Graded Increased Oxygen Administration Improved Oxygenation and Mitigated Oxidative Stress after Resuscitation from Severe Hemorrhagic Shock

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ABSTRACT

Background: The optimal oxygen administration strategy during resuscitation from hemorrhagic shock (HS) is still controversial. Improving oxygenation and mitigating oxidative stress simultaneously seem to be contradictory goals. To maximize oxygen delivery while minimizing oxidative damage, the authors proposed the notion of gradually increased oxygen administration (GIOA), which entails making the arterial blood hypoxemic early in resuscitation and subsequently gradually increasing to hyperoxia, and compared its effects with normoxic resuscitation, hyperoxic resuscitation, and hypoxemic resuscitation in severe HS.

Methods: Rats were subjected to HS, and on resuscitation, the rats were randomly assigned to four groups (n = 8): the normoxic, the hyperoxic, the hypoxemic, and the GIOA groups. Rats were observed for an additional 1 h. Hemodynamics, acid–base status, oxygenation, and oxidative injury were observed and evaluated.

Results: Central venous oxygen saturation promptly recovered only in the hyperoxic and the GIOA groups, and the liver tissue partial pressure of oxygen was highest in the GIOA group after resuscitation. Oxidative stress in GIOA group was significantly reduced compared with the hyperoxic group as indicated by the reduced malondialdehyde content, increased catalase activity, and the lower histologic injury scores in the liver. In addition, the tumor necrosis factor-α and interleukin-6 expressions in the liver were markedly decreased in the GIOA group than in the hyperoxic and normoxic groups as shown by the immunohistochemical staining.

Conclusions: GIOA improved systemic/tissue oxygenation and mitigated oxidative stress simultaneously after resuscitation from severe HS. GIOA may be a promising strategy to improve resuscitation from HS and deserves further investigation. (Anesthesiology 2015; 123:1122-32)

What We Already Know about This Topic

- Improving oxygenation and mitigating oxidative stress simultaneously during resuscitation from severe hemorrhagic shock seem to be contradictory goals.
- This study tested a candidate resuscitation strategy: gradually increased oxygen administration, which involves making the arterial blood hypoxemic during the early moments of resuscitation, followed by a gradual increase to a hyperoxic state. The authors hypothesized that gradually increased oxygen administration would improve oxygenation without enhancing oxidative stress during resuscitation.

What This Article Tells Us That Is New

- Gradually increased oxygen administration improved systemic/tissue oxygenation and mitigated oxidative stress simultaneously after resuscitation from severe hemorrhagic shock.

EMORRHAGIC shock (HS) remains a major cause of death in trauma patients.1,2 Intravascular volume and oxygen delivery are impaired during HS.3 Common treatment algorithms involve immediate bleeding control, appropriate fluid resuscitation, and adequate oxygen administration.4-7 Oxygen administration is supposed to alleviate the adverse effects of hypoxemia and tissue hypoxia. Hyperoxic resuscitation, which can be achieved by breathing a high fraction of inspiration oxygen (FiO2), was reported to increase blood pressure, ameliorate the acid–base balance, and increase tissue oxygen partial pressure.8-10 Currently, hyperoxic resuscitation is generally applied during the clinical management of HS.11-13 However, researchers and clinicians are more aware of the damage that oxygen may cause. Heckbert et al.14 reported that among those who survived more than or equal to 24 h after resuscitation from HS, 39% developed infection and 24% developed organ failure. Considerable evidence suggests that the burst of oxygen-derived free radicals as a result of hyperoxia is a major contributing factor to the pathogenesis of damage and dysfunction secondary to HS and subsequent resuscitation.11,15-18 To minimize oxidative injury, research has been carried out regarding a novel oxygen administration strategy called hypoxemic resuscitation, which is the gradual acclimatization from hypoxemia to normoxia.19-22 It was believed that by reducing oxygen substrate...
for free radical production, oxidative stress can be limited. However, although hypoxic resuscitation might alleviate oxidative injury, as its name implies, the amount of oxygen provided is likely to be inadequate, which might counteract the beneficial effects on survival. Overall, the optimal medical oxygen administration strategy is still controversial, and improving oxygenation and mitigating oxidative stress simultaneously during resuscitation from severe HS seem to be contradictory goals. To balance the benefits and the harms associated with hyperoxia and hypoxemia, the authors proposed and tested a candidate resuscitation strategy: gradually increased oxygen administration (GIOA), which involves making the arterial blood hypoxemic during the early moments of resuscitation and followed by a gradual increase to a hyperoxic state. We hypothesized that GIOA would improve oxygenation without enhancing oxidative stress, and this procedure was compared with normoxic resuscitation, hyperoxic resuscitation, and hypoxicemic resuscitation.

Materials and Methods

Animals

The study was approved by the Institutional Animal Care and Use Committee of the Academy of Military Medical Sciences (IACUC No: AMMS-2013-016) and was conducted in adherence to the Guide for the Care and Use of Laboratory Animals. Adult male Wistar rats (280 to 340 g body weight) were purchased from Vital River (Beijing, China) and housed in a controlled environment with a 12-h light/dark cycle. The animals fasted overnight with ad libitum water.

Surgical Procedures

The rats were anesthetized with an intraperitoneal injection of 50 mg/kg sodium pentobarbital and placed in a supine position on a warming pad (TMS-202, Softron, Beijing, China) that was maintained at 37° ± 0.1°C throughout the experiment. Supplemental doses of 10 mg/kg sodium pentobarbital were given at 30 min after the initiation of resuscitation and followed by a gradual increase to a hyperoxic state. We hypothesized that GIOA would improve oxygenation without enhancing oxidative stress, and this procedure was compared with normoxic resuscitation, hyperoxic resuscitation, and hypoxicemic resuscitation.

Experimental equipment. Subsequently, the central vein was exposed, isolated, and cannulated with polyethylene catheter (Tuoren Medical, Beijing, China) through the superior vena cava. The two femoral arteries and the left femoral vein were used to withdraw blood for the measurement of central venous blood gas.

Arterial and central venous blood gases were measured using a blood gas analyzer (ABL90, Radiometer, Copenhagen, Denmark) after stabilization (baseline [BL]), after the induction of HS (post-HS), after completion of resuscitation (PR), and 1-h postresuscitation (1-h PR). The abdominal skin right above the liver was incised, and then the probe was inserted 5 mm into the liver. The tissue temperature was also measured for temperature compensation.9

HS Model

After surgical preparation, the rats were allowed a 10-min stabilization period. HS was induced by bleeding the animals at the rate of 0.4 ml/min to achieve a mean arterial pressure (MAP) of 38 mmHg using a syringe pump (LZS-AJ10, Softron). MAP was thereafter maintained at 35 to 40 mmHg for 1 h by reinfusion of the shed blood or further withdrawal at the rate of 0.3 ml/min. The rats were spontaneously breathing room air during HS.

Resuscitation and Observation

At the end of HS, the rats were randomly assigned to one of four groups: the normoxic group in which the FiO2 was 0.21; the hyperoxic group in which the FiO2 was 0.5; the hypoxicemic group in which the FiO2 increased from 0.11 to 0.21 by 0.02 per 10 min; and the GIOA group in which the FiO2 increased from 0.11 to 0.21 by 0.02 per 5 min and from 0.21 to 0.50 by 0.05 per 5 min (fig. 1).

Immediately after shock, the animals were resuscitated by first returning all of the collected blood at the rate of 0.4 ml/min, followed by administering twice the shed blood volume as lactated Ringer’s solution warmed at 37°C at the rate of 0.8 ml/min. The resuscitation period lasted for 1 h, and the animals were observed for an additional 1 h.

During resuscitation, the rats breathed spontaneously through a cone mask connected to 2 flowmeters (FL-3610ST and FL-3610C, OMEGA, Stamford, CT). One flowmeter was connected to oxygen and the other to nitrogen, and different oxygen concentrations were achieved by adjusting the flowmeters. Total flow was set as 900 ml/min, making sure that rats received oxygen at the specific FiO2 we set. The flow did not affect the normal breathing of the rats.

At the end of the experiment, the animals were killed by a lethal intravenous dose of sodium pentobarbital. The liver tissues were harvested and stored in liquid nitrogen for further processing.

Measurements and Calculations

MAP, pulse pressure (PP), and heart rate (HR) were recorded using a multiple-channel recorder (MP150 Research System, Biopac System Inc., Montreal, Canada) every 10 min during HS and resuscitation and every 30 min during observation. The PltO2 was recorded at the same time point.

Arterial and central venous blood gases were measured using a blood gas analyzer (ABL90, Radiometer, Copenhagen, Denmark) after stabilization (baseline [BL]), after the induction of HS (post-HS), after completion of resuscitation (PR), and 1-h postresuscitation (1-h PR).
Liver malondialdehyde content, superoxide dismutase (SOD) activity, catalase activity, and myeloperoxidase activity were determined using detection kits (A003-1, A001-3, A007-1, and A004, respectively) purchased from Nanjing Jiancheng Bioengineering Institute (Jiangsu, China). Liver tissue was homogenized in cold normal saline to prepare a 10% homogenate and then centrifuged at 1,000 rpm (SORVALL Biofuge Primo R, Thermo Fisher Scientific, Waltham, MA) for 6 min, after which the supernatant was collected for determination. After reaction with the tested reagents in the detection kits, the collected supernatants were analyzed spectrophotometrically (SpectraMax M5, Molecular Devices, Sunnyvale, CA) at 532-, 405-, 450-, and 460-nm absorbance, respectively.

Histologic Examination and Microscopic Scoring
After fixation in 4% formalin, the livers were dehydrated, embedded in paraffin, and stained with hematoxylin and eosin. The samples were examined by light microscopy and scored on a 4-point scale by two pathologists blinded to experimental condition. Briefly, analysis was performed on 35 randomly chosen high-power fields in each slide. Grading of the severity of liver injury was as follows: grade 0, minimal or no evidence of injury; grade 1, slight injury consisting of cytoplasm vacuolization and focal nuclear pyknosis; grade 2, moderate injury with extensive nuclear pyknosis, cytoplasmic hypereosinophilia, and loss of intercellular borders; grade 3, severe necrosis with disintegration of hepatic cords, hemorrhage, and neutrophil infiltration.23,24

Immunohistochemistry Staining and Evaluation
The liver sections of 4-μm thick were deparaffinized in xylene and rehydrated through a graduated alcohol series to distilled water. Sections were then placed in citrate buffer and microwaved for 15 min for antigen retrieval. After blocking endogenous peroxidase for 10 min and protein for 5 min, diluted anti-tumor necrosis factor (TNF)-α antibody (1:200, Santa Cruz Biotechnology, Dallas, TX) and anti-interleukin (IL)-6 antibody (1:200, Santa Cruz Biotechnology) were applied, respectively, for 1 h. Then the slides were incubated with biotin-labeled secondary antibody and detected with diaminobenzidine (Sigma, St. Louis, MO). Nucleuses were counterstained with Mayer hematoxylin. Negative controls were performed by omitting primary antibodies. After staining, 10 high-magnification fields of each section were chosen randomly. The average proportion of positive cells in each field was calculated. Blind examination was performed by two pathologists.

Statistical Analysis
The data are expressed as the means ± SD, and statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). We didn’t conduct a priori statistical power calculation. The sample size was decided based on the related papers with similar study design.22 For the malondialdehyde content, catalase activity, SOD activity, myeloperoxidase activity, histologic examination, and immunohistochemistry evaluation, differences between groups were compared using ANOVA with Student–Newman–Keuls post hoc testing for multiple comparisons. For the physiologic parameters and blood gases, the differences were compared using two-way repeated measures ANOVA with main effects of “group” and “time, and the “group × time” interaction. When the interaction was statistically significant, pairwise comparisons between groups were performed at various time points. When the interaction was not statistically significant, the data were averaged and analyzed across all time points. Values of \( P < 0.05 \) were considered significant.
Results
A total of 43 male Wistar rats were enrolled in this study. Four animals were used for measuring the relationship between $P_{aO_2}$ and $FIO_2$. Three animals had abnormal BL values, and four animals died during bleeding because of the individual variances, which were eliminated from further analysis. Therefore, the experiments included eight animals of each of the four groups.

Figure 2 illustrates the relationship between $P_{aO_2}$ and $FIO_2$. $P_{aO_2}$ was 32.0 ± 2.1 mmHg when the $FIO_2$ was set at 0.11 and increased accordingly as the $FIO_2$ increase. $P_{aO_2}$ was 240.0 ± 10.1 mmHg when the $FIO_2$ was set at 0.50.

Gas Exchange
Table 1 depicts the gas exchange throughout the experiment. The arterial hemoglobin concentrations were comparable in the four groups. Because of the administration of the high $FIO_2$, the $PvO_2$ (ANOVA analysis: $p(group) = 0.0391$, $p(time) < 0.0001$, $p(group \times time \text{ interaction}) = 0.0336$) and $Paco_2$ (ANOVA analysis: $p(group) = 0.5480$, $p(time) < 0.0550$, $p < 0.0001$, $p(group \times time \text{ interaction}) = 0.0336$) decreased suddenly in the hypoxemic group. $PvO_2$ (ANOVA analysis: $p(group) = 0.5981$, $p(time) < 0.0001$, $p(group \times time \text{ interaction}) = 0.2406$) decreased suddenly in the hypoxic group at 1-h PR. These data showed that the hyperoxic and GIOA groups could restore blood pressure more effectively.

Figure 3C illustrates the time course of HR in the four groups. HR decreased to approximately 270 beats per minute during shock induction and recovered progressively during the shock period and the resuscitation phase. There was no significant difference among groups throughout the experiment (ANOVA analysis: $p(group) = 0.2702$, $p(time) < 0.0001$, $p(group \times time \text{ interaction}) = 0.0229$) values were higher in the hyperoxic and GIOA groups compared with the normoxic and hypoxic groups at PR.

Hemodynamics
No group differences in MAP (fig. 3A) and PP (fig. 3B) levels were observed at BL. The MAP and PP levels deteriorated during blood withdrawal; however, they were comparable among the groups, suggesting that the HS model was established successfully in all groups. On resuscitation, the MAP levels (ANOVA analysis: $p(group) = 0.0006$, $p(time) < 0.0001$, $p(group \times time \text{ interaction}) < 0.0001$) in the hyperoxic and the GIOA groups soon recovered toward the normal level and were significantly higher compared with the hypoxic group throughout the resuscitation phase and were higher compared with the normoxic group in the latter 30 min of resuscitation. In the PR phase, the MAP levels were not significantly different among the groups. Interestingly, PP (ANOVA analysis: $p(group) = 0.5981$, $p(time) < 0.0001$, $p(group \times time \text{ interaction}) = 0.2406$) decreased suddenly in the hypoxic group at 1-h PR. These data showed that the hyperoxic group could restore blood pressure more effectively.

Acid–Base Status
Table 2 illustrates the arterial acid–base status. After HS, all groups had lower pH, base excess, and $HCO_3$ and higher lactate levels compared with BL, with no significant differences among groups, suggesting a comparable severity of HS. Although recovery was observed in all groups after resuscitation, the acid–base status tended to be better in the hypoxemic and GIOA groups.

Systemic and Tissue Oxygenation
The central venous oxygen saturation ($ScvO_2$; ANOVA analysis: $p(group) = 0.0391$, $p(time) < 0.0001$, $p(group \times time \text{ interaction}) = 0.2207$) and $PaO_2$ (ANOVA analysis: $p(group) = 0.5480$, $p(time) < 0.0550$, $p < 0.0001$, $p(group \times time \text{ interaction}) = 0.0336$) of the high $FIO_2$, the $PvO_2$ (ANOVA analysis: $p(group) = 0.0006$, $p(time) < 0.0001$, $p(group \times time \text{ interaction}) = 0.0336$) were higher in the hyperoxic and GIOA groups compared with the normoxic group in the latter 30 min of resuscitation. Because of the administration of the high $FIO_2$, the $PaO_2$ was 240.0 ± 10.1 mmHg when the $FIO_2$ was set at 0.50.
Gradually Increased Oxygen Administration

Liver Oxidative Stress and Antioxidant Status

To test whether the GIOA group had reduced lipid peroxidation, the malondialdehyde content (fig. 5A) in the liver at 1-h PR was detected. Malondialdehyde in the hyperoxic group was significantly higher compared with the normoxic, hypoxemic, and GIOA groups, and no significant differences were observed between the other three groups. SOD activity (fig. 5B) was comparable among all of the groups. Catalase activity (fig. 5C) was significantly lower in the hyperoxic group compared with the hypoxemic group and GIOA group. Neutrophil accumulation in the liver was measured by determining the myeloperoxidase activity (fig. 5D). Myeloperoxidase activity in the hyperoxic group was significantly higher compared with the normoxic group and numerically higher compared with the hypoxemic and GIOA groups.

Histopathology

The hyperoxic group showed more disordered structure of hepatic lobule, more severe inflammatory cell infiltration and fatty degeneration of hepatocytes, and more obvious hepatic cell oncosis and liver cell cord derangement compared with the other three groups (fig. 6A). The histologic
liver injury scores were significantly lower in the normoxic, hypoxic, and GIOA groups than that in the hyperoxic group. No significant difference was observed among the normoxic, hypoxic, and GIOA groups (fig. 6B). Then we investigated the expression levels of TNF-α and IL-6 with immunohistochemical staining (fig. 7, A and B). Quantitative analysis showed that the percentage of cells positive for TNF-α or IL-6 was significantly lower in the hypoxic and GIOA groups when compared with the normoxic and hyperoxic groups (P < 0.05, respectively). There was no significant difference between the hypoxic and GIOA groups (P > 0.05, fig. 7, C and D).

Discussion

For the first time, this study proposed the notion of GIOA and compared its effects with normoxic resuscitation, hyperoxic resuscitation, and hypoxic resuscitation in a rat HS model. The main findings are that GIOA (1) restored blood pressure, ameliorated the acid–base status, and improved systemic/tissue oxygenation to an extent comparable with hyperoxic resuscitation and (2) mitigated oxidative stress to an extent comparable with hypoxic resuscitation.

The rationale for this study was based on three observations. First, an increased oxidative stress has been identified to be associated with poor outcomes in critically ill patients.25 The pioneering studies by Douzinas et al.26,27 showed that hypoxic resuscitation with FiO2 that gradually increased from hypoxia to normoxia could reduce oxidative injury, as manifested by lower malondialdehyde levels, a higher ratio of reduced to total glutathione, and lower levels of TNF-α, IL-1β, IL-6, and IL-8. This is understood as a consequence of reducing the “fuel” that drives the fire of oxidative stress by limiting the amount of oxygen available during the reperfusion phase.21 Second, serum lactate levels remained abnormally high after hypoxic resuscitation, 26 indicating the presence of tissue hypoxia. Accordingly, hypoxic resuscitation may not be an optimal oxygen administration strategy, and efforts to improve systemic and tissue oxygenation are needed. Third, starting cardiopulmonary bypass with high FiO2 was reported to produce reoxygenation injury, and this oxygen-related damage is reduced by controlling

Table 2. Acid–Base Status

<table>
<thead>
<tr>
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<th>BL</th>
<th>PS</th>
<th>PR</th>
<th>1-h PR</th>
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<tr>
<td>pH</td>
<td>7.41 ± 0.02</td>
<td>7.29 ± 0.06</td>
<td>7.36 ± 0.06</td>
<td>7.43 ± 0.07</td>
</tr>
<tr>
<td>Normoxic</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hyperoxic</td>
<td>7.42 ± 0.02</td>
<td>7.30 ± 0.09</td>
<td>7.38 ± 0.05</td>
<td>7.49 ± 0.03</td>
</tr>
<tr>
<td>Hypoxic</td>
<td>7.39 ± 0.03</td>
<td>7.30 ± 0.06</td>
<td>7.38 ± 0.05</td>
<td>7.47 ± 0.04</td>
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<tr>
<td>GIOA</td>
<td>7.42 ± 0.03</td>
<td>7.31 ± 0.05</td>
<td>7.39 ± 0.04</td>
<td>7.48 ± 0.03</td>
</tr>
<tr>
<td>BE (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoxic</td>
<td>2.8 ± 0.7</td>
<td>-13.3 ± 2.7</td>
<td>-4.1 ± 3.8</td>
<td>-3.1 ± 5.9</td>
</tr>
<tr>
<td>Hyperoxic</td>
<td>2.8 ± 1.1</td>
<td>-12.9 ± 3.4</td>
<td>-0.3 ± 1.8</td>
<td>0.5 ± 2.6</td>
</tr>
<tr>
<td>Hypoxic</td>
<td>2.0 ± 1.2</td>
<td>-12.7 ± 3.1</td>
<td>-3.5 ± 3.6</td>
<td>-1.9 ± 3.9</td>
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<tr>
<td>GIOA</td>
<td>3.1 ± 1.3</td>
<td>-11.7 ± 1.8</td>
<td>-0.1 ± 2.4</td>
<td>1.3 ± 2.3</td>
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<tr>
<td>HCO3− (mmol/L)</td>
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<tr>
<td>Normoxic</td>
<td>27.9 ± 0.6</td>
<td>11.8 ± 2.5</td>
<td>20.8 ± 3.0</td>
<td>21.0 ± 5.2</td>
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<td>Hyperoxic</td>
<td>27.7 ± 1.1</td>
<td>12.3 ± 2.4</td>
<td>23.5 ± 3.3</td>
<td>23.5 ± 2.6</td>
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<td>Hypoxic</td>
<td>27.2 ± 1.1</td>
<td>12.4 ± 2.7</td>
<td>20.8 ± 3.0</td>
<td>21.3 ± 4.3</td>
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<tr>
<td>GIOA</td>
<td>28.2 ± 1.1</td>
<td>12.9 ± 2.0</td>
<td>24.7 ± 2.2*†</td>
<td>24.7 ± 2.5</td>
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<td>Lactate (mmol/L)</td>
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<td></td>
</tr>
<tr>
<td>Normoxic</td>
<td>0.7 ± 0.2</td>
<td>8.6 ± 1.8</td>
<td>3.4 ± 1.7</td>
<td>2.8 ± 2.0</td>
</tr>
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<td>Hyperoxic</td>
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<td>8.2 ± 2.1</td>
<td>1.7 ± 1.7‡§</td>
<td>2.0 ± 1.1</td>
</tr>
<tr>
<td>Hypoxic</td>
<td>0.7 ± 0.2</td>
<td>7.6 ± 1.8</td>
<td>3.4 ± 1.5</td>
<td>2.4 ± 1.4</td>
</tr>
<tr>
<td>GIOA</td>
<td>0.9 ± 0.4</td>
<td>8.5 ± 1.4</td>
<td>1.7 ± 0.6*†</td>
<td>1.6 ± 0.7</td>
</tr>
</tbody>
</table>

All data are expressed as mean ± SD. *P < 0.05 values in the GIOA group differ from those in the normoxic group. †P < 0.05 values in the GIOA group differ from those in the hypoxic group. ‡P < 0.05 values in the hyperoxic group differ from those in the normoxic group. §P < 0.05 values in the hypoxic group differ from those in the hyperoxic group.

BE = base excess; BL = baseline; GIOA = gradually increased oxygen administration; PR = postresuscitation; PS = postshock.

Fig. 4. Central venous oxygen saturation (A) and liver tissue oxygen partial pressure (B) throughout the experiment. BL = baseline; GIOA = gradually increased oxygen administration; PR = postresuscitation; PS = postshock. §P < 0.05 values in the hyperoxic group differ from those in the normoxic group; †P < 0.05 values in the hyperoxic group differ from those in the hypoxic group; ¶P < 0.05 values in the GIOA group differ from those in the normoxic group; ȻP < 0.05 values in the GIOA group differ from those in the hypoxic group. All data are expressed as mean ± SD.
the circumstances of the reoxygenation period (gradually increasing \( \text{Pao}_2 \) from 30 to 400 mmHg).28

On the basis of these experiences, we can form the idea of GIOA—sudden exposure to hyperoxia during resuscitation causes a burst of oxidative stress, whereas the gradual acclimatization from hypoxemia to hyperoxia is supposed to be well tolerated during HS and subsequent resuscitation. Figure 8 illustrates the rationality of making the arterial blood hypoxemic at the early moments of resuscitation. Abrupt reoxygenation of the ischemic cell and tissue with hyperoxic resuscitation will cause oxidative injury. Not only does proper hypoxemia at the early moments of resuscitation prevent the worsening of cell and tissue hypoxia but it may also prime animals for a less aggressive reperfusion response. The oxygen supply with GIOA may better fit with the critical oxygen demand during resuscitation from HS.

Currently, the liver is considered to be one of the first organs to be subjected to the hypoxic insult inflicted by HS.29 It has been reported that 20% of patients in hypovolemic shock would exhibit some degree of liver dysfunction, and as many as 5% of patients who survive 24 h after HS may ultimately suffer from hepatic failure.30 In this study, the levels of malondialdehyde were reduced and the catalase activity was restored at 1-h PR in the GIOA group compared with the hyperoxic group, indicating that GIOA not only reduced the oxidant-mediated injury but also stimulated the antioxidant activity.31 In addition, the TNF-\( \alpha \) and IL-6 expressions in the liver were markedly decreased in the GIOA group than in the hyperoxic and normoxic group as shown by the immunohistochemical staining (fig. 7). These data demonstrate that GIOA indeed mitigated oxidative stress.

Moreover, we have shown that in the GIOA group, acid-base status was ameliorated, as manifested by higher base excess.
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and HCO₃⁻ levels and lower lactate levels, and tissue/systemic oxygenation was improved, as manifested by higher ScvO₂ and PltO₂, indicating that GIOA could not only decrease oxidative stress but could also increase systemic/tissue oxygenation.

In fact, the idea of GIOA is in line with the notion of postconditioning (PoC). PoC, a series of ischemia/reperfusion or hypoxia/reoxygenation cycles applied at the onset of reperfusion or reoxygenation, is a recently described novel approach to reduce the deleterious effects of ischemia-reperfusion injury.³²,³³ It is reported to reduce oxidative stress, reduce mitochondrial calcium overload, improve endothelial function, and reduce inflammation.³²,³⁴ PoC is considered likely to be an easy and effective manifestation of gradual treatment.³⁵,³⁶

Evidence from PoC indicates that the early moments of reperfusion were important in the pathogenesis of postischemic injury. The sudden reintroduction of abundant oxygen to the ischemic tissue will cause a burst of oxidative stress.³⁷,³⁸ However, GIOA not only focuses on the onset of reperfusion to activate the protective response but also emphasizes the gradual process from hypoxemia to hyperoxia to alleviate the possible adverse effects of hypoxic conditions. GIOA can be considered to be another manifestation of gradual treatment.

There is accumulating evidence that gradual treatment will play a more critical role in the treatment of HS.³⁹–⁴¹

It is worth noting that in this study, hypoxemic resuscitation did not seem to reduce oxidative stress compared with normoxic resuscitation, which is in disagreement with the findings of Douzinias et al. This discrepancy may be because of the different severities of the HS models and/or the possible instability of hypoxemic resuscitation. In addition, invasive mechanical ventilation can contribute to the existing oxidative injury during HS,⁴²,⁴³ and interactions between higher concentrations of oxygen and mechanical ventilation may augment the injury.⁴⁴,⁴⁵ To rule out the possible influence of ventilators and the interaction, this study used a cone mask, and this might have reduced the oxidative stress difference between the normoxic group and the hypoxemic group.

There are several limitations to this study. The power of this study was limited to identify mortality differences between groups. However, in another research of our group, we found that GIOA group had a significantly higher 96-h survival rate compared with the normoxic and the hyperoxic groups (Yujing Yin, PhD, Xin Luo, PhD, and Hong Zhou, PhD, Institute of Transfusion Medicine, Academy of Military Medical Sciences, Beijing, China, April 2015, unpublished results). In addition, the 1-h observation period after resuscitation might be too short for the development of oxidative injury, and longer observation periods may result in more significant differences in oxidative stress. Further research is required to identify the long-term effects of GIOA and the details of GIOA, such as how to determine the initial concentration of GIOA and how quickly the FiO₂ should change.

In conclusion, our study shows for the first time that GIOA improved systemic/tissue oxygenation and mitigated oxidative stress simultaneously after resuscitation from severe HS. Our study provides novel insight into the oxygen administration strategy, and GIOA seems to be a simple and promising strategy to improve resuscitation from HS.

**Acknowledgments**

The authors thank Jing Yang, M.D. (Institute of Transfusion Medicine, Academy of Military Medical Sciences, Beijing, China), and Weiwei Liu, Ph.D. (Consulting Center of Biomedical Statistics, Academy of Military Medical Sciences, Beijing, China), for their advice regarding the data analysis.

This work was supported by the National High Technology Research and Development Program of China, Beijing, China (2012AA021902) and National Natural Science Foundation of China, Beijing, China (81300751).
Fig. 7. Immunohistochemistry. (A) Representative immunohistochemistry staining images showed the expression of tumor necrosis factor (TNF)-α protein in the liver tissues. (B) Representative immunohistochemistry staining images showed the expression of interleukin (IL)-6 protein in the liver tissues. (C) Quantification analysis for the percentage of TNF-α–positive cells. (D) Quantification analysis for the percentage of IL-6–positive cells. GIOA = gradually increased oxygen administration. †P < 0.05 values in the hyperoxic group differ from those in the hypoxemic group; £P < 0.05 values in the hyperoxic group differ from those in the GIOA group. ¶P < 0.05 values in the GIOA group differ from those in the normoxic group.

Fig. 8. Rationality for making the arterial blood hypoxemic at the early moments of resuscitation. GIOA = gradually increased oxygen administration.

Competing Interests
The authors declare no competing interests.

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Signed Simpson Stereoscopic Photoportrait, Blind-stamped Lennie

On the first major avenue beneath Edinburgh Castle Rock, Princes Street, and just a long scone’s throw from the (Sir Walter) Scott Monument, the family business of Scottish master optician James Lennie sold eyewear, jewelry, perfume, and photographic apparatus. The Lennies’ corner shop at 46 Princes Street was only two Georgian city blocks from Queen Street and just under five blocks total from 52 Queen Street, the home of Sir James Young Simpson from 1845 until his death in 1870. Simpson’s stereoscopic photoportrait (top) bears the blind-stamp "ANSE / 46 PRINCES ST / Edinburgh" on front. On back is the imprinted autograph (bottom) of the Professor of Midwifery who pioneered chloroform anesthesia, "J Y Simpson." (Copyright © the American Society of Anesthesiologists, Inc.)

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