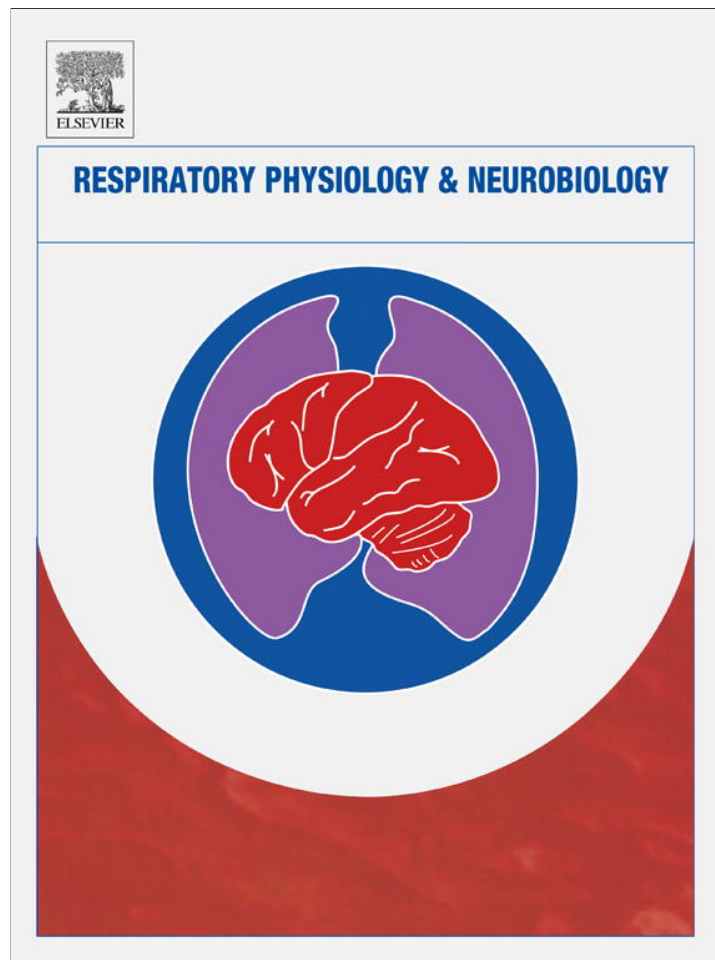


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## The effects of a single mild dose of morphine on chemoreflexes and breathing in obstructive sleep apnea

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### ABSTRACT

The effect of morphine on breathing and ventilatory chemoreflexes in obstructive sleep apnea (OSA) is unknown. It has been assumed that acute morphine use may induce deeper respiratory depression in OSA but this has not been investigated. We evaluated awake ventilatory chemoreflexes and overnight polysomnography on 10 mild-moderate OSA patients before and after giving 30 mg oral controlled-release morphine. Morphine plasma concentrations were analysed. We found a 30-fold range of morphine plasma concentrations with the fixed dose of morphine, and a higher plasma morphine concentration was associated with a higher CO<sub>2</sub> recruitment threshold (VRT) ( $r=0.86$ ,  $p=0.006$ ) and an improvement in sleep time with SpO<sub>2</sub> < 90% (T90) ( $r=-0.87$ ,  $p=0.005$ ) compared to the baseline. The improvement in T90 also significantly correlated with the increase of VRT ( $r=-0.79$ ,  $r=0.02$ ). In conclusion, in mild-to-moderate OSA patients, a single common dose of oral morphine may paradoxically improve OSA through modulating chemoreflexes. There is a large inter-individual variability in the responses, which may relate to individual morphine metabolism.

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### 1. Introduction

Opioids are commonly used in a number of clinical settings, including treatment of pain, trauma, cancer and in opioid maintenance treatment program. The number of opioid prescriptions has increased dramatically in the past decade. In the USA, the therapeutic use of methadone and oxycodone increased by 824% and 660%, respectively, between 1997 and 2003 (US Department of Justice and Drug Enforcement Administration, 2005). In Australia, the number of Pharmaceutical Benefits Scheme (PBS) opioid prescriptions increased three-fold, from 2.4 million in 1992 to 7.0 million in 2007 (Leong et al., 2009). Meanwhile, mortality rates from unintentional drug overdose have also increased substantially, with deaths attributed primarily to prescription opioid analgesics (more than

90%) (Centres for Disease Control and Prevention, 2007; Hall et al., 2008; Okie, 2010). In Australia, there was a three-fold increase in the number of hospitalisations as a result of unintentional overdose by opioids other than heroin and methadone from 1998/99 to 2006/07 (National Hospital Morbidity Database, 2008). Death from opioids is nearly always due to respiratory arrest (Caplehorn and Drummer, 1999; Gutstein and Akil, 2005). Acute opioid use can reduce vital ventilatory chemoreflexes and cause severe hypoventilation (Bailey et al., 2000), with the immediate cause of death often being pulmonary oedema secondary to prolonged hypoventilation (Caplehorn and Drummer, 1999).

During sleep, respiration is naturally depressed and mainly under automatic neural-chemical control (Douglas, 2000). Acute opioid use significantly reduces protective chemoreflexes, and patients have an increased risk of respiratory arrest during sleep (Dempsey et al., 2010). As a common disease, obstructive sleep apnea (OSA) is characterised by repetitive pauses in breathing during sleep due to the collapse and/or narrowing of the upper airway, and is usually associated with a reduction in blood oxygen saturation. The effect of opioids on OSA is unknown. No carefully designed clinical trial has investigated the effect of opioids in OSA (Chung et al., 2008; Macintyre et al., 2011). Current knowledge is based on observational case studies and retrospective

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analysis, and most have involved multiple drugs during perioperative procedures, limiting firm conclusions. At the same time, OSA has become a major concern for anaesthesia care providers (Benumof, 2002; Chung et al., 2008). Significant adverse respiratory outcomes have been reported in cases of obese patients with OSA during perioperative management (Benumof, 2002; Agro et al., 2004). The American Society of Anesthesiologists has issued practice guidelines for the perioperative management of OSA patients to reduce the risk of adverse outcomes (Gross et al., 2006). However, relevant recommendations were primarily based on the consensus of consultants' opinions (Gross et al., 2006; Chung et al., 2008). Similarly, sleep-disordered breathing was listed as a likely contributor to all opioid-related deaths mainly based on an expert panel's opinion (Webster et al., 2011). In contrast, a few recent reviews and reports have questioned whether OSA is an independent risk factor for perioperative adverse events (Sabers et al., 2003; Ahmad et al., 2008; Ankichetty et al., 2011; Macintyre et al., 2011; Weingarten et al., 2011). These reviews suggest that these adverse events may be related to co-existing obesity (Weingarten et al., 2011). Therefore clinical experimental trials are needed to investigate the effect of opioids on breathing during sleep including how these effects may relate to actual plasma drug levels. In the present study, we hypothesised that a commonly used single dose of oral morphine would impair awake ventilatory chemoreflexes and breathing during sleep in OSA patients and this would be related to plasma morphine levels.

## 2. Methods

This experiment was conducted as a part of a proof-of-concept study examining the potential for the antibiotic minocycline to reverse opioid-induced respiratory depression. Data on minocycline are not reported. The study was conducted at the Clinical Sleep Laboratory of Royal Prince Alfred Hospital (RPAH), a major teaching hospital of the University of Sydney. The study protocol was approved by Sydney South West Area Health Service (SSWAHS) Ethics Review Committee (Protocol No. X10-0268 & HREC/10/RPAH/476). Written consent forms were signed by all patients. The Australian & New Zealand Clinical Trial Registry number is ACTRN12610001074088.

### 2.1. Patients and procedure

Thirteen men with mild-moderate OSA were recruited from the sleep clinics of the Royal Prince Alfred Hospital and the associated Woolcock Institute of Medical Research from October 2010 to December 2010. Only men were included due to potential ventilatory chemoreflex changes in women during the menstrual cycle (White et al., 1983). We excluded regular opiate users and those who had a history of adverse effects from opioids or minocycline, history of drug abuse, current CPAP users, current or recent severe physiological or psychological illness including severe cardiovascular (hypertension) or CNS diseases, and those with another severe sleep disorders, or concurrent use of other medications that might interfere with the study drugs.

All patients underwent a baseline visit with overnight polysomnography (PSG) and awake ventilatory chemoreflex tests. Only those patients with apnea-hypopnea index (AHI)  $\geq 10$  and oxygen saturation ( $Sp_{O_2}$ ) nadir between 70 and 90% were included and asked to come back for the intervention study.

In the intervention visit, patients finished dinner at 5 pm, and took a single oral dose of 30 mg slow-release morphine (MS Contin, Mundipharma Pty Limited, Sydney, Australia) at 5:30 pm. The drug will reach peak concentration at about 3 h post-dose and have around a 12 h duration of effect. Between 9 and 9:30 pm, patients

were tested for awake ventilatory chemoreflexes. Between 9:30 and 10 pm, 5 ml of venous blood was taken for drug concentration analyses. At 10 pm (lights off time), the PSG sleep study started and was recorded continuously until 7 am the next morning.

### 2.2. PSG

In-lab standard full PSGs (Alice 5, Philips Respironics, Andover, MA, USA) were monitored, including 4 channels of electroencephalogram (EEG), 2 channels of electrooculogram (EOG), chin electromyogram (EMG), anterior tibial EMG, electrocardiogram (ECG), body position, nasal pressure, chest and abdomen movements, and  $Sp_{O_2}$ . PSG recordings were scored using Rechtschaffen and Kales criteria (Rechtschaffen and Kales, 1968), by an experienced sleep technologist who was blinded to treatment allocation. Respiratory events and arousals were scored according to standard Chicago and ASDA criteria respectively (American Sleep Disorders Association, 1992; AASM Task Force, 1999). AHI was calculated by dividing the total number of apneas and hypopneas by the total sleep time (hours). Oxygen desaturation index (ODI) was calculated by dividing the total number of  $\geq 3\%$   $Sp_{O_2}$  dips by the total sleep time (hours).

### 2.3. Ventilatory chemoreflex testing

Central chemosensitivity,  $CO_2$  ventilatory recruitment threshold (VRT) and basal minute ventilation ( $V_E$ ) were measured using a fully computerised system using Duffin's modified chemoreflex test (Duffin, 2010, 2011). An advantage of the Duffin's modified rebreathing method is that VRT can be directly measured rather than being estimated using an extrapolated line. Central chemosensitivity was determined by testing the slope of iso-oxic hyper-oxic (holding oxygen constant at 150 mmHg) ventilatory response to  $CO_2$ , as a 10 min test while the patient was awake (Fig. 1). The procedure included a 5 min hyperventilation and a 5 min of rebreathing through a closed circuit. During the hyperventilation, end-tidal  $P_{CO_2}$  was controlled between 19 and 25 mmHg. The computer then switched the valve and the patient rebreathed for 5 min through a bag containing a mix gas of 6% of  $CO_2$  and 94%  $O_2$ . The  $P_{O_2}$  in the circuit was held constant at 150 mmHg. The computer continuously analysed  $O_2$  consumption over the past 3 breaths and used a prediction model to determine how much  $O_2$  to feed into the circuit. The VRT and central chemosensitivity (the slope of  $P_{CO_2}$  plotted against minute ventilation) were analysed through purpose-built software. An example is shown in Fig. 1.

### 2.4. Drug analyses

Plasma morphine concentrations were analysed at the laboratory of the Discipline of Pharmacology, The University of Adelaide. Plasma morphine concentrations were measured by LC/MS using a previously validated procedure (Somogyi et al., 2008). The intra- and inter-assay validation data showed accuracy  $> 90\%$  and precision  $< 15\%$  on quality control samples. The lower limits of quantification were 1 ng/ml.

### 2.5. Statistical analysis

The main outcomes of interest were respiratory depression related parameters including overnight  $Sp_{O_2}$  nadir, percent of sleep time with  $Sp_{O_2} < 90\%$  (%T90), central chemosensitivity and VRT between baseline and morphine night. Descriptive data were expressed as mean  $\pm$  SD, unless otherwise stated. Pair-wise comparisons were tested by paired *t*-test or Wilcoxon signed-rank test depending on normality of data distribution. Associations were

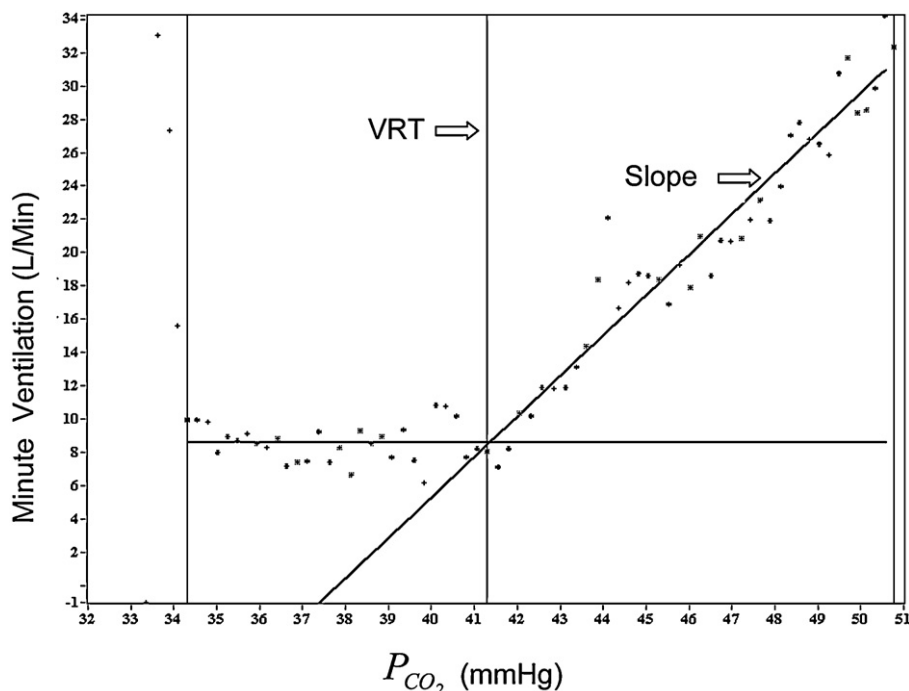


Fig. 1. An example of the ventilatory chemoreflex analyses from our data. “Slope” is the central chemosensitivity. “VRT” is the CO<sub>2</sub> ventilatory recruitment threshold.

tested by either Pearson’s or Spearman’s tests also based on normality of distribution. A *p*-value of less than 0.05 was considered as significant. Analyses were performed using SPSS (version 17; SPSS, Chicago, IL, USA).

3. Results

Thirteen OSA patients were originally invited to participate. One declined due to a busy work schedule, and another due to concerns about potential side effects of morphine. Of the 11 patients randomised, one withdrew from the study due to severe nausea attributed to morphine. Ten patients completed the protocol. They had an average age of 47.6 ± 8.4 (range 37–65) years, BMI of 28.5 ± 3.2 (range 23.9–35.8) kg/m<sup>2</sup>. All the patients had baseline AHI between 10 and 30/h. None of them were CPAP users.

Two blood sample tubes were damaged during the interstate shipment, and hence were excluded from the blood related analysis. Average plasma morphine concentration is 7.25 ± 6.04 ng/ml. The patient who withdrew from the study with severe nausea had a blood morphine concentration of 2.25 ng/ml.

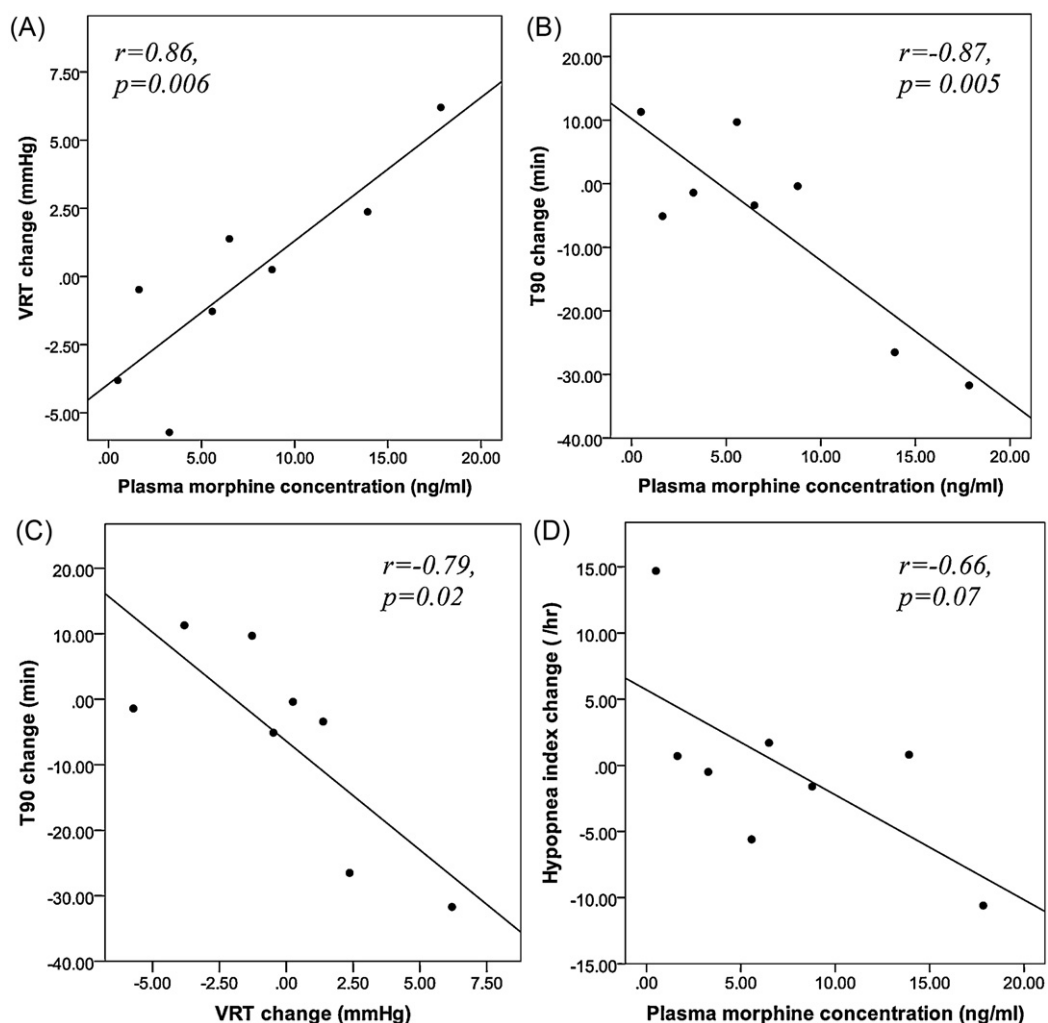
The comparison of key ventilatory chemoreflex and PSG sleep and breathing parameters between the morphine arm and baseline is shown in Table 1. Compared to baseline, the administration of 30 mg slow release morphine did not cause statistically significant respiratory depression in any key PSG and ventilatory chemoreflex parameter. There was an average 33% reduction in central chemosensitivity in the “morphine plus placebo” night, but the difference did not reach statistical significance (*p* = 0.18). There was a significant reduction in % rapid eye movement (REM) sleep (*p* < 0.05) with morphine use, but the reduction did not cause major change in REM related AHI or sleep time with SpO<sub>2</sub> < 90% (T90) (Table 1). Average SpO<sub>2</sub> nadir during sleep paradoxically improved 4.4% with morphine use but did not reach significance (*p* = 0.17).

However, blood analyses showed that there was a large inter-individual difference (30 fold range) in morphine plasma concentration for the fixed dose of 30 mg oral controlled-release morphine (Fig. 2). There was a significant positive correlation between a higher plasma morphine concentration in the

morphine arm and the increase of the VRT from baseline (*r* = 0.86, *p* = 0.006) (Fig. 2, Panel A). The higher plasma morphine concentration was also significantly associated with an improvement in the T90 from baseline (*r* = -0.87, *p* = 0.005) (Fig. 2, Panel B). In addition, the increase in VRT significantly correlated with reduction in T90 (*r* = -0.79, *p* = 0.02) (Fig. 2, Panel C). Furthermore, we also found the higher plasma morphine concentration tended to correlate with an improvement in hypopnea index compared to the baseline (*r* = -0.66, *p* = 0.07), but not with the change in apnea index (*r* = -0.30, *p* = 0.46) (Fig. 2, Panel D). No significant correlation was found between the change of central chemosensitivity and VRT or morphine concentration.

Table 1 Comparison of ventilatory chemoreflex and PSG parameters in the morphine arm and in baseline.

	Morphine	Baseline	<i>p</i>
V <sub>E</sub> -basal (l/min)	12.06 ± 4.26	12.59 ± 5.29	0.721
VRT (mmHg)	46.99 ± 2.48	47.02 ± 4.59	0.98
Central chemosensitivity (l/min/mmHg)	1.45 ± 0.75	2.16 ± 1.26	0.185
TST (min)	371.20 ± 56.96	351.67 ± 56.93	0.066
SE (%)	80.67 ± 10.62	80.00 ± 9.37	0.801
REM (%)	10.78 ± 3.76	15.95 ± 6.47	0.042
SWS (%)	16.83 ± 10.36	20.66 ± 6.33	0.323
Arl (/h)	17.80 ± 7.67	21.82 ± 9.92	0.256
CSA (min)	1.87 ± 3.61	0.51 ± 1.18	0.254
OSA (min)	13.51 ± 16.77	10.59 ± 8.34	0.578
Hypopnea (min)	37.73 ± 25.48	40.68 ± 27.14	0.535
CAI (/h)	0.99 ± 1.80	0.29 ± 0.64	0.248
Hypopnea Ratio (%)	0.78 ± 0.16	0.77 ± 0.20	0.828
ODI (/h)	12.06 ± 12.06	10.15 ± 6.35	0.878
AHI (/h)	22.15 ± 17.08	19.54 ± 6.91	0.799
AHI-REM (/h)	28.46 ± 21.90	33.06 ± 18.19	0.514
AHI-NREM (/h)	21.18 ± 17.71	17.33 ± 9.46	0.424
SpO <sub>2</sub> low (%)	83.50 ± 7.34	79.10 ± 7.74	0.173
%T90	1.83 ± 2.08	2.81 ± 3.72	0.551
T90-REM (min)	1.37 ± 1.78	1.969 ± 2.58	0.438
T90-NREM (min)	3.46 ± 5.39	5.34 ± 8.86	0.6



**Fig. 2.** Between the morphine arm and baseline, significant associations were found between individual plasma morphine concentration and the change of awake VRT (Panel A), and the change of Sleep Time with  $Sp_{O_2} < 90\%$  (T90) (Panel B). Panel C shows the association between the change of VRT and the change of T90 min. Panel D shows that a higher plasma morphine concentration tended to correlate with an improvement in hypopnoea index compared to the baseline. The changes were calculated by (morphine arm – baseline).

#### 4. Discussion

In contrast to our hypothesis, a commonly used single dose of oral morphine did not worsen breathing during sleep in this group of patients with mild-to-moderate sleep apnea. There was a strong correlation between higher plasma morphine concentrations and increased  $CO_2$  thresholds. However, paradoxically, this change in chemoreflex was linearly correlated with improvement in OSA. We propose that there is an intrinsic mechanistic link between the use of a mild dose of morphine, the decrease of ventilatory chemosensitivity, the increase of VRT/rhythm re-initiation threshold, the increase of  $CO_2$  reserve, and the improvement of mild-moderate OSA (Fig. 3).

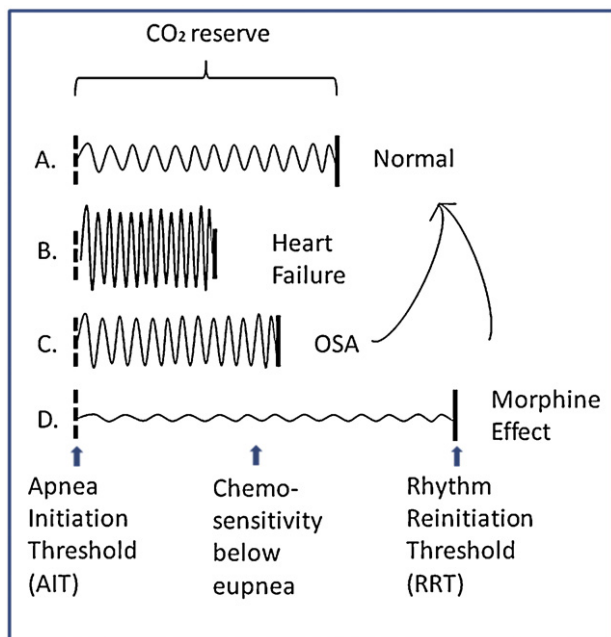
##### 4.1. Inter-individual variability of morphine concentration

In our study, for the fixed dose of 30 mg oral controlled-release morphine, there was a 30-fold range in plasma morphine concentrations. And the response variability is significantly associated with the large inter-individual variability in plasma morphine concentration. Those showing no or little response had very low plasma morphine concentration (Fig. 2). The large metabolism and respiratory variability may partly explain why opioids are a major cause of death by prescription medications, and why the opioid dose

titration period is extremely dangerous (Capehorn and Drummer, 1999; Ready, 2000; Centres for Disease Control and Prevention, 2007). Australian data showed that the relative risk (RR) of fatal accidental drug toxicity for patients in the first two weeks of methadone maintenance was 6.7 times that of heroin addicts not in the treatment program, and 97.8 times that of patients who had been on maintenance for more than two weeks (Capehorn and Drummer, 1999). The variability may also explain why our pair-wise group comparisons were mostly not significant given a relevant small sample size, i.e. the group comparison did not take consideration of the large inter-individual difference in morphine plasma concentration. Our approach in this study is therefore mainly for concentration-effect, as a basic principle of clinical pharmacology.

##### 4.2. Morphine effect on VRT and central chemosensitivity

For the first time, our study showed a strong correlation between a higher plasma morphine concentration and the increase of directly measured VRT. Elevated  $CO_2$  threshold by opioids have been inferred in previous human and animal studies using indirect estimate of  $P_{CO_2}$  threshold by extrapolating ventilatory response slope line (Berkenbosch et al., 1994; Lalley, 2004; Teppema et al., 2008). Morphine (Berkenbosch et al., 1994), M6G (Teppema et al.,



**Fig. 3.** Potential mechanism of acute morphine effect on breathing instability in OSA. We would like to emphasise that the effect we refer to is that of a mild dose of acute morphine on mild-to-moderate OSA. To make it easier to compare between the CO<sub>2</sub> reserves, we present each condition as starting from the same “apnea initiation threshold” (AIT).

2008) and fentanyl (Lalley, 2004) were found to increase estimated  $P_{CO_2}$  threshold in cats. The effect has also been reported in a human study through observing of a right shift of the steady-state CO<sub>2</sub> response curve with morphine injection (Bourke and Warley, 1989). Importantly, increased CO<sub>2</sub> recruitment threshold usually related with decreased central chemosensitivity (Duffin, 2010). In the present study, mean central chemosensitivity reduced 33% with morphine across the patient group. Although, this effect was not statistically significant, the magnitude of the effect was comparable to previous work showing a 42% reduction in ventilatory responses to hypercapnia before and after administration of 7.5 mg of morphine sulphate subcutaneously in six normal subjects (Weil et al., 1975). Data in cats have also shown a similar 30% reduction in CO<sub>2</sub> sensitivity following intravenous 0.15 mg/kg morphine (Berkenbosch et al., 1997). An obvious question is why we did not find similar concentration effect in central chemosensitivity. A likely explanation is that measurement variability for central chemosensitivity is much higher than VRT. A recent study investigated variability of Duffin method and found that VRT has a minimal between day measurement variability (coefficient of variation  $\approx 3$ ), while the variability for central chemosensitivity is around 10 fold higher (Jensen et al., 2010). This would suggest that for a small sample size, it could be much easier to find a physiological response correlated with VRT, while group comparison is more suitable for chemosensitivity. In summary, our data may generally suggest a combination effect of increased VRT and reduced central chemosensitivity with morphine use.

#### 4.3. Morphine effect on breathing stability during sleep

A surprising finding from our study is that, for the first time, we demonstrated a paradoxical improvement in oxygenation during sleep in patients with OSA with higher plasma morphine concentrations (Fig. 2, Panel B), and moreover, the improvement of the oxygenation in OSA was linked to a higher VRT (Panel C). These findings may be counter-intuitive when considering the effects of

narcotic overdose on breathing but in this study of a standard single dose of oral morphine are congruent with recent advances in the understanding of respiratory control during wake and sleep in patients with OSA (Dempsey, 2004; Dempsey et al., 2004; White, 2005; Younes, 2008; Edwards et al., 2012).

Our VRT was measured by beginning with 5 min of hyperventilation with end-tidal  $P_{CO_2}$  between 19 and 25 mmHg, levels lower than the VRT. Following this, rebreathing is initiated to allow  $P_{CO_2}$  to increase, but ventilation does not increase until  $P_{CO_2}$  crosses the VRT, where we observed ventilation linearly increasing in response to hypercapnia. This is demonstrated in Fig. 1. This mechanism is analogous with the breathing seen in OSA, with apnea occurring after a period of ventilatory overshoot, there are still respiratory tone but ventilation does not increase until  $P_{CO_2}$  crosses the rhythm reinitiation threshold (RRT) (Dempsey, 2004). From the above mechanisms, we believe that it is reasonable to estimate that VRT during awake is parallel to RRT during sleep, and could be around 3 mmHg higher due to the wakefulness drive. Similarly, it is reasonable to believe that a high central chemosensitivity (the slope response in Fig. 2) measured during awake represent a high chemical drive during sleep (Mateika et al., 2004; Beecroft et al., 2006).

During sleep, CO<sub>2</sub> reserve, which is the difference in  $P_{CO_2}$  between apnea initiation threshold (AIT) and RRT, is a key determinant of breathing instability (Dempsey, 2004; Dempsey et al., 2004) (Fig. 3). A narrower CO<sub>2</sub> reserve indicates a greater breathing instability, and a widened CO<sub>2</sub> reserve leads to a greater breathing stability (Dempsey, 2004; Dempsey et al., 2004). Typical examples are “Cheyne-Stokes” respiration in congestive heart failure patients and the effect of hypoxia in high altitude, where CO<sub>2</sub> reserve becomes much narrower with frequent disordered-breathing events. CO<sub>2</sub> reserve is highly labile and varies inversely with the slope of ventilatory response below eupnea (Dempsey et al., 2004). OSA has been characterised with high loop gain/chemical drive/chemosensitivity which can cause ventilatory overshoot, and the repetitive pattern is crucial in precipitating a cyclic sleep-disordered breathing pattern (White, 2005; Dempsey et al., 2010). In our OSA patients, the mild dose of morphine may reduce ventilatory chemosensitivity, and therefore the controller gain and the chance of cyclic ventilatory overshoot, thus improve OSA (Edwards et al., 2012; Wang et al., 2011). On the other hand, the increased VRT in our OSA patients may indicate an increased RRT and a widened CO<sub>2</sub> reserve, and a greater breathing stability during sleep. As shown in Fig. 3, we suspect the two factors act together and play the key role for the underlying mechanism. The improved oxygenation with higher concentrations of morphine, in our sample of OSA patients and the trend of significant correlation between plasma morphine concentration and the change of the hypopnea index support this potential mechanism (Fig. 2, Panel D). The positive effect on OSA was not reflected in studying the group as a whole, probably as a consequence of the individual variability in morphine concentrations (Table 1, Fig. 2). Nevertheless, although no significant differences were demonstrated, the mean  $Sp_{O_2}$  nadir in these 10 OSA patients increased from 79.1% in baseline to 83.5% in the morphine arm, and the T90 decreased from 2.81 to 1.83 min (Table 1).

#### 4.4. Clinical implications

It will be important in the future to examine the effects of higher doses of morphine, but it is unlikely the lower doses that were used in this study have a negative impact on patients with mild-moderate sleep apnea. The American Society of Anesthesiologists has issued practice guidelines for the perioperative management of OSA patients to reduce the risk of adverse outcomes (Gross et al., 2006). However, relevant recommendations were

primarily based on the consensus of consultants' opinions (Gross et al., 2006; Chung et al., 2008). No properly designed prospective clinical study has investigated the effect of opioids on OSA (Chung et al., 2008; Macintyre et al., 2011). Interestingly, a retrospective study compared 234 OSA patients with matched controls did not find OSA is a risk factor for adverse events among patients undergoing outpatient surgical procedures (Sabers et al., 2003). Evidence supporting an increased risk of perioperative complications in OSA patients often reported in patients who also have significant obesity (Macintyre et al., 2011). A large retrospective review of 797 patients found that obesity rather than OSA severity is associated with post-operative and overall complication rates (Weingarten et al., 2011). Our patients mostly had moderate OSA. Patients with more obesity, more severe OSA and a highly collapsible airway may possibly worsen their sleep disordered breathing with even modest doses of opioid. Opioids do suppress upper airway muscle activity in animals (Hajiha et al., 2009). A specifically designed study with a larger sample size and measurements of upper airway collapsibility, overnight loop gain/chemoreflex testing is needed to better investigate the effects of opioids on a wider range of patients with OSA.

We speculate that our findings may suggest an additional direction in pharmacological treatment of sleep apnea in certain patients. We (Wang et al., 2011) and others (Eckert et al., 2011; Edwards et al., 2012) have identified certain respiratory phenotypes that may characterise sub-groups of OSA patients that will improve sleep apnea following use of CNS depressants. In these patients, the use of safe doses of a respiratory depressant may modulate the chemoreflexes by alteration of the VRT or/and chemical drives/loop gain.

#### 4.5. Limitations

It is important to recognise that our findings are preliminary based on a proof-of-concept study limited by a low dose of opioid and less severe OSA patients. These choices of patients and opioid dosage were required by safety and ethical considerations. We would expect to see a higher dose of morphine cause more significant respiratory depression. With the large inter-individual variability in opioid concentrations, this factor may well be crucial in determining which patients develop respiratory depression or respiratory arrest following opioid administration. Ideally, future studies can adopt double-blind, placebo-controlled design with an extra arm testing over-night ventilatory chemoreflexes using mechanical ventilation techniques. It could provide direct evidence for our proposed mechanism by comparing the measurements of sleep parameters like ventilatory response to CO<sub>2</sub> above and below eupnea, RRT, AIT and CO<sub>2</sub> reserve, with awake chemoreflex parameters. Furthermore, we could ideally include peripheral chemoreflex test as part of the awake chemoreflex test which could better explain the potential mechanisms (Wang et al., 2011). We did not test this as we have very limited window of time after the slow-release morphine taking effect (9 pm) and before sleep time (10 pm). For the same reason, we could not repeatedly test the chemoreflexes to assess potential variability of the tests.

#### 5. Conclusions

In mild-to-moderate OSA patients, a single common dose of oral morphine may paradoxically improve OSA through modulating chemoreflexes. There is a large inter-individual variability in the responses which may relate to individual morphine metabolism. These data question the assumption that small doses of opioids are harmful to patients with mild-to-moderate OSA, and may have implications for OSA pharmacological treatment.

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