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Review

Effect of Pre/Postconditioning at Temporary Clipping

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ABSTRACT

Intracranial aneurysms and their treatment is one of the leading problems of neurosurgery that create high mortality and morbidity. The technique of safe clipping is as generally used depends on the temporary occlusion of the cerebral vasculature during surgery. However, there is no exact data about temporary clipping or timing of this procedure.

Preconditioning by exposure to sublethal hypoxic stress, hours or days before severe hypoxia, decreases cell death, and this resistance of the brain to injury is known as ischemic tolerance. Brief alternating periods of reperfusion-reocclusion at the beginning of reperfusion is defined as postconditioning. Cerebral ischemic pre/postconditioning protects against stroke, but is clinically feasible only when the occurrence of stroke is predictable.

Brief, repetitive occlusion and release of the main trunk of a vessel during early aneurysm surgery or before long-lasting temporary artery occlusion may protect the brain against later possible vasospasm/ischemia.

KEYWORDS: Aneurysm, Postconditioning, Preconditioning, Temporary clipping

■ INTRODUCTION

*“that which does not kill us makes us stronger”
Nietzsche*

Intracranial aneurysms and its treatment is still one of the leading problems of neurosurgery. Modern medical era has developed different treatment modalities but the importance of surgery still continues. The technique of safe clipping as generally used depends on the temporary occlusion of the cerebral vasculature during surgery. It may lessen the risk of intraoperative aneurysm rupture and also allows evacuation of intramural calcification and thrombosis before definitive clipping in large aneurysms.

Elective temporary occlusion in the treatment of intracranial aneurysms was first performed by Jefferson in 1928. He used a modified Michel clip for proximal vessel control. In 1947, Henry Schwartz manufactured a clip that could be applied with a modified uterine forceps for the purpose of temporary

vessel occlusion with the help of George Bishop (55). In 1957, a modified Cairns clip was used in two cases of aneurysm by Gibbs (55). Temporary clamping and moderate hypothermia in the treatment of aneurysms were reported by Suzuki et al. in 1969. The authors pointed that intermittent reperfusion allowed prolongation of the total time of temporary occlusion (52). After the late 1970s, there were an increasing number of reports on the use of precautionary temporary artery occlusion in the surgical management of giant aneurysms (4, 20, 51, 53). Ljunggren et al. reported that occlusion was well tolerated at the middle cerebral artery (MCA) for up to 20 minutes in 1983 (31). The routine use of both proximal and distal temporary clipping was pioneered by Suzuki (8). After Ausman's paper in 1985, many articles have reported the routine use of temporary artery occlusion in large series of patients (2, 8, 44).

However, there is no agreement on the time of temporary clipping and its application to protect the patient from focal cerebral ischemia and associated neurologic injury (8, 13, 21, 28, 38, 44, 55).



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Intraoperative aneurysm rupture and ischemia due to prolonged temporary clipping are direct causes of mortality and morbidity of aneurysm surgery (3, 9, 14, 59). However, sometimes prolonged occlusion is mandatory for complete clipping. The period of stroke-free temporary clipping varies depending on the clinical factors and the occluded vessel (13).

Monitoring of brain tissue oxygen concentration (PtiO₂) has been used to detect changes in brain oxygenation due to temporary clipping (9). Cerejo et al. showed that there were significant decrease (20% or more, compared with the basal value) in PtiO₂ values after temporary clipping (9).

Motoyama et al. studied the reliability of combined use of transcranial and direct cortical motor evoked potential (MEP) monitoring during unruptured aneurysm surgery (35). Decrease or disappearance of direct MEP waves were recovered immediately after re-application of the clip and release of the temporary clip and they showed that combined transcranial and direct cortical MEP recording may improve the feasibility and reliability of MEP monitoring during unruptured aneurysm surgery (35).

Ischemic events can occur even in cases of aneurysm surgery. Organisms respond with protective mechanisms to recurrent insults and this resistance of the brain to ischemic injury is known as ischemic tolerance (IT). IT induced by several paradigms represents an important phenomenon of central nervous system (CNS) adaptation to sublethal short-term ischemia (17).

Ischemic preconditioning (IP) was first introduced by Murry (36) in the heart and later Schurr et al. and Kitagawa et al. worked on this subject in the brain (26, 47). The molecular mechanisms underlying IT are not yet fully understood. Many experimental and clinical studies have been performed to understand the nature of the neuroprotective mechanism regarding extreme metabolic stress, such as hypoxia/ anoxia/ ischemia (25, 41). Global ischemia, focal ischemia, cerebral hypoxia, cortical spreading depression, hypo/hyperthermia, heat shock and various pharmacological agents can play a role in preconditioning (30). In 1991, Burda et al. showed that graded postischemic reoxygenation could be used as a neuroprotective tool to prevent secondary postischemic damage in nervous tissue (6). Later Danielisova et al. documented that the duration of the sublethal ischemic episode (for 3–8 min) and the time that had elapsed between the second ischemia are important (10). After induced IT by IP, SOD and CAT were significantly increased after 5 hours and 1 and 2 days of reperfusion (11).

Older patient age, poor grade of hemorrhage, location of aneurysm, size of aneurysm, and the risk of intraoperative aneurysm rupture are other factors that affect the potential risk of stroke (13). Ferch et al. observed a trend for an increased incidence of stroke in patients in whom temporary vessel occlusion was performed for more than 10 minutes in their retrospective analysis and pointed that early surgery, and the use of single prolonged clip placement rather than repeated shorter episodes were associated with a higher risk of stroke (13). Contrary to other authors, Ferch et al. concluded that

intraoperative aneurysm rupture did not affect stroke risk and only poorer clinical grade and increasing age were significantly associated with symptomatic stroke risk (13).

There are two concepts based on experimental studies. Temporary or continuous occlusion of vessels can be used to protect the brain from ischemia (12, 16, 38, 49). The temporary occlusion times were longer in the studies in which the rate of stroke was lower when continuous compared with intermittent occlusion was performed (13, 38, 44).

In a series of 100 normothermic, normotensive patients Samson et al. suggested that 15 to 20 minutes was the maximum period of occlusion that could be safely sustained by the help of etomidate protection. They found that 31 minutes was the cut off value for clinical and radiological evidence of cerebral infarction (44). Evoked potential failure has been used as an indicator of dense ischemia in cerebral tissue by several authors (15, 34). Sensory evoked potentials were lost approximately 9 minutes after temporary clipping. If recirculation was reestablished within 20 minutes of the occlusion, the rate of clinical sequelae was very low (34).

Intraoperative monitoring of cortical blood flow has also been used to define the safe limits of temporary vessel occlusion in the literature (39).

Mild hypothermia and mannitol administration was used to prevent cerebral infarction (38). Ogilvy et al. used intravenous mannitol and induced systemic hypertension and mild hypothermia prior to and during planned temporary vessel occlusion. They concluded that stroke develops when temporary clipping stands more than 20 minutes and intraoperative aneurysm rupture was very significantly associated with stroke outcome (38). There is a 10-minute time gap of infarction times between Ogilvy and Samson. This time difference might be because one group had hypothermia and hypertension induction while Samson, et al. used the normothermic, normotensive anesthetic technique (38, 44).

Protection of cooling in ischemic conditions is a well-documented subject in the literature, both in the clinical setting and animal studies (18, 19, 22, 24, 27). Mack et al. showed that longest occlusion times could be achieved by using a combination of global deep hypothermia and cardiac standstill but had a high mortality rate of 12% at one month and fair or poor outcome rate of 20% (32).

The Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) was a randomized trial of mild systemic hypothermia (33°C) in 1000 patients undergoing surgery to treat an acutely ruptured intracranial aneurysm. The study showed that hypothermia did not significantly affect neurologic or neuropsychologic outcomes. However, supplemental drug administration was not considered in the study (21, 56). Todd et al. pointed out that patients who had temporary clip durations greater than or equal to 20 min had less favorable outcomes but they did not mention the indications of temporary clipping (21).

Aneurysms that were located on arteries with perforating vessel segments appeared to have poor tolerance for long

occlusion times (28, 44). For example, Samson et al. showed infarction rates of 41% for the basilar group and 7% for the internal carotid artery (44). Lavine et al. performed an intermittent temporary clip application with no standardization for the number or duration of reperfusion episodes and showed that infarction rates from undergoing intermittent temporary clip application was lower than the continuous episode of ischemia, which was a contradiction of the results of Ogilvy et al. (28, 38).

Five minutes of reperfusion after every 10 minutes of ischemia produced by intraluminal occlusion of the MCA in rats resulted in significantly smaller infarction volumes compared to continuous ischemia as demonstrated by Goldman et al. (16). A decrease in infarction size and decreased cortical neuronal damage have shown by Steinberg et al. in another model of interrupted focal ischemia (49). However, there are also conflicting results with the damage of reperfusion in different animal models (5, 46, 57).

One of the main concerns about intermittent clip applications was reperfusion injury that was discovered to be the significant component of ischemic injury (33, 48).

Selman et al. showed that intermittent or continuous occlusion was not important for the volume of infarction. They compared the infarct volumes with intermittent and continuous occlusion in normotensive and spontaneously hypertensive rats and concluded that spontaneously hypertensive rats had a greater volume of infarction than normotensive rats independent of the occlusion type (46).

Group comparisons of Glasgow Coma Scale (GCS) and Glasgow Outcome Scale (GOS) scores were performed by using the Kruskal-Wallis test. Subgroup analysis for multiple comparisons was performed by using the Mann-Whitney test with Bonferroni correction. Sex was compared among groups by the chi-square test. Correlation analysis was performed for examining the relationship between GCS and GOS scores and the Spearman correlation coefficient was computed. $P < 0.05$ was set at statistical significance and SPSS 20.0 was used for performing statistical analyses.

In the analysis of our 544 aneurysm series, there was no significant difference with respect to distribution of age between groups ($p=0.285$). There was a significant difference

for sex between the groups ($p < 0.001$). In subgroup analysis, there was a significant difference between Gr1 and Gr2 ($p < 0.001$), Gr1 and Gr4 ($p=0.015$), Gr2 and Gr3 ($p < 0.001$), Gr2 and Gr5 ($p < 0.001$), Gr3 and Gr4 ($p=0.009$), Gr4 and Gr5 ($p=0.005$) and Gr5 and Gr6 ($p=0.017$) but no difference was found between G1 and Gr3 ($p=0.434$), Gr1 and Gr5 ($p=0.228$), Gr1 and Gr6 ($p=0.094$), Gr2 and Gr4 ($p=0.166$), Gr2 and Gr6 ($p=0.147$), Gr3 and Gr5 ($p=0.845$), Gr3 and Gr6 ($p=0.052$), Gr4 and Gr6 ($p=0.069$) (Table I). No difference was found between the groups according to GCS scores ($p=0.295$), but there was a significant difference between the groups according to GOS scores ($p=0.010$). A significant difference was found between Group 1 and Group 5 with respect to subgroup analysis ($p=0.003$) and the GOS score of group 5 was higher than Group 1 (Table II).

Comparisons according to GCS and GOS scores of the groups are given in Table III. There was no difference between the temporary and direct clipped-groups according to the values of GCS and GOS (respectively $p=0.188$, $p=0.162$). A significant relationship between GCS and GOS scores was found according to the results of the correlation analysis ($r=0.37$; $p < 0.001$).

Transient ischemic events contribute to the development of stroke as tissue injury during the ischemic period and as reperfusion injury. Free oxygen radicals play an important role in postischemic tissue injury (58).

Repetitive interruption of blood flow at the onset of tissue perfusion after an ischemic period has been defined as postconditioning (61). The effectiveness of postconditioning in different organs such as the heart, kidney, muscles, skin, and intestinal mucosa were studied (30). Zhao et al. showed that three cycles of 30 seconds interruptions of blood flow in the dog coronary arteries following 60 minutes of ischemia decreased the infarct area from a mean of 47% to 11% (61). Many experimental studies have proven the neuroprotective effects of ischemic postconditioning (6, 54, 62, 63). Hippocampal CA1 neuronal protection by postconditioning was shown by Burda and Danielisová in two different models (7, 11). Jiang and Turkkan proved the value of postconditioning in spinal cord injury models (23, 58).

Taşkapılıoğlu et al. showed that preconditioning, postconditioning, and pre/post conditioning have preventive effects

Table I: Comparison of Groups According to Demographic Variables. Gr₁: MCA, Gr₂: ACoA, Gr₃: Pcomm, Gr₄: BA, Gr₅: other Localisations, Gr₆: Multiple

		Gr ₁ (n=147)	Gr ₂ (n=192)	Gr ₃ (n=59)	Gr ₄ (n=5)	Gr ₅ (n=75)	Gr ₆ (n=66)	p-value
Sex	f/m	85/62	68/124	38/21	0/5	44/21	30/36	<0.001
	Median	50.5	50	51	46	49	53	
Age	Min.-Max.	20-84	12-85	25-85	42-65	16-75	20-74	0.285
	Mean	51.78	49.97	52.77	48.80	47.38	52.03	
	St.Dev.	11.22	12.12	13.41	9.52	13.64	11.39	

MCA: middle cerebral artery, **ACoA:** anterior communicating artery, **Pcomm:** posterior communicating artery, **BA:** basilar artery, **f:** female, **m:** male.

Table II: Comparisons between Groups Based on GCS and GOS Scores

		Gr ₁ (n=147)	Gr ₂ (n=192)	Gr ₃ (n=59)	Gr ₄ (n=5)	Gr ₅ (n=75)	Gr ₆ (n=66)	p-value
GCS	Median	15	15	15	15	15	15	0.295
	Min.-Max.	4-15	5-15	7-15	8-15	7-15	4-15	
	Mean	14.01	14,55	14.56	13.60	14.69	14.35	
	St.Dev.	2.43	1.21	1.28	3.13	1.04	1.84	
GOS	Median	5	5	5	3	5	5	0.010
	Min.-Max.	1-5	1-5	1-5	1-5	1-5	1-5	
	Mean	3.99	4.22	4.17	3.00	4.57	4.21	
	St.Dev.	1.50	1.28	1.25	1.58	1.02	1.22	
Pairwise Comparisons for GOS ($\alpha^*=0.003$)								
	Gr ₁ - Gr ₂ : p=0.328			Gr ₂ - Gr ₃ : p=0.384			Gr ₃ - Gr ₅ : p=0.004	
	Gr ₁ - Gr ₃ : p=0.941			Gr ₂ - Gr ₄ : p=0.029			Gr ₃ - Gr ₆ : p=0.643	
	Gr ₁ - Gr ₄ : p=0.085			Gr ₂ - Gr ₅ : p= 0.013			Gr ₄ - Gr ₅ : p=0.016	
	Gr₁- Gr₅: p=0.003			Gr ₂ - Gr ₆ : p=0.820			Gr ₄ - Gr ₆ : p=0.073	
	Gr ₁ - Gr ₆ : p=0.563			Gr ₃ - Gr ₄ : p=0.084			Gr ₅ - Gr ₆ : p=0.023	

Table III: Comparisons Between GCS and GOS Scores of Groups: 1 Intermitant Clip; 2 Direct Clip

clip	GCS	GOS
1 (n=213)	15 (5-15)	5 (1-5)
2 (n=331)	15 (4-15)	5 (1-5)
p-value	0.188	0.162

against cerebral ischemia in a rat focal cerebral model of ischemia that was induced by suture occlusion of the middle cerebral artery (54).

Ischemic postconditioning mechanisms underlying neuroprotection were thought to be similar to those underlying cardioprotection, which involves decreased neutrophil accumulation and endothelial dysfunction, decreased mitochondrial permeability, decreased apoptotic cell death and phosphatidylinositol 3-kinase pathway activation (63).

Xing et al. reported that six cycles of middle cerebral artery occlusion 30 seconds apart produced neuroprotection via inhibition of apoptosis (60). Danielisova et al. reported that delayed postconditioning, when applied 48 hours after ischemia, provides neuroprotection (11).

Nemethova et al. used a 2 or 3 days of reperfusion followed by 5 minutes of ischemia and another 1 day of reperfusion for detecting the immunoreactivity of antioxidant enzymes and proteins that were related to apoptosis in postconditioning. They showed that the increased expression of antioxidant enzymes and prevention of ischemia-induced increase of the pro-apoptotic protein Bax (37).

There are also growing data about ischemic preconditioning indicating that it not only has a protective effect on the same tissue, but can also express its protection in remote tissues and organs, known as remote ischemic postconditioning (IPC) (29).

There is little knowledge on the mechanism of postconditioning effect. Improvement at the cerebral blood flow, prevention of cytochrome c translocation, activation of protein kinase Akt., and activation of the phosphoinositide 3-kinase-linked pathway have been described in animal models (30). Ren et al. showed that delayed postconditioning with 6 cycles of 15 minutes occlusion/15 minutes release of the ipsilateral common carotid arteries protected against focal ischemia in a rat model (42).

Angina prior to myocardial infarction resulted in smaller infarct size and has been shown to be protective both in the animal model and human studies. (43).

Upregulation of endogenous pathways by stimuli causing trauma in the central nervous system may lead to neuroprotection by increasing the endurance to ischemia or trauma (54). Timely opening of the occluded vessels will provide reperfusion. However, reperfusion injury that may take place through overproduction of free radicals is the pending threat (54).

Cerebral ischemic pre/postconditioning protects against stroke, but is clinically feasible only when the occurrence of stroke is predictable. Stroke development in neurosurgical practice is commonly seen during aneurysm surgery while utilizing temporary clip application. Ischemic tolerance is determined by both the degree of the perfusion defect, and

the duration of ischemia. Prompt recanalisation with shorter duration of ischemic insult will be more beneficial for the viability of the neural tissues (45, 54).

Ischemic preconditioning was first shown to develop days after the first insult. However, Perez-Pinzon et al. then reported that a short time, like 30 minutes, subsequent to the injury was enough for the development of the expected protective effect of the insult (40). A rat model with 2 hours occlusion performed 24 hours after 10 minutes of preconditioning showed a decreased cerebral infarct volume (54).

Similar pathways and molecules take place in pre and postconditioning but their roles and timing are different in each condition (50). Reperfusion injury is expressed as endothelial and microvascular dysfunction, impaired blood flow, metabolic dysfunction, cellular necrosis, and apoptosis (1).

There are some limitations in our series. First, this is a retrospective analysis. There was no statistical difference between intermittent and direct clipped groups in our series but generally temporary clips were used for ruptured and amorphous aneurysms.

In conclusion, repetitive occlusion and release of the main trunk of a vessel during early aneurysm surgery or before long-lasting temporary artery occlusion may protect the brain against later possible vasospasm/ischemia. Studies on the precise temporal characteristics of pre- and postconditioning, or both, in the brain and determination of the presence of a therapeutic role are very important.

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