A mathematical model of CO₂ effect on cardiovascular regulation

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Magosso, Elisa, and Mauro Ursino. A mathematical model of CO₂ effect on cardiovascular regulation. Am J Physiol Heart Circ Physiol 281: H2036–H2052, 2001.—The effect of changes in arterial CO₂ tension on the cardiovascular system is analyzed by means of a mathematical model. The model is an extension of a previous one that already incorporated the main reflex and local mechanisms triggered by O₂ changes. The new aspects covered by the model are the O₂-CO₂ interaction at the peripheral chemoreceptors, the effect of local CO₂ changes on peripheral resistances, the direct central neural system (CNS) response to CO₂, and the control of central chemoreceptors on ventilation and tidal volume. A statistical comparison between model simulation results and various experimental data has been performed. This comparison suggests that the model is able to simulate the acute cardiovascular response to changes in blood gas content in a variety of conditions (normoxic hypercapnia, hypocapnic hypoxia, and hypercapnic hypoxia). The model ascribes the observed responses to the complex superimposition of many mechanisms simultaneously working (baroreflex, peripheral chemoreflex, CNS response, lung-stretch receptors, local gas tension effect), which may be differently activated depending on the specific stimulus under study. However, although some experiments can be reproduced using a single basal set of parameters, reproduction of other experiments requires a different combination of the mechanism strengths (particularly, a different strength of the local CO₂ mechanism on peripheral resistances and of the CNS response to CO₂). Starting from these results, some assumptions to explain the striking differences reported in the literature are presented. The model may represent a valid support for the interpretation of physiological data on acute cardiovascular regulation and may favor the synthesis of contradictory results into a single theoretical setting.

hypercapnia; hypocapnic hypoxia; chemoreceptors; lung-stretch receptors; central neural system response

Carbon dioxide is known to have a significant impact on the cardiovascular system. Experimental studies in animals suggest that hypocapnia causes a depression of the central vasomotor neurons (34, 35, 38) and abates the peripheral chemoreflex response (4, 20, 30–32); the opposite effects occur during hypercapnia (16, 34, 35, 38). Moreover, CO₂ is known to be a vasodilator of many peripheral vascular beds (including the brain, heart, and skeletal muscle) (6, 15, 18, 28, 44, 53). Furthermore, in conditions when ventilation is free to change, hypercapnia provokes an increase in lung inflation, thus stimulating slowly adapting pulmonary-stretch receptors with myelinated A fibers; the latter cause tachycardia and vasodilation in the vascular beds under sympathetic reflex control (10, 11). Finally, changes in systemic arterial pressure (SAP), which often accompany hypercapnia or hypocapnia, modulate the action of the baroreflex control system, which, in turn, exerts a powerful control on several cardiovascular parameters.

Even though the main mechanisms involved in the cardiovascular response to CO₂ changes have been familiar for many years, their final effects on cardiovascular quantities are far from being completely recognized. Although several experiments indicate that hypercapnia causes an increase in total peripheral resistance (TPR), tachycardia, and an increase in mean SAP, others report a significant decrease in total systemic resistance and a decrease in heart rate (HR) (5, 25, 48, 50, 54, 61). Moreover, changes in cardiac output (CO) exhibit an almost equal dispersion in both directions during both increasing and decreasing PCO₂.

These apparent contradictions of experimental data can ensue from the extreme complexity of the entire cardiovascular control system, characterized by the nonlinear superimposition among multiple mechanisms operating simultaneously. Individual variability, differences in the experimental setup (for instance free vs. artificial ventilation), or a variance in hemodynamic conditions (for instance in the SAP level or in metabolism) may bring about a different balance between regulatory actions, thus resulting in opposing final changes of the same regulated quantities.

A further aspect that requires particular attention is that changes in blood PCO₂ almost always occur together with O₂ pressure changes (for instance during hypocapnic hypoxia or asphyxia). Because the regulatory actions triggered by changes in PO₂ and PCO₂ share several common afferent pathways and utilize the...
CARDIOVASCULAR RESPONSE TO CO₂ CHANGES

The cardiovascular response to CO₂ becomes exceedingly complex (1). Mathematical modeling and computer simulation techniques have often been advocated as important tools to investigate the complexity of physiological control systems in rigorous quantitative terms. In recent years, we formulated a mathematical model of the short-term cardiovascular regulatory response to acute isocapnic hypoxia (59). The model includes the arterial baroreflex, the peripheral chemoreflex, the lung-stretch receptors, the hypoxic response of the central neural system (CNS), and the local O₂ effect on the vascular beds with a higher metabolic requirement. With that model, we were able to summarize several different experimental results concerning acute hypoxia into a single theoretical setting (60).

The main limitation of the previous model was the absence of CO₂ mechanisms, i.e., the model could be used to investigate hypoxia in isocapnic conditions only. The aim of the present subsequent study is to include the effect of blood P_{CO₂} into the previous mathematical model in accordance with present physiological knowledge. This may be important 1) to provide a theoretical framework for the analysis of physiological experiments characterized by changes in P_{CO₂}; and 2) to provide possible explanations for the differences observed among experimental results. In particular, we aspire to analyze the putative role of each mechanism in the cardiovascular response to CO₂.

This paper is structured as follows. First, the mathematical model is briefly described in qualitative terms, laying stress on the new aspects only. Second, physiological results concerning normoxic hypercapnia, hypocapnic hypoxia, and hypercapnic hypoxia are simulated. Finally, a sensitivity analysis on the main mechanisms is performed to gain a deeper understanding on the possible rationale for experimental differences.

Glossary

- **Cv_{vb,02}** Oxygen gas concentration in venous (v) blood leaving brain (b), ml O₂/ml blood
- **Cv_{vb,02n}** Oxygen gas concentration in venous blood leaving brain under normal (n) conditions, ml O₂/ml blood
- **Cv_{vj,02} j = h, m** Oxygen gas concentration in venous blood leaving heart (h) and skeletal muscle (m), respectively, ml O₂/ml blood
- **D_{Vp}** Time delay of ventilatory response to peripheral chemoreceptors (p), s
- **D_{Vc}** Time delay of ventilatory response to central chemoreceptors (c), s
- **f_{ab}** Baroreceptor afferent (ab) activity, spikes/s
- **f_{ac}** Afferent chemoreceptor (ac) activity, spikes/s
- **f_{aj} j = h, p, v** Activity in the efferent sympathetic (s) fibers to heart, peripheral resistances, and veins, respectively, spikes/s
- **f, K_{H}** Parameter related with the strength of the afferent chemoreceptor response to CO₂, dimensionless
- **g_{ccoj} j = h, p, v** Gains of the central chemoreceptor sympathetic (ccs) response to CO₂ acting on heart, peripheral resistances, and veins, respectively, s⁻¹ mmHg⁻¹
- **g_{j,02} j = h, m, b** Gain of the local O₂ response on the coronary (h), muscular (m), and cerebral (b) vascular beds, respectively, ml blood/ml O₂
- **g_{Vp}** Gain of ventilatory response to peripheral chemoreceptors, l/min
- **g_{Vc,ib}g_{Vc,i}** Gain of ventilatory response to central chemoreceptors (h during hypercapnia, l during hypocapnia), l/min·mmHg⁻¹·s⁻¹
- **G_{bp}** Cerebral peripheral hydraulic conductance, ml/mmHg⁻¹·s⁻¹
- **G_{bpm}** Basal (n) value of cerebral peripheral hydraulic conductance, ml/mmHg⁻¹·s⁻¹
- **k_{j,CO₂} j = h, m** Parameter related to the central gain of the CO₂ effect, coronary and muscular bed, respectively, mmHg
- **k_{isc,aj} j = h, p, v** Parameter related to the central gain of the hypoxic (ischemic) response, mmHg
- **k_{ac}** Parameter related to the central gain of the afferent chemoreceptor response, mmHg
- **Pa_{CO₂,n}** P_{CO₂} basal value (n), mmHg
- **P_{O₂,ac}** Oxygen pressure at the central point of the afferent chemoreceptor response, mmHg
- **P̃_{O₂,aj}** Oxygen pressure at the central point of the hypoxic (ischemic) response, mmHg
- **R_{jp} j = h, m** Coronary and skeletal muscle resistance (hydraulic), respectively, mmHg·s·ml⁻¹
- **R_{jpm} j = h, m** Normal coronary and skeletal muscle resistance (hydraulic), respectively, mmHg·s·ml⁻¹
- **RR** Respiratory rate, breaths/min
- **V** Ventilation, l/min
- **ΔV_{p}** Change in ventilation induced by activation of peripheral chemoreceptors, l/min
- **ΔV_{c}** Change in ventilation induced by activation of central chemoreceptors, l/min

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The model includes the pulsating heart, the vascular system, and various regulatory actions. Description of the regulatory mechanisms, in turn, distinguishes between the different information from several groups of receptors (arterial baroreceptors, peripheral chemoreceptors, and lung-stretch receptors), the response of the CNS to changes in \( \text{PO}_2 \) and \( \text{PCO}_2 \), the activity of the efferent sympathetic fibers directed to the heart and peripheral vessels, the vagus activity, the response of various effectors to the efferent activity of neural fibers, the local effect of \( \text{O}_2 \) and \( \text{CO}_2 \) on peripheral resistances, and the ventilation response to peripheral and central chemoreceptor drive. A block diagram summarizing the main aspects of the regulatory actions is shown in Fig. 1.

The description of the pulsating heart and of the entire vascular system is unchanged compared with that used in previous studies (57, 59), where all details can be found. Hence, these parts of the model are not described again for the sake of brevity.

**Afferent information.** The arterial baroreceptors respond to changes in both the instant value of SAP and its rate of change; slowly adapting lung-stretch receptors respond to changes in VT. Both responses include a static characteristic and a first-order dynamic. The response of both groups of receptors is the same as that used in the previous paper (59).

The model of the peripheral chemoreceptors also includes a dynamic block and a static nonlinear characteristic. Description of the latter has been modified compared with that used in the previous paper (59) to account for the nonlinear peripheral interaction between \( \text{O}_2 \) and \( \text{CO}_2 \) pressure changes. As in the previous work, the static curve relating chemoreceptor activity to arterial \( \text{PO}_2 \)(\( \text{PaO}_2 \)) during normocapnia exhibits an hyperbolic trend (4) with an upper saturation level. This behavior has been reproduced using a combination of exponential functions. The static relationship linking chemoreceptor activity to \( \text{PCO}_2 \) during normoxia exhibits a lower threshold and a monotonic increase (20, 30–32). These data can be reproduced reasonably well through a logarithmic curve. Finally, experimental and clinical results demonstrate that hypoxia reinforces the chemoreceptor response to hypercapnia and vice versa (20, 30–32); this behavior involves a multiplicative relationship between the individual \( \text{O}_2 \) and \( \text{CO}_2 \) static curves and a progressive shift of the lower threshold to the left during hypoxia (see Eqs. 1–2 in APPENDIX).

Examples of the chemoreceptor response to \( \text{PCO}_2 \) changes, evaluated in steady-state conditions at different arterial oxygen levels, are shown in Fig. 2 and are compared with experimental data. The parameters in these curves have been given to reproduce experimental results by Fitzgerald et al. (20) and Lahiri et al. (30–32). The chemoreceptor time constant \( \tau_{ac} \) has been given the value of 2 s based on data by Rutherford and Vatner (51).

**Efferent neural pathways.** The efferent pathways in the model comprise both sympathetic and parasympathetic (vagal) neural fibers. The activity in these efferent fibers is a nonlinear monotonic function of the weighted sum of activities from baroreceptors, chemoreceptors, and lung-stretch receptors, where the weights may be positive or negative. Moreover, afferent information is compared with an offset term; in the case of sympathetic activity, the latter is modulated by hypoxia in the CNS and by \( \text{CO}_2 \) changes in the medulla (see CNS response).

As justified in previous studies (57, 59), we assumed that sympathetic activity decreases with a negative monoeponential function in response to inhibitory afferent information, whereas it increases exponentially up to a saturation level in response to excitatory inputs (see APPENDIX, Eq. 3). An important modification of the present work, compared with the previous, is that we used different equations to describe...
the sympathetic activity to the heart ($f_{sh}$), to the peripheral resistance ($f_{sp}$), and to the veins ($f_{sv}$). In fact, experimental data on the CNS response to hypocapnia and hypercapnia can be reproduced reasonably well only assuming a dissimilar sympathetic action on arterioles and veins (see RESULTS). The weights connecting baroreceptors, peripheral chemoreceptors, and lung-stretch receptors to sympathetic neurons have been given the same values as in the previous work (59). In contrast, the offset term depends not only on hypoxia of the CNS, but also on the CO$_2$ level in supraspinal neural structures (especially the medulla).

The vagal fibers are directed to the heart only and contribute to the control of HR. Their dependence on the activity of afferent information is the same as that used previously (59).

Fig. 1. Block diagram describing the interactions among regulatory mechanisms according to the present model. CNS, central neural system.

Fig. 2. Steady-state activity in the afferent chemoreceptor fibers ($f_{ac}$) vs. arterial PCO$_2$ (PaCO$_2$), plotted at different levels of arterial PO$_2$ (PaO$_2$) ranging from deep hypoxia (top left) to hyperoxia (bottom right). Continuous lines are model simulation curves obtained at different levels of PaO$_2$. Experimental data are from Fitzgerald and Parks (20) ($\triangle$, $\ast$, $\times$, $\circ$) and from Lahiri and Delaney (31) ($\circ$) in cats, at corresponding levels of PaO$_2$. 

![Diagram of cardiovascular response to CO$_2$ changes](http://example.com/diagram.png)
**CNS response.** The model assumes that changes of Po2 and PCO2 affect the sympathetic activity directly by modifying the offset term in the equation linking sympathetic response to the afferent information (Eqs. 4–7 in APPENDIX). Both mechanisms include a static characteristic and a first-order, low-pass dynamic.

Various experimental results suggest that the effect of CNS hypoxia on the sympathetic drive is quite negligible until Po2 is lowered below a given threshold and then it increases dramatically. This behavior has been reproduced using a sigmoidal function. According to data reported in Koehler et al. (25), this threshold is higher for the cardiac sympathetic activity (50–60 mmHg) and lower for the sympathetic activity directed to peripheral vessels (35–40 mmHg). All parameters describing the static and dynamic aspects of CNS hypoxia have been given to mimic data by Koehler et al. (25) and Downing et al. (16).

A direct role of the CNS on the cardiovascular response to CO2 is stressed by experiments in cats and rats (34, 35, 37). These experiments show that hypocapnia can produce a decrease in arterial pressure and total systemic resistance independently of the input from arterial baroreceptors and peripheral chemoreceptors. The opposite effect is evident during hypercapnia. Moreover, superfusion of the ventral medulla with hypercapnic fluid causes a sympathetically mediated increase in HR and augments sympathetic activity to the forelimb, hindlimb, and kidney (36). Results of the previous experiments can be simulated reasonably well assuming that the offset term of sympathetic activity (i.e., the quantity θ in Eq. 3) depends linearly on PCO2 changes. The slope of these relationships for the arterioles, venules, and the heart have been given to mimic experimental results by Lioy et al. (34) and Downing et al. (16) (see RESULTS). The time constant of the central CO2 mechanism has been taken from the arterial pressure time pattern reported in Lioy and Trzebski (37) following CO2 stimulation of central chemosensitive areas.

**Cardiovascular effectors for the reflex control.** As explained above, in the present work the sympathetic activity is subdivided into three distinct branches. The first is directed to systemic arterioles in the splanchnic, muscular, and nonautoregulated extrasplanchnic vascular beds and modifies the peripheral resistance. The second is directed to the peripheral veins and modifies venous unstrained volumes in the same vascular beds. Finally, sympathetic activity to the heart affects heart period and the end-systolic elastance in the right and left ventricles. The vagal activity works on the heart only by modulating heart period. Each effector response includes a pure delay, a monotonic static function, and a first-order, low-pass dynamic. Equations are formally identical to those used in a previous work (59) and hence are not repeated for brevity.

**Local effect of O2 and CO2.** We assume that hypoxia in the coronary, brain, and skeletal muscle circulation causes vasodilation through a local mechanism. It is well known that the local O2 effect can be ascribed to two concurrent mechanisms, i.e., a direct effect of O2 on smooth muscle tension in the arteriolar wall and an indirect effect mediated by the release of vasodilatory metabolites (adenosine, pH, etc.) by the hypoxic tissue. Because the aim of this model is not to analyze the synergetic action of these mechanisms in detail and to assess their individual role, but just to simulate the overall O2 effect on peripheral resistances, we used a simple empirical equation for each compartment. In this equation, we assumed that the controlled quantity for the local O2 regulation is O2 concentration in the venous blood leaving the compartment. This choice is appropriate because venous O2 concentration is influenced by both the arterial O2 content and local blood flow, as well as by tissue O2 consumption rate; hence, its changes reflect all stimuli (direct and indirect) affecting the vascular bed.

Accordingly, the peripheral hydraulic resistance in the locally regulated vascular beds is linearly related to O2 venous concentration via a first-order dynamic, i.e., resistance decreases when O2 venous concentration falls below the basal level (Eqs. 8–9 and 12–13 in APPENDIX). All parameters of this regulation have been given the same values as in the previous work (59).

O2 venous concentration is computed from knowledge of arterial Po2 (PaO2) (which is an input for the model) by imposing a mass balance between O2 extraction rate and O2 consumption rate. To this end, the O2- and CO2-carrying capacity of blood are computed from Po2 and PCO2 by using the equations proposed by Spencer et al. (52), which account for the Bohr and Haldane effects. Throughout the present simulations the O2 consumption rate is assumed to remain constant in the brain and skeletal muscle. By contrast, consumption rate in the heart is proportional to the average power of the cardiac pump.

According to several authors, CO2 has an important vasodilatory effect on the cerebral, coronary, and skeletal muscle vascular beds. This effect has been simulated, during normoxia, through a static nonlinear relationship, linking peripheral resistance to arterial PCO2 (PaCO2), and a first-order, low-pass dynamic. The static relationships have been assigned to mimic experimental data by Reivich (45) to the cerebral vascular bed, by Case et al. (6) to the coronary circulation, and by Kontos et al. (28), Radawski et al. (44), and Stowe et al. (55) to the skeletal muscle circulation (Eqs. 10–11 and 14–15 in APPENDIX). The time constant of this mechanism has been given a value taken from Ursino and Lodi (58), where more details can be found.

By example, Fig. 3 shows the relationship linking peripheral resistance to PaCO2 in the skeletal muscle vascular bed during normoxia in the absence of any sympathetic influence.

![Fig. 3. Percent changes of peripheral muscle resistance (Rmp) in the skeletal muscle vascular bed vs. local (PCO2) measured by Refs. 28, 44, and 55 in conditions where only the local mechanism is active. Continuous line represents model results simulated by giving a value for the local vasodilatory effect of CO2 as in Table 1 (kPCO2 = 142.8 mmHg). The large dispersion among experimental data is remarkable.](http://ajpheart.physiology.org/10.1152/ajpheart.00388.2001)
(i.e., only the local CO₂ effect is effective in these experiments). As clearly shown in Fig. 3, experimental data exhibit a very large dispersion. The basal parameter values for the model (continuous line in Fig. 3) have been chosen to mimic cases with a moderate peripheral reactivity to CO₂. However, as shown in RESULTS, a stronger reactivity must be hypothesized to explain data by others (48–50).

**Control of V and VT.** $V$ is regulated by both central and peripheral chemoreceptors. Because both effects are largely additive in most physiological conditions (7), we can write (Eq. 16 in APPENDIX)

$$V = V_n + \Delta V_p + \Delta V_c$$

where $V$ represents ventilation and the three terms on the right-hand side of the previous equation denote the normal level of ventilation (i.e., ventilation during normoxia and normocapnia, $V_n$), and the changes in ventilation induced by stimulation of peripheral ($\Delta V_p$) and central chemoreceptors ($\Delta V_c$), respectively. The effect of each group of chemoreceptors has been simulated using a simple first-order linear differential equation with a pure delay (Eqs. 17 and 18 in APPENDIX) (3, 8, 9, 55).

The input quantity for the peripheral mechanism is the afferent activity in the arterial chemoreceptor fibers; as shown in Fig. 2, the latter implicates a nonlinear multiplicative O₂-CO₂ interaction. The value of the peripheral chemoreceptor gain has been assigned to reproduce the ventilatory response to a hypoxic stimulus ($PaO_2 = 40$ mmHg) in isocapnic condition reported by Reynolds and Milhorn (46) (Fig. 4).

The input for the central mechanism are changes in $PCO_2$, assuming that, in physiological conditions, variations of $PCO_2$ in blood and in the medulla surface are proportional. This is the assumption adopted in most recent mathematical models of ventilatory control fitted to experimental data (3, 8, 9). The central chemoreceptor gain has been given two different values during hypercapnia and hypocapnia, reflecting the existence of two regions separated by a break point in the relationship “ventilation vs. $PaCO_2$” (7). During hypercapnia the value of the central chemoreceptor gain, together with the peripheral chemoreceptor gain assigned previously, furnishes a ventilation increase per millimeter mercury of $PCO_2$ change (2.4 l·min⁻¹·mmHg⁻¹) in the range reported in the literature (7, 19, 43). During hypocapnia, the ventilation change exhibits low CO₂ sensitivity (7). The pure delay and time constant of peripheral chemoreceptors has been taken from the works of others (3, 8, 9, 55). The pure delay and the time constant of central chemoreceptor control have higher values according to the same authors. An example of the ventilatory response to a hypercapnic stimulus is shown in Fig. 5, top, and compared with clinical data (47).

Finally, because the input quantity for lung-stretch receptors are changes in VT, we need a relationship linking $V$, VT, and respiratory rate (RR). Clinical data in humans (17, 23, 46, 47) suggest that, during moderate hypoxia or moderate hypercapnia, the increase in $V$ can be almost completely ascribed to changes in VT. In contrast, during severe hypoxia and severe hypercapnia, changes in RR become evident, too; as a consequence, VT increases less than $V$. The relationship linking VT and $V$ can be reproduced fairly well using an empirical mathematical equation (Eq. 19 in APPENDIX); the latter is shown in Fig. 6 and compared with clinical data on humans. Changes in VT during hypercapnia and hypoxia are also shown in Figs. 4 and 5 (bottom) and compared with the data by Reynolds et al. (46, 47).

The set of differential equations has been numerically solved on Pentium-based personal computers by using the Runge-Kutta-Fehlberg 4/5 algorithm with adjustable step length (maximum allowed integration step 0.01 s, memorization step 0.01 s). To this end, we used the software package SIMNON (SIMNON/PCW for Microsoft Windows, version 3.0, SSPA Maritime Consulting; Göteborg, Sweden) designed for simulation of ordinary differential equations. Because all hemodynamic quantities are pulsating in nature, the mean
values during each heart period were computed from stored data using the trapezoidal integration method.

All new mathematical equations are reported in APPENDIX. The parameter numerical values with references can be found in Table 1. All other parameters and equations, necessary to complete the model, can be found in a previous study (59).

RESULTS

In all subsequent figures, experimental data taken from the literature are presented as means ± SE. Just in a few cases, SE are not presented because they could not be acquired from the original publication. Moreover, to quantitatively assess the adequacy of fitting, a statistical Student’s t-test has been performed between the model prediction and the corresponding experimental data in all cases where the experimental SE was available. Three levels of statistical significance are used as the following: *P < 0.1, **P < 0.05, and ***P < 0.01.

CO₂ response of the CNS. A preliminary group of simulations was performed to give a numerical value to the parameters characterizing the CNS response to local CO₂ changes. To this end, the action of baroreceptors, peripheral chemoreceptors, and lung-stretch receptors was excluded from the model to simulate conditions occurring in artificially ventilated animals after the vagi, carotid sinus, and aortic nerves were cut (34). Exclusion of these mechanisms was achieved by artificially maintaining the input quantities of these groups of receptors at their basal value throughout the simulations, i.e., these receptors work in open-loop conditions with an input quantity different from that used in the rest of the cardiovascular model. PaCO₂ was then changed from 20 to 50 mmHg. The parameter affecting HR (\( g_{\text{cesj}} \) in Eq. 6 on APPENDIX) was assigned to reproduce the HR increase measured by Downing et al. (16) in dogs (~40 beats/min increase if PCO₂ of the CNS superfusate is increased by ~80 mmHg). The parame-

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**Fig. 5.** Time pattern of minute \( \dot{V} \) (top) and VT (bottom) simulated with the model (left) and measured by Reynolds et al. (47) (right) in response to a 25-min step hypercapnia (PaCO₂ = 56 mmHg). Clinical data are means ± SE for 14 subjects.

**Fig. 6.** Plot of the steady-state relationship between VT and minute \( \dot{V} \) according to the present model (continuous line). Clinical data are from Dripps and Comroe (17), Hey et al. (23), and Reynolds and Milhorn (46).
CARDIOVASCULAR RESPONSE TO CO2 CHANGES  

Afferent Chemoreflex Pathway  
\[ f_{ac, max} = 12.3 \text{ s}^{-1} \]  \[ f_{ac, min} = 0.835 \text{ s}^{-1} \]  \[ f = 1.4 (20, 31, 32) \]  \[ k_{ac} = 29.27 \text{ mmHg} \]  

Efferent Sympathetic Pathway  
\[ f_{es, max} = 60 \text{ s}^{-1} \]  \[ f_{es, 0} = 16.11 \text{ s}^{-1} \]  \[ k_{es} = 0.0675 \text{ s}^{-1} \]  \[ k_{es, sp} = 2 \text{ mmHg} \]  

CNS Response  
\[ \dot{P}_{O_{2}, sp} = 30 \text{ mmHg} \]  \[ k_{inc, sp} = 2 \text{ mmHg} \]  

Blood Flow Local Control  
\[ V_{c} = 7 \text{ l/min} \]  \[ \dot{V}_{O_{2}, c} = 3.6 \text{l/min} \]  \[ D_{V_{c}} = 7s \]  \[ D_{V_{c}} = 8s \]  

Ventilatory Response  
\[ \dot{V}_{O_{2}, n} = 1.8 \text{l/min} \]  \[ \dot{V}_{O_{2}, n} = 0.12 \text{l/min} \]  

See text definitions of all abbreviations.

The assumption of a higher local CO2 reactivity in the skeletal muscle used in the simulation of Fig. 9 can be further validated by comparing model prediction with the data reported by Richardson et al. (48) after sympathetic blockade of the forearm (Fig. 9B). In this particular simulation, we assumed that the skeletal muscle vascular bed is not under sympathetic control [i.e., muscle peripheral resistance \( R_{mpn} \) was held constant in Eq. 12 of the APPENDIX to mimic local sympathetic blockade], whereas all other parameters in the model were given the same value used in Fig. 9A. The values of skeletal muscle resistance and local blood flow measured by Richardson et al. (48) in this condition agree with those obtained by the model, confirming the existence of a high local CO2 reactivity.

Hypercapnia during controlled ventilation. Several authors analyzed the effect of hypercapnia on cardiovascular variables in anesthetized animals with controlled ventilation plus hyperoxia. In these experiments affecting peripheral resistance and CO \( g_{ccsp} \) and \( g_{ccsv} \) were given to reproduce the changes in the main hemodynamic quantities observed by Lioy et al. (34) in the rat. A comparison between model predictions and experimental results is shown in Fig. 7 for two different values of parameter \( g_{ccsp} \). It is worth noting that experimental data can be reproduced reasonably well assuming that the CNS response to CO2 does not significantly affect the venous unstressed volume. This assumption, however, will be removed when simulating other experiments (see Normoxic hypercapnia). Significant statistical differences between simulated and real data are evident only during severe hypercapnia.

Normoxic hypercapnia. Figure 8 shows the percent changes in the main hemodynamic quantities simulated with the model in response to an acute +10 mmHg increase in \( P_{aCO_{2}} \) performed at constant \( P_{O_{2}} = 80 \text{ mmHg} \), i.e., the same basal value as in Ref. 25. This simulation was performed with all mechanisms working in closed-loop conditions. Results are compared with those computed from data reported in Koehler et al. (25). The agreement is satisfactory with no significant statistical difference.

However, Richardson et al. (48) observed a different pattern of hemodynamic quantities in healthy male volunteers during normoxic hypercapnia, i.e., a decrease in total systemic resistance with a notable rise in CO. As is shown in Fig. 9A, very significant differences occur if one tries to simulate these results using the basal parameter values shown in Table 1. Conversely, results by Richardson et al. (48) can be reproduced quite well by the model assuming a stronger local vasodilatory effect of CO2 on the skeletal muscle vascular bed and a different strength for the CNS response to CO2 on the heart and peripheral vessels. In particular, data by Richardson et al. can be satisfactorily reproduced assuming that activation of the CNS response to hypercapnia causes vasoconstriction of peripheral veins (thus increasing mean filling pressure and venous return), whereas these receptors have a negligible role on HR and peripheral resistance (see Fig. 9 for the parameters used).
ments, owing to artificial ventilation, lung-stretch receptors have no role in the regulation, hence their input was maintained constant throughout the simulations. Two different examples are shown in Fig. 10 (50, 61) and compared with model predictions. In the experiments by Wendling et al. (61), TPR increases during hypercapnia, whereas CO decreases. This result can be reproduced by using the basal set of parameters, but just assuming a reduction in the strength of the CNS response on HR and on TPR. The last changes may reflect the use of anesthesia during the experiment.

In contrast, Rothe et al. (50) observed a decrease in TPR during hypercapnia and a concomitant increase in CO. Moreover, in this experiment, mean filling pressure increased significantly suggesting the occurrence of venoconstriction. These results, which largely differ from those by Wendling et al. (61), can be reproduced rather well at different levels of PaCO₂ assuming a stronger local vasodilatory effect of CO₂ on peripheral vessel and a different impact of central chemoreceptors on cardiovascular parameters (i.e., venoconstriction with almost no role on resistance and HR). These parameter changes are similar to those already used to simulate experiments by Richardson et al. (48) (see Fig. 9).

Hypocapnic hypoxia. Figure 11 shows the percent changes in the main hemodynamic quantities simulated in response to an acute hypoxia, with a concomitant decrease in PaCO₂. Two different examples are
reported and compared with data obtained by Krasney and Koehler (29) in dogs and Kontos et al. (27) on human volunteers. The agreement between model simulation results and data by Krasney and Koehler (29) is satisfactory, using the basal parameter set without statistical differences. In contrast, very significant statistical differences are evident to mean SAP and TPR if model predictions are compared with data by Kontos et al. (27). However, these differences can be overcome if

the strength of the peripheral chemoreceptor response to CO₂ is just moderately increased (from $K_{H}^{3}$ to $K_{H}^{4.7}$, see Eq. 1 in APPENDIX).

Hypercapnic hypoxia. Figure 12 shows the percent changes in the main hemodynamic quantities simulated in response to acute hypercapnia + acute hypoxia. Comparison is performed with two different experimental results in dogs (25, 49). Figure 12A shows that the model is able to reproduce the experimental
results by Koehler et al. (25) fairly well using the basal set of parameters. However, we can observe that HR and so CO are overestimated. In contrast, the results by Rose et al. (49) (see Fig. 12B) exhibit a significant decrease in TPR during hypercapnia + hypoxia. The model can approximately simulate this behavior only assuming that the CNS response to CO2 has scarce effect on resistance and HR and assuming a stronger vasodilatory effect of CO2 on peripheral vascular beds. It is interesting to observe that the latter changes conform to those already hypothesized to simulate data by Richardson et al. (48) and Rothe et al. (50).

Finally, it is worth noting that, in all cases, HR increases much more in the model than in the experiments, which is reflected in overestimation of the CO level. This model limitation is commented in DISCUSSION.

Sensitivity analysis. Because the cardiovascular responses to CO2 pressure changes reported in the literature show striking differences from one case to another (5, 25, 38, 48, 50, 54, 61), we found it useful to perform a sensitivity analysis on the role of the individual mechanisms. To this end, Fig. 13 shows the percent changes in the main hemodynamic quantities simulated with the model in response to a PaCO2 increase from 40 to 60 mmHg during normoxia (PaO2 = 95 mmHg) first when all mechanisms are intact and then after selective exclusion of a single mechanism. The individual mechanism was eliminated by opening the corresponding feedback loop and maintaining the input quantity at the basal level, thus excluding the corresponding regulatory action. However, when excluding the CNS response to CO2, we also excluded the action of central chemoreceptors on ventilation, i.e., all central influences are simultaneously withdrawn.

The results show that the baroreflex plays a pivotal role in avoiding excessive derangement in the main hemodynamic quantities during hypercapnia. In the absence of this mechanism, in fact, any change in CO2 pressure would evoke very large changes in SAP and HR.

Fig. 11. Steady-state percent changes in mean SAP, CO, HR, and TPR simulated with the model in response to acute hypoxia associated with hypocapnia (hypocapnic hypoxia). Final levels of hypoxia and hypocapnia used in these simulations are shown in the corresponding panels. A: mean values ± SE from Krasney and Koehler (29); B: mean values ± SE from Kontos et al. (27). In the second experiment, the starting level of PaO2 was as low as 75 mmHg. All model parameters used to simulate the first experiment are as in Table 1. Two simulations have been performed for the second experiment. The first simulation used the same parameter values as in Table 1. However, significant statistical differences are evident as to SAP and TPR. These differences can be overcome using a higher strength for the peripheral chemoreceptor response to CO2 (K_H = 4.7 instead of K_H = 3.0 in Eq. 1 in APPENDIX). ***P < 0.01.

Fig. 12. A: steady-state percent changes in mean SAP, CO, HR, and TPR simulated with the model in response to an acute 10-mmHg increase in PaCO2 associated with a simultaneous reduction in PaO2 (from 80 to 40 mmHg) (hypoxic hypercapnia). All parameters for feedback mechanisms are as in Table 1. Experimental data are mean values from Koehler et al. (25). SE are not shown because they were not reported in the original paper at this level of hypoxia. B: percent changes in the same quantities measured by Rose et al. (49) (mean values ± SE) at a greater level of hypoxia. These changes can be roughly simulated with the model assuming a poor CNS response to CO2 (g_corp = 0 mmHg−1·s−1, g_corv = 0 mmHg−1·s−1, g_cosh = 0 mmHg−1·s−1) and a strong local vasodilatory effect (k_m,CO2 = 8.3 mmHg, k_h,CO2 = 7.7 mmHg). However, it is still worth noting the existence of a great overestimation of HR by the model, which is reflected in overestimation of CO and mean SAP, too.
The lung-stretch receptors contribute strongly to the increase in HR during hypercapnia and attenuate the peripheral resistance increase caused by peripheral and central chemoreceptor activation. In particular, in the absence of this mechanism the tachycardia nor-

The CNS response and peripheral chemoreceptors have a similar effect on SAP in that their elimination reduces the arterial pressure increase by ~50%, mainly through a reduction in TPR, whereas CO is almost unaffected. However, the mechanism of action is different in the two cases. The absence of peripheral chemoreceptors provokes a greater tachycardia in accordance with the idea that activation of this group of receptors reduces HR primarily through an increase in vagal tone. However, CO remains almost unchanged due to a decrease in sympathetic venous tone. In contrast, suppression of CNS response plus central chemoreceptors causes a fall in HR, both via a direct action on the cardiac sympathetic tone and via the reduction in the ventilatory response (which, in turn, stimulate lung-stretch receptors). Nevertheless, CO remains rather constant because the reduction of ventilation results in an increase of sympathetic tone to the veins (via the withdrawal of lung-stretch receptors activity).

As it is clear from the previous analysis, the syner-

gical-antagonistic interactions among the various reg-

Discussion

The major aim of the present work was to extend a

previous model of short-term cardiovascular regulation to account for the effect of PacO2 changes on cardiovascular parameters. The new aspects incorporated include the nonlinear O2-CO2 interaction at the peripheral chemoreceptors, the direct CNS response to CO2 changes, the role of central chemoreceptors on ventilation, and the local CO2 effect on peripheral resistances. The parameter values characterizing these individual mechanisms have been given on the basis of specific physiological experiments in which the contribution of each mechanism could be adequately assessed independently of the others. Subsequently, we verified that the integrated action of all these mechanisms joined with the regulatory actions described in the previous work (i.e., the baroreflex response, the hypoxic CNS response, the action of lung-stretch receptors, and the local oxygen effect) is able to reproduce experimental results reasonably well in a variety of experimental conditions (normoxic hypercapnia, hypercapnia with artificial ventilation, hypoxic hypercapnia, and hypocapnic hypoxia). At present, we are not aware of other models able to summarize all these regulatory actions into a single theoretical structure. In fact, although various models of the baroreflex control have been presented in previous years (21, 22, 42), no one describes the effect of changes in gas tension on cardiovascular parameters in accurate quantitative terms.

The present model may have several important implications: it may be useful to summarize present physiological knowledge, it may help the rational interpretation of physiological data, and it may constitute the core of future software packages of didactic value. In perspective, the model may also be of value in the clinical practice, especially in the analysis of physiological conditions characterized by acute changes in blood gas content. In addition, it might be combined with other models describing lung mechanics, gas exchange processes, pharmacokinetics, and/or electrolyte disorders. These areas of explorations may permit deeper comprehension of the interaction between the cardiovascular system and other physiological systems, often studied separately. For instance, the model may be useful to study the effect of respiratory pathologies on cardiovascular quantities and/or to analyze the transport of various substances (not only O2, but also drugs or anesthetics) in different hemodynamic conditions. To this end, however, the model should be enriched with other aspects, not considered presently, such as equations for gas exchange at the alveoli, lung mechanics, pH balance, and capillary exchange.

In the following, the main results obtained with the present simulations are critically discussed.

Normoxic hypercapnia. When arterial O2 content is maintained at its basal level, the model furnishes a
typical cardiovascular response to hypercapnia. This is characterized by a significant ventilation increase (Fig. 5) and a moderate increase in mean SAP, HR, and TPR, whereas CO exhibits insubstantial changes (Fig. 8). As clarified by the sensitivity analysis reported in Fig. 13, this response is the result of the complex superimposition among the various mechanisms simultaneously operative. In particular, according to Fig. 13, the model ascribes the increase in total systemic resistance to the synergistic action of the peripheral chemoreceptors and of the CNS response to CO2. Selective elimination of these mechanisms, in fact, attenuates the rise in TPR during hypercapnia. Conversely, the increase in HR results from the CNS response and the simultaneous stimulation of lung-stretch receptors (secondary to the ventilation increase). Finally, it is worth noting the pivotal role played by the baroreflex control in buffering excessive cardiovascular derangement. In the absence of this mechanism, in fact, even a moderate hypercapnia would result in large increases in mean SAP and HR.

Although the results in Fig. 8 coincide with experimental data in awake dogs by Koehler et al. (25), significant discrepancies can be observed when comparing these results with those of others. An example of such striking differences is provided by the classic experiment in human volunteers by Richardson et al. (48). In these trials (see Fig. 9), hypercapnia still induces a rise in mean SAP and HR, but these changes are now associated with a significant decrease in TPR and a large increase in CO. Our model is still able to mimic this specific response, but using a different combination of parameters affecting peripheral resistance and venous unstressed volume. In fact, to reproduce Richardson’s data with the model, we had to presuppose a stronger local vasodilatory effect of CO2 on the skeletal muscle vascular bed and an increase in the sympathetic activity to peripheral veins during hypercapnia (the latter increases mean filling pressure and CO). Conversely, the sympathetic activity to peripheral arterioles should not increase significantly. The hypothesis of a stronger local vasodilatory effect of CO2 in Richardson’s experiment is further confirmed by data measured by this author in the forearm during hypercapnia after local sympathetic blockade (Fig. 9B).

Hypercapnia with artificial ventilation. The significant differences in the response to CO2 visible between Figs. 8 and 9 are not exceptional but correspond to other findings in the physiological literature. For instance, as shown in Fig. 10, comparable differences can be also observed in experiments performed in artificially ventilated dogs, i.e., without lung-stretch receptors. According to some authors, the main consequence of hypercapnia is a moderate arterial hypertension with an increase in TPR, whereas CO exhibits either inconclusive changes (54) or moderate reduction (61). The model can reproduce this scenario fairly well using the basal parameter set (but just assuming a weakening of central chemoreceptors, which can be due to anesthesia). Conversely, Rothe et al. (50) observed a progressive decrease in total resistance when increasing the hypercapnic level up to 90 mmHg; moreover, these authors observed a progressive increase in central blood volume and mean filling pressure, indicating active vasoconstriction through sympathetic activation. Results by Rothe et al. can be reproduced quite well assuming a strong local vasodilatory effect of CO2 on peripheral resistances and the existence of sympathetic vasoconstriction from the CNS response. According to this idea, Rothe et al. suggested that about 30% of the observed increase in mean filling pressure arises from receptors in the brain. The latter scenario is similar to that hypothesized when simulating the experimental results by Richardson (48), revealing remarkable analogies between the two cases.

Hypercapnic hypoxia. Similar differences in the response to CO2 can also be noticed by comparing the experimental results by Koehler et al. (25) and Rose et al. (49) during hypercapnic hypoxia in conscious dogs. According to experimental results by Koehler et al., the model suggests that moderate hypoxia (40 mmHg) with hypercapnia results in a significant increase in SAP, CO, and HR, whereas total systemic resistance exhibits only an inconsistent change. The model explains these results ascribing the increase in HR to activation of lung-stretch receptors and to the CNS response (stimulated both by hypoxia and hypercapnia) and the increase in CO to the increase in mean filling pressure, caused by peripheral chemoreceptor activation. Meanwhile, TPR remains almost unchanged because it depends on various antagonistic actions. In fact, the CNS response and the peripheral chemoreceptor activation work to increase resistance in reflexly regulated vascular beds, whereas the strong stimulation of lung-stretch receptors and the local vasodilatory effect of CO2 and O2 conspire to reduce systemic resistance in the reflexly and the metabolic regulated vascular beds, respectively.

If greater levels of hypoxia are simulated during hypercapnia, the model forecasts a further progressive rise in mean SAP, HR, and CO, whereas TPR remains rather constant (unpublished simulations). Conversely, contradictory scenarios are recounted in the physiological literature.

Koehler et al. (25), in their fundamental work on awake dogs, also reported experimental data obtained at deeper levels of hypoxia (down to ~30 mmHg). These results display that, at deeper levels of hypercapnic hypoxia, total systemic resistance and mean SAP exhibit a greater increase, whereas HR and CO settle at a saturation level, proximal to the level attained at 40 mmHg PaO2. On the contrary, Rose et al. (49) describe a completely different result on conscious dogs. In their work, systemic hemodynamic changes during combined hypercapnia and deep hypoxia (PaO2 = 33 mmHg) comprehend a rise in mean SAP and a notable increase in HR and CO, whereas total systemic resistance decreases significantly. Once again, the model can account for the decrease in TPR observed by Rose et al. ascribing it to a stronger local vasodilatory effect of CO2.
An important limit of the present model is that it predicts a very large increase in HR during severe hypoxia + hypercapnia. In contrast, both data by Koehler et al. (25) and Rose et al. (49) suggest that HR cannot increase >50% of baseline in the same condition. It is probable that severe asphyxia involves some protective mechanism for the heart, limiting it from excessive cardioacceleration.

**Hypocapnic hypoxia.** The model is able to reproduce the cardiovascular response to hypocapnic hypoxia reasonably well, both in awake dogs (29) and human volunteers (27), even though the second simulation may benefit from a moderate change in the peripheral chemoreceptor sensitivity to CO2.

In conclusion, the present model is able to provide a plausible theoretical summary of many different physiological data reported in the clinical literature. However, reproduction of the different results requires formulation of alternative scenarios and the use of different parameters characterizing the mechanism strengths. A first scenario is characterized by the presence of strong vasoconstrictive mechanisms (especially caused by activation of peripheral and central chemoreceptors) during hypercapnia, which counterbalance the local vasodilatory effects. In contrast, vasoconstriction is scarce. As a consequence, TPR increases or remains unchanged, whereas CO exhibit inconsistent changes (25, 61). A second scenario is characterized by the prevalence of local vasodilation and probably also by active venoconstriction from central chemoreceptors. In this scenario, TPR decreases and CO exhibits a large rise (48–50). The reasons for these different scenarios may be numerous: large variabilities among individual subjects or between animal species, the alerting response in awake subjects, the effect of anesthesia in anesthetized animals, or differences in local metabolism.

In general, the present study emphasizes the extreme complexity of the system regulating cardiovascular parameters following acute changes in blood gas content, and the study points out that the analysis of this system may significantly benefit from a rigorous quantitative approach based on mathematical models and computer simulation techniques. Explication of experimental results with the help of the model may provide important indications on the role of the individual mechanisms, may allow differences among contradictory findings to be better understood, and may provide suggestions on the existence of further regulatory actions, which deserve deeper theoretical and experimental studies.

**APPENDIX**

Only equations concerning the new aspects of the model are presented. They describe chemoreceptor afferent pathways, efferent sympathetic activity, CNS response, the local O2 and CO2 effects on peripheral resistances, the control of ventilation, and tidal volume. All other equations are unchanged compared with the previous study (59), where an accurate description can be found.

**Afferent Chemoreflex Pathway**

The model of peripheral chemoreceptors includes a static function and a first-order linear dynamic. The static characteristic has been modified compared with that used in the previous paper (59), to account for the nonlinear peripheral interaction between PO2 and Pco2 changes. As in the previous work, we assume that the chemoreceptor activity is a sigmoid function of PAO2 at constant level of PCO2. The static response to changes in PACO2 during normoxia has been reproduced through a logarithmic curve with a lower threshold, below which the activity approaches zero. In accordance with experimental data (31), PACO2 threshold decreases as the intensity of hypoxia increases. Finally, the overall chemoreceptor static response exhibits a multiplicative interaction between the O2 and CO2 functions. Hence, the following equations hold

\[ \varphi_{ac}(PaO_2, PaCO_2) = \begin{cases} 0 & \text{if } PaO_2 < 40 \\
\frac{\exp \left( \frac{PaO_2 - PaO_2^min}{k_{ac}} \right)}{1 + \exp \left( \frac{PaO_2 - PaO_2^max}{k_{ac}} \right)} & \text{if } 40 < PaO_2 < 80 \\
\frac{K_H}{1 - 2.7 \left( \frac{PaO_2 - 80}{30} \right)} & \text{if } PaO_2 > 80 \\
\frac{K_H}{1 - 1.2} & \text{if } PaO_2 < 40 \\
\end{cases} \]

\[ \frac{df_{ac}}{dt} = \frac{1}{\tau_{ac}} \cdot (-f_{ac} + \varphi_{ac}) \]

where \( f_{ac} \) is the frequency discharge in the chemoreceptor afferent fibers, \( f_{ac,max} \) and \( f_{ac,min} \) are the upper and lower saturation levels of the sigmoid, \( PO2_{2ac} \) is arterial PO2 at the central point of the sigmoid, \( k_{ac} \) is a parameter with the dimension of pressure related to the slope of the sigmoid at the central point, \( PACO2_{2ac} \) is PaCO2 basal value (i.e., 40 mmHg), and \( f \) and \( K_H \) are constant parameters tuned to reproduce the CO2 static response. Finally, \( \tau_{ac} \) is the time constant of the mechanism.

**Efferent Sympathetic Pathways**

The efferent sympathetic pathways in the model comprise fibers to the vessels and those to the heart. Compared with the previous study, the former have been distinguished between sympathetic fibers to the arteries (\( f_{ap} \)) that modify peripheral resistances of the splanchnic, skeletal muscle, and extraplanchnic vascular beds and sympathetic fibers to the veins (\( f_{sv} \)) that affect unstressed venous volumes of the same compartments. Cardiac sympathetic fibers (\( f_{ah} \)) work on HR and contractility.

As in the previous paper (59), we assume that efferent sympathetic activities are a monoexponential function of the weighted sum of afferent information from baroreceptors, peripheral chemoreceptors, and lung-stretch receptors. Weighting factors may be positive or negative, depending on whether afferent information exerts an inhibitory or excitatory effect on sympathetic activity. Furthermore, afferent information is compared with an offset term, which is modulated by hypoxia in the CNS and by Pco2 changes in the medulla (see CNS response). Hence...
H2050
CARDIOVASCULAR RESPONSE TO CO2 CHANGES

\[ f_{sj} = \begin{cases} f_{sa,x} + (f_{sa,0} - f_{sa,x}) \cdot \exp[k_{sa} \cdot (W_{b,sa} \cdot f_{ab})] \\ f_{sa,max} + W_{c,sa} \cdot f_{ac} + W_{p,sa} \cdot f_{ap} - \theta_{sj} \end{cases} \]

\[ j = h, p, v \]

where \( f_{sa}, f_{sa,x} \), and \( f_{sa,0} \) are afferent activities from baroreceptors, peripheral chemoreceptors, and lung-stretch receptors, respectively; \( W_{b,sa}, W_{c,sa}, W_{p,sa} \) (\( j = h, p, v \)) are used to distinguish sympathetic activity to heart, peripheral resistances, and veins, respectively) are corresponding sympathetic activities, and \( \theta_{sj} \) (\( j = h, p, v \)) are the offset terms. Finally, \( k_{sa}, f_{sa,x}, f_{sa,0}, \) and \( f_{sa,max} \) are constant parameters \( f_{sa,max} > f_{sa,0} > f_{sa,x} \); \( f_{sa,max} \) is the saturation level above which the sympathetic activity cannot increase.

CNS Response

To reproduce the CNS response, the model assumes that the offset terms \( \theta_{sj} \) (\( j = h, p, v \)) in Eq. 3 depend on \( P_{O_2} \) and \( P_{CO_2} \); both mechanisms include a static characteristic and a first-order, low-pass dynamic.

According to experimental evidence, parameters \( \theta_{sj} \) (\( j = h, p, v \)) depend on \( P_{O_2} \) through a static sigmoidal function; the latter remains near zero until \( P_{O_2} \) is higher than a certain threshold and then increases rapidly to a saturation. The threshold is higher for cardiac sympathetic nerves (50–60 mmHg) than for peripheral sympathetic activity (35–40 mmHg). We have

\[ \omega_{sj}(P_{O_2}) = \frac{\chi_{sj}}{1 + \exp\left(\frac{P_{O_2} - P_{O_2,sj}}{k_{sc,uj}}\right)} \quad j = p, h, v \]

where \( \chi_{sj} \) is the saturation of the hypoxic response, \( P_{O_2,uj} \) is the value of \( P_{O_2} \) at the central point of the sigmoidal function, \( k_{sc,uj} \) is a parameter with the dimension of pressure related to the slope of the static function at the central point, and \( \tau_{sc} \) is the time constant of the mechanism. Finally, \( \Delta \theta_{O_2,uj} \) represents the change in the offset term caused by the CNS hypoxia.

Dependence of offset terms on \( P_{CO_2} \) includes a static linear function and a first-order, low-pass filter. This allows experimental results to be reproduced quite well (16, 34, 37).

Hence

\[ \frac{d\Delta \theta_{O_2,uj}}{dt} = \frac{1}{\tau_{oc}} \cdot (\Delta \theta_{O_2,uj} + \omega_{sj}) \quad j = p, h, v \]

where \( \chi_{uj} \) (\( j = h, p, v \)) are the constant gain factor tuned to reproduce experimental results, \( P_{O_2,uj} \) is the basal value of \( P_{O_2} \), \( \tau_{oc} \) is the time constant, and \( \Delta \theta_{O_2,uj} \) represents the change in the offset term caused by central chemoreceptor stimulation.

Finally, the values of the offset terms to be used in Eq. 3 are obtained by assuming a linear interaction between \( O_2 \) and \( CO_2 \) responses

\[ \theta_{sj} = \theta_{sn} - \Delta \theta_{O_2,uj} - \Delta \theta_{CO_2,uj} \quad j = p, h, v \]

where \( \theta_{sn} \) represents the offset term in basal condition, i.e., during normocapnia and normoxia.

Blood Flow Local Control

Hypoxia causes vasodilation in the vascular beds with higher metabolic requirements (coronary, cerebral, and skeletal muscle circulation). As in the previous work, the local effect of \( O_2 \) on these vascular beds has been mimicked by assuming that hydraulic peripheral conductance (i.e., the inverse of peripheral resistance) decreases linearly with venous \( O_2 \) concentration through a first-order, low-pass dynamics.

According to several authors, cerebral vessel tone is profoundly affected by alterations in \( P_{ACO_2} \). The effect of \( CO_2 \) on the cerebrovascular resistance has been described through a static relationship (taken from Ref. 45) and a first-order, low-pass filter, which mimics the mechanism dynamic. Finally, we assume that the two local mechanisms (\( O_2 \) and \( CO_2 \)) interact in an additive manner on cerebral hydraulic conductance \( G_{b} = 1/R_{bp} \), where \( R_{bp} \) is brain peripheral hydraulic conductance (for a more detailed description of this parameter, see the hydraulic analog in Ref. 59). Hence, the local metabolic control of cerebral blood flow is governed by the following equations

\[ G_{bp} = G_{b}\psi (1 + x_{b,O_2} + x_{b,CO_2}) \quad (8) \]

\[ \frac{dx_{b,O_2}}{dt} = \frac{1}{\tau_{O_2}} \cdot [-x_{b,O_2} - g_{b,O_2} \cdot (C_{b,O_2} - C_{b,O_2,n})] \quad (9) \]

\[ \frac{dx_{b,CO_2}}{dt} = \frac{1}{\tau_{CO_2}} \cdot [-x_{b,CO_2} + \phi_{b}(P_{CO_2})] \quad (11) \]

where \( x_{b,O_2} \) and \( x_{b,CO_2} \) are state variables representing the effect of \( O_2 \) and \( CO_2 \) on cerebral circulation, \( C_{b,O_2} \), \( C_{b,O_2,n} \), indicates its value under normal conditions, and \( g_{b,O_2} \) is a constant gain factor. \( A, B, C, \) and \( D \) are constant parameters taken from Reivich (45), and \( \tau_{O_2} \) and \( \tau_{CO_2} \) are the time constants of the two mechanisms. Finally, \( G_{b}\psi \) is a constant parameter denoting the basal value of peripheral cerebrovascular conductance, which is not under reflex control.

Several experimental results (6, 15, 28, 44, 53) reveal that variation in arterial \( P_{CO_2} \) can affect coronary and muscular vascular resistances, too. According to these authors, coronary and muscular vascular resistances decrease linearly with \( P_{ACO_2} \) until a saturation level that indicates maximal resistance reduction is reached. In the model, the effect of \( CO_2 \) on coronary \( (R_{cap}) \) and muscular peripheral resistance \( (R_{cap}) \) has been described through a sigmoidal static relationship with an upper and lower saturation level. The sensitivity at the central point of the sigmoid is much less for \( R_{cap} \) than for \( R_{cap} \), which is in agreement with experimental data. The static relationship has been arranged in series with a first-order, low-pass dynamics to reproduce the temporal pattern of the mechanism.

Hence, the local control of coronary and muscular peripheral resistances is governed by the following equations

\[ R_{cp} = R_{cp} \cdot \frac{(1 + x_{c,CO_2})}{(1 + x_{c,O_2})} \quad j = h, m \]

\[ \frac{dx_{c,CO_2}}{dt} = \frac{1}{\tau_{CO_2}} \cdot [-x_{c,CO_2} - g_{c,CO_2} \cdot (C_{c,CO_2,n} - C_{c,CO_2,n})] \quad j = h, m \]

AAJP-Heart Circ Physiol • VOL 281 • NOVEMBER 2001 • www.ajpheart.org

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1 - \exp \left( \frac{\text{PaCO}_2 - \text{PaCO}_2^n}{k_j} \right) \\
1 + \exp \left( \frac{\text{PaCO}_2 - \text{PaCO}_2^n}{k_j} \right) \\
\Phi_j(\text{PaCO}_2) = \frac{d\text{x}_{j,\text{CO}_2}}{dt} = \frac{1}{\tau_{\text{CO}_2}} \left[ -x_{j,\text{CO}_2} + \Phi_j(\text{PaCO}_2) \right] \\
\text{where } x_{j,\text{O}_2} \text{ and } x_{j,\text{CO}_2} (j = h, m) \text{ are state variables representing the effect of O}_2 \text{ and CO}_2 \text{ on coronary and muscular circulation, respectively; } C_{j,\text{O}_2} (j = h, m) \text{ represents O}_2 \text{ concentration in venous blood leaving the heart and skeletal muscle; } C_{j,\text{CO}_2} (j = h, m) \text{ indicates its value under normal conditions; } g_{j,\text{O}_2} (j = h, m) \text{ is a constant gain factor; } k_j (j = h, m) \text{ is a parameter with the dimension of pressure related to the slope of the sigmoidal function at the central point; and } \tau_{\text{O}_2} \text{ and } \tau_{\text{CO}_2} \text{ are the time constants of the two mechanisms. The normal peripheral resistance (R_p) in Eq. 12 is a constant parameter in the coronary compartment (j = h), because this vascular bed is not under reflex control; whereas it is not constant in skeletal muscle compartment (j = m), because it depends on the action of sympathetic nerves (see Ref. 59 for more details).}

As in the previous paper, O}_2 \text{ venous concentration in each compartment (i.e., } C_{j,\text{O}_2} \text{ with } j = h \text{, m) has been computed by imposing a mass balance between O}_2 \text{ extraction and O}_2 \text{ consumption rate and using the equations proposed by Spencer et al. (52) for O}_2 \text{ and CO}_2 \text{ transport in blood.}

**Ventilation and Tidal Volume Control**

Ventilation (V) is regulated by both peripheral and central chemoreceptors. In most physiological conditions the two mechanisms interact in a linear way. Hence, the final value of V is computed as follows

\[ V = V_n + \Delta V_p + \Delta V_c \]

where \( V_n \) is a constant value that represents the basal level of V (i.e., during normocapnia and normoxia), \( \Delta V_p \) and \( \Delta V_c \) are the changes induced by stimulation of peripheral and central chemoreceptors, respectively. The contribution of each group of chemoreceptors has been provided by a first-order linear differential equation with a pure delay. In the model, the input quantity for the peripheral feedback is the afferent activity in the arterial chemosensitive fibers, whereas the central mechanism responds to variations of \( \text{PCO}_2 \) in arterial blood. Hence, we have

\[ \frac{d\Delta V_p}{dt} = \frac{1}{\tau_p} \left( -\Delta V_p + g_v \left[ f_{ac}(t - D_{V_p}) - f_{ac,n} \right] \right) \]

\[ \frac{d\Delta V_c}{dt} = \frac{1}{\tau_c} \left( -\Delta V_c + g_v \left[ \text{PaCO}_2(t - D_{V_c}) - \text{PaCO}_2^n \right] \right) \]

where \( f_{ac} \) is the afferent chemoreceptor activity provided by Eq. 2, \( f_{ac,n} \) is its basal value (i.e., the value computed during normoxia and normocapnia). \( \text{PaCO}_2 \) is the normal value of \( \text{P}_\text{CO}_2 \) in arterial blood (i.e., 40 mmHg), \( g_v \) and \( g_v' \) are gain factors (peripheral and central, respectively) tuned to reproduce ventilatory responses to arterial gas perturbations described in the clinical and physiological literature. The \( g_v \) has been given two different values during hypocapnia (\( g_v \text{h} \) if \( \text{PaCO}_2 > \text{PaCO}_2^n \)) and during hypocapnia (\( g_v \text{h} \) if \( \text{PaCO}_2 < \text{PaCO}_2^n \)), reflecting the existence of two regions separated by a break-point in the relation “ventilation vs. \( \text{ PaCO}_2 \)” (7).

Finally, \( D_{V_p}, \Delta V_p, \tau_v, \text{ and } \tau_V \) are pure delay and time constants of the two mechanisms, respectively. Because lung stretch receptors are sensitive to changes in tidal volume (VT), an equation relating \( V \), VT, and respiratory rate (RR) is necessary. Clinical data (17, 23, 46, 47) have been reproduced by using an empirical relationship linking \( V \) to VT

\[ \text{VT} = 0.15 \left( V + 1 \right)^{0.65} \]

Finally, RR can immediately be computed from V and VT

\[ \text{RR} = \frac{V}{VT} \]

**REFERENCES**


