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Individual modeling of oxygen capture by the human lungs

M.-Y. Kang[a], T. Hua-Huy[b], S. Günther[b], F. Aubourg[b], A.T. Dinh-Xuan[b], B. Sapoval[a,*]

[a] Physique de la Matière Condensée, CNRS, Ecole Polytechnique, 91128 Palaiseau, France
[b] Service de Physiologie-Explorations Fonctionnelles, Hôpital Cochin, AP-HP, Université Paris Descartes, 75014 Paris, France

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ABSTRACT

It has been proposed that oxygen capture by the human lungs depends on four determinants: ventilation, cardiac output, oxygen partial pressure in the inspired air and the venous blood. Indeed, the theoretical-numerical model proposed recently by Kang et al. was able to interpret the known empirical relation between the average of the determinants and the average oxygen capture called VO_2. This method is tested here at the individual level in a group of 31 subjects submitted to standard pulmonary function testing and cardiopulmonary exercise testing. For this, an inverse method is used in which individual cardiac output is predicted from the clinical test data. Comparison to the cardiac output deduced from Fick principle confirms that the dynamic model is a "microscopic" justification of the "macroscopic" Fick principle. It shows that in addition to the four determinants, two secondary determinants, namely hemoglobin concentration and Bohr effect, expressed here through P_{50}, play significant roles.

1. Introduction

In 2004, John B. West, reviewing classic papers on pulmonary gas exchange of the last century, formulated the idea that capture of oxygen depends on four primary determinants (West, 2004): ventilation (VE), perfusion (Q), and oxygen partial pressure in the air (PIO_2) and in the mixed venous blood (PvO_2). This implies a considerable simplification of the global respiratory function which results from a complex interaction between supply and demand. The supply involves convective transfer in the bronchial tree followed by diffusion and gas capture in the pulmonary acini.

In 2013, Foucquier et al. suggested considering the pulmonary acinus as a "machine" being able to transfer oxygen from air to blood (Foucquier et al., 2013). In this work, the blood was considered as a simple sink. The complete oxygen capture theory, taking into account non-linear characters of hemoglobin (Hb) – O_2 saturation, was proposed by Kang et al. (2015). Here, oxygen capture is determined by the above mentioned determinants: gaseous determinants, ventilation per acinus VE_{ac} and PIO_2, and blood (circulatory) determinants, perfusion per acinus Q_{ac} and PvO_2. If the acinus morphology is known (Haefeli-Bleuer and Weibel, 1988), the theoretical-numerical machinery used in Kang et al. (hereafter referred as the model) yields the spatial-temporal distribution of oxygen capture in the acinus. By taking its average over space and time, one obtains the acinar oxygen capture $VO_{2,ac}$, schematically represented in Fig. 1.

Results are obtained by solving interactively the equations for O_2 convection-diffusion-permeation dynamics in the acinar airways and hemoglobin saturation dynamics in the capillaries. In Kang et al. (2015), the comparison between numerical predictions made on "averaged" global lungs and corresponding "averaged" physiological data was found to be satisfactory. The object of our work is to study the same comparison at the *individual* level. Its goal is then to check to what extent the computation results are valid individually by compared to individual clinical tests.

Unfortunately, usual clinical tests do not include the measurement of cardiac output nor measurement of PvO_2, two of the entrance determinants of the model. For this reason, we use an *inverse* method. It means a method to *retrieve* a quantity that is difficult to measure from the values of quantities that are routinely measured in clinical situations. For instance, if one knows VO_2, one can deduce the cardiac output Q for a given set of VE, PIO_2 and PvO_2. This is what we want to test in this work by applying the inverse method to a cohort of individuals.

A set of clinical test data from pulmonary function testing (PFT) and cardiopulmonary exercise testing (CPET) is used to retrieve Q for each individual. Absence of measured PvO_2 in routine clinical tests restricts the study to two situations, rest and peak exercise, where PvO_2 values can be reasonably postulated: $PvO_2 = 40$ mmHg at rest and $= 20$ mmHg at peak exercise. The results are then compared to corresponding Q values deduced from the Fick principle, the general

* Corresponding author.
E-mail address: bernard.sapoval@polytechnique.edu (B. Sapoval).

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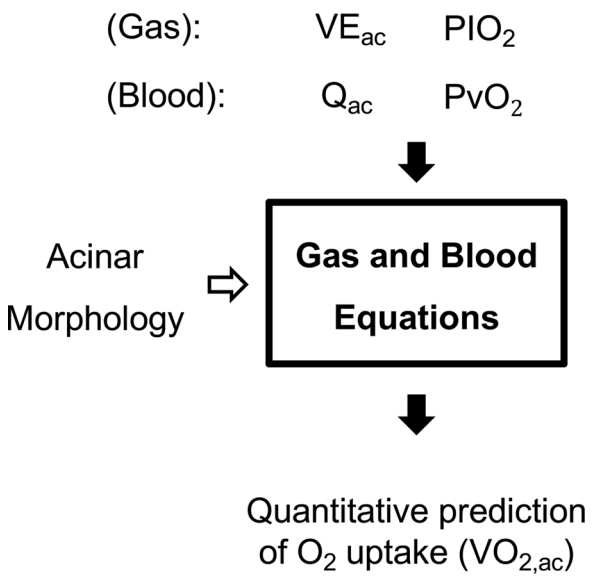

Fig. 1. Summary of the dynamic oxygen uptake model by Kang et al. (2015). Given the average morphology of an acinus, one computes the O_2 uptake in terms of VO_2 for given ventilation per acinus VE_{ac}; blood flow rate per acinus Q_{ac}; oxygen partial pressure in the inspired gas PIO_2; and the mixed venous oxygen partial pressure PvO_2.

conservation principle of O_2 transfer. This will constitute the first validity test of the dynamic oxygen uptake theory in its direct application to the *individual* respiratory system.

Besides the above primary determinants, there exist secondary determinants:

- the respiratory rate f,
- the dead space volume V_D,
- the hemoglobin concentration in blood [Hb],
- P_{50} as a simple indicator of the individual O_2-Hb dissociation curve.

Our second objective is then to examine to what extent the prediction accuracy can be improved by introducing these secondary determinants. This is investigated in two steps. Firstly, we compute Q using individual values *for the sole primary determinants* and average values for the secondary determinants (Table 1). This is called below a "Simplified approach".

Secondly, we present a systematic study of the role of the individual values of secondary determinants. Thus, the results will indicate which parameters amongst these four are the most important to reach good predictions.

2. Methods

2.1. Determination of the individual acinar primary determinants

The model deals with oxygen capture at acinus level. The basic hypothesis used here is that all the individuals in this study have identical acini, the average acinus being considered as a "standard" (Haefeli-Bleuer and Weibel, 1988). A precise description of this standard morphology being composed of a symmetric arborescence obeying Haefeli-Bleuer and Weibel measurements is given in Foucquier et al (2013).

Table 1
Average values for the secondary determinants.

Name	Notations	Values
Respiration frequency	f	12 (rest), 30 (peak exercise)
Dead space volume	V_D	170 mL
Hemoglobin concentration	[Hb]	13.4 g/dL (women), 14.6 g/dL (men)[7]
O_2 pressure for 50% saturation	P_{50}	26 mmHg[6]

Since we work at acinus level, the global primary determinants measured in the clinical tests need to be converted to the acinus level. The number of acini for each individual is first computed as

$$N_{ac} = (TLC - V_D) / \text{single acinus volume} \quad (1)$$

where TLC is the total lung capacity and the "average" single acinar volume set to be equal to 187 mm^3 (Haefeli-Bleuer and Weibel, 1988). Once the number of acini for each individual is known, one finds the acinar ventilation and VO_2 by dividing them by N_{ac} such that

$$VE_{ac} = VE / N_{ac} \quad (2)$$

$$VO_{2,ac} = VO_2 / N_{ac} \quad (3)$$

In all cases, PIO_2 is equal to 150 mmHg. Implementing variations of ± 3 mmHg found in the measurements did not yield any noticeable change in the predictions.

Using the individual determinant values, the acinus perfusion Q_{ac} is sought by searching iteratively the solution of

$$g(Q_{ac}, VE_{ac}, PIO_2, PvO_2, f, V_D, [Hb], P_{50}) - VO_{2,ac} = 0$$

where $g(\ldots)$ denotes the forward application of the model that yields $VO_{2,ac}$ for given determinants (see Kang et al. (2015) for details of numerical methods). One can then retrieve the global cardiac output by multiplying it by N_{ac}: $Q = Q_{ac} \times N_{ac}$.

2.2. Simplified inverse approach through pre-calculated solutions

The prediction of Q is possible *without* the aid of computers by using pre-calculated solutions of the standard acinus functioning with average secondary determinants. Solutions are given by the VO_2 graph consisting of a set of isolines of $VO_{2,ac}$ for a range of VE_{ac} and Q_{ac} shown in Fig. 2.

The following describes step by step how this process is implemented. A specific denoted as M17, marked with an asterisk * in the Tables of the results section, is chosen as an example.

- First, M17's number of acini can be obtained by plugging M17's TLC and V_D values into Eq. (1): $N_{ac}(M17) = (8.1\text{-}0.224)/(187 \times 10^6) = 42{,}117$. Note that V_D at peak exercise is used to compute N_{ac}.
- Then, applying the Eq.s (2) and (3) to clinical test data at rest (Table 4) leads to $VE_{ac} = VE/N_{ac}(M17) = 10.8$ L/min / 42,117 = 256 µL/min and $VO_{2,ac} = VO_2/N_{ac}(M17) = 0.301$ L/min / 42,117 = 7.1 µL/min.

Using these two parameters, one can obtain the corresponding Q_{ac} value from the iso-VO_2 graph at rest for [Hb] = 14.6 g/dL. This process is graphically illustrated in Fig. 2(a). The horizontal red arrow from left to right represents M17's VE_{ac} and M17's $VO_{2,ac}$ is highlighted by a thick blue line. Thus, by drawing a vertical line from this intersection, one gets Q_{ac} of 154 µL/min. Multiplying by N_{ac}, the global perfusion Q of M17 = 6.5 L/min is obtained. *This is the result of the inverse approach.* Fig. 2(b) shows that prediction for M17 at peak exercise can be also made in the same way by using the standard graphs calculated for peak exercise such as VE_{ac} = 1819 µL/min, $VO_{2,ac}$ = 49.5 µL/min → Q_{ac} = 356 µL/min and Q = 15 L/min. Higher resolution graphs for two typical [Hb] = 13.4 g/dL (females) and 14.6 g/dL (males) are given in **Appendix A** (rest) and **Appendix B** (peak exercise). Note that these graphs are universal. Because they correspond to a single standard acinus, they are valid whatever each individual size.

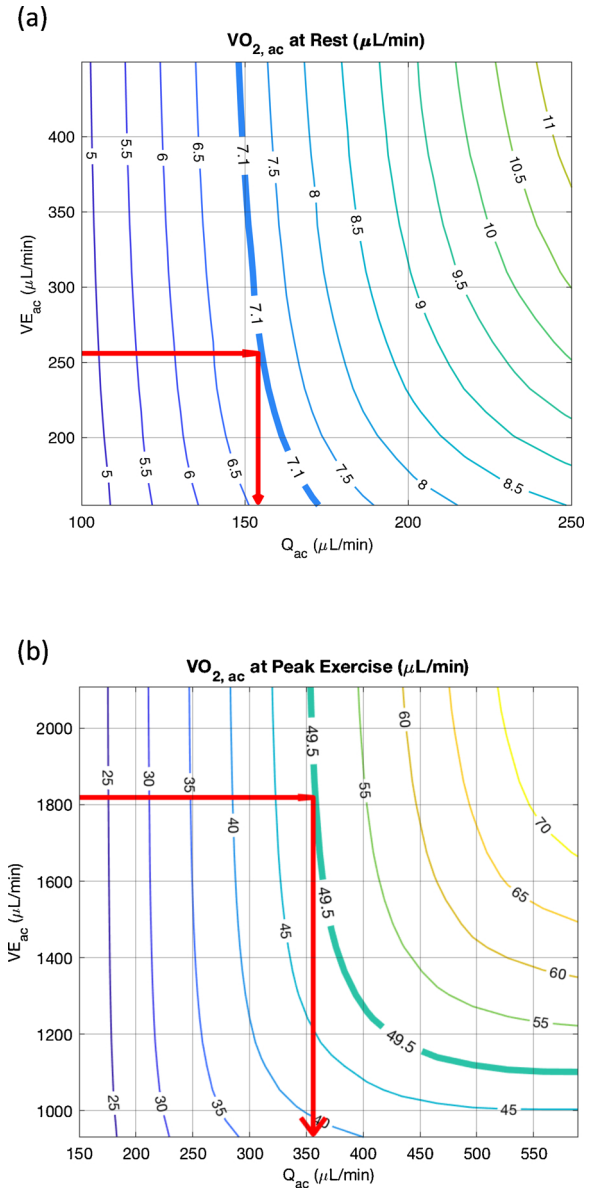

Fig. 2. Graphs for standard acinus functioning. Iso-$VO_{2,ac}$ lines are drawn as a function of VE_{ac} and Q_{ac} (a) at rest being computed for PvO_2 = 40 mmHg and (b) at peak exercise being computed for PvO_2 = 20 mmHg. For both, [Hb] = 14.6 g/dL (male) and values in Table 1 are used. Thick arrow lines illustrate the Simplified prediction process for the individual (M17). See Method for more details. Higher resolution graphs are given in Appendices A and B.

2.3. Calibration through Fick principle

Fick principle expresses the conservation of oxygen flux along the respiratory chain (Cotes et al. 2006). It relates the volumetric Q with VO_2 and saturation of arterial (SaO_2) and mixed venous blood (SvO_2). In terms of the Hb content, it is written as below (derivation given in **Appendix C**).

$$Q_{Fick}\,(L/min) = 0.72\,(g/ml_{STP}) \times VO_2\,(ml_{STP}/min) / \{[Hb]\,(g/L) \times (SaO_2 - SvO_2)\} \quad (4)$$

One can then calculate Q_{Fick} for each subject from experimental VO_2 knowing (SaO_2-SvO_2). Due to the low resolution of the experimental SaO_2, we used experimental PaO_2 with the individual O_2-Hb dissociation curve to get SaO_2. The same conversion was conducted to have individual SvO_2 from the assumed values of PvO_2 = 40 mmHg at rest and 20 mmHg at peak exercise.

2.4. O_2-Hb dissociation curve

Among a variety of its expressions, a simplest form of the curve, so-called the Hill-curve, was implemented, which is written

$$SaO_2 = (PaO_2/P_{50})^n/(1 + (PaO_2/P_{50})^n)$$

Using this relation, the measured P_{50} values allow to approximately take account of individual variations related to the shift of the curve due to Bohr effect. In all cases, n was fixed to 2.7 (Frank et al., 1997).

2.5. Clinical tests

2.5.1. Patients

Consecutive patients addressed to the Department of Physiology (Cochin Hospital, Paris, France) for exploring dyspnoea on exertion between January 2015 and December 2017 were included in this study. Patients underwent PFT and CPET on the same day. Patients with either obstructive or restrictive lung diseases, or chronic heart diseases were excluded from the cohort.

All study processes were approved by our institutional ethic committee (Hôpital Cochin, AP-HP, Paris, France), and complied with the World Medical Association Declaration of Helsinki as all functional tests were routinely performed for diagnostic and therapeutic purposes. Informed consents were signed by all patients.

2.5.2. Pulmonary function testing

PFT measuring total lung capacity (TLC), forced vital capacity (FVC), and forced expiratory volume in one second (FEV1), was performed using the whole-body plethysmography (MasterScreen BodyDiff, Carefusion, Hoeschberg, Germany) with a standard methodology and quality controls according to the American Thoracic Society and the European Respiratory Society (ATS/ERS) recommendations (Macintyre et al., 2005; Miller et al., 2005; Wanger et al., 2005).

2.5.3. Cardiopulmonary exercise test

CPET was performed using a maximal or symptom-limited incremental protocol (American Thoracic Society, 2003) on an electromagnetically braked cycle ergometer with breath-by-breath measurements (Schiller CS-200, Schiller AG, Baar, Switzerland). Oxygen uptake (VO_2), carbon dioxide output (VCO_2), and minute ventilation (VE) were obtained by computer calculations (Vmax Spectra Series V229, SensorMedics, Hoeschberg, Germany). Patients were continuously monitored by a 12-lead electrocardiogram and pulse oximeter (Oxi-3 Pulse Oximeter, Radiometer A/S, Copenhagen, Denmark). Pneumotachograph, oxygen and carbon dioxide sensors were calibrated before each test. Predicted peak VO_2 was calculated using Hansen and Wasserman's equation (Hansen et al., 1984). Single radial arterial blood gas sampling was performed at rest, during the 5-min baseline period, and a second sample at the peak of exercise using the sample tool heparinized plastic capillary for arterial blood collection (Roche Microsampler Protect, ref 05772494, AVL Cobas®, Roche, Mannheim, Germany). Arterial O_2 (SaO_2) and CO_2 partial pressures (PaO_2 and $PaCO_2$) were determined using a blood gas analyser (Radiometer ABL800 FLEX, Radiometer A/S, Copenhagen, Denmark).

The main protocol consists of 4 successive phases: baseline recording at rest (5 min), warming-up (3 min), incremental exercise (6 to 12 min), and recovery (5 min). Work rate (or power output) was set

Table 2
Basic anthropometric and physiologic data, 31 subjects.

Name	Sex	Age	Height(cm)	Weight (kg)	TLC (L)	N_{ac}
F1	F	27	170	75	5.11	25825
F2	F	31	172	64	6.06	31686
F3	F	37	170	89	5.45	27838
F4	F	45	167	53	6.01	30973
F5	F	45	169	66	6	30793
F6	F	46	168	54	5.6	28633
F7	F	53	166	60	6.08	31597
F8	F	62	160	65	5.16	26448
F9	F	65	159	52	5.76	29568
F10	F	65	160	63	5.76	29649
M1	M	18	177	60	6.74	34988
M2	M	19	183	68	6.51	33907
M3	M	20	186	72	7.26	37795
M4	M	21	175	60	6.48	33515
M5	M	32	175	60	7.03	36651
M6	M	36	176	87	6.2	32201
M7	M	37	176	76	7.85	39828
M8	M	46	187	101	7.85	41009
M9	M	52	186	67	8.66	44999
M10	M	53	183	81	7.09	37026
M11	M	54	172	62	7.13	36887
M12	M	55	178	88	7.93	40781
M13	M	58	175	80	6.51	33116
M14	M	59	174	92	6.99	36374
M15	M	66	172	86	7.08	36484
M16	M	67	171	62	6.23	31450
M17*	**M**	**68**	**181**	**81**	**8.1**	**42117**
M18	M	69	184	91	7.39	38102
M19	M	71	180	89	7.89	41143
M20	M	71	184	81	7.41	38183
M21	M	73	176	76	7.09	35922
Avg. ± SD		49 ± 17	175 ± 8	73 ± 13	6.72 ± 0.9	34693 ± 4794

TLC: Total Lung Capacity, N_{ac}: Number of the acini in the lung computed by Equation (1). * denotes a case subject randomly chosen for explaining how the Simplified computation is made (see the text in **Methods**).

between 20 W and 40 W during the warming-up period, increased by 10 to 20 W/min during the incremental phase, and returned to the warming-up level during the 2-min active recovery phase depending on the subject's anthropometric data (age, sex, height, and weight) (American College of Chest Physicians, 2003). The cycling frequency was maintained stable during CPET, varying from 60 to 70 rounds per minute (rpm) as indicated by a digital display on the ergometer monitor. End test criteria were symptoms, such as unattainable 60-rpm pedalling, unsustainable dyspnoea or leg fatigue, chest pain, ECG abnormalities (ventricular tachycardia, sustained ventricular tachycardia, …), systolic blood pressure > 250 mmHg or diastolic blood pressure > 130 mmHg. The recovery period comprised a first 2-min active phase with patient keeping cycling at reduced rate (40–60 rpm), followed by a 3-min passive phase with resting ventilatory parameters and ECG recording on cycle ergometer.

3. Results

3.1. Results of the clinical tests

Anthropometric and physiologic data of the 31 subjects (21 men) are detailed in Table 2. Individual data of the secondary determinants are presented in Table 3. All subjects had normal values of lung volumes (TLC, FVC, and FEV1). At rest, the average VO_2 was $4.5 \pm 0.87\ ml.kg^{-1}.min^{-1}$ (Mean ± Standard derivation) and results of arterial blood gas (ABG) were within normal ranges (PaO_2, SaO_2 and $PaCO_2$). All subjects were capable to maintain the CPET until exhaustion (exercise duration between 7 and 13 min). VO_2 and VE at peak exercise increases in average a 6-fold as compared to the baseline values (at rest) and the respiratory exchange ratio (RER) increased from 0.83 ± 0.06 to 1.23 ± 0.07 at peak of exercise. The overall average of the CPET and PFT are summarized in **Appendix D**.

3.2. Results of the inverse methods

Inverse predictions were first conducted for the two cases, Simplified and Full computations. The former considers individual values of the four primary determinants only while the latter uses both the primary and the secondary determinants for calculations. Individual values of predictions for the two cases together with Q_{Fick} and the clinical test data are provided in Tables 4 and 5.

4. Discussion

One observes in the last lines of Tables 4 and 5, that the simplified inverse prediction shows reasonably good agreement with Q_{Fick}. This is indicated by the values of the correlation coefficient between $Q_{Inverse}$ and Q_{Fick} which are found to be 0.86 at rest and 0.92 at peak exercise. But the use of secondary determinants (Full columns in the Tables 4 and 5) improves strongly the quality of the predictions. The correlation coefficients are now 0.98 at rest and 0.997 at peak exercise.

The quality of the inverse prediction can also be tested using the ratio of $Q_{Inverse}$ to Q_{Fick}. Using the data of Tables 4 and 5, one obtains:

Table 3
Individual data of the secondary determinants for rest and peak exercise.

Name	[Hb] (g/dL)	V_D (L)	Rest *f* (min^{-1})	P_{50} (mmHg)	V_D (L)	Peak *f* (min^{-1})	**P_{50} (mmHg)**
F1	15	0.151	18	24.7	0.281	20	28.4
F2	12.4	0.115	23	25.8	0.135	40	26.6
F3	14.2	0.217	18	24.9	0.244	30	31.9
F4	14.2	0.193	12	26.0	0.218	30	27.6
F5	10.4	0.161	15	26.0	0.242	43	26.7
F6	13.3	0.219	18	26.3	0.246	34	29.5
F7	13.7	0.178	20	26.7	0.171	30	28.1
F8	14.8	0.130	18	25.2	0.214	28	27.5
F9	13.6	0.144	13	23.1	0.231	28	29.6
F10	12.2	0.190	22	24.9	0.216	30	25.3
M1	15.6	0.205	19	26.4	0.197	33	29.1
M2	16.2	0.192	29	26.6	0.169	38	28.7
M3	14.7	0.186	23	26.4	0.192	38	30.3
M4	15.7	0.126	16	25.2	0.213	26	28.6
M5	16.9	0.156	16	26.4	0.176	40	27.9
M6	15.1	0.157	17	25.7	0.179	35	28.1
M7	17.1	0.293	18	25.2	0.402	38	27.1
M8	17	0.171	26	25.6	0.181	37	27.2
M9	14.3	0.204	20	26.2	0.245	30	27.7
M10	15.7	0.236	18	25.7	0.166	26	28.1
M11	11.2	0.226	15	27.5	0.232	30	29.7
M12	15	0.259	19	25.8	0.304	28	28.6
M13	15.6	0.187	32	25.1	0.317	42	25.9
M14	17.6	0.135	17	26.6	0.188	28	27.6
M15	16.6	0.202	22	25.6	0.257	29	26.8
M16	16.8	0.184	20	26.0	0.349	36	27.5
M17*	**15.8**	**0.178**	**21**	**26.2**	**0.224**	**31**	**26.8**
M18	15	0.266	12	26.2	0.265	27	28.2
M19	15.3	0.194	18	26.3	0.196	30	27.9
M20	16.4	0.234	18	26.5	0.270	31	27.8
M21	15	0.192	20	25.2	0.373	25	28.6
Avg. ± SD	14.9 ± 1.7	0.190 ± 0.041	19 ± 4	25.8 ± 0.8	0.235 ± 0.062	32 ± 5	28.0 ± 1.3

[Hb]: Hemoglobin concentration, V_D: dead space volume, *f*: respiration frequency, P_{50}: O_2 partial pressure for 50% saturation.

- Simplified study: mean of $Q_{Inverse}/Q_{Fick}$ = 1.02 with a standard deviation = 0.11.
- Full study: mean of $Q_{Inverse}/Q_{Fick}$ = 0.98 with a standard deviation = 0.05.

The "Full study" induces then a strong reduction of the standard deviation by a factor of more than 2. In the case of peak exercise only, the mean $Q_{Inverse}/Q_{Fick}$ value is 0.96 with *a standard deviation of only* 0.02. Remaining uncertainties are probably due to inevitable experimental errors or to slightly dispersed PvO_2.

Then, one may ask which, amongst the four secondary determinants, are more important in order to improve the predictions. To answer this question, a systematic study has been conducted. Total of 12 sets of individuals determinants were considered: 4 groups of non-invasive ones (simplified, V_D only, *f* only, both V_D and *f*) and 3 groups of invasive ones (simplified, [Hb] only, both [Hb] and P_{50}). Fig. 3 plots $Q_{Inverse}$ versus Q_{Fick} with the associated average and the standard deviation of $Q_{Inverse}/Q_{Fick}$ for each case. This figure can be read easily if one observes that horizontal lines correspond respectively to no use of individual [Hb] and $P_{50,}$ then second line, use of individual [Hb], and third line, use of both individual [Hb] and P_{50}.

The columns follow the same type of rule. The first column corresponds to average values of Table 1 for V_D and *f*. The second column corresponds to the use of individual values for V_D and so on for the 3rd and 4th column.

One observes that the main increases in precision are found going from the top to bottom lines, corresponding to the use of the determinants obtained by blood sampling ([Hb] and P_{50}). On the contrary, the role of V_D and *f* or both are minor.

5. Conclusion and perspectives

Hahn and Farmery, in their review paper entitled "Gas exchange modelling: no more gills, please", stressed major limitations of the conventional gas exchange models, mainly the underlying assumption of steady-state and continuous flow which is appropriate only for fish gills (Hahn and Farmer, 2003). The oxygen capture model proposed by Kang et al. (2015) overcame these limitations by taking fully into account the dynamics of O_2 convection-diffusion-permeation in the airways and the dynamics of O_2-Hb saturation in the pulmonary capillaries; it was first validated against average data of O_2 capture in the literature. The present study confirms its validity at the *individual* level by comparing its prediction of individual cardiac outputs to the Fick principle of respiration. A particular striking result is the 3% standard deviation obtained whatever the individual V_D and *f* values are, provided that one uses subject-specific [Hb] and P_{50}.

Table 4
Clinical test data and results of the inverse method at Rest.

	Clinical test data			$Q_{Inverse}$(L/min)		Q_{Fick} (L/min)
	VE (L/min)	VO_2 (L/min)	PaO_2 (mmHg)	Simplified†	Full‡	
F1	11.2	0.368	100	9.7	10.1	9.2
F2	8.5	0.241	103	5.8	6.4	6.6
F3	11.5	0.358	88	9.1	11.8	9.8
F4	7.3	0.229	95	5.6	5.3	5.6
F5	10.7	0.365	97	9.5	12.4	12.0
F6	10.9	0.273	101	6.5	7.0	6.8
F7	10.0	0.275	102	6.6	6.4	6.4
F8	11.0	0.349	96	9.0	8.8	8.6
F9	6.1	0.228	83	5.8	7.1	7.8
F10	10.7	0.259	85	6.1	7.8	8.4
M1	14.6	0.438	106	9.9	9.9	9.1
M2	15.3	0.376	91	8.2	7.8	7.8
M3	15.3	0.4	107	8.7	8.9	8.8
M4	8.6	0.309	94	7.2	7.0	7.2
M5	8.8	0.276	91	6.1	5.2	5.6
M6	11.1	0.34	98	7.7	7.8	7.8
M7	12.4	0.268	90	5.7	5.4	5.9
M8	14.3	0.43	98	9.6	9.2	8.9
M9	12.9	0.336	92	7.2	7.4	8.1
M10	13.7	0.366	102	8.0	8.2	8.1
M11	8.3	0.209	105	4.5	5.3	5.6
M12	13.9	0.418	94	9.3	10.3	9.8
M13	17.8	0.403	103	8.7	9.5	9.3
M14	8.4	0.242	101	5.3	4.2	4.5
M15	13.3	0.399	98	9.0	9.0	8.5
M16	9.8	0.248	92	5.4	4.9	5.2
M17*	**10.8**	**0.301**	**89**	**6.5**	**6.1**	**6.7**
M18	11.7	0.382	95	8.7	8.9	8.6
M19	10.9	0.299	95	6.5	6.2	6.6
M20	10.8	0.343	92	7.7	7.2	7.0
M21	11.9	0.317	110	6.9	7.5	7.4
correlation§				0.86	0.98	

*: the subject chosen as an example for Simplified prediction, †: study that uses the average values of the secondary determinants given in Table 2, ‡: study where all four subject-specific secondary determinants (f, V_D, [Hb], P_{50}) are taken into account through recalculation using (11), §: values of the correlation coefficient for $Q_{Inverse}$ and Q_{Fick}.

Table 5
Clinical test data and results of the inverse method at Peak exercise.

	Clinical test data			$Q_{Inverse}$(L/min)		Q_{Fick} (L/min)
	VE (L/min)	VO_2 (L/min)	PaO_2 (mmHg)	Simplified†	Full‡	
F1	56.7	1.60	109	12.6	10.7	11.0
F2	54.5	1.37	119	10.7	11.4	11.9
F3	72.1	1.93	104	15.1	12.7	13.2
F4	46.9	1.23	121	9.7	8.8	9.1
F5	60.5	1.27	114	9.8	12.5	13.2
F6	52.5	1.39	111	11.0	10.3	10.6
F7	50.8	1.48	114	11.7	10.8	11.2
F8	42.7	1.33	104	10.8	9.4	9.6
F9	43.3	1.28	89	10.2	9.4	9.7
F10	58.3	1.41	111	11.0	12.4	13.1
M1	80.7	2.41	109	17.5	15.2	15.8
M2	64.0	1.98	113	14.5	12.3	12.6
M3	123.3	3.42	110	24.6	22.2	23.2
M4	50.4	1.88	114	14.5	12.8	12.3
M5	99.7	2.41	115	17.2	14.1	14.9
M6	89.2	2.43	102	17.5	16.0	16.9
M7	101.0	2.30	124	16.4	13.7	14.3
M8	111.2	3.11	118	22.4	18.6	19.4
M9	81.1	2.32	122	16.8	16.4	16.9
M10	87.1	2.55	107	18.4	16.2	17.0
M11	62.3	1.81	115	13.2	15.8	16.2
M12	95.6	2.65	98	19.1	17.5	18.5
M13	94.2	2.14	101	15.3	14.4	15.4
M14	57.6	1.44	112	10.3	8.2	8.6
M15	74.4	2.34	108	17.2	14.9	15.3
M16	63.3	1.33	102	9.5	8.0	8.5
M17*	**76.6**	**2.08**	**102**	**15.0**	**13.6**	**14.4**
M18	78.3	2.32	102	16.9	15.6	16.2
M19	84.3	2.30	109	16.5	15.0	15.8
M20	54.9	1.73	114	12.7	11.0	11.0
M21	61.6	1.83	101	13.3	12.4	12.6
correlation§				0.92	0.997	

*: the subject chosen as an example for Simplified prediction, †: study that uses the average values of the secondary determinants given in Table 2, ‡: study where all four subject-specific secondary determinants (f, V_D, [Hb], P_{50}) are taken into account through recalculation using (11), §: values of the correlation coefficient for $Q_{Inverse}$ and Q_{Fick}.
PFT: pulmonary function test; CPET: cardiopulmonary exercise test; SD: standard derivation; BMI: body mass index; Hb: haemoglobin; TLC: total lung capacity; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; SpO_2: fraction of oxygen-saturated haemoglobin measured by pulse oximetry; PPO: peak power output; W: Watt; VO_2: oxygen uptake/consumption; VE: minute ventilation; HR_{peak}: peak heart rate; O_2 pulse: oxygen pulse, oxygen uptake for every heart beat at peak exercise; RER: respiratory exchange ratio; PaO_2: arterial partial pressure of oxygen; SaO_2: fraction of oxygen-saturated haemoglobin measured by arterial blood gas analysis; ABG: arterial blood gas; p50: partial pressure of oxygen to achieve 50% haemoglobin saturation; y: year (s); n: number of person; W: watt(s).
Comparisons between Men and Women groups were performed on IBM SPSS Statistics (Version 20) using t-Student test.

This type of agreement is exceptional in lung physiology. It indicates indirectly that the basis of this study is realistic for normal healthy respiration. Let us mention for instance the role of the acinus morphology. Fick principle is over a century older than the acinus morphology detailed description given by Haefeli-Bleuer and Weibel (1988). The values of Q_{Fick} are obtained *without* any consideration about the acinus morphology while our graphs, such as Fig. 2, depend directly on the acinus morphology. The fact that both agree with the above striking precision confirms the validity of the dynamic theory of oxygen capture together with the quality of the approximations used, in particular that of healthy homogeneous lungs. It confirms that the oxygen uptake model is a “microscopic” justification of the “macroscopic” Fick principle. This makes the oxygen uptake theory a good candidate to study more complex pathological situations like that of emphysematous acini.

In conclusion, this study is the first personalized application and check of the dynamic oxygen uptake theory. The proposed inverse method has a practical advantage compared to the use of Fick principle. The inverse method does not need to know the values of PaO_2, which is in fact a result of O_2 capture, to deduce cardiac output. This fact allows for a simple graphical approximation of Q with reasonable accuracy. One could employ easily the dynamic model by using the high-resolution maps provided in the Appendices with detailed explanations given in the Methods. Moreover, this shows that in addition to the four primary determinants of respiration, two secondary determinants,

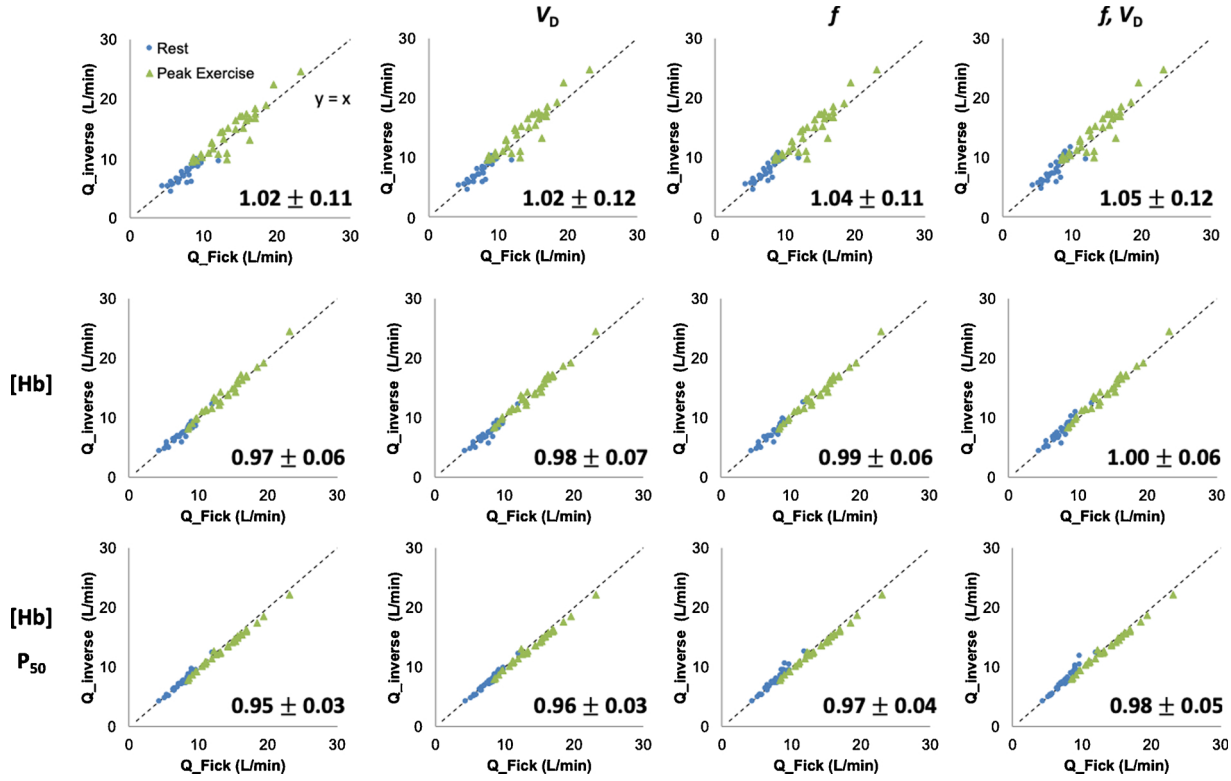

Fig. 3. Results of different improvement strategies of the $Q_{Inverse}$ predictions as compared to Q_{Fick}. Notations on the top and the left display the secondary determinants used for the predictions. Notation on the top is applied to the all three cases in the corresponding vertical column. Notations on the left is applied to the 4 cases in the corresponding horizontal lines. Constant values listed in Table 1 are used unless otherwise stated. For example, the figure located at the cross section of [Hb] and V_D is a result for individual [Hb] and V_D values and standard *f* and P_{50} values. The upper-left case corresponds to the Simplified study and the lower-right case corresponds to the Full study (see text). A dashed line in a diagonal direction indicates the identity line (y = x). The average ± standard deviation of the ratio $Q_{Inverse}/Q_{Fick}$ are displayed for each study.

hemoglobin concentration [Hb] and Bohr effect, expressed here through P_{50}, play significant roles.

The fact that the method works for both rest and peak exercise indicates that the same theory would also work for any value of PvO_2 corresponding to moderate exercise. It can then be considered as a performing tool that would allow a future study to tackle the problem of finding Q by embedding the Fick principle into the dynamic O_2 uptake model. If this attempt succeeds, the inverse method will be free from the needs for PvO_2. Then, one could take full advantage of the dynamic theory by converting VO_2 to Q (or PvO_2) in real time through an adapted model.

Declaration of Competing Interest

No conflicts of interest, financial or otherwise, are declared by the author(s).

Author contributions

M.Y.K., B.S. conception and design of research; T.H.H., F.A. performed experiments; M.Y.K., B.S. analyzed data; M.Y.K., B.S. interpreted results of experiments; M.Y.K. prepared figures; M.Y.K., B.S. drafted manuscript; M.Y.K., T.H.H., S.G., A.T.D.X., B.S. edited and revised manuscript; M.Y.K., T.H.H., S.G., F.A., A.T.D.X., B.S. approved final version of manuscript.

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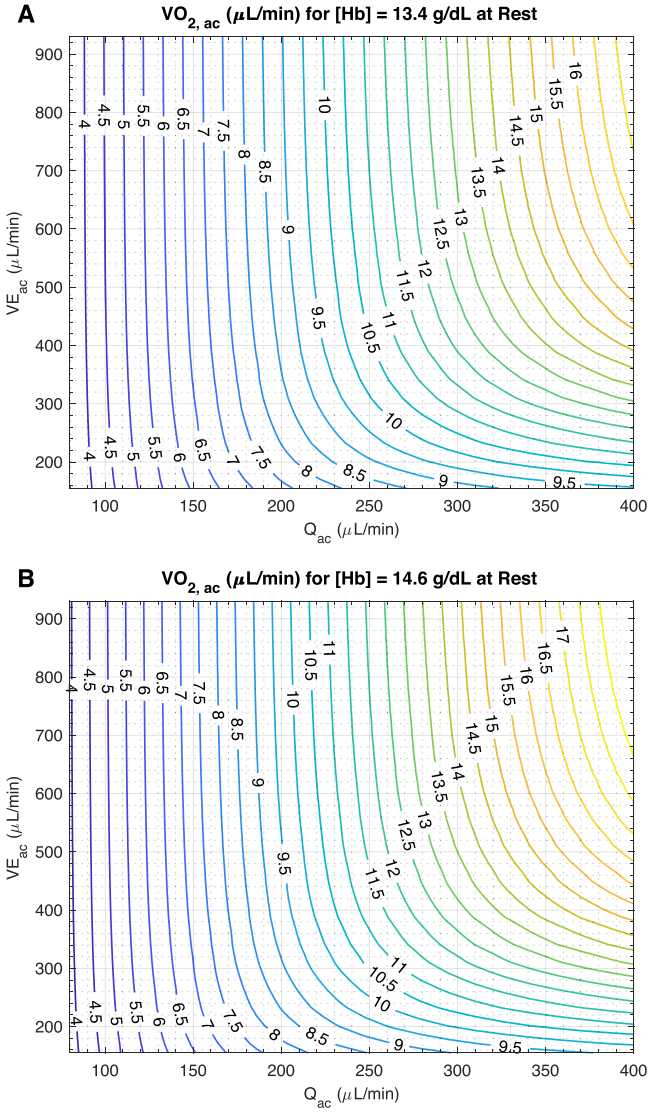
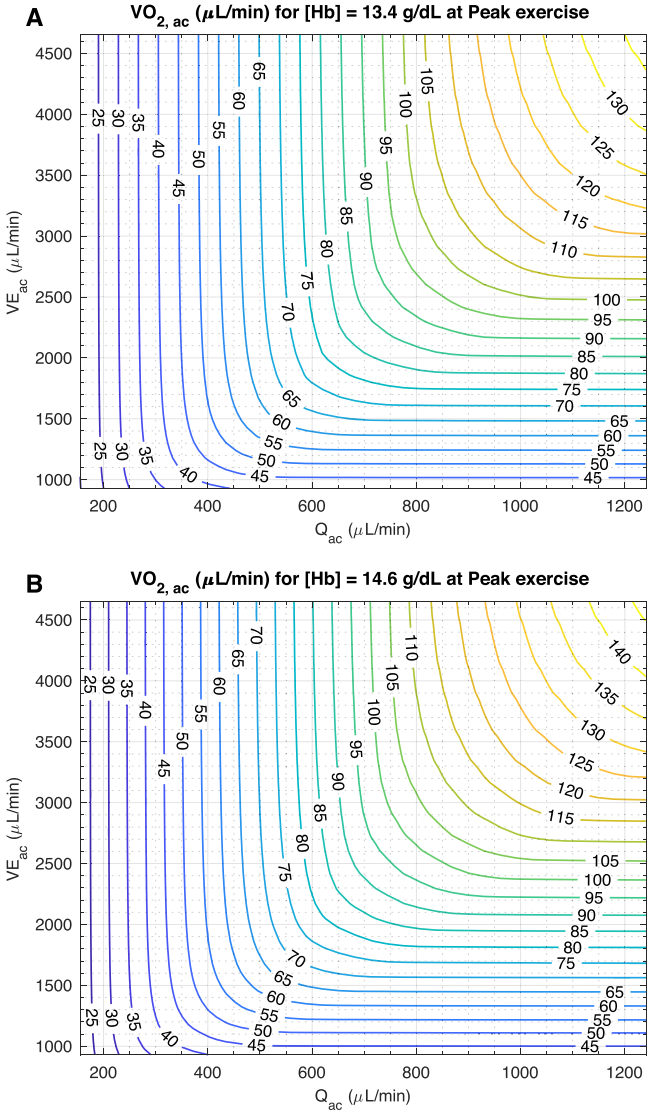
Appendix A. High resolution VO_2 graphs of the standard acinus at rest for Simplified prediction. It is recommended to use (A) for female and (B) for male subjects



Appendix B. High resolution VO_2 graphs of the standard acinus at Peak exercise for Simplified prediction. It is recommended to use (A) for female and (B) for male subjects



Appendix C. Fick principle as a function of blood hemoglobin content

The Fick principle is a conservation principle, namely the conservation of the oxygen flux. The flux of oxygen in the gas is VO_2. The flux of oxygen in the blood is the hydrodynamic flux Q (L/min) times the quantity of oxygen per unit volume of blood. The number of Hb molecules per unit volume of blood is the mass of Hb per unit volume [Hb] in g/L divided by the mass of a single Hb molecule which is equal to the Hb molecular mass Hb_{mole} divided by the Avogadro number N_A. If one takes account of the fact that each Hb molecule carries 4 oxygen molecules times the blood saturation, one can write Fick's principle in the following manner:

$$VO_2\ (\text{molecules/min}) = Q\ (\text{L/min}) \times [Hb]\ (\text{g/L}) \times N_A / Hb_{mole}\ (\text{g}) \times 4(SaO_2 - SvO_2) \quad (C.1)$$

To obtain VO_2 in ml_{STP} per minute, one has to divide VO_2 (molecules/min) by $N_A/22{,}400$ ($ml_{STP}{}^{-1}$). Then, with Hb_{mole} = 64,458 g (Van Beekvelt MC et al.), it is written as

$$VO_2\ (ml_{STP}/\text{min}) = 1.39\ (ml_{STP}/\text{g}) \times Q\ (\text{L/min}) \times [Hb]\ (\text{g/L}) \times (SaO_2 - SvO_2) \quad (C.2)$$

or

$$Q_{Fick}\ (\text{L/min}) = 0.72\ (\text{g}/ml_{STP}) \times VO_2\ (ml_{STP}/\text{min}) / \{[Hb]\ (\text{g/L}) \times (SaO_2 - SvO_2)\} \quad (C.3)$$

Equation (C.3) is used in this study to compute Q_{Fick} from the measured VO_2, [Hb] and SaO_2. As for SvO_2, the values of PvO_2 = 40 mmHg (rest), 20 mmHg (peak), which are the same as being used for the predicitions, are converted to the saturation by means of the oxygen dissociation curve with individual P_{50} values.

Appendix D. Data from pulmonary function and cardiopulmonary exercise tests (n = 31)

	Men (n = 21)	Women (n = 10)
Age, y	49.8 ± 19.1 (18 – 73)	47.6 ± 13.6 (27 – 65)
Weight, kg	77.1 ± 12.3 (60 – 101) **	64.1 ± 11.2 (52 – 89)
Height, m	1.79 ± 0.05 (1.71 – 1.87) ***	1.66 ± 0.05 (1.59 – 1.72)
BMI, kg/m^2	24.2 ± 3.7 (19.2 – 30.4)	23.2 ± 3.6 (19 – 30.8)
Hb, g/dL	15.6 ± 1.4 (11.2 – 17.6) **	13.4 ± 1.4 (10.4 – 15)
PFT		
TLC, litre	7.21 ± 0.66 (6.2 – 8.66) ***	5.70 ± 0.36 (5.11 – 6.08)
TLC, % predicted	100.3 ± 7.7 (86 – 112)	110.5 ± 9.0 (94 – 122) **
FVC, litre	4.66 ± 0.68 (3.52 – 5.74) ***	3.61 ± 0.48 (2.40 – 4.18)
FVC, % predicted	102.1 ± 11.2 (81 – 117)	113.4 ± 16.4 (93 – 143) *
FEV_1, litre	3.81 ± 0.64 (2.88 – 5.22) **	2.99 ± 0.55 (1.74 – 3.63)
FEV_1, % predicted	104.3 ± 12.9 (84 – 126)	108.4 ± 14.7 (80 – 130)
Resting SpO_2, %	95.6 ± 0.9 (94 – 97)	95.8 ± 1.0 (94 – 97)
CPET		
PPO, W	169 ± 37 (105 – 250) ***	108 ± 21 (90 – 160)
PPO, % predicted	81 ± 14 (53 – 108)	84 ± 16 (58 – 106)
$VO_{2\ max}$, $ml.min^{-1}$	2228 ± 493 (1332 – 3421) ***	1428 ± 207 (1227 – 1929)
$VO_{2\ max}$, $ml.kg^{-1}.min^{-1}$	29.3 ± 7.1 (15.6 – 47.5) **	22.5 ± 2.2 (19.2 – 25.8)
VO_{2max}, % predicted	92 ± 15 (54 – 110)	93 ± 16 (73 – 115)
VE, l/min	80.5 ± 19.4 (50.4 – 123.3) ***	53.8 ± 8.8 (42.7 – 72.1)
VE, % predicted	60.7 ± 12.6 (40 – 84)	52.5 ± 9.3 (43 – 70)
HR_{peak}, $beats.min^{-1}$	153 ± 23 (109 – 194)	155 ± 10 (141 – 173)
HR_{peak}, % predicted	86 ± 9 (64 – 98)	86.5 ± 6 (76 – 96)
O_2 pulse, $ml.min^{-1}.b^{-1}$	14.7 ± 3.1 (10.2 – 22.1) ***	9.3 ± 1.5 (7.5 – 12.3)
O_2 pulse, % predicted	108 ± 20 (68 – 144)	107 ± 18 (82 – 137)
RER	1.21 ± 0.07 (1.08 – 1.37)	1.23 ± 0.08 (1.09 – 1.35) *
PaO_2, mmHg	109.4 ± 7.3 (98 – 124)	109.6 ± 9.1 (89 – 121)
SaO_2, % (Radial ABG)	95.9 ± 0.8 (94 – 97)	95.9 ± 1.4 (93 – 97)
p50	28 ± 1 (26 – 30)	28.1 ± 1.8 (25 – 32)

PFT: pulmonary function test; CPET: cardiopulmonary exercise test; SD: standard derivation; BMI: body mass index; Hb: haemoglobin; TLC: total lung capacity; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; SpO_2: fraction of oxygen-saturated haemoglobin measured by pulse oximetry; PPO: peak power output; W: Watt; VO_2: oxygen uptake/consumption; VE: minute ventilation; HR_{peak}: peak heart rate; O_2 pulse: oxygen pulse, oxygen uptake for every heart beat at peak exercise; RER: respiratory exchange ratio; PaO_2: arterial partial pressure of oxygen; SaO_2: fraction of oxygen-saturated haemoglobin measured by arterial blood gas analysis; ABG: arterial blood gas; p50: partial pressure of oxygen to achieve 50% haemoglobin saturation; y: year(s); n: number of person; W: watt(s).

Comparisons between Men and Women groups were performed on IBM SPSS Statistics (Version 20) using t-Student test. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

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