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Exaggerated Carotid Sinus Massage Responses Are Related to Severe Coronary Artery Disease in Patients Being Evaluated for Chest Pain

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Summary

Background: Previous studies have reported that carotid sinus massage responses are associated with advancing age and carotid or coronary artery disease.

Hypothesis: This study was undertaken to investigate the potential role of carotid sinus hypersensitivity as a marker for the presence of coronary artery disease, and especially left main stem disease, in patients who were referred for evaluation of chest pain.

Methods: Toward this end, carotid sinus stimulation with simultaneous recordings of the electrocardiogram and aortic pressure was performed before coronary arteriography in 150 selected consecutive patients (mean age 59.4 ± 9 years) who were referred for evaluation of chest pain.

Results: Coronary artery disease was present in 118 patients (78.7%); of these, 35 had single-vessel disease, 35 had double-vessel disease, 33 had triple-vessel disease, and 15 had left main stem with or without such vessel disease. Carotid sinus hypersensitivity was found in 40 patients (26.6%). The incidence of hypersensitivity in patients with single-, double-, or triple-vessel disease and left main stem disease was 8.5, 14.2, 57.5, and 73.3%, respectively. Stepwise multiple logistic regression analysis revealed that left main stem disease was significantly and independently related to the presence of carotid sinus hypersensitivity ($p < 0.05$). In addition, the presence of hypersensitivity had 73.3% sensitivity, 86.2% specificity, and 96.3% negative predictive value for the presence of left main stem disease.

Conclusion: In patients being evaluated for suspected ischemic heart disease, carotid sinus massage responses are related to severe coronary disease. The absence of hypersensitivity may reflect absence of left main stem disease.

Key words: carotid sinus hypersensitivity, left main stem coronary artery disease

Introduction

The carotid sinus as a part of the baroreceptor system plays an important role in the normal reflex regulation of the cardiovascular system.[1, 2] Carotid sinus massage (CSM) frequently serves as an important diagnostic aid in deciphering cardiac arrhythmias and has been regarded as a useful therapeutic maneuver in relieving anginal pain or acute pulmonary edema in patients with coronary artery disease (CAD) or hypertension.[3–5] In addition, previous studies have suggested that carotid sinus hypersensitivity (CSH) is associated with advancing age and coronary or carotid artery disease.[6–8] The aim of the present study was to assess the possible relationship between CSH and the presence or absence of severe CAD in patients who were referred for evaluation of chest pain by coronary angiography.

Subjects and Methods

Study Population

The study group included 210 consecutive patients, in sinus rhythm, who were referred for coronary angiography for evaluation of chest pain and/or abnormal noninvasive test results suggestive of ischemic heart disease.

From our study we excluded (1) patients in whom CSM could induce risk (such as patients with recent cerebrovascular infarction, ulcerated carotid atherosclerotic plaque, or total carotid artery occlusion detected by ultrasonography, uncontrolled hypertension, and unstable angina or recent acute myocardial infarction), and (2) patients in whom the interpreta-

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tion of coronary angiography was obscured (such as patients with coronary bypass graft or percutaneous transluminal coronary angioplasty). Also, we excluded patients with cardiomyopathy, valvulopathy, sinus dysfunction, or persistent sinus bradycardia below 50 beats/min and any systemic disease. Finally, 150 patients fulfilling the above criteria were selected.

After a detailed history, all patients underwent a physical examination, chest x-ray, electrocardiogram (ECG), and an ultrasound examination of the heart and carotid arteries. The institutional ethics committee of our hospital approved the study protocol that included an evaluation of risk factors for cardiovascular diseases, carotid sinus massage, and coronary angiography—left ventriculography. Written informed consent was obtained from all patients after a detailed description of the procedure.

Evaluation of Risk Factor Variables

The risk factor variables that were evaluated in this study included age, hypercholesterolemia (defined as total plasma cholesterol > 210 mg/dl in the previous 12 months, or documented hypercholesterolemia requiring lipid-lowering drug therapy), hypertension (coded as present if there was any history of high blood pressure or if the blood pressure measured at the hospital had at least twice exceeded 150 mmHg systolic or 95 mmHg diastolic), diabetes mellitus (defined as patient history of diabetes requiring treatment, or Hb A_{1c} value > 8%), smoking behavior (if the patient had smoked for > 20 pack-years), and family history (coded as positive if a first degree relative had had a serious coronary event before the age of 60).[9]

Carotid Sinus Massage

Carotid sinus massage was performed in the catheterization laboratory, after overnight fasting, just before coronary angiography. Cardiovascular medications were discontinued for at least five drug half lives before CSM was performed and premedication was not administered. A pigtail, fluid-filled catheter was advanced to the ascending aorta through a 7F sheath placed into the right femoral artery in order to record the aortic pressure.

A temporal pacemaker electrode was advanced to the right ventricle through a 5F sheath placed into the right femoral vein and was on standby. Two surface ECG leads were also monitored continuously. Carotid sinus massage was performed 20 min after the instrumentation and before coronary angiography to allow patients to relax and for hemodynamic parameters to stabilize, and also to exclude any effect of the contrast medium on the carotid sinus reflex. Electrocardiogram and aortic pressure tracings were recorded simultaneously on a Honeywell multichannel strip chart recorder (Honeywell Medical Electronic Division, New York, N.Y., USA) at paper speeds of 25 and 50 mm/s.

The technique used to perform the test has been previously described.[2, 3, 6] In brief, with the patient in the supine position, during normal respiration, the carotid sinus region was identified and the massage was gently applied for 5 s in a progressive fashion: we began our stimulation basically with a light touch to observe the response and then we increased the strength of the stimulation in successive attempts. If there was no response, pressure was increased for an additional 5 s. The direction of the compression in the carotid bifurcation was usually against the vertebral spine. We made sure that the pressure applied did not occlude the carotid artery by simultaneous palpation of the ipsilateral temporary artery pulse. The massage was terminated prematurely only if an asystole longer than 3 s resulted. To reestablish control conditions after the massage of the sinus was completed, we repeated the CSM on the other side 2 min later.

The massage was carried out by the same investigator who was blinded to clinical history of the patients, including the results of the ischemic workup, with the same intensity in order to maintain uniformity of stimulus. Simultaneous recording of the aortic pressure and the ECG started 10 s before and continued during and after CSM until arterial pressure and heart rate returned to baseline levels.

The following variables from the ECG and the aortic pressure recordings were measured (Fig. 1): (1) Max R-R (in s): the longest R-R interval on the ECG recording during carotid sinus massage. (2) Max AoP Fall (in mmHg): the difference between baseline systolic aortic pressure (average of 5 consecutive beats) immediately before CSM and the lowest systolic pressure during massage or immediately after massage termination.

According to their exaggerated response to CSM, our patients were classified into three types: patients with cardioinhibitory type (characterized by the provocation of ventricular asystole of a 3 s minimum duration), vasodepressor type (characterized by the provocation of a decrease in systolic aortic pressure of at least 50 mmHg or a decrease of 30 mmHg in the presence of neurologic symptoms), and mixed type (a combination of cardioinhibitory and vasodepressor types).[2, 3, 10, 11] In patients who exhibited asystole > 3 s, the CSM was repeated after the intravenous administration of 0.02 mg/kg atropine in order to eliminate heart rate slowing and to allow the differentiation of the pure cardioinhibitory type, the vasodepressor type, or the mixed type.

To test the reproducibility of CSM responses, we repeated the CSM in 15 patients 30 min after the first massage and before coronary angiography. We found a significant correlation ($r = 0.80$) between the results of the first and second massage as far as both normal and exaggerated responses are concerned.

Coronary Angiography

Coronary angiography and left ventriculography were performed using the standard Judkins technique. The percentage of diameter stenosis was calculated by quantitative coronary angiography with a commercially available automated coronary analysis system (DCI-S, Phillips Medical System, Bothell, Wash., USA). Coronary artery disease was defined as diameter stenosis of > 50% in at least one major coronary artery. According to the number of diseased vessels, our patients were classified into the following five groups : Group 1:

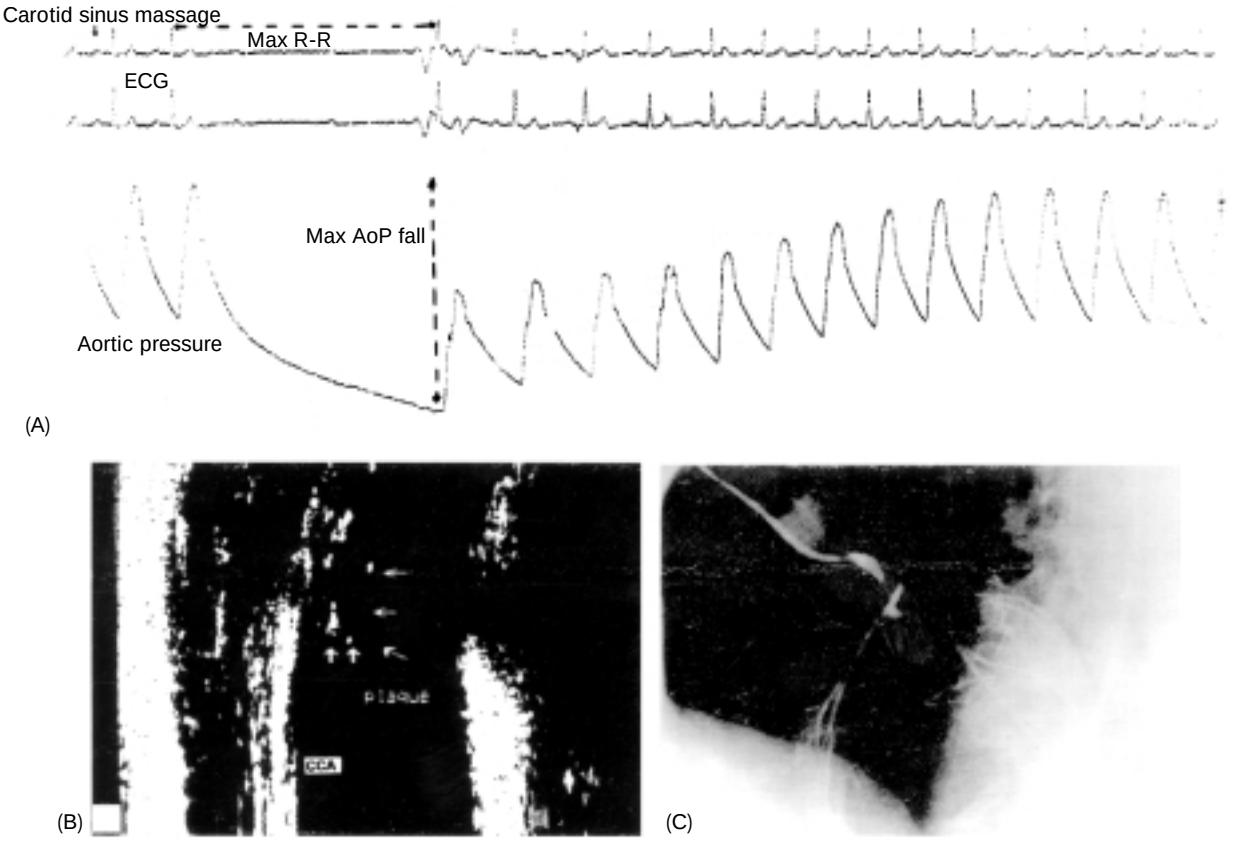

FIG. 1 (A) Recordings of simultaneous intra-aortic pressure and two-lead electrocardiogram (ECG) before, during, and after carotid sinus massage in a patient. With the onset of right carotid massage, there is an increased responsiveness regarding the heart rate and the aortic pressure. See text for definitions of intervals. (B) Coronary angiography of this patient shows left main stem coronary artery disease and triple-vessel disease in the left anterior oblique with cranial angulation view.

no vessel disease, Group 2: single-vessel disease, Group 3: double-vessel disease, Group 4: triple-vessel disease, and Group 5: left main stem (LMS) CAD (with or without such vessel disease).

Statistical Analysis

Data were expressed as mean ± standard deviation. For comparison between means, the paired Student's *t*-test or the chi-square test was used where appropriate. Logistic regression analysis was applied to identify possible predictors of a dichotomous dependent variable. A value of $p < 0.05$ was accepted as statistically significant.

Results

Clinical Features

The study group consisted of 127 men and 23 women with a mean age of 59.4 years (range 34–79). Of these, 91 (60.7%) were smokers, 64 (42.7%) had hypercholesterolemia, 63 (42%) had hypertension, 35 (23.3%) had diabetes mellitus, and 22 (14.7%) had positive family history.

Coronary Angiographic Findings

Coronary angiography revealed CAD in 118 patients (78.7%). In particular, 35 patients (23.3%) had single-vessel disease, 35 patients (23.3%) had double-vessel disease, 33 patients (22 %) had triple-vessel disease, and 15 patients (10%) had LMS-CAD. The remaining 32 patients (21.3%) had coronary arteries without critical stenosis. Furthermore, the ejection fraction was 52 ± 10 % (range 25–75).

Carotid Sinus Massage Responses

The procedure of CSM was carried out without any morbidity. The mean values of max R-R interval and max AoP fall was 1.63 s (range 0.5–13) and 30.8 mmHg (range 5–70), respectively.

The CSM responses, according to the massage on the left and the right carotid sinus, did not differ ($p = 0.38$). Almost all patients (147 of the 150) had some heart rate slowing and a decrease in blood pressure with CSM.

Carotid sinus hypersensitivity was found in 40 patients (26.6%). The mean values of the Max R-R interval was 3.84 s (range 0.60–13.00) and Max AoP fall was 43.5 mmHg (range 20–70).

TABLE I Clinical characteristics of the hypersensitive population

Age (years)	64.8 ± 8.11
Sex (male/female)	34/6
Smoking (%)	28 (70.0)
Hypertension (%)	17 (42.5)
Positive family history (%)	10 (25)
Diabetes mellitus (%)	10 (25)
Hypercholesterolemia (%)	29 (72.5)

Cardioinhibitory type response was present in 29 patients (72.5%), vasodepressor type in 5 patients (12.5%), and mixed type in 6 patients (15%). Only three of the patients with CSH had a history of dizziness and confusion interfering with their daily activity. In these patients, CSM was sufficient to reproduce spontaneous symptoms and they were found to belong to the cardioinhibitory type. The clinical characteristics of these patients are presented in Table I. We noticed a stepwise increase in the percentage of hypersensitive patients as the age increased: The incidence of CSH was 15.4% in patients aged 40–49 years, 25.9% in patients 60–69 years, and 52.9% in patients age 70–79 years.

Relation of Carotid Sinus Responses to Coronary Artery Disease

The incidence of CSH in patients without CAD was 6.2% (2/32) while in patients with CAD it was 32.2% (38/118). Accordingly, CSH was present in 3 of 35 patients (8.5%) with single-vessel disease, in 5 of 35 patients (14.2%) with double-vessel disease, in 19 of 33 patients (57.5%) with triple-vessel disease, and in 11 of 15 patients (73.3%) with LMS-CAD (Fig. 2).

Forward stepwise logistic regression analysis revealed that only the presence of LMS-CAD was independently related to the presence of CSH (Table II). Moreover, CSM responses show a satisfactory sensitivity (73.3%) and specificity (78.5%) and a high negative predictive value (96.3%) for the presence of LMS -CAD (Table III).

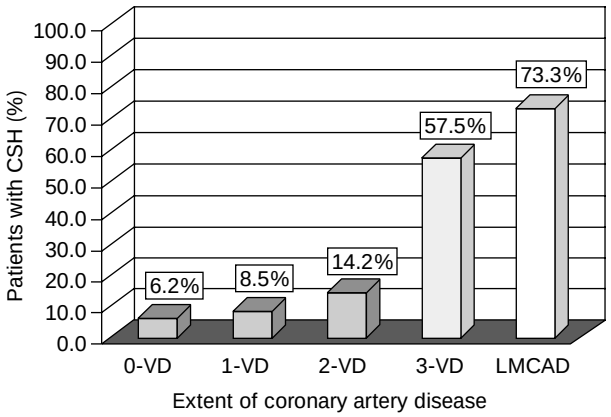

FIG. 2 Plot showing distribution of patients with carotid sinus hypersensitivity (CSH) as a function of the extent of coronary artery disease. 0-VD = coronary arteries without critical stenosis, 1-VD = single-vessel disease, 2-VD = double-vessel disease, 3-VD = triple-vessel disease, LMCAD = left main coronary artery disease.

Discussion

In this study we reported the close relationship between CSM responses and the severity and extent of atherosclerosis in the coronary arteries in patients evaluated for suspected ischemic heart disease. The major finding of our study was that CSH is independently related to LMS-CAD and furthermore, in this study population, the absence of CSH reflects the absence of LMS-CAD.

TABLE II Stepwise multiple logistic regression coefficients for the relationship between night variables and carotid sinus hypersensitivity

Variables	Coefficient (b)	Wald	p Value
Left main stem coronary artery disease	1.99 ± 0.78	6.46	0.011
Constant	−2.45 ± 0.34		

The variables age, male sex, smoking, diabetes mellitus, hypertension, heredity, hypercholesterolemia, triple-vessel coronary disease, and ejection fraction did not enter the equation, according to the selection criteria (probability for entry < 0.05, probability of removal > 0.01).

TABLE III Carotid sinus hypersensitivity as predictor for coronary artery disease and left main stem coronary disease

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Prediction of				
Coronary artery disease (%)	32.2	93.7	95	27.2
Left main stem coronary disease (%)	73.3	78.5	27.5	96.3

Carotid Sinus Massage Responses and Atherosclerotic Disease

Previous studies have reported an association between CSH and atherosclerotic vascular disease.[5, 6] Brown *et al.* were the first to show that the exaggerated response to CSM in the presence of symptomatic CAD is associated with the total CAD score;[11] however, possible additional associations between CSM responses and the severity of CAD have not been well addressed. To investigate this issue further, we focused our attention on the exact relation between CSH and LMS-CAD. Thus, in the present study using CSM in a series of consecutive patients evaluated for suspected ischemic heart disease, the incidence of CSH was increased in proportion to the severity of CAD: from 6% in the patients with no vessel disease to 57 and 73% in patients with triple-vessel disease and LMS-CAD, respectively. In addition, carotid sinus responses appear to be related to the absence of LMS-CAD, since CSH had a high negative predictive value (96.3%) for the presence of LMS-CAD.

Indications of Carotid Sinus Stimulation

In the past, CSM has been considered to be a useful diagnostic and therapeutic maneuver in patients with angina pectoris.[3, 5, 12, 13] In 1928, Wassermann and Weber were the first to suggest that carotid sinus pressure may relieve anginal pain.[5] Lown and Levine reported the diagnosis of CAD in patients in their late thirties and early forties who complained of atypical chest pain, exhibited nonspecific alterations in ST segments and T-wave complexes, and responded to mild and brief CSM with partial or complete heart block.[3] Since LMS-CAD is a disease of high morbidity and mortality, evidence derived from CSM responses could be very helpful in the evaluation and treatment of these patients until the definite diagnosis can be made by cardiac catheterization. Obviously, CSM cannot replace the already existing, noninvasive tests for the evaluation of CAD, such as stress test, echo-dobutamine, and so forth, and probably the greatest clinical value of CSM is clarifying the type or the mechanism of different rhythm disturbances and confirming the presence of hypersensitivity.[3, 14, 15] Taken into consideration that manipulation of the carotid sinus can be accomplished at the bedside and, when done properly, carries little risk,[16] we suggest that CSM is a simple, safe, noninvasive test, at bedside, that may provide useful information in everyday clinical practice in selected patients under evaluation for chest pain.

Mechanisms of Carotid Sinus Hypersensitivity

Although the mechanisms of the relation between atherosclerotic disease and exaggerated carotid sinus responses are not fully understood, it is currently believed that the bulk of the abnormalities in the carotid sinus reflex is present in the central nervous system, especially in the cardiovascular regulation centers.[1, 2, 17–19] The structural changes and the decreased distensibility in the large elastic arteries, which may result in ineffective central afferent-efferent coupling,[17, 20, 21] could explain the decreased baroreflex sensitivity and resetting of carotid sinus baroreceptors in atherosclerosis. Apart from the abovementioned mechanical component, the accompanied endothelial dysfunction with the resulting defect in endogenous production of prostacyclin enhances formation of oxygen-free radicals and platelet aggregation and contributes to the impaired baroreceptor activity.[18, 22–24] Keeping in mind that the severity of carotid artery disease is strongly and consistently associated with the coronary status and especially with LMS-CAD,[25, 26] we suggest that our findings are in agreement with the above concept.

Limitations

Several factors may have limited the apparent strength of the relation we found between CMS responses and LMS-CAD. First, we studied a group of consecutive patients who were referred for coronary angiography for suspected ischemic heart disease. This selection bias means that our findings regarding the relation of carotid sinus responses with the presence of LMS-CAD are relevant only to this special group of patients and may not be applicable to the general population.

Also, although we discontinued the cardiovascular medication for at least five drug half lives before CMS was performed, we cannot exclude the possibility that the observed carotid sinus responses have been influenced by the induced hyperadrenergic state in a group of patients who were previously being treated with beta blockers.[20] Second, regardless of the method of analysis, coronary angiography frequently underestimates the severity of atherosclerotic disease, although it is a reasonable method for measuring the extent and severity of CAD. Also, the classification of CAD extent based on the number of diseased vessels may not be as precise as other specific indices such as the Gensini score. However, this classification is very common in every day clinical practice and consequently the relation of CSH to the diseased vessels is of practical value. Finally, as it has been suggested by others in similar studies, the reproducibility of the response to CSM may not be as high;[2, 10] however, in this study, we observed a good reproducibility of the CMS responses either performed invasively or noninvasively. A possible explanation for our good reproducibility is that we used a standardized stimulation protocol.

Conclusion

In patients who were referred for evaluation of chest pain, CSM responses are significantly related to the presence of LMS-CAD. The absence of CSH may reflect absence of LMS-CAD.

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