The $T_{L,NO}/T_{L,CO}$ ratio cannot be used to exclude pulmonary embolism

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Summary

Background The existing screening modalities for pulmonary embolism (PE), such as D-dimer and clinical prediction rules, have low positive predictive values. With its capability to indicate pulmonary vascular abnormalities, the ratio of the transfer factor of the lungs for nitric oxide and the transfer factor of the lungs for carbon monoxide ($T_{L,NO}/T_{L,CO}$) might be an additional discriminating parameter.
Methods Carbon monoxide/Nitric oxide diffusion measurements were performed on unselected patients seen on the emergency department for which due to suspected PE a computed tomography pulmonary angiogram (CTPA) was ordered.
Results A total of 28 patients were included, PE was found in 12 on CTPA. Median $T_{L,NO}/T_{L,CO}$ ratio was 4·09 (interquartile range (IQR) 3·83–4·40) in the no PE group versus 4·00 (IQR 3·78–4·32) in the PE group ($P = 0{\cdot}959$). Median alveolar volume was 77·1% of predicted in the no PE group versus 71·0% of predicted in the PE group ($P = 0{\cdot}353$). Median $T_{L,CO}$ was 75·8% of predicted in the no PE group versus 68·8% of predicted in the PE group ($P = 0{\cdot}120$). Median $T_{L,NO}$ was 69·3% of predicted in the no PE group versus 60·5% of predicted in the PE group ($P = 0{\cdot}078$).
Conclusion The presented data indicate that the $T_{L,NO}/T_{L,CO}$ ratio cannot be used to exclude PE.

Introduction

Due to its potentially lethal consequences, pulmonary embolism (PE) needs to be ruled out when suspected. The nowadays widely used tools to select patients with suspicion of PE are D-dimer (Stein *et al.*, 2004) and Wells score (Wells *et al.*, 2000). Positive D-dimer or high Wells score warrants further investigation. Current gold standard to confirm or exclude PE is a computed tomography pulmonary angiogram (CTPA) (Konstantinides & Torbicki, 2014). In over 75% of all CTPAs requested due to suspected PE, the disease can be safely ruled out (Stein *et al.*, 2006). To prevent unnecessary irradiation and admissions due to the need for prehydration, an additional fast and cheap tool to exclude PE is desirable. With its capability to indicate pulmonary vascular abnormalities, the $T_{L,NO}/T_{L,CO}$ ratio might be such a tool.

The transfer factor of the lungs (T_L) for a gas can be described by the Roughton–Forster equation:

$$\frac{1}{T_L} = \frac{1}{D_m} + \frac{1}{\theta V_C},$$

in which D_m indicates the membrane diffusion capacity, θ the binding capacity of the gas with the erythrocytes and V_C the pulmonary capillary blood volume (Roughton & Forster, 1957). In the case of carbon monoxide (CO), the transfer factor is more weighted by θV_C than on D_m. In the case of nitric oxide (NO), θV_C is much greater than D_m (Guenard *et al.*, 1987). Therefore, the transfer factor of NO ($T_{L,NO}$) is more dependent on D_m than on θV_C. Hughes and van der Lee have shown that, given that Dm_{NO} equals αDm_{CO} (in which α is a theoretic constant), the ratio of $T_{L,NO}$ and the transfer factor for CO ($T_{L,CO}$) is dependent on the D_m/V_C ratio and α. As α is (assumed to be) a constant, the $T_{L,NO}/T_{L,CO}$ ratio is a reflection of the D_m/V_C ratio without the need of further assumptions. A rise of this ratio might thus suggest pulmonary vascular abnormalities (Hughes & van der Lee, 2013). The $T_{L,NO}/T_{L,CO}$ ratio has been reported to be increased in heavy smokers (Van der Lee *et al.*, 2009), chronic thromboembolic pulmonary hypertension and diffuse parenchymal lung disease (Van der Lee *et al.*, 2006). In the case of PE, one would expect V_C to be decreased and therefore $T_{L,NO}/T_{L,CO}$ to be increased. This has been investigated in prone anesthetized sheep by Harris *et al.* (2004) who reported a significant higher $T_{L,NO}/T_{L,CO}$ ratio after pulmonary artery obstruction compared to baseline. To the best of our knowledge, the $T_{L,NO}/T_{L,CO}$

ratio in PE has not yet been reported in humans. Therefore, the aim of this study was to investigate the value of the $T_{L,NO}/T_{L,CO}$ ratio in the exclusion of PE.

Methods

Design

This study was conducted at Medisch Spectrum Twente in Enschede, the Netherlands, in combination with another research project on the value of volumetric capnography in PE. Inclusion criteria were as follows: patients at the emergency department with suspected PE for which a CTPA scan was requested due to either elevated Wells score or D-dimer and age ≥ 18 years. Exclusion criteria were as follows: hemodynamic instability, pregnancy and oxygen administration. After inclusion, capnography and CO/NO diffusion measurements were performed within 4 h after the request for a CTPA was filed and before the results of the CTPA were reported to the pulmonologist. Both the local ethics committee and the board of directors of Medisch Spectrum Twente approved the study protocol.

Measurements

Carbon monoxide/Nitric oxide diffusion was measured on the MasterScreen™ PFT Pro system (CareFusion, Höchberg, Germany) using the single-breath method with a breath-hold time of 10 s and an inspired NO fraction of 50 ppm. According to the ATS/ERS guidelines, a measurement was considered repeatable when the results of at least two tests were within 10% of the highest resulting values for $T_{L,CO}$ and $T_{L,NO}$ and the vital capacity (VC) was at least 85% of the highest VC measured before the diffusion test (Macintyre *et al.*, 2005). Predicted values for $T_{L,CO}$, K_{CO} and alveolar volume were provided by the MasterScreen™ PFT Pro software. Predicted values for $T_{L,NO}$ and K_{NO} were calculated using the prediction equations of Van der Lee *et al.* (2007).

Statistical analysis

Continuous variables are expressed as median with interquartile range (IQR); categorical variables as counts with corresponding percentages. Baseline differences between the groups with and without PE were for continuous variables compared using the Mann–Whitney *U*-test. For categorical variables, the chi-square test or Fisher's exact test was used as appropriate. Diagnostic performances of $T_{L,CO}$, $T_{L,NO}$ and the $T_{L,NO}/T_{L,CO}$ ratio were quantified with the area under the curve (AUC) of the receiver operating characteristic curve. All AUCs were tested against the null hypothesis that the true area is equal to 0·5. Differences were considered significant if the statistic P is smaller than 0·05. Data were analysed using SPSS version 22 (SPSS Inc., Chicago IL, USA).

Results

Subjects were included from the end of July 2014 till the begin of May 2015. During this period, 36 patients were approached for participation in the study. Five of the approached patients refused participation, leading to 31 included subjects. PE was found in 13 patients on CTPA. Diffusion measurements failed in three patients (two no PE, one PE). Characteristics and presenting symptoms of the included patients are provided in Table 1. Three patients in both groups had a history of previous PE or deep venous thrombosis ($P = 1{\cdot}000$). In the group without PE, three patients had known airflow obstruction versus no patients with known airflow obstruction in the PE group ($P = 0{\cdot}238$). Wells score, D-dimer levels and the number of abnormal chest X-rays were significantly higher in the PE group compared to the no PE group. No other significant differences in characteristics were found.

Table 1 Patient characteristics.

	No PE (*n* = 16)		PE (*n* = 12)		
	Median	IQR	Median	IQR	*P*-value
Age, year	56	(42–69)	49	(41–67)	0·415
Females, n (%)	9	(56·3)	6	(50·0)	0·743
Height, cm	177	(168–183)	177	(166–184)	0·816
Weight, kg	83	(72–95)	78	(63–98)	0·378
BMI, kg m^{-2}	29·0	(24·2–33·7)	25·3	(23·2–28·5)	0·137
Active smoker, n (%)	6	(37·5)	2	(16·7)	0·401
Wells score	2·8	(0·0–3·0)	3·0	(3·0–4·5)	0·011*
D-dimer, μg L^{-1}	804	(640–1758)	2820	(1097–6049)	0·001*
Abnormal CXR, n (%)	1	(6·3)	9	(75·0)	0·000*
Thoracic pain, n (%)	13	(81·3)	8	(66·7)	0·418
Dyspnoea, n (%)	11	(68·8)	10	(83·3)	0·662

Data are presented as median (interquartile range) unless stated otherwise.
BMI, body mass index; PE, pulmonary embolism; DVT, deep venous thrombosis.
*A statistically significant difference ($P<0{\cdot}05$).

Results of the measurements are provided in Table 2. A boxplot of the distribution of the $T_{L,CO}/T_{L,NO}$ ratio in the no PE and PE groups is given in Fig. 1. No statistically significant differences between the PE and no PE groups were found. $T_{L,CO}$, $T_{L,NO}$ and alveolar volume were all lowered (<80% of predicted) in both the PE and no PE groups. AUC of the $T_{L,NO}/T_{L,CO}$ ratio was 0·453 (95% confidence interval (CI) 0·230–0·676, P = 0·676). The AUCs of all diffusion parameters were also not statistically significant higher than 0·5.

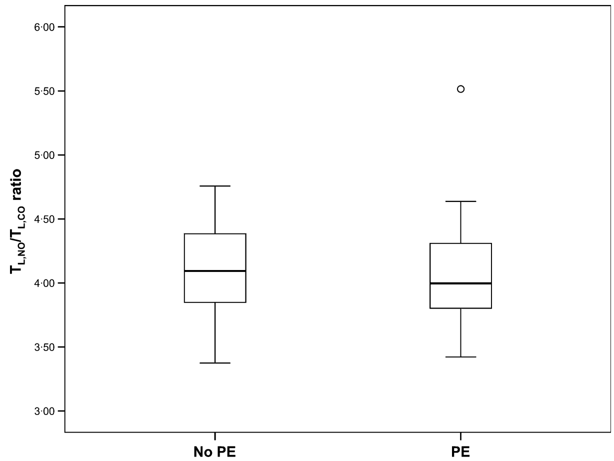

Figure 1 Boxplots of the distribution of the $T_{L,NO}/T_{L,CO}$ ratio in the no pulmonary embolism (PE) and PE groups. The value of the $T_{L,NO}/T_{L,CO}$ ratio found in healthy subjects by Van der Lee *et al.* (2006) was 4·36 ± 0·6.

Discussion

Due to the results of Harris *et al.*, and the physiological theory behind the $T_{L,NO}/T_{L,CO}$ ratio, it was expected that the ratio is increased in PE compared to no PE patients. Our data show lowered $T_{L,CO}$ and $T_{L,NO}$ and normal $T_{L,NO}/T_{L,CO}$ ratios in both groups. The value of $T_{L,CO}$ in PE has been investigated several times. Wimalaratna *et al.* (1989) for instance reported a $T_{L,CO}$ in PE patients of <75% of predicted which failed to normalize within three months in most cases (Wimalaratna et al., 1989). Oppenheimer *et al.* report decreased $T_{L,CO}$ values in chronic thromboembolic disease Oppenheimer *et al.* (2006), but it is hard to compare these values to acute PE. In 2011, Piirilä *et al.* reported lowered $T_{L,CO}$ in acute PE similar to the values found by Wimalaratna *et al.* (74% of predicted) which were still lowered after seven months (Piirilä *et al.*, 2011). The $T_{L,CO}$ values we found (69% of predicted) are comparable with the results of both Wimalaratna *et al.* and Piirilä *et al.*

Besides the difference in $T_{L,CO}$, Piirilä *et al.* also investigated other parameters (including D_m and V_C). Although they did not find a significant difference in D_m/V_C ratio (on which the $T_{L,NO}/T_{L,CO}$ ratio is dependent) and V_C between the PE group and the healthy controls, they did observe significant lower values of D_m in the PE group compared to the healthy controls in both the acute phase and after seven months. Moreover, they reported a (weak) correlation between D_m and the extent of the PE measured by central embolism mass (r = 0·31, P = 0·047). Piirilä *et al.* argue that D_m is influenced more by the reduction in alveolar volume compared to V_C. As $T_{L,NO}$ is directly related to D_m, this argument agrees with the finding of Van der Lee *et al.* (2007) that $T_{L,NO}$ is influenced more by a reduction in alveolar volume than $T_{L,CO}$. Moreover, in PE patients of <75% of predicted which failed to normalize within three months in most cases (Wimalaratna et al., 1989). a trend towards lower $T_{L,CO}$ and $T_{L,NO}$ compared to predicted in the PE group compared to the no PE group can be seen from Table 2 (although not statistically significant due to a small number of subjects). Concluding, the present findings do not correspond with the

Table 2 Results of the CO/NO diffusion measurements.

	No PE (*n* = 16)		PE (*n* = 12)		
	Median	IQR	Median	IQR	*P*-value
IVC (L)	3·03	(2·33–3·73)	2·86	(2·26–3·71)	0·834
IVC % predicted	81·6	(70·0–93·0)	66·4	(61·1–90·5)	0·330
VA (L)	4·79	(3·96–5·19)	4·40	(3·53–5·57)	0·516
VA % predicted	77·1	(65·5–87·8)	71·0	(65·0–81·4)	0·353
$T_{L,CO}$ (mmol kPa^{-1} min^{-1})	7·16	(5·27–8·90)	6·62	(5·21–7·45)	0·330
$T_{L,CO}$ % predicted	75·8	(62·9–89·6)	68·8	(58·5–75·7)	0·120
K_{CO} (mmol kPa^{-1} min^{-1}L^{-1})	1·47	(1·35–1·62)	1·46	(1·20–1·80)	0·926
K_{CO} % predicted	99·9	(85·8–111·7)	100·5	(87·7–107·3)	0·610
$T_{L,NO}$ (mmol kPa^{-1} min^{-1})	29·9	(23·0–37·9)	25·8	(20·0–30·3)	0·286
$T_{L,NO}$ % predicted	69·3	(57·0–76·1)	60·5	(46·6–68·9)	0·078
K_{NO} (mmol kPa^{-1} min^{-1} L^{-1})	6·10	(5·24–7·10)	5·98	(5·33–6·81)	0·642
K_{NO} % predicted	89·5	(76·4–95·5)	83·9	(77·0–91·1)	0·330
$T_{L,NO}/T_{L,CO}$	4·09	(3·83–4·40)	4·00	(3·78–4·32)	0·959

Data are presented as median (interquartile range) unless stated otherwise.
IVC, inspiratory vital capacity; VA, alveolar volume; $T_{L,CO}$, transfer factor of the lungs for carbon monoxide; K_{CO} transfer coefficient of the lungs for carbon monoxide; $T_{L,NO}$, transfer factor of the lungs for nitric oxide; K_{NO}, transfer coefficient of the lungs for nitric oxide.

data of Harris *et al.* found in sheep but are consistent with earlier measurements of $T_{L,CO}$ in PE in humans.

First of all, a probable cause of the lack in increased $T_{L,NO}/T_{L,CO}$ ratios might be the relatively small extent of the pulmonary emboli included in the current study, as hemodynamic unstable and oxygen-dependent patients were excluded. Moreover, recent research showed that total occluding emboli result in perfusion defects (Ikeda *et al.*, 2014), and in non-occluding emboli, a slight decrease in both D_m and V_C can be expected. Finally, hypocapnic bronchoconstriction might shift ventilation towards well-perfused regions (Tsang *et al.*, 2009) which could also diminish the negative effects of PE on the diffusion capacity of the lungs.

Detailed inspection of the current data reveals another possible explanation for the lack in increased $T_{L,NO}/T_{L,CO}$ ratios. The measured alveolar volume is decreased in both groups (77·1% of predicted in the no PE group versus 71·0% of predicted in the PE group). This decreased alveolar expansion is likely to be caused by the thoracic pain of which almost all patients suffered (see Table 1). This hypothesis is supported by the reduced inspiratory VC in both groups, indicating an extrathoracic restriction. A reduced alveolar volume greatly influences the measured transfer factors. A reduction in alveolar volume will decrease the surface area and increase the thickness of the alveolar–capillary membrane (and therefore decreases D_m and thus $T_{L,NO}$). $T_{L,CO}$ is approximately equal dependent on D_m and V_C and is therefore less dependent on a decrease in alveolar volume. Therefore, the $T_{L,NO}/T_{L,CO}$ ratio decreases with a decrease in alveolar volume (Glénet *et al.*, 2007; Van der Lee *et al.*, 2007). This might explain the slightly lowered $T_{L,NO}/T_{L,CO}$ ratios found in our data. In the data of van der Lee *et al.*, an alveolar volume of 70–80% of its value at total lung capacity (TLC) results in a measured $T_{L,NO}/T_{L,CO}$ ratio of approximately 4·00 (Van der Lee *et al.*, 2007) which corresponds with the now presented data. The previous reports of Wimalaratna *et al.* and Piirilä *et al.* on $T_{L,CO}$ in PE do not report alveolar volumes compared to its predicted value. They do report K_{CO} compared to its predicted value. Piirilä *et al.* report normal K_{CO} values indicating decreased alveolar volumes which correspond with our data. Surprisingly, Wimalaratna *et al.* report lowered K_{CO} values when compared to their predicted value (calculated from mean data). This difference can be caused by changes between 1989 and now in measurement protocol and the reference equations used to calculate predicted values.

Conclusion

Our data indicate that the $T_{L,NO}/T_{L,CO}$ ratio cannot be used in the exclusion of PE. Lowered $T_{L,CO}$ and $T_{L,NO}$ combined with normal K_{CO} and K_{NO} were noted in both the no PE and the PE group. The decrease in transfer factors is likely to be caused by the decreased alveolar volume (possibly due to thoracic pain) which was also noted in both groups. The present findings do not correspond with the $T_{L,NO}/T_{L,CO}$ ratio found in sheep but are consistent with earlier measurements of $T_{L,CO}$ in pulmonary embolism in humans.

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Conflict of interests

The authors declare to have no conflict of interests.

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