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CORRESPONDENCE

Exposure at high altitude and exercise altered membrane diffusion capacity of the lung

To the Editors:

In an article published in a recent issue of the *European Respiratory Journal*, DEHNERT *et al.* [1] report various measurements made after climbing at high altitude. Among them were carbon monoxide (CO) transfer measurements. I was surprised by the finding of an increase in the transfer factor of the lung for CO ($T_{L,CO}$) at altitude, as an article presently in press [2], already published in abstract form [3], in which $T_{L,CO}$ and the transfer factor of the lung for nitric oxide ($T_{L,NO}$) decreased slightly but significantly at altitude. At 5,000 m, two thirds of the subjects decreased their $T_{L,NO}$ by >5% after a short maximal exercise. This discrepancy could be due to the fact that DEHNERT *et al.* [1] divided the measured value at altitude by a factor <1 which, in fact, should only be used to estimate the predicted values at altitude. Altitude hypoxia, due to reduced capillary oxygen pressure, increases the conductance of blood for CO and, therefore, the CO transfer. Thus, if one wants to compare the results obtained at altitude to those at sea level, we should either multiply the measured results by this factor or express the results as % predicted, taking into account the equation cited in DEHNERT *et al.* [1] for the predicted value at altitude. When looking for a detection of interstitial oedema, NO transfer would be more sensitive than CO, as the former is mainly dependent on the membrane conductance and the latter is dependent on both membrane and blood conductances [4].

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From the authors:

H. Guénard points out a discrepancy of the transfer factor of the lung for carbon monoxide ($T_{L,CO}$) measurements between data published in his group's abstract [1] and data we reported recently [2]. DE BISSCHOP *et al.* [1] observed a small but significant decrease in $T_{L,CO}$ in acclimatised subjects after maximal exercise at 5,000 m, which H. Guénard considers to be in disagreement with the small increase we found in nonacclimatised subjects at rest at 4,559 m. He suggests that the discrepancy is due to an erroneous calculation of diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) on our part. Furthermore, he points out that transfer factor of the lung for nitric oxide ($T_{L,NO}$), which was also slightly decreased in the study of DE BISSCHOP *et al.* [1], is a better measure of diffusion than $T_{L,CO}$, since nitric oxide uptake is dependent only on membrane conductance and is not influenced by blood conductance.

First, we need to emphasise that corrections of the $D_{L,CO}$ measurements for altitude were done properly. The equipment used in the study performed an automated correction of $D_{L,CO}$ for the lower oxygen tension at altitude according to the formula given by MACINTYRE *et al.* [3]:

$$D_{L,CO,Alt} = D_{L,CO}/(1+0.0031 \times (P_{I,O_2,Alt}-150))$$

where $D_{L,CO}$ and $D_{L,CO,Alt}$ are the measured single-breath $D_{L,CO}$ at low altitude and that predicted for altitude, respectively, $P_{I,O_2,Alt}$ is the inspiratory oxygen tension (P_{I,O_2}) at altitude, and 150 mmHg is the assumed at sea level.

As pointed out by H. Guénard, this formula predicts $D_{L,CO}$ at high altitude based on measurements performed at low altitude. Since our values measured at high altitude were compared with the baseline values at low altitude, the automated correction multiplied the measured values by $(1+0.0031 \times (P_{I,O_2}-150))$, *i.e.* by a term that is less than one. In addition, data were corrected for changes in haemoglobin concentration according to the formula given by MACINTYRE *et al.* [3]. We apologise for not having explained these corrections in more detail.

One needs to consider that the diffusing capacity measurement, based as it is on gas diffusion at the alveolar level, is not

very sensitive to any early interstitial oedema formation. The work of J.C. Parker and colleagues (reviewed in EFFROS and PARKER [4]) shows that the alveolar capillary endothelium at rest has permeability only to hydrostatic stress of ~5% compared with the larger upstream pulmonary artery endothelium. This means that the vast majority of fluid filtration of the lung vasculature occurs away from the alveolar capillary barrier. This notion is supported by only minor changes in $D_{L,CO}$ in subjects with radiographically evident high-altitude pulmonary oedema in our study [2].

The technique of measuring diffusing capacity of the lung for NO ($D_{L,NO}$) was not available at the time of the study. H. Guénard suggests that we might have, therefore, missed evidence of interstitial oedema. This method is, however, not a perfect test for diffusion measurement either, because about of a third of NO uptake resistance is dependent upon the erythrocytes. Therefore, $D_{L,NO}$ is not just a reflection of changes in the alveolar capillary membrane [5] as H. Guénard proposes.

We also want to point out that the level of acclimatisation and physical activity of subjects were very different between these two studies and, thus, preclude direct comparison. DE BISSCHOP *et al.* [1] examined subjects that had acclimatised over 1 week at an altitude of 5,000 m after maximal exercise, while we examined nonacclimatised subjects at rest (4, 20 and 44 h after climbing) at 4,559 m [2]. Exercise at low [6] and high altitude [7] can cause mild interstitial oedema. Several studies suggest that a prolonged stay at high altitude may be associated with interstitial fluid accumulation in systemic tissues. This was shown for subcutaneous tissue [8] at 2,300 m and for mild pericardial effusion at 5,200 m, which increased over the first 7 days [9]. Furthermore, a small decrease in lung compliance compatible with mild interstitial pulmonary oedema was measured by PELLEGRINO *et al.* [10] after 2 days of rest at 3,611 m and 1 day of rest at the same location, where we found no change in lung compliance during the first 48 h at altitude after more rapid ascent.

We thank H. Guénard for making us look again in detail at the published data, because we discovered that table 3 contained erroneous $D_{L,CO}$ values that had been corrected for altitude, in addition to the automated adjustment made by the computer of the body plethysmograph. We encountered problems with the submission of the large tables and were asked several times to repeat the uploading which, at one stage, lead to the submission of an old version of table 3. We apologise for this error and for not detecting it when proof reading. We assure that the description and discussion of the data in the paper were correct. A corrected version of table 3 has been published in the current issue of the *European Respiratory Journal*, as part of an Author Correction that highlights and rectifies this mistake [11].

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