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PREDICTION OF SYMPTOMATIC VASOSPASM AFTER SUBARACHNOID HEMORRHAGE: THE MODIFIED FISHER SCALE

OBJECTIVE: We developed a modification of the Fisher computed tomographic rating scale and compared it with the original Fisher scale to determine which scale best predicts symptomatic vasospasm after subarachnoid hemorrhage.

METHODS: We analyzed data from 1355 subarachnoid hemorrhage patients in the placebo arm of four randomized, double-blind, placebo-controlled studies of tirilazad. Modified Fisher computed tomographic grades were calculated on the basis of the presence of cisternal blood and intraventricular hemorrhage. Crude odds ratios (OR) reflecting the risk of developing symptomatic vasospasm were calculated for each scale level, and adjusted ORs expressing the incremental risk were calculated after controlling for known predictors of vasospasm.

RESULTS: Of 1355 patients, 451 (33%) developed symptomatic vasospasm. For the modified Fisher scale, compared with Grade 0 to 1 patients, the crude OR for vasospasm was 1.6 (95% confidence interval [CI], 1.0–2.5) for Grade 2, 1.6 (95% CI, 1.1–2.2) for Grade 3, and 2.2 (95% CI, 1.6–3.1) for Grade 4. For the original Fisher scale, referenced to Grade 1, the OR for vasospasm was 1.3 (95% CI, 0.7–2.2) for Grade 2, 2.2 (95% CI, 1.4–3.5) for Grade 3, and 1.7 (95% CI, 1.0–3.0) for Grade 4. Early angiographic vasospasm, history of hypertension, neurological grade, and elevated admission mean arterial pressure were identified as risk factors for symptomatic vasospasm. After adjusting for these variables, the modified Fisher scale remained a significant predictor of vasospasm (adjusted OR, 1.28; 95% CI, 1.06–1.54), whereas the original Fisher scale was not.

CONCLUSION: The modified Fisher scale, which accounts for thick cisternal and ventricular blood, predicts symptomatic vasospasm after subarachnoid hemorrhage more accurately than original Fisher scale.

KEY WORDS: Computed tomography, Subarachnoid hemorrhage, Vasospasm

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Symptomatic vasospasm after subarachnoid hemorrhage (SAH) is a serious complication that occurs in 20 to 40% of patients (4). Initial computed tomographic (CT) findings such as thick cisternal subarachnoid clot and intraventricular hemorrhage (IVH) have been identified as predictors of symptomatic vasospasm (3, 5, 7, 8, 11, 17, 24, 26–28). The clearance of cisternal clot, either spontaneously or mechanically, has been associated with a reduced risk of vasospasm (15, 16, 18, 19, 29, 34).

The Fisher CT grading scale (6) is the most commonly used method of assessing SAH on CT scans. This grading scale does not, however, account for patients with thick cisternal blood and concomitant intraventricular or intraparenchymal blood. In fact, two studies have found that the Fisher scale did not significantly correlate with the development of symptomatic vasospasm (29, 31). Recently, we assessed the value of individual components of admission CT scans to predict symptomatic vasospasm or CT infarction from vasospasm. On the basis of these analyses, we proposed a new CT rating scale that identifies patients with both the thick cisternal clot and IVH. Compared with the original Fisher scale, this new scale had superior predictive value for symptomatic deterioration or infarction caused by vasospasm (5). In the present study, our goal was to validate these findings in a

larger, multicenter patient population by comparing the predictive value of the original Fisher scale with our new scale: the modified Fisher scale.

METHODS AND MATERIALS

Patient Population

We retrospectively reviewed data from patients enrolled in four prospective, randomized, double-blind, placebo-controlled trials of tirilazad conducted worldwide from 1991 to 1997 (9, 14, 20, 21). All patients had angiographically documented saccular aneurysms, and SAH was diagnosed by CT scans or lumbar puncture if the initial CT scan was negative. Exclusion criteria were age under 18 years, nonsaccular aneurysm, severe concomitant illness or cardiovascular complications, pregnancy/lactation, placement of a detachable coil in the ruptured aneurysm, and use of steroids or calcium channel blockers other than nimodipine. All patients were treated with nimodipine for 14 days after admission.

Admission CT Risk Factors

Admission CT scans were classified by the local investigator at the time of admission as demonstrating diffuse or localized thick subarachnoid blood, diffuse or localized thin subarachnoid blood, or no SAH. Explicit criteria for classifying blood as thick or thin, or focal or diffuse, were not applied. In addition, the presence or absence of IVH was noted and graded as present or absent. On the basis of these ratings, we assigned each patient an admission original and modified Fisher scale score (*Table 1*). The modified Fisher CT SAH rating scale criteria are as follows: Grade 0, no SAH or IVH; Grade 1, focal or diffuse, thin SAH, no IVH; Grade 2, focal or diffuse, thin SAH, with IVH; Grade 3, focal or diffuse, thick SAH, no IVH; and Grade 4, focal or diffuse, thick SAH, with IVH (*Fig. 1*). The Fisher scale (6) was defined as follows: Grade 1, no or focal, thin SAH; Grade 2, diffuse, thin SAH; Grade 3, focal or diffuse, thick SAH; and Grade 4, focal or diffuse, thin or no SAH, with significant intracerebral hemorrhage (ICH) or IVH.

TABLE 1. Classification of modified and original Fisher scale scores from admission computed tomographic ratings used in the tirilazad database[a]

SAH classification	IVH	Fisher grade	Modified Fisher grade
Diffuse, thick SAH	Present	3	4
	Absent	3	3
Localized, thick SAH	Present	3	4
	Absent	3	3
Diffuse, thin SAH	Present	4	2
	Absent	2	1
Localized, thin SAH	Present	4	2
	Absent	1	1
No SAH	Present	4	2
	Absent	1	0

[a] SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage.

Non-CT Risk Factors

Other variables that were tested for possible associations with symptomatic vasospasm included demographic factors (age, sex, and race), past medical history (hypertension, diabetes), admission clinical features (neurological grade classified according to the World Federation of Neurological Surgeons scale (33), mean arterial pressure on admission, and admission radiological features (aneurysm size $\geq$ 12 mm and the presence of early moderate to severe angiographic vasospasm, defined as angiographic luminal narrowing of the intracranial arteries documented within 48 h of SAH onset, not caused by other intrinsic disease). Data on transcranial Doppler ultrasonography were not recorded in the tirilazad database.

Definition of Outcome Variables

Symptomatic vasospasm was defined as clinical symptoms between Days 5 and 12 after SAH such as worsening headache, stiff neck, insidious onset of confusion or decline in level of consciousness, or focal deficits not clinically or radiographically attributable to other causes. Neurological worsening was defined as an increase of two or more points in the motor score to the National Institutes of Health Stroke Scale lasting for 8 hours or more or a decrease of two or more points in the modified Glasgow Coma Score (2, 10).

Statistical Analysis

Data analyses were performed with commercially available statistics software (SPSS version 12.0; SPSS, Inc., Chicago, IL). For the purposes of this analysis, patients assigned a modified Fisher scale score of 0 were combined with Group 1 to serve as a reference group for the calculation of odds ratios. Continuous variables were dichotomized based on clinical cut-points or median values. χ^2 analysis was used to test associations between categorical variables. Student's t test was used for normally distributed and the Mann-Whitney U test for non-normally distributed continuous variables.

The risk of symptomatic vasospasm associated with each level of the original and modified Fisher scales was evaluated by calculating crude odds ratios (and 95% confidence intervals) referenced to a scale score of 1. Univariate analysis was performed to detect significant associations between non-CT risk factors and symptomatic vasospasm. The modified Fisher and Fisher CT scales were then added separately to a multiple logistic regression model controlling for significant univariate predictors of symptomatic vasospasm to calculate an adjusted odds ratio, expressing the incremental risk of developing symptomatic vasospasm for each level of the scale. Significance was set at $P \leq 0.05$.

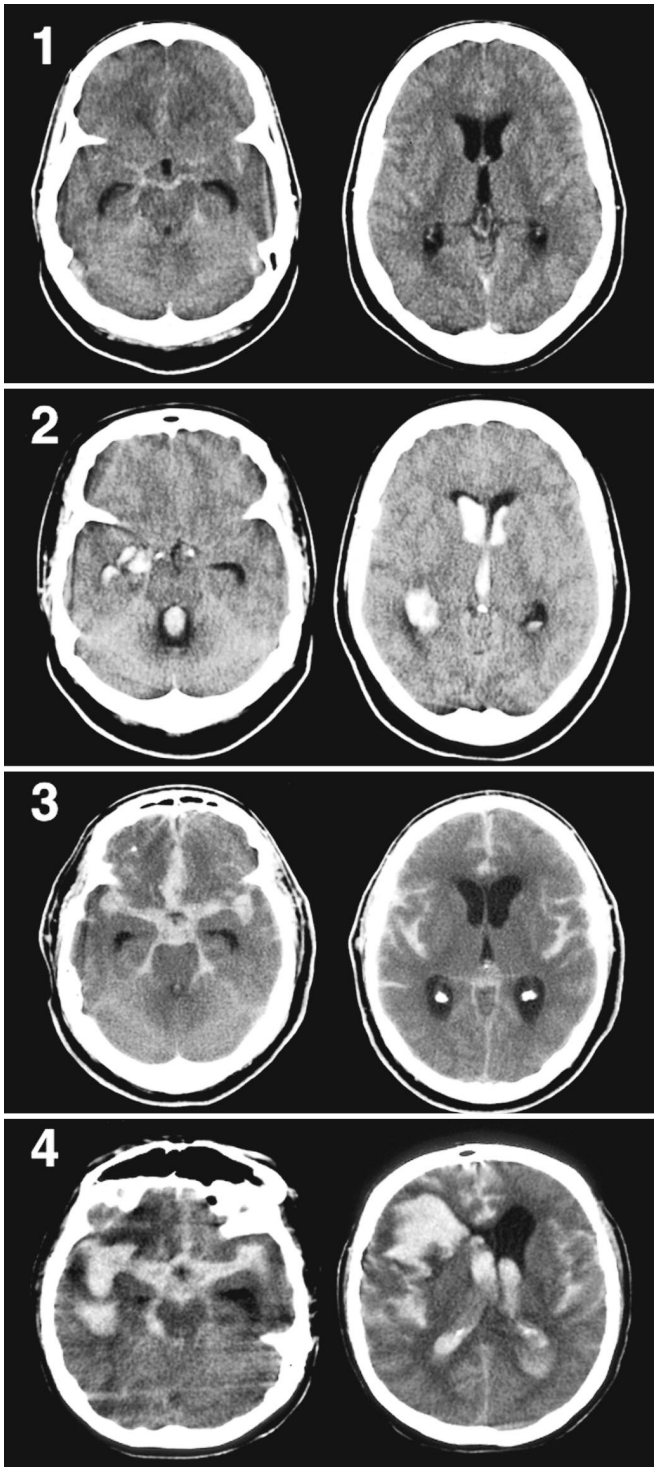

FIGURE 1. *CT scans demonstrating the modified Fisher CT rating scale.* Grade 1 *(minimal or diffuse thin SAH without IVH), indicating low risk for symptomatic vasospasm;* Grade 2 *(minimal or thin SAH with IVH);* Grade 3 *(thick cisternal clot without IVH), indicating intermediate risk for symptomatic vasospasm; and* Grade 4 *(cisternal clot with IVH), indicating high risk for symptomatic vasospasm (*from*, [5]).*

RESULTS

Of the 3552 SAH patients enrolled, we included 1378 placebo-treated patients to minimize any treatment effect tirilazad may have on the measured outcomes. Twenty-three patients who did not have an evaluation of the admission CT scan were excluded, leaving 1355 patients for inclusion in our analysis, 451 (33%) of whom developed symptomatic vasospasm.

The modified Fisher scale showed a stronger association with symptomatic vasospasm than the original Fisher scale. Each modified Fisher grade was referenced to Grade 0 and 1 combined because only 20 (2%) patients had a modified Fisher grade of 0. The risk of developing vasospasm progressively increased with each level of the modified Fisher grade (*Table 2*). Conversely, using the original Fisher scale, the risk of developing vasospasm was highest for Grade 3 and then decreased for Grade 4 (*Figs. 1* and *2*).

Univariate non-CT clinical and radiographic predictors of symptomatic vasospasm included moderate to severe early angiographic vasospasm ($P = 0.017$), mean arterial pressure $\geq$ 112 mm Hg ($P = 0.016$), history of hypertension ($P = 0.001$), and poor World Federation of Neurological Surgeons grade ($P = 0.005$). A multivariate model including these variables was created, and each CT rating scale was separately added to this model to calculate an adjusted odds ratio expressing the incremental risk of developing symptomatic vasospasm for each level of the scale. The modified Fisher scale remained a significant and independent predictor of symptomatic vasospasm. For each increase in scale level, the odds of symptomatic deterioration increased by 28% (*Table 2*). Conversely, the Fisher scale did not remain an independent predictor of vasospasm.

DISCUSSION

The Fisher CT rating scale is widely used for prognostication after SAH, yet its utility for predicting clinical vasospasm remains controversial (29, 31). In their seminal description of the scale in 47 SAH patients, Fisher et al. (6) noted that a grade of 3, indicative of thick cisternal clot, was highly predictive of angiographic and symptomatic vasospasm. For the past 25 years, neurosurgeons have relied on the presence of Fisher 3 blood to identify patients at high risk for complications from vasospasm.

One weakness of the Fisher scale, however, is the manner in which ICH and IVH is handled. In the original article, Grade 4 included patients with significant ICH or IVH, but only if thin diffuse or focal SAH was present. However, confusion has arisen because some patients can have thick SAH in addition to significant amounts of ICH or IVH (30). In our previous study of 276 patients enrolled in the Columbia University SAH Outcomes Project, we found that both thick cisternal SAH and biventricular IVH were independently predictive of delayed cerebral ischemia from vasospasm and that this risk was additive (5). On the basis of these findings, we

TABLE 2. Risk of symptomatic vasospasm according to the original and modified Fisher computed tomographic rating scales[a]

	Percent classified to grade	Percent within grade with symptomatic vasospasm	Odds ratio[b]	95% confidence interval	*P*
Modified Fisher scale					
1 Focal or diffuse thin SAH, no IVH[c]	21.6	24	—	—	—
2 Focal or diffuse thin SAH, with IVH	10.8	33	1.58	1.02–2.46	0.042
3 Thick SAH present, no IVH	33.9	33	1.59	1.14–2.22	0.006
4 Thick SAH present, with IVH	33.7	40	2.20	1.58–3.05	< 0.001
Adjusted odds ratio for incremental risk of symptomatic vasospasm for each scale level			1.28	1.06–1.54	0.010
Fisher scale					
1 Focal thin SAH	8.1	21	—	—	—
2 Diffuse thin SAH	10.9	25	1.26	0.70–2.23	0.442
3 Thick SAH present	67.7	37	2.18	1.35–3.51	0.001
4 Focal or diffuse thin SAH, with significant ICH or IVH	13.3	31	1.71	0.98–2.98	0.060
Adjusted odds ratio for incremental risk of symptomatic vasospasm for each scale level			1.1	0.84–1.43	0.488

[a] SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage.
[b] Adjusted values were calculated controlling for other significant predictors of vasospasm (early angiographic vasospasm, history of hypertension, neurological grade, and mean arterial pressure).
[c] Includes 20 patients classified to modified Fisher 0 (no SAH or IVH present).

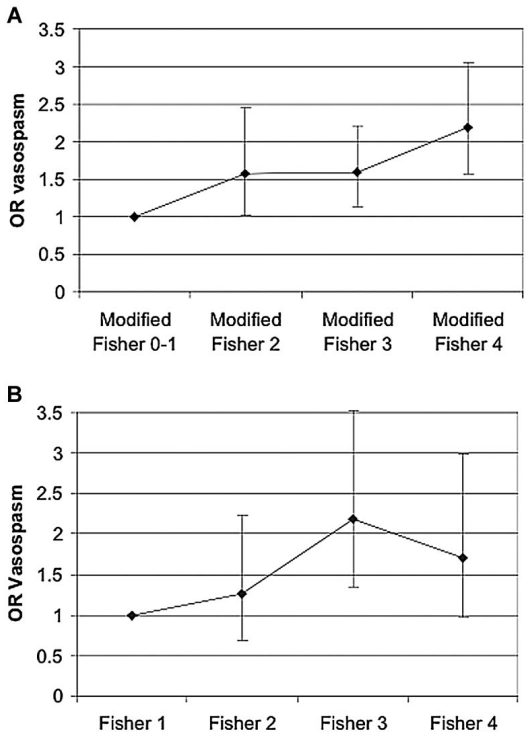

FIGURE 2. *Line graphs showing odds ratios for risk of symptomatic vasospasm in original and modified Fisher CT rating scales. Risk of vasospasm progressively increases for each modified Fisher grade* (A)*, whereas risk for vasospasm peaks for Fisher Grade 3 and then decreases* (B)*.* OR*, odds ratio.* Vertical bars *represent 95% confidence intervals.*

developed a new scale that assigned a score of 1 if no thick cisternal clot or bilateral IVH was present, 2 if bilateral IVH was present, 3 if thick cisternal clot was present, and 4 if both were present. The ability of this scale to predict symptomatic ischemia from spasm was superior to the original scale, with a positive predictive value of approximately 10% for a score of 1, approximately 20% for a score of 2 or 3, and 40% for a score of 4.

In this study, we sought to verify our previous findings in a separate cohort of SAH patients. The original scale has been modified slightly (and, therefore, renamed) because the tirilazad database only classified patients according to the presence or absence of IVH. Accordingly, in this study, we used the presence of any IVH, rather than biventricular IVH, to classify patients as having a modified Fisher score of 2 or 4. In our original article, the presence of any IVH was nearly as significant a predictor of delayed ischemia as was biventricular IVH.

We have confirmed that, although the risk of vasospasm peaks for Grade 3 and then decreases on the original Fisher scale, the modified Fisher scale displays an increasing risk as the grade increases, making it a more intuitive tool. Moreover, we found that the modified Fisher scale score was significantly associated with symptomatic vasospasm after controlling for other clinical predictors of spasm, whereas the original Fisher scale was not. In all likelihood, the added predictive power of the modified Fisher scale comes from the way that IVH is incorporated into its rating system. In keeping with our previous findings, we found that the risk of vasospasm was equally high in patients with IVH or thick cisternal clot and

highest if both of these findings were present (5). Although the literature to date has shown conflicting evidence regarding the association of IVH and vasospasm (1, 3, 11, 27), the present study confirms our original observation of a consistent relationship between these two variables.

In our multivariate analysis, we identified poor clinical grade, moderate to severe early angiographic vasospasm, history of hypertension, and admission mean arterial pressure as predictors of symptomatic vasospasm. These associations have been confirmed in the entire cohort of patients that participated in the tirilazad trials, including those treated with study drug (23). We were unable to test other previously identified risk factors, such as transcranial Doppler velocities, cigarette smoking, and hyperglycemia, because they were not recorded in this database, and no additional data on these patients are available (2, 4, 5, 11–13, 22, 25–27). The inclusion of additional vasospasm risk factors might have yielded a more robust multivariate model.

Other limitations of this study also deserve mention. Most importantly, our study relied on a reconstruction of the CT rating scores based on previously collected variables rather than direct review and rating of the films by a study physician. The CT scans in the tirilazad trials were read by the local investigators and assigned to one of four groups on the basis of a global impression rather than explicit criteria. Although the interobserver reliability of this CT rating system was not formally tested, the reliability of the Fisher scale is only moderate (κ, 0.50–0.62) (32). This was probably the case for the classification scheme we analyzed as well. However, our study confirms that even when CT evaluations are based on global impressions, the modified Fisher scale is a better predictor of vasospasm risk than the original scale. The addition of specific classification criteria in future studies might further improve its predictive value. Similarly, the reliability of the clinical diagnosis of symptomatic vasospasm may be diminished by observer bias and varying definitions (35). For this reason, it would have been desirable to assess for associations between the scales and infarction from vasospasm. However, the tirilazad database did not specify mechanism of infarction. Because infarction from surgical retraction, catheterization related embolic stroke, herniation, vasospasm, and any other potential cause were grouped together, a specific analysis was not possible. Confirmation of symptomatic vasospasm with angiographic evidence of spasm may also have added specificity. Finally, because only surgically treated patients were included in the tirilazad database, our conclusions may not be applicable to patients undergoing coil embolization of an aneurysm.

In conclusion, our findings indicate that a simple modification of the widely used Fisher CT rating scale can improve its predictive value. A prospective study is needed to confirm these results and to determine whether the modified Fisher scale should be routinely incorporated into clinical practice. Studies are also needed to elucidate the mechanisms by which IVH can increase the risk of developing delayed cerebral ischemia after SAH.

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COMMENTS

This is a valuable contribution to the subarachnoid hemorrhage (SAH) literature. Although the Fisher scale has served us well since it was introduced by the great Millar Fisher 25 years ago, the authors have validated a modified version as more predictive of symptomatic vasospasm in 1355 patients who were treated with a placebo in four tirilazad trials conducted in the 1990s. The new scale includes a Grade 0 (no blood visible in the subarachnoid space or ventricles) and then, similar to the original, Grades 1 through 4 distinguishing between thin (Grades 1 and 2) and thick (Grades 3 and 4) subarachnoid clot. What is new in the modified scale is an assessment of intraventricular blood clot, the presence of which increases the risk of vasospasm and accounts for Grades 2 (thin SAH plus intraventricular hemorrhage [IVH]) and 4 (thick SAH plus IVH). It seems that separating thick and thin SAH was more or less subjective and that there is no distinction between focal or diffuse subarachnoid clot. Similarly, the amount of IVH is not taken into account: it is simply present or absent. Using odds ratios, the authors demonstrate quite clearly that the modified scale predicts symptomatic vasospasm better than the old one. It also eliminates another problem with the original scale in which Grade 3 has the highest vasospasm risk and Grade 4 is somewhat lower, which is counterintuitive and, at times, confusing. It is possible that those patients with truly thick and diffuse subarachnoid clot (visible on several axial cuts and distributed in multiple cisterns) combined with casting and dilatation of the ventricular system are at the highest risk for vasospasm, but the database the authors explored did not allow this separate analysis. From a pathophysiological point of view, it is not entirely clear why the presence of IVH heightens the risk of symptomatic vasospasm because IVH alone is only very rarely complicated by vasospasm. Ventricular hemorrhage reflects a greater overall clot burden and may also indicate an injured brain more sensitive to a secondary ischemic insult. These authors were the first to recognize the significance of IVH on the development of vasospasm and should be credited for confirming their original observation and providing us with an improved "Modified Fisher Scale."

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The authors have modified the Fisher computed tomographic (CT) grading scale for prediction of symptomatic cerebral vasospasm after SAH and have compared it to the original scale using data from the tirilazad database. The modified Fisher scale was found to be a significant predictor of vasospasm, whereas the original scale was not after adjusting for appropriate variables.

This is a simple modification and preliminarily seems to be an improvement over the original scale. There are some limitations to the current study as the authors nicely point out, and these data await confirmation in subsequent, and preferably prospective, investigation.

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In this report, Frontera et al. have used the large tirilazad database to compare the predictive value of a modification of the Fisher CT scale with the original Fisher scale. Unlike the original grading system, the scale proposed by these authors takes into account the presence or absence of intraventricular hemorrhage, in addition to the

amount of subarachnoid blood. In this study, the modified scale was a more accurate predictor of vasospasm than the original scale. The original scale described by Fisher in a landmark article in 1980 has numerous shortcomings, as outlined by these authors. Because of these limits, the Fisher scale is no longer used in multicenter clinical trials of aneurysmal SAH. Nevertheless, the Fisher scale continues to be used routinely in clinical practice because it is easy to memorize and has very good interobserver agreement while still correlating with the development of symptomatic vasospasm. Frontera et al. have convincingly shown once again that their modification of the original Fisher scale is a better predictor of vasospasm. However, I suspect that the original scale, for the reasons previously outlined, will continue to be used widely in neurosurgery units across the globe.

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In this article, the authors review the database from four randomized double-blind, placebo-controlled studies of tirilazad. Using this database, they modified the original Fisher grading scale for SAH. The authors find that by modifying the original scale using the presence or absence of IVH for thick and thin SAH, their ability to predict the incidence of spasm is higher than when the Fisher scale alone is used. Of course, the original Fisher scale was developed at a time when CT scanning was crude by today's standards. The reason that the original demarcation of less than 1 mm or greater than 10 mm of blood was made on the Fisher scale was because, at that point, 10-mm cuts were the standard thickness that CT scans provided.

Although the authors note in several places that the modified Fisher scale displays an increased risk of spasm as the grade increases, this is not strictly true. As seen in *Table 2*, the modified Fisher scale produces the same incidence of vasospasm for Grade 2 and 3 patients with identical odds ratios. It is of interest that they again document the relationship in the Fisher grading scale for Grade 4 patients with intraventricular or intraparenchymal clot in whom the incidence of vasospasm drops down compared with the thick subarachnoid clot. This makes sense, given the fact that in both the condition of intraventricular and intraparenchymal hematoma, a large component of clot does not have access to the subarachnoid space and subarachnoid vessels and, therefore, the incidence of vasospasm would be expected to be less.

What the authors have provided us with is a three-grade system. The modified Grades 2s and 3s could actually be combined to create a single grade. The authors' study reiterates the point that in many patients with dense subarachnoid clot, vasospasm can be predicted. The big question is what treatments should be different in these patients compared with those with low risk for vasospasm.

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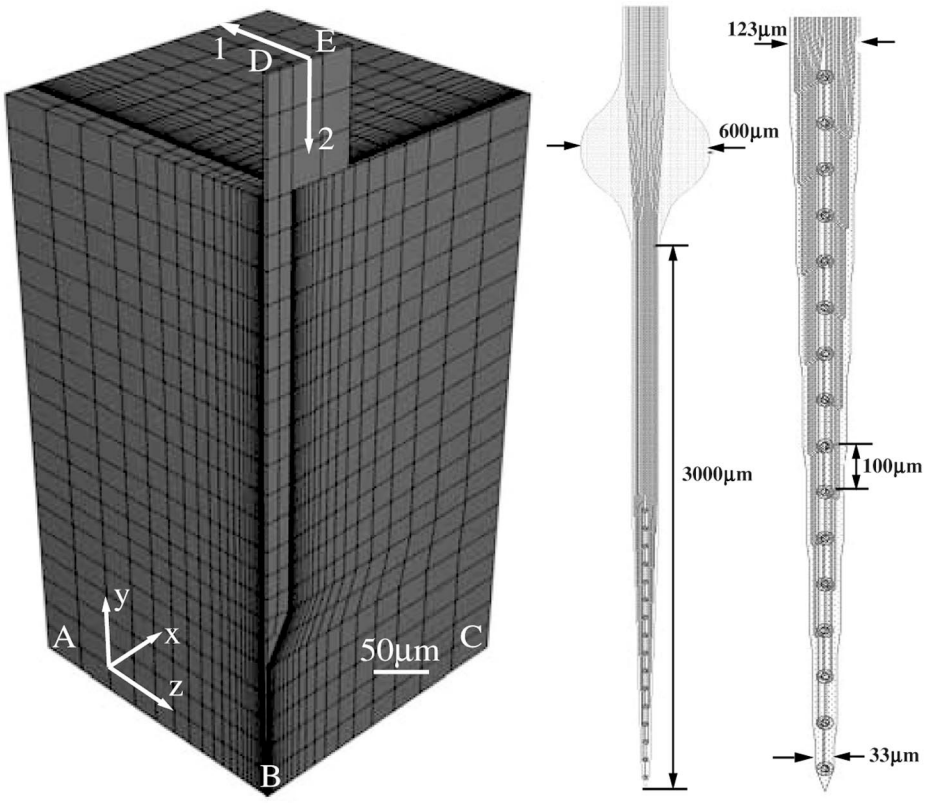

Micromotion simulation of chronically implanted microelectrodes. *3D finite-element model (FEM) of a probe-brain tissue system (left) and schematics of single shank Michigan probes (right) used to simulate and evaluate the mechanical properties of micromotion and tissue response in an effort to analyze the effects of tethering forces, probe-tissue adhesion, and stiffness of the probe substrate. (Subbaroyan J, Martin DC, Kipke DR: A finite-element model of the mechanical effects of implantable microelectrodes in the cerebral cortex.* **J Neural Eng** *2:103–113, 2005.)*