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Inhalation Effect of Heated Helium-Oxygen Mixture and Nitric Oxide on Gas Exchange Parameters in Patients with Polytrauma and Pulmonary Contusion

Yuri E. Kostyrya[1,2]*, Nikolay I. Gulyaev[1], Roman E. Lakhin[3], Anna F. Kostyrya[4]

[1] National Medical Research Center for High Medical Technologies — A. A. Vishnevsky Central Military Clinical Hospital, Ministry of Defense of the Russia, 1 Novy township, Krasnogorsk Urban District, 143420 Moscow Region, Russia
[2] Clinical Hospital, Medical and Sanitary Unit, Ministry of Internal Affairs of Russia for Moscow, 3a Novaya Ipatovka Str., 127299 Moscow, Russia
3 S. M. Kirov Military Medical Academy, 6 Academician Lebedev Str., B, 194044 St. Petersburg, Russia
[4] Moscow City Oncology Hospital No. 62, Moscow City Health Department, 27 Istra Township, Krasnogorsk Urban District, 143515 Moscow Region, Russia

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***Correspondence to:** Yuri E. Kostyrya, urry.k@yandex.ru

Summary

The heated helium-oxygen mixture (t-He/O_2, heliox) reduces resistance in the airways and improves ventilation in affected zones of the lungs. Inhaled nitric oxide (NO) is a selective pulmonary vasodilator that lowers pressure in the pulmonary artery and enhances the ventilation-perfusion matchig, which also contributes to the optimization of oxygenation.

The aim of the study is to assess the efficacy and safety of adding inhaled NO, t-He/O_2, and their combination to standard respiratory therapy in patients with polytrauma and pulmonary contusion.

Materials and Methods: We conducted an open prospective randomized study. 186 patients were divided into 4 groups: the NO group (n=43), the t-He/O_2 group (n=49), the t-He/O_2 + NO group (n=48), and the control group (oxygen therapy, O_2, n=46). The respiratory therapy course lasted 12 days. We assessed the dynamics of computed tomography (MSCT) signs of pulmonary contusion, as well as the arterial blood gas (ABG) parameters (PaO_2, $PaCO_2$, SaO_2, lactate, pH) on days 1, 4, 8, and 12.

Results. The most remarkable improvements were documented in the combination therapy group (t-He/O_2 + NO). By day 12, this group showed a statistically significant 69% reduction in the extent of lung injury on MSCT (p=0.018), an increase in PaO_2 to 95.1 mm Hg (p< 0.001), a decrease in $PaCO_2$ to 35.8 mm Hg (p< 0.001), and a reduction in lactate to 1.38 mmol/L (p=0.0025). The same parameters in the monotherapy groups NO or t-He/O_2 also markedly improved compared to the control group (O_2). No therapy-related adverse events were reported.

Conclusion. Employment of inhaled t-He/O_2 and NO, especially in combination, as a part of the total care plan of patients with polytrauma and pulmonary contusion, contributes to a significant improvement in gas exchange and regression of radiographic signs of lung tissue injury. Thereby, described method is recommended for early respiratory therapy in intensive care units.

Keywords: helium-oxygen mixture; heliox; inhaled nitric oxide; polytrauma; pulmonary contusion; respiratory therapy; blood gas composition

Highlight. A 12-day respiratory therapy course with inhaled NO and heated helium-oxygen mixture accelerates recovery from pulmonary contusion and improves gas exchange parameters in patients with polytrauma.

Conflict of interest. The authors declare no conflict of interest.

Information about the authors:
Yuri E. Kostyrya: https://orcid.org/0009-0006-1037-8607
Nikolay I. Gulyaev: https://orcid.org/0000-0002-7578-8715
Roman E. Lakhin: https://orcid.org/0000-0001-6819-9691
Anna F. Kostyrya: https://orcid.org/0009-0001-0453-4910

Introduction

Polytrauma remains one of the leading causes of mortality and disability among working-age individuals, representing a significant medical and social issue, particularly for the healthcare system of law enforcement agencies [1–5]. A distinctive pathophysiological feature of polytrauma is the syndrome of mutual buffering, where the simultaneous presence of two or more injuries causes a disproportionate worsening of patient's overall health status due to destructive synergy between co-occurring conditions [3–6]. Pulmonary contusion,

as a common component of polytrauma, is an independent risk factor for the development of acute respiratory failure (ARF), prolongs the duration of mechanical ventilation (MV), and increases overall mortality [2–5, 7, 8].

The mainstay of respiratory support for a pulmonary contusion is respiratory therapy aimed at optimizing oxygenation and ventilation. The search for adjunctive methods that can improve gas exchange and shorten the time needed for lung function recovery is an important issue in intensive care.

Helium-oxygen mixture (heliox), due to helium's low density, reduces resistance in the airways and improves ventilation in areas with turbulent flow, which could theoretically be beneficial in the edema and obstruction accompanying pulmonary contusion [9–13]. Thermal modification of the heated heliox, namely heating it immediately before inhalation to 70–90°C, may further improve the rheological properties of sputum and mucociliary clearance. Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator that reduces pulmonary artery pressure and improves ventilation-perfusion matching, thereby also helping optimize oxygenation [14–17].

Numerous studies have confirmed that nitric oxide (NO) is a fundamental regulator of metabolic processes in all living organisms, exhibiting a wide range of biological effects. These findings have helped elucidate the mechanisms by which NO functions in biological systems. The physicochemical properties of neutral NO molecules, which are produced in the human body through enzymatic synthesis, explain their dual action on target organs. NO molecules can both regulate and exert cytotoxic effects on cells and tissues [16, 18–21].

NO is a key mediator involved in a wide range of biochemical processes that are critically important for regulating physiological functions at the cellular level. Its role in signaling, both intercellular and intracellular, helps maintain the body's homeostasis. In particular, in the cardiovascular system, NO induces vasodilation by activating an endothelium-dependent mechanism of relaxation of vascular smooth muscle [8, 17, 18, 20].

The main effect of inhaled nitric oxide on the body is its direct action on the vessels of the pulmonary circulation, through which various mechanisms of improved gas exchange are effectuated. In addition, its direct regulatory effect on the smooth muscle of the bronchial tree helps reduce resistance to the gas mixture flowing through it [14–17]. The advantage of heated heliox in pathological bronchoconstriction lies in its very low viscosity and high flowability, which ensure a high capacity to penetrate the alveoli and provide a direct thermal effect [9–13].

Despite the well-established effects of helium-oxygen mixtures and nitric oxide individually, data on simultaneous use of both — especially in combination of iNO with heated heliox — in patients with traumatic lung injury are limited.

The aim of the study: to evaluate the efficacy and safety of adding inhaled nitric oxide (NO), heated heliox, and their combination to standard respiratory therapy in patients with polytrauma and pulmonary contusion.

Materials and Methods

An open-label, single-center, interventional, prospective, randomized clinical study was conducted in the intensive care units of the National Medical Research Center for High Medical Technologies — A. A. Vishnevsky Central Military Clinical Hospital of the Russian Ministry of Defense (A. A. Vishnevsky NMRC HMT) from September 2023 to May 2025. The study was approved by the Ethics Committee of A. A. Vishnevsky NMRC HMT (research project «Helium,» protocol No. 14/23 dated July 20, 2023; research project «Helium+», protocol No. 2/25 dated February 27, 2025).

Totally 15,846 patients with multiple trauma were subjected to chest MSCT screening upon admission to the medical facility. Of these, 468 patients had lung injury as the predominant problem in the setting of polytrauma, manifested as pulmonary contusion and respiratory failure without signs of inflammation. A total of 192 patients meeting the inclusion criteria were selected for the study (all men; mean age 31 ± 7 years). Of these, 186 completed the study protocol in full, and 6 patients were excluded because of emerging inflammatory changes in pulmonary tissue in four, and acute kidney injury requiring renal replacement therapy in two patients (Fig. 1).

Inclusion criteria: patients of both genders aged 18–65 years with a confirmed diagnosis of polytrauma and pulmonary contusion (based on emergency chest MSCT), signs of respiratory failure ($SaO_2 \leqslant 95\%$, $PaO_2 \leqslant 80$ mm Hg), who signed informed consent.

Exclusion criteria: isolated chest trauma; bacterial pneumonia at admission; severe organ pathology (renal dysfunction with a glomerular filtration rate below 30 mL/min/1.73 m², need for hemodialysis, liver failure with signs of cytolysis, decompensated diabetes mellitus, oncologic or hematologic diseases); need for extracorporeal membrane oxygenation (ECMO); and participation in other clinical trials.

Group allocation: 186 patients who met the inclusion criteria were randomized using sealed envelopes into 4 groups:

Group 1 (NO), $n = 43$: standard of care + NO inhalations at a dose of 30 ppm via the Tianox device (AIT-NO-O1, according to Technical Specifications TU 32.50.21-001-07623615-2017), twice a day for 20 minutes each session.

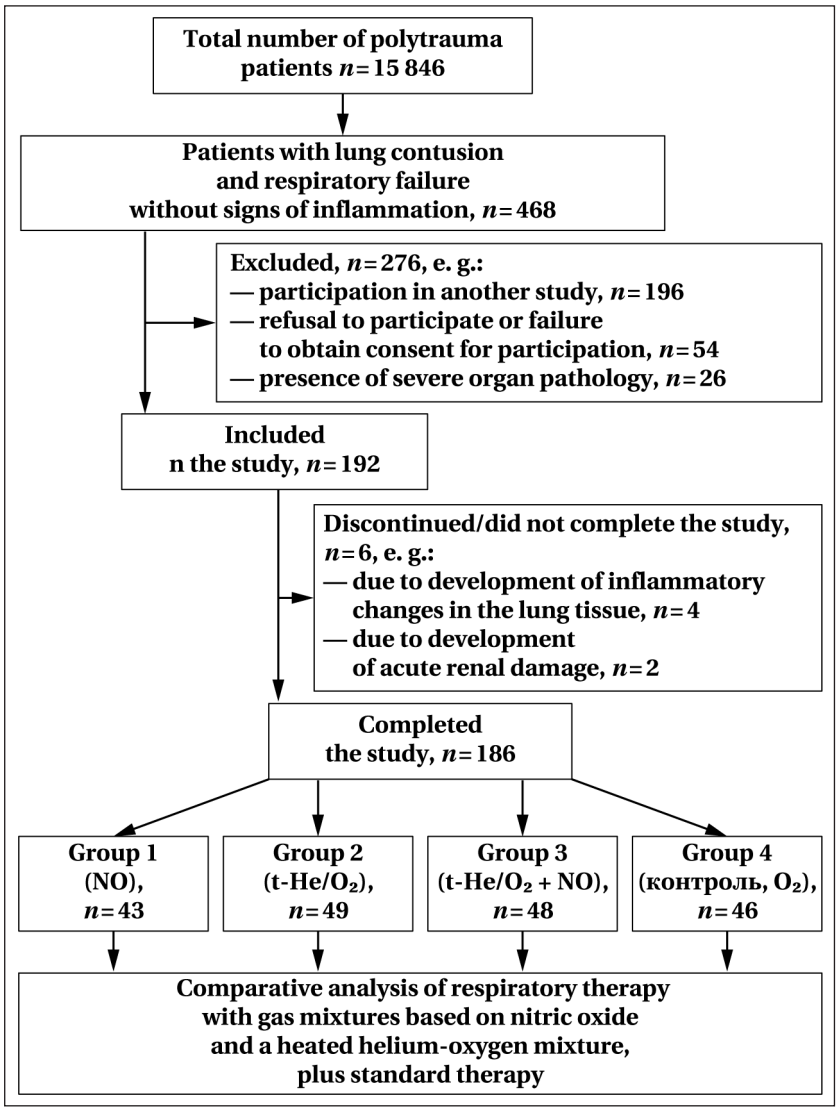

Fig. 1. Flowchart of patient selection for the study.

Group 2 (t-He/O_2, heated heliox), $n=49$: standard of care plus inhalations of heated helium-oxygen mixture (65–75% He, 25–35% O_2, temperature 70–90°C) administered via the Heliox Extreme device (RZN 2016/3988, TU 9444-001-0116489960-2015) twice daily for 20 minutes.

Group 3 (t-He/O_2 + NO), $n=48$: standard of care + co-inhalations (t-He/O_2 + NO) according to the same regimen.

Group 4 (control, O_2), $n=46$: standard of care plus oxygen therapy via a Venturi mask (O_2 flow rate of 6 L/min) twice daily for 20 minutes.

Standard therapy in all groups was administered in accordance with current clinical guidelines and included adequate pain management, respiratory support when indicated, antibacterial therapy, and infusion therapy.

Measured parameters. The study's primary endpoint was the change in PaO_2 (arterial oxygen partial pressure) by day 8 of therapy. In addition to PaO_2, changes in several arterial blood gas (ABG) parameters ($PaCO_2$, SaO_2, lactate, pH) and MSCT-based extent of pulmonary lesion resolution were assessed. Evaluations were performed at baseline (day 1) and on days 4, 8, and 12 of therapy. The severity of lung contusion was assessed using a modified classification: CT-1 (mild), CT-2 (moderate), and CT-3 (severe) [8].

Sample size justification. The sample size was calculated for the primary endpoint, namely the change in PaO_2 (arterial oxygen partial pressure) by day 8 of therapy. Based on a retrospective analysis of medical records of patients with polytrauma and pulmonary contusion at our center, the minimum clinically meaningful between-group difference was set at 12 mm Hg. The standard deviation (*SD*) of PaO_2 in the study population was 7.0 mm Hg.

The statistical calculation was performed using G*Power software (version 3.1.9.7, Universität Düsseldorf, Germany) for a one-way analysis of variance (ANOVA) with four groups. The following values were considered statistically significant: significance level $\alpha=0.05$ (two-sided), statistical power $(1–\beta)=0.80$, and expected effect size Cohen's $f=0.50$ (corresponding to a ratio of the difference in means to the standard deviation, $\triangle/SD \approx 12/7=1.71$, converted to f for four groups).

To control Type I error in multiple pairwise comparisons, we used the Bonferroni correction: the number of comparisons among the four groups was 6, so the adjusted significance level was $\alpha\_adj = 0.05 / 6 \approx 0.0083$.

Calculation result: the minimum required sample size was 21 patients per group. Taking into account possible attrition (about 10% due to the development of inflammatory changes, acute kidney injury, and other reasons), the planned group size was set at 23 patients.

In fact, after randomization and the exclusion of 6 patients, each group included 43 to 49 patients, which was 1.9–2.1 times more than the calculated minimum. Statistical power was calculated for a one-way analysis of variance (ANOVA) with four groups, a total sample size of $n=192$, a significance level of $\alpha=0.05$, and Cohen's $f=0.50$, using G*Power software (version 3.1.9.7, Universität Düsseldorf,

Table 1. Anthropometric, clinical, and laboratory parameters of patients.

Parameters	Parameter values in the groups				*p*
	NO, *n* = 43	t-He/O_2, *n* = 49	t-He/O_2 + NO, *n* = 48	O_2 *n* = 46	
Age, years	32 ± 7	30 ± 6	30 ± 7	32 ± 6	0.779
Gender, m	43 (100%)	49 (100%)	48 (100%)	46 (100%)	0.999
Height, cm	175 ± 6	174 ± 5	175 ± 7	173 ± 7	0.741
Weight, kg	76.8 ± 6.8	77.4 ± 8.1	75.9 ± 8.6	77.2 ± 7.6	0.861
Body mass index, kg /m²	25.6 ± 4.8	24.9 ± 5.3	25.1 ± 4.9	25.8 ± 5.6	0.863
BMI > 25kg/m²	12 (28%)	16 (32%)	17 (35%)	14 (30%)	0.902
HR, bpm	92 ± 14	86 ± 12	88 ± 15	90 ± 14	0.668
Pulmonary lesion MSCT (on admission)*, scores	1.96 (1.45–2.47)	1.92 (1.36–2.56)	2.0 (1.39–2.61)	1.94 (1.33–2.55)	0.675
PaO_2 (on admission) mm Hg	72.1 ± 6.9	74.3 ± 9.7	73.1 ± 8.4	72.8 ± 8.8	0.807
$PaCO_2$ (on admission) nm Hg	47.2 ± 6.8	48.4 ± 7.6	48.3 ± 7.7	47.0 ± 7.5	0.850
SaO_2 (on admission), %	91.6 ± 1.4	92.3 ± 2.1	91.9 ± 1.9	92.0 ± 2.2	0.780
Lactate level (on admission), mmol/L	4.12 ± 0.78	3.86 ± 1.12	3.92 ± 0.84	4.01 ± 1.22	0.766
pH (on admission)	7.33 ± 0.07	7.32 ± 0.07	7.32 ± 0.07	7.33 ± 0.07	0.886
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extremities*	2.3(1–4)	2.4(1–4)	2.3(1–4)	2.4(1–4)	0.950
head*	2.6(1–4)	2.5(1–4)	2.5(1–4)	2.6(1–4)	0.953
neck*	0.3(0–1)	0.2(0–1)	0.3(0–1)	0.3(0–1)	0.841
face*	0.2(0–1)	0.2(0–1)	0.2(0–1)	0.3(0–1)	0.841
chest*	9(9–9)	9(9–9)	9(9–9)	9(9–9)	0.999
abdomen*	2.8(1–4)	2.6(1–4)	2.7(1–4)	2.8(1–4)	0.964
external* and other trauma	2.2(1–4)	2.4(1–4)	2.3(1–4)	2.0(1–4)	0.790

Note. Data in Tables 1 and 2 are presented as *M* ± *SD*, where *M* is the arithmetic mean and *SD* is the standard deviation. ISS1 — severity of combined injury by body region according to the Injury Severity Score (ISS), scores. * — Data are presented as *Me*, the median, (*Q1–Q3*) — lower and upper quartiles.

Germany) for the specified parameters. Power was approximately 1.00 (or 100%). Even after applying the Bonferroni correction, statistical power remained very high (99%), ensuring the reliability of the conclusions for all planned between-group comparisons.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel LTSC MSO (16.0.14332.20761) (Microsoft Corp., Redmond, Washington 98052-6399, USA). The normality of distributions was assessed using the Shapiro–Wilk test and Pearson's χ^2 test. Variables that followed a normal distribution were described using arithmetic means *(M)*, standard deviations *(SD)*, and 95% confidence intervals (95% CI). In cases of non-normal distribution of quantitative data, they were described using the median *(Me)* and the lower and upper quartiles *(Q1–Q3)*. Continuous numerical data from independent samples were compared using Student's *t*-test, while paired samples were compared using the *t*-test for dependent observations. Differences between groups involving variables with non-normally distributed data were assessed using the Mann–Whitney *U* test and the Wilcoxon signed-rank test. Proportions in groups and categorical variables were compared using Pearson's chi-square test or Fisher's exact test (when the outcome frequency was less than 10%). Differences in group mean values were assessed using analysis of variance (ANOVA). The results of multiple comparisons were adjusted using Tukey's method for pairwise mean differences and a significance-level correction (Bonferroni adjustment). As a quantitative measure of effect when comparing relative measures, odds ratios *(ORs)* were used, with 95% confidence intervals calculated. Differences were considered statistically significant at $p < 0.05$.

Generative artificial intelligence. No generative AI technologies were used in creating this article.

Results

Baseline characteristics of the groups: patients' baseline demographic, clinical, and laboratory parameters were comparable in all four groups ($p > 0.05$), confirming the validity of the randomization (Table 1). All patients were male, which was related to epidemiology of polytrauma. Patients' mean age was 31 ± 7 years. Moderate lung contusion (CT-2) predominated, accounting for 77% of cases.

Dynamics of MSCT findings: on day 12 of follow-up, the most remarkable reduction in the volume of pulmonary involvement was observed in the combination therapy group t-He/O_2+NO (69% decrease from baseline, $p = 0.018$) and in the t-He/O_2 group (62% decrease, $p = 0.044$). In the NO group, the regression was 54% ($p = 0.09$), and in the O_2 control group, 42% ($p = 0.230$) (Fig. 2).

Dynamics of ABG panel parameters. SaO_2: by day 4, SaO_2 had increased significantly in all study groups compared with the control group ($p < 0.05$), reaching its highest value in the t-He/O_2+NO group (96.6%). By day 12, SaO_2 had stabilized at 97.4% in

Table 2. Dynamics of monitored ABG parameters over 12 days of therapy.

Parameters, day	Parameter values in the groups			
	NO, $n=43$	t-He/O_2, $n=49$	t-He/O_2 + NO, $n=8$	O_2 $n=46$
SaO_2, %				
1st	91.6±1.4	92.3±2.1	91.9±1.9	92.0±2.2
4th	95.6±1.1*	96.1±1.3*	96.6±1.1*	94.0±2.2
8th	96.1±1.3	97.8±1.1	98.9±0.7	94.7±1.9
12th	96.6±1.4	98.8±0.8	99.1±0.8	95.0±2.8
p, 1-e and 12th	$p<0.001$	$p<0.001$	$p<0.001$	$p=0.285$
PaO_2, mm Hg				
1-e	72.1±6.9	74.3±9.7	73.1±8.4	72.8±8.8
4th	82.7±5.9	85.8±6.3	86.7±5.6	81.3±7.1
8th	88.1±6.9	95.3±4.5	95.1±4.4	82.8±4.8
12th	92.8±5.1	97.1±1.9	98.3±0.9	90.1±8.2
p, 1-e and 12th	$p<0.001$	$p<0.001$	$p<0.001$	$p=0.036$
$PaCO_2$, mm Hg				
1st	47.2±6.8	48.4±7.6	48.3±7.7	47.0±7.5
4th	43.2±5.8	42.4±4.6	40.9±6.1	45.2±6.5
8th	39.2±3.2	36.4±2.6	36.1±2.1	42.4±6.1
12th	37.2±4.1	36.1±2.3	35.9±2.7	39.8±4.5
p, 1-e and 12th	$p=0.015$	$p<0.001$	$p<0.001$	$p=0.110$
Arterial blood lactate, mmol/L				
1st	4.12±0.78	3.86±1.12	3.92±0.84	4.01±1.22
4th	2.66±0.62*	2.12±0.68*	2.06±0.74*	3.1±1.18
8th	1.78±0.84	1.54±0.91	1.48±0.88	2.45±1.32
12th	1.82±0.96	1.36±0.85	1.38±0.84	2.34±1.14
p, 1st and 12th	$p=0.017$	$p=0.003$	$p=0.003$	$p=0.144$
Arterial blood pH				
1st	7.33±0.07	7.32±0.07	7.32±0.07	7.33±0.07
4th	7.36±0.07	7.36±0.07	7.36±0.07	7.36±0.07
8th	7.39±0.07	7.40±0.07	7.40±0.07	7.35±0.07
12th	7.38±0.07	7.42±0.07	7.43±0.07	7.36±0.07
p, 1st and 12th	$p=0.481$	$p=0.155$	$p=0.116$	$p=0.667$

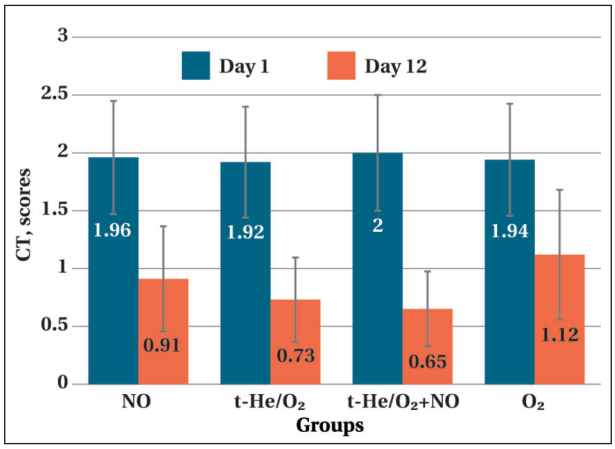

Fig. 2. Changes in CT findings of pulmonary contusion in the groups.

the study groups vs 95.0% in the control group (Table 2).

PaO_2. A significant increase in PaO_2 by day 8 was observed in all groups; however, the increase was most remarkable in the t-He/O_2 and t-He/O_2+NO groups (to 95.3 and 95.1 mmHg, respectively; $p<0.001$), exceeding the values in the control group (82.8 mmHg, $p=0.040$) (Table 2).

$PaCO_2$. A statistically significant decrease in $PaCO_2$ by day 8 was observed in the t-He/O_2 group (36.4 mm Hg, $p=0.027$) and the t-He/O_2+NO group (36.1 mm Hg, $p=0.030$). No significant changes were observed in the control group ($p=0.110$) (Table 2).

Lactate. By day 4, all study groups showed a significant decrease in lactate compared with baseline ($p<0.05$), whereas the change in the control group was not significant ($p=0.443$). By day 12, lactate concentrations in the t-He/O_2 and t-He/O_2 + NO groups reached 1.36 and 1.38 mmol/L, respectively, which was lower than in the control group (2.34 mmol/L) (Table 2).

pH. No intergroup differences were found in the dynamics of arterial blood pH ($p>0.05$), although there was a trend toward faster physiological recovery to normal reference ranges in the groups treated with t-He/O_2 (Table 2).

Safety. Throughout the entire follow up period, no adverse events related to NO or t-He/O_2 inhalation therapy were reported. The highest methemoglobin level recorded was 1%.

Discussion

The results of the study show that adding respiratory therapy with inhalations of NO and, in particular, with heated helium-oxygen mixture to standard of care in patients with polytrauma and pulmonary contusion leads to a significantly greater improvement in gas exchange parameters compared with oxygen therapy alone.

The greatest effectiveness of the heated heliox + NO combination can be explained by its impact on different links in the pathogenesis of respiratory failure in pulmonary contusion. Inhaled NO, as a selective vasodilator, presumably improved perfusion in ventilated lung areas, thereby reducing shunting [16, 22–24]. Heated heliox, by lowering breathing mixture density and possibly through the mucolytic effect of warmed, humidified gas, may have helped improve gas flow distribution and patency of the distal airways, reducing areas of hypoventilation [11–13, 20, 25]. The synergistic combination of these effects probably led to the fastest improvement of PaO_2, $PaCO_2$, and lactate values to normal ranges in group 3.

Similar effects were reported in a systematic review and meta-analysis [26] that included 8 studies with a total of 1,097 patients with pneumonia, showing that adding He/O_2 to standard therapy may improve oxygenation regardless of the He/O_2 inhalation protocol used. During the COVID-19 pandemic, He/O_2 inhalation improved oxygenation, helping to shorten the duration of oxygen therapy and reduce mortality [9, 10, 27]. The use of He/O_2 inhalation in preoperative preparation reduces the incidence of postoperative complications [25].

An important finding is the significant reduction in lactate levels in all study groups by day 4. Since hyperlactatemia in critically ill patients often reflects tissue hypoperfusion and oxygen debt, its rapid decline during use of the studied methods may indicate improved peripheral oxygenation and overall hemodynamics, which is consistent with the known effects of NO on microcirculation [9, 14, 17].

The complete absence of adverse events is consistent with the literature indicating the high safety of both low-dose inhaled NO [8, 18, 24] and heliox therapy [9, 11, 27] when used short-term in patients without severe pulmonary hypertension.

The limitations of this study include its open-label design, which is related to the technical characteristics of the equipment used, as well as its single-center setting, which may limit the generalizability of the results. A promising direction is to conduct multicenter studies using blinding to assess the impact of these methods on more hard endpoints: duration of mechanical ventilation, length of ICU stay, and all-cause mortality.

Clinical relevance: the proposed respiratory support methods are low-cost, noninvasive, and can be rapidly deployed in hospital settings and military field medical facilities. Their use may help stabilize polytrauma patients more quickly, shorten intensive care stays, and improve outcomes, which is of great importance for medical support in emergency zones.

Conclusion

Adding inhalations of either nitric oxide (30 ppm) or heated helium-oxygen mixture to standard respiratory therapy in patients with polytrauma and pulmonary contusion leads to a significant improvement in gas exchange parameters (PaO_2, SaO_2, $PaCO_2$), as well as a more rapid reduction in arterial blood lactate, compared with standard oxygen therapy.

The combined use of heated heliox and nitric oxide inhalations shows the most pronounced positive effect on gas exchange dynamics and on the resolution of CT signs of contusion-related lung injury, indicating a possible synergistic effect between the two methods.

All inhalation treatments demonstrated a favorable safety profile when used over a 12-day treatment course.

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