Communications to the Editor

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MOSAIC Acronym

To the Editor:

Dr. Tsung O. Cheng’s point1 is well taken. The acronym is derived from the original study protocol: “A multicentre, multinational, prospective, randomized, double-blind study to compare the effectiveness of Moxifloxacin Oral tablets to Standard oral antibiotic regimen given as first-line therapy in out-patients with Acute Infective exacerbations of Chronic bronchitis.”

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Reference
1 Cheng TO. What is a MOSAIC Study? Chest 2004; 126: 1000–1001

Nitric Oxide Diffusing Capacity on Exercise

To the Editor:

The excellent article by Zavorsky et al (March 2004)1 expands our knowledge of lung diffusing capacity on exercise, but it is not quite true to state that no study has compared the diffusion capacity of the lung for nitric oxide (DLNO)/diffusion capacity of the lung for carbon monoxide (DLCO) ratio using a single-breath technique during various exercise intensities. In our original study,2 we measured single-breath DLNO and DLCO in three male patients at rest and at 75 W, 125 W, and 175 W of bicycle ergometer-induced exercise (the 50 W in the methods of that article is a typographic error). The results can be deduced from Figure 2 in our study, but in contrast to Zavorsky et al,1 we found that single-breath DLNO/DLCO declined from 4.4 (rest), 3.8 (75 W), 3.9 (125 W), to 3.7 (175 W). In agreement with their study,1 however, we observed a linear rise in DLNO with workload, and I have today performed a linear regression of DLNO on alveolar volume (VA) and workload for our data, which yields the model DLNO = 12.3 × VA + 0.27 × workload + 66.2, which is agreeably close to their result.

Why did we find a decline in DLNO/DLCO with increasing exercise? A decline in DLNO/DLCO has been observed in mild hypoxia,3 which increases the specific blood transfer conductance for carbon monoxide but not the specific blood transfer conductance for nitric oxide. In our study,2 subjects held their breath for 7.5 s rather than 5 s, as done by Zavorsky et al,1 whose inspired gas mixture contained 21% oxygen prior to addition of nitric oxide, whereas ours contained 17%. Our subjects could therefore have been more hypoxic. The other cause of reduced DLNO/DLCO is a reduction in membrane diffusion capacity (DM)/pulmonary capillary blood volume (VC). This has been demonstrated for measurements at reduced lung volume that will affect DM and hence DLNO to a greater extent than VC and hence DLCO.2 The mechanism of increased lung diffusion on exercise is believed to be recruitment of closed pulmonary capillaries and further dilatation of those already open. Recruitment will merely increase the number of available alveoli of uniform DM/VC without affecting the overall ratio. Dilatation, however, will increase capillary volume in proportion to the cube of capillary diameter, but surface area and hence DM only by the square. It is conceivable that by virtue of subject selection or training (in our case lack of!) that dilatation rather than recruitment effected our observed increase in DLNO and decline in DLNO/DLCO.

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References

Diffusion Capacity for Nitric Oxide and Carbon Monoxide

To the Editor:

We read with interest the article by Zavorsky et al1 about the relationship between the diffusion capacity of the lung for nitric
nitric oxide (DLNO) and exercise. Their study was well performed, but leaves some serious matters concerning the methods and results. First, after reading the section concerning the calculation of diffusion capacities and pulmonary capillary blood flow (Vc), it still is unclear to us how the investigators determined the Vc. The determination of the specific blood transfer conductance for carbon monoxide (θCO) is essential in calculating the product 1/θCO × Vc. In the past years, different equations have been used to calculate the θCO, as Borland et al stated in their reply to Heller et al. Zavorsky et al do not describe which equation they used. As the results of the Vc are higher than expected, as much as 134% higher than in previous studies, we think a clearer description of methodology is necessary. As the authors state in their discussion, a probable cause for the high Vc lies in the high DLNO values they determined.

A second issue is the calculation of membrane diffusing capacity for carbon monoxide (DMCO), defined as DLNO/1.94, which is solely based on the theoretical relationship between the DLNO and diffusion capacity of the lung for carbon monoxide (DLCO). A recent study revealed a higher DLNO/DMCO ratio of 2.42. Other research constantly shows a higher DLNO/DMCO ratio than the expected 1.94.

A third concern is the extremely high inspiratory nitric oxide levels used. The most obvious reason for this is the use of the electrochemical cell, because the cell is less sensitive than the chemiluminescence analyzers other investigators have used. Zavorsky et al state that the nitric oxide backpressure varies between 11 ppb and 66 ppb. This estimate is much too high; Pietropaoli et al showed values of 2 to 3 ppb in healthy subjects at high exhalation flows. The use of the very high nitric oxide levels can lead to vasodilatation, which can explain the significantly higher DLCO obtained with the simultaneous DLNO measurements.

We think the overall findings of the investigators holds up, namely the dependence of DLNO on alveolar volume, and the linear increment of DLCO and DLNO with increasing workload, but the absolute values of pulmonary membrane diffusing capacity and Vc are to be interpreted with caution. Because of the fact there are still no exact values of θCO and specific blood transfer conductance for nitric oxide, we would like to propose the recommendation to publish and interpret the values of DLCO and DLNO, in which the latter gives more insight to the true function of the alveolarcapillary membrane than the first, instead of publishing pulmonary membrane diffusing capacity and Vc values, which are difficult to interpret.

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REFERENCES

2. 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

To the Editor:

I would like to express sincere thanks to Dr. Borland for commenting on our recent article. Dr. Borland previously investigated the diffusion capacity of the lung for carbon monoxide (DLCO) and diffusion capacity of the lung for nitric oxide (DLNO) in three subjects at various exercise levels and increased levels of inspired oxygen, which was missing from our discussion. In the present study, we looked at higher workloads and the effect of hypoxia (15% inspired oxygen). The hypoxic inspiratory gas should have resulted in an alveolar P02 of approximately 90 mm Hg in our subjects. We hypothesized that the reduced inspiratory oxygen concentrations may have increased the blood transfer conductance for carbon monoxide (θCO) by approximately 14%, allowing for the 6% overestimation of DLCO that we observed. As such, the DLNO/DMCO ratio of 4.52 that we report may actually be slightly higher in normoxia since the blood transfer conductance for nitric oxide (θNO), unlike θCO, is not affected by hypoxia. The data by Borland and Cox do indeed show that the DLNO/DMCO ratio rises with escalating inspired oxygen concentrations. We have since corrected the problem of inspiring low oxygen concentrations during a DLNO maneuver by using a higher concentration of nitric oxide (900 ppm) in a NO/N2 tank, and thus the dilution in the inspiratory bag is minimal (the oxygen concentration is now approximately 20%). We have also added an oxygen analyzer that directly measures the inspiratory oxygen concentrations prior to inhalation to verify normal oxygen delivery to the alveolus. Nevertheless, this does not change the fact that inspired oxygen concentrations were the same at rest and throughout all levels of exercise, and thus the DLNO/DMCO ratios were maintained.

We also appreciate Drs. van der Lee and Zanen for their comments on the methodology chosen. We would like to clarify some of their concerns. In determining pulmonary capillary blood volume (Vc), a main factor is the specific θCO. We used the following formula by Roughton and Forster: 1/θCO = 0.73 + 0.0055 × (P02). The alveolar P02 and hemoglobin concentration were standardized to 120 mm Hg and 146 g/L, respectively, and therefore 1/θCO was 1.426. We acknowledge that the Vc at rest was approximately 25% larger than the expected 92.4-mL predicted values for healthy male populations (1/predicted Vc = –0.0201 × height in meters + 0.047). However, there are several reasons for this higher value as presented our discussion. First, the DLCO at rest in our study was approximately 10% larger than either the predicted or our measured values when 232 ppm of nitric oxide (balance N2) gases were added to the CO/He/O2 diffusion mixture. The addition of NO/N2 gases from a 232 ppm NO tank (balance N2) most likely diluted the inspiratory bag of oxygen, and consequently resulted in a higher overall DLCO. We have performed some calculations, and if we reduced the overall exaggerated resting DLCO by 10% in our study from 46 to 42 mL/min/mm Hg, the Vc would have been reduced from 116 mL to approximately 99 mL according to the formula by Roughton and Forster, which follows: 1/DLCO = 1/DMCO + 1/θCO × Vc, where DMCO is membrane
diffusion capacity for carbon monoxide. A value of 99 mL is closer to the predicted value of 92.4 mL. This brings us to a second and related reason why the DLCOs at rest and during exercise may have been slightly elevated. As reported in our discussion, the alveolar PO2 was reported as 120 mm Hg. However, due to the dilution of CO/He/O2 diffusion mixture with the 232 ppm NO (balance N2), the oxygen concentrations in the inspiratory bag may have been approximately 15%. As such, the alveolar PO2 during inspiration would have decreased to approximately 90 mm Hg and therefore that would increase CO by 14%, resulting in an overall increase in DLCO. Therefore, if we take the DLCO value of 42 mL/min/mm Hg that was obtained from the DLco method (NO/N2 mixture is absent), and use the L/9C0 value of 1.252, according to Roughton and Forster, the VC will have further decreased to 58.5 mL and would be much closer to the predicted value of 92.4 mL. We have since corrected the problem of having the subjects inspire low oxygen concentrations during a DLNO maneuver by using a higher concentration of nitric oxide (900 ppm) in a NO/N2 tank, and thus the dilution in the inspiratory bag is minimal (the oxygen concentration is now approximately 20%). We have verified the modifications in our laboratory by looking at a group of male subjects (mean height, 181.4 ± 6.8 cm; weight, 86.4 ± 9.5 kg [± SD]), and the average VC at rest was 84 ± 21 mL calculated from simultaneous measurement of nitric oxide and carbon monoxide gases from the single-breath method. This is quite close to the predicted value.4

Their second issue is concerning the calculation of DMCO. As mentioned in our article,1 we decided to use the theoretical ratio of 1.97 since the diffusivity of nitric oxide is approximately 1.97 times greater than carbon monoxide. Other authors6–9 have used 1.97 as the theoretical ratio of DLNO to DMCO during single-breath maneuvers. The ratio of 2.42 has been determined during rebreathing maneuvers,10,11 not single breath as was the case in the present study. Interestingly, a ratio of 2.42 results in a resting DMCO of 86.9 mL/min/mm Hg, a value more in line with the current normative values. Obviously, more research is required to determine the true DLNO to DMCO in humans.

Their third concern is that we used high levels of nitric oxide gas (mean concentration on inspiration, 67 ppm). Previous studies12–15 have used 40 to 50 ppm of NO during a single-breath maneuver, while other studies have had subjects rebreathe between 20 ppm and 40 ppm for at least 16 s10,11 to 5 min,14 so our inspiratory nitric oxide levels are not that high as van der Lee and Zanen have suggested. Nevertheless, these studies10,11,14 demonstrated that there is no effect of either repeated single-breath maneuvers or rebreathing maneuvers on pulmonary gas exchange and lung diffusion capacity, so we are confident that the inspiratory levels of nitric oxide from our study did not cause vasodilation of the pulmonary capillaries leading to the high DLCO levels. In fact, data in our laboratory have shown that even four repeated single-breath maneuvers interspersed with 5 min rest does not increase DLNO or DLCO.

Despite the concerns with the methods, the overall findings of our study1 holds up, namely the dependence of DLNO on alveolar volume and workload, and that the relationship between DLNO vs workload, and DLCO vs workload is linear. We appreciate the comments by Drs. van der Lee and Zanen.

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References
8 Tamhane RM, Johnson RL Jr., Hsia CC. Pulmonary membrane diffusion capacity and capillary blood volume measured during exercise from nitric oxide uptake. Chest 2001; 120:1850–1856

French Health System: More Work Is Needed

To the Editor:

We are flattered by the article1 and the editorial2 on the French system of homecare. It is nice to know that our system has been noticed and recognized. However, things change continuously, and the world changes around us. Your article describes the system up to the year 2000, and since then things have changed. ANTADIR is facing challenges related to rising health costs in France and structural changes in the health service industry that have forced regional associations to make choices of direction.

Attempts to simplify reimbursement procedures and to reduce costs have led to a weakening of the Observatory as in-depth data are more difficult to accumulate. Doctors “in the field” find it

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