



## ORIGINAL RESEARCH

# Arterial Blood Gas and Rotational Thromboelastometry Parameters in Healthy Rescuers Incidentally Exposed to Nitroglycerin, Nitrogen Compounds, and Combustion Products

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**Introduction**—Acute exposure to nitrogen compounds combined with a massive inhalation of air pollutants can influence respiratory and cardiovascular symptoms and coagulation abnormalities in accidentally exposed healthy adults during cave detonation operations.

**Methods**—Italian alpine and cave rescuers widened a cave in the Abisso Luca Kralj in Trieste, Italy. Volunteers inside the cave were accidentally exposed to the fumes from an uncontrolled detonation of blasting gelatin microcharges. We performed a retrospective cohort study on the clinical data, arterial blood gas analysis, and rotational thromboelastometry parameters from the rescuers involved in the accident.

**Results**—Ninety-three healthy rescuers were involved in the uncontrolled detonation: 47 volunteers handled a mixture of nitrogen compounds (blaster group), and 46 volunteers did not (nonblaster group). After the accident, statistically significant differences ( $P < 0.05$ ) in arterial blood gas values were observed between the groups, with a pattern of mild respiratory acidosis with hypercapnia in the nonblaster group and severe mixed acid-base disorder with hypoxia and hypercapnia in the blaster group. Mild hyperfibrinolysis was observed in 44 volunteers in the blaster group, as were associated bleeding symptoms in 34 volunteers; no significant coagulation modifications were recorded in the nonblaster group.

**Conclusions**—Respiratory acidosis with hypoxia, hypercapnia, a compensatory metabolic response, and mild hyperfibrinolysis were probably related to the combined effect of nitrogen compounds and the inhaled toxic products of detonation. Therefore, each element exerts a determinant effect on promoting the biological toxicity of the others.

**Keywords:** cave rescue, air pollutants, pulmonary gas exchange, coagulation, acid-base disorders, hyperfibrinolysis

## Introduction

The cave widening group (CWG), a part of the Italian alpine and cave rescue (IACR), uses blasting gelatin (a mixture of nitroglycerin, nitrogen compounds, and chalk) to enlarge narrow portions of the caves, facilitating patient evacuation if an accident occurs. The physicians

on the medical commission of the IACR must be present at procedures. An evaluation of volunteer vital signs and parameters (heart rate [HR], arterial blood pressure, and oxygen saturation measured with pulse oximetry [ $S_pO_2$ ]), arterial blood gas exchange function, and coagulation function is required before starting an enlargement procedure, in accordance with our protocol.

During cave widening, the CWG volunteers handle explosive materials that can permeate the human body by inhalation or skin absorption, despite the use of personal protective equipment. Thus, the medical commission

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equips each volunteer with a large, full-face respirator with eye protection against dust, organic vapors, odors, fumes, sawdust, and asbestos, as well as full-body suits and gloves to protect against chemicals and gases. In addition, detonation gases remain in the air because of the narrow space in the cave, despite the use of portable air purifiers and toxic gas detectors during enlargement procedures. Thus, IACR volunteers may be subjected to prolonged inhalation of combustion products.

Detonating microcharges lead to the release of various combustion products, particularly carbon monoxide (CO), resulting in concentration-dependent symptoms ranging from headache, tachycardia, dyspnea, and seizures to death. The binding affinity of CO for hemoglobin (Hb) is greater than that of oxygen (O<sub>2</sub>), resulting in the formation of carboxyhemoglobin (COHb). This alteration decreases the oxygen-carrying capacity of blood and impairs the release of O<sub>2</sub> from Hb. During microcharge detonation, high concentrations of carbon dioxide (CO<sub>2</sub>) can also be released into the air, leading to tachypnea, tachycardia, fatigue, nausea and vomiting, syncope, convulsions, coma, and death. Nitric oxide (NO) can also be present. High doses of inhaled NO (>100 parts per million [ppm]) appear to promote lung injury, potentially owing to concurrent nitric dioxide (NO<sub>2</sub>) formation. The toxicologic effects of high-dose NO<sub>2</sub> inhalation in humans are related to airway reactivity with diffuse inflammation that presents clinically as dyspnea, followed by pulmonary edema and death.<sup>1</sup>

Vasodilatation is the primary consequence of nitroglycerin and nitrogen compound toxicity, and it results in hypotension with tachycardia, headache, dyspnea, coma, and death. Methemoglobinemia is a consequence of nitrate overdose,<sup>2</sup> and clinical manifestations can include grayish pigmentation of the skin, the presence of chocolate-colored blood, central cyanosis, dizziness, headache, anxiety, dyspnea, symptoms of low cardiac output, somnolence, seizures, reduced consciousness, respiratory depression, shock, and death.<sup>2</sup>

Other toxic effects from nitrogen compounds caused by nitrous oxide exposure have been shown to be associated with neurologic symptoms including headache, dizziness, euphoria due to hypoxia, vitamin B<sub>12</sub> deficiency, and megaloblastic anemia. In addition to regulating vascular tone, nitric oxide inhibits platelet adherence to endothelial cells and aggregation.<sup>3</sup>

The Abisso Luca Kralj cave is a sinkhole in the dolomite rocks of the karst near Trieste, Italy. Airborne dust produced from the explosion of dolomite rocks contains high concentrations of calcium ions, magnesium ions, and hydroxyl ions that increase the pH of the biofilm on the exposed surface of the cornea and the oral and airway mucosa, resulting in ophthalmic damage, airway

and skin irritation, and ulcerative lesions of the mouth and esophagus.

We investigated whether nitroglycerin and nitrogen compounds influence coagulation changes in response to hypoxia<sup>4</sup> resulting from the toxic effects of the combustion products from blasting gelatin. Subsequently, data from the widening of the Abisso Luca Kralj and its effects on the rescuers were investigated.

## Methods

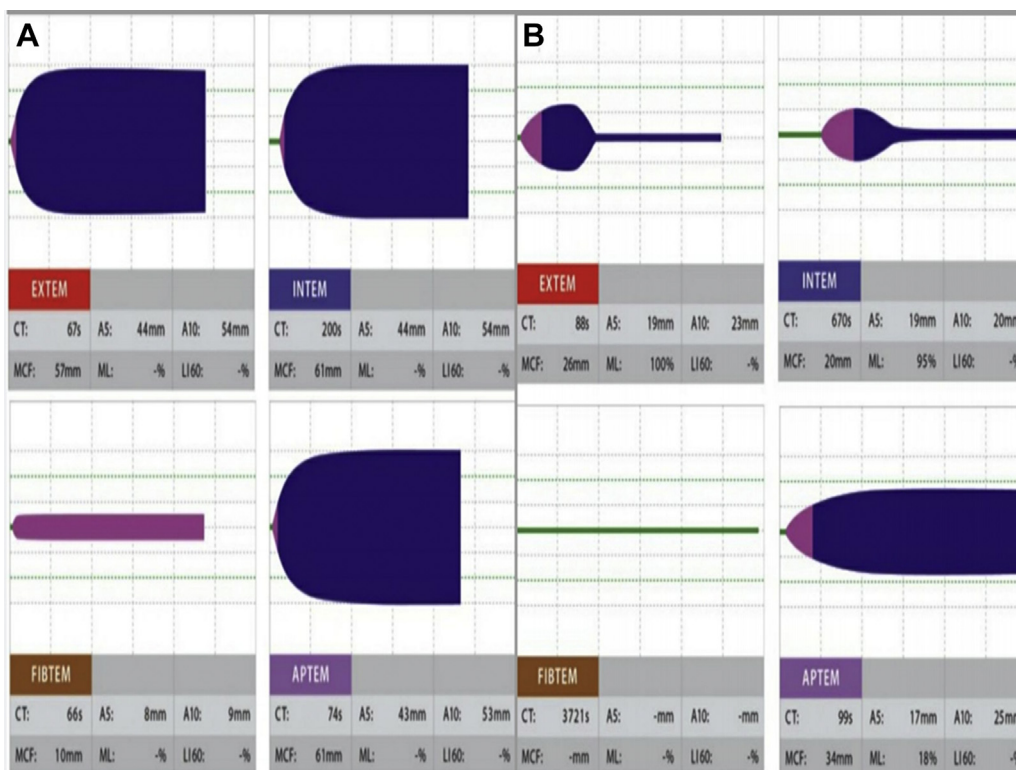
This retrospective cohort study analyzed clinical data from CWG rescuers from IACR who were accidentally exposed to fumes from an uncontrolled detonation of blasting gelatin microcharges during the widening of the cave Abisso Luca Kralj.

This study was approved by the cave ethics committee of the IACR ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT04201860). It adhered to the STROBE statement and the Declaration of Helsinki for ethical principles for medical research involving human subjects. Written informed consent was obtained from all rescuers.

Before starting the operations for cave enlargement, the rescuers were divided into 10 teams, 9 teams with 9 volunteers (5 explosive specialists and 4 speleologists) and 1 team with 12 volunteers (2 explosive specialists and 10 speleologists) at each point of microcharge placement. The speleologists assisted the explosive specialists during the progression through the cave. The volunteers did not have any exposure to nitroglycerin, nitrogen compounds, or combustion products in the 6 mo before the study.

Forty-seven healthy volunteers handled, manufactured, and blasted the explosive microcharges (blaster group, BG), and 46 healthy volunteers did not have contact with the explosives (nonblaster group, NBG). Three hundred microcharges were packed and blasted. Each rescuer in the BG packed 6 microcharges and handled blasting gelatin for an average of 85 min. The composition of the blasting gelatin was 50% nitroglycerin, 41% diglycerin tetranitrate, 8% nitrocellulose, and 1% chalk.

All rescuers were equipped with a large, full-face respirator with eye protection (3M full facepiece reusable respirator 6000 series, Milan, Italy) and wore full-body suits (DuPont C3122T TN Tychem 5000 coveralls, Wilmington, DE) and gloves (Chemstop 30 cm [12 in] blue cut-resistant, impact-resistant PVC-coated gloves, Superior Glove, Ontario, Canada) that protected them from chemicals and gases. An air purification system was activated; it consisted of a series of portable air purifiers (Trotec, TAC 750 E, Trotec International GmbH & C. Sas, Verona, Italy) with filters for airborne dust, fumes,



**Figure 1.** ROTEM variables. A, The results are presented in a normal graphical plot. B, The results indicate hyperfibrinolysis and reduced clot firmness.<sup>12</sup>

and vapors. One volunteer in each team used a handheld gas detector (MineARC, Aura-PT 4 gas detector, Mine-ARC Systems, Perth, Australia) to monitor the gas levels within their immediate surroundings continuously. The handheld gas detectors were able to monitor the thresholds of O<sub>2</sub>, CO, CO<sub>2</sub>, and NO<sub>2</sub> gases instantaneously and

provided visual and vibration alerts. The allowed thresholds of toxic gases were CO <10 ppm, CO<sub>2</sub> <800 ppm, and NO<sub>2</sub> <5 ppm.<sup>5</sup>

An advanced medical presidium (AMP) was placed outside the cave. The AMP is a light and pneumatic tent-type structure from which a voluntary staff of doctors and

**Table 1.** Characteristics of rescuers

	Groups		P value
	NBG (n=46) n (%) or mean±SD	BG (n=47) n (%) or mean±SD	
Age, y	37±9	40±10	0.887
Sex			
Female	10 (11)	5 (22)	0.169
Male	36 (89)	42 (78)	
Smoking			
No	35 (74)	30 (65)	0.331
Yes	12 (26)	16 (35)	
BMI (kg·m <sup>2</sup> )	23.8±2.7	24.9±3.3	0.099
HR (beats·min <sup>-1</sup> )	85±17	92±12	0.014
DP (mm Hg)	74±6	70±7	0.013
SP (mm Hg)	128±12	122±13	0.027
S <sub>p</sub> O <sub>2</sub> (%)	95±19	98±1	0.193

BMI, body mass index; DP, diastolic pressure; HR, heart rate; SP, systolic pressure; S<sub>p</sub>O<sub>2</sub>, oxygen saturation.

**Table 2.** Parameters investigated at 2 follow-up times within the groups

Parameters	NBG (n=46)		BG (n=47)	
	Follow-up (mean±SD)		Follow-up (mean±SD)	
	T0	T1	T0	T1
pH	7.39±0.03	7.32±0.05	7.39±0.02	7.25±0.06
PO <sub>2</sub> (mm Hg)	106±19	75±9	96±13	65±5
PCO <sub>2</sub> (mm Hg)	37±4	50±7	38±4	58±5
HCO <sub>3</sub> <sup>-</sup> (mmol·L <sup>-1</sup> )	24±3	22±2	23±2	20±1
BE (mmol·L <sup>-1</sup> )	1±2	-6±2	0±1	-11±4
Na (mmol·L <sup>-1</sup> )	138±4	137±4	140±4	140±4
K (mmol·L <sup>-1</sup> )	4.3±0.4	4.3±0.4	4.2±0.5	4.2±0.5
iCa (mg·dL <sup>-1</sup> )	4.5±0.3	4.7±0.3	4.8±0.4	4.2±0.3
Hct (%)	45±6	45±6	45±4	45±4
S <sub>p</sub> O <sub>2</sub> (%)	95±19	92±3	98±1	87±2
eT (°C)	36.7±0.2	37.6±0.2	37.0±0.3	37.6±0.3
Hb (g·dL <sup>-1</sup> )	15±1	15±1	15±1	14±1
Glu (mg·dL <sup>-1</sup> )	97±12	95±9	77±7	73±8

BE, base excess; eT, epi tympanic temperature; Glu, glucose; Hb, hemoglobin; HCO<sub>3</sub><sup>-</sup>, bicarbonate; Hct, hematocrit; iCa, ionized calcium; K, potassium; Na, sodium; PCO<sub>2</sub>, partial pressure of carbon dioxide; pH, arterial blood; PO<sub>2</sub>, partial pressure of oxygen; S<sub>p</sub>O<sub>2</sub>, oxygen saturation measured by pulse oximetry.

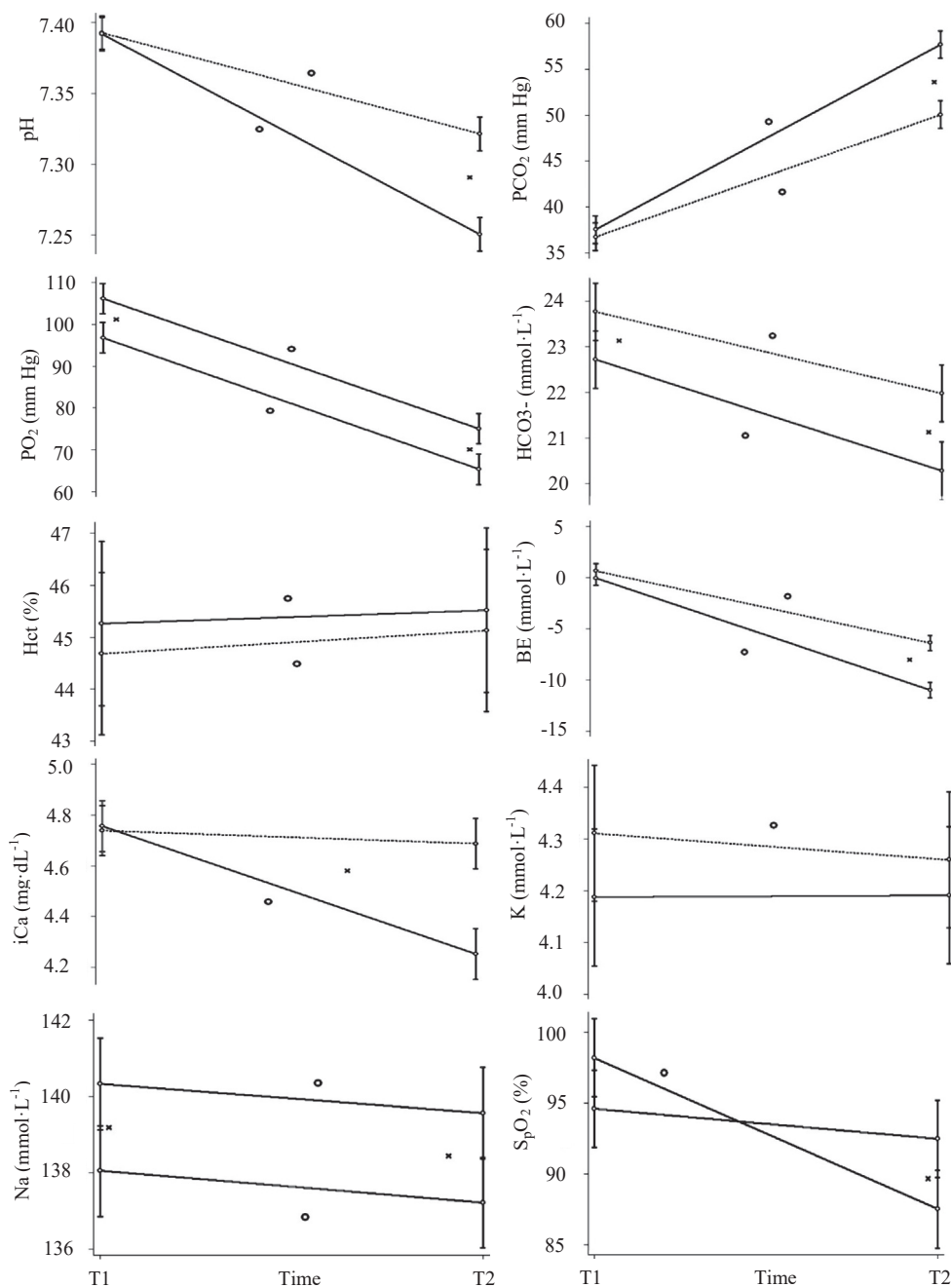
nurses operates.<sup>6</sup> The medical rescue team consisted of 2 anesthesiologists and 4 nurses with training in prehospital trauma life support and advanced cardiac life support protocols.<sup>7</sup> The anesthesiologists were also trained in the extended focused assessment with sonography for trauma (e-FAST) protocol. They performed the e-FAST assessment using double head convex (3.5-5.0 MHz) plus linear (7.5-10.0 MHz) color Doppler wireless transducers (wireless double head ATL linear/convex color Doppler echography probe, ATL s.r.l., Milan, Italy) connected to a tablet. The e-FAST protocol was performed to obtain scans of the abdominal, pleural, and pericardial space and bilateral lungs to detect free intraperitoneal, intrathoracic, and pericardial fluid and pneumothorax and to exclude the possibility of organ injuries. During the anterolateral chest scan, the number of B-lines was summed for a qualitative evaluation of lung congestion; up to 15 B-lines per single intercostal space was considered evocative for pulmonary congestion or edema.<sup>8</sup> The images from the e-FAST examination were captured and stored in the tablet.

The following data were collected before the rescuers entered the cave (T0): age, sex, body mass index (BMI), smoking status, HR, arterial blood pressure (diastolic pressure [DP] and systolic pressure [SP]), S<sub>p</sub>O<sub>2</sub>, epi tympanic temperature (eT), arterial blood gas analysis (ABGA), and hemostatic measurements (HMs). The vital signs were recorded using a multiparametric monitor (ARGUS PRO LifeCare2, SCHILLER AG, Baar, Switzerland), and eT was measured using an epi tympanic

probe (Braun ThermoScan PRO 6000 ear thermometer, Kronberg im Taunus, Germany).

The following blood gas tests were performed using an iSTAT handheld blood analyzer (iSTAT handheld; Abbott Point of Care, Inc.; Princeton, NJ) with CG8+ cartridges with arterial reference ranges: sodium (Na 138–146 mmol·L<sup>-1</sup>), potassium (K 3.5–4.9 mmol·L<sup>-1</sup>), ionized calcium (iCa 4.5–5.3 mg·dL<sup>-1</sup>), glucose (Glu 70–105 mg·dL<sup>-1</sup>), hematocrit (Hct 38–51%), hemoglobin (Hb 12–17 g·dL<sup>-1</sup>), pH (7.35–7.45), partial pressure of carbon dioxide (PCO<sub>2</sub> 35–45 mm Hg), partial pressure of oxygen (PO<sub>2</sub> 80–105 mm Hg), concentration of hydrogen carbonate (HCO<sub>3</sub> 22–26 mmol·L<sup>-1</sup>), base excess (BE [-2]- [+3] mmol·L<sup>-1</sup>), and arterial oxygen saturation (SaO<sub>2</sub> 95–98%).<sup>9,10</sup> A venous blood sample was obtained by venipuncture using a 21-gauge needle. Blood was collected in vacuum tubes (BD vacutainerVR citrate tubes 3.2%), and the first 3 mL of blood was always discarded.

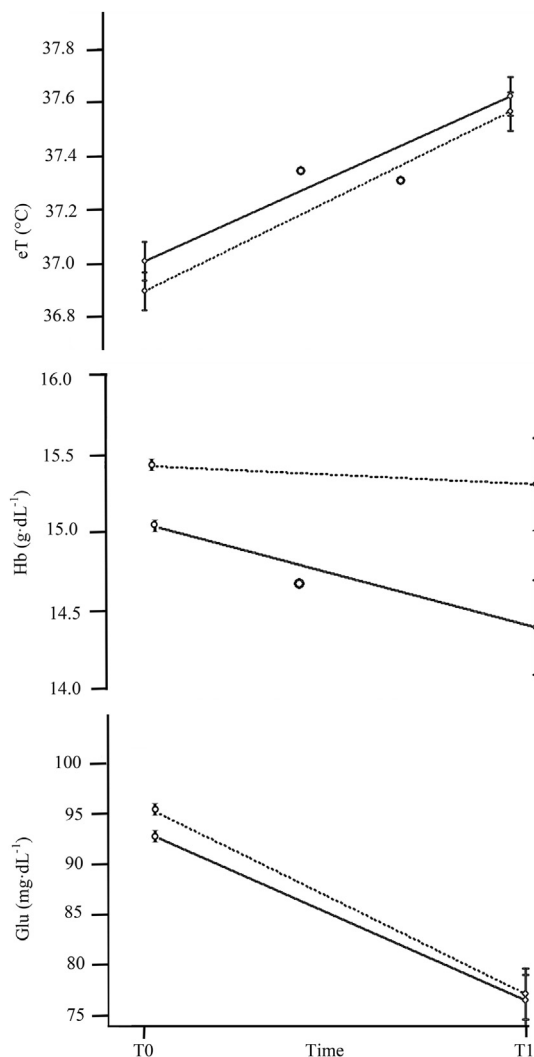
The HMs were evaluated using thromboelastometry (ROTEM delta analyzer, Tem International GmbH, München, Germany). Rotational thromboelastometry (ROTEM) is easy to use as a point-of-care assay in an emergency setting; it produces rapid graphical and numerical results for hemostatic status and is able to detect and quantify the cause of coagulopathy.<sup>11</sup> ROTEM measurements were performed within 30 min after blood sample collection and at least 15 min after venipuncture. The device temperature was set to 37°C, and the maximum runtime was 120 min.



**Figure 2.** Changes in blood gas parameters within the 2 groups over time (predicted mean with 95% confidence interval). **o** and **x** indicate significant differences within and between groups, respectively, at  $P < 0.05$ . The solid line indicates the blaster group (BG), and the dashed line indicates the nonblaster group (NBG). pH, arterial blood pH;  $PO_2$ , partial pressure of oxygen;  $PCO_2$ , partial pressure of carbon dioxide;  $HCO_3^-$ , bicarbonate; BE, base excess; Na, sodium; K, potassium;  $iCa$ , ionized calcium; Hct, hematocrit;  $S_pO_2$ , arterial oxygen saturation measured by pulse oximetry.

The ROTEM delta analysis was performed in parallel on the 4 channels using the following reagents: EXTEM to evaluate the extrinsic coagulation pathway, INTEM for the intrinsic coagulation cascade, FIBTEM to evaluate

the fibrinogen concentration, and APTEM for the detection of hyperfibrinolysis. These data resulted in a graphical plot (TEMogram) of clot firmness over time. Figure 1 shows normal and abnormal TEMograms.<sup>12</sup>



**Figure 3.** Changes over time for epitympanic temperature, glucose, and hemoglobin within the 2 groups (predicted mean with 95% confidence interval). o and x indicate significant differences within and between groups, respectively, at  $P < 0.05$ . The solid line indicates the blaster group (BG), and the dashed line indicates the nonblaster group (NBG). eT, epitympanic temperature; Hb, hemoglobin; Glu, glucose.

The following parameters were considered in the present study: clotting time (CT) in seconds and amplitudes of clot firmness as measured in millimeters at 5 (A5), 10 (A10), and 20 (A20) min after the start of clot formation, including maximum clot firmness.

Under aseptic conditions, the radial artery was punctured, and 1 mL of blood was subjected to ABGA. When gas exchange disorders were detected using the ROTEM delta analyzer, the volunteer was forbidden to go into the cave.

The iSTAT and ROTEM delta analyzers were placed in the AMP outside of the cave. Each rescuer recorded the duration of blasting gelatin handling using a

chronometer that was started at the first moment each volunteer handled the explosive. The detonation of microcharges at each point was remote-controlled, and the volunteers were in a safe place 50 m from the detonation area. Ten detonation sites were placed, with 30 microcharges at each site. One detonation was allowed at a time, and after each detonation, the purification devices were set to clean the air inside the cave until the gas detectors recorded a safe breathing level.<sup>5</sup>

After uncontrolled detonation, each volunteer exited the cave as soon as possible and immediately reached the AMP (T1); the following parameters were recorded: HR, DP, SP,  $S_pO_2$ , eT, ABGA, and HMs. Symptoms related to the toxic gas levels were also recorded. The e-FAST assessment was performed.

### STATISTICAL ANALYSIS

Descriptive statistics were calculated for all the variables in the study and reported as the mean  $\pm$  SD or frequency, depending on the scale level and distribution. The  $\chi^2$  test or Fisher's exact test was used to analyze categorical variables. Continuous variables were tested for normality with the Shapiro-Wilk test and analyzed using the independent-samples t test to compare means or the Wilcoxon rank-sum test when adequate. A  $P < 0.05$  was considered statistically significant. Repeated-measures analysis of variance with the group (BG versus NBG) as the between-subjects factor and time as the within-subjects factor was used to assess the presence of significant differences in the blood parameters investigated between the groups. The statistical analysis was performed using STATA 14 software.<sup>13</sup>

### Results

Ninety-three volunteers went inside the cave. Table 1 shows the baseline characteristics recorded before they entered the cave; significant differences in the HR, DP, and SP between the groups were reported.

During the enlargement procedure, the remote controller for the detonation malfunctioned, resulting in the uncontrolled blasting of all the microcharges simultaneously and a subsequent blackout of the cave electric network.

The purification devices stopped working, and acceptable toxic gas levels were likely exceeded within a few minutes. The atmosphere of the cave was saturated by fumes and vapors from the uncontrolled detonation. The thresholds of the detected toxic gases were impossible to obtain because all rescuers had to escape from the cave rapidly without concern for their protective equipment, which resulted in serious damage. In addition, they

lost the handheld gas detectors because of the dangerous environment of the cave; thus, the volunteers from the 2 groups were exposed to toxic levels of combustion products in the narrow portions of the cave. All volunteers reached the AMP outside the cave after an average of 110 min.

After the accident, significant differences were confirmed in the following parameters between the NBG and BG: HR ( $134 \pm 14$  beats·min<sup>-1</sup> vs  $119 \pm 13$  beats·min<sup>-1</sup>,  $P < 0.001$ ), DP ( $92 \pm 10$  mm Hg vs  $85 \pm 9$  mm Hg,  $P = 0.003$ ), and SP ( $171 \pm 15$  mm Hg vs  $124 \pm 24$  mm Hg,  $P < 0.001$ ).

Table 2 summarizes the results of the ABGA at 2 follow-up visits within the groups. The changes in each blood gas parameter over time and the differences between the 2 groups investigated using the repeated measures analysis of variance model are shown in Figures 2 and 3.

As reported in Figure 2, no statistically significant differences in the pH, PCO<sub>2</sub>, HCO<sub>3</sub><sup>-</sup>, BE, Hct, iCa, K, and S<sub>p</sub>O<sub>2</sub> values were observed between the rescuers in the BG and NBG ( $P > 0.05$ ) before entering the cave, whereas statistically significant differences in PO<sub>2</sub>, HCO<sub>3</sub><sup>-</sup>, and Na values were noted ( $P < 0.05$ ). After the accident, statistically significant differences ( $P < 0.05$ ) were observed in the following blood gas values within the groups: pH, PO<sub>2</sub>, PCO<sub>2</sub>, HCO<sub>3</sub><sup>-</sup>, BE, iCa, Na, and S<sub>p</sub>O<sub>2</sub>. Figure 2 shows the differences in the ABGA within the groups. The explosive specialists exhibited a more significant loss of bicarbonate, and hypocalcemia was recorded (Figure 2). No differences in eT and Glu were observed at T0 between the BG and NBG; Hb levels decreased over time, with a significant difference between the 2 groups observed at T1 ( $P < 0.05$ ), as reported in Figure 3.

No respiratory disturbances were reported in either group before entering the cave. After the uncontrolled detonation, respiratory symptoms such as cough, tachypnea, and respiratory distress were noted in 41 volunteers in the BG and 6 volunteers in the NBG, with a statistically significant difference between the 2 groups ( $P < 0.05$ ). Rescuers in the BG with respiratory symptoms had diffuse wheezing on chest evaluation.

AN e-FAST assessment of the volunteers in both groups was performed, but no free intraperitoneal, intrathoracic, or pericardial fluid, pneumothorax, or organ injuries were noted. Bleeding from the nose and gums and blood-stained oral secretions were present in 34 volunteers in the BG and 12 volunteers in the NBG ( $P < 0.05$ ).

All volunteers had a normal TEMogram at T0. After the accident, the following HMs were recorded on average in 44 volunteers in the BG:  $270 \pm 10$  s for CT (normal range: 100–240),  $33 \pm 15$  mm for maximum clot firmness (normal range: 50–72), alpha angle of  $51 \pm 5^\circ$ ,

A5 of  $20 \pm 4$  mm, A10 of  $27 \pm 8$  mm, and A20 of  $34 \pm 13$  mm. Complete clot lysis was reported after 60 min. In contrast, no significant TEMogram modifications were recorded in the NBG at T1.

In AMP, peripheral venous access (16 G) was obtained in 12 rescuers from the BG with tachypnea, wheezing, respiratory distress with hypoxia and hypercapnia, and TEMogram abnormalities. They received an intravenous injection of a total of 500 mL of crystalloid solution and noninvasive ventilatory support with oxygen via a Venturi mask ( $12$  L·min<sup>-1</sup>). Two hundred micrograms of nebulized salbutamol and 250 mg of intravenous hydrocortisone were also administered to these rescuers.<sup>14</sup> They were rapidly hospitalized.

## Discussion

In this study, we investigated the short-term changes in arterial blood gas and ROTEM parameters in healthy rescuers who handled nitroglycerin and nitrogen compounds and were accidentally exposed to blasting gelatin fumes in an austere environment.

Potential confounders, such as age, sex, smoking status, and BMI, had no significant influence on the models. Before the rescuers entered the cave, significant differences in their HR, DP, and SP were likely due to the BG rescuers transporting the tools for microcharge packing without being exposed to the explosives before data collection.

Little scientific evidence is available to support the hypothesis that acid-base disorders in healthy adults are related to exposure to nitroglycerin<sup>15</sup> and the nitrogen compounds in blasting gelatin. Nitrogen compounds in blast form at airborne concentrations up to lethal inhalation levels (eg, 3000 ppm) have minimal skin penetration ability, but skin absorption and reservoir effects have been described.<sup>16</sup> Potential secondary inhalation should be avoided by removing the outer layer of protective clothing. Decontamination and movement into an area of enhanced ventilation are also advised.<sup>16</sup> In the austere environment of the cave, with poor ventilation, decontamination of the full-body suits was not possible. In addition, after uncontrolled detonation, the rescuers seriously damaged their protective equipment. Thus, during microcharge packing or detonation, molecules of nitroglycerin and nitrogen compounds remained on the suits and then were probably inhaled or remained on the skin of the explosive specialists during their escape from the cave, penetrating into the body.

Nitroglycerin reduces pulmonary artery pressure<sup>17</sup> because it is metabolized to NO, which is a potent vascular smooth muscle relaxant in vascular endothelial

cells.<sup>18</sup> Inhaled nitroglycerin and NO easily cross the alveolar-capillary barrier and stimulate soluble guanylate cyclase in the smooth muscle of the microcirculatory network near the alveoli,<sup>19</sup> producing pulmonary vasodilation with a reduction in pulmonary artery pressure, pulmonary vascular resistance, and right ventricular afterload while avoiding systemic hypotension.

Therefore, nitroglycerin and nitrogen compounds produce vasodilation with a reduction in pulmonary vascular resistance and an increase in blood flow to these areas, whereas acute exposure to toxic gases may rapidly induce inflammatory responses, oxidative injury, and the death of bronchial epithelial cells before ultimately impairing the respiratory membrane of the lungs.<sup>20</sup> Thus, after uncontrolled detonation, we speculate that the respiratory epithelium of the rescuers in the BG was more permeable to inhaled toxic molecules from the combustion pollutants, with a subsequent increase in absorption from the pulmonary to systemic circulation. Consequently, nitroglycerin and nitrogen compounds were not directly responsible for respiratory acidosis, but they enhanced the toxicity of the other gaseous pollutants. Under this condition, pulmonary gas exchange function was impaired, resulting in severe respiratory acidosis with hypoxia and hypercapnia and a compensatory metabolic response. This biological mechanism might also explain the differences in HR, SP, and DP between the groups at the 2 follow-up time points. After the accident, the increased absorption of air pollutants may also have influenced the systemic vasculature. In effect, the short-term inhalation of air particulate pollutants over the allowed threshold causes acute arterial vasoconstriction by generating systemic inflammation and cytokine production,<sup>21</sup> which are possibly related to the free radical activity of components in particulate matter<sup>22</sup> and to the impairment of large artery endothelial function.<sup>23</sup> In addition, exposure to acute and massive concentrations of nitrous oxide presumably present in the atmosphere of the cave after the accident might promote beta-adrenergic activation with increased cardiac output, HR, and blood pressure.

A possible explanation for the conflicting findings of our research is that vasodilatation is the primary consequence of nitroglycerin and nitrogen compound toxicity on the one hand, and arterial vasoconstriction with higher HR and blood pressure in the BG may be related to the inhalation of particulate air pollution and gaseous pollutants on the other hand.

Glycemia and Hb levels decreased in all rescuers, with significant differences in Hb levels between the 2 groups. We hypothesize that the decrease in Hb levels might be related to bleeding from the airways, or presumably due to hemodilution because rescuers with bleeding symptoms

drank water because of thirst (1500 mL, on average) during the evacuation from the cave. However, lung inhalation injury, inhalation burn injury, or other bleeding sources were not excluded in rescuers who were bleeding, especially because their personal protection equipment was destroyed and they were exposed to the airborne dust produced from the explosion of dolomite rocks.

Primary blast injuries are a complex type of trauma resulting in damage to gas-containing organs such as the lungs.<sup>24</sup> The shock wave from detonations can lead to mild blast injury to the lungs owing to increased intrathoracic pressure or chemical/thermal damage, leading to acute inflammatory responses<sup>25</sup> with small artery reactive hyperemia and pulmonary capillary rupture.<sup>26</sup> Based on this information, we hypothesize that this lung injury may have resulted in the airway bleeding observed in the 2 groups, potentially because all rescuers were exposed to gases for 110 min, on average. A chest x-ray and bronchoscopy would be necessary but was impractical in the context. The literature lacks clear evidence for the use of lung ultrasonography as a suitable tool for diagnosing mild blast injury to the lung and concurrent pulmonary bleeding in adults<sup>27–29</sup>; thus, in this experience, lung ultrasonography could not confirm the diagnosis of mild blast injury to the lung because no organ injuries were noted.

A pattern of mild hyperfibrinolysis<sup>30</sup> was observed, especially in explosive specialists. Fibrinolysis related to shockwave trauma has a wide spectrum of activity with a complex multifactorial process that is often affected by the amount of tissue injury the individual sustains.<sup>31</sup> The ROTEM delta analysis provided a picture of hemostasis due to the ability to assess coagulation factors, platelet function, and fibrinolytic activity.<sup>32</sup> Thus, we hypothesize that inhaled NO-releasing agents may increase fibrinolytic capacity<sup>33</sup> and modulate clotting by decreasing coagulation protein function and platelet function.<sup>34</sup> In addition, a decreased pH combined with a low calcium level may also influence clot and platelet function, resulting in mild coagulopathy predisposing the individual to increased bleeding<sup>35,36</sup> such that the effect of one factor may enhance the effects of the others.

## LIMITATIONS

This retrospective cohort study analyzed clinical data from rescuers involved in a cave accident. The incident was not planned, but it provided an opportunity to perform our research, which could be considered the principal limitation of the study.

After the accident, we were unable to clearly determine which agent(s) caused changes in arterial blood gas and ROTEM parameters because the threshold of the toxic gases detected was impossible to record. We



hypothesize that the rescuers were exposed to toxic gas levels over the allowed threshold for the entire time spent exiting the cave.

In addition, the rescuers were significantly exposed to many other toxic agents not measured by the detectors, such as dust, quartz, and other volatile compounds. We could not collect these data because of the harsh environment and the emergency situation, which was another limitation of this study. Another important drawback of this research was the lack of methemoglobinemia and lactate values in the arterial blood gas tests; the cartridges used for our iSTAT handheld blood analyzer did not include these parameters, and we were unable to collect these data. Although methemoglobin intoxication was suspected, the clinical signs required to confirm this diagnosis were not recorded. Sulfur dioxide and cyanide may also have been liberated in the blast and might have contributed to the clinical symptoms related to uncontrolled detonation. Unfortunately, we were unable to measure their levels in the atmosphere of the cave using handheld gas detectors, which were not able to detect these gases; in addition, all rescuers lost their handheld gas detectors during their escape from the cave. Last, a kappa test was not used for interrelater reliability for the clinical examination or e-FAST, which is another limitation of this research.

## Conclusions

The higher blood pressure, respiratory acidosis with hypoxia, hypercapnia, a compensatory metabolic response, and mild hyperfibrinolysis were probably related to a combined effect of nitrogen compounds and the inhaled toxic products of the detonation. Each element exerts a determinant effect in promoting the biological toxicity of the others. This information could be useful for providing a strategy for future clinical interventions in individuals with acute exposure to nitrogen compounds combined with massive inhalation of air pollutants.

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