40 Influence of anaesthesia and analgesia on the control of breathing
New Concept in Respiratory Function

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Most agents used to induce and maintain general anaesthesia or to relieve pain or suppress the responses to pain change the control of breathing drastically. They affect the chemical control of breathing, behavioural control or, most often, both. Chemical or metabolic control of breathing is coupled to metabolism and depends on the chemical composition of arterial blood (pH, PCO2, PO2) and brainstem interstitial fluid (pH, brain tissue PCO2). Chemical control occurs during non-rapid-eye-movement sleep and anaesthesia. Behavioural control adjusts breathing in specific situations such as speech, exercise, pain, arousal and stress. An example of agents that affect both control systems are the volatile halogenated anaesthetics. For example, halothane depresses ventilation by abolishing peripheral drive from the chemoreceptors at the carotid bodies, by general depression of respiratory centres in the central nervous system (CNS), and by the suppression of the function of motor neurones, intercostal muscles and the diaphragm (all involved in the chemical control of breathing) and also by the loss of wakefulness drive (behavioural control).

We have previously reviewed the effect of anaesthetics and opioids on ventilation. In this review we will consider issues that have been neglected up to now but have important clinical implications: (i) how to test the effects of drugs on chemical and behavioural ventilatory control; (ii) the role of free-radical species in the depression of the response of the carotid bodies to hypoxia caused by anaesthetics; (iii) the respiratory pharmacodynamics of morphine and its metabolite, morphine-6-glucuronide (M6G); (iv) modelling of the interaction of opioids and anaesthetics on ventilatory control.

Assessing the effect of drugs on ventilatory control

Classical physiology dictates that chemical control is tested by measuring ventilatory responses to inhaled carbon dioxide and/or reduced inspired oxygen concentrations or inspiratory resistive loads. Behavioural control is best tested by measuring the effect of one or more drugs on resting variables such as ventilation (i.e. without any inspired carbon dioxide) or end-tidal/arterial carbon dioxide concentration (PETCO2, PaCO2). Interestingly, recent studies indicate that C50 values (i.e. the drug concentration causing 50% depression of ventilation) obtained either from studies on chemical control of breathing using a fixed increased PETCO2 as input to the chemical control system, or from studies of the dynamic effect of the drugs on resting ventilation and PaCO2, which

do take into account the dynamics and kinetics of carbon dioxide, were of the same order of magnitude. For example, the C50 of alfentanil for depression of ventilation at a raised fixed PETCO2 (about 1 kPa above resting values) is about 75 ng ml-1, while the C50 derived from resting ventilation (i.e. without any inspired carbon dioxide) is 60 ng ml-1. However, current models of the effect of drugs on resting ventilation that take into account carbon dioxide dynamics and kinetics have not described the `true' opioid effect on chemical control (i.e. the parallel shift of the ventilatory carbon dioxide response to greater PCO2 values) but are only able to describe the effect of opioids on behavioural control (i.e. the reduction of the slope of the ventilatory carbon dioxide response). Opioids and anaesthetics probably have different C50 values for their effect on chemical control (measured from their effect on the slope of the ventilatory carbon dioxide response) and for their effect on behavioural control (as determined from resting ventilation and resting PCO2). The similar C50 values observed for alfentanil's effect on behavioural and chemical control (see above) may just be coincidence.

If the effects of drugs on resting ventilation are measured without taking into account the dynamics and kinetics of carbon dioxide, extremely high C50 values are obtained. For example, C50 values of alfentanil become greater than 300 ng ml-1. If the kinetics and dynamics of carbon dioxide and the drug are not considered, the study results may depend on the rate of drug infusion. For example, a relatively large bolus of remifentanil may cause immediate apnoea because of the direct depressant effect, while a slow remifentanil infusion will reduce ventilation but will not cause apnoea since there is time for carbon dioxide to accumulate and enhance respiratory drive (i.e. central carbon dioxide drive) despite depression of the chemosensors and/or the respiratory centres in the CNS by the opioid.

Most studies on the influence of anaesthetics and opioids on respiration are done with healthy volunteers.. This has advantages, avoiding the effects of underlying disease, surgery, inflammation, sleep deprivation etc. However, in real life, respiration in perioperative patients is related to the fragile balance between depression by sedation, sleep and the effect of anaesthetics and opioids on respiratory sensors and neurones on the one hand and stimulation from pain, stress, inflammation and activated chemoreflexes on the other. However, these stimulatory effects activate behavioural control without affecting chemical control much. In patients recovering from abdominal surgery, the ventilatory response to a progressive asphyxic stimulus (i.e. the gradual occurrence of hypoxia and hypercapnia as may occur during obstructive and central apnoea) was depressed by about 25%, despite opioid pain relief and high levels of C-reactive protein (a measure of stress and inflammation). This suggests impaired chemical control of breathing and a poor response to chemical stimuli that are frequent after surgery (hypoxia, hypercapnia and acidosis).

The effects of drugs on control of breathing in healthy volunteers, using inspired carbon dioxide and lowered concentrations of oxygen, are crucial to define their pharmacological effects. Single measurements of PETCO2, inspired minute ventilation and arterial oxygen saturation have very limited value to predict responses of patients to a hypoxic/hypercapnic stimulus as would occur during obstructive apnoea.

Free-radical species and anaesthesia-induced depression of hypoxic drive

In hypoxia, the body responds with a swift (and sometimes life-saving) increase in minute ventilation caused by activation of the peripheral chemoreceptors in the carotid body. The carotid bodies are strategically situated at the bifurcation of the common carotid arteries (in a sense they are the guards of oxygen delivery to the brain). The glomus type-I cells of the carotid bodies, which are thought to contain oxygen-sensing mechanisms, release neurotransmitters in response to hypoxic stimulation. These transmitters activate postsynaptic receptors located on afferent fibres of the carotid sinus nerve that have their cell bodies in the petrosal ganglion. Their central axons terminate in the nucleus tractus solitarii. In animals and humans, the ventilatory response to isocapnic hypoxia has two components: a fast component with a time constant of 2–10 s and a slow component with a time constant of 60–90 s. The fast component is caused by activation of the carotid bodies, while the slow component is related to central modulation of the carotid body response (e.g. central neuronal dynamics or short-term potentiation of breathing). This latter mechanism stabilizes hypoxic breathing, so that a brisk hyperventilatory response to hypoxia causing hypocapnia does not result in apnoea or periodic breathing.

Inhalational (halothane, isoflurane, enflurane and sevoflurane) and i.v. anaesthetics (propofol) reduce the hypoxic drive even at low or subanaesthetic concentrations. The C50 values for halothane, isoflurane, sevoflurane and propofol for reduction of the hypoxic drive (0.08, 0.10, 0.27 end-tidal volume percent and 600 ng ml-1 plasma concentration, respectively) are all much less than the C50 for loss of consciousness. The sites of action on the hypoxic drive are different, however. Inhalational anaesthetics affect both the fast and slow components of the acute hypoxic response, but propofol affects only the slow component. This suggests that propofol acts at sites within the CNS, whereas inhalational anaesthetics act both within the CNS and at the carotid bodies to reduce the hypoxic response. The direct effect of low-dose inhalational anaesthetics on the carotid bodies in humans is further shown by the following: i) after 20 min of isocapnic hypoxia, the sudden introduction of isoflurane (end-tidal concentration 0.125%) causes a rapid (within 15–30 s) reduction of hypoxia-driven ventilation; ii) the fast component of the ventilatory response to hypercapnia (i.e. the component arising at the carotid bodies) is affected by low-dose halothane, isoflurane and sevoflurane while the central component is left unchanged; iii) 0.1 MAC halothane affects the acute ventilatory response to moderate metabolic acidosis (which acts by stimulation of the peripheral chemoreceptors) by about 60%.

The mechanisms of oxygen sensing at the carotid bodies and how inhalational anaesthetics (halothane having the largest effect) impair oxgyen sensing remain poorly understood. Over the last decade, studies have shown that low oxygen decreases the open probability of potassium channels and causes membrane depolarization, an influx of calcium ions and release of neurotransmitters. The precise identity of the potassium channels for oxygen sensing is unknown and may differ between species (e.g. TASK channels in the rat and Kv channels in the rabbit). Exactly how low oxygen increases the conductance of potassium channels is unknown, but may involve sensitivity to reactive oxygen species (ROS) and changes in redox status. Reactive species, on the other hand, may also be involved in oxygen sensing but at this stage their exact role remains obscure.

In hypoxic conditions, volatile anaesthetics, particularly halothane, cause formation of reactive species, leading to lipid peroxidation and mild liver damage. In the guinea pig,

this effect can be prevented by antioxidant treatment. Volatile anaesthetics such as halothane increase the conductance of potassium channels, especially TASK channels, possibly by binding to a specific cytoplasmic C-terminal site that is also required for neurotransmitter inhibition of the channel.

The findings that low oxygen closes potassium channels which by themselves are sensitive to ROS, and that halothane is not only able to open potassium channels but also produces ROS (particularly in hypoxia) raise the question whether halothane may reduce the hypoxic response by producing ROS or affecting the redox state of the carotid body. We studied this in healthy volunteers by giving an antioxidant mixture (a-tocopherol and ascorbic acid) and measuring the acute hypoxic response. The antioxidants prevented depression of the hypoxic response by 0.13 MAC halothane. Subjects pretreated with antioxidants had no depression of the ventilatory response by halothane (), while subjects given placebo showed 50–60% depression. Antioxidants by themselves had no effect on the response to hypoxia.

Since antioxidants prevent the depression of the response to hypoxia by halothane, the agent could be acting through reactive species generated by its reductive metabolism. An increase in the concentration of reactive species would then depress the hypoxic response by opening ROS-sensitive potassium channels. Another explanation could be that the antioxidants alter cellular redox state or the concentration of ROS, and this could affect the binding of halothane to the potassium channel. Additional studies are needed to clarify this.

In animals, the effect of halothane on the hypoxic response differs between species (). In goats, an endtidal concentration of 0.5% does not significantly depress the hypoxic drive, but similar concentrations cause depression in cats and rabbits, with a greater effect in cats. Note that goats produce large quantities of ascorbic acid and may thus be better protected against the adverse effects of ROS and free radicals. Cats produce low quantities of ascorbic acid, which may explain their greater susceptibility to halothane than rabbits, which produce more ascorbic acid. Humans cannot synthesize ascorbic acid and so may be more vulnerable to the adverse effects of ROS. These species differences could also originate from differences in potassium channel types and/or splice variants that initiate the hypoxic response and their difference in anaesthetic sensitivity.

In healthy volunteers we found that antioxidants also prevented the depression of the acute hypoxic response by 0.1 MAC isoflurane—a volatile anaesthetic that also can produce reactive species, albeit to a lesser degree than halothane. (Note that the depression from isoflurane is also smaller than from halothane.) Desflurane (0.1 MAC), on the other hand, is metabolized very little, with very little production of reactive species and does not impair the hypoxic response (). It is interesting that propofol, which has antioxidant properties, does not depress the carbon dioxide sensitivity of the peripheral chemoreflex loop nor the fast carotid-body-mediated component of the hypoxic response. Altogether, these findings in animals and humans suggest that the depressant effect of anaesthetics on the hypoxic response may be related to their pro-oxidant properties but further studies are needed to confirm this.

Further work, including dose—response studies, are needed to determine the clinical importance of a possible involvement of ROS in the effects of volatile anaesthetics. Although respiratory depression after surgery is probably caused mainly by opioid analgesics, interaction (synergism) between opiates and residual anaesthetic may impair

the responses of some patients to hypercapnic and hypoxic loads (e.g. obstructive apnoea). Postoperative hypoxia is associated with delayed wound healing and increased occurrence of wound infection, myocardial ischaemia, tachycardia and acute cognitive disturbances. Particular care is required in the management of patients with sleep-disordered breathing, which is common in the general population. It would be interesting to study if antioxidant treatment could reduce postoperative hypoxia, which could provide a new method of preventing potentially serious or life-threatening adverse effects after anaesthesia with inhalational anaesthetics.

Respiratory pharmacodynamics of morphine and its metabolite M6G

M6G is an important active metabolite of morphine in humans. About 10% of morphine is metabolized to M6G. Both morphine and M6G act at opioid receptors, predominantly at m-opioid receptors. Despite their many side-effects, opioids, and especially morphine, remain the most important agents for the treatment of severe acute and chronic pain.

The site of action of morphine and M6G on respiration, antinociception and thermoregulation has been studied in mice lacking the m-opioid receptor (that is exon 2 m-opioid receptor gene (MOR-1 gene) knockout mice). Morphine and M6G caused profound analgesia (morphine:M6G potency ratio 1:10), hypothermia and overt respiratory depression (a reduction in ventilatory frequency without affecting tidal volume) in mice with intact m-receptors. However, neither morphine nor M6G had any antinociceptive or respiratory effect in the MOR-1 knockout mice. This confirms that m-opioid receptors are the essential molecular targets of morphine and other m-opioids on both respiratory control and pain response. Agents acting at m-opioid receptors will depress respiration but the degree may depend on the affinity of the opioid to the various splice variants of the MOR-1 gene (vide infra). Other important findings were greater ventilatory frequencies in the knockout mice compared with their wild-type littermates and an increase in respiratory frequency in response to hypercapnia of similar magnitude in both genotypes after naloxone. This suggests that the m-opioid receptor moderates the respiratory rhythm. The role of the m-opioid receptor is small, however, and the naloxone results suggest that the d-opioid receptor has a more important role.

In humans and animals, the effects of morphine (and other m-opioids) on ventilatory control differ according to sex. This is not surprising considering other observations of sex differences in opioid analgesia (see Sarton and colleagues for a review). Morphine is a more potent analgesic and respiratory depressant in women, which is a pharmacodynamic not a pharmacokinetic effect. These experimental findings support clinical observations of greater opioid consumption in men for treatment of postoperative pain and more respiratory events in young women after i.v. fentanyl. It is not clear if the differences in opioid pain response and the respiratory effects have a single mechanism. Sex differences in opioid pain relief are probably related to differences in opioid receptor density or affinity in brain sites involved in pain control. These differences are possibly related to long-term developmental and organizational effects of sex steroids that occur in prenatal and early postnatal life, causing differences in brain neurobiology and structure (sexual dimorphism) between men and women. The cause of sex differences in opioid respiratory effect may also be related to the differences in opioid-induced sedation. Greater sedative effects of opioids in women relative to men could cause the greater

depression of the ventilatory response to hypercapnia and hypoxia in women compared with men.

We recently calculated the respiratory potency of morphine and M6G in humans. The influences of morphine 0.13 mg kg-1 and M6G 0.2 mg kg-1 on normoxic ventilation and the ventilatory response to isocapnic hypoxia were compared with PETCO2 kept constant at 6 kPa. Morphine depressed ventilation more, both for normoxic ventilation (morphine:M6G potency ratio 20:1) and hypoxic ventilation (morphine:M6G potency ratio 50:1). The greater potency ratio with hypoxia was surprising. With a concentration of morphine that reduced normoxic ventilation by 25%, ventilation during hypoxia was depressed by more than 50%. For M6G, depression of ventilation during hypoxia was only 15% at concentrations that caused 25% depression of normoxic ventilation. In terms of the infusion rate needed for a steady-state effect, an infusion rate of 9 mg kg-1 per min for morphine would cause 25% depression of hypercapnic and hypoxic ventilation. At these infusion rates, steady-state plasma concentrations are 20–30 nM. The M6G infusion rate required for 25% depression of hypercapnic ventilation is 20 mg kg-1 min-1, while 40 mg kg-1 min-1 is needed to depress hypoxic ventilation by 25%. The plasma concentrations would be 500 nM and 900 nM for 25% depression of hypercapnic and hypoxic breathing, respectively. These results are clinically relevant as they show that M6G has less effect on the chemoreflex response to hypoxia compared with morphine. As far as we know, M6G is the only opioid for which depression of hypoxic ventilation requires greater doses than for depression of normoxic ventilation. These differences between M6G and other opioids may be from activation of pathways involving different G-protein receptor complexes, or activation of non-opioid receptors by M6G causing respiratory stimulation. However, the respiratory effects of opioids should always be viewed in light of their analgesic effects. So far, there are few good studies of the pharmacokinetics and pharmcodynamics of M6G analgesia. We have preliminary data that M6G has a C25 value of 275 nM, which is 2–4 times greater than the C25 value causing depression of hypercapnic and hypoxic ventilation. This observation supports earlier reports of a dissociation of the respiratory and analgesic effect of M6G. In contrast, the C25 for morphine analgesia is equivalent to the values observed for respiratory effect.

Finally, it has long been suggested that morphine's toxicity is caused in part by accumulation of M6G in the body. In humans, 5–10% of morphine is metabolized in the liver to M6G. After an analgesic dose of morphine 0.13 mg kg-1, the M6G concentration reaches 60 nM within 1 h of morphine infusion. For M6G to cause significant respiratory depression, plasma concentrations need to be greater than 600–800 nM. This suggests that after a morphine bolus or short-duration infusion, the respiratory effects are unrelated to M6G production or accumulation, at least in patients with normal renal function. Morphine and M6G concentrations in patients receiving patient-controlled analgesia morphine after surgery are very variable and in some cases an appreciable M6G effect could occur, particularly in patients with poor renal function. However, despite increased M6G plasma concentrations, respiratory depression by M6G seems of limited importance relative to the respiratory effect of morphine. The relative resistance to the effect of M6G may have a genetic basis. A recent report of no toxicity (sleepiness and sedation) in a patient with renal impairment after morphine administration, despite high M6G blood concentrations (1600 nM), was related to a mutation in the m-opioid receptor (A118G

single nucleotide polymorphism). In contrast, another patient with poor renal function who had a non-mutated m-opioid receptor showed signs of sedation and sleepiness when M6G plasma concentrations were high.

Response surface modelling of opioid—anaesthetic interaction on ventilatory control

An important advantage of combining an opioid and an anaesthetic compared with use of single agents is the synergistic increase in anaesthetic effect, such as reducing autonomic and somatic responses to noxious stimuli (laryngoscopy, intubation, surgery, skin closure, extubation, pain). This means that less drug is needed to achieve the same effect. Since even low doses of anaesthetics, opioids and hypnotics can depress respiration when they are combined, it is surprising that the effects of combinations have been studied infrequently in humans. We recently modelled the interaction of opioid and anaesthetic (sevoflurane—alfentanil; remifentanil—propofol) on ventilatory control. We used a three-dimensional representation of the concentration—response relationship for combinations of drugs to express the interaction (additive, synergistic or antagonistic) for all possible combinations. All of these interactions are possible in different regions of the response surface. This gives advantages compared with isoboles (or iso-effect curves) which only indicate the interaction of drug combinations yielding a constant effect, such as 25% or 50% reduction in an effect (e.g. C25 or C50).

The usual model of pharmacodynamic effect is the sigmoid EMAX model. However, this model does not always represent clinical respiratory behaviour, so we used a more empirical model of the form:

$$y = a(1-xb) \quad (1)$$

This model of drug effect has the following advantages over the classic sigmoid EMAX model. (i) It allows zero effect at a finite drug concentration, which can occur in complex non-linear systems such as ventilatory control (i.e. abrupt central apnoea after a bolus drug infusion). In contrast, the classical sigmoid EMAX model only gives a zero effect when the drug concentration is infinite. (ii) It can predict negative responses as drug concentration is increased. For example, ventilation can increase in response to a hypoxic challenge at halothane MAC values of 0.2 or less, but will decrease rather than increase when 1 MAC halothane is breathed. (iii) Because drug—effect relationships are sometimes strikingly linear, especially when only a limited part of the dose—response relationship is explored, this can be modelled easily by setting parameter b to 1 (see also).

To model interactions between two drugs we extended the model:

$$E(C1, C2) = E0 \{1 - (U1 + U2)b\ INT\} \quad (2)$$

where E is measured respiratory effect (such as the magnitude of the acute hypoxic response or baseline ventilation) at concentrations C of drugs 1 and 2, E0 is the baseline effect, U1 and U2 are the concentrations of drugs 1 and 2 divided by their respective C50 values, and INT expresses interaction between the drugs (INT=1 would represent no interaction; INT > 1 expresses synergy). The model can be expanded easily by adding more drugs: U1 + U2 + U3 + °.

We present two examples of opioid—anaesthetic interaction expressed as a response surface. The first (alfentanil—sevoflurane) is of limited clinical importance since this combination is seldom used in spontaneously breathing patients. However, we studied

this interaction because we could easily measure the agents in plasma (alfentanil) and exhaled gas (sevoflurane) and used this as an example for further studies.

Alfentanil—sevoflurane interaction

Respiratory responses were measured in nine healthy volunteers using 10–12 drug combinations in each subject. The study was designed so that at the greatest drug combinations the response to hypoxia was virtually absent at a fixed PETCO2 (C50). The concentration causing 50% reduction of minute ventilation was 75 ng ml-1 and 1.5 end-tidal volume percent for alfentanil and sevoflurane, respectively, when these agents were given separately. The combination was strikingly synergistic. Maximum synergy occurred with an alfentanil:sevoflurane ratio of 0.7. In other words, considering the respective C50 values and the linear dose—response relationships, concentrations that give maximum synergy would be a fraction or multiple of 26.7 ng ml-1 for alfentanil and 0.24 end-tidal percent for sevoflurane. For example, maximum synergy causing 25% reduction of minute ventilation occurs with 13.4 ng ml-1 alfentanil and 0.12 end-tidal percent sevoflurane. Interestingly, the interaction of the two agents on the hypoxic drive was additive. However, the hypoxic response was much more sensitive to the effects of the opioid and anaesthetic: C50 values were 15.7 ng/ml for alfentanil and 0.27 end-tidal percent for sevoflurane. This indicates that the hypoxic test is more sensitive for assessing the effects of anaesthetics and opioids on the control of breathing.

Remifentanil—propofol interaction

These two agents are commonly used for monitored anaesthesia care or conscious sedation in patients having minor surgery under local anaesthesia or diagnostic procedures. Knowing the separate effects and the interaction of these agents on both chemical and behavioural control of breathing is important clinically and will guide their practical use. Synergistic effects were seen on resting ventilation (i.e. with no inspired carbon dioxide), resting PCO2, and ventilatory response to carbon dioxide (see and). However, each variable showed different degrees of synergy: resting ventilation showed the greatest interaction, followed by resting carbon dioxide and finally ventilation at a fixed PETCO2. The differences in synergy may be related to the fact that resting variables and ventilation measured when carbon dioxide is increased are affected differently by chemical and behavioural control of breathing (see also above). Ventilation at an increased carbon dioxide is predominantly controlled by chemical factors; the arousal state of the patient or volunteer has little influence. In contrast, for resting variables apart from a chemical component there is a large behavioural component. For example, if the subject/patient falls asleep suddenly there will be a large effect on respiration, possibly apnoea. This may have enhanced the synergy between the two drugs for resting ventilation relative to ventilation at a high fixed carbon dioxide. Furthermore, in contrast to studying the effect of drugs on ventilation at a fixed carbon dioxide (where the effect is tested in `open-loop' conditions), effects on resting ventilation are tested under `closed-loop' conditions. Changes in ventilation are caused by the tested drugs acting on the respiratory centres in the CNS and on the carotid bodies and then by the effect of the resulting changes in arterial and brain tissue PCO2 on breathing. This is a further reason for the observed differences in synergy.

The clinical relevance of both studies is that a fast-onset opioid should not be given rapidly with an anaesthetic. If given slowly, then sufficient carbon dioxide will be

retained so that respiration will continue. Sudden changes in wakefulness or sudden increases in blood concentration of either drug would cause irregular breathing or apnoea.

In summary, more clinical studies are needed on the interaction of anaesthetics and opioids on the behavioural and chemical control of breathing. The interactions described here are important clinically because they show synergistic effects on resting ventilation and carbon dioxide at relatively low drug concentrations (as would be used in monitored anaesthesia care). At these concentrations, the interaction of opioids and anaesthetics on suppression of somatic and autonomic responses is additive. The interaction between remifentanil and propofol for maintenance of i.v. anaesthesia (using abolition of cardiovascular, autonomic and somatic responses to laryngospcopy, intubation and intra-abdominal surgery) was additive when drug concentrations were in the clinical range, but synergistic when concentrations were greater (propofol > 8 mg ml-1).

Concluding remarks

Accurate and reliable measurement of the control of breathing (that is chemical control vs behavioural control) is not easy. However, since respiratory depression is a serious and sometimes life-threatening side-effect of anaesthetics and opioid use, further studies investigating their effects (and their interaction) on breathing should be encouraged. So far, a potent, effective anaesthetic or opioid without respiratory depression remains an illusion, so it is important to address the issue of prevention of respiratory depression. This would benefit all patients after general anaesthesia, but particularly those with poor ventilatory control (such as patients with sleep apnoea, the morbidly obese, women more than men, the aged, and patients with congenital hypoventilation syndrome). Finally, the effects of drugs on the complex interation between behavioural and chemical control of breathing has not been studied sufficiently despite the obvious relevance to clinical practice.

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