Computer simulation clarifies mechanisms of carbon dioxide clearance during apnoea

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Running title: CO_2 clearance during apnoeic oxygenation

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Abstract

Background. Apnoeic oxygenation can come close to matching the oxygen demands of the apnoeic patient but does not facilitate carbon dioxide (CO_2) elimination, potentially resulting in dangerous hypercapnia. Numerous studies have shown that high flow nasal oxygen (HFNO) administration prevents hypoxaemia, and appears to reduce the rate of rise of arterial CO_2 partial pressure ($PaCO_2$), but evidence is lacking to explain these effects.

Methods. We extended a high-fidelity computational simulation of cardio-pulmonary physiology to include modules allowing variable effects of (a) cardiogenic oscillations affecting intrathoracic gas spaces, (b) gas-mixing within the anatomical deadspace, (c) insufflation into the trachea or above the glottis, and (d) pharyngeal pressure oscillation. We validated this model by reproducing the methods and results of five clinical studies on apnoeic oxygenation.

Results. Simulated outputs best matched clinical data for model selection of parameters reflecting (a) significant effects of cardiogenic oscillations on alveoli, both in terms of strength of the effect (4.5 cmH_2O) and percentage of alveoli affected (60%), (b) augmented gas-mixing within the anatomical deadspace in HFNO, and (c) pharyngeal pressure oscillations between 0 and 2 cmH_2O at 70 Hz.

Conclusion. Cardiac oscillations, deadspace gas-mixing and micro-ventilation induced by pharyngeal pressure variations appear to be important mechanisms that combine to facilitate clearance of CO_2 during apnoea. Evolution of high-flow oxygen-insufflation devices should take advantage of these insights, potentially improving apnoeic gas exchange.

Keywords: Apnoea; Carbon Dioxide; Computer Simulation; Respiratory Physiology.

Apnoea is common following induction of anaesthesia and during emergence. Accumulation of carbon dioxide (CO_2) occurs predictably during apnoea, since CO_2 is no longer removed from the alveoli to any significant degree once tidal ventilation ceases.[1] It has been recognized that while apnoeic oxygenation (i.e. mass inflow of oxygen via an open airway occurring during apnoea) alone can largely match the oxygen demands of the subject, it does not prevent a potentially dangerous rise in the concentration of arterial CO_2. Gaseous mixing in the anatomical deadspace with generation of low-volume, tidal ventilation through cardiogenic volume changes in the alveoli and tracheobronchial airspaces are likely to be important physiological mechanisms facilitating gas exchange during apnoea.[2-6] Several studies [7-9] have shown that nasal cannulae delivering high-flow, humidified oxygen (HFNO) can increase apnoea time substantially, by preventing hypoxaemia with only modest rises in the arterial partial pressure of carbon dioxide ($PaCO_2$). However, no clear evidence has been offered to explain this phenomenon.

We extended and validated a high-fidelity computational simulator of human cardio-pulmonary physiology against published data on human apnoea, and used this model to conduct an *in silico* investigation of the mechanisms of transport and exchange of gases and the clearance of CO_2 during apnoeic oxygenation. Computational simulation offers a fresh approach to research into otherwise inaccessible clinical questions and is particularly well suited to research in anaesthesia and critical care. Due to the emergency nature of work in these clinical specialties, it is difficult to recruit patients to studies examining crisis scenarios; it is also difficult to assure appropriate matching, blinding, stratification and control of confounders. Furthermore, *in silico* models of individual subjects and pathologies are configurable, reproducible and free of ethical limitations.

The aim of this study is to investigate the mechanisms of CO_2 clearance and exchange of gases during apnoeic oxygenation, under the hypothesis that cardiogenic oscillation, gas-

mixing in the anatomical deadspace and pharyngeal pressure are key physiological mechanisms during open-airway apnoea.

Methods

Model description

Our study used the Interdisciplinary Collaboration in Systems Medicine (ICSM) suite of physiological simulations; these comprise highly-integrated computational models of the pulmonary and cardiovascular systems, which have been described in detail elsewhere.[10-16] The model has been widely validated and used to investigate apnoea in adults,[17-19] parturients,[20, 21] and children.[22]

The model includes a series deadspace volume, 100 independently-configurable alveolar compartments and 19 in-series cardiovascular compartments. The series deadspace (SD) is located between the airway and the alveolar compartments and it is simulated as a series of stacked, rigid laminae ($N_{lam} = 50$) of equal volume. The static total volume of the series deadspace is set to 150 ml[23, 24] (representing a 70-kg adult) and each lamina, j, has a known fraction ($f^{x}_{(SD,j)}$) of gas x.

The pressure of each alveolar compartment is described by a cubic function:

$$p_i = ((10 \cdot v_i - 300)^3/6600) - P_{ext,i} \quad v_i > 0 \qquad for\ i = 0, \dots, N_{alv} \qquad [1]$$

$$p_i = 0 \qquad otherwise$$

Equation [1] determines the alveolar pressure p_i in cmH_2O for the i^{th} of N_{alv} alveolar compartments for the given volume of alveolar compartment, v_i, in millilitres. $P_{ext,i}$ (per alveolar unit, in cmH_2O) represents the effective net pressure generated by the sum of the effects of factors outside each alveolus.[14]

Full details of the model are provided in the Supplementary Data.

We recently developed and added four new modules to the existing ICSM suite, preliminary validated against an experimental animal study.[25]

Cardiogenic oscillations module

The effect of cardiac oscillations on alveolar compartments was described using the following equation:

$$P_{osc,i} = K_{osc} \cdot \varphi \qquad for\ i = 0, \dots, N_{osc} \qquad \text{where } N_{osc} \leq N_{alv} \qquad [2]$$

$P_{osc,i}$ represents the pressure generated by the heart, and acting on the alveolar compartment i. K_{osc} is a variable parameter representing the strength of the effect of cardiogenic oscillations on alveoli, due to the alveoli being compressed by the heart and/or trans-pulmonary blood volume. N_{osc} is a variable parameter reflecting the number of alveolar compartments that are affected by cardiogenic oscillations. The parameter φ is the ventricular activation function, equal to 1 at the peak of systolic contraction and 0 during maximal diastolic relaxation.

Thus, the final equation describing the pressure of each alveolar compartment is:

$$p_i = ((10 \cdot v_i - 300)^3/6600) - P_{ext} - P_{osc,i} \qquad [3]$$

More detail is presented in the Supplementary Data.

Anatomical deadspace gas-mixing module

A variable parameter σ was added to the calculation of $f^{x}_{(SD,j)}$ representing the proportion of gas mixing between adjacent laminae of the series deadspace. The parameter σ allows for varying degrees of mixing between adjacent layers; $\sigma = 1$ indicates complete mixing of gases between layers representing the effects of extreme turbulent flow, while $\sigma = 0$ indicates no mixing of gases.

Further detail is presented in the Supplementary Data.

Tracheal insufflation module

To reproduce the effects of tracheal gas insufflation (or gas inflow at the top of the series deadspace), the flow of gas entering the series deadspace is determined by the variable parameters, r_{insuff}, representing the rate of insufflation in L·min^{-1} and l_{insuff}, representing the location of insufflation in different positions across the series deadspace.

Further detail is presented in the Supplementary Data.

Pharyngeal pressure

As a result of high flow through the nasopharynx, we hypothesised an oscillating pressure P_{phar} above the glottis. This could be tuned in terms of its frequency and amplitude:

$$P_{phar} = A \cdot \sin(\frac{\pi}{f})^2 \quad (4)$$

where, A is the amplitude of the pressure in cmH_2O and f is the frequency in Hz. This phenomenon can be effectively disabled by setting A to zero.

Further detail is presented in the Supplementary Data.

Clinical data used for model calibration and validation

To calibrate and validate the ICSM simulator with the new modules as a tool for studying apnoeic oxygenation, the methods of five previous clinical studies were reproduced [8, 26-29], selected for their complete descriptions of subjects (weight, body mass index, functional residual capacity, [FRC]), the reproducibility of methods and the detail of results. Approval from a research ethics committee was not sought, since the data were obtained from previously published literature. The ICSM simulator was set to replicate the mean of the patient group described in each study (i.e., using the mean weight and mean FRC) and was subjected to the same intervention as the study subjects. Model simulations were run on a 64-

bit Intel Core i7 3.7 GHz Windows 7 personal computer, running Matlab version R2017a MathWorks Inc. MA, USA.

The studies selected are described below:

Frumin and co-workers[26] studied apnoeic oxygenation in eight healthy men. Patients were denitrogenated by breathing 100% oxygen for a minimum of 30 mins (at flow rate of oxygen of at least 8 $L \cdot min^{-1}$). Following the denitrogenation, apnoea persisted for 30-55 min with an oxygen flow rate of 200 ml per minute through an endotracheal catheter. Arterial blood gases and oxygen saturation during and after apnoeic oxygenation were measured. The methodology for the denitrogenation and for the apnoea were reproduced in our model. Therefore, the following "population normal" values were assumed in modelling the subject group: weight 70 kg, BMI 24 $kg \cdot m^{-2}$, ventilatory minute volume 420 m1 × 12 min^{-1}, oxygen consumption 3.3 $mL \cdot kg^{-1} \cdot min^{-1}$, FRC 43 mL·kg before the induction of anaesthesia and 20% less after the induction of anaesthesia, alveolar dead space 10% of tidal volume and venous admixture 1% of cardiac output.

Fraioli and co-workers[27] studied the pulmonary and cardiovascular effects of apnoeic oxygenation in man. The authors studied apnoeic oxygenation in 13 patients undergoing Jako-laryngoscopy and 18 patients having other minor surgical procedures. After 10 minutes of pulmonary denitrogenation with 100% oxygen the apnoeic period was begun via a pharyngeal catheter (Jako-laryngoscopy) and endotracheal tube (for patients having minor surgical procedure). Arterial blood gases, pH and pulmonary function studies were assessed. We replicated the methodology for the patient population having minor surgical procedures. The subject group was modelled by using the same "population normal" values used in modelling Frumin's subjects, except for the oxygen consumption and the FRC values that at induction of anaesthesia were decreased by 26% and 27%, respectively, as reported in the paper.

Berthoud and co-workers[28] studied six morbidly obese (BMI 49 $kg \cdot m^{-2}$) and six matched non-obese patients (BMI 23.1 $kg \cdot m^{-2}$) undergoing anaesthesia. Subjects were anesthetized after denitrogenation (8 $L \cdot min^{-1}$ 100% oxygen) and were subsequently apnoeic until tracheal intubation. The time taken for desaturation of oxyhaemoglobin to 90% during apnoea was recorded and arterial blood gases measured. FRC of the subjects was not measured in the study, so the ICSM simulator was set up with values for FRC of 43 $mL \cdot kg^{-1}$ for the non-obese and 14 $mL \cdot kg^{-1}$ for the morbidly obese [30] and FRC was assumed to decrease by 20% and 50% on induction of anaesthesia in healthy and in obese patients, respectively. [30] The minute ventilation before the induction of anaesthesia was configured as 420 mL × 12 min^{-1} for the non-obese subjects and 420 mL × 16 min^{-1} for the obese group. The airway was modelled as obstructed after the induction of anaesthesia up to the point of tracheal intubation.

Baraka and co-workers[29] investigated the effectiveness of nasopharyngeal oxygen insufflation at a rate of 5 $L \cdot min^{-1}$ in delaying the onset of haemoglobin desaturation during the subsequent apnoea in morbidly obese patients (study group: BMI 41.8 $kg \cdot m^{-2}$) following pre-oxygenation using tidal volume breathing for 3 min (10 L min^{-1} 100% oxygen) as compared to pre-oxygenation alone (control group: BMI 42.7 $kg \cdot m^{-2}$). Apnoea was allowed to continue until SpO_2 fell to 95% or until 4 min had elapsed from the onset of apnoea. The time from the onset of apnoea until SpO_2 fell to 95% was compared between the two groups. The subject group was modelled by using the same values used in modelling Berthoud's subjects.

Gustafsson and co-workers[8] studied apnoeic oxygenation in adults under general anaesthesia using HFNO in anesthetized patients. Patients were pre-oxygenated using 40 $L \cdot min^{-1}$ 100% oxygen, for at least 3 minutes and at the onset of apnoea, the flow of oxygen was increased to 70 $L \cdot min^{-1}$ 100% oxygen, and maintained throughout anaesthesia. Arterial

blood gases, arterial pH and saturation were recorded. The subject group was modelled by using the same values used in modelling Frumin's subjects.

Data collection

In all simulations, the following model outputs were recorded every 5 msec: arterial partial pressure of oxygen (PaO_2) and CO_2 ($PaCO_2$), arterial oxygen saturation (SaO_2), arterial pH, and cardiac oscillations volume (i.e. tidal volume generated by cardiac oscillations). The variable parameters of the new modules of the ICSM simulator were calibrated against Frumin's paper [26] and published values for passive tidal volume generated by cardiac oscillations in humans (4–11 ml).[31] The parameters were tuned to provide the closest possible match between the reported clinical data and the modelled data.

Data considered from the five clinical investigations were: the rate of rise of $PaCO_2$ and arterial pH (Frumin[26], Fraioli[27], Gustafsson[8]); PaO_2 increase (Fraioli[27]), time to reach SaO_2 90% and corresponding $PaCO_2$ (Berthoud[28]); time to reach SaO2 95% (Baraka[29]). All data are presented in this manuscript as mean (standard deviation, [SD]).

Results

Parameter-tuning to match previously published data resulted in the cardiogenic oscillations module being configured as follows: $K_{osc} = 4.5$ cm H_2O and $N_{osc} = 60\%\ N_{alv}$, producing a passive, oscillation-induced, tidal volume of 9 ml during apnoea.[31]

In the anatomical deadspace gas-mixing module, the optimal value of the parameter σ was found to be 0.3. Once a satisfactory fit and behaviour of the model was found for this dataset, the model was validated against the other 4 studies Fraioli,[27] Berthoud,[28] Baraka [29] and Gustasfsson.[8]

For validation of the model against Gustafsson's study,[8] in which the authors did not use classical apnoeic oxygenation but rather HFNO, we tuned the parameter (σ) from 0.3 to 1. Adding a pharyngeal pressure with a frequency of 70 Hz and an amplitude tuned to be between 1 and 2 cmH_2O[32] achieved an even closer match to the data.

The complete results of the model validation against the clinical studies,[8, 26-29] performed with and without the effect of cardiogenic oscillations and gas-mixing in the anatomical deadspace, are reported in Table 1.

Fig. 1 shows the $PaCO_2$ and arterial pH time courses during apnoeic oxygenation when recreating the methodology and subject group of Fraioli's work.[27] Enabling the effect of cardiac oscillations ($K_{osc} = 4.5$ cmH_2O and $N_{osc} = 60\%\ N_{alv}$) and the gas-mixing deadspace ($\sigma = 0.3$), the model results for the classical apnoeic studies[26-29] were within 36% of the values found clinically in all cases and within 15% in most cases, and for the HFNO study[8] results were within 1% ($K_{osc} = 4.5$ cmH_2O, $N_{osc} = 60\%\ N_{alv}$ and $\sigma = 0.6$).

The model results obtained against the data from Gustafsson's study[8] are as follows. In the study, the mean apnoea time was 22.5 (4.5) min, SpO_2 never reduced below 91%, the rate of

increase in $PaCO_2$ was 0.24 (0.05) kPa·min^{-1}, and arterial pH decreased from 7.44 (0.04) to 7.14 (0.01). Using the simulator with the effect of cardiac oscillations and the deadspace gas mixing, configured as previously, (i.e. $K_{osc} = 4.5$ cmH_2O, $N_{osc} = 60\%\ N_{alv}$ and $\sigma = 0.3$) and insufflating 30 L·min^{-1} at the glottis, the increase in $PaCO_2$ was 0.40 kPa·min^{-1}, SaO_2 was constant at 99%, and arterial pH decreased from 7.40 to 7.13. By increasing the parameter σ (series deadspace gas mixing) from 0.3 to 1, the rate of rise of $PaCO_2$ was reduced to 0.36 kPa·min^{-1} and arterial pH decreased from 7.40 to 7.15.

Adding the effect of high frequency pressure variation in the pharynx (above the glottis) with an amplitude equal to 1 cmH_2O, σ equal to 1 and glottic insufflation at 30 L·min^{-1}, the rate of rise of CO_2 fell again to 0.28 kPa·min^{-1}. Increasing the amplitude to 2 cmH_2O, we obtained a similar dynamic $PaCO_2$ time course as was presented in the clinical data, with a non-linear pattern – an initial rapid increase in $PaCO_2$ that gradually levelled-off during the apnoeic period (Fig. 2). The final best fit between the model and the clinical data was achieved by setting $\sigma = 0.6$ and $r_{insuff} = 13$ L·min^{-1}, producing a rate of $PaCO_2$ increase equal to 0.24 kPa·min^{-1}, and a decrease in arterial pH from 7.40 to 7.22.

Discussion

To our knowledge, the mechanisms underlying gas-mixing during apnoea have so far been studied only in animal models.[5, 6, 33] We investigated the mechanisms of transport and exchange of gases and the clearance of CO_2 during apnoea *in silico*, by configuring a high-fidelity computational physiological modelling of cardiovascular and pulmonary system against five previous studies of apnoea in human subjects. Our results provide strong support for the hypothesis that augmented gas-mixing in the anatomical deadspace along with the provision of micro-ventilation via cardiogenic oscillations are key physiological mechanisms providing clearance of carbon dioxide and oxygenation during open-airway apnoea, and that pharyngeal pressure oscillation is an important factor augmenting CO_2 clearance during HFNO. In all cases, enabling the effects of cardiac oscillation, gas-mixing in deadspace and pharyngeal pressure in our model produced model outputs that were closer to the data available in clinical studies.

The ICSM simulation suite was shown to be capable of accurately predicting the results of several previous clinical investigations with human subjects. The simulator performed well in steady state conditions, but more importantly, also when physiological variables were changing quickly. Some deviations between simulator predictions and the clinical results were observed, as expected, due to imperfect matching of the modelled subjects to the patient group or to unquantified variation in the clinical subjects. For example, Berthoud[28] and Baraka[29] did not measure FRC, but the ICSM simulator required a value for FRC to configure study subjects; thus, we used a value of FRC for obese subjects taken from another study.[30]

Our study allowed the separation of the contributing physiological mechanisms involved in apnoea in order to study the behaviour of each mechanism individually. By integrating cardiac oscillations, anatomical deadspace gas-mixing modules and oxygen insufflation

into/above the trachea into our model, we could evaluate different degrees of mixing between adjacent layers in the series deadspace on clearance of CO_2 and a range of flow rates of oxygen on ventilation and oxygenation during apnoea. For the validation of the model against Gustafsson's study,[8] in which the authors used high-flow nasal oxygen, we initially found a rate of rise of $PaCO_2$ equal to 0.40 $kPa \cdot min^{-1}$ using the configuration of parameters used for the other four studies. Subsequent adjustment of model parameters governing gas-mixing in the series deadspace and glottic oxygen-insufflation rate allowed us to reduce this value closer to that found clinically; further addition of high-frequency glottic pressure variation (soft tissue "wobble") brought the model predictions very close to those found clinically, lending support to the hypothesis that such mechanisms are important, and informing our understanding of their relative strengths and importance.

Thus, during classical apnoeic oxygenation (without HFNO) the physiological mechanisms for the clearance of CO_2 are represented by a combination of relatively small amount of gas-mixing in the anatomical deadspace and generation of ventilation through cardiac oscillations; it is not possible to determine which factor has the greatest importance. During open-airway apnoea with HFNO, the combination of cardiac oscillations together with a high degree of gas-mixing in the anatomical deadspace and with the high-frequency glottic pressure appear to be the physiological mechanisms for CO_2 clearance, and the most important contribution is provided by high-frequency pressure oscillation in the pharynx.

Future evolution of high-flow, upper-airway, oxygen-insufflation devices could take advantage of the mechanisms proposed here, since it is likely that gas-exchange facilitated by high-flow nasal cannulae is achieved via a combination of the mechanisms proposed in this manuscript noting that potentially only a fraction of the total delivered gas reaches the trachea. The new additions that we have made to the ICSM simulator could also assist with the development of apnoeic oxygenation devices, such as THRIVE,[8] in different clinical

scenarios, such as term pregnancy, severe lung disease and rapid sequence induction.

Limitations of the study include the possibility that subjects were not modelled exactly, e.g. not considering fully the effect of muscle relaxants. However, the modelling of the subjects was performed before the recreation of the methodologies, and was thus blinded. Although we have validated the model against published data, future work will focus on collection and incorporation of new clinical data to further evolve the detail and veracity of the simulation suite, allowing us to investigate the effect of pathological conditions that may modify the dynamics of apnoea.

Authors' contributions

Design of initial model: JGH

New module development: ML, AD, JGH, DGB

Validation of the model: ML, JGH, DGB, AD

Interpretation of results. ML, AD, MC, DGB, JGH

Writing and final approval of manuscript: ML, AD, MC, DGB, JGH

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Declaration of Interest

None declared.

Supplementary Data

Supplementary Data are available online.

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Table

Table 1. Validation of the model against the five clinical studies with and without the effect of cardiac oscillations and gas-mixing deadspace.

	Clinical Data		**Model**			
		Cardiac Oscillations	ON	ON	OFF	OFF
		Gas mixing	ON	OFF	ON	OFF
Frumin[26]						
Rate of rise $PaCO_2$ ($kPa \cdot min^{-1}$)	0.40 (0.07)		0.40	0.95	0.98	0.98
Minimum level of arterial pH	6.72		7.08	6.88	6.87	6.87
Fraioli[27]						
Rate of rise $PaCO_2$ ($kPa \cdot min^{-1}$)	0.43 (0.04)		0.50	0.84	0.84	0.84
PaO_2 increase (%)	30.1 (24)		26.4	47.8	47.7	47.9
Arterial pH decrease (min^{-1})	0.02 (0.00)		0.02	0.02	0.02	0.02
Berthoud[34]						
Time to SaO_2=90% obese (s)	196 (80)		184	181	181	181
$PaCO_2$ at SaO_2=90% obese (kPa)	6.20 (1.1)		6.79	6.79	6.79	6.79
Time to SaO_2=90% non-obese (s)	595 (142)		500	495	495	493
Baraka[34]						
Time to SaO_2=95% study (s)	240 (0)		240	240	240	240
Time to SaO_2=95% control (s)	145 (27)		187	206	190	206
Gustafsson[8]						
Rate of rise $PaCO_2$ ($kPa \cdot min^{-1}$)	0.24 (0.05)		0.24	0.90	0.54	0.91
Arterial pH decrease (min^{-1})	0.06 (0.00)		0.01	0.02	0.01	0.02

Cardiogenic Oscillations: ON the effect of cardiac oscillations is enabled ($K_{osc} = 4.5$ cmH$_2$O and $N_{osc} = 60\%\ N_{alv}$); OFF the effect of cardiac oscillations is disabled $K_{osc} = 0$ cmH$_2$O and $N_{osc} = 0\%\ N_{alv}$;

Gas Mixing: ON effect of gas mixing is enabled ($\sigma = 0.3$ for the studies of Frumin, Fraioli, Berthoud, and Baraka and $\sigma = 0.6$ for Gustafsson's study); OFF the effect of gas mixing is disabled ($\sigma = 0$).

For the results of model validation against Gustassfon's study, the pharyngeal pressure is set to 2 cmH$_2$O and the rate of oxygen insufflation is equal to 13 L min^{-1}.

Results from the clinical studies are presented as mean (SD).

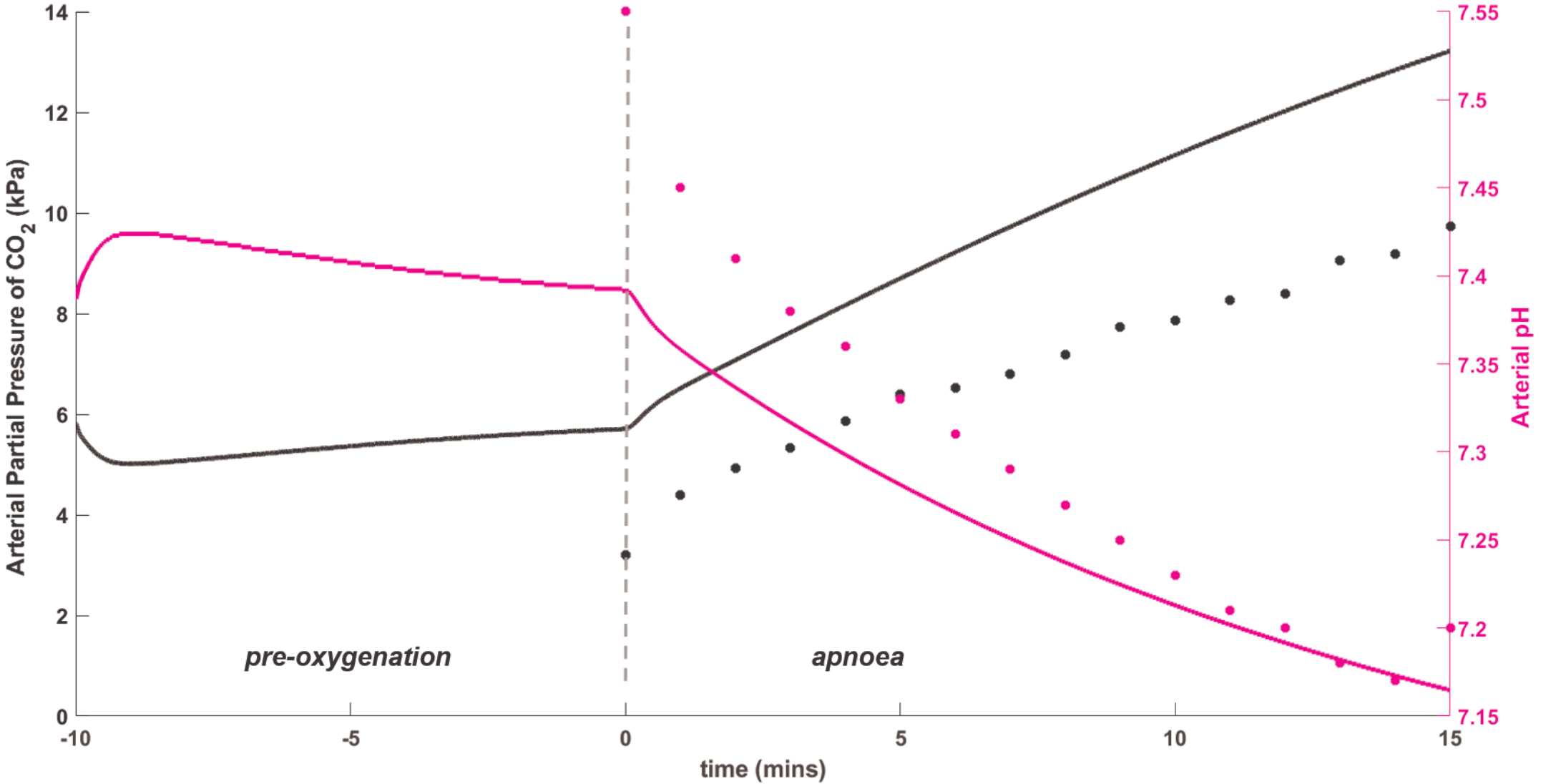
Figure legends

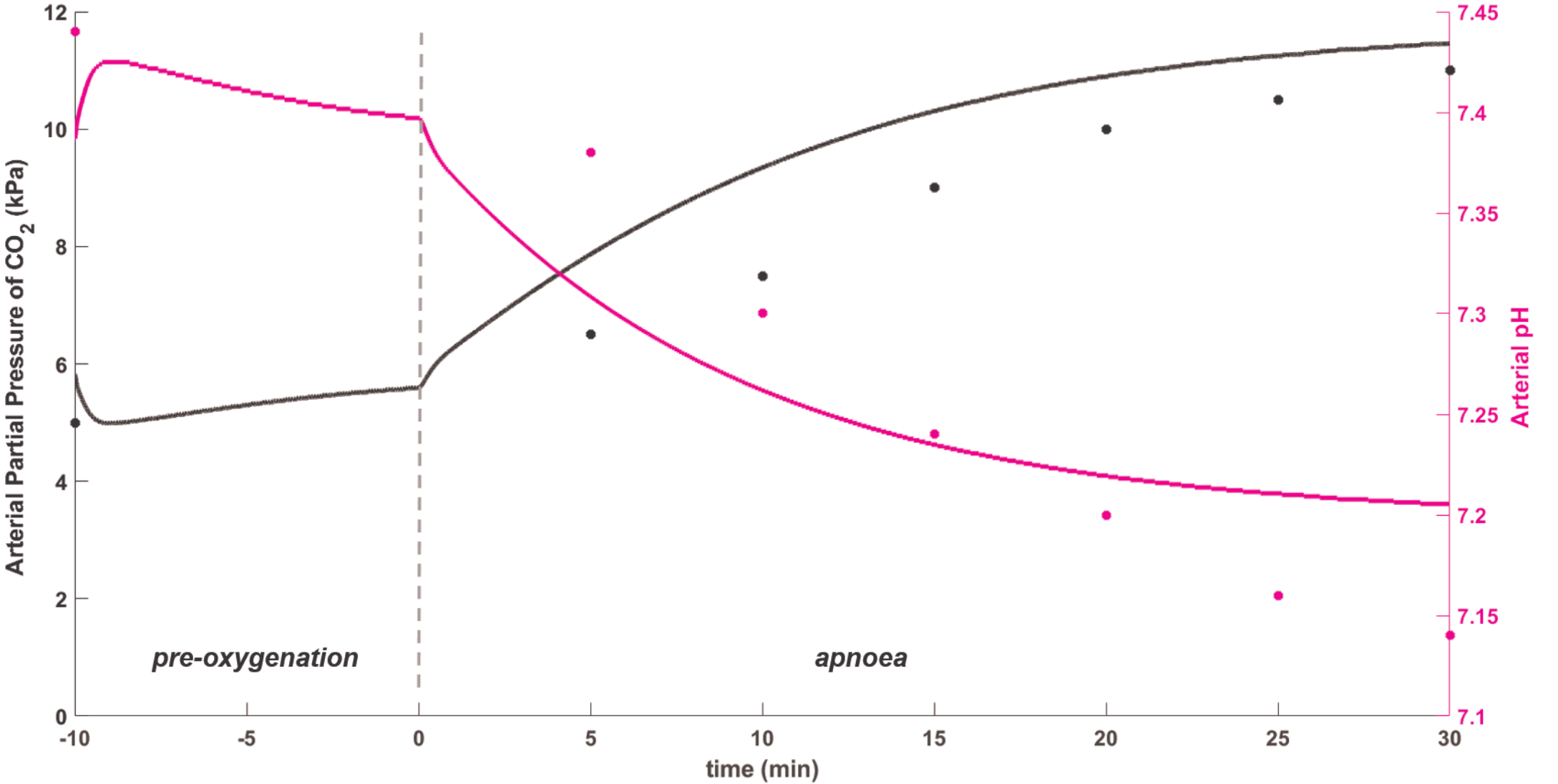
Fig. 1

Time-course of $PaCO_2$ (black) and arterial pH (pink) for the output model (straight line) and the clinical investigation of Fraioli's study[27] (dots). The grey dashed line indicates the beginning of apnoea after pre-oxygenation.

Fig. 2

Time-course of $PaCO_2$ (black) and arterial pH (pink) for the output model (straight line) and the clinical investigation of Gustafsson and co-workers[8] (dots). The grey dashed line indicates the beginning of apnoea after pre-oxygenation.


Arterial Partial Pressure of CO_2 (kPa)
Arterial pH
time (mins)
pre-oxygenation
apnoea
14
12
10
8
6
4
2
0
7.55
7.5
7.45
7.4
7.35
7.3
7.25
7.2
7.15
-10
-5
0
5
10
15


Arterial Partial Pressure of CO_2 (kPa)
Arterial pH
time (min)
pre-oxygenation
apnoea
12
10
8
6
4
2
0
7.45
7.4
7.35
7.3
7.25
7.2
7.15
7.1
-10
-5
0
5
10
15
20
25
30