Preconditioning With Repeated Hyperbaric Oxygen Induces Myocardial and Cerebral Protection in Patients Undergoing Coronary Artery Bypass Graft Surgery: A Prospective, Randomized, Controlled Clinical Trial

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Objectives: To evaluate the cerebral and myocardial protective effects of hyperbaric oxygen preconditioning in both on-pump and off-pump coronary artery bypass graft surgery.

Design: A prospective, randomized, single-blinded study including patients scheduled for elective on-pump or off-pump surgery between December 2007 and February 2009.

Setting: A tertiary care university teaching hospital.

Participants: Forty-nine elective on-pump or off-pump coronary artery bypass graft surgery patients.

Interventions: Patients were randomized to either the control (15 patients with on-pump procedure and 10 patients with off-pump procedure, respectively) or hyperbaric oxygen (HBO; 14 patients with on-pump procedure and 10 patients with off-pump procedure, respectively) groups. Patients in the HBO groups underwent preconditioning for 5 days before surgery.

Measurements and Main Results: On-pump coronary artery bypass graft surgery patients preconditioned with HBO had significant decreases in S100B protein, neuron-specific enolase, and troponin I perioperative serum levels compared with the on-pump control group. Postoperatively, patients in the on-pump HBO group had a reduced length of stay in the intensive care unit and a decreased use of inotropic drugs. Serum catalase activity 24 hours postoperatively was significantly increased compared with the on-pump control group. In the off-pump groups, there was no difference in any of the same parameters.

Conclusions: Preconditioning with HBO resulted in both cerebral and cardiac protective effects as determined by biochemical markers of neuronal and myocardial injury and clinical outcomes in patients undergoing on-pump coronary artery bypass graft surgery. No protective effects were noted in off-pump coronary artery bypass graft surgery.

KEY WORDS: cerebral protection, ischemia/reperfusion, myocardial protection, hyperbaric oxygen, preconditioning, coronary artery bypass graft surgery

Despite advances in surgical techniques and anaesthetic management, ischemia-reperfusion injury remains an inevitable event of cardiac surgery, resulting in significant postoperative complications and multiple-organ dysfunction. To date, brain injury after cardiopulmonary bypass (CPB) for cardiac surgery has been well documented. Sequela can be as mild as postoperative cognitive dysfunction and postoperative delirium and as severe as stroke.1 The etiology of cerebral injuries probably represents a complex interaction among cerebral microemboli, global cerebral hypoperfusion, inflammation, cerebral temperature modulation, genetic susceptibility, and ischemia-reperfusion injury.2 Ischemia-reperfusion injury during CPB also leads to myocardial stunning, necrosis, or apoptosis that manifest clinically either acutely as low cardiac output or chronically as heart failure.3

Preconditioning is the application of an intervention to activate endogenous protective mechanisms to potentially lessen the morphologic and functional sequelae of a subsequent ischemia insult. The phenomenon of ischemic preconditioning was first described in a canine myocardium ischemia-reperfusion injury model4 and subsequently was shown in the brain.5 Since then, intense research in the field of pharmacology ensued to identify agents such as volatile anaesthetic agents6,7 and ischemic preconditioning8-10 that could duplicate the protective effects of preconditioning after cardiac surgery.

Animal studies have shown that the hyperbaric oxygen (HBO) preconditioning could induce ischemia tolerance, resulting in protection against myocardial or central nervous system ischemia.11-18 Reactive oxygen species induced by HBO preconditioning may play an important role in providing myocardial protection during interventions that involve an inevitable episode of ischemia-reperfusion injury, whether in the setting of thrombolysis, percutaneous coronary angioplasty, or cardiac surgical revascularization.13 Previous reports from the authors’ laboratory showed that HBO preconditioning caused the activation of antioxidative enzymes and related genes in the central nervous system, including catalase (CAT), superoxide dismutase, and heme oxygenase-1.14-17 Despite the increasing number of basic science publications on this issue, studies describing HBO preconditioning in the clinical practice of cardiac surgery remain scarce. Clinical studies showed that using HBO as an adjunct treatment in patients with either acute myocardial infarction or undergoing a percutaneous coronary intervention improved myocardial function and reduced clinical restenosis.19-22 To date, only a few studies have investigated the preconditioning effects of HBO in the human brain and myocardium. In 2005, Alex et al22 observed that repetitive pretreatment with 3 sessions of HBO before on-pump coronary artery bypass graft (CABG) surgery reduced neuropsychometric dysfunction and modulated the inflammatory response after CPB. More recently, Yogaratnam et al23 reported that preconditioning with 1 session of HBO before on-pump CAGB surgery improved left ventricular stroke work post-CABG surgery while reducing intra-

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PRECONDITIONING WITH HBO

operative blood loss, intensive care unit (ICU) length of stay, and postoperative complications.

Presently, it remains unclear whether repetitive HBO preconditioning has a clinical protective effect against cerebral or myocardium injury in on-pump CABG surgery patients and whether this modality of preconditioning has the same protective effect for patients undergoing off-pump CABG surgery. Based on the previously described available laboratory and clinical evidence, the authors of this study hypothesized that repeated HBO preconditioning would induce both myocardial and cerebral protective effects in patients undergoing either on-pump or off-pump surgery. The objective of this study was to determine whether HBO preconditioning could decrease the release of cerebral and myocardial biochemical markers such as S100B protein, neuron-specific enolase (NSE), and troponin I (cTnI) in the peri- and post-CABG surgery period. The primary endpoint of this study was to show that repeated HBO preconditioning leads to a statistically significant ($p < 0.05$) decrease in the release of S100B and NSE. The secondary endpoints of this study were to assess the effects of HBO preconditioning on serum troponin I, inotrope usage, ventilator hours, length of ICU stay, postoperative length of hospital stay, hemodynamic parameters, and serum CAT activity.

METHODS

This study was performed according to the Declaration of Helsinki and relevant Chinese laws. The study protocol was approved by the Ethics Committee of Xijing Hospital (approval number 200712315) and was registered on ClinicalTrials.gov (http://clinicaltrials.gov/) with the registration number NCT00817791. All subjects provided written informed consent before inclusion in the study.

Between December 2007 and February 2009, 51 patients scheduled to undergo first-time elective CABG surgery with the use of either CPB (on-pump) or off-pump CABG surgery were recruited. Exclusion criteria included concomitant aortic or valvular surgery, female sex, emergency procedures, age >80 years, ejection fraction (EF) <35%, previous cerebrovascular disease, claustrophobia, history of pneumothorax, middle ear disease, repeat CPB, and repeat thoracotomy either during or after the procedure.

Sample size calculations were based on detecting differences among treatment groups in the changes of S100B and NSE from the initial to the end of the HBO preconditioning session. The primary objective was to determine whether HBO preconditioning could decrease the release of cerebral and myocardial biochemical markers such as S100B protein, neuron-specific enolase (NSE), and troponin I (cTnI) in the peri- and post-CABG surgery period. The primary endpoint of this study was to show that repeated HBO preconditioning leads to a statistically significant ($p < 0.05$) decrease in the release of S100B and NSE. The secondary endpoints of this study were to assess the effects of HBO preconditioning on serum troponin I, inotrope usage, ventilator hours, length of ICU stay, postoperative length of hospital stay, hemodynamic parameters, and serum CAT activity.

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Pre-, peri-, and postoperative clinical data for the study population were collected. Inotrope scores at different times after ICU arrival were calculated as dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100) + isoprenaline (×100). The total inotrope dose was calculated by adding the doses of dopamine and other drugs (in μg/min) and assigning an equivalent value for each inotropic drug. For example, the dose of 10 μg/kg/min of dopamine was assigned an equivalent value for each 0.1 μg/kg/min of epinephrine. Hemodynamic parameters including heart rate (HR), mean arterial blood pressure (MAP), central venous pressure (CVP), pulmonary arterial pressure (PAP), pulmonary arterial wedge pressure (PAWP), and cardiac output (CO) were measured at different time points from preinduction to ICU arrival using a pulmonary artery catheter during surgery.

SPSS version 10.0 for Windows was used for statistical analysis (SPSS Inc, Chicago, IL). All continuous variables were expressed as mean ± standard error, and discrete variables were presented as frequencies and percentages. Analysis of categoric variables was performed with the chi-square test. Analysis of continuous variables was performed with the independent t test and a 2-way analysis, and multiple comparisons were made with post hoc least significant difference comparisons. A value of p < 0.05 was considered statistically significant.

RESULTS

A total of 51 patients initially were enrolled in the study. One patient undergoing on-pump CABG surgery in the control group subsequently was excluded because of an intraoperative event of blood loss necessitating secondary CPB. Another patient undergoing off-pump CABG surgery in the HBO group withdrew from the study because of ear pain during the 1st HBO session. Therefore, data were available from 49 patients. Perioperative data in the on-pump or off-pump CABG groups have been summarized in Table 1.
No surgical deaths occurred, and no patient suffered stroke and/or transient ischemic attack, but 1 patient who underwent the on-pump procedure in the control group and 1 patient who underwent the off-pump procedure in the HBO group experienced postoperative delirium. One patient who underwent the on-pump procedure in the control group required transient postoperative inotropic support with an intra-aortic balloon pump because of hemodynamic instability.

There was no difference between the HBO group and the control group in mechanical ventilation time and the length of stay in patients who underwent the on-pump or off-pump procedure (Fig 2). The ICU length of stay in the HBO group was significantly shorter than in the control group in patients who underwent the on-pump procedure (85.9 ± 10.8 hours v 59.4 ± 5.8 hours, p < 0.05, Fig 2). In patients who underwent the off-pump procedure, the ICU length of stay was not significantly different between the HBO and control groups.

No differences in hemodynamic parameters, including HR, MAP, CVP, PAP, PAWP, and CO, were identified among groups of patients who underwent on-pump (Fig 3) or off-pump (Fig 4) procedures. In patients who underwent on-pump surgeries, inotropic scores in the HBO group at 24 and 36 hours after ICU arrival (10.2 ± 1.1 and 9.6 ± 1.1 μg/kg/min, respectively) were lower than the inotropic scores in the control group (6.9 ± 0.8 and 6.7 ± 0.8 μg/kg/min, respectively, p < 0.05, Fig 5). There were no significant differences in inotropic scores during the first 48 hours after arrival in the ICU between the control and HBO groups of patients who underwent off-pump surgery.

In patients who underwent on-pump surgery, the serum S100B concentration 1 hour after cross-clamp removal and at the time of ICU arrival (82.18 ± 11.45 and 60.42 ± 8.8 pg/mL, respectively) was significantly lower in the HBO group compared with the control group (138.21 ± 9.66 and 89.74 ± 4.4 pg/mL, respectively; p < 0.01, Fig 6). Serum NSE concentrations measured from 6 hours to 24 hours postoperatively (35 ± 3.14, 31.85 ± 2.4, and 30.3 ± 2.04 ng/mL) were decreased significantly in the HBO group compared with the control group (43.7 ± 2.38, 39.41 ± 2.09, and 37.99 ± 2.54 ng/mL, p < 0.05, Fig 6). In contrast, serum S100B and NSE concentrations were similar between the HBO and the control group at the different test points in the groups of patients who underwent off-pump surgery (Fig 6).

Serum cTnI levels in the on-pump HBO group were significantly lower at all 6 time points (from 1 hour after cross-clamp removal to 48 hours postoperatively) compared with the on-pump control group (p < 0.05, Fig 7). In patients who underwent off-pump surgery, there

![Fig 2](image-url)  
Comparison of the primary clinical outcomes in the HBO and control groups of patients who underwent either on-pump or off-pump surgery. Data were presented as mean ± standard error (range bars); *p < 0.05 compared with the control group. Abbreviations: ICU LOS, the length of ICU stay; post-op LOS, the length of postoperative hospital stay; Ven-support, ventilation support time. (Color version of figure is available online.)
was no significant difference in serum cTnI levels between the HBO and control groups \((p > 0.05, \text{Fig } 7)\).

Finally, serum CAT activity increased from \(1.31 \pm 0.29 \text{ U/mL} \) preoperatively to \(3.73 \pm 0.46 \text{ U/mL} \) postoperatively in the on-pump control group \((p < 0.01)\) and from \(1.74 \pm 0.38 \text{ U/mL} \) to \(6.1 \pm 0.62 \text{ U/mL} \) in the on-pump HBO group \((p < 0.01)\). Serum CAT activity was higher 24 hours postoperatively in the on-pump HBO group than the on-pump control group \((p < 0.01)\). There was no difference in CAT activity at any time points either within or between the 2 off-pump groups (Fig 8).

**DISCUSSION**

To the authors’ knowledge, the current study is the first clinical trial to assess the cardiac and neurologic protective effects of repeated HBO preconditioning in on-pump and off-pump CABG surgery patients. Some clinical studies have evaluated the protective effects of HBO preconditioning in patients undergoing on-pump CABG surgery. In 2005, for example, Alex et al\(^22\) observed that 3 HBO sessions at 24, 12, and 4 hours before CPB could reduce neuropsychometric dysfunction and modulate inflammatory responses after CPB. Yogaratnam et al\(^23\) reported that preconditioning with 1 session of HBO before on-pump CABG surgery improved left ventricular stroke volume after CABG surgery, reduced intraoperative blood loss, decreased ICU length of stay, and minimized postoperative complications. Previous studies conducted by the authors of the current study found that 5 days of HBO preconditioning performed before spinal ischemia resulted in improved neurologic and histopathology outcomes compared with only 3 days of HBO preconditioning in a rabbit model.\(^{14,15}\) This provided the rationale for selecting 5 sessions of HBO preconditioning in the present study.

Compared with the previously cited clinical studies, there are 3 novel findings in the present study. First, repeated preconditioning by HBO (five 70-minute sessions conducted once per day at 2.0 ATA) reduced the release of S100B, NSE, and cTnI during and after CPB in patients undergoing on-pump CABG surgery. In turn, the patients’ clinical outcomes, such as the length of ICU stay and the use of inotropic drugs postsurgically, were improved. Second, HBO preconditioning activated a protective pathway involving the antioxidative effect (determined by an increase in CAT activity), which could be linked to the observed beneficial effects. Finally, HBO preconditioning had no protective effect in patients undergoing off-pump CABG surgery.

There are conflicting results regarding the estimation of brain injury after cardiac surgery by the neurobiochemical markers of S100B and NSE.\(^{28-30}\) The half-life of S100B in blood is 25 minutes; therefore, S100B and NSE levels could at least partly reflect cerebral injury postsurgically. On the basis of this pathophysiologic background, S100B and NSE were used to assess the cerebral effects of HBO preconditioning in patients undergoing elective CABG surgery. These results showed significant differences in S100B 1 hour after the removal of the clamp and upon arrival in the ICU. Significant differences in serum NSE levels also were found postoperatively in patients undergoing on-pump CABG surgery.
CABG surgery who were preconditioned using HBO. No significant differences in S100B and NSE levels were noted in the control and HBO groups of patients who underwent off-pump CABG surgery. Thus, CPB is a crucial factor. A study by Bonacchi et al. reported a strong correlation between CPB time and the release of S100B and NSE. The correlation between HBO preconditioning and neuronal biomarkers may suggest a link between the anti-inflammatory or antioxidative action of HBO preconditioning and the release of biomarkers or neuronal clinical or subclinical injury.

The results of the current study found that patients undergoing the on-pump procedure who were preconditioned with HBO had a significantly shorter stay in the ICU, which was consistent with the results of Yogaratnam et al. These results were also similar to those of Sharifi et al. who reported that using HBO before or immediately after a percutaneous coronary intervention could reduce clinical restenosis and had a statistically significant reduction in composite adverse cardiac events. In contrast to Yogaratnam et al. who reported that HBO preconditioning did not decrease postoperative cTnT release statistically in patients undergoing CABG surgery who were preconditioned using HBO, significant differences in S100B and NSE levels were noted in the control and HBO groups of patients who underwent off-pump CABG surgery. Thus, CPB is a crucial factor. A study by Bonacchi et al. reported a strong correlation between CPB time and the release of S100B and NSE. The correlation between HBO preconditioning and neuronal biomarkers may suggest a link between the anti-inflammatory or antioxidative action of HBO preconditioning and the release of biomarkers or neuronal clinical or subclinical injury.

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on-pump CABG surgery, this study found that in patients undergoing on-pump CABG surgery, cTnI release in the HBO group was reduced compared with the control group from 1 hour after cross-clamp removal to 24 hours after surgery. This decrease in cTnI release suggests that HBO preconditioning could prevent myocardial injury induced by CPB. There were no significant differences in cTnI release between patients in the HBO and control group who underwent off-pump CABG surgery. It is possible that the difference between the Yogaratnam et al’s study and the current study relates to the repetitive HBO preconditioning sessions used in this study compared with the single preconditioning used by Yogaratnam et al. In the current study, the measured hemodynamic parameters were not clinically or statistically different in the patients who were preconditioned with 5 sessions of HBO and subsequently underwent either on-pump or off-pump CABG surgeries. Whether preconditioning protocol factors such as pressure, frequency, or time before surgery contributed to the different results should be investigated in further studies.

Previous studies from the authors’ laboratory16,17 and other studies32 indicated that HBO preconditioning could induce ischemic tol-

![Fig 6. Changes in serum S100B and NSE levels in patients who underwent either on-pump or off-pump surgery. Data were presented as mean ± standard error (range bars); *p < 0.01; #p < 0.05 compared with the control group. Abbreviations: post-op, postoperative; pre-indu, preinduction of anesthesia; pre-CPB, before CPB onset; removal, after cross-clamp removal. (Color version of figure is available online.)](image)

![Fig 7. Changes in serum cTnI levels in patients who underwent either on-pump or off-pump surgery. Data were presented as mean ± standard error (range bars); *p < 0.05 compared with the control group. Abbreviations: post-op, postoperative; pre-indu, preinduction of anesthesia; pre-CPB, before CPB onset; removal, after cross-clamp removal. (Color version of figure is available online.)](image)
erance against cerebral and spinal cord ischemia through upregulation of a series of antioxidant enzymes and related genes. The current study further confirmed the involvement of antioxidants by measuring serum CAT release before and subsequent to surgery. Serum CAT activities in patients in the HBO group were increased significantly compared with the control group in on-pump CABG patients 24 hours postsurgically. Therefore, it is possible that, by preconditioning patients with HBO, an endogenous antioxidative protective pathway was initiated when patients subsequently were exposed to a further robust release of reactive oxygen species, as occurs during CPB surgery. The reactive oxygen species scavenging ability was improved by HBO preconditioning.

The systemic increase in oxidative stress during on-pump CABG surgery has been well documented. \textsuperscript{33} CPB causes the release of superoxide by the xanthine-oxidase system. \textsuperscript{34} Luyten et al\textsuperscript{35} reported that the total antioxidant capacity had a maximum increase of 60%. This finding was consistent with the current study in that the CAT activity was significantly elevated 24 hours after surgery compared with the time point of preinduction in patients undergoing on-pump procedures in both subgroups.

HBO preconditioning appears to have no protective effects for patients undergoing off-pump CABG surgery. This study found that almost all of the outcome measures (such as clinical outcomes and biochemical markers) were not statistically different between the 2 subgroups of patients who underwent off-pump CABG surgery. Previous studies showed that off-pump surgery is a more physiologic and less traumatic procedure associated with less cardiac cTnI release and lower oxidative stress than on-pump CABG surgery. \textsuperscript{34,36} Derkach et al\textsuperscript{37} reported that patients undergoing off-pump CABG surgery had shown no increase in the concentration of either S100B or NSE. Therefore, the protective effects of HBO preconditioning may only manifest when there is a relatively severe injury, such as on an off-pump procedure and not in off-pump CABG surgery patients.

There were several limitations to the present study. First, the small sample size inherently limited interpretation of the results; however, to prevent the bias caused by recruitment, the operative and perioperative factors were standardized as much as possible. Previous studies suggested that women were at higher risk for perioperative neurologic deficits and result in poorer surgical outcomes than men. \textsuperscript{38,39} Although both men and women can be preconditioned, the phenomenon of a sex-specific response to a variety of preconditioning occurs in experimental myocardial or cerebral ischemia. Women may require a more substantial injury stimulus to become preconditioned. \textsuperscript{40} Kitano et al\textsuperscript{41} found that the neuroprotective effect of isoflurane preconditioning administered to male mice before middle cerebral artery occlusion was not observed in female mice and, indeed, potentiated injury in adult female mice. To avoid the influence of sex, female patients were excluded from this study. Nonetheless, the small sample size and early postoperative clinical outcomes of patients in the present study were not clinically sufficient to evaluate the effects on the reduction of morbidity and mortality. A final determination of effect would need to include a larger sample size and a long-term clinical outcomes assessment and would need to be a multicenter study. In addition, only 2 biochemical markers (S100B and NSE) were measured to assess cerebral injury in this study. It is unknown whether this observed decrease in biochemical indices of neurologic injury is correlated with improved function outcome. To further evaluate the neuroprotective effects of HBO preconditioning, other assessment methods of brain injury after cardiac surgery, such as magnetic resonance imaging and cognitive functions, would need to be performed in future studies.

In conclusion, this study revealed that nonischemic preconditioning with HBO reduced the elevation of biomarkers of neurologic and cardiac injury and improved clinical outcomes in patients undergoing on-pump CABG surgery. The protective effects of HBO preconditioning may be associated with the endogenous antioxidant activity. In this study, HBO preconditioning had no protective effects in patients undergoing off-pump CABG surgery.

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