

CORRESPONDENCE

Physiological changes in respiratory function associated with ageing

To the Editor:

We read with interest the review of JANSSENS *et al.* [1] entitled "Physiological changes in respiratory function associated with ageing", more specifically the subheading devoted to changes in arterial oxygenation and ventilation-perfusion (V'/Q') relationships. Although the seminal study of WAGNER *et al.* [2] was addressed in full, it was a shame that they did not discuss the more recent comprehensive work of our group in this field [3]. We extensively investigated the distributions of V'/Q' ratios in 64 healthy individuals aged 18–71 yrs. The principal findings of that study were: 1) that V'/Q' imbalance, but not increased intrapulmonary shunting, did increase with age as previously expected; 2) that the increase over the span of ~50 yrs was physiologically very small; 3) that most of the variance in V'/Q' mismatch in this cohort of subjects was not due to ageing and remained unsettled; and 4) that the fall in arterial partial pressure of oxygen (PO_2) with age was also quite small but was internally consistent with the V'/Q' changes measured independently.

V'/Q' relationships were characterized in most of these healthy individuals by narrow distributions that widened slightly with age together with a trivial shunt of <1% of the cardiac output in 90% of cases. Both the second moments (dispersions) of pulmonary blood flow (Log SDQ) and of alveolar ventilation (Log SDV) increased by ~0.1 between 20–70 yrs. Accordingly, the dispersion of pulmonary perfusion (Log SDQ) increased from 0.36–0.47, akin to a decrease of oxygen tension in arterial blood (Pa_{O_2}) of only ~6 mmHg. Only 10% of the total variance was attributed to age. A similar amount was due to intrasubject variability, but none was due to variations in other factors, such as forced expiratory volume in one second (FEV₁), FEV₁/forced vital capacity (FVC) ratio, weight or height. We did not measure closing volume and it is therefore likely that age could disturb V'/Q' matching as a result of increases in closing volume. However, since the latter mechanism is highly unlikely to influence V'/Q' relationships in young healthy individuals [4], and since the variance of the dispersion of pulmonary blood flow was as large amongst the subset of young as that of old individuals, we would postulate that increased closing volume is not a determinant factor of the variance in V'/Q' homogeneity.

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To the Editor:

With great interest, we read the review article by JANSSENS *et al.* [1] concerning physiological changes in respiratory function associated with ageing. The authors have summarized in the abstract that "Physiological ageing of the lung is associated with dilatation of alveoli, enlargement of airspaces, decrease in exchange surface area and loss of supporting tissue for peripheral airways ("senile emphysema"), changes resulting in decreased static elastic recoil of the lung and increased residual volume and functional residual capacity". Although the functional and structural alterations of the respiratory system with ageing were sophisticatedly described in the article, we are not in agreement with the authors that physiological ageing of the lung is determined as the senile emphysema.

Because the airspace enlargement including ductectasia and loss of elastic recoil of the lung are commonly investigated in aged humans without noxious insults [2–4], VERBEKEN *et al.* [5, 6] proposed that the structural and functional characteristics caused by isolated airspace enlargement seen in the elderly as "senile lung (ageing lung)", were differentiated from senile emphysema by the absence of alveolar wall destruction. The ductectasia and airspace enlargement without alveolar wall destruction was quantitatively assessed by morphometric indices, *e.g.* mean linear intercept (MLI) and destructive index (DI), while the loss of lung elastic recoil was assessed by the left-sided shifts of pressure-volume curves of lungs and by the exponential equivalent K [7].

However, it is difficult in human lungs to separate the true age effect, *i.e.*, the physiological ageing effect, from the cumulative environmental effects, *i.e.*, the combination of physiological and pathological ageing effects, since the human respiratory system is open to the environment, continuously exposing the lung to a variety of pollutants. Although senescence-accelerated mouse (SAM) is a good model to investigate the differences between physiological ageing of the lung, *i.e.*, ageing lung or senile lung, and pathological ageing of the lung, *i.e.*, cigarette smoke-related airspace enlargement [7–10], it has been reported that aged mice under protected circumstances using a filter cage do not exhibit the airspace enlargement or alveolar wall destruction [11]. In contrast, several canine studies revealed that long-term exposure to air pollutants at ambient levels might cause bronchitis lesions and emphysematous lesions in dogs [12]. In humans, it has been suggested that cutaneous hypersensitivity to common aeroallergens is a significant independent predictor of subsequent decline of lung function among middle-aged and older males with no history of asthma [13]. MEYER *et al.* [14] also reported that neutrophil migration and

low-grade inflammation existed in lower airways of many clinically normal, older individuals. These results indicate that long-term exposure to environmental pollution during life-time, rather than age, plays an important role in the development of airspace enlargement in later life. Thus, physiological ageing should be named the senile lung or ageing lung. "Senile emphysema" may be a condition of pathological ageing of the lung, since emphysema increases in frequency with age and is found most frequently in patients in the seventh decade [3, 15].

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From the authors:

We read with interest the comments made by Rodriguez-Roisin *et al.* as to the age-related changes in ventilation-perfusion ratio (V'/Q') heterogeneity and the implication of increased closing volume (CV) as a possible explanation for increased V'/Q' heterogeneity in older healthy subjects.

Rodriguez-Roisin *et al.* refer to an excellent study analysing, by the multiple inert gas technique changes in pulmonary V'/Q' inequality with age in 64 healthy individuals aged 18–71 yrs [1].

The observation that the decrease in oxygen tension in arterial blood (P_{a,O_2}) with ageing is small is indeed consistent with the observations of GUÉNARD *et al.* [2] and DECLAUX *et al.* [3] who did not find any significant correlations between age and changes in P_{a,O_2} and suggest that normal values for P_{a,O_2} are in the range of 11.2 ± 1.0 kPa (84 ± 7.5 mmHg; mean \pm SD) in healthy elderly subjects, which is well above results obtained by previously published regression equations [4].

However, we have a few comments on the assertion that increased CV is not a determinant factor in increased V'/Q' heterogeneity in the elderly and on the data on which Rodriguez-Roisin *et al.* base their assumption: 1) The study referred to includes 64 patients of a mean age of 37 ± 14 yrs (mean \pm SD); only our subjects (6%) are aged ≥ 60 yrs, the eldest being 71 and only 10 subjects are aged ≥ 55 yrs (15%). These data are therefore hardly representative of the physiological changes in the respiratory system of elderly subjects, which were the focus of our review [5]; 2) the proportion of subjects with low V'/Q' areas ($>0.75\%$ of cardiac output) is 75% for the small number of subjects aged ≥ 60 yrs ($n=4$), versus 6.7% for those aged <60 yrs, suggesting an increase in V'/Q' mismatch in these "young" elderly subjects, although this was not statistically significant; 3) the CV increases with age; however, data published by LEBLANC *et al.* [6] suggest that the CV may equal the functional residual capacity (FRC) only when subjects reach ~ 65 yrs of age ($FRC - CV = 1.95 - (0.03 \times \text{age (yrs)})$): in younger subjects, the increase in closing volume may not have a significant repercussion on V'/Q' homogeneity; 4) the increase in CV with ageing is most probably not linear; the increase in CV is accelerated after the age of 50 yrs, and follows a curvilinear (exponential) equation ($\Delta N_2 (\% \cdot L^{-1}) = 0.85 + 0.0929 \times \text{age} - 6.302$); this emphasizes the importance of studying a large group of older subjects to document the interaction between CV and V'/Q' mismatch [7]; 5) CRAPO *et al.* [8] suggests that the age-associated anatomic-pathological modifications in small and distal airways, which may affect and increase the CV, become physiologically significant in much older individuals than those studied by CARDUS *et al.* [1].

Based on available data, we believe therefore that increased CV cannot presently be excluded as an explanation for V'/Q' mismatch in the old and very old; the answer to this problem will necessitate studies similar to that published by CARDUS *et al.* [1] including a larger population of older subjects. Information extrapolated from studies including younger adults may not reflect the physiological changes which occur in the very old.

We agree with TERAMOTO *et al.* that the homogeneous enlargement of alveolar ducts and airspaces, without signs of inflammation or destruction described in our review [5] should be considered as "senile lung" and not as "senile emphysema". Whether the appearance of the characteristic parenchymal alterations of the "senile lung" is related to a low grade inflammation in the distal airways, as a reaction to environmental pollutants, or is just the result of "wear and tear" alterations in the collagen and elastin framework, warrants further studies.

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Postural drainage techniques and gastro-oesophageal reflux in infants with cystic fibrosis

To the Editor:

Recently PHILLIPS *et al.* [1] added to the body of knowledge relating to gastro-oesophageal reflux (GOR) in cystic fibrosis (CF). I noted with interest the high incidence of GOR (73%) found in their study of 11 children with CF of <2.5 yrs. This reinforces the sentiment that GOR is an important issue that needs to be considered in the management of young children with CF.

In their article, PHILLIPS *et al.* [1] state that "holding the baby: head downwards positioning for physiotherapy does not cause gastro-oesophageal reflux". This is different to the findings of three independent studies on this topic over the past fifteen years [2–4]. I would like to comment on some of the significant differences between the studies that may have contributed to their different results and conclusions.

We studied 20 infants of <5.6 months newly diagnosed with CF. Eighteen of the infants were <3 months, 15 of those were ≤2 months; the other two were 4.4 and 5.6 months [4]. This large group of very young infants with CF is different to the group of 11 infants and toddlers with CF aged up to 27 months of PHILLIPS *et al.* [1].

They chose six positions, of which two positions were 20° head down lying on the left and right side and two positions were 15° head down lying on the left and right side, both with a quarter turn towards supine (the other two positions were horizontal and head up). We studied four positions: supine horizontal, prone with 30 head-down tilt and lying on the left and right side with 30° head-down tilt. We studied those four

studied those four positions as they were what we were using and teaching the parents of infants with CF at our clinic.

I noted with interest that the widely prescribed prone with head down tilted position [5] was not included in the study of PHILLIPS *et al.* [1]. FOSTER *et al.* [2] found a mean oesophageal pH of 2.8 during chest physiotherapy in the prone position in their study of ten children with CF. The prone position was associated with the lowest mean pH of the four standard positions that they studied.

In considering the title of the study of PHILLIPS *et al.* [1], I was puzzled by their acknowledgement that "in some infants it is possible that the head-down tipped positions may worsen GOR. Therefore, individual evaluation of physiotherapy is recommended for infants undergoing lower oesophageal pH monitoring in whom clearance of excess secretions is indicated". Does this suggest that some of the 11 patients with CF may have had episodes of GOR during chest physiotherapy?

What the study of PHILLIPS *et al.* [1] may imply is that, first, by excluding the prone head-down tilted position and reducing the angle of head-down tilt, the likelihood of increasing episodes of reflux is reduced. Secondly, the older the infant with CF, the lower the likelihood of increased episodes of GOR during chest physiotherapy. Whether the prone position should be used for infants with CF, by how much we need to decrease the angle of head-down tilt and at what age in infancy and early childhood GOR during chest physiotherapy becomes less of an issue is open to debate and further research.

Newborn screening has resulted in the commencement of daily chest physiotherapy in very young infants (often ~6–8 weeks of age) at many centres. There is substantial evidence that there is a high incidence of gastro-oesophageal reflux in infants with cystic fibrosis. I, therefore, believe that when prescribing a chest physiotherapy regimen for infants with cystic fibrosis, the unique infant differences compared to older patients should be considered, and further longer-term research should be undertaken. The main objective is to provide chest physiotherapy for infants with cystic fibrosis that is optimally effective in terms of promoting clearance of pulmonary secretions and that does not have iatrogenic effects. In the words of ORENSTEIN [6] "Respiratory disease may also provoke reflux more indirectly by prompting the use of therapies that provoke reflux. These therapies include . . . postural drainage.

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From the authors:

We thank B.M. Button for showing interest in our study. There are a number of reasons for the discrepancies between our own [1] and previous studies [2–4]. In their abstract, FOSTER *et al.* [2] conclude that chest physical therapy may precipitate gastro-oesophageal reflux (GOR), but they do not state whether the subjects were tipped; one position described is "upright". VANDENPLAS *et al.* [3] investigated physiotherapy using head-downwards positioning; however, each treatment lasted 30 min and included the intermittent use of abdominal thrusts and tracheal rubs to stimulate coughing. It is documented that the control subjects also suffered regurgitation and vomiting during "physiotherapy". BUTTON *et al.* [4] compared a "standard" physiotherapy regimen (SPT) using tipped-down positions with a "modified" regimen (MPT) excluding all tipped postures. They concluded GOR was increased in the SPT but not with the MPT, but, as TAYLOR and THRELFALL [7]

pointed out, there was no significance difference in reflux indices between the regimens, and, in the head-downwards positions, acid refluxate was cleared faster.

In clinical practice, we assess each infant to determine which segments of the lungs need clearing before treating. We ensure, however, that, during the course of a day, all lobes are treated and thus, in our study design, we included the lingula and middle lobes, which other studies have not. The lateral segments of the lower lobes were treated; prone head tilted down was not indicated. Regarding the exact angle of head-downwards tip in this age group, physiotherapy is most frequently performed by parents/carers with the infant on a pillow on the knees. The legs of the adult carer are positioned to allow different tipped positions. No previous study describes how the angle of tip was attained or indeed how it was precisely maintained. Nor, in clinical practice, is it likely to be measured by busy mothers in a home setting.

As with other studies, our own contains relatively small numbers of children. In the group we studied, there was no evidence that the head-down tipped position induced gastro-oesophageal reflux in any infant. However, neither we nor anyone else can exclude the possibility that there may be individuals who were not in the study in whom this is not the case. Our study does not "imply" anything; we concluded that, in patients of this age, using standard techniques for chest physiotherapy, head-down tilt does not cause gastro-oesophageal reflux; indeed, it is in the sitting postural drainage position that gastro-oesophageal is most likely. These postural changes are compatible with physiological understanding. We agree that extrapolation outside the specific conditions and subjects of any study should be performed with caution, and certainly what is needed is high quality research-based evidence with proper statistical analysis, rather than mere "beliefs" and "words".

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