4 Majoor CJ, Kamphuisen PW, Zwinderman AH, *et al.* Risk of deep vein thrombosis and pulmonary embolism in asthma. *Eur Respir J* 2013; 42: 655–661.
5 Johannesdottir SA, Horváth-Puhó E, Dekkers OM, *et al.* Use of glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. *JAMA Intern Med* 2013; 173: 743–752.
6 Stuijver DJ, Majoor CJ, van Zaane B, *et al.* Use of oral glucocorticoids and the risk of pulmonary embolism: a population-based case-control study. *Chest* 2013; 143: 1337–1342.

Eur Respir J 2014; 43: 1534–1535 | DOI: 10.1183/09031936.00157813 | Copyright ©ERS 2014

*T*LNO/*T*LCO ratio is not the end of the road

To the Editor:

As our team analysed in detail the physiological meaning of the transfer factor of the lung for nitric oxide (*T*LNO)/transfer factor of the lung for carbon monoxide (*T*LCO) ratio [1], it seems interesting to extend the analysis to patients. This has been done elegantly by HUGHES and VAN DER LEE [2]. This ratio, which has the advantage of simplicity, nevertheless has some disadvantages. 1) In a given cohort of homogenous patients, values are widely scattered and a given value cannot, therefore, be used as a strong predictor of a disease. For example, pulmonary hypertension patients have, as a mean, higher *T*LNO/*T*LCO than healthy controls; however, a normal value does not exclude the disease. 2) The interpretation of an alteration in this ratio always makes allusions to capillary lung volume (*V*c) and membrane conductance for carbon monoxide (*D*mCO) variables, which stand behind this ratio. So why don't we used these variables directly? The answer is well known: we do not know the right values of the carbon monoxide and nitric oxide conductance of haemoglobin (specific conductance (θ)), which are necessary to the calculation of *V*c and *D*m. However, although we thought in 1987 that the conductance for nitric oxide could be taken as infinite [3], we have since changed our minds, as, at that time, we used the recommended carbon monoxide specific conductance of ROUGHTON and FORSTER [4], which was incorrect, as explained later by FORSTER [5]. The work of BORLAND *et al.* [6] added experimental arguments leading us to consider that the conductance of nitric oxide has a finite value.

What are the right values for θNO and θCO. Following the *in vitro* work of CARLSEN and COMROE [7], θNO is 4.5 mmHg·min^{-1} and the FORSTER [5] recommended value for θCO in normoxia is 0.58 mmHg·min^{-1}, the ratio of these conductances (θNO/θCO) would be 7.7. It can be demonstrated using the ROUGHTON and FORSTER [4] equation for the two gases that the *T*LNO/*T*LCO ratio cannot be greater than θNO/θCO, *i.e.* 7.7 [8]. As the upper normal value of *T*LNO/*T*LCO reaches approximately 5.5–6.0 in most reports [2, 9], a θNO value $<$4.5 or a θCO value $>$0.58 are unlikely as they would lead to a decrease in θNO/θCO to $<$7.7. It could be suggested that both conductances might be lower than these *in vitro* values; however, it seems highly unlikely that both *in vitro* values were overestimated, and no published θCO value is $<$0.58 mmHg·min^{-1} in normoxia. Interestingly, using the aforementioned θNO/θCO leads to increased *D*m [8], reaching the morphometric value of WEIBEL *et al.* [10]. This reasoning has sharp consequences for the interpretation of both *T*LCO and *T*LNO as, if the θNO/θCO value of 7.7 is confirmed, it would lead us to consider that *T*LCO is mainly dependent on *V*c, as *T*LNO would be equally dependent on *D*m and *V*c. Thus, *T*LCO would appear to be a vascular marker and *T*LNO would be the only marker sensitive to membrane alterations.

*T*LNO/*T*LCO ratio appears to be a step in our knowledge of diffusion, not the end: the road is still open.

@ERSpublications
The practical use of the *T*LNO/*T*LCO ratio in a clinical setting remains uncertain http://ow.ly/tRTAs

Jean-Benoit Martinot[1] and Hervé Jean-Pierre Guénard[2]
[1]Dept of Pneumology, St Elisabeth Hospital, Namur, Belgium. [2]Dept of Physiology, University Bordeaux 2, Bordeaux, France.

Correspondence: J-B. Martinot, St Elisabeth Hospital, 15 Place Louise Godin, 5000 Namur, Belgium. E-mail: martinot.j@scarlet.be

Received: Jan 16 2014 | Accepted: Jan 23 2014

Conflict of interest: None declared.

References

1 Glénet SN, De Bisschop C, Vargas F, *et al.* Deciphering the nitric oxide to carbon monoxide lung transfer ratio: physiological implications. *J Physiol* 2007; 582: 767–775.
2 Hughes JM, van der Lee I. The $T_{L,NO}/T_{L,CO}$ ratio in pulmonary function test interpretation. *Eur Respir J* 2013; 41: 453–461.
3 Guenard H, Varene N, Vaida P. Determination of lung capillary blood volume and membrane diffusing capacity in man by the measurements of NO and CO transfer. *Respir Physiol* 1987; 70: 113–120.
4 Roughton FJ, Forster RE. Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. *J Appl Physiol* 1957; 11: 290–302.
5 Forster RE. Diffusion of gases across the alveolar membrane, *In:* Fishman AP, ed. Handbook of Physiology. Bethesda, American Physiological Society, 1987; pp. 71–88.
6 Borland CD, Dunningham H, Bottrill F, *et al.* Significant blood resistance to nitric oxide transfer in the lung. *J Appl Physiol* 2011; 108: 1052–1060.
7 Carlsen E, Comroe JH Jr. The rate of uptake of carbon monoxide and of nitric oxide by normal human erythrocytes and experimentally produced spherocytes. *J Gen Physiol* 1958; 42: 83–107.
8 Martinot JB, Mulè M, de Bisschop C, *et al.* Lung membrane conductance and capillary volume derived from the NO and CO transfer in high-altitude newcomers. *J Appl Physiol (1985)* 2013; 115: 157–166.
9 Aguilaniu B, Maitre J, Glénet S, *et al.* European reference equations for CO and NO lung transfer. *Eur Respir J* 2008; 31: 1091–1097.
10 Weibel ER, Federspiel WJ, Fryder-Doffey F, *et al.* Morphometric model for pulmonary diffusing capacity. I. Membrane diffusing capacity. *Respir Physiol* 1993; 93: 125–149.

Eur Respir J 2014; 43: 1535–1536 | DOI: 10.1183/09031936.00012314 | Copyright ©ERS 2014

Doxycycline in lymphangioleiomyomatosis: not all questions are answered

To the Editor:

We read with interest the article by CHANG *et al.* [1], which demonstrated doxycycline to have no effect on pulmonary function tests (PFTs) and is unlikely to have a potential benefit in lymphangioleiomyomatosis (LAM). An increase in metalloproteinases (MMPs) is considered one of the pathways involved in the pathogenesis of cystic lung destruction in LAM. As a result, doxycycline, a MMP inhibitor, may represent a potential therapeutic target [2–6].

One factor that could have determined a lack of effect on PFTs in the present study was that patients with LAM, treated with doxycycline, had moderate impairment in PFTs when compared with those receiving placebo, which had mild impairment. A recent nonrandomised study from our group has already suggested that patients who would most benefit with doxycycline are those with mild functional impairment [7]. Moreover, the small number of patients included may have limited the results in the present study.

From our previously published study [7], we re-evaluated the effect of the use of doxycycline (100 $mg \cdot day^{-1}$) in 24 patients for 3 years on PFTs. Baseline mean $\pm$ SD forced expiratory volume in 1 s (FEV_1) and diffusion capacity of the lungs for carbon monoxide (D_{LCO}) were 2.30 $\pm$ 0.67 L (81 $\pm$ 21% pred) and 18 $\pm$ 6.6 $mL \cdot min^{-1} \cdot mmHg^{-1}$ (69 $\pm$ 23% pred), respectively. After 3 years, there was a significant reduction in FEV_1 (2.09 $\pm$ 0.71 L; $p<0.001$) and in D_{LCO} (15.8 $\pm$ 6.2 $mL \cdot min^{-1} \cdot mmHg^{-1}$; $p=0.04$). Rate of decline in FEV_1 in 3 years was -73 $mL \cdot year^{-1}$. The majority of patients ($n=20$; 83%) showed a decrease in FEV_1. From the 13 patients that had a stabilisation of or an increase in FEV_1 after receiving doxycycline for 1 year, 11 patients continued follow-up and showed a reduction in FEV_1 after three years (group stabilisation/increase). From 18 patients that showed a reduction in FEV_1 in the first year, 13 continued follow-up and demonstrated the same tendency after 3 years (group decrease), figure 1.

The annual rate of decline in FEV_1 in the present study was slightly greater (-90 mL in the placebo group and -123 mL in the doxycycline group) compared with that observed in the re-evaluation performed by our group (-73 mL in patients that received doxycycline) and with that identified in the study of Taveira-DaSilva and colleagues (-75 mL) [1, 8]. Can we assign a greater decline in FEV_1 identified in the doxycycline group in the present study to a greater impairment in baseline pulmonary function? We believe that there is still no response to this question.

Although doxycycline reduces the levels of MMPs in patients with LAM, we also agree with the authors that based on these recent studies the potential mechanism of action of doxycycline in LAM may be independent of the blockade of MMPs [1, 2, 6, 7].