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Matched Cohort Analysis of the Effects of Limb Remote Ischemic Conditioning in Patients with Aneurysmal Subarachnoid Hemorrhage

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Abstract

Background—Remote ischemic conditioning (RIC) is a powerful innate response to transient subcritical ischemia that protects against severe ischemic insults at distant sites. We have previously shown the safety and feasibility of limb RIC in aneurysmal subarachnoid hemorrhage (aSAH) patients, along with changes in neurovascular and cerebral metabolism. In this study we aim to detect the potential effect of an established lower-limb conditioning protocol on clinical outcomes of aSAH patients.

Methods—Neurologic outcome (modified Rankin Scale [mRS]) of patients enrolled in a prospective trial (RIPC-SAHA) was measured. A matching algorithm was applied to identify control patients with aSAH from an institutional departmental database. RIC patients underwent 4 lower-limb conditioning sessions, consisting of 4 five-minute cycles per session over nonconsecutive days. Good functional outcome was defined as mRS of 0 to 2.

Results—The study population consisted of 21 RIC patients and 61 matched controls. There was no significant intergroup difference in age, gender, aneurysm location, clipping versus coiling, Fisher grades, Hunt and Hess grades, or vasospasm. RIC was independently associated with good outcome (OR: 5.17; 95% CI: 1.21–25.02). RIC also showed a trend toward lower incidence of stroke (28.6% vs. 47.5%) and death (4.8% vs. 19.7%).

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Compliance with Ethical Standards: The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. This research involved human participants. This study was conducted with Institutional Review Board approval and participants gave informed consent before taking part.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

Azim N. Laiwalla, Yinn Cher Ooi, Raymond Liou, and Nestor R. Gonzalez declare that they have no conflicts of interest.

Conclusions—Lower-limb RIC following aSAH appears to have a positive effect in the functional outcomes of patients with aSAH. While this effect is consistent with prior preclinical studies, future trials are necessary to conclusively evaluate the effects of RIC for aSAH.

Keywords

aneurysm; neurologic outcomes; remote ischemic preconditioning; stroke; subarachnoid hemorrhage

Introduction

Remote ischemic conditioning (RIC) is a powerful endogenous mechanism whereby sublethal episodes of ischemia temporarily protect against subsequent lethal ischemic insults at distant sites [1]. In animal models, RIC of the limb has been shown to be effective in protecting against global and focal cerebral ischemia [2–5]. In humans, lower-limb RIC induces ischemic muscle changes, resulting in transient metabolic shifts consistent with sublethal ischemia that may be used to protect distant organs [6]. Prior clinical studies have demonstrated the safety of limb RIC in patients with aneurysmal subarachnoid hemorrhage (aSAH) and the mechanism's potential to produce neurovascular and cerebral metabolic changes [7,8]. Several authors have suggested the potential role of RIC in aSAH patients; however, the exact benefits remain unclear [9,10]. Recent randomized clinical trials reported the efficacy of RIC in stroke prevention in patients with intracranial atherosclerosis and carotid endarterectomy, but this has not been shown in aSAH [11,12]. The goal of this study is to evaluate the potential effect of an established lower-limb conditioning protocol on functional outcomes of patients with aSAH.

Methods

Study Design

To evaluate the potential effect of lower-limb RIC in patients with aSAH, we performed a retrospective cohort study of patients originally enrolled in the Remote Ischemic Preconditioning in Subarachnoid Hemorrhage (RIPC-SAH) trial ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01158508) # NCT01158508) versus a matched control group. The study was conducted with institutional review board approval. The details of the RIPC-SAH study protocol and results of the safety endpoints have been previously published [8]. For the present study a matching algorithm was used to retrospectively identify a control group of individuals with aSAH from our institutional departmental database. The algorithm accounted for known factors affecting outcomes of aSAH [13–16]. Patients were identified matching for age within 4 years, gender, exact Hunt and Hess (H&H) grade, and Fisher grade after intervention for elevated intracranial pressure (ICP). To increase the power of the study, an allocation rate of 3:1 was used between controls and cases. The same neurocritical care team was involved in the management of the RIC and control groups. Table 1 summarizes the inclusion and exclusion criteria for the RIPC-SAH study, which were also applied to the control cohort.

Both RIC and control patients received standard-of-care management of aSAH, including early protection of the aneurysm, calcium channel blocker treatment, and external

ventricular drainage placement for signs of elevated ICP. In the ICU, patients were treated with moderate hypertension and hypervolemia, and monitored with central venous catheters, arterial lines, and/or Swan-Ganz catheters. Furthermore, ICU patients underwent daily transcranial Doppler (TCD) ultrasonography and continuous electroencephalography (EEG). Patients with TCD velocities that increased over serial monitoring, TCD velocities that surpassed established TCD thresholds, or with deterioration in neurological examination, received neurological imaging with endovascular treatment for vasospasm, as needed [16,17]. MRI imaging included DWI, GRE, FLAIR, T2, COW TOF MRA, ASL, PWI, CEMRA, and post-contrast T1-GRE sequences. CT imaging included non-contrast CT, CTA brain and neck, and CT perfusion scans.

The protocol of RIC consisted of 4 RIC sessions of the lower limb over multiple nonconsecutive days, performed within 2 to 12 days following aneurysm rupture. Each session included 4 inflation cycles lasting 5 minutes, with 5 minutes of cuff deflation between all of the cycles. Inflation pressure was initiated at 20 mm Hg above the patient's known baseline systolic blood pressure and was increased until the dorsalis pedis pulse was abolished, as verified by Doppler ultrasonography. This pressure was maintained through the inflation cycle.

Endpoint measurements

The standard dichotomized modified Rankin Scale (mRS) at discharge was used as primary endpoint, with good functional outcome defined as mRS 0 to 2 and poor functional outcome as mRS 3 to 6 [18,19]. Secondary endpoints included the development of (1) vasospasm during hospitalization, as determined by catheter angiography and/or transcranial Doppler (TCD) ultrasonography, and (2) ischemic stroke, as determined by MRI and/or CT.

Sample-size calculation

Using the approach described by Kelsey et al., a total sample size of 76 was calculated to be sufficient to detect a minimum odds ratio of 4.0 in favor of the RIC group for good outcome, with α of 0.05 and 80% power [20]. This calculation was based on the expected proportion of good outcomes of 25% with current standard of care, according to Hop et al [21].

Statistics

Statistical analysis was performed with JMP®, version 11 (SAS Institute Inc., Cary, NC, 1989–2007). All authors participated in the analysis of the data. Descriptive statistics were generated for demographic and clinical assessments to characterize the study populations in both groups. Contingency 2×2 tables with the numbers of treated and untreated patients with good and poor outcomes were created, from which the odds ratio was calculated. A chi-square test of significance was applied with α of 0.05.

Logistic regression models were used to account for the possible effects of covariates not corrected by the matching algorithm. A full model was built using the covariates age, gender, aneurysm location, treatment (coiling vs. clipping), Fisher grade, H&H grade, presence of intraventricular hemorrhage/intraparenchymal hemorrhage (IVH/IPH), and group (RIC vs. control). Backward and forward stepwise model building regression with

minimum BIC and AIC stopping rules were used to generate a parsimonious model. Odds ratios of the significant variables were calculated from the parsimonious model with their corresponding 95% confidence intervals. The models' significance was tested with the chi-square test. Entropy RSquare, misclassification rate, and the area under the curve of their receiver operating characteristics were utilized to evaluate their fitness.

To evaluate for potential effects of time of management in RIC compared to historical controls, a correlation matrix between time of treatment and mRS was constructed. Spearman's correlation was used to evaluate its significance.

Results

Patient Population

The RIC group consisted of 21 patients, ages ranging from 22 to 76 years (mean = 50.81, SD = 12.73), with 14 females (66.7%) and 7 males (33.3%). The matching algorithm identified 61 control patients, ages ranging from 20 to 77 years (mean = 52.03, SD = 11.95), and consisted of 41 females (67.2%) and 20 males (32.8%). Demographic data and clinical presentation grades (Fisher and H&H grades) are summarized in Table 2.

The location of the ruptured aneurysm was classified as anterior or posterior circulation for each patient. Twelve of 21 RIC (57.1%) and 41 of 61 control (67.2%) patients had ruptured aneurysms in the anterior circulation. The remaining 9 RIC (42.9%) and 20 control (32.8%) patients had ruptured aneurysms in the posterior circulation. There was no significant difference in the proportions of patients treated with clipping or coiling between RIC patients and controls. Endovascular coiling was performed in 13 RIC (61.9%) and 38 control (62.3%) patients, with surgical clipping performed in 8 (38.1%) and 23 (37.7%) of the RIC and control patients, respectively.

Clinical Outcomes

Nine of 21 RIC (42.9%) patients had good outcomes, while only 14 of 61 control (23.0%) patients had good outcomes. Four of 21 RIC (19.1%) patients had no neurological deficits (mRS 0) versus 4 of 61 controls (6.6%). There was 1 (4.8%) death in the RIC group and 12 (19.7%) in the control group. The complete list of clinical outcomes is summarized in Table 3.

Whereas a larger proportion of RIC patients were affected by vasospasm, a smaller proportion suffered ischemic stroke as compared to the control group. Vasospasm was observed in 17 of 21 RIC (81.0%) and 42 of 61 control (69.0%) patients, while 6 of 21 RIC (28.6%) and 29 of 61 control (47.5%) patients suffered strokes. Neither vasospasm nor stroke occurrence was found to be statistically different between groups, although RIC patients showed a trend toward lower incidence of stroke (28.6% vs. 47.5%).

The multiple logistic regression models (summarized in Table 3) showed that RIC is significantly associated with good outcome, while higher Fisher and H&H grades are associated with a lower likelihood for good outcome. The logistic equation for the parsimonious model is expressed as follows:

$$\ln[\text{good outcome}] = 14.91 + (1.64 * \text{group}) + (-4.02 * \text{Fisher grade}) + (-1.80 * \text{H\&H grade}) + (1.40 * \text{IVH/IPH})$$

where group: control = 0 and RIC = 1; IVH/IPH: no = 0 and yes = 1

The odds ratio of good outcome for patients treated with conditioning was 5.17 (95% CI: 1.21–25.02). Patient outcome (mRS) had no significant correlation with the time period in which patients presented and were treated (Spearman's ρ -0.18, p = 0.11). (Figure 1.)

Discussion

Remote ischemic conditioning is a powerful innate response to transient ischemia that confers protection against subsequent severe ischemia at distant sites [1]. Several preclinical models have demonstrated that this phenomenon protects against cerebral ischemia [2–5]. The clinical potential of conditioning is underscored by the high morbidity and mortality of aSAH and the ease of application of RIC with relatively low risk for injury [22,23].

The efficacy of remote ischemic conditioning in animal models has prompted human trials for acute ischemic stroke. In a randomized study of patients undergoing carotid endarterectomy, two 10-minute episodes of limb RIC produced a nonsignificant reduction of saccadic latency deteriorations, suggesting potential neuroprotective effects [12]. In a longer-term randomized control trial, bilateral limb RIC performed twice daily for 300 days conferred neuroprotection in patients with symptomatic intracranial arterial stenosis, as demonstrated by a reduction in the incidence of recurrent stroke, shortened average time to recovery after stroke, and improved cerebral perfusion [11]. These clinical findings, along with those from preclinical studies, point to the presence of endogenous neural protective mechanisms inducible by RIC.

RIC holds potential for the prevention of delayed neurological deficits following aSAH. The established time course for vasospasm and delayed ischemic neurological deficits following aSAH permits timely application of RIC before the peak risk of vasospasm and stroke [1]. Previous studies have evaluated the effects of the RIC protocol used in this study on limb-muscle ischemia, demonstrating increase in lactate and in the lactate-pyruvate ratio, without variation in glycerol, indicating transient muscle ischemia without permanent cell damage [6]. The effects of RIC on the cerebral vasculature and local metabolites have also been investigated. TCD measurements of patients undergoing RIC indicated transient cerebral vasodilation over the duration of conditioning. Brain microdialysis demonstrated a persistent reduction in the lactate-pyruvate ratio as well as in glycerol 25 to 54 hours after the final conditioning stimulus [7]. Subsequent studies confirmed the safety and feasibility of lower-limb RIC in patients hospitalized with aSAH [6–9]. RIC did not cause deep vein thrombosis or mechanical or permanent ischemic injury to the preconditioned limb [8].

With the specific conditioning regimen of 4 five-minute alternating cycles of ischemia, RIC was found to be associated with good outcomes in the multiple logistic regression models. Additionally, there was a trend toward lower incidence of stroke and death, and a higher incidence of patients without aSAH-related disability (mRS 0) in the RIC group. These

findings further substantiate the potential benefit of RIC in the management of aSAH and suggest an actual effect of the administered dose. While our retrospective study suggests potential positive effects in aSAH patient outcomes, the true efficacy of conditioning for the management of ischemic stroke or aSAH will require pivotal confirmatory clinical trials.

Our analysis showed that there was no significant correlation of discharge mRS with the period of time of aSAH, a factor introduced by the use of a historic control cohort that could not be corrected with the matching design. Furthermore, after corrections for other strong predictors in the multiple logistic regression models, RIC stands as an important individual predictor for good outcome. In concordance with the literature, well-recognized factors that predict vasospasm, including Fisher and H&H grades, were also predictors of outcomes in our model [14,16].

Limitations

The main limitations of this study are its retrospective nature and the use of historic controls. This limits the conclusion and generalizability of the data presented. However, our study shows a trend toward a positive effect of RIC on aSAH patient outcome, and identified an effect size that may help to pave the way for future prospective randomized trials. To increase the validity of the data, a matching algorithm was created to identify controls that accounted firsthand for the most important predictors in aSAH outcomes and had the exact same inclusion and exclusion criteria as the RIC-treated cases. Unavoidable with retrospective studies of this nature, patients enrolled in the rigid protocol of the RIPC-SAHA trial may have benefited from care that differed from that of the controls. Regression analyses were performed to account for covariates that could not be corrected by the matching algorithm, and in both the full and parsimonious models, RIC was associated with good outcomes. To address the limitation introduced by using historic controls, the potential effect of time of treatment on outcome was evaluated and found to be insignificant. We speculate this is due to the pioneering work of our neurocritical care team in the development of management strategies for vasospasm and subarachnoid hemorrhage that were recently adopted by other centers [24–27]. An additional limitation of this study was the relatively small sample size of the RIC group. The detection of an effect required a larger population, which was compensated for by creating an ~3:1 allocation with the control group. This study evaluated the effects of limb RIC in clinical outcomes with a particular protocol, and therefore, the evaluation of other regimens would require further studies.

Conclusions

Remote ischemic conditioning using the protocol described appears to have a positive effect on the functional outcomes of patients with aSAH, reflected by an improvement in mRS scores. The detection of this directionally appropriate effect, consistent with evidence from prior preclinical and clinical models, requires future trials to conclusively evaluate the effects of RIC for aSAH.

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References

1. Koch S, Gonzalez N. Preconditioning the human brain: proving the principle in subarachnoid hemorrhage. *Stroke*. 2013; 44:1748–1753.10.1161/STROKEAHA.111.000773 [PubMed: 23598525]
2. Zhao H-G, Li W-B, Li Q-J, Chen X-L, Liu H-Q, Feng R-F, et al. Limb ischemic preconditioning attenuates apoptosis of pyramidal neurons in the CA1 hippocampus induced by cerebral ischemia-reperfusion in rats. *Sheng Li Xue Bao*. 2004; 56:407–412. [PubMed: 15224159]
3. Jin RL, Li WB, Li QJ, Zhang M, Man XH, Sun XC, et al. The role of extracellular signal-regulated kinases in the neuroprotection of limb ischemic preconditioning. *Neurosci Res*. 2006; 55:65–73.10.1016/j.neures.2006.01.006 [PubMed: 16530867]
4. Dave KR, Saul I, Prado R, Busto R, Perez-Pinzon MA. Remote organ ischemic preconditioning protect brain from ischemic damage following asphyxial cardiac arrest. *Neuroscience Letters*. 2006; 404:170–175.10.1016/j.neulet.2006.05.037 [PubMed: 16781056]
5. Ren C, Gao X, Steinberg GK, Zhao H. Limb remote-preconditioning protects against focal ischemia in rats and contradicts the dogma of therapeutic time windows for preconditioning. *Neuroscience*. 2008; 151:1099–1103.10.1016/j.neuroscience.2007.11.056 [PubMed: 18201834]
6. Bilgin-Freiert A, Dusick JR, Stein NR, Etchepare M, Vespa P, Gonzalez NR. Muscle microdialysis to confirm sublethal ischemia in the induction of remote ischemic preconditioning. *Transl Stroke Res*. 2012; 3:266–272.10.1007/s12975-012-0153-1 [PubMed: 24323782]
7. Gonzalez NR, Hamilton R, Bilgin-Freiert A, Dusick J, Vespa P, Hu X, et al. Cerebral hemodynamic and metabolic effects of remote ischemic preconditioning in patients with subarachnoid hemorrhage. *Acta Neurochir Suppl*. 2013; 115:193–8.10.1007/978-3-7091-1192-5_36 [PubMed: 22890668]
8. Gonzalez NR, Connolly M, Dusick JR, Bhakta H, Vespa P. Phase I Clinical Trial for the Feasibility and Safety of Remote Ischemic Conditioning for Aneurysmal Subarachnoid Hemorrhage. *Neurosurgery*. 2014; 75:590–598.10.1227/NEU.0000000000000514 [PubMed: 25072112]
9. Koch S, Katsnelson M, Dong C, Perez-Pinzon M. Remote ischemic limb preconditioning after subarachnoid hemorrhage: a phase Ib study of safety and feasibility. *Stroke*. 2011; 42:1387–1391.10.1161/STROKEAHA.110.605840 [PubMed: 21415404]
10. Koch S, Sacco RL, Perez-Pinzon MA. Preconditioning the brain: moving on to the next frontier of neurotherapeutics. *Stroke*. 2012; 43:1455–1457.10.1161/STROKEAHA.111.646919 [PubMed: 22461331]
11. Meng R, Asmaro K, Meng L, Liu Y, Ma C, Xi C, et al. Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. *Neurology*. 2012; 79:1853–1861.10.1212/WNL.0b013e318271f76a [PubMed: 23035060]
12. Walsh SR, Nouraei SA, Tang TY, Sadat U, Carpenter RH, Gaunt ME. Remote ischemic preconditioning for cerebral and cardiac protection during carotid endarterectomy: results from a pilot randomized clinical trial. *Vasc Endovascular Surg*. 2010; 44:434–439.10.1177/1538574410369709 [PubMed: 20484064]
13. Teunissen LL, Rinkel GJ, Algra A, van Gijn J. Risk factors for subarachnoid hemorrhage: a systematic review. *Stroke*. 1996; 27:544–549.10.1161/01.STR.27.3.544 [PubMed: 8610327]
14. Claassen J, Bernardini GL, Kreiter K, Bates J, Du YE, Copeland D, et al. Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: the Fisher scale revisited. *Stroke*. 2001; 32:2012–2020.10.1161/hs0901.095677 [PubMed: 11546890]
15. Molyneux A. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *The Lancet*. 2002; 360:1267–1274.10.1016/S0140-6736(02)11314-6

16. Gonzalez NR, Boscardin WJ, Glenn T, Vinuela F, Martin NA. Vasospasm probability index: a combination of transcranial doppler velocities, cerebral blood flow, and clinical risk factors to predict cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Journal of Neurosurgery*. 2007; 107:1101–12.10.3171/JNS-07/12/1101 [PubMed: 18077946]
17. Oskouian RJ, Martin NA, Lee JH, Glenn TC, Guthrie D, Gonzalez NR, et al. Multimodal Quantitation of the Effects of Endovascular Therapy for Vasospasm on Cerebral Blood Flow, Transcranial Doppler Ultrasonographic Velocities, and Cerebral Artery Diameters. *Neurosurgery*. 2002; 51:30–43.10.1097/00006123-200207000-00005 [PubMed: 12182433]
18. Weisscher N, Vermeulen M, Roos YB, De Haan RJ. What should be defined as good outcome in stroke trials; a modified Rankin score of 0–1 or 0–2? *J Neurol*. 2008; 255:867–874.10.1007/s00415-008-0796-8 [PubMed: 18338195]
19. Duncan PW, Jorgensen HS, Wade DT. Outcome measures in acute stroke trials: a systematic review and some recommendations to improve practice. *Stroke*. 2000; 31:1429–1438.10.1161/01.STR.31.6.1429 [PubMed: 10835468]
20. Kelsey, JL.; Whittemore, AS.; Evans, AS.; Thompson, WD. *Methods in observational epidemiology*. New York: Oxford University Press; 1996.
21. Hop JW, Rinkel GJ, Algra A, van Gijn J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. *Stroke*. 1997; 28:660–664. [PubMed: 9056628]
22. Cahill J, Zhang JH. Subarachnoid hemorrhage: is it time for a new direction? *Stroke*. 2009; 40:S86–S87.10.1161/STROKEAHA.108.533315 [PubMed: 19064787]
23. Dezfulian C, Garrett M, Gonzalez NR. Clinical Application of Preconditioning and Postconditioning to Achieve Neuroprotection. *Transl Stroke Res*. 2012; 4:19–24.10.1007/s12975-012-0224-3 [PubMed: 24323188]
24. Duckwiler G. Balloon angioplasty and intra-arterial papaverine for vasospasm. *Journal of Stroke and Cerebrovascular Diseases*. 1997; 6:261–263. [PubMed: 17895012]
25. Vespa PM, Nuwer MR, Juhász C, Alexander M, Nenov V, Martin N, et al. Early detection of vasospasm after acute subarachnoid hemorrhage using continuous EEG ICU monitoring. *Electroencephalogr Clin Neurophysiol*. 1997; 103:607–615. [PubMed: 9546487]
26. Vespa PM. Acute presentation and early intensive care of acute aneurysmal subarachnoid hemorrhage. *Journal of Stroke and Cerebrovascular Diseases*. 1997; 6:230–234. [PubMed: 17895003]
27. Vespa PM, Nenov V, Nuwer MR. Continuous EEG monitoring in the intensive care unit: early findings and clinical efficacy. *J Clin Neurophysiol*. 1999; 16:1–13. [PubMed: 10082088]

Fig. 1.

Plot of Modified Rankin Scale (mRS) at Discharge versus Aneurysmal Subarachnoid Hemorrhage (aSAH) Date. There was no significant correlation of discharge mRS with time of aSAH. Graphic produced by JMP®, version 11 (SAS Institute Inc., Cary, NC, 1989–2007)

Table 1

Inclusion and Exclusion Criteria for Remote Ischemic Preconditioning in Subarachnoid Hemorrhage Trial Enrollment.

Inclusion Criteria
<ul style="list-style-type: none">• Patient age between 18 and 80 years• Patient or appropriate surrogate capable of providing signed, informed consent• aSAH confirmed by CT or lumbar puncture with aneurysm origin confirmed by catheter or CT angiography• Ruptured aneurysm protected by coiling or clipping
Exclusion Criteria
<ul style="list-style-type: none">• Unprotected ruptured intracranial aneurysm• Pregnancy• History or physical exam findings of peripheral vascular disease, deep vein thrombosis, peripheral neuropathy, or lower extremity bypass

Table 2

Summary of Demographics and Clinical Presentation Grades between Remote Ischemic Conditioning and Control Groups. Chi-square method was used to compare proportions among groups.

Demographics	Control Group	RIC ^a Group
No. of patients	61	21
Age – years		
Mean (SD)	52.03 (11.95)	50.81 (12.73)
Gender – No. (%)		
Female	41 (67.2%)	14 (66.7%)
Male	20 (32.8%)	7 (33.3%)
Aneurysm Location – No. (%)		
Posterior circ.	20 (32.8%)	9 (42.9%)
Anterior circ.	41 (67.2%)	12 (57.1%)
Treatment – No. (%)		
Clipping	23 (37.7%)	8 (38.1%)
Coiling	38 (62.3%)	13 (61.9%)
Fisher – No. (%)		
2	8 (13.1%)	3 (14.3%)
3	53 (86.9%)	18 (85.7%)
Hunt and Hess – No. (%)		
1	6 (9.8%)	2 (9.5%)
2	9 (14.8%)	3 (14.3%)
3	18 (29.5%)	6 (28.6%)
4	14 (23.0%)	5 (23.8%)
5	14 (23.0%)	5 (23.8%)
IVH/IPH ^b – No. (%)		
No	27 (44.3%)	8 (38.1%)
Yes	34 (55.7%)	13 (61.9%)

Mean age difference calculated using a two-sided t-test. There were no significant differences between the groups.

^aRemote ischemic conditioning,

^bIntraventricular hemorrhage/intraparenchymal hemorrhage

Table 3

Prediction Model for the Probability of Outcome in Patients with Aneurysmal Subarachnoid Hemorrhage. Built with backward and forward stepwise regression with minimum BIC and AIC stopping rules.

Variable	Functional Outcome		Full		Parsimonious	
	Poor (mRS 3)	Good (mRS 2)	Beta coefficient	p-value	Beta coefficient	p-value
Age – years						
Mean (SD)	52.12 (10.76)	50.70 (14.70)	0.07	0.12		
Gender – No. (%)						
Female	37 (67.3)	18 (32.7)	0.51	0.71		
Male	22 (81.5)	5 (18.5)		Male code 1		
Location – No. (%)						
Anterior	39 (73.6)	14 (26.4)	0.09	0.92		
Posterior	20 (68.9)	9 (31.0)		Anterior code 1		
Group – No. (%)			2.03	0.02	1.64	0.03
Control	47 (77.1)	14 (22.9)				
RIC ^a	12 (57.1)	9 (42.9)		RIC code 1		
Treatment – No. (%)						
Coiling	35 (68.6)	16 (31.4)	2.73	0.02		
Clipping	24 (77.4)	7 (22.6)				
Fisher grade – No. (%)			–5.55	0.005	–4.02	0.006
2	2 (18.2)	9 (81.8)				
3	57 (80.3)	14 (19.7)				
H&H ^b grade – No. (%)			–2.28	<0.001	–1.80	<0.001
1	1 (12.5)	7 (87.5)				
2	5 (41.7)	7 (58.3)				
3	18 (75)	6 (25)				
4	17 (89.5)	2 (10.5)				
5	18 (94.7)	1 (5.3)				
IVH/IPH ^c – No. (%)			1.40	0.25	1.40	0.15

Variable	Functional Outcome			Full		Parsimonious	
	Poor (mRS 3)	Good (mRS 2)		Beta coefficient	p-value	Beta coefficient	p-value
Yes	40 (85.1)	7 (14.9)		IVH/IPH code 1			
No	19 (54.3)	16 (45.7)					

Model Test

Chi-square	<0.001	<0.001
RSquare	0.55	0.45
Misclassification Rate	0.12	0.13

RIC is significantly associated with good outcome. Higher Fisher grade and H&H grades are associated with a lower likelihood for good outcome.

^aRemote ischemic conditioning,

^bHunt and Hess,

^cIntraventricular hemorrhage/intraparenchymal hemorrhage