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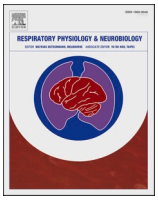

Impaired diffusion at submaximal lung inflation in asthma and copd patients

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ABSTRACT

Introduction: Dissolved-phase ^{129}Xe MRI metrics suggest that gas diffusion may be more compromised at submaximal lung inflation compared to maximal inflation. We hypothesized that this diffusion deficit could be detected by comparing the carbon monoxide transfer coefficient (Kco) at submaximal lung inflation to that measured routinely at total lung capacity (TLC).

Methods: Asthma and COPD patients performed carbon monoxide diffusion tests, first at maximal lung inflation for routine Kco and alveolar volume VA and then, at a 30 % reduced inflation (redux; obtaining Kco_{redux} and VA_{redux}). At both inflations mixing efficiency was determined as VA/TLC and VA_{redux}/TLC_{redux} to examine a potential effect on Kco_{redux}/Kco behavior.

Results: In normal subjects (n=36), median Kco_{redux}/Kco amounted to 130 [IQR:122–136]% as expected for normal Kco recruitment response. However, 60 % of asthma patients (49/83) and 80 % of COPD patients (44/55) showed reduced Kco recruitment at submaximal inflation (Kco_{redux}/Kco<122 %). In the asthma group, with otherwise normal routine Kco, Kco_{redux}/Kco was significantly correlated with RV/TLC ratio (r=-0.53;P<0.001), but not with VA/TLC. In COPD patients, all with abnormal routine Kco, abnormal Kco_{redux}/Kco response occurred in those patients with lower FEV_1, higher RV/TLC and lower VA/TLC (P<0.01 for all).

Conclusion: Sizeable portions of COPD and asthma patients showed a lack of normal Kco recruitment at submaximal lung inflation, related to high RV/TLC. In asthma, this was the case despite normal Kco at full lung inflation, suggesting that hyperinflation at lung volumes less than TLC affects the carbon monoxide diffusion rate constant by distorting pulmonary capillaries and alveolar–capillary membranes.

1. Introduction

In a clinical setting, the single breath transfer factor for carbon monoxide is routinely measured during a breath hold at full inflation. The resulting transfer factor for carbon monoxide (DLco) is the product of two primary measures (a) transfer coefficient Kco, reflecting the rate of CO disappearance across the gas-blood barrier, and (b) alveolar volume VA at which CO disappearance occurs; thus, DLco = Kco x VA (Hughes and Pride, 2012). The DLco value declines when measurements are made at lung inflations less than total lung capacity (TLC); at 70 % TLC, the rate of CO uptake (Kco) increases to approximately 130 % of its value at TLC. This volume dependent increase or "recruitment" of Kco is well documented for normal subjects (Stam et al., 1994; Johnson, 2000; Macintyre et al., 2005), but systematic studies using the standard single breath test in patients with respiratory disease are lacking. In asthma and COPD, for example, the Kco increase at lower lung inflation could be attenuated due to a less compliant pulmonary capillary bed (related to vascular pruning) (Ash et al., 2018; Estépar et al., 2013), an increase in heterogeneity of perfusion or ventilation at lung inflations closer to physiological breathing.

Although diffusing capacity measurement maneuvers closer to the normal breathing range such as rebreathing (Hsia et al., 1995) or tidal breathing (Snyder et al., 2005) are more physiologically relevant, the single breath measurement at maximal lung inflation is currently the standard procedure. Using this routine measurement of Kco as a reference point, we hypothesized that in patients with asthma and COPD, the normal Kco increase at lower lung inflation (Kco_{redux}/Kco) might be compromised. In patients with COPD, Kco_{redux}/Kco may pick up an increase in the diffusion deficit already visible at full inflation, but in patients with asthma where Kco is usually normal (Collard et al., 1994), Kco_{redux}/Kco might reveal a diffusion deficit otherwise unnoticed. To assess a potential influence of ventilation heterogeneity on Kco_{redux}/Kco behavior in asthma and COPD, we measured the VA/TLC ratio (Roberts et al., 1990; Kaminsky et al., 2014) both at full and reduced inflation.

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2. Methods

Patients with a clinical diagnosis of asthma or COPD who presented to the outpatient clinic for full lung function testing had an additional – i.e., third – single breath diffusing capacity measurement at a reduced inflation (UZ Brussel ethics approval BUN1432023000161). From the two standard single breath diffusing capacity measurements at full inflation, VA and Kco were calculated, and accepted if the inter-measurement variation was < 5 %: from the measurement at reduced inflation, VA_{redux} and Kco_{redux} were determined (MasterScreenPFT; SentrySuite, Vyaire, Mettawa, IL, USA). A maximum deviation of 10 % was allowed from the target VA_{redux} of 70 % VA; Kco_{redux} was corrected for this, assuming a linear dependence within this VA range (Stam et al., 1994). We then determined Kco_{redux}/Kco, where Kco_{redux}/Kco =100 % means that Kco does not change with inflation level, i.e., no Kco *recruitment* response. Patients were not included for analysis when plethysmographic TLC was outside limits of normal (z-scores for TLC below −1.645 or over +1.645). A normal group of non-smokers without any history of lung disease was included as a control. We specifically excluded subjects over 50 to avoid accelerated age-dependent deterioration of lung function indices such as ventilation heterogeneity and RV/TLC (Verbanck et al., 2016). To estimate ventilation heterogeneity at full and reduced lung inflation, VA/TLC and VA_{redux}/TLC_{redux} were determined, where TLC_{redux} was computed as plethysmographic RV plus the inhaled volume from the reduced inflation diffusion test.

3. Results

Eighty-three asthma patients (48±18(SD) years; FEV_1=85±14 % pred; DLco=90±13 %pred), fifty-five COPD patients (67±8 years; FEV_1=63±17 %pred; DLco=61±19 %pred) and thirty-six normal subjects (36±13years; FEV_1=98±10 %pred; DLco=93±11 %pred) were studied. Median value and interquartile [IQR] range of VA_{redux}/VA was 69 [61–77]%. The corresponding Kco_{redux}/Kco values were 130 [122–136]% in normal controls. We then used the first quartile (Q1) for Kco_{redux}/Kco in the control group to stratify the asthma and COPD patients into subgroups corresponding to a "normal" and "abnormal" Kco_{redux} recruitment response at the lower lung inflation (Table 1). Significant impairment of Kco_{redux}/Kco recruitment was seen in 60 % of the asthmatic and 80 % of the COPD patients.

Values for VA/TLC were similar at both inflations in the control group. In the patient groups, VA/TLC values were generally lower (i.e., ventilation heterogeneity was increased) and VA_{redux}/TLC_{redux} was significantly smaller than VA/TLC (P<0.001 for all subgroups according to Kco_{redux} recruitment response). In the asthma cohort, VA/TLC or VA_{redux}/TLC_{redux} did not distinguish between patients with or without abnormal Kco_{redux}/Kco recruitment response (Table 1). In fact, age and RV/TLC were the only significant discriminating features between asthma patients with or without attenuated Kco_{redux}/Kco. When performing a multiple regression including age and RV/TLC, but also FEV_1 and DLco (for their borderline significance) as potential contributors, an abnormal Kco_{redux}/Kco response was only significantly related to asthma patients' baseline RV/TLC (adjusted R^2=0.28; P<0.001). Fig. 1 shows the distribution of individual Kco_{redux}/Kco versus RV/TLC values in the asthma and COPD patients. In the COPD cohort, greater Kco_{redux}/Kco attenuation was associated with more severe obstructive impairment (lower FEV_1), more hyperinflation (higher RV/TLC) and greater ventilation heterogeneity (lower VA/TLC) at both inflation levels, but Kco_{redux}/Kco attenuation was independent of DLco or Kco.

Table 1
Lung function in asthma and COPD patients stratified according to Kco recruitment response.

		Normals (n=36)		Asthma (n=83)					COPD (n=55)				
				abnormal Kco recruitment response		normal Kco recruitment response			abnormal Kco recruitment response		normal Kco recruitment response		
				(Kco_{redux}/Kco<Q1) (n=49)		(Kco_{redux}/Kco>Q1) (n=34)			(Kco_{redux}/Kco<Q1) (n=44)		(Kco_{redux}/Kco>Q1) (n=11)		
Male/Female		15 M/21 F		23 M/26 F		19 M/15 F			30 M/14 F		9 M/2 F		
		mean	SD	mean	SD	mean	SD	P	mean	SD	mean	SD	P
age	(years)	36	13	53	17	40	16	**0.001**	68	8	64	8	0.12
BMI	(kg/m^2)	25.3	3.6	25.7	4.0	24.7	3.8	0.3	26.6	3.4	27.1	3.7	0.7
FEV_1	(%pred)	98	11	84	11	89	14	0.06	60	17	77	14	**0.003**
	(z-score)	−0.3	1.0	−1.7	1.3	−1.3	1.7	0.2	−4.8	2.8	−2.4	1.7	**0.010**
FEV_1/FVC	(%)	82 %	6 %	75 %	8 %	77 %	9 %	0.3	56 %	10 %	67 %	12 %	**0.003**
	(z-score)	0.2	1.0	−0.9	1.4	−0.6	1.6	0.5	−3.6	1.3	−1.7	2.5	**0.001**
DLco	(%pred)	93	11	88	13	93	10	0.06	58	18	66	16	0.2
	(z-score)	−0.5	0.9	−1.0	1.2	−0.6	0.8	0.06	−4.5	2.3	−3.6	1.9	0.2
Kco	(%pred)	96	10	96	16	99	11	0.3	70	19	73	14	0.6
	(z-score)	−0.3	0.8	−0.4	1.2	−0.1	0.9	0.3	−2.2	1.5	−2.0	1.1	0.6
VA	(%pred)	91	9	87	9	89	9	0.3	78	10	85	9	0.08
	(z-score)	−1.0	1.0	−1.3	0.9	−1.2	1.0	0.4	−2.1	1.0	−1.5	0.8	0.06
RV/TLC	(%)	28 %	6 %	40 %	9 %	32 %	8 %	**<0.001**	50 %	8 %	40 %	7 %	**<0.001**
	(z-score)	0.1	1.0	1.3	1.1	0.6	1.3	**0.007**	2.6	1.8	0.9	1.7	**0.007**
TLC	(%pred)	98	9	98	9	98	9	0.9	102	10	97	10	0.14
	(z-score)	−0.2	0.9	−0.2	0.9	−0.2	0.9	0.9	0.1	0.9	−0.3	0.9	0.15
VA/TLC	(%)	92 %	4 %	89 %	7 %	91 %	6 %	0.2	77 %	9 %	88 %	6 %	**0.001**
VA_{redux}/TLC_{redux}	(%)	91 %	8 %	83 %	11 %	85 %	10 %	0.4	67 %	14 %	79 %	7 %	**0.012**

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; DLco: diffusing capacity for carbon monoxide; Kco: transfer coefficient for carbon monoxide; DLco and Kco corrected for Hb concentration; VA: alveolar volume corresponding to Kco; RV: residual volume; TLC: total lung capacity; VAredux/TLCredux: ratio of VA/TLC at reduced volume. %predicted and z-scores based on reference values in ref (Verbanck et al., 2016); for both VA and TLC % pred and z-scores, reference values for TLC are considered.
Q1: first quartile of Kco_{redux}/Kco values obtained in normal subjects (see text for details).
P-value: comparison between patients with normal and abnormal Kco recruitment response, within asthma and COPD groups.

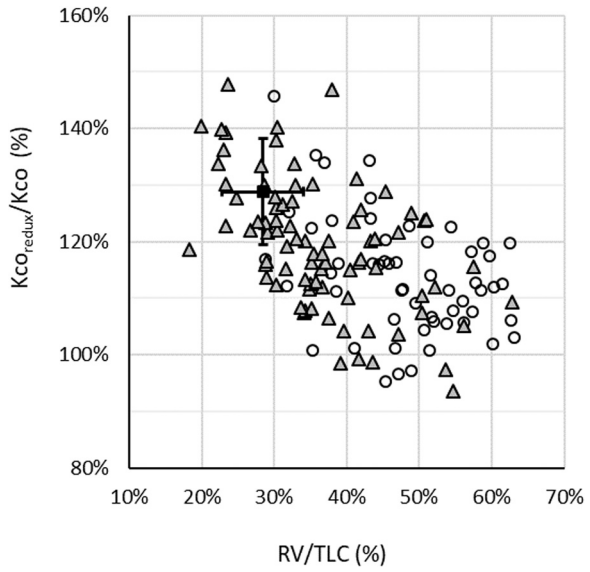

Fig. 1. Extent of Kco increase at reduced lung inflation (Kco_{redux}) relative to that routinely obtained at maximal inflation (Kco) obtained in asthma (n=83; grey triangles) and COPD (n=55; open circles) patients, and its relationship to the residual volume – total lung capacity (RV/TLC) ratio. Normal values for RV/TLC and Kco_{redux}/Kco values are also shown (avg±SD bars) for comparison.

4. Discussion

In this study, we identified groups within our asthma and COPD patients for whom Kco does not increase with reduced lung inflation as is expected in a normal lung. This diffusion deficit at lower lung inflations closer to physiological lung volumes appears to affect particularly those COPD or asthma patients with elevated RV/TLC. In COPD patients, impaired diffusion at lower inflation was more generally associated with worse disease severity in terms of FEV_1 and poorer gas mixing, but in asthma patients it was not.

4.1. Kco recruitment: mechanisms

We focused on Kco (the rate of uptake of alveolar CO) and its increase (or "recruitment") when the clinical single breath diffusion test is performed at lung volumes close to 70 % of the standard VA. In normal subjects, Kco at 70 % VA is typically expected to be 130 % of that at 100 % VA, as was verified in our control group. According to the Roughton–Forster equation, 1/Kco (~ VA/DLco) is determined by the sum of the VA/DM and VA/θVc ratios where DM is the alveolar–capillary membrane diffusing capacity, θ is the reaction rate of uptake of CO by blood and Vc is the pulmonary microcirculatory blood volume (Hughes and Pride, 2012). As VA decreases, the VA/DM ratio remains virtually unchanged but the VA/θVc ratio decreases because Vc does not change (Stam et al., 1991). The constant Vc at reduced lung expansion is the reason for the "recruitment" of Kco occurring at submaximal lung inflation. When the single breath diffusion test was performed at submaximal alveolar volumes, the normal recruitment response was impaired in 60 % of our patients with asthma and 80 % of those with COPD. Possible explanations are a) volume-dependent worsening of inspired CO distribution and mixing (increased ventilatory inhomogeneity), or b) impairment of the normal Vc and DM responses to VA change.

4.2. Increased ventilatory heterogeneity

Impaired gas mixing may contribute to an underestimation of actual Kco transfer during the standard single breath maneuver (Piiper and Sikand, 1966; Verbanck et al., 2008). The VA/TLC ratio in both patients groups suggests the presence of ventilation heterogeneity at both inflation levels (Table 1). If ventilation heterogeneity (or airway closure) were present at VA_{redux} and less so at VA, VA_{redux}/TLC_{redux} would be reduced and more so than VA/TLC, which is the case in both patient groups. In the COPD group, those patients who failed to show "recruitment" of Kco at submaximal lung inflation had a significantly greater impairment of ventilation distribution in terms of the VA/TLC ratio, both at reduced VA and maximal VA. In the asthma group, there was no difference in VA_{redux}/TLC_{redux} or VA/TLC between the normal and abnormal Kco recruitment subgroups. Hence, we may assume that heterogeneity of ventilation distribution had a role in the lack of "recruitment" of Kco in COPD, but that this was not the case in the asthma patients.

4.3. Pulmonary capillary blood volume (Vc) and/or alveolar capillary membrane surface area and thickness

Microvascular irregularities are a more likely cause for the observed failure to recruit Kco at submaximal alveolar volumes, since Kco is a "window on the pulmonary microcirculation" (Hughes, 2003). Reduced plasticity (compliance) and recruitment of the capillary bed (or "drop–out" of micro–vessels) is a possibility. The low Kco_{redux}/Kco values observed in the COPD patients is consistent with dissolved-phase ^{129}Xe MRI metrics, where the membrane-to-gas and red-blood-cell-to-gas ratios increased, as expected, at lower compared to fuller lung inflation in normal controls, but the increase was less in elderly normals or COPD patients (Garrison et al., 2023).

State-of-the-art analysis of CT lung images with quantification of the vasculature provides another clue for the observed Kco_{redux}/Kco behavior (Ash et al., 2018; Estépar et al., 2013; McIntosh et al., 2023). These studies report vascular pruning in COPD (Ash et al., 2018) but also in asthma (Estépar et al., 2013) where redistribution of blood volume from the larger to the smaller pulmonary vessels was seen to occur after two years of anti-IL-5Rα treatment (McIntosh et al., 2023). Clearly, there will be loss of small blood vessels in the emphysematous changes which occur in COPD; in asthma, inflammatory remodeling of blood vessels may be a factor. In addition, pulmonary capillary and/or alveolar–capillary membrane distortion in regions of hyperinflation might explain the association with RV/TLC seen in both asthma and COPD (Table 1, Fig. 1). Measurements in rapidly frozen lungs have shown how local hyperinflation (and possibly a reduced capillary-alveolar pressure gradient) could reduce capillary width and red cell density (Glazier et al., 1969). In fact, in the case of asthma, the association of abnormal Kco recruitment response with RV/TLC, but not with VA/TLC, lends further support to some form of hyperinflation-related distortion at the blood-gas barrier.

While this study showed that abnormality in Kco recruitment was linked to different factors in asthma and COPD patients, the consistent association with an elevated RV/TLC in both patient groups suggests that a Kco recruitment deficit might also occur to some extent in a normal ageing lung where an accelerated RV/TLC increase is seen around 50 years (Verbanck et al., 2016). In this sense, our study suggests that it might be useful to measure Kco recruitment in subjects aged 20–80 years. Specifically, it might be possible link the biphasic RV/TLC increase with ageing to a deficit in Kco recruitment, against the backdrop of a steady Kco decrease with age, which remains largely unexplained (Hughes and Pride, 2012).

5. Conclusion

The new finding in this study is that DLco and Kco values in stable asthma, generally considered to be normal, may be compromised if the routine DLco measurement is repeated at lung volumes less than the customary TLC. The exact mechanism remains to be fully understood, but distortion or pruning of alveolar–capillary geometry at lung volumes less than maximal is a possibility.

CRediT authorship contribution statement

Sylvia Verbanck: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mike Hughes:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization.

Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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Author contributions

S.V. is the guarantor of the manuscript. S.V. performed data analysis; S.V and M.H. co-wrote the manuscript.

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