



### Quantification of lobar gas exchange: a proof-of-concept experimental study

Journal:	<i>British Journal of Anaesthesia</i>
Manuscript ID	BJA-2021-00447-HH283.R1
Article Type:	Correspondence
Date Submitted by the Author:	n/a
Complete List of Authors:	Gallifant, Jack; King's College London Faculty of Life Sciences and Medicine, Centre for Human and Applied Physiological Sciences Cronin, John; King's College London School of Medical Education, Centre for Human and Applied Physiological Sciences Formenti, Federico; King's College London Faculty of Life Sciences and Medicine, Centre for Human and Applied Physiological Sciences
Keywords:	Bronchoscopy, lung, oxygen consumption, pulmonary gas exchange, lung function tests

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44

# Quantification of lobar gas exchange: a proof-of-concept experimental study

Jack Gallifant<sup>1</sup>, John N. Cronin<sup>1,2,@</sup> and Federico Formenti<sup>1,3,4,@</sup>

<sup>1</sup> Centre for Human and Applied Physiological Sciences, School of Basic and Medical Biosciences, King’s College London, London, UK  
<sup>2</sup> Department of Anaesthesia, Guy's and St Thomas' NHS Foundation Trust, London, UK  
<sup>3</sup> Nuffield Division of Anaesthetics, University of Oxford, Oxford, UK  
<sup>4</sup> Department of Biomechanics, University of Nebraska Omaha, Omaha, NE, USA

**@ Corresponding authors:**  
Dr Federico Formenti, e-mail: [federico.formenti@outlook.com](mailto:federico.formenti@outlook.com); telephone +442078486292; fax +442078486325, and Dr John N. Cronin, e-mail: [john.n.cronin@kcl.ac.uk](mailto:john.n.cronin@kcl.ac.uk)

**Address:** Centre for Human and Applied Physiological Sciences, School of Basic and Medical Biosciences, King’s College London, London, SE1 1UL, United Kingdom

**Authors’ contributions:** JNC and FF designed the experiments; JNC and FF performed the experiments; JG and JNC analysed the data; JG, JNC and FF interpreted the data; FF contributed to financial support. All authors critically revised the manuscript.

**Sources of funding:** We acknowledge support from the Medical Research Council (MC\_PC\_17164).

**Declarations of interest:** The authors declare that they have no conflicts of interest.

**Running title:** measurement of lobar oxygen uptake

**Total number of words:** 1,037

**Total number of references:** 10

**Keywords:** Bronchoscopy, lung, oxygen consumption, pulmonary gas exchange, lung function tests

Editor - The prediction of post-operative lung function helps to stratify lung cancer patients' risk of mortality and potential suitability for resection <sup>1</sup>. Carbon monoxide transfer factor ( $T_{LCO}$ ) and forced expiratory volume in 1 s ( $FEV_1$ ) tests are commonly used to determine diffusing capacity and degree of airway obstruction respectively, and to predict post-resection dyspnoea, assuming they would decrease in proportion to the number of lung segments resected. These tests provide global indicators of lung function, but cannot distinguish between functional contributions from different lobes. Gas exchange occurs heterogeneously, differing between lung regions in health and disease <sup>2</sup>, and this heterogeneity may be exaggerated by lung cancer, limiting the usefulness of whole-lung function tests. Estimates of post-operative  $FEV_1$  based upon computed tomography (CT) measurements of resected lung volume <sup>3</sup>, or quantitative ventilation/perfusion scintigraphy <sup>1</sup> may be more informative. However, these methods are limited by a poor correlation between post-operative  $FEV_1$  and functional capacity, where maximal oxygen uptake is more sensitive <sup>4</sup>.

Quantifying lobar contribution to overall pulmonary gas exchange could provide more accurate predictions of post-operative lung function. For example, if a diseased lobe contributes minimally to gas exchange, its resection will unlikely have major functional impacts.

The aim of our study was to measure oxygen uptake at the lobar level in a proof-of-concept experimental study. A fibre optic sensor was used to measure the tidal variation in lobar partial pressure of oxygen ( $PO_2$ ), and whole-lung CT to quantify lobar tidal volume; these measurements combined were used to calculate lobar oxygen uptake.

This study, conducted in the Hedenstierna Laboratoriet at Uppsala University, Sweden received ethical approval (AREC ref.C98/16) and conformed with the NIH and ARRIVE guidelines <sup>5</sup>.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Two male domestic pigs (weight: 29 kg) were studied in dorsal recumbency under general anaesthesia and mechanical ventilation via tracheostomy. Details of the anaesthesia protocol are presented elsewhere <sup>6</sup>. Mechanical ventilation was delivered by a Servo-I ventilator (Maquet, Germany) in pressure-control mode with tidal volume of 10 mL kg<sup>-1</sup>, respiratory rate 12 breaths per minute, inspiratory:expiratory (I:E) ratio of 1:2, and inspiratory rise time of 0 s so each breath consisted of 1.67 s of inspiration and 3.33 s of expiration. A saline lavage surfactant-depletion lung-injury model was induced in one pig to study heterogeneous lungs <sup>6</sup>.

Cardiopulmonary variables (IntelliVue M8004A, Philips Healthcare, Netherlands; Capnomac Ultima, Datex-Ohmeda, WI) and lobar PO<sub>2</sub> (OxyLite Pro, Oxford Optronix, UK) were continuously monitored, with analogue signals converted to digital form using PowerLab (ADInstruments, New Zealand), recorded with LabChart version 8.2.1 (ADInstruments, New Zealand) at a sampling rate of 10 Hz throughout. Data were processed using R version 3.6.2 ([www.r-project.org](http://www.r-project.org)).

PO<sub>2</sub> was recorded with fibre optic sensors with a response time of <150 ms in air <sup>7</sup>. The sensor's working principle is based on luminescence quenching by oxygen of a fluorophore embedded in a polymer material; technical details are presented elsewhere <sup>7-10</sup>. The fine-bore sensor was inserted into a bronchoscope until the sensor tip was visible inside the main bronchus entering a lobe, with the bronchoscope itself remaining within the large airways. Data for ~12 breaths were collected in each lobe and averaged to produce a single breath per lobe. PO<sub>2</sub> tidal variation was calculated as the peak-to-trough difference in the averaged breath. Tidal variation in lobar PO<sub>2</sub> (kPa) was then converted to tidal variation in oxygen concentration [ $\Delta$ PO<sub>2</sub>

(%)], dividing by 101.3 kPa. This experiment could not be completed in the CT scanner, so lobar PO<sub>2</sub> measurements were completed just before CT imaging.

Whole-lung volume CT scans (Somatom Definition Flash, Siemens, Germany) were recorded during end-inspiratory and end-expiratory breath-holding manoeuvres (under the same ventilation conditions as during the lobar PO<sub>2</sub> experiment) to measure lobar tidal volume. Lobar volumes were calculated via segmentation at 3 mm intervals using Slicer version 4.1; figure 1A, B and C illustrate the segmentation process. Gas volumes were then calculated as

$$\text{Lobar Gas volume (mL)} = \text{Lobar volume (cm}^3\text{)} \times \frac{-[\text{Mean voxel density (HU)}]}{1000}$$

and **lobar oxygen uptake** calculated by multiplying tidal gas volume (difference between end-inspiratory and end-expiratory lobar gas volumes) by DeltaPO<sub>2</sub> (%).

Further methodological details are presented in the Supplementary data.

Supplementary Table 1 shows the baseline characteristics of the animals studied. Cardiorespiratory parameters were within the normal or expected range, with a lower P/F ratio in the lung injury model (15.1 kPa) than in the control (61.5 kPa). In order to achieve normoxia, the inspired oxygen concentration was higher in the lung injury model (0.7 vs control 0.4).

Figure 1D illustrates the lobar PO<sub>2</sub> tidal variation, greater in the saline lavage lung injury model than in the control pig.

Figure 1 inset table presents lobar PO<sub>2</sub>, end-inspiratory, end-expiratory and tidal volumes, and the associated **lobar oxygen uptake**. PO<sub>2</sub> tidal variation ranged from 4.7 to 20.3 kPa in different lobes. Lobar tidal volume ranged from 12.9 to 75.1 mL, with **lobar oxygen uptake** ranging

from 0.6 to 11.9 mL breath<sup>-1</sup>. Figure 1E shows oxygen uptake in both animals, visualising the difference between lobes, and overall pulmonary oxygen uptake between animals.

We demonstrated the feasibility of a novel technique to calculate lobar oxygen uptake in mechanically ventilated control and saline lavage lung injury pig models. Study limitations include the small sample size and use of porcine models that do not fully replicate all the features of the human respiratory system. Data were collected at rest, assuming proportional contributions during exercise, when functional limitation likely occurs. Nevertheless, the lung injury model used resulted in heterogeneous lung injury and hypoxaemia, and was sufficient to determine differences in lobar and overall oxygen uptake compared with the control.

The distribution of lobar contribution to gas exchange can vary significantly, even in patients with similar overall lung function, but tests currently used to predict lung function following lung cancer resection cannot determine gas exchange at the lobar level. Following refinement, the technique proposed here could provide valuable insight into the proportion of oxygen uptake associated with a given lobe and support the decision on patients' suitability for lobar resection. Although this technique was tested under conditions of general anaesthesia and mandatory ventilation, its working principle would remain valid in spontaneous breathing, allowing the technique's use in the outpatient setting. The technique is clinically feasible given the widespread use of both bronchoscopy and CT imaging in lung cancer diagnosis.

Acknowledgements

1  
2  
3 140 We are grateful to Dr Rongsheng Chen and Oxford Optronix for making the fibre optic oxygen  
4  
5 141 sensors available, and to the staff in the Hedenstierna Laboratoriet and in the Radiology  
6  
7 142 Department, Uppsala University Hospital, including Agneta Roneus, Kerstin Ahlgren, Mariette  
8  
9 143 Anderson, Liselotte Pihl, Maria Swälas, Monica Segelsjö, Göran Hedenstierna, Anders  
10  
11 144 Larsson and Miklos Lipcsey for their support with the data collection.  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For Peer Review

References

1 Lim E, Baldwin D, Beckles M, et al. Guidelines on the radical management of patients with lung cancer. *Thorax* 2010; **65**: iii1-iii27

2 Wagner PD. The physiological basis of pulmonary gas exchange: implications for clinical interpretation of arterial blood gases. *European Respiratory Journal* 2015; **45**: 227-43

3 Papageorgiou CV, Antoniou D, Kaltsakas G, Koulouris NG. Role of quantitative CT in predicting postoperative FEV1 and chronic dyspnea in patients undergoing lung resection. *Multidisciplinary Respiratory Medicine* 2010; **5**: 188

4 Wang J-S, Abboud RT, Wang L-M. Effect of Lung Resection on Exercise Capacity and on Carbon Monoxide Diffusing Capacity During Exercise. *Chest* 2006; **129**: 863-72

5 Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. *PLoS Biology* 2010; **8**: e1000412

6 Lachmann B, Robertson B, Vogel J. In Vivo Lung Lavage as an Experimental Model of the Respiratory Distress Syndrome. *Acta Anaesthesiologica Scandinavica* 1980; **24**: 231-6

7 Chen R, Formenti F, Obeid A, Hahn CE, Farmery AD. A fibre-optic oxygen sensor for monitoring human breathing. *Physiological measurement* 2013; **34**: N71-81

8 Formenti F, Bommakanti N, Chen R, et al. Respiratory oscillations in alveolar oxygen tension measured in arterial blood. *Scientific Reports* 2017; **7**: 7499

9 Formenti F, Chen R, McPeak H, Matejovic M, Farmery AD, Hahn CE. A fibre optic oxygen sensor that detects rapid PO2 changes under simulated conditions of cyclical atelectasis in vitro. *Respiratory Physiology & Neurobiology* 2014; **191**: 1-8



1  
2  
3 167 10 Crockett DC, Cronin JN, Bommakanti N, et al. Tidal changes in PaO<sub>2</sub> and their relationship  
4  
5 168 to cyclical lung recruitment/derecruitment in a porcine lung injury model. *British Journal of*  
6  
7 169 *Anaesthesia* 2019; **122**: 277-85  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For Peer Review

Figure caption

**Figure 1. Computed tomography scans and associated 3D reconstruction of the porcine lung, lobar partial pressure of oxygen (lobar PO<sub>2</sub>) measured during a respiratory cycle, and lobar and whole lung oxygen uptake.**

Panels A and B show the same axial slice from the same pig; panel A is the original image, and panel B shows the lobes labelled by colour (Left Caudal= green, Left Cranial= yellow, Right Accessory= red, Right Caudal= orange, Right Cranial= pink, Right Middle= blue). This colour coding is used in panels C, D and E also.

Panel C is a three-dimensional reconstruction of the control pig lungs at end-inspiration, viewed in the anterior-posterior direction. The model is labelled as follows: I= inferior, S= superior, R= right, L= left.

Panel D shows the lobar partial pressure of oxygen (PO<sub>2</sub>) recorded with fibre optic technology at each 0.1 s interval during a respiratory cycle for each lobe (data averaged over at least 3 cycles); dashed and solid lines show values respectively for the control and saline lavage lung injury pig. The shaded (left) and clear (right) regions in panel D indicate inspiration and expiration respectively. Recordings were made during pressure-controlled mechanical ventilation, with tidal volume 10 mL kg<sup>-1</sup>, I: E 1:2 and respiratory rate 12 breaths per minute.

Panel E shows lobar and whole lung oxygen uptake (mL min<sup>-1</sup>).

Inset table: lobar densities and volumes were calculated from CT images recorded during end-inspiratory and end-expiratory breath holding manoeuvres. Lung segmentation started at the bifurcation of the trachea. Rounding to the nearest % performed. PO<sub>2</sub> = Partial pressure of oxygen, HU= Hounsfield units, C= Control pig, SL= Saline lavage lung injury model.

194 **Figure 1, Inset table.**

Lobe	Animal	PO <sub>2</sub>					Density	Volume			Oxygen uptake	
		Mean	Max	Min	Delta	Delta	Mean	End-Inspiratory	End-Expiratory	Tidal	per breath	Proportion of total lung
		kPa					HU	mL			mL breath <sup>-1</sup>	%
<b>Left</b>	C	45.6	53.6	37.5	16.1	<b>16</b>	-247.5	105.2	30.1	<b>75.1</b>	11.9	<b>38</b>
<b>Caudal</b>	SL	29.8	36.4	26.8	9.6	<b>9</b>	-367.4	112.3	51.3	<b>61.0</b>	5.8	<b>29</b>
<b>Left</b>	C	37.3	48.9	28.6	20.3	<b>20</b>	-450.1	97.1	50.6	<b>46.5</b>	9.3	<b>30</b>
<b>Cranial</b>	SL	30.7	36.2	27.9	8.3	<b>8</b>	-548.3	95.9	52.0	<b>43.9</b>	3.6	<b>18</b>
<b>Right</b>	C	52.0	55.0	50.3	4.7	<b>5</b>	-334.8	23.8	10.9	<b>12.9</b>	0.6	<b>2</b>
<b>Accessory</b>	SL	30.8	36.7	27.2	9.4	<b>9</b>	-571.2	43.8	17.7	<b>26.1</b>	2.4	<b>12</b>
<b>Right</b>	C	53.3	58.1	50.6	7.6	<b>8</b>	-153.6	59.5	15.3	<b>44.3</b>	3.3	<b>11</b>
<b>Caudal</b>	SL	29.6	32.9	26.6	6.3	<b>6</b>	-341.4	104.2	46.6	<b>57.6</b>	3.6	<b>18</b>
<b>Right</b>	C	51.1	57.0	47.9	9.1	<b>9</b>	-451.4	86.4	45.1	<b>41.3</b>	3.7	<b>12</b>
<b>Cranial</b>	SL	26.4	29.4	24.4	5.0	<b>5</b>	-562.6	84.1	48.0	<b>36.1</b>	1.8	<b>9</b>
<b>Right</b>	C	48.9	52.5	45.4	7.1	<b>7</b>	-472.6	75.9	40.1	<b>35.8</b>	2.5	<b>8</b>
<b>Middle</b>	SL	31.9	35.4	29.5	5.9	<b>6</b>	-672.3	115.3	69.8	<b>45.5</b>	2.7	<b>13</b>

195

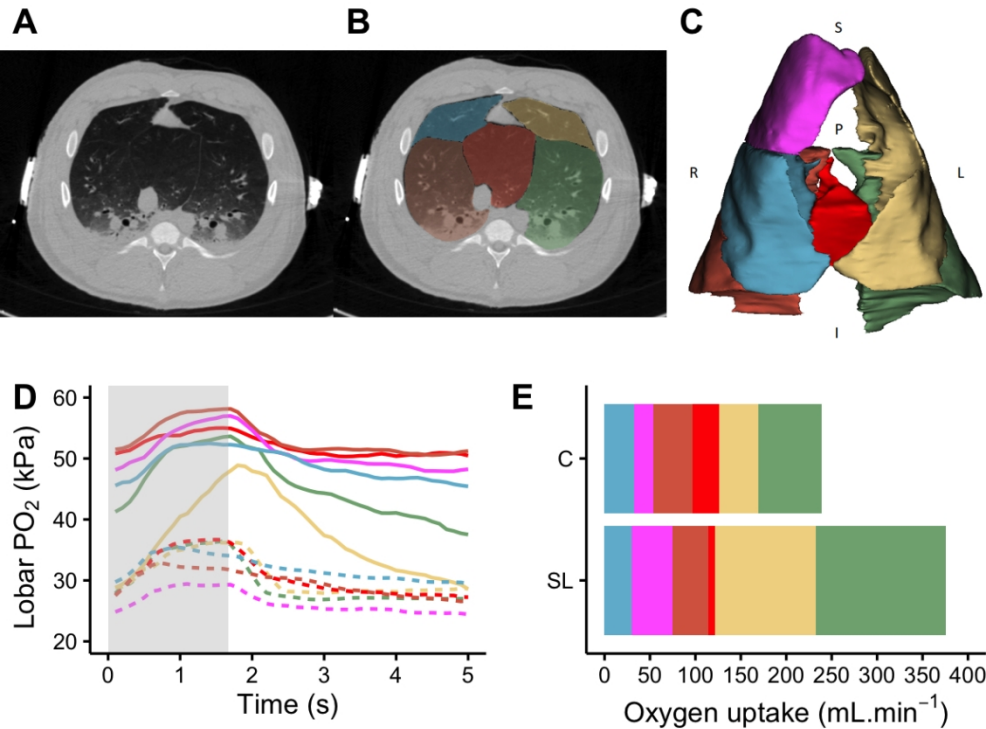


Figure 1. Computed tomography scans and associated 3D reconstruction of the porcine lung, lobar partial pressure of oxygen (lobar PO<sub>2</sub>) measured during a respiratory cycle, and lobar and whole lung oxygen uptake.

Panels A and B show the same axial slice from the same pig; panel A is the original image, and panel B shows the lobes labelled by colour (Left Caudal= green, Left Cranial= yellow, Right Accessory= red, Right Caudal= orange, Right Cranial= pink, Right Middle= blue). This colour coding is used in panels C, D and E also.

Panel C is a three-dimensional reconstruction of the control pig lungs at end-inspiration, viewed in the anterior-posterior direction. The model is labelled as follows: I= inferior, S= superior, R= right, L= left. Panel D shows the lobar partial pressure of oxygen (PO<sub>2</sub>) recorded with fibre optic technology at each 0.1 s interval during a respiratory cycle for each lobe (data averaged over at least 3 cycles); dashed and solid lines show values respectively for the control and saline lavage lung injury pig. The shaded (left) and clear (right) regions in panel D indicate inspiration and expiration respectively. Recordings were made during pressure-controlled mechanical ventilation, with tidal volume 10 mL kg<sup>-1</sup>, I: E 1:2 and respiratory rate 12 breaths per minute.

Panel E shows lobar and whole lung oxygen uptake (mL min<sup>-1</sup>).

Inset table: lobar densities and volumes were calculated from CT images recorded during end-inspiratory and end-expiratory breath holding manoeuvres. Lung segmentation started at the bifurcation of the trachea. Rounding to the nearest % performed. PO<sub>2</sub> = Partial pressure of oxygen, HU= Hounsfield units, C= Control pig, SL= Saline lavage lung injury model.

423x317mm (72 x 72 DPI)