—**Original**—

Clinical Usefulness of the Common Carotid Artery Blood Flow Velocity Ratio as Measured by an Ultrasonic Quantitative Flow Measurement System: Evaluation With Respect to Prevalence of Ischemic Heart Disease

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Abstract

The present study evaluated the clinical usefulness of the measurement of common carotid artery blood flow velocity by an ultrasonic quantitative flow measurement system (QFM), and its correlation with the prevalence of ischemic heart disease (IHD). The subjects in this study included 287 patients (149 men and 138 women; mean age, 67.6 ± 11.0 years) being treated as outpatients. Bilateral common carotid artery blood flow velocity was measured using a QFM-1100 (Hayashi Denki Co., Ltd.). The "high to low velocity ratio" (H/L ratio) was calculated by dividing the higher value by the lower value of the velocity of the common carotid artery. In 43 of 287 patients, we used an SSA-270 ACE (Toshiba Co., Ltd) to determine the presence of plaque and measure intimal-medial thickness (IMT) in the common carotid arteries. The mean H/L ratio was 1.45, with a median value of 1.25. The patients were stratified into subgroups based on H/L ratios from 1.0 and above in 0.1 increments in order to compare the prevalence rates of IHD. The prevalence rates in groups with H/L ratios of 1.3 and greater were significantly higher than those in the group with H/L ratios less than 1.3. In logistic regression analysis, the unadjusted H/L ratio was an independent risk factor for IHD at ratios from greater than 1.1 to greater than 1.6. The age-adjusted H/L ratio was an independent risk factor for IHD at ratios from greater than 1.1 to greater than 1.4. IMT was significantly higher in patients with a H/L ratio of 1.4 or greater versus patients with a ratio less than 1.4 (1.154 ± 0.417 mm vs. 0.421 ± 0.425 mm; $p<0.05$). The prevalence of carotid artery plaque was also significantly higher in patients with a H/L ratio of 1.4 or greater versus patients with a ratio of less than 1.4 (76.5% vs. 38.5%; $p<0.03$). Therefore, determination of the carotid artery H/L ratio by means of QFM may be clinically useful in screening patients for coronary artery lesions. (J Nippon Med Sch 2001; 68: 482—489)

Key words: ultrasonic quantitative flow measurement system (QFM), blood flow velocity of common carotid arteries, ischemic heart disease, intimal-medial thickness of common carotid arteries

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Introduction

Reported advances in the prevention of ischemic heart disease (IHD) include lipid lowering therapy and various coronary artery interventions[1-3]. These preventive strategies are primarily targeted at patients before the development of myocardial infarction. Recent studies have reported the measurement of intimal-medial thickness (IMT) of the common carotid arteries to be clinically useful in predicting the presence of cardiovascular lesions[4-6]. However, the high cost of equipment for measuring IMT has limited its more widespread clinical use as a screening tool. An ultrasonic quantitative flow measurement system (QFM) has been developed to specifically measure blood flow in the common carotid arteries. The price of B-mode ultrasonography is about ten million yen. QFM is much less expensive to perform than B-mode ultrasonography, and the cost is about one-fourth to one-third that of B-mode ultrasonography, required to measure IMT. A correlation between carotid artery blood flow assessed by QFM with cerebrovascular diseases has been reported[7]. However, no similar correlation with IHD has previously been investigated.

In this study, we examined the relationship between the carotid artery blood flow velocity assessed by QFM and the prevalence of IHD, and the influence of other risk factors.

Materials and Methods

Subjects

Between March 1993 and November 1997, 287 outpatients recruited in this study by the Division of Geriatric Medicine at Nippon Medical School Hospital. All patients received an explanation of the test procedures and gave informed consent to participate in the study. The patients fasted overnight before blood samples were drawn. A diagnosis of angina pectoris was confirmed by a history of symptoms of angina and typical changes on exercise stress testing and 24-hour Holter monitoring. In addition, 24-hour Holter monitoring was used to detect arrhythmias and silent myocardial ischemia. A diagnosis of previous myocardial infarction was based on a history of acute myocardial infarction in association with electrocardiography (ECG) and serum enzyme changes. If there were suspected changes on ECG, further cardiac echocardiography or nuclear cardiac imaging studies were performed to confirm the presence of an infarct lesion. Any patient diagnosed with myocardial infarction or symptoms of angina pectoris was considered to have IHD.

Table 1 shows the clinical characteristics of the study participants. The mean age was 67.6 years, and 51.9% of the patients were men. There were 138 patients with diabetes mellitus and 159 patients with hypertension. A total of 65 patients (22.6%) had both diabetes and hypertension. A total of 63 patients (22.0%) were diagnosed with IHD. This included 37 patients with angina pectoris only, 20 patients with a history of myocardial infarction only, and 6 patients with both angina pectoris and a history of myocardial infarction. All patients with hypertension were receiving antihypertensive therapy. The mean systolic blood pressure was 142.6 ± 19.7 mmHg, and the mean diastolic blood pressure was 79.7 ± 10.5 mmHg. There were 22 patients treated with statines. The prevalence of statine

Table 1 Characteristics of the 287 study participants

Characteristic	Value *
n (male / female)	287 (149/138)
Age (years old)	67.6 ± 11.0
Body mass index (kg/m^2)	22.5 ± 3.6
Diabetes mellitus	138 (48.1%)
Hypertension	159 (55.4%)
Ischemic heart disease	63 (22.0%)
Angina pectoris	43 (15.0%)
Myocardial infarction	26 (9.1%)
Pack-years of smoking †	24.2 ± 34.5
Blood pressure (mmHg)	
Systolic	142.6 ± 19.4
Diastolic	79.7 ± 12.1
Total cholesterol (mg/d*l*)	210.5 ± 43.8
Triglyceride (mg/d*l*)	124.5 ± 65.3
Uric acid (mg/d*l*)	5.5 ± 1.8
Fasting plasma glucose (mg/d*l*)	127.7 ± 46.7
Velocity of common carotid artery (cm/s)	15.3 ± 6.5
High to low velocity ratio of carotid artery	1.45 ± 0.64

* Plus-minus value are mean ± SD.

† Pack-years of smoking are for those who had a history of smoking.

administration was significantly lower in groups with H/L ratios of 1.4 and greater than in the group with H/L ratios less than 1.4 (10.3% vs. 2.9%; $p<0.05$).

QFM, carotid artery plaque, and IMT examination

Common carotid artery blood flow velocity was measured bilaterally using the QFM-1100 (Hayashi Denki Co., Ltd). QFM was measured between 9 and 9:30 AM by a single operator who was blinded with respect to the clinical characteristics of the patients. The patients were examined supine with the neck extended and the probe in the anterolateral position. All measurements of QFM were made in the longitudinal plane on both common carotid arteries. The blood flow Doppler signal was measured at the point of maximum and sharpest signal intensity. The "high to low velocity ratio" (H/L ratio) was calculated by dividing the higher value by the lower value of the velocity of the common carotid artery.

In 43 of the 287 patients studied between January 1997 and November 1997, carotid artery plaque and IMT were measured by ultrasound (SSA-270 ACE, Toshiba Co., Ltd) after completion of QFM. **Table 2** shows the clinical characteristics of the subjects whose carotid artery plaque and IMT were studied.

Statistical Analysis

All of the data was input into a computerized database and analyzed using SPSS (Statistical Package Version 10.0; SPSS Inc, Chicago, Illinois USA). The data presented in this report are expressed as mean values ± standard deviations. Categorical variables were compared by Chi-squared analysis (Yates' correction used if necessary). Continuous variables were compared by Student's *t* test. Logistic regression analysis was used for multivariate analysis. In addition to an elevated H/L ratio of the common carotid arteries, 2 sets of explanatory variables were used, including age, tobacco lifelong dose, the presence of diabetes mellitus, gender (ie, male sex), systolic blood pressure, uric acid, total cholesterol, and triglyceride (model 1); diastolic blood pressure instead of systolic blood pressure (model 2). Differences were considered statistically significant at a P value of less than 0.05.

Table 2 Characteristics of the subjects, who studied carotid artery plaque and IMT, according to H/L ratio

H/L ratio	<1.4	≧ 1.4	P Value
n (male /female)	26 (12/14)	17 (6/11)	
Age (years old)	68.8 ± 8.6	68.7 ± 8.1	0.969
Body mass index (kg/m^2)	22.4 ± 3.5	22.8 ± 3.3	0.692
Diabetes mellitus	16 (61.5%)	9 (52.9%)	0.753
Hypertension	16 (61.5%)	14 (82.5%)	0.187
Ischemic heart disease	1 (3.8%)	8 (47.1%)	0.001
Angina pectoris	0 (0%)	6 (35.3%)	0.002
Myocardial infarction	1 (3.8%)	2 (11.8%)	0.552
Pack-years of smoking †	32.2 ± 42.7	26.2 ± 34.7	0.634
Blood pressure (mmHg)			
Systolic	142.8 ± 20.1	150.8 ± 18.6	0.194
Diastolic	80.4 ± 10.0	85.9 ± 10.5	0.092
Total cholesterol (mg/d*l*)	216.3 ± 48.8	224.5 ± 16.3	0.583
Triglyceride (mg/d*l*)	120.2 ± 70.8	115.2 ± 44.6	0.797
Uric acid (mg/d*l*)	6.0 ± 1.8	4.8 ± 1.0	0.016
Fasting plasma glucose (mg/d*l*)	135.2 ± 50.4	130.7 ± 42.5	0.766
Velocity of common carotid artery (cm/s)	13.4 ± 4.6	12.8 ± 3.7	0.649
IMT of the common carotid artery (mm)	1.15 ± 0.42	1.42 ± 0.43	0.048
Carotid artery plaque	10 (38.5%)	13 (76.3%)	0.027

IMT : Intimal-medial thickness

Plus-minus value are mean ± SD.

† Pack-years of smoking are for those who had a history of smoking.

Results

The mean velocity of common carotid arteries was 15.3 ± 6.5 cm/second (range = 2.9 to 64.3 cm/second). The mean value for the carotid artery H/L ratio was 1.45, and the median value was 1.25. In 38 patients (chosen on the bases of availability), the H/L ratio was re-measured 5～7 days later; the coefficient of variation was 16.2%. Of these 38 patients, on the first measurement, the H/L ratios of 21 patients were less than 1.4 and those of 19 patients were less than 1.4 on the second measurement. The H/L ratios in one patient were 1.34 (first) and 1.45 (second), and in another patient, 1.37 (first) and 1.44 (second). In these 38 patients, we used the first measurement data.

Fig. 1 compares the prevalence of IHD in different subgroups of patients stratified on the basis of a carotid artery H/L ratio from 1.0 and above in 0.1 increments. The prevalence of IHD was significantly different among the groups (p<0.001). The prevalence rates in groups with ratios of 1.3 to less than 1.5, 1.6 to less than 1.7, and 2.0 and greater were significantly higher than in the group with ratios of 1.0 to less than 1.1. The prevalence rates in groups with ratios of 1.3 to less than 1.7 and 2.0 and greater were also significantly higher than in the group with ratios of 1.2 to less than 1.3. The prevalence rates in groups with ratios of 1.7 to less than 1.8, 1.8 to less than 1.9, and 2.0 and greater were not significantly different form those in the group with ratios of 1.0 to less than 1.1, nor in the group with ratios of 1.2 to less than 1.3. But the prevalence rates in groups with ratios of 1.7 and greater were significantly higher than in the group with ratios of 1.0 to less than 1.1 (30.0% vs. 6.2%; p < 0.005) and also significantly higher than in the group with ratios of 1.2 to less than 1.31 (30.0%vs. 3.6%; p<0.001).

Table 3 shows the odds ratio for the prevalence of IHD as a function of the carotid artery H/L ratio. A total of 10 groups were defined and stratified by H/L ratios ranging from greater than 1.1 to greater than 2.0 in 0.1 increments. The prevalence of IHD in each group was the dependent variable. The data were analyzed with respect to each factor variable, including the unadjusted H/L ratio, the age-adjusted H/L ratio, and the H/L ratio adjusted for all other "model 1" factor variables. The unadjusted H/L ratio was an independent risk factor for IHD at ratios from greater than 1.1 to greater than 1.6. The age-adjusted H/L ratio was an independent risk factor for IHD at ratios from greater than 1.1 to greater than 1.4. None of the other baseline characteristics were significant risk factors. **Table 4** shows the results of logistic regression analyses using the "model 1" factors. The "age" and the "H/L ratio of 1.4 or greater" were independent variables for ischemic heart disease. When analyses were performed using the "model 2" factors,

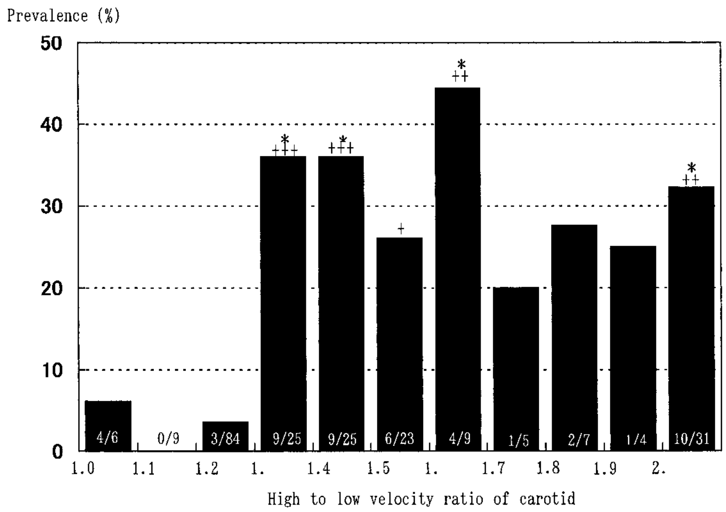

Fig. 1 Prevalence of the presentation of ischemic heart disease as a function of the high to low velocity ratio of the carotid artery
*p<0.05 vs. 1.0–1.1 group, +p<0.05, ++p<0.01, +++p<0.001 vs. 1.2–1.3 group

Table 3 Odds ratio of the presentation of ischemic heart disease as a function of high to low velocity ratio of the carotid artery

High to low velocity ratio of carotid artery	Prevalence of IHD #	Unadjusted		Adjusted for age		Adjusted for age and other risk factors †	
		Odds Ratio (95%CI)	P value	Odds Ratio (95%CI)	P value	Odds Ratio (95%CI)	P value
>1.1	59/222 (26.6%)***	5.517 (1.922—15.835)	0.001	5.843 (2.013—16.959)	0.001	5.843 (2.013—16.969)	0.001
>1.2	59/213 (27.7%)***	6.698 (2.342—19.157)	0.000	6.672 (2.312—19.254)	0.000	6.672 (2.321—19.254)	0.000
>1.3	42/129 (32.6%)***	3.149 (1.748—5.674)	0.000	2.814 (1.545—5.126)	0.001	2.814 (1.545—5.126)	0.001
>1.4	33/104 (31.7%)**	2.370 (1.342—4.186)	0.003	2.128 (1.190—3.805)	0.011	2.128 (1.190—3.805)	0/011
>1.5	24/79 (30.4%)*	1.891 (1.045—3.420)	0.035	—		—	
>1.6	18/56 (32.1%)*	1.958 (1.024—3.745)	0.042	—		—	
>1.7	14/47 (29.8%)	—		—		—	
>1.8	13/42 (31.0%)+	—		—		—	
>1.9	11/35 (31.4%)	—		—		—	
>2.0	10/31 (32.3%)	—		—		—	

Prevalence of IHD : Prevalence of ischeminc heart disease in group with greater H/L ratio group.
† Risk factors were systolic blood pressure, pack-years smoking, body mass index, uric acid, total cholesterol, triglyceride, sex, and history of diabetes mellitus.
+ $p<0.1$, * $p<0.05$, ** $p<0.01$, *** $p<0.001$ by Chi squared test.

Table 4 Logistic regression analysis of the presence of ischemic heart disease

Variable	β Coefficient	Standard Error	P	Odds Ratio	95%CI
Age	0.063	0.018	0.000	1.065	1.029—1.102
H/L ratio>1.4	0.779	0.307	0.011	2.128	1.190—3.805
Smoking value	0.000	0.000	0.266	1.000	1.000—1.001
Body mass index	0.051	0.046	0.271	1.052	0.961—1.151
Uric acid	0.042	0.085	0.616	1.043	0.884—1.231
Total cholesterol	0.003	0.004	0.498	1.003	0.995—1.010
Triglyceride	0.000	0.003	0.953	1.000	0.995—1.005
Male sex	0.131	0.367	0.721	1.140	0.555—2.341
Diabetes mellitus	0.301	0.334	0.366	1.352	0.703—2.599
Systolic blood pressure	− 0.010	0.008	0.205	0.990	0.974—1.006

the results were the same as with the "model 1" factors.

IMT was significantly greater in patients with H/L ratios of 1.4 or greater compared to patients with ratios of less than 1.0. The prevalence of carotid artery plaque was also significantly higher in patients with H/L ratios of 1.4 or greater versus patients with ratios of less than 1.4 (**Table 2**).

Discussion

Measurement of IMT by B-mode ultrasonography is reported to be a clinically useful, noninvasive means of predicting the presence of cardiovascular lesions. QFM was actually available in clinical settings prior to the development of equipment for B-mode ultrasonography. However, few studies have investigated the clinical usefulness of QFM[7,8] and there are no prior reports of the equipment used in this study being used to measure blood flow velocity. QFM is used to calculate blood flow velocity. The blood flow in the carotid arteries is measured by sequential ultrasound exposure with an exposure frequency of 5 MHz at 10° angle differences. The two ultrasound echoes are then analyzed by a Doppler method[9,10]. This technique measures the velocity of flow through a linear vessel; the flow rate is also calculated from the measured vessel diameter. The measured values have been found to correlate well with actual flow rates. Uematsu et al.[7] reported that the ratio of left to right common carotid artery blood flow helped to identify cerebrovascular lesions. In measurements of blood flow in tortuous vessels and vessels with plaque, they reported abnormally high blood flow velocities in areas of carotid artery stenosis. However, details of abnormal carotid artery morphology were not discussed, and the data were not examined by multivariate analysis.

In our study, we performed stratified analysis of the data regarding the prevalence of IHD as a function of the H/L ratio. We found that a ratio of 1.3 and greater was associated with a higher prevalence of IHD. However, because the risk factors for atherosclerosis varied among patients, we also examined the data by multivariate analysis to assess the effect of each risk factor. Multivariate analysis showed that H/L ratios of greater than 1.1, 1.2, 1.3, and 1.4 were independent risk factors for IHD. Therefore, patients with carotid artery H/L ratios of 1.4 or greater should be considered a high risk group for the presence of IHD.

Kimura et al.[11] studied patients with internal carotid artery obstruction and normal carotid arteries by ultrasound technique and angiography. They compared blood flow velocity between patients and normal subjects. The H/L ratio was less than 1.4 in patients with normal carotid arteries. Among patients with internal carotid artery obstruction, the H/L ratio was 1.4 and greater in all patients with obstruction due to atherosclerosis and in all but one patient with obstruction due to a cardiogenic source. However, no results were reported about what increase in the H/L ratio best correlated with clinical findings.

The high coefficient of variation (16.2%) for determination of the H/L ratio suggests relatively poor reproducibility; thus, reliability of the procedure for absolute quantitative measurement may be low. Nevertheless, reproducibility is good with respect to classifying patients with H/L ratios below or above a cutoff value of 1.4. The two patients in this study who were classified differently based on the first and second measurements both had H/L ratios near 1.4. Therefore, the clinical usefulness of the H/L ratio is not based on absolute values. Rather, H/L ratios of 1.4 and above are clinically useful in identifying patients at higher risk for atherosclerosis.

Longitudinal stretching of arteries is associated with the process of aging, and results in blood vessel tortuosity. QFM has mainly been performed in elderly patients with suspected carotid artery atherosclerosis. Thus, tortuosity of the carotid arteries was present in many of the patients studied. The lack of reports evaluating use of this equipment may be because of its inability to measure IMT and sometimes less than satisfactory reproducibility of blood flow measurements. We believe that some of the disparity between results during developmental testing and results in actual clinical practice may be because of its original design based on the premise of measuring flow in linear blood vessels. Therefore, the present study evaluated the clinical usefulness of measuring the H/L ratio by direct measurement only of carotid artery blood flow. In some patients studied, we also measured IMT of the common carotid arteries. We found higher IMT values and an increased presence of plaque in patients with greater H/L ratios. These findings suggest that greater H/L ratios are associated with higher rates of vessel tortuosity and irregularity of the vessel inner walls.

In our study, multivariate analysis of each risk factor for atherosclerosis showed that an increased carotid artery H/L ratio and age acted as independent risk factors for IHD. None of the other baseline characteristics were significant risk factors. These findings were in some disagreement with other reports[1,12-14]. Mannami et al.[15] performed carotid artery ultrasound studies in apparently healthy Japanese subjects. They found that cardiovascular risk factors strongly correlated with the presence of carotid artery atherosclerosis. The prevalence of severe lesions of 50% or greater was similar to that in Europe and the United States. It seems unlikely that our findings represent unique characteristics of Japanese subjects. Most of the present study subjects were being treated for various medical conditions. Prospective cohort studies using large number of subjects are required to confirm the present observation.

The limitations of the present study are follows. First, the number of study subjects was small and all of them were outpatients. Prospective cohort studies using large number of subjects are required to confirm the present observation. Second, we did not examine the drug, taken by the study subjects. Many large clinical intervention trials using demonstrated a beneficial effect on the progression of atherosclerosis accompanied by a reduction in cardiovascular events[1,16,17]. In the present study, the prevalence of statine administration was significantly lower in groups with H/L ratios of 1.4 and greater than in the group with H/L ratios of less than 1.4 (10.3% vs. 2.9%; $p<0.05$). Many trials showed that the effects of antiplatelet therapy prevent cardiovascular events [18]. These issues also need to be addressed by studies in a larger number of patients. Third, the H/L ratio in patients with bilateral common carotid stenosis should be low. Therefore, the H/L ratio, measured by QFM, may be a clinically unusable index in patients with severe atherosclerosis. Several authors have commented on nonuniformity in findings between the left and right carotid arteries with respect to the onset and development of atherosclerosis. Caplan et al.[19] notes that atherosclerosis does not begin or develop as a uniform process in both common carotid arteries. The resulting geometric and morphologic differences between the left and right sides leads to differences in the shear stresses acting on the blood vessel walls[20]. Ultrasound studies by Gnasso et al.[21] showed that atherosclerosis of the carotid arteries begins as an asymmetrical process. They reported lower shear stresses on the side with milder atherosclerosis. We did not measure shear stress in our study. Thus, we were unable to make comparisons with the data from other studies.

In conclusion, we used QFM to measure blood flow velocity in the common carotid arteries. Patients with H/L ratios of greater than 1.4 had an increased prevalence of IHD. We therefore believe that QFM is clinically useful in screening patients for coronary artery lesions.

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