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Effects of pain and arousal on the control of breathing

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Introduction

> *Breathing is the only coordinated skeletal muscle act that continuously fulfills and seamlessly integrates continuous metabolic and intermittent behavioral functions without normally disrupting the efficiency of either in the process*
>
> *F. Plum [1].*

The control of breathing is a complex physiological process that results from the integration of multiple dynamic inputs. The perioperative period represents a particularly dynamic situation, requiring adjustment of the level of ventilation on a moment-to-moment basis as the result of multiple conflicting requirements. The autonomic or metabolic controller adjusts ventilation depending on the level of arterial pH, Pa_{o_2}, and Pa_{co_2}, and has been extensively studied and reviewed [2–4]. The stimulation of the central chemoreceptors in the medulla with carbon dioxide or the stimulation of the peripheral chemoreceptors in the carotid bodies with hypoxemia (or also with hypercapnia or acidemia) results in a relatively prompt increase in ventilation (over seconds to minutes). Ventilation increases linearly with hypercapnia and desaturation.

However, the relative magnitude of the contribution of these chemoreflexes in determining ventilation is uncertain under many circumstances, and it would appear that only under (deep) anesthesia or nonrapid eye movement (NREM) sleep [5] are the chemoreflexes the sole determinants of ventilation. However, even with most levels of anesthesia (e.g., supra minimum alveolar concentration [MAC] concentrations of inhalational anesthetics), painful surgical stimuli that do not elicit a purposeful movement will elicit a change in ventilation. The role of chemoreflexes in determining resting ventilation in awake subjects is subject to some controversy [6,7] and it may be that a "wakefulness drive", as proposed by Fink [8], plays a major part, possibly accounting for the often irregular breathing that is observed at rest.

There are many other factors arising from peripheral (nociceptors, lung receptors, muscle stretch receptors, etc.) or central (cortical, limbic, hypothalamic, etc.) structures that normally affect ventilation and, under certain circumstances, can completely override the autonomic controller (e.g., speech, vomiting, voluntary breath holding, yawning, sighing, etc.), at least for some period of time. The autonomic system does ultimately prevail, as seen by the involuntary termination of voluntary breath holding. Figure 1 illustrates some of the complex interconnections between the metabolic and nonmetabolic ventilatory control pathways. This brief review will focus on the ventilatory effects of pain and arousal, two stimuli that are important during the perioperative period, and how the effects of these stimuli are modified by pharmacological agents used in anesthesiology.

Traditional ventilatory control—the chemoreflex loops

The hypercapnic and hypoxic responses mediated by central and peripheral chemoreflexes [2,3] have been extensively studied, but their relative contribution to the control of normal resting ventilation is still controversial [6,7,9]. They at least function as reflexes to ensure that oxygen and carbon dioxide levels in the blood do not get too far out of the normal range without an increase in ventilation. Traditionally, it has been assumed that arterial carbon dioxide plays the major role

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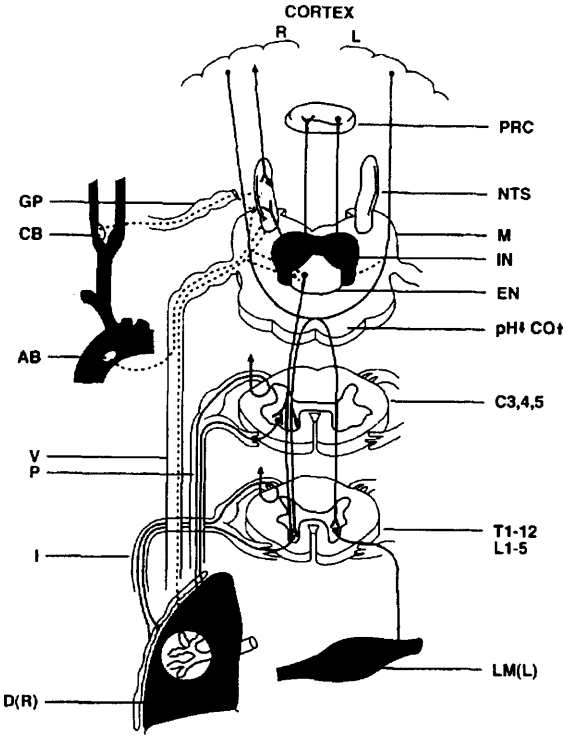

Fig. 1. Neuroanatomic connections involved with ventilatory control. The respiratory centers in the brain stem, including the inspiratory (*IN*) and expiratory (*EN*) neurons in the medulla (*M*), the nucleus tractus solitarius (*NTS*), and the pontine respiratory complex (*PRC*), all receive input from the peripheral chemoreceptors, primarily the carotid bodies (*CB*) via the glossopharyngeal nerve (*GP*), but there is also some input from the aortic bodies (*AB*) via the vagus (*V*) nerve. Ascending connections from the NTS to the cortex are illustrated *on the right*. There are also chemoreceptors near the surface of the medulla (separate from the respiratory centers) that are sensitive to a decrease in pH and an increase in CO_2. The phrenic nerve (*P*) innervates the diaphragm (*D*) from cervical levels *C3*, *4*, and *5*, and the intercostal (*I*) nerve from the thoracic spinal segments innervates the intercostal muscles. Two cortical spinal tracts are shown. *On the right*, the descending tract crosses the pyramidal dessication to reach the motor neurons in the anterior horn, innervating, for example, leg muscles (*LM*). *On the left*, the descending cortical spinal tract connects to the medullary centers (*dotted lines*), as well as to the phrenic and intercostal motoneurons (from Guz [59], with permission)

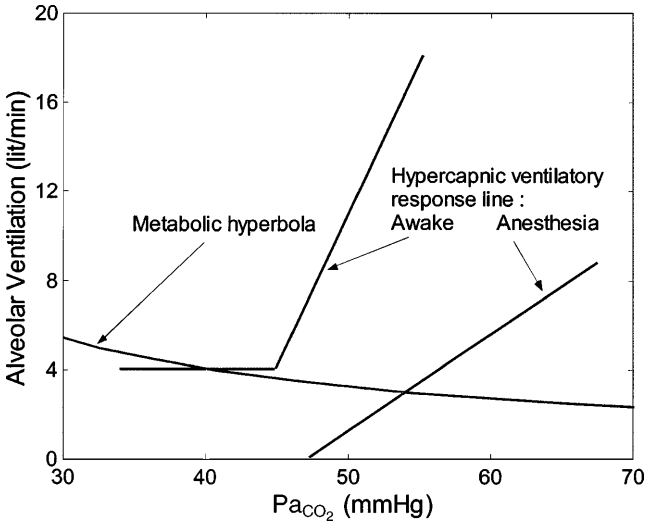

Fig. 2. During anesthesia, ventilation is determined by the intersection of the metabolic hyperbola and the hypercapnic ventilatory response line. Note that, in the range of Pa_{co_2} shown, the metabolic hyperbola is quite "flat" and a relatively small change in alveolar ventilation will cause a large increase in Pa_{co_2}. The hypercapnic response is quite shallow and the resulting CO_2 level is only 5–6 mmHg above the apneic threshold. When awake, resting ventilation is determined more by the wakefulness drive than by the intersection of the hypercapnic response and the metabolic hyperbola. This is shown by the flat "dogleg" in the awake response (see text for further discussion)

in determining resting ventilation. Because the ventilatory sensitivity to oxygen does not start until the Pa_{o_2} falls below approximately 80 mmHg [10], changes in resting ventilation will have little effect on the hypoxic stimulus. However, the response to hypercapnia is linear, and in anesthetized animals there is a so-called apneic threshold where the CO_2 stimulus is sufficient to initiate and sustain ventilation. This threshold can also be observed by direct measurement of the firing rate in the carotid sinus nerve, although the threshold may be considerably less than the ventilatory threshold. Because there is also an inverse relationship between alveolar ventilation and Pa_{co_2} (the metabolic hyperbola), the intersection of these two relationships has been thought to determine the resting ventilation and Pa_{co_2} in the steady state (Fig. 2). There is also a very strong interaction between hypoxia and hypercapnia (asphyxia response). Hypoxia increases the slope (gain) of the ventilation response to CO_2. Conversely, hypercapnia increases the sensitivity to hypoxia (increases the slope of the ventilation–desaturation relationship). This interaction takes place in the carotid bodies. In addition, if hypoxia lasts more than 5 min, there is a progressive decline in ventilation. This decline requires stimulation of the carotid bodies [11] and is only part of the very complex ventilatory response to hypoxia [12].

Sleep eliminates many of the effects of behavioral control, and the CO_2 chemoreflex then determines ventilation. The exception is rapid eye movement (REM) sleep, when a behavioral-type control seems to dominate [13]. While there is a slight decrease in ventilation during slow-wave sleep (SWS) and a resulting slight rise in CO_2, this is probably due to the removal of the wakefulness drive and the dependence on the chemoreflexes to determine the unstimulated ventilation. However, this does not mean that in the awake state the wakefulness drive and the chemoreflexes are simply additive.

The effects of sleep on the hypoxic and hypercapnic chemoreflexes are less certain, but there seems to be a reduction in the hypoxic response [14–16]. Conceptually, this is an important observation, as it indicates there are possible state-modulated changes in the chemoreflex gain and not just additive changes in the ventilatory level. This change in gain may result in an alteration of ventilatory pattern or rhythm in patients with sleep apnea or in patients in the postoperative period [17,18].

Arousal, behavioral, and voluntary effects

Although it is obvious that there are considerable behavioral, involuntary (coughing, sneezing, yawning, sighing, changes in emotional state, etc.), and voluntary (breath-holding, talking, singing, etc.) inputs to respiration, the amount of stimulation to breathing when there are no overt behavioral effects (quiet resting ventilation) has been difficult to quantify. Indeed, the common observation that when one person in a group yawns, often other members of the group will yawn would seem to indicate that the involuntary responses can be triggered by external behavioral stimuli. Fink [8] showed that voluntary or mechanical hyperventilation in awake subjects to CO_2 levels below the apneic threshold (Fig. 2) did not cause apnea or even hypoventilation. He then concluded that there was a substantial "wakefulness" drive to breathe and that this accounted for the "dog-leg" or "hockey-stick" seen in the awake CO_2 response. Because these experiments with induced hypocapnia are, by necessity, not steady-state, interpretation of the amount of the wakefulness drive and its interaction with the chemoreflex drives is difficult. When the respiratory centers are stimulated by the carotid bodies in animals [19] or by cortical command in humans [20], there is short-term potentiation of ventilation that tends to maintain ventilation at previous levels even when isocapnia is maintained during the transition [21]. Other studies using rebreathing techniques have found that there are contributions from both the CO_2 chemoreflex and a wakefulness drive to resting ventilation [6]. However, it is clear that different stimuli at rest can not only alter the variability of the ventilatory pattern (frequency and tidal volume) but also the total ventilation [13,22,23]. In careful experiments in nonanxious subjects, Shea et al. [22] found that visual and auditory input resulted in significant increases in ventilation with frequency being stimulated the most when the input had "meaning" (i.e., when subjects were listening to a story). The specific type of cortical activity may also be important, as Mador and Tobin [23] found that mental arithmetic did not increase the breath-to-breath tidal volume variability, but audiovisual stimulation did.

It is clear that behavioral drives can have substantial influence on ventilation and the pattern of breathing, but it is not as clear which neurological pathways are involved (Fig. 1) and whether there is direct cortical modulation of the brainstem respiratory centers. Anatomical and functional pathways apparently exist, linking cortical and limbic systems to the brainstem respiratory centers, as well as to spinal motoneurons [24–26], although not all studies have been able to demonstrate a direct functional connection to respiratory centers [27].

Two pathological conditions have provided more insight into the anatomical and functional connections between the metabolic and the behavioral control systems. Breathing during conditions that eliminate behavioral control ("locked-in syndrome") [1,28] or metabolic control (Ondine's curse or congenital hypoventilation syndrome) [29–31] provides interesting information about the interaction between these two systems. In Ondine's curse syndrome (which has been best studied in its congenital form), there is a greatly diminished or absent chemoreflex that is manifest as hypoventilation or even ventilatory failure when the patient is drowsy or asleep, while awake resting ventilation is adequate but shows increased variability. With the locked-in syndrome, a lesion (e.g., stroke) in the ventral pons and lower midbrain interrupts the motor tracts and, except for the eye muscles, the patient has lost all voluntary movement. Breathing shows less variability than normal.

Because the congenital hypoventilation syndrome seems to be a heterogeneous set of disorders without a specific genetic or anatomical defect, it has been difficult to relate studies in these patients to normal respiratory control [32]. However, many of these patients are able to breathe adequately while awake, although their ventilation is much more irregular than normal, but they become profoundly hypercapnic when asleep. Evidently this drive during wakefulness does not require actual "conscious" command of each breath, but the awake "state" is sufficient to generate a respiratory rhythm.

In the locked-in syndrome, a lesion in the ventral pons prevents volitional motor behavior, including respiration [33]. These patients have a spontaneous regular breathing pattern (like that during NREM sleep) and an intact hypercapnic response, and an easily demonstrable apneic threshold with passive mechanical hyperventilation [33]. While no volitional ventilatory increase can be made, changes in emotional state do affect the ventilatory pattern, indicating intact connections from the limbic system to the respiratory centers [28]. In normal subjects, Masaoka and Homma [34] found that anxiety increased respiratory frequency (with no increase in heart rate) and that respiratory-related neural activity existed in limbic and paralimbic areas [35]. In-

terestingly, Spicuzza et al. [36] found that yoga practitioners had a lower hypoxic ventilatory response independent of their breathing frequency.

Effects of pain

Common clinical observation shows that pain has pronounced effects on ventilation, and pain is used frequently to stimulate breathing in patients with relative overdoses of substances which depress respiration. The pain pathways from peripheral receptors to the central nervous system (CNS) are quite complex [37], with connections that either bypass the respiratory centers (e.g., the spinothalamic track) or have major connections in the pons (e.g., the spinomesencephalic tract). Thus, there are many ways in which pain might stimulate ventilation without needing intact cortical structures [38], implying that the effects of pain are not obtained solely through "arousal" of higher centers. Waldrop et al. [38] found that heating the skin of either anesthetized or decerebrate cats to 51°C caused an approximately 50% increase in phrenic nerve activity, but that a 41°C stimulus did not, indicating the activation of nociceptive afferents.

While pain clearly increases ventilation, it seems to do so by resetting resting ventilation, without affecting the chemoreflexes [39–41]. Duranti et al. [39] utilized both cutaneous electrical stimulation and ischemic pain via an arm tourniquet and found that tidal volume and breathing frequency were both increased, with a resulting increase in ventilation and decrease in partial pressure end-tidal CO_2 ($P_{ET_{CO_2}}$). With the most severe ischemic pain, $P_{ET_{CO_2}}$ was reduced from 42.3 ± 1.2 to 33.1 ± 3.0 mmHg. They did not investigate whether these stimuli changed the hypoxic or hypercapnic sensitivities.

Borgbjerg et al. [42] also used a forearm tourniquet pain test that achieved a visual analogue scale (VAS) pain score of approximately 4 (although they observed a decrease in the VAS score during the 3 min of tourniquet inflation, so the initial score may represent more of an anxiety effect rather than just pain) and found no effect on the slope of the CO_2 response measured by a rebreathing technique. However, they did not report the resting ventilation or $P_{ET_{CO_2}}$, so it is difficult to determine the magnitude of painful stimulation. In a carefully designed study, using transcutaneous electrical pain, Sarton et al. [40] assessed the effects of pain on chemoreflexes. Their painful stimulus was rated at approximately 5 by the subjects, on a 0–10 numeric scale. This resulted in a mild stimulation of resting ventilation, with the $P_{ET_{CO_2}}$ only decreasing to 36.0 ± 2.3 mmHg from a control value of 38.3 ± 2.5 mmHg. They then investigated the effects of this stimulus on the hypercapnic and initial hypoxic responses, and on the response after 15 min of hypoxia. As there was no significant change in any of the chemoreflex sensitivities, they concluded that pain caused an increase in "a chemoreflex-independent tonic ventilatory drive" [40]. It is not certain if a more painful stimulus would have had any effect on the chemoreflexes.

Rather than applying pain, Bourke [43] used regional anesthesia to relieve pain from severe trauma to an upper extremity and found that relief of pain decreased ventilation and the slope of the hypercapnic response. These patients had moderate to severe pain, with VAS pain scores of 7.1 ± 1.1, but did not have a significant resting hypocapnia ($P_{ET_{CO_2}}$ prior to the block was 39.6 ± 0.08). Although the lidocaine and epinephrine that the patients received for the block could have had respiratory effects, these effects were not felt to be significant. Because there were no preinjury measurements of the response slope, it could not be determined if the preblock slope was greater than normal (i.e., stimulated by pain).

Drug effects on the interactions between behavioral and metabolic control

Drugs used in anesthesia are designed to prevent pain and arousal (although the potency of inhalational anesthetics is commonly measured by MAC, which directly measures neither perception of pain nor arousal). The relative potencies of the drugs between their analgesic/hypnotic effects and their effects on ventilation are quite variable. Opioids can result in an apnic, conscious patient (chemoreflex, autonomic breathing may be completely absent), who, when asked, may be able to voluntarily breathe. Conversely, patients under inhalational anesthesia may be unconscious, but will breathe adequately and increase their breathing with a painful stimulus. The effects of drugs on the autonomic or metabolic control of breathing have recently been reviewed [44,45].

Even under relatively deep anesthesia, i.e., 1 MAC of inhalational anesthetics, a painful stimulus will elicit a ventilatory response even when there is no cardiovascular or somatic response [46,47], but this stimulus does not appear to increase the sensitivity of the chemoreflexes [48]. Under stable enflurane anesthesia, surgical stimulation causes a progressive increase in tidal volume over at least ten breaths, but only the first breath after the stimulation shows any alteration in timing (interestingly an increase, not a decrease, in inspiratory time [T_I] and expiratory time [T_E], which would seem to be more related to a transient reflex "breath-hold" with stimulation) [49]. This contrasts with painful stimulation in awake subjects, in whom electrical stimulation caused a decrease in T_I and T_E with little change in tidal volume

(V_T) [39]. However, in the awake study, obviously a much less painful stimulation was used, and the averaging of multiple breaths may have prevented the observation of a transient decrease in ventilatory frequency.

Hyperventilation readily causes apnea in the anesthetized patient, in contrast with the maintenance of ventilation in the awake subject [50]. Even sedation with nitrous oxide (75% inspired, although the administration of the nitrous oxide was not in steady-state and the brain concentration may have been less) resulted in loss of the wakefulness drive and apnea upon termination of voluntary hyperventilation [51]. The apneic intercept (see Fig. 2) is also shifted to the right by sevoflurane and to the left by surgical stimulation [52].

The effects of low doses of inhalational anesthetics are the most interesting. Halothane at 0.1 MAC levels markedly depresses the acute hypoxic response (AHR) [48], but other inhalational anesthetics may have less depression [53–55]. However, audiovisual stimulation seems to affect the hypoxic response. In a study specifically designed to investigate the effects of audiovisual stimulation on the depression of the hypoxic ventilatory response, van den Elsen et al. [56] found no difference in hypoxic response when the subjects watched a music video compared with when they kept their eyes closed. However, during sedation with 0.1 MAC, the audiovisual stimulation increased the hypoxic chemosensitivity from 0.27 ± 0.06 to $0.47 \pm 0.13\,l \cdot min^{-1} \cdot \%\,sat^{-1}$. This latter sensitivity was not different from the control experiments either with or without audiovisual stimulation. Similarly, Foo et al. [57] found that sleep depressed the acute hypoxic response in subjects breathing 0.1 MAC isoflurane compared with when they were awake and listening to music. However, that study did not have control responses without isoflurane with which to compare the findings. There is also a pronounced interaction between opioids and sleep, with a markedly increased depression of the hypercapnic chemoreflex during sleep [58]. The mechanism whereby audiovisual stimulation reverses a specific drug effect on the hypoxic response (without any effect on the hypoxic response without the drug) remains obscure.

The interaction of pain with drug effects on chemoreflexes is apparently different from the effects of audiovisual stimulation. In the study by Borgbjerg et al. [42], morphine did not affect the slope of the hypercapnic response, either with or without experiment pain. Sarton et al. [54] found a similar result with low-dose (0.23%) sevoflurane. Again using pain from electrical stimulation (VAS pain score of 4.5–5.5), they found no reversal of the depression of hypoxic chemosensitivity ($0.48 \pm 0.15\,l \cdot min^{-1} \cdot \%\,sat^{-1}$ sevoflurane and no pain and $0.46 \pm 0.12\,l \cdot min^{-1} \cdot \%\,sat^{-1}$ sevoflurane during pain). Sevoflurane did depress hypoxic sensitivity by 30%, and without sevoflurane, pain did not affect this sensitivity.

Summary

Ventilatory drive can become unstable in the immediate postoperative period when the patient is affected by many drugs, may fall asleep, and has varying levels of pain. The control of ventilation can only be understood in the context of these multiple inputs, both nonchemical and chemoreflex-related, that are integrated together to produce the breath-by-breath ventilatory drive. While the chemoreflexes are the most completely studied, it is clear that, during the perioperative period, many other influences may play a dominant role. Pain seems to affect ventilation by an additive stimulation, and it does not alter the chemoreflex response depressed by either opioids or inhalational anesthetics, although the available studies are not complete. In contrast, arousal, while not affecting the hypoxic response in unsedated patients, may reverse the depression of the hypoxic response caused by inhalational anesthetics.

References

1. Plum F (1992) Breathing is controlled independently by voluntary, emotional, and metabolically related pathways. Arch Neurol 49:441–441
2. Cunningham DJC, Robbins PA, Wolff CB (1986) Integration of respiratory responses to changes in alveolar partial pressures of CO_2 and O_2 and in arterial pH. In: Fishman AP, Cherniack NS, Widdicombe JG, Geiger SR (eds) Handbook of Physiology. The Respiratory System, Vol II. American Physiological Society, Bethesda, pp 475–528
3. Honda Y, Tani H (1999) Chemical control of breathing. In: Altose MD, Kawakami Y (eds) Control of Breathing in Health and Disease. Marcel Dekker, New York, pp 41–87
4. Caruana-Montaldo B, Gleeson K, Zwillich CW (2000) The control of breathing in clinical practice. Chest 117:205–225
5. Phillipson EA, Bowes G (1986) Control of breathing during sleep. In: Cherniack NS, Widdicombe JG (eds) The Respiratory System: Control of Breathing. American Physiology Society, Bethesda, pp 649–690
6. Mahamed S, Ali AF, Ho D, Wang B, Duffin J (2001) The contribution of chemoreflex drives to resting breathing in man. Exp Physiol 86:109–116
7. Corfield DR, Roberts CA, Guz A, Murphy K, Adams L (1999) Modulation of the corticospinal control of ventilation by changes in reflex respiratory drive. J Appl Physiol 87:1923–1930
8. Fink BR (1961) Influence of cerebral activity in wakefulness on regulation of breathing. J Appl Physiol 16:15–20
9. Corfield DR, Morrell MJ, Guz A (1995) The nature of breathing during hypocapnia in awake man. Respir Physiol 101:145–159
10. Akiyama Y, Kawakami Y (1999) Clinical assessment of the respiratory control system. In: Altose MD, Kawakami Y (eds) Control of Breathing in Health and Disease. Marcel Dekker, New York, pp 251–287
11. Dahan A, Ward DS, van den Elsen M, Temp J, Berkenbosch A (1996) Influence of reduced carotid body drive during sustained hypoxia on hypoxic depression of ventilation in humans. J Appl Physiol 81:565–572
12. Powell FL, Milsom WK, Mitchell GS (1998) Time domains of the hypoxic ventilatory response. Respir Physiol 112:123–134
13. Shea SA (1996) Behavioural and arousal-related influences on breathing in humans. Exp Physiol 81:1–26

14. Douglas NJ, White DP, Weil JV, Pickett CK, Martin RJ, Hudgel DW, Zwillich CW (1982) Hypoxic ventilatory response decreases during sleep in normal men. Am Rev Respir Dis 125:286–289
15. Berthon-Jones M, Sullivan CE (1982) Ventilatory and arousal responses to hypoxia in sleeping humans. Am Rev Respir Dis 125:632–639
16. Corfield DR, Roberts CA, Griffiths MJ, Adams L (1999) Sleep-related changes in the human "neuromuscular" ventilatory response to hypoxia. Respir Physiol 117:109–120
17. Rosenberg J, Rasmussen GI, Wojdemann KR, Kirkeby LT, Jorgensen LN, Kehlet H (1999) Ventilatory pattern and associated episodic hypoxaemia in the late postoperative period in the general surgical ward. Anaesthesia 54:323–328
18. Rosenberg J, Wildschiodtz G, Pedersen MH, von Jessen F, Kehlet H (1994) Late postoperative nocturnal episodic hypoxaemia and associated sleep pattern. Br J Anaesth 72:145–150
19. Eldridge FL, Gill-Kumar P (1980) Central neural respiratory drive and afterdischarge. Respir Physiol 40:49–63
20. Swanson GD, Ward DS, Bellville JW (1976) Posthyperventilation isocapnic hyperpnea. J Appl Physiol 40:592–596
21. Folgering H, Durlinger M (1983) Time course of posthyperventilation breathing in humans depends on alveolar CO_2 tension. J Appl Physiol 54:809–813
22. Shea SA, Walter J, Pelley C, Murphy K, Guz A (1987) The effect of visual and auditory stimuli upon resting ventilation in man. Respir Physiol 68:345–357
23. Mador MJ, Tobin MJ (1991) Effect of alterations in mental activity on the breathing pattern in healthy subjects. Am Rev Respir Dis 144:481–487
24. Orem J, Trotte RH (1994) Behavioral control of breathing. News Physiol Sci 9:228–232
25. Davenport PW, Reep RL (1995) Cerebral cortex and respiration. In: Dempsey JA, Pack AI (eds) Regulation of Breathing. Marcel Dekker, New York, pp 365–388
26. Horn EM, Waldrop TG (1998) Suprapontine control of respiration. Respir Physiol 114:201–211
27. Corfield DR, Murphy K, Guz A (1998) Does the motor cortical control of the diaphragm "bypass" the brain stem respiratory centres in man? Respir Physiol 114:109–117
28. Munschauer FE, Mador MJ, Ahuja A, Jacobs L (1991) Selective paralysis of voluntary but not limbically influenced automatic respiration. Arch Neurol 48:1190–1192
29. Severinghaus JW (1962) Ondine's curse—failure of respiratory center automaticity while awake. Clin Res 10:122
30. Gozal D (1998) Congenital central hypoventilation syndrome: an update. Pediatr Pulmonol 26:273–282
31. Shea SA (1997) Life without ventilatory chemosensitivity. Respir Physiol 110:199–210
32. Gozal D, Harper RM (1999) Novel insights into congenital hypoventilation syndrome. Curr Opin Pulm Med 5:335–338
33. Heywood P, Murphy K, Corfield DR, Morrell MJ, Howard RS, Guz A (1996) Control of breathing in man; insights from the "locked-in" syndrome. Respir Physiol 106:13–20
34. Masaoka Y, Homma I (2001) The effect of anticipatory anxiety on breathing and metabolism in humans. Respir Physiol 128:171–177
35. Masaoka Y, Homma I (2000) The source generator of respiratory-related anxiety potential in the human brain. Neuroscience Lett 283:21–24
36. Spicuzza L, Gabutti A, Porta C, Montano N, Bernardi L (2000) Yoga and chemoreflex response to hypoxia and hypercapnia. Lancet 356:1495–1496
37. Millan MJ (1999) The induction of pain: an integrative review. Prog Neurobiol 57:1–164
38. Waldrop TG, Millhorn DE, Eldridge FL, Klingler LE (1984) Respiratory responses to noxious and non-noxious heating of skin in cats. J Appl Physiol 57:1738–1741
39. Duranti R, Pantaleo T, Bellini F, Bongianni F, Scano G (1991) Respiratory responses induced by the activation of somatic nociceptive afferents in humans. J Appl Physiol 71:2440–2448
40. Sarton E, Dahan A, Teppema L, Berkenbosch A, van den Elsen M, van Kleef J (1997) Influence of acute pain induced by activation of cutaneous nociceptors on ventilatory control. Anesthesiology 87:289–296
41. Becerra LR, Breiter HC, Stojanovic M, Fishman S, Edwards A, Comite AR, Gonzalez RG, Borsook D (1999) Human brain activation under controlled thermal stimulation and habituation to noxious heat: an fMRI study. Magn Reson Med 41:1044–1057
42. Borgbjerg FM, Nielsen K, Franks J (1996) Experimental pain stimulates respiration and attenuates morphine-induced respiratory depression: a controlled study in human volunteers. Pain 64:123–128
43. Bourke DL (1993) Respiratory effects of regional anesthesia during acute pain. Reg Anesth 18:361–365
44. Ward DS, Temp JA (1997) Neuropharmacology of the control of ventilation. In: Biebuyck J, Lynch C, Maze M, Saidman LJ, Yaksh TL, Zapol W (eds) Anesthesia: Biologic Foundations. Lippincott-Raven, Philadelphia, pp 1367–1394
45. Ward DS (1998) Inhalational anesthetics and control of breathing during hypoxia. Anesth Clin North Am 16:77–88
46. Rosenberg M, Tobias R, Bourke D, Kamat V (1980) Respiratory responses to surgical stimulation during enflurane anesthesia. Anesthesiology 52:163–165
47. Eger EI, Dolan WM, Stevens WC, Miller RD, Way WL (1972) Surgical stimulation antagonizes the respiratory depression produced by Forane. Anesthesiology 36:544–549
48. Knill RL, Gelb AW (1978) Ventilatory responses to hypoxia and hypercapnia during halothane sedation and anesthesia in man. Anesthesiology 49:244–251
49. Sutherland RW, Drummond GB (1996) Effects of surgical skin incision on respiration in patients anaesthetized with enflurane. Br J Anaesth 76:777–779
50. Hickey RF, Fourcade HE, Eger EI, Larson CP Jr, Bahlman SH, Stevens WC, Gregory GA, Smith NT (1971) The effects of ether, halothane, and Forane on apneic thresholds in man. Anesthesiology 35:32–37
51. Northwood D, Sapsford DJ, Jones JG, Griffiths D, Wilkins C (1991) Nitrous oxide sedation causes post-hyperventilation apnoea. Br J Anaesth 67:7–12
52. Nishino T, Kochi T (1994) Effects of surgical stimulation on the apnoeic thresholds for carbon dioxide during anaesthesia with sevoflurane. Br J Anaesth 73:583–586
53. Temp JA, Henson LC, Ward DS (1992) Does a subanesthetic concentration of isoflurane blunt the ventilatory response to hypoxia? Anesthesiology 77:1116–1124
54. Sarton E, Dahan A, Teppema L, van den Elsen MJLJ, Olofsen E, Berkenbosch A, van Kleef J (1996) Acute pain and central nervous system arousal do not restore impaired hypoxic ventilatory response during sevoflurane sedation. Anesthesiology 85:295–303
55. Foo IT, Martin SE, Lee RJ, Drummond GB, Warren PM (1995) Interaction of the effects of domperidone and sub-anaesthetic concentrations of isoflurane on the immediate and sustained hypoxic ventilatory response in humans. Br J Anaesth 74:134–140
56. van den Elsen MJLJ, Dahan A, Berkenbosch A, DeGoede J, van Kleef J, Olievier ICW (1994) Does subanesthetic isoflurane affect the ventilatory response to acute isocapnic hypoxia in healthy volunteers? Anesthesiology 81:860–867
57. Foo IT, Martin SE, Fried MJ, Douglas NJ, Drummond GB, Warren PM (1995) Does sleep enhance the effect of subanesthetic isoflurane on hypoxic ventilation? Anesth Analg 81:751–756
58. Forrest WH Jr, Bellville JW (1964) The effect of sleep plus morphine on the respiratory response to carbon dioxide. Anesthesiology 25:137–141
59. Guz A (1997) Brain, breathing and breathlessness. Respir Physiol 109:197–204