ORIGINAL RESEARCH LETTER

Low D_{LCO} predicts all-cause hospital admissions in patients with reduced left ventricular ejection fraction or diastolic dysfunction

To the Editor:

The diffusing capacity of the lung for carbon monoxide (D_{LCO}) can be decreased in many disease states, including COPD and interstitial lung disease [1, 2]. Low D_{LCO} can also be seen in those with clinically relevant congestive heart failure (CHF) due to its deleterious consequences on lung volumes, perfusion and gas exchange efficiency [3, 4]. Pulmonary function testing results are frequently available in patients with CHF. D_{LCO} measurements have previously been shown to impact exercise capacity in CHF patients with either reduced or preserved left ventricular ejection fraction (LVEF) [5–7]. Impaired D_{LCO} has also been suggested as a potential predictor of negative clinical outcomes in CHF [8]. We, therefore, aimed to determine if patients with reduced LVEF or isolated diastolic dysfunction on echocardiography and a low D_{LCO} are at a higher risk of hospital admissions than their counterparts with a preserved D_{LCO}. Confirmation of this hypothesis would support the need for closer monitoring of CHF patients who also present with a reduced D_{LCO}.

We performed a retrospective review at Montfort Hospital (Ottawa, ON, Canada), a large urban academic centre, to identify all patients who underwent echocardiography (1 January 2016 to 30 June 2017) and pulmonary function testing, including D_{LCO} measurements by single-breath carbon monoxide uptake. We charted all-cause hospital admissions between 1 January 2016 and 31 December 2018 for all subjects. LVEF was determined by the biplane Simpson method and the American Society of Echocardiography guidelines were used for the evaluation of left ventricular diastolic function [9]. D_{LCO} % predicted results were determined for each patient using the 2017 Global Lung Function Initiative reference values [10]. A reduced D_{LCO} was defined as a result below the lower limit of normal.

A total of 363 individuals underwent both echocardiography and D_{LCO} measurements; 128 (35.3%) had at least one admission to the hospital. 131 patients had evidence of cardiac dysfunction (40% with a decreased LVEF *versus* 60% with isolated diastolic dysfunction). 66 of these subjects (50.4%) had a reduced D_{LCO} (33 from both the reduced LVEF and isolated diastolic dysfunction groups). Cigarette smoking status was similar in those with a low or preserved D_{LCO}, with 26% and 29%, respectively, reporting being lifelong nonsmokers. ANOVA revealed that D_{LCO} had an independent relationship with all-cause hospital admissions ($p<0.01$). Indeed, patients with cardiac dysfunction and a low D_{LCO} were admitted to the hospital more frequently than those with a preserved D_{LCO} (mean of 1.29 *versus* 0.45 admissions, $p<0.01$). Subjects with a moderate or severe decrease of D_{LCO} (⩽60% predicted) were at an even higher risk of hospitalisation (mean of 1.64 admissions, $p<0.01$) compared with those with only a mild decrease (mean of 0.87 admissions) (table 1). No significant difference was seen amongst patients with a low D_{LCO} when comparing individuals with a reduced LVEF *versus* isolated diastolic dysfunction ($p=0.25$). The mean±SD predicted D_{LCO} in these two groups was 54±15% and 55±15%, respectively.

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A low D_{LCO} should be valued as a predictor of all-cause hospital admissions in patients with reduced LVEF or isolated diastolic dysfunction. The severity of the impairment seen on D_{LCO} testing also appears to affect the risk of hospitalisation. https://bit.ly/3e4r8bH

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TABLE 1 All-cause hospital admissions in patients with reduced left ventricular ejection fraction or diastolic dysfunction (n=131) dependent on diffusing capacity of the lung for carbon monoxide (D_{LCO}) measurements

D_{LCO}	Patients n (%)	Mean all-cause hospital admissions (95% CI)
⩾LLN	65 (49.6)	0.45 (0.18–0.71)
<LLN	66 (50.4)	1.29 (0.89–1.68)
⩽60% predicted	36 (27.5)	1.64 (1.00–2.28)

LLN: lower limit of normal.

We also sought to investigate whether these findings would remain significant taking into consideration the % predicted forced expiratory volume in 1 s (FEV_1) and the presence of airflow limitation, given the potential confounding effects from pulmonary disease on D_{LCO}. As expected, the mean FEV_1 was lower in the group with a reduced D_{LCO} (73% *versus* 93% predicted, respectively). Patients with a decreased D_{LCO} also had evidence of airflow limitation on spirometry more often (55% *versus* 28%). Of note, FEV_1 did not have a meaningful effect on all-cause hospital admissions (p=0.08). A reduced D_{LCO} was also a predictor of hospitalisations in individuals (25 out of 79 patients) with cardiac dysfunction and a FEV_1 ⩾80% predicted (mean of 0.84 *versus* 0.30 admissions, p=0.01). In keeping with these results, D_{LCO} remained an independent predictor of hospitalisations after adjustment for FEV_1 (p=0.02). In the subgroup of patients with cardiac dysfunction but no airflow limitation present (n=77), subjects with a low D_{LCO} (n=30) still had an increased risk of admission (mean of 1.10 *versus* 0.36 admissions, p<0.01).

Our analysis revealed that a low D_{LCO} predicts all-cause hospital admissions in patients with reduced LVEF or isolated diastolic dysfunction. There was a nearly threefold increase in mean hospitalisations in those with a reduced D_{LCO}. The severity of the impairment seen on D_{LCO} testing also appeared to affect the risk of hospitalisation. It is interesting to note that no significant relationship with all-cause hospital admissions was found when using FEV_1. Thus, impairment in gas exchange efficiency seems more relevant than the severity of airflow limitation in predicting this negative outcome in these patients.

Low D_{LCO} could reflect worse pulmonary perfusion secondary to impaired cardiac output and endothelial dysfunction in the lung capillaries [3, 4]. Repeated episodes of pulmonary oedema, increased interstitial fluid and alveolar–capillary membrane thickening might play a role. Increased ventilation–perfusion mismatch is an important determinant of a low D_{LCO}. The association of poor pulmonary perfusion with ventilation distribution abnormalities could have also influenced our results [11–14]. Regardless of the underlying mechanisms, these abnormalities are expected to worsen as the extracardiac manifestations of impaired ventricular function become more relevant. A reduced D_{LCO} may reflect the potentiating effects of negative cardiopulmonary interactions on chronic breathlessness, thereby increasing the likelihood of the patient being admitted to hospital [15].

What are the implications of our results? First and foremost, our data provide novel support to the notion that patients with impaired systolic and/or diastolic function and a reduced D_{LCO} should be flagged as being at a higher risk of admission to the hospital. Secondly, they set the stage for prospective studies looking at changes in D_{LCO} as the treatment of the underlying cardiac dysfunction is optimised. If so, it is conceivable that a higher D_{LCO} over time could be associated with a lower risk of hospitalisation, particularly when there is a direct cause–effect relationship between ventricular function and a low D_{LCO}. Thirdly, the advent of reliable point-of-care D_{LCO} measurement systems raises the perspective that easily accessible results could play an unexplored role in the longitudinal follow-up of these patients. Finally, the added value of the diffusion coefficient (K_{CO}=D_{LCO}/alveolar volume) in those with preserved D_{LCO} also merits investigation since a low K_{CO} but normal D_{LCO} indicates impaired gas exchange efficiency, which might be related to abnormal pulmonary perfusion due to cardiovascular disease [15].

Our analysis does have some inherent limitations given that it is a retrospective review from objective testing results. Despite the fact that a reduced D_{LCO} remained a strong predictor of hospitalisations even when removing subjects with airflow limitation or a FEV_1 <80% predicted, we cannot rule out that a low D_{LCO} may have been negatively influenced by other concomitant pathologies, including pulmonary disease. The relatively small number of events also precluded further investigating the potential effects of worsening ventricular function on our main outcome. The confounding effects of anaemia should also be considered as well as the deleterious effects of recent smoking.

In conclusion, D_{LCO} measurements provide meaningful clinical information to help predict hospital admissions in patients with CHF. As pulmonary function testing is frequently available in these patients, our data indicate that those with a reduced D_{LCO} should be monitored more closely in an attempt to reduce the burden of repeated hospital admissions.

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References

1 Pellegrino R, Viegi G, Brusasco V, *et al.* Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26: 948–968.
2 Neder JA, Berton DC, Muller PT, *et al.* Incorporating lung diffusing capacity for carbon monoxide in clinical decision making in chest medicine. *Clin Chest Med* 2019; 40: 285–305.
3 Neder JA, Rocha A, Alencar MC, *et al.* Current challenges in managing comorbid heart failure and COPD. *Expert Rev Cardiovasc Ther* 2018; 16: 653–673.
4 Neder JA, Rocha A, Berton DC, *et al.* Clinical and physiologic implications of negative cardiopulmonary interactions in coexisting chronic obstructive pulmonary disease-heart failure. *Clin Chest Med* 2019; 40: 421–438.
5 Agostoni P, Bussotti M, Palermo P, *et al.* Does lung diffusion impairment affect exercise capacity in patients with heart failure? *Heart* 2002; 88: 453–459.
6 Agostoni P, Bussotti M, Cattadori G, *et al.* Gas diffusion and alveolar capillary unit in chronic heart failure. *Eur Heart J* 2006; 27: 2538–2543.
7 Olson T, Johnson B, Borlaug B. Impaired pulmonary diffusion in heart failure with preserved ejection fraction. *JACC Heart Fail* 2016; 4: 490–498.
8 Guazzi M, Pontone G, Brambilla R, *et al.* Alveolar-capillary membrane gas conductance: a novel prognostic indicator in chronic heart failure. *Eur Heart J* 2002; 23: 467–476.
9 Nagueh SF, Smiseth OA, Appleton CP, *et al.* Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016; 29: 277–314.
10 Stanojevic S, Graham BL, Cooper BG, *et al.* Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J* 2017; 50: 1700010.
11 Wright RS, Levine MS, Bellamy PE, *et al.* Ventilatory and diffusion abnormalities in potential heart transplant recipients. *Chest* 1990; 98: 816–820.
12 Olson T, Beck KC, Johnson BD. Pulmonary function changes associated with cardiomegaly in chronic heart failure. *J Card Fail* 2007; 13: 100–107.
13 Guazzi M. Alveolar gas diffusion abnormalities in heart failure. *J Card Fail* 2008; 14: 695–702.
14 Siegel JL, Miller A, Brown LK, *et al.* Pulmonary diffusing capacity in left ventricular dysfunction. *Chest* 1990; 98: 550–553.
15 Magnussen H, Canepa M, Zambito PE, *et al.* What can we learn from pulmonary function testing in heart failure? *Eur J Heart Fail* 2017; 19: 1222–1229.