Research Square

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Effects of micro-pressure oxygen, diffuse oxygen supply, and nasal cannula oxygen on physiological and psychological outcomes in high-altitude migrants: a randomized controlled trial

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Abstract

Background

High-altitude hypoxia imposes persistent physiological and psychological stress on migrant populations, leading to impaired oxygenation, cardiovascular compensation, hematological alterations, and increased vulnerability to negative emotional symptoms. Although oxygen therapy is widely used as a non-pharmacological intervention for high-altitude hypoxic strain, the comparative efficacy of different oxygen-delivery modalities remains insufficiently understood. This study compared the effects of micro-pressure oxygen, diffuse oxygen supply, and nasal cannula oxygen on physiological and psychological outcomes in high-altitude migrants residing in Lhasa, Xizang.

Methods

In this randomized controlled trial, 80 eligible university students who had migrated from low-altitude areas to Lhasa (3650 m) were allocated in a 1:1:1:1 ratio to micro-pressure oxygen, diffuse oxygen supply, nasal cannula oxygen, or no-intervention control. Seventy-five participants were included in the final analysis (micro-pressure oxygen, n = 19; diffuse oxygen supply, n = 18; nasal cannula oxygen, n = 18; control, n = 20). The intervention lasted for 20 consecutive days. Physiological outcomes included peripheral oxygen saturation (SpO_2), heart rate (HR), hemoglobin (Hb), and hematocrit (Hct). Depression was the primary psychological outcome measured using the Symptom Checklist-90 (SCL-90). Outcomes were analyzed using 4-group × 2-time mixed analyses of variance.

Results

Significant group-by-time interactions were observed for SpO_2 [$F_{(3,71)} = 4.303$, $p = 0.008$, $\eta_p^2 = 0.154$], HR [$F_{(3,71)} = 3.794$, $p = 0.014$, $\eta_p^2 = 0.138$], Hb [$F_{(3,71)} = 3.591$, $p = 0.018$, $\eta_p^2 = 0.132$], Hct [$F_{(3,71)} = 7.002$, $p < 0.001$, $\eta_p^2 = 0.328$], and depression [$F_{(3,71)} = 2.980$, $p = 0.037$, $\eta_p^2 = 0.112$]. For the primary psychological outcome, compared with the control group, the mean differences in pre–post changes in depression scores were − 5.55 points for micro-pressure oxygen (95% CI − 9.45 to − 1.65, $p = 0.006$), − 4.99 points for diffuse oxygen supply (95% CI − 8.95 to − 1.04, $p = 0.014$), and − 4.27 points for nasal cannula oxygen (95% CI − 8.23 to − 0.32, $p = 0.035$). For SpO_2, the corresponding mean differences in change were 2.37 percentage points (95% CI 0.88 to 3.86, $p = 0.002$), 1.44 percentage points (95% CI − 0.07 to 2.96, $p = 0.061$), and 2.28 percentage points (95% CI 0.77 to 3.79, $p = 0.004$), respectively. For HR, the mean differences were − 11.53 bpm (95% CI − 19.67 to − 3.40, $p = 0.006$), − 3.41 bpm (95% CI − 11.66 to 4.85, $p = 0.413$), and − 10.91 bpm (95% CI − 19.16 to − 2.65, $p = 0.010$), respectively. For Hb, the corresponding differences were − 5.33 g/L (95% CI − 15.02 to 4.37, $p = 0.277$), − 4.41 g/L (95% CI − 14.24 to 5.42, $p = 0.374$), and − 15.74 g/L (95% CI − 25.57 to − 5.91, $p = 0.002$), respectively. For Hct, the mean differences were − 4.34 percentage points (95% CI − 7.69 to − 0.99, $p = 0.012$), − 3.13 percentage points (95% CI − 6.52 to 0.27, $p = 0.071$), and − 7.71 percentage points (95% CI − 11.10 to − 4.31, $p < 0.001$), respectively. No adverse events were observed in any group.

Conclusions

All three oxygen interventions improved selected physiological and psychological outcomes in high-altitude migrants, but their effect profiles differed. Micro-pressure oxygen showed the broadest pattern of improvements in oxygenation, HR, and depression; diffuse oxygen supply improved oxygenation and depression; and nasal cannula oxygen showed more prominent reductions in Hb and Hct. These findings provide preliminary evidence to inform the selection of oxygen-delivery strategies in high-altitude settings.

1 Introduction

At altitudes above 3000 meters, the core environmental characteristics are hypobaric hypoxia, which can markedly suppress aerobic metabolism and trigger systemic stress responses [1]. Acute or prolonged exposure to high-altitude hypoxic environments induces compensatory changes in the cardiovascular and hematological systems, manifested as increased heart rate, elevated blood pressure, excessive erythrocyte proliferation, and increased blood viscosity [2–4]. In severe cases, it may lead to acute mountain sickness and even life-threatening high-altitude illnesses such as high-altitude cerebral edema [5, 6]. Meanwhile, hypoxic stress directly impairs central nervous system function and emotional regulatory circuits, significantly increasing the risk of psychological and behavioral problems, including anxiety, depression, somatization, and cognitive dysfunction, thereby forming a distinctive pattern of physiological–psychological comorbidity in high-altitude migrant populations [7].

High-altitude hypoxia mediates physiological and psychological impairments through multiple systemic pathways: High-altitude hypoxia can induce a series of cardiovascular and hematological adaptations, including activation of the sympathetic-adrenal system, increased heart rate, elevated pulmonary arterial pressure [8, 9], and sustained upregulation of erythropoietin, resulting in increased hemoglobin (Hb) concentration and hematocrit (Hct). Excessive compensatory erythrocytosis may increase blood viscosity and further contribute to the development of chronic high-altitude diseases, such as high-altitude polycythemia and cor pulmonale at high altitude [10–12]. In addition, hypoxia induces oxidative stress damage, neurotransmitter imbalance, and sleep disturbances, thereby exacerbating internal homeostatic dysregulation [13, 14]. Epidemiological studies, field observations, and animal models consistently demonstrate that hypoxic exposure can directly induce negative emotional states such as depression and anxiety. The core mechanism involves hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis, and the degree of activation is significantly positively correlated with the severity of depression [7, 15, 16].

High-altitude hypoxia induces persistent physiological–psychological adverse effects through multisystem pathways, highlighting the urgent need for safe, accessible, and low–side-effect interventions. The preventive effect of staged ascent is limited [17], and pharmacological interventions are associated with adverse reactions and restricted applicability [18]. Therefore, oxygen therapy, characterized by its noninvasive nature, high efficiency, and favorable safety profile, has become the preferred non-pharmacological strategy for alleviating hypoxic injury and preventing or treating acute and chronic high-altitude diseases [19, 20]. Currently, mainstream oxygen intervention methods include nasal cannula oxygen therapy, diffuse oxygen supply, and mild hyperbaric oxygen therapy. Nasal cannula oxygen therapy, as the most commonly used individualized oxygen delivery method, can significantly increase blood oxygen saturation, reduce respiratory rate, and improve the hypercompensatory state of the circulatory system [21, 22]. Diffuse oxygen supply achieves simultaneous oxygen supplementation for multiple individuals by creating a localized oxygen-enriched environment, effectively improving blood oxygen levels, reducing heart rate, alleviating high-altitude discomfort, and enhancing sleep quality [23, 24]. Mild hyperbaric oxygen therapy delivers high-concentration oxygen under pressures of 1–2 ATA, enhancing tissue oxygenation and reducing oxidative stress [25]; it can not only improve respiratory function and blood oxygen

status in high-altitude workers [26], but also alleviate depressive symptoms, improve sleep, and enhance the efficacy of psychotropic medications [27, 28].

Although the protective effects of oxygen interventions have been widely demonstrated, the differences in efficacy and underlying mechanisms among various oxygen delivery methods remain unclear. With the comprehensive promotion of oxygen supply infrastructure in high-altitude regions, clarifying the integrated effects of different oxygen therapy modalities on physiological and psychological health is of significant practical importance. Previous studies have confirmed that standardized oxygen therapy can stabilize blood oxygen levels, reduce heart rate, reverse abnormal elevations in erythrocytes and hemoglobin, and decrease the risk of high-altitude heart disease [20]. Moreover, significant differences exist in the effects of different oxygen therapy approaches [21, 29]. However, current research still has several critical limitations: most studies focus on a single oxygen therapy modality, lacking head-to-head comparisons among the three mainstream approaches; evaluation metrics are primarily limited to isolated physiological indicators, with insufficient integration of physiological and psychological outcomes; and most studies are based on simulated hypoxic environments, with a scarcity of high-quality field evidence conducted in real high-altitude settings among migrant populations. These gaps result in a lack of evidence-based guidance for high-altitude oxygen therapy strategies, hindering the implementation of precision and individualized health management.

Based on this, the present study adopts a randomized controlled design to simultaneously compare the effects of mild hyperbaric oxygen, diffuse oxygen supply, and nasal cannula oxygen therapy, along with a blank control, on the physiological and psychological health of high-altitude migrant populations in a real high-altitude environment in Lhasa, Tibet (altitude 3650 m). The study aims to: (1) determine the effects of the three oxygen therapies on key physiological indicators, including blood oxygen saturation, heart rate, hemoglobin, and hematocrit; (2) quantitatively evaluate the effects of the three oxygen therapies on psychological dimensions such as depression, anxiety, and somatization as measured by the SCL-90; and (3) compare the differential effects among the three oxygen therapy modalities to identify the optimal intervention strategy.

Research hypotheses:

We hypothesized that, relative to the no-intervention control, each oxygen intervention would increase SpO_2, reduce HR, and attenuate hematological compensation, as reflected by lower Hb and Hct after intervention.

We hypothesized that each oxygen intervention would reduce the prespecified primary psychological outcome of SCL-90 depression scores relative to the control group; changes in the other SCL-90 dimensions were treated as secondary outcomes.

We further hypothesized that the magnitude and pattern of change would differ across modalities, with micro-pressure oxygen and diffuse oxygen supply showing larger overall improvements in oxygenation and depression than nasal cannula oxygen.

2 Methods

2.1 Participants

An a priori sample-size calculation was conducted in G*Power for a repeated-measures within–between interaction with four groups and two measurements. Assuming a medium effect (f = 0.25), α = 0.05, power = 0.90,

a pre–post correlation of 0.50, and a nonsphericity correction of 1.00, the minimum total sample was 64. We targeted 80 participants (20 per group) to allow for attrition and improve precision. A researcher independent of participant recruitment generated the computer-based random allocation sequence. Participants were allocated in a 1:1:1:1 ratio, with 20 participants per group; no stratified randomization was used. The allocation sequence was concealed in sequentially numbered, opaque, sealed envelopes that were opened only after enrollment and completion of baseline assessment. Research staff who were not involved in sequence generation recruited and enrolled participants. An independent researcher implemented the allocations. Because the interventions were visibly different, participants and intervention providers were not blinded; outcome assessors and statisticians remained blinded to group allocation. Five participants discontinued: one in the micro-pressure oxygen group, two in the diffuse oxygen group, and two in the nasal cannula oxygen group; no participants withdrew from the control group. Withdrawals were attributed to scheduling conflicts or health-related reasons. Thus, 75 participants were included in the final analysis: micro-pressure oxygen (n = 19; 9 males, 10 females; age 23.52 ± 2.06 years), diffuse oxygen (n = 18; 9 males, 9 females; age 22.45 ± 3.01 years), nasal cannula oxygen (n = 18; 9 males, 9 females; age 22.76 ± 2.29 years), and control (n = 20; 10 males, 10 females; age 23.37 ± 2.57 years). Age and duration of residence did not differ significantly among groups (ps > 0.05). No adverse events were observed in any group.

Inclusion criteria were as follows: (1) birthplace at an altitude below 1500 meters, with no history of long-term residence or living in high-altitude regions before adulthood; (2) no history of long-term oxygen therapy and no recent exposure to oxygen chambers or oxygen inhalation; (3) residence in Lhasa for 1–2 years, with no history of prolonged absence due to suspension of schooling, exchange programs, or other special circumstances, except for winter and summer vacations; (4) exclusion of severe psychiatric disorders such as schizophrenia, affective disorders, and intellectual disability, as well as major physical or neurological diseases; (5) absence of chronic cardiopulmonary diseases, hematological disorders, or severe underlying diseases; (6) normal or corrected-to-normal vision.

This study was approved by the Ethics Committee of Xizang University. All participants signed informed consent forms prior to the experiment and received compensation after completion of the study.

2.2 Materials

2.2.1 Physiological Indicators

Peripheral blood oxygen saturation (SpO_2) and HR were recorded using a Yuwell pulse oximeter (YX303). At both assessments, participants rested seated for at least 10 min; three readings were obtained at 1-min intervals after the signal stabilized, and their mean was analyzed. On the morning before the intervention period and again on the morning after the final intervention day, each participant provided 5 mL of venous blood after fasting for more than 10 h. Blood was obtained from all 80 randomized participants at baseline; post-intervention sampling was completed for the 75 participants retained in the final analysis. Immediately after blood collection, SpO_2 and HR were measured on site, followed by the psychological assessment. Samples were analyzed at Xizang Fukang Hospital with a Mindray BC-5390 automated hematology analyzer and matched reagents.

2.2.2 Psychological Indicators

The Symptom Checklist-90 (SCL-90) is a 90-item self-report inventory assessing nine symptom dimensions: somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Reported validity coefficients range from 0.77 to 0.99 [30].

Depression was prespecified as the primary psychological outcome because the study hypotheses and prior high-altitude oxygen literature focused on depressive symptoms; the total score and the other eight symptom dimensions were analyzed as secondary psychological outcomes.

2.3 Procedure

The randomized controlled study lasted 22 days. Baseline measurements were obtained on the morning of Day 1, followed by 20 consecutive intervention days (Days 2–21); post-intervention measurements were obtained on the morning of Day 22, after the final intervention day. At both assessment points, the order was fasting venous blood collection, on-site SpO_2 and HR measurement after seated rest, and then SCL-90 completion in a quiet laboratory. This fixed sequence and morning schedule were used to improve comparability across time points. The experimental procedure is illustrated in Fig. 1.

2.3.1 Phase I: Pre-test

On the morning of Day 1, after a fast of more than 10 h, 5 mL of venous blood was collected from each randomized participant. Participants then rested seated for at least 10 min; SpO_2 and HR were measured with the YX303 pulse oximeter, and the SCL-90 was completed afterward in a quiet laboratory. Participants subsequently received their intervention instructions and schedules.

2.3.2 Phase II: Intervention

Except for the control group (which did not receive any intervention), the remaining three groups underwent the following interventions:

Micro-Pressure Oxygen Intervention Group:

A soft micro-pressure oxygen chamber with negative-ion function (NBYY-HYDT-003; Ningbo Yangyu Health Technology Co., Ltd.) was used. The chamber was elliptical (height 2.13 m, width 2.5 m, floor area 7.88 m^2). The value 0.42 ATA denotes the pressure increment above the local ambient pressure in Lhasa (approximately 0.64 ATA), yielding a chamber absolute pressure of approximately 1.06 ATA. This modest pressure increment was selected to restore the chamber pressure to near sea-level atmospheric pressure while avoiding the substantially higher pressures used in conventional clinical hyperbaric oxygen therapy; this approach is consistent with prior micro-pressure reoxygenation work in high-altitude migrants[31, 32]. The device supplied oxygen at a nominal concentration of 100%. Each 90-min session comprised 30 min of compression, 30 min at target pressure with oxygen delivery, and 30 min of decompression. Sessions occurred each afternoon for 20 consecutive days.

Diffuse Oxygen Intervention Group:

Normobaric diffuse oxygen was delivered through a centralized system compliant with YYT0187-94. The device output pressure was 0.5 MPa, terminal flow was 10 L/min, and oxygen concentration at the oxygen outlet was 93% ± 3%. Oxygen was released into a relatively enclosed room to increase ambient oxygen concentration; 93% ± 3% describes the gas supplied by the equipment, not the FiO_2 inhaled by participants. Participants remained in the oxygen-enriched room for 2 h each afternoon for 20 consecutive days.

Nasal Oxygen Intervention Group:

A Yuwell 6 L medical molecular-sieve oxygen concentrator (7F-6W; registration No. 20162081398) delivered oxygen through bilateral nasal cannulae with heated humidification (distilled water, 37°C). Oxygen flow was set at 5–6 L/min. The concentrator output oxygen concentration was 93% ± 3%; this value refers to gas leaving the device and should not be interpreted as the participant's actual fraction of inspired oxygen (FiO_2), which also depends on inspiratory flow, breathing pattern, cannula fit, and room-air entrainment. Oxygen was administered for 2 h each afternoon for 20 consecutive days.

2.3.3 Phase III: Post-test

On the morning of Day 22, after the final intervention day and a fast of more than 10 h, 5 mL of venous blood was collected from each participant who completed the study. Participants then rested seated for at least 10 min. SpO_2 and HR were measured with the same YX303 pulse oximeter; three stable readings were obtained at 1-min intervals and averaged. Participants subsequently completed the SCL-90 in a quiet laboratory.

2.4 Data Analysis

Data were analyzed using SPSS 27.0. Continuous variables are presented as means and standard deviations. A 4 (group: micro-pressure oxygen, diffuse oxygen supply, nasal cannula oxygen, and control) × 2 (time: pre-intervention and post-intervention) mixed ANOVA was conducted for each outcome, with group as the between-subjects factor and time as the within-subject factor. Because the within-subject factor had only two levels, the sphericity assumption was automatically satisfied and no sphericity test or correction was required. Significant group-by-time interactions were followed by simple-effects analyses and LSD pairwise comparisons[33]. If the interaction effect was significant, simple effect analysis was further conducted to reveal the differences in changes among different groups at each time point. Meanwhile, η_p^2 was calculated to evaluate the proportion of variance in the dependent variable explained by the independent variable. Python (pandas, SciPy, statsmodels, seaborn, etc.) was used to perform one-way ANOVA on each indicator (ΔSpO2, ΔHeart rate, ΔDepression, ΔHemoglobin, ΔHematocrit) to test the differences among different intervention groups. On the basis of statistically significant overall differences, the least significant difference (LSD) method was further used for pairwise comparisons. The standard error was estimated based on the mean square error (MSE) of the ANOVA residuals, and the t values and corresponding two-sided *p* values for the mean differences between groups were calculated. The significance level was set at α = 0.05.

3 Results

The primary outcomes of this study were changes in SpO_2, HR, hematological indicators, and SCL-90 depression subscale scores before and after the intervention.

3.1 Descriptive Statistics of the Four Groups Before and After Intervention

Descriptive statistical analyses were conducted on the psychological indicators (SCL-90) and physiological indicators (hematological parameters) of the four groups before and after the intervention (all results are presented in Supplementary Table 1, with significant results shown in Table 1). In addition, one-way ANOVA was performed to examine baseline levels of all indicators across the four groups prior to the intervention. The results indicated that, except for Hct (see Section 3.2), there were no significant differences among the four groups at

baseline for any of the measured indicators ($p > 0.05$) (see Supplementary Table 2), suggesting that the groups were equivalent before the intervention.

Table 1
Descriptive statistics of psychological and physiological indicators in the four groups before and after intervention (M ± SD)

	pre-test				post-test			
	Nasal Cannula Oxygen	**Diffusion Oxygen**	**Micro-Pressure Oxygen**	**Control Group**	**Nasal Cannula Oxygen**	**Diffusion Oxygen**	**Micro-Pressure Oxygen**	**Control Group**
SpO_2(%)	91.39 ± 2.43	92.56 ± 2.41	91.68 ± 2.21	92.25 ± 2.31	93.67 ± 1.33	94.00 ± 1.14	94.05 ± 1.81	92.25 ± 2.05
Heart rate (bpm)	91.33 ± 14.88	83.61 ± 10.84	86.68 ± 16.55	85.70 ± 14.65	81.28 ± 12.05	81.06 ± 7.24	76.00 ± 10.18	86.55 ± 15.59
Hb (**g/L**)	175.67 ± 17.87	169.56 ± 16.49	168.42 ± 12.14	162.20 ± 14.28	156.72 ± 11.03	163.22 ± 11.77	162.89 ± 15.95	162.00 ± 13.44
Hct (%)	49.69 ± 4.66	48.31 ± 3.97	48.27 ± 4.44	45.65 ± 3.32	42.24 ± 2.69	45.43 ± 4.45	44.19 ± 3.91	45.90 ± 3.90
Depression	21.72 ± 4.11	20.89 ± 6.54	20.32 ± 4.88	21.00 ± 4.21	19.00 ± 2.70	17.44 ± 3.33	16.32 ± 3.65	22.55 ± 7.54

3.2 Results of Repeated Measures ANOVA for Physiological and Psychological Indicators

Only indicators with significant differences are reported in the repeated measures ANOVA results (see Fig. 2); other indicators showed no significant interaction effects (all results are presented in Supplementary Table 3).

For SpO_2, the group-by-time interaction was significant [$F_{(3, 71)} = 4.303$, $p = 0.008$, $\eta_p^2 = 0.154$]. The analyzed sample sizes were 19 in the micro-pressure oxygen group, 18 in the diffuse oxygen group, 18 in the nasal cannula oxygen group, and 20 in the control group. At post-intervention, compared with the control group, the estimated mean differences were 1.80 percentage points for micro-pressure oxygen (95% CI 0.07 to 3.54, $p = 0.026$), 1.75 percentage points for diffuse oxygen supply (95% CI − 0.01 to 3.51, $p = 0.026$), and 1.42 percentage points for nasal cannula oxygen (95% CI − 0.34 to 3.18, $p = 0.065$). Within-group comparisons showed that SpO_2 increased significantly from baseline in the micro-pressure oxygen group (mean change = 2.37 percentage points, 95% CI 1.30 to 3.44, $p < 0.001$), diffuse oxygen group (mean change = 1.44 percentage points, 95% CI 0.35 to 2.54, $p = 0.011$), and nasal cannula oxygen group (mean change = 2.28 percentage points, 95% CI 1.18 to 3.37, $p < 0.001$), whereas no significant change was observed in the control group (p = 1.000).

For HR, the group-by-time interaction was significant [$F_{(3, 71)} = 3.794$, $p = 0.014$, $\eta_p^2 = 0.138$]. The analyzed sample sizes were 19, 18, 18, and 20 in the micro-pressure oxygen, diffuse oxygen, nasal cannula oxygen, and control groups, respectively. At post-intervention, compared with the control group, the estimated mean differences were − 10.55 bpm for micro-pressure oxygen (95% CI − 21.88 to 0.78, $p = 0.083$), − 5.49 bpm for diffuse oxygen supply (95% CI − 16.99 to 6.00, $p = 0.295$), and − 5.27 bpm for nasal cannula oxygen (95% CI − 16.76 to 6.22, $p = 0.295$). Within-group comparisons showed that HR decreased significantly from baseline in the micro-pressure oxygen group (mean change = − 10.68 bpm, 95% CI − 16.51 to − 4.86, $p < 0.001$) and nasal cannula oxygen group (mean

change = − 10.06 bpm, 95% CI − 16.04 to − 4.07, p = 0.001), but not in the diffuse oxygen group (p = 0.398) or control group (p = 0.766).

For Hb, the group-by-time interaction was significant [$F_{(3, 71)}$ = 3.591, p = 0.018, η_p^2 = 0.132]. The analyzed sample sizes were 19, 18, 18, and 20 in the micro-pressure oxygen, diffuse oxygen, nasal cannula oxygen, and control groups, respectively. At post-intervention, compared with the control group, the estimated mean differences were 0.89 g/L for micro-pressure oxygen (95% CI − 11.49 to 13.28, p = 0.847), 2.94 g/L for diffuse oxygen supply (95% CI − 9.61 to 15.50, p = 0.799), and − 2.28 g/L for nasal cannula oxygen (95% CI − 14.83 to 10.28, p = 0.799). Within-group comparisons showed that Hb decreased significantly from baseline only in the nasal cannula oxygen group (mean change = − 15.94 g/L, 95% CI − 23.08 to − 8.81, p < 0.001). Changes were not significant in the micro-pressure oxygen group (p = 0.117), diffuse oxygen group (p = 0.201), or control group (p = 0.953).

For Hct, the group-by-time interaction was significant [$F_{(3, 71)}$ = 7.002, p < 0.001, η_p^2 = 0.228]. The analyzed sample sizes were 19, 18, 18, and 20 in the micro-pressure oxygen, diffuse oxygen, nasal cannula oxygen, and control groups, respectively. At post-intervention, compared with the control group, the estimated mean differences were − 1.71 percentage points for micro-pressure oxygen (95% CI − 5.11 to 1.68, p = 0.268), − 0.47 percentage points for diffuse oxygen supply (95% CI − 3.91 to 2.97, p = 0.715), and − 3.67 percentage points for nasal cannula oxygen (95% CI − 7.11 to − 0.22, p = 0.030). Within-group comparisons showed that Hct decreased significantly from baseline in the micro-pressure oxygen group (mean change = − 4.08 percentage points, 95% CI − 6.48 to − 1.69, p = 0.001), diffuse oxygen group (mean change = − 2.87 percentage points, 95% CI − 5.34 to − 0.41, p = 0.023), and nasal cannula oxygen group (mean change = − 7.46 percentage points, 95% CI − 9.92 to − 4.99, p < 0.001), but not in the control group (p = 0.829). Because baseline Hct differed among groups, these post-intervention comparisons are not equivalent to baseline-adjusted estimates and should be interpreted cautiously. A separate ANCOVA or baseline-adjusted linear model is required to obtain adjusted mean differences.

For depression, the prespecified primary psychological outcome, the group-by-time interaction was significant [$F_{(3, 71)}$ = 3.349, p = 0.024, η_p^2 = 0.124]. The analyzed sample sizes were 19, 18, 18, and 20 in the micro-pressure oxygen, diffuse oxygen, nasal cannula oxygen, and control groups, respectively. At post-intervention, compared with the control group, the estimated mean differences were − 6.23 points for micro-pressure oxygen (95% CI − 10.44 to − 2.03, p < 0.001), − 5.11 points for diffuse oxygen supply (95% CI − 9.37 to − 0.84, p = 0.005), and − 3.55 points for nasal cannula oxygen (95% CI − 7.81 to 0.71, p = 0.055). Within-group comparisons showed that depression scores decreased significantly from baseline in the micro-pressure oxygen group (mean change = − 4.00 points, 95% CI − 6.79 to − 1.21, p = 0.006) and diffuse oxygen group (mean change = − 3.44 points, 95% CI − 6.31 to − 0.57, p = 0.019). The decrease in the nasal cannula oxygen group did not reach statistical significance (mean change = − 2.72 points, 95% CI − 5.59 to 0.15, p = 0.063), and no significant change was observed in the control group (p = 0.260). No adverse events were observed in any group.

Changes in psychological and physiological indicators before and after intervention in each group are shown in Fig. 2.

3.3 Effects of Pre-test and Post-test Differences on Physiological and Psychological Indicators

One-way ANOVA was used to examine the effects of oxygen interventions on improvements in physiological and psychological indicators, with a focus on depression, SpO_2, HR, Hb, and Hct, by comparing the change score for each variable calculated as the post-test value minus the pre-test value (Δ = post-test − pre-test; see Fig. 3 and Supplementary Table 4 for detailed results).

For SpO_2, the results showed a significant main effect of group, $F_{(3,71)} = 4.303$, $p = 0.008$, $\eta_p^2 = 0.154$. LSD-corrected pairwise comparisons indicated that increases in the mild hyperbaric oxygen group (2.37) and nasal oxygen group (2.28) were significantly greater than in the control group (0).

For HR, the results showed a significant main effect of group, $F_{(3,71)} = 3.794$, $p = 0.014$, $\eta_p^2 = 0.138$. LSD-corrected pairwise comparisons indicated that reductions in the mild hyperbaric oxygen group (− 10.68) and nasal oxygen group (− 10.06) were significantly greater than in the control group (0.85).

For Hb, the results showed a significant main effect of group, $F_{(3,71)} = 3.591$, $p = 0.018$, $\eta_p^2 = 0.132$. LSD-corrected pairwise comparisons indicated that the reduction in the nasal oxygen group (− 18.95) was significantly greater than that in the mild hyperbaric oxygen group (− 5.53), diffuse oxygen group (− 6.34), and control group (− 0.20).

For Hct, the results showed a significant main effect of group, $F_{(3,71)} = 7.002$, $p < 0.001$, $\eta_p^2 = 0.228$. LSD-corrected pairwise comparisons indicated that reductions in the mild hyperbaric oxygen group (− 4.08) and nasal oxygen group (− 7.46) were significantly greater than in the control group (0.25), and that the reduction in the nasal oxygen group (− 7.46) was significantly greater than that in the diffuse oxygen group (− 2.87).

For depression, the results showed a significant main effect of group, $F_{(3,71)} = 3.349$, $p = 0.024$, $\eta_p^2 = 0.124$. Further pairwise comparisons with LSD correction indicated that improvements in the mild hyperbaric oxygen group (− 4.00), nasal oxygen group (− 3.44), and diffuse oxygen group (− 2.72) were significantly greater than in the control group (1.55).

4 Discussion

This study employed a randomized controlled design to systematically compare the effects of three oxygen intervention modalities—micro-pressure oxygen, diffuse oxygen supply, and nasal oxygen inhalation—on the physiological and psychological health of high-altitude migrant populations. The results showed that all three oxygen interventions were able, to varying degrees, to ameliorate the adverse effects of high-altitude hypoxia, although their patterns of action differed markedly. Micro-pressure oxygen demonstrated the most comprehensive effects in increasing SpO_2, reducing HR, and alleviating depressive symptoms; diffuse oxygen supply was effective in stably improving SpO_2 and relieving depression; nasal oxygen inhalation showed a unique advantage in reducing hematological compensatory indicators such as Hb and Hct. These findings suggest that different oxygen therapy modalities may influence the adaptive status of high-altitude migrants through distinct physiological pathways and exhibit differentiated intervention characteristics.

Because participants had lived at 3650 m for 1–2 years, the findings should not be interpreted as reversal of an acute altitude response. Ventilatory, cardiovascular, and hematological acclimatization likely reduced the magnitude of untreated hypoxic strain and may partly explain the modest between-group differences for some outcomes. Nevertheless, acclimatization in lowland migrants is variable and may remain incomplete; permanent high-altitude residence does not necessarily fully compensate for environmental hypoxia [34, 35]. The observed

changes therefore suggest that supplemental oxygen can modify residual physiological or psychological strain in an acclimatized population, but the absence of a low-altitude comparison prevents attribution of these effects specifically to high-altitude exposure.

4.1 Physiological Changes:

4.1.1 Core Physiological Adaptation Indicators Under Hypobaric Hypoxia (SpO_2 and HR):

The results for SpO_2 showed a significant interaction between group and time. After the intervention, the SpO_2 levels in the mild hyperbaric oxygen group and the diffuse oxygen group were significantly higher than those in the control group, and the SpO_2 levels in all three intervention groups were significantly higher after the intervention than before the intervention. Difference-value analysis further indicated that the increases in SpO_2 in the mild hyperbaric oxygen group and the nasal oxygen group were significantly greater than that in the control group. This result is consistent with previous studies on oxygen therapy at high altitude [32]. Mild hyperbaric oxygen increases ambient pressure and oxygen partial pressure, thereby increasing alveolar oxygen partial pressure and the amount of physically dissolved oxygen in the blood, which more effectively improves tissue oxygenation [31]. Diffuse oxygen supply creates a localized oxygen-enriched environment, allowing individuals to continuously receive oxygen supplementation under natural conditions, and can effectively counteract high-altitude hypoxia [36, 37]. High-flow nasal cannula (HFNC) can improve oxygenation and reduce the work of breathing by delivering heated and humidified gas at high flow rates, providing a more stable fraction of inspired oxygen (FiO_2), reducing entrainment of room air during inspiration, flushing anatomical dead space in the upper airway, and generating a certain level of positive end-expiratory pressure [38]. In the present study, the between-group differences for nasal oxygen therapy were relatively modest, which may be influenced by factors such as the set flow rate, actual FiO_2 achieved, breathing pattern (oral vs. nasal), adherence to device use, duration of intervention, and timing of outcome measurement. A systematic review and meta-analysis by Thiruvenkatarajan et al. [39] generally supports that HFNC can reduce the incidence of hypoxemia and decrease the need for airway interventions; however, considerable heterogeneity exists, and the magnitude of effect varies across different populations and clinical settings. This suggests that, in scenarios requiring rapid and marked improvement in SpO_2, the two “environment-level” interventions—mild hyperbaric oxygen and diffuse oxygen supply—may be preferable options. Taken together, active oxygen supplementation can effectively improve the oxygenation status of high-altitude migrants. Among the modalities tested, mild hyperbaric oxygen and diffuse oxygen supply showed clearer advantages in between-group comparisons, whereas nasal oxygen inhalation, although showing a positive trend of improvement, demonstrated relatively limited between-group superiority. This also indicates that, in situations requiring rapid correction of hypoxic status, mild hyperbaric oxygen and diffuse oxygen supply may have greater practical advantages.

HR likewise showed a significant group × time interaction. After the intervention, only the mild hyperbaric oxygen group had a significantly lower HR than the control group; within-group comparisons showed that HR in both the mild hyperbaric oxygen group and the nasal oxygen group was significantly lower after the intervention than before the intervention. Difference-value analysis also demonstrated that the reductions in HR in the mild hyperbaric oxygen group and the nasal oxygen group were significantly greater than that in the control group. HR is a sensitive indicator reflecting cardiac workload and sympathetic nervous tension. High-altitude hypoxia

activates the sympathetic nervous system, resulting in compensatory tachycardia to meet the body's oxygen demand [40]. Mild hyperbaric oxygen can rapidly increase blood oxygen levels, reduce the compensatory burden on the heart, and promote a shift in autonomic nervous function toward parasympathetic dominance [32, 41]. Nasal oxygen inhalation may also relieve sympathetic tension to some extent, thereby reducing HR [42]. High-flow nasal oxygen therapy can reduce respiratory rate, alleviate the work of breathing, and improve cardiopulmonary interactions to a certain extent, thereby contributing to reductions in HR and cardiac workload [43]. However, no significant between-group advantage of nasal oxygen therapy was observed in the present study. This may be because the benefits of HFNC are primarily demonstrated in acute hypoxemic conditions or high-risk settings (e.g., anesthesia or respiratory failure), where it plays a key role in preventing hypoxemia and providing respiratory support [44]. In contrast, the participants in this study were relatively stable high-altitude migrants, whose baseline HR regulation is more strongly influenced by long-term hypoxic adaptation mechanisms [34]. In summary, the findings of this study suggest that the more prominent intervention effect of mild hyperbaric oxygen may be related to its greater capacity to improve oxygenation. Although nasal oxygen inhalation did not show endpoint differences as clearly as those observed for the control group in between-group comparisons, the pre–post changes within the group still suggest that it has physiological significance and potential application value in HR regulation.

4.1.2 Hematological Compensation Indicators Under Hypobaric Hypoxia (Hb and Hct)

Both Hb and Hct showed significant group × time interactions, although their patterns of change differed. Hb decreased significantly only in the nasal oxygen group, and the magnitude of decrease was significantly greater than that in the other three groups. Hct decreased significantly after all three interventions, with the reductions in the nasal oxygen group and mild hyperbaric oxygen group being significantly greater than that in the control group, and the reduction in the nasal oxygen group being significantly greater than that in the diffuse oxygen group. Prolonged high-altitude hypoxia can promote erythropoiesis through the HIF–EPO pathway, leading to compensatory increases in Hb and Hct. Excessive elevation increases blood viscosity and raises the risk of chronic mountain sickness [40, 45]. Nasal oxygen therapy, through continuous and regular oxygen delivery, may alleviate renal tissue hypoxia, thereby downregulating HIF pathway activity and reducing erythropoietin (EPO) secretion, ultimately suppressing excessive erythropoiesis [46, 47]. Diffuse oxygen supply showed a weaker effect on hematological parameters, which may be attributed to its limited ability to increase effective oxygen partial pressure. Compared with active oxygen delivery modalities such as mild hyperbaric oxygen and high-flow nasal cannula, diffuse oxygen supply primarily improves ambient oxygen concentration and only indirectly increases inspired oxygen partial pressure. Consequently, its effects on alveolar oxygen tension and arterial oxygenation are relatively modest and may be insufficient to substantially alter renal oxygen sensing, thereby exerting a limited inhibitory effect on the HIF–EPO pathway. This difference suggests that the regulation of erythropoiesis by oxygen therapy may depend more on the magnitude of effective oxygen partial pressure elevation than on the mode of oxygen delivery itself.

Although participants were randomly assigned to groups in this study, baseline differences in Hct were present among groups. To reduce the influence of baseline differences on the results, the present study additionally conducted pre–post difference-value analyses. The results showed that the reductions in Hct in the nasal oxygen group and the mild hyperbaric oxygen group remained significantly greater than that in the control group, and that the reduction in the nasal oxygen group was significantly greater than that in the diffuse oxygen group, suggesting that the intervention effect was genuine. Nevertheless, when interpreting Hct-related results, the influence of

baseline differences should still be taken into account, and future studies with larger samples are needed for further validation.

4.2 Psychological Changes:

The main effect of time, the main effect of group, and the interaction effect were all significant for depression scores. After the intervention, depression scores in all three oxygen intervention groups were significantly lower than those in the control group and were also significantly lower than their own pre-intervention levels. Difference-value analysis showed that the magnitude of improvement in depression was significantly greater in all three intervention groups than in the control group, with more pronounced improvements in the mild hyperbaric oxygen group and the diffuse oxygen group. This result is consistent with studies showing that hyperbaric oxygen can improve depressive symptoms in high-altitude populations, and that 20 sessions of hyperbaric oxygen intervention can significantly reduce depression scale scores in high-altitude migrants [41]. Oxygen intervention may exert its effects through both physiological and psychological pathways: physiologically, improvement of hypoxia may alleviate excessive activation of the HPA axis and improve abnormalities in the metabolism of neurotransmitters such as serotonin, thereby relieving depression [48, 49]; psychologically, diffuse oxygen supply is less restrictive, and the mild hyperbaric oxygen environment is quiet and comfortable, both of which may improve the intervention experience and generate positive emotional effects [50]. The present study did not directly assess relevant neural or endocrine indicators, and these mechanisms therefore still require further verification.

Taken together, the present study found that the effect patterns of the three oxygen interventions diverged clearly: mild hyperbaric oxygen showed a relatively favorable overall effect in improving SpO_2, reducing HR, and alleviating depressive symptoms, making it suitable for individuals who require rapid improvement in oxygenation status and reduction of cardiovascular burden; diffuse oxygen supply showed clear effects on improving oxygenation and mood, and also features multi-person sharing, higher comfort, and fewer activity restrictions [36], suggesting promising applicability in long-term scenarios such as residential and occupational settings; although nasal oxygen inhalation did not show between-group superiority in improving SpO_2 as clearly as mild hyperbaric oxygen and diffuse oxygen supply, it performed particularly well in reducing Hb and Hct, suggesting that it may have special value in the long-term regulation of hematological adaptation. Each of the three methods has its own strengths, and there is no single modality that can be regarded as the “absolutely optimal” option in all circumstances; rather, selection should be made according to different scenarios and needs.

Limitations

This study has several limitations. First, the sample was modest and drawn from one university, limiting generalizability. Second, participants had already lived at high altitude for 1–2 years, and no low-altitude group was included; consequently, the study cannot separate residual high-altitude-specific effects from responses that might also occur in healthy low-altitude residents. Third, participants could not be blinded, and the no-intervention control did not match treatment attention, expectations, time commitment, or environmental context, which is especially important for self-reported depression. Fourth, exposure duration was not matched: micro-pressure oxygen sessions lasted 90 min, whereas diffuse oxygen and nasal cannula oxygen sessions lasted 2 h. Differences among modalities may therefore reflect both delivery method and oxygen dose or contact time. Fifth, baseline Hct imbalance may have influenced the apparent magnitude of change; change-score analysis does not fully eliminate this concern, and a prespecified baseline-adjusted ANCOVA is warranted in future work. Sixth, LSD post hoc tests were relatively permissive given the number of outcomes and comparisons, increasing the risk of

type I error; the findings require confirmation using a more conservative multiplicity procedure such as Holm, Tukey, or Bonferroni adjustment. Seventh, the intervention lasted only 20 days, and long-term maintenance is unknown. Finally, EPO, HIF-1α, cortisol, HR variability, neurotransmitters, and other proposed mediators were not measured, so mechanistic explanations remain speculative rather than experimentally established.

Future Directions

Future studies may expand the sample size and conduct multicenter research, extend the duration of intervention and follow-up, measure molecular and neuroendocrine indicators to clarify mechanisms, and, at the same time, incorporate comfort, adherence, and cost considerations to establish more practical oxygen therapy regimens for high-altitude environments.

Conclusion

In conclusion, this study demonstrates that all three active oxygen supplementation modalities can, to a certain extent, improve the physiological and psychological status of high-altitude migrants, although their patterns of action differ substantially. Micro-pressure oxygen more prominently improves oxygenation, reduces HR, and alleviates depression; diffuse oxygen supply has clear effects on improving oxygenation and mood and offers greater advantages for environmental application; nasal oxygen inhalation shows more prominent effects in regulating Hb and Hct. These findings provide preliminary evidence for the refined selection of different oxygen therapy strategies in high-altitude environments and also lay a foundation for more in-depth mechanistic studies and translational application research in the future.

Abbreviations

ATA
atmospheres absolute
CI
confidence interval
CG
control group
Hb
hemoglobin
Hct
hematocrit
HR
heart rate
MPO
micro-pressure oxygen
SCL-90
Symptom Checklist-90
SpO_2
peripheral oxygen saturation.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Xizang University. Written informed consent was obtained from all participants before enrollment.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Author Contributions

Peng Dang:performed statistical analysis and drafted the manuscript. **Xuemei Zhang:**recruited participants and assisted with data collection. **Chun Zheng**:recruited participants and assisted with data collection. **Hai-lin Ma:** led project administration and secured funding. **Zian Liu**: recruited participants, assisted with data collection, and conceived and designed the study. All authors contributed to data interpretation and approved the final manuscript.

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Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Figures

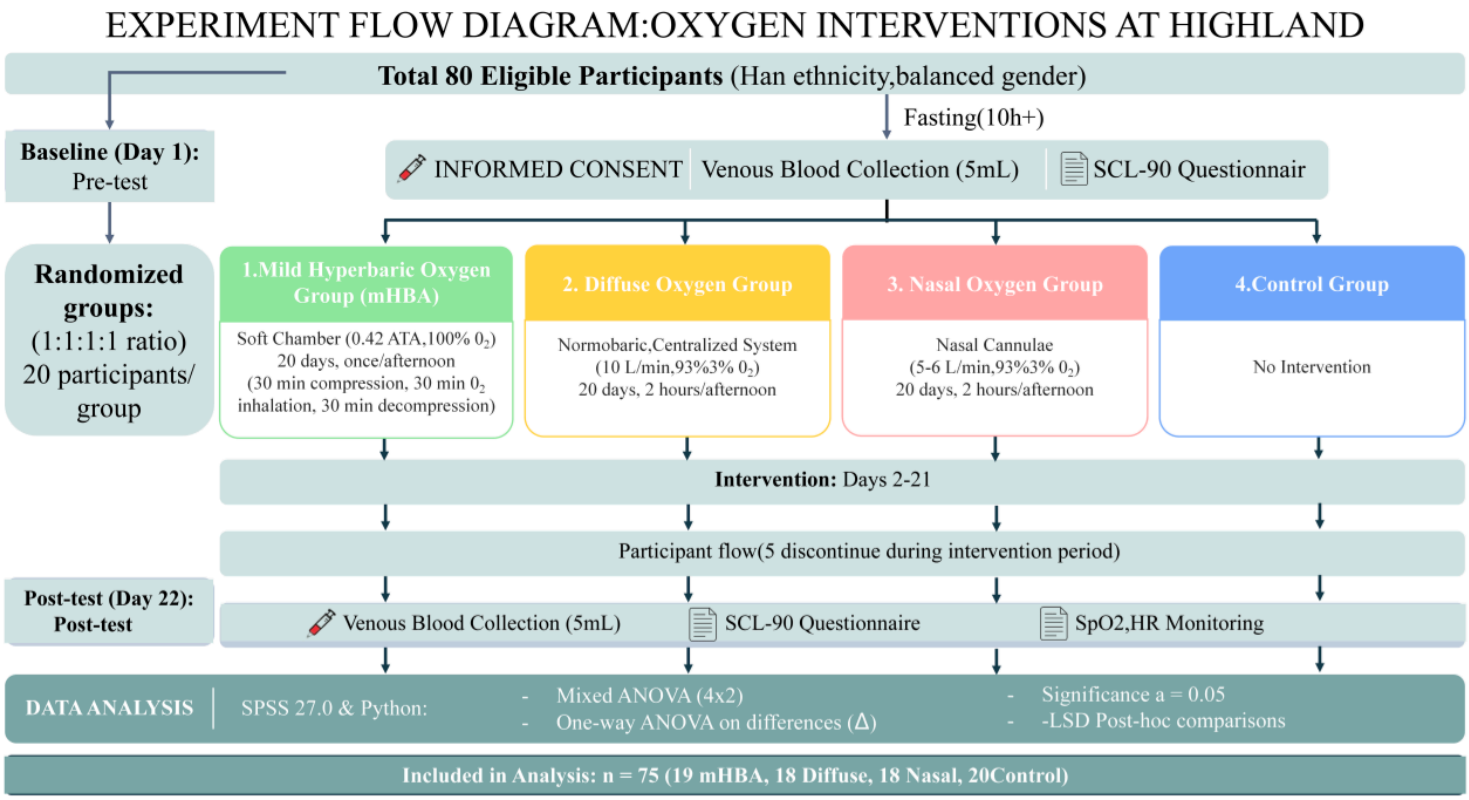


Figure 1

CONSORT flow diagram of participant recruitment and analysis. Eighty participants were randomized equally to four groups. After five withdrawals, 75 participants were analyzed (micro-pressure oxygen, n = 19; diffuse oxygen, n = 18; nasal cannula oxygen, n = 18; control, n = 20).

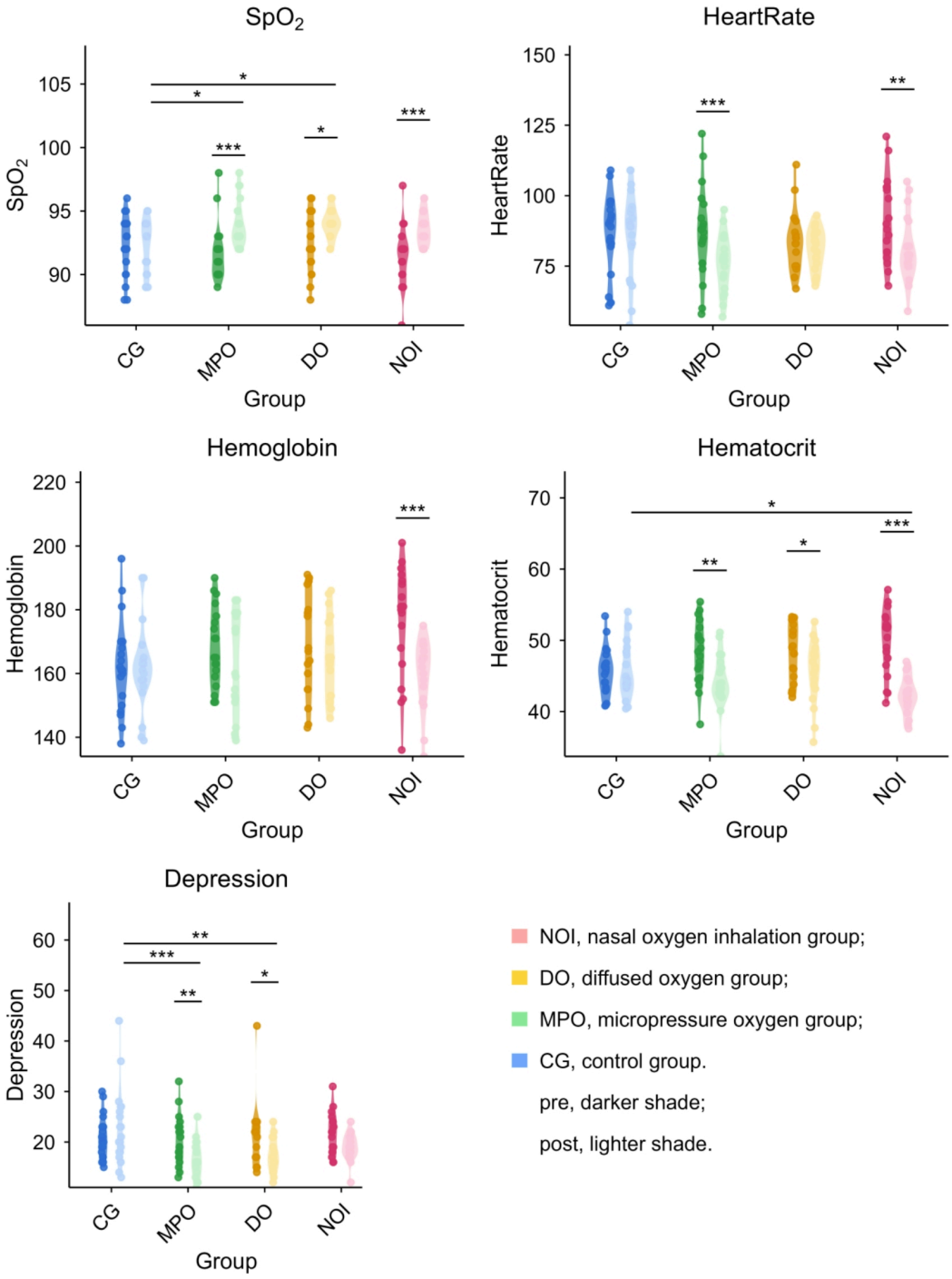


Figure 2

Pre–post changes in physiological and psychological outcomes. SpO_2, peripheral oxygen saturation; HR, heart rate; Hb, hemoglobin; Hct, hematocrit. In each group, the front violin represents baseline and the rear violin represents post-intervention values. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

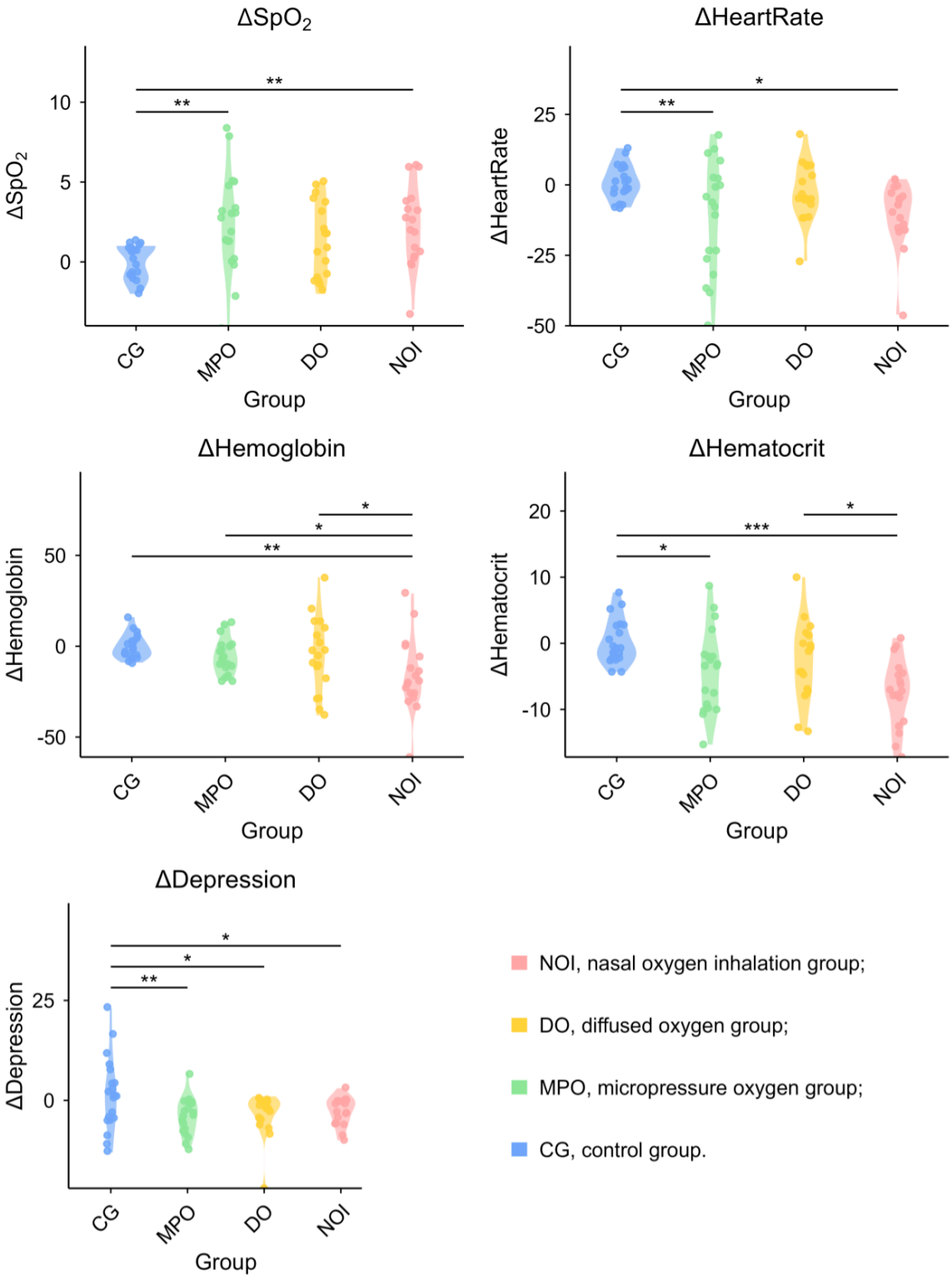


Figure 3

Between-group differences in outcome change scores. Change was calculated as post-intervention minus baseline. Negative values indicate reductions in HR, Hb, Hct, and depression; positive values indicate increases in SpO_2. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Supplementary Files

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