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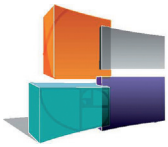

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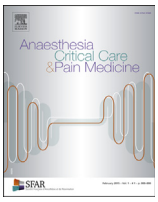

Original Article

# Dexmedetomidine to facilitate non-invasive ventilation after blunt chest trauma: A randomised, double-blind, crossover, placebo-controlled pilot study☆

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ABSTRACT

*Background:* Although non-invasive ventilation (NIV) is recommended in patients with chest trauma, this procedure may expose to discomfort and even failure due to agitation or excessive pain. We tested the impact of dexmedetomidine on the duration of the first session of NIV.
*Methods:* This randomised, crossover study enrolled 19 patients with blunt chest trauma who needed NIV. During one cycle comprising two NIV sessions, patients received in a random order an intravenous infusion of dexmedetomidine (0.7 mcg/kg/h) and placebo (saline solution) that was initiated 60 min prior to NIV. Dexmedetomidine (or placebo) was titrated to maintain a Richmond Agitation Sedation Scale (RASS) score between 0 and −3. A 6-h washout period was observed between NIV sessions. The reproducibility of the drug-related effects was tested during a second cycle of two NIV sessions.
*Results:* During the first cycle, dexmedetomidine prolonged the duration of NIV compared to placebo: 280 min (118–450) (median, 25–75th quartiles) versus 120 min (68–287) respectively, corresponding to a median increased duration of 96 min (12–180) ($P = 0.03$). Dexmedetomidine was associated with a lower score for RASS: −0.8 (−1.0;0.0) versus 0.0 (−0.5;0.0) ($P < 0.01$), and reduced respiratory discomfort according to the 10 cm visual similar scale: 0.6 cm (0.0–3.0) versus 2.2 cm (0.0–5.3) ($P = 0.05$). Pain scores, morphine consumption, and blood gas measurements were comparable between groups. No difference in the duration of non-invasive ventilation was found during the second cycle.
*Conclusions:* In this pilot trial, dexmedetomidine could facilitate the acceptance of the first session of non-invasive ventilation for patients with chest trauma.
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## 1. Introduction

The use of non-invasive mechanical ventilation (NIV) in patients with severe blunt chest trauma has been associated with reduced tracheal intubation rate, length of intensive care unit (ICU) stay and/or incidence of ventilator-associated pneumonia [1–4]. However, respiratory comfort and control of chest wall pain, agitation and anxiety is a prerequisite to reduce the incidence of NIV failure in this trauma population. Thoracic epidural analgesia for blunt thoracic trauma is the most examined technique [5,6]. However, strong evidence is lacking to firmly recommend this modality over others in chest trauma [7,8]. Furthermore, the use of epidural analgesia is limited in critically ill trauma patients due to several contraindications [6]. One alternative is the use of hypnotics and/or opioids, inducing respiratory depression and possibly aggravating the morbidity of chest trauma.

In this context, dexmedetomidine could be an alternative to improve NIV tolerance. Dexmedetomidine is a short-acting

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alpha-2 adrenoreceptor agonist that provides sedation and analgesia with no significant respiratory depression and a reduced risk of delirium [9,10]. It was found to improve patient ability to communicate with their caregiver [11] and reduce intubation duration in patients with agitated delirium [12]. Dexmedetomidine was found preferable to benzodiazepine sedatives in critically ill, mechanically ventilated patients in the most recent guidelines [13]. While a few randomised studies have explored the dexmedetomidine effects in non-trauma patients managed with NIV [14–16], none have studied its impact in patients with chest trauma. We then planned a pilot study to test the effects of dexmedetomidine on the duration of NIV in critically ill patients who needed NIV. Using a randomised, double-blind, crossover, placebo-controlled trial, we hypothesised that dexmedetomidine could provide respiratory comfort and lead to a longer duration of NIV session compared to placebo.

## 2. Methods

This prospective, randomised, double-blind, crossover, placebo-controlled pilot study was conducted between September 2015 and February 2017 in a surgical intensive care unit. The Institutional Review Board of Sud-Est V approved the study (IRB#15-CHUG-23) on July 1st 2015, and clinical trial authorisation was obtained from the National Agency for Medicines and Health Products Safety (ANSM#150652A-31) on June 16th 2015. Written informed consent was obtained from all patients prior to randomisation. The study was registered with ClinTrials.gov, number NCT02537366 on September 1st, 2015, https://clinicaltrials.gov/ct2/show/NCT02537366.

### 2.1. Participants

Critically ill adult patients were considered for study participation if they had a significant blunt chest trauma with an impact on outcome as reflected by a Thorax Trauma Severity Score (TTSS) higher than 6 (range: 0–25) [17], and if they required NIV and arterial catheter monitoring according to the in-charge physician. Non-inclusion criteria were the use of an epidural catheter for analgesia, agitation as defined by a Richmond Agitation Sedation Scale (RASS) score higher than +2, concomitant administration of midazolam, propofol or ketamine, tracheal intubation and extubation prior to screening for inclusion, treatment with clonidine or dexmedetomidine in the past 8 hours, long-term treatment with neuroleptics, use of NIV prior randomisation, pregnancy, spinal cord injury, patient refusal and contraindications to the NIV and/or to dexmedetomidine: imminent indication of tracheal intubation, Glasgow Coma Scale score less than 9, craniofacial trauma, non-drained complete pneumothorax, airway obstruction, vomiting, active gastro-intestinal bleeding, haemodynamic instability, ventricular arrhythmia, acute cardiac failure, and heart block without pacemaker use. In addition, a score of 0–3 on the Visual Analog Scale (VAS; 0–10 cm) for pain at rest was required in all patients at the time of inclusion. Patients received acetaminophen (1 g × 4 daily) and a continuous intravenous infusion of nefopam (80 mg daily).

### 2.2. Study protocol

The cycle included two NIV sessions during which patients randomly received an intravenous continuous infusion of dexmedetomidine (Dexdor®, Baxter France Benelux, Guyancourt, France) and placebo (0.9% sodium chloride solution). The allocation of the treatment order was determined by means of a computer-generated random table by blocks of four. A nurse working in another ICU prepared the dexmedetomidine (400 mcg/40 mL) and placebo solutions. In-charge physicians and nurses were blind to the assigned treatments that were indiscernible in appearance and volume of infusion, and undisclosed in verbal or written reports. The infusion was initiated 60 min prior to NIV at the same rate for both treatments, corresponding to 0.7 mcg/kg/h of dexmedetomidine without a loading dose. Dexmedetomidine (or placebo) was then titrated by 0.2 mcg/kg/h every 60 min (up to a maximum dose of 1.3 mcg/kg/h) to maintain a RASS score between 0 and −3. A 6-h washout period was observed between two NIV sessions accounting for 1-h contextual half-life of dexmedetomidine. Patients received neither tested drug nor NIV during this 6-h interval (Fig. 1).

Following the start of infusion, the patient could have a morphine titration (2 mg every 5 min) if the 10-cm VAS pain score exceeded 3. Patients were then instructed to use a Patient-Controlled Analgesia (PCA) device that was set to deliver a 1-mg dose of morphine with a 7-min lockout time.

Following initiation of these treatments, NIV (Evita Infinity® V500, Dräger France, Antony, France) was delivered through a full-face mask with initial settings as follows: inspiratory positive airway pressure at 8 cm $H_2O$, positive end-expiratory airway pressure at 4 cm $H_2O$, and fraction of inspired oxygen to achieve pulse oximetry higher than 92%.

### 2.3. Study outcomes

The primary outcome was the duration of NIV session to reflect comfort and NIV tolerance. The maximal target duration of NIV was 8 hours. The NIV session was discontinued if the patient had a RASS score higher than +2, was grabbing and pulling the NIV mask off, requested to stop the NIV session, or if there was an indication of invasive ventilation according to previously defined criteria [1]. The development of serious adverse effects could be a cause of NIV discontinuation whether they were due to NIV intolerance, or to the use of dexmedetomidine, i.e. heart rate less than 40 beats/min, mean arterial pressure less than 55 mmHg, RASS score of −4 or −5.

Secondary outcomes included the hourly measurements by nurses of RASS score and the hourly measurements of self-rated 10-cm VAS for pain and respiratory discomfort during each NIV

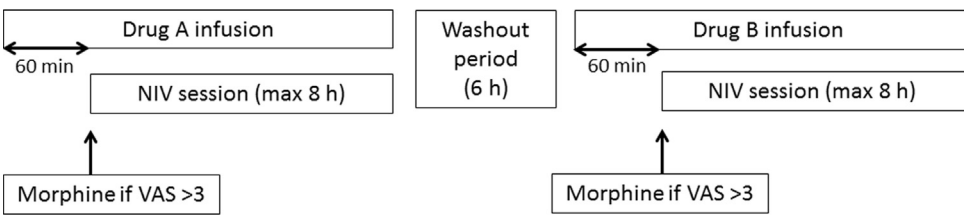


**Fig. 1.** Timeline diagram of one cycle with two non-invasive ventilation (NIV) sessions. Each patient received 1-h drug infusion then a morphine titration if the Visual Analog Scale (VAS) for pain exceeded 3, and NIV session for a maximal duration of 8 hours. A 6-h washout period was observed prior to starting the second sequence. The second cycle started after 6-h washout period according to the same sequence. During the study period, patients received multimodal analgesia, i.e. acetaminophen, nefopam and morphine patient-controlled analgesia.

session. Other outcomes included the amount of morphine consumed, the differences in arterial blood gases ($PaO_2$, $PaCO_2$) and pH measured at the start and end of each NIV session, and side effects of dexmedetomidine. There was no delirium assessment.

### 2.4. Additional study

The reproducibility of the drug-related effects was tested during a second cycle of two NIV sessions using similar crossover design. This second cycle was initiated 6 hours following the completion of the first cycle whatever the time of the day. The allocated order for treatments was the same between the first and the second cycle.

### 2.5. Statistical analysis

The trial was designed to have a power of 90% to detect a clinically significant intra-individual difference in the primary outcome of a NIV session duration lasting more than 50% with dexmedetomidine with the use of a two-sided type 1 error of 0.05. NIV session duration was estimated 180 min ± 180 min with placebo according to other studies in non-trauma patients [18,19]. Assuming that the correlation of the two NIV sessions duration would be 0.7 for each patient and assuming an increased NIV duration by 120 min with dexmedetomidine, we calculated that 18 patients would be needed to detect this difference. To account for unexpected technical difficulties, a sample of 20 patients was planned (nQuery, Statistical Solutions Ltd, Cork, Ireland).

Results are given as the median (25–75th percentiles) for continuous variables, frequencies and percentages for categorical variables. The *AB/BA* design accounting for a period effect, also known as Collaboration in Research and Methodology for Official Statistics (CROS) analysis, was used to analyse changes in outcomes between dexmedetomidine and placebo [20]. We assumed no carry-over effect using this study design with a 6-h washout period. Student *t*-test or non-parametric Mann–Whitney and Wilcoxon tests were used for the CROS analysis of normally or non-normally distributed variables, respectively. The reproducibility of treatment effects with repeated NIV sessions was determined by comparing results obtained in first cycle with those from second cycle; this occurred only for statistically different results between treatments found on first cycle. Statistical significance was declared when $P \leq 0.05$ (Stata version 15.0, Stata Corp., College Station, TX, USA).

## 3. Results

Among 99 patients assessed for participation in the study, 20 were randomised (Fig. 2). The 59 patients who did not meet inclusion criteria had no arterial catheter ($n = 18$), contraindication to NIV ($n = 15$), tracheal intubation ($n = 12$), a TTSS equal or lower than 6 ($n = 11$), spinal cord injury ($n = 1$), epidural analgesia ($n = 1$), and age less than 18 years ($n = 1$). One randomised patient was excluded from the study because of participation in another randomised study. Nineteen patients were therefore included in the intention-to-treat analysis. Due to bradycardia during the first cycle, one patient was excluded from the second cycle.

Baseline characteristics of the study population are shown in Table 1. Patients were enrolled in the study within 627 min (425–1742) of their admission to the intensive care unit. No patient required thoracic surgery while staying in ICU. Supplemental oxygen (2–10 L/min) via nasal cannula or facial mask was required for all patients. At the time of randomisation, patients had a VAS pain score of 2 (0–2), a RASS score of 0 (0–0), and a respiratory discomfort of 2 (0–5). Patients were discharged from the ICU after a median length of stay of 8 days (5–12).

### 3.1. Primary outcome

During the first cycle of NIV sessions, the median dose of dexmedetomidine was 0.7 mcg/kg/h (0.4–0.7). Prior to the NIV session, there was a lower mean arterial blood pressure with dexmedetomidine compared to placebo, while heart rate was comparable between treatments (Table 2). Dexmedetomidine prolonged the duration of NIV compared to placebo: 280 min (118–450) versus 120 min (68–287), resulting in an intra-individual increased NIV duration by 96 min (12–180) ($n = 19$ patients; $P = 0.03$) (Fig. 3). Patients who received dexmedetomidine first were less likely to tolerate NIV for longer duration during their second exposure with placebo (Fig. 3).

The main reason for NIV discontinuation prior to the maximal duration of 8 hours per session was the patient refusal to continue the NIV session due to discomfort: 15 with placebo, 14 with dexmedetomidine. The other reasons to stop NIV were a RASS score higher than +2 (1 with placebo and 1 with dexmedetomidine) and the NIV mask being pulled off (3 with placebo and 2 with dexmedetomidine). Considering patients who requested to stop their NIV session, the NIV duration was significantly longer with dexmedetomidine: 298 min (182–417) versus 162 min (72; 275) ($P = 0.05$).

### 3.2. Secondary outcomes

Dexmedetomidine was associated with a lower RASS score compared to placebo: −0.8 (−1.0;0.0) versus 0.0 (−0.5;0.0), respectively ($n = 19$ patients; $P < 0.01$) (Fig. 4). The VAS score for respiratory discomfort was also lower with dexmedetomidine: 0.6 (0.0–3.0) versus 2.2 (0.0–5.3), respectively ($n = 19$ patients;

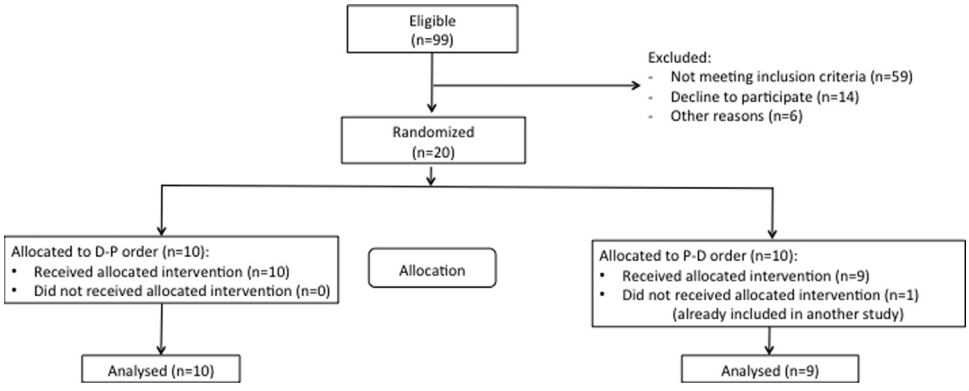


**Fig. 2.** Flowchart of patients included in the study. D: dexmedetomidine; P: placebo.

**Table 1**
Characteristics of the 19 included patients. Data are expressed as median [25th; 75th percentile] unless otherwise specified.

| Variables | Value |
|---|---|
| Age, years | 56 [29; 67] |
| Sex, male/female, *n* | 17/2 |
| Mechanism of injury, *n* | |
| Road traffic accident | 11 |
| Skiing accident | 3 |
| Fall | 5 |
| Injury Severity Score (ISS) | 24 [20; 25] |
| Simplified Acute Physiology Score (SAPS) II | 32 [22; 37] |
| Thorax Trauma Severity Score (TTSS) | 9 [7; 10] |
| Pneumothorax, *n* | |
| Drained | 11 |
| Not drained | 4 |
| Associated vertebral trauma, *n* | 11 |
| Rib fractures, *n* | |
| 1 to 3 | 2 |
| 3 to 6 | 5 |
| >3 bilateral | 4 |
| Flail chest | 8 |
| Abbreviated Injury Scale (AIS) maximum ≥ 3 | |
| Thorax AIS ≥ 3, *n* | 19 |
| Head and neck AIS ≥ 3, *n* | 1 |
| Abdomen AIS ≥ 3, *n* | 3 |
| Limb AIS ≥ 3, *n* | 3 |
| Variables on admission | |
| Heart rate, beats/min | 92 [75; 112] |
| Mean arterial blood pressure, mmHg | 90 [80; 98] |
| Respiratory rate, cycle/min | 17 [14; 19] |
| Pulse oximetry, % | 100 [98; 100] |
| $PaO_2$, mmHg[a] | 104 [94; 135] |
| $PaCO_2$, mmHg | 43 [37; 47] |
| Arterial pH | 7.39 [7.34; 7.40] |

[a] Data were obtained under supplemental oxygen (2–10 L/min) for all patients.

$P = 0.05$). The VAS score for pain was however comparable between dexmedetomidine and placebo: 1.3 (1.0–3.0) versus 2.9 (0.5–5.0), respectively ($n = 18$ patients; $P = 0.11$). Morphine consumption during the NIV session was not affected with the treatment: 1 mg (0–3) versus 1 mg (0–4), respectively ($n = 19$ patients; $P = 0.74$).

**Table 2**
Physiological data and respiratory pattern during the non-invasive ventilation (NIV) session while patients were receiving dexmedetomidine and placebo ($n = 19$ patients). Haemodynamics and arterial blood gases were measured when NIV session was initiated (Start) and terminated (End). Changes (Δ) in arterial blood gases were compared between dexmedetomidine and placebo. Data are expressed as the median [25th; 75th percentile].

| Variables | Dexmedetomidine | Placebo | *P*-value |
|---|---|---|---|
| Mean arterial blood pressure, mmHg | | | |
| Start | 70 [63; 86] | 90 [77; 95] | 0.04 |
| End | 75 [66; 83] | 88 [78; 97] | 0.04 |
| Heart rate, beats/min | | | |
| Start | 84 [65; 95] | 84 [77; 106] | 0.50 |
| End | 80 [63; 99] | 84 [77; 99] | 0.55 |
| $PaO_2$, mmHg | | | |
| Start | 98 [85; 130] | 113 [87; 119] | |
| End | 104 [81; 124] | 92 [74; 117] | |
| $\Delta PaO_2$ | 5 [−20; 33] | −18 [−72; 35] | 0.95 |
| $PaCO_2$, mmHg | | | |
| Start | 43 [37; 50] | 42 [36; 45] | |
| End | 45 [39; 49] | 42 [36; 45] | |
| $\Delta PaCO_2$ | −0.0 [−0.3; 0.3] | −0.0 [−0.2; 0.1] | 0.51 |
| Arterial pH | | | |
| Start | 7.39 [7.36; 7.41] | 7.39 [7.37; 7.42] | |
| End | 7.40 [7.37; 7.41] | 7.40 [7.37; 7.41] | |
| ΔpH | 0.00 [−0.01; 0.01] | 0.01 [0.00; 0.02] | 0.78 |
| Tidal volume, mL | 655 [532; 733] | 636 [463; 787] | 1 |
| Respiratory rate | 18 [15; 20] | 17 [14; 21] | 0.52 |
| End-expiratory pressure | 5 [4; 5] | 5 [4; 5] | 1 |
| Fraction of inspired oxygen | 40 [35; 40] | 40 [35; 40] | 0.81 |

A 4-mg morphine titration was required in one patient only during his first NIV session. During the administration of dexmedetomidine, there was one episode of bradycardia and five episodes of arterial hypotension. Three patients required the concomitant infusion of norepinephrine at a median dose of 2.5 mcg/kg/min. Accordingly, a lower mean arterial blood pressure was found with dexmedetomidine compared to placebo during the NIV session (Table 2). The NIV settings, respiratory pattern and changes in arterial blood gases and pH measurements during the NIV session were comparable between treatments. No excessive sedation was found with dexmedetomidine. No patient required tracheal intubation or suffered nosocomial pneumonia.

### 3.3. Additional study

During the second cycle, two patients (1 with dexmedetomidine, 1 with placebo) accomplished the first NIV session but refused the second NIV session of this cycle; their NIV duration was given as 0 minutes. The median dose of dexmedetomidine was 0.7 mcg/kg/h (0.6–0.7). No difference in the duration of NIV sessions was found with the treatment: 180 min (80–245) (dexmedetomidine) versus 150 min (74–282) (placebo) ($n = 18$ patients; $P = 0.71$). The RASS score obtained with dexmedetomidine was significantly lower compared to placebo: −0.2 (−1.0;0.0) versus 0.0 (−0.4;0.0), respectively ($n = 16$ patients; $P < 0.01$).

## 4. Discussion

In a population of patients with blunt chest trauma managed with NIV, the introduction of dexmedetomidine improved NIV tolerance, as reflected by a clinically relevant effect of more than 50% duration of the first NIV session, a deeper level of sedation and less respiratory discomfort compared to placebo. No effects on pain scores and morphine consumption were found in these patients who had controlled pain within 0–3 VAS at rest. This dexmedetomidine-induced effect on NIV duration was not reproducible during a subsequent session. Findings of this pilot study indicate that dexmedetomidine could be an adjunct therapeutic option to transiently reduce respiratory discomfort and facilitate the acceptance of NIV in patients with chest trauma. This adds to the recent guidelines suggesting the preferential use of dexmedetomidine over benzodiazepines for mechanically ventilated patients [13].

This study has several strengths. Its crossover design permitted a gain in statistical power compared to a parallel trial. Patients acted as their own control and were blind to treatment order. All patients had a significant chest trauma as reflected by a median TTSS of 9 (7–10) needing an admission to the intensive care unit. They required pneumothorax drainage ($n = 11$), supplemental oxygen to normalise blood oxygenation, and NIV to facilitate thoracic physiotherapy according to the French guidelines [21]. A TTSS of more than 6 was found to have an impact on outcome after chest trauma [17,22]. With no significant pain at rest as prerequisite, patients received dexmedetomidine (or placebo) at a rate of 0.7 mcg/kg/h one hour prior to starting the first NIV session in order to optimise the drug effect [10]. Although this sequential order seemed as the most efficient to maximise the NIV tolerance, two patients refused the second NIV session of the second cycle. This sequential order differed from a parallel trial in which dexmedetomidine was given after the initiation of NIV and which showed no benefit on NIV tolerance [16].

Respiratory distress following chest trauma is multifactorial and includes pain, rib fractures, flail chest, pleural effusions, and lung contusions. Placing the patient under invasive mechanical ventilation increases the risk of ventilator-associated pneumonia. The use of NIV in cooperative patients was proposed to overcome

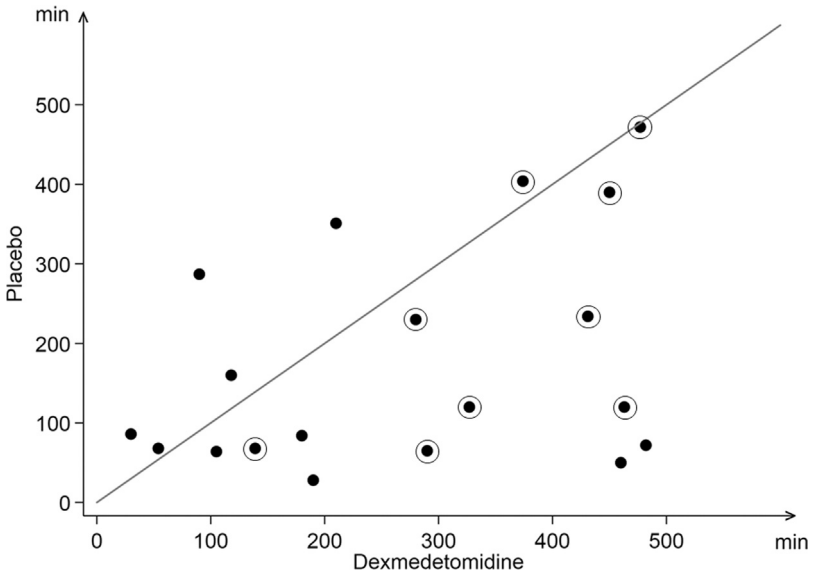


**Fig. 3.** Duration (min) of non-invasive ventilation (NIV) session for the 19 included patients. Each patient underwent two NIV sessions, one with dexmedetomidine and the other with placebo in a random order. Dexmedetomidine was associated with significantly longer NIV duration compared to placebo. Patients with a circle received dexmedetomidine first.

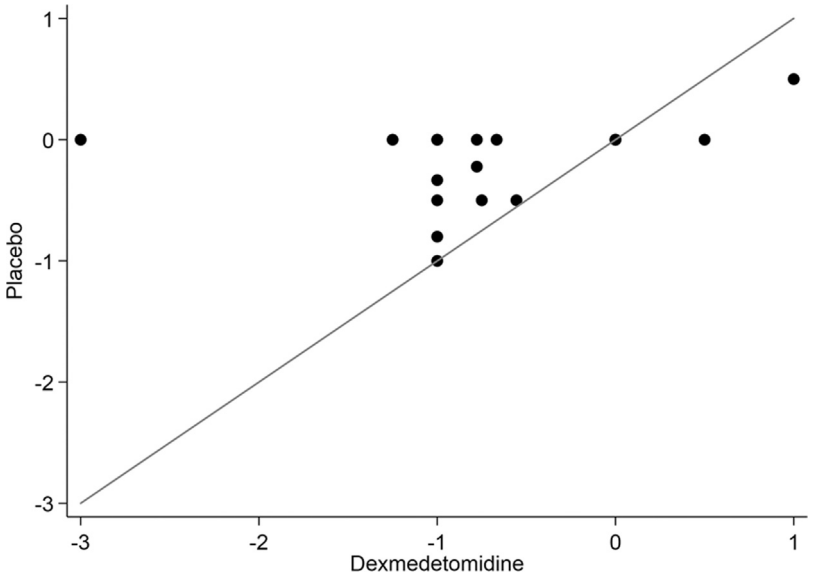


**Fig. 4.** Richmond Agitation Sedation Scale score during non-invasive ventilation (NIV) session for the 19 included patients (3 circles had more than one patient). Each patient underwent two NIV sessions, one with dexmedetomidine and the other with placebo in a random order. Dexmedetomidine was associated with significantly lower Richmond Agitation Sedation Scale scores compared to placebo.

this issue [23]. In the three randomised studies having tested NIV in chest trauma, pain was controlled with epidural analgesia or intravenous remifentanil infusion [1,3], or with a midazolam infusion and a morphine-PCA device [2]. However, the use of epidural analgesia is not always possible in critically ill trauma patients [6], and opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are often associated with side effects. In addition, recent guidelines only weakly recommend considering the use of epidural analgesia and multimodal analgesia (i.e., NSAIDs, pregabalin/gabapentin, acetaminophen) in chest trauma patients [8].

As an alternative, dexmedetomidine has already been tested for its ability to improve NIV tolerance in non-trauma patients. In patients who refused to continue NIV due to discomfort, dexmedetomidine was shown to achieve the expected level of sedation and improve NIV tolerance [24]. This drug was associated with a lower tracheal intubation rate compared to midazolam in patients who had discomfort with previous NIV sessions [14]. Patients in acute respiratory failure were shown to tolerate NIV for longer durations following dexmedetomidine compared to placebo [16]. In the present crossover study, chest trauma patients under dexmedetomidine had significantly increased duration of NIV compared to placebo. This was associated with a reduced respiratory discomfort while differences in RASS scores could be viewed as mild. There was no first exposure effect, i.e. patients who received dexmedetomidine first had no better experience that would tolerate NIV for a longer period during the exposure with placebo (Fig. 3).

Despite the improved NIV tolerance, dexmedetomidine had no effect on pain scores and morphine consumption. This is not

surprising given that dexmedetomidine was administered in patients in whom the control of chest wall pain at rest was prerequisite and who had received multimodal analgesia (i.e., acetaminophen, nefopam) prior to initiating dexmedetomidine. The present study also shows that the dexmedetomidine-induced NIV tolerance was not reproducible during the subsequent cycle of NIV sessions. Nevertheless, a longer duration of NIV at the first session with dexmedetomidine may facilitate the further acceptance of this modality. Side effects associated with dexmedetomidine, i.e. bradycardia and arterial hypotension should be considered.

Our study, however, has limitations. First, it is a single-centre study, which therefore does not account for large variations in patient management procedures across centres. Our findings thus require external validation on a larger population. Second, despite all presenting a significant chest trauma, our enrolled patients were selected to ensure none had chest wall pain or agitation at baseline, and none were in cardio-respiratory failure. Whether the use of dexmedetomidine can be transposed to other medical conditions, in particular significant pain at rest also warrants further investigation. Third, while we found no nosocomial pneumonia among our enrolled patients, their limited number excludes any conclusion about the impact of NIV on the morbidity of chest trauma. Little is known about the benefits of an early use of NIV in this clinical condition [25].

## 5. Conclusion

In this pilot study, dexmedetomidine provided respiratory comfort and transiently improved the duration of NIV session for patients with blunt chest trauma. Dexmedetomidine could be viewed as an adjunct therapy to facilitate the acceptance of this modality in this clinical setting.

## Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

## Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

## Disclosure of interest

Dr. Jean-Francois Payen reports past fees from Baxter Healthcare Corporation. The other authors declare that they have no competing interest.

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## Authors' contributions

Study design/planning: BD, TTB, JLB, and JFP.
Study conduct: BD, TTB, AG, and DF.
Data analysis: BD, TTB, LGA, PB, JLB, and JFP.
Writing paper: BD, TTB, PB and JFP.
Revising paper: all authors.

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