



Impact of atrial septal defect closure on diffusing capacity for nitric oxide and carbon monoxide

To the Editor:

Secundum atrial septal defects (ASDs) are one of the most common congenital heart diseases and cause left-to-right shunting through the interatrial septum. The major indication for closure is a haemodynamically significant shunt, defined as a pulmonary-to-systemic flow ratio ≥ 1.5 with pulmonary vascular resistance < 5 Wood units [1]. We investigated the diffusion mechanism in a small cohort of ASD patients before and after percutaneous closure to study the physiological impact of an ASD and its successful closure.

The diffusing capacity for carbon monoxide ($DLCO_c$) is currently the test of choice to assess pulmonary gas transfer in clinical practice. $DLCO_c$ comprises both the alveolar–capillary membrane diffusion for carbon monoxide ($DMCO$) as well as the binding rate of carbon monoxide to haemoglobin and pulmonary capillary blood volume (V_{cap}) [2]. Nitric oxide binds 1500 \times faster to haemoglobin and is therefore less affected by haemoglobin concentration and V_{cap} [3]. So, the diffusing capacity for nitric oxide ($DLNO$) reflects more of an alveolar–capillary membrane diffusion, whereas $DLCO_c$ is largely represented by V_{cap} rather than the membrane diffusion [4]. Both gases combined yield the $DLNO/DLCO_c$ ratio which sheds light on the possible causes of diffusion impairment [5].

In this prospective observational study, 42 adult ASD patients were referred for percutaneous closure in a tertiary centre for congenital heart disease within a 13-month period. Percutaneous ASD closure was performed under general anaesthesia for transoesophageal echocardiographic guidance of an Amplatzer Septal Occluder implantation (Abbott Vascular BV, Santa Clara, CA, USA). At baseline and 6 months after closure, spirometry and pulmonary carbon monoxide/nitric oxide diffusing capacity testing were conducted on a MasterScreen PFT (Jaeger, Wurzburg, Germany) conforming to standardised European guidelines [6–8], from which predicted value calculations were also derived. Diffusing capacity for carbon monoxide/nitric oxide was measured simultaneously using the single-breath technique in a seated position with a 4–6 s breath-hold time. Inspiratory concentrations were 0.15% for carbon monoxide, 21% for oxygen and 60 ppm for nitric oxide. The first 750 mL of exhaled gas was discarded as the washout volume. Haemoglobin levels were obtained by venepuncture. This study conformed to the amended Declaration of Helsinki. All patients provided informed consent according to local medical ethical committee regulations.

Statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY, USA). The two-tailed paired t-test was used for comparing pre- and post-procedural data. Differences between previous/current smokers and non-smokers were analysed using the two-tailed independent t-test. Correlations were linearly tested with a Pearson correlation coefficient. A p-value < 0.05 was considered statistically significant.

Of the 42 consecutive patients planned for percutaneous ASD closure, patients with incomplete baseline pulmonary assessment ($n=10$), misdiagnosed patent foramen ovale ($n=1$) and surgical conversion ($n=2$)



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Atrial septal defects are characterised by a low $DLNO/DLCO_c$ ratio in diffusion testing. Successful percutaneous closure shows an increase in $DLNO/DLCO_c$ ratio and vital capacity through correction of a hyperdynamic pulmonary circulation. <http://ow.ly/Rqkc30o5yMM>

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were excluded. The study cohort comprised 29 patients (mean±SD age 50±14 years; 66% female; ASD size 18±7.6 mm; forced expiratory volume in 1 s (FEV1) 3.02±0.96 L (98±16% predicted)) with paired testing (median (interquartile range (IQR)) 20 (11–34) days pre-closure; median 6.0 (5.5–6.0) months post-closure). 14 patients (48%) were previous/current smokers (median (IQR) 3.2 (0.7–23) pack-years).

Post-closure spirometry showed a significant increase in forced vital capacity (FVC) (3.76±1.17 to 3.90±1.17 L (103±16 to 108±15% predicted); $p<0.001$) and a decrease in FEV1/FVC ratio (0.79±0.07 to 0.77±0.08 (100±8.0 to 98±9.0% predicted); $p=0.02$). Diffusing capacity changes are shown in figure 1. Breath-hold time was 5.39±0.48 s pre- and 5.41±0.48 s post-closure ($p=0.88$). Alveolar volume (VA) increased nonsignificantly (82±10%–83±10%, $p=0.08$). DLCOc and DLCOc/VA (KCO) significantly decreased post-closure ($\Delta-6\pm6\%$ and $\Delta-9\pm9\%$, respectively), parallel to a significant reduction in V_{cap} ($\Delta-4\pm11\%$). Indeed, changes in DLCOc and V_{cap} were linearly correlated ($r=0.63$; $p<0.001$). DLNO did not significantly decrease ($\Delta-2\pm6\%$); however, the DLNO/VA (KNO) did ($\Delta-4\pm6\%$), and the changes in DLNO and DMCO were significantly correlated ($r=0.79$; $p<0.001$). Combined, this resulted in a significant increase in DLNO/DLCOc ratio (from 4.36±0.32 to 4.54±0.32), which was inversely correlated with V_{cap} ($r=-0.82$; $p<0.001$). In previous/current smokers, the effect of closure was more evident in KCO and V_{cap} , presumably due to their slightly lower VA compared to non-smokers.

This study is the first to describe the diffusing capacity of a small cohort of adult ASD patients before and after successful percutaneous closure. To summarise the results, baseline DLCOc and DLNO were slightly lower than predicted with a relatively higher KCO than KNO, suggesting a mechanistic cause of pulmonary hypercirculation such as reduced VA rather than an alveolar–membrane diffusion impairment in ASD patients. Post-procedurally an increase in the DLNO/DLCOc ratio was observed, which corresponded to a relatively stronger decrease in DLCOc than DLNO by significant reduction of pulmonary capillary blood volume after ASD closure.

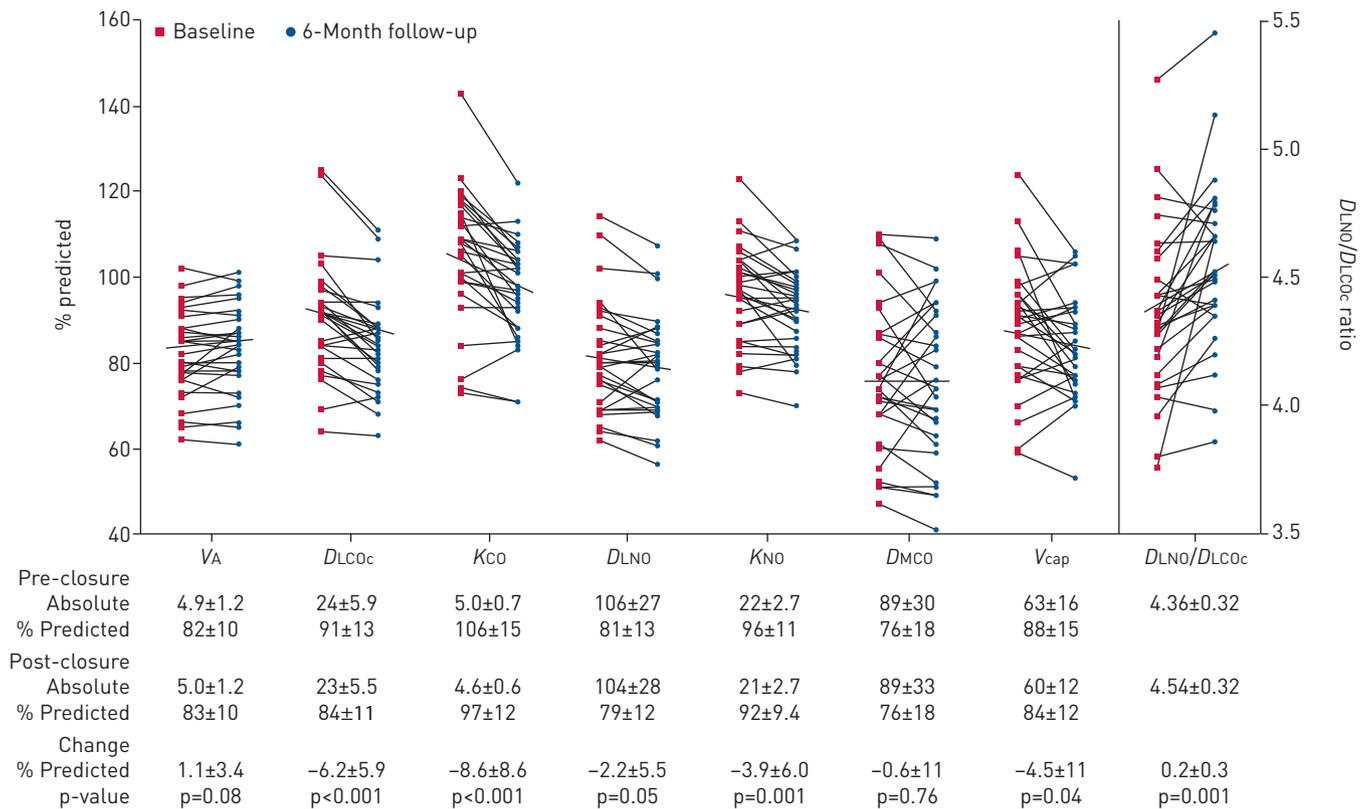


FIGURE 1 Pulmonary diffusion parameters before and after secundum atrial septal defects (ASD) closure. Diffusion test parameters at baseline and 6-month post-procedural follow-up in 29 adult ASD patients, shown as percentages of predicted values (left y-axis) or in absolute value (right y-axis). Data are presented as mean±SD. VA: alveolar volume (L); DLCOc: haemoglobin-corrected diffusing capacity for carbon monoxide ($\text{mL}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}$); KCO: transfer coefficient for carbon monoxide ($\text{mL}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}\cdot\text{L}^{-1}$); DLNO: diffusing capacity for nitric oxide ($\text{mL}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}$); KNO: transfer coefficient for nitric oxide ($\text{mL}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}\cdot\text{L}^{-1}$); DMCO: alveolar–capillary membrane diffusing capacity for carbon monoxide ($\text{mL}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}$); V_{cap} : capillary volume (mL).

Percutaneous ASD closure is the first choice of treatment as it is less invasive and involves a shorter hospital stay than surgical closure [9]. Also, surgical closure is known to impair pulmonary function due to the cardiopulmonary bypass and surgical scar, which affects respiratory resistance and lung compliance [10]. The percutaneous closure technique therefore provides a unique model to assess pulmonary function changes which are fully attributable to left-to-right shunt closure. Indeed, ASD closure instantly corrects right heart and pulmonary arterial volume overload and thereby significantly improves spirometry [11], which the present study confirms.

In this study cohort, both baseline $DLCO_c$ and $DLNO$ were lower than predicted based on age, sex and height. Both diffusion capacities depend on the VA [12], which was also reduced at baseline. This is confirmed by the higher values for KCO and KNO , yielding a KCO higher than the predicted value and a KNO within the normal range. This may indicate a certain pulmonary restriction [13], very possibly due to ASD-based pulmonary vascular engorgement and right heart enlargement. Also, overall alveolar–capillary membrane diffusion seems adequate especially in well-ventilated areas [14]. Interstitial oedema in ASD patients is therefore either absent, or altogether does not significantly influence diffusing capacity in this patient population.

After successful percutaneous ASD closure, $DLCO_c$ and KCO significantly decreased. Due to their interdependence, both can be attributed to the significant reduction in pulmonary capillary volume. $DLNO$ did not decrease as much post-closure, which correlated strongly to the unchanged $DMCO$, *i.e.* the actual alveolar–capillary membrane diffusing capacity. Thus, most likely the increased $DLNO/DLCO_c$ ratio after closure is mainly caused by the reduction in pulmonary capillary volume. Regarding the seemingly low percentage predicted capillary volume at baseline ($88\pm 15\%$), it must be noted that both capillary volume and $DMCO$ are the determinants of $DLCO_c$. Considering that the $DLCO_c$ was well below the expected mean value of 100% of predicted in this cohort ($91\pm 13\%$), the capillary volume percentage of 88% is relatively high. This is one of the main arguments for using combined nitric oxide and carbon monoxide diffusion testing; a $DLNO/DLCO$ ratio is a valuable addition to the interpretation of diffusing capacity [5].

Hence, the most prominent effect of percutaneous ASD closure on diffusion is an increase in the $DLNO/DLCO$ ratio by reduction of capillary volume. Its impact is two-fold: 1) this seems to correct an abnormally high diffusing capacity for carbon monoxide, and 2) it enables an increase in VA and consequently of vital capacity.

This study supports a wider use of additional nitric oxide diffusion testing. Currently, the routine clinical test gas for measuring diffusing capacity is carbon monoxide, for which the European Respiratory Society/American Thoracic Society standards have been recently updated [7]. Several studies have promoted the use of combined carbon monoxide and nitric oxide measurements for more accurate information on diffusing capacity [4, 5, 8]. This study confirms that combined $DLCO_c$ and $DLNO$ testing facilitates understanding of the mechanism underlying the effect of percutaneous ASD closure. Should $DLCO_c$ have been measured alone, we could not have excluded alveolar–capillary membrane diffusion impairment in ASD patients. Furthermore, by combined diffusion testing, the presence of left-to-right shunting is evident from a low $DLNO$, $DLCO_c$ and $DLNO/DLCO_c$ ratio. The recently published standardisation for nitric oxide diffusion testing [8] paves the way for combined testing in the management of cardiovascular disease [15].

This study has several limitations. Diffusion capacities were measured during a mean 5.4 ± 0.5 s breath-hold time so percentages of predicted values may be underestimated for carbon monoxide; however, paired pre- and post-procedural changes were the main point of interest. In some patients, the changes were smaller than the minimal detectable changes for diffusion testing [8], which in future studies can perhaps be prevented by including patients with a pulmonary-to-systemic ratio of ≥ 2.0 . Also, this study included a limited ASD cohort with 6-month follow-up, therefore larger studies with longer follow-up are needed to confirm our findings. Measuring total lung capacity may have aided the study by potentially eliminating pulmonary restrictive disease in ASD patients. Finally, in this descriptive study, the clinical relevance of certain parameters, such as increased $DLNO/DLCO$ ratio, remains difficult to interpret for clinicians. Future studies are needed to determine the merits of these findings; the present study merely demonstrates that subtle haemodynamic changes in the pulmonary circulation after ASD closure can be detected by advanced pulmonary function testing.

In conclusion, the present study is the first to describe the diffusing capacity of adult ASD patients before and after successful percutaneous closure. At baseline, ASD-based left-to-right shunting is evident from a low $DLNO/DLCO_c$ ratio. The physiological effect of successful percutaneous ASD closure is demonstrated by a post-procedural significant increase in the $DLNO/DLCO_c$ ratio and normalisation of excessive diffusion through correction of an ASD-induced hyperdynamic pulmonary circulation. Hence, combined

carbon monoxide and nitric oxide diffusion testing is applicable for a physiological evaluation of ASD closure.

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Author contributions: M. Nassif had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. M. Nassif, R.P. van Steenwijk, I. van der Lee, P.J. Sterk, B.J.M. Mulder and R.J. de Winter contributed substantially to the study conception and design. M. Nassif and J.M. Hogenhout acquired the data. M. Nassif, R.P. van Steenwijk, I. van der Lee, F.H.C. de Jongh, P.J. Sterk, J.G.P. Tijssen and R.J. de Winter substantially contributed to data analysis and interpretation. M. Nassif has drafted the submitted article. All authors have critically revised the submitted article for important intellectual content, provided final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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