

## RESPIRATION AND THE AIRWAY

# High-inspired oxygen concentration further impairs opioid-induced respiratory depression

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### Editor's key points

- It is important to understand the effects of opioids on ventilatory parameters.
- This study investigated the ventilatory effects of opioids under different inspired oxygen concentrations.
- Increased inspired oxygen resulted in greater opioid-induced respiratory depression.
- Opioid-related respiratory depression was not detected by Sp<sub>O<sub>2</sub></sub> monitoring when supplemental oxygen was given.

**Background.** Hyperoxaemia depresses the output of peripheral and central chemoreceptors. Patients treated with opioids often receive supplemental oxygen to avert possible decreases in oxygen saturation (Sp<sub>O<sub>2</sub></sub>). We examined the effect of a single dose of remifentanyl in healthy volunteers inhaling room air vs air enriched with 50% oxygen.

**Methods.** Twenty healthy volunteers received i.v. 50 µg remifentanyl (infused over 60 s) at anormoxic (N) or hyperoxic (F<sub>I</sub>O<sub>2</sub> 0.5, H) background on separate occasions. Minute ventilation (V<sub>i</sub>), respiratory rate (RR), end-tidal P<sub>CO<sub>2</sub></sub>, and Sp<sub>O<sub>2</sub></sub> were collected on a breath-to-breath basis. The occurrence of apnoea was recorded.

**Results.** During normoxia, remifentanyl decreased V<sub>i</sub> from 7.4 (1.3) [mean (sd)] to 2.2 (1.2) litre min<sup>-1</sup> (P<0.01), and during hyperoxia from 7.9 (1.0) to 1.2 (1.2) litre min<sup>-1</sup> (P<0.01; H vs N: P<0.001). RR decreased from 13.1 (2.9) to 6.1 (2.8) bpm during N (P<0.01) and from 13.2 (3.0) to 3.6 (4.0) bpm during H (P<0.01; H vs N: P<0.01). During normoxia, Sp<sub>O<sub>2</sub></sub> decreased from 98.4 (1.5) to 88.6 (6.7)% (P<0.01), while during hyperoxia, Sp<sub>O<sub>2</sub></sub> changed from 99.7 (0.7) to 98.7 (1.0)% (P<0.001). Apnoea developed in two subjects during normoxia and 10 during hyperoxia.

**Conclusions.** Respiratory depression from remifentanyl is more pronounced in hyperoxia than normoxia as determined from minute ventilation, end-tidal P<sub>CO<sub>2</sub></sub>, and RR. During hyperoxia, respiratory depression may be masked when measuring Sp<sub>O<sub>2</sub></sub> as pulse oximetry remains in normal values during the first minutes of respiratory depression.

**Keywords:** analgesics; hyperoxia; hypoventilation; hypoxia; monitoring; opioids; oxygen; remifentanyl; respiration; respiratory depression; respiratory rate; ventilatory depression

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Opioids are essential instruments in the treatment of moderate-to-severe pain. However, the use of opioids comes with a variety of side-effects; of which, opioid-induced respiratory depression is potentially life-threatening.<sup>1</sup> Spontaneously breathing patients on opioid therapy often receive supplemental oxygen to prevent the occurrence of decreases in Sp<sub>O<sub>2</sub></sub>. Oxygen is a potent modifier of the ventilatory control system.<sup>2,3</sup> It directly interacts with breathing by decreasing the activity of the peripheral chemoreceptors at the carotid bodies and modifies central drive by decreasing the slope of the ventilatory carbon dioxide response of the central chemoreceptors in the brainstem.<sup>2</sup> Little is known on the interaction of high-inspired oxygen concentration and opioid therapy on breathing. Since opioids activate µ-opioid receptors expressed on neurones in brain areas involved in chemosensitivity and rhythmogenesis,<sup>4</sup> it is reasonable to assume that they interact in their effects on breathing.

In the current proof-of-concept study, we measured the effect of a single bolus dose of remifentanyl (50 µg) on ventilation in healthy volunteers inhaling a normoxic vs a hyperoxic gas mixture. We tested the opioid remifentanyl, as this opioid is short acting, a potent depressant of ventilation, and is increasingly used in spontaneously breathing patients for a variety of indications, including labour pain, procedural analgesia and sedation, and postoperative pain relief.<sup>5–8</sup>

We hypothesize that remifentanyl during hyperoxia impairs ventilation more than during normoxia, due to the combined effects of remifentanyl and oxygen.

## Methods

Testing the effect of the inspired oxygen condition on opioid-induced respiratory depression was the primary endpoint of the study. Furthermore, a secondary endpoint of the study was the ability of reductions in minute ventilation

to be detected by coincident reductions in respiratory rate (RR) and/or oxygen saturation as displayed on monitoring equipment.

### Volunteers

Twenty healthy male ( $n=10$ ) and female ( $n=10$ ) volunteers (aged 18–28 yr, BMI 23–29 kg m<sup>-2</sup>, weight 73–89 kg) were enrolled in the study after approval of the protocol by the Human Ethics Committee of the LUMC (Commissie Medische Ethiek, LUMC, Leiden, The Netherlands). All subjects gave informed consent before the measurements.

### Study design

During breathing of either a normoxic gas mixture (inspired fraction 0.21) or a hyperoxic gas mixture (inspired fraction 0.5), the subjects received an i.v. infusion of 50 µg remifentanyl (Ultiva, GlaxoSmithKline, Zeist, The Netherlands) over 90 s. From 5 min before the opioid administration until 10 min after the start of drug infusion, the following parameters were measured and collected on a breath-to-breath basis for further analysis: minute ventilation ( $V_i$ ), tidal volume, inspired and end-tidal oxygen concentrations, end-tidal  $P_{CO_2}$ , RR ( $F$ ), and  $Sp_{O_2}$ . All subjects breathed through a facemask connected to a pneumotachograph and differential pressure transducer (#4813, Hans Rudolph, Myandotta, MI, USA). The pneumotachograph was connected to a custom-made gas mixing system that was connected to oxygen, nitrogen, and carbon dioxide gas containers via three mass-flow controllers (Bronkhorst High-Tec, Veenendaal, The Netherlands). The mass-flow controllers were controlled by a computer allowing the inhalation of preset inhaled gas mixtures. The airway gas flow signal of the pneumotachograph was integrated to yield a volume signal. The signal was calibrated with a motor-driven piston pump (volume 1 litre at 20–30 strokes min<sup>-1</sup>). Corrections in volume were made for changes in gas viscosity due to changes in inhaled oxygen concentration. Inspired and expired oxygen and carbon dioxide concentration were measured with a Capnomac monitor (Datex, Helsinki, Finland).  $Sp_{O_2}$  was measured with a finger pulse oximeter (Masimo, Irvine, CA, USA). Each subject performed two experiments, one during the inhalation of a normoxic gas mixture (normoxia) and the other during inhalation of a hyperoxic gas mixture (inspired fraction 0.5) with 10–20 min between experiments. The sequence between runs

was randomized. Oxygen inhalation preceded the drug infusion by 15 min. Heart rate and ECG were monitored throughout the studies.

### Apnoea

Apnoea is defined in our study as the absence of spontaneous breathing as detected by the absence of flow through the pneumotachograph for at least 20 s. In case the apnoeic episode lasted for 90 s, the subject was encouraged to take one or multiple breaths.

### Power and statistical analysis

The study was powered (based on data on remifentanyl effect on breathing from our laboratory)<sup>8</sup> to detect a difference in minute ventilation of 2 litre min<sup>-1</sup> between normoxia and hyperoxia with an  $SD$  of 3 litre min<sup>-1</sup>,  $\alpha=0.05$ , and  $\beta=0.8$ . This resulted in a sample size of 20 (Sigplot v 12 for Windows, Systat Software, Inc., San Jose, CA, USA).

The data were averaged over 1 min periods. The following two intervals were used in the data analysis: baseline (obtained during the 1 min period before drug infusion) and peak ventilatory depression (the 1 min in which the measured variable displayed its lowest, for  $V_i$ ,  $F$ , and  $Sp_{O_2}$ , or highest, for end-tidal  $P_{CO_2}$ , value). The effects of remifentanyl and oxygen treatment on  $V_i$ ,  $F$ , end-tidal  $P_{CO_2}$ , and  $Sp_{O_2}$  were tested by the two-tailed paired  $t$ -tests or Wilcoxon signed-rank tests, with  $P<0.05$  considered significant. The analyses were performed in SigmaPlot version 12 for Windows (Systat Software, Inc.). Data are presented as mean ( $SD$ ) unless otherwise stated.

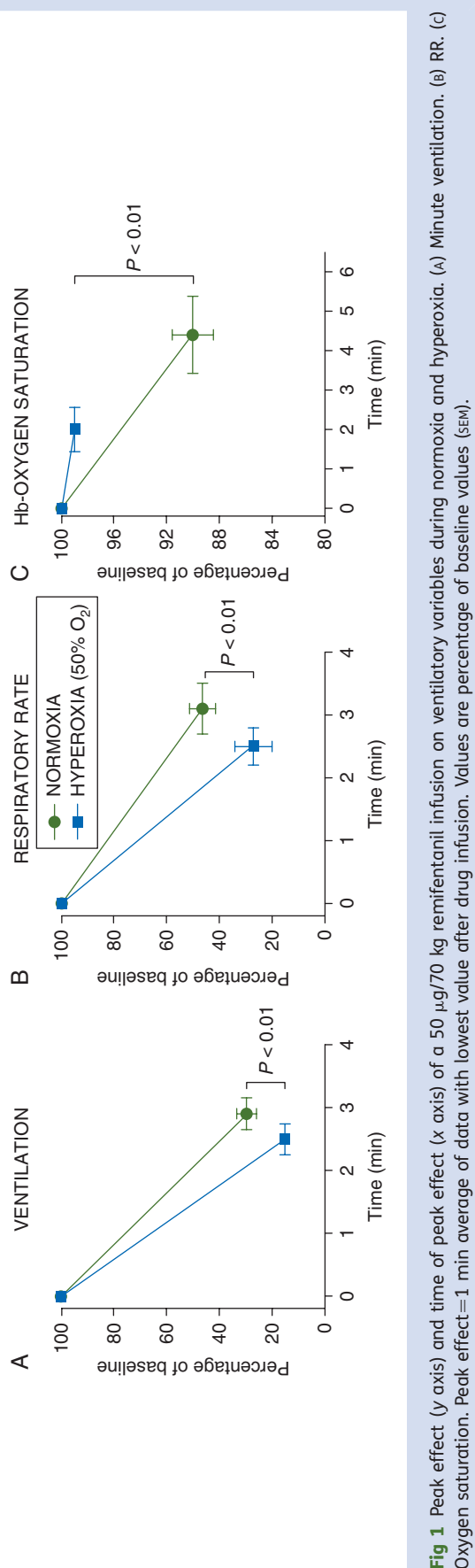
### Results

The mean ( $SD$ ) pre-drug baseline variables not affected by oxygen therapy were inspired minute ventilation [normoxic  $V_i$  7.4 (1.3) litre min<sup>-1</sup> and hyperoxic  $V_i$  7.9 (1.0) litre min<sup>-1</sup>], RR [normoxic  $F$  13.1 (2.9) bpm and hyperoxic  $F$  13.2 (3.0) bpm], and end-tidal  $P_{CO_2}$  [normoxia 5.1 (0.5) kPa and hyperoxia 5.2 (0.4) kPa]. End-tidal  $P_{O_2}$  varied between oxygen conditions: 13.3 (0.5) and 40 (1.0) kPa in normoxia and hyperoxia, respectively. Similarly,  $Sp_{O_2}$  was greater during hyperoxia: normoxic  $Sp_{O_2}$  98.4 (1.5) % and hyperoxic  $Sp_{O_2}$  99.7 (0.7) % ( $P<0.05$ ).

The effect of the oxygen condition on remifentanyl-induced respiratory depression is shown in Figure 1 and Table 1. Two subjects developed apnoea during normoxia,

**Table 1** Effect of remifentanyl on respiratory variables. Values are mean ( $SD$ ). \* $P<0.01$  vs baseline. # $P<0.05$  vs normoxic baseline. Baseline=1 min average before drug infusion. Peak effect=1 min average of data with lowest value after drug infusion. N, normoxia; H, hyperoxia

	Normoxia		Hyperoxia		Peak effect H vs N
	Baseline	Peak effect	Baseline	Peak effect	
Ventilation (litre min <sup>-1</sup> )	7.4 (1.3)	2.2 (1.2)*	7.9 (1.0)	1.2 (1.2)*	$P<0.01$
Respiratory rate (bpm)	13.1 (2.9)	6.1 (2.8)*	13.2 (3.0)	3.6 (4.0)*	$P<0.01$
$Sp_{O_2}$ (%)	98.4 (1.5)	88.6 (6.7)*	99.7 (0.7)#	98.7 (1.0)	$P<0.001$
End-tidal $P_{CO_2}$ (kPa)	5.1 (0.5)	5.7 (0.3)*	5.2 (0.4)	6.1 (0.6)*	$P<0.01$



**Fig 1** Peak effect (y axis) and time of peak effect (x axis) of a 50 µg/70 kg remifentanyl infusion on ventilatory variables during normoxia and hyperoxia. (A) Minute ventilation. (B) RR. (C) Oxygen saturation. Peak effect = 1 min average of data with lowest value after drug infusion. Values are percentage of baseline values (SEM).

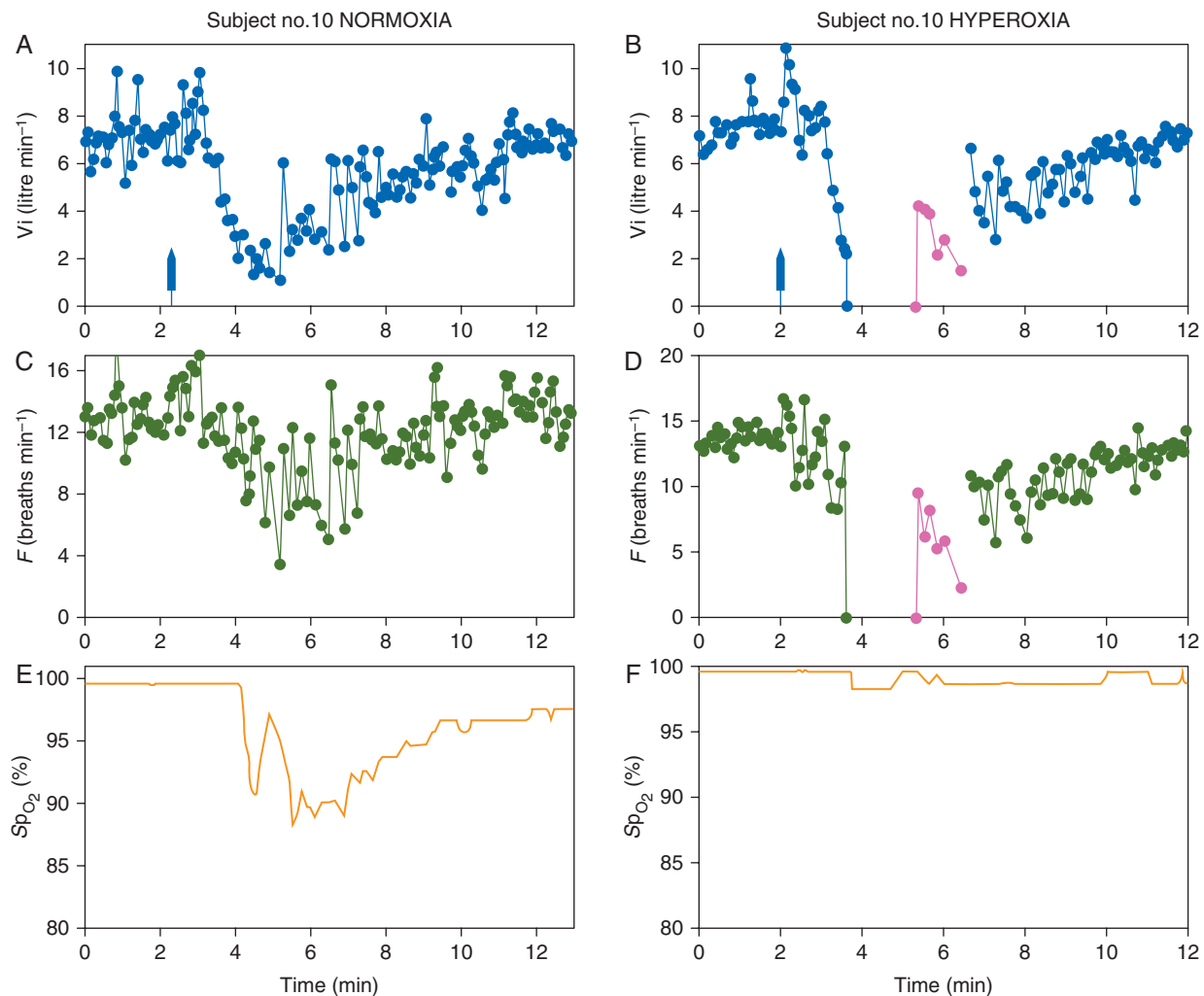
while these two plus an additional eight subjects developed apnoea during hyperoxia (hyperoxia vs normoxia:  $P < 0.05$ ). Under normoxic and hyperoxic conditions, ventilation decreased to 2.2 (1.2) and 1.2 (1.2) litre  $\text{min}^{-1}$ , respectively (hyperoxia vs normoxia:  $P < 0.01$ ). RR decreased to 6.1 (2.8) bpm (normoxia) and 3.6 (4.0) bpm (hyperoxia; hyperoxia vs normoxia:  $P < 0.01$ ). End-tidal  $P_{\text{CO}_2}$  increased to 5.7 (0.3) kPa (normoxia) and 6.1 (0.6) kPa (hyperoxia,  $P < 0.01$ ). During normoxia,  $\text{SpO}_2$  decreased to 88.6 (6.7)%, and during hyperoxia,  $\text{SpO}_2$  decreased to 98.7 (1.0)% (hyperoxia vs normoxia:  $P < 0.001$ ).

In Figure 2, two examples from one subject are given for the effect of remifentanyl on respiratory variables during normoxia and during hyperoxia. During normoxia, the 50 µg remifentanyl infusion caused a decrease in inspired minute ventilation (but breathing was maintained) with RR decreasing to a 4 bpm low and  $\text{SpO}_2$  was reduced to 90% (Fig. 2A, c, and e). During hyperoxia, 50 µg remifentanyl caused apnoea as was observed both in inspired minute ventilation and RR (Fig. 2B and d), while no clinically relevant change in  $\text{SpO}_2$  occurred (Fig. 2F). Despite the lack of change in  $\text{SpO}_2$ , the subject was encouraged after more than 60 s of apnoea to take some breaths (in pink in Fig. 2d).

## Discussion

The main findings of our study are that respiratory depression from remifentanyl is more pronounced in hyperoxia than normoxia. The greater effect of remifentanyl during hyperoxia was apparent in various respiratory variables: minute ventilation, RR, and end-tidal  $P_{\text{CO}_2}$ . Furthermore, apnoea developed in two subjects during normoxia and 10 during hyperoxia. The greater effect of remifentanyl during hyperoxia was not observed in  $\text{SpO}_2$  as during hyperoxia, pulse oximetry remains in normal values during the first minutes of respiratory depression.

The effect of oxygen on the ventilatory control system is complex and not well understood. Hyperoxia reduces the output of the peripheral chemoreceptors by 80–100% and the output of the ventral medulla chemoreceptors by 15–20%.<sup>2,3</sup> Apart from these depressant effects, there are also indications of a stimulatory effect from hyperoxia on breathing, related to a diminished brain blood flow, a reduction in the Haldane effect, and release of stimulatory agents (e.g. nitric oxide and glutamate) in the brain compartment.<sup>2,9,10</sup> In the current study, we showed that while hyperoxia does not affect pre-drug baseline ventilation, it does enhance remifentanyl-induced respiratory depression. Opioid receptors are abundantly expressed in the respiratory control centres, including the brainstem (e.g. in the pre-Bötzinger complex, central chemoreceptors) and possibly the peripheral chemoreceptors.<sup>4</sup> Also higher centres that relay to the ventilatory control centres express opioid receptors, including the insula, thalamus, and anterior cingulate cortex.<sup>4</sup> While opioid overdosing is associated with life-threatening apnoea, there is ample evidence for the respiratory depressant effects of opioids in the clinical dose range. For example, exogenous



**Fig 2** Examples of the effect of a 50 µg remifentanyl infusion on minute ventilation (A and B), RR (C and D), and Hb-oxygen saturation (E and F) in one subject (subject no. 10) during normoxia (A, C, and E) and hyperoxia (B, D, and F). A greater respiratory depressant effect was observed in hyperoxia (with a 90 s period of apnoea). In pink, a series of breaths taken by the subject upon request of the investigators. Since these are imposed breaths, they were not taken into account in the analysis. The blue syringes indicate the remifentanyl infusion.

opioids reduce ventilatory drive in a dose-dependent manner in volunteers, and in patients with obstructive sleep apnoea, opioids increase the nightly occurrence of central apnoeas.<sup>1 11</sup> We surmise that the enhanced depression of ventilation when remifentanyl is administered during hyperoxia is due to an additive effect of the opioid and the oxygen-induced reduced ventilatory drive.

Although some beneficial effects of hyperoxia have been described (antiemetic, decrease in wound infections), our data indicate that supplemental oxygen may exacerbate opioid-induced respiratory depression. Hyperoxia has been shown to negatively impact clinical outcomes such as the negative relationship between supranormal oxygen concentrations and outcome after various cardiovascular events.<sup>12–14</sup> A 13.3 kPa increase in oxygen arterial partial pressure increases the (in-house) mortality risk after a cardiac arrest by 24%.<sup>13</sup> Similar observations are made when supplemental

oxygen is given after a cerebrovascular ischaemic event.<sup>12</sup> The detrimental effects of hyperoxia include increases in vascular resistance, decreased cardiac output, and worsening reperfusion injury.<sup>13 14</sup>

In the current study, we just measured the effect of two oxygen levels. Future studies should address the effect of greater variations in inspired oxygen fractions (e.g. from 0.3 to 1.0). Possibly at the lower end ( $F_{I_{O_2}}$  0.3), the influences on opioid-induced respiratory depression are smaller. We do not think the absence of blinding in our study influenced the outcome since all subjects were unaware of possible effects of high oxygen on ventilation and remained uninformed on the concentration of oxygen they inspired during the studies. Whether the absence of blinding affected the investigators remains unknown but since data acquisition and analysis were automated, we also do not think that this had a major impact on the study



outcome. We did not measure arterial  $P_{CO_2}$  in our studies but relied on end-expiratory  $P_{CO_2}$ . Since we did not obtain end-expiratory  $P_{CO_2}$  values during apnoea (which predominantly occurred under hyperoxic conditions), we may have underestimated the respiratory depression during hyperoxia in terms of  $P_{CO_2}$ .

Whether our findings have direct clinical implications is difficult to conclude from our data. Indeed, while hyperoxia enhances opioid-induced respiratory depression, the decrease in breathing activity may be detected in time when using appropriate monitoring devices, such as RR measurements or capnography. When using  $Sp_{O_2}$  monitoring, the reduced breathing activity during hyperoxia may be observed only when the alveolar oxygen stores are depleted (as occurs during prolonged opioid-induced respiratory depression/apnoea and/or upper airway obstruction). This will cause a delay in detection as has observed by others and us.<sup>15 16</sup> Since respiratory depression coincides with increases in arterial  $P_{CO_2}$ , hypercapnia-induced sympathetic activation may cause hypertension and tachycardia, which may affect patient outcome. Further studies in patients with and without comorbidities (e.g. pulmonary and cardiac disease, obstructive sleep apnoea with recurrent nightly hypoxic events, obese patients, opioid-tolerant patients, carotid body resected patients),<sup>17</sup> using a variety of opioids and routes of administration, are required to corroborate our findings in a clinical setting and address the issue of the complex interactive effects of oxygen and underlying disease on opioid-induced respiratory depression. For example, Brown and colleagues<sup>18 19</sup> showed that both in children and in rodents, previous recurrent hypoxic events (as occurs in obstructive sleep apnoea patients) increase opioid sensitivity.

In conclusion, as studied in 20 healthy volunteers, opioid-induced respiratory depression is greater during breathing of a hyperoxic gas mixture compared with a normoxic gas mixture (i.e. room air). The steep reductions in minute ventilation in the presence of opioid were apparent from reductions in RR under normoxic and hyperoxic conditions, but not from reductions in  $Sp_{O_2}$  when supplemental oxygen was administered.

## Declaration of interest

R.P.M. is the editor-in-chief of the *British Journal of Anaesthesia*.

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