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REVIEW

Effects of brain hypoxia on ventilation

A. Berkenbosch, J. DeGoede*

CONTENTS

1. Introduction

For over a century it has been known that a lack of oxygen in the blood stimulates breathing. In 1868 PFLUEGER [69] postulated that hypoxia directly stimulates the respiratory centres in the medulla oblongata. This view was not challenged until the discovery of the peripheral chemoreceptors, first of the aortic and later of the carotid bodies, by J.F. Heymans, C. Heymans and co-workers in the years 1927–1931. They performed experiments demonstrating that stimulation of ventilation by hypoxia was nearly absent when the nerve connections of the carotid and aortic bodies with the medullary respiratory centres were disrupted [36]. Occasionally they observed a decrease in ventilation in their denervated anaesthetized dogs upon the induction of hypoxia. By 1940, most of the evidence indicated that, in anaesthetized denervated animals, hypoxia led to a depression of ventilation [79]. This depressant effect of hypoxia was thought to be of central origin, *i.e.* an action of hypoxia on central nervous structures in the brain. In very lightly anaesthetized dogs, whose peripheral chemoreceptors had been denervated, MOYER and BEECHER [64] reported that, after an initial decrease, hypoxia gave rise to increased tachypnoeic ventilation. Upon deepening the anaesthesia, hypoxia depressed ventilation in the same animals. Chemodenervated conscious dogs [23, 90] and cats [29, 60] react qualitatively in the same way. There are therefore at least three modes of action of hypoxia on the respiratory controller: stimulation of the peripheral chemoreceptors, depression of the respiratory centres and central stimulation. The latter effect is only observed at severe hypoxia. At moderate hypoxia, the main effects appear to be peripheral stimulation and central depression.

* Department of Physiology, University of Leiden, P.O. Box 9604, 2300 RC Leiden, The Netherlands.

In this article, we will review the depressant effects of hypoxia in adult and newborn human subjects, although information about central depressant effects of hypoxia on ventilation in adult human beings is scarce. The phenomenon that hypoxia depresses ventilation in newborn infants is described in many studies, since depressant effects overrule the stimulatory effects of hypoxia in most cases. Quantitative data about the stimulatory and depressant effects of hypoxia in human beings are lacking. This is because non-invasive techniques which quantitatively separate peripheral from central effects were, up till now, not reliable. The action of hypoxia on the respiratory control system should not be taken by itself. The change in ventilation induced by hypoxia will alter the alveolar CO_2 tension, which itself is a powerful signal for the respiratory controller. Most of the information about the effects of hypoxia stems from animal experiments. Therefore the results of animal studies will also be discussed in some detail in this review.

2. Separation of central and peripheral effects of oxygen

Several methods have been tried to separate the effects of hypoxia on peripheral chemoreceptors from the effects on structures of the central nervous system. We mention: 1) denervation of peripheral chemoreceptors; 2) artificial perfusion of isolated structures; 3) analysis of the dynamic behaviour of the respiratory control system.

2.1. *Denervation studies*

The notion that hypoxia in the central nervous system depresses ventilation originates from experiments on unanaesthetized decerebrated cats whose carotid bodies had been denervated [81]. The

depressant effect of hypoxia in chemodenervated anaesthetized animals has been frequently reported [52, 67, 80, 81]. Apnoea often occurs in such preparations, indicating that the depressant effects are severe.

In awake chemodenervated animals, ventilation is already depressed at light levels of hypoxia. However, at deeper levels of hypoxia (fractional inspired O_2 concentration (F_{IO_2}) <0.13), ventilation starts to rise by an increase in breathing frequency at constant tidal volume [23, 29, 60, 90]. This hypoxia-induced tachypnoea is extremely sensitive to even small amounts of anaesthetics. Administration of dopa, xanthines such as caffeine or aminophylline and 2% CO_2 in the inspirate suppresses the phenomenon. It is believed that this central stimulating effect of hypoxia is of suprapontine origin as it is absent in decerebrate, unanaesthetized animals [29, 81]. There is some evidence that it is due to depletion of brain catecholamines by hypoxia [29, 60]. It is not clear whether this hypoxia-induced tachypnoea also occurs in newborn animals. It was not observed by BUREAU *et al.* [14] in awake, chemodenervated newborn lambs, but they also did not observe a depressant effect of hypoxia in their lambs. However, in other chemodenervated newborn animals (kittens), a clear depression was observed [80].

There are only a few studies on humans in whom the carotid bodies have been resected [1, 38–40, 58, 89]. Upon a hypoxic challenge, some individuals show a decrease in ventilation, while others show a small increase. To what extent the aortic bodies contribute to the remaining effect of hypoxia when the carotid bodies have been removed is unknown. From these studies in carotid body resected man, it is not clear if hypoxia depresses ventilation. It is, however, generally believed that this is so.

2.2. *Artificial perfusion of isolated structures*

A second method to separate central and peripheral drives uses artificial perfusion of isolated structures. In cross-perfusion experiments on anaesthetized dogs, LEE and MILHORN [55] showed that when the carotid bodies of a dog were perfused with the blood of a donor dog, inhalation of hypoxic gas mixtures by the recipient dog depressed ventilation even at moderate levels of hypoxia (P_{aO_2} 6.7 kPa). They also observed that, besides a shift to higher P_{aCO_2} levels, the ventilatory response to inhaled CO_2 had a diminished slope, the decrease in the slope becoming less by an increased peripheral chemoreceptor drive. Recently it has been shown that, in anaesthetized cats, hypoxia applied only to the ponto-medullary region caused an appreciable depression of ventilation, whether the pons and medulla were anaesthetized or not [2, 5]. The depressant effect of medullary hypoxia was most pronounced at P_{aO_2} levels below normoxia, but it was also manifest going from hyperoxia to normoxia. The central CO_2 sensitivity, however, was not diminished during central hypoxia.

2.3. *Dynamic behaviour of the respiratory control system*

2.3.1. *Non-isocapnic studies*

A decrease of inspired O_2 causes an immediate increase of ventilation. However, this increase is only transient because, after a few minutes, ventilation falls back towards its prehypoxic level. In the steady-state with inspired O_2 concentrations of about 12–14%, ventilation in adult humans is virtually the same as when breathing air [34, 42, 56, 77], but is frequently below control levels in both pre- and full-term human infants [11, 19, 73, 75, 77]. Inhalation of gas mixtures with an oxygen concentration below 12% causes sustained hyperventilation in the steady-state in adult man and most adult mammals in contrast to newborn mammals [8, 10, 12, 13, 15, 32, 51, 80]. There is an overwhelming number of reports on this so-called biphasic response in newborns (for recent reviews see [33, 43, 76, 88]). The first phase of the response is presumably due to stimulation of the peripheral chemoreceptors, as it is absent in chemodenervated animals [14, 52]. It is remarkable that the second phase in non-isocapnic experiments has received so much attention from paediatricians. Many suggest that it is a unique feature of ventilation in newborns; however, it is also observed in adult man [34, 42, 77] and other mammals [16, 17]. Contrary to most studies in adults, the CO_2 tension of newborns is not kept constant during the induction of hypoxia. Due to the washout of CO_2 by the increased ventilation, there is decreased stimulation of central and peripheral chemoreceptors. Therefore, upon induction of hypoxia, there will always be a fall in

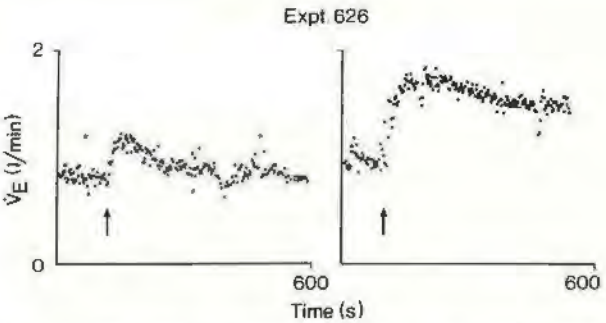

Fig. 1. Ventilatory response to a hypoxic step in the anaesthetized cat. Left panel: time course of the breath-by-breath ventilation of a cat following a stepwise change (indicated by the arrow) from air to 10.5% O_2 in the inspirate. P_{aO_2} fell from 12.5 to 4.6 kPa at the end of the hypoxic challenge which lasted about 10 min. P_{aCO_2} at the start was 4.3 kPa and at the end 3.9 kPa. Note that ventilation at the end of the hypoxic challenge is about the same as the prehypoxic value. Right panel: Ventilatory response to isocapnic (P_{aCO_2} 4.3 kPa) induction of hypoxia in the same cat. At the arrow, the P_{aO_2} was changed stepwise from 12.5 kPa to 5.8 kPa. Both responses show a biphasic pattern. The peak ventilation under non-isocapnic conditions is much lower, as the increase in ventilation immediately lowers the P_{aCO_2}. This counteracts the stimulatory effect of hypoxia by a lessened potentiation of CO_2 and O_2 at the level of the peripheral chemoreceptors, and by washout of CO_2 from brain tissue at the site of the central chemoreceptors. $\dot{V}_E$: minute ventilation.

ventilation after the initial increase, when the arterial CO_2 tension is not kept constant (fig. 1). It follows from the steady-state solution of the respiratory control system [21, 22, 31, 57] that, during moderate hypoxia, only a small increase in ventilation would occur. This increase may be too small to be detected, because of unavoidable scatter in the data. A change in ventilation also depends on whether the metabolic CO_2 production and the dead-space ventilation change. Several authors have shown that, in newborns who are not kept at a thermoneutral temperature, metabolic rate decreases due to hypoxia [10, 20, 37, 61, 62, 68]. This decrease in metabolic rate contrasts with the absence of change in adult animals exposed to the same hypoxic stimulus [20]. Only in adult small animals is a decrease of metabolism also observed [37]. As a result, steady-state ventilation may be lower than the prehypoxic value in newborns or small animals not kept at the thermoneutral level. Changes in dead-space ventilation due to alterations in breathing frequency or changes in the ventilation-perfusion ratio in the lung also ultimately determine gas exchange. In some newborns, breathing frequency in the steady-state is lower during hypoxia than in normoxia [8, 33, 73, 75], so that dead-space ventilation may be lower. Changes in metabolic rate and dead-space ventilation, together with a decrease in arterial CO_2 tension, may partly explain the unaltered or even diminished ventilation in newborns in the steady-state during hypoxia. Thus no firm conclusions about the physiological mechanisms can be drawn from non-isocapnic studies. By keeping the arterial CO_2 constant during the induction of hypoxia, changes in metabolic rate and dead-space ventilation cannot contribute to the development of the biphasic response in ventilation.

2.3.2. *Isocapnic studies*

When hypoxia is induced isocapnically, ventilation increases rapidly (fig. 1). In anaesthetized cats this increase is followed by a decrease and a new steady-state is reached in about 10 min [5, 24]. The early rise in ventilation is due to stimulation of the peripheral chemoreceptors, while the secondary fall in ventilation must be of central origin since it was absent when the brainstem was kept hyperoxic by artificial perfusion [24]. Sudden isocapnic relief of hypoxia shows an undershoot in the ventilatory response. We are unaware of similar studies in other animals. In man, SWANSON *et al.* [85] reported that two out of their six subjects, when subjected to an end-tidal PO_2 of 7 kPa for 5 min, slowly developed a secondary fall in ventilation. Rapid induction of progressive isocapnic hypoxia, followed by rapid relief, shows a hysteresis in the ventilatory response, which is thought to be caused by a depressant effect of hypoxia [92]. WEIL and ZWILLICH [91] reported a 25% decrease in minute ventilation in man, compared to the early rise after 10 min of isocapnic hypoxia (PaO_2 6 kPa). In the studies of KAGAWA *et al.* [45] and EASTON *et al.* [26], all subjects showed an appreciable secondary fall in ventilation starting after about 5 min. It is interesting that, in man, ventilatory depression develops much more slowly than in cats; hence, a secondary fall in ventilation is not manifest in most experiments on adult humans when hypoxia is induced for five to ten min only [72].

There are few reports on studies in which hypoxia is induced isocapnically in newborns. In anaesthetized and vagotomized piglets, three to five days old, phrenic nerve activity first increased to 180% of control after a change in PaO_2 from 46 to 4.4 kPa, but thereafter phrenic nerve activity returned to a mean value of 104% of control [53]. In newborn human babies (6 h to 11 days), BRADY and CERUTI [11] observed that there was an initial increase in ventilation with hypoxia during the first minute, but that during the second and third minutes, ventilation decreased. In older babies (13 days), a greater and sustained increase in ventilation was seen [11]. Taken together, the biphasic response to hypoxia of newborns and adults appears therefore to differ only quantitatively. To further study the effects of hypoxia on ventilation, it is essential to quantitatively separate central and peripheral effects. Development of the non-invasive dynamic end-tidal forcing technique for isocapnic changes in O_2 tension would furnish a valuable tool in this respect. Briefly, with this technique, the inspired gas is manipulated so that the end-tidal O_2 tension is forced to follow a prescribed pattern (*e.g.* square wave) in time, keeping the end-tidal CO_2 tension constant. The ventilatory response, measured on a breath-by-breath basis, is then separated into a slow and fast component, using an appropriate mathematical model (see [24]).

3. Depressant effects of hypoxia

Most of the evidence for a central depressant effect of hypoxia in man stems from indirect studies in which the time course of the ventilatory response to hypoxia is followed ([26, 41, 45, 91, 92]; see section 2.3.2.). Occasionally in man, the steady-state ventilation in response to isocapnic hypoxia is even lower than the prehypoxic value [41, 45]. Some volatile anaesthetics are known to depress the peripheral chemoreflex in man. For instance, halothane at a concentration of 1 MAC (minimum anaesthetic concentration) nearly abolishes the response of the peripheral chemoreceptors to hypoxia [47]; ventilation diminishes when going to hypoxia. This may be due to the central depressant effect of hypoxia on ventilation. More direct evidence is obtained from animal experiments in which the peripheral chemoreceptors are denervated (section 2.1.) or isolated structures are perfused (section 2.2.). It is not clear at which level of hypoxia depression of ventilation occurs. In the perfusion experiments of VAN BEEK *et al.* [2], in which hypoxia was exclusively applied to the pons and medulla oblongata, hypoxic depression was found at light levels of hypoxia (PaO_2 10 kPa). In

other studies, it was shown to occur at moderate hypoxia (Pa_{O_2} 5 kPa) [6, 29, 90] or only at severe hypoxia (Pa_{O_2} 3 kPa) [63].

The results on the effects of brain hypoxia on respiratory reflexes from central chemoreceptors are confusing. In anaesthetized cats [2] and awake ponies [28], central CO_2 responsiveness was not depressed unlike the central CO_2 sensitivity in anaesthetized dogs [55] and awake goats [86]. In adult man, the central CO_2 sensitivity during hypoxia remained constant [4]. In preterm babies, the overall CO_2 response is depressed [74] during hypoxia. However, it should be remarked that it is important to keep Pa_{O_2} constant within a few tenths of a kPa during measurement of CO_2 response curves during hypoxia. This was not the case in the study of RIGATTO *et al.* [74], so that the finding of a depressed CO_2 sensitivity should be viewed with caution.

The amount of ventilatory depression by brain hypoxia is appreciable. From the data of EASTON *et al.* [26] and KAGAWA *et al.* [45], it can be inferred that, in adult humans, it amounts to 60–80% of the stimulatory effect on the peripheral chemoreceptors. In anaesthetized cats, about half of the stimulatory effect is counteracted by the central depressant effect of hypoxia [2]. Data from newborns are insufficient to estimate the degree of depression. However, in newborn babies [11] and piglets [53], it is at least as big as the stimulatory effect. In newborn lambs, the central depressant effect seems to be far less [14, 15, 70].

4. Mechanisms of depressant effects of hypoxia

Although the existence of a central depressant effect of hypoxia on ventilation is firmly established, the underlying physiological mechanisms are obscure. Many mechanisms have been suggested, but their relative importance for the depression of ventilation is unknown.

Cerebral blood flow (CBF) in human beings is increased by hypoxia [18]. As a consequence, there is less ventilatory stimulation from central chemoreceptors due to increased washout of acid metabolites from brain tissue [55, 92]. The influence of cerebral blood flow on the control of breathing has been recently reviewed [35, 78]. It is important to emphasize that there appears to be a continuous change in CBF over the whole Pa_{O_2} range from hyperoxia to hypoxia [3, 9, 44], contrary to earlier studies in which it was reported that CBF increased only below a threshold of 6.7 kPa [49]. In newborns, the changes in CBF seem to be even greater than in adults [46, 48, 54, 71]. The time constant of the change in CBF upon a change in Pa_{O_2} in adult cats and goats is about 30 s [3, 25]. In the cat, a step change into isocapnic hypoxia quickly increased ventilation, which later declined with a time constant consistent with the decline in ventilation by washout of CO_2 from a brain compartment [24]. In man, the time course of the change in cerebral blood flow is not known; the slower decline in ventilation following hypoxia might be due to a much slower increase in CBF. Measuring at the surface of the medulla oblongata in rabbits, NOLAN and DAVIES [66] reported an increase in pH shortly after the induction of hypoxia, which probably reflects a decrease in brain tissue P_{CO_2}. In cats, an alkalotic shift in ventral medullary pH following mild hypoxia was observed with a concomitant diminution in ventilation [65]. However, this increase in pH was only transient and fell towards baseline values after 4 min while ventilation continued to decrease. Evidence is mounting that the pH is not the unique stimulus of the central chemoreceptors, but that there is probably a much greater CO_2 effect [82, 87]. Brain tissue P_{CO_2} measured on the ventral surface of the medulla [27] or the cerebro-spinal fluid P_{CO_2} as an index of brain tissue P_{CO_2} [67] decreased upon induction of isocapnic hypoxia. These findings support the view that changes in CBF play an important role in the depressant effect of hypoxia on ventilation.

Hypoxia influences the rate of synthesis or release of putative neurotransmitters or modulators. Even at mild hypoxia, a direct and indirect involvement of O_2 on the synthesis of several neurotransmitters has been suggested [30]. Changes in the concentration of GABA could effect ventilatory control, but these changes reach significance only at deep levels of hypoxia. In adult humans, hypoxic ventilatory depression is not altered by naloxone, so it is presumably not mediated by endorphins [45]. This may be different in newborn rabbits, where naloxone influences the depressant effect when it is applied in relatively high doses [32]. Hypoxia below 6.7 kPa raises the levels of adenosine in brain tissue [93]. MILLHORN *et al.* [59] reported that cats pretreated with theophylline, an antagonist of adenosine, showed significantly less respiratory inhibition than the untreated ones and they suggested that an impairment of neuronal function by adenosine could play a role in the depression of ventilation. Adenosine, however, has also been implicated in the regulation of blood flow [93], so that its depressant effect might partly depend on its vasodilatory action on brain blood vessels.

There is no increase in brain lactate, adenosine diphosphate and adenosine monophosphate concentrations nor a decrease in adenosine triphosphate and phosphocreatine or brain oxygen uptake down to a Pa_{O_2} of 6.7 kPa [83]. Therefore, there is no convincing evidence that changes in concentrations of neurotransmitters and in brain metabolism, leading to direct depression of medullary respiratory neuronal activity, play an important role in the depressant effect of hypoxia on ventilation down to a Pa_{O_2} of 6.7 kPa.

Hypoxia is reported to have a direct depressant effect on respiratory neurons [84]. However, neural activity is also expected to be decreased when recordings are made from neurons on which afferents from central chemoreceptors impinge, when these chemoreceptors are less stimulated, for instance due

to washout of CO_2 by an increase in CBF. We wish to remark that the finding after an application of hypoxia, an additional hypoxic change still elicits a (transient) increase in ventilation cannot be used as an argument against central neural depression [13], since depression of respiratory neurons does not necessarily imply that a further challenge has no stimulatory effect.

In newborns, hypoxia may influence lung mechanics [50, 51] and thus influence the relationship between output from the integrating respiratory centres and ventilation. LAFRAMBOISE *et al.* [51] have recently shown that mouth occlusion pressure at 200 ms, an index of central output, remains elevated throughout the hypoxic response, although the ventilation showed a biphasic response with hypoventilation in the second phase.

There is some evidence that the peripheral chemoreflex adapts during steady-state hypoxia. In newborn lambs, removal of a hypoxic stimulus induces less decrease in ventilation when the preceding hypoxia was induced by a steady-state method than by progressive hypoxia [15]. There is recent evidence from experiments in lambs that, in the first hours after birth, there is a resetting of hypoxic sensitivity. A few days after birth, spontaneous chemoreceptor discharge in normoxia is similar to that of adult animals [7, 8]. In adult man the abrupt induction of hypoxia for 25 min gives rise to a much bigger overshoot in ventilation than removal of the same stimulus [26], although it should be remarked that the ventilatory off-response in the study of EASTON *et al.* [26] was only followed up for about 5 min.

5. Concluding remarks

Over the years, a considerable amount of work has been done on the effects of hypoxia on ventilation. It has been established that hypoxia stimulates ventilation both through the peripheral chemoreceptors and through a central mechanism which is unmasked in the unanaesthetized state after peripheral chemodenervation. Besides these stimulatory effects, brain hypoxia depresses ventilation. A number of mechanisms have been proposed to play a role in the cerebral effects of hypoxia on ventilation. However, opinions are divided about the importance of these mechanisms. This situation is partly due to a lack of well designed experiments from which the importance of the proposed mechanisms can be inferred. For instance, this has led to the erroneous notion that the biphasic response of ventilation to hypoxia is a unique feature of newborns. Future work should be directed towards quantitative assessment of the contribution of the several suggested mechanisms during different physiological conditions. Measurement of the response to hypoxia in newborns under isocapnic conditions should provide valuable information, although, as aptly summarized by RIGATTO [76], the technical facilities and the experimental difficulties of performing experiments on newborn infants are formidable. It would be very interesting to further develop the dynamic end-tidal forcing technique for isocapnic changes in O_2 tension, in order to separate central and peripheral effects of hypoxia. This will greatly improve our understanding of the role of hypoxia in ventilation.

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