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REVIEW

Studying the control of breathing in man

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ABSTRACT: The control system of breathing can be considered as a closed-loop system, consisting of two subsystems: the controlling system and the controlled system. Both subsystems are defined by their input-output relationships. In the controlling system the input is the blood gas value; the output is some parameter of ventilation. The controlled system is characterized by an input of ventilation, and an output of blood gas values. In the closed-loop situation the control of breathing can be influenced by outside "disturbances", threatening to disrupt the regulation of the constancy of the internal environment. When studying the control of breathing, and therefore studying the strengths or defects of this homeostatic system, one has to decide whether one intends to investigate the closed-loop or the open-loop situation, and which defect in a subsystem may be the cause of a disrupted homeostasis. What non-feedback stimuli may be active at the moment of the investigation? How can they be kept constant or eliminated? What possible effects from drugs, beverages, nutrients (possibly consumed hours earlier) may still be present? In particular, the output parameters of the controlling system should be carefully chosen to represent that part of the system that one intends to investigate. Disruptions of the control of breathing may have serious consequences for several categories of patients, *e.g.* those with chronic obstructive pulmonary disease (COPD), asthma, sleep apnoea, sudden infant death syndrome, several neurological syndromes, and the hyperventilation syndrome. Adequate investigation of the control of breathing in these patients is of great importance for their treatment.
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In the normal resting and awake human the level of ventilation is driven by two major stimuli. The most important is the CO_2-stimulus which functions in the homeostatic control system of the body for pH/Pco_2. The control system for CO_2 has a feedback loop. The second important drive is a non-feedback drive, from neuronal structures that mediate wakefulness or the level of arousal. Furthermore body temperature, certain hormones, open or closed eyes, any motor activity, listening to music, adrenal-sympathetic tone, the degree of filling of the urinary bladder, recently imbibed beverages such as coffee or alcohol, and the type of nutrition all contribute to the level of resting ventilation and consequently have to be controlled when studying the regulation of ventilation.

There are two major groups of ventilatory stimuli: feedback stimuli and non-feedback stimuli. The former are the chemical stimuli: pH, carbon dioxide tension (Pco_2) and oxygen tension (Po_2) of the arterial blood or interstitial fluid, that are detected by chemoreceptors, and are altered by the level of ventilation. The latter are hormonal or neuronal stimuli, the intensity of which is not affected by the level of ventilation. Both types of stimuli may interact with the other, so that studying the ventilatory effects of, *e.g.*, CO_2 means that all other stimuli have to be kept constant or changed in a quantifiable way.

Chemical control of breathing

A block diagram of the feedback loops in the chemical control of breathing is shown in figure 1. Gas exchange takes place in the lungs, resulting in certain levels of Po_2 and Pco_2 and a certain pH in the arterial blood. The peripheral chemoreceptors sense the blood gas levels and convert them into neuronal signals which are transmitted to the brainstem neuronal respiratory centre. The pH/Pco_2 homeostasis of the most vulnerable of all tissues, the central nervous system, is sensed by the central chemoreceptors at the ventral medullary surface. Afferent signals from both chemoreceptors are processed in the ponto-medullary neuronal respiratory centre. The output of this centre is transmitted to the motor neurones of the respiratory muscles at the appropriate spinal levels. The activity of these muscles changes the configuration of the thorax, and consequently changes the

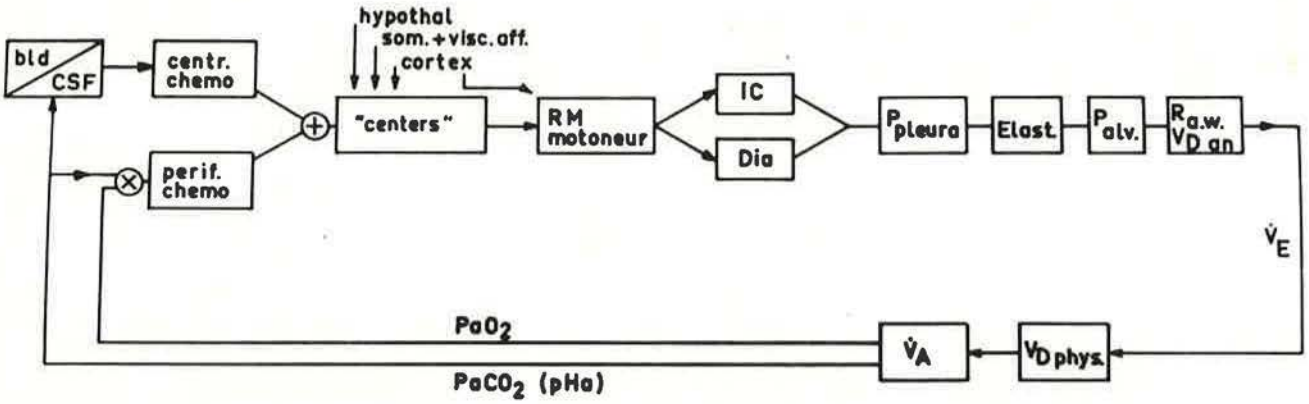

Fig. 1. – Block diagram of the ventilatory control system. bld: blood; CSF: cerebro spinal fluid; centr chemo: central chemoreceptors; perif chemo: peripheral chemoreceptors; centres: "respiratory centres" in pons and brainstem; RM motoneur: spinal motor neurones of the inspiratory muscles; IC: intercostal inspiratory muscles; Dia: diaphragm; Ppleura: pleural pressure; Elast: elastic properties of the lung parenchyma; Palv: alveolar pressure; Raw: airway resistance; VDan: anatomical deadspace; VDphys: physiological deadspace; hypothal: hypothalamus; som+visc aff: somatic and visceral afferents; cortex: forebrain cortex; $\dot{V}_E$: total ventilation; $\dot{V}_A$: alveolar ventilation Pao_2: arterial oxygen tension; $Paco_2$: arterial carbon dioxide tension; pHa: arterial pH.

pleural pressure. These pleural pressure swings, after modification by the elastic properties of the parenchyma of the lungs, cause alterations of pressure in the alveoli. Depending on the flow resistance in the airways, more or less air is moved in or out of the lungs. The net gas exchange in the alveoli is determined by the relative deadspace ventilation, by the dilution of the "fresh" air in the residual volume, by the diffusion process over the alveolar-capillary membrane, and by the ventilation-perfusion ratio.

Basically the properties of this chemical control loop can be studied in two ways: 1) the ventilatory control loop (as shown in fig. 1) can be kept functionally intact. Its ability to maintain homeostasis for Po_2 and pH/Pco_2 in the presence of external disturbances can be tested. This type of study is carried out, *e.g.*, when blood gas levels are measured in humans after administration of drugs, when exercising, during sleep, or under psychological influences such as hypnosis or mental stress; 2) the ventilatory control loop can be opened, and arterial- or end-tidal-Po_2 or Pco_2 can be kept at desired levels so that ventilation does not influence blood gas values, as is done when making CO_2 or O_2 response curves; or the blood gas levels do not influence ventilation as in paralysed subjects who are artificially ventilated.

In both open- and closed-loop studies, subsystems of the control system can be studied. These subsystems are then defined and characterized by their input-output relationships. The two major subsystems of the ventilatory control system are the "controlling" and the "controlled" system. The controlling system is defined as the subsystem with an input of a blood gas value; and the output is a ventilatory parameter such as minute ventilation, pleural pressure, respiratory muscle electromyograph (EMG), mouth pressure, etc. The controlled system is defined as having as the input (alveolar) ventilation, and as the output the arterial (interstitial) pH or arterial blood gas values. The input-output relationships determine the gains in these subsystems.

Analogous to technical control systems, some of the properties of the ventilatory control system are being described by some authors in terms of a "set-point": a certain blood gas value that should be maintained. A set-point in technical control systems is a signal that is absolutely constant, and independent of changes in the environment. The measured value of the controlled parameter in these technical control systems is compared to this reference signal. When there is a difference between both signals, the control system is activated and the difference between the controlled parameter and the reference value is minimized. If such a set-point mechanism were present in the ventilatory controlling system, this would presuppose a (presumably neuronal) comparator system, where the afferent chemoreceptor signals are compared to some constant signal representing a desirable blood gas level. There is no neurophysiological evidence for the existence of such set-points in the control of breathing [1].

An alternative approach in describing the function of the control system is based on the view that, in the closed-loop situation, the controlling and the controlled systems have to be in equilibrium: the output of the controlling system is the input of the controlled system and *vice versa*. Thus the intact control system has to include the characteristics of both the controlled system (metabolic hyperbolae) and of the controlling system (CO_2- and O_2-response curves). When plotting these input-output relationships of both subsystems, the result is that the total control system settles in the crossing of both lines. This is called the "working point" (fig. 2). Changes in the ventilatory response curves or in the metabolic hyperbolae change the position of this working point.

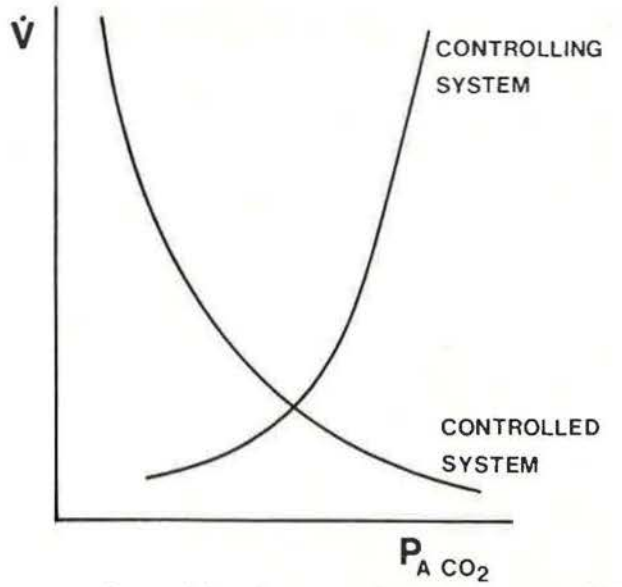

Fig. 2. – Characteristics of the controlling, and of the controlled subsystem in the ventilatory control system. The characteristics of the controlling system are described by the CO_2-response curve: the input parameter is alveolar (arterial) P_{CO_2} (P_{ACO_2}); the output parameter is ventilation ($\dot{V}$). The controlled system is characterized by the metabolic hyperbola: input ventilation, output alveolar P_{CO_2}. In the closed-loop situation, the control system has to settle in the point where the input of the controlling system equals the output of the controlled system, and *vice-versa*. This crossing point of both characteristics is called the working point of the control system.

Closed-loop studies

In the closed-loop situation of the chemical control system, the basic question is "how adequate is the chemical control loop in maintaining homeostasis for P_{O_2} and P_{CO_2}, in spite of a disturbance from outside this control system?" This "disturbance", is often a change in a non-feedback drive, or the application of a certain drug. Consequently, the parameters that are studied in such investigations are the blood gas levels of P_{CO_2} and P_{O_2} or arterial pH. Drugs that have been investigated in such a way include: alcohol, caffeine, sedatives, hormones (progesterones, adrenaline, thyroxine), endorphins, respiratory stimulants such as doxapram and almitrine, opiates and their antagonists, etc. [2–7].

The effects of wakefulness and sleep are often studied in the closed-loop situation. Even when awake, open or closed eyes make a difference in arterial P_{CO_2} [8]. Slow wave sleep generally depresses ventilation, whereas rapid eye movement (REM) sleep is eucapnic or even hypocapnic [9]. Mental stress tests cause respiratory alkalosis [10].

In open-loop studies more or less adequate attempts are being made to keep these non-feedback factors constant by making the subjects read, watch a neutral television programme, or listen to quiet music [11].

Exercise is a potent non-feedback ventilatory stimulus. The mechanism of this stimulus has been studied intensively, but has not yet been elucidated. During light to moderate exercise the arterial blood gas levels remain constant. Both the metabolic hyperbola and the CO_2-response curve change in such a way that the working point remains at the resting P_{CO_2} level. Only at higher submaximal exercise levels in normals, is there an increase in ventilation which is disproportionate to the increase in metabolism (CO_2 production), resulting in a disruption of the normal ventilatory control and in a lowered P_{CO_2}. The exercise level at which the ventilation increases more than the CO_2 production, resulting in hypocapnia, is sometimes used to determine the "anaerobic threshold". This is misleading; there is substantial evidence that this relative hyperventilation is not a respiratory compensation of a metabolic acidosis, caused by the anaerobic metabolism and lactate production. Patients with "McArdle's disease" cannot make lactate, but do show such a relative hyperventilation and hypocapnia [12]. Furthermore, if lactacidosis is pre-existent before the exercise test, at a certain exercise level there is still a disproportionate increase in ventilation, resulting in hypocapnia and respiratory alkalosis [13].

Sensory input from proprioceptors can profoundly affect the control of breathing. In particular, afferent signals from spindles in the intercostal muscles have potent effects in this respect [14–17]. These effects have to be taken into account when studying control in loaded breathing, *e.g.* in chronic obstructive pulmonary disease (COPD) patients, or in pharmacological studies with drugs that depress the activity of the gamma-motor neurone system in the intercostal muscles [18].

A rather unsuspected source of disturbances of ventilatory control in the closed-loop situation is the filling state of the urinary bladder: distension of the bladder causes a decrease in the amplitude and frequency of breathing [19].

The controlled system

The controlled system is defined as having an input of ventilation, and an output of arterial blood gas values. In anaesthesia and in intensive care medicine with patients on respirators, working with the characteristics of this controlled system is part of daily practice. The graphic representation of this input-output relationship for CO_2 is called the "metabolic hyperbola". The position of this hyperbola is determined by CO_2 production and thus by metabolism. It is, therefore, not surprising that the characteristics of this controlled system are altered by substantial changes in nutrients [20, 21].

Furthermore, in situations like haemodialysis, CO_2 is eliminated from the body via the dialysis bath [22, 23]; since the arterial P_{CO_2} remains normal, the characteristics of the controlling system have to change also.

The transfer function from ventilation to blood gas values is affected by the mechanical properties of the lungs and airways: airway resistance (asthma, COPD), compliance of the lungs (pneumonia, adult respiratory distress syndrome (ARDS)) and compliance of the thorax (scoliosis, thoracic trauma).

The controlling system

The controlling system is defined as having an input of arterial blood gas values, and a ventilatory parameter as

output. The graphic representation of the input-output relationship is called a ventilatory response curve to CO_2 or to O_2. Depending on the degree of invasiveness with which the experimenter and the subjects are prepared to comply, the real input to the chemoreceptors can be measured in indirect or more direct ways. The same is true for the output parameters of this controlling system. In extreme invasiveness this means that arterial Po_2 and Pco_2 and pH of cerebrospinal fluid (CSF-pH) are measured directly or, on the other hand, minimal invasiveness is approached when end-tidal partial pressures are measured and thought to be representative of the real stimuli. Output parameters can be measured in even more ways, ranging from electroneurograms of phrenic or intercostal nerves, EMG's of the corresponding muscles, minute ventilation, to plethysmography of thoracic and abdominal displacements. It is clear that a description of the controlling system is completely dependent on the input and output parameters actually measured. They have to be stated clearly, and conclusions from the studies have to be restricted with regard to the way the system is investigated. For instance, in COPD patients the end-tidal partial pressures of O_2 and CO_2 are often not representative of the arterial values, and the ventilation is not a good measure of the output from the respiratory centres [24]. The problems concerning measurement of the various ventilatory output parameters in COPD patients were shown by SCANO *et al.* [25], who compared diaphragmatic EMG, mouth occlusion pressure ($P_{0.1}$), and mean inspiratory flow (VT/TI). They found very different responses to changes in end-tidal CO_2 with these three output parameters.

Input parameters for the controlling system

For the O_2 control loop the input parameter that is actually sensed by the arterial chemoreceptors is the arterial Po_2. In experimental conditions this parameter can be measured directly by arterial blood sampling, or by an indwelling Po_2-electrode. If it is desirable to be less invasive, the arterial Po_2 can be approximated by the end-tidal value. However, one has to bear in mind that even in normal subjects there can be an arterial-alveolar Po_2 gradient of up to 1.5 kPa. This gradient changes as ventilation changes. Alveolar Po_2 measurement requires a fast O_2-analyser with a response time of about 0.1 s. Transcutaneous Po_2-electrodes are useful for trend monitoring, but not for measurements of an input parameter in ventilatory control studies. The oxygen saturation (Sao_2) measured with a pulse-oximeter can well be used as an input parameter. The shapes of the oxygen-response curve and of the haemoglobin oxygen dissociation curve fortuitously make rectilinear ventilation-Sao_2 relationships that can be described by very simple mathematical equations. However, one must bear in mind that the stimulus for the chemoreceptors is Po_2 and not Sao_2. Measurement of Sao_2 as input stimulus may be wrong in situations of carbon monoxide intoxication, in the presence of a substantial amount of abnormal haemoglobins, in very severe anaemia, and in situations where the oxygen dissociation curve is substantially shifted [26].

The CO_2 control loop has two sensors that detect the input stimulus: the peripheral and central chemoreceptors. The former sense arterial Pco_2/pH. There is good evidence that the receptor mechanism measures arterial pH changes, irrespective of whether they are brought about via respiratory (CO_2) or metabolic ("fixed acid") mechanisms [27]. In normal subjects end-tidal Pco_2 is a good representation of arterial Pco_2; this end-tidal Pco_2 value can be measured with any fast-responding device such as a capnograph or a mass spectrometer. The stimulus for the central chemoreceptors is more complex and can hardly be measured directly. There is a transfer factor from the extracellular Pco_2/pH in the interstitial fluid around the central chemoreceptors to the arterial blood. Cerebral blood flow and active ion transport across the blood-brain barrier play an important role in this transfer. There also seem to be independent pH and Pco_2 effects on these chemoreceptors [28].

The closest one can get to this actual stimulus is sampling cerebrospinal fluid (CSF) by suboccipital puncture [29] or by lumbar puncture [30]. When attempting to measure these stimuli as directly as possible, one also has to be as invasive as possible. In these conditions, one of the basic physical laws should not be forgotten: any measurement on a system influences the system. In the case of invasive measurement of blood gas or CSF values the subjects will either hyperventilate or hold their breath during the procedure and, therefore, change their Pco_2/pH values.

Methods have been developed to separate the central and peripheral chemoreceptor effects by using the different temporal responses of the two chemoreceptor systems to step changes in end-tidal Pco_2 (dynamic end-tidal forcing (DEF)-technique). The ensuing ventilatory change can be separated into a fast and a slow component. The time constants and the gains from these two components can be derived mathematically [31]. The final evidence that these fast and slow responses could really be attributed to peripheral and central chemoreceptor responses, respectively, was discovered in animal experiments with separate perfusion of carotid and vertebral arteries [32]. Using the DEF-technique requires computerized shaping of the inspiratory Pco_2 profile, plus computer analysis and curve fitting of the ventilatory response. In normoxia, the peripheral chemoreceptor control loop for Pco_2 contributes 34% to the total gain in the CO_2 control loop [31]. In hypoxic conditions there is an interaction between O_2- and CO_2-stimuli in the peripheral chemoreceptors: hypoxia increases the CO_2-sensitivity, and hypercapnia increases the hypoxic sensitivity.

Output parameters of the controlling system

The output of the ponto-medullary respiratory neuronal centre consists of the neuronal signals travelling in the spinal cord to the motor neurones of the respiratory muscles. Also descending signals from the corticospinal

tract, mediating volitional respiratory commands, project to these motor neurones. Both groups of signals travel in separate tracts that can be lesioned independently and can give rise to different clinical syndromes with a dysregulation of breathing [33].

The output from the spinal motor neurones of the respiratory muscles to the muscles themselves travels in peripheral nerves such as the phrenic nerve and intercostal nerves. In contrast to the widely used quantification of this neuronal output in animal experiments, these output parameters have not yet been used in humans.

The next station in the output from the controlling system, the electrical activity of the respiratory muscles has, however, been used successfully by many investigators. Electromyographic activity of the respiratory muscles can be recorded with needle- or wire-electrodes (*e.g.* in the parasternal intercostal muscles), electrodes on an oesophageal balloon (diaphragm), or surface electrodes (intercostals, diaphragm, and accessory muscles). Usually EMG-activity is rectified and integrated. When performed correctly, these recorded and quantified EMG's can be used as output parameters of the respiratory controlling system [34].

The contraction of the inspiratory muscles causes pressure changes in the pleural space. These pressure changes are a result of the combined activity of all respiratory muscles. They can be measured with an oesophageal balloon. This output parameter of the controlling system can be modified by the compliance of the lungs and the thoracic wall. Measurement of oesophageal pressure swings can be very useful when airway obstruction makes the measurement of ventilation an unreliable output parameter, as in COPD or obstructive sleep-apnoea or hypopnoea. The transdiaphragmatic pressure only gives an indication of the contribution of the diaphragm to the pleural pressure swings. Interpretation of the measurements of oesophageal *vs* transdiaphragmatic pressure is complex [35, 36].

The pleural pressure swings are transmitted to the alveoli, the transfer factor being the elastic properties of the parenchyma of the lung. Measurement of alveolar pressure can also be used as an output parameter. Occluding the airway for a very short time (0.1 s) makes the pressure in the mouth equilibrate with the alveolar pressure. Thus, it is possible to measure mouth pressure ($P_{0.1}$) as being representative of alveolar pressure when there is no airflow during the occlusion [37].

This type of measurement presupposes that 0.1 s is a short enough time for load compensating reflexes not to come into effect, and long enough for equilibration of alveolar and mouth pressures. This is certainly true in normal subjects; in COPD patients this may not quite be the case but the $P_{0.1}$ output parameter in these patients is always a closer approximation of the respiratory centre activity than is the output measured from minute ventilation. Furthermore, the $P_{0.1}$ is a reliable output parameter only if the neuromuscular system is not diseased, weakened, or fatigued.

One of the least invasive output measurements is the quantification of respiratory movements of the thorax and of the abdomen. The aim of these methods is to measure volume displacements. Use of magnetometers gives a measurement of linear displacement. Magnetometers in both anterior-posterior and in lateral direction give a better approximation of volume. However, most magnetometers measure displacements *vs* a fixed-point, and consequently are subject to movement artifacts.

The application of coils around the thorax and abdomen measures changes in the volume of the cylinder that is surrounded by the coils. This respiratory inductive plethysmographic (RIP) signal can be used satisfactorily as an output parameter, provided that rather complex calibration procedures have been applied, and that the subject absolutely does not change position after the calibration procedure. It is claimed that RIP can measure diaphragmatic and intercostal contributions to the respiratory tidal volume [38]. This presupposes that all thoracic cage movement is made by the intercostal muscles, and that abdominal wall displacements are only a result of diaphragmatic contractions. These suppositions cannot be maintained in view of recent insights of mechanical effects of respiratory muscles [36]. The RIP signal is, therefore, very useful in non-invasive qualitative or semi-quantitative assessment of ventilation and thoracic and abdominal movements. Ambulatory monitoring of breathing, or monitoring during sleep, can be performed with RIP, keeping in mind that only semi-quantitative (increase/decrease) assessment of breathing can be carried out.

Ventilation measured at the mouth and nose is the final output parameter of the controlling system. The way in which the subject is connected to any apparatus influences the measurement. A face-mask over mouth and nose increases tidal volume, and lowers respiratory frequency, as compared to a mouthpiece and noseclip [39, 40]. Volume displacement can be measured as volume (spirometer) or as integrated flow (pneumotachograph). Both types of measurement are useful in specialized situations, depending on the required frequency response, resistance and inertia in the system, open or closed breathing systems, etc. [41].

Subsystems within the controlling system

Using two or more of the measurements described above, it is possible to describe the transfer factors in various subsystems in the output system of the controlling system. Comparing quantified EMG-activity and oesophageal (or transdiaphragmatic) pressure gives an impression of the electromechanical coupling in the inspiratory muscles [42]. This transfer factor changes in muscle weakness, fatigue, and change of position on the length-tension diagram of the muscle.

The EMG-ventilation relationship is another parameter to quantify electromechanical coupling. This relationship is also affected by the resistance in the airways.

CO_2-response curves

One of the methods most widely used to test the properties of the controlling system in the open-loop situation

is to construct the CO_2-response curve. The relationship between alveolar (arterial) Pco_2 and minute ventilation is determined by the functioning of the chemoreceptors, the brain stem neuronal respiratory centre, the descending neuronal pathways, the respiratory muscles, and by the mechanical properties of lungs and airways. Furthermore, it is assumed that all non-feedback inputs to the controlling system are in standard conditions. Considering this multitude of factors affecting the Pco_2-ventilation relationship, it is not surprising that there is a huge range of normal values: from 3–33 $l \cdot min^{-1} \cdot kPa^{-1}$ [26, 41]. It is, therefore, very difficult to distinguish between normal and pathological ventilatory responses to CO_2. Perhaps the only criterion in this respect should be: a response or not. There are three basic methods for determining CO_2-sensitivity: the steady-state method, the rebreathing method, and the dynamic end-tidal forcing technique. In the steady-state method the alveolar (arterial) Pco_2 is elevated for a sufficient time to obtain a steady ventilatory response. The time constant depends on the equilibration rate of the extracellular fluid compartment around the central chemoreceptors, on the adaptation of cerebral blood flow to the changed Pco_2, and on the time constant of the neuronal circuitry in the brainstem. The time to reach a steady-state ventilation in hypercapnia ranges, according to various authors, from 5 min [31] to 20–25 min [1]. This is the classical "Oxford" method [43].

In the rebreathing method, as described by READ [44], the subject rebreathes a mixture of 7% CO_2 in oxygen. Various authors have modified this method by using breathing of gas mixtures with or without CO_2 in the starting condition. Both steady-state and rebreathing methods yield the same slopes, the latter curves being shifted to the right, *i.e.* higher Pco_2 levels.

In the DEF-technique the inspiratory Pco_2 is changed abruptly; the ventilatory response is analysed by computer models based on a two compartment model for central and peripheral chemoreceptor loops. This method has been validated in animal studies [32]. Also, in carotid body resected subjects this method yields only one slow, central component [31].

The shape of the CO_2-response curve has been the subject of discussions. The classical Oxford approach is description by means of a straight line. Undoubtedly this is mathematically the simplest description. However, in their review in 1986, CUNNINGHAM *et al.* [43] discussed the problems of ventilation around the normal value of Pco_2, and considered the possibility of a so called "dog-leg" in normoxia. FOLGERING *et al.* [45] found curvilinear CO_2-responses which can be described by an exponential equation or by two straight lines. In the lower ranges of CO_2-responses in particular, interactions can occur between the CO_2-stimulus and the exercise stimulus [46] or stimuli from hypothalamic centres [47–49].

The ventilatory CO_2-sensitivity is affected by hormones, drugs, alcohol, endorphins [2–5], is reduced at older ages [50–52], seems to be lower in females than in males, and changes during the menstrual cycle [6, 53]. The effect of athletic training is equivocal; reduced as well as augmented CO_2-responses in athletes have been described [54–55]. In spite of the fact that resting ventilation in the sitting position is higher than in the supine position, the ventilatory response to CO_2 seems to be unaffected by posture [56]. In chronically hypercapnic patients the ventilatory response to CO_2 increased after a carbohydrate meal that raised the respiratory exchange ratio [21]. Obstructive pulmonary disease, especially of the blue and bloating type is accompanied by low CO_2-sensitivity [24, 57].

Vibration of the thoracic wall increases CO_2-sensitivity considerably [16]. A 5 min period of hypoxia increases the CO_2-sensitivity for 40 min [58]. Increased body temperature gives a higher slope [59]. Increased gravity only shifts the CO_2-response curve to lower Pco_2 levels, with no significant change in slope [60]. Daily successive CO_2-response curves seem to increase the slope [61]. Hypnosis decreases CO_2-sensistivity [62]. Personality, familial, racial and genetic influences have also been described [63].

Hypoxic response curves

In hypoxic ventilatory responses the time constant of the ventilatory response is relatively short: about 18 s [26]. Therefore, no distinction is generally made between steady-state and non-steady-state responses. As previously mentioned, the actual stimulus for the peripheral chemoreceptors is the arterial Po_2. If this parameter is used in the description of the O_2-controller, the adequate equation is of a hyperbola:

$$\dot{V}E=\dot{V}O+A/(Pao_2-C)$$

In this equation $\dot{V}O$ is the horizontal asymptote; C is the vertical asymptote; and A is the shape parameter. The normal values of A range from 40–280, and C has the value of 32 [26] (note that these values are based on Po_2 values in mmHg). When the Sao_2 is used as an input stimulus, the ventilatory response can be described by a linear equation with a negative slope. The normal range of this slope is 0.16–1.76 $l \cdot min^{-1} \cdot \%$ desaturation^{-1} [41]. When breathing hypoxic mixtures, the subjects hyperventilate and blow off CO_2. Due to the interaction between the O_2- and CO_2-stimuli, this leads to a decreased hypoxic response. Therefore, it is necessary to maintain a constant arterial Pco_2 level during a hypoxic response, by adding an adequate amount of CO_2 to the inspiratory air.

Another source of error in the hypoxic response is the fact that the hypoxic depression of the central nervous system counteracts the stimulatory effect of the peripheral chemoreceptors. This leads to a biphasic response: the initial increase in ventilation from the chemoreceptor stimulation is somewhat diminished later by the central hypoxic depression. Other theories about this biphasic hypoxic response include adaptation of the peripheral chemoreceptor and increases in cerebral blood flow due to the hypoxia.

Hypoxia is a potentially dangerous condition. Recording of hypoxic response curves should be carried out

with constant monitoring of the subject and his arterial Po_2 or Sao_2 (transcutaneous Po_2 monitoring is insufficient and too slow in this situation) and preferably also with ECG-monitoring. A clinician should be present.

Clinical applications

In several clinical situations the control of breathing is disrupted. In more severe COPD patients, in respiratory muscle dysfunction, and in pharmacological suppression of the chemoreflexes, one finds hypoventilation and respiratory acidosis. On the other hand, a respiratory alkalosis occurs in conditions such as pneumonia, pneumothorax, pulmonary embolism, heart failure, early acute asthma, interstitial lung diseases, and in several neurological conditions. Oscillations in the system with alternating hypercapnic and hypocapnic periods can be seen in Cheyne-Stokes breathing, when either the controller gain is changed grossly (as in terminal patients), or when there are time-lags in the control system (very low cardiac outputs). Increasing the cardiac output or the CO_2-stimulus eliminates this pathological breathing pattern.

Various drugs affect ventilatory control. Anaesthetics, sedatives, alcohol and certain analgesics depress the controller gain resulting in a ventilatory insufficiency and hypercapnia. They depress the wakefulness drive, or the activity in the medullary neuronal respiratory centre. Most of them do not seem to affect the chemoreceptor activity in animal experiments. Caffeine, almitrine, doxapram, progesterone, adenosine, adrenaline and high doses of salicylate increase the gain in the controlling system. Some of them act specifically on the peripheral chemoreceptors.

Theophylline has a special place since it has its stimulatory effects on both the controlling system and the conductivity of the airways in the controlled system. The possible effect of theophylline on respiratory muscles is not yet clear.

In situations where the CO_2 production is increased, such as exercise, carbohydrate alimentation and intraperitoneal CO_2 loading [64], the gain in the controller is increased. When the CO_2 production seems to be reduced, *e.g.* in haemodialysis where CO_2 is removed in the dialysate, the controller gain is also reduced [22, 65]. These patients become slightly hypoxic. It is not yet clear how this CO_2-flux is perceived by the organism, and how it affects the control mechanisms. Respiratory oscillations in blood gas values may be the cause. Further research in this field is certainly needed.

In neonates and babies under one year, there is a risk of sudden infant death syndrome (SIDS). There are indications that defects in the controlling system of breathing during sleep may play a role in this affliction. Constructing CO_2-response curves in sleeping near-miss SIDS children will identify high risk children by the absence of a response [66, 67]. It can be speculated that older patients with "Pickwick's syndrome" could be survivors of near-miss SIDS.

In asthmatic patients both the controlled and the controlling systems are affected: bronchoconstriction impedes a normal gas exchange in the controlled system. On the other hand, stimulation of irritant receptors in the airways stimulates ventilation and makes the asthmatic hyperventilate in the early stages of an attack. In the past, the carotid bodies of some of these patients have been denervated in order to diminish the sensations of dyspnoea. The results did not warrant a widespread use of this procedure. These chemodenervated patients did not have a hypoxic response any more [31], nor did they react to drugs like doxapram or almitrine. Some arteriosclerotic patients have been chemodenervated accidentally during carotid endarterectomy.

The COPD patients can be subdivided into two groups: those who maintain their Pco_2/pH homeostasis, and those who do not. They are also called "pink puffers" and "blue bloaters" or "fighters" and "quitters", respectively. In these patients, it is not clear what properties of the controlling or of the controlled system makes one patient eucapnic, and another hypercapnic. There are indications that the CO_2-responses in the eucapnic group are steeper than in the hypercapnic group [14]. There are also indications that the O_2-sensitivity is a familial trait that may determine CO_2 retention [57]. The theory that CO_2 retention in some COPD patients is a result of the high-frequency breathing pattern, as proposed by Sorli *et al.* [68], should be re-evaluated. Their hypercapnic patients were on diuretics. Many diuretics cause a metabolic alkalosis and, therefore, eliminate part of the chemical ventilatory drive.

During sleep when the wakefulness drive is diminished the hypoventilation may be of such an extent that some COPD patients become hypoxic. Obesity and hypertension increase the risk of nocturnal hypoxia. Sleep studies with polysomnography of respiratory parameters and arterial oxygen saturation are indicated in these patients. In a group of COPD patients there is a fair correlation between daytime arterial Po_2 and sleep desaturations [9]. In the experience of this author the daytime oxygen saturation in the individual patient is insufficiently predictive for the frequency and depth of nightly desaturations.

Neurological syndromes such as cerebral tumours, cerebrovascular accidents, Shy-Drager syndrome, Locked-in syndrome, give rise to dysregulation of ventilation, either awake or asleep. Descending pathways from the corticospinal tract or from the reticulospinal tracts can be severed separately by accidents, or iatrogenically by neurosurgical interventions. Corticospinal tract lesions make voluntary breathing movements impossible, and reticulospinal tract lesions make automatic breathing impossible: breathing has to be performed consciously, and stops during sleep [33].

Psychological stress, high sympathetic-adrenergic tone and possible high activity in hypothalamic emotional centres all contribute to the hyperventilation syndrome. In this syndrome the normal control of breathing is abandoned by the individual. The normal negative CO_2-feedback is often inverted into a positive feedback. When such a patient is hypocapnic, adding CO_2 to the inspiratory air, as occurs when rebreathing into a plastic bag,

diminishes ventilation in about 40% of cases. This increases the arterial P_{CO_2} even more, until the P_{CO_2} values have reached a normocapnic level. When for some reason the ventilation in the hyperventilation patient is increased, it remains high for a considerable time after the stimulus is taken away. This "flywheel phenomenon" has also been described in animal experiments [69, 70], and in a mild form in normal human subjects [71]. The hyperventilation and the ensuing respiratory alkalosis can cause a cerebral vasoconstriction so that the oxygen supply to the brain is temporarily impaired and the patient faints. The dysregulation of ventilation in the hyperventilation syndrome might not give rise to grave clinical conditions, but it occurs in many patients (about 10% of all patients seeking medical help [72]), is sometimes difficult to diagnose [73], and can be very disabling for the individual.

Conclusions

When studying the control of breathing, one has to decide whether one wants to investigate the closed-loop or the open-loop situation, and which non-feedback stimuli may be active at the moment of the investigation. How can they be kept constant or eliminated? What possible effects from drugs, beverages or nutrients possibly taken hours earlier, may still be present? The output parameters of the controlling system in particular must be carefully chosen to represent that part of the system that one intends to investigate.

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RÉSUMÉ: Le système de contrôle de la respiration peut être considéré comme un système à circuit fermé, formé de deux sous-systèmes : le système contrôleur et le système contrôlé. Les deux sous-systèmes sont définis par leurs relations "input-output". Dans le système contrôleur, l'input est la valeur des gaz du sang, et l'output l'un ou l'autre paramètre de ventilation. Le système contrôlé est caractérisé par un input de ventilation et un output de valeur des gaz du sang. Dans une situation de circuit fermé, le contrôle de la respiration peut être influencé par des "troubles" extérieurs, menaçant de rompre la régulation ou la stabilité de l'environnement interne.Lorsqu'on étudie le contrôle de la respiration, et donc les forces ou des déficiences de ce système homéostatique, on doit réaliser si l'on désire investiger la situation en circuit fermé ou la situation en circuit ouvert, et quelle déficience dans quel sous-système pourrait être la cause de rupture de l'homéostasie. Quels "stimuli" non-feedback peuvent-ils intervenir au moment de l'investigation? Comment peut-on les maintenir constants? ou les éliminer? Quels effets possibles provenant de médicaments, de boissons, ou d'aiments, pris plusieurs heures auparavant, pourraient-ils encore être présents? Ce sont surtout les paramètres de output du système contrôleur qui doivent être choisis soigneusement pour être représentatifs de cette partie du système que l'on souhaite investiger. Des troubles du contrôle de la respiration peuvent avoir des conséquences sérieuses pour toute une série de patients comme les BPCO, les asthmes, les apnées du sommeil, la mort subite du nourrisson, différents syndromes neurologiques et le syndrome d'hyperventilation. Une investigation adéquate du contrôle de la respiration chez ces patients est d'une grande importance pour leur traitement.