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EDITORIAL

Hypoxic pulmonary hypertension in man: what minimum daily duration of hypoxaemia is required?

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It is recognized that chronic alveolar hypoxia is the major cause of pulmonary hypertension in chronic respiratory diseases [1]. Accordingly, this form of secondary pulmonary hypertension is often termed hypoxic pulmonary hypertension. The acute effects of alveolar hypoxia (hypoxic vasoconstriction) must in fact be distinguished from the long-term effects (pulmonary vascular "remodelling") and both effects contribute to increased pulmonary vascular resistance and increased pulmonary artery pressure. The threshold value of hypoxaemia under which the risk of developing pulmonary arterial hypertension (PAH) becomes elevated, is 55–60 mmHg, which is equivalent to an oxygen saturation of 88–90%. This level is generally required in patients who are candidates for long-term oxygen therapy [2–4].

In chronic respiratory diseases, and particularly in chronic obstructive pulmonary disease (COPD), hypoxaemia is most often permanent, being observed during both daytime and night-time. Indeed, it is subjected to fluctuations and hypoxaemia may worsen during exercise (*e.g.* walking) and during sleep. In one particular disease, obstructive sleep apnoea syndrome (OSAS), hypoxaemia may be limited to night-time, that is to sleep. This sleep-related hypoxaemia can also be observed in the early stages of chronic respiratory diseases, such as COPD [5], cystic fibrosis and restrictive lung disease, when daytime hypoxaemia is not yet present. This has raised the question: can isolated nocturnal hypoxaemia induce pulmonary hypertension in humans? In other terms, what minimum daily duration of hypoxaemia is required to generate permanent (night-time and daytime) pulmonary hypertension? Apart from its theoretical interest, the answer to this question may have some practical importance. As an example, if it is demonstrated that COPD patients without significant daytime hypoxaemia (arterial oxygen tension (P_{a,O_2}) >60 mmHg) but with sleep-related hypoxaemia, develop pulmonary hypertension, it will be justified to prescribe them nocturnal oxygen therapy.

At the present time it is not known what the daily minimum requirement is for developing PAH and whether isolated nocturnal (sleep-related) hypoxaemia is sufficient for that purpose. Indeed, experimental studies cannot be performed in humans for evident ethical reasons. However, indirect arguments can be obtained, first, from experimental data collected in animals and, secondly, from observations made in the best clinical "model" of sleep-related hypoxaemia, which is the OSAS.

In this issue of the *European Respiratory Journal*, McGuire and Bradford [6] present the results observed in rats with alternating periods of normoxia and hypercapnic hypoxia every 30 s for 8 h per day, for 5 days per week, for 5 weeks, as a model of the intermittent blood gas changes which occur in sleep disordered breathing in humans, and particularly in OSAS. They have observed that chronic intermittent hypercapnic hypoxia caused a significant increase in pulmonary arterial pressure (PAP) from 20.7±6.8–31.3±7.2 mmHg. It also increased right ventricular weight and haematocrit. These results support the idea that nocturnal episodic hypercapnic hypoxia causes pulmonary hypertension in the absence of continuous hypoxia. However, the authors have carefully concluded that "it is unclear how these results in rats might transpose to humans with OSAS".

It must be underlined that the rat model used by McGuire and Bradford [6] is a good one for the changes that occur during central sleep apnoeas (periodic breathing), but is probably not a good model in OSAS, the most frequent cause of sleep disordered breathing in humans. Indeed, in contrast to central apnoeas, obstructive breaths are characterized by markedly negative intrathoracic pressures, inducing acute haemodynamic changes [7, 8] that could have long-term cardiovascular consequences. But it must also be emphasized that the effects of repetitive episodic hypoxia on PAP in animals have not been previously investigated, the remarkable study by Fletcher *et al.* [9] having been devoted to systemic pressure and right ventricular weight but not to PAP. In this regard, the study by McGuire and Bradford [6] adds substantially to the knowledge in this field.

It is known from earlier experimental studies, all performed in rats [10–12], that intermittent hypoxia (2–8 $h \cdot day^{-1}$) induces right ventricular hypertrophy. It is also known from the study by Kay [13] that experimental hypoxic pulmonary hypertension, observed in rats after 4 weeks in a hypobaric chamber, is corrected after recovery in room air, but not if intermittent normoxia (8 and 16 $h \cdot day^{-1}$) is used during recovery. From these studies and the present one by McGuire and Bradford [6] it can be concluded that in rats intermittent hypoxia, with repetitive episodes mimicking sleep apnoeas or not, with associated hypercapnia or not, causes pulmonary hypertension and right ventricular hypertrophy. Are

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these experimental results transposable to humans? Are they confirmed by clinical observations made in OSAS patients?

In fact, the majority of OSAS patients do not exhibit permanent (diurnal) PAH. In the study by CHAOUAT *et al.* [14], which included 220 consecutive, unselected OSAS patients, only 37 (17%) of the patients had PAH defined by a resting PAP $\geqslant$20 mmHg. Furthermore, PAH was generally associated with daytime hypoxaemia (24/37 patients) and less often with hypoxaemic hypercapnia (15/37 patients). Hypoxaemia and hypercapnia were strongly linked to the presence of an obstructive ventilatory defect (COPD) and were also observed in some patients with a restrictive defect (severe obesity). These results were in agreement with the earlier findings by BRADLEY *et al.* [15] who showed that "cor pulmonale" was infrequent (6/50 patients) in OSAS and was exclusively observed in patients exhibiting daytime alveolar hypoventilation and an obstructive ventilatory defect. Taken together these data do not support the hypothesis that PAH can develop in OSAS patients in the absence of daytime hypoxaemia.

However, there is still controversy in this field and other results [16, 17] would favour this hypothesis. SAJKOV *et al.* [16] have observed the presence of PAH in 11/27 OSAS patients without associated pulmonary or heart disease. Hypoxaemia was very slight in this group (P_{a,O_2}=72.2±7.6 mmHg). Their cohort was rather small and PAP was not measured by right heart catheterization but estimated from pulsed Doppler measurement. LAKS *et al.* [17] have found PAH in 42/100 patients, six of whom had a normal daytime P_{a,O_2} ($\geqslant$80 mmHg), but the wedge pressure was not measured and PAH could have been of the postcapillary type in some of their markedly overweight patients (mean body mass index (BMI)=38 kg·m^{-2}). More recently, BADY *et al.* [18] have found PAH in 12/44 patients without COPD; the PAH group differed by a lower P_{a,O_2} (but hypoxaemia was very mild) and by the presence of marked obesity (BMI= 37.4±6.0 kg·m^{-2}).

Thus, permanent PAH may be present in some OSAS patients without significant daytime hypoxaemia, but the vast majority of OSAS patients never develop PAH. The risk of PAH is indeed increased in those OSAS patients who exhibit an associated COPD or a severe obesity or a combination of both. Interestingly, there is no relationship between the severity of OSAS, expressed by the apnoea/hypopnoea index and the presence of PAH [14, 15, 17]. Almost all studies agree on the fact that PAH is generally of mild degree in OSAS patients (PAP most often in the range 20–35 mmHg) [14, 17, 18], which is very similar to COPD.

Another "model" of intermittent hypoxaemia in humans is sleep-related hypoxaemia in COPD patients not exhibiting significant daytime hypoxaemia. This nocturnal desaturation is not uncommon in COPD [5, 19] and it has been hypothesized that it could lead to permanent PAH [20]. Initial studies [19, 21] have shown that nocturnal desaturators had a higher PAP than nondesaturators, the daytime P_{a,O_2} being >60 mmHg in all patients. A more recent study [22] that included a much larger number of patients (n=94) has shown no difference in PAP between desaturators and nondesaturators. PAP was not correlated with the degree and duration of nocturnal hypoxaemia. A further study from the same multicentric group [23] has clearly shown that nocturnal oxygen therapy given to sleep-desaturators, whose daytime P_{a,O_2} was >60 mmHg, did not modify the evolution of pulmonary haemodynamics over a period of 2 yrs in comparison to nocturnal desaturators not receiving nocturnal oxygen therapy. These results in COPD patients do not support the hypothesis that (isolated) sleep-related hypoxaemia is sufficient for inducing PAH in COPD patients, and they suggest that the prescription of nocturnal oxygen therapy in isolation is not justified in COPD patients.

It thus appears that there is discrepancy between experimental data and the results of clinical studies, and that the observations made in animals cannot automatically be transposed to humans. It must be recalled that marked interindividual differences in the response of the pulmonary circulation to hypoxia have been observed in healthy individuals [24, 25] as well as in chronic obstructive pulmonary disease and obstructive sleep apnoea syndrome patients [25, 26]. Accordingly, in obstructive sleep apnoea syndrome "responders" to alveolar hypoxia repetitive elevations of pulmonary arterial pressure during sleep may lead, with time, to pulmonary vascular remodelling, even in the absence of daytime hypoxaemia, as speculated by SAJKOV and coworkers [16, 27]. This could explain the presence of permanent pulmonary arterial hypertension in at least a few patients without daytime hypoxaemia.

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