Evidence for an Ischemic Preconditioning Effect on Cerebral Vasospasm in Patients with Aneurysmal Subarachnoid Hemorrhage

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Introduction

Numerous studies show that transient exposure to mild ischemia renders the brain resistant to a subsequent more severe ischemic stimulus, a concept known as preconditioning. Excitingly, this phenomenon has recently been demonstrated in subarachnoid hemorrhage (SAH), as mice transiently exposed to hypoxia developed an eNOS-mediated reduction vasospasm and neurological deficits following experimental SAH; however, this has never been studied in humans. In the present study, we hypothesize that patients with pre-existent steno-occlusive vascular disease experience ischemic preconditioning resulting in reduced SAH-induced cerebral vasospasm.

Methods

Retrospective case-controlled data from six high-volume SAH centers from 2006-2011 were pooled. Only Fisher 3-4 patients were included. The effect of pre-existing steno-occlusive vascular disease (extra - and intra-cranial atherosclerotic disease, and peripheral vascular disease) on the following endpoints was studied: angiographic vasospasm, symptomatic vasospasm, and delayed stroke. Multivariate logistic regression analysis was performed with the following covariables; age, gender, Hunt-Hess grade, neurological deficit on admission, aneurysm size, aneurysm location and type of aneurysm treatment.

Results

A total of 1043 patients were included, of which 359 (34.4%) had pre-existent vascular disease, 684 (65.6%) did not. Of those patients that had pre-existent vascular disease, 119 (33.1%) developed radiographic vasospasm, 69 (19.2%) symptomatic vasospasm and 58 delayed stroke (16.2%). Of those patients that did not have pre-existent vascular disease, 318 (46.5%) developed radiographic vasospasm, 173 (25.3%) symptomatic vasospasm, 107 (15.6%) delayed stroke.

In univariate analysis, pre-existent condition was significantly less likely to have angiographic vasospasm (P<.0001) and less symptomatic vasospasm (P=.033), but no difference in delayed stroke. (Table 1) In multivariate analysis, pre-existent condition was significantly less likely to experience angiographic vasospasm (odds ratio=0.71, 95% CI=[.515, .969], p=.031), however there was no difference in symptomatic vasospasm or delayed stroke. (Table 2) More specifically, patients with pre-existing cerebrovascular disease were significantly less likely to have radiographic vasospasm (p<.001). But, there were no statistical differences in symptomatic vasospasm or spasm-related cerebral infarction.(Table 3)

Conclusions

These retrospective case-controlled data are the first evidence in human patients that ischemic preconditioning has an effect on cerebral vasospasm in patients with aneurysmal SAH.

Any pre-existing vascular disease and pre-existing cerebrovascular disease protect against angiographic vasospasm, but does not seem to have an effect on symptomatic vasospasm or delayed stroke. This will warrant further investigation with larger prospective studies.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Discuss role of the ischemic preconditioning in association with the incidence of vasospasm; 2) Discuss risk factors associated with the development of vasospasm

Table 1. Patient outcomes by pre-existing vascular disease status

	Overall (n=1043)	Pre-existing vascular disease		p-value
		No (n=684)	Yes (n=359)	
Angiographic vasospasm				
No	606 (58.1%)	366 (53.5%)	240 (66.9%)	<.001
Yes	437 (41.9%)	318 (46.5%)	119 (33.1%)	
Symptomatic vasospasm				
No	801 (76.8%)	511 (74.7%)	290 (80.8%)	.033
Yes	242 (23.2%)	173 (25.3%)	69 (19.2%)	
Stroke				
No	878 (84.2%)	577 (84.4%)	301 (83.8%)	.900
Yes	165 (15.8%)	107 (15.6%)	58 (16.2%)	

Table 2. A multivariate model for primary endpoints (radiographic vasospasm, symptomatic vasospasm, and spasm-related cerebral infarction)

Variable	Odds ratio	95% CI for odds ratio		P-value
		Lower	Upper	
Radiographic vasospasm				
Age (each year increase)	0.97	0.966	0.980	<.001
Clipping vs. coiling	1.7	1.27	2.32	<.001
Pre-existent vascular disease	0.71	0.515	0.969	.031
Symptomatic vasospasm				
Age (each year increase)	0.98	0.962	0.989	<.001
Female vs. men	1.3	1.15	1.49	<.001
Aneurysm location (anterior vs. posterior)	1.4	1.10	1.72	.005
H-H grade*	NA	NA	NA	<.05
Radiographic cerebral infarction				
Age (each year increase)	0.97†	0.956	0.989	.001
Female vs. men	1.4	1.06	1.77	.015
Clipping vs. coiling	1.7	1.29	2.14	<.001

Table 3. Patient outcomes by pre-existing cerebrovascular disease only

	Overall (n=1043)	Pre-existing cerebrovascular disease		p-value
		No (n=722)	Yes (n=321)	
Angiographic vasospasm				
No	606 (58.1%)	389 (53.9%)	217 (67.6%)	<.001
Yes	437 (41.9%)	333 (46.1%)	104 (32.4%)	
Symptomatic vasospasm				
No	801 (76.8%)	545 (75.4%)	256 (79.8%)	.132
Yes	242 (23.2%)	177 (24.5%)	65 (20.2%)	
Cerebral infarction				
No	878 (84.2%)	611 (84.6%)	267 (83.2%)	.554
Yes	165 (15.8%)	111 (15.4%)	54 (16.8%)	