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Conceptual Idea of Digital Computer Model of Human Respiratory System

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DIGITAL SIMULATION AND EXPERIMENTAL EVALUATION OF THE CO₂-H⁺ CONTROL OF PULMONARY VENTILATION

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Previous models of the CO₂-H⁺ control of ventilation have been concerned with either the response to CO₂ inhalation\(^1\)\(^2\) or the response to perfusion of the surface of the medulla with mock cerebrospinal fluid having a high Pco₂\(^3\). Simulations of both responses with the same model have not been attempted. The purpose of the present study was two fold; first to develop such a model and, second, to obtain experimental data from which to develop and evaluate this and future models.

**Experimental Data**

By use of the black box approach to the human respiratory system, one can obtain a considerable amount of useful information. One possible view of the respiratory system was black boxed as illustrated in Figure 1. The system inputs are the inspired concentrations of oxygen and carbon dioxide (F\(_{I}\)O\(_2\), F\(_{I}\)CO\(_2\)) and the outputs are respiratory frequency (f), tidal volume (V\(_T\)), and alveolar oxygen and carbon dioxide partial pressures (P\(_A\)O\(_2\), P\(_A\)CO\(_2\)). Minute ventilation (V) is computed secondarily from tidal volume and respiratory frequency. We will be concerned with the step responses to F\(_{I}\)CO\(_2\) only. Responses to sudden changes in F\(_{I}\)O\(_2\) with and without end-tidal P\(_{E}\)CO\(_2\) controlled at normal levels have also been obtained by the authors, but since they do not directly pertain to the portion of the system described in this paper they will be omitted\(^4\).

Subjects used were healthy males in their third decade of life. The instrumentation used is described in detail elsewhere by Holldom and Milhorn\(^5\) and is shown schematically in Figure 2. The input side of the apparatus consisted of a five-way valve through which the operator selected either room air or the stimulus mixture supplied from a 60-liter meteorological balloon, which was in turn supplied from a commercial compressed gas cylinder. The subject breathed through a mouth-piece connected to a respiratory valve system consisting of two Rudolph valves arranged in parallel. This arrangement was found to be the best compromise between low resistance and the desired low dead space. Expiratory flow was measured by a heated Fleisch pneumotachograph and Statham pressure transducer. The flow signal was detected by a trigger circuit which produced a short-duration pulse output at the end of each expiration. Gas was continuously sampled through needles inserted into the mouthpiece and was analyzed by a Beckman LB-1 infrared CO\(_2\) analyzer and a Thermox fuel cell oxygen analyzer. The flow signal, the trigger pulses, and the continuous outputs of the oxygen and carbon dioxide analyzers were recorded on four channels of a magnetic tape using a Sanborn 3907 FM magnetic tape system. After an experimental session, the recorded data was played back, demodulated, digitized, and calculations performed by a Digital Equipment Corporation PDP-9 digital computer. For each breath, the computing routine calculated the tidal volume by integration of the flow signal and the respiratory period by measuring the elapsed time between trigger pulses. From this, the respiratory frequency and minute ventilation associated with that breath were calculated. The highest carbon dioxide and lowest oxygen values occurring during the breath were also determined and stored as approximations of the alveolar concentrations. The occurrence of a receive pulse on the trigger channel was used by the program to initiate and terminate processing of input data for each breath.

After the calculations for the entire experimental run had been performed, the breath-by-breath values for tidal volume, respiratory frequency, minute ventilation, and alveolar oxygen and carbon dioxide were printed out and also stored as a data file on magnetic tape. The stored data could then be averaged into 10-sec intervals and displayed on a storage oscilloscope or plotted out by an on-line incremental drum plotter. All data files for a given stimulus concentration could also be accessed by another program and processed to give mean values and standard errors for each of the five variables.

Each experiment consisted of a 20-min prestimulus period breathing room air, a 25-min period breathing the stimulus mixture, and another 20-min off-transient period breathing room air. The stimulus mixtures were either 3, 5, 6, or 7 percent carbon dioxide in air provided by commercial sources. The subjects were placed in a semi-recumbent position in a comfortable recliner chair and listened to a stereophonic music through headphones. The music was provided both to relieve boredom and to mask out any ambient sounds occurring in the room during the course of the experiment. If necessary, instructions could be transmitted to the subject by the operator by use of an FM "wireless microphone" tuned to the frequency on which the music was being broadcast. All equipment was situated so that the subject could not observe the actions of the operator, the indication of any instrument, or the manipulation of any valve or control. Air from a compressed air tank was allowed to escape into the room during the periods when the stimulus mixture was not filling the reservoir bag so that the subject would not get an auditory cue when the stimulus was applied or removed. Subjects were not told which stimulus mixture they were to receive, and most underwent a "blank" experimental run in which compressed air was used in place of the CO\(_2\) stimulus gas in order to detect the presence of voluntary effort, psychic effects, etc., on the part of the subject.

The stimulus gas mixture was allowed to come to temperature equilibrium with the room air by passage through two series humidifier/heat exchangers and the reservoir balloon. Gas flow rates were kept low enough to prevent positive pressure from
developing in the balloon and to allow time for temperature equilibrium with the room air to be achieved. The degree of humidification provided by the humidifiers was such that subjects were unable to differentiate between room air and humidified compressed air from the reservoir balloon in several runs.

The experimental results for tidal volume, respiratory frequency, and minute ventilation are plotted in Figures 3-5. It can be seen from Figures 3 and 4 that a characteristic dissociation of the frequency and tidal volume on-transients occurs at each stimulus concentration with tidal volume changing rapidly in the first transients, while the frequency rises very gradually throughout the stimulus period. Alveolar Pco2 and P02 transients for all stimulus levels are given in Figure 6.

The steady-state values and transient half-times for the ventilatory variables are summarized in Table 1 and those for the gas pressures in Table 2. Several trends can be noted. The on-transient half-times for respiratory frequency steadily increase with increasing stimulus level while those for tidal volume increase in a nearly linear fashion. Ventilation on-transient half-times also steadily increase with increasing stimulus level. The on-transient half-times for alveolar Pco2 become progressively smaller as the stimulus level is increased. The half-times for the Pco2 on-transients remain essentially constant until the 7 per cent level is reached. At this concentration the half-time becomes significantly larger. The off-transient half-times for respiratory frequency, tidal volume and minute ventilation all decrease with increasing stimulus concentration. Again it can be noted that the trend of the alveolar oxygen half-time is opposite to that of the other variables. The half-times for alveolar Pco2 are essentially constant for all inspired CO2 values. As the Pco2 on-transients, the Pco2 off-transients are the fastest ones observed. The off-transients for every variable except alveolar Pco2 are faster than the on-transient.

### Computer Simulation

The model was divided into a controlled system and a controlling system. The former is illustrated in Figure 7. It consists of a lung compartment, a cerebrospinal fluid compartment, a peripheral sensor compartment, and a lumped tissue compartment. Arterial blood and venous blood were given their own CO2 dissociation curves, and all tissues, for simplicity, were assumed to have the dissociation curve of brain tissue. In actuality, this is not a bad assumption when this curve is compared to those of the other major tissues. Cerebral blood flow was assumed to be a steady-state function of arterial Pco2 and a first-order lag, as was the blood flow to the lumped tissue compartment. Blood flow to the peripheral compartment was assumed to be constant. Cardiac output was then the sum of the individual flows. Circulation times were considered to be variable depending on the instantaneous flow rates.

The controlling system is shown in Figure 8. Ventilation is considered to be the sum of two components, a peripheral chemoreceptor component and a central chemoreceptor component. Each of these is determined by use of a function curve and a weighting function (w = 0.88). The inputs to the two functions are assumed to be peripheral chemoreceptor hydrogen ion concentration (CpHCS) and central chemoreceptor hydrogen ion concentration (CpHCS). Alveolar ventilation (VA) is determined from minute ventilation as follows: tidal volume is computed from minute ventilation by use of a function curve based on data from the literature. Physiological deadspace (Vd) is then computed from tidal volume based on data from the literature. Minute ventilation is divided by tidal volume to obtain respiratory frequency. Respiratory frequency is then multiplied by deadspace to obtain minute deadspace (Vd) which is subtracted from minute ventilation to give alveolar ventilation.

Viewing the central chemoreceptor as being located somewhere between cerebrospinal fluid and deep brain tissue, a Pco2 gradient between cerebrospinal fluid Pco2 (PcSFco2) and deep brain tissue Pco2 can be described by

\[ P_{co2} = P_{co2} + (PcSF_{co2} - P_{co2}) \exp(-760QcsS X/10) \]  

In which Qcs is the blood flow in the neighborhood of the central sensor, S is the slope of the CO2 dissociation curve D is the diffusion coefficient of CO2, and X is the depth beneath the surface. PcSF in this equation becomes the central receptor Pco2 (PcSco2) at a value of X equals to its depth beneath the surface. The pH at this point is

\[ pH_{cs} = 6.14 \log \left( \frac{(C_{so2} - C_{so2_{CSO2}}}{760}) \right) \]  

and the hydrogen ion concentration is

\[ C_{H^+} = \exp(-2.303pH_{cs}) \]
from human subjects, as might be expected, is not available for comparison. However, Mitchell et al. did perform a similar experiment in anesthetized cats (Figure 12). A qualitative comparison can, therefore, be made. As can be seen, the response of the model appears to be similar in form to the response of the anesthetized cat. In addition, using responses of the model to both CO₂ inhalation and CSF perfusion, the controller relationships of previous models were compared to the present one. Although differences in responses to CO₂ inhalation did occur with each controller relationship, they were not greatly different. The responses to CSF perfusion, however, varied greatly, the present relationship giving the most satisfactory result. The responses of the model were also similar for CO₂ inhalation when the single central sensor was replaced by one monitoring cerebrospinal fluid H⁺ concentration and contributing 23 per cent of the central ventilatory drive and another monitoring deep brain tissue H⁺ concentration and contributing 77 per cent of the central ventilatory drive. The responses to cerebrospinal fluid perfusion, however, were considerably different in each case.

References
TABLE 1. Summary of steady-state values and half-times for minute ventilation, tidal volume, and respiratory frequency.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>PI\textsubscript{CO}_2</th>
<th>PRESTIMULUS CONTROL</th>
<th>25-MINUTE VALUE</th>
<th>ON-TRANSIENT t\textsubscript{1/2} (seconds)</th>
<th>OFF-TRANSIENT t\textsubscript{1/2} (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minute Ventilation (liters/min)</td>
<td>0.03</td>
<td>6.3</td>
<td>11.25</td>
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<td>43</td>
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<td>17.40</td>
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<td>0.07</td>
<td>6.0</td>
<td>41.44</td>
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<tr>
<td>Tidal Volume (liters)</td>
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<td>Respiratory Frequency (breaths/min)</td>
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<td>25.5</td>
<td>225</td>
<td>23</td>
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* Not sufficiently well-defined to measure transient half-times.
<table>
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<th>VARIABLE</th>
<th>P_{CO_2}</th>
<th>PRESTIMULUS CONTROL</th>
<th>25-MINUTE VALUE</th>
<th>ON-TRANSIENT t(_\frac{1}{2}) (seconds)</th>
<th>% OVERSHOOT</th>
<th>OFF-TRANSIENT t(_\frac{1}{2}) (seconds)</th>
<th>% UNDERSHOOT</th>
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<td>126.0</td>
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<td>F_{AO_2} (mm Hg)</td>
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<td>132.1</td>
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<td>F_{AO_2} (mm Hg)</td>
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<td>56.2</td>
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<td>0</td>
<td>6.0</td>
<td>72</td>
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Figure Captions

1. The respiratory system as a black box.

2. Data collection system.

3. Transient tidal volume responses to steps of 3, 5, 6, and 7 per cent CO\textsubscript{2} in inspired air.

4. Transient respiratory frequency responses to steps of 3, 5, 6, and 7 per cent CO\textsubscript{2} in inspired air.

5. Transient minute ventilation responses to steps of 3, 5, 6, and 7 per cent CO\textsubscript{2} in inspired air.

6. Transient responses of alveolar PCO\textsubscript{2} and PO\textsubscript{2} to steps of (a) 3%, (b) 5%, (c) 6%, and (d) 7% CO\textsubscript{2} in inspired air.

7. The controlled system.

8. The controlling system.

9. Determination of central receptor depth (see text for explanation).

10. Transient minute ventilation responses of the model to steps of 3, 5, 6, and 7 per cent CO\textsubscript{2} in inspired air.

11. Transient tidal volume and alveolar PCO\textsubscript{2} responses of the model to a step of CO\textsubscript{2} in cerebrospinal fluid.

12. Transient tidal volume and alveolar PCO\textsubscript{2} responses of an anesthetized cat to a step of CO\textsubscript{2} in cerebrospinal fluid.
Figure 1

Figure 2
Figure 5

Figure 6

V (liters/min)
Figure 8
Figure 9

Figure 10
Figure 11

Figure 12