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REVIEW

Effects of intermittent hypoxia on pulmonary haemodynamics: animal models *versus* studies in humans

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ABSTRACT: The aim of this review was to analyse the effects of intermittent hypoxia (IH) on pulmonary haemodynamics, comparing results of animal experiments with results of clinical studies.

In animal investigations even short hypoxic exposure, continuously or in short repeated episodes mimicking obstructive sleep apnoea (OSA), leads to pulmonary artery remodelling and to pulmonary hypertension (PH). Results of investigations on effects of nocturnal IH on pulmonary haemodynamics in patients with chronic obstructive pulmonary disease (COPD) are discordant. Earlier studies reported the development of mild PH in subjects desaturating during sleep, while more recent investigations did not confirm those findings.

Alveolar IH developing during apnoeic episodes during sleep in OSA patients is a disease-induced model to study its effects on pulmonary haemodynamics. In the majority of studies in OSA patients pulmonary arterial pressure remained within normal values. PH was found in patients with OSA accompanied by COPD and/or extreme obesity.

People commuting between lowland and high altitude due to their employment, are also repeatedly exposed to IH. Results of clinical investigations suggest that it did not lead to the development of permanent PH.

The mechanisms of discrepancies between effects of intermittent hypoxia in animal models and in humans remain to be studied.

KEYWORDS: Animal models, chronic obstructive pulmonary disease, high altitude, obstructive sleep apnoea syndrome, pulmonary circulation, remodelling

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In 1946 VON EULER and VON LILJESTRAND [1] from the Karolinska Institute in Stockholm published results of their experiments on the effects of various interventions on pulmonary arterial pressure (PAP), performed in cats. One of the interventions applied consisted of giving experimental animals hypoxic mixtures to breathe. Breathing of a hypoxic mixture (10.5% of oxygen) resulted in an acute increase in PAP. PAP quickly normalised once the experimental animals were given atmospheric air to breathe. VON EULER and VON LILJESTRAND [1] were the first to demonstrate that the reaction of pulmonary arteries to hypoxia was the opposite to that observed in the systemic circulation in which hypoxia induces vasodilatation [2]. They also, in the discussion section of the paper, put forward a hypothesis explaining the purpose of the described reaction writing: ''It is also required however, that the blood becomes distributed to the different parts of the lung in such a way, that the alveolar air will give off oxygen and take up carbon dioxide (CO_2) fairly evenly throughout the lungs''. They were right. A few years later a concept of ventilation/perfusion relationships in the lung was documented [3].

One year later hypoxic pulmonary vasoconstriction (HPV) was confirmed in healthy man. Investigations were performed in the cardiorespiratory laboratory at Bellevue Hospital, New York, USA directed by A. Cournand and D.W. Richards, Jr. MOTLEY *et al*. [4] performed pulmonary artery catheterisation in five healthy subjects. Mean PAP averaged 13 mmHg whilst subjects were breathing air. During hypoxic

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mixture breathing, 10% of oxygen was given and mean PAP rose considerably to 23 mmHg. Cardiac output was measured by the Fick method. During hypoxic exposure pulmonary vascular resistance (PVR) doubled, mainly due to vasoconstriction as there was no significant change in the cardiac output.

Two authors of those two seminal investigations were later awarded the Nobel Prize. U.S. von Euler, together with B. Katz and J. Axelrod, were awarded the Nobel Prize in 1970 for the discovery of noradrenaline. In 1956, A. Cournand received a joint prize together with W. Forssmann and D.W. Richards, Jr. for the introduction of cardiac catheterisation into clinical practice.

HYPOXIC PULMONARY VASOCONSTRICTION AND VASCULAR REMODELLING

BARER *et al.* [5] found, in animal experiments, that reduction of the alveolar oxygen pressure to <70 mmHg elicits strong pulmonary vasoconstriction. HPV is common in mammals. However, there are important interspecies differences in HPV. The rabbit shows almost no reaction to hypoxia. Cattle present the strongest vasoconstriction. In man hypoxic vasoconstriction is weaker than in the rat [6].

There is also great individual variability in HPV among humans. NAEIJE *et al*. [7] demonstrated that in healthy man, individual HPV varied from almost no reaction to very strong vasoconstriction. LAKS *et al*. [8] found that, during hypoxic exposure in individual subjects, the increase in mean PAP varied between 2–15 mmHg.

After some debate about the site of hypoxic constriction in the pulmonary vascular bed it was demonstrated that hypoxia constricts pulmonary muscular arteries, vessels of <1 mm in diameter. [9–12]. Despite many years of extensive investigations, the mechanism of HPV is still under debate. A current theory suggests that reduced oxygen pressure inhibits smooth muscle cell voltage–dependent potassium channels, resulting in membrane depolarisation, the influx of calcium and muscle fibre shortening [13, 14]. Two such channels, Kv_2, and $Kv_{1.5}$, have been described [15]. In addition to intrinsic smooth muscle cell reactivity to hypoxia, altered endothelium-mediated relaxation of pulmonary arteries involving nitric oxide may also play a role [16]. Also, acidosis enhances HPV [17].

PROLONGED HYPOXIA

Whilst short exposure to hypoxia causes HPV, prolonged hypoxia results in remodelling of distal branches of pulmonary arteries. Experiments in rats kept in hypoxic conditions showed that new muscle and endothelial cells appear in the walls of pulmonary muscular arteries during the first days of continuous hypoxia [18–21].

Hypertrophy and hyperplasia of the medial muscular coat and intimal hypertrophy, muscularisation and fibrosis, remodel the pulmonary microcirculation. Lengthening of the resistance segment, thickening of the wall and narrowing of the lumen result in a durable increase in PVR and an increase in the right ventricle afterload, leading to pulmonary hypertension (PH) and finally to right ventricular hypertrophy [22].

In man, the character of remodelling is somewhat different than in the rat. Hypertrophy of the circular muscular layer between internal and external elastic laminae is less prominent. More important are changes in the intima. Longitudinal bundles of smooth muscle develop, together with endothelial proliferation, and fibroelastosis [23–26]. Intensive remodelling also takes place in the pulmonary arterioles. In healthy man, the pulmonary arterioles are thin walled vessels without a muscular layer. Prolonged hypoxia leads to muscularisation of the arterioles and the development of intimal changes similar to that observed in the muscular arteries contributing further to the increase in PVR.

INTERMITTENT HYPOXIA IN ANIMAL MODELS

Several investigations have been performed in rats, evaluating effects of intermittent hypoxia (IH) on pulmonary haemodynamics [27–31]. Severe hypoxia was applied in a hypobaric chamber for 4–8 $h \cdot day^{-1}$, 5–7 days a week, with a total of 13–24 exposures. Oxygen pressure in the inspired air ranged from 56 mmHg [30] to 70 mmHg [31]. The results were fairly uniform. Even the shortest exposure to hypoxia resulted in an increase in right ventricle systolic pressure, and right ventricular weight. Remodelling of pulmonary muscular arteries after IH was similar to that observed in rats exposed to prolonged hypoxia [20, 21, 32, 33].

Another model of IH studied in animals was mimicking pathophysiology of obstructive sleep apnoea (OSA) by applying rapid changes in the composition of inspired gases. MCGUIRE and BRADFORD [34] exposed experimental rats to consecutive 30 s periods of severe hypoxia followed by 30 s of normoxia for 8 $h \cdot day^{-1}$ for 5 weeks. During that time, mean PAP increased from 20.7 ± 6.8 to 31.3 ± 7.2 mmHg ($p<0.01$) and right ventricular mass index increased from 0.25 to 0.31 ($p<0.05$) indicating right ventricle hypertrophy.

FAGAN [35] performed similar experiments in mice exposed to 2 min of hypoxic environment (10% of oxygen), followed by 2 min of normoxia, for 8 $h \cdot day^{-1}$ for 4 weeks. Right ventricle systolic pressure increased from 30 to 36 mmHg and right ventricle mass index increased from 0.22 to 0.27. Both changes were significant ($p<0.01$). FAGAN [35] also found that the number of muscular arterioles in the lung of rats exposed to IH significantly increased ($p<0.005$).

INTERMITTENT HYPOXIA IN COPD PATIENTS

The development of alveolar hypoxia in chronic obstructive pulmonary disease (COPD) is a long process. It has been noted that at first, alveolar hypoxia may appear during sleep. In normal man sleep induces important changes to breathing. Resetting of the respiratory centre to a higher arterial CO_2 tension [36], decreased motor neurone output [37], decreased intercostal muscle activity [38], an increase in airway resistance [39] and decrease in functional residual capacity [40] have been reported. All those changes lead to hypoventilation [41], especially during rapid eye movement sleep [42]. Episodes of alveolar hypoventilation lead to a small decrease in arterial oxygen pressure, with no clinically important effect on oxygen transport.

In patients with COPD, breathing disorders induced by sleep are more pronounced [40, 43–44]. Ventilation/perfusion mismatching, the main mechanism of hypoxaemia in COPD, also increases during sleep [45].

Hypoxaemia during sleep in COPD patients was first reported by ROBIN [46] and later confirmed by several authors using an elaborate method of multiple arterial blood sampling [47–49]. The introduction of noninvasive oximetry allowed for the continuous monitoring of arterial blood saturation [50, 51]. The appearance and severity of nocturnal arterial blood desaturations have generally been related to the arterial blood gas status during wakefulness [52].

However, it was found that some COPD patients who are normoxaemic during the day develop hypoxaemia during sleep. The prevalence of nocturnal desaturation in COPD patients preserving satisfactory oxygenation while awake was not well established. FLETCHER *et al*. [53] found nocturnal desaturation in 25% of 135 COPD patients, defining desaturation as a fall in S_{a,O_2} below 90% for 5 min or more with a nadir of 85% or lower. LEVI-VALENSI *et al*. [54] found nocturnal desaturation in 18 out of 40 COPD patients, defining desaturation as spending >30% of sleep time in saturation below 90%. It was found that overnight oxygen supplementation prevented nocturnal desaturation episodes [55].

Nocturnal desaturation reflects episodes of alveolar hypoxia. Simultaneous continuous recordings of arterial blood saturation and PAP during sleep in COPD patients showed that desaturation dips coincided with the increase in PAP [55, 56].

Contrary to the uniform results of experiments in animals showing that IH leads to development of PH, the results of studies on the effects of IH on pulmonary haemodynamics in patients with COPD were rather contradictory. In one study [57], pulmonary haemodynamics were investigated in 16 patients desaturating during sleep and in 10 nondesaturating patients. In both groups mild PH at rest was found. During steady state exercise, PAP increased significantly more ($p<0.01$) in desaturating patients than in nondesaturators.

The authors of another study [58] demonstrated that nocturnal oxygen supplementation in desaturating patients prevented the progression of PH, during a 3-yr follow-up trial. In one multicentre investigation, survival in 169 desaturating and nondesaturating patients not treated with oxygen was analysed [59]. Desaturating patients presented a significantly worse ($p<0.02$) survival curve compared to nondesaturators.

More recently, a series of similar investigations were performed in Europe. In the first study [60], 94 COPD patients with diurnal arterial oxygen tension (P_{a,O_2}) >55 mmHg were divided into 66 desaturating patients and 28 nondesaturators. In both groups mean PAP was slightly <20 mmHg. Also, on exercise, increase in PAP was of the same magnitude in desaturators and nondesaturators.

In the second investigation [61], 76 desaturating COPD patients, spending >30% of sleep in saturation below 90%, were divided into two groups. A total of 41 of them received nocturnal oxygen supplementation and 35 served as controls. After 2 yrs of follow-up, changes in PAP were insignificant in both groups.

Also, the survival rate in 68 COPD patients, both desaturators and nondesaturators not treated with oxygen, matched for diurnal P_{a,O_2}, FEV1 and followed up for 4 yrs, was not significantly different [62].

The differences in the results of those two series of studies could be explained by the different number of investigated patients, their selection and, perhaps, effects of other factors leading to PH in COPD. The patients included in the studies by FLETCHER and colleagues [57, 58] presented with mild PH at entry and some of them with signs of left ventricle dysfunction, whereas patients in the studies by CHAOUAT and colleagues [60, 61] presented with borderline PAP.

INTERMITTENT HYPOXIA IN COPD PATIENTS ON LONG-TERM OXYGEN TREATMENT

Patients with severe COPD and permanent hypoxaemia, treated with domiciliary oxygen, may also experience IH. Such patients usually present with permanent PH. Oxygen should be given continuously, but the majority of patients interrupt oxygen breathing several times a day. SELINGER *et al*. [63] recorded PAP continuously in COPD patients undergoing long-term oxygen treatment (LTOT). Whilst patients were breathing oxygen, mean PAP was stable, slightly >30 mmHg. Interruption of oxygen administration resulted in a steady increase in mean PAP up to 40 mmHg. A simultaneous rise in the calculated driving pressure across the pulmonary vascular bed confirmed that the rise in the PAP was due to pulmonary vasoconstriction.

In severe COPD patients, desaturation may also appear during oxygen breathing. Continuous 24-h pulse oximetry was recorded in COPD patients treated with domiciliary oxygen. Desaturation episodes were observed during some daily activities and during sleep while patients were breathing oxygen [64–67].

It is difficult to assess how those pulmonary vasoconstriction episodes caused either by interruption of oxygen breathing or despite oxygen breathing, affect long-term pulmonary haemodynamics.

ZIELIŃSKI *et al*. [68] followed-up 95 COPD patients, with very advanced disease, starting on LTOT. Mean oxygen breathing hours was 14.5 $h \cdot day^{-1}$. Pulmonary artery catheterisation had been performed at entry and repeated every 2 yrs, up to 6 yrs. A small reduction in mean PAP and mean PVR was observed after the first 2 yrs of treatment, followed by stabilisation of mean PAP and of mean pulmonary vascular resistance for the remaining 4 yrs of observation. The mean PAP at entry was 25 ± 7 mmHg and 26 ± 6 mmHg at 6 yrs. It seems that breathing oxygen for 14.5 $h \cdot day^{-1}$ is sufficient to prevent the progression of PH in patients undergoing LTOT. Other authors have reported a reduction of PAP after LTOT [69, 70]. Based on these data it seems that short, intermittent episodes of hypoxia do not aggravate PH in severe COPD patients.

INTERMITTENT HYPOXIA IN OBSTRUCTIVE SLEEP APNOEA

OSA is a very common disease, defined as an intermittent repeatable cessation of airflow to the lung due to closure of the airway at a pharyngeal level. Cessation of airflow leads to progressive asphyxia and increased respiratory effort, leading to brief arousal from sleep and restoration of airway patency. The patient then returns to sleep and the sequence of events is

repeated. In patients with severe OSA, episodes lasting 20–40 s may appear 300–400 times per night. An apnoeic episode results in alveolar hypoxia and HPV. In patients with OSA, large swings of intrathoracic pressure during apnoea greatly affect intravascular PAP. To assess HPV during apnoeic episodes, true transmural PAP has to be measured [71]. HPV is resolved at the resumption of breathing [72].

The first polysomnographic recordings in patients with OSA included monitoring of PAP [73, 74]. Patients with severe OSA demonstrated an increase in PAP during apnoeic episodes.

In early studies assessing pulmonary haemodynamics during the day, based on a limited number of patients with severe OSA, PH was found in the majority of subjects studied [75–77]. However, many of the subjects also presented with signs of COPD and diurnal hypoxaemia. Larger, nonselected groups of OSA patients were collected by WEITZENBLUM [78] and CHAOUAT [79] of the Strasbourg group. Among 220 consecutive patients with OSA diurnal PH (mean PAP 26 ± 5.8 mmHg) was found in 17%. The majority of patients with PH presented with signs of COPD [79]. CHAOUAT *et al*. [79] concluded that in the majority of patients, PH could be explained by diurnal hypoxaemia due to COPD or obesity-induced hypoventilation.

Similar findings have been reported by SANNER *et al*. [80]. They found PH in 20% of OSA patients. Patients with PH presented with restrictive impairment of ventilatory reserves due to obesity. Permanent hypoventilation in severely obese patients with OSA may be the main cause of development of pulmonary hypertension [81].

HAWRYLKIEWICZ *et al*. [82] studied 67 patients with severe OSA and 17 patients with OSA complicated by COPD, called the overlap syndrome [83]. In patients with OSA (mean apnoea-hypopnoea index $=62 \pm 22$) mild PH (mean PAP $= 24 \pm 3.6$ mmHg) was found in 11 subjects. A total of 56 patients presented with normal PAP (mean 14.2 ± 2.8 mmHg). Patients with PH were younger, more obese and had a higher number of apnoeic episodes than subjects with normal PAP. The overnight arterial blood oxygen saturation was not significantly different between patients with normal PAP and patients with PH, suggesting that the nocturnal desaturation did not play an important role in the development of PH. In contrast to patients with ''pure'' OSA, among 17 patients with the overlap syndrome, only three subjects had normal PAP (mean $=12.3 \pm 3.1$ mmHg) and 14 presented with moderate PH (mean PAP $=26.8 \pm 5.1$ mmHg).

However, there are a number of studies demonstrating that PH is rather frequent in patients with OSA. LAKS *et al*. [84] found PH in 42 of 100 OSA patients. Patients with PH were older, had higher CO_2 arterial tension (P_{a,CO_2}), lower arterial oxygen tension and lower FEV1. Such a constellation of signs suggests that some of those patients belonged to the group of the overlap syndrome.

Recently, BADY *et al*. [85] found PH in 12 out of 44 patients with ''pure'' OSA. Patients with PH had significantly lower daytime arterial oxygen tension, higher daytime CO_2 tension, more severe nocturnal hypoxaemia, and higher body mass index (BMI). Stepwise multiple regression analysis showed that mean PAP was positively correlated with BMI and negatively with P_{a,O_2}. Also, SAJKOV *et al*. [86] reported PH in 12 out of 27 patients with OSA. His results should be cautiously analysed, as in that study PAP was measured indirectly using the echo-Doppler method.

The large differences in the literature concerning the prevalence of PH in patients with OSA may perhaps be related to behavioural factors [87–89] genetic predisposition [6, 7, 90], severity of obesity [91] or left ventricle dysfunction [80].

SHORT-TERM HYPOXIA AT HIGH ALTITUDE

At sea level, the oxygen pressure in the inspired air (P_{i,O_2}) is equal to 150 mmHg. At an elevation of 3,000 m, P_{i,O_2} is one third lower than at sea level. People born and living in Leadville, Colorado, USA, 3,100 m above sea level (ASL), have mild PH (mean PAP=24 mmHg) [92]. At the elevation of 5,000 m, $P_{i,O2}$ equals 75 mmHg. Aimara and Ketchua Indians inhabiting the high altitude plateau in the Andes, Bolivia and Peru living at elevations ~4000 m ASL, have moderate PH (mean PAP=27–28 mmHg) [93–95]. During a 6-week simulated ascent to Mount Everest, Nepal, in a hypobaric chamber (P_{i,O_2}at the summit=43 mmHg), healthy volunteers developed moderate PH (mean PAP $=34 \pm 3$ mmHg), partly unresponsive to oxygen breathing [96].

Hypertrophy of the muscular layer in pulmonary muscular arteries and arterioles is a prominent feature of remodelling in people permanently living at high altitude [97] in distinction to changes observed in patients with COPD [25]. It may be hypothesised that high altitude hypoxia-induced structural changes in pulmonary arteries develop rather rapidly in normal man. The only partial reduction of PH during oxygen breathing in subjects exposed to 6 weeks of hypoxia simulating ascent to Mount Everest implies that there were structural changes in the pulmonary arteries in addition to vasoconstriction [96]. Indian soldiers deployed in the very high mountains (~6,000 m ASL) for 18 weeks developed signs of right heart failure. Pulmonary artery catheterisation performed a few days after the descent to low altitude showed that the soldiers still had mild PH, mean PAP=26 mmHg. PH completely resolved after 12 weeks of recovery at lowland [98].

SHIFT WORK AT HIGH ALTITUDE

In the last 20 yrs a new type of exposure to high altitude has developed. To assure uninterrupted functioning of high altitude mines and telescope stations, commuting of the working staff between low and high altitude has become more and more frequent. The pattern of commuting varies from hours to weeks at high altitude balanced by an equal time at sea level or moderate altitude. The medical and physiological consequences of indefinitely repeated exposure to high altitude are poorly understood [99, 100].

There is very little data concerning effects of intermittent hypoxia of high altitude on pulmonary haemodynamics. One investigation was performed in the Collahuasi copper mine, Chile [101]. Miners working there spend 7 days at altitude ranging from 3,800–4,600 m ASL. The working shift is followed by a 7-day holiday at sea level. A total of 29 miners, mean age 25 yrs, were followed up for 2.5 yrs. One of the variables studied was PAP, assessed at sea level by an echocardiographic method. Initial measurement showed

normal PAP. There was no increase in the PAP measured four times during the 31 months of follow-up. At each investigation, after initial measurements were taken whilst breathing air, subjects were asked to breathe a hypoxic mixture, mimicking conditions at the level of the mine. Pulmonary vasoconstriction of fairly constant magnitude was observed.

Another study on pulmonary haemodynamics in miners working in the gold mine situated in the Tien-Shan Mountains in Kyrgyzstan was recently published by SARYBAEV *et al*. [102]. A total of 26 healthy Caucasian males, mean age 42±9 yrs were studied. They had been working at the mine for 4 weeks at elevations ranging from 3,700–4,200 m ASL followed by 4-week holidays at low altitude. Pulmonary haemodynamics were assessed by the echocardiographic method. The first examination was performed at low altitude on return from holidays. The mean calculated PAP ranged from 10–18 mmHg (mean=14.7±2.7 mmHg). Second measurements were performed at the end of the 4-week working shift at 3,700 m ASL, P_{i,O_2}=89 mmHg. The individual increase in mean PAP was very variable, ranging between 3–19 mmHg (mean PAP=25.8±8.3 mmHg). Ten subjects with the strongest hypoxic vasoconstriction, with an increase in PAP under hypoxic condition of >10 mmHg, were selected and followed up for the next 2 yrs.

Consecutive measurements were performed yearly at high altitude at the end of the working shift. Initially in those 10 subjects, mean PAP at low altitude was 15±2 mmHg and increased to 28±4 mmHg at high altitude. Mean PAP during the next 2 yrs remained unchanged. During the last measurements a hyperoxic test was performed. Subjects received 100% oxygen to breathe for 30 min. The mean PAP fell to 18± 2.7 mmHg, confirming that PH was induced by HPV and was reversible.

The results of these two studies suggested that prolonged exposure to intermittent high altitude hypoxia at elevations ~4,000 m ASL did not lead to permanent PH, contrary to permanent dwellers at high altitude who, at similar altitudes, suffer from moderate PH.

However, there is an exception to that rule. There is one ethnic group living in the high mountains who do not develop PH. Tibetans, by a long process of adaptation, are almost free from hypoxic pulmonary vasoconstriction and hypertension [103, 104].

WHY ARE THERE DIFFERENCES IN EFFECTS OF INTERMITTENT HYPOXIA IN ANIMALS AND IN HUMANS?

The discrepancy between the results of animal experiments and those of clinical studies in humans is difficult to explain. Donald Heath, a researcher with great experience in the field of pulmonary circulation at sea level and at high altitude, suggested that the rat is a bad model of hypoxic PH [105]. In rats, muscularisation of pulmonary arteries is the most prominent feature of hypoxic remodelling, whereas in man, endothelial proliferation and fibroelastosis play a crucial role.

Also, hypoxia applied in animal experiments has been much more severe than the hypoxia developing in the disease state in humans. This could result in a different severity of vasoconstriction and remodelling. In animals with normal lungs alveolar hypoxia is fairly uniform, contrary to uneven distribution of inspired air in patients with COPD or OSA. This may result in large regional differences in hypoxic pulmonary vasoconstriction, and in remodelling.

It is also possible that an episode of hypoxic pulmonary vasoconstriction in humans must last a certain time before it initiates reactions leading to arterial wall remodelling [106]. Another cause of discrepancy may be related to an individual susceptibility to the hypoxic stimulus [107].

CONCLUSIONS

In animal models, intermittent severe hypoxia leads to the development of pulmonary hypertension irrespective of hypoxia/normoxia intervals. Intermittent hypoxia in man seems to exert only a small, probably clinically unimportant, effect on pulmonary haemodynamics.

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