An Integrated Mathematical Model of the Human Cardiopulmonary System: Model Development

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Abstract - Several cardiovascular and pulmonary models have been proposed in the last few decades. However, very few have addressed the interactions between these two systems. Our group has developed an integrated cardiopulmonary model that mathematically describes the interactions between the cardiovascular and respiratory systems along with their main short-term control mechanisms. The model has been compared to human and animal data taken from published literature. Due to the volume of the work, the paper is divided in two parts. The present paper is on model development and normophysiology, while the second is on the model’s validation on hypoxic and hypercapnic conditions. The cardiopulmonary model incorporates cardiovascular circulation, respiratory mechanics, tissue and alveolar gas exchange, as well as short-term neural control mechanisms acting on both the cardiovascular and the respiratory functions. The model is able to simulate physiological variables typically observed in adult humans under normal and pathological conditions and to explain the underlying mechanisms and dynamics.

New & Noteworthy - This paper describes a novel integrated mathematical model of the cardiovascular and respiratory systems that includes the main cardiorespiratory interactions and short-term regulation mechanisms. Model results under normal resting conditions are similar to those observed in average populations.

Introduction

Life depends on the interactions between the cardiovascular and respiratory systems. The harmonious balance of such interactions maintains vital physiological variables, such as blood flow and blood oxygen content, within specific ranges. The cardiovascular and respiratory systems interact via several mechanisms, continuously, in a complex and non-linear manner. Oxygen (O₂) and carbon dioxide (CO₂) are exchanged between pulmonary capillary blood and alveolar air, and the efficacy of such exchange depends on the success of their coupling. Furthermore, the amount of blood pumped by the heart and the degree of vessel vasoconstriction affect the blood gas transport delay, which is a key determinant of O₂ and CO₂ blood contents. These, in turn, modulate the depth and frequency of respiratory efforts via the action of specific receptors (chemoreceptors), which become active when O₂ and CO₂ blood contents are out of their normal ranges. Mechanical interactions also exist due to the fact that the chest contains the respiratory system and a significant portion of the cardiovascular system. These are particularly important during mechanical ventilation (MV), when elevated intra-thoracic pressure could compromise ventricular filling and stroke volume, thus reducing arterial blood pressure (ABP). ABP, in turn, modulates the activity of specific cardiovascular receptors (baroreceptors) that induce neural activity changes in both the sympathetic and parasympathetic branches of the autonomic nervous system (ANS), ultimately affecting
heart rate, cardiac contractility and vasomotor tone. Mechanisms outside ANS control also exist. Local autoregulation and central nervous system (CNS) ischemic response are such examples. These become active in extreme conditions, such as severe hypoxia, to preserve perfusion and oxygen supply to vital organs (e.g. brain and coronary arteries).

Mathematical modeling and computer simulation can improve the understanding of such complex interrelations and provide an efficient quantitative tool for the analysis and synthesis of cardiopulmonary dynamics. By using computer simulations, investigators can conduct virtual physiological experiments, test new hypotheses, and predict the effects of particular treatments or clinical maneuvers. Such simulations can be used in clinical decision making for diagnostic and therapeutic medicine.

Pioneering work in cardiorespiratory modeling was done by Grodins et al. in the 1950s (30,31) and by Guyton and his co-workers in the 1970s (32). However, due to the physiological knowledge and limited computational power of the time, the interactions between the cardiovascular and respiratory systems were not completely described. In the past few decades, thanks to the advancement in computational technology, scientific activity in this field has notably increased, and modeling complexity presented in the literature (9,10,13,35,36,37,41,43,44,64,67,69) has grown to more accurately describe physiological mechanisms and their dynamics. However, the majority of these models are primarily either cardiovascular or pulmonary and thus do not permit a comprehensive exploration of cardiopulmonary response to different acute conditions. Very few models have tried to address the strong dynamic interactions between the cardiovascular and respiratory systems albeit with some limitations. For instance, the models by Ursino and Magosso (44,69) are to our opinion the most exhaustive in terms of the cardiovascular control mechanisms but lack respiratory and gas exchange components. The models by Cheng et al. (9,10), which include Ursino's cardiovascular system and control models, include description of respiratory mechanics and gas exchange, but are more focused on the interactions between sleep mechanisms and the autonomic nervous system rather than on cardiorespiratory interactions. On the other hand, models by Lu et al. (41,43) are detailed in their description of the mechanical interactions between the respiratory and cardiovascular systems and do include gas exchange, but are less detailed in cardiovascular and respiratory neural control.

Our group has developed an integrated model to overcome some of the above limitations by including finer cardiorespiratory interactions and short-term control mechanisms. The model is the result of a multi-year effort and only preliminary results have been presented in previous papers (2,7,27). The model is presented in two separate papers: Model Development; and Model Validation under Hypercapnia and Hypoxia. The present (first) paper provides a rigorous description of the model including results and comparison against human and animal data, in normal conditions, taken from literature. The companion (second) paper (8) includes validation against human data under hypercapnic and hypoxic conditions. The model incorporates essential features from existing models and represents a substantial extension of the models by Ursino and Magosso (44,69). Their studies were mainly focused on analyzing the cardiovascular response to hypercapnic and hypoxic stimuli; the respiratory system was not explicitly considered. Arterial $Po_2$ and $Pco_2$ were fed to the models as external inputs, and the
gas exchange process was completely ignored. Here, separate sub-models of respiratory mechanics, gas exchange in lungs and tissues, gas transport in blood, and respiratory control mechanisms have been added to attain an integrated cardiopulmonary model that is able to run in closed-loop mode requiring inspiratory air gas content ($F_{\text{i,}O_2}$ and $F_{\text{i,}CO_2}$) and total blood volume as the only inputs. The model is able to generate physiological variable values typically observed in adult humans under normal, hypercapnic and hypoxic conditions and explain the underlying mechanisms and dynamics. Furthermore, after further ad hoc validation, the model may be used to simulate different disease conditions by appropriately varying parameter values prior to or during simulations, as well as therapeutic interventions.

**Model Development**

The present cardiopulmonary model (CP Model) incorporates cardiovascular circulation, respiratory mechanics and gas exchange, along with their main short-term control mechanisms. A schematic block diagram of the model is shown in Fig. 1, where the interconnections among the different subsystems are highlighted. The **Cardiovascular System** and the **Respiratory System** interact via the **Gas Exchange and Transport** module. This module describes the gas exchange processes in the lungs and the systemic tissues, along with the gas transport throughout the circulatory system. Both the cardiovascular and respiratory systems are subject to their own control mechanisms, identified in the block diagram as the **Cardiovascular Control System** and the **Respiratory Control System** modules, respectively. Particularly, the cardiovascular function is regulated by the **Autonomic Nervous System** (ANS) that integrates the afferent information provided by the **Baroreceptors**, **Peripheral Chemoreceptors** and **Lung Stretch Receptors** modules. Local **Autoregulation** mechanisms are also included along with a central nervous system (CNS) mediated response to acute ischemic conditions (**CNS Ischemic Response**). The respiratory function is assumed to be governed by the superposition of control mechanisms mediated by both the **Peripheral Chemoreceptors** and the **Central Chemoreceptors**, which modulate the activity of the **Respiratory Muscles** acting on the **Lung Mechanics** module. This, in turn, can also be driven by the action of an external **Mechanical Ventilator**. In the following sections, a qualitative description of these different components is provided. Following a control-theory approach, the cardiovascular and the respiratory systems are first described in the absence of regulatory actions (uncontrolled system). Description of their feedback control mechanisms is subsequently provided. A complete set of equations describing the model is presented in the **Appendix** section.

**The Uncontrolled Cardiovascular System Model**

The cardiovascular component of our CP Model is largely based on the work of Ursino and Magosso (44,69). However, modifications were introduced allowing more details of the heart-lung interactions, and the integration of the cardiovascular module on one side, and of the lung mechanics and the gas exchange modules, on the other side. As shown in
the schematic diagram in Fig. 2, the model includes a pulsatile heart, a pulmonary
circulation and a systemic circulation. The heart model includes both left and right hearts
along with their corresponding chambers (atria and ventricles) and valves (mitral, aortic,
tricuspid and pulmonary). The systemic circulation is subdivided into five districts
arranged in parallel describing blood circulation into the coronary, brain, skeletal muscle,
splanchnic (comprising the liver, the spleen, and the gastro-intestinal organs) and the
remaining extrasplanchnic (kidney, skin, bones, etc.) vascular beds. This distinction is
necessary since, as will be described later, autonomic and local cardiovascular regulatory
mechanisms exert different actions on each compartment. The hemodynamics in both
systemic and pulmonary circulations distinguish between large arteries, peripheral vessels
(combining arterioles and capillaries) and veins. The modifications with respect to the
original model formulation presented in (44,69) are: 1) A pulmonary shunt compartment
has been added in parallel to the pulmonary peripheral circulation between the
pulmonary artery and the pulmonary veins (anatomical shunting) to account for the
amount of blood that does not pass through the pulmonary capillaries and hence does not
participate in gas exchange; 2) An additional compartment representing the thoracic
veins, which return blood to the right atrium, has been included in the systemic
circulation; 3) The effects of respiration on venous return and cardiac output (respiratory
pump) have been modeled by considering intrapleural pressure \( P_{pl} \) as the reference
extravascular pressure for those compartments that are located inside the thoracic cavity
(heart, lungs and thoracic veins); all remaining compartments are assumed to be subject
to extravascular atmospheric pressure \( P_{atm} \); 4) As a consequence of respiration,
transmural pressure in the systemic veins can become negative at their point of entrance
in the thoracic cavity; to account for this phenomenon, venous valves have been included
by inserting an ideal diode both upstream and downstream of each systemic venous
compartment thus preventing retrograde blood flow (45). With these modifications, the
cardiovascular model includes a total of 20 compartments that are listed in Fig. 2.

1) The Circulation Model: Each vascular compartment shown in Fig. 2 is described
through traditional windkessel models (67,73), i.e. as the arrangement of a hydraulic
resistance \( R_j \) which accounts for pressure energy losses, and a hydraulic compliance \( C_j \)
which determines the blood volume stored in each compartment at a given pressure. For
those compartments where inertial forces in blood are relevant, i.e. the large pulmonary
and systemic arteries, an inertance \( L_j \) is also included as a third parameter of the
corresponding windkessel-type model. The general windkessel single-compartment model
with inertance is illustrated in Fig. 3. Equations relating pressures \( P \) and flows \( Q \) in the
vascular system are obtained by enforcing conservation of mass principles for each
vascular compartment of Fig. 2 (see Appendix). The pressure-volume \( PV \) relationship of
each vascular compartment is assumed to be linear, except for the thoracic veins
compartment. The assumption of linear \( PV \) relationship allows constant and
pressure-independent compliances \( C_j \). Hence, the volume of each of these
compartments is computed as the sum of the unstressed component \( V_{u,j} \) and the excess
volume component \( V_{e,j} \), which is associated with the increase in the transmural
pressure:
where \( P_{tm,j} \) is the transmural pressure of the \( j \)-th compartment. On the other hand, the thoracic veins compartment is modeled via a non-linear collapsible \( PV \) relationship. This choice can be justified by considering the typical \( PV \) relationship of a blood vessel shown in Fig. 4. It is quite linear near the unstressed volume (volume at zero transmural pressure), concaves upward, gradually increases in slope at higher volumes, and concaves downward as the volume decreases and the vessel collapses (18). In arteries and capillaries, transmural pressure is typically high and the operating point along the \( PV \) curve is such that a linear approximation is valid (17,65). In contrast, in the venous circulation the intravascular pressure is low; should any positive extravascular pressure exist, the vessel will collapse. This situation is most likely to occur in the thoracic veins, under the effects of a positive intrathoracic pressure (such as during mechanical ventilation). The non-linear \( PV \) relationship of the thoracic veins compartment has been derived by combining features of slightly different \( PV \) curves proposed in the literature for the vena cava compartment (9,49):

\[
P_{tm,tv} = \begin{cases} 
D_1 + K_1 \cdot (V_{tv} - V_{u,tv}) - \Psi & V_{tv} \geq V_{u,tv} \\
D_2 + K_2 \cdot e^{V_{tv,\text{min}}} - \Psi & V_{tv} < V_{u,tv}
\end{cases}
\]

with \( \Psi = K_{xp}/(e^{K_{xx}} - 1) \)
Finally, note that in solving the model equations for the pressure variables, atmospheric pressure has been assumed to be zero and hence the resulting values of $P_j$ in Fig. 3 represent above-atmospheric values.

2) The Heart Model: The model of the pulsatile heart remains unchanged compared to that one used in (44,69), where an accurate description can be found. The only modification introduced is the inclusion of the intrapleural pressure as the external reference pressure acting outside the heart chambers.

The Respiratory System Model

As shown in Fig. 1, the model of the respiratory system includes the descriptions of the lung mechanics and the respiratory muscles. The tidal-breathing lung mechanics model is based on previous work by Rideout (55) and Fukui (26) and has been modified to include chest wall and intrapleural pressure dynamics. Figure 6 shows the equivalent pneumatic circuit representing the lung mechanics model. It consists of the series arrangements of four segments, namely the larynx, the trachea, the bronchea and the alveoli. Each segment has been represented by a linear resistance and a linear compliance, which describe the dissipative and the elastic forces that act on the respiratory system during normal breathing. Inertial forces have not been considered because they have negligible effects within the physiological breathing frequencies (50).

The model can be driven by either an external pressure $P_{vent}$ representing the pressure provided by the ventilator, as in the case of mechanically ventilated patients, or by an internal generator $P_{mus}$ representing the pressure generated by the respiratory muscles, as in the case of spontaneously breathing patients. The chest wall has been modeled as a passive compliant element whose pressure-volume characteristic has been assumed linear and hence described by a constant compliance term, $C_{cw}$. This is a good approximation in the volume range of quiet breathing (2.5 to 3 L), according to the typical assumption of sigmoidal $PV$ relationship (6). The chest wall viscous resistance to flow has been neglected, as this typically has a small contribution to the overall respiratory system resistance in both healthy and diseased states (23,29). The respiratory muscle generator is connected to the chest wall compliance, which acts on the pleural space whose internal pressure $P_{pl}$ is transferred to those segments lying within the chest cavity, i.e. trachea, bronchea and alveoli.

In the present study, since the model was used to simulate spontaneous breathing conditions, the action of the external pressure generator $P_{vent}$ is nullified and the airway pressure $P_{ao}$ is always assumed to be equal to atmospheric pressure. However, the external pressure generator could be applied in order to simulate artificial ventilation conditions, or even superimposed to the action of the internal pressure generator to account for simultaneously natural and artificial breathing.

The respiratory muscle pressure generator (internal pressure generator), $P_{mus}$, has been modelled based on the average profile proposed by Mecklenburgh (46). This has been reproduced as a piece-wise continuous function consisting of an inspiratory parabolic profile and an exponential expiratory profile. Particularly, under the assumption of complete passive exhalation with no recruitment of the expiratory muscles (reasonable
for minute ventilation values up to 40 L/min (15)), $p_{mus}$ is assumed to decrease from 0 to its minimum end-inspiratory value during the inhalation phase and to gradually return to 0 during exhalation, according to:

$$p_{mus}(t) = \begin{cases} 
-P_{mus,min} \cdot \frac{t^2}{T_I \cdot T_E} + \frac{P_{mus,min} \cdot T_I}{T_I \cdot T_E} \cdot t & t \in [0, \; T_I] \\
\frac{P_{mus,min}}{1-e^{-\frac{T_E}{\tau}}} \cdot (e^{-\frac{(t-T_I)}{\tau}} - e^{-\frac{T_E}{\tau}}) & t \in [T_I, \; T_E]
\end{cases}$$

where $T_I$ and $T_E$ represent the duration of the inspiratory and expiratory phases, respectively, $T$ is the respiratory period, $P_{mus,min}$ is the minimum end-inspiratory pressure value representing the amplitude of the inspiratory efforts, and $\tau$ is the time constant of the exponential expiratory profile. The inspiratory and expiratory times are considered fixed fractions of the respiratory period $T$:

$$T_I + T_E = T = 60/RR$$
$$T_I = T_E \cdot IE_{ratio}$$

where $RR$ is the respiratory rate (expressed in breaths/min) and $IE_{ratio}$ is the inspiratory-expiratory time ratio. The muscle pressure waveform is repeated with the respiratory period. The expiratory $p_{mus}$ time constant, $\tau$, is assumed to be directly proportional to the expiratory time $T_E$, and the inspiration-expiration time ratio, $IE_{ratio}$, is assumed to be fixed during a simulation. Hence, the $p_{mus}$ profile is fully parameterized via the two quantities $RR$ and $P_{mus,min}$, whose values are assumed to vary from breath to breath and are computed at the beginning of each respiratory cycle as output of the chemoreceptors module (see Respiratory Control Model section).

Outputs of the lung mechanics model are the instantaneous pressures and volumes of each compartment, along with the instantaneous air flow into and out of them. The equations for pressures and flows are obtained by solving the electrical circuit shown in Fig. 6 based on conservation of mass principles. Volumes are then computed taking into account the unstressed components (see Eq. 1). To allow interaction between the lung mechanics and the gas exchange model (see Fig. 1), the dead space is also considered and its instantaneous volume is computed as the sum of the volumes of the three compartments that do not participate in gas exchange, i.e. larynx, trachea and bronchie. Hence, differently from the majority of the models available in literature (9,71), dead space is not assumed to be rigid but its volume is constantly changing throughout a respiratory cycle. As a consequence of the elastic dead space assumption, part of the total air flow entering the lung, denoted as $\dot{V}_d$, is spent to inflate the dead space and does not contribute to the effective flow that reaches the alveoli, denoted as $\dot{V}_A$. Furthermore, since the difference between the volumes of $O_2$ and $CO_2$ that are exchanged between alveoli and pulmonary capillary over a respiratory cycle is typically very small, the net air flow that is transferred from the alveoli to the pulmonary blood is neglected and the inhaled tidal volume over a respiratory cycle is assumed exactly equal to the corresponding exhaled tidal volume.
The Gas Exchange and Transport Model

The model of gas exchange and transport describes the oxygen ($O_2$) and carbon dioxide ($CO_2$) exchange between pulmonary capillaries and lungs and between systemic capillaries and tissues, along with $O_2$ and $CO_2$ transport by blood throughout the circulatory system. As shown in the block diagram of Fig. 7, the model is made of three components, namely the Lung Gas Exchange, the Tissue Gas Exchange and the Venous Pool Gas Transport. Circulatory transport delays, $\tau_{LT}$ and $\tau_{VL}$, are included in the model to account for the time that it takes for blood to transport gases from the lungs to the systemic tissues and from the thoracic veins back to the pulmonary capillaries. Gas transport throughout the venous pool is instead explicitly modeled since blood flow in the venous section is typically slow and hence this section accounts for most of the circulatory blood transport delay. Only $O_2$ and $CO_2$ gas species are considered in the model, with nitrogen ($N_2$) and other air gas components neglected. In the following, a detailed description of the three submodels is provided.

1) The Lung Gas Exchange: The lung gas exchange model includes anatomical dead space, alveoli, pulmonary capillaries (also belonging to the pulmonary peripheral compartment of the cardiovascular system) and right to left pulmonary shunts. A schematic block diagram is shown in Fig. 8. It receives total airflow ($V$), alveolar airflow ($V_a$), dead space ($V_d$) and alveolar volume ($V_A$) as inputs from the lung mechanics model, and pulmonary peripheral volume ($V_{pp}$) and blood flows through the pulmonary beds ($Q_{pa}, Q_{pp}$ and $Q_{ps}$) as inputs from the cardiovascular model. Furthermore, the lung gas exchange model is obviously interconnected to the tissue gas exchange model, as shown in Fig. 7, as it requires as inputs the delayed venous gas concentrations $\tilde{C}_{v,\text{gas}}$ as well (where gas indicates either $O_2$ and $CO_2$). External inputs to the lung gas exchange model are the gas fractions in the inspired air, $F_{i,\text{gas}}$. Outputs of the model are the concentrations of gas in the pulmonary capillaries ($C_{pp,\text{gas}}$), which are then converted into arterial blood gas concentrations ($C_{a,\text{gas}}$). These are computed by applying conservation of mass to each of the three compartments in Fig. 8 for each gas species, and assuming that every compartment is homogenous and perfectly-mixed. Gases are assumed to be ideal, and gas fractions in the lungs are related to their corresponding partial pressures via the ideal gas law. Blood gas concentrations are related to their corresponding partial pressures via empirical dissociation curves (60) that are easily invertible and have been validated and used in previous cardiopulmonary models. These dissociation functions take into account both the Haldane and the Bohr effects. Finally, equilibrium between pulmonary capillaries and alveoli in terms of gas partial pressures is assumed to happen instantaneously. The complete set of equations governing the lung gas exchange model is reported in the Appendix section.

2) The Tissue Gas Exchange and Venous Pool Gas Transport: The tissue gas exchange model accounts for the $O_2$ consumption and $CO_2$ production of tissues and organs at the level of the systemic capillaries, whereas the venous pool gas transport model describes $O_2$ and $CO_2$ transport through the systemic and thoracic veins. A schematic diagram of the combined model is shown in Fig. 9. The model receives as input the
delayed arterial gas concentrations from the lung gas exchange model, $\bar{C}_{a,\text{gas}}$, and
provides as output the gas concentrations in the mixed venous blood, $C_{v,\text{gas}}$, computed
at the exit of the thoracic veins compartment. Furthermore, the tissue gas exchange
model is connected with the cardiovascular model since it requires blood flows and
volumes in the different systemic vascular beds as input as well. As shown in Fig. 9, tissue
gas exchange is assumed to happen at the level of the five systemic peripheral
compartments (coronary, brain, skeletal muscle, splanchnic and extrasplanchnic
compartments). Each compartment supplies blood to a organ/tissue (or group of
organs/tissues) that is modeled as a simple container, characterized by a constant volume
$V_{T,jp}$, where the subscript $jp$ indicates the $j$-th systemic peripheral compartment. Blood
and tissues are assumed to form a combined homogenous blood-tissue compartment that
is characterized by gas concentrations $C_{jp,\text{gas}}$ and total volume given by the sum of the
tissue volume $V_{T,jp}$ and the blood volume $V_{jp}$ of the corresponding systemic peripheral
compartment by which it is supplied. Oxygen consumption and carbon dioxide production
are assumed to happen within these combined blood-tissue compartments at constant
rates, $M_{O_2,jp}$ and $M_{CO_2,jp}$, respectively. Venous blood concentrations $C_{v,\text{gas}}$ are
computed by applying conservation of mass principles to each compartment shown in Fig.
9, under perfectly-mixed phase assumption and considering that $M_{O_2,j}$ and $M_{CO_2,j}$ are
set. The complete set of equations governing the model is reported in the Appendix
section.

**The Cardiovascular Control Model**

The cardiovascular control model includes the main short-term regulation
mechanisms (time duration < 1-2 min) that act on the cardiovascular function in response
to acute hemodynamic and blood gas composition perturbations. The model is based on
the previous work of Ursino and Magosso (44,69) and a high-level schematic block
diagram highlighting its input-output interconnections is shown in Fig. 10. Briefly, the
model includes the action of carotid sinus baroreceptors, peripheral chemoreceptors, lung
stretch receptors, autoregulation mechanisms and a CNS directly mediated ischemic
response. The afferent information coming from baroreceptors, chemoreceptors and lung
stretch receptors is first processed at the level of the Autonomic Nervous System (ANS),
which in turn modulates sympathetic and parasympathetic activities in the neural efferent
pathways. Sympathetic and parasympathetic neural fibers, then, control the
cardiovascular system via modifications of heart period ($HP$), maximum ventricular
contractilities ($E_{\text{max},lv}$ and $E_{\text{max},rv}$), resistances of the systemic peripheral beds ($R_{jp}$)
and systemic venous unstressed volumes ($V_{u,jp}$). The heart period is assumed to depend
on a balance between sympathetic and parasympathetic activities, whereas all other
effectors are assumed under the control of sympathetic fibers only. Circulation in the
most vital vascular beds, i.e, the coronary and the brain compartments, is assumed to be
independent of the ANS modulation, being only affected by local autoregulation
mechanisms. Finally, the effect of a CNS ischemic response is modeled by assuming that
arterial blood gas partial pressures ($P_{aO_2}$ and $P_{aCO_2}$) can alter the sensitivity of the
efferent sympathetic fibers to the stimuli coming from the afferent receptors (baroreceptors, chemoreceptors and lung stretch receptors).

The mathematical equations governing the model have been taken from (44,69), where detailed explanation can be found. However, the equations pertaining to the afferent peripheral chemoreceptors pathway (see Fig. 10) have been replaced with a more detailed model proposed in (68). Motivations for this choice have been reported in a previous paper (2) and more details are included in the next section, since this model is also used in the respiratory control module.

The Respiratory Control Model

The respiratory control model includes both the peripheral and the central chemoreceptors. Reflexes arising from mechanoreceptors, such as the Hering-Breuer reflexes, are not taken into account as these are believed to play a major role only at high tidal volumes. A schematic block diagram of the model is shown in Fig. 11. The central chemoreceptors are assumed to be sensitive to arterial $P_{CO_2}$, whereas the peripheral chemoreceptors are assumed to be sensitive to both arterial $P_{O_2}$ and $P_{CO_2}$. The central and peripheral chemoreceptors directly affect the respiratory frequency, $RR$, and the amplitude of the respiratory muscle pressure generator, $P_{mus,min}$ (see The Respiratory System Model section). This inclusion is an essential feature that differentiates our integrated cardiopulmonary model from other large scale models presented in literature. The majority of these models, in fact, assumes that chemoreceptors act on the respiratory system either by directly changing minute ventilation $V_e$ (9,11,44,70) or by modifying tidal volume $V_T$ and respiratory rate $RR$ (19,20), hence ultimately affecting minute ventilation. In these models, a set of static or dynamic equations coupling $P_{aO_2}$ and $P_{aCO_2}$ (or some surrogates of these variables) to $V_e$ (or $V_T$ and $RR$) is used to describe the entire respiratory control system, bypassing the physiological link between chemoreceptors and respiratory muscles. Very few models account for the relationship between blood gas contents and respiratory efforts (26,42,43), expressed in terms of either intrapleural pressure $P_{pl}$ or respiratory muscle pressure $P_{mus}$, and even fewer make a distinction between mechanisms affecting respiratory efforts amplitude and mechanisms affecting respiratory rate (42,43).

As supported by experimental studies performed on humans (61), there is no active interaction included in the model between the two distinct central and peripheral chemoreceptor mechanisms. Hence, the central and the peripheral contributions to the ventilation response, in terms of variations in $RR$ and $P_{mus,min}$, are assumed to be additive. Contributions from the chemoreceptors are then added to the basal values of $RR$ and $P_{mus,min}$ generated by the intrinsic respiratory rhythm generator that produces a wakefulness drive when chemoreceptors are not stimulated.

A detailed description of the input-output relationships of the central and peripheral chemoreflex has been provided in a previous paper (2) and complete equations are reported in the Appendix section. Briefly, the central chemoreceptor mechanism is described as a first-order dynamic system with a pure delay, having as input the variation
of $P_{CO_2}$ in the arterial blood with respect to a set-point value $P_{aCO_2,n}$. The peripheral chemoreflex, on the other hand, is described as a two-stage transduction mechanism where $P_{aO_2}$ and $P_{aCO_2}$ are first transduced into electrical activity of the peripheral chemoreceptor fibers, $f_{apc}$, that is then converted into variations of amplitude and frequency of the respiratory muscle generator. The first-stage transduction mechanism obeys the same model of the afferent peripheral chemoreceptor pathway, proposed by Ursino and Magosso (68), which has been used in the cardiovascular control model. This takes into account a multiplicative interaction between $O_2$ and $CO_2$ at the peripheral chemoreceptor level and it has been validated using experimental data from animals under a variety of combined $O_2$ and $CO_2$ stimuli. The second stage is described via relationships analogous to those used for the central chemoreceptors (that is, as a first-order dynamic system with a pure delay), the input being the variations in $f_{apc}$ with respect to a set-point value $f_{apc,n}$.

Parameter Assignment

All the parameters of the CP Model have been assigned with reference to a 70-Kg healthy subject. Most of them are based on previous studies, but some have been modified or newly introduced. They are summarized in Tables I-VII, along with the corresponding literature references when applicable. In the following sections, the choice of the parameter values for each subsystem will be discussed with particular emphasis on the new parameters and their modifications with respect to previous studies.

Vascular System

The parameters of the uncontrolled vascular system model have been taken from (44,69), where detailed justifications about their values can be found. However, some parameters needed to be adjusted or defined to reflect the aforementioned modifications (see Model Development section) introduced to the original model structure presented in these previous works. Particularly: 1) Resistance and compliance values of the pulmonary peripheral and pulmonary shunt compartments have been assigned to reflect the fact that 1.7% of the total blood flow coming out of the pulmonary arteries ($Q_{pa}$ in Fig. 2) enters the pulmonary shunts and the remaining 98.3% enters the pulmonary capillaries (33). Furthermore, it has been assumed that the parallel arrangement of pulmonary shunt and pulmonary peripheral compartments provides the equivalent resistance and compliance values as used in (44,69). 2) The values of the thoracic veins parameters have been given based on (9,49). 3) As a consequence of the introduction of the thoracic veins compartment, the venous compliance values in all the parallel systemic districts have been reduced by 30% relative to the values used in (44,69), so that the total venous compliance is maintained as suggested in (45). 4) To compensate for the added excess volume due to the introduction of the negative intrapleural pressure, the basal value of the unstressed volume in every vascular compartment within the thoracic cavity has been reduced by 12% relative to the values used in the previous studies (44,69). 5) The
compliance of the overall systemic peripheral circulation has been redistributed among the five parallel districts in order to guarantee realistic and valid simulation results based on literature. All the parameters characterizing the uncontrolled vascular system in basal condition (without the action of the regulatory mechanisms) are reported in Table I and II, along with their corresponding reference source.

**Heart**

The parameters characterizing the heart model have been given the same value used in previous studies (44,67,69). For the sake of brevity, these parameters are not listed here and the interested reader can refer to the previous studies for the details.

**Lung Mechanics**

The parameters of the lung mechanics model (resistances, compliances and unstressed volumes of the four respiratory mechanics compartments) have been assigned starting from values reported in (26,55). However, some adjustments have been made in order to account for the newly introduced pleural pressure and chest wall dynamics and to reproduce realistic simulated lung volumes typically observed in normal subjects under quiet breathing conditions. Particularly: 1) The chest wall compliance $C_{cw}$, not included in (26,55), has been assigned a value based on (71). 2) The amplitude and frequency of the respiratory muscle pressure generator $P_{mus}$ in basal conditions (without the action of the respiratory control model) have been assigned in order to attain a tidal volume of about 500 mL and a respiratory rate of 12 breaths/min (72); 3) The initial conditions for the five different pressure nodes in Fig. 6 (state variables) have been assigned assuming that at time $t = 0$ corresponding to the end exhalation time, all the pressures in the lungs equilibrate to atmospheric pressure whereas the intrapleural pressure has a subatmospheric value of -5 cmH$_2$O (72); 4) The unstressed volume of the alveolar compartment has been modified in order to produce an end expiratory lung volume equal to normal functional residual capacity (FRC), based on the following equation:

$$V_{u,A} = FRC + C_A \cdot P_{p,EE} - V_{l,EE} - V_{l,EE} - V_{b,EE}$$ (6)

where $P_{p,EE}$ is the pleural pressure value at end exhalation, $V_{l,EE}$, $V_{l,EE}$ and $V_{b,EE}$ represent the end-expiratory volumes of the larynx, trachea and bronchea, respectively, and FRC is 2.4 L (72). 5) Finally, the value of the time constant $\tau$, governing the exponential expiratory $P_{mus}$ profile, has been assumed to be equal to 1/5 of the expiratory time to allow enough time for lung emptying, and a value of 0.6 has been used for the inspiratory-expiratory time ratio based on the fact that the normal physiological $IE_{ratio}$ is between 1:2 and 1:1.5 (52). All the parameters of the lung mechanics model are reported in Table III, along with their corresponding reference source when applicable.
The parameters describing the gas exchange and transport model can be subdivided into parameters pertaining to the lung gas exchange model, parameters pertaining to the tissue gas exchange model, and parameters pertaining to blood transport, i.e. the two circulatory transport delays $\tau_{LT}$ and $\tau_{VL}$ (see Fig. 7).

The parameters characterizing the lung gas exchange model can be further divided into 3 different groups: 1) parameters pertaining to the environmental conditions (e.g. atmospheric pressure, $O_2$ and $CO_2$ gas fractions in air, and saturated water vapor pressure at body temperature), which have been given typical values under the assumption of normal environmental conditions; 2) parameters pertaining to the $O_2$ and $CO_2$ dissociation curves, which have been taken from (60); 3) parameters pertaining to the physiological status of the subject (percentage of pulmonary shunts, $sh$, and hemoglobin content, $Hgb$), which have been chosen to simulate a 70 Kg healthy adult male. The values of the parameters are reported in Table IV for each group.

As for the tissue gas exchange model, the only parameters involved are the tissue volumes ($V_{T,jp}$) and the $O_2$ and $CO_2$ metabolic rates ($M_{O_2,jp}$ and $M_{CO_2,jp}$), where $j$ corresponds to the different combined blood-tissue compartments. The values of $V_{T,jp}$ have been assigned based on literature data, whereas the values of the metabolic rates have been assigned as follows. First, the values of $M_{O_2}$ for the brain, coronary and skeletal muscle compartments have been taken from (44,69). Then, the values of $M_{O_2}$ for the splanchnic and extrasplanchnic compartments have been given based on the assumption that total $O_2$ consumption rate is 250 mL/min (33) and that the ratio $M_{O_2,sp}/M_{O_2,ep}$ is 7.384 (12). Finally, the values of $M_{CO_2}$ for the different compartments have been computed by assuming that the total $CO_2$ production rate is 210 mL/min (33), corresponding to a respiratory quotient of 0.84, and that the $M_{CO_2}$ ratio between compartment $i$ and compartment $j$ is equal to the corresponding $M_{O_2}$ ratio between the same compartments.

The values of the blood transport delays have been assigned from literature. Some adjustments were made in order to reflect the fact that part of the circulatory delay has been explicitly taken into account in the venous pool transport model. Particularly, the time delay from lungs to tissue, $\tau_{LT}$, has been given the same value used in (43) and (66).

As for the veins to lungs time delay, $\tau_{VL}$, a value of 10 sec has been chosen considering that a value of 25 sec has been used in the model by Lu et al. (43) for the overall tissue-to-lungs delay. This choice is then equivalent to the assumption that a time delay of around 15 sec can be attributed to the systemic and the thoracic veins compartments. All the parameters of the tissue gas exchange model are reported in Table V, along with the corresponding reference source.

Respiratory Control

As we mentioned in the Model Development section, the majority of the ventilation control models presented in the literature assumes a very simplified structure of the
respiratory control system. Hence, assignment of the parameters pertaining to the respiratory control model based on previous models available in literature was not always possible. When no reference values were available, the parameters were then calibrated so as to fit experimental data obtained from healthy volunteers under specific respiratory challenges (53,54).

Referring to Fig. 11, the choice of the respiratory control model parameters is now explained in detail.

1) All the parameters of the 1st stage transduction mechanism in the peripheral chemoreceptor model, equivalent to the model presented by Ursino and Magosso (68), have been maintained to their original values in (68).

2) The values of the central and peripheral chemoreflex time delays ($D_c$ and $D_p$, respectively) as well as the set point values for $P_{aCO_2}$ and $f_{apc}$ have been taken from (44).

3) The two time constants ($\tau_{p,A}$ and $\tau_{p,f}$) and two gains ($G_{p,A}$ and $G_{p,f}$) of the peripheral chemoreceptors model, for which reference values were not available, were calibrated based on the experimental data from isocapnic hypoxia (reduced O$_2$ with controlled CO$_2$) experiments reported by Reynolds and Milhorn (54). These data show the response to a 10-minute step input from room air to an 8% O$_2$ mixture (hypoxia) of a group of 10 healthy male volunteers in terms of tidal volume ($V_t$), respiratory rate ($RR$), minute ventilation ($V_e$), alveolar O$_2$ partial pressure ($P_{AO_2}$) and alveolar CO$_2$ partial pressure ($P_{ACO_2}$). During the experiments, alveolar CO$_2$ partial pressure was artificially controlled (isocapnia) and kept at a normal physiological value below chemoreceptor activation threshold. In order to calibrate the four aforementioned parameters, similar experimental conditions were replicated in the CP Model: the hypoxic stimulus was simulated by imposing a $F_{iO_2}$ step input from 21% (room air) to 8% with the same duration as that one used in the experiments (10 minutes), whereas the isocapnic condition was simulated by including a negative feedback controller that changed $F_{iCO_2}$ level dynamically in order to maintain $P_{ACO_2}$ at its normal range (around 40 ±2 mmHg (14)). Multiple isocapnic hypoxia simulations were run, starting with default guessed values of the unknown parameters and using the errors between the model predicted $V_t$ and $RR$ waveforms and the corresponding experimental data to guide the parameters’ fine-tuning. As shown in Fig. 12, the problem of fine-tuning the time constants and gains of the peripheral chemoreceptors model can indeed be approached as a typical system identification problem. The system is excited with a step input ($F_{iO_2}$) and the responses ($V_t$ and $RR$) are measured. Due to the isocapnic condition, the central chemoreceptors are not stimulated and the measured responses are entirely due to the activation of the peripheral chemoreceptors. Hence, the only unknown parameters to be identified are the two time constants ($\tau_{p,A}$ and $\tau_{p,f}$) and the two gains ($G_{p,A}$ and $G_{p,f}$) in the peripheral chemoreceptors model, while all other parameters remain fixed. Note that despite the availability of numerical techniques to solve this specific system identification problem, the fine-tuning of the model parameters was performed manually because our goal was only to achieve qualitative agreement between model-simulated and experimental data. In fact, trying to obtain a strict quantitative agreement was scientifically irrelevant, due to
the large variability of responses existing even among healthy subjects.

4) The two time constants ($\tau_{c,A}$ and $\tau_{c,f}$) and two gains ($G_{c,A}$ and $G_{c,f}$) of the central chemoreceptors model, for which it was not possible to obtain reference values from literature, were also assigned following a process similar to the one described above (for the time constants and gains of the peripherhal chemeoreceptors). In this case, the unknown parameters were calibrated based on the experimental data reported by Reynolds et al. (53) related to hypercapnic conditions (increased CO$_2$). The data contain the average respiratory responses (time profiles of $V_T$, $RR$, $V_e$, $P_{AO_2}$ and $P_{ACO_2}$) observed across 14 subjects after a 25-minute hypercapnic step input from normal room air to 7% CO$_2$. Similarly to what is described above, in order to assign the unknown parameters, the experimental conditions were first simulated in the CP Model starting with guessed default values for $\tau_{c,A}$, $\tau_{c,f}$, $G_{c,A}$ and $G_{c,f}$. Then, an iterative calibration process was performed, where the errors between model outputs ($V_T$ and $RR$) and experimental data were used to guide parameter fine tuning. Throughout this process, the parameters of the peripheral chemoreceptors model were fixed to the values found in the previous calibration step. Again, the problem of fine-tuning the parameters is seen as a typical system identification problem (see Fig. 13), where the system is excited with a known step input ($F_{I,CO_2}$) and the responses ($V_T$ and $RR$) are measured. Note that in this case, unlike the isocapnic hypoxia case above, where only the peripheral chemoreceptors were activated, the $V_T$ and $RR$ responses are determined by contributions from both the central and peripheral chemoreflex mechanisms. However, since the parameters of the peripheral chemoreceptors model were maintained fixed throughout the calibration process, it was still possible to isolate the contribution from the central chemoreceptors and identify the parameters that allowed to fit the experimental results. Note that even in this case, during the parameter adjustment process, only qualitative agreement between model predictions and experimental data was sought and no attempt to minimize the corresponding error via numerical techniques was made.

All the parameters of the respiratory control model are provided in Table VI, along with the corresponding reference source when applicable. The results from the hypercapnia and isocapnic hypoxia simulations, obtained via the parameter calibration procedures described above, are included in the companion paper (8).

Cardiovascular Control

Since the cardiovascular control model is formally equivalent to the models by Ursino and Magosso (44,69), except for the afferent peripheral chemoreceptors pathway that is based on (68), all of its parameters have been taken from these previous models (44,68,69). However, some of the parameters related to the autoregulation mechanism and the balance of the afferent information from the different receptors, operated at the level of the ANS, have been modified with respect to their original values presented in (44,69). This was necessary in order to reproduce the typical cardiovascular response to hypercapnia and hypoxia observed in the healthy population and reported in the literature (3,38,47,62). In fact, simulations of hypercapnia and hypoxia using the nominal
parameter values reported in (44,69) produced cardiovascular responses that were not in agreement with the experimental data reported in the literature, particularly in terms of heart rate (HR) and arterial blood pressure (ABP) changes. Hence, a sensitivity analysis (SA) of the impact of model parameters on cardiovascular outputs during hypercapnia and hypoxia was conducted to assess which parameters contributed the most to the above mentioned discrepancies between model-predicted and experimental responses. Particularly, the parameters of the cardiovascular control model were ranked based on the local sensitivity matrix according to the procedure suggested by Ellwein et al. (22).

As a result of this SA, 11 parameters were identified as the most sensitive and their values were modified compared to their initial values proposed in (44,69). Here, for the sake of brevity, the details of the SA procedure are not reported and only the values of the modified parameters are listed in Table VII. The interested reader can refer to previous publications (44,68,69) for a list of the additional unchanged parameters. The comparison between model simulated responses to hypoxia and hypercapnia with the experimental counterparts are shown in the companion paper (8).

Results

The combined model has 78 differential equations, more than 70 algebraic equations and 240 parameters associated with its components. Table VIII shows the distribution of the state variables, model parameters and main outputs of this integrated cardiopulmonary model. The model was programmed in Matlab-Simulink (The Mathworks Inc.) and the numerical integration of the differential equations was performed using the 4th order Runge-Kutta method with fixed-step size.

A reasonable reproduction of variables typically observed on a general healthy adult population is the basis for further applications of our integrated cardiopulmonary model. To verify the ability of the present model in these regards, we analyze the model's predicted outputs in normal resting conditions and we present a comparison with waveforms or average values typically observed in humans. Particularly, our analysis includes the model behavior both in terms of mean values, i.e. averaged values over a respiratory or cardiac cycle, and intra-cycle (respiratory or cardiac cycle) values. In presenting the results, major emphasis is put on the new aspects of the model compared to previous work (44,69). All model results are based on 1000-sec simulations using the parameter values reported in Table I-VII.

Hemodynamics

Table IX summarizes the static values of the relevant clinical hemodynamic variables that the CP model generates, and compares them with values typically measured on healthy humans in normal resting conditions. The table shows that the model-predicted outputs are within normal physiological ranges of the general population.

Figure 14 shows a representative simulated left ventricle P-V loop, along with the pressure and volume time profiles over an entire cardiac cycle. The model is thus able to
capture the typical features of a realistic P-V loop, both in terms of shape and amplitude. For the specific cardiac cycle shown in the figure, the left ventricular volume ranged from 132 mL (end-diastolic volume) to 53 mL (end-systolic volume) providing a stroke volume of 79 mL and an ejection fraction of 79/132, or 59%. Note that these values slightly change from one cardiac cycle to the next because of variations of intrapleural pressure and the effects of cardiovascular control mechanisms that induce cyclic changes in heart rate, ventricular contractility and afterload.

Figure 15 compares model-generated left and right ventricular output flows to experimental waveforms (43). Both the amplitude and duration of the simulated flow waveforms resemble the experimental data. The left ventricular flow has a higher peak value and shorter time duration compared with the right ventricular flow. For the specific cardiac cycle shown in Fig. 15, the left ventricle peak flow is 688.5 mL/s and the right ventricle peak flow is 484.5 mL/s; the left ventricle ejection phase lasts for 0.192 s, whereas the right ventricle ejection phase lasts for 0.252 s. This is due to the greater contractility and higher afterload of the left ventricle, as compared to the right. Numerical integration of the flow waveforms over the entire cardiac cycle gives the values of left and right ventricular stroke volume as 79.21 mL and 79.32 mL, respectively. Hence, despite the dissimilarities in amplitude and time duration, the areas enclosed by the two waveforms are essentially the same.

**Respiratory Mechanics**

Figure 16 shows the pressure and flow waveforms generated by the lung mechanics model in normal resting conditions, when the chemoreceptors are silent and RR and $P_{\text{mus, min}}$ are equal to their basal values. At the beginning of inspiration, alveolar pressure equals atmospheric pressure, i.e. zero pressure. During inspiration, the negative $P_{\text{mus}}$ drives pleural pressure to decrease from its resting value of -5 cmH$_2$O to about -8 cmH$_2$O, which in turn decreases alveolar pressure below atmospheric value and allows air to flow into the mouth, trachea, bronchae and alveoli. At the end of inspiration, when the respiratory muscles start relaxing, pleural pressure returns to its baseline value and alveolar pressure becomes slightly positive allowing air to flow out of the lung. The tidal volume produced by the model is approximately 540 mL, 40 mL of which are spent in ventilating the dead space and the remaining flowing into the alveoli to participate to gas exchange (see Fig. 16). This is in agreement with normal physiological behavior under quiet breathing conditions (72).

Figure 17 compares a model-simulated airflow waveform during a typical breathing cycle to an experimental tracing from a normal subject. As evident from Fig. 17a, the simulated inspiratory flow pattern has the typical dome shape that has been reported in the literature (51), with the peak flow being reached early in the inspiratory part of the cycle. However, some discrepancies between simulated and experimental data can be observed in terms of time and amplitude of the maximum and minimum peak flow. These discrepancies could be ascribed to the high intra-subject variability in the respiratory patterns and, as shown in Fig. 17b, can be reduced via slight modifications of some of the parameters of the respiratory muscle pressure model (e.g. $P_{\text{mus, min0}}, IE_{\text{ratio}}$ and $\tau$).
Figure 18 shows the comparison between a model-simulated pleural pressure waveform and an experimental tracing of intrapleural pressure from a dog during spontaneous breathing conditions. Again, even though some discrepancies can be observed in terms of timing and amplitude of pleural pressure swings, Fig. 18 shows that the model-simulated intrapleural pressure dynamics resemble those observed in vivo.

**Gas Exchange and Transport**

The main outputs of the gas exchange and transport model are summarized in Table X in terms of their mean values over one respiratory cycle and compared with typical values in resting healthy humans. Furthermore, in Figs. 19-22, the time profiles of partial pressures at different levels throughout the cardiopulmonary system are shown. Particularly, Fig. 19 shows the variation of arterial $O_2$ and $CO_2$ partial pressures, along with the lung volume waveform. Arterial $P_{O_2}$ and $P_{CO_2}$ are relatively constant and oscillate around their mean values, 98.9 and 39.55 mmHg respectively (see Table X), in synchrony with the respiratory cycle. Arterial $P_{O_2}$ varies from 96.93 to 100.8 mmHg, it increases during inhalation and decreases during exhalation. The opposite is valid for $P_{acO_2}$, which oscillates between 37.89 and 41.06 mmHg. The mean values of the simulated $P_{aO_2}$ and $P_{acO_2}$ waveforms are in agreement with the values typically observed in healthy humans from arterial blood gas analysis (ABG test) during normal resting conditions (see Table X). Comparison of model generated $P_{aO_2}$ and $P_{acO_2}$ fluctuations with corresponding human data is more difficult to obtain due to the lack of continuous $P_{aO_2}$ and $P_{acO_2}$ measurements available in the literature. However, $P_{aO_2}$ fluctuations of $\pm$ 1-4 mmHg in synchrony with the respiratory cycle and in the same direction as those generated by the model have been reported in animal studies performed on cats and lambs. Furthermore, the magnitudes of the model generated fluctuations agree with those reported in previous simulation studies (24,39). It is worth noticing that cardiogenic oscillations are present in the simulated $P_{aO_2}$ and $P_{acO_2}$ profiles, a phenomenon that has been reported by previous investigators as well (24,26). This is essentially due to the coupling between the tidal respiratory model and the pulsatile cardiovascular model, which is an essential feature of our integrative modeling approach. Figure 20 shows the variations of blood gas composition in the venous section in terms of partial pressure. Variations of $P_{vO_2}$ and $P_{vCO_2}$, like those in arterial $P_{O_2}$ and $P_{CO_2}$, are affected by the respiratory cycle events, but the effects of blood pulsatility are less evident due to the filtering introduced by the venous circulation. The mean values of $P_{vO_2}$ and $P_{vCO_2}$ are also in the typical ranges observed in normal resting subjects (see Table X). Figure 21 shows the comparison between model-simulated alveolar $P_{O_2}$ and $P_{CO_2}$ waveforms and their expected physiological counterparts as shown in physiology textbooks (14,26). Clearly, the dynamics predicted by the model are different from their physiological counterparts. For instance, the simulated waveforms contain higher-frequency dynamics that can be attributed to cardiogenic events, in addition to lower frequency variations that are related to the respiratory events. This generates the appearance, in the simulated $P_{O_2}$ and $P_{CO_2}$ waveforms, of plateau phases superimposed to monotonic fall and rise periods in synchrony with the respiratory events.
In contrast, the physiological counterparts do not contain the aforementioned high-frequency dynamics, as the effects of blood pulsatility are typically ignored in traditional physiology textbooks. Nevertheless, the overall trend of the simulated $P_{O_2}$ and $P_{CO_2}$ waveforms with respect to the respiratory cycle events is in agreement with the expected behavior reported in the literature. Particularly, at the beginning of the inspiratory phase, alveolar $P_{CO_2}$ rises to a maximum and $P_{O_2}$ drops to a minimum; this represents the period during which dead space air is entering the alveoli. This is followed by a period of rapidly increasing $P_{O_2}$ and falling $P_{CO_2}$, which reflects the effects of the introduction of fresh inspired air into the alveoli. The maximum $P_{O_2}$ and minimum $P_{CO_2}$ are reached toward the end of the inspiratory phase, when maximum dilution with fresh air has been achieved. During the expiratory phase, the partial pressure variations change direction, with $P_{O_2}$ progressively falling and $P_{CO_2}$ progressively rising. This reflects the effects of continued gas exchange during a period when no fresh air is supplied to the alveoli.

Finally, Fig. 22 shows a comparison between the model-generated dead space $P_{CO_2}$ and a typical time-based capnographic waveform obtained in normal adult patients over a single respiratory cycle (63). The simulated dead space $P_{CO_2}$ resembles the capnogram in terms of both shape and amplitude, even though some minor differences can be observed. First, the baseline in the simulated dead space $P_{CO_2}$ tracing is slightly above zero (see Table X), whereas the normal capnogram has a zero baseline value. Second, during the inhalation phase the capnographic waveform suddenly reaches the zero baseline value and remains flat until early exhalation; this is not the case for the simulated dead space $P_{CO_2}$ waveform, probably because the capnographic waveform is obtained by sampling the airflow at the mouth, whereas the simulated $P_{CO_2}$ waveform is representative of a lumped dead space compartment that is between the atmospheric air and the internal alveolar compartments.

**Heart-lung Interactions**

As mentioned in the *Introduction* section, heart-lung interactions take a variety of forms. Mechanical interactions are one of these forms and are mainly due to the effects of intrathoracic pressure on venous return and cardiac function. During inhalation, venous return (VR) increases due to the decreasing intrapleural pressure that produces a shift in blood volume from the systemic to the pulmonary circulation. The variations in VR are associated with variations in cardiac performance: the increased VR during inhalation improves right ventricular filling and preload, thus generating an increase in right ventricular output flow and stroke volume according to the Frank-Starling mechanism. The effects of inspiration on the left ventricle are in the opposite direction: the decreasing intrapleural pressure affects the pulmonary vasculature, which acts as a capacitance reservoir that holds more blood so that left ventricular filling is reduced with the consequent drop in left ventricular output flow and stroke volume via the Frank-Starling mechanism. The situation is reversed during expiration, when intrapleural pressure gradually returns to baseline. In this case, VR and right ventricular output flow are reduced, whereas more blood is forced from the pulmonary vasculature into the left heart and hence left ventricular output flow is increased. The variations of intrathoracic
Pressure associated with the respiratory events also have effects on systemic arterial pressure. Systolic, diastolic and pulse arterial pressures are lowest during inspiration and highest at the peak of expiration. These variations result partially from transmission of intrathoracic pressure to the ascending and thoracic aorta, and partially from the respiratory-related changes in left ventricular output flow (58), discussed above. Reductions in systolic blood pressure during inhalation of about 4-5 mmHg have been reported in the literature (58) and variations of more than 5 mmHg are considered signs of pathological conditions and are commonly referred to as “pulsus paradoxus” (48).

The present model is able to account for such mechanical interactions between heart and lungs, thanks to the inclusion of the intrapleural pressure as the reference external pressure for the vascular compartments that lie within the thoracic cavity (see Model Development section). Figure 23 shows the simulated time profiles of venous return (computed in the model as the instantaneous flow entering the right atrium), left and right ventricular output flow and stroke volume, along with the pleural pressure waveform over few representative respiratory cycles. The model-predicted hemodynamic changes driven by respiratory events are qualitatively in agreement with the physiological mechanisms described above: venous return and right ventricular stroke volume rise during inspiration and fall during exhalation, whereas left ventricular stroke volume variations have opposite direction. The model predicts an inspiratory rise in right ventricular stroke volume of about 7 mL, which agrees well with the expected variations in normal condition (5 mL according to (58)). On the other hand, the model predicted changes in left ventricular stroke volume are slightly underestimated: only 1.16 mL inspiratory fall with respect to the end-exhalation value. The effects of respiration are visible in the systemic arterial blood pressure waveform ($P_{sa}$) as well, as shown in Fig. 24 where the systolic and diastolic $P_{sa}$ values are plotted together with the pleural pressure waveform over a few consecutive respiratory cycles. The model-predicted changes in systolic and diastolic blood pressure are qualitatively in agreement with the expected behavior: systolic and diastolic blood pressure drop during inhalation and rise during exhalation. However, even in this case, the model-predicted variations are smaller than what is typically observed in normal subjects: 0.7 mmHg model-predicted reduction in systolic blood pressure, corresponding to about 0.5% of the end-exhalation value, as compared to 4 mmHg and 3% variation in normal subjects (58). Possible reasons for such discrepancy between model results and experimental observations will be explained in the Discussion section and these aspects might be the subject of future study.

Another well-known physiological mechanism of cardiorespiratory interactions is the respiratory sinus arrhythmia (RSA). RSA is a naturally occurring variation in heart rate ($HR$) in synchrony with the respiratory cycle, whereby $HR$ increases during inhalation and decreases during exhalation. The model, in its present form and with its nominal parameter values, is able to partially reproduce RSA by capturing only certain aspects of the phenomenon. Particularly, the model-simulated $HR$ does vary within a respiratory cycle, but the magnitude of the variations (0.8 beats/min) is underestimated compared to what is typically observed in normal subjects under resting conditions (about 5 beats/min). Furthermore, the timing of the model-simulated $HR$ variations is slightly out of phase with respect to the respiratory events, resulting in $HR$ decrease during inhalation.
Manipulations of some model parameters (e.g. reduction of the basal respiratory rate $RR_0$) have shown to be effective in improving both the amplitude and the timing mismatches, with slight effects on the model-simulated respiratory and gas exchange variables (moderate $P_{aO_2}$ increase and $P_{aCO_2}$ decrease with respect to their normal baseline values). Due to the preliminary nature of these results we have decided not to cover these aspects in the present paper and leave the RSA topic as the subject of future investigations, as will be mentioned in the Discussion section.

**Discussion**

This paper presents an integrated mathematical model of the cardiovascular and respiratory systems and their interactions. It comprises the following physiological systems and mechanisms: heart (four chambers), systemic circulation (arteries, five peripheral and five venous compartments), pulmonary circulation (arteries, vessels, veins, and shunt), lung mechanics (larynx, trachea, bronchi, alveoli, pleural cavity, and diaphragmatic muscle), thoracic cavity, autonomic nervous system (sympathetic and vagal), local autoregulation, central nervous system ischemic response, as well as gas exchange (lung and tissue) including Bohr and Haldane effects. It is the fruit of a multi-year effort and is presented in two papers: the present paper describes the model development and verification under normal physiological conditions, while the companion one (8) describes the response under hypercapnic and hypoxic conditions. The model contains close to 150 equations divided almost equally between ordinary differential and algebraic equations. The results suggest good fidelity between the model’s output and published human data in normo-physiological (see Figs. 15, 17, 18, 21, 22 and Tables IX, X) as well as hypercapnic and hypoxic conditions (companion paper). There are close to 70 state variables that can be outputted, or observed, from the model (like pressures, flows, and gas concentrations) and around 240 parameters that represent physical properties and geometry of the anatomy (like alveolar compliance, bronchial resistance, left ventricular elastance, and systemic vascular resistance).

To facilitate its usage, the model has been coupled with a stand-alone Graphical User Interface (GUI). This allows the user to directly interact with the model via a web application (http://cardiopulmonarymodel.com/).

The main aspects that deserve a discussion are the integrative nature of the model, and the potential benefits of its future applications for the physiological/clinical community.

Most previous models focused on a single aspect of the overall cardiorespiratory system (such as respiratory mechanics, cardiovascular regulation, or ventilation control). The main objective of the present work is to combine these partial descriptions and allow the cardiorespiratory dynamics to ensue from an integrated model, consisting of many sub-systems that are mixed and continuously influence each other in a multi-feedback, multi-scale arrangement. This fully integrative perspective will unfold more of the richness and complexity of the cardiovascular system. A possible concern is that the model contains too many parameters (about 240) to be really fitted to any individual subject. This
criticism is certainly correct. However, we think that tailoring the model to individual cases does not require all parameters to be fine-tuned, but only those that are crucial to the specific physiological aspects under investigation. For instance, if the objective of a study is to investigate individual variability in ventilation, only parameters characterizing respiratory mechanics and ventilation control can be tuned. The model can simulate individual variations in these aspects, and then can furnish indications on how a change in respiratory mechanics and ventilation is reflected in the other parts of the model (cardiac, metabolic, hemodynamical, etc.) still assumed in the prototypical configuration.

The present model has many potential applications. First, it can be used as an educational tool, to illustrate and explain the complexity of the cardiorespiratory relationships, and the possible consequences of specific parameter changes. To this regard, the high number of parameters constitutes an advantage rather than a limitation of the model, providing a more complete illustration of many aspects at the anatomical, physiological and functional level.

Second, the model can be used as a research tool to elucidate the physiological reasons for the variability of cardiorespiratory quantities observed across different individuals in healthy condition. For instance, assuming that some parameters can vary within a physiological range in healthy individuals, the model can produce a range of physiological waveforms for each different parameter set. In other words, model complexity can be exploited to explain this intrinsic “irregularity” of the healthy condition, a crucial aspect in physiology and clinics, which often lacks a rigorous scientific characterization.

Another important application of the model is the analysis of cardiorespiratory responses to acute perturbations (posture change, metabolic alteration, hemorrhage, change in air gas content, etc.). In fact, one function of feedback regulatory mechanisms (that represent an essential part of the present model) is to cope with acute changes of the internal, or external, environment, in order to regulate vital and metabolic functions. An example will be illustrated in the second companion paper (8), devoted to a thorough investigation of the model response to hypoxia and hypercapnia.

Finally, an important future use of the model is to simulate and analyze cardiorespiratory pathologies. This aspect, however, requires future validation studies. In the present paper and in the second companion one, we have not investigated pathological conditions: all simulations were performed using a single parameter set, representing a generic healthy individual. Hence, we have no present validation on disease states. Nevertheless, we claim that the model has the potential to investigate pathological conditions, thanks to two important features. First, we incorporated a multitude of physiological mechanisms in a single theoretical setting, providing a more complete description than any previous comparable model. Second, all model parameters have a clear physiological/functional meaning. This may allow the description of pathologies to be implemented on the basis of a true physiological knowledge, in an effort to reproduce where and how a disease affects the cardiopulmonary system. All these aspects can have enormous impacts, both in education programs and, in perspective, in helping clinical reasoning. Application of the model to the simulation of diseases will require a) understanding which parameters may be potentially affected by the pathology; b) testing the effect of these parameter changes in the model; c) comparing the modified
model waveforms with data available from clinical measurements.

Once the model has been used to simulate a specific pathology, it may then be used to simulate therapeutic interventions. Interventions, on the other hand, can only be simulated if the appropriate therapy has an input path to one of the sub-models. For instance, a mechanical ventilator has a direct path to the lung mechanics sub-model.

Finally, if enough knowledge is not available to fully characterize a pathology in terms of mechanisms involved and parameter values, the model may be used as a reverse engineering tool. For instance, one can try to identify which parameter changes produce derangements of vital quantities in agreement with clinical observations, and generate new physiological hypotheses about the origins of a specific pathology.

Now that we have described the salient characteristics of the model, it is equally important to discuss its main limitations. Limitations discussed below will be targets of future improvements.

First, the model does not include several organs and regulatory mechanisms that affect the cardiopulmonary system. Particularly: 1) It does not possess a kidney and no fluid balance is computed; we have not included equations for fluid exchange at the capillaries, under hydraulic and oncotic pressure gradients. Hence, the blood volume is constant, and the only way to modify it is via a hemorrhagic shock. 2) The model focuses on short-term regulation and hence does not include long-term control mechanisms like the Renin-Angiotensin-Aldosterone system. 3) The metabolism module is limited to constant metabolic rates of the different organs and does not include acid-base balance. 4) There is no thermoregulation and no thermal nor humidity factors affect the lungs.

In addition, as pointed out in the Results section, the effects of respiration on arterial blood pressure and left ventricular stroke volume are slightly underestimated. This discrepancy may be due to the fact that the present model does not account for ventricular interdependence via the septum, which may play an important role in explaining the reduced left ventricular stroke volume during inhalation. The left and right ventricles, in fact, share a common pericardial space and are separated by a mobile intraventricular septum. When the right ventricular diastolic volume increases during inhalation, the septum tends to shift to the left, reducing left ventricular compliance and causing a further reduction in stroke volume (25). Another reason for the underestimated effects of respiration on systemic arterial pressure may be related to the fact that the lumped systemic arterial compartment in the model is not subject to intrapleural pressure, whereas in reality the ascending and the thoracic aorta are within the thoracic cavity and hence are directly affected by intrapleural pressure variations. Further expansion of the model to specifically address these limitations is envisioned.

Finally, the model is unable to fully reproduce the physiological RSA phenomenon (see Results section). To this regard, it is worth mentioning that the physiological origins of RSA are still arguments of debate in the physiological community. The two current competing theories are: 1) RSA is the result of baroreflex mediated variations in HR, triggered by the blood pressure fluctuations associated with the respiratory events (21); 2) RSA is a centrally mediated mechanism independent of baroreflex activation (21). Thus, if the central origin theory was confirmed, the discrepancy between model-simulated RSA and the corresponding physiological observations, pointed out in the Results section, might be
justified since the present model does not include such mechanism and hence would certainly not be able to account for it. On the other hand, if the baroreflex was solely responsible for the origin of RSA, then in principle the model should be able to correctly reproduce RSA. Hence, justification of the aforementioned discrepancy would be more challenging. These, along with the effects of parameter modifications (e.g. basal respiratory rate $RR_0$) on the simulated RSA, will be the topic of further investigation and future model development.

In conclusion, we have developed a novel integrated cardiopulmonary model. The level of rigor included in each sub-model reflects current available knowledge. The author’s hope is to contribute to the understanding of our cardiopulmonary system in a deterministic way, so we can better quantify our physiological knowledge and ultimately make more informed clinical decisions, leading to a better quality of life.
APPENDIX

In the following section a quantitative description of the model is provided. Only equations concerning the new aspects of the model and the modifications introduced with respect to the previous models upon which the present one is build are presented. They describe the circulatory system, the lung mechanics, the lung gas exchange, the tissue gas exchange and venous pool gas transport, and the respiratory control.

**The Circulatory System**

The equations describing the circulatory system have been obtained by enforcing conservation of mass and balance of forces for each vascular compartment in Fig. 2.

**Systemic Circulation:**

\[
C_{sa} \cdot \frac{dP_{sa}}{dt} = Q_{lv,o} - Q_{sa} \tag{A-1}
\]

\[
L_{sa} \cdot \frac{dQ_{sa}}{dt} = P_{sa} - P_{ep} - R_{sa} \cdot Q_{sa} \tag{A-2}
\]

\[
V_{sa} = C_{sa} \cdot P_{sa} + V_{u,sa} \tag{A-3}
\]

\[
C_{p,eq} \cdot \frac{dP_{ep}}{dt} = Q_{sa} - \sum_j Q_{jp} \tag{A-4}
\]

\[
P_{ep} = P_{sp} = P_{mp} = P_{bp} = P_{hp} \tag{A-5}
\]

\[
Q_{jp} = \begin{cases} 
\frac{P_{jp} - P_{jv}}{R_{jp}} & P_{jp} \geq P_{jv} \\
0 & P_{jp} < P_{jv} 
\end{cases} \tag{A-6}
\]

\[
V_{jp} = C_{jp} \cdot P_{jp} + V_{u,jp} \tag{A-7}
\]

\[
C_{sv} \cdot \frac{dP_{sv}}{dt} + \frac{dV_{u,sv}}{dt} = Q_{sp} - Q_{sv} \tag{A-8}
\]

\[
C_{mv} \cdot \frac{dP_{mv}}{dt} + \frac{dV_{u,mv}}{dt} = Q_{mp} - Q_{mv} \tag{A-9}
\]

\[
C_{hv} \cdot \frac{dP_{hv}}{dt} = Q_{hp} - Q_{hv} \tag{A-10}
\]

\[
P_{ev} = \frac{1}{C_{ev}} \cdot [V_{tot} - V_{sa} - V_{hp} - V_{bp} - V_{mp} - V_{sp} - V_{ep} - V_{hv} - V_{bv} - V_{mv} - V_{sv} - \\
V_{tv} - V_{ra} - V_{rv} - V_{hv} - V_{bv} - V_{mv} - V_{sv} - V_{tv} - V_{ra} - V_{rv} - V_{pa} - V_{pp} - V_{ps} - V_{pv} - \\
V_{la} - V_{tv} - V_{u,ev}] \tag{A-12}
\]
\[ Q_{jv} = \begin{cases} \frac{p_{jv} - p_{tv}}{R_{jv}} & \text{if } p_{jv} \geq p_{tv} \\ 0 & \text{if } p_{jv} < p_{tv} \end{cases} \quad (A-13) \]

\[ V_{jv} = C_{jv} \cdot p_{jv} + V_{u,jv} \quad (A-14) \]

\[ \frac{dV_{tv}}{dt} = \Sigma_j Q_{jv} - Q_{tv} \quad (A-15) \]

\[ Q_{tv} = \frac{p_{tv} - p_{ra}}{R_{tv}} \quad (A-16) \]

\[ p_{tv} = p_{pl} + p_{tm, tv} \quad (A-17) \]

where \( j = e, s, m, b, h \) indicates the specific systemic compartment, \( C_{p, eq} = \sum_j C_{jp} \) is the equivalent peripheral compliance given by the parallel arrangement of the 5 different systemic peripheral compartments and \( p_{tm, tv} \) is given by Eq. 2 (see Model Development section). Note that for the extrasplanchnic systemic veins pressure, \( p_{ev} \), the conservation of mass equation has been replaced by an algebraic compatibility equation (Eq. A-12) in order to guarantee that the total volume of blood (\( V_{tot} \)) contained in the cardiovascular system is constant at any time during the simulations.

**Pulmonary Circulation:**

\[ C_{pa} \cdot \frac{d(p_{pa} - p_{pl})}{dt} = Q_{rv, o} - Q_{pa} \quad (A-18) \]

\[ L_{pa} \cdot \frac{dQ_{pa}}{dt} = p_{pa} - p_{pp} - R_{pa} \cdot Q_{pa} \quad (A-19) \]

\[ V_{pa} = C_{pa} \cdot (p_{pa} - p_{pl}) + V_{u,pa} \quad (A-20) \]

\[ (C_{ps} + C_{pp}) \cdot \frac{d(p_{pp} - p_{pl})}{dt} = Q_{pa} - Q_{ps} - Q_{pp} \quad (A-21) \]

\[ Q_{pp} = \frac{p_{pp} - p_{pv}}{R_{pp}} \quad (A-22) \]

\[ Q_{ps} = \frac{p_{ps} - p_{pv}}{R_{ps}} \quad (A-23) \]

\[ p_{ps} = p_{pp} \quad (A-24) \]

\[ V_{pp} = C_{pp} \cdot (p_{pp} - p_{pl}) + V_{u,pp} \quad (A-25) \]

\[ V_{ps} = C_{ps} \cdot (p_{ps} - p_{pl}) + V_{u,ps} \quad (A-26) \]

\[ C_{pv} \cdot \frac{d(p_{pv} - p_{pl})}{dt} = Q_{pp} + Q_{ps} - Q_{pv} \quad (A-27) \]

\[ Q_{pv} = \frac{p_{pv} - p_{la}}{R_{pv}} \quad (A-28) \]
\[ V_{pv} = C_{pv} \cdot (P_{pv} - P_{p1}) + V_{u,pv} \]  

\[(A-29)\]

**The Heart**

The equations describing the heart model are formally equivalent to those reported in (44,69), but modifications have been introduced in order to account for the presence of intrathoracic pressure.

**The Lung Mechanics**

The equations describing the lung mechanics model have been obtained by applying conservation of mass to the electrical analog shown in Fig. 6.

\[ C_l \cdot \frac{dP_l}{dt} = \frac{P_{ao} - P_l}{R_{ml}} - \frac{P_l - P_{tr}}{R_{lt}} \]  

\[(A-30)\]

\[ C_{tr} \cdot \frac{d(P_{tr} - P_{pl})}{dt} = \frac{P_l - P_{tr}}{R_{lt}} - \frac{P_{tr} - P_b}{R_{tb}} \]  

\[(A-31)\]

\[ C_b \cdot \frac{d(P_b - P_{pl})}{dt} = \frac{P_{tr} - P_b}{R_{tb}} - \frac{P_b - P_A}{R_{bA}} \]  

\[(A-32)\]

\[ C_A \cdot \frac{d(P_A - P_{pl})}{dt} = \frac{P_b - P_A}{R_{bA}} \]  

\[(A-33)\]

\[ C_{cw} \cdot \frac{d(P_{pl} - P_{mus})}{dt} = \frac{P_l - P_{tr}}{R_{lt}} \]  

\[(A-34)\]

\[ \dot{V} = \frac{P_{ao} - P_l}{R_{ml}} \]  

\[(A-35)\]

\[ \dot{V}_A = \frac{P_l - P_{tr}}{R_{lt}} \]  

\[(A-36)\]

\[ V_l = C_l \cdot P_l + V_{u,l} \]  

\[(A-37)\]

\[ V_{tr} = C_{tr} \cdot (P_{tr} - P_{pl}) + V_{u,lr} \]  

\[(A-38)\]

\[ V_b = C_b \cdot (P_b - P_{pl}) + V_{u,b} \]  

\[(A-39)\]

\[ V_A = C_A \cdot (P_A - P_{pl}) + V_{u,A} \]  

\[(A-40)\]

\[ V_D = V_l + V_{tr} + V_b \]  

\[(A-41)\]

The equations describing the profile of the respiratory muscle generator \( P_{mus} \) have been provided in the *Model Development* section (see Eq. 4).

**Lung Gas Exchange**

\[ V_D \cdot \frac{dF_{D,02}}{dt} = u(\dot{V}) \cdot \dot{V} \cdot (F_{I,02} - F_{D,02}) \]

\[ +u(-\dot{V}) \cdot \dot{V}_A \cdot (F_{D,02} - F_{A,02}) \]

\[(A-42)\]
blood, and Eq. A-56 is used to compute \( O_2 \) saturation in the arterial blood.

Note: \( \theta \) is the Heaviside step function and it is introduced to make Eqs. A-42, A-43, A-44, A-45 valid both during inhalation and exhalation; \( K \) is a proportionality constant that allows to convert volumes from BTPS (body temperature pressure saturated) to STPD (standard temperature pressure dry) conditions; the term 1.34 in Eq. A-56 is the oxygen capacity (expressed in ml of \( O_2 \) per g of Hgb) and the term 0.003/100 represents the solubility of \( O_2 \) in blood (expressed in ml of \( O_2 \) per ml of blood per mmHg).

**Tissue Gas Exchange**

The complete equations describing the tissue gas exchange model are the following:

\[
(V_{T,hp} + V_{hp}) \cdot \frac{dc_{hp,O2}}{dt} = Q_{hp,in} \cdot (\tilde{C}_{a,O2} - C_{hp,O2}) - M_{O2, hp}
\]

(A-57)

\[
(V_{T,bp} + V_{bp}) \cdot \frac{dc_{bp,O2}}{dt} = Q_{bp,in} \cdot (\tilde{C}_{a,O2} - C_{bp,O2}) + M_{CO2, hp}
\]

(A-58)

\[
(V_{T,bp} + V_{bp}) \cdot \frac{dc_{bp, CO2}}{dt} = Q_{bp,in} \cdot (\tilde{C}_{a, CO2} - C_{bp, CO2}) - M_{O2, bp}
\]

(A-59)

\[
(V_{T,mp} + V_{mp}) \cdot \frac{dc_{mp,O2}}{dt} = Q_{mp,in} \cdot (\tilde{C}_{a,O2} - C_{mp,O2}) - M_{O2, mp}
\]

(A-60)

\[
(V_{T,mp} + V_{mp}) \cdot \frac{dc_{mp, CO2}}{dt} = Q_{mp,in} \cdot (\tilde{C}_{a, CO2} - C_{mp, CO2}) + M_{CO2, mp}
\]

(A-61)

\[
(V_{T,ep} + V_{ep}) \cdot \frac{dc_{ep,O2}}{dt} = Q_{ep,in} \cdot (\tilde{C}_{a,O2} - C_{ep,O2}) - M_{O2, ep}
\]

(A-62)

\[
(V_{T,ep} + V_{ep}) \cdot \frac{dc_{ep, CO2}}{dt} = Q_{ep,in} \cdot (\tilde{C}_{a, CO2} - C_{ep, CO2}) + M_{CO2, ep}
\]

(A-63)

\[
(V_{T,sp} + V_{sp}) \cdot \frac{dc_{sp,O2}}{dt} = Q_{sp,in} \cdot (\tilde{C}_{a,O2} - C_{sp,O2}) - M_{O2, sp}
\]

(A-64)

\[
(V_{T,sp} + V_{sp}) \cdot \frac{dc_{sp, CO2}}{dt} = Q_{sp,in} \cdot (\tilde{C}_{a, CO2} - C_{sp, CO2}) + M_{CO2, sp}
\]

(A-65)
where $Q_{j,p,in}$ is the blood flow entering the $j$-th peripheral compartment (see Fig. 9 legend for further definition of subscripts).

**Venous Pool Gas Transport**

\[ V_{hv} \cdot \frac{dC_{hv,O2}}{dt} = Q_{hp} \cdot (C_{hp,O2} - C_{hv,O2}) \]  
\[ V_{hv} \cdot \frac{dC_{hv,CO2}}{dt} = Q_{hp} \cdot (C_{hp,CO2} - C_{hv,CO2}) \]  
\[ V_{bv} \cdot \frac{dC_{bv,O2}}{dt} = Q_{bp} \cdot (C_{bp,O2} - C_{bv,O2}) \]  
\[ V_{bv} \cdot \frac{dC_{bv,CO2}}{dt} = Q_{bp} \cdot (C_{bp,CO2} - C_{bv,CO2}) \]  
\[ V_{mv} \cdot \frac{dC_{mv,O2}}{dt} = Q_{mp} \cdot (C_{mp,O2} - C_{mv,O2}) \]  
\[ V_{mv} \cdot \frac{dC_{mv,CO2}}{dt} = Q_{mp} \cdot (C_{mp,CO2} - C_{mv,CO2}) \]  
\[ V_{ev} \cdot \frac{dC_{ev,O2}}{dt} = Q_{ep} \cdot (C_{ep,O2} - C_{ev,O2}) \]  
\[ V_{ev} \cdot \frac{dC_{ev,CO2}}{dt} = Q_{ep} \cdot (C_{ep,CO2} - C_{ev,CO2}) \]  
\[ V_{sv} \cdot \frac{dC_{sv,O2}}{dt} = Q_{sp} \cdot (C_{sp,O2} - C_{sv,O2}) \]  
\[ V_{sv} \cdot \frac{dC_{sv,CO2}}{dt} = Q_{sp} \cdot (C_{sp,CO2} - C_{sv,CO2}) \]

**Respiratory Control**

The respiratory control model affects the respiratory system via modifications in the amplitude, $P_{mus,min}$, and the frequency, $RR$, of the respiratory muscle pressure generator $P_{mus}$ (see Fig. 11), according to:

\[ P_{mus,min} = P_{mus,min0} + \Delta P_{mus,min} + \Delta P_{mus,min} \]  
\[ RR = RR_0 + \Delta RR_c + \Delta RR_p \]
where $P_{\text{mus, min}0}$ is the basal value of the respiratory muscle pressure amplitude, $RR_0$ is the basal value of the respiratory muscle pressure frequency, $\Delta RR_c$ and $\Delta P_{\text{mus, min}c}$ are the variations in respiratory rate and respiratory muscle pressure amplitude induced by the central chemoreceptors, and $\Delta RR_p$ and $\Delta P_{\text{mus, min}p}$ are the variations in respiratory rate and respiratory muscle pressure amplitude induced by the peripheral chemoreceptors.

The central chemoreceptors mechanism has been described as a first-order dynamic system, whose input-output relationships are governed by the following equations (2):

$$\frac{d\Delta P_{\text{mus, min}c}}{dt} = \frac{-\Delta P_{\text{mus, min}c} + G_{cA} u_c}{\tau_{cA}}$$  \hspace{1cm} (A-81)$$
$$\frac{d\Delta RR_c}{dt} = \frac{-\Delta RR_c + G_{cf} u_c}{\tau_{cf}}$$  \hspace{1cm} (A-82)$$

with $u_c(t) = P_{aCO2}(t - D_c) - P_{aCO2,n}$

where $D_c$ is a delay that accounts for the time it takes to blood to travel from the systemic arteries to the central chemosensitive area in the brain, $G_{cf}$ and $G_{cA}$ are the gains of the $P_{\text{mus}}$ amplitude and frequency control mechanisms, respectively, $\tau_{cf}$ and $\tau_{cA}$ are the corresponding time constants and $P_{aCO2,n}$ is the arterial $O_2$ partial pressure set-point value.

The peripheral chemoreceptors mechanism has been described as a two-stage transduction mechanism (see Model Development section). The 1st stage has been taken from previous work (68), where complete equations are provided. The 2nd stage has been described similarly to the central mechanism as the first-order dynamic system (2) as below:

$$\frac{d\Delta P_{\text{mus, min}p}}{dt} = \frac{-\Delta P_{\text{mus, min}p} + G_{pA} u_p}{\tau_{pA}}$$  \hspace{1cm} (A-83)$$
$$\frac{d\Delta RR_p}{dt} = \frac{-\Delta RR_p + G_{pf} u_p}{\tau_{pf}}$$  \hspace{1cm} (A-84)$$

with $u_p(t) = f_{aCP}(t - D_p) - f_{aCP,n}$

where $D_p$ is a delay that accounts for the time it takes to blood to travel from the systemic arteries to the peripheral chemosensitive area, $G_{pf}$ and $G_{pA}$ are the gains of the $P_{\text{mus}}$ amplitude and frequency control mechanisms, respectively, $\tau_{pf}$ and $\tau_{pA}$ are the corresponding time constants and $f_{aCP,n}$ is the afferent peripheral chemoreceptor activity set-point value.

**Cardiovascular Control**

The equations describing the cardiovascular control model are taken from (44,69). The only modification is in the description of the afferent peripheral chemoreceptor
mechanism, as described in the *Model Development* section.
References


Figure Legend

Fig. 1. Block diagram of the CP Model. $C_{wO2}$ and $C_{wCO2}$, O$_2$ and CO$_2$ gas concentrations in the venous blood, respectively; $P_{aO2}$ and $P_{aCO2}$, O$_2$ and CO$_2$ arterial blood partial pressures, respectively; $ABP$, arterial blood pressure; $P_{pl}$, pleural pressure; $P_{mus}$, respiratory muscle pressure.

Fig. 2. Schematic diagram of the cardiovascular system model. $P$, pressure; $Q$, blood flow; $MV$, mitral valve; $AV$, aortic valve; $TV$, tricuspid valve; $PV$, pulmonary valve. Subscripts: $la$, left atrium; $lv$, left ventricle; $lv, o$, left ventricle output; $sa$, systemic arteries; $sp$, splanchnic peripheral compartment; $sv$, splanchnic veins; $ep$, extrasplanchnic peripheral compartment; $ev$, extrasplanchnic veins; $mp$, skeletal muscle peripheral compartment; $mv$, skeletal muscle veins; $bp$, brain peripheral compartment; $bv$, brain veins; $hp$, coronary peripheral compartment; $hv$, coronary veins; $tv$, thoracic veins; $ra$, right atrium; $rv$, right ventricle; $rv, o$, right ventricle output; $pa$, pulmonary artery; $pp$, pulmonary peripheral circulation; $sh$, pulmonary shunt; $pv$, pulmonary veins; $pl$, pleural space.

Fig. 3. Single-compartment windkessel-type model. $P$, intravascular pressure; $Q$, outgoing blood flow rate; $R$, resistance; $C$, compliance; $L$, inertance; $j$, $j+1$, $j-1$, compartment index; $P_{ref}$, extravascular pressure reference (atmospheric pressure or intrapleural pressure, depending on the location of $j$).

Fig. 4. Typical $PV$ relationship of a blood vessel. $PC$, transmural pressure; $V_c$, volume; $V_{cu}$, unstressed volume. Reproduced from (65).

Fig. 5. $PV$ relationship of the thoracic veins compartment according to Eq. 2. $P_{tm, tv}$, transmural pressure; $V_{tv}$, volume; $V_{lu, tv}$, unstressed volume; $K_{sv}$, volume below which $\Psi$ becomes dominant.

Fig. 6. Lung mechanics model. $P$, pressure; $R$, resistance; $C$, compliance; $\dot{V}$, total air flow; $\dot{V}_a$, alveolar air flow. Subscripts: $ao$, airway opening; $l$, larynx; $tr$, trachea; $b$, bronchae; $A$, alveoli; $pl$, pleural space; $cw$, chest wall.

Fig. 7. Schematic diagram of the gas exchange and transport model highlighting the alveolar and tissue components, the venous pool gas transport block and the blood transport delays. $C_{a,gas}$, arterial blood gas concentrations; $C_{v,gas}$, mixed venous blood gas concentrations; $\tau_{LT}$, transport delay from lungs to systemic tissues; $\tau_{VL}$, transport delay from thoracic veins to lungs; $\hat{C}_{a,gas}$, gas concentrations in the blood that enters the tissue gas exchanger; $\hat{C}_{v,gas}$, gas concentrations in the blood that enters the lung gas exchanger; $\dot{V}_{O2}$ and $\dot{V}_{CO2}$, O$_2$ and CO$_2$ gas flow between alveoli and pulmonary capillaries, respectively; $M_{O2}$ and $M_{CO2}$, metabolic O$_2$ consumption and CO$_2$ production rates in the systemic tissues, respectively. The subscript $gas$ indicates either O$_2$ or CO$_2$.

Fig. 8. Schematic diagram of the lung gas exchange model. $\dot{V}$, total air flow; $\dot{V}_a$, alveolar air flow; $V_d$, dead space volume; $V_A$, alveolar volume; $F_{i,gas}$, gas fractions in the inspired air; $F_{d,gas}$, gas fractions in the dead space; $F_{a,gas}$, gas fractions in the alveoli; $\dot{V}_{O2}$ and $\dot{V}_{CO2}$, O$_2$ and CO$_2$ gas flow between alveoli and pulmonary capillaries, respectively; $C_{v,gas}$, gas concentrations in the blood that enters the pulmonary capillaries; $C_{pp,gas}$, gas concentrations in the pulmonary capillaries; $C_{a,gas}$, gas concentrations in the arterial blood; $Q_{pa}$, blood flow from the pulmonary arteries; $sh$, shunt percentage; $Q_{pp}$, blood flow at the exit of the pulmonary capillaries; $Q_{sh}$, blood flow at the exit of the pulmonary shunt compartment.

Fig. 9. Schematic diagram of the tissue gas exchange and venous pool gas transport model. $\hat{C}_{a,gas}$, gas concentration at the entrance of the systemic peripheral compartments; $C_{p,p,gas}$, gas concentration in the $j$-th combined blood-tissue compartment; $C_{v,gas}$, gas concentrations in the $j$-th systemic venous
Fig. 15. Model-predicted flows (continuous line) compared with reported experimental data (dotted line). Diastolic and the end-systolic pressure/volume functions, respectively. The two dotted lines tangent to the P-V loop at the point 1 and 3 represent the stroke volume SV and the opening and closing points of the heart valves: 1, mitral valve opening point; 2, aortic valve opening point; 3, aortic valve closing point; 4, mitral valve closing point. The four cardiac phases (a, b, c and d) are shown along with the stroke volume SV and the opening and closing points of the heart valves: 1, mitral valve opening point; 2, aortic valve opening point; 3, aortic valve closing point; 4, mitral valve closing point. The two dotted lines tangent to the P-V loop at the point 1 and 3 represent the diastolic and the end-systolic pressure/volume functions, respectively.
Top: left ventricle output flow \((Q_{lv,o})\). Bottom: right ventricle output flow \((Q_{rv,o})\). The experimental data have been redrawn from Fig. 7 of (43).

Fig. 16. Pressure, volume and flow waveforms generated by the lung mechanics model. (A) From top to bottom: Respiratory muscle pressure \((P_{mus})\), pleural pressure \((P_{pt})\), alveolar pressure \((P_A)\) and air flow. (B) From top to bottom: Lung volume \((V_L)\), alveolar volume \((V_A)\) and dead space volume \((V_D)\).

Fig. 17. Comparison between simulated and experimental airflow waveforms. Dashed line: pneumotachogram from a normal subject showing patterns of flow in quiet mouth breathing; reproduced from (51). Continuous line: model generated airflow. (A) Simulated data obtained using the nominal parameter values reported in Table III; (B) Simulated data obtained after modifying the parameters \(P_{mus,mino}, I_{Eratio}\) and \(\tau\) in the respiratory muscle pressure generator model.

Fig. 18. Comparison between simulated and experimental pleural pressure waveforms. (A) Tracing of pleural pressure from a dog in supine position during spontaneous breathing; reproduced from (16). (B) Model generated pleural pressure waveform. Note that the time division in both figures is 1 sec and the scales of the two figures have been adjusted to allow for visual comparison.

Fig. 19. Time profiles of model generated arterial \(O_2\) and \(CO_2\) partial pressures. From top to bottom: total lung volume \((V_L)\), partial pressure of oxygen in the arterial blood \((P_{aO2})\) and partial pressure of carbon dioxide in the arterial blood \((P_{aCO2})\).

Fig. 20. Time profiles of model generated mixed venous \(O_2\) and \(CO_2\) partial pressures. From top to bottom: total lung volume \((V_L)\), partial pressure of oxygen in the mixed venous blood \((P_{vO2})\) and partial pressure of carbon dioxide in the mixed venous blood \((P_{vCO2})\).

Fig. 21. Time profiles of \(O_2\) and \(CO_2\) partial pressures in the alveolar space during a respiratory cycle. Top figure: model simulations; Bottom figure: expected behavior from literature (14,26).

Fig. 22. Comparison between model generated \(CO_2\) partial pressure in the dead space (top figure) and a representative normal time-based capnogram (bottom figure)(63).

Fig. 23. Mechanical effects of respiration on cardiovascular function. From top to bottom: time profiles of intrapleural pressure \((P_{pt})\), venous return \((VR)\), right ventricular output flow \((Q_{rv,o})\), right ventricular stroke volume \((SVr)\), left ventricular output flow \((Q_{lv,o})\) and left ventricular stroke volume \((SVl)\).

Fig. 24. Mechanical effects of respiration on systemic arterial pressure. From top to bottom: time profiles of intrapleural pressure \((P_{pt})\), systemic arterial pressure \((P_{sa})\), systolic blood pressure \((SBP)\) and diastolic blood pressure \((DBP)\).
Lung Gas Exchange

Arterial Blood

\( \dot{V}_{CO_2} \)

\( \dot{V}_{O_2} \)

Venous Blood

\( \tilde{C}_{v,gas} \)

\( \tau_v \)

Venous Pool Gas Transport

\( C_{v,gas} \)

Tissue Gas Exchange

\( \tilde{C}_{a,gas} \)

\( M_{CO_2} \)

\( M_{O_2} \)

Arterial Blood

\( C_{a,gas} \)

\( \tau_L \)
## TABLE I
PARAMETERS OF THE VASCULAR SYSTEM IN BASAL CONDITION (Eqs. A-1-A-29 in Appendix)

<table>
<thead>
<tr>
<th>Compliance, ml/mmHg</th>
<th>Unstressed Volume, ml</th>
<th>Resistance, mmHg \cdot s \cdot ml^{-1}</th>
<th>Inertance, mmHg \cdot s^2 \cdot ml^{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{sa}$ = 0.28 (69)</td>
<td>$V_{u,sa} = 0$ (69)</td>
<td>$R_{sa} = 0.06$ (69)</td>
<td>$L_{sa} = 0.22 \times 10^{-3}$ (69)</td>
</tr>
<tr>
<td>$C_{sp}$ = 1.1532 [MODEL]</td>
<td>$V_{u,sp} = 274.4$ (69)</td>
<td>$R_{sp0} = 2.49$ (69)</td>
<td></td>
</tr>
<tr>
<td>$C_{ep}$ = 0.8184 [MODEL]</td>
<td>$V_{u,ep} = 134.64$ (69)</td>
<td>$R_{ep0} = 1.35$ (69)</td>
<td></td>
</tr>
<tr>
<td>$C_{mp}$ = 0.1488 [MODEL]</td>
<td>$V_{u,mp} = 24$ (69)</td>
<td>$R_{mp0} = 19.71$ (69)</td>
<td></td>
</tr>
<tr>
<td>$C_{hp}$ = 0.8184 [MODEL]</td>
<td>$V_{u,hp} = 10.73$ (69)</td>
<td>$R_{hp,n} = 6.6667$ (69)</td>
<td></td>
</tr>
<tr>
<td>$C_{bp}$ = 0.0788 [MODEL]</td>
<td>$V_{u,bp} = 50.26$ (69)</td>
<td>$R_{bp,n} = 0.038$ (69)</td>
<td></td>
</tr>
<tr>
<td>$C_{pa}$ = 0.0986 [MODEL]</td>
<td>$V_{u,pa} = 98.21$ (69)</td>
<td>$R_{pa} = 0.05$ (69)</td>
<td></td>
</tr>
<tr>
<td>$C_{pp}$ = 0.76 (69)</td>
<td>$V_{u,pp} = 0$ (69)</td>
<td>$R_{pp} = 0.023$ (69)</td>
<td></td>
</tr>
<tr>
<td>$C_{ps}$ = 0.0986 [MODEL]</td>
<td>$V_{u,ps} = 0$ (69)</td>
<td>$R_{ps} = 0.009$ (69)</td>
<td></td>
</tr>
<tr>
<td>$C_{pv}$ = 25.37 (69)</td>
<td>$V_{u,pv} = 105.6$ [MODEL]</td>
<td>$R_{pv} = 5.2588$ [MODEL]</td>
<td></td>
</tr>
</tbody>
</table>

See text and Fig. 2 for explanation of symbols and subscripts.
Note the use of subscripts 0 and n in the unstressed volumes and resistances that are subject to control mechanisms.
Total blood volume ($V_{tot}$) is 5,300 mL.
TABLE II
PARAMETERS OF THE THORACIC VEINS (Eqs. 2-3)

<table>
<thead>
<tr>
<th>PV Relationship</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_1 = 0.3855 \text{ mmHg}$ (9)</td>
<td>$K_a = 0.001 \text{ mmHg s mL}^{-1}$ (9)</td>
</tr>
<tr>
<td>$K_1 = 0.15 \text{ mmHg/mL}$ (9)</td>
<td>$V_{t,v,\text{max}} = 350 \text{ mL}$ (9)</td>
</tr>
<tr>
<td>$V_{t,v} = 130 \text{ mL}$ (9)</td>
<td>$R_{tv,0} = 0.025 \text{ mmHg s mL}^{-1}$ (9)</td>
</tr>
<tr>
<td>$D_2 = -5 \text{ mmHg}$ (9)</td>
<td>$K_{x,p} = 2 \text{ mmHg}$ (49)</td>
</tr>
<tr>
<td>$K_2 = 0.4 \text{ mmHg}$ (9)</td>
<td>$K_{x,v} = 8 \text{ mL}$ (49)</td>
</tr>
<tr>
<td>$V_{t,v} = 50 \text{ mL}$ (9)</td>
<td>$V_{t,v} = 50 \text{ mL}$ (9)</td>
</tr>
</tbody>
</table>

See text and references for explanation of symbols.
### TABLE III


<table>
<thead>
<tr>
<th>Compliance, L/cmH₂O</th>
<th>Unstressed Volume, ml</th>
<th>Resistance cmH₂O · s · L⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₁ = 0.00127 (26)</td>
<td>Vₘ₁ = 34.1 (26)</td>
<td>Rₚ₁ = 1.021 (55)</td>
</tr>
<tr>
<td>C₂ = 0.00258 (26)</td>
<td>Vₘ₂ = 6.63 (26)</td>
<td>Rₚ₂ = 0.3369 (55)</td>
</tr>
<tr>
<td>C₃ = 0.0131 (26)</td>
<td>Vₘ₃ = 18.7 (26,55)</td>
<td>Rₚ₃ = 0.3063 (55)</td>
</tr>
<tr>
<td>C₄ = 0.2 (26)</td>
<td>Vₘ₄ = 1.263 [MODEL]</td>
<td>Rₚ₄ = 0.0817 (55)</td>
</tr>
</tbody>
</table>

Additional parameters:
- Cₓₙ = 0.2445 L/cmH₂O (71) FRC = 2.4 L (72)
- RR = 12 breaths/min (72)
- IEratio = 0.6 [MODEL]
- P_LER = −5 cmH₂O (72)
- P_SAC = −5 cmH₂O [MODEL]
- τ = Tₑ/5 [MODEL]

See text and Fig.6 for explanation of symbols and subscripts.

Note the use of subscript 0 for the parameters that are subject to control mechanisms.
TABLE IV

<table>
<thead>
<tr>
<th>Environmental conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>( F_{\text{O}_2} = 21.0379 % )</td>
<td>( P_{\text{em}} = 760 \text{ mmHg} )</td>
</tr>
<tr>
<td>( F_{\text{CO}_2} = 0.0421 % )</td>
<td>( P_{\text{ex}} = 47 \text{ mmHg} )</td>
</tr>
<tr>
<td>( K = 1.2103 )</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dissociation curves (60)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{sat,O}_2} = 9 \text{ mmol/L} )</td>
<td>( C_{\text{sat,CO}_2} = 86.11 \text{ mmol/L} )</td>
</tr>
<tr>
<td>( h_1 = 0.3836 )</td>
<td>( h_2 = 1.819 )</td>
</tr>
<tr>
<td>( \alpha_1 = 0.03198 \text{ mmHg}^{-1} )</td>
<td>( \alpha_2 = 0.05591 \text{ mmHg}^{-1} )</td>
</tr>
<tr>
<td>( \beta_1 = 0.008275 \text{ mmHg}^{-1} )</td>
<td>( \beta_2 = 0.03255 \text{ mmHg}^{-1} )</td>
</tr>
<tr>
<td>( K_1 = 14.99 \text{ mmHg} )</td>
<td>( K_2 = 194.4 \text{ mmHg} )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physiological status</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{sh} = 1.7 ) (33)</td>
<td>( \text{Hgb} = 15 \text{ g/dL} ) (72)</td>
</tr>
</tbody>
</table>

See Fig.8 for explanation of symbols.
<table>
<thead>
<tr>
<th>Compartment</th>
<th>Tissue Volume ml</th>
<th>$O_2$ Consumption Rate ml/min</th>
<th>$CO_2$ Production Rate ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronaries</td>
<td>284(40)</td>
<td>24 (44.69)</td>
<td>20.16 [MODEL]</td>
</tr>
<tr>
<td>Brain</td>
<td>1300(70)</td>
<td>47.502 (44.69)</td>
<td>39.9017 [MODEL]</td>
</tr>
<tr>
<td>Skeletal Muscles</td>
<td>31200(59)</td>
<td>51.6 (44.69)</td>
<td>43.344 [MODEL]</td>
</tr>
<tr>
<td>Splanchnic</td>
<td>2673(4,28,56)</td>
<td>108.419 [MODEL]</td>
<td>91.0720 [MODEL]</td>
</tr>
<tr>
<td>Extrasplanchnic</td>
<td>262(57)</td>
<td>14.683 [MODEL]</td>
<td>12.3337 [MODEL]</td>
</tr>
</tbody>
</table>

**Blood Transport Delays**

$\tau_{LT} = 18$ s (43,66) \hspace{1cm} $\tau_{VL} = 10$ s [MODEL]
TABLE VI
PARAMETERS OF THE RESPIRATORY CONTROL MODEL (Eqs. A-79-A-84 in Appendix)

<table>
<thead>
<tr>
<th></th>
<th>Peripheral Chemoreceptors</th>
<th>Central Chemoreceptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_p$</td>
<td>7 s (44)</td>
<td></td>
</tr>
<tr>
<td>$\tau_{p,A}$</td>
<td>83 s [MODEL]</td>
<td></td>
</tr>
<tr>
<td>$G_{p,A}$</td>
<td>$1310 , \text{cmH}_2\text{O} \cdot \nu^{-1}$ [MODEL]</td>
<td>$850 , \text{cmH}_2\text{O} \cdot \text{mmHg}^{-1}$ [MODEL]</td>
</tr>
<tr>
<td>$\tau_{p,f}$</td>
<td>$147.78$ s [MODEL]</td>
<td></td>
</tr>
<tr>
<td>$f_{apc,n}$</td>
<td>3.7 spikes/s (44)</td>
<td></td>
</tr>
<tr>
<td>$D_c$</td>
<td>8 s (44)</td>
<td></td>
</tr>
<tr>
<td>$\tau_{c,A}$</td>
<td>105 s [MODEL]</td>
<td></td>
</tr>
<tr>
<td>$G_{c,A}$</td>
<td>$850 , \text{cmH}_2\text{O} \cdot \text{mmHg}^{-1}$ [MODEL]</td>
<td>$0.9$ breaths/min $\cdot$ mmHg$^{-1}$ [MODEL]</td>
</tr>
<tr>
<td>$\tau_{c,f}$</td>
<td>400 s [MODEL]</td>
<td></td>
</tr>
<tr>
<td>$P_{aCO_2,n}$</td>
<td>40 mmHg (44)</td>
<td></td>
</tr>
</tbody>
</table>

$\nu = \text{spikes/s}$. See Fig. 11 for explanation of symbols.
<table>
<thead>
<tr>
<th></th>
<th>Afferent Lung Stretch Receptors Pathway</th>
<th>Efferent Sympathetic Pathway</th>
<th>Autoregulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$G_{a sr}$</td>
<td>$= 11.76$ spikes $\cdot$ L$^{-1} \cdot$s$^{-1}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$W_{b,sp}$</td>
<td>$= -1.1375$</td>
<td>$W_{pc,sp}$ $= 1.716$</td>
<td>$g_{b,O_2}$</td>
</tr>
<tr>
<td>$W_{sr,sp}$</td>
<td>$= -1.0806$</td>
<td>$W_{sr,sp}$ $= -0.3997$</td>
<td>$g_{h,O_2}$</td>
</tr>
<tr>
<td>$W_{b,sv}$</td>
<td>$= -1.75$</td>
<td></td>
<td>$g_{m,O_2}$</td>
</tr>
<tr>
<td>$W_{b,sh}$</td>
<td>$= -1.75$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

See (44,69) for explanation of symbols.
<table>
<thead>
<tr>
<th>State Parameters</th>
<th>State Variables</th>
<th>Parameters</th>
<th>Outputs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular System</td>
<td>17</td>
<td>74</td>
<td>43</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>5</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Gas Exchange and Transport</td>
<td>26</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>Cardiovascular Control</td>
<td>26</td>
<td>104</td>
<td>8</td>
</tr>
<tr>
<td>Respiratory Control</td>
<td>4</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Variable</td>
<td>Model Simulation</td>
<td>Normal Range</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------</td>
<td>--------------------</td>
<td></td>
</tr>
<tr>
<td>Arterial Pressure mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>90.74</td>
<td>70-105 (1)</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>122.79</td>
<td>90-140 (34)</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>78.86</td>
<td>60-90 (34)</td>
<td></td>
</tr>
<tr>
<td>Venae Cavae Pressure mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>3.79</td>
<td>2-14 (34)</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>2.72</td>
<td>0-8 (34)</td>
<td></td>
</tr>
<tr>
<td>Right Atrium Pressure mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.7</td>
<td>2-6 (1)</td>
<td></td>
</tr>
<tr>
<td>Right Ventricle Pressure mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>24.45</td>
<td>15-28 (34)</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>-1.2</td>
<td>0-8 (34)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Artery Pressure mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>24.41</td>
<td>15-28 (34)</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>7.38</td>
<td>5-16 (34)</td>
<td></td>
</tr>
<tr>
<td>Left Atrium Pressure mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4</td>
<td>2-6 (1)</td>
<td></td>
</tr>
<tr>
<td>Left Ventricle Pressure mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>122.79</td>
<td>90-140 (34)</td>
<td></td>
</tr>
<tr>
<td>End-diastolic</td>
<td>0.2</td>
<td>4-12 (34)</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Model Simulation</td>
<td>Normal Value</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>Arterial $P_{O2}$ mmHg</td>
<td>98.9</td>
<td>100 (14)</td>
<td></td>
</tr>
<tr>
<td>Arterial $P_{CO2}$ mmHg</td>
<td>39.55</td>
<td>40 (14)</td>
<td></td>
</tr>
<tr>
<td>Mixed Venous $P_{O2}$ mmHg</td>
<td>42.3</td>
<td>40 (14)</td>
<td></td>
</tr>
<tr>
<td>Mixed Venous $P_{CO2}$ mmHg</td>
<td>43.5</td>
<td>46 (14)</td>
<td></td>
</tr>
<tr>
<td>Mixed Venous $C_{O2}$ mL/dL</td>
<td>15.11</td>
<td>15 (1)</td>
<td></td>
</tr>
<tr>
<td>Mixed Venous $C_{CO2}$ mL/dL</td>
<td>52.07</td>
<td>53 (5)</td>
<td></td>
</tr>
<tr>
<td>Alveolar $P_{O2}$ mmHg</td>
<td>100.7</td>
<td>104 (14)</td>
<td></td>
</tr>
<tr>
<td>Alveolar $P_{CO2}$ mmHg</td>
<td>39.5</td>
<td>40 (14)</td>
<td></td>
</tr>
<tr>
<td>Dead Space $P_{O2}$ mmHg</td>
<td>148.5*</td>
<td>149.2* (14)</td>
<td></td>
</tr>
<tr>
<td>Dead Space $P_{CO2}$ mmHg</td>
<td>1.47*</td>
<td>0.3* (14)</td>
<td></td>
</tr>
</tbody>
</table>

* Dead space $P_{O2}$ and $P_{CO2}$ values are maximum and minimum values obtained within a respiratory cycle, respectively.