The \( \text{DL}_{\text{NO}}/\text{DL}_{\text{CO}} \) ratio: Physiological significance and clinical implications

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A B S T R A C T

\( \text{DL}_{\text{NO}}/\text{DL}_{\text{CO}} \) directly measures the ratio of the diffusing capacities of the lung for nitric oxide (NO) and carbon monoxide (CO). In terms of the Roughton and Forster (1957) equation, \( 1/\text{DL} = 1/\text{Dm} + 1/\text{Vc} \), where \( \text{Dm} \) is the membrane (Dm) and \( \text{Vc} \) is the red cell component of the overall diffusing conductance (DL); \( \text{DL}_{\text{NO}} \) mostly reflects the Dm component and \( \text{DL}_{\text{CO}} \) the \( \text{Vc} \) red cell component.

The \( \text{DL}_{\text{NO}}/\text{DL}_{\text{CO}} \) ratio is positively related to the \( \text{DmNO}/\text{Vc} \) ratio and the CO red cell resistance (1/\( \text{VcCO} \)) as a percentage of the total resistance (1/\( \text{DLCO} \)), independent of the absolute values of \( \text{DLNO} \) or \( \text{DLCO} \). In clinical studies, a raised \( \text{DLNO}/\text{DLCO} \) ratio (≥ 110% predicted versus a control group), plus a low \( \text{DLNO} \) and \( \text{DLCO} \) (<67% pred), predicts pulmonary vascular disease, while a low \( \text{DLNO}/\text{DLCO} \) ratio, with similarly reduced \( \text{DLNO} \) and \( \text{DLCO} \), is associated with interstitial lung disease with fibrosis. More clinical studies are needed, and reference values need to be better defined.

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1. Introduction

In the clinical setting, the diffusing capacity of the lung (DL) is usually measured with the single breath carbon monoxide (CO) uptake technique (\( \text{DL}_{\text{CO}} \)). The method has undergone little change since the original description (Ogilvie et al., 1957). In 1983–9, the measurement of diffusing capacity using an inert haemoglobin (Hb)-reactive gas, nitric oxide (NO), was introduced (Guénard et al., 1989; Borland and Higenbottam, 1989), employing the same single breath technique. Both tracer gases (CO and NO) were inhaled from the same reservoir (together with an inert volume-marker gas, usually helium). The ratio of \( \text{DLNO} \) to \( \text{DLCO} \) in normal subjects was about 5.0 (Borland and Higenbottam, 1989). This fivefold ratio is caused by the different properties of NO versus CO, as they traverse the blood-gas barrier; the greatest difference lies in the more rapid (about 300-fold) uptake rate of NO versus CO by intracapillary haemoglobin.

It is too early to say whether the \( \text{DLNO} \) will replace the \( \text{DLCO} \) as the best test of the diffusing capacity of the lung. At the present time, measurement of the \( \text{DLNO} \) is always accompanied by a simultaneous \( \text{DLCO} \) measurement. In this article, we will review the physiological processes responsible for the fivefold difference in the NO-CO uptake rates, and consider the clinical implications of an abnormally high or low \( \text{DLNO}/\text{DLCO} \) ratio.

2. \( \text{DLNO} \) versus \( \text{DLCO} \): differences and similarities

The conductance of CO from gas to blood is given by the classical equation (Roughton and Forster, 1957):

\[
1/\text{DLCO} = 1/\text{DmCO} + 1/\text{VcCOVc}
\]  

(1)

where \( 1/\text{DLCO} \) is the lung resistance to CO transfer (the reciprocal of the conductance), \( 1/\text{DmCO} \) (the molecular diffusion resistance of the lung membranes – from the surfactant lining layer to the red cell membrane – and \( 1/\text{Vc} \) is the resistance to CO transfer within the red cell. The sum of the red cell and membrane resistances, which are in series, are the components of the overall resistance, \( 1/\text{DLCO} \times 0 \) and \( \text{Vc} \) are defined under Nomenclature. The same equation applies to NO uptake:

\[
1/\text{DLNO} = 1/\text{DmNO} + 1/\text{VNOVc}
\]  

(2)

The molecular diffusive conductance for NO in lung tissue (∼ tissue solubility/MW−2) is 1.97 times that for CO; thus, the \( \text{DmNO}/\text{DmCO} \) ratio, designated \( \alpha \), is 1.97. The ratio of the red cell conductances for NO versus CO, \( \theta_{\text{NO}}/\theta_{\text{CO}} \), on the best available evidence from in vitro and in vivo experiments (Guénard et al., 2016), at an alveolar \( \text{PO}_2 \approx 100 \text{mmHg} \), is 4.5/0.56 = 8.01. \( \theta_{\text{CO}} \) is \( \text{O}_2 \)-sensitive, but \( \theta_{\text{NO}} \) is essentially \( \text{O}_2 \)-insensitive (Borland and Cox, 1991).
2.2. $\theta_{NO}$ and $\theta_{CO}$ and absolute values of $DmCO$ and $Vc$

Using Eq. (1) only (the classical method, measuring $DLCO$ at normal and hyperoxic alveolar $PO_2$), estimates of $DmCO$ in normal subjects at rest are in the range 40–60 mL min$^{-1}$ mmHg$^{-1}$ (Hughes and Bates, 2003), rising to 130–180 with combined NO and CO inhalation using Eqs. (3) and (4) and a finite value for $\theta_{NO}$ (Zavorky et al., 2017). $Vc$ goes in the opposite sense, from 80 to 100 mL with the hyperoxic $DLCO$ to 65–85 mL with the combined $DLNO-DLCO$ measurement. If an infinite $\theta_{NO}$ is taken, so that $DmCO = 0.5 DmNO$ (Eq. (5)), estimated $DmCO$ falls and $Vc$ rises towards the values found with the classical $DLCO$ multi-step $O_2$ technique. The higher values of $DmCO$, using the NO-CO analysis and a finite $\theta_{NO}$, are more in line, particularly on exercise ($DmCO \sim 260 \text{ mL min}^{-1} \text{ mmHg}^{-1}$ (Zavorky et al., 2004)) with morphometric measurements (representing the theoretical maximum values) of 280 mL min$^{-1}$ mmHg$^{-1}$ (Gehr et al., 1978). This concordance of physiologic with morphometric values for $DmCO$ is some justification, albeit indirect, for the use of the simultaneous NO-CO inhalation technique, coupled with a finite value for $\theta_{NO}$. But, the issue of finite versus infinite $\theta_{NO}$ is still a matter for debate.

3. $DLNO/DLCO$ ratio: physiological interpretation

With the classical analysis (Eq. (1)), the resistance split between $1/DLCO$ and $1/\theta_{CO}Vc$ was about 50:50 (Hsia et al., 1995). On clinical grounds, the $DLCO$ data from pulmonary vascular disease and anaemia seemed to favour a 25:75 partition between the membrane resistance, $1/DLCO$ (25%) and the red cell resistance, $1/\theta_{CO}Vc$ (75%), and this was supported by calculations of $DmCO$ and $Vc$, using more recent estimates (Forster, 1987) of the $1/\theta_{CO} – PO_2$ relationship (Hughes and Bates, 2003). Recent work using the NO-CO method with finite values for $\theta_{NO}$ (and, of course, $\theta_{CO}$) suggest that the red cell resistance percentage for $1/DLCO$ is much less (c.37%), and that $1/DLNO$ is dominated by the membrane resistance (63%) (Borland et al., 2010). In simple terms, $1/DLNO$ represents $1/(DmNO\theta_{NO})$, and $1/DLCO$ reflects $1/Vc$; thus, $DLNO/DLCO$ is an expression of two related ratios, $DmNO/Vc$ and the $Rc/Rtot$ fraction for CO (Fig. 1, Table 1).

4. Relationship between $DLNO/DLCO$ and $DmCO/Vc$

For this analysis, we have computed theoretical $DLNO$, $DLCO$ and $DLNO/DLCO$ values in terms of Eqs. (3) and (4) using the generally accepted value for $\theta_{NO}$ (Carlsen and Comroe, 1958) and a newly published equation for the $1/\theta_{CO} - PO_2$ relationship based on both in vitro and in vivo data (Guénard et al., 2016). Fig. 1 shows a curvilinear relationship between $DmCO/Vc$ and $DLNO/DLCO$, which is independent of the absolute values of $DLNO$ and $DLCO$, as shown in Table 1. Thus, on the basis of $DmNO/DmCO$ of 1.97 ($\alpha$) and $\theta_{NO}/\theta_{CO}$ ($\Psi$) of 8.01, $DmCO/Vc$ can be predicted from the $DLNO/DLCO$ ratio. $Rc/Rtot$ behaves similarly to $DmCO/Vc$.

5. $DLNO/DLCO$ ratio in health and disease

5.1. Normal values

In the period 2007–8, three groups published reference values for $DLNO$ in European (van der Lee et al., 2007; Aguilaniu et al., 2008) and North American (Zavorky et al., 2008a,b) adult populations. There were some important differences. The subjects in the North American study were younger and more athletic; two studies used the less sensitive electrochemical cell for NO analysis and a breath hold time (BHT) of 4 s (Aguilaniu et al., 2008) and 5.5 s (Zavorky et al., 2008a,b), and one a high sensitivity chemilumines-

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Fig. 1. Ratio of carbon monoxide (CO) membrane diffusing capacity (DmCO) to pulmonary capillary volume (Vc), DmCO/Vc, and red cell diffusion resistance (Rrc) for CO as a percentage of total (Rtot) CO diffusion resistance, Rrc/Rtot%, plotted against ratio of diffusing capacities for nitric oxide (NO) and CO (DmNO/DmCO) for normal male, aged 45 years, height 175 cm. Individual points calculated using Eqs. (3) and (4), and the computer programme in the on-line supplement of Zavorsky et al. (2017). The relationship is given by the equation DmCO/Vc = 0.0536*exp(−0.7465*DLNO/DLCO) and Rrc/Rtot% = 69.805 ln(DmNO/DmCO) − 31.963.

Table 1

Computations, using Eqs. (3) and (4) with &theta;NO and &theta;CO from Guénard et al. (2016), at constant DmNO/DmCO ratios (High, Normal and Low), showing that the DmNO/Vc ratio and red cell diffusion resistance for CO as percent total diffusion resistance (Rrc/Rtot%) do not depend on absolute values of DmNO and DmCO, only on the DmNO/DmCO ratio. All values except DmCO/Vc are as percent predicted normal for male aged 45 years, height 1.75 m (from on-line supplement, Zavorsky et al., 2017*).

<table>
<thead>
<tr>
<th>DmNO/DmCO</th>
<th>DmNO %</th>
<th>DmCO %</th>
<th>DmNO %</th>
<th>Vc %</th>
<th>DmCO/Vc</th>
<th>Rrc/Rtot%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH</td>
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<td>100</td>
<td>83</td>
<td>153</td>
<td>70</td>
<td>4.53</td>
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<td></td>
<td>6.0</td>
<td>85</td>
<td>70</td>
<td>131</td>
<td>59</td>
<td>4.55</td>
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<tr>
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<td>2.07</td>
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<tr>
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<td>70</td>
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<td>2.08</td>
</tr>
<tr>
<td>LOW</td>
<td>3.5</td>
<td>84</td>
<td>119</td>
<td>58</td>
<td>156</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>51</td>
<td>72</td>
<td>35</td>
<td>94</td>
<td>0.77</td>
</tr>
</tbody>
</table>

DmCO: membrane diffusing capacity for carbon monoxide.
Vc: pulmonary capillary volume.
* 100% predicted = 166 (DmNO), 33.5 (DmCO), 166 (DmCO) 75 (Vc), 2.22 (DmCO/Vc), 80 (Rrc/Rtot%); units are ml.min\(^{-1}\) mmHg\(^{-1}\), except for Vc (ml) and DmCO/Vc and Rrc/Rtot (dimensionless).

Table 2

Effects of acute and chronic exposure to the hypoxia of altitude in healthy lowlanders and highlanders, except for one study of highlanders with chronic mountain sickness (CMS). All results are as % of sea level controls for each study. Values >90% > 110% are in bold-italic, DmCO and Vc computed from DmNO and DmCO using Eqs. (3) and (4).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>n</th>
<th>Altitude exposure</th>
<th>DmNO/DmCO</th>
<th>DmNO %</th>
<th>DmCO %</th>
<th>DmCO %</th>
<th>Vc %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.1 Martinot et al. (2013)</td>
<td>Lowlanders</td>
<td>25</td>
<td>2–3 days at 4300 m. Peru.</td>
<td>92</td>
<td>121</td>
<td>131</td>
<td>108</td>
<td>138</td>
</tr>
<tr>
<td>A.2 Faoro et al. (2014)</td>
<td>Lowlanders</td>
<td>13</td>
<td>2–4 days at 50050 m. Nepal.</td>
<td>93</td>
<td>103</td>
<td>112</td>
<td>94</td>
<td>120</td>
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<tr>
<td>C.1 de Bisschop et al. (2010)</td>
<td>Lowlanders</td>
<td>16</td>
<td>4 days at 4000 m. Bolivia.</td>
<td>86</td>
<td>84</td>
<td>97</td>
<td>73</td>
<td>111</td>
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<td>D.1 Groepenhoff et al. (2012)</td>
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<td>15</td>
<td>4 days at 4300 m.</td>
<td>83</td>
<td>127</td>
<td>155</td>
<td>102</td>
<td>183</td>
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<tr>
<td>A.2 Martinot et al. (2013)</td>
<td>Lowlanders</td>
<td>25-7-8 days, 4300 m</td>
<td>100</td>
<td>107</td>
<td>107</td>
<td>108</td>
<td>107</td>
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<tr>
<td>E. Taylor et al. (2016)</td>
<td>Lowlanders</td>
<td>7</td>
<td>40 days at 5150 m. Nepal.</td>
<td>106</td>
<td>117</td>
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<td>126</td>
<td>104</td>
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<td>8</td>
<td>4000 m. Bolivia.</td>
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<td>110</td>
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<td>B.2 Faoro et al. (2014)</td>
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<td>5150 m. Nepal</td>
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<td>185</td>
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<tr>
<td>D.2 Groepenhoff et al. (2012)</td>
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<td>4300 m. Peru.</td>
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<td>132</td>
<td>167</td>
<td>101</td>
<td>208</td>
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<tr>
<td>D.3 Groepenhoff et al. (2012)</td>
<td>Highlanders with CMS</td>
<td>13</td>
<td>4300 m. Peru.</td>
<td>77</td>
<td>148</td>
<td>194</td>
<td>110</td>
<td>253</td>
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</tbody>
</table>

* Corrected for polycythaemia to the standard haemoglobin level (13.4–14.6 g dl\(^{-1}\)).
Table 3
Clinical studies of DLNO/DLCO ratios with related values and indices. All values are as percent of study controls. DmCO/Vc, DmCO and Vc were computed for patients and controls using Eqs. (3) and (4), and expressed as % of control. Rows arranged in descending order of DLNO/DLCO ratios (% control) and in three sections (A > 110%, B > 110% > 95%, C < 95%).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Diagnosis</th>
<th>N1</th>
<th>DLNO/DLCO</th>
<th>DLNO %</th>
<th>DLCO %</th>
<th>DmCO/Vc</th>
<th>DmCO %</th>
<th>Vc %</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>van der Lee et al. (2006)</td>
<td>PAH2</td>
<td>26</td>
<td>114</td>
<td>58</td>
<td>65</td>
<td>148</td>
<td>69</td>
<td>40</td>
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<tr>
<td>Borland et al. (1996)</td>
<td>PAH1</td>
<td>12</td>
<td>111</td>
<td>65</td>
<td>62</td>
<td>143</td>
<td>82</td>
<td>57</td>
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<tr>
<td>Degano et al. (2009)</td>
<td>HPS1</td>
<td>11</td>
<td>111</td>
<td>71</td>
<td>66</td>
<td>127</td>
<td>80</td>
<td>63</td>
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<tr>
<td>GROUP B</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>van der Lee et al. (2009)</td>
<td>COPD: GOLD 13</td>
<td>68</td>
<td>110</td>
<td>95</td>
<td>86</td>
<td>110</td>
<td>95</td>
<td>86</td>
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<td>Smokers: GOLD 05</td>
<td>168</td>
<td>107</td>
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<td>Zavrasky et al. (2008a,b)</td>
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<td>71</td>
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<tr>
<td>Monard and Guénard (1990)</td>
<td>COPD: GOLD 3–4</td>
<td>10</td>
<td>94</td>
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<td>56</td>
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<td>Barisione et al. (2016)</td>
<td>NSIP6</td>
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<td>UIP–ILD10</td>
<td>30</td>
<td>89</td>
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<td>BMT11</td>
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<td>87</td>
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<td>80</td>
<td>35</td>
<td>43</td>
<td>52</td>
<td>28</td>
<td>54</td>
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</tbody>
</table>

1 number of patients in each study.
2 pulmonary artery hypertension, 77% of whom had chronic thromboembolic disease.
3 idiopathic pulmonary arterial hypertension.
4 hepatopulmonary syndrome based on arterial hypoxaemia and positive contrast-enhanced echocardiography.
5 GOLD staging of COPD severity (FEV1/FVC < 0.7). GOLD 1 = FEV1% predicted ≥ 80%: GOLD 2 = FEV1% predicted < 80%: GOLD 3 – 4 = FEV1% predicted < 50%.
6 GOLD 0: asymptomatic smokers without airflow obstruction (FEV1/FVC > 0.7).
7 chronic heart failure.
8 diffuse interstitial lung disease with fibrosis.
9 non-specific interstitial pneumonia, associated with inflammation and fibrosis.
10 usual interstitial pneumonia with lung fibrosis.
11 patients selected for bone marrow transplantation for haematological malignancies.

Figure 2. Plot of diffusing capacities for nitric oxide (NO) and carbon monoxide (CO) and their ratio (DLNO/DLCO), membrane diffusing capacity for carbon monoxide (DmCO), and the DmCO/pulmonary capillary volume ratio (DmCO/Vc) (on the ordinate) versus alveolar volume (~lung volume minus anatomic dead space) as % maximum (~TLC minus dead space) while normal subjects voluntarily changed lung expansion (50% VA max is about FRC). Note DLNO, DmCO and DmCO/Vc are more volume sensitive than DLCO itself, implying that Vc is independent of lung expansion change, and that DmCO is relatively independent, due to the influence of Vc. The figure was reproduced from Zavrasky et al. (2017), and data were derived from van der Lee et al. (2007) and Hughes and van der Lee (2013).
5.3. Exercise

The ERS–ATS Task Force (Zavorsky et al. 2017) has reviewed DLNO exercise studies. DLNO and DLCO increase linearly as cardiac output and oxygen consumption increase, but with more scatter for the DLNO relationship. With exercise, pulmonary vascular pressures increase and more alveolar surface is available for gas exchange from the opening up of closed capillary units in the alveolar septa (recruitment) and dilatation of already patent vessels. This recruitment and dilatation increases DmNO and DmCO (“more” membrane now takes part in NO and CO transfer). In addition, DLCO will increase as capillary volume (VC) increases (this will be a smaller effect for DLNO). As a result, the DLNO/DLCO ratio decreases linearly with increasing power output (Tamhane et al. 2001) by about 17–28% from rest to maximum exercise, or by 0.06 units for each 1.0 L min⁻¹ increase in cardiac output (Zavorsky et al., 2007). In sarcoidosis with parenchymal fibrosis, the DLNO/DLCO ratio fell similarly from rest to exercise (Phansalkar et al., 2004).

5.4. Change in lung expansion (ΔVA)

In healthy subjects, DLNO and DLCO are measured at maximum inflation, i.e. at a breath hold at total lung capacity (TLC). In the single breath test, this breath hold lung volume is measured by inert gas dilution from gas expired after the breath hold. A subtraction of “non-gas exchanging” volume is made (instrumental plus anatomic dead space) and an “alveolar volume” (VA) calculated. This VA at TLC (−VAmax) is about 94% (SD 7%) of a separately measured TLC by multi–breath dilution (Roberts et al., 1990; van der Lee et al., 2007); this difference (from 100%) is 3–4% greater than expected from the anatomic dead space, and reflects incomplete alveolar mixing in the 10 s breath hold time.

Normal subjects can voluntarily stop the initial inspiration to TLC at a submaximal volume (VA50%max to VA90%max) and DLNO and DLCO and their components measured at different levels of alveolar expansion (van der Lee et al., 2007). In Fig. 2, as the alveoli reduce in size (down to 50% VAmax), the reduction in DLNO exceeds that of DLCO and the DLNO/DLCO ratio falls. This is because ΔDmNO is more driven by ΔDmNO than the more VC-weighted DLCO. VC changes little as the lung becomes smaller; for example, the change in DmCO/VC is almost the same as the change in DLCO itself. In the clinical setting, extrapulmonary restriction which reduces VA to 50% max should reduce the DLNO/DLCO ratio to 80% predicted.

5.5. Implication for DLNO/DLCO if VA is reduced other than by expansion loss

VA can be reduced by alveolar destruction or filling with fluid or inflammatory tissue. This may be local (e.g. pneumonectomy) or diffuse. A 50% loss of VA in pneumonectomy results in a DLCO of 60% of predicted max, not 50%, because the blood flow and volume per unit alveolar volume in the remaining lung increases DLCO by capillary dilatation and recruitment (Hughes and Pride, 2012). This “compensatory” effect (mediated by an increase in KCO to 110–120% predicted) might be less for DLNO (though DLNO is also blood volume sensitive), so DLNO/DLCO might fall; there is no data one way or the other. A third cause of VA reduction is poor distribution of the inhaled marker gases; this occurs in airflow obstruction when the separately measured TLC exceeds the single breath VA. The effect on DLNO/DLCO is difficult to predict.

5.6. DLNO/DLCO ratios in altitude-induced hypoxia

There have been several studies of the effects of acute and chronic exposure to the hypoxia of altitude dwelling (summarised in Table 2). All values, including those for permanent residents (highlanders) are expressed as percent of that at sea level in the “lowlanders”. Except for study A2 (Table 2) the effect of acute (2–4 days) altitude exposure (rows A1, B1, C1, D1) is a fall in DLNO/DLCO, but the changes in the various components in Table 2 are more variable; the most consistent change is a rise in VC, probably due to an increase in cardiac output and pulmonary capillary recruitment and dilatation. After 40 days exposure (study E), VC appears to have returned to the sea level value, but this is only a single study. In a comparison of lowlanders and highlanders (acute versus chronic exposure) – B1-2, C1-2 and D1-2 – highlanders have large increases in DLNO, DmCO, DmCO and VC, with reductions in DLNO/DLCO. Highlanders have secondary polycythaemia, which is particularly marked in those with chronic mountain sickness (CMS) – D3. The high haemoglobin explains a large part of the high DLCO and VC.

The main changes are probably a) an increase in pulmonary blood flow (~cardiac output) on acute exposure (high DLNO, DLCO and VC) and b) secondary polycythaemia increasing DLCO and VC with chronic (lifelong) exposure through an expansion of the alveolar membrane surface (↑DmNO in 2/3 studies); interestingly, Faoro et al. (2014) reported an increased VA in highlanders, as did Martinot et al. (2013) in 2/3 day exposure in lowlanders. Capillary recruitment (DmCO and VC) must also occur.

5.7. DLNO/DLCO ratios in pulmonary and cardiac disease

Most of the clinical studies to date are listed in Table 3. Each study had their own controls (normal subjects) and all patient values are reported as “% control”. This is important because, at this early stage in the development of the DLNO, the “control” DLNO/DLCO varies widely from study to study (from 3.9 to 5.4).

In Table 3 (Group A), high DLNO/DLCO (>110% control) ratios plus DLCO and/or DLNO values <67% predicted normal are associated with pulmonary vascular disease, either pulmonary arterial hypertension or the pulmonary capillary remodelling and dilatation of the hypertapulmonary syndrome (HPS). In all three studies, DLNO and DLCO are low, but the DmCO/VC ratio is high. The reduction in VC is greater than the reduction in the membrane conductance (DmCO).

In Group B (Table 3), DLNO/DLCO ratios are normal (110–97% control). Those studies with a reduced DLCO (<80% control) are also associated with pulmonary hypertension, either arterial (Farha et al., 2013) or venous hypertension (chronic heart failure, Magini et al., 2015). The Magini et al. (2015) study (DmCO and VC have been recalculated via the on-line supplement in Zavorsky et al., 2017) is interesting because the reduction in VC is greater than the reduction in DmCO. In previous studies, using the normoxic–hyperoxic DLCO analysis, the opposite has been found (Puri et al., 1995). The van der Lee et al. (2006) study in ILD will be discussed later.

In Group C, a low DLNO/DLCO (<95% control) was seen in destructive lung disease. Where the DLCO and/or DLNO values were <67% predicted normal (or, for Barisone et al., 2014; Dressel et al., 2009, where only the DLNO was <67% predicted), the pathological process was (in 4/6 examples) interstitial lung disease with diffuse fibrosis, or in one instance (Moinard and Guérard, 1990) destruc
tive emphysema. The study of van der Lee (2006) in ILD (mostly sarcoidosis) with a normal DLNO/DLCO ratio (Group B), but reduced DLNO and DLCO, is an anomaly: the computed DmCO% was greater than the VC%, whereas in the last four studies in Group C (with DLNO/DLCO <95% controls) the opposite was the case. At present, there is no obvious explanation.

In summary, a high DLNO/DLCO is associated with pulmonary vascular disease and a low DLNO/DLCO with alveolar destruction (emphysema or fibrosis). The pattern of changes in DmCO/VC (Table 3) and in Rcr/Rtot% (data not shown) mirror those of DLNO/DLCO, but DmCO/VC and Rcr/Rtot% are computed variables, whereas DLNO/DLCO is directly measured.
6. Conclusions
1. The ultra–rapid reaction of NO with red cell haemoglobin implies that NO conductance (DLNO) from alveolar gas to pulmonary capillary blood mostly measures the alveolar–capillary membrane diffusion capacity (Dm), but because of the slower reaction of CO with oxygenated haemoglobin, DLCO mainly reflects red cell conductance, and will be reduced when pulmonary capillary volume (Vc) is compromised.
2. The DLNO/DLCO ratio, according to the Roughton and Forster (1957) equation, is positively related to the Dm/Vc ratio and to the red cell resistance fraction (Rc/Rtot) in a curvilinear manner (Fig. 1).
3. The relationship between DLNO/DLCO and Dm/Vc or Rc/Rtot% is independent of the absolute values of DLNO or DlCO (Table 1).
4. The response of lowlanders to acute exposure to high altitude is variable, but there is a trend for a reduced DLNO/DLCO and a high Vc, probably due to capillary recruitment. With longer exposure, and in native highlanders, there is secondary polycythemia, and a larger fall in DLNO/DLCO and rise in Vc, even after Hb correction (Table 2).
5. In clinical studies, three patterns emerged for the DLNO/DLCO ratio: A) high (≥110% predicted), associated with pulmonary vascular disease; B) normal (<110% >95%) in mild to moderate COPD, chronic heart failure and morbid obesity; C) low (<95%) associated with moderate to severe COPD, cystic fibrosis, but predominantly with interstitial lung disease with fibrosis (Table 3).
6. Because of a wide spread of DLNO/DLCO values in healthy controls between studies (ranging from 3.9 to 5.4), we recommend each laboratory uses their own healthy controls.

References

Zavorsky, G.S., Cao, M., Murias, J.M., 2008a. Reference values of pulmonary diffusing capacity for nitric oxide in an adult population. Nitric Oxide 18, 70–79.