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Modeling Cardio-Respiratory System Response to Inhaled CO_2 in Patients with Congestive Heart Failure

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Abstract— **In this paper we examine a cardiovascular-respiratory model of mid-level complexity designed to predict the dynamics of end-tidal carbon dioxide (CO_2) and cerebral blood flow velocity in response to a CO_2 challenge. Respiratory problems often emerge as heart function diminishes in congestive heart failure patients. To assess system function, various tests can be performed including inhalation of a higher than normal CO_2 level. CO_2 is a key quantity firstly because any perturbation in system CO_2 quickly influences ventilation (oxygen perturbations need to be more severe). Secondly, the CO_2 response gain has been associated with respiratory system control instability. Thirdly, CO_2 in a short time impacts the degree of cerebral vascular constriction, allowing for the assessment of cerebral vasculature function. The presented model can be used to study key system characteristics including cerebral vessel CO_2 reactivity and ventilatory feedback factors influencing ventilatory stability in patients with congestive heart failure. Accurate modeling of the dynamics of system response to CO_2 challenge, in conjunction with robust parameter identification of key system parameters, can help in assessing patient system status.**

I. INTRODUCTION

The respiratory and cardiovascular systems are linked in many ways resulting in complex system responses to perturbations and stresses. These links can lead to a number of clinical conditions when the pumping of the heart becomes impaired due to deterioration in heart tissue as seen in the condition known as congestive heart failure (CHF). In this paper, a model of the cardiovascular-respiratory system response to a ventilatory CO_2 challenge in patients with CHF is presented. To assess system function, a number of tests can be performed including the single breath CO_2 test and a test of continuously inhaling air with a higher than normal CO_2 level. CO_2 is a key quantity for several reasons. Firstly, perturbations in inhaled CO_2 will quickly influence respiratory chemosensors (O_2 perturbations typically need to be more severe to register an effect). Secondly, the CO_2 ventilatory response gain has been associated with respiratory system control instability. Thirdly, CO_2 impacts the degree of cerebral vascular constriction, so that altering blood CO_2 provides a way to assess cerebral vasculature function. Focusing on CHF patient physiology in the combined cardiovascular-respiratory model is motivated by interest in clinical problems that may be influenced by CO_2 responsiveness. Other cardio-respiratory modeling studies examining links between CO_2 and O_2 and cardio-respiratory behavior include [1],[2],[3],[4].

A. Respiration and chronic heart failure

When cardiac output is reduced, the time needed to transport CO_2 and O_2 levels in the lungs to the respiratory chemosensors that monitor blood gas levels is increased. These sensors are located in the carotid bodies (peripheral sensors) and in central brain tissue (central sensors). An increase in transport time implies an increased time delay in the feedback control of ventilation depending on this information. This delay can, in combination with other factors, induce instabilities in the ventilatory control system, leading to apnea, periodic breathing, disturbed sleep patterns, and sleep arousal [5], [6], [7], [8].

An increase in CO_2 in the brain will increase stimulation of the central chemosensors which in turn will support an increase in ventilation as compensation. At the same time efficient vascular vasodilation in response to increased CO_2 can lead to increased cerebral blood flow (CBF) which acts to wash out the (CO_2) induced H^+ ions that stimulate the central chemosensors. This in turn will reduce the ventilatory drive response to central stimulation, acting as a kind of buffer of the ventilatory response to increased CO_2, working to smooth that response. Recent studies [9] have investigated cerebral CO_2 reactivity in CHF for patients with sleep apnea. The results indicated that CHF patients exhibit reduced cerebrovascular response to changes in CO_2 induced through an inhalation of air with increased CO_2 content. This reduced reactivity may impede CO_2 modulation of CBF which might in turn support instabilities in breathing patterns by contributing to ventilatory overshoot during hypercapnia and undershoot during hypocapnia.

The above discussion illustrates that system interactions are complex, emphasizing the need for models that reflect the complexity and allow for evaluation of the patient status.

B. Clinical tests of respiratory function

The single breath CO_2 test can be used to assess the peripheral chemosensor response [10], [11] since the central chemosensor response occurs only after an additional transport time delay reflecting the distance between the peripheral and central sensor sites. A second test involving continuous inhalation of air with a constant 5% CO_2 level, which is the test implemented in this paper, has been used to examine normal and compromised cerebrovascular reactivity [9], [12].

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To model the inhaled CO_2 test with sufficient accuracy to allow for system evaluation, factors that influence the time constants of CO_2 dynamics must be accurately portrayed. Research and modeling studies indicate that the slower time constants involved in loading the tissue CO_2 stores influence the end-tidal observed partial pressures [13], [14], [15].

II. Modeling CO_2 and O_2 exchange

The model discussed in this paper builds on a model developed by Olufsen, Ellwein et al [16], [17], [18], extended to include details of gas tissue exchange following the pattern given in [13]. The model is a lumped parameter compartmental model based on blood flow mass balances for systemic and pulmonary arteries and veins and blood gas mass balance for general tissue and brain tissue compartments. The model is designed to predict the measurable pulsatile quantities of systemic arterial blood pressure p_{sa}, cerebral blood flow velocity CBFV, and partial pressure of expiratory CO_2 p_{exp,CO_2}. Cerebral vascular resistance was controlled via estimation of parameters connected via a piece-wise linear spline similar to the approach used in [18]. The general model is extended and adapted here to quantify responses to a 5% CO_2 inhalation test in a resting CHF patient. Hence the model can be used to examine the possibility (experimentally observed in [9]) that patients with CHF and central sleep apnea have an attenuated cerebrovascular responsiveness.

Given the focus of this study, we describe the important model features in the respiratory submodel including the addition of tissue capillary compartments to reflect time constants correctly (Fig. 1):
(a) This model takes airflow data as input and so the respiratory feedback control loop is not modeled in this initial study. However, cerebral blood velocity is predicted in response to a CO_2 challenge.
(b) Conducting tubes in the airway passages are not able to exchange CO_2 and O_2 with pulmonary capillaries. The volume of air breathed in to fill these tubes is waisted in terms of respiratory function (termed anatomical dead space). In addition some alveoli are collapsed or under-supplied with capillary blood also reducing effective air volume involved in CO_2 and O_2 exchange (termed physiological dead space). These dead spaces influence dynamics and reduce the effectiveness of ventilation since a higher dead space requires higher minute ventilation to achieve the same level of CO_2 and O_2 exchange. Hence dead space needs to be modeled.
(c) As mentioned above, the time constants reflecting the loading of CO_2 tissue stores influences dynamics and therefore capillary compartments interfacing and exchanging blood gases with the tissue compartments are included.

A. Lung compartment

The respiratory equations are provided for a generic gas (either CO_2 or O_2) since the modeling details are parallel for these two blood gases. Let A denote the alveolar compartment; then the quantity of alveolar gas is given by

$$V_{A,g} = V_A F_{A,g},$$

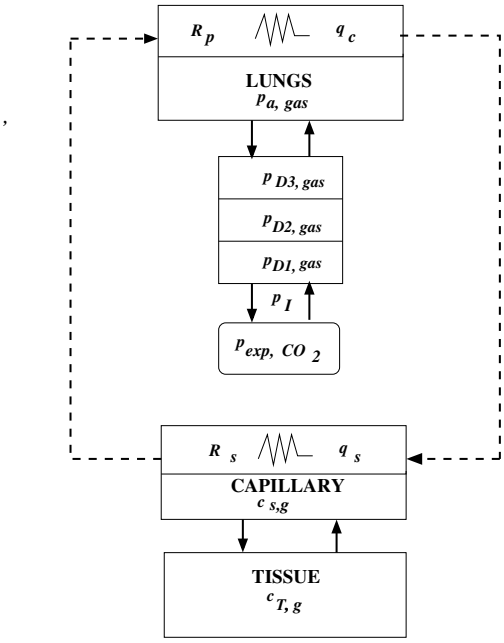

Fig. 1. Block diagram of respiratory submodel.

which is the product of alveolar volume V_A [ml] and gas fractioxn $F_{A,g}$. The change in quantity of alveolar gas is represented by a mass balance relation involving two sources of exchange. The first source involves blood gases transported to and from the lungs via the pulmonary circulation with exchange of gases by passive diffusion at the pulmonary capillary/alveoli boundary, The second source is the gas exchange with the environment carried out via inspiration and expiration. Let subscript p represent the pulmonary compartment. Reflecting these two sources of mass exchange, we arrive in a standard way at the relation:

$$\frac{dV_{A,g}}{dt} = F_{A,g}\frac{dV_A}{dt} + V_A\frac{dF_{A,g}}{dt} = \frac{dV_A}{dt}F_{i,g} + q_p(c_{v,g} - c_{a,g}).$$

In this representation $F_{i,g}$ denotes the fraction of gas in the air that is either being inspired or expired into the alveolar compartment (the i changes for inspiration and expiration). Also, c, p, and q represent concentration, partial pressure, and blood flow respectively, while subscripts a and v represent systemic arterial and venous compartments, p the pulmonary compartment, and g a generic gas. We will incorporate the anatomical dead space as described below. In the above equation $i = D_3$ indicates inspiration, since the interface with the alveolar compartment is the final dead space compartment during inspiration. That is, during inspiration, inspired air coming into the alveoli is coming from this last adjacent dead space region. We can also set $i = A$ which indicates expiration since air leaving the alveoli is alveolar air equilibrated with the pulmonary capillaries.

Conversion to partial pressures in the gas phase is via the ideal gas law. We also convert blood gas values in STPD to units of BTPS (hence the coefficient 863) appropriate for the lung compartment. In addition, we assume a 2% shunt in pulmonary blood flow. This can be taken to reflect leakage

of blood from the right to left heart chambers, thereby being diverted from the pulmonary reaching the capillary network. It can also reflect alveolar physiological dead space (loss of gas exchange due to collapsed alveoli or alveoli without adequate exposure to capillary flow). Therefore only 98% of the cardiac output is assumed to become oxygenated and reduced in CO_2 content. Collecting these observations we arrive at the following expression (background details can be found at [16], [19].

$$V_A \frac{dp_{A,g}}{dt} = \begin{cases} \text{during inspiration:} \\ \frac{dV_A}{dt}(p_{D_3,g} - p_{A,g}) \\ \qquad +0.98 \cdot 863 q_p (c_{v,g} - c_{a,g}), \\ \text{during expiration:} \\ 0.98 \cdot 863 q_p (c_{v,g} - c_{a,g}). \end{cases} \quad (1)$$

The thin alveolar wall allows for almost immediate equilibration of gases between the alveoli denoted by A and the pulmonary capillaries; thus we assume that the concentrations of blood gases is the same in the pulmonary capillaries and in the systemic arteries. In terms of partial pressures we have $p_{A,g} = p_{sa,g}$ as an auxiliary equation.

Connected to the alveolar compartment are three dead space compartments of equal volume with a total volume representing anatomical dead space. Each dead space is considered a well-mixed compartment with units V_{BTPS}, in ml. Material balance equations for the dead space compartments reflect change in gas levels due to airflow, with opposite directions of flow for inspiration versus expiration. The relation $F_{A,g} = p_{A,g}/713$ holds, and equation units are all in BTPS. Thus, following in a similar way the derivation of (1) and similaar to the approach in [10] we have.

$$\begin{aligned} \text{Inspiration: } V_{D_1} \frac{dp_{D_1,g}}{dt} &= \frac{dV_A}{dt}(p_{I,g} - p_{D_1,g}), \quad (2) \\ V_{D_i} \frac{dp_{D_i,g}}{dt} &= \frac{dV_A}{dt}(p_{D_{i-1},g} - p_{D_i,g}), \text{ i=2,3.} \\ \text{Expiration: } V_{D_i} \frac{dp_{D_i,g}}{dt} &= \frac{dV_A}{dt}(p_{D_i,g} - p_{D_{i+1},g}), \text{ i=1,2,} \\ V_{D_3} \frac{dp_{D_3,g}}{dt} &= \frac{dV_A}{dt}(p_{D_3,g} - p_{sa,g}). \end{aligned}$$

Pressure $p_{I,g}$ [mmHg] is the partial pressure of the gas in the inspired air, while the subscript D_i denotes a dead space compartment. Hence during inspiration and expiration we have reversal of air flow inputs and outputs.

B. Tissue compartment

Standard mass balance equations describe respiration in the tissue compartments. The following symbol convention will be used: c represents concentration [$\text{ml}_{\text{gas}}/\text{ml}_{\text{blood}}$], subscript T represents a generic tissue compartment which can be chosen to be systemic tissue or brain tissue. Generic gas quantity is denoted by g and gas fractional amount by F. Venous flow [ml/sec] is denoted by v and arterial flow [ml/sec] by a. We denote the total amount A of a gas in a tissue compartment by $A_{T,g}$ [ml] which is given by

$$A_{T,g} = V_{T,g} c_{T,g}.$$

This equation describes $A_{T,g}$ [ml] by the product of the effective tissue volume V [ml] (constant) available for the gas and the concentration c [$\text{ml}_{\text{gas}}/\text{ml}_{\text{blood}}$] of the gas in the volume. Related to the tissue compartment T we include a capillary blood compartment (denoted by S) interfacing with the tissue compartment which then returns the gas to the blood stream leaving the capillary compartment. The change in amount of gas in the tissue compartment T depends on the amount of gas produced or consumed by metabolism M [ml/sec] and the amount added or removed by diffusion with the capillary compartment S. The change in capillary compartment S gas volume depends in turn on the removal by the bloodstream q_T [ml/sec] the gas from the capillary compartment and any diffusion of gas into or out of the tissue compartment T. For the change in gas in the generic tissue compartment we have:

$$\begin{aligned} \frac{dA_{T,g}}{dt} &= \frac{dV_{T,g}}{dt} c_{T,g} + V_{T,g} \frac{dc_{T,g}}{dt} \\ &= M_{T,g} - D_{T,g}(c_{T,g} - c_{S,g}). \end{aligned}$$

and for the change in gas in the capillary compartment, the equation includes a term for diffusion between tissue and capillary and term for mass balance of gas entering and leaving the capillary compartment via blood flow q_T:

$$\begin{aligned} \frac{dA_{S,g}}{dt} &= \frac{dV_{S,g}}{dt} c_{S,g} + V_{S,g} \frac{dc_{S,g}}{dt} \\ &= q_{T,g}(c_{a,g} - c_{S,g}) + D_{T,g}(c_{T,g} - c_{S,g}). \end{aligned}$$

In the above, $D_{T,g}$ = diffusion capacity for a gas (depends on use of partial pressures or concentrations values), $V_{T,g}$ = effective tissue volume for a gas, $V_{S,g}$ = effective capillary blood volume for a gas (approximately 1% of $V_{T,g}$), and $q_{T,g}$ = blood flow through the capillary compartment.

Note, the concentration in the systemic arteries (i.e., in the body and the brain) are the same, since no metabolism has been accounted for on this side. Hence we denote the arterial concentration for c_a [$\text{ml}_{\text{gas}}/\text{ml}_{\text{blood}}$]. Assuming $dV_{T,g}/dt = 0$, this equation reduces to the generic equation for exchange between tissue compartment and capillary blood for carbon dioxide to

$$V_{T,g} \frac{dc_{T,g}}{dt} = M_{T,g} - D_{T,g}(c_{T,g} - c_{S,g}). \quad (3)$$

and for removal of gas by capillary flow out of the tissue compartment:

$$V_{S,g} \frac{dc_{S,g}}{dt} = q_{T,g}(c_{a,g} - c_{S,g}) + D_{T,g}(c_{T,g} - c_{S,g}). \quad (4)$$

III. RESULTS

Model simulations indicate consistent and physiological behavior of all states in response to the inhaled 5% CO_2 test. Figure 2 gives end-tidal CO_2 (model and data) increasing from steady state in response to a 5% CO_2 inhalation. In this figure the model does not include capillary compartments and the simulated end-tidal CO_2 (dark blue) continues to increase compared to measured data (light blue). Figure 3 simulates end-tidal CO_2 with capillary compartments and the dynamics match the data in Figure 2. Figure 4 gives CBFV simulation

and data during 5% CO_2 inhalation (CBFV increases do to vascular dilation). These results indicate reasonable time constants and dynamic matching for the CHF patient data.

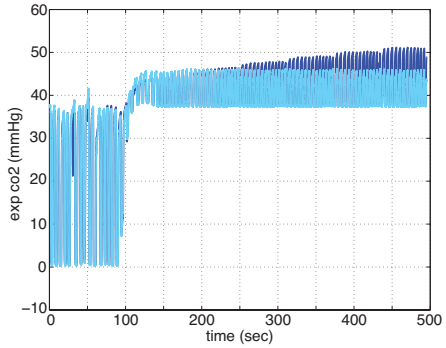

Fig. 2. End-tidal CO_2 simulation (no capillary compartment) comparison to data (simulations in dark blue). CO_2 varies with inspiration-expiration

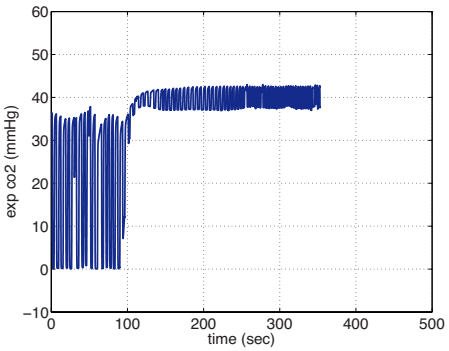

Fig. 3. End tidal CO_2 simulation (with capillary compartments).

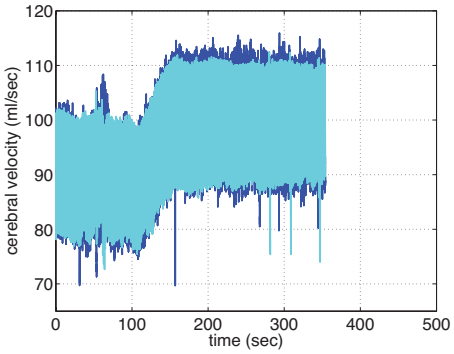

Fig. 4. Cerebral blood flow velocity simulation comparison to data (simulations in dark blue) CBFV varies with inspiration-expiration.

IV. CONCLUSIONS AND FUTURE WORKS

The model discussed here tracks both end-tidal CO_2 and cerebral blood flow velocity in response to the inhaled 5% CO_2 test in a CHF patient. Simulations indicate the need for a tissue capillary compartment to buffer the effects of slow time constants in the tissue region which will influence end-tidal dynamics. This model takes ventilatory data as input and so the feedback control loop is not modeled in this initial study. Other delays in the compartmental exchange are not included in this initial study but will be included in future work. Initial parameter estimation results will be refined using sensitivity analysis and subset selection to improve the speed and robustness of the estimates.

V. ACKNOWLEDGMENTS

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