Control of breathing: effects of analgesic, anaesthetic and neuromuscular blocking drugs

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"Breathing is truly a strange phenomenon of life, caught midway between the conscious and unconscious, and peculiarly sensitive to both ..."

D.W. Richards (1953)

Throughout the history of anaesthesia, a major cause of morbidity and mortality has been failure of ventilation. In the past, this was usually attributed to anaesthetics causing excessive "central depression." In recent years, it has become evident that many anaesthetic agents are not simply non-specific central depressants of breathing but rather have discrete and sometimes potent actions on various mechanisms of breathing control. Knowledge of these specific actions can be helpful to the clinician in anticipating the particular circumstances of anaesthesia and the postanaesthetic period in which ventilation is most likely to be seriously impaired.

The purpose of this presentation is to provide an up-to-date review of the important effects of commonly used anaesthetic, analgesic and neuromuscular blocking drugs on resting ventilation and mechanisms of breathing control in humans. These effects will be considered with reference to a simple model.

Model of breathing control

The system which regulates breathing consists of three basic elements: inputs, controllers and effectors¹ (see Figure). There are two separate controllers: (1) a primary

FIGURE Schematic representation of ventilatory control system.

brain stem controller concerned with automatic (or involuntary) breathing and (2) a secondary cerebral controller which superimposes behavioural (or voluntary) influences on ventilation. The brain stem controller receives and integrates various inputs and then sends impulses through motor neurons to the effectors or ventilatory muscles. The cerebral controller directs the same effectors but its inputs are complex and poorly understood.

The inputs to the brain stem controller provide the drive for automatic breathing. Since this controller is fundamentally concerned with maintaining oxygenation and acid/base homeostasis, its principle inputs arise from chemoreceptors which sense variables of oxygen and acid/base balance. Two sets of chemoreceptors perform this function: one in the medulla sensitive to brain PCO_2 - $[\text{H}^+]$ activity; the other in the carotid bodies reactive to the PO_2 and PCO_2 - $[\text{H}^+]$ of arterial blood. The effective input of each appears at thresholds of PO_2 and/or PCO_2 - $[\text{H}^+]$ and then increases in relation to reductions of PO_2 and/or increments of PCO_2 - $[\text{H}^+]$. A second type of input to the automatic controller arises from the non-specific neural activity or "traffic" in the brain stem reticular formation. Although not as well characterized, this input likely mediates the effects of wakefulness and noxious stimulation on breathing.² The wakefulness-related input adds only slightly to normal resting chemoreceptor drive, but becomes critically important when the chemoreceptor input is severely impaired. If, for example, chemoreceptor drive is abolished – as with a low PCO_2 and high PO_2 – an input related to wakefulness can take over and maintain breathing at about two-thirds normal values.³ Other types of input originate with the mechanoreceptors of the lungs and chest wall and the baroreceptors of the cardiovascular system. These are not pertinent to this presentation.

The effectors of the system are the two groups of muscles that achieve ventilation: (1) the muscles of the

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upper airway (e.g., genioglossus and posterior cricoarytenoids) and (2) the muscles of the chest wall (diaphragm, intercostals and accessories). Each group displays two types of activity: (1) intermittent or phasic and (2) continuous or tonic.^{4,5} The phasic activity generates inspiration. That of the upper airway muscles enlarges the airway with each breath; that of the chest wall muscles acts to inflate the lungs. The tonic activity performs certain "postural" functions. That of the genioglossus helps to keep the airway open between breaths⁴ and that of the diaphragm helps maintain the end-expiratory lung volume (i.e., FRC) in the supine position.⁵

Sedatives/hypnotics/tranquillizers

This varied group of CNS depressants, which includes the barbiturates, phenothiazines and benzodiazepines, has no important effect on resting breathing if given in doses that produce only sedation or light sleep. However, these agents do impair certain mechanisms of breathing control and as a result may affect breathing in vulnerable patient groups. Sedative/hypnotics can reduce the ventilatory responses to chemoreceptor stimuli, i.e., added CO₂,⁶ and/or hypoxaemia.⁷ In patients who have chronic ventilatory failure (e.g., with COPD) and thus reduced responses to chemoreceptor stimuli related to disease, the added depressive effect of these drugs can be sufficient to worsen ventilatory failure and precipitate a respiratory crisis⁸ – especially in association with loss of wakefulness or sleep.⁹ Sedative/hypnotics also suppress the normal tone of the effector muscles of the upper airway.¹⁰ In patients with the obstructive sleep apnoea syndrome and an anatomical predisposition to upper airway obstruction, this relaxing effect is believed to be responsible for an increase in the number and severity of apnoeas during sleep.¹¹

Narcotic analgesics

All narcotic analgesics (morphine, meperidine, fentanyl, etc.) are potent ventilatory depressants. Equi-analgesic doses of individual agents have quantitatively similar effects. In the usual analgesic doses, they depress breathing primarily by reducing the breathing rate and increase PaCO₂ 3 or 4 mmHg. These effects increase with dose until, at the point of loss of consciousness or "sleep," periodic breathing or apnoea occurs. Those agents that possess both agonist and antagonist activity (e.g., nalbuphine) display a ceiling of ventilatory depression at moderate doses. However, this is of little therapeutic advantage since their analgesic effect is limited too.¹²

Narcotics also alter the mechanisms of breathing control. Accompanying the changes in resting breathing and PaCO₂ are dose-related reductions of the responses to

chemoreceptor stimuli, both added CO₂ and hypoxaemia.¹³ Thus, patients who have ventilatory failure and pre-existing impaired responses to these stimuli are also more sensitive to narcotic effect.⁸

As responses to chemoreceptor stimuli are obtunded by a narcotic, ventilation becomes more dependent upon the input of wakefulness. Thus, loss of wakefulness – as with natural nonREM sleep – appears to potentiate narcotic induced ventilatory depression.¹⁴ The magnitude of this effect is modest at an ordinary analgesic dose,¹⁴ but can be dramatic in the presence of a larger dose, in which case loss of wakefulness or sleep may precipitate severe hypopnoea or apnoea.¹⁵ Such sleep induced apnoea can be reversed by arousing the patient and prompting him to breathe, i.e., by making use of the wakefulness and/or behavioural control mechanisms.

Any drug or drug combination which abolishes wakefulness has the potential to greatly exaggerate narcotic depression of breathing. For example, a larger dose of narcotic by itself may reduce breathing only modestly. However, the addition of a small dose of sedative or tranquillizer which, with the narcotic, induces sleep can result in marked hypopnoea or apnoea.¹⁵ Thus when a narcotic and a tranquillizer are given together, as in neuroleptanalgesia, the dose of narcotic should be judicious and limited to that which is necessary to relieve pain (see below). Anaesthetizing doses of volatile anaesthetics also potentiate narcotic-induced ventilatory depression, such that even a relatively small dose of narcotic given during anaesthesia may cause severe hypoventilation or apnoea.

Noxious stimulation or pain increases the brain stem neural activity and effectively antagonizes the depression of ventilation associated with analgesic doses of narcotic. When using a narcotic to treat acute pain, one can virtually always administer it to the point of pain relief without concern for depressed breathing, regardless of the absolute dose required. This important point is too often forgotten in clinical practice.

Certain ventilatory effects of narcotic pertain to particular methods of administration. Rapid intravenous administration of a moderate to large dose can induce muscle spasm and rigidity of the chest wall to an extent that severely limits ventilation.¹⁶ N₂O potentiates this effect and neuromuscular blockade effectively abolishes it. Epidural or subarachnoid administration of a relatively small dose of water-soluble narcotic (e.g., morphine) occasionally causes profound ventilatory depression which is delayed and apparently due to slow transport of morphine in the spinal CSF to the brain stem.¹⁷ Old age, respiratory disease and/or concomitant parenteral narcotic predispose to this effect.¹⁷ Chronic pain and/or narcotic tolerance may be protective.

Inhalational and intravenous anaesthetics

The modern halogenated anaesthetics (halothane, isoflurane and enflurane) are also potent ventilatory depressants, but only when given in doses that produce loss of wakefulness and anaesthesia. At such doses, they reduce ventilation and tidal volume, increase breathing frequency and elevate PaCO_2 – all in proportion to anaesthetic depth. The magnitude of hypoventilation varies considerably amongst equipotent doses of individual agents. At 1.0 MAC, halothane increases the average PaCO_2 value to about 45 mmHg while isoflurane increases it to 50 mmHg and enflurane to over 65 mmHg (making enflurane in oxygen unacceptable for spontaneous breathing). Contrary to popular expectation, depression of ventilation does not increase with anaesthetic duration – but rather decreases, in a kind of “adaptation”.¹⁸ Surgical stimulation usually counteracts depression somewhat, reducing the PaCO_2 about 5 mmHg.¹⁹

Halogenated agents have several important actions on the mechanisms of breathing control.

First, they obtund responses to all chemoreceptor stimuli,^{19–21} independent of surgical stimulation.²² At anaesthetic doses, the slope of the response to added CO_2 is depressed in a dose-related fashion – more or less in parallel with the changes in resting ventilation and PaCO_2 .¹⁹ Thus, patients with pre-existing impaired CO_2 responsiveness, such as those with COPD, hypoventilate more during anaesthesia.²⁰ This insensitivity to added CO_2 during anaesthesia is the rationale for avoiding rebreathing in all spontaneously breathing patients since rebreathing increases the CO_2 level much more when the CO_2 response slope is reduced.

More severely affected are the reactions to hypoxaemia and to added $[\text{H}^+]$ or metabolic acidemia. Anaesthetic doses of halogenated agents completely abolish these responses such that ventilation is unaffected by either the oxygen tension or the acidity of the blood.²¹ Subanaesthetic doses markedly suppress them.²¹ Accordingly, those patients who depend upon the input of hypoxaemia or acidemia to sustain ventilation (e.g., the COPD patient who has lost his sensitivity to CO_2 or the patient with acute metabolic acidemia requiring hyperventilation to defend $[\text{H}^+]$) will breathe inadequately during and following anaesthesia. Further, if acute hypoxaemia or metabolic acidemia develop during or after anaesthesia, neither ventilatory compensation nor signs of respiratory distress appear.

Second, anaesthesia abolishes wakefulness and thereby renders ventilation completely dependent upon chemoreceptor input.^{3*} In the case of the halogenated anaesthetics, chemoreceptor input relates solely to CO_2 .²¹ Thus any factor during halogenated hydrocarbon anaesthesia which removes the CO_2 stimulus (passive hyperventila-

tion) or completely suppresses CO_2 responsiveness (e.g., sufficient narcotic) abolishes all ventilatory activity and results in apnoea. These factors are made use of in instituting “controlled apnoea” for controlled ventilation.

This dependence on CO_2 -related input can give rise to a particular hazard during early recovery from anaesthesia in which controlled ventilation has been employed and conditions for “controlled apnoea” continue to exist, i.e., (1) the PCO_2 level remains below its stimulating threshold and/or (2) CO_2 responsiveness remains markedly impaired. A drowsy but awake patient may breathe adequately in these circumstances (due to the input of wakefulness) but loss of wakefulness can precipitate severe hypopnoea or apnoea. Since wakefulness cannot be assured throughout the recovery period† and since early postanaesthetic levels of halogenated agent continue to render CO_2 the only reliable chemoreceptor stimulus,²¹ continuous breathing during recovery must be considered to be still completely dependent upon CO_2 . Accordingly, at the end of anaesthesia involving controlled ventilation, both a stimulating level of CO_2 and an adequate CO_2 response must be provided for the recovery period. The presence of wakefulness and ventilation during wakefulness does not guarantee adequate breathing throughout the recovery period.

Third, the halogenated agents cause a preferential depression of certain functions of the effector system. In anaesthetic doses, they markedly suppress the activity of upper airway muscles of the tongue, predisposing to airway obstruction. This action is potent and evident at even subanaesthetic doses.²³ They also preferentially depress intercostal muscle activity and the tonic activity of the diaphragm at end-expiration.^{24,25} The selective loss of intercostal activity reduces the thoracic or rib cage contribution to spontaneous ventilation.²⁴ The relaxation of the diaphragm at end-expiration, together with the loss of intercostal activity, is likely the principal factor responsible for the reduced end-expiratory volume (FRC) during anaesthesia (with either spontaneous or controlled ventilation).⁵ The reduced FRC undoubtedly underlies the microatelectasis, pulmonary shunting and impairment of oxygen uptake associated with anaesthesia.²⁵

The importance of these various effects on effector muscle activity depends at least in part upon the structural and mechanical characteristics of the ventilatory system.

*The addition of noxious stimulation during anaesthesia adds to chemoreceptor drive²² and may reduce the threshold of chemoreceptor input, but does not alter the basic dependence of ventilation upon this input.

†Knill RL, Moote CA, Skinner MI, Rose EA, Lim G. The early post anaesthetic state is primarily light NREM sleep (unpublished observations).

For example, compared to a patient with normal airway anatomy, an obese patient who has excessive fat about the upper airway is more susceptible to airway obstruction from loss of upper airway muscle activity. Similarly, an obese patient with added fat weighing upon the abdomen and chest wall suffers a greater reduction of FRC and a more severe impairment of oxygenation from loss of diaphragm tone.

The intravenous barbiturate anaesthetics (thiopentone methohexitone) have similar effects on breathing and the breathing control system except they do not cause a preferential loss of the response to hypoxaemia. Ketamine and nitrous oxide (N_2O) are unique in having no effect on resting breathing in typical clinical doses. Including these latter agents in an anaesthetic mixture – and thereby decreasing the dose of other agents – can substantially reduce overall ventilatory depression. Thus, while enflurane 1.0 MAC alone causes an unacceptable degree of ventilatory depression, a 1.0 MAC mixture of enflurane and N_2O 70 per cent permits adequate spontaneous breathing.²⁶

Neuromuscular blocking drugs

The ventilatory effects of the neuromuscular blocking agents (succinylcholine, tubocurarine, pancuronium, etc.) result solely from their actions on the neuromuscular junctions of effector muscles. Their effect on individual muscle groups varies considerably. Amongst the muscles of the chest wall, the expiratory abdominal muscles and intercostals are the most sensitive, the inspiratory intercostals somewhat less so and the diaphragm least of all.^{27,28} At typical clinical doses of pancuronium, expiratory force is abolished but the diaphragm is only slightly impaired.²⁹

The effector muscles which are the most readily compromised by the neuromuscular blocking agents are those of the upper airway. With increasing doses of tubocurarine, the earliest clinically detectable ventilatory effect is obstruction of the upper airway.³⁰ Upper airway resistance increases³¹ and inspiratory flow decreases²⁸ before there are important reductions of vital capacity or chest wall muscle strength. This is sometimes due to an inability to clear (i.e., swallow) secretions but more often due to soft tissue collapse – no doubt the result of weakened muscles of the pharynx, tongue and/or jaw. Thus, in managing neuromuscular blockade and its recovery, one must be attentive not only to the ventilatory muscles of the chest wall but in particular to those which maintain the airway.

Conclusion

Analgesic, anaesthetic and neuromuscular blocking drugs interfere with the ventilatory system in several discrete

and specific ways. Awareness of their various actions improves clinical rationale for the safe management of ventilation in the peri-anaesthetic period.

References

- 1 Berger AJ, Mitchell RA, Severinghaus JW. Regulation of respiration. *N Engl J Med* 1977; 297: 92–7, 138–43, 194–200.
- 2 Orem JM. Central neural interactions between sleep and breathing. In: Saunders NA, Sullivan CE (Eds). *Sleep and Breathing*. New York: Marcel Dekker, 1984; 91–135.
- 3 Fink BR, Hanks EC, Ngai SH, Papper EM. Central regulation of respiration during anesthesia and wakefulness. *Ann NY Acad Sci* 1963; 109: 892–9.
- 4 Harper RM, Sauerland EK. The role of the tongue in sleep apnea. In: Guilleminault C, Dement WC (Eds). *Sleep Apnea Syndromes*. New York: Alan R. Liss, 1978; 219–34.
- 5 Muller N, Volgyesi G, Becker L, Bryan MH, Bryan AC. Diaphragmatic muscle tone. *J Appl Physiol* 1979; 47: 279–84.
- 6 Catchlove RFH, Kafer ER. The effects of diazepam on the ventilatory response to carbon dioxide and on steady-state gas exchange. *Anesthesiology* 1971; 34: 9–13.
- 7 Hirshman CA, McCullough RE, Cohen PJ, Weil JV. Effect of pentobarbital on hypoxic ventilatory drive in man: preliminary study. *Br J Anaesth* 1975; 47: 963–8.
- 8 Wilson RH, Hoseth W, Dempsey ME. Respiratory Acidosis. *Am J Med* 1954; 17: 464–70.
- 9 Gold MI, Reichenberg S, Freeman E. Respiratory depression in the sedated bronchitic patient: rapid version of the CO_2 response curve. *Anesthesiology* 1969; 30: 492–9.
- 10 Bonora M, St. John WM, Bledsoe TA. Differential elevation by protriptyline and depression by diazepam of upper airway respiratory motor activity. *Am Rev Respir Dis* 1985; 131: 41–5.
- 11 Dolly FR, Block AJ. Effect of flurazepam on sleep-disordered breathing and nocturnal oxygen desaturation in asymptomatic subjects. *Am J Med* 1982; 73: 239–43.
- 12 Gal TJ, DiFazio CA, Moscicki J. Analgesic and respiratory depressant activity of nalbuphine: a comparison with morphine. *Anesthesiology* 1982; 57: 367–74.
- 13 Weil JV, McCullough RE, Kline JS, Soda IE. Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. *N Engl J Med* 1975; 292: 1103–6.
- 14 Knill RL, Moote CA, Skinner MI, Rose EA, Lok PYK. Morphine-induced ventilatory depression is potentiated by non-REM sleep. *Can J Anaesth* 1987; 34: S101–2.
- 15 Severinghaus JW. Ventilation and anesthesia – dangerous interactions. In: Mushin WW, Severinghaus JW, Tiengo M, Gorini S (Eds). *Physiological Basis of Anaesthesiology*. Padua: Piccin Medical Books, 1975; 201–19.
- 16 Comstock MK, Carter JG, Moyers JR, Stevens WC.

- Rigidity and hypercarbia associated with high dose fentanyl induction of anesthesia. *Anesth Analg* 1981; 60: 362-3.
- 17 Gustafsson LL, Schildt B, Jacobsen K. Adverse effects of extradural and intrathecal opiates: report of a nationwide survey in Sweden. *Br J Anaesth* 1982; 54: 479-86.
 - 18 Fourcade HE, Larson CP Jr, Hickey RF, Bahlman SH, Eger EI II. Effects of time on ventilation during halothane and cyclopropane anesthesia. *Anesthesiology* 1972; 36: 83-8.
 - 19 Munson ES, Larson CP Jr, Babad AA, Regan MJ, Buechel DR, Eger EI II. The effects of halothane, fluroxene and cyclopropane on ventilation: a comparative study in man. *Anesthesiology* 1966; 27: 716-28.
 - 20 Pietak S, Weenig CS, Hickey RF, Fairley HB. Anesthetic effects on ventilation in patients with chronic obstructive pulmonary disease. *Anesthesiology* 1975; 42: 160-6.
 - 21 Knill RL, Clement JL. Ventilatory responses to acute metabolic acidemia in humans awake, sedated, and anesthetized with halothane. *Anesthesiology* 1985; 62: 745-53.
 - 22 Lam AM, Clement JL, Knill RL. Surgical stimulation does not enhance ventilatory chemoreflexes during enflurane anaesthesia in man. *Can Anaesth Soc J* 1980; 27: 22-8.
 - 23 Hwang JC, St John WM, Bartlett D Jr. Respiratory-related hypoglossal nerve activity: influence of anesthetics. *J Appl Physiol* 1983; 55: 785-92.
 - 24 Tusiewicz K, Bryan AC, Froese AB. Contributions of changing rib cage-diaphragm interactions to the ventilatory depression of halothane anesthesia. *Anesthesiology* 1977; 47: 327-37.
 - 25 Hedenstierna G, Tokics L, Strandberg A, Lundquist H, Brismar B. Correlation of gas exchange impairment to development of atelectasis during anaesthesia and muscle paralysis. *Acta Anaesthesiol Scand* 1986; 30: 183-91.
 - 26 Lam AM, Clement JL, Chung DC, Knill RL. Respiratory effects of nitrous oxide during enflurane anesthesia in humans. *Anesthesiology* 1982; 56: 298-303.
 - 27 De Troyer A, Bastenier J, Delhez L. Function of respiratory muscles during partial curarization in humans. *J Appl Physiol* 1980; 49: 1049-56.
 - 28 Gal TJ, Arora NS. Respiratory mechanics in supine subjects during progressive partial curarization. *J Appl Physiol* 1982; 52: 57-63.
 - 29 Donati F, Antzaka C, Bevan DR. Potency of pancuronium at the diaphragm and the adductor pollicis muscle in humans. *Anesthesiology* 1986; 65: 1-5.
 - 30 Cash PT, Hoekstra CS. Preliminary curarization in electric convulsive shock therapy. *Psychiatric Quarterly* 1943; 17: 20-34.
 - 31 Dodgson BG, Knill RL, Clement JL. Curare increases upper airway resistance while reducing ventilatory muscle strength. *Can Anaesth Soc J* 1981; 28: 505-6.