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Effect of ischemic preconditioning on brain tissue gases and pH during temporary cerebral artery occlusion

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Summary

Previous studies have demonstrated that a brief period of ischemia protect against subsequent severe ischemic insults to the brain, i.e. preconditioning. We evaluated the effects of ischemic preconditioning, produced by 2 min proximal temporary artery occlusion, on brain tissue gases and acidity during clipping of cerebral aneurysm.

Twelve patients with aneurysmal subarachnoid hemorrhage were recruited. All patients received standard anesthetics. After craniotomy, a calibrated multiparameter catheter was inserted to measure oxygen (PtO_2) tension, carbon dioxide ($PtCO_2$) tension and pH (pHt) in tissue at risk of ischemia during temporary artery occlusion. In patients assigned to the preconditioning group, proximal artery was occluded initially for 2 min and was allowed to reperfuse for 30 min. All patients underwent cerebral artery occlusion for clipping of aneurysm. The rate of change in PtO_2, $PtCO_2$ and pHt after artery occlusion were compared between groups using unpaired *t* test.

Baseline brain tissue gases and pHt were similar between groups. Following artery occlusion, the decline in PtO_2 and pHt were significantly slower in the preconditioning group compared with the routine care group.

These results suggested that ischemic preconditioning attenuates tissue hypoxia during subsequent artery occlusion. Brief occlusion of the proximal artery may be a simple maneuver for brain protection during complex cerebrovascular surgery.

Keywords: Cerebral ischemia; ischemic preconditioning; cerebral oxygenation.

Introduction

Ischemic preconditioning refers to an endogenous mechanism for brain protection against ischemia. In this phenomenon, a transient episode of minor cerebral ischemia produces tolerance to subsequent prolonged ischemic injury [2, 3, 6]. Cerebral ischemic preconditioning has been well defined in a variety of animal models after focal or global ischemia [2, 3, 6, 10]. There are however, few data to support the existence of ischemic preconditioning in human. In a number of observational studies, outcomes after ischemic strokes are generally better among patients with preceding transient ischemic attacks (TIAs) in the same vascular territory [1, 8, 11–14]. These data suggested that prodromal TIA induces protective response to subsequent ischemia. However, more recent data refuted these observations [5].

Unfortunately, despite its important therapeutic implications, in vivo ischemic preconditioning cannot be confirmed in TIA model because of the ethical and practical difficulties. However, it is possible to study patients undergoing microsurgical clipping of cerebral aneurysm. During this operation, proximal artery is often occluded temporarily to facilitate surgical dissection of the aneurysm, thus render the distal brain tissue at risk of ischemic damage. We hypothesized that brief episode of ischemia followed by reperfusion confers tolerance to subsequent ischemic injury during temporary artery occlusion. We evaluated the effect of ischemic preconditioning on brain tissue gases and acidity in patients undergoing clipping of cerebral aneurysm.

Materials and methods

After approval from the Clinical Research Ethics Committee, we studied 12 patients undergoing microsurgical clipping of aneurysm following subarachnoid hemorrhage (SAH). Patients were excluded if they were younger than 18 years or if there was a clinical plan not to apply temporary artery occlusion during surgery. Written informed consents were obtained from the patients or their relatives.

All patients received nimodipine infusion 1–2 mg/h. Monitoring included invasive arterial and central venous pressure measurements, electrocardiogram, capnography, pulse oximetry and oesophageal temperature recordings. Anesthesia was induced and maintained with target controlled infusions of propofol (3–4 μg/ml) and remifentanil (6 ng/ml). Neuromuscular blockade was achieved with ro-

curonium infusion (0.5 mg/kg/h). The lungs were ventilated with an air/oxygen mixture to maintain normocarbia. The inspired oxygen concentration was set as 30%. A warming blanket (Bair Hugger 505, Augustine Medical, Eden Prairie, MN) was used to maintain normothermia throughout the procedure.

We measured brain tissue oxygen (PtO_2), carbon dioxide tensions ($PtCO_2$) and acidity (pHt) with a calibrated multiparameter catheter (Neurotrend, Diametrics Medical, Minneapolis, MN). This catheter, 0.5 mm in diameter, incorporated a miniaturized optode electrode, two fibreoptic hydrogen electrodes and a thermocouple for PtO_2, pHt, $PtCO_2$ and brain temperature recordings, respectively. After a standard pteronial craniotomy was performed, the catheter was inserted into the ipsilateral middle frontal gyrus. Thirty minutes of equilibration was allowed. Readings were downloaded on a personal computer using a purposely designed data acquisition program.

Patients were randomly assigned to receive either ischemic preconditioning or routine care. In patients allocated to the preconditioning group, proximal feeding artery was briefly clamped for 2 min using a specifically designed, low-force, vascular clip. This was followed by 30 min reperfusion. In patients allocated to the routine care group, artery was exposed but not clamped. All patients then underwent cerebral artery occlusion for clipping of aneurysm. Immediately prior to artery occlusion, a bolus dose of thiopentone 2–3 mg/kg was given IV to produce electroencephalographic burst suppression. Arterial pressure was maintained within 20% of baseline using phenylephrine infusion. All patients were reviewed again one week after surgery for any development of new neurologic deficit.

The primary outcome measure in this study was the rate of change in PtO_2, $PtCO_2$ and pHt. As the delivery of substrates was interrupted with artery occlusion, a change in tissue gases and acidity is a measure of tissue vulnerability to ischemia. Therefore, a steep change in tissue gases or acidity indicates rapid depletion of intracellular substrate and accelerated energy failure. We calculated the rate of change in PtO_2, $PtCO_2$ and pHt during the first four minutes after temporary artery occlusion using linear regression. Values were compared between groups using Mann-Whitney test. Results are presented as median (range). A P value of less than 0.05 was considered significant.

Results

All twelve patients completed the study. Patient characteristics are listed in Table 1. Demographic data in the preconditioned patients were similar to that receiving routine care. The median (range) time from SAH to surgery was 47 (28–81) h in the preconditioned group and 53 (30–77) h in the routine care group, $P = 0.54$. The median (range) duration of temporary artery occlusion in the preconditioned group, 7.5 (6.1–13.6) min was also similar to that in the routine care group, 6.8 (5.0–15.1) min, $P = 0.73$. There was no intraoperative complication.

Following catheter equilibration, baseline values in the preconditioned group, pHt 7.11 (7.05–7.30), PtO_2 17 (13–29) mmHg, $PtCO_2$ 49 (32–58) mmHg, were similar to that in the routine care group, pHt 7.15 (7.03–7.28), PtO_2 20 (12–26) mmHg, $PtCO_2$ 53 (35–60) mmHg. After temporary artery occlusion, PtO_2 and pHt decreased and $PtCO_2$ increased in all patients (Fig. 1). But the rate of change in PtO_2 and pHt in the preconditioned patients was significantly slower than the controls (Fig. 2). However, the difference in the rise of $PtCO_2$ was small and was not statistically significant. PtO_2 in all patients receiving routine care fell below 10 mmHg before release of temporary artery occlusion, whereas only two of the preconditioned patients had ischemic change in PtO_2. A week after surgery, only one patient the routine care group had neurologic deficit. Proximal artery was occluded for 9 min in this patient. There was no adverse effect associated with catheter insertion.

Table 1. *Patient characteristics and severity of subarachnoid hemorrhage*

	Routine care	Ischemic preconditioning	*P* Values
No. of patients	6	6	
Age (year)	58 (38–72)	53 (40–69)	0.76
Body weight (kg)	72 (44–81)	59 (41–85)	0.89
Gender (Male/Female)	3/3	4/2	0.18
WFNS grade ≤ 3	3	4	0.80
Fisher's grade ≤ 3	4	3	0.82
Medical history			
– Hypertension	5	6	1.00
– Diabetes mellitus	4	3	0.37
– Current smoker	3	4	0.37
Location of ruptured aneurysm			
– Anterior cerebral artery	4	3	0.37
– Middle cerebral artery	2	3	

Values are median (range) or number of patients. *WFNS* World Federation of Neurological Surgeons.

Discussion

This study confirms the existence of ischemic preconditioning in humans. The changes in brain tissue gases and acidity suggested that the preconditioned patient will tolerate a longer period of ischemia during temporary artery occlusion for clipping of cerebral aneurysm. We are however, unable to detect a better outcome after ischemic preconditioning, mainly due to the small sample size. A larger study recruiting over 380 patients will be required to demonstrate the efficacy and safety of ischemic preconditioning during aneurysm surgery.

Ischemic preconditioning has been extensively evaluated in a number of animal models [2, 3, 6, 10]. On

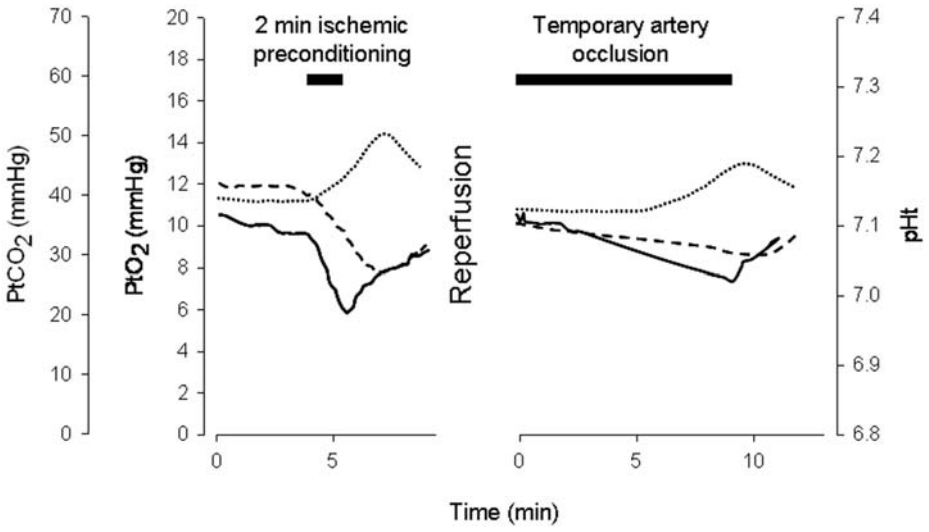

Fig. 1. Changes in tissue oxygen (PtO_2, *solid line*), carbon dioxide tension ($PtCO_2$, *dotted line*), and acidity (*pHt*, *dashed line*) following 2 min ischemic preconditiong, 30 min reperfusion and then temporary artery occlusion for clipping of cerebral aneurysm

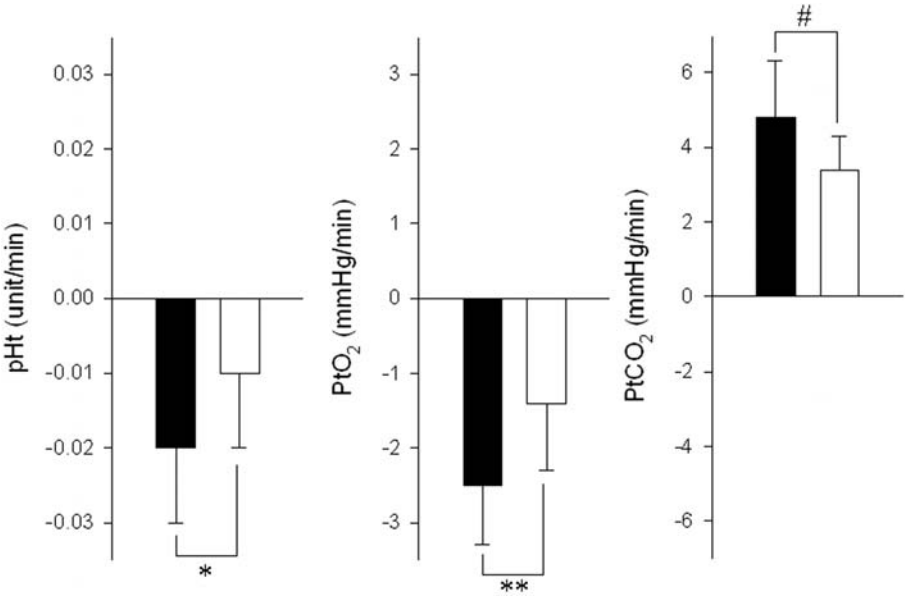

Fig. 2. Rate of change in tissue oxygen (PtO_2), carbon dioxide tension ($PtCO_2$) and acidity (pHt) after temporary artery occlusion in patients receiving prior ischemic preconditioning (black bar) or routine care (empty bar). $*P = 0.02$; $**P = 0.04$; $\#P = 0.07$

average, preconditioning with focal or global ischemia of 2–20 min duration, reduced the infarct size by 53% (range 20–91%) after subsequent prolonged ischemia [8]. While there is little difference among animal species, treatment efficacy depends largely on the duration of ischemia during induction of preconditioning and the interval to subsequent ischemia [2, 3, 6, 9, 10]. In the present study we induced preconditioning by 2 min proximal artery occlusion. This is followed by an inter-ischemic reperfusion for 30 min. This experimental paradigm is feasible during clinical practice and has been shown to produce the maximum protection against prolonged ischemia in rats [9].

The clinical evidence for ischemic preconditioning remains scanty in humans. The traditional TIA model suggested that prior occurrence of TIA decreases the severity of subsequent stroke [1, 8, 11–14]. However, it is not known whether the diverse etiologies of stroke

may have biased the findings. A recent study of 180 patients with TIA and subsequent stroke within the next 90 days, showed no correlation between timing or duration of TIA and disability of subsequent stroke [5]. Nevertheless, the application of the TIA model is limited because neither the TIA itself nor the subsequent stroke can be staged. The use of ischemic preconditioning is more encouraging during proximal temporary artery occlusion for aneurysm surgery. Two observational studies suggested that repetitive brief occlusion of the proximal artery with intermittent reperfusion reduces the risk of stroke compared with uninterrupted ischemia of similar duration [4, 7]. Our data are in accord with these findings that brief occlusion of the proximal artery induces ischemic tolerance.

The underlying mechanism of ischemic preconditioning remains unclear. However, *N*-methy-D-asparate receptor activation would appear to be the primary event during induction of preconditioning [2, 3, 6, 10]. Subsequent delayed protection is best explained by genetic remodeling [2, 6, 10].

In conclusion, a brief (2 min) proximal artery occlusion induces tolerance to subsequent ischemia, 30 min apart. This is a simple and effective technique for brain protection when prolonged proximal artery occlusion is required during complex aneurysm surgery.

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