asystole was not induced by carotid sinus massage after administration of atropine sulfate in these patients. In the sole patient with a vasodepressor response, a decrease in systolic pressure by 80 mmHg was observed, although the heart rate was kept constant by administration of atropine.

The 7 patients with cardioinhibitory carotid sinus syndrome were treated with dual-chamber pacing. The patient with vasodepressor carotid sinus syndrome received oral propranolol.

During a follow-up period of $48 \pm 11$ months, all of the patients remained asymptomatic with treatment. Carotid sinus massage during the follow-up period in the 7 patients with cardioinhibitory carotid sinus syndrome revealed ventricular asystolic intervals of $4.3 \pm 1.4$ s prior to treatment, $4.0 \pm 1.6$ s at $34 \pm 11$ months and $4.0 \pm 2.5$ s at $48 \pm 11$ months after treatment. Although no significant differences were found, wide variations in asystolic intervals were demonstrated in each patient at the three examinations. All 7 patients had asystolic intervals of 3 s or longer with marked sinus bradycardia before treatment, while 4 patients and 3 patients had similar prolonged asystolic intervals during the second and third follow-up examinations, respectively (Fig. 1). In the remaining patients, 3 showed asystolic intervals longer than 2 s at both the second and third tests, and only 1 patient responded with an asystolic interval of less than 2 s at the third test. Therefore, most of the patients repeatedly demonstrated abnormal responses to carotid sinus massage at three different occasions. The differences in asystolic intervals between prior to treatment (first) and the third test were significantly greater than those between the first and the second test ($2.4 \pm 1.2$ s vs $0.7 \pm 0.6$ s; $p<0.05$). In the patient with vasodepressor carotid sinus syndrome, a decrease in systolic blood pressure of at least 50 mmHg was reproducibly induced by carotid sinus massage three times during the follow-up period.

All of the patients had symptoms during the initial carotid sinus massage. Moreover, 6 had symptoms during the second testing and 4 had symptoms during the third testing. Fig. 2 shows the surface electrocardiogram during carotid sinus massage in a patient with the cardioinhibitory carotid sinus syndrome. The ventricular asystolic interval induced by carotid sinus massage was $4.0$ s prior to treatment, $3.7$ s 44 months after treatment and $8.0$ s 58 months after treatment. Fig. 3 shows the surface electrogram during carotid sinus massage in another patient with the cardioinhibitory carotid sinus syndrome. The ventricular asystolic interval was $7.2$ s prior to treatment, $6.5$ s 45 months after treatment and $5.1$ s 58 months after treatment. Thus, variable and abnormal responses to carotid sinus massage during long-term follow-up were demonstrated in these 2 patients.
Reproducibility of Carotid Sinus Hypersensitivity

A. Prior to treatment

B. 44 months after treatment (pacemaker implantation)

C. 58 months after treatment (pacemaker implantation)

Fig. 2. Carotid sinus massage (CSM) in a patient with the cardioinhibitory carotid sinus syndrome. A sinus pause of 4.0 s during CSM and a surface electrocardiographic (lead I) recording are shown prior to treatment (upper strip). Following 44 months of treatment, repeat CSM produces ventricular asystole for 3.7 s during temporary cessation of DDD pacing (middle strip). Following 58 months of treatment, ventricular asystole of 8.0 s with a sinus pause and atrioventricular block are induced by CSM (lower strip).

A. Prior to treatment

B. 45 months after treatment (pacemaker implantation)

C. 58 months after treatment (pacemaker implantation)

Fig. 3. Carotid sinus massage (CSM) in another patient with cardioinhibitory carotid sinus syndrome. The upper, middle and lower strips demonstrate ventricular asystolic periods of 7.2 s prior to treatment, 6.5 s after 45 months of treatment and 5.1 s after 58 months of treatment (lead aVF). The response to CSM gradually diminished in this particular patient.

DISCUSSION

Patients with carotid sinus syndrome do not necessarily possess abnormal sinus node function. In fact, most studies have revealed that a high percentage of these patients have normal sinus node function. Similarly, patients in our study had no evidence of sinus node dysfunction during electrophysiologic testing, despite the presence of a predominant vagal state in three of these patients. It is still unknown whether the site of hypersensitivity in patients with carotid sinus syndrome is in the reflex arc, the central connection, or the target organ. Nevertheless, ventricular asystole or reduction in blood pressure can be induced by carotid sinus massage. Thus, this procedure can play an important role in the diagnosis of this syndrome.

The natural history of patients with carotid sinus syndrome after treatment has been studied and the recurrence of symptoms has been observed in these patients. However, patients with carotid sinus syndrome who undergo cardiac pacing and other modes of treatment often become asymptomatic, so that it is unknown whether the disappearance of symptoms following treatment is due to effective treatment or spontaneous remission of symptoms. Moreover, whether or not abnormal hemodynamic and electrical responses associated with carotid sinus massage persist during long-term follow-up has not been demonstrated despite the recurrence of clinical symptoms.

Our study demonstrates the long-term reproducibility of carotid sinus hypersensitivity with a temporary cessation of cardiac pacing or oral administration of drugs in patients with carotid sinus syndrome. In about half of the patients with carotid sinus syndrome, symptomatic asystolic intervals longer than 3 s were repeatedly demonstrated by carotid sinus massage during long-term follow-up. Furthermore, in each patient, wide variations in asystolic intervals were observed at different follow-up periods despite the absence of clinical symptoms.

The difference in the long-term response to carotid sinus massage in each patient was probably associated with the variable vagal response to baroreceptor stimulation. Nevertheless, patients with carotid sinus syndrome have an increased and variable baroreflex sensitivity.

In conclusion, most patients with carotid sinus syndrome demonstrated long-term reproducibility of carotid sinus hypersensitivity without recurrence of symptoms, while the abnormal responses to carotid sinus massage varied during long-term follow-up. Therefore, the absence of symptoms in these patients may be due to the beneficial effects of treatment rather than to the spontaneous remission of symptoms.

REFERENCES

2. Walter PF, Crawley IS, Dorney ER: Carotid sinus hypersensitivity and syncope. Am J Cardiol 1978; 41: 396—403
13. Narula OS, Shanto N, Vasquez M, Towne WD,

Japanese Circulation Journal Vol 59, January 1995