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CLINICAL AND POPULATION STUDIES

Hemodynamic Environments for the Progression of Carotid Stenosis: The NHO Carotid CFD Study

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BACKGROUND: Hemodynamic stress plays an important role in the development of atherosclerosis. It is difficult to sufficiently predict the progression of atherosclerosis and consequent stenosis based on known risk factors alone. This may be partly because the hemodynamic environments that promote stenosis progression remain unclear. The carotid bifurcation is the preferred site of atherosclerosis. In this prospective observational study, we sought to identify hemodynamic predictors of carotid stenosis progression.

METHODS: Computational fluid dynamics analysis was performed using arterial geometry and flow velocity specific to individual patients. Hemodynamic metrics were compared by multivariate analysis between the presence or absence of stenosis progression, using known risk factors as confounding factors.

RESULTS: A total of 545 patients were enrolled, and 361 stenotic arteries in 313 patients were analyzed, 38 of which had progressive stenosis. Among the carotid arteries with 30% to 55% area stenosis, those with stenosis progression had significantly lower time-averaged wall shear stress (WSS; odds ratio [OR], 0.078 [95% CI, 0.012–0.492]; *P*=0.0067) distal to the stenosis site and significantly higher oscillatory shear index (OR, 2.37 [95% CI, 1.17–4.82]; *P*=0.016). Among carotid arteries with 56% to 70% stenosis, those with stenosis progression had significantly higher time-averaged WSS (OR, 2.36 [95% CI, 1.19–4.72]; *P*=0.014) and transverse WSS (OR, 3.03 [95% CI, 1.45–6.34]; *P*=0.0033), a metric for multidirectional WSS disturbance, at the stenotic site and significantly higher transverse WSS (OR, 2.30 [95% CI, 1.20–4.42]; *P*=0.012) at the distal site. Arteries with 71% to 99% stenosis and stenosis progression had significantly higher oscillatory shear index (OR, 1.91 [95% CI, 1.05–3.47]; *P*=0.033) at the distal site.

CONCLUSIONS: These data suggest the specific hemodynamic environments involved in the stenosis progression at bifurcation and that hemodynamic risk for stenosis progression differs depending on the degree of stenosis. Combining these hemodynamic predictors with known risk factors may allow a more accurate selection of cases at high risk of progression.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atherosclerosis ■ carotid stenosis ■ hemodynamics ■ risk ■ stents

Atherosclerosis is the major cause of peripheral vascular diseases, including cerebral and myocardial infarction, and is caused by an interactive combination of hemodynamic and biological factors with underlying diseases, such as diabetes, hypertension, and dyslipidemia.[1,2] Hemodynamic stress is one of the factors most directly related to the onset of atherosclerosis and is one of the most important parameters in the biomechanics of atherosclerosis.[1–6] Therefore, it is important to examine the pathogenesis of atherosclerosis from a hemodynamic perspective. Nonetheless, the role of hemodynamics in atherosclerosis pathogenesis has not yet been sufficiently clarified.

Computational fluid dynamics (CFD) analysis is a suitable method for examining the hemodynamics in atherosclerosis. This is because wall shear stress (WSS),

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Nonstandard Abbreviations and Acronyms

3D	3-dimensional
CAS	carotid artery stenting
CEA	carotid endarterectomy
CFD	computational fluid dynamics
ICA	internal carotid artery
NHO	National Hospital Organization
OR	odds ratio
OSI	oscillatory shear index
TAWSS	time-averaged wall shear stress
transWSS	transverse wall shear stress
WSS	wall shear stress

considered the most important hemodynamic factor in atherosclerosis, cannot yet be reliably evaluated using current experimental methods, whereas CFD analysis allows the evaluation of WSS with high accuracy.[7] Previous studies by various researchers have demonstrated that plaque development usually occurs in the low WSS region, oscillating disturbances of WSS are also involved, and plaque rupture, the final stage of plaque formation and vascular stenosis, occurs in the high WSS region.[1–12] However, the hemodynamic environments that induce the progression of plaque formation and consequent stenosis progression due to atherosclerosis remain unclear.

The hemodynamic environment is highly dependent on vascular geometry, and atherosclerosis is known to occur primarily at arterial bifurcations and the aortic arch.[8,13–15] Among these locations, the carotid bifurcation is one of the most common sites of arterial stenosis due to atherosclerosis, and carotid stenosis is one of the main lesion responsible for atherosclerotic ischemic stroke.[3,16–18] Therefore, we established a prospective observational clinical study—the NHO Carotid CFD Study (National Hospital Organization Carotid Computational Fluid Dynamics; University Hospital Medical Information Network ID: URL: https://www.umin.ac.jp/ctr; Unique identifier: UMIN000025903)—by enrolling and examining patients with carotid stenosis who underwent 3-dimensional (3D) imaging of the carotid artery and carotid ultrasonography. The purpose of the NHO Carotid CFD Study was to use CFD analysis to examine differences in the hemodynamic environments between patients in whom stenosis progressed over a 2-year observation period and those in whom it did not, and thereby identify hemodynamic risk factors for stenosis progression.

Highlights

- We performed a prospective observational study on the progression of carotid stenosis utilizing computational fluid dynamics analysis. A total of 544 patients were enrolled, with 361 stenoses analyzed in 313 cases, 38 of which had progressive stenosis.
- In the initial stage of stenosis (30%–55% area stenosis), arteries with stenosis progression were significantly associated with a low and oscillatory shear environment, while in the moderate stenosis stage (56%–70% area stenosis), higher wall shear stress with enhanced multidirectional disturbance was associated with stenosis progression. For moderate-to-severe stenosis (71%–99% area stenosis), oscillatory wall shear stress was significantly stronger distal to the stenosis site in arteries with progressive stenosis.
- These sets of evidence suggest that the hemodynamic environments that induce stenosis progression depend on the degree of stenosis and that both the magnitude and disturbance of the wall shear stress are important factors.
- By combining the obtained hemodynamic predictors of stenosis progression with known risk factors for progression, it will be possible to more accurately select high-risk cases, which will be useful for future treatment strategies.
- The possible role of hemodynamics in the progression of stenosis suggests the potential for a prophylactic agent against stenosis; namely, blood flow-sensing inhibitors such as P2X4 inhibitors may be able to reduce stenosis progression.

MATERIAL AND METHODS

Availability of Data

The authors declare that all supporting data are available within the article or its Supplemental Material. The raw data of this study cannot be released because the patient information analyzed in this study was obtained with written consent under the condition that it be used only by the NHO Carotid CFD study office.

Regulatory Requirements and Ethics

This study was conducted in accordance with the World Medical Association Declaration of Helsinki Ethical Guidelines for Medical Research Involving Human Subjects, the Act on the Protection of Personal Information, and the Act on the Protection of Personal Information Held by Independent Administrative Institutions. The conformity of research protocols and other documents with applicable guidelines was approved by the NHO central ethics review board on December 5, 2016. Written consent was obtained for patient enrollment. Case enrollment was conducted at 28 institutions (see Supplemental Material for a list of participating institutions).

Enrollment of Patients and Eligibility Criteria

The enrollment period was from January 2017 to March 2019, and the observation period was 2 years after enrollment. Patients meeting all of the following criteria were eligible for enrollment: at least 1 prior carotid 3D contrast-enhanced computed tomography angiography examination (the reason for the

examination did not necessarily have to be carotid stenosis); carotid artery stenosis with an area stenosis of at least 30% on carotid ultrasonography; age of >20 years; and provision of written consent. Patients with postradiation carotid stenosis, aortitis syndrome, fibromuscular dysplasia, dissection carotid stenosis, or congenital carotid stenosis; patients after carotid endarterectomy (CEA) or carotid artery stenting (CAS; with the exception that patients with contralateral unoperated stenotic lesions could be enrolled); and patients who could not undergo 3D contrast-enhanced computed tomography angiography due to contrast allergy or severe renal dysfunction were excluded.

During the observation period, patients were generally required to undergo carotid ultrasonography at intervals of 1 year from the time of enrollment. Because this was an observational study, the doctor in charge could decide the interval of the examination depending on the case, but the final examination was scheduled 2 years after enrollment. Observation was terminated in the event of occlusion of the subject's carotid artery, death, or withdrawal of consent by the subject.

The enrollment was conducted in accordance with the STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology Statement) and the STROBE checklist was submitted to the journal's editorial office.

CFD Modeling and Postprocessing

CFD analysis was performed on each case that met the eligibility criteria, according to the method used in our previous report,[19] which will be briefly described here.

First, the geometries of the carotid artery were extracted from the volume data set of 3D contrast-enhanced computed tomography angiography images and reconstructed as realistic 3D vessel geometry data. Mimics and 3-matic software (Materialise, Leuven, Belgium) were used for this process. Next, computational meshes were created for the geometry data using Mixed-Element Grid Generator in 3D.[20,21] Because quantification of WSS is important in this study, suitable layer meshes were inserted along the vessel wall. The total number of elements in the computational meshes was ≈3 to 10 million, depending on the individual case. The computational meshes were then used for blood flow simulation using ANSYS CFX (ANSYS, Canonsburg, PA). The basic equations solved were the 3D, unsteady, incompressible Navier-Stokes equations. Blood was treated as a Newtonian fluid with a density of 1050 kg/m^3 and a viscosity of 0.0035 Pa·s, and the vessel wall was assumed to be rigid. The setting of the boundary conditions is important in CFD analysis. Individual vessel diameters and peak-systolic and end-diastolic velocities were measured with the Doppler ultrasound technique on common carotid arteries and internal carotid arteries (ICAs) of each patient to compute the corresponding flow rates. In the case of severe ICA stenosis, if only the flow rate in the common carotid artery is used as input and was calculated, most of the blood flow would be simulated as flow into the external carotid artery. However, unless the ICA is nearly occluded, more blood flow actually traverses the ICA because of the higher demand for cerebral blood flow (Murray law[22] cannot be assumed). To correct for this issue, the flow rate in the ICA in addition to that in the common carotid artery was entered in all cases. A typical pulsatile waveform shape from the literature[23] was scaled to the patient-specific peak-systolic and end-diastolic flow rates as CFD boundary conditions.

The results obtained from the blood flow simulations were used to calculate the distribution of the following 6 hemodynamic metrics throughout the vessel: time-averaged WSS (TAWSS), time-averaged WSS gradient,[24] oscillatory shear index (OSI),[25] gradient oscillatory number,[26] transverse WSS (transWSS),[27] and normalized transWSS.[28] TAWSS and time-averaged WSS gradient are the time-averaged magnitudes of WSS and WSSG, respectively; OSI and gradient oscillatory number quantify the temporal disturbances in WSS and WSSG, respectively; transWSS quantifies the disturbances in WSS in a specific direction (perpendicular to the main flow); and normalized transWSS is a dimensionless quantity obtained by dividing transWSS by TAWSS. The mathematical formulas used for the hemodynamic metrics are shown in Table S1. The value of each hemodynamic index was the average of the values of the luminal surface of the vessel in the stenotic, distal, and proximal areas.

Outcomes

For purposes of the present analysis, 3 regions of the stenotic carotid were defined: the stenotic area where the stenosis was present, the proximal area from the upstream end of the stenosis to 10 mm proximal, and the distal area from the downstream end of the stenosis to 10 mm distal.[19]

In this study, stenosis progression is defined as an increase of at least 15% in arteries with 30% to 70% area stenosis at initial enrollment, at least 10% in arteries with 71% to 90% initial stenosis, and at least 5% or vessel occlusion in arteries with 91% or greater initial stenosis on carotid echocardiography.

For patients who underwent CEA or CAS after enrollment, postoperative restenosis was defined as a postoperative area stenosis >50%.[29]

The value of the hemodynamic metric depends largely on the stenosis rate.[24–28] Therefore, hemodynamic metrics of progressive and nonprogressive stenotic arteries were compared among 3 subgroups defined according to the area stenosis of 30% to 55%, 56% to 70%, and 71% to 99% at registration.

Statistical Analysis

The continuous data are reported as means±SD. The binary data are reported as the frequency and percentage. The distributions of hemodynamic metrics of the carotid arterial wall obtained by CFD analysis, that is, TAWSS, time-averaged WSS gradient, OSI, gradient oscillatory number, transWSS, and normalized transWSS, are presented as means±SD.

Each hemodynamic variable was standardized by dividing by the SD so that it was easy to compare the odds ratio (OR) among variables. The ORs with 95% CIs and *P* values were calculated by multivariate analysis using logistic regression models 1 factor at a time because many of the hemodynamic metrics are highly correlated with each other[19,28] (the formulas for each hemodynamic metric are shown in Table S1).

At the time this study was initiated, there had been no comparable prospective study in this research area. Therefore, we initiated this research in an exploratory manner with the goal of enrolling as many cases as possible from a limited number of participating centers within a defined time frame. Therefore,

sample size and power calculations were not performed before performing the study. Because the sample size of this study was not large, the statistical power may not have been sufficient. Therefore, we did not correct for the effects of age or sex, as this only increases multiplicity.

We adopted the approach recommended by Rothman and Lash in their epidemiology textbook,[30] selecting variables for multivariate analysis based on previously reported clinical priorities, rather than based on their *P* value–based statistical significance in the univariate analysis. Each hemodynamic metric was adjusted for the known risk factors of age, sex, hypertension, diabetes, dyslipidemia, primary area stenosis, smoking history, daily drinking history, history of taking an antiplatelet drug, and history of taking a statin.[1]

The multivariate analysis using logistic regression models was also used to compare the presence or absence of restenosis after CEA or CAS.

Values of $P<0.05$ were considered statistically significant. Complete-case analysis was performed. All analyses were conducted using JMP ver. 17.2.0 software (SAS, Cary, NC). All statistical analyses were performed under the supervision of our coauthor and a biostatistician.

RESULTS

Number of Registered Patients

During the enrollment period, 544 patients were enrolled. Of these, 195 cases were excluded due to withdrawal of consent (3 cases), nonconformity with eligibility criteria (2 cases), death during the observation period (20 cases), termination of attendance at the facility (123 cases), or deficiencies in image or other data (47 cases), and the remaining 349 cases were analyzed. The number of patients who did not undergo CEA or CAS during the observation period was 313, accounting for 361 arteries, of which 38 arteries showed progression of stenosis. For the background of these cases, see Table 1. Of the 36 patients (36 arteries) who underwent the surgery during the observation period, 6 showed progression of stenosis. For the background of these cases, see Table S2. There were 13 cases of symptomatic cerebral infarction.

Comparison of Hemodynamic Metrics Between Progressive and Nonprogressive Stenotic Arteries

Comparison of the arteries with progressive and nonprogressive stenosis in the group with area stenosis of 30% to 55% at registration revealed that OSI (OR, 2.37 [95% CI, 1.17–4.82]; $P=0.016$) was significantly higher, and TAWSS (OR, 0.078 [95% CI, 0.012–0.492]; $P=0.0067$) and time-averaged WSS gradient (OR, 0.013 [95% CI, 0.0004–0.429]; $P=0.014$) were significantly lower in the progressive stenosis group for the distal site (Table 2; Figure). In the group with area stenosis of 56% to 70%, TAWSS (OR, 2.36 [95% CI, 1.19–4.72]; $P=0.014$) and transWSS (OR, 3.03 [95% CI, 1.45–6.34]; $P=0.0033$) at the stenotic site and gradient oscillatory number (OR, 2.12 [95% CI, 1.16–3.89]; $P=0.014$) and transWSS (OR, 2.30 [95% CI, 1.20–4.42]; $P=0.012$) at the distal site were significantly higher in the progressive stenosis group (Table 3; Figure). In the group with area stenosis of 71% to 99%, OSI (OR, 1.91 [95% CI, 1.05–3.47]; $P=0.033$) at the distal site was significantly higher in the progressive stenosis group (Table 4; Figure). No significant differences were found for the other metrics.

Comparison of Hemodynamic Environments After CEA or CAS Between the Presence or Absence of Restenosis

There was no significant difference in any of the hemodynamic metrics at enrollment between the carotid arteries that underwent restenosis and those that did not (Table S3).

DISCUSSION

Among hemodynamic parameters potentially involved in atherosclerosis, the magnitude of WSS has attracted particular attention; it has been widely believed that low WSS plays a major role at atherosclerosis onset and that high WSS plays a major role in plaque rupture, one of the final stages of the disease.[2,7–12] Low WSS in the carotid artery is associated with intimal tunica media thickening and formation of carotid bifurcation plaques.[9,31] However, the role of hemodynamics in the progression of atherosclerosis, namely, the progression of vascular stenosis, has remained unclear. The results of the present study suggest that examination of arterial stenosis caused by atherosclerosis from a hemodynamic perspective may be useful in elucidating its pathogenesis.

Low and Oscillatory WSS During Plaque Formation

It has been reported that arterial geometry is a predictor of arterial wall thickening.[9,16,17] Physiological hemodynamic mechanisms do not function well in arterial segments with relatively less mobile geometries where blood flow is slower than along the contralateral arterial wall, such as the outer arterial wall of a carotid bifurcation or the inner arterial wall of the aortic arch, and are prone to atherosclerosis.[32] In addition, differences in carotid arterial geometry also affect the hemodynamic environment at the carotid bifurcation.[16,17] Low and oscillatory shear environment induced by these vessel geometries was suggested to trigger plaque formation by Ku et al[13] as early as 1985, and several later reports supported this hypothesis.[4,5,33] In the context of these reports, oscillatory shear represents the degree of unidirectional flow

Table 1. Background of Cases With Progressive and Nonprogressive Carotid Arteries

		30%–55%		56%–70%		71%–99%	
	Stenosis	Progressive	Nonprogressive	Progressive	Nonprogressive	Progressive	Nonprogressive
	No. of arteries	16	76	12	131	10	116
	Female, %	4 (25)	14 (18)	2 (17)	28 (21)	2 (20)	21 (18)
	Age, y	72.8±8.4	72.5±6.7	73.8±7.7	75.0±7.5	75.9±7.3	72.5±8.0
	Initial stenosis rate, %	42.9±9.1	44.9±8.0	61.5±4.5	62.9±4.3	80.0±5.2	81.7±7.6
	Hypertension, %	9 (56)	62 (82)	9 (75)	95 (73)	9 (90)	89 (77)
	Hyperlipidemia, %	10 (63)	40 (53)	5 (42)	58 (44)	7 (70)	53 (46)
	Diabetes, %	1 (6)	17 (22)	8 (67)	38 (29)	4 (40)	41 (35)
	Smoking, %	9 (56)	48 (63)	8 (67)	83 (63)	8 (80)	73 (63)
	Daily drinking	3 (19)	21 (28)	5 (42)	48 (37)	5 (50)	39 (34)
	Antiplatelet, %	6 (38)	40 (53)	10 (83)	87 (66)	7 (70)	76 (66)
	Statin, %	12 (75)	40 (53)	8 (67)	69 (53)	6 (60)	64 (55)
Stenotic area	TAWSS, Pa	0.922±0.492	0.911±0.615	1.58±1.01	1.06±0.69	1.78±0.99	1.98±2.66
	TAWSSG, Pa/mm	0.0625±0.0910	0.0509±0.0818	0.130±0.141	0.111±0.221	0.344±0.709	0.213±0.422
	OSI (–)	0.0554±0.0503	0.0606±0.0444	0.0413±0.0208	0.0506±0.0292	0.0450±0.0271	0.0369±0.0245
	GON (–)	0.101±0.054	0.111±0.058	0.0883±0.0438	0.0954±0.0428	0.0837±0.0363	0.164±0.171
	transWSS, Pa	0.101±0.039	0.102±0.055	0.159±0.082	0.111±0.054	0.159±0.079	0.158±0.170
	NtransWSS (–)	0.208±0.096	0.206±0.090	0.182±0.061	0.194±0.061	0.189±0.047	0.164±0.057
Distal area	TAWSS, Pa	0.493±0.249	1.09±0.65	1.33±0.77	1.17±0.80	1.75±1.77	1.76±1.63
	TAWSSG, Pa/mm	0.0144±0.0124	0.0372±0.0517	0.0943±0.1663	0.0631±0.1097	0.420±1.236	0.0973±0.2055
	OSI (–)	0.0745±0.0400	0.0351±0.0335	0.0401±0.0291	0.0268±0.0247	0.0414±0.0414	0.0236±0.0190
	GON (–)	0.115±0.048	0.0881±0.0528	0.130±0.071	0.0882±0.0464	0.104±0.065	0.0844±0.0520
	transWSS, Pa	0.0695±0.0284	0.0952±0.0534	0.147±0.080	0.0977±0.0525	0.185±0.233	0.147±0.154
	NtransWSS (–)	0.218±0.0784	0.151±0.080	0.164±0.077	0.137±0.066	0.145±0.065	0.128±0.054
Proximal area	TAWSS, Pa	0.521±0.317	0.577±0.363	0.689±0.431	0.602±0.414	0.561±0.304	0.726±0.724
	TAWSSG, Pa/mm	0.0175±0.0176	0.0195±0.0346	0.0271±0.0403	0.0347±0.0794	0.0489±0.0845	0.0419±0.1004
	OSI (–)	0.0666±0.0512	0.0516±0.0468	0.0353±0.0288	0.0506±0.0459	0.0586±0.0561	0.0614±0.0545
	GON (–)	0.106±0.057	0.101±0.054	0.0814±0.0413	0.0987±0.0605	0.113±0.085	0.114±0.081
	transWSS, Pa	0.0668±0.0343	0.0693±0.0501	0.0656±0.0291	0.0666±0.0461	0.0882±0.0629	0.0881±0.0756
	NtransWSS (–)	0.198±0.103	0.170±0.099	0.134±0.057	0.163±0.098	0.196±0.112	0.191±0.115

GON indicates gradient oscillatory number; transWSS, transverse wall shear stress; NtransWSS, normalized transverse wall shear stress; OSI, oscillatory shear index; TAWSS, time-averaged wall shear stress; and TAWSSG, time-averaged wall shear stress gradient.

disturbance, that is, periodic flow reversal in the direction of the main axis of flow.[8]

Hemodynamic Risk Factors for Stenosis Progression in Arteries With an Area Stenosis of 30% to 55%

In the stage shortly after the onset of stenosis, that is, in arteries with an area stenosis of 30% to 55% at the first registration measurement, a significant environment of low and oscillatory shear was found downstream of the stenosis site in the progressive stenosis group (Table 2). The results of the present study suggest that low and oscillatory shear environment is associated with pathogenesis not only during carotid plaque formation but also at early stage of carotid stenosis. This may be due to the original carotid artery geometry before the stenosis occurred. The classic low and oscillatory shear may be induced by the vascular geometry, which may have the effect of promoting not only plaque formation but also stenosis development and early stenosis progression.

Hemodynamic Risk Factors for Stenosis Progression in Arteries With an Area Stenosis of 56% to 70%

In the arteries with mild-to-moderate stenosis (area stenosis of 56%–70%), the hemodynamic environment associated with stenosis progression was different from the low and oscillatory shear environment found in the early stages of stenosis. That is, contrary to the initial stage of stenosis, the magnitude of WSS was significantly higher at the site of stenosis in arteries with progressive stenosis compared with nonprogressing arteries (Table 3). With regard to WSS

Table 2. Comparisons of Hemodynamic Metrics Between Progressive and Nonprogressive Carotid Arteries With an Area Stenosis of 30%–55%

30%–55%	Metrics	OR	95% CI lower	95% CI upper	*P* value	AICc
Stenotic area	TAWSS	1.06	0.89	1.04	0.85	97.9
	TAWSSG	1.40	0.79	2.50	0.25	96.8
	OSI	0.68	0.35	1.35	0.27	96.7
	GON	0.62	0.30	1.29	0.20	96.2
	transWSS	0.91	0.50	1.67	0.76	97.8
	NtransWSS	0.83	0.43	1.60	0.57	97.6
Distal area	TAWSS	0.078*	0.012	0.492	0.0067*†	82.3
	TAWSSG	0.013*	0.0004	0.429	0.014*†	86.3
	OSI	2.37*	1.17	4.82	0.016*†	91.3
	GON	1.32	0.70	2.49	0.39	97.2
	transWSS	0.36	0.13	1.02	0.054	92.5
	NtransWSS	1.83	0.89	3.75	0.10	95.0
Proximal area	TAWSS	0.88	0.46	1.68	0.70	97.8
	TAWSSG	2.57	0.001	4425	0.80	97.9
	OSI	1.34	0.72	2.48	0.35	97.1
	GON	1.04	0.57	1.92	0.89	97.9
	transWSS	0.91	0.49	1.70	0.77	97.9
	NtransWSS	1.22	0.66	2.26	0.53	97.6

Each hemodynamic variable was divided by the standard deviation so that it was easy to compare the OR among variables. The ORs with 95% CIs and *P* values were calculated by multivariate analysis using logistic regression models 1 factor at a time. Each hemodynamic metric was adjusted for the known risk factors of age, sex, hypertension, diabetes, dyslipidemia, primary area stenosis, smoking history, daily drinking history, history of taking an antiplatelet drug, and history of taking a statin. AICc indicates corrected Akaike information criterion; GON, gradient oscillatory number; NtransWSS, normalized transverse wall shear stress; OR, odds ratio; OSI, oscillatory shear index; TAWSS, time-averaged wall shear stress; TAWSSG, time-averaged wall shear stress gradient; and transWSS, transverse wall shear stress.

*Odds ratio of hemodynamic metric with significant *P* value.

†$P<0.05$.

disturbances, transverse WSS, an index that evaluates the degree of disturbance in multiple directions relative to the flow direction,[27,34] rather than OSI, was significantly enhanced at both the stenotic and distal sites, and the disturbance of the WSS gradient was also enhanced distal to the stenosis.

Several previous reports have investigated potential explanations for the effects of stenosis degree on the hemodynamic environment.[35–37] Guo et al[35] used CFD techniques to examine the hemodynamic environment of 60 patients with carotid bifurcation stenosis ranging from 10% to 95% and reported a correlation between stenosis degree and geometric parameters of bifurcation. Regarding changes in the magnitude of WSS, Kumar and Shah[36] simulated the hemodynamic environment in arteries with degrees of stenosis ranging from 10% to 80% and found a clear relationship between the degree of stenosis and hemodynamic changes. They suggested that WSS was particularly affected, exhibiting increases at both the entry and exit zones of the stenosis, and may contribute to endothelial injury and plaque formation. Mahalingam et al[37] examined changes in the degree of WSS disturbance. They quantitatively calculated parameters affecting turbulence in the coronary arteries at 0%, 30%, 50%, and 70% stenosis and found that the transition from laminar to turbulent flow begins at 50% stenosis and that blood flow is turbulent for all area stenosis above 70%.

Although Bijari et al[17] suggest that carotid bifurcation geometry is an independent predictor of wall thickening only in the early stages of wall thickening, vessel geometry is a possible factor contributing to these hemodynamic differences. We have reported that the hemodynamic distributions of stenotic carotid arteries after artificial release of the stenosis are significantly different from those of normal carotid arteries that have not developed stenosis.[19] We also reported that carotid arteries with a smaller ratio of the external carotid artery diameter to the common carotid artery diameter are more likely to develop severe stenosis, suggesting that arterial geometry may play a role in the progression of stenosis. Therefore, in progressive stenosis cases in the present analysis, there may have been geometry changes that induced higher WSS and a greater degree of multidirectional WSS disturbance. This could be due not only to the arterial geometry before the stenosis occurred but also to changes in the arterial shape due to atherosclerosis and adaptive remodeling during the process of stenosis progression, which could have induced a hemodynamic environment that would promote stenosis progression.

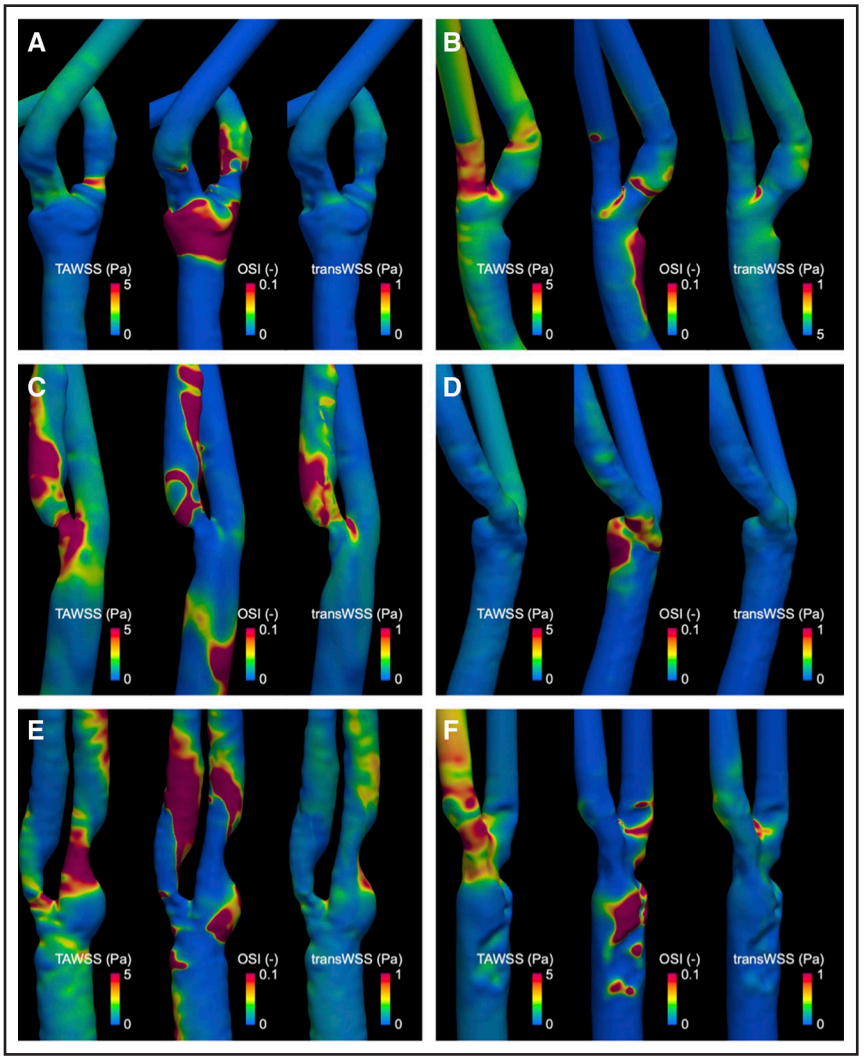

Figure. Representative images of hemodynamic metrics at registration of arteries with and without progressive stenosis.
Representative images of time-averaged wall shear stress (TAWSS), oscillatory shear index (OSI), and transverse wall shear stress (transWSS) between an artery with progressive stenosis (**A**, **C**, and **E**) and an artery with nonprogressive stenosis (**B**, **D**, and **F**) in the group with area stenosis of 30% to 55% (**A** and **B**), 56% to 70% (**C** and **D**), and 71% to 99% (**E** and **F**) at registration.

Hemodynamic Risk Factors for Stenosis Progression in Arteries With an Area Stenosis of 71% to 99%

For moderate-to-severe stenosis (71%–99% stenosis rate), oscillatory WSS was significantly stronger distal to the stenosis site in arteries with progressive stenosis (Table 4). Thus, it was characteristic that WSS disturbances were enhanced downstream of the stenosis site at all stenosis rate stages in the arteries with progressive stenosis compared with the nonprogressive arteries. However, the type of WSS disturbance differed at each stage. Although oscillatory disturbance was enhanced in the early stages of stenosis, multidirectional disturbance was enhanced at moderate stenosis rates, and as stenosis rates became stronger, oscillatory disturbance was again enhanced. In general, blood flow patterns are relatively simple in the early stages of stenosis, and oscillatory disturbances of WSS can occur distal to the stenosis, but multidirectional disturbances are unlikely. On the contrary, in mild-to-moderate stenosis, the shape of the stenosis changes in a complex, nonaxisymmetric manner, and the WSS disturbance is likely to become more multidirectional. In moderate-to-severe stenosis, although the vascular geometry is complex, the type of WSS disturbance may change from multidirectional to oscillatory due to reduced flow rate. Thus, it is important to consider not only the magnitude of WSS but also the WSS disturbance.[38,39] Under physiological conditions, coronary blood flow is helical, and the helical intensity has been reported to help reduce the disturbance of arterial blood flow in normal arteries, with a protective effect against atherosclerosis.[8] This helical flow is known to be disturbed at the bifurcation.

Hemodynamic Risk Factors for Plaque Rupture and Onset of Ischemic Events

Plaque rupture in severe carotid artery stenosis is one of the main causes of symptomatic ischemic stroke. Due to the small number of patients with symptomatic cerebral infarction, statistical analysis of hemodynamic risk factors for plaque rupture and associated ischemic events was not possible in this prospective study. Zhao et al[18] conducted a cross-sectional cohort-comparison

Table 3. Comparisons of Hemodynamic Metrics Between Progressive and Nonprogressive Carotid Arteries With an Area Stenosis of 56%–70%

56%–70%	Metrics	OR	95% CI lower	95% CI upper	*P* value	AICc
Stenotic area	TAWSS	2.36*	1.19	4.72	0.014*†	81.4
	TAWSSG	0.96	0.45	2.02	0.90	87.8
	OSI	0.60	0.27	1.35	0.22	86.1
	GON	0.83	0.43	1.64	0.60	87.5
	transWSS	3.03*	1.45	6.34	0.0033*†	77.9
	NtransWSS	0.83	0.42	1.64	0.59	87.5
Distal area	TAWSS	1.14	0.63	2.03	0.65	87.6
	TAWSSG	1.14	0.63	2.05	0.66	87.6
	OSI	1.58	0.85	2.91	0.14	85.8
	GON	2.12*	1.16	3.89	0.014*†	81.7
	transWSS	2.30*	1.20	4.42	0.012*†	80.7
	NtransWSS	1.62	0.80	3.29	0.17	86.0
Proximal area	TAWSS	1.42	0.74	2.70	0.29	86.8
	TAWSSG	0.69	0.27	1.75	0.43	86.8
	OSI	0.74	0.34	1.60	0.44	87.2
	GON	0.91	0.43	1.94	0.80	87.7
	transWSS	1.32	0.66	2.63	0.43	87.2
	NtransWSS	0.90	0.43	1.89	0.77	97.7

Each hemodynamic variable was divided by the standard deviation so that it was easy to compare the OR among variables. The ORs with 95% CIs and *P* values were calculated by multivariate analysis using logistic regression models 1 factor at a time. Each hemodynamic metric was adjusted for the known risk factors of age, sex, hypertension, diabetes, dyslipidemia, primary area stenosis, smoking history, daily drinking history, history of taking an antiplatelet drug, and history of taking a statin. AICc indicates corrected Akaike information criterion; GON, gradient oscillatory number; NtransWSS, normalized transverse wall shear stress; OR, odds ratio; OSI, oscillatory shear index; TAWSS, time-averaged wall shear stress; TAWSSG, time-averaged wall shear stress gradient; and transWSS, transverse wall shear stress.

*Odds ratio of hemodynamic metric with significant *P* value.

†$P<0.05$.

observational study of 352 patients using carotid artery echocardiography to compare WSS, OSI, and the turbulence index around carotid bifurcation plaques in patients with and without symptomatic ischemic stroke, and reported that higher WSS and OSI on the downstream surface of plaque were significantly associated with ischemic stroke. However, several reports indicate that plaque rupture, which can cause symptomatic cerebral infarction, occurs in the high shear stress region upstream of the plaque surface rather than downstream.[9] Another study in patients with coronary artery disease reported that high WSS proximal to an atherosclerotic lesion is a predictor of myocardial infarction.[11] It is unclear whether plaque rupture is more likely to occur upstream, downstream, or both upstream and downstream of the plaque lesion, and whether these 2 theories can be reconciled. In the present study, the magnitude of WSS was not significantly involved in the progression of stenosis of carotid arteries with moderate-to-severe stenosis. The PROSPECT study (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) prospectively followed high-risk acute coronary syndrome patients in the United States and Europe and found that low endothelial shear stress in coronary artery lesions is an independent prognostic factor for future development of high-risk thin-fiber atheroma.[10] The PROSPECT researchers concluded low endothelial shear stress is a major factor in the development and progression of atherosclerosis as a potent inflammatory and atherogenic stimulator.

Novelty of the Present Study

Compared with these hemodynamic analyses of plaque development and rupture, hemodynamic analyses of stenosis progression are much less common. To our knowledge, there has been no prospective observational study like the present study, even one including other vessel sites. In a retrospective study, Goudot et al[40] reported on the progression of carotid stenosis. They examined whether wall shear rate and energy loss coefficient calculated by Doppler ultrasound could predict the progression of atherosclerotic carotid artery disease in 74 patients and found no significant association between these metrics and disease progression. It has been reported that coronary arteries, as well as carotid arteries, are prone to atherosclerosis at bifurcations.[14] Involvement of low WSS due to aspects of vessel geometry,

Table 4. Comparisons of Hemodynamic Metrics Between Progressive and Nonprogressive Carotid Arteries With an Area Stenosis of 71%–99%

71%–99%	Metrics	OR	95% CI lower	95% CI upper	*P* value	AICc
Stenotic area	TAWSS	0.90	0.40	2.03	0.80	93.9
	TAWSSG	1.20	0.66	2.20	0.54	93.6
	OSI	1.21	0.69	2.13	0.50	93.5
	GON	1.02	0.54	1.94	0.94	93.9
	transWSS	1.08	0.49	2.35	0.84	93.9
	NtransWSS	1.41	0.74	2.68	0.29	92.8
Distal area	TAWSS	0.96	0.48	1.90	0.90	93.9
	TAWSSG	1.46	0.75	2.86	0.27	91.9
	OSI	1.91*	1.05	3.47	0.033*†	88.8
	GON	1.43	0.83	2.47	0.19	92.4
	transWSS	1.23	0.68	2.22	0.50	93.5
	NtransWSS	1.57	0.77	3.22	0.21	92.4
Proximal area	TAWSS	0.67	0.22	2.00	0.47	93.3
	TAWSSG	1.01	0.55	1.83	0.98	93.9
	OSI	0.74	0.35	1.57	0.42	93.3
	GON	0.77	0.36	1.67	0.50	93.5
	transWSS	0.86	0.41	1.78	0.67	93.8
	NtransWSS	0.83	0.40	1.73	0.62	93.7

Each hemodynamic variable was divided by the standard deviation so that it was easy to compare the OR among variables. The ORs with 95% CIs and *P* values were calculated by multivariate analysis using logistic regression models 1 factor at a time. Each hemodynamic metric was adjusted for the known risk factors of age, sex, hypertension, diabetes, dyslipidemia, primary area stenosis, smoking history, daily drinking history, history of taking an antiplatelet drug, and history of taking a statin. AICc indicates corrected Akaike information criterion; GON, gradient oscillatory number; NtransWSS, normalized transverse wall shear stress; OR, odds ratio; OSI, oscillatory shear index; TAWSS, time-averaged wall shear stress; TAWSSG, time-averaged wall shear stress gradient; and transWSS, transverse wall shear stress.

*Odds ratio of hemodynamic metric with significant *P* value.

†$P<0.05$.

such as large bifurcation angles, has been reported.[15,38] Because the hemodynamic risk factors associated with plaque development and rupture are similar in carotid and coronary arteries,[2,7–12] the same may be true for the hemodynamic environment at the stenosis.

Clinical Contributions

The hemodynamic predictors of stenosis progression obtained in the present study may be clinically useful. By combining the obtained hemodynamic predictors of stenosis progression with known risk factors for progression, it will be possible to more accurately select high-risk cases, which will be useful for future treatment strategies such as management of underlying disease, lifestyle modification, and monitoring with imaging examinations at short intervals. In particular, for patients at high hemodynamic risk in the early stages of stenosis, measures taken early in the disease may prevent progression.

Studies on the pathogenesis of atherosclerosis based on the magnitude and disturbance of WSS are gradually reaching an academic consensus.[2] The properties of WSS have been studied primarily by modeling with CFD analysis.[2,8] For clinical application of CFD analysis, it is important to be able to obtain analysis results promptly and in a simplified manner. With the continuous improvement of the computer performance-cost ratio in CFD analysis, WSS has been recognized as one of the useful parameters for diagnosis of atherosclerosis, and CFD analysis is being actively promoted in clinical practice. Because attempts are also being made to use CFD analysis software as an adjunctive diagnostic tool for determining treatment strategy during endovascular treatment of coronary artery stenotic lesions,[8,12] the hemodynamic stenosis progression predictors obtained in this study may be useful in determining the treatment strategy. Because coronary arteries are greatly deformed by the beating heart wall, the Fluid–Structure Interaction method, which also takes into account the deformation of the vessel wall, may be effective, but its use is currently limited by the difficulty of setting initial conditions for the stress state.[41]

Pharmacological Targeting of Blood Flow–Sensing Pathways: P2X4 Inhibitors

The present results support pharmacological targeting of blood flow–sensing pathways for the prevention of stenosis progression. Such pharmacological intervention would

prevent the vessels from sensing the hemodynamic stress that is triggering the progression of stenosis. We have been trying to determine whether blood flow–sensing inhibitors can be clinically applied to prevent the rupture of cerebral aneurysms. We have focused on the significant involvement of hemodynamic factors in the development, growth, and rupture of cerebral aneurysms.[34,42–44] In our basic study using animal models of experimentally induced cerebral aneurysms[42] and also in a retrospective cohort study,[43] we reported that inhibition of the P2X4 purinoceptor, which is involved in the blood flow–sensing system of vascular endothelial cells,[45] prevents the initiation and growth of cerebral aneurysms, suggesting the possibility of using P2X4 inhibitors such as paroxetine to prevent rupture of cerebral aneurysms. The present study suggests that, as with cerebral aneurysms, hemodynamic factors play a major role in the progression of atherosclerotic arterial stenosis. In fact, in basic experiments using an animal model of carotid stenosis, we have obtained data suggesting that the progression of stenosis was significantly suppressed in P2X4-knockout mice compared with wild-type mice, although the data are still in the stage of presentation at international conferences.[46] Therefore, inhibitors of P2X4, including paroxetine, may suppress the progression of carotid stenosis and could have potential as prophylactic agents for carotid stenosis in addition to antiplatelet agents and statins. As paroxetine is currently used as a clinical antidepressant,[47] it could be a candidate for drug repositioning.

Limitations

There are several limitations to this study. First, the CFD analysis was a simulation and did not fully represent the actual hemodynamic distributions of the carotid artery because it assumed a rigid arterial wall. Therefore, the CFD analysis did not take into account the effects of stretching or the direct mechanical effects of beating on the arteries. While some have reported that the rigid wall assumption is valid for blood flow modeling of relatively large diameters, such as carotid arteries,[48] others have reported that this assumption impacts the results.[49] Second, we were unable to search for hemodynamic risks related to postoperative restenosis or the development of symptomatic cerebral infarction due to the small number of cases. Third, with regard to generalizability, this study was designed for stenosis in the carotid bifurcation and thus its results may not be applicable to other vascular bifurcations, such as the coronary bifurcation, due to the respective differences in vessel diameter and blood flow rate. Fourth, because this study is observational, a large number of cases, 195 out of 544, were excluded from the analysis. Fifth, the high correlation between several pairs of hemodynamic metrics used in this study could have led to inflated standard errors, unstable estimates, and overestimating effect sizes.

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Disclosures

None.

Supplemental Material

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