A High Prevalence of Intracranial Stenosis in Patients with Coronary Artery Disease and the Diagnostic Value of Transcranial Duplex Sonography

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Background: According to the data from the population-based Rotterdam study, intracranial carotid artery calcification detected by computed tomography is very common and contributed to 75% of all strokes. The aim of the present study was to estimate the prevalence of intracranial stenosis (IS) using noninvasive transcranial color-coded duplex sonography (TCCS) in neurologically asymptomatic patients with coronary artery disease (CAD). *Methods:* Three hundred and eighty-nine patients with angiographically-confirmed, severe CAD were included prospectively. All of them were examined using extracranial and TCCS. *Results:* Out of 389 patients (age 66.7 ± 9.2, 39-88), 237 (61%) were diagnosed with 3 vessels disease and 152 patients (39%) with left stem disease with/without 3 vessels damage. Transcranial sonography revealed at least 1 IS in 63.6% of echo positive patients (220/346). IS was found in 127 (61.4%) patients with 3 vessels disease, 20 patients (58.8%) with isolated left stem disease, and 73 patients (69.5%) with 3 vessels and left stem disease ($P = .305$). In the case of significant (≥50%) extracranial internal carotid artery stenosis, intracranial stenosis were detected in 84.8% (50 of 59), in the case of mild (<50%) stenosis, in 59.2% (170 of 287), $P < .001$. *Conclusions:* It was found that two thirds of patients with advanced CAD have a silent IS. TCCS is a reliable method for the evaluation of intracranial atherosclerosis in such patients in order to gain useful information about cerebrovascular disease as a risk factor for stroke.

Key Words: Coronary artery disease—intracranial stenosis—transcranial ultrasonography—color Doppler—atherosclerosis

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Introduction

The most common causes of death in the world are ischemic heart disease and stroke: 7.4 million and 6.7 million per year, respectively.[1] According to the data from a case-control autopsy study, the presence of atherosclerotic plaques in coronary and intracerebral arteries is found in 80.4% of cases.[2] Data from the population-based Rotterdam study recently revealed that intracranial atherosclerosis is very common in elderly white persons (the overall prevalence being 82.2%) and that the calcification of the internal carotid artery (ICA) detected using CT is associated with an increased risk of stroke and mortality.[3-5] Data from earlier angiographic studies showed a very poor patient prognosis in the presence of intracranial ICA atherosclerosis, a marker for advanced atherosclerotic disease.[6-9] However, ultrasonic data on the prevalence of asymptomatic intracranial stenosis (IS) is lacking in patients with advanced coronary artery disease (CAD). A study previously conducted by Valaikiene together with a team of investigators from Regensburg University demonstrated that transcranial color-coded duplex sonography (TCCS) allows highly successful imaging of the C1 and C5 segments of the intracranial ICA.[10,11]

The purpose of the present prospective study was to establish the prevalence of asymptomatic IS in patients with angiographically-proven 3 vessels and left stem CAD using TCCS.

Materials and Methods

Patients

All the patients were white descent Lithuanians who were studied and treated at Vilnius University Hospital Santaros Clinics from March 02, 2010 to December 31, 2014.

Inclusion criteria: adult patients with angiographically-confirmed 3 vessels and/or left stem CAD.

Exclusion criteria: heart rhythm disorders (chronic atrial fibrillation or flutter), heart valve disease, a myocardial infarction (MI) within the last 6 weeks, a ventricular aneurysm, neurological focal symptoms after a previous stroke, and decompensated chronic diseases.

The study was approved by the Vilnius Regional Biomedical Research Ethics Committee, Lithuania. Informed consent was obtained from all of the subjects.

Methods

All the patients were examined using coronary angiography, extracranial color-coded duplex sonography (ECCS), and TCCS. Each patient was evaluated by a neurologist before the ultrasound examination.

Information about the cardiovascular risk factors of the study patients was obtained from an interview and laboratory blood tests. Obesity, which was defined as a body mass index greater than or equal to 30 (weight in kilograms divided by the square of the height in meters), hypercholesterolemia as total cholesterol greater than or equal to 6.2 mmol/l (≥239 mg/dL) and/or current use of cholesterol−lowering medications, hypertension as systolic pressure greater than and equal to 140 mm Hg, diastolic pressure greater than or equal to 90 mm Hg or current use of antihypertensive medications, diabetes mellitus as fasting glucose levels greater than or equal to 7.0 mmol/L (≥126 mg/dL) or current use of diabetes medications, and smoking as never or ever smoked were assessed.

To minimize interinvestigational variability, all ultrasound examinations were performed by a single experienced investigator (J.V.) in the same ultrasound laboratory. Sonographic examinations were performed using standard General Electric (GE) color duplex sonography systems with a linear probe (5−8 MHz) for extracranial insonation and a low frequency sector probe (2−3.5 MHz) for transcranial insonation (GE Healthcare, Tokyo, Japan). A standard ECCS was performed to evaluate atherosclerotic lesions before a TCCS. The peak systolic velocity (PSV), end diastolic velocity, and mean blood flow velocity of the distal extracranial ICA were registered. The stenotic lesions of the ICA were classified according to North American Symptomatic Carotid Endarterectomy Trial criteria.[12] Standard TCCS examinations were performed on the basis of previous studies.[10,11] The evaluation of the middle cerebral artery (MCA) M1, anterior cerebral artery (ACA) A1, and posterior cerebral artery (PCA) P1 or P2 segments was performed using a transtemporal axial scanning plane and the ICA C1 and C5 segments using strictly defined coronal anterior and posterior scanning planes. Transnuchal insonation was used for imaging the basilar artery (BA) and vertebral artery (VA) V4 segments. An angle correction was applied in all cases when the intracranial artery length was greater than or equal to 15−20 mm, except for the ICA segments. Due to its tortuous course, the insonation angle was kept at 0° during all velocity measurements. Stenosis of the intracranial ICA was diagnosed in accordance with the established TCCS criteria.[11] In short, stenosis greater than or equal to 50% was established when the PSV and C1/ICA index (division of the mean flow velocities) were more than the mean normal age-dependent value ± 2 standard deviations. Stenosis less than 50% was established in the presence of elevated PSV and/or high−intensity low−frequency signals, but a normal C1/ICA index. Stenosis or occlusion of the remaining arteries of the Circle of Willis was diagnosed in accordance with the earlier published criteria.[13,14] In the case of collateralization through the anterior and/or posterior communicating artery, the increased velocities in the ACA A1 segment and/or the PCA P1 segment were considered compensatory, not stenotic. The cases of bilateral high−grade ICA stenosis or occlusion with increased flow velocities in the VA and BA were described as nonclassifiable, as it was difficult to define the impact of the compensatory component on the increased flow velocities.

Those patients with a poor transtemporal bone window were classified as echo negative if the image quality of at

least 1 segment of the investigated intracerebral arteries (ICA C1 and C5, MCA M1, PCA P1/P2) was insufficient. Those patients with a good transtemporal bone window that allowed sufficient imaging for a bilateral evaluation of all the listed arterial segments were classified as echo positive.

Statistical Analysis

Data analysis was performed using Statistical Package for the Social Sciences (version 17, SPSS) and Statistica Version 10 for Windows. When comparing categorical variables, chi-square or Fisher's exact tests were used. When comparing quantitative variables between the 2 groups, the t test (continuous normal distributed variables) or the Mann-Whitney U test (continuous skewed variables) was used. Risk factors and the presence of IS were checked using an analysis of logistic regression. The significance level was fixed at a P value of .05.

Sample size

In the aforementioned autopsy study,[2] the expected rate of any intracerebral artery lesions was approximately 64%, ICA lesions occurring in 48% of the cases. On the basis of these values, the number of patients that had to be included in order to estimate the number of intracranial lesions in advanced CAD when the deviation from the real lesion rate was less than 5% was calculated with a 95% level of confidence. It was established that 355 patients needed to be investigated in order to estimate the total rate of intracerebral arteries lesions, 384 patients to estimate the intracranial ICA lesion rate. Therefore, a decision was made to include at least 384 patients with 3 vessels and/or left stem CAD, confirmed by angiography. An equation, based on normal approximation, was used to calculate the sample volume (n) or required number of patients: $n = Z_{\beta}^2 \frac{p(1-p)}{e^2}$, $\beta = 1 - \frac{\alpha}{2}$; where e: maximal tolerable deviation from the real rate, p: proportional part of patients with expected lesions, α: significance level, Z_{β}: standard normal β: quantile of the random variable.

Results

The characteristics of the study population are presented in Table 1.

In the coronary angiography, out of 389 patients (male 72.8%, female 27.2%), 3 vessels CAD was diagnosed in 237 patients (60.9%), 3 vessels and left stem CAD in 115 patients (29.6%), and left stem CAD in 37 patients (9.5%). The distribution of cardiovascular risk factors was without significant difference in all 3 groups. After an initial evaluation, 289 patients underwent coronary artery bypass grafting (CABG), 53 underwent percutaneous transluminal coronary angioplasty, and 47 patients were prescribed drug treatment.

Table 1. *Baseline characteristics of study patients (n = 389)*

Age, y (mean ± SD)	66.7 ± 9.2
Sex, female	106 (27.2%)
Hypertension	382 (98.2%)
Diabetes mellitus	86 (22.1%)
Dyslipidemia	354 (91.0%)
Obesity	146 (37.5%)
Myocardial infarction	196 (50.4%)
PTCA	142 (36.5%)
Peripheral artery disease	43 (11.1%)
Smoker (past or current)	172 (44.2%)
Family history of CVD	173 (44.5%)
History of stroke/TIA	12 (3.1%)

Abbreviations: CVD, cardiovascular diseases; PTCA, percutaneous transluminal coronary angioplasty; SD, standard deviation; TIA, transient ischemic attack.

Data are presented as numbers of patients with percentages in parentheses.

ECCS Data

The obstructive ICA lesions according to North American Symptomatic Carotid Endarterectomy Trial criteria are presented in Table 2. Significant ICA stenosis (≥50%) was diagnosed in 62 patients (81 ICA), i.e., 36 of 237 (15.2%) in the 3 vessels CAD patient group, 5 of 37 (13.5%) in left stem group, and 21 of 115 (18.3%) in the 3 vessels and left stem CAD group ($P = .696$). In comparing the distribution of greater than or equal to 50% ICA stenotic lesions in the CAD patient groups with and without left stem stenosis, no significant difference was found (36 of 237 versus 26 of 152), $P = .615$.

High-grade (≥70%) obstructive lesions were diagnosed in 39 of 389 patients and 50 of 778 (6.4%) ICAs.

The distribution of the main risk factors between the 3 CAD groups was nonsignificant, with the exception of obesity demonstrating a borderline difference ($P = .05$).

TCCS Data

An insufficient transtemporal bone window was established in 11.1% (43 of 389) of the patients. The overall

Table 2. *Obstructive lesions of extracranial ICA according to the NASCET (n = 389 patients, 778 ICA)*

ICA	Number (%)
Normal	66 (8.5%)
<50% stenosis	629 (80.8 %)
≥50% stenosis	83 (10.7%)
50%-69% stenosis	33 (4.2%),
70%-99% stenosis	29 (3.7%)
Occlusions	21 (2.7%)
All obstructive lesions	712 (91.5%)

Abbreviations: ICA, internal carotid artery; NASCET, North American Symptomatic Carotid Endarterectomy Trial.

Data are presented as numbers of patients ICA with percentages in parentheses.

identification rate of intracranial segments was 91.5% (4628 of 5057): MCA: 90.1% (701 of 778), ACA: 85.9% (668 of 778), ICA C1: 88.3% (687 of 778), ICA C5: 88.3% (687 of 778), PCA: 92.7% (721 of 778), and BA and VA: 99.7% (388 of 389 and 776 of 778).

Further analysis included only echo positive patients (346 of 389) with a bilateral transtemporal bone window sufficient for the evaluation of all the major arterial segments. At least 1 IS was diagnosed in 220 of the 346 echo positive patients (63.6%), i.e., 127 (61.4%) in the 3 vessels CAD, 20 (58.8%) in the left stem CAD, and 73 (69.5%) in the 3 vessels CAD and left stem CAD patient group, $P = .305$.

The most common localization of hemodynamic disorders in the echo positive patient group was the C1 segment of the intracranial ICA: 35.2% (242 of 687), followed by MCA: 10.7% (75 of 701), BA: 9.8% (38 of 388), VA: 9.4% (73 of 776), ACA: 8.1% (54 of 668), PCA: 6.1% (44 of 721), and ICA C5: 5.2% (36 of 687).

The analysis of the risk factor distribution in patients with and without IS showed an established difference in the IS group, i.e., in older patients (OR, 1.67; 95% CI, 1.32−2.11; $P < .001$), female patients (OR, 1.44; 95% CI, 1.08−1.91; $P = .013$), patients without an MI history (OR, .69; 95% CI, .56−.87; $P = .02$), and smoking patients (OR, .79; 95% CI, 10.63-.99; $P < .048$). The EuroSCORE was greater in the IS group (mean ± standard deviations, 1.97 ± 2.5 versus 1.42 ± 1.2; $P < .001$), the logistic regression showed OR 1.93; 95% CI, .98-3.79; $P = .058$. There was no significant difference between the groups when comparing body mass index, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TAG), creatinine level, peripheral artery disease (PAD), diabetes mellitus (DM), stroke or transient ischemic attack history, obesity, obstructive lung disease, or familial anamnesis ($P > .05$).

In order to prevent the influence of extracranial carotid obstructive lesions on the velocity values of the intracranial arteries, further IS analysis was carried out after excluding those patients with a greater than or equal to 50% ICA stenosis. The overall identification rate of the intracranial segments in the patient group (n = 327, mean age 66 ± 1.3, female 87, 26.6%) was 91.6% (3893 of 4251), i.e. MCA: 89.9% (587 of 654), ACA: 86.2% (564 of 654), ICA C1: 88.4% (578 of 654), ICA C5: 88.5% (579 of 654), PCA: 92.5% (605 of 654), VA: 100% (654 of 654), and BA 92.7% (326 of 327). At least 1 IS was diagnosed in 174 of the 291 echo positive patients (59.8%), i.e. 99 (56.9%) in the 3 vessels CAD patient group,−16 (55.2%) in the left stem CAD patient group, and 55 (65.5%) in the 3 vessels CAD and left stem CAD patient group, $P = .378$.

The most common localization of hemodynamic disorders in the echo positive patient group was also the intracranial ICA, i.e. 31.5% (182 of 578) in the C1 segment and 1.9% (11 of 579) in the C5 segment. Six patients with greater than or equal to 50% stenosis in the C5 (n = 7 stenosis) were excluded from the further analysis due to a possible poststenotic flow impact on the velocities of the ICA C1 segment. In analyzing the hemodynamic C1 changes, less than 50% stenosis was found in 18.3% (106 of 578) and greater than or equal to 50% stenosis in 13.1% (76 of 578). Additionally, stenosis of the MCA was diagnosed using TCCS in 9.5% (56 of 587), VA: in 7.3% (48 of 654), ACA: in 5.7% (32 of 564), PCA: in 4.1% (25 of 605), and BA: in 5.2% (17 of 326).

Those patients with IS were older ($P < .001$), had a higher prevalence of past or current smoking ($P = .016$), dyslipidemia ($P = .04$), or an MI history ($P = .004$), or were female ($P = .035$).

The hemodynamic values (extracranial PSV, end diastolic velocity, mean blood flow velocity of the ICA, and CCA) in patients with normal C1 segment values, compared to those in patients with less than 50% stenosis, were without significant difference.

ECCS and TCCS Data Analysis

In the case of a greater than or equal to 50% stenosis of the extracranial ICA (n = 62), after the exclusion of the 3 echo negative patients, IS was diagnosed in 84.8% (50 of 59). In the case of a less than 50% ICA stenosis (n = 327), after the exclusion of the 40 echo negative patients, IS was diagnosed in 59.2% (170 of 287). Thus, there was significantly more IS in the patient group with greater than or equal to 50% stenosis of the extracranial ICA ($P < .001$). A comparison of the hemodynamic parameters of the carotid artery in cases of a normal, stenotic less than 50%, and stenotic greater than or equal to 50% C1 segment of the intracranial ICA is presented in Table 3.

Discussion

Cardiovascular diseases remain a leading cause of death in the world.[15] Despite a remarkable decline in the number of deaths from ischemic heart disease in the European Union (over 30% for male and female) over the past decade, Lithuania remains the state with the highest mortality rate from ischemic heart disease (772.6 of 484.2 deaths per 100,000 for male/female inhabitants), exceeding the average (132/100,000) more than fourfold (European Commission statistics). As expected, this cross-sectional study of patients with advanced CAD showed an asymptomatic IS rate of 63.6%. To the present authors' knowledge, this is the first ultrasound study about IS detection using TCCS in patients with CAD. The results of the present study correlate with the neuroimaging and post−mortem examination data. A case−control autopsy of fatal strokes (n = 339) showed an intracranial plaque/stenosis rate of 62.2%. Coronary artery plaques were diagnosed in 80.4% (152 of 200) of the cases in that patients group. The authors presumed that an IS of 30% or more could be the cause of death due to a thrombus superposition at the site of an ulcerated plaque[2]. Analogous results were obtained from the neuroimaging studies; in the MRA studies, 64% (90 of 140) of the patients scheduled for a CABG operation had an IS. Patients with a higher atherosclerotic score were considered to be at high risk of stroke

Table 3. *Comparing of hemodynamical parameters of carotid artery, in cases of normal, stenotic <50% and ≥50% C1 segment of intracranial ICA*

	Normal values*		<50% stenosis		>=50% stenosis		
	Mean	SD	Mean	SD	Mean	SD	*P*
C1 PSV	76.24	17.56	119.74	23.63	157.96	27.66	<0.001
C1 EDV	29.94	8.01	42.88	11.49	57.52	13.52	<0.001
C1 MFV	45.37	10.53	68.50	14.05	91.00	17.26	<0.001
C5 PSV	48.98	11.31	58.43	15.12	53.63	13.70	<0.001
C5 EDV	20.16	6.43	21.74	5.99	19.63	6.42	0.097
C5 MFV	29.76	7.20	33.97	8.20	30.96	8.23	<0.001
C1/ICA	1.19	0.35	1.62	0.42	2.82	0.63	<0.001
C1/CCA	1.31	0.41	2.00	0.58	2.85	061	<0.001
C5/ICA	0.82	0.26	0.90	0.28	0.93	0.29	0.091
C5/CCA	0.86	0.26	0.99	0.30	0.97	0.29	0.002

Abbreviations: CCA: common carotid artery; ICA: internal carotid artery; C1 and C5: intracranial segments of ICA; C1/ICA, C1/CCA, C5/ICA, C5/CCA: divisions of mean flow velocities; EDV: end diastolic velocity; PSV: peak systolic velocity; MFV: mean flow velocity; SD: standard deviation.

All velocities are given in centimeters per second.

*Age dependent [11].

and *off-pump* CABG (instead of *on-pump*) was performed in order to prevent a stroke.[16]

Taking into account that the patients of the present study were relatively old (67 ± 9 years), the overall identification rate of intracranial segments using TCCS without contrast was 91.7%, in line with the data of other authors.[17-22] After the exclusion of those patients with greater than or equal to 50% ICA stenosis, the identification rate remained the same. 93% of the PCA P1/P2 segments, 90% of the MCA M1 segments, 88% of the ICA C1 and C5 segments, and 86% of the ACA A1 segments were identified transtemporally. It should be noted that the identification rate of the distal ICA in the previous studies[10,11] was higher (C1: 100/98% and C5: 98/94%, in 2002 and 2008, respectively) as well as in the Eggers et al study (100% and 97%, respectively). In the present authors' opinion, their younger age and correspondingly better acoustic bone windows account for this difference. Despite the ultrasound data about the limitations of transcranial insonation due to temporal bone thickness, especially in female, black, and older patients,[23-25] a complete transtemporal examination was successfully performed in 89% of the older patients with advanced CAD.

The present study, based on the TCCS data, showed that the most common location of all the hemodynamic disorders in patients with a sufficient transtemporal bone window was the intracranial ICA (40.4%), predominantly in the C1 segment (35.2%). Significantly, fewer stenotic lesions were diagnosed in the MCA (10.7%), BA (9.8%), VA (9.4%), ACA (8.1%), and PCA (6.1%). The data is in line with the results of previous angiographic studies, which demonstrated that the majority of intracranial atherosclerotic lesions are located in the distal ICA.[26] However, according to the results of earlier ultrasound studies, the most common IS location was the MCA.[25] This could be explained by the fact that the distal ICA was not examined in most of the ultrasound studies owing to the opinion that noninvasive intracranial ultrasound imaging of the ICA was unavailable. The very first data about the use of the TCCS technique for the examination of the distal ICA by employing strictly defined coronal scanning planes was published in 2002.[10] Later, the TCCS criteria for a significant stenosis of the distal intracranial ICA were established together with a team of investigators from Regensburg University.[11] Afterwards a successful examination study of all the intracranial ICA segments using coronal and axial imaging planes was published.[27]

Comparing the data from the present study with the authors' earlier angiographic data, a 72% (36 of 50) tandem stenosis of the ICA was found, i.e. when various atherosclerotic changes in the extracranial ICA were in coexistence with changes in the intracranial ICA. However, high-grade (≥50%) extra-/IS was diagnosed in only 5% (4 of 80) of all patients.[11] The difference in the results was possibly influenced by the characteristics of the patients. The majority of previous study subjects (68%) were stroke patients and only 17% had CAD. In the present study, all the patients had advanced CAD and only 3% (12 of 389) had had a transient ischemic attack or a minor stroke without functional disability. The risk analysis for asymptomatic IS revealed older age, female gender, smoking, arterial hypertension, and a history of cerebrovascular events and MI have significant influence. However, the frequency of the cardiovascular risk factors and IS among patients with and without left stem CAD showed no significant difference, despite a well-accepted clinical opinion about the higher risk of patients with left stem CAD compared to those with 3 vessels CAD.

It should be noticed that there were significantly fewer patients with an MI history in the group of patients with

asymptomatic IS (P = .002). The possibility cannot be excluded that some of the patients with acute MI were not admitted into the hospital and/or did not survive. Perhaps the early detection of asymptomatic IS might predict severe treatable CAD and the employment of appropriate treatment could help them to survive by avoiding a fatal MI.

According to the data from the recently published Rotterdam study, intracranial atherosclerosis is very common in the elderly European population (mean age, 69.5 years). Using a head CT, it was established that calcification of the ICA is a marker for intracranial atherosclerosis.[3] The authors compared the overall 82% intracranial ICA calcification rate with the calcification rate of other vascular beds: 82% of the coronary arteries, 93% of the aortic arch, and 73% of the extracranial carotid arteries.[5] Calcification of the intracranial ICA was diagnosed in 80%−97% of the cases in the 65 and over age group.[3] It contributed to 75% of all strokes during the 6 year observation period.[4] The presented results differ from those of previous reports which concluded that the cause of a stroke in 10%−30% of cases was extracranial atherosclerosis in Europeans, but intracranial arterial disease in people of Asian and African descent.[6,28-30]

Moreover, it is well−known that the nonenhanced CT perfectly detects calcification, but is unable to visualize part of the vulnerable plaques of great clinical significance. Heterogeneous plaques with hypodense/isodense components are the most common in daily carotid duplex ultrasound practice and may potentially be the source of embolization in the brain and eye. The present study demonstrates that it is possible to evaluate the status of intracranial circulation by using noninvasive TCCS for most of the coronary patients (89%). TCCS is a relatively cheap and easily repeatable method without radiation or a contrast agent.

Based on a prospective study conducted on Asian subjects (n = 201, mean age 50.5 ± 8.0), Yoon et al were the first to show that IS may be an independent risk factor for central nervous system complications after CABG in at least Asian patients.[31] The authors supported a preoperative evaluation of the intracranial arteries as a risk assessment for CABG surgery. A longitudinal study of white-descent CABG patients with advanced CAD and IS is still needed to prove the relationship between the presence of IS and perioperative and long-term results in respect to cardiovascular/cerebrovascular morbidity and mortality.

In conclusion, patients with 3 vessels and/or left stem CAD have an increased risk of asymptomatic IS, especially those with significant extracranial ICA stenosis. The most prevalent region of IS is the C1 segment of the distal ICA. TCCS is a reliable method for diagnosing IS and providing important prognostic information in patients with advanced CAD. The diagnosis of subclinical intracerebral atherosclerosis allows appropriate measures to be taken for preventing stroke and decreasing the risk of cerebrovascular morbidity and mortality.

Supplementary Materials

Supplementary data to this article can be found online at doi:10.1016/j.jstrokecerebrovasdis.2018.12.023.

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