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Original Article

Oxidative stress is associated with the gastric mucosa lesion of the Tibetans with high-altitude polycythemia

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Abstract: Objective: High plateau is a special low-oxygen environment, resulting in pathogenesis of high-altitude polycythemia (HAPC). Gastric mucosal lesion (GML) is a common complication of HAPC. In this study, the effect of oxidative stress involved in HAPC-induced GML was studied to understand how oxidative stress function in HAPC-induced GML. Methods: The gastric tissues of 24 subjects (11 HAPC-induced GML patients and 13 healthy controls) were detected through immunohistochemical and histopathological analysis, and three genes related to oxidative stress were detected by Western blot and RT-PCR. Results: Compared with healthy controls, there was a significant increase in the number of red blood cells, gastric vessels, and diameters of gastric mucosal vessels in HAPC-induced GML patients ($P < 0.05$). Moreover, more red blood cells were distributed in gastric tissue not only in vascular levels but also in the tissue space ($P < 0.05$). Furthermore, expression of oxidative stress-related molecules (CAT, NQO1, and NRF2) was significantly higher in the HAPC-induced GML patients than that in the healthy controls. The pathologic changes showed that GML presents following with HAPC and that up-regulation of CAT, NQO1, and NRF2 indirectly reflects the increase of reactive oxygen species (ROS) and oxidative stress. *Conclusions*: Altogether, these results demonstrate that dysregulation of oxidative stress-related molecules might improve GML through the regulation of oxidative stress. These findings provide novel insight for the effect of oxidative stress on gastric lesions induced by HAPC.

Keywords: High-altitude polycythemia, gastric mucosal lesion, oxidative stress, CAT, NQO1, NRF2

Introduction

Tibetan Plateau residents usually encountered a common phenomenon hypobaric hypoxia and may present anemia which is related to the deficiency of red blood cells and/or hemoglobin and oxygen transfer [1]. It has been reported that almost 18% residents in the Tibetan Plateau present excessive erythrocytosis, defined as high-altitude polycythemia (HAPC) [2].

Long-term high-altitude hypoxia has varying effects on the digestive system, and the gastrointestinal tract is one of the commonly affected systems due to increased sensitivity [3]. In addition, some previous papers have reported gastric mucosal lesion (GML) is the concomitant disease followed by HAPC which is difficult to deal with [4-6]. Moreover, blood flowing in the micro-vessels (arterioles, capillaries) has also been proven to play an important role in the maintenance of structure and functions of gastrointestinal mucosa [7, 8].

Reactive oxygen species (ROS) generate in the human body during various metabolic processes and play a dual role in biological systems [9]. At low concentrations, ROS play physiological roles in cellular responses, such as defense against infectious agents and a number of cellular signaling systems [10, 11]. ROS can be an important damage mediator to break off cell structures (lipids and membranes, proteins and nucleic acids) at high concentrations [12, 13]. Over-production of ROS from either endogenous or exogenous is usually termed oxidative stress [14].

ROS are produced within the gastrointestinal (GI) tract; however, there is little understanding of oxidative stress involved in HAPC-induced GML. In this study, the role of high-altitude hypoxic environment was investigated in physi-

Table 1. Demographic character and clinic features of participants

	GML (n = 11)		Nomal (n = 13)		*P* value
	Mean	SD	Mean	SD	
Age	43.0	5.0	43.0	3.6	0.9914
Height	170.6	5.0	169.1	4.1	0.6411
Weight	72.4	10.0	70.0	8.0	0.5596
Oxygen saturation	78.5	1.7	85.6	1.1	< 0.0001
Heart rate	92.2	12.9	75.4	10.8	0.0039
Systolic pressure	130.2	14.9	114.2	12.3	0.0136
Diastolic blood pressure	88.5	9.8	74.8	7.8	0.0022
RBC	6.9	0.2	4.9	0.5	< 0.0001
HGB	228.2	9.4	161.5	12.8	< 0.0001
HCT	685.7	31.5	476.2	40.6	< 0.0001

ological function of human gastrointestinal mucosa to illustrate the role of oxidative stress in the pathogenesis of HAPC-induced GML in the Tibetans.

Material and methods

Participants

HAPC was defined with hemoglobin (Hb) concentration > 21 g/dl for male and > 19 g/dl for female by the 2004 Qinghai International High Altitude Medicine Conference [2]. The severity of blood mucosal lesion was classified according to hematoxylin-eosin (HE) staining of gastric tissues: the number of red blood cells and vessels, as well as the aggregation degree of red blood cells. The histopathological changes were diagnosed according to the Operative Link on Gastritis Assessment (OLGA) staging system [15]. On July 2013, 24 subjects (indigenous and have lived in their regions for over 30 years) from Lhasa, Nagqu, Shannan, and Rigaze of Tibet with an average altitude of 3600 to 4800 m were screened in this study. All subjects were divided into two groups: the GML group with an average oxygen saturation 78.5% (11 diagnosed with HAPC-induced GML) and the control group with an average oxygen saturation 85.6% (13 healthy Tibetans without HAPC and GML) (**Table 1**). Each patient was matched to a control including gender, age, birthplace, lifestyle, diet, body mass index (BMI), height of living location, work intensity, helicobacter pylori infection, and non-steroidal anti-inflammatory drugs (NSAIDs) application. BMI and per capita income as main factors affecting gastric injury caused by inflammation were carefully considered [16]. All subjects were native male Tibetans within 40-45 years of age. Subjects with chronic pulmonary diseases; chronic respiratory disorders or secondary polycythemia due to hypoxemia cau sed by certain chronic diseases; severe diseases of the heart, brain, lungs, liver, kidneys, endocrine system and hematopoietic system; alcohol abuse, drug addiction, poor mental health or other conditions inappropriate for gastroscopy; obstructed gastrointestinal tract, and medical histories such as recent gastrointestinal bleeding were excluded. Gastric mucosa and peripheral venous blood were sampled for following tests.

The experimental protocol was established based on the ethical guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the People's Hospital of Tibet Autonomous Region, Lasha, China. Written informed consent was obtained from the individual participant.

H&E staining and immunohistochemical analysis

Gastric mucosa collected from 24 subjects was fixed in 4% neutral formaldehyde solution, gradually dehydrated in gradient ethanol, then embedded in paraffin and sliced into 5 μm thick sections to double stain with both hematoxylin and eosin, then sealed with neutral gum. Finally, the number of gastric mucosal vessels and erythrocytes in one field, and diameter of 5 gastric vessels were calculated.

The sliced sections were added with methanol solution including 0.3% hydrogen peroxide and placed for 30 minutes, then washed with 0.01 M PBS for 3 times (5 minutes per time). Subsequently, anti-catalase antibody (rabbit anti-human, 1:200 dilutions, Proteintech™, ABCAM, USA) was added and incubated at 4°C for overnight (16 h). After washing 3 times with 0.01 M PBS, horseradish peroxidase secondary antibody (goat anti-rabbit, 1:200, proteintech™, ZSGB-BIO, China) were added and incubated for 30 minutes, then washed three times.

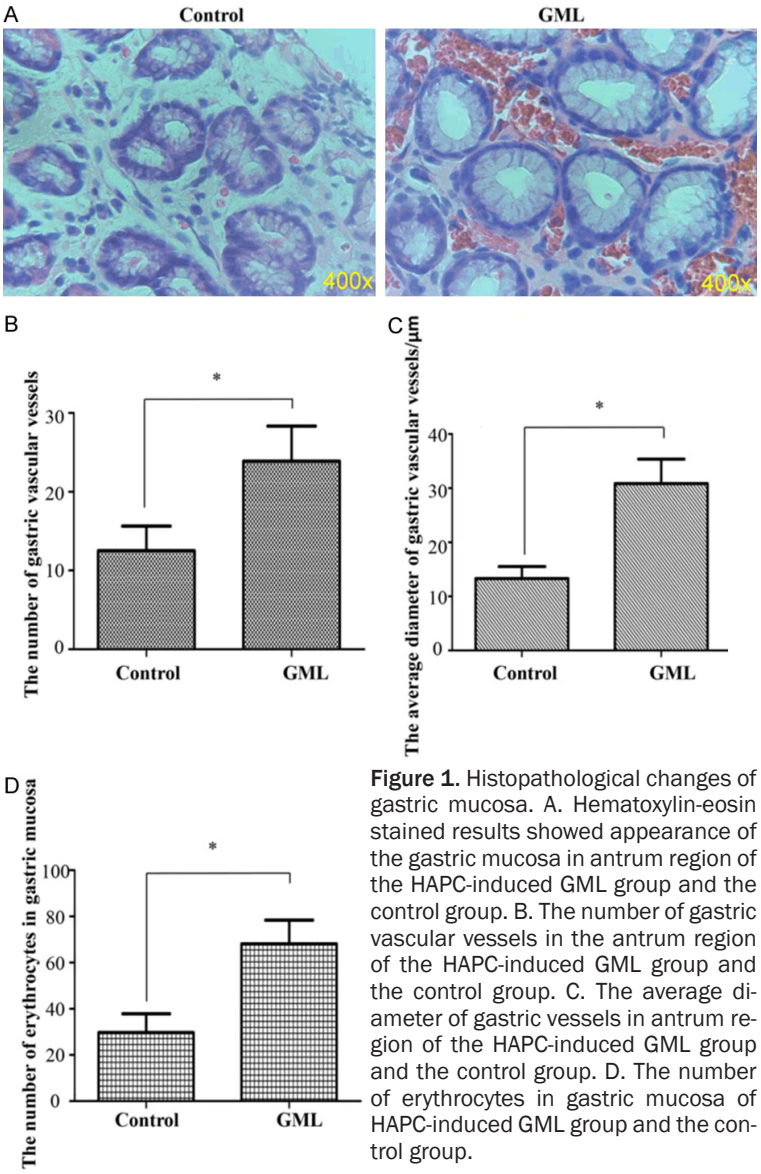

Figure 1. Histopathological changes of gastric mucosa. A. Hematoxylin-eosin stained results showed appearance of the gastric mucosa in antrum region of the HAPC-induced GML group and the control group. B. The number of gastric vascular vessels in the antrum region of the HAPC-induced GML group and the control group. C. The average diameter of gastric vessels in antrum region of the HAPC-induced GML group and the control group. D. The number of erythrocytes in gastric mucosa of HAPC-induced GML group and the control group.

Finally, the staining process was developed with the DAB color kit (ZSGB-BIO, China), and the expression and distribution of Catalase (CAT) was observed.

Western blot analysis

Total protein was isolated from gastric mucosa and assayed for CAT and NAD(P)H quinone oxidoreductase1 (NQO1) by Western blotting. After adding protein lysis buffer and three-cycle freezing and thawing, the cell supernatant was collected to extracted protein, and then the protein concentration was determined by BCA assay. After that, 10 μg protein from each cell lysate was separated on a 10% sodium dodecyl-sulfate-polyacrylaminde gels (SDS-PAGE), then transferred to a poly-vinylidene fluoride (PVDF) membrane. After sealing, the membranes were incubated at 4°C for overnight and washed. Later, primary antibodies (rabbit anti-human, 1:1000 dilutions, Proteintech™, ABCAM, USA) to CAT/NQO1 were added and incubated at 37°C for 2 hours, then probed with corresponding secondary antibody (goat anti-rabbit, 1:1000, proteintech™, ZSGB-BIO, China) at 37°C for 2 hours, then washed three times with PBS. Finally, with X-ray film exposure and photograph, expression of CAT and NQO1 was measured using Quantity One software with the internal control protein of β-actin.

Real time quantitative reverse transcription polymerase chain reaction (RT-PCR)

Total RNA of the collected gastric mucosal samples were extracted using guanidine thiocyanate-phenol-chloroform. After DNase digestion, Agilent-Bioanalyzer (Agilent, Palo Alto, CA, USA) was used to assess RNA quantification and purity at 260/280 nm. Then denaturing agarose gel electrophoresis was performed to measure RNA integrity and genome DNA contamination.

Subsequently, RNA samples were reverse-transcribed using a reverse transcriptase reaction kit (ABI biosystems, Foster City CA, USA). The primers were designed as follows: CAT, forward primer, 5'-GACTTTTTACATCCAGGTCAT-3', reverse primer, 5'-GACCAGTTTACCAACTGG-3'; NQO1, forward primer, 5'-GAA AGGATGGGAGGTGGTGG-3';reverseprimer,5'-CAGACTCGGCAGGATACTG AAAG-3'; NRF2, forward primer, 5'-TTCAGCCAGCCCAGCACAT-3', reverse primer, 5'-GCAGTCATCAAAGTACAAAGCATCT-3'; β-Actin, forward primer, 5'-GAAGATCAAGATCATTGCTCCT-3', reverse primer, 5'-TACTCCTGCTTGCTG ATCCA-3'. SYBR Green PCR Master Mix and 7500 Fast real-time PCR detection system (ABI Biosystems, Foster City CA, USA) were used to perform PCR with the amplified conditions: 94°C

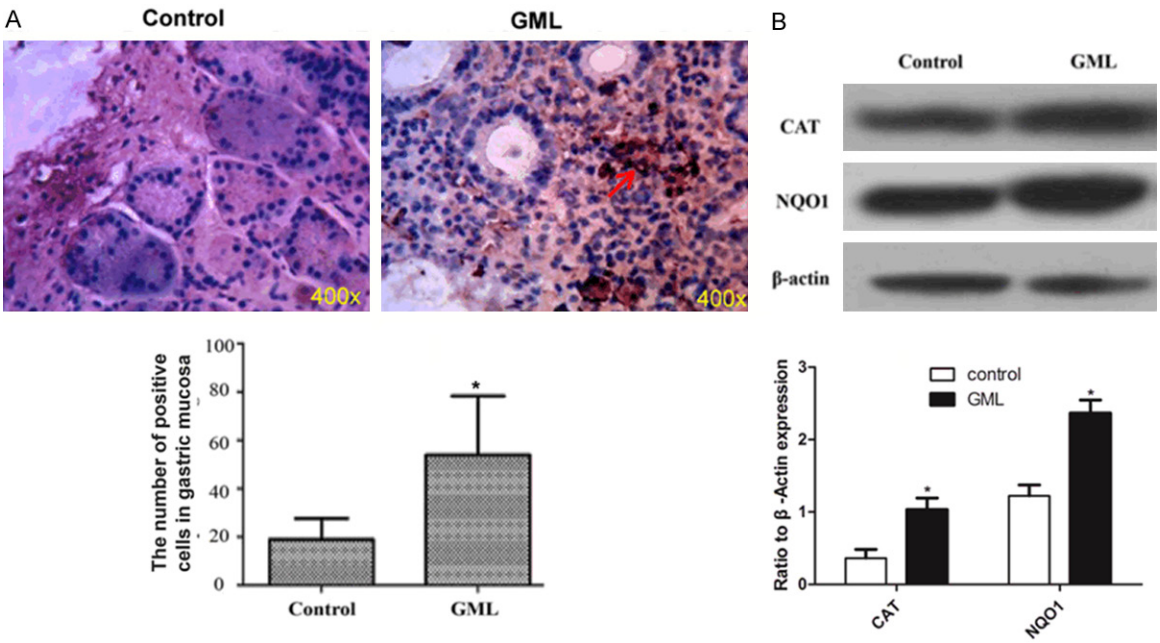

Figure 2. Expression of Catalase and NQO1. A. Expression of Catalase assessed by immunohistochemistry, the arrow points to the Catalase positive cells, brown or dark brown indicated a higher positive rate. B. Quantitative analysis of Catalase and NQO1 assessed by Western blotting.

for 2 minutes; 45 cycles of 94°C for 20 seconds, 53°C for 30 seconds and 60°C for 40 seconds. Then the relative expression value was calculated by $2^{-\Delta\Delta Ct}$ method.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 software package (SPSS Inc, Chicago, IL, USA). Data are expressed as from two independent experiments. Statistical differences between the groups were compared using Student's t-test. Chi-square (χ^2) test was used for expression correlation analysis. A *P*-value of less than 0.05 was considered statistically significant.

Results

Histopathological changes

In our study, 24 subjects including 11 Tibetans diagnosed with HAPC-induced GML patients and control group with 13 healthy Tibetans without HAPC and GML were screened (**Table 1**), there was no statistical difference in age, weight and height between the GML group and the control group ($P > 0.05$), but the heart rate, systolic pressure, diastolic blood pressure showed up-regulated in GML group ($P < 0.05$). The average oxygen saturation of GML subjects was lower than that of nomal subjects, and the RBC (red blood cell), HGB (hemoglobin), HCT (hematocrit) level in GML group was higher than that in control group ($P < 0.05$). H&E staining revealed that in the healthy controls, the duct was in normal structure with suitable amounts of blood vessels and red blood cells (**Figure 1A**). While in the HAPC-induced GML patients, the duct was destroyed. A large number of red blood cells were gathered in gastric vessels. Parietal cells are over-proliferated in gastric biopsies. The number of gastric cells is decreased while the volume and diameter of gastric vessels is increased compared with those in the healthy controls.

As it shown in **Figure 1B**, the number of gastric vascular vessels was significantly higher in the stomach of HAPC-induced GML patients than those in the healthy controls (23.67 ± 3.84 and 12.50 ± 2.07). The average diameter of gastric vessels was also significantly higher in the stomach of HAPC-induced GML patients than those in the healthy controls (30.76 ± 9.33 and 13.20 ± 4.49) (**Figure 1C**). In addition, the number of erythrocytes in gastric mucosa was significantly higher in the stomach of HAPC-induced GML patients than those from healthy controls (150.46 ± 67.31 and 28.81 ± 11.63) (**Figure 1D**), which showed that erythrocytes

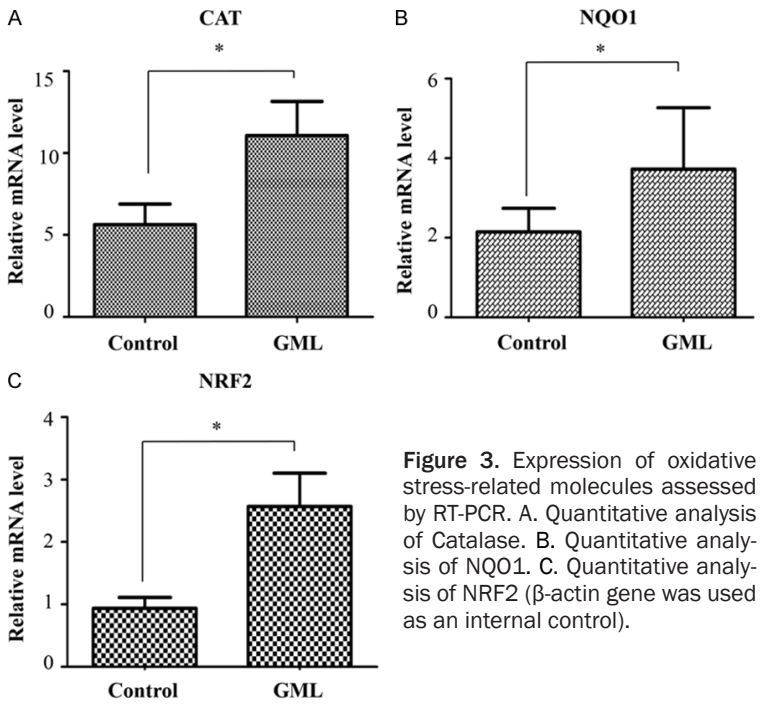

Figure 3. Expression of oxidative stress-related molecules assessed by RT-PCR. A. Quantitative analysis of Catalase. B. Quantitative analysis of NQO1. C. Quantitative analysis of NRF2 (β-actin gene was used as an internal control).

are distributed in blood vessels together with tissue space, suggesting that high altitude could lead to increase the number of gastric vessel and cause the injury of the stomach.

Expression of oxidative stress-related molecules in HAPC-induced GML

To explore the relation between oxidative stress and GML induced by HAPC, expression of CAT and NQO1 was analyzed and found to be significantly higher in the HAPC-induced GML patients than that in the healthy controls through immune-histochemistry (**Figure 2A**) and Western blotting (**Figure 2B**). Expression of CAT, NQO1, and nuclear factor-E2-related factor-2 (NRF2) were analyzed through RT-PCR. The results show that expression of CAT, NQO1, and NRF2 was significantly higher in the HAPC-induced GML patients than that in the healthy controls (**Figure 3**), which was in accordance with the results of immunohisto-chemistry and Western blotting.

Correlation analysis between four blood parameters and three oxidative stress-related molecules in HAPC-induced GML

Hemoglobin (HGB), red blood cells (RBC), white blood cells (WBC) and platelets (PLT) are needed for healthy blood, which have strong ties to oxidative stress. As shown in **Figure 4**, the levels of three blood parameters (HGB, RBC, and PLT) and three oxidative stress-related genes (CAT, NQO1, and NRF2) were negatively correlated (two-tailed Spearman's correlation, $P < 0.05$), while the levels of WBC showed no correlation with three oxidative stress-related genes (CAT, NQO1, and NRF2) levels (two-tailed Spearman's correlation, $P > 0.05$).

Discussion

Recently, hypoxia has been proven to decrease blood flow to the gastric mucosa, which results in ischemia and subsequent destruction of the mucosal lining [3]. Gastric mucosal ischemia which results from microvascular thrombosis caused by excessive polycythemia may contribute to GML. This research was performed with the gastric tissues of heavy HAPC-induced GML patients and healthy controls through histopathological analysis. The results show that compared with healthy controls there was a significant increase in the number of red blood cells, gastric vessels, the diameters of gastric mucosal vessels in HAPC-induced GML patients. In addition, more red blood cells were distributed in gastric tissue not only in vessels but also in the tissue space. Furthermore, the number of vacuoles increased in gastric mucosal cells. These pathologic changes suggest that in order to transfer enough oxygen to tissues, the number of red blood cells and gastric vessels increased and resulted in gastric mucosal lesion.

Oxygen free radicals (nitric oxide (NO), superoxide anion, and reactive oxygen species (ROS)) in excessively high amounts can provoke "oxidative stress" and detrimentally affect living organisms. Free radicals have been proven to be related to the pathogenesis of diverse gastrointestinal (GI) diseases, such as gastritis, gastroesophageal reflux disease (GERD), etc. [17]. ROS are produced within the gastrointestinal (GI) tract, overproduction of ROS can causes oxidative damage to cell structures (lipids and membranes, proteins and nucleic acids), paradoxically, many ROS mediated responses can induce "redox homeostasis" to protect the cells

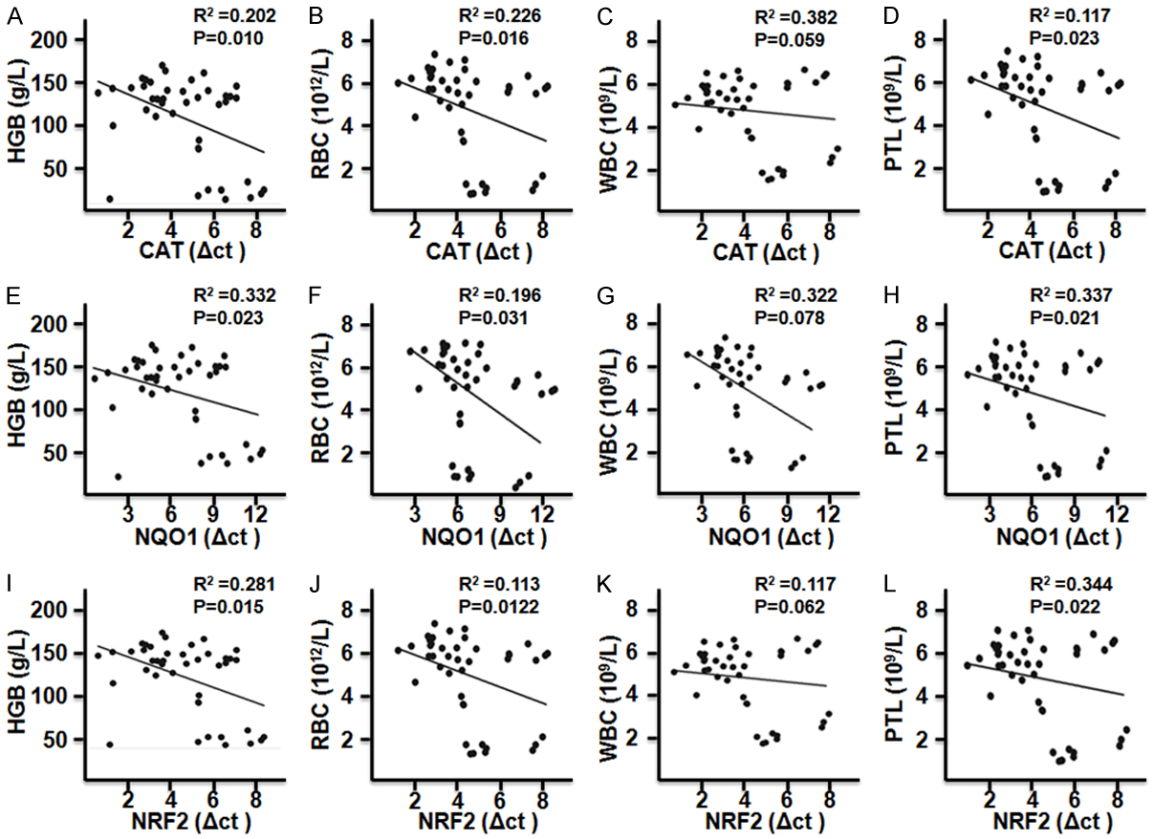

Figure 4. Correlation analysis between four blood parameters and three oxidative stress-related molecules in HAPC-induced GML by Chi-square (χ^2) test.

against oxidative stress [14, 18]. Excessive ROS in the human body could be balanced through the antioxidant action of non-enzymatic antioxidants as well as antioxidant enzymes, such as superoxide dismutase (Cu, Zn-SOD, Mn-SOD), catalase, glutathione peroxidase [19-21]. Catalase, which is an enzyme located in the cells of plants, animals and aerobic (oxygen requiring) bacteria, could efficiently promote the conversion of hydrogen peroxide to water and molecular oxygen, which significantly decreases the detrimental effects of ROS [22-24]. On the other hand, NAD (P) H quinone oxidoreductase1 (NQO1) as an inducible enzyme, catalyzes two electron reduction of quinone to the redox-stable hydroquinone [25, 26]. Moreover, it has been suggested that NQO1 is involved in an important protective mechanism against oxidative damage [27]. Furthermore, the nuclear factor-E2-related factor-2 (NRF2) could be translocated into the nucleus as a transcription factor upon oxidative signals and bind to ARE which resides in the promoter regions of many phase II detoxifying and antioxidant genes including NQO1 [28, 29]. Therefore, the NRF2-ARE-NQO1 axis could function against oxidative damage.

When exposure to high altitude, partial pressure of oxygen decreased, antioxidant enzyme system showed decreased activity and effectiveness, while the formation of reactive oxygen and nitrogen species (RONS) increased [30]. Many studies have demonstrated that ROS participates in the pathogenesis of gastric mucosal damage by various irritants. In addition, inhibiting ROS could effectively reduce the toxic effect oxidative damage to gastric mucosal [31-33]. In addition, increased ROS can induce depletion of antioxidants and increase the expression of oxidative stress-related genes [17].

In this study, expression of oxidative stress-related molecules was tested through immunohistochemistry, Western blot and RT-PCR to investigate the effect of oxidative stress on GML induced by HAPC. Expression of CAT, NQO1, and NRF2 was significantly higher in the HAPC-induced GML patients than that in the

healthy controls, which indirectly means ROS and oxidative stress increased in the HAPC-induced GML patients. Furthermore, three blood parameters (HGB, RBC, and PLT) levels and three oxidative stress-related genes (CAT, NQO1, and NRF2) levels were negatively correlated. Therefore, all the results clarify that dysregulation of oxidative stress-related molecules related to the pathogenesis of GML induced by HAPC and might improve GML through the regulation of oxidative stress.

In conclusion, microvessel density and diameter of gastric mucosal vessels as well as the number of erythrocytes are significantly higher in GML patients with HAPC compared with healthy controls, which suggests that HAPC induced the occurrence of gastric mucosal lesion. Moreover, dysregulation of oxidative stress-related molecules might improve GML in HAPC patients through the regulation of oxidative stress. But further integrated analysis is still necessary to provide more precise information about the HAPC-induced GML. Finally, our results would contribute to further future studies for the treatment against gastric lesions induced by HAPC.

Disclosure of conflict of interest

None.

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