DYNAMIC SIMULATION OF HUMAN VENTILATORY REGULATION

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In order to investigate the regulation of respiration under various conditions, a dynamic model of the human ventilatory system has been developed. This model describes the flows of oxygen and carbon dioxide between the atmosphere and the tissues, as well as the chemical regulation of breathing.

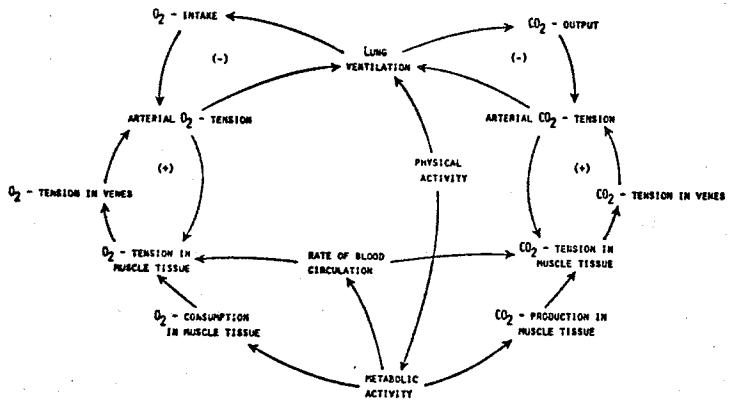

Fig. 1 Simplified causal loop diagram for the human respiratory system. While several of the relationships can be reduced to fundamental physical and chemical laws, others are still not fully understood. By means of our model one can test alternative formulations of these relationships and establish the conditions under which the model responds correctly to exogenous stimuli. Besides responses to changes in the level of physical activity, the model has also been used to examine the respiratory response to changes in the composition and pressure of the inspired air.

The blood is the major store of oxygen and carbon dioxide in the body. Since it is also the transport medium, the blood plays a central role for the dynamic performance of the system. For each of the two gasses, the blood stores are divided into three arterial, three venous, and three capillary compartments.

Oxygen and carbon dioxide are also present in the tissues and in the lungs and airways. These spaces are represented by four compartments: muscle tissue, nonmuscle tissue, dead space, and alveolar space. The dead space is in series with the lung alveoles, which are ventilated with half-wave sinusoidal in- and expiratory flows. The amplitudes hereof and the duration of expiration are computed from the expired minute volume which again is determined from the arterial gas tensions. Both the central (i.e. located in the brain) and the peripheral (located in the arteries of the neck) ventilatory drive are represented in the model. The first of these is taken to respond to the carbon dioxide pressure in the third arterial compartment, while the second responds to the oxygen and carbon dioxide pressures in the first arterial compartment. The model also includes a "neural factor" which is taken to be linearly dependent on the intensity of muscular metabolism.

The transport of gas between the capillary blood and the alveolar/tissue spaces is described by means of a simplified diffusion model. It is not assumed that the blood reaches equilibrium with the alveolar air or with the tissues it perfuses, and variations in the blood circulation rate, the capillary volume, and the effective capillary diffusion constants with the level of metabolic activity can thus be taken into account. Interactions between the saturation degree of hemoglobin with oxygen and the chemical binding of carbon dioxide (Haldane effect) as well as between the carbon dioxide pressure and the physical solubility of oxygen (Bohr effect) are included in the model.

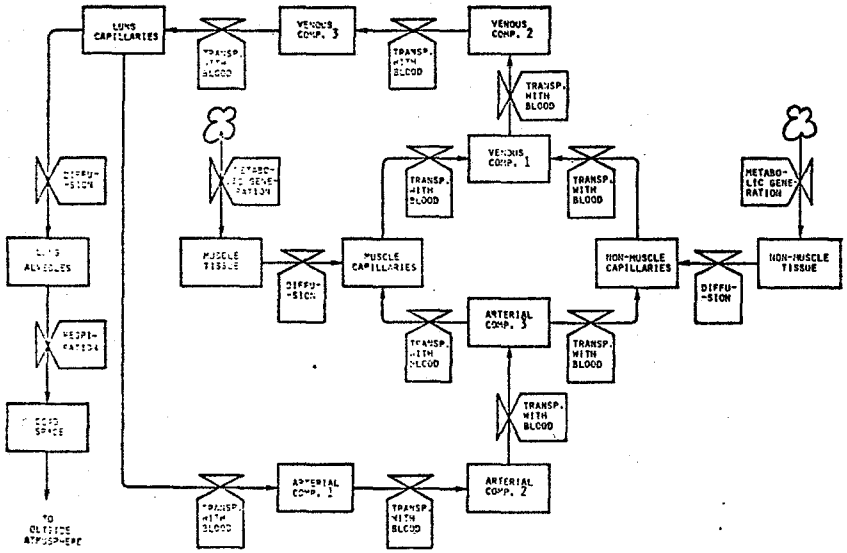

Fig. 2 System dynamics representation of the (material) flow of carbon dioxide in the human body. CO_2 is produced in the tissues by oxidative burning of nutrients (metabolic generation), diffuses through the capillary membrane into the blood, and is transported to the lung capillaries. Here, CO_2 diffuses into the alveoles from which is is removed through expiration. A similar diagram applies for oxygen.

When testing the model with a step increase in muscular metabolism (simulating a transition from rest to physical activity), the model reproduces clinical observations for the variation in ventilation as well as in arterial oxygen and carbon dioxide pressures. The model also reproduces the respiratory response to changes in the composition of the inspired air. Combined with a model of the Hafnia A anaesthetic system, the respiration model has hereafter been used to examine the dynamic interactions between a patient and the anesthetic system under conditions not amenable to clinical

investigation, i.e. when the fresh gas flow falls below a certain threshold value, and the patient starts to rebreath his own expiration.

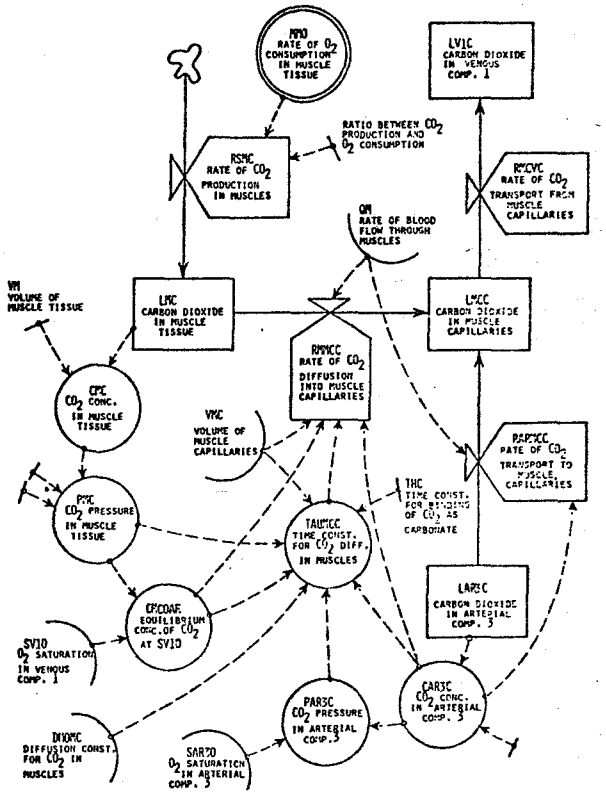

Fig. 3 Detail of system dynamics flow diagram showing the flow of CO_2 from muscle tissue into muscle capillary blood. The inter-dependent processes of CO_2 diffusion through the capillary membrane, chemical binding of CO_2 as carbonate, liberation of O_2 from hemo-globin, and diffusion of O_2 into the tissues were treated in detail in a separate model (with a much shorter time scale), and the results hereof were used to construct the relationships of the ventilatory system model.

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In order to investigate the regulation of breathing under various conditions, we have developed a dynamic model of the human respiratory and cardio-vascular systems. The model describes the flows of oxygen and carbon dioxide between the atmosphere and the tissues as well as the chemical regulation of breathing in a rather detailed manner. When testing the model with a step increase in muscular metabolism (simulating a transition from rest to physical activity), it reproduces clinical observations for the variation in ventilation and in arterial oxygen and carbon dioxide pressures. The model also reproduces the respiratory response to changes in the composition of the inspired air. Combined with a model of the Hafnia A anaesthetic system, the respiratory system model has finally been used to examine the life-threathening dynamical run-away effects which may occur, if the fresh gas flow is reduced too much, and the patient starts to rebreathe his own expiration.

INTRODUCTION

Physiological systems usually have a rather complicated non-linear feed-back structure which causes them to show a varity of dynamical behaviours, and human physiology is therefore a natural area for system dynamics modeling.

Often one finds, that a relatively well established explanation of the various causal relations in a physiological system exists, but that it is less certain whether these mechanisms actually can

account for the phase relations, delays and/or characteristic periods observed in practice. One may also find that some parts of a physiological system are known in detail, while other parts of the same system are little understood and difficult to investigate experimentally because of various intervening feed-back loops. Finally, there are a number of physiological phenomena that are important to understand (for instance to design a proper medical treatment), but for which clinical experiments are restricted because they would expose the involved persons to unacceptable risks.

In all of these situations, computer modeling can provide a significant contribution to our understanding of the systems. Simulation is usually the only manner in which one can perform a true dynamical analysis of a complex feed-back system to determine whether the accepted causal relations are correct or not. By means of a simulation model, one can infer the form of certain unknown relations (or the magnitude of unknown parameters) by adjusting model output to real system behaviour, and computer modeling is also a valuable alternative where clinical experiments are restricted by ethical (economic or other) considerations. Human physiology is therefore not only a natural but also a scientifically very interesting area for system dynamics modeling.

In this paper we present a dynamic model of the human respiratory system. It is known that the main control of the respiratory system takes place through neural processes which regulate the depth of inspiration and the rate of breathing according to the metabolic needs of the body. Agents in this regulation are chemoreceptors in the brain and in the arteries of the neck which respond to changes in the local oxygen and carbon dioxide tensions.

While the principal mechanism in the chemical regulation of breathing thus are known, a number of problems remain unsolved and controversial. After more than 100 years of investigation it is still uncertain, for instance, whether the existing theory can give an adequate explanation to the enhanced breathing accompanying muscular exercise[1,2]. The detailed form of the relations between arterial gas pressure and ventilatory drive is not well established, and other kinds of stimuli (the nature of which are in debate) may be involved.

For these reasons we have developed a model which can simulate the most common experimental situations (such as a transition from rest to physical activity) with a sufficient accuracy to allow a detailed comparison with clinical results obtained at the Institute of Physiology, Aarhus University and elsewhere. Combined with a model of the Hafnia A anaesthetic system, the respiratory system model has also been used to examine the dynamical interactions between a patient and the anaesthetic system under conditions not amenable to clinical investigation, i.e. when the fresh gas flow falls below a certain threshold value, and the patient starts to rebreathe his own expiration. A more detailed account of this work was presented at the 6th International Conference on System Dynamics.[3]

SYSTEM DESCRIPTION

The human organism requires energy to maintain life and to perform its many functions. All of this energy is ultimately derived from the oxidative burning of nutrients in the tissues, and it is well-known that the carbon dioxide hereby produced is transported with the blood to the lung capillaries. Here, the carbon dioxide diffuses into the alveolar air to be finally eliminated through the lung (pulmonary) ventilation. At the same time oxygen diffuses from the lung alveoles into the blood with which it is transported back to the tissues.

The metabolic rate (oxygen consumption and carbon dioxide production) varies according to the state of activity, and for muscle tissue it may increase almose abruptly by up to a factor of 15 at the transition from rest to exercise.

To match these requirements, and to maintain an adequate supply of oxygen to the vital organs (brain and heart) under all circumstances, the respiratory and cardiovascular (heart plus blood vessels) systems must be extremely well controlled. At the same time, in order that the enzymatic processes in the tissues can take place appropriately, a stable ionic environment is required. Carbon dioxide through the formation of carbonic acid plays an important role for maintaining this internal homeostasis, and the carbon dioxide pressure must therefore be kept relatively constant.

For the cardiovascular system both the total blood flow (cardiac output) and the distribution of the flow between the various organs are regulated[4]. The local part of this control takes place through receptors that respond to the build up of metabolic products with signals to a group of small muscles that control the cross sections of the arterioles leading the blood to the capillaries of the active tissue. The alveoles are dilated when more oxygen is needed, and the additional blood flow increases the supply of oxygen and expands the capacity for removing carbon dioxide. At the same time, the additional supply of blood presumably by itself widens the capillaries of the tissue and hereby increases the effective diffusion constants for oxygen and carbon dioxide, so that the two gasses can pass more readily across the capillary membrane separating blood from intercellular fluid.

As the resistance to the blood flow through the working muscle is reduced, the blood pressure in the systemic (body) arteries tends to fall. This pressure must be maintained, however, to secure the oxygen supply to the brain and heart, and as a response to signals from pressure sensitive receptors in the arterial walls, the heart starts to work faster and increases the circulatory rate. At the same time, the cross section of arterioles of less vital organs (the gastrointestinal tract, the skin and non-working muscles) are reduced, so that the blood flow through these organs decreases.

Both the depth of inspiration and the rate of breathing are controlled by the arterial oxygen and carbon dioxide tensions, such that both a reduction in the oxygen pressure (PO_2) and a build-up of carbon dioxide stimulate ventilation. The carbon dioxide pressure (PCO_2) is the more powerfull of the two controllers, and it is worth noticing that significant synergetic effects occur in the regulation, so that the ventilatory response to a simultaneously reduced PO_2 and elevated PCO_2 is considerably stronger than the sum of the responses to each of these stimuli separately.

Actually, rather than by the partial pressure of CO_2, lung ventilation may be controlled by the arterial concentration of hydrogen ions (H^+). In the present analysis, however, changes in the H^+-concentration are assumed to be caused by variations in PCO_2 according to the reaction

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows HCO_3^- + H^+,$$

and other sources to changes in the acid-base status of the blood (such as the production of lactid acid) are not represented.

Two groups of receptors are involved in the chemical regulation of breathing. One group, the central chemoreceptors, is situated in the brain and responds to changes in the H^+-concentration in the brain's intercellular fluid. The other group, the peripheral chemoreceptors, is located in the arteries of the neck and responds both to changes in PO_2 and in PCO_2. While they are the only important receptors that respond to arterial PO_2, the peripheral chemoreceptors only play a minor role in the CO_2-dependent H^+-regulation.

During heavy muscular exercise, alveolar ventilation may increase by a factor of 10 or 20 to supply the additional oxygen requirements and remove the excess carbon dioxide produced. Apparently, however, the chemical control mechanisms just discussed are not sufficient to explain the ventilatory response to exercise.

Clinical experiments show an abrupt increase in ventilation at the unset of exercise and well before any build-up of CO_2 in the arterial blood can have occurred. This initial increase, which amounts to 30-50% of the final steady state increase in ventilation to be reached after several minutes, is often strong enough to produce an increase in arterial oxygen pressure for a short period after the exercise has started. Moreover, at very high working loads, the steady state alveolar ventilation is found to increase relatively more than the oxygen consumption and to produce arterial oxygen pressures above and carbon dioxide pressures below normal values. To explain these effects one may assume (as we have done in the model) that there is a direct stimulatory influence on ventilation from a working muscle. The manner in which this mechanism functions, however, is not known at all.

In the blood, oxygen is present both in physical solution and chemically bound to hemoglobin in the red blood cells. Because of its relatively low solubility in water, of the 200 ml of oxygen carried by 1 ℓ of arterial blood, less than 3 ml are physically dissolved, and more than 98% is bound in the blood cells. The extend to which oxygen combines with hemoglobin depends upon the oxygen tension. This relationship, the oxygen-hemoglobin saturation curve, increases rather rapidly from about 15% saturation of hemoglobin with oxygen at PO_2 = 10 mmHg to about 90% saturazion at PO_2 = 60 mmHg.

In muscle tissue at rest the oxygen tension is typically 40 mmHg and at this pressure about 75% of the hemoglobin remains saturated and only about 25% of the oxygen carried with the blood is given off to the cells. When the muscle starts to work, however, the local PO_2 decreases towards zero, and the release of oxygen from the blood increases considerably.

Above 80 mmHg of oxygen tension, further increase in PO_2 only produces a very small increase in the amount of oxygen bound to a given amount of hemoglobin. This flat part of the saturation curve ensures a full supply of oxygen even if the oxygen pressure in the lungs should fall somewhat below its normal value of 105 mmHg (at sea level). High levels of muscular activity, for instance, will be associated with moderate reductions in the alveolar PO_2.

The binding of oxygen to hemoglobin also depends upon the hydrogen ion concentration in such a way that an increased carbon dioxide pressure (by increasing the H^+-concentration) reduces the affinity of hemoglobin to oxygen. Since the carbon dioxide pressure in muscle tissue increases with increasing activity, the blood flowing through the capillaries of a working muscle releases more oxygen, than it would do, had the oxygen pressure been the only determining factor. In the same way, the temperature increase which occurs in a working muscle, facilitates the dissociation of oxygen from hemoglobin.

Of the carbon dioxide supplied to the blood from the working cells, a significant fraction combines with water (to form carbonic acid and bicarbonate) or with hemoglobin. Due to these processes,

the relationship (dissociation curve) between total CO_2-concentration and PCO_2 is nonlinear with PCO_2 increasing almost exponentially with the blood CO_2-concentration. Furthermore, the dissociation curve depends upon the degree of hemoglobin saturation with oxygen, such that (venous) blood with low O_2-saturation at the same CO_2-tension can carry more carbon dioxide than fully saturated (arterial) blood.

To sum up the above discussion, Fig. 1 shows a causal loop diagram of the most significant mechanisms involved in the control of the respiratory and cardiovascular systems. The cardiac output influences the transfers of O_2 and CO_2 in the lungs because at high circulatory rates, the blood no longer reaches equilibrium with the alveolar air during the time it takes to pass the lung capillaries. The dotted curve in Fig. 1 represents the postulated direct stimulatory effect on ventilation from muscular exercise.

SYSTEM DYNAMICS MODEL

Our model of the human respiratory and cardiovascular systems is structured around the physical flows of oxygen and carbon dioxide between the atmosphere and the tissues. In Figs. 2 and 3 we have illustrated the magnitudes of these flows for a normal person at rest at sea level. At the same figures, we have indicated the partial pressures of the two gasses in the inspired and expired air as well as in the arteries, veins and tissues of the body. At rest, the lung ventilation is typically $V_T \cong 5\ell$ (air)/min, and the cardiac output is $Q \cong 5\ell$ (blood)/min.

Fig. 4 shows a system dynamics representation of the material flow of carbon dioxide from metabolic generation in muscle and non-muscle tissue to expiration. The paths followed by carbon dioxide and oxygen through the body are similar, and the model representation of the material flow of oxygen is therefore identical in structure, although some of the rates have opposite directions. Blood is the major store of the two gases in the body, and because it is also the transport medium, it plays a central role for the dynamic performance of the system. For this reason a relatively detailed representation of the circulation has been attempted.

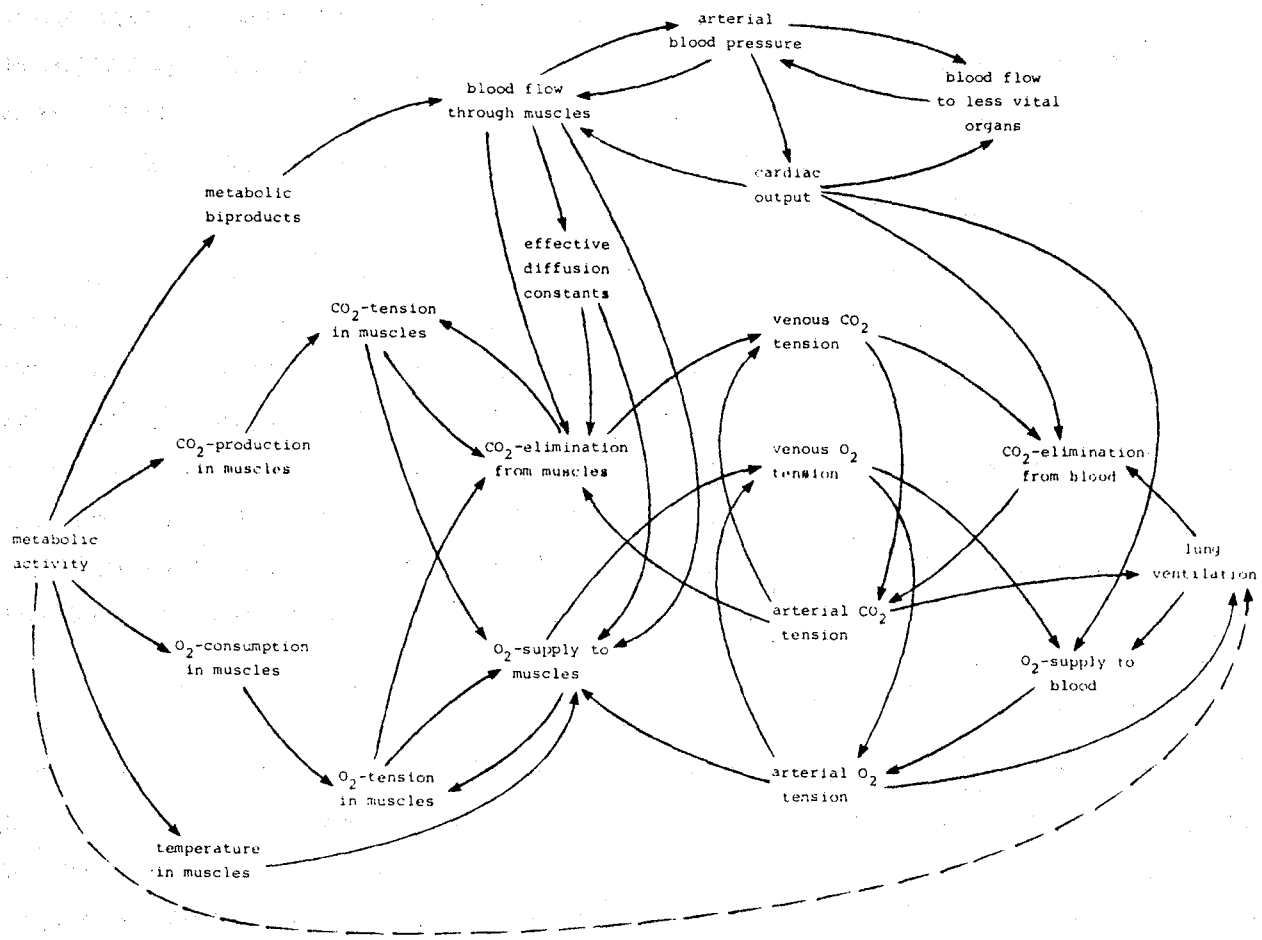


Figure 1. Causal loop diagram for the most significant mechanisms involved in the control of the respiratory and cardiovascular systems.

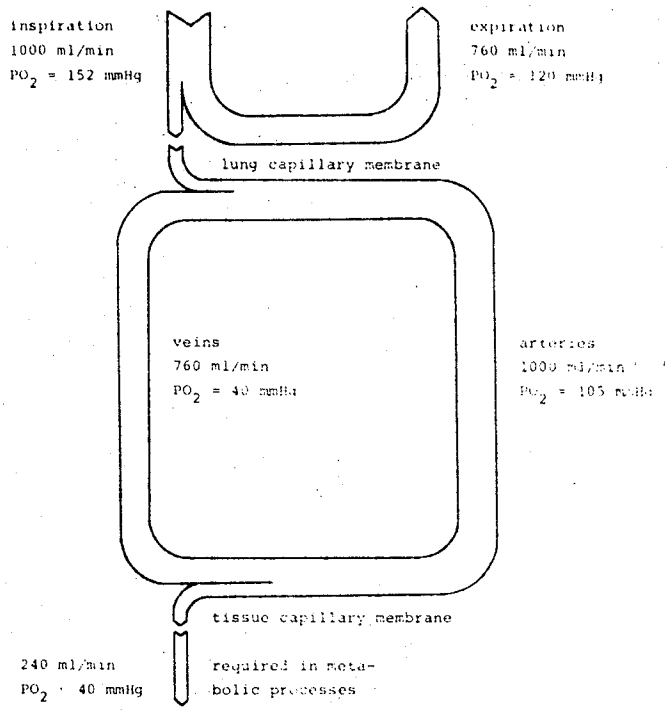


Figure 2. Flows of oxygen for a normal person at rest at sea level. Also indicated are the corresponding partial pressures of oxygen.

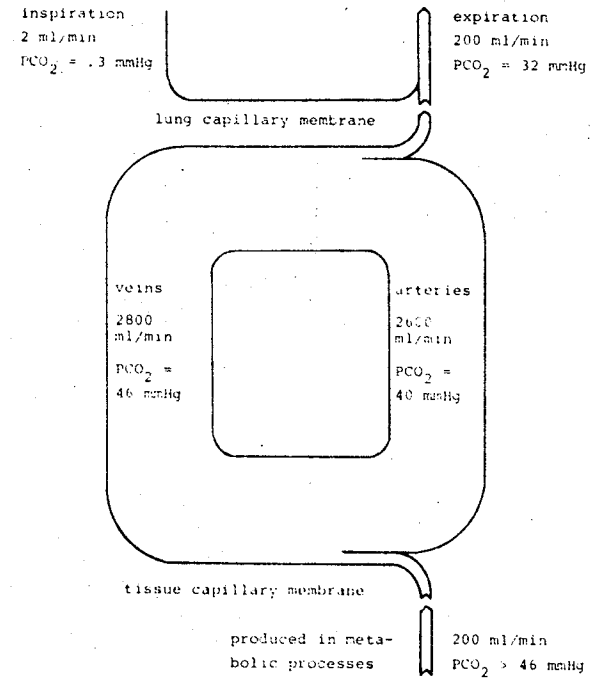


Figure 3. Similar flows and partial pressures for carbon dioxide. The carbon dioxide production is typically 80% of the oxygen consumption.

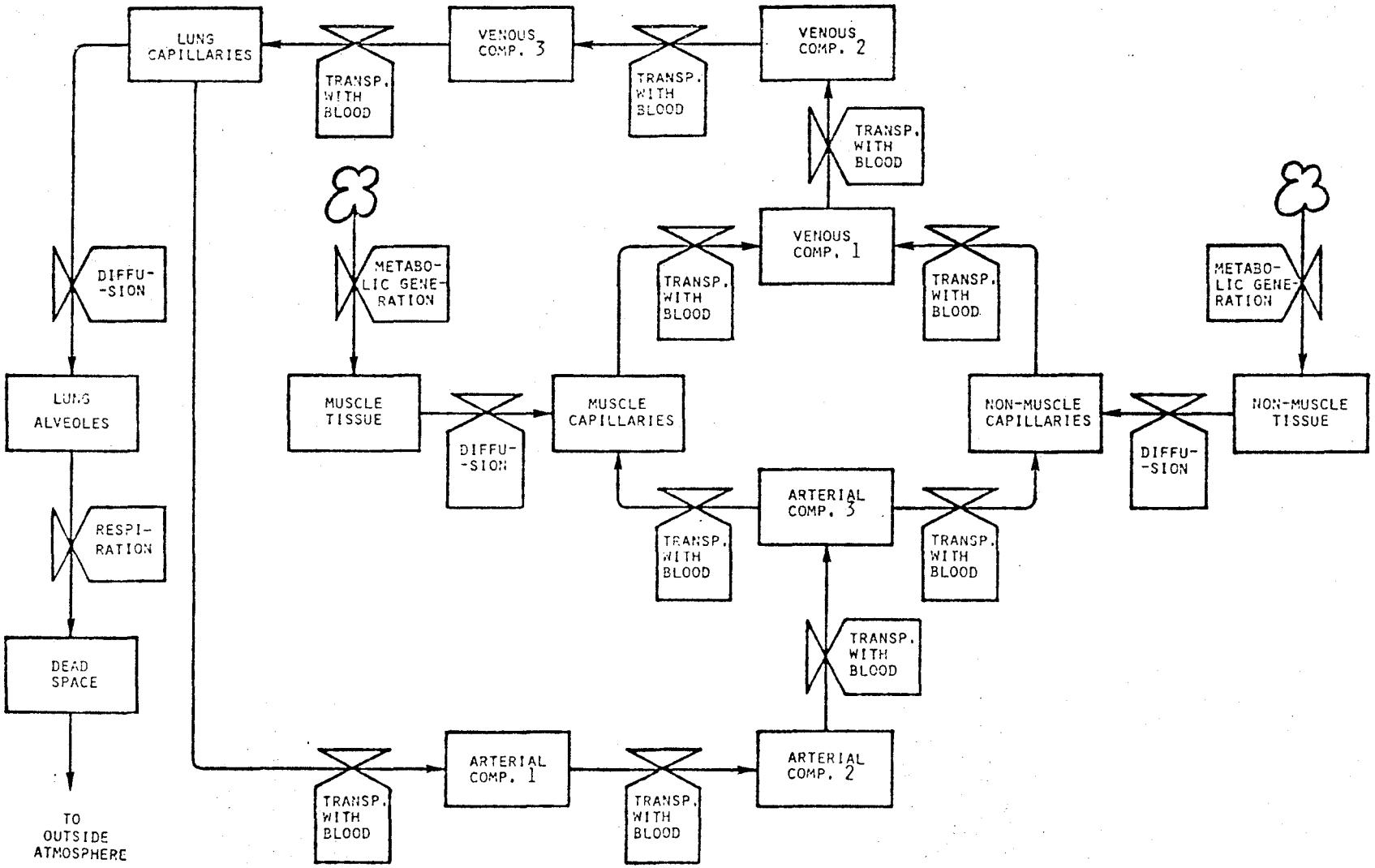


Figure 4. System dynamics representation of the material flow of carbon dioxide from metabolic generation to expiration.

The tissue stores of carbon dioxide are shown as two levels, one representing the stores in muscle tissue, the other the stores in non-muscle tissue. This division is necessary to simulate muscular exercise and the associated redistribution of the blood flow. At rest, the metabolic rates (basic metabolic oxygen consumption) for muscle and non-muscle tissue are BMEMO = 70 ml oxygen/min and BMENO = 180 ml oxygen/min, respectively. To simulate the response of the respiratory system to muscular exercise, BMEMO is treated as an exogeneous variable which is increased either by a STEP or a RAMP function, starting with the system in equilibrium at rest. The respiratory quotient (the ratio between the rates of carbon dioxide production and oxygen consumption) is assumed to be constant, RQ = .8.

Carbon dioxide is also present in the gas of the lungs and airways. These spaces are represented by two levels, one representing the dead-space and one the alveolar space. The rates of gas transport between these two levels and between the dead-space and the atmosphere are calculated as the ventilatory flow multiplied by the concentration of gas in the level from which the flow is directed. These concentrations are calculated as the amount of the particular gas divided by the total volume of the compartment.

The blood gas stores have been divided first into arterial, venous and capillary gas stores. Because the gas transfer between the blood and the tissues, respectively the alveolar air, takes place across the capillary membrane, there are three levels representing the amounts of gas in the blood of the muscle-, non-muscle-, and pulmonary capillaries. The lung capillaries connect the arterial and venous levels in one end of the circuit, while the two sets of tissue capillaries connect them at the other end.

In the great central vessels there is only limited longitudinal mixing, and during transient stages the change in the gas content of the blood cannot be assumed to start simultaneously at all locations along the vessel. Therefore the arterial and venous blood gas stores have been divided into three serial levels, and thus there are 9 levels representing the total blood gas stores of each of the gases.

The rates connecting any two of these levels are calculated as the blood flow multiplied by the concentration of gas in the level from which the flow is directed. This concentration is calculated as the amount of gas in the level divided by the blood volume in that part of the circulation.

For the blood levels it is necessary to convert from concentration of a gas to its partial pressure and vice versa. For both gases the dissociation curve (which is the relationship between concentration and partial pressure) is non-linear. For carbon dioxide it is approximated by an exponential function. Following the conversion a correction for the influence of the saturation of hemoglobin with oxygen (Haldane effect) is carried out. This correction is a simple linear interpolation between two exponential functions, one representing the dissociation curve in fully oxygenated blood, and the other the dissociation curve in fully deoxygenated blood. The conversion from partial pressure to concentration is carried out by means of a reverse procedure.

For oxygen the conversion from concentration (or rather saturation) to partial pressure is by means of two table functions, one covering the range of saturation from 0 to 90%, the other covering the range from 90 to 100%. This division is necessary because the slope of the dissociation curve is small in the high range. The Bohr effect (the dependence of hemoglobin saturation with oxygen on carbon dioxide pressure) is calculated from the carbon dioxide tension using an exponential function[5]. The conversion from partial pressure to saturation is by means of carfully matched inverse table functions.

In the gaseous compartments these conversions are simple since there is a linear relationship between concentration and partial pressure.

In the tissues the carbon dioxide dissociation curve is also approximated by an exponential function, while the oxygen dissociation curve is described by a table function.

As discussed in the next section, the rate of gas transfer between the tissues (respectively the alveolar air) and the corresponding capillary blood is calculated by means of a separate relatively detailed diffusion model. With this formulation, it is not assumed that the blood reaches equilibrium with the tissue it perfuses.

Fig. 5 shows the model formulation of the rate of carbon dioxide diffusion from muscle tissue to muscle capillary blood RMMCC. This rate is a function of the blood flow through the muscles QM, the volume of the muscle capillaries VMC, the concentration of carbon dioxide in the blood arriving at the muscles CAR3C, the carbon dioxide concentration of blood in equilibrium with the carbon dioxide and oxygen pressures in the muscles CMCOAF, and the time constant TAUMCC describing the rate at which this equilibrium is approached. This time constant TAUMCC is again a function of the volume of the muscle capillaries VMC, the effective diffusion constant for carbon dioxide across the muscle capillary membrane DMOMC, the time constant for binding of CO_2 as bicarbonate THC, and the differences both in carbon dioxide pressures and in corresponding equilibrium blood concentrations between the arterial blood arriving at the muscles and the muscle tissue itself. It is ensured in the model, both that the total blood volume remains constant, and that incorrect changes in gas pressures or concentrations are not introduced as a consequence of the redistribution of blood flow between muscles and non-muscles.

As shown in the flow-diagram of Fig. 6, the overall pulmonary ventilation VE (equivalent to the minute-volume in liters of air per minute) is calculated as the sum of three entities. The first of these CEN describes the ventilatory drive from the central chemoreceptors in the brain, the second PER represents the ventilatory drive from the peripheral chemoreceptors in the arteries of the neck, and the third MAF represents the assumed direct ventilatory stimulation from exercising muscles.

CEN is assumed to be a piecewise linear function of the carbon dioxide pressure in the third arterial compartment. PER is also assumed to vary with the arterial carbon dioxide pressure in a linear fashion, but the slope of this relation is taken to increase hyperbolically with decreasing oxygen pressure. Moreover, to account for the different locations of the two sets of chemoreceptors relative to the circulation, the carbon dioxide pressure used to calculate PER is that of the second arterial compartment. Finally MAF (contribution from muscle neural afferents) is taken to be proportional to the intensity of muscular exercise as measured by the increase in metabolic rate.

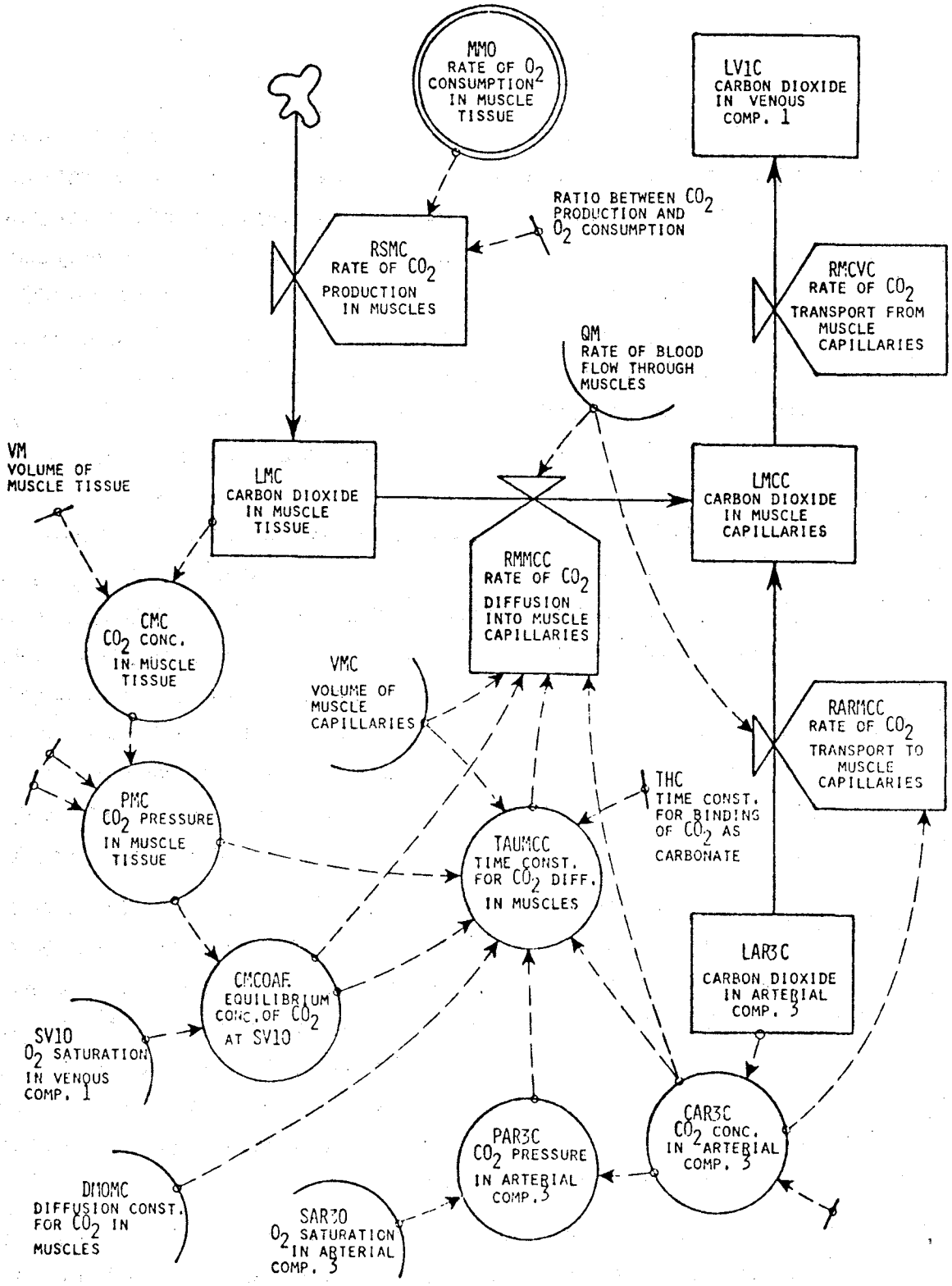
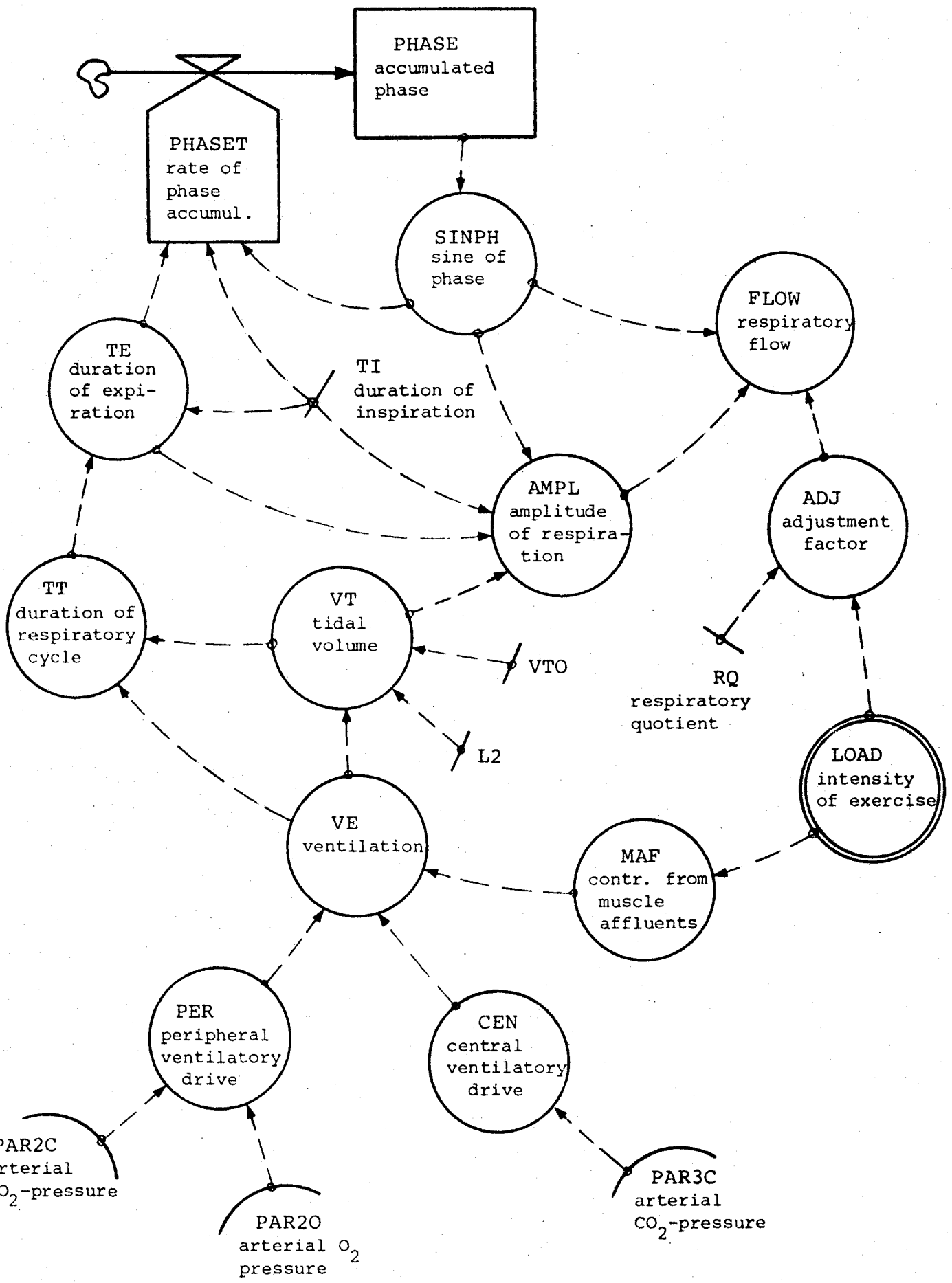


Figure 5. Part of the total flow diagram for the respiratory and cardiovascular systems showing the calculation of the rate at which carbon dioxide diffuses from muscle tissue to muscle capillary blood.


PHASE
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adjustment
factor
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duration of
respiratory
cycle
VT
tidal
volume
VTO
RQ
respiratory
quotient
L2
LOAD
intensity
of exercise
VE
ventilation
MAF
contr. from
muscle
affluents
PER
peripheral
ventilatory
drive
CEN
central
ventilatory
drive
PAR2C
arterial
CO_2-pressure
PAR2O
arterial O_2
pressure
PAR3C
arterial
CO_2-pressure

The tidal volume VT (or the depth of respiration in liters of air per inspiration) is taken to be a linear function of overall pulmonary ventilation. The duration of the respiratory cycle can hereafter be obtained as TT = VT/VE. The duration of inspiration TI is assumed to be constant, so that the duration of expiration becomes TE = TT-TI.

To obtain the magnitude of the respiratory flow at a given moment FLOW, we must know both the amplitude AMPL and the phase PHASE of this flow. PHASE accumulates during a simulation at the rate of π/TI during an inspiration and π/TE during an expiration. The sign of the auxillary variable SINPH = SIN(PHASE) is used to distinguish between the two, and at the same time the product of SINPH and AMPL gives the instantaneous magnitude of FLOW. The amplitude of the respiratory flow AMPL is obtained from the tidal volume VT and the durations TI and TE, using again the sign of SINPH to distinguish between the in- and expiratory phases of the respiratory cycle.

For a normal person at rest, the duration of a respiratory cycle is about .1 min (10-12 respirations per minute), and during exercise the duration may be considerably reduced. On the other hand, it takes 5-10 min for the respiratory system to reach steady state after the unset of muscular exercise. As a result, a simulation with our model usually involves several hundred respiratory cycles. Since the respiratory quotient has been assumed to be less than unity (RQ = .8), carbon dioxide production does not balance oxygen production, and the expired volume of air is somewhat smaller than the inspired volume. Over several hundred cycles, this becomes a significant effect, which in our model is accounted for through the load-dependent auxillary variable ADJ.

Another thing is that a simulation over several hundred cycles is just at the edge of what our DYNAMO II compiler can manage. Considerable care must be given to the formulation of some of the equations to avoid the accumulation of computational errors. Even then, accumulating errors in the model give rise to a slight tendency for the lung volume to decrease. We have therefore (through ADJ, but not shown in the flow-diagram) introduced a negative feed-back which controls the average lung volume.

DIFFUSION MODEL

For a normal person at rest it takes the blood approximately .75 sec to pass through the lung capillaries. Short as it may seem, oxygen and carbon dioxide diffuse so rapidly across the capillary membrane, that this period is enough for the blood to reach complete equilibrium with the alveolar air.

When a person starts to exercise, however, the circulatory rate is increased, and at a sufficiently high level of exercise, the blood passes so quickly through the lung capillaries that equilibrium between blood and alveolar air can no longer be attained. This reduces the efficiency of the gas exchange in the lungs, and together with the finite ability of the heart to increase the circulatory rate, it sets a limit to the function of the respiratory and cardiovascular systems during high levels of muscular activity.

We have found it important to include this effect (together with the similar effect occuring in the muscle capillaries) into our model. On the other hand, a model which simulates the respiratory response over 5-10 min can not at the same time give a detailed description of processes which take place in fractions of seconds. For this reason, we have developed a separate model for the diffusion of oxygen and carbon dioxide across a capillary membrane. The results obtained with this (diffusion) model have then been approximated by an analytical expression of all the significant variables, and this expression has been used in the larger model of the respiratory and cardiovascular systems.

The diffusion model considers the exchange of gas between the alveolar air and a particular volume of blood passing through the lung capillaries. The capillary volume is divided into 75 consecutive sections along the blood flow. However, instead of considering the exchange og gas for each of these sections separately and introducing equations of continuity for the transport of gas between the sections, the whole diffusion process is discussed in a coordinate system which follows the flow of blood. Each time step thus moves the considered blood volume from one section to the next, and after 75 steps of integration, the blood volume has passed all the way through the capillaries. In this formulation, the diffusion model takes the form shown in Fig. 7.

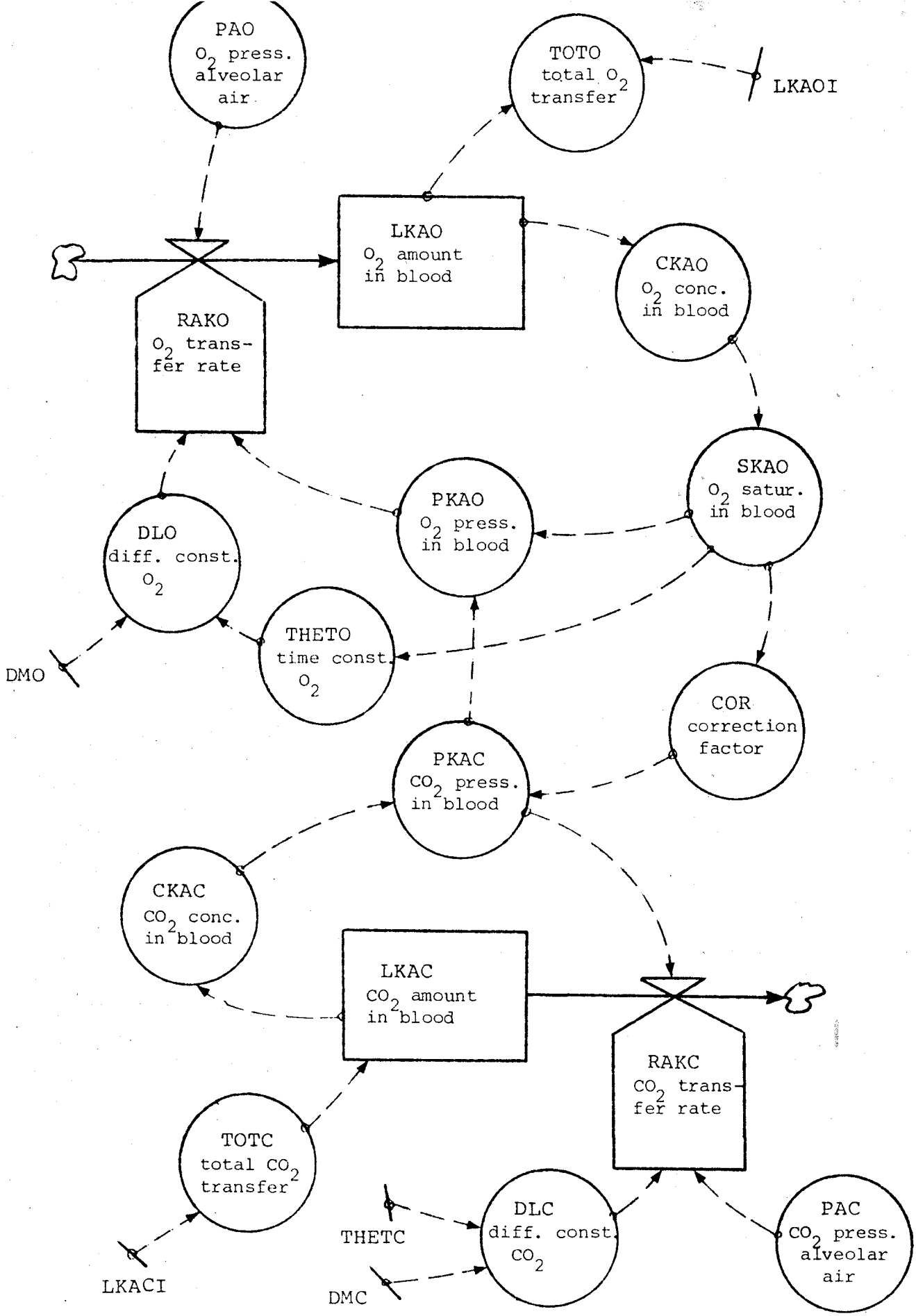

Figure 7. Flow diagram describing the diffusion of oxygen and carbon dioxide across a capillary wall.

At any given moment, the rate of oxygen transfer between alveolar air and lung capillary blood RAKO is determined by the difference between the oxygen pressure in the alveoles PAO and in the blood PKAO times an effective diffusion constant for oxygen DLO. In the same way the rate of carbon dioxide transfer RAKC is determined by the difference between the carbon dioxide pressure in the capillary blood PKAC and in the alveolar air PAC multiplied by an effective diffusion constant for carbon dioxide DLC.

The amount of oxygen in the considered blood volume LKAO determines the oxygen concentration CKAO and the corresponding hemoglobin saturation with oxygen SKAO. Together with the carbon dioxide pressure in the blood PKAC, the oxygen saturation SKAO determines the oxygen pressure PKAO according to the saturation curve(s). The effective diffusion constant for oxygen is dependent both upon the diffusion constant DMO for the actual diffusion across the capillary membrane and upon the time constant THETO for the binding of oxygen to hemoglobin. Usually, the diffusion across the capillary wall is the slower of the two processes, and therefore the one that most effectively controls DLO.

Similarly, the amount of carbon dioxide in the considered blood volume LKAC determines the carbon dioxide concentration CKAC and the corresponding partial pressure PKAC. The carbon dioxide pressure PKAC is also dependent upon the degree of oxygen saturation SKAO as described through the correction factor COR. (At this point, the actual model formulation is a little more complicated, involving also the hydrogen ion concentration in the blood). The effective diffusion constant for carbon dioxide is again determined from the actual diffusion constant DMC and from the time constant THETC for the transformation of carbon dioxide into bicarbonates. For carbon dioxide, the actual diffusion is usually the faster of the two processes.

The accumulated transfer of oxygen and carbon dioxide during the passage of the lung capillaries, respectively TOTO and TOTC, are obtained as the difference between LKAO and LKAC and the similar quantities LKAOI and LKACI for the blood arriving at the lungs.

Fig. 8 shows an example of the results obtained in a simulation with the diffusion model. We have here plotted the variation of the oxygen pressure, the rate of oxygen transfer and the accumu-

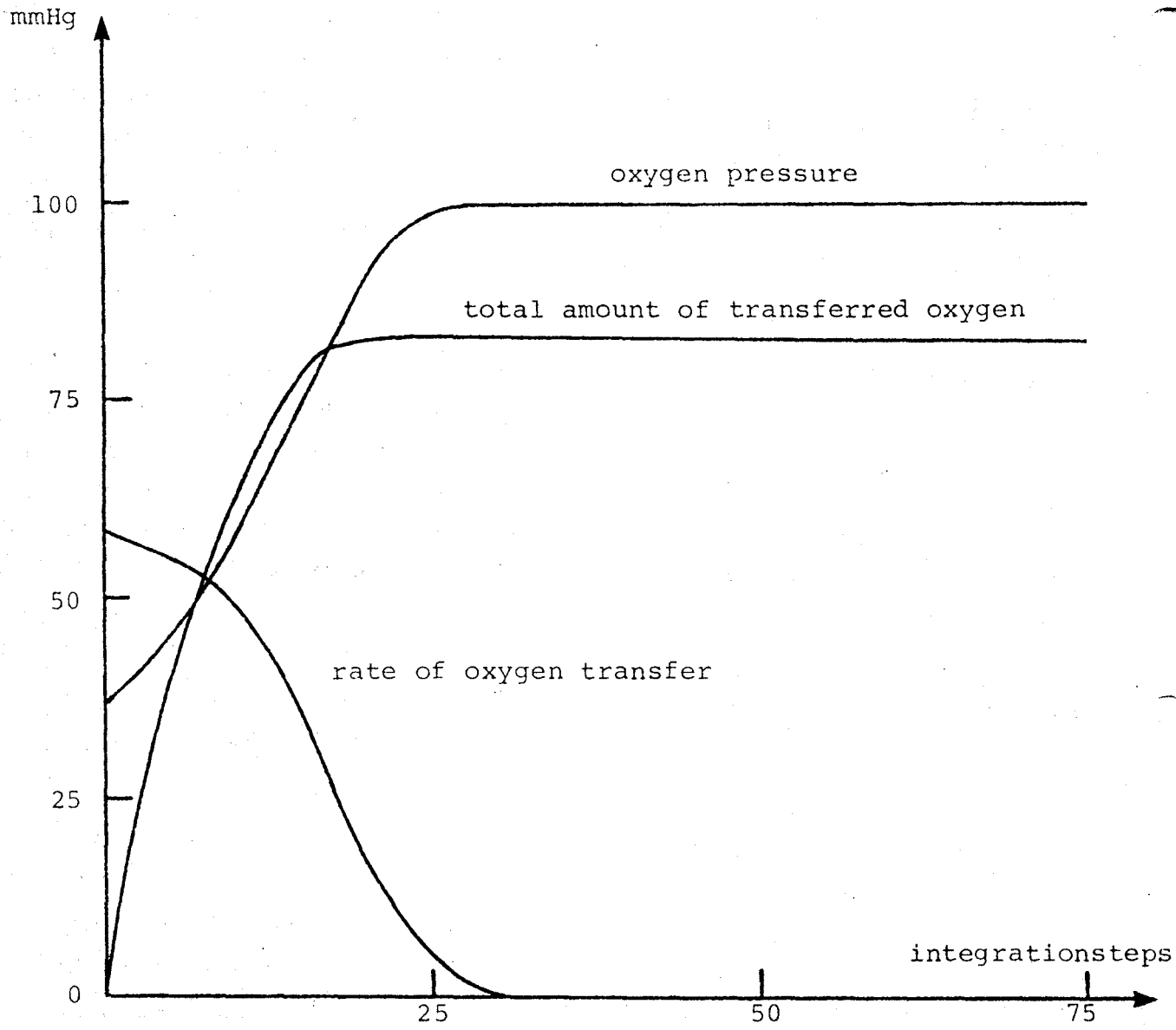

Figure 8. Typical simulation results for the transfer of oxygen from alveolar air to lung capillary blood.

In this simulation, the blood reaches equilibrium with the alveolar air well before it leaves the lungs. If the cirkulatory rate is increased by a factor of 3 - 4, however, this will no longer be the case.

lated oxygen transfer during a passage of the lung capillaries. The oxygen pressure in the incoming blood has been assumed to be 37 mmHg, and the oxygen pressure in the lung alveoles 100 mmHg. The circulatory rate is relatively low, and the blood fully equilibrates with the alveolar air well before leaving the lungs.

By performing a number of such simulations with varying initial oxygen and carbon dioxide pressures (PV30 and PV3C, respectively), with varying alveolar oxygen and carbon dioxide pressures (PAO and PAC, respectively), and with varying circulatory rates Q we have found that the transfer of oxygen per unit time in the lung capillaries with sufficient accuracy can be approximated by

$$\text{RALLCO} = Q \times \left[\text{CKAO}\{\text{PAO},\text{PAC}\} - \text{CKAO}\{\text{PV3O},\text{PV3C}\}\right] \times \left[1 - \exp\{-\text{ALPHA} \times \text{VKAP}/(Q \times \text{TAU})\}\right]$$

with

$$\text{TAU} = \left[\frac{\text{VKAP}}{\text{DMO}} + \frac{1}{\text{THETO}\{\text{SV3O}\}}\right] \times \left[\frac{\text{CKAO}\{\text{PAO},\text{PAC}\} - \text{CKAO}\{\text{PV3O},\text{PV3C}\}}{\text{PAO} - \text{PV3O}}\right]$$

VKAP is here the volume of the lung capillaries. CKAO{PAO,PAC} is the oxygen concentration for blood in equilibrium with the alveolar air, CKAO{PV3O,PV3C} is the oxygen concentration of the incoming blood (arriving from the 3rd venous compartment), and SV3O is the oxygen saturation for the incoming blood. The best overall approximation is obtained for ALPHA = 1.3. Similar expressions apply to the transfer of carbon dioxide in the lungs as well as to the transfer of both gasses in muscle tissue (see e.g. the determination of the rate of CO_2 diffusion from muscle tissue to muscle capillary blood in Fig. 5).

SIMULATION RESULTS AND DISCUSSION

Fig. 9 shows a typical example of the results obtained with the respiratory system model when simulating the transition from rest to physical activity. Here we have plotted the total oxygen consumption (in a scale from 0 to 2000 ml oxygen/min), the overall lung ventilation (in a scale from 0 to 40 l air/min), the circulatory rate (in a scale from 0 to 20 l blood/min), the partial pressures of oxygen in muscle tissue, non-muscle tissue and ve-

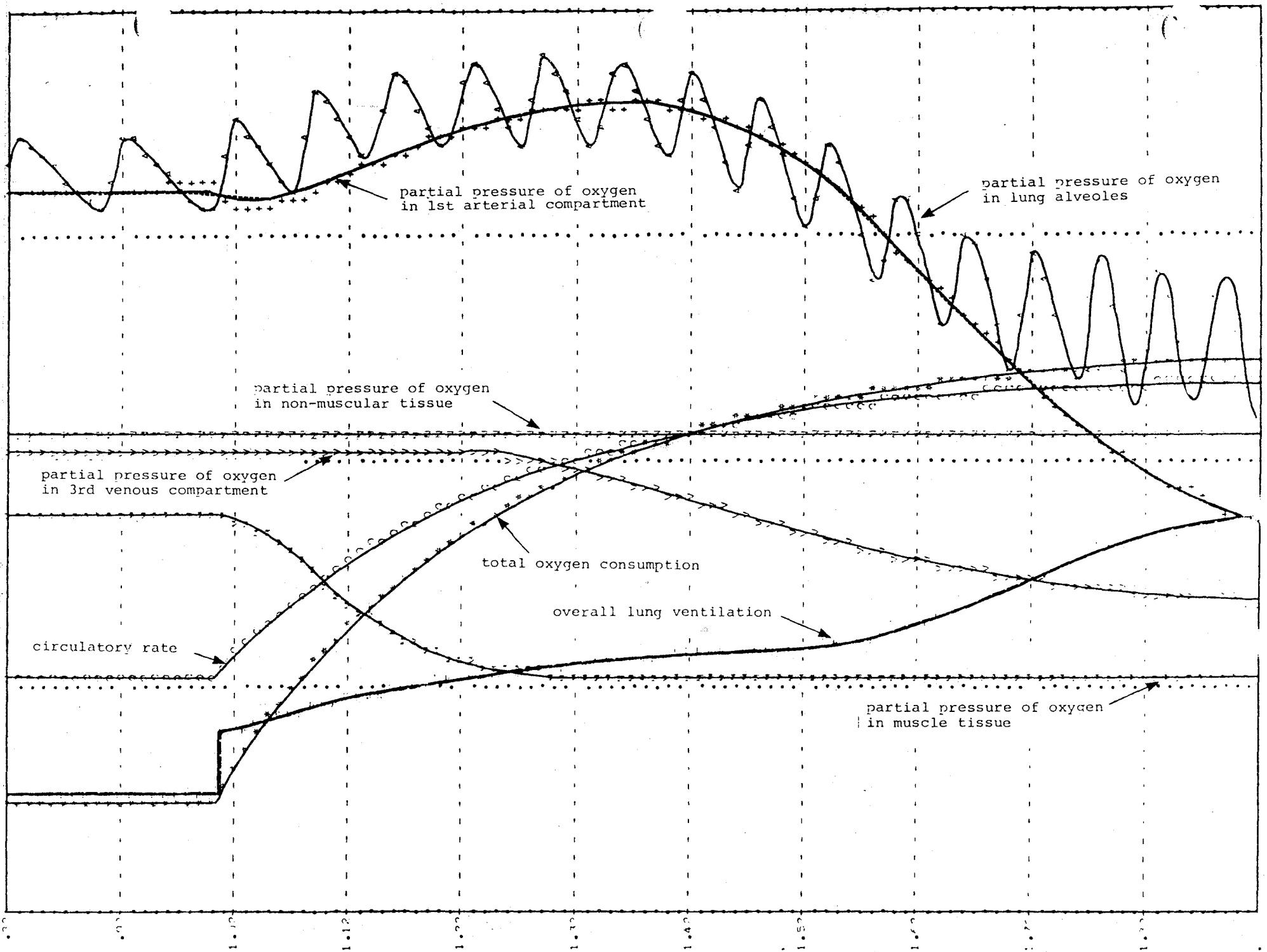

Figure 9. Respi... ry resp... to the start of exercise.

nous blood (in a scale from 0 to 80 mmHg), and the partial pressures of oxygen in arterial blood and lung alveoles (in a scale from 70 to 110 mmHg).

Initially at rest, the values of the various variables are:

oxygen consumption	250 ml oxygen/min
lung ventilation	5,2 l air/min
cardiac output	5,0 l blood/min
oxygen pressure in muscle tissue	35 mmHg
oxygen pressure in non-muscle tissue	43 mmHg
oxygen pressure in venous blood	41 mmHg
oxygen pressure in arterial blood	103 mmHg

The simulation is run over 10 min, of which Fig. 9 shows the printout for the period from .82 min to 1.92 min. With a smoothing period of .25 min, a muscular activity corresponding to an additional oxygen consumption of 1000 ml oxygen/min is introduced at time 1.00 min. In the model, this causes the circulatory rate to increase from its initial value of 5,0 l blood/min towards 12.0 l blood/min. The time delays involved in this regulation, have not been modeled in detail, however.

Due to the assumed direct stimulatory effect from the working muscles, the overall ventilation immediately rises from 5.2 to 8.1 l air/min, and ventilation hereafter continues to rise in accordance with the development in muscular activity. Manifesting itself as an increase both in depth and rate of breathing, the enhanced ventilation can also be observed as an increase both in amplitude and frequency of the oscillatory component in the alveolar oxygen pressure. As a consequence of the increased ventilation, also the average oxygen pressure in the lung alveoles starts to increase, and this again causes the arterial oxygen pressure to rise.

At the same time, the increased oxygen consumption causes the oxygen pressure in the muscles to decrease. After a certain (circulatory) delay, the oxygen pressure in the veins also starts to fall, while the oxygen pressure in non-muscle tissue remains virtually constant throughout the entire simulation. (This latter result is partly a consequence of neglecting the time constants involved in the regulation of the blood flow). After about

.2 min, the oxygen pressure in muscle tissue reaches a new steady state at 20 mmHg, and from then on the supply of oxygen to the muscles exactly balances their metabolic requirements. The rest of the system, however, is still far from steady state.

After a delay of about .3 min, the falling oxygen content in the venous blood reaches the lungs, and the partial pressure of oxygen in both the lung alveoles and the arterial blood starts to decrease. Together with the accompanying build-up of carbon dioxide in the arterial blood this causes a renewed stimulation of the ventilation, now through the two sets of chemoreceptors. The overall lung ventilation increases, and the oscillatory component in the alveolar oxygen pressure becomes faster and more pronounced.

In the beginning, the average oxygen pressure in the lungs follows the decrease in arterial oxygen pressure. About .7 min after the unset of exercise, however, the cirulatory rate has become so high, and the venous oxygen pressure so low that the diffusion of oxygen no longer is rapid enough to secure equilibrium between the alveolar air and the blood leaving the lungs. The arterial oxygen pressure then falls below the oxygen pressure in the lungs.

A final steady state for the respiratory system is not reached until 3-4 min after the unset of exercise. This steady state is shown in the left hand side of Fig. 10 which is another part of the same printout as Fig. 9, but now running from 5.84 to 6.94 min. The values attained by the various variables in steady state are:

oxygen consumption	1250 ml oxygen/min
lung ventilation	22 l air/min
cardiac output	12 l blood/min
oxygen pressure in muscle tissue	20 mmHg
oxygen pressure in non-muscle tissue	43 mmHg
oxygen pressure in venous blood	26 mmHg
oxygen pressure in arterial blood	90 mmHg

At time 6.00, the muscular exercise is suspended, and Fig. 10 shows how the respiratory and cardiovascular systems gradually return to their initial equilibrium conditions.

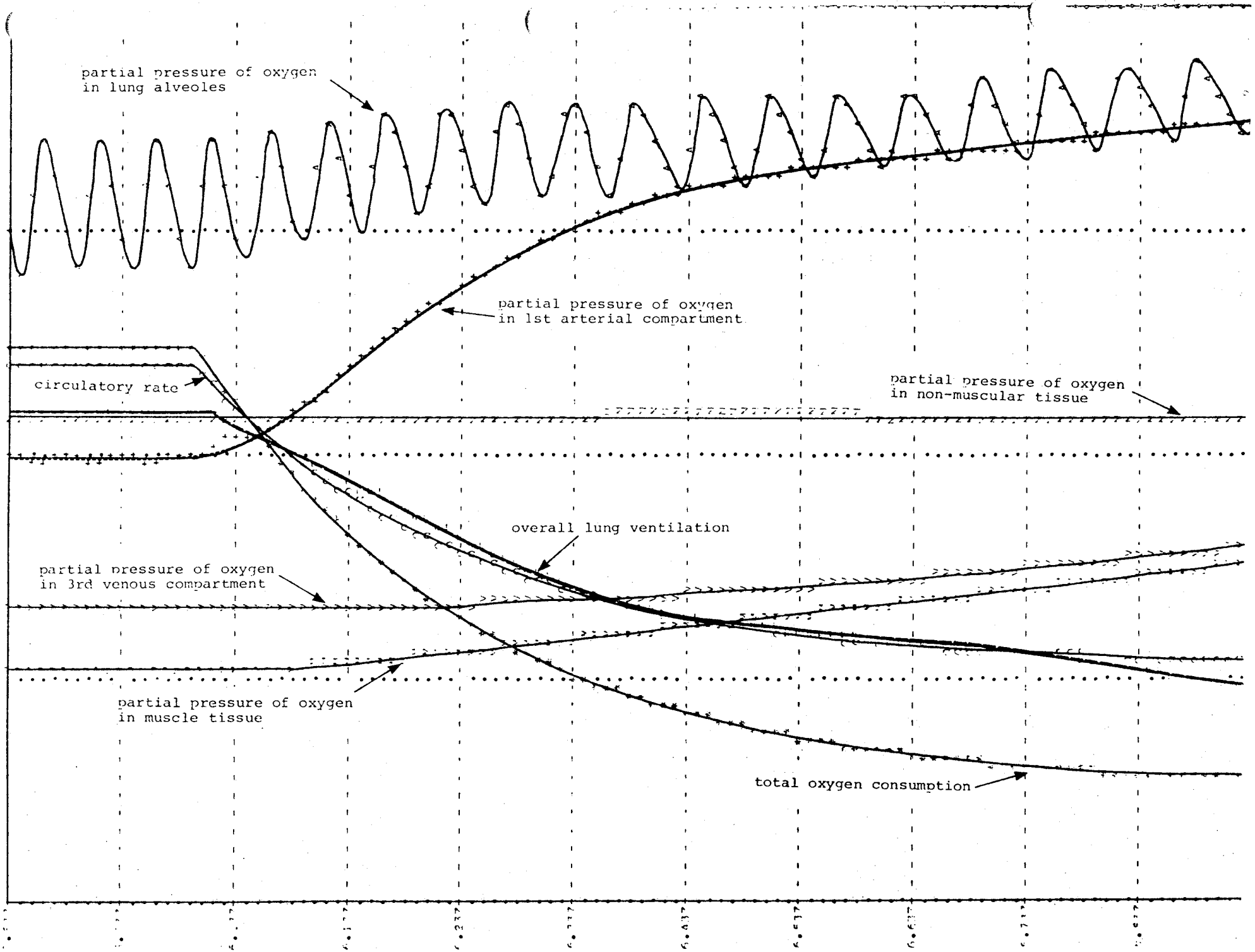

Figure 10. Respiratory response to the termination of exercise.

In our model we have assumed the following general forms for the three components in the ventilatory regulation:

$$CEN = D \times CLIP(PAR3C - B, 1, PAR3C, B + 1)$$

for the contribution from the central chemoreceptors,

$$PER = \frac{A \times D}{PAR2O-C} CLIP(PAR2C - B, 1, PAR2C, B + 1)$$

for the contribution from the peripheral chemoreceptors, and

$$MAF = CLIP(G3 \times LOAD + H3, 0, LOAD, 1)$$

for the contribution from muscular neural afferents.

By comparing simulation results with clinical results we have found the set of parameters

A = 17 mmHg
B = 38 mmHg
C = 32 mmHg
D = 4000 ml air/min/mmHg
G3 = 5 ml air/ml oxygen
and H3 = 2500 ml air/min

to give a satisfactory agreement.

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