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Effects of hydromorphone and dexmedetomidine on diaphragmatic function in patients with acute exacerbation of chronic obstructive pulmonary disease receiving noninvasive ventilation

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Abstract

Sedative and analgesic agents may negatively influence diaphragmatic performance. This study sought to compare the effects of dexmedetomidine (DEXM) and hydromorphone (HM) on diaphragmatic function among patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) undergoing noninvasive ventilation (NIV). In this open-label randomized controlled trial, 80 patients were randomly assigned to either the HM or DEXM group, with primary endpoints being the alterations in diaphragmatic thickening fraction (DTF) and diaphragmatic excursion (DE). Secondary endpoints included length of hospital stay, duration of NIV, and hospital mortality rates. Safety assessments involved monitoring fluctuations in mean arterial pressure (MAP), heart rate, respiratory rate (RR), minute ventilation, episodes of respiratory depression or hypotension, as well as variations in arterial partial pressure of carbon dioxide and oxygenation index. Results indicated that both DEXM and HM groups exhibited significant increases in DE and DTF ($p<0.05$). However, DE improvements were notably superior in the HM group than in the DEXM group ($p=0.024$). Additionally, NIV duration was significantly reduced in the HM group compared with the DEXM group ($p=0.033$). There were no significant differences between groups regarding length of hospital stay or in-hospital mortality ($p>0.05$). The DEXM group experienced a more pronounced reduction in MAP ($p=0.032$), while the RR reduction was significantly greater in the HM group ($p=0.003$). A significant interaction between group assignment and time was observed for RR ($p=0.023$). Incidents of clinically significant hypotension were infrequent and comparable between groups ($p>0.05$). Neither group showed evidence of respiratory depression nor any detrimental impact on overall respiratory function. The findings suggest that HM may better preserve diaphragmatic function during NIV in AECOPD. Although HM was well tolerated, clinicians should remain cautious regarding potential drug accumulation and avoid prolonged administration.

Key words: hydromorphone, dexmedetomidine, diaphragm, chronic obstructive pulmonary disease, acute exacerbation.

Introduction

Chronic obstructive pulmonary disease (COPD) remains a significant global health concern and continues to be ranked third among leading causes of death worldwide [1]. AECOPD constitutes a major reason for hospital admissions among elderly patients. NIV is considered the primary therapeutic option for acute respiratory failure associated with AECOPD, as it decreases the necessity for endotracheal intubation and enhances clinical outcomes [2,3]. However, severe diaphragmatic dysfunction occurs in approximately 25% of hospitalized AECOPD patients receiving NIV, and such dysfunction is associated with difficult weaning and poorer outcomes [4-6]. Therefore, diaphragmatic function in AECOPD patients has received increasing attention.

Multiple factors can impair diaphragmatic function in COPD patients, yet the adverse effects of analgesic and sedative drugs on the diaphragm have only recently been recognized. Studies have demonstrated that sedation is linked to diaphragmatic dysfunction in patients with sepsis [7]. In mechanically ventilated rats, DEXM impaired diaphragmatic function and increased oxidative stress; midazolam induced more severe dysfunction during sedation than DEXM and propofol, while propofol reduced diaphragmatic electromyographic activity in mechanically ventilated pediatric patients [8-10]. However, the effects of opioid drugs on diaphragmatic function remain unclear. Oxidative stress has been identified as a key contributor to diaphragmatic dysfunction in COPD, whereas HM has been shown to attenuate oxidative stress [11,12], suggesting a potential protective effect of HM on the diaphragm.

Recent systematic reviews and meta-analyses have shown that analgesia and sedation improve NIV tolerance and reduce the need for endotracheal intubation, demonstrating clear clinical benefits. Although current guidelines provide no specific recommendations for the use of analgesia and sedation during NIV, DEXM is often regarded as a preferred option [13,14]. However, the increased risk of bradycardia and hypotension associated with DEXM use in patients with acute respiratory failure should not be ignored [15]. Therefore, identifying safer alternatives that minimize diaphragmatic dysfunction is essential for AECOPD patients undergoing NIV.

This study aimed to evaluate and compare the effects of HM and DEXM on diaphragmatic function, clinical outcomes, and safety in patients with AECOPD receiving NIV.

Materials and Methods

An open-label randomized controlled trial was performed between July 2024 and October 2025 at Chongqing University Fuling Hospital. The ethics approval for this investigation was granted by the Ethics Committee of Chongqing University Fuling Hospital (approval number: 2024CDFSFLYYEC-061, approval date: 17/07/2024). Written informed consent was secured from all patients or their authorized representatives prior to inclusion in the study.

Patients

All included patients have been diagnosed with and met the diagnostic standards outlined by the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD 2024) [16].

Inclusion criteria: (1) age 50–85 years; (2) initiation of NIV for one or more of the following indications: (a) respiratory acidosis ($PaCO_2$ ≥45 mmHg and pH ≤7.35); (b) severe dyspnea with clinical signs suggestive of respiratory muscle fatigue or increased work of breathing; or (c) persistent hypoxemia despite supplemental oxygen therapy[16].

Exclusion criteria: (1) chronic use of home NIV therapy; (2) presence of neuromuscular disorders; (3) malignant diseases; (4) severe shock requiring norepinephrine dosage ≥ 1.0 μg/kg/min; (5) decompensated hepatic impairment defined by a Child-Pugh score exceeding 6; (6) severe renal dysfunction (creatinine clearance < 30 mL/min); (7) known allergy or hypersensitivity to DEXM or HM; (8) inability to attain targeted sedation or analgesia or concurrent administration of other sedative or analgesic medications; (9) NIV application lasting less than 24 hours; (10) hospitalization period either shorter than 7 days or extending to 30 days or more; (11) requirement for invasive mechanical ventilation during the study period due to clinical worsening; (12) refusal to provide informed consent.

Randomization

Participants were allocated to either the HM or DEXM groups through a randomization process generated via the RAND() function of Microsoft Excel software, employing a 1:1 allocation ratio and randomized block sizes. Group assignment codes were concealed within sealed, sequentially numbered envelopes.

Intervention

Patients in the DEXM group received a continuous infusion of DEXM at 0.2–0.7 μg/kg/h,

whereas those in the HM group received HM at 0.1–0.2 μg/kg/h. Analgesia and sedation were titrated according to the visual analog scale (VAS) and Bispectral Index (BIS) monitoring. Infusion rates were adjusted to maintain VAS ≤ 3 and BIS 80–90. All other management followed current guidelines.

Outcomes

The primary outcomes were changes in DE and DTF [17], assessed by ultrasound on day 1 (D1) and day 7 (D7) after enrollment.

Secondary outcomes included NIV duration, length of hospital stay, and in-hospital mortality.

Safety outcomes included changes in HR, MAP, RR, and MV. These parameters were evaluated before intervention (T0), at the time of first achieving therapeutic targets (TTA), and at 12 hours (T12) and 24 hours (T24) after the intervention. Safety outcomes also included the incidence of respiratory depression (RR < 8 breaths/min) [18], hypotension (MAP < 65 mmHg) [19], hypotension requiring intervention, arterial partial pressure of carbon dioxide ($PaCO_2$), and oxygenation index (PaO_2/FiO_2) assessed on D7.

Sample size and statistical analysis

The required sample size calculation was conducted using MedCalc Statistical Software (version 20.0.14), based on previously collected unpublished data. Calculations indicated that 32 participants per group would provide 90% power at an alpha level of 0.05 (two-tailed).

Data analysis was carried out using IBM SPSS Statistics (version 21.0). Continuous variables following a normal distribution were summarized as mean ± standard deviation (SD), with intergroup comparisons made through independent two-sample t-tests and intragroup comparisons via paired t-tests. Repeated measures data underwent analysis using repeated-measures ANOVA (RM-ANOVA). Continuous variables without a normal distribution were represented by median values and interquartile ranges, and differences between groups were analyzed with the Mann-Whitney U test, while intragroup variations were examined using Wilcoxon signed-rank tests. Categorical variables were assessed using either χ^2 or Fisher's exact tests, as appropriate. Subgroup analyses were conducted according to GOLD groups. Statistical significance was defined as a p-value less than 0.05.

Results

Between July 2024 and October 2025, a total of 151 AECOPD patients initially met the inclusion criteria and underwent screening for study eligibility. Subsequently, 118 eligible individuals were randomly allocated into two treatment arms. After excluding 38 subjects, 80 patients (40 assigned to the DEXM group and 40 assigned to the HM group) successfully completed the trial protocol. A detailed study flowchart is depicted in Figure 1.

The average age of enrolled patients was 74 years. At baseline, the two groups exhibited no statistically significant differences regarding demographic characteristics such as age, sex, presence of comorbid conditions, CURB-65 scores, or laboratory values related to organ functionality and markers of infection (all $P > 0.05$). The comprehensive baseline characteristics are presented in Table 1.

Primary outcomes

On day 1, diaphragmatic excursion (DE) did not differ significantly between the HM and DEXM groups ($P = 0.668$). However, by day 7, DE was significantly greater in the HM group compared with the DEXM group ($P = 0.024$). Moreover, both groups demonstrated a significant improvement in DE from day 1 to day 7 ($P < 0.05$) (Table 2).

Regarding diaphragmatic thickening fraction (DTF), no significant intergroup differences were identified on day 1 or day 7 (all $P > 0.05$). Nevertheless, significant within-group increases in DTF occurred between days 1 and 7 in both treatment arms ($P < 0.05$) (Table 2).

In post-hoc subgroup analyses, DM and DTF on day 7 were significantly greater in the HM group compared with the DEXM group among patients in the combined GOLD A/B subgroup ($P < 0.05$), whereas no significant intergroup difference was observed in the GOLD E subgroup ($P > 0.05$) (*Supplementary Table 1*).

Secondary outcomes

Patients in the HM group experienced significantly reduced NIV durations compared to those in the DEXM group ($P = 0.033$). In contrast, no significant differences emerged between groups concerning hospital stay length or in-hospital mortality rates ($P > 0.05$) (Table 2).

In post-hoc subgroup analyses, no significant intergroup differences in NIV durations, hospital stay length, and in-hospital mortality rates were observed between the DEXM group and the HM group ($P > 0.05$) (*Supplementary Table 1*).

Safety outcomes

HR exhibited no significant differences between the HM and DEXM groups ($P = 0.598$). However, HR significantly declined at T12 and T24 compared with baseline (T0) in both groups ($P < 0.001$). Additionally, HR in the DEXM group was significantly lower at T12 and T24 relative to values measured at TTA ($P < 0.05$) (Figure 2A).

MAP demonstrated no significant group-by-time interaction ($P > 0.05$). However, MAP values at TTA, T12, and T24 were significantly reduced in the DEXM group relative to the HM group ($P = 0.032$). Moreover, a significant decline in MAP was observed in both groups at TTA, T12, and T24 compared to baseline (T0) ($P < 0.001$) (Figure 2B).

A significant group-by-time interaction was noted for RR ($P = 0.023$). RR was significantly lower in the HM group than in the DEXM group at TTA, T12, and T24 ($P = 0.003$). Furthermore, RR significantly decreased from baseline (T0) at TTA, T12, and T24 in both groups ($P < 0.001$). Additionally, within the HM group, RR at T24 was lower than at TTA ($P < 0.05$) (Figure 2C).

MV showed no significant intergroup differences between the HM and DEXM groups ($P = 0.663$). Nevertheless, MV significantly decreased in both groups at TTA, T12, and T24 compared with baseline (T0) ($P < 0.001$) (Figure 2D).

Hypotension was reported in 7 patients (17.5%) in the DEXM group and 3 patients (7.5%) in the HM group, with no statistically significant difference ($P > 0.05$). Hypotension necessitating medical intervention occurred equally in two patients (5.0%) per group ($P > 0.05$). No instances of respiratory depression were identified during the study (Table 3).

No significant differences emerged between groups regarding arterial PCO_2 or PaO_2/FiO_2 on either day 1 or day 7 (all $P > 0.05$). Nonetheless, both parameters exhibited statistically significant improvements from day 1 to day 7 within each group ($P < 0.05$) (Table 3).

Discussion

The main clinical manifestations of diaphragmatic dysfunction include reduced DE, decreased muscle strength, and abnormal structural parameters [20]. Despite advances in diagnostic techniques, assessment of diaphragmatic function remains inconsistent across clinical settings [21]. Ultrasound is currently the only noninvasive and non-ionizing imaging technique widely available for direct evaluation of diaphragmatic function and is particularly useful for patients with AECOPD. It allows quantitative assessment by measuring diaphragmatic thickness, DE, and DTF, and has been shown to be reliable, valid, and

reproducible [22]. Reduced DE, a characteristic feature of diaphragmatic dysfunction in COPD, is closely associated with pulmonary function, subjective symptoms, and exercise capacity, and declines progressively with disease progression [23]. DTF is also an important parameter for assessing diaphragmatic function, although its clinical value in COPD remains controversial [24]. In this study, compared with DEXM, HM was more favorable for the recovery of DE in AECOPD patients receiving NIV, especially in patients of GOLD A/B groups, thereby contributing to the preservation of diaphragmatic function.

AECOPD is strongly associated with exacerbated airway inflammation and increased airflow limitation caused by multiple factors [25,26]. Air trapping resulting from airflow limitation is one of the major pathophysiological mechanisms underlying acute exacerbations and dyspnea [27,28]. Studies have shown that reduced DE is primarily caused by air trapping, rather than by dynamic hyperinflation or impaired muscle strength [29,30]. Persistent air trapping increases residual volume, keeping the diaphragm flattened and limiting its contraction, ultimately leading to decreased DE [31]. As precipitating factors are controlled and airway inflammation subsides, airflow limitation improves and residual volume decreases, allowing DE recovery [32,33], consistent with our findings. Furthermore, several studies have demonstrated that diaphragmatic dysfunction is associated with prolonged mechanical ventilation and weaning failure [34,35]. DE has been shown to predict weaning success [36]. Therefore, better DE may reflect stronger spontaneous breathing ability, facilitating earlier NIV withdrawal, which aligns with our results. This may also be related to the ability of opioid analgesics to alleviate dyspnea, modulate respiratory drive, reduce RR, and prolong expiratory time, thereby decreasing residual volume [37].

The potential adverse effects of analgesia and sedation should not be ignored. DEXM exerts a more pronounced effect on blood pressure in patients with AECOPD, although the overall incidence of hypotension remains low. A meta-analysis also confirmed that DEXM increases the risk of bradycardia and hypotension during NIV in patients with acute respiratory failure [15].

In contrast, HM may have a greater effect on respiration and potential for drug accumulation, yet it did not increase the risk of respiratory depression or carbon dioxide retention. Another study reported that HM had no significant effect on ventilatory function or arterial carbon dioxide tension in patients receiving palliative treatment for dyspnea, while significantly reducing dyspnea severity and RR [38]. The risk of HM accumulation may increase with age, as studies have shown that elderly individuals have prolonged half-life and reduced

clearance of HM [39,40], thereby increasing the likelihood of accumulation. Overall, both agents appeared to be safe for AECOPD patients receiving NIV, although close monitoring is recommended. It is also worth exploring whether combined administration could reduce adverse effects. A previous study found that HM and DEXM combination therapy reduced the required HM dose and decreased the incidence of HM-related side effects [41]. However, further research is needed to confirm these findings.

This study has several limitations. Diaphragmatic measurements may have been influenced by NIV, and continuous assessment of dynamic diaphragmatic changes was not performed. Patients who required endotracheal intubation were excluded, and long-term prognostic follow-up was not conducted.

Conclusions

We concluded that HM may better preserve diaphragmatic function during NIV in AECOPD, contributing to the recovery of DE and shortening NIV duration. Although well tolerated, clinicians should remain cautious of drug accumulation and avoid prolonged use. Despite no significant improvement in clinical outcomes, further studies with optimized intervention protocols, including placebo controls, combination therapy, or larger sample sizes, are warranted to explore potential benefits. In addition, the effect of analgesic and sedative therapy on the long-term risk of acute exacerbations in COPD patients remains to be clarified in further studies.

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Online supplementary material:
Supplementary Table 1. Primary and secondary outcomes stratified by GOLD classification.

Table 1. Patients' demographic, clinical and laboratory characteristics.

Variable	DEXM group (n=40)	HM group (n=40)	p
Age (years)	72.90±8.35	74.22±7.79	0.465
Sex, n(%)			0.217
Female	14(35.0)	9(22.5)	
Male	26(65.0)	31(77.5)	
Comorbidities, n(%)			
Hypertension	13(32.5)	19(47.5)	0.171
Coronary artery disease	12(30.0)	14(35.0)	0.633
Diabetes	7(17.5)	12(30.0)	0.189
Autoimmune disease	1(2.5)	1(2.5)	1.000
CURB-65 score	3(2,4)	3(2,3)	0.799
Creatinine (μmol/L)	86.06±37.00	90.47±43.67	0.628
Total bilirubin (μmol/L)	12.67(9.92,18.40)	13.68(7.69,17.82)	0.573
NT-proBNP (ng/mL)	1313(370,3948)	2060(431,4713)	0.610
WBC ($\times 10^9$/L)	8.65(6.28,12.11)	7.86(6.36,10.95)	0.405
Neutrophil percentage (%)	80.35±11.07	76.53±10.05	0.110
CRP (mg/L)	19.28(5.82,51.42)	20.79(6.92,41.42)	0.893
PCT (ng/mL)	0.12(0.07,0.28)	0.16(0.07,0.38)	0.739

DEXM, dexmedetomidine; HM, hydromorphone; CURB-65, severity score for community-acquired pneumonia; CRP, C-reactive protein; PCT, procalcitonin.

Table 2. Primary and secondary outcomes.

Variable		DEXM group (n=40)	HM group (n=40)	p
Primary outcome				
DE (cm)	D1	3.15±1.24	3.27±1.26	0.668
	D7	4.03±1.33#	4.74±1.44#	**0.024**
DTF (%)	D1	88.39±50.31	85.52±48.11	0.795
	D7	128.54±68.89#	137.30±74.66#	0.587
Secondary outcomes				
Duration of NIV(hours)		181±103	134±89	**0.033**
Length of hospital stay (days)		13.50±5.12	13.03±4.57	0.663
In-hospital mortality,n(%)		0(0)	3(7.5)	0.241

DEXM, dexmedetomidine; HM, hydromorphone; DE, diaphragmatic excursion; DTF, diaphragmatic thickening fraction;NIV: Noninvasive ventilation. Time points: D1 = the first day after enrollment; D7 = the seventh day after enrollment. Significance symbols: #$p<0.05$ compared to D1.

Table 3. Safety outcomes.

Variable		DEXM group (n=40)	HM group (n=40)	p
Hypotension,n(%)		7(17.5)	3(7.5)	0.176
Hypotension requiring intervention,n(%)		2(5.0)	2(5.0)	1.000
Respiratory depression,n(%)		0(0.0)	0(0.0)	—
PCO_2(mmHg)	D1	67.50±20.03	67.43±20.09	0.987
	D7	56.18±10.74#	57.35±13.50#	0.668
PaO_2/FiO_2	D1	217.53±69.30	229.20±71.13	0.459
	D7	270.10±73.40#	271.02±89.62#	0.960

DEXM, dexmedetomidine; HM, hydromorphone;PCO_2, arterial carbon dioxide partial pressure; PaO_2/FiO_2, oxygenation index. Time points: D1 = the first day after enrollment; D7 = the seventh day after enrollment. Significance symbols: #$p<0.05$ compared to D1.

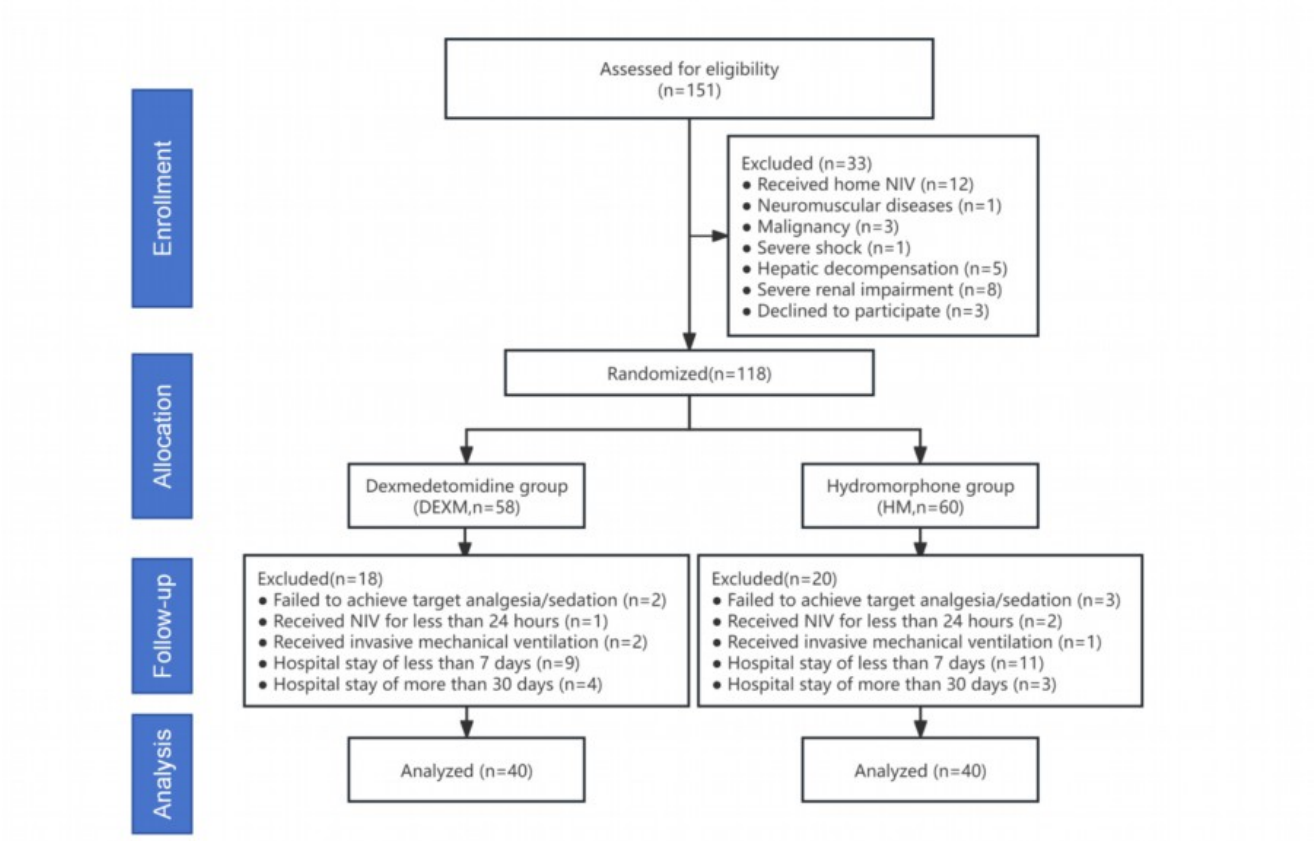

Figure 1. Flowchart of the study.

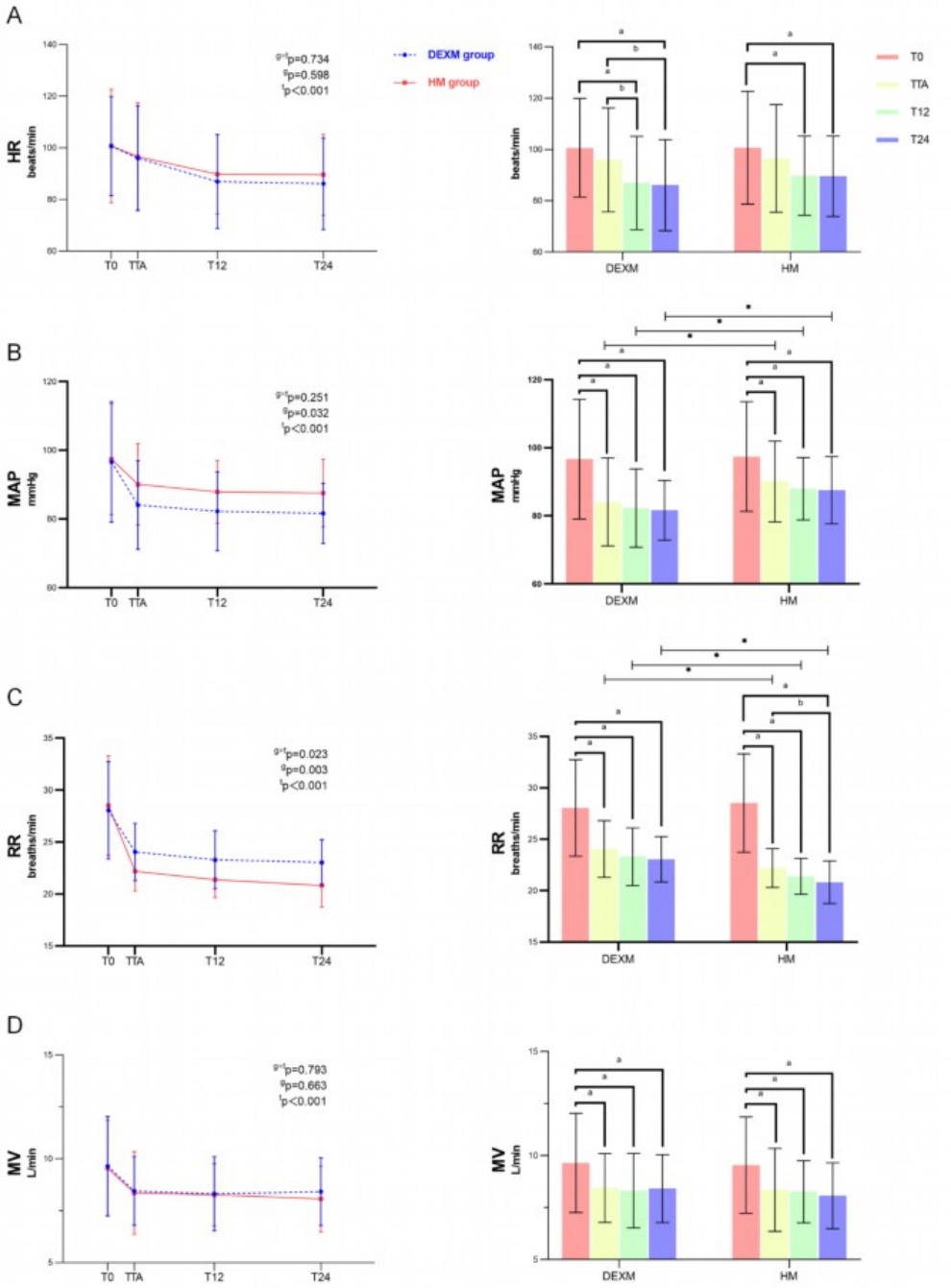

Figure 2. Changes in heart rate, mean arterial pressure, respiratory pressure, and minute ventilation during the first day of the study. DEXM, dexmedetomidine; HM, hydromorphone; HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate; MV, minute ventilation. Time points: T0 = before the intervention; TTA = at the first therapeutic-target-achieving time; T12 = 12 h post-intervention; T24 = 24 h post-intervention. Statistical effects: g × tp = group × time interaction; gp = group effect; tp = time effect. Significance symbols: a = $p < 0.05$ compared to T0; b = $p < 0.05$ compared to TTA; * = $p < 0.05$ compared to DEXM group.