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Effects of Clonidine on Breathing during Sleep and Susceptibility to Central Apnoea

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Abstract

We hypothesized that administration of clonidine would decrease the hypocapnic apnoeic threshold (HAT) and widen the CO_2 reserve during non-REM sleep.

Methods—Ten healthy subjects (4 females) (age 22.3±3.0 years; BMI 25.5±3.4 kg/m^2) were randomized to receive placebo or 0.1 mg/45Kg of clonidine on 2 separate nights. Ventilation and upper airway resistance were monitored during wakefulness and sleep. Two separate experiments were performed: Protocol 1 (n=8), CO_2 reserve, HAT and HcVR were determined using non-invasive hyperventilation (NIV) to induce hypocapnia for at least 3 minutes; Protocol 2 (n=6), peripheral hypocapnic ventilatory response (HcVR) was determined by NIV using short (3 breaths) hyperventilation.

Results—Clonidine decreased the systolic blood pressure by 12±10 mmHg but did not affect baseline ventilation or upper airway resistance during wakefulness or sleep. Protocol (1), Clonidine was associated with decreased HAT relative to placebo (37.3±3.3 vs. 39.7±3.4 mmHg, $P<0.05$), increased CO_2 reserve (-3.8±1.3 vs. -2.8±1.2 mmHg, $P< 0.05$), and decreased HcVR (1.6±0.6 vs. 2.5±1.3 L/min/mmHg, $P<0.05$). Protocol (2), administration of clonidine did not decrease peripheral HcVR compared to placebo (0.5±0.3 vs. 0.7±0.3 L/min/mmHg, P=NS).

Conclusion—Clonidine is associated with diminished susceptibility to hypocapnic central apnoea without significant effect on ventilation or upper airway mechanics. Reduced susceptibility to hypocapnic central apnoea is not explained by the peripheral chemoreceptor pathway. This suggests a central rather than a peripheral effect of clonidine on the susceptibility to hypocapnic central apnoea.

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1. Introduction

Clonidine, a selective α2-adrenergic agonist, is increasingly used as an anesthetic adjuvant, owing to its salutary profile of enhancing preoperative sedation, reducing intraoperative anesthetic requirement, and potentiating postoperative analgesia (Ghignone et al., 1986; Ghignone et al., 1988; Pawlik et al., 2005). Recent study has demonstrated a beneficial effect of clonidine premedication in patients with OSA, who were undergoing ENT surgical procedures (Pawlik et al., 2005). Specifically, the authors showed that clonidine was associated with decreased requirements for intra-operative anesthetics and postoperative opioids without adverse effects on ventilation or hemodynamic variables. Overall, clinical studies in humans suggest that administration of clonidine preoperatively before general anesthesia enhances the effects of anesthetics without adverse consequences on respiration in patients with sleep apnoea (Chung et al., 2008).

Studies investigating clonidine's physiological effects on sleep and breathing in humans are very limited (Issa 1992; Autret et al., 1977). Issa et al in 1992 showed that clonidine administration before sleep to patients with obstructive sleep apnoea improved nocturnal hypoxia with disappearance of sleep apnoea during REM sleep. The mechanism of improvement in sleep related breathing disturbances and hypoxemia however was not thoroughly investigated and thought to be due to REM suppressant effect.

The purpose of this study was to determine the effect of clonidine on breathing during sleep in healthy humans and to determine the physiological effect of clonidine on upper airway mechanics and ventilation particularly the propensity to hypocapnic central apnoea during NREM sleep. We hypothesized that clonidine decreases the susceptibility to hypocapnic central apnoea during non-REM sleep. To this end, we measured sleep and ventilatory parameters and calculated the CO_2 reserve and hypocapnic apnoeic threshold (HAT) to assess susceptibility to hypocapnic central apnoea in healthy men and women. Results of this study have previously been reported in the form of abstracts (Grullon et al., 2011).

2. Methods

2.1. Subjects

The Human Investigation Committee of the Wayne State University and the VA Medical Center approved the experimental protocol. An informed written consent was obtained and subjects had a screening polysomnography. We studied healthy individuals free of sleep apnoea. Female subjects were not pregnant nor on birth control pills.

Subjects were randomized and blinded to receive a single dose of either placebo or 0.1 mg/45 Kg of clonidine orally prior to sleep over 2 separate nights. Non-invasive ventilation (NIV) was used to assess the hypocapnic apnoeic threshold (HAT) and determine the hypocapnic ventilatory response (HcVR) after the random administration of clonidine and placebo.

2.2. Measurements

In addition to standard polysomnography including EEG and chin EMG, airflow was measured by a pneumotachometer connected to a tight-fitting nasal mask. Tidal volume (V_T) was obtained by integrating the pneumotachograph flow signal. End-tidal carbon dioxide (P_{ETCO2}) was measured with a gas analyzer. Supraglottic pressure was measured with a pressure tipped catheter (Millar®), positioned in the hypopharynx.

2.3. Non-invasive Ventilation (NIV)

Protocol 1—We used NIV to induce hyperventilation using a 10 cmH_2O pressure support for at least 3 minutes resulting in a hypopnea or central apnoea. NIV was terminated during expiration to the baseline expiratory positive airway pressure (EPAP=4.0 cmH_2O) for a minimum of 3 minutes. The hyperventilation trials were repeated at higher pressure support (1-2 cmH_2O) until central apnoea was obtained. If central apnoea followed NIV trial, hyperventilation trials were repeated at lower pressure support (1-2 cmH_2O) to the nearest hypopnea to an apnoeic threshold.

Protocol 2—To measure the peripheral response to hypocapnia before it reaches central chemoreceptors we used a recently described brief hyperventilation method (Xie et al., 2006) by applying NIV 3 breaths only then assessed the ventilatory response immediately after NIV is terminated. NIV was terminated during expiration to the baseline EPAP for a minimum of 3 minutes.

2.4. Data Analysis

Baseline wake and sleep monitoring: Sleep, ventilation, non-invasive blood pressure and upper airway resistance (R_{UA}) were monitored in each subject to assess the effect of clonidine vs. placebo during wakefulness and sleep. Periods of ten breaths from wakefulness and stable non-REM sleep were measured after clonidine or placebo administration to assess baseline ventilation (V_I, V_T, F_B, T_I, T_E, P_{ETCO2}, O_2Sat) and upper airway resistance, which were then summarized as mean±SD. Segments were selected and analysis was performed in blinded fashion.

Protocol 1—After stable sleep is achieved, in each hyperventilation trial (figure 1) the control period was represented by the average of five breaths immediately preceding the onset of mechanical ventilation. The hyperventilation data were the calculated average of the last five NIV breaths prior to the ventilator being turned back to the baseline EPAP. The change in P_{ETCO2} (ΔP_{ETCO2}) was calculated as the difference between the control period and the last 5 NIV breaths. Hypocapnic apnoeic threshold (HAT) was defined as the measured P_{ETCO2} at which the apnoea closest to the last hypopnea occurred. The CO_2 reserve was defined as ΔP_{ETCO2} between control and central apnoea. Hypocapnic ventilatory response (HcVR) was defined as the ratio of change in minute ventilation from control to post-NIV recovery divided by the ΔP_{ETCO2} from control to NIV.

Protocol 2—In each short hyperventilation trial the control period was represented by the average of five breaths immediately preceding the onset of NIV. The hyperventilation data were the calculated average of the three NIV breaths. The change in P_{ETCO2} (ΔP_{ETCO2}) was

calculated as the difference between the control period and the 3 NIV breaths. The peripheral hypocapnic ventilatory response (HcVR) was defined as the ratio of change in minute ventilation from control to post-NIV recovery divided by the $\Delta P_{ET^{CO}2}$ from control to NIV.

2. 5. Statistical analysis

A repeated-measures analysis of variance was used to compare each dependent variable (V_I, V_T, F_B, T_I, T_E, $P_{ET}CO_2$, O_2Sat, R_{UA} and mean arterial pressure) during wakefulness and sleep under clonidine vs. placebo. A paired t-test was used to compare the mean values of sleep and chemoresponsiveness parameters ($P_{ET^{CO}2}$, HAT, CO_2 reserve, HcVR and peripheral HcVR) under clonidine vs. placebo for protocol 1 and 2. To assess the relationship between the chemoresponsiveness and the effect of clonidine on blood pressure, a Pearson correlation analysis was used.

3. Results

3.1. Effect of clonidine on ventilation and sleep in healthy human

We studied 10 healthy subjects (4 females), free of sleep apnoea as confirmed by polysomnography (age 22.3±3.0 years; BMI 25.5±3.4 kg/m^2, and neck circumference 35.8±2.3 cm). We found that a single dose of oral clonidine did not affect sleep architecture or nocturnal respiration, relative to placebo as shown in table 1. The administration of clonidine orally lowered the systolic blood pressure by 12±10 mmHg (120±6 to 107±9 mmHg, *p*=0.02) but did not affect baseline ventilation, timing, or oxygenation during wakefulness or during non-REM sleep (table 2).

3.2 Effect of clonidine on upper airway resistance during wakefulness and sleep

Upper airway resistance (R_{UA}) during inspiration was measured in 10 subjects under clonidine vs. placebo first during wakefulness (prior to sleep onset) and then during stable non-REM sleep. We found that a single dose of oral clonidine did not affect R_{UA} during wakefulness or sleep, relative to placebo as shown in figure 2. Likewise, no significant difference was found in inspiratory or expiratory respiratory timing or in mid-inspiratory flow under clonidine relative to placebo during wakefulness or sleep (table 2).

3.3. Effect of clonidine on the susceptibility to hypocapnic central apnoea and chemoresponsiveness during sleep

Eight healthy subjects completed this protocol. Each subject completed two separate nights after random administration of either clonidine or placebo. The oral administration of clonidine decreased the HAT relative to placebo as depicted in figure 3B for the whole group (37.3±3.3 vs. 39.7±3.4 mmHg; P<0.05). Similarly CO_2 reserve increased under clonidine (-3.8±1.3 vs. placebo -2.8±1.2 mmHg; P< 0.05) (figure 3C) and hypocapnic ventilatory response (HcVR) decreased (1.6±0.6 vs. placebo 2.5±1.3 L/min/mmHg; P<0.05) (figure 3D). There was no correlation between the change in the CO_2 reserve and the change in systolic and diastolic blood pressure (r=0.05 and 0.34, respectively; *p*=NS) or between HcVR and blood pressure (systolic or diastolic) (r=0.70 and -0.04, respectively; *p*=NS).

3.4. Effect of clonidine on the peripheral chemoresponsiveness during sleep

Six subjects were included to assess the effect of clonidine on the peripheral chemoresponsiveness. Figure 4 illustrates the clonidine vs. placebo effect on ventilatory chemoresponse after short hyperventilation during sleep. There was no significant difference in the baseline P_{ETco2} or in the peripheral hypocapnic ventilatory response (0.5±0.3 vs. 0.7±0.3 L/min/mmHg, p=NS).

4. Discussion

Our study demonstrated several novel and significant findings regarding the physiological effects of clonidine on breathing during non-REM sleep. (1) Clonidine did not affect ventilation or sleep in humans despite a modest drop in blood pressure. (2) Clonidine did not affect upper airway resistance during wake or sleep relative to placebo. (3) Clonidine administration was associated with lower apnoeic threshold relative to placebo. (4) Clonidine widened the CO_2 reserve without affecting baseline end-tidal CO_2 or ventilation. (5) The mechanism of action responsible for the clonidine effect in reducing the susceptibility to hypocapnic central apnoea is not by the peripheral chemoresponsiveness pathway.

4.1. Methodological Considerations

Our laboratory has used NIV to induce hypocapnic central apnoea in humans during non-REM sleep in multiple studies (Rowley et al., 2006; Salloum et al., 2010; Sankri-Tarbichi et al., 2009; Zhou et al., 2000). Nevertheless, several considerations may influence the interpretation of the findings. First, we studied the effect of a single dose (0.1 mg/45Kg) of clonidine, which precludes assessing a dose response of this drug on ventilation and sleep. Second, we studied only healthy non-hypertensive, non-obese and non-apnoeic individuals, all of which influence the hypocapnic apnoeic threshold and/or CO_2 reserve. Our goal to study healthy individuals was to understand the physiological effects of clonidine independent of co-morbidities. The next step should be to confirm our findings in patients with sleep disordered breathing, particularly those with hypertension. Third, our healthy subjects were studies during spontaneous but reduced total sleep due to heavy instrumentation, the physiological effects of clonidine vs. placebo on sleep may not be generalized to the general population. Although clonidine plasma concentrations were not measured, clonidine has a half-life of 12 h it is therefore unlikely that it decreased over the sleep period. Clonidine dose was weight- based similar to previous studies (Hall et al., 2006) to avoid significant hypotension. Fourth, although 1 mmHg drop in CO_2 is small drop but it is sufficient to induce central hypopnea and /or apnoea in healthy humans (Badr et al., 1995; Xie et al., 2006). Using non-invasive hyperventilation to measure the apnoeic threshold is based on the assumption that the central to end-tidal PCO2 difference remained constant and that the cerebral blood flow response to the hypocapnia did not change. In addition the cerebral blood flow response to CO2 is assumed to be unchanged by Clonidine. In addition our analysis included only trials with stable non-REM sleep state to ensure that sleep state changes did not influence the apnoeic threshold. Finally, to assess peripheral vs. central effect of clonidine on ventilatory response during non-REM sleep, a short hyperventilation technique described recently in normal human subjects was used (Xie et al., 2006). The

clonidine effect on changes in cerebral blood flow and on the chemoreflex control of breathing during wakefulness however were not tested and further studies will be needed using modern chemoreflex assessment technique (Ainslie et al., 2009).

4.2. Effect of clonidine on sleep and breathing

We noted that a single dose of clonidine (0.1 mg/45Kg), which decreased blood pressure, did not affect baseline ventilation or upper airway resistance during wakefulness or sleep. Likewise, the sleep stages, efficiency and apnoea-hypopnea index were similar between clonidine and placebo. Due to the insufficient REM sleep in placebo nights, the clonidine effect on REM suppression could not be assessed. Therefore, oral clonidine at modest doses prior to sleep is safe and does not affect baseline ventilation during wakefulness or sleep in healthy normotensive individuals.

4.3. Effect of clonidine on the susceptibility to hypocapnic central apnoea during non-REM sleep

Clonidine is a selective alpha-2 agonist which was introduced as an anti-hypertensive agent in the early 1970s by its sympathoinhibitory activity in the in the rostral ventrolateral medulla (Fairbanks et al., 2009). We noted that clonidine oral administration was associated with decreased in propensity to develop hypocapnic central apnoea which manifested by lower hypocapnic apnoeic threshold and chemoresponsiveness to CO_2 relative to placebo. This novel finding may have significant clinical implications for the management of certain sleep apnoea phenotypes especially those that are associated with cardiovascular co morbidities.

4.4. Mechanism(s) of decreased susceptibility to hypocapnic central apnoea

We considered several possible mechanisms of decreased susceptibility to hypocapnic central apnoea after oral administration of clonidine, including the effect of decreased blood pressure on peripheral baroreceptor, CO_2 effects on the peripheral chemoreceptors, or the activation of central α 2-adrenergic receptors in the medulla (Haxhiu et al., 1995).

Decreased blood pressure alone is an unlikely cause given the lack of relationship between the change in blood pressure and hypocapnic apnoeic threshold, CO_2 reserve, or hypocapnic ventilatory response during non-REM sleep. There is evidence that alpha 2-adrenergic receptors located specifically in the locus coeruleus, are responsible on the modulation effect of chemosensitivity and respiratory regulation in animal preparations (Biancardi et al., 2008; Voituron et al., 2012). Moreover, other studies performed on rat brain cells demonstrated that the CO_2 effects on the chemoreceptors are centrally located in the locus coeruleus and not affected by peripheral chemoreceptors input (Fairbanks et al., 2009).

The effects of clonidine on the apnoeic threshold, and widening CO_2 reserve was due to decreased hypocapnic CO2 chemoreflex sensitivity. Our findings corroborate previous studies that demonstrated decreased hypercapnic ventilatory response following clonidine administration in awake humans (Foo et al., 1996; Ooi et al., 1991; Penon et al., 1991). In fact, the change in hypocapnic ventilatory response in the present study was similar to the reported hypercapnic ventilatory response in the study by Penon et al (1991) who found that

administration of oral clonidine to awake humans which was associated with a decrease in the slope of the ventilatory response to CO_2, from 2.06 ± 0.70 L/min/torr to 1.33±0.67 L/min/torr after 2 hours. Likewise Ooi et al (1991) observed decreased ventilatory response to CO_2 after epidural and intravenous demonstration of clonidine in awake humans. Interestingly, decreased CO_2 responsiveness was interpreted as a central depressant effect whereas we interpret this finding as a protective particularly during non-REM sleep, mitigating the ventilatory effects of hypocapnia and decreasing the propensity to develop hypocapnic central apnoea.

We did not find a significant effect of clonidine on the peripheral ventilatory response to hypocapnia. However, we cannot exclude a clonidine effect on hypoxia chemoreceptor sensitivity or the cerebral blood flow as we tested the hypocapnic effect only (Foo et al., 1996; Kaczynska and Szereda-Przestaszewska, 2006). It is possible that hypoxia and CO_2 are sensed through different mechanisms by the carotid body glomus cells. Likewise, the hypoglossal nerve carries sensory peripheral chemoreceptor information to the nucleus of the solitary tract NTS, where the signal is integrated and processed.

Clonidine is a mixed Imidazoline (I-1) / adrenergic (alpha-2) receptors agonist. One possibility that clonidine exerts its sympathoinhibitory effects located centrally at α_2-adrenergic receptors or at imidazoline receptors (I-1) in the ventrolateral medulla (Haxhiu et al., 1995). It has been reported previously in animal models that the clonidine effect on the Imidazoline receptors, decreases the tonic cervical sympathetic nerve activity and blood pressure, but does not affect the CO_2 threshold (Haxhiu et al., 1995). On the other hand, the alpha 2-adrenergic effect of clonidine attenuates the cervical sympathetic response to CO_2 and may have relative inhibitory effect on the respiratory muscles. In our study, we found that clonidine at a lower dose was effective in decreasing the susceptibility to central apnoea. It is possible that lower doses of clonidine in humans have a preferential effect on alpha-2 than Imidazoline receptors leading to a decreased hypocapnic apnoeic threshold and chemosensitivity to CO_2. This interpretation is supported by the fact that when Moxonidine, a clonidine derivative with higher affinity to Imadozoline receptors, was administered to anesthetized cats it decreased the sympathetic activity without altering CO_2 sensitivity (Haxhiu et al., 1995).

4.5. Therapeutic implications

Clonidine as a sympathoinhibitory agent offers a unique pharmacological treatment for central sleep-disordered breathing such as in heart failure, stroke, or narcotics mediated central apnoea. It is estimated that up to 40% of compensated heart failure patients have central sleep apnoea, which is associated with increased mortality (Javaheri et al., 1996; Javaheri 2006). The augmentation of sympathetic activity in cardiovascular disease and heart failure is common and could be responsible for the development of central sleep disordered breathing. Thus sympathoinhibitory agent, such as alpha 2-agonist, could become a potential therapeutic target for central apnoea in heart failure.

Opiate-induced central sleep apnoeaapnoea is a common problem that could be reduced by the use of clonidine's anti-nociceptive effects, including an opiate sparing effect or use in those with opiate-induced sleep apnoea (Javaheri et al., 2008). Furthermore, a recent study

showed that when clonidine was given preoperatively a significant postoperative opioid-sparing effect was observed which may reduce the risk of preoperative sleep apnoea (Chung et al., 2008; Pawlik et al., 2005).

In summary, we have shown that clonidine, a sympathoinhibitory agent and alpha-2 agonist, reduced the susceptibility for hypocapnic central apnoea during non-REM sleep. Clonidine did not affect peripheral chemosensitivity to hypocapnia; therefore central sympathetic activity inhibition by its α_2-adrenergic receptor activity is the likely mechanism. Clonidine may have important clinical applications especially in patients with cardiovascular disease, post-operatively and in patients with opiate induced sleep disordered breathing. Further studies are needed to ascertain the exact mechanism of action and confirm its therapeutic action in clinical settings.

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References

Ainslie P, Duffin J. Integration of cerebrovascular CO_2 reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. Am J Physiol Regul Integr Comp Physiol. 2009; 296(5):1473–1495.

Autret A, Minz M, Beillevaire T, et al. Effect of clonidine on sleep patterns in man. Eur J Clin Pharmacol. 1977; 12:319–322. [PubMed: 598402]

Biancardi V, Bicego KC, Almeida MC, et al. Locus coeruleus noradrenergic neurons and CO2 drive to breathing. Pflugers Arch. 2008; 455:1119–1128. [PubMed: 17851683]

Chung SA, Yuan H, Chung F. A Systemic Review of Obstructive Sleep Apnoea and Its Implications for Anesthesiologists. Anesthesia & Analgesia. 2008; 107:1543–1563. [PubMed: 18931212]

Fairbanks CA, Stone LS, Wilcox GL. Pharmacological profiles of alpha 2 adrenergic receptor agonists identified using genetically altered mice and isobolographic analysis. Pharmacol Ther. 2009; 123:224–238. [PubMed: 19393691]

Foo IT, Warren PM, Drummond GB. Influence of oral clonidine on the ventilatory response to acute and sustained isocapnoic hypoxia in human males. Br J Anaesth. 1996; 76(2):214–220. [PubMed: 8777100]

Ghignone M, Quintin L, Duke PC, Kehler CH, et al. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. Anesthesiology. 1986; 64(1):36–42. [PubMed: 3942335]

Ghignone M, Noe C, Calvillo O, et al. Anesthesia for ophthalmic surgery in the elderly: the effects of clonidine on intraocular pressure, perioperative hemodynamics, and anesthetic requirement. Anesthesiology. 1988; 68(5):707–716. [PubMed: 3285731]

Grullon KR, Sankri-Tarbichi A, Rowley JA, et al. Influence of Alpha 2 Receptors Agonist on Susceptibility to Hypocapnic Central Apnoea during NREM Sleep in Healthy Individuals. Am J Respir Crit Care Med. 2011; A5285

Hall DL, Tatakis DN, Walters JD, et al. Oral Clonidine Pre-treatment and Diazepam/Meperidine Sedation. Journal of Dental Research. 2006; 85(9):854–858. [PubMed: 16931871]

Haxhiu MA, Dreshaj IA, Erokwu B, et al. Effect of I1-imidazoline receptor activation on responses of hypoglossal and phrenic nerve to chemical stimulation. Ann N Y Acad Sci. 1995; 763:445–462. [PubMed: 7677359]

Hedrick MS, Dwinell MR, Janssen PL, et al. Differential respiratory muscle recruitment induced by clonidine in awake goats. J Appl Physiol. 1998; 84:1198–1207. [PubMed: 9516185]

Issa FG. Effect of clonidine in obstructive sleep apnoea. Am Rev Respir Dis. 1992; 145:435–439. [PubMed: 1736753]

Javaheri S, Malik A, Smith J, et al. Adaptive pressure support servoventilation: a novel treatment for sleep apnoea associated with use of opioids. J Clin Sleep Med. 2008; 4:305–310. [PubMed: 18763420]

Javaheri S, Parker TJ, Wexler L, et al. Effect of theophylline on sleep-disordered breathing in heart failure. N Engl J Med. 1996; 335:562–567. [PubMed: 8678934]

Javaheri S. Acetazolamide improves central sleep apnoea in heart failure: a double-blind, prospective study. Am J Respir Crit Care Med. 2006; 173:234–237. [PubMed: 16239622]

Kaczynska K, Szereda-Przestaszewska M. Clonidine-evoked respiratory effects in anaesthetized rats. Exp Physiol. 2006; 91(1):269–275. [PubMed: 16282369]

O'Halloran KD, Herman JK, Bisgard GE, et al. Clonidine induces upper airway closure in awake goats. Respir Physiol. 2000; 123:165–176. [PubMed: 11007984]

O'Halloran KD, Herman JK, Bisgard GE, et al. Differential effects of clonidine on upper airway abductor and adductor muscle activity in awake goats. J Appl Physiol. 1999; 87:590–597. [PubMed: 10444617]

Ooi R, Pattison J, Feldman SA, et al. The effects of intravenous clonidine on ventilation. Anaesthesia. 1991; 46(8):632–633. [PubMed: 1909506]

Pawlik MT, Hansen E, Waldhauser D, et al. Clonidine premedication in patients with sleep apnoea syndrome: a randomized, double-blind, placebo-controlled study. Anesth Analg. 2005; 101:1374–1380. [PubMed: 16243997]

Penon C, Ecoffey C, Cohen SE, et al. Ventilatory response to carbon dioxide after epidural clonidine injection. Anesth Analg. 1991; 72(6):761–764. [PubMed: 1903615]

Rowley JA, Zhou XS, Diamond MP, et al. The determinants of the apnoea threshold during NREM sleep in normal subjects. Sleep. 2006; 29:95–103. [PubMed: 16453986]

Salloum A, Rowley JA, Mateika JH, et al. Increased propensity for central apnoea in patients with obstructive sleep apnoea: effect of nasal continuous positive airway pressure. Am J Respir Crit Care Med. 2010; 181:189–193. [PubMed: 19762565]

Sankri-Tarbichi AG, Rowley JA, Badr MS, et al. Expiratory pharyngeal narrowing during central hypocapnic hypopnea. Am J Respir Crit Care Med. 2009; 179:313–319. [PubMed: 19201929]

Smith I, Lasserson TJ, Wright J, et al. Drug therapy for obstructive sleep apnoea in adults. Cochrane Database Syst Rev. 2009:1–77.

Voituron N, Hilaire G, Quintin L, et al. Dexmedetomidine and clonidine induce long-lasting activation of the respiratory rhythm generator of neonatal mice: Possible implication for critical care. Respiratory Physiology & Neurobiology. 2012; 180:132–140. [PubMed: 22108092]

Xie A, Skatrud JB, Puleo DS, et al. Influence of arterial O2 on the susceptibility to posthyperventilation apnoea during sleep. Journal of Applied Physiology. 2006; 100(1):171–177. [PubMed: 16179400]

Zhou XS, Rowley JA, Demirovic F, et al. Effect of testosterone on the apnoeic threshold in women during NREM sleep. J Appl Physiol. 2003; 94:101–107. [PubMed: 12391093]

Zhou XS, Shahabuddin S, Zahn BR, et al. Effect of gender on the development of hypocapnic apnoea/hypopnea during NREM sleep. J Appl Physiol. 2000; 89:192–199. [PubMed: 10904052]

Highlights

1. Clonidine did not affect ventilation or upper airway resistance during wake or sleep relative to placebo.
2. Clonidine administration is associated with lower apneic threshold relative to placebo.
3. Clonidine widens the CO_2 reserve without affecting baseline end-tidal CO_2 or ventilation.
4. The mechanism of action responsible for the clonidine effect in reducing the susceptibility to hypocapnic central apnea is likely centrally mediated.

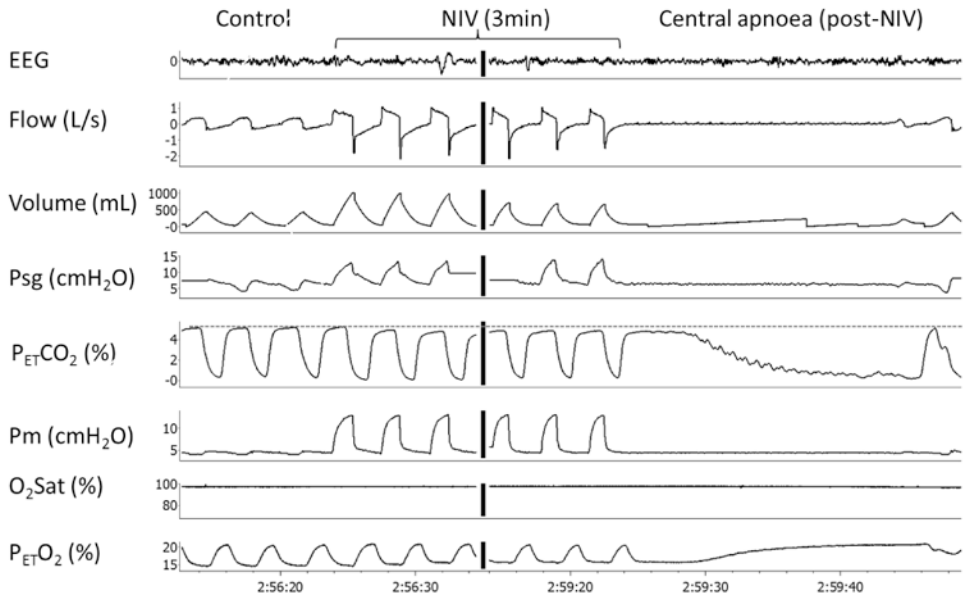

Figure 1.

Polygraph tracing of a non-invasive ventilation (NIV) trial during N2- sleep followed by central apnoea in one representative subject to calculate the hypocapnic apnoeic threshold. Dashed line indicates the level of end-tidal CO_2.

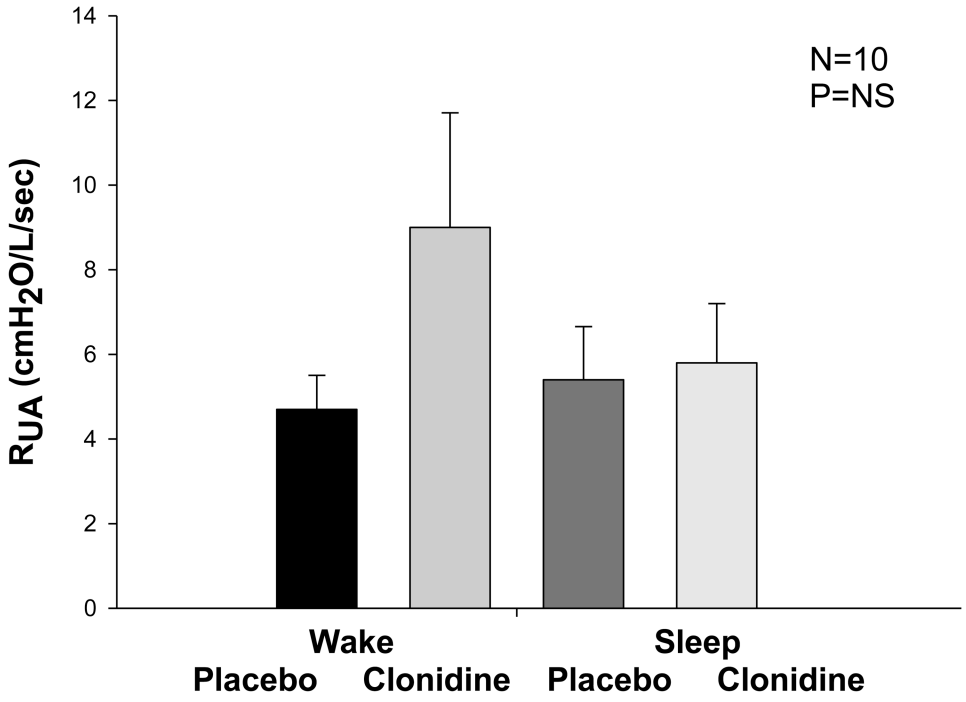

Figure 2.

Grouped data for inspiratory upper airway resistance during wake and non-REM sleep under clonidine vs. placebo. All presented data are mean SE.

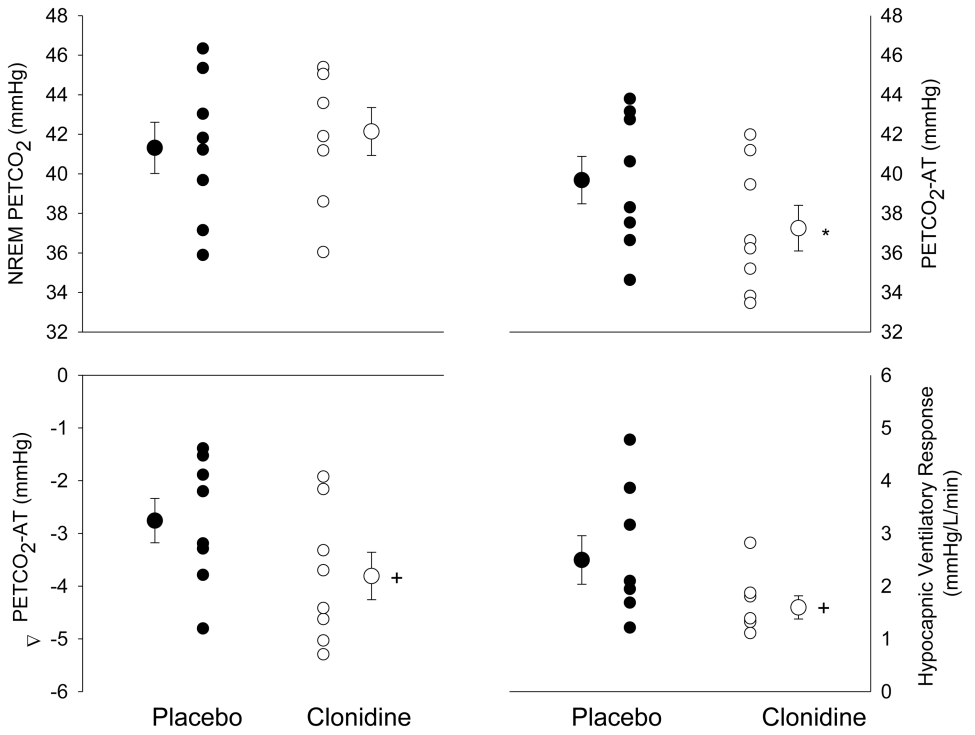

Figure 3.

Effect of clonidine (open circles) vs. placebo (closed circles) on chemoresponsiveness. **A**, End-Tidal-CO_2 ($P_{ET}CO_2$) during non-REM sleep measured under placebo and clonidine (p= NS). **B**, Apnoeic threshold ($P_{ET}CO_2$-AT) under placebo and clonidine. Note that $P_{ET}CO_2$-AT decreased under the effect of clonidine (*p=0.02). **C**, individual and group data for CO2 reserve for placebo vs. clonidine. Note that CO_2 reserve increased under the effect of clonidine (+p=0.01). **D**, individual and group data comparing hypocapnic ventilatory response during sleep for placebo vs. clonidine. Note that hypocapnic ventilatory response decreased under the effect of clonidine (+p=0.04). All presented data are mean ± SE.

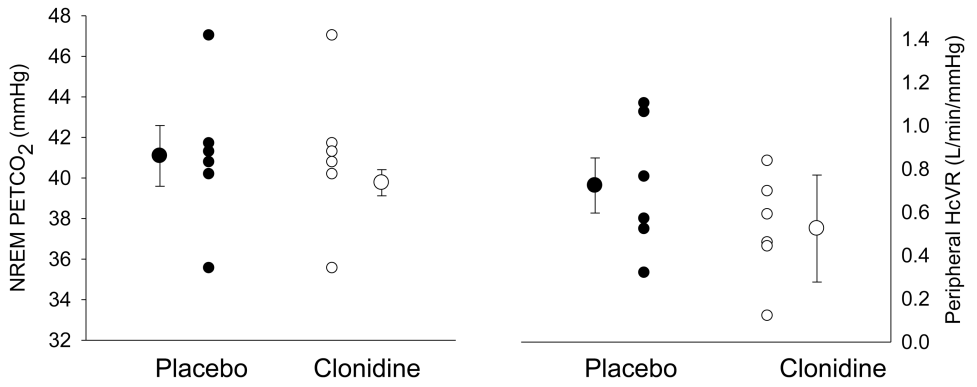

Figure 4.

Individual and group mean data (mean ± SE) comparing: **A**. end-tidal-CO_2 ($P_{ET}CO_2$) during Non-REM sleep under the effect of placebo (closed circles) and clonidine (open circles) (*p*= NS), **B**, peripheral hypocapnic ventilatory response (HcVR) for placebo vs. clonidine (*p*=NS).

Table 1

Sleep Parameters (N=10)

	Placebo	Clonidine
TST (min)	92.3± 63.7	92.1± 62.7
N1 (%)	20.6± 10.9	17.1± 7.3
N2 (%)	60.3± 14.9	72.1± 13.7
SWS (%)	14.3± 15.1	9.1± 12.2
REM (%)*	3.4± 5.6	1.6± 3.4
Sleep Efficiency (%)	74.8± 20.2	73.1± 16.9
Sleep Latency (min)	10.9± 13.7	8.9± 8.3
Latency to REM (min)*	130.0± 0.0	82.3± 47.5
AHI (event/hr)	0.6± 2.0	0.5± 0.8

All data Mean ± SD

TST, total sleep time; N1, Stage 1 non-REM sleep; N2, Stage 2 non-REM sleep; SWS, Slow wave sleep; REM, Rapid Eye Movement, AHI, apnea hypopnea index.

* Only one subject had REM sleep in Placebo and only three subjects had REM in clonidine nights.

Table 2

Ventilatory parameters (N=10)

	Wake		Non-REM Sleep	
	Placebo	**Clonidine**	**Placebo**	**Clonidine**
V_I (L/min)	7.6± 1.6	6.7± 1.5	6.9± 0.9	6.7± 1.3
V_T (L)	0.53± 0.14	0.52± 0.19	0.46± 0.05	0.43± 0.08
F_B (breath/min)	14.7± 2.7	14.1± 4.8	15.2± 1.7	16.1± 3.4
T_I (sec)	2.0± 0.4	2.2± 1.1	1.9± 0.2	1.8± 0.3
T_E (sec)	2.3± 0.6	2.7± 1.2	2.2± 0.4	2.0± 0.5
T_I/T_{TOT} (sec)	0.47± 0.04	0.45± 0.04	0.46± 0.04	0.48± 0.07
$P_{ET}CO_2$(mmHg)	40.2± 4.2	39.0± 4.2	40.9± 3.0	40.6± 4.0
O_2Sat (%)	96.2± 1.5	96.2± 1.6	96.0± 2.0	96.2± 1.1

(Mean ± SD)

V_I, inspiratory minute ventilation; V_T, tidal volume; F_B, breathing frequency; T_I, inspiratory time; T_E, expiratory time; F_B, frequency; $P_{ET}CO_2$, End-tidal CO_2; O_2Sat, oxygen saturation; R_{UA},, upper airway resistance.