CASE REPORT

Attenuation of hypoxic ventilatory response after recovery from chronic hypoxaemia in a case of pulmonary A-V fistula

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Attenuation of hypoxic ventilatory response after recovery from chronic hypoxaemia in a case of pulmonary A-V fistula. S. Kobayashi, M. Nishimura, K. Miyamoto, Y. Kawakami. ©ERS Journals Ltd 1994.
ABSTRACT: We studied respiratory chemosensitivity in a patient with pulmonary arterio-venous (AV) fistulae before and after surgical removal of the lesions.

The patient had had moderate hypoxaemia with hyperventilation before the operation. When first studied, 21 days following surgery, both hypoxic and hypercapnic ventilatory responses were found to be lower than they were preoperatively. During the next 1–2 months, hypoxic ventilatory response continued to fall significantly to a steady value, whereas hypercapnic response showed no further fall.

There has been no previous report of such a phenomenon in humans after recovery from chronic hypoxaemia.
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The effect of chronic hypoxaemia on ventilatory control has been extensively studied in humans. After many years of hypoxic exposure, the magnitude of the hyperventilation decreases in association with reduced hypoxic ventilatory response (HVR), which is called hypoxic desensitization [1]. It is commonly found in natives of high altitude with lifelong hypoxia [2–5], or in children with cyanotic congenital heart disease [6, 7]. After relief of the prolonged hypoxaemia, the blunted HVR has been reported to be normalized [6, 8] ,or to remain unchanged [7].

The present patient with pulmonary arterio-venous (AV) fistulae had moderate hypoxaemia, which seemed to have persisted for many years. We studied HVR and hypercapnic ventilatory response (HCVR) before and after surgical removal of the lesions, with particular emphasis on the time course of the recovery process and the difference of the two responses. After relief of the hypoxaemia, the magnitude of HVR began to decline over several weeks and gradually reached a steady value in about two months. To our knowledge, this is the first report of an attenuation of HVR after recovery from very prolonged hypoxaemia.

Case presentation

A 21 year old man was admitted to the hospital for the evaluation of cyanosis, which had been noticeable since he was a junior high school student (age 12–15). He was cyanotic on the lips and nails with marked clubbing of the fingers. Physical examination of the chest revealed no abnormality. The chest roentgenogram showed multiple nodules in the left lower lobe, the sizes of which

ranged 1.2–3.8 cm in diameter. All nodules had two tortuous bands connecting to the left hilum. A pulmonary arteriographic study confirmed the diagnosis of AV fistulae. Major fistulae of large size were localized in the left lower lobe, although several minute ones were distributed in bilateral upper lobes. The surgical removal of the left lower lobe was chosen as a therapeutic approach.

Before the operation, peripheral blood cell analysis revealed that there was moderate polycythaemia due to sustained hypoxaemia (red blood cell count $5.8 \times 10^6 \cdot mm^{-3}$, haemoglobin 18.2 $g \cdot dl^{-1}$, haematocrit 52%), which recovered to a normal value one month after the operation (red blood cell count $4.89 \times 10^6 \cdot mm^{-3}$, haemoglobin 15.2 $g \cdot dl^{-1}$, haematocrit 48%). Chemical and serological analyses of the blood showed no particular abnormalities. The whole blood 2,3-diphosphoglyceric acid (2,3-DPG), which had been elevated to 2.84 $\mu mol \cdot ml^{-1}$ before the operation, returned to a normal value of 2.02 $\mu mol \cdot ml^{-1}$.

Before the operation, arterial blood gas (ABG) analysis whilst breathing room air in a supine position revealed moderate hypoxia with hypocapnia (pH 7.42, arterial oxygen tension (Pa_{O_2}) 7.9 kPa (59 mmHg), arterial carbon dioxide tension (Pa_{CO_2}) 4.7 kPa (35 mmHg), calculated arterial oxygen saturation (Sa_{O_2}) 91%). Although Pa_{O_2} was elevated to 19.9 kPa (149 mmHg) after 20 min of 100% O_2 inhalation, Pa_{CO_2} was different from the value whilst breathing room air, despite sufficient arterial oxygenation (pH 7.45, Pa_{CO_2} 4.5 kPa (34 mmHg)). The right-to-left shunt value was calculated as 32% whilst breathing 100% O_2 (using the shunt equation and assuming an arterio-venous O_2 content difference of 4.5 volume %). One month after the operation, the shunt value was decreased to 8.6% (pH 7.39, Pa_{O_2}

68 kPa (510 Torr) and Paco$_2$ 5.3 kPa (39.8 Torr) during 100% O$_2$ inhalation), and Pao$_2$ under room air was elevated to 11.6 kPa (87 mmHg) in association with the normalization of Paco$_2$ (pH 7.40, PaCO$_2$ 5.6 kPa (42 mmHg)).

Before the operation, there were no significant pulmonary function disturbances (vital capacity (VC) 3.92 *l* (86% predicted value), forced expiratory volume in one second (FEV$_1$) 3 61 *l*, FEV$_1$/forced vital capacity (FVC) 92%, total lung capacity (TLC) 6.75 *l* (110% pred), functional residual capacity (FRC) 3.70 *l* (115% pred), residual volume (RV/TLC 42%, diffusion capacity of the lungs for carbon monoxide (DLCO/VA) 32.0 ml·min^{-1}·kPa·*l*$^{-1}$ (73%). Twenty one days after the left

lower lobectomy, lung volumes significantly decreased (VC 2.68 *l* (59% pred), FEV$_1$ 2.44 *l*, FEV$_1$/FVC 91%, TLC 4.67 *l* (77%pred), FRC 2.81 *l* (88% pred), RV/TLC 38%, DLCO/VA 31.7 ml·min^{-1}·kPa·*l*$^{-1}$ (72% pred).

Ventilatory response tests were conducted before the operation and on days 21, 28, 40, 72 and 200 postoperation. For these tests, we used the system developed in our laboratory, which can control end-tidal carbon dioxide and oxygen tension (PETCO$_2$ and PETO$_2$) simultaneously and independently in a predetermined [9]. The results are shown in figure 1. The patient was in a supine position and breathed spontaneously through a mouthpiece. Minute ventilation ($\dot{V}$E) was calculated every 15 s by integrating the expiratory airflow.
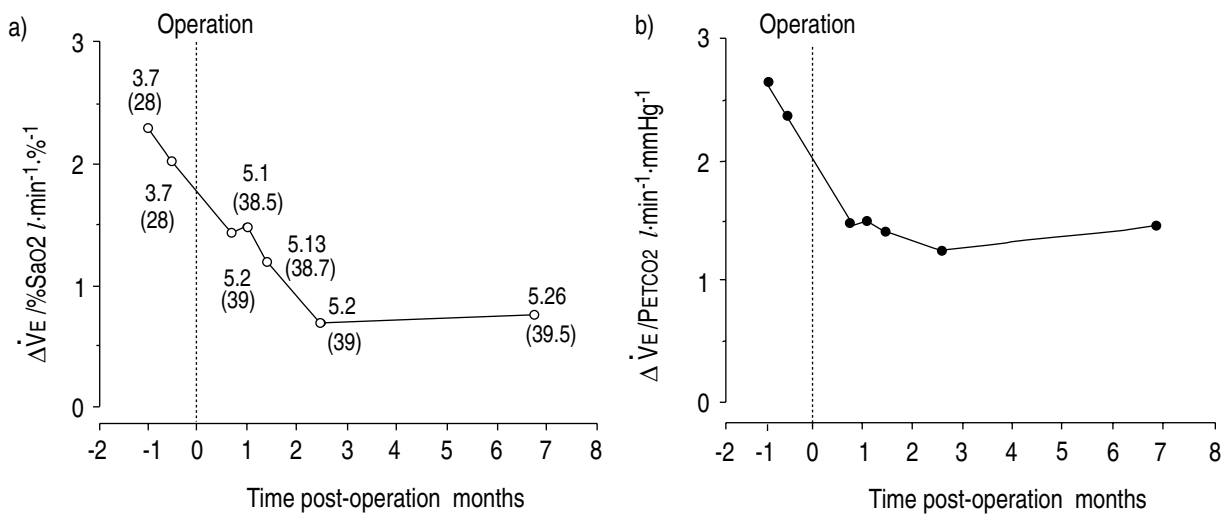

Fig. 1. – Change in: a) hypoxic ventilatory response (HVR, *l*·min^{-1}·%$^{-1}$) and b) hypercapnic ventilatory response (HCVR *l*·min^{-1}·mmHg^{-1}) after recovery from prolonged hypoxaemia. When first studied 21 days following surgery, both HCVR and HVR were found to be lower than they were preoperatively. During the next 1–2 months, HVR continued to fall significantly to a steady value, whereas HCVR showed no further fall. The mean values of end-tidal carbon dioxide tension (PETCO$_2$, mmHg) under which the HVR tests were conducted, are indicated in kPa (mmHg in parentheses). Note PETCO$_2$ in mmHg in b) Conversion factor 7.5 mmHg=1 kPa. $\dot{V}$E: minute ventilation; Sao$_2$: arterial oxygen saturation.
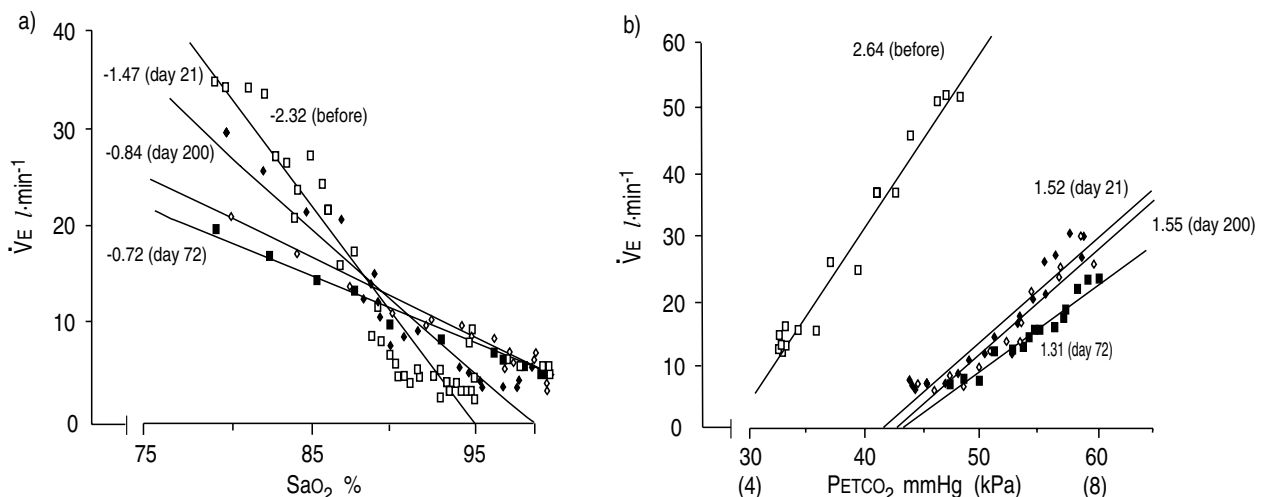

Fig. 2. – Change in position of a) hypoxic ventilatory response (HVR) and b) hypercapnic ventilatory response (HCVR) after recovery from hypoxaemia with regression slope. The HVR regression slope (*l*·min^{-1}·%$^{-1}$) decreased from a very high preoperative value to a high normal value by 72 days postoperatively. The preoperative response was not linear, showing almost no increase of ventilation as Sao$_2$ fell from 97% to 90%, his resting air breathing value, below which it became steep. On the other hand, there was a reduction in the slope value (*l*·min^{-1}·mmHg^{-1}) of the HCVR line, which was associated with its rightward shift, so that the Pco$_2$ intercept was positioned at a higher value (right). This may indicate an increased respiratory central excitability in the chronically hypoxic state. ☐ : before operation; ◆ : day 21 postoperation; ■ : day 72 postoperation; ◇: day 200 postoperation; Pco$_2$: carbon dioxide tension. For further abbreviations see legend to figure 1.

For the HVR test, after a steady ventilation was achieved whilst inhaling hyperoxic gas for 10 min (pre-operation 40% O_2, postoperation 25% O_2), the inspiratory O_2 content was progressively lowered within 5 min until Sao_2, monitored by a finger-tip pulse oximeter, finally reached 80%, whilst $Petco_2$ was kept isocapnic at the hyperoxic level. (The mean values of $Petco_2$, under which the tests were conducted, are indicated in parenthesis in figure 1). For the HCVR test, after a steady state of ventilation was obtained by inhaling 3% CO_2, the inspiratory CO_2 content was gradually raised within 5 min until $\dot{V}E$ reached 50 $l \cdot min^{-1}$ (the subject's symptom limit) or $Petco_2$ finally reached 8.0 kPa (60 Torr), whilst Sao_2 was kept hyperoxic. The magnitudes of HVR and HCVR were evaluated by the slope value of the $\dot{V}E$-Sao_2 regression line and that of the $\dot{V}E$-$Petco_2$ regression line, respectively.

The magnitude of HVR before the operation was 2.32 $l \cdot min \cdot \%^{-1}$, which was above the normal range. (The mean value for healthy subjects in our laboratory is 0.50 ± 0.20 (2SEM) $l \cdot min \cdot \%^{-1}$). At three weeks after the operation, the HVR value was 1.47 $l \cdot min \cdot \%^{-1}$, which then further declined and seemed to reach a steady value in about two months (0.72 and 0.84 $l \cdot min \cdot \%^{-1}$ at postoperative day 72 and 200, respectively). Similarly, the HCVR value decreased from 19.8–11.4 $l \cdot min^{-1} \cdot kPa^{-1}$ (2.64 to 1.52 $l \cdot min^{-1} \cdot mmHg^{-1}$) in the initial three weeks. The HCVR curve shifted right, so that the Pco_2 intercept was positioned at a higher value (fig. 2). However, after that, there was no obvious change of the slope value or position of the HCVR curve, in contrast to the change in HVR line.

Discussion

The HVR and HCVR values, measured three weeks after recovery from hypoxaemia, were smaller than those before the operation. This might be partly attributed to the lobectomy, since the loss of lung volume acts as elastic loading on ventilation. The ratio of HVR/VC, which was arbitrarily calculated in order to correct the altered lung volume, was similar before and after the operation (before 0.59; after 0.55). On the other hand, the ratio of HCVR/VC was slightly smaller after the operation (before 5.03, after 4.28). Several factors might influence these results. Firstly, the preoperative HVR value might be underestimated, since the effect of the chronic hypoxic ventilatory depression might not have been sufficiently eliminated, although the preoxygenation time before the test was set for about 10 min whilst inhaling a hyperoxic gas. Secondly, since the $Paco_2$ during the test was higher after surgery (reflected by the elevated $Petco_2$), the HVR value seemed to be overestimated postoperatively. Thirdly, the preoperative HCVR value might be overestimated, since the elevation of Pao_2 during the test seemed to be insufficient for hyperoxic chemodenervation due to the shunts before the operation. Therefore, in the initial few weeks, both HVR and HCVR seemed to decrease regardless of the loss in lung volume.

However, in the following period, the time-dependent change was different for HVR and HCVR. The magnitude of HVR further declined over several weeks and reached a steady value in about two months, whilst that of HCVR was maintained at a relatively constant level throughout the term. The coefficient of variations of the ventilatory response tests in our laboratory and others are reported to be in the range of 10–20% when measured repeatedly with an interval of about one week, which seemed to confirm the reliability of these tests [10]. Therefore, the attenuation of the HVR value could not simply be attributed to the measurement variation. On the other hand, the chest wall wound healing process after operation, if anything, might increase the ventilatory response values time-dependently over months.

The effect of chronic hypoxaemia on ventilatory control has been extensively documented in human beings, especially in residents at high altitude. It is generally known that after very prolonged exposures, from many years to a lifetime, ventilation appears to decrease in association with decreased ventilatory responsiveness to hypoxia, which is called hypoxic desensitization [1]. This loss of hypoxic response is commonly found in natives of high-altitude with lifelong hypoxia [2–5], and in children with cyanotic congenital heart disease [6, 7]. The desensitization can also be acquired later in life after many years of hypoxic exposure in nonnative residents of high altitude [1, 3, 11]. These changes are sometimes associated with a moderate but less pronounced decrease in hypercapnic response [3].

On the other hand, after recovery from prolonged hypoxaemia, the blunted HVR has been reported to be normalized [6, 8], or remain unchanged [7]. Although the present patient had been exposed to hypoxaemia for at least 7 yrs (he was cyanotic since he was in junior high school), the result of the HVR test seem to be the opposite of what was expected from his prolonged hypoxaemia. There have been no reports that described the change in HVR after revovery from such long term hypoxaemia in a patient with pulmonary AV fistulae. There may be several reasons why hypoxic desensitization was not obvious in this case. Firstly, such desensitization is thought to be acquired as a function of the duration and, perhaps, the severity of hypoxic exposure [3, 11, 12]. More severe hypoxia may accelerate the development of desensitization. In humans, when exposed to moderate altitude, hypoxic desensitization may require as long as 20 yrs to be fully expressed, although the adaptation process takes place in the order of some 7 yrs [3]. Since it is largely limited to persons hypoxic from the time of birth, neonatal hypoxic exposure may be an important factor [4, 5]. In the present case, the duration and/or severity of hypoxic exposure might have been insufficient for the development of hypoxic desensitization.

On the other hand, there is another form of hypoxic adaptation, termed ventilatory acclimatization [2, 13, 14], which is known to be associated with an increased ventilatory response to carotid body stimulation [2, 11, 13, 15–18]. There is a general enhancement of central nervous system (CNS) responsiveness both to peripheral and to central ventilatory stimuli. It is initiated by

hypoxic stimulation of the carotid bodies, leading to hyperventilation and hypocapnic alkalosis, which reduce cerebral blood flow (CBF) toward normal from its initial hypoxically elevated level. This time-dependent alteration in CBF may in return influence the results of the ventilatory response tests.

The dominant influence of ventilatory acclimatization seemed to remain in the present case. Several findings support this idea. Firstly, O_2 administration did not fully normalize the hyperventilation before surgery, although the elimination of chronic hypoxic ventilatory depression might partly influence the result. It is known that the increased ventilation in acclimatization is not rapidly reversed by acute normoxia [16]; it is more persistent when the hyperventilation continues for longer periods or hypocapnia is allowed to supervene. Secondly, hypoxic acclimatization is characterized by a left shift and increased slope of the HCVR curve, as was observed in this case [2, 13, 16, 17]. These are thought to be combined effects of altered sensitivity in the carotid bodies and a decreased bicarbonate ion in the respiratory centre. Thirdly, the period required for the recovery of HVR was in accord with previous reports. The increased response due to acclimatization is known to persist for months after return to low altitude [12]. On the other hand, the relatively rapid correction of the HCVR curve seemed to reflect the acid-base adjustments of cerebrospinal bicarbonate ion near the respiratory centre, which needs several weeks to occur. There must have been different acclimatization mechanisms for HVR and HCVR, since their recovery processes were different.

The specific mechanisms for hypoxic acclimatization in disorders with right-to-left shunts are still uncertain. They may include altered sensitivity of the carotid body itself or changes in CNS processing of chemoreceptor information [2, 11, 14–18]. In the present case, the HVR value before surgery was markedly above the normal range in our laboratory. Since the patient had significant right-to-left shunts, there might have been some endogenous mediators passing through the fistulae and potentially stimulating the carotid bodies. This may be the reason why the hypoxic desensitization was not obvious in this case. The attenuation of HVR after removal of the fistulae may partly reflect the elimination of such stimulatory effects on the carotid bodies. On the other hand, the effect of hypoxic pulmonary vasoconstriction should be noted. The shunt fraction would increase as inhalational hypoxia progressed, since it would increase resistance in normal lung arterioles and drive more blood through the anatomic shunts. This increasing shunt may have increased the arterial Pa_{CO_2} somewhat as Sa_{O_2} fell, thus further stimulating the ventilatory response. This mechanism can not be entirely excluded, since we did not measure the blood P_{CO_2} values.

To the best of our knowledge, this is the first report that observed a time-dependent attenuation of HVR after recovery from prolonged hypoxaemia in a patient with pulmonary AV fistulae. Further studies are required to decide whether the phenomenon observed in this case can be generalized for most hypoxic patients with this disorder.

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