MODELLING OF THE RESPIRATORY SYSTEM FOR EXERCISE CONDITIONS: A CASE STUDY IN PHYSIOLOGICAL SYSTEM SIMULATION

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Abstract

This paper provides a brief review of respiratory control system models and associated computer simulations for human subjects during exercise. It also describes the development of a model of the human respiratory system for a range of exercise intensities. This dynamic model, which is compartmental in form and is based on ordinary differential equations and algebraic relationships, puts particular emphasis on the representation of the individual tissue compartments and especially the skeletal muscle compartment, which is considered in particular detail. The structure of the model is described and variables of the model are discussed, highlighting those that are readily measurable in contemporary exercise experiments. The form of the model is used to help to identify possible reasons for the relative lack of success of modelling and simulation methods in this particular field of research in the past. Suggestions are also made, with illustrative examples, of ways in which experimentation and model-related activities could be more closely integrated to the benefit of future research on exercise physiology. Conclusions are presented regarding the present status of modelling and simulation methods in respiratory physiology during exercise and proposals are made for a strategy that might allow researchers to use available modelling and simulation tools more effectively.

Keywords: Respiratory system, Control, Exercise, Simulation model, Validation.

Presenting Author's biography

Husni Thamrin is a research student at University of Glasgow. He is also a member of staff at the Universitas Muhammadiyah Surakarta, Indonesia. His main research activity is in control system modelling and simulation, especially in the context of biomedical systems applications.

ISBN 978-3-901608-32-2

1 Introduction

The human body has a large number of control systems. These include neural and mechanical systems, such as those involved in the control of erect posture and body movement, as well as many chemical systems, such as those controlling the level of blood glucose and the regulation of arterial blood pressure. Most of these systems are negative feedback control systems where we can identify control actions that tend to reduce or eliminate deviations of the system output from normal levels. For example, a high concentration of blood carbon dioxide stimulates pulmonary ventilation in an attempt to restore the concentration back to normal levels. Some systems, however, contain elements of feedforward operation as is proposed by some investigators in modelling the respiratory control system during exercise.

Due to their complexity, the systems of the human body have become a focal point for much activity involving computer-based modelling and simulation. Traditional linear control theory also provides a useful framework within which to discuss physiological control mechanisms, but detailed quantitative investigation of most of these systems requires the use of computer-based methods. Engineering control systems usually operate in a more or less linear fashion under normal conditions and have identifiable and known set point values. Physiological systems, on the other hand, rarely have any identifiable set points and the normal steady-state operating condition results from nonlinear interactions between elements arranged in series and, in some cases, multiple closed loops. Among the objectives of modelling work of this kind is the testing of hypotheses about physiological systems, the analysis of dysfunctions of various kinds or the investigation of diseased conditions.

Interest in modelling in the case of exercise physiology includes, for example, gaining a more complete understanding of the mechanisms involved in the relevant physiological systems, evaluation of different strategies for training in sports and rehabilitation and assessment of levels of medication and other forms of treatment. Simulation and experimentation used together can often provide valuable insight that is difficult to obtain using experimental methods alone.

Although computer simulation techniques have been widely used in modelling some aspects of the respiratory system in humans and in other mammals, not much progress appears to have been made in using these techniques successfully in the study of the dynamic response of the cardio-respiratory system to exercise, especially over higher exercise intensities when subsystem responses typically begin to lose their original proportionality for increments in exercise rate and associated functions. The application of computer simulation techniques and control system methods of analysis to cardio-respiratory control dynamics in exercise has been confined largely to statistical modelling of experimental data sets, but with considerable success. However, there has been less work on the application of such experimental modelling methods to structural dynamic models based on putative physiological control mechanisms.

2 Models of the respiratory control system

Many models of the human respiratory system have been developed and many published examples of such models can be found (e.g.[1-4]). The precise form of these models depends on the intended application and this may range from the testing of specific hypotheses concerning clinical phenomena, such as periodic breathing, to the development of real-time simulators for medical education and training. Efforts have also been made to model sub-systems to describe some specific aspects of the system in considerable detail, for example the mechanical properties of the lungs (e.g. [5]), gas exchanging properties of the lungs (e.g. [6]), the effect of breathing higher than normal levels of CO_2 or anaesthetic gases (e.g.[7,8]), respiratory anaerobiosis in skeletal muscle [9], and respiratory control mechanisms during exercise [10,11].

What is clear from these studies is that models successfully developed for a particular application have a form that is specific to the situation being considered. Although it is possible to have a general form of model that successfully describes a physiological system for a number of different applications, those applications must be taken carefully into account during the development of the model. A single very general model is unlikely to be completely appropriate for a range of different uses. A model intended for a particular purpose must be thoroughly tested and validated for that specific application before being used. Since validation should always be applied iteratively during the model development process it is vital that all the intended applications should be taken fully into account throughout the whole process of model development and testing.

3 A model of the respiratory system under exercise conditions.

In this study, we are attempting to develop a dynamic model of the human respiratory system for the conditions of exercise across the complete range of exercise intensity. The formulation and parameter values are taken as far as possible from published literature based on the results of experimental investigations. The model is functional in form and information about the dynamic properties of each

ISBN 978-3-901608-32-2

sub-model within it has been taken directly from experimental findings and from published information. Modelling investigations of this kind have been attempted in the past, but there is no generally agreed and generally accepted simulation model available that adequately describes the comprehensive cardio-respiratory behaviour of humans during exercise. The level of exercise has been limited typically to the lowest domain, known as moderate exercise, where steady-state proportionality of the system response to the imposed work-rate increment is generally agreed to hold.

Using such a model, we may be able to discern whether a mathematical and computer-based formulation based on reported laboratory observations can match results of other observations. Deficiencies in this quantitative description should, hopefully, direct us towards the aspects of current understanding of the system that require further experimental investigation or to areas of the model that do not fully reflect the complex interactions occurring in the real system.

3.1 Model structure

The model has been developed using a number of lumped compartments. This is a simplified and idealised representation of the corresponding real system. It is intended to be applicable to cycle-ergometer exercise in healthy young subjects at sea level. In physiological terms the model, which has the structure shown in Figure 1, involves work rate as the input and partial pressures of oxygen and carbon dioxide and associated ventilation levels for oxygen and carbon dioxide as outputs. There are six main compartments and a number of time delay elements that represents the time to transport gases between muscle and lung.

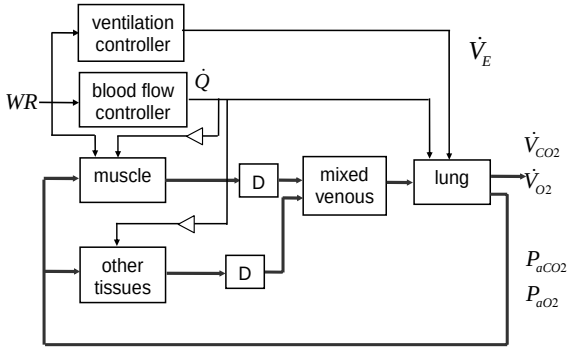

Figure 1. Block diagram of respiratory control system model for conditions of exercise below lactate threshold.

The most important of these compartments in physiological terms are a single lumped compartment representing muscle and another representing the lung. The compartment shown as "other tissues" in Figure 1 represents other parts of human body that do not play a direct and active role during exercise. The blood flow from the heart compartment (the cardiac output) depends on the exercise work rate, as do the muscle oxygen consumption and ventilation. The simplifying assumption is made that all of the increases of pulmonary oxygen uptake and cardiac output during exercise are associated with the exercising muscle compartment.

In terms of linear system theory, analysis of experimental results for moderate intensity exercise suggests that the dominant dynamic response of many of the compartments can be approximated by a single exponential. This "fundamental" component in ventilation and pulmonary gas exchange is almost always preceded by an initial transient component (e.g. [12-18]). The overall dynamic response of the system to changes in work rate is thus often described as biphasic, (i.e. having two components). The initial component of the response has been termed phase 1 with the fundamental and more dominant component being phase 2.

3.1.1 Muscle

The flow of respiratory gases, i.e. oxygen and carbon dioxide, through compartments has to obey the Fick principle, which is a form of the law of mass conservation. Thus, for the muscle compartment, the relevant equations are:

$$C_{vMO2} = C_{aMO2} - \frac{\dot{Q}_{O2}}{\dot{Q}_M}$$

$$C_{vMCO_2} = C_{aMCO_2} + \frac{\dot{Q}_{CO_2}}{\dot{Q}_M}$$

where C_{vMX} is the concentration of respiratory gas in the muscle vein, C_{aMX} is the concentration in the muscle artery, $\dot{Q}_M$ is the blood flow to the muscle compartment and $\dot{Q}_X$ is the muscle gas production or consumption, where the subscript X refers to either O_2 or CO_2.

The muscle oxygen consumption ($\dot{Q}_{O2}$) can be estimated using the measurement of phosphocreatine (PCr) turnover with Phosphorus Magnetic Resonance Spectroscopy (PMRS). For moderate exercise conditions, $\dot{Q}_{O2}$ exhibits a first-order linear system behaviour with a fundamental time constant similar to that of the oxygen uptake ($\dot{V}_{O2}$) [13,14,19]. Upon reaching a steady state, $\dot{V}_{O2}$ (and also $\dot{Q}_{O2}$) has risen by a value proportional to the exercise work rate (*WR*). Thus, in mathematical terms:

$$\Delta\dot{V}_{O2} = 10WR$$

where $\Delta\dot{V}_{O2}$ has units of ml/min and WR has units of watts [19-21].

The consumed oxygen is assumed to react instantly in the muscle producing carbon dioxide according to the equation:

$$\dot{Q}_{MCO2} = RQ.\dot{Q}_{MO2}$$

where RQ = 0.95 is the muscle respiratory quotient. Muscle has the capability to store CO_2, largely as bicarbonate. The associated transient is of first order.

3.1.2. Blood flow

Blood flow kinetics may be represented by a fundamental component involving a single exponential, but many investigators have suggested a second component involving an initial rise known as phase 1 [18,22-24]. For example, data from [18] for the case of an experiment involving a change from rest to 40W exercise suggest that the time constant for phase 1 is of the order of 5.5s and the gain is 86% of the total steady state gain. This is a significant component. Beat by beat measurements of limb blood flow confirms the biphasic nature of muscle blood flow with phase 1 settling rapidly in 3-7s with phase 2 delayed by 15-20s [24].

From the total cardiac output at rest of 5 l/min, 0.75 l/min goes to muscle and during exercise the cardiac output increment may be assumed to go entirely to the exercising muscle [25] according to the equation:

$$\Delta\dot{Q} = 0.05WR + 5$$

3.1.3. Ventilation

The ventilation $\dot{V}_E$ changes in a biphasic manner during a step increase of exercise [16]. Ventilation has been shown to be linearly related to carbon dioxide output at the mouth, $\dot{V}_{CO2}$, over a wide work-rate range [26,27]. In healthy young adults the $\dot{V}_E$-$\dot{V}_{CO2}$ slope is approximately 24.6 [28-30] with a small $\dot{V}_E$ intercept of 3.2 l/min [30]. Thus,

$$\dot{V}_E = 24.6\dot{V}_{CO2} + 3.2$$

The knowledge of $\dot{V}_E$ can then be used to calculate P_{aO2} and P_{aCO2} using the following equations:

$$P_{aCO2} = \frac{863 \cdot \dot{V}_{CO2}}{\dot{V}_E \cdot (1 - V_D / V_T)}$$

$$P_{aO2} = 147 - \frac{863 \cdot \dot{V}_{O2}}{\dot{V}_E \cdot (1 - V_D / V_T)}$$

which provide the feedback from the body compartments through the arterial blood. As the variable regarded as the effective set point quantity in the respiratory control system, it is expected that P_{aCO2} will be constant during exercise below the lactate threshold.

3.1.4. Other compartments

Fick's principle applies to gas exchange in the lung and in the compartment representing the tissues other than muscle. In that latter compartment, equations similar to those for the muscle compartment have been used.

In the mixed venous compartment, different concentrations of gases from the muscle compartment and other tissues compartments are mixed to provide the value of venous gas concentration for the blood which flows to the lung.

Blood has a capability to store oxygen and carbon dioxide. The model uses Kelman's equations found in [31,32] to represent the pressure – content relationship of gases in the blood.

4 Simulation results for moderate intensity exercise

A simulation model has been developed using MATLAB and SIMULINK for conditions of moderate exercise. Parameter values and static conditions appropriate to this type of situation have been derived from the physiological literature and a number of tests have been carried out on the simulation model for a work rate of 100W. At this level of exercise it can be assumed that the lactate threshold has not been exceeded, which means that lactate and metabolically produced protons have not accumulated in the exercising muscle or blood.

Under static conditions close correspondence has been found between steady state values of key variables of the model and values obtained from the literature and from experimentation. For example, the steady state value of partial pressure of carbon dioxide (P_{aCO2}) was maintained at the baseline value, i.e. a value for the unloaded exercise condition of 40 mmHg. Similarly, the partial pressure of oxygen (P_{aO2}) attained a value of 103 mmHg, which is not significantly different from the baseline value of 100 mmHg. The respiratory exchange ratio (RER) was found to increase during steady state exercise, as has been widely demonstrated experimentally (e.g. [33]).

Responses of the system for dynamic conditions at the onset of 100W exercise are depicted in figure 2 and 3. Biphasic characteristic can be observed for $\dot{V}_{CO2}$ and for $\dot{V}_{O2}$. During phase 1 the increase of muscle oxygen consumption and carbon dioxide production has not had an effect in the lung so the dynamic responses of $\dot{V}_{CO2}$ and $\dot{V}_{O2}$ during this phase are shaped by the phase 1 characteristics of ventilation $\dot{V}_E$ and cardiac output $\dot{Q}$. That is why phase 1 has been termed "cardiodynamic" (e.g. [34]).

During phase 2, the dynamic response in terms of $\dot{V}_{O2}$ is more dependent on metabolic changes in the

muscle as the shape of the response for that variable reflects very much the shape of the response for $\dot{Q}_{O2}$ [13,15]. Similar dependency appears to apply for the $\dot{V}_{CO2}$ response.

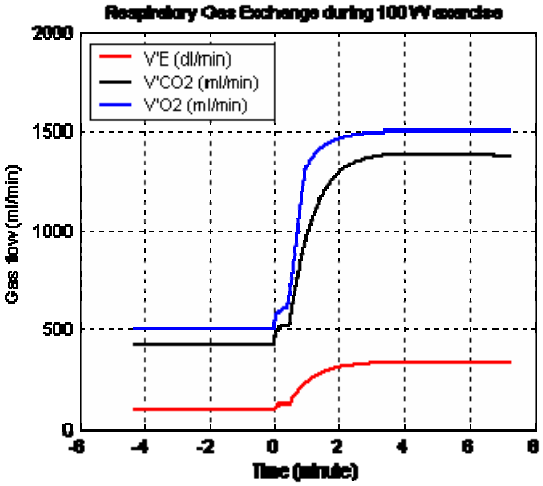

Figure 2. Profile of the respiratory gas exchange at the onset of moderate exercise

Many observers have suggested that, in terms of control theory, the arterial partial pressures can be regarded as the controlled outputs of the respiratory system. The responses shown in figure 3 can be used to support that suggestion because they show that the steady state levels of both variables attain a value similar to the controlled baseline value.

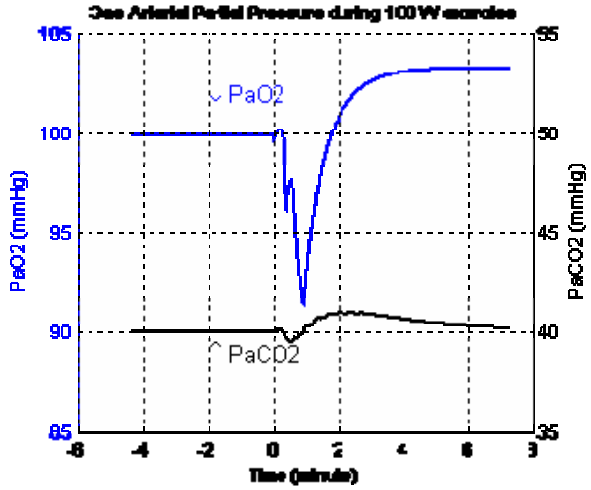

Figure 3. Oxygen and carbon dioxide partial pressure after a step change of moderate exercise (100W)

During phase 1, the variables P_{aO_2} and P_{aCO_2} are largely unchanged. The increase of $\dot{V}_E$ should have altered both P_{aO_2} and P_{aCO_2} but this change is compensated by a synchronous increase in the value of $\dot{Q}$.

During phase 2, P_{aO_2} falls transiently and then rapidly increases back to its controlled steady state value. Similarly, P_{aCO_2} also changes in a transient fashion before tending back towards its controlled steady state value. During the transients, fluctuations are observable on both the P_{aO_2} and P_{aCO_2} curves.

5 Discussion and conclusions

One of the inherent difficulties with models that are developed using anatomical and physiological principles is that values of parameters have to be estimated from experimental data and models also have to be validated using experimental data. The data sets used for parameter estimation should be quite separate and distinct from those used for external validation of the model and this can introduce practical difficulties in biological experimentation where day-to-day variability of subjects can be significant and issues such as fatigue have to be taken into account.

Problems of non-identifiability of individual parameters and associated non-uniqueness of estimates are common in modelling situations of this kind which involve initial assumptions about appropriate model structures and subsequent estimation of parameters from available experimental data. The more general the model, and the wider the intended range of applications, the greater are the difficulties in applying such methods. By keeping the model structure relatively simple and by relating it directly to experimental evidence gathered from the literature and from new experiments it has been possible to minimise issues of structural uncertainty and non-identifiability of parameters.

Methods of modelling that aim to produce a minimally parameterised model that is testable using measured response data (in addition to the data sets used for estimation of parameters) have many advantages. Failure to fully acknowledge this may well be one important reason why simulation models of the respiratory system developed so far have contributed little to developments in the field of exercise physiology. Previous modelling studies have often attempted to represent, within a single simulation, a number of quite separate aspects of the system in considerable detail, including respiratory mechanics, gas exchange and control. Inevitably such models have involved large numbers of compartments and even larger numbers of parameters associated with those compartments. In some cases a means of introducing non-perfect behaviour, representative perhaps of diseased or abnormal situations, has also been included within the model. This increases the potential difficulties of parameter estimation and external validation even further.

In the current work the aim has been to focus attention on the compartments of the model that are believed to be of greatest significance in terms of the ventilatory and gas exchange responses. The most

ISBN 978-3-901608-32-2

important of these is undoubtedly the muscle compartment and the main contribution in this work has been the inclusion of a muscle model which includes elements of CO_2 storage dynamics.

The simulation results have highlighted issues concerned with the dynamics of the respiratory system at the onset of exercise where gas arterial partial pressures have temporarily deviated from their controlled value. Such deviations are not unexpected considering the fact that the oxygen uptake and carbon dioxide outflow have different dynamic responses compared with the ventilation. In the past, some investigators have assumed these variables to be constant when examining the transient behaviour of the muscle during exercise (e.g. [22]), which would reduce the accuracy of their analysis. The present model can be used in such a situation to improve the analysis.

Gas arterial partial pressures are expected to have fluctuations that are attributable to the breath-by-breath respiration cycle. In this simulation a non-cyclical ventilation profile has been used yet a fluctuation is observed in the P_{aCO_2} and P_{aCO_2} curves during transients. Investigations based on the model suggest that this simulation result is associated with the properties of a closed-loop system containing a pure time delay.

Although the model for the 100W exercise level has been successfully tested in most respects, further work is necessary to extend the model to allow it to be used for exercise levels in the high intensity domains. This is a region for which less physiological information is available and the task of modelling the system is significantly more challenging than the for the case at lower levels of exercise. However, models for high intensity exercise conditions will still be based on the relatively simple structure shown in Figure 1. The compartmental approach to modelling of the overall system based on relatively simple and proven sub-models still applies.

In the high intensity domains, the muscle O_2 consumption profile shows non linearity in terms of the response to an increase of exercise work rate. A larger increase of $\dot{Q}_{O2}$ is observed for the same increase in exercise. At work rates within the domain of heavy exercise, $\dot{Q}_{O2}$ may still reach a steady value but the rate of increase may be as high as 13 ml/min/W [13]. At higher work rates $\dot{Q}_{O2}$ increases towards an asymptotical steady state value but this limiting value is never achieved because of the effects of fatigue.

Another important aspect to be dealt with at the level above lactate threshold is the production and accumulation of lactic acid in the muscle and blood. The human body has metabolic processes that may cease to function for conditions of extreme acidity. Fortunately the human body has some mechanisms to reduce this problem. Blood, for example, has chemical buffers which function to maintain its acidity near its normal pH level of 7.4. The most important buffer of the blood is the bicarbonate (HCO_3^-) which has an equilibrium equation:

$$H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

When lactic acid drains into the blood stream, more carbonic acid (H_2CO_3) will be formed to reduce the amount of proton (H^+). When the blood flows through the lung, carbonic acid will be transformed into H_2O and CO_2. The CO_2 will be released into the lung which will increase the level of $\dot{V}_{CO2}$.

At the lower level of acidity, the respiratory controller can stimulate the lung to ventilate more quickly. This "hyperventilation" will force more CO_2 to come out of the blood, which enables bicarbonate to bind more protons hence reducing acidity. Hyperventilation results in the values of P_{aCO_2} and P_{aO_2} shifting from the "normal" control levels. This phenomenon may be interpreted as the change in set point of the ventilation controller by the human body to protect itself against acidity.

6 Acknowledgements

The authors gratefully acknowledge the assistance and support provided for this project by Professor Susan Ward of the Institute of Membrane and Systems Biology, University of Leeds, UK.

The authors also wish to express their gratitude to the Ministry of Education, the Republic of Indonesia who provide funding for this research through the TPSDP project.

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ISBN 978-3-901608-32-2