Carotid sinus hypersensitivity: evaluation of the vasodepressor component

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ABSTRACT The basis of the vasodepressor response in patients with carotid sinus hypersensitivity (CSH) is unknown, and prevention of recurrent vasodepressor-induced hypotension in these patients has not been possible. In this study we assessed the effectiveness of atrioventricular sequential pacing and pharmacologic interventions in the prevention of carotid sinus massage (CSM)-induced vasodepressor responses in eight patients with CSH. Maintenance of constant heart rate (80 beats/min) and atrioventricular synchrony (atrioventricular interval 150 msec) with sequential pacing did not significantly alter mean CSM-induced fall in systolic pressure (CSM control, $-60 \pm 12$ mm Hg vs CSM with atrioventricular sequential pacing, $-48 \pm 19$ mm Hg). Similarly, neither pharmacologic muscarinic blockade nor combined muscarinic and $\beta$-adrenergic blockade significantly attenuated CSM-induced fall in systolic pressure (CSM with atropine, $-43 \pm 16$ mm Hg; CSM with atropine plus propranolol, $-47 \pm 18$ mm Hg; both $p = NS$ vs atrioventricular sequential pacing alone). On the other hand, intravenous norepinephrine and oral ephedrine blunted the CSM-induced drop in systolic pressure (CSM with norepinephrine, $-19 \pm 12$ mm Hg; CSM with ephedrine, $-21 \pm 11$ mm Hg; both $p < .01$ vs atrioventricular sequential pacing alone). Thus, vasodepressor responses were not prevented by control of heart rate, maintenance of atrioventricular synchrony, pharmacologic muscarinic blockade, or combined muscarinic and $\beta$-adrenergic blockade, but were attenuated by drugs believed to be predominantly $\alpha$-adrenergic agonists. Consequently, atrioventricular sequential pacing alone may be inadequate to prevent hypotension in patients with pronounced vasodepressor responses, whereas administration of vasoconstrictors such as ephedrine may diminish symptoms.


IN PATIENTS with hypersensitive carotid sinus syndrome (CSH), symptoms of dizziness or syncope result from transient diminished cerebral perfusion due to an exaggerated cardiovascular response to carotid sinus baroreceptor stimulation.1 Three types of responses have been described: (1) a cardioinhibitory response in which marked sinus bradycardia and/or transient atrioventricular block result in systemic hypotension, (2) a vasodepressor response in which arterial hypotension occurs in the absence of marked bradycardia, and (3) a mixed response in which both cardioinhibitory and vasodepressor factors contribute to hypotension.2

The cardioinhibitory response in patients with CSH appears to be the result of muscarinic receptor stimulation by efferent parasympathetic neural impulses, since both sinus bradycardia and paroxysmal atrioventricular block can be prevented or reversed by administration of atropine.1,2 In contrast, the basis of the vasodepressor response is unknown, and consequently treatment of individuals exhibiting symptoms of dizziness or syncope due primarily to a vasodepressor response is often unsatisfactory. The purpose of this study was to evaluate potential therapeutic avenues for patients with vasodepressor-induced hypotension. To this end, we examined the effectiveness of both pacing techniques and pharmacologic interventions in preventing the vasodepressor response in patients with CSH.

Methods

Eight patients (all men from 49 to 84 years old) with recurrent syncope were included in this study. All patients underwent careful neurologic and cardiac evaluation, including invasive electrophysiologic studies, to exclude other causes of syncope.
Patients were included in the study group only if no other cause of syncope could be established, and if criteria for diagnosis of CSH were present (see definitions below).

Patients were fasting and unsedated at the time of the studies reported here and, except in the studies of long-term oral ephedrine therapy, none received cardiovascular drugs within five drug half-lives before the study. After percutaneous puncture of the femoral vein, two quadrripolar No. 6F electrode catheters for pacing and recording were advanced under fluoroscopic control and one each was positioned at the lateral wall of the right atrium and at the right ventricular apex. An arterial catheter was placed percutaneously within the brachial or femoral artery. Systemic arterial pressure, three to five surface electrocardiographic leads, and intracardiac electrograms were recorded simultaneously with a multichannel photographic recorder (Electronics for Medicine VR-16) at paper speeds of 25 and 50 mm/sec.

**Carotid sinus stimulation.** All studies were performed while patients were supine. Care was taken to ensure absence of carotid artery bruits before initiation of carotid sinus stimulation. Ten seconds of carotid sinus massage (CSM) was applied, with firm pressure, to the carotid artery just below the angle of the mandible. Simultaneous recording of systemic pressure and the surface electrocardiogram commenced 10 sec before CSM and was continued during and after CSM until arterial pressure returned to the control level. To provide reproducible mechanical pressure with CSM, the same investigator performed the carotid stimulation during each study. Respiration was monitored during CSM to ensure that no apnea or Valsalva effect was present.

Initially, CSM was applied while patients were in sinus rhythm, alternating between left and right sides. A minimum of three carotid sinus stimulation procedures were performed on each carotid sinus, with a rest interval of 4 to 6 min between massages. Since the cardiovascular responses to CSM were frequently unilateral, only the carotid sinus demonstrating the maximum vasodepressor response was stimulated for the remainder of the study.

**Study protocol.** Control heart rate and blood pressure response to CSM was documented in each patient over a 30 to 40 min control period. CSM was then repeated three to five times during each of the following pacing and/or pharmacologic interventions during the same day and on subsequent study days: (1) Atrioventricular sequential pacing was performed with an atrioventricular interval of 150 msec at a heart rate of 80 beats/min. (2) Pharmacologic muscarinic blockade (0.04 mg/kg iv atropine sulfate) was induced during sinus rhythm. (3) Combined muscarinic and β-adrenergic blockade was induced during atrioventricular sequential pacing and intravenous atropine, as described above, plus 0.2 mg/kg iv propranolol were given. This combined atropine-propranolol dose has been reported to effect pharmacologic muscarinic and β-adrenergic receptor blockade in man. (4) Norepinephrine was administered intravenously to achieve short-term, predominantly α-adrenergic agonist activity. The infusion began at a rate of 1 μg/min and CSM was repeated. The dose was then increased in increments of 1 μg/min to a maximum rate of 5 μg/min, or until a CSM-induced decline in systolic arterial pressure to less than 15 mm Hg was observed. (5) Ephedrine, 75 to 150 mg/day orally, was given. Patients were reevaluated 48 to 96 hr after initiation of ephedrine therapy.

**Definition of terms.** A cardioinhibitory response to CSM was defined as ventricular asystole exceeding 3000 msec. A vasodepressor response to CSM was defined as either a minimum decrease in systolic arterial pressure of 50 mm Hg or reproduction of symptoms in association with a 30 mm Hg or greater decrease in systolic arterial pressure., both either occurring in the absence of marked bradycardia or persisting in the presence of fixed-rate atrioventricular sequential pacing.

**Limitations of methods.** A potential limitation of this study is the variable nature of CSM. The mechanical effects of manual CSM cannot be quantified as precisely or applied in as reproducible a fashion as can negative pressure during application of neck suction. However, to our knowledge neck suction devices have not yet been evaluated systematically in patients with CSH. In two patients in this study, neck suction to ~60 mm Hg failed to induce a response, whereas right CSM reproducibly resulted in both bradycardia and a vasodepressor response. In two other patients (Nos. 1 and 6), asymmetric neck anatomy resulting from previous surgery prevented application of neck suction.

**Data analysis.** The maximum decrease in systemic arterial pressure during CSM was determined as the difference between control systemic pressure (average of 5 consecutive beats) immediately before CSM and the lowest arterial pressure during sinus rhythm or atrioventricular sequential pacing after initiation of CSM. Values are expressed as negative differences (mm Hg) for both systolic and mean arterial pressures. The mean arterial pressure was calculated as diastolic pressure plus one-third of the pulse pressure. To analyze the vasodepressor component, and eliminate the effect of heart rate differences, the changes in arterial pressure induced by CSM during drug interventions were compared with CSM-induced changes in arterial pressure observed during atrioventricular pacing. The maximum prolongation of the RR interval induced by CSM was obtained from a simultaneously recorded surface electrocardiogram. All values are expressed as mean ± SD. All tests of statistical significance were performed with Student’s paired t test, and a p value of .05 or less was considered indicative of significance.

**Results**

**Clinical features.** Table 1 summarizes clinical findings in the eight patients. All patients were referred for unexplained recurrent syncope. Patients 1, 3, and 6 had previously undergone radical neck operations and local irradiation for malignancy. Syncope developed late after surgery (15, 6, and 6 months, respectively) in these three patients. Patient 8 developed syncope while being treated with radiation therapy for a tonsillar lymphoma. Electrocardiographic recordings at the time of syncope were available in two patients. (Nos. 4 and 5.) Patient 4 had documented atrial and ventricular asystole and, despite implantation of a single-chamber ventricular-inhibited pacing system before his referral to us, he continued to have episodes of syncope. Patient 5 had both marked sinus bradycardia and paroxysmal third-degree atrioventricular block with syncope (figure 1).

**Heart rate and blood pressure response to CSM.** Typical changes in heart rate and arterial pressure induced by CSM are illustrated in figure 2, and changes in arterial pressure are summarized for the patient group in table 2 and figure 3. All patients except patient 6 demonstrated CSM-induced bradycardia. Four patients (Nos. 4, 5, 7, and 8) had RR prolongations greater than 3000 msec.
In four patients (patients 1, 3, 6, and 7) the response to CSM was unilateral. Three of these patients, as noted above, had previously undergone neck operations plus radiation therapy; the carotid sinus manifesting the greater responsiveness was ipsilateral to the previous surgery. Two patients (Nos. 2 and 4) demonstrated essentially equivalent right and left CSH. In patient 5 there was dissociation of the cardioinhibitory and vasodepressor responses bilaterally; left CSM resulted in a primarily cardioinhibitory response, and right CSM resulted in a primarily vasodepressor response. Similarly, patient 8 demonstrated atrioventricular block with ventricular asystole and marked vasodepressor response with right carotid sinus stimulation, but a vasodepressor response only during left CSM.

Although patients were in the supine position at time of study, while in sinus rhythm all manifested a significant decrease in arterial pressure when CSM was applied (drop in systolic pressure, \(-60 \pm 12\) mm Hg [p < .001]; mean drop, \(-42 \pm 8\) mm Hg [p < .001]) (table 2, figure 3).

**Effect of atrioventricular sequential pacing on vasodepressor response.** Despite atrioventricular sequential pacing to maintain a constant heart rate, prevent atrioventricular block, and maintain atrioventricular synchrony, statistically significant CSM-induced vasodepressor responses persisted (drop in systolic

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Symptoms</th>
<th>Associated conditions</th>
<th>ECG</th>
<th>Therapy</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>Syncope x 3</td>
<td>Squamous cell carcinoma of neck; previous right hemimandiblectomy and local irradiation</td>
<td>Normal</td>
<td>75 mg/day ephedrine</td>
<td>Asymptomatic for 5 months until death from cancer</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>Syncope; recurrent dizziness</td>
<td>Possible coronary artery disease</td>
<td>Normal</td>
<td>AV sequential pacemaker; 100 mg/day ephedrine</td>
<td>Asymptomatic for 11 months</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>Syncope; numerous episodes while eating</td>
<td>Metastatic epidermoid carcinoma to the neck; previous bilateral neck dissection and radiation</td>
<td>Normal</td>
<td>100 mg/day ephedrine</td>
<td>Asymptomatic for 16 months until death from cancer</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>Recurrent syncope despite VVI pacing</td>
<td>VVI Pacing for documented atrial and ventricular asystole</td>
<td>Ventricular paced rhythm</td>
<td>AV sequential pacemaker; 150 mg/day ephedrine</td>
<td>Asymptomatic for 15 months</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>Syncope</td>
<td>Paroxysmal third-degree AV block; single-vessel coronary artery disease</td>
<td>First-degree AV block</td>
<td>120 mg/day ephedrine</td>
<td>Recurrent third-degree AV block on ephedrine alone; AV sequential pacemaker implanted</td>
</tr>
<tr>
<td>6</td>
<td>49</td>
<td>Multiple syncope</td>
<td>Previous left radical neck dissection for squamous cell carcinoma</td>
<td>Normal</td>
<td>120 mg/day ephedrine; NaCl tablets</td>
<td>Recurrent syncope despite therapy</td>
</tr>
<tr>
<td>7</td>
<td>84</td>
<td>Multiple syncope</td>
<td>None</td>
<td>Normal</td>
<td>AV sequential pacemaker; 75 mg/day ephedrine</td>
<td>Asymptomatic &lt;6 months</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>Syncope</td>
<td>Tonsillar lymphoma; symptoms developed during radiation therapy</td>
<td>Normal</td>
<td>AV sequential pacemaker; 75 mg/day ephedrine</td>
<td>Asymptomatic &lt;6 months</td>
</tr>
</tbody>
</table>

ECG = electrocardiogram; VVI = ventricular-inhibited; AV = atrioventricular.

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**TABLE 1**
Clinical findings in the eight male subjects
pressure, $-48 \pm 19$ mm Hg [$p < .001$]; mean drop, $-32 \pm 11$ mm Hg [$p < .001$]) (figure 3). Furthermore, in the group as a whole there was no statistically significant difference between the CSM-induced decreases in arterial pressure before and after initiation of atrioventricular sequential pacing (figure 4). In only one patient (No. 1) did atrioventricular sequential pacing appear to attenuate the vasodepressor response, while in six patients CSM-induced arterial hypotension was essentially unaltered by fixed-rate pacing. Atrioventricular sequential pacing was not performed in patient 6 since he maintained resting sinus tachycardia throughout CSM and exhibited no significant bradycardiac response.

**Temporal relationship of hypotension to CSM.** Temporal responses of heart rate and arterial pressure during and after CSM are summarized in table 3. The spectrum of temporal changes is illustrated by examples from results in patients 4 and 6 (figure 5). The maximum hypotensive response to CSM in patient 4 occurred 16 sec after initiation of CSM, and return to control arterial pressure did not occur until 38 sec after the nadir of the blood pressure response. In contrast, patient 6 had early onset of the vasodepressor response (10 sec after onset of CSM), but arterial pressure recovered with a marked overshoot within 6 sec of the nadir of the fall in blood pressure.

**Effect of drugs on CSM-induced vasodepressor response.** The blood pressure and heart rate responses to CSM after drug interventions in patient 4 are illustrated in figure 6, and findings in the group as a whole are summarized in figure 7.

**Atropine.** The mean maximum prolongation of RR interval induced during CSM was shortened in all patients after atropine administration (control, 3303 ± 3187 msec; after atropine, 681 ± 140 msec; $p < .001$). However, atropine did not significantly influence the hypotensive response to CSM even when heart rate effects were eliminated by atrioventricular sequential pacing (figure 7). Thus, atropine prevented the cardioinhibitory response, but not the vasodepressor response.

**Atropine plus propranolol.** Despite administration of both atropine and propranolol and maintenance of atrioventricular sequential pacing, CSM continued to induce a decline in arterial pressure to a level that was not significantly different from the control value (figure 7).

**Norepinephrine.** The minimum effective infusion rate of norepinephrine (i.e., the infusion rate reducing the CSM-induced fall in pressure to $\leq 15$ mm Hg) varied among the patients (range 1 to 5 $\mu$g). Mean heart rate during infusion of the drug was not significantly different from control heart rate (84 ± 13 vs 87 ± 24 beats/min; NS). Nonetheless, norepinephrine significantly blunted the hypotensive response to CSM (figures 6 and 7). Of note is that during norepinephrine infusion the mean systolic arterial pressure was 145 ± 25 mm Hg and mean diastolic arterial pressure was 86 ± 9 mm Hg. Thus, norepinephrine significantly diminished the vasodepressor component without producing a marked hypertensive response.

**Ephedrine.** At the time of the ephedrine study mean systolic arterial pressure was 137 ± 25 mm Hg and mean diastolic pressure was 75 ± 9 mm Hg, which were not significantly different from control pressures at the first study. However, the resting heart rate during the ephedrine study was significantly increased as compared with control heart rate at the first study (98 ± 18 vs 84 ± 20 beats/min, $p < .03$). During short-term administration of oral ephedrine the arterial hypotensive response to CSM during atrioventricular sequential pacing was significantly diminished, but not completely ablated (figure 7).
Follow-up. Patients 1 and 3 remained symptom free on ephedrine therapy alone but died from cancer 5 and 16 months, respectively, after initiation of treatment. Patient 6 continued to have syncope while on ephedrine therapy both alone and in conjunction with attempted volume expansion by salt loading. Although local introduction of anesthetic into the vicinity of the left carotid sinus transiently ablated susceptibility to vasodepressor-induced hypotension, patient 6 declined a surgical denervation procedure and continues to have recurrent syncopal episodes. The remaining five patients demonstrated CSM-induced cardioinhibi-

### TABLE 2
Response to CSM

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Control arterial pressure during sinus rhythm (mm Hg)</th>
<th>Control heart rate</th>
<th>Carotid sinus involved</th>
<th>Maximum decline in arterial pressure (mm Hg) Systolic</th>
<th>Mean</th>
<th>Maximum RR prolongation (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>144/70</td>
<td>89</td>
<td>Right</td>
<td>-56</td>
<td>-38</td>
<td>2,235</td>
</tr>
<tr>
<td>2</td>
<td>132/86</td>
<td>87</td>
<td>Right and left</td>
<td>-50</td>
<td>-39</td>
<td>2,280</td>
</tr>
<tr>
<td>3</td>
<td>158/88</td>
<td>77</td>
<td>Left</td>
<td>-50</td>
<td>-39</td>
<td>1,150</td>
</tr>
<tr>
<td>4</td>
<td>134/86</td>
<td>88</td>
<td>Right and left</td>
<td>-56</td>
<td>-39</td>
<td>1,200 (paced)</td>
</tr>
<tr>
<td>5</td>
<td>156/84</td>
<td>60</td>
<td>Right (CI); left (VDP)</td>
<td>-48</td>
<td>-30</td>
<td>3,100</td>
</tr>
<tr>
<td>6</td>
<td>138/95</td>
<td>120</td>
<td>Left</td>
<td>-79</td>
<td>-56</td>
<td>530</td>
</tr>
<tr>
<td>7</td>
<td>142/72</td>
<td>61</td>
<td>Right</td>
<td>-66</td>
<td>-42</td>
<td>10,050</td>
</tr>
<tr>
<td>8</td>
<td>150/78</td>
<td>108</td>
<td>Right (CI + VDP); left (VDP)</td>
<td>-74</td>
<td>-49</td>
<td>5,880</td>
</tr>
</tbody>
</table>

CI = cardioinhibitory response; VDP = vasodepressor response.
TABLE 3
Temporal response of heart rate and arterial pressure to CSM

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Time to maximum RR interval (seconds)</th>
<th>Time to recovery of control RR interval (seconds)</th>
<th>Time to maximum hypotension (systolic pressure &lt; 90 mm Hg) (seconds)</th>
<th>Time to recovery of arterial pressure (systolic pressure &gt; 90 mm Hg) (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.8</td>
<td>13.5</td>
<td>12</td>
<td>NA</td>
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<tr>
<td>2</td>
<td>4.9</td>
<td>12.8</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>2.4</td>
<td>11.8</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>(paced)</td>
<td>(paced)</td>
<td>15</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>14.8</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>(no RR prolongation)</td>
<td></td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>12.5</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>2.5</td>
<td>16.0</td>
<td>18</td>
<td>84</td>
</tr>
</tbody>
</table>

All values are seconds. NA = measurement not available.

tory responses as well as vasodepressor responses, indicating the need for cardiac pacing. All five patients received dual-chamber pacemakers (DDD) based on current conventional treatment practice. In addition, these five patients continued on oral ephedrine therapy, and all remain symptom free at 5 to 18 months of follow-up.

Discussion
Systemic hypotension, often unassociated with marked bradycardia, is an important but poorly understood phenomenon in patients with transient neurologic symptoms resulting from CSH. This study, in which vasodepressor responses in symptomatic patients with CSH were evaluated in the presence of cardiac pacing and pharmacologic interventions, provides four principal observations regarding the vasodepressor response in man. First, in contrast to the bradycardic response, which is usually of nearly immediate onset and rapid resolution, the temporal sequence of CSM-induced hypotension is varied; the nadir of the hypotensive response generally occurred within 10 to 15 sec after the onset of CSM, and hypotension was sustained for a varying period of time (range 6 to 84 sec) after termination of the initiating stimulus. Second, atrioventricular sequential pacing alone is often inadequate to prevent marked hypotension. Third, neither muscarinic receptor blockade alone (atropine) nor combined muscarinic and β-adrenergic blockade (atropine-propranolol) prevent CSM-induced hypotension. Finally, drugs with predominantly α-adrenergic-agonist activity, when administered acutely as well as chronically, blunt the hypotensive response. The latter findings suggest a therapeutic alternative and a potentially fruitful area of research for future studies assessing the neural mechanisms of the vasodepressor response in man.

Temporal response of heart rate and blood pressure chambers. Little is known about the temporal response of heart rate and recovery of blood pressure in patients with CSH. Brown et al. studied the heart rate and blood pressure responses to CSM in patients with coronary artery disease. The time to maximum RR interval (4.6 ± 1.9 sec) and time to return to control RR interval (11.6 ± 3.9 sec) reported by Brown et al. are similar to those we observed (table 3). On the other hand, the time to recovery of arterial pressure observed in our patients (range 6 to 84 sec) was more varied and generally more prolonged than the duration of the hypotensive response (20.0 ± 6.0 sec) reported by Brown et al. The prolonged return of vasodepressor-associated hypotension may account for the develop-

FIGURE 3. Graphs depicting effect of CSM on arterial pressure during sinus rhythm and atrioventricular sequential pacing in the eight patients. Ordinate indicates arterial pressure. Systolic pressure is shown with solid lines and diastolic pressure with hatched lines. CSM during sinus rhythm and atrioventricular sequential pacing induced a significant decline in both systolic and diastolic pressure (p < .001). Furthermore, there was no significant difference between the fall in arterial pressure with CSM and atrioventricular sequential pacing and that during sinus rhythm (p > .05).
ment of symptoms despite the brief initiating event in spontaneous episodes of dizziness and syncope in patients with CSH.

Effect of drugs on the vasodepressor response. Although circulatory reflexes from the carotid baroreceptors have been investigated in man, the mechanisms responsible for the vasodepressor response in those with CSH have not been systematically evaluated. Human and animal studies have demonstrated that electrical stimulation of the carotid sinus nerve is accompanied by a fall in peripheral vascular resistance. In addition, activation of the arterial baroreceptors induced by a rise in arterial pressure produces increased afferent nerve activity and a reflex fall in peripheral vascular resistance. It has been suggested that this vasodilation is mediated by passive reflex withdrawal of sympathetic vascular tone and by active neurohumoral vasodilators. Furthermore, the existence of cholinergic sympathetic vasodilator fibers has been demonstrated in animals and it has been suggested that these fibers are active in man during stress. In addition, a recent study suggested that cholinergic vasodilation occurred as part of the carotid baroreflex in man. However, the failure of muscarinic-receptor blockade to blunt the arterial hypotension induced by CSM in our patients suggests that cholinergic sympathetic activity is an unlikely contributor to the vasodepressor response in CSH. Likewise, the recently described inhibition by acetylcholine of norepinephrine release from sympathetic nerve endings seems an unlikely explanation for CSM-induced hypotension.

FIGURE 4. Histogram depicting CSM-induced decline in systolic, diastolic, and mean arterial pressure during sinus rhythm and atrioventricular sequential pacing. There was no statistically significant difference observed between CSM-induced hypotension with atrioventricular sequential pacing and sinus rhythm (p > .05). C = control sinus rhythm; AV = atrioventricular sequential pacing.

FIGURE 5. Temporal response of arterial hypotension induced by CSM in patients 4 and 6. Electrocardiographic leads are shown in the top half of each tracing and arterial pressure in the bottom half. Patient 4 demonstrated prolonged recovery of CSM-induced arterial hypotension. On the other hand, patient 6 had rapid recovery of arterial pressure with a hypertensive response. See text for discussion.
**FIGURE 6.** The effect of drug interventions on CSM-induced arterial hypotension in patient 4. Electrocardiographic leads I, II, and III are shown in the top portion of each tracing and arterial pressure is shown in the bottom portion. A. As illustrated in the top panel CSM during atioventricular sequential pacing resulted in a pronounced decline in arterial pressure. Both atropine (middle panel) and atropine-propranolol (lower panel) failed to abolish CSM-induced hypotension. B. Norepinephrine administered at 1 μg/min (top panel) blunted the arterial hypotension. Oral ephedrine, 150 mg/day (bottom panel) also attenuated CSM-induced hypotension.
given the lack of efficacy of high-dose atropine in our patients.

Stimulation of β-adrenergic receptors can produce hypotension by direct peripheral vasodilatation. Recently, elevated levels of epinephrine were reported in a subject with vasovagal syncope. In our patients the failure of β-adrenergic-receptor blockade to prevent the hypotensive response to CSM suggests that neither neural nor humoral β-adrenergic-receptor activity was responsible for the vasodepressor response.

Norepinephrine is an endogenous sympathetic neurotransmitter that regulates vascular tone by its α-adrenergic-agonist properties and regulates heart rate and myocardial contractile force through its β-adrenergic effects. Although previous investigators have shown that norepinephrine can directly increase myocardial contractile force in man, the doses used in this study have previously been demonstrated to primarily increase peripheral vascular resistance and have little influence on cardiac output. Although measurements of catecholamine levels can be used to assess sympathetic neural activity, determination of norepinephrine levels was not attempted in this study because of the relatively brief and rapidly changing nature of the hemodynamic events. Thus, although the antihypotensive effect of norepinephrine observed in our patients appeared to be a result of α-adrenergic vasoconstrictive influence on the peripheral circulation, the precise location of the defect in adrenergic neuroregulatory system could not be determined. However, none of our patients demonstrated orthostatic hypotension. Thus, it seems unlikely that depletion of norepinephrine from sympathetic nerve terminals or reduction in α-receptor density produced the hypotensive response.

An exaggerated physiologic response to baroreceptor stimulation may have been involved. Mechanical stimulation of the peripheral mechanoreceptor results in cardiac slowing and hypotension. It is possible that the profound vasodepressor responses observed in our patients were the result of an exaggerated suppression of resting sympathetic outflow. Inappropriate suppression of adrenergic neurohumoral activity (as measured by plasma norepinephrine levels) has been implicated in a patient with glossopharyngeal neuralgia and syncope. Whether abnormalities in the peripheral baroreceptor, afferent nerves, central vasomotor centers, or efferent pathways are responsible for hypotension cannot be determined from our data.

The sympathomimetic agent epinephrine has complex cardiovascular effects that include both direct adrenergic-agonist activity and stimulation of norepinephrine release. In addition, it possesses positive inotropic properties. We did not attempt a detailed assessment of the hemodynamic and inotropic effects of epinephrine in this study. Consequently, the observation that the drug blunted the vasodepressor response may have resulted from its cardiac stimulatory and peripheral vasoconstrictive properties.

Clinical implications and limitations of the study. The findings of this study suggest that there is a spectrum of cardiovascular responses to CSM in patients with CSH. Mixed vasodepressor and cardioinhibitory responses may be common. Therefore, patients with apparent cardioinhibitory responses during electrocardiographic monitoring should also be carefully screened for vasodepressor responses, since failure to document hypotension during CSM may lead to inadequate therapy.
Previous observations suggest that atrioventricular sequential pacing is the treatment of choice for patients who demonstrate cardioinhibitory and vasodepressor components of CSH. However, in only one of our patients did atrioventricular sequential pacing significantly diminish CSM-induced hypotension. Thus, findings in this study suggest that even pacing may not be sufficient therapy in many patients with mixed cardioinhibitory and vasodepressor responses. On the other hand, although these studies were carried out in patients in the supine position, our results suggest that oral vasoconstrictive drugs such as ephedrine may be useful adjunctive treatment in some patients who demonstrate vasodepressor responses. However, although ephedrine was well tolerated in our patients, its lack of long-term efficacy in some patients, the potential hazards of its use in elderly patients and individuals with underlying coronary artery disease, and its sympathomimetic side effects are important potential limitations to its widespread application.

We express our gratitude to the staff of the cardiac catheterization laboratory, to the cardiology fellows who assisted in these studies, and to Wendy Markuson and Barry L. S. Detloff for assistance in the preparation of this manuscript.

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_Circulation_. 1985;71:927-936
doi: 10.1161/01.CIR.71.5.927

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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