The cardiovascular response to hypoxia is the result of a multitude of concomitant mechanisms that superimpose in vivo in complex nonlinear ways. These include local vasodilation, the peripheral chemoreflex, the lung inflation reflex, and the hypoxic response of the central nervous system (CNS) (1, 24, 34).

It is well known that the vascular beds in organs with the higher metabolic rate (especially the heart, brain, and skeletal muscle) dilate in response to severe hypoxia. Blood flow to these organs may disproportionately increase when arterial PO₂ (PaO₂) is decreased below 30 mmHg (7, 24). This local vasodilatory effect would result in a significant arterial hypotension if it is not counteracted by vasoconstriction in other vascular beds. This is provided by activation of the peripheral chemoreflex, which causes vasoconstriction in the splanchnic and renal circulation as well as in the skeletal muscle. Because of the previous responses, hypoxia causes a significant redistribution of the available blood flow from the organs with a lower metabolic need toward those with a higher metabolic demand.

The pattern described above, however, is further complicated by changes in ventilation, which activate stretch receptors in the lung (13), and by the hypoxic response of the CNS (19). Moreover, cardiovascular and ventilatory adjustments to hypoxia modify other hemodynamic and metabolic quantities [especially systemic arterial pressure (SAP) and arterial PCO₂ (PaCO₂)], the change of which elicits the secondary action of additional control mechanisms. Arterial pressure variations trigger the baroreflex system, whereas changes in PCO₂ activate the central chemoreceptors located in the medulla, modulate the response of peripheral chemoreceptors, and have a local effect on blood vessels. Of course, the final cardiovascular response depends on the integration of all these components, in part excitatory and in part inhibitory, and on their relative magnitude (12).

Because of the multiplicity of factors that superimpose nonlinearly, the final result of hypoxia is not easily predictable by use of only qualitative reasoning. The use of mathematical models and of computer simulation techniques may be of great value to deepen our comprehension of the problem in physiological investigation and in clinical practice. Mathematical models permit the nonlinear interactions among the different mechanisms and the effect of their individual variability to be accounted for in rigorous quantitative terms.

Several models of short-term cardiovascular regulation have been proposed in the past decades with different purposes (3, 21, 22). However, we are not aware of any model that brings together all mechanisms triggered by hypoxia and their complex mutual interactions into a single theoretical setting. In recent years, we formulated a mathematical model of the baroreflex control in pulsating conditions that is able to account for many aspects of the short-term arterial pressure regulation (46, 47). The
model includes a pulsatile heart, systemic and pulmonary circulations, the afferent and efferent neural pathways, and four effectors for the regulation. With that model, we were able to address several important aspects of the baroregulation, such as the importance of venous unstressed volume control, the role of pulsatility, and the dependence of the Starling law on baroreceptor activation.

The aim of this work is to significantly extend the previous model to include some of the main cardiovascular mechanisms involved in the acute response to isocapnic hypoxia. The new mechanisms include the local vasodilatory effect of O₂, the effect of peripheral chemoreceptors and lung stretch receptors on the heart and blood vessels, and hypoxia of the CNS. Furthermore, all these mechanisms interact with the baroreflex response included in the previous model.

In this version of the model (46, 47), we did not consider changes in PaCO₂; i.e., the only input quantity for the model is PaO₂. For this reason, all the experimental conditions refer to isocapnic hypoxia only. The reason is that analysis of the interaction between hypoxia and PCO₂ changes would confound interpretation of physiological results and require a more complex model, including description of gas exchange at the lungs and tissues, and the inclusion of additional control loops (such as central chemoreceptors in the medulla).

In the present report the main aspects of the model are presented, and its capacity to reproduce the pattern of the cardiovascular response to hypoxia is shown. In a subsequent related study, a sensitivity analysis on the role of the main parameters will be performed to underline the role of each mechanism and the impact of individual parameter variations (48).

QUALITATIVE MODEL DESCRIPTION

The present model represents an extension of a baroreflex mathematical model described in a recent report (46). The major changes are in the analysis of the cardiovascular response to hypoxia. They include 1) a separate description of the vascular beds in organs with higher metabolic need (brain, coronary, and skeletal muscle circulation) and the local effect of hypoxia on these vascular beds, 2) the afferent information from peripheral chemoreceptors and its effect on the efferent (sympathetic and parasympathetic) neural pathways, 3) the effect of peripheral chemoreceptors on tidal volume (Vₜ) and the consequent response of lung stretch receptors, further affecting the efferent neural pathways, and 4) the direct effect of hypoxia of the CNS.

A block diagram showing the main relationships between afferent and efferent neural information, the effector responses, and the local role of O₂ is presented in Fig. 1. The main characteristics of the model are summarized in qualitative terms, with particular emphasis on the new aspects. Model equations are reported in the APPENDIX; parameter values can be found in Tables 1–3. All parameters have been computed with reference to a 70-kg subject.

Vascular Compartments

The hydraulic analog of the vascular system is described in Fig. 2. It includes 14 different vascular compartments. Three of the compartments are used to describe the pulmonary circulation, differentiating among the large pulmonary arteries, the pulmonary peripheral circulation, and the pulmonary veins. The systemic circulation includes 11 compartments. The first represents the large systemic arteries. The others describe the peripheral and venous circulation in five different compartments arranged in parallel: the compartments of the organs with higher metabolic need (brain, coronary, and skeletal muscle circulation), the splanchnic circulation, and the remaining extrasplanchnic vascular beds. A distinction among these compartments is of paramount importance, since regulatory mechanisms exert a different action on them (24, 28, 46).

Each compartment includes a hydraulic resistance (R), a hydraulic compliance (C), and the unstressed volume (V₀). The inertial effects (L) have been included only in the large artery compartments, where blood acceleration is maximal. Equations relating pressures and flows in the vascular system have been written by enforcing the conservation of mass at all nodes in Fig. 2 and the equilibrium of forces at L.

Heart

The model of the pulsating heart is the same as in the previous model (46), where an accurate description can be found. Briefly, in the model, each atrium is described as a passive compliance, whereas the activity of the ventricles is simulated by means of a variable-elastance model (43). Shifting from the end-diastolic to the end-systolic pressure-volume curve is governed by a pulsating activation function, with period T. Heart period and the slope of the end-systolic curve are modified by the efferent neural activities. Finally, the model includes a simplified description of the atrioventricular and aortic (or pulmonary) valves, each mimicked as an ideal diode.

Local Vasodilatory Effect of Hypoxia

Hypoxia causes significant vasodilation in the coronary, brain, and skeletal muscle circulation. The local effect of O₂ in these vascular beds has been reproduced with the assumption that the hydraulic peripheral conductance (i.e., the reciprocal of resistance of peripheral circulation in skeletal muscle, brain, and coronary vascular bed in Fig. 2) linearly depends on the decrease in O₂ concentration in venous blood via first-order low-pass dynamics. The time constant of the low-pass filter represents the time necessary for the mechanism to reach about two-thirds of its final response. The choice of venous O₂ concentration instead of arterial concentration as the regulatory stimulus agrees with data of several authors (29), who reported that O₂ acts on peripheral vessels mainly indirectly, through the effect of hypoxia in the surrounding tissue, rather than by a direct action on smooth muscle tension. O₂ concentration in the venous blood leaving each compartment (brain, heart, and skeletal muscle) has been computed by writing a mass balance equation between O₂ extraction and O₂ consumption rate. O₂ concentration in the arterial blood is computed as a function of PaO₂ (which is an input quantity for the model) by using the equations for O₂ dissociation in blood proposed by Spencer et al. (44). These may allow the role of CO₂ and the Bohr effect to be easily included in future work. Finally, we assumed that O₂ consumption rate in brain and skeletal muscle remains constant throughout the present simulations. By contrast, O₂ consumption rate in the heart is proportional to the average power of the cardiac pump (work per unit time). The latter term has been calculated by low-pass filtering the instantaneous power of the two ventricles.
Afferent Pathways

Baroreceptor afferent pathway. The afferent information from the arterial baroreceptors is described by means of a first-order dynamic block, which exhibits a static and a rate-dependent gain, in series with a sigmoidal static characteristic. However, because experimental evidence suggests that chemoreceptors have no rate-dependent component in their response to PO₂ (6), we preferred to adopt simple exponential functions. This behavior has been reproduced using a combination of exponential trend (5). However, chemoreceptor activity cannot increase indefinitely but flattens at a saturation level. This behavior has been reproduced using a combination of exponential functions.

Afferent information from lung stretch receptors. Inflation of lungs at low pressure activates slowly adapting lung stretch receptors with vagal myelinated A fibers (1). In the model the afferent activity of these receptors depends on changes in V₄, which, in turn, are elicited by the peripheral chemoreceptor activation (see Effect of Peripheral Chemoreceptors on Ventila-

Table 1. Parameters characterizing the vascular system in the basal condition

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unstressed Volume, ml</th>
<th>Hydraulic Resistance, mmHg · s⁻¹ · ml⁻¹</th>
<th>Inertance, mmHg · s² · ml⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cᵥᵥᵥₙ</td>
<td>0.28</td>
<td>Vᵥᵥᵥₙ = 0</td>
<td>Rᵥᵥᵥₙ = 0.06</td>
</tr>
<tr>
<td>Cᵥᵥᵥₜ</td>
<td>2.05</td>
<td>Vᵥᵥᵥₜ = 274.4</td>
<td>Rᵥᵥᵥₜ = 3.307</td>
</tr>
<tr>
<td>Cᵥᵥᵥₑ</td>
<td>0.668</td>
<td>Vᵥᵥᵥₑ = 134.64</td>
<td>Rᵥᵥᵥₑ = 3.52</td>
</tr>
<tr>
<td>Cᵥᵥᵥₚ</td>
<td>0.525</td>
<td>Vᵥᵥᵥₚ = 105.8</td>
<td>Rᵥᵥᵥₚ = 4.48</td>
</tr>
<tr>
<td>Cᵥᵥᵥₑ</td>
<td>0.358</td>
<td>Vᵥᵥᵥₑ = 72.13</td>
<td>Rᵥᵥᵥₑ = 6.57</td>
</tr>
<tr>
<td>Cᵥᵥᵥₛ</td>
<td>0.119</td>
<td>Vᵥᵥᵥₛ = 24</td>
<td>Rᵥᵥᵥₛ = 19.71</td>
</tr>
<tr>
<td>Cᵥᵥᵥₑ</td>
<td>61.11</td>
<td>Vᵥᵥᵥₑ = 1,121</td>
<td>Rᵥᵥᵥₑ = 0.038</td>
</tr>
<tr>
<td>Cᵥᵥᵥₑ</td>
<td>20</td>
<td>Vᵥᵥᵥₑ = 550</td>
<td>Rᵥᵥᵥₑ = 0.04</td>
</tr>
<tr>
<td>Cᵥᵥᵥₑ</td>
<td>15.71</td>
<td>Vᵥᵥᵥₑ = 432.14</td>
<td>Rᵥᵥᵥₑ = 0.05</td>
</tr>
<tr>
<td>Cᵥᵥᵥₑ</td>
<td>10.71</td>
<td>Vᵥᵥᵥₑ = 294.64</td>
<td>Rᵥᵥᵥₑ = 0.075</td>
</tr>
<tr>
<td>Cᵥᵥᵥₑ</td>
<td>3.57</td>
<td>Vᵥᵥᵥₑ = 98.21</td>
<td>Rᵥᵥᵥₑ = 0.224</td>
</tr>
<tr>
<td>Cᵥᵥₚ</td>
<td>0.76</td>
<td>Vᵥᵥₚ = 0</td>
<td>Rᵥᵥₚ = 0.023</td>
</tr>
<tr>
<td>Cᵥᵥₑ</td>
<td>5.80</td>
<td>Vᵥᵥₑ = 123</td>
<td>Rᵥᵥₑ = 0.0894</td>
</tr>
<tr>
<td>Cᵥᵥₑ</td>
<td>25.37</td>
<td>Vᵥᵥₑ = 120</td>
<td>Rᵥᵥₑ = 0.0056</td>
</tr>
</tbody>
</table>

C, compliance; Vᵥᵥᵥₙ, unstressed volume; R, hydraulic resistance; L, inertance; sa, systemic arterial; sp, splanchnic peripheral; ep, extraplanchnic peripheral; mp, skeletal muscle peripheral; hp, brain peripheral; cp, coronary peripheral; sv, splanchnic venous; ev, extraplanchnic venous; mv, skeletal muscle venous; bv, brain venous; hv, coronary venous; pa, pulmonary arterial; pp, pulmonary periphera; pv, pulmonary venous. Total blood volume (Vᵥᵥᵥₐₚ) is 5,300 ml.
Crv,02 n
Cvh,02 n
Basal values of parameters for local metabolic regulation (Eqs. 41–48)

thetic and parasympathetic neural fibers. The activity in
Efferent Neural Pathways
The response includes a static relationship that is quite
be positive or negative. Furthermore, the afferent informa-
tion also includes an offset term, which, in the case of
Efferent Neural Pathways
The efferent pathways in the model consist of sympa-
thetic and parasympathetic neural fibers. The activity in
these efferent fibers is a nonlinear monotonic function of
the overall afferent information. The latter, in turn, is the
weighted sum of activities from baroreceptors, chemore-
ceptors, and lung stretch receptors, where the weights may
be positive or negative. Furthermore, the afferent informa-
tion also includes an offset term, which, in the case of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cm,02n</td>
<td>0.155</td>
<td>Mm</td>
</tr>
<tr>
<td>Cvh,02n</td>
<td>0.14</td>
<td>Mh</td>
</tr>
<tr>
<td>Csh,02n</td>
<td>0.11</td>
<td>Mhn</td>
</tr>
<tr>
<td>Vbn</td>
<td>12,660 mmHg · ml · s⁻¹</td>
<td></td>
</tr>
<tr>
<td>O₂ dissociation curve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>9 mmol/l</td>
<td>α</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>α</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>β</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>K</td>
</tr>
</tbody>
</table>

See APPENDIX for explanation of symbols.
sympathetic fibers, is modulated by hypoxia in the CNS (see below).

The vagal fibers are directed to the heart only and participate in the heart period control. By contrast, sympathetic activity is directed to the heart and blood vessels. An important modification of the present work, compared with the previous study, is that we used two different equations to describe the sympathetic activity to the heart ($f_{sh}$) and to blood vessels ($f_{sp}$). This choice is justified by the observation that cardiac and peripheral sympathetic activities do not change in parallel but exhibit disparate variations in response to afferent information from chemoreceptors and lung stretch receptors, as well as in response to CNS hypoxia.

As justified in a previous study (46), we assumed that sympathetic activity decreases with a negative monoeXponential relationship in response to inhibitory afferent information, whereas it increases exponentially up to a saturation level in response to excitatory inputs. Similarly, inhibitory afferent information causes an increase in vagal activity, thus slowing heart rate, whereas excitatory information causes a reduction in the vagus frequency.

As described in PARAMETER ASSIGNMENT AND SIMULATION OF THE INDIVIDUAL COMPONENTS, the weighting factors and offset term have been given to mimic the effect of receptor stimulation on heart rate and systemic resistance observed experimentally.

**Effect of CNS Hypoxia**

We assumed that hypoxia modifies the offset term in the nonlinear input-output function of sympathetic nerves, thus altering sympathetic outflow. According to Koehler et al. (27), CNS hypoxia has a significant effect on heart rate and cardiac contractility in awake animals even at moderate hypoxia, whereas its effect on peripheral vessels becomes evident only at lower levels of Po2. Hence, in the model, cardiac and peripheral sympathetic nerves are under CNS control. Dependence of the offset term on Po2 includes a nonlinear
static function and first-order low-pass dynamics. The static function has been chosen so that CNS hypoxia has almost no effect until \( P_{O_2} \) reaches a given threshold; then its effect increases abruptly. According to data reported previously (27, 41), the threshold is higher for cardiac sympathetic nerves (50–60 mmHg) than for peripheral sympathetic activity (35–40 mmHg).

**Effect of Peripheral Chemoreceptors on Ventilation**

The aim of this work is not to study ventilation control but to use \( V_T \) changes as input for the lung stretch receptors. Hence, the effect of peripheral chemoreceptor activity on \( V_T \) has been simulated using a simple first-order linear differential equation with a pure delay. This is the description normally adopted in a clinically oriented model of ventilation control (39).

**Cardiovascular Effectors for Reflex Control**

The effectors for the reflex control are the same as those described previously (46): they include the response of the systemic peripheral resistance and of venous unstressed volume (in the splanchnic, skeletal muscle, and other extraspinal compartments) to activation of peripheral sympathetic nerves, the response of heart contractility to cardiac sympathetic nerves, and the response of heart period to cardiac sympathetic nerves and the vagus. The only important difference between this study and the previous study is that peripheral resistance and venous unstressed volume in the cerebral and coronary circulations (i.e., in the branches b and h in Fig. 2) are assumed to be independent of neural influences, being mainly affected by local vasodilatory stimuli. As in the previous study, the reflex response of each effector includes a pure delay, a monotonic static function, and first-order linear dynamics.

According to the previous description, peripheral resistance in the skeletal muscle circulation \( R_{mp} \) is subjected to a double control: the local effect of \( O_2 \) and the activity of efferent sympathetic nerves. In the model the interaction between these two mechanisms on \( R_{mp} \) is assumed to be multiplicative in nature. This choice is justified by the observation that skeletal muscle blood flow during deep hypoxia increases significantly, despite sympathetic activation (28).

**PARAMETER ASSIGNMENT AND SIMULATION OF THE INDIVIDUAL COMPONENTS**

Here we discuss how a value has been assigned to all parameters that characterize the new portions of the model. For each new subsystem (Fig. 1), a comparison is presented with experimental results to illustrate the input-output relationships and to reveal agreement between model curves and real data. The effect of the nonlinear interactions among the different parts is studied in RESULTS and, to a greater extent, in the companion article (48).

**Vascular System**

The parameters that characterize the heart and the vascular system (i.e., resistances, capacitances, and inertial terms in Fig. 2) have been given the same values used previously (46). The only important difference is that the extraspinal systemic circulation has been subdivided into the parallel arrangement of brain, coronary, and skeletal muscle vascular beds (branches b, h, and m in Fig. 2) and of the other extraspinal vascular beds (e.g., kidney, etc., branch e in Fig. 2). The individual parameters of these branches in the basal condition have been given with the assumption that normal blood flow entering the brain is ~14–15% of total cardiac output (32), coronary blood flow is 4–5% (4), and skeletal muscle blood flow is ~22% (33). Finally, we assumed that the parallel arrangement of segments m, h, b, and e provides the same parameter values used in the previous study (46) for the overall extraspinal circulation.

**Heart**

Parameters describing heart function have been given the same value used previously (46).

**Local Vasodilatory Effect of Hypoxia**

The \( O_2 \) consumption rate in the locally regulated vascular beds has been given according to data reported elsewhere (33). The gains of the regulatory mechanism have been assigned to reproduce experimental results on animals (18, 28, 36, 37, 45). These represent the percent changes in blood flow in the compartments at different levels of \( P_{O_2} \). Figure 3 shows the percent changes of cerebral blood flow at different levels of \( P_{O_2} \); the model curve is compared with the pattern of cerebral blood flow vs. \( P_{O_2} \) measured elsewhere (36, 37, 45).

The time constant of the local regulation has been assigned by assuming that \( O_2 \) exerts its action on cerebral, skeletal muscle, and coronary vessels mainly through the release of vasodilatory factors (such as adenosine) in the perivascular space (49). Values derived from the previous work suggest a time constant of ~10 s.

**Afferent Pathways**

**Arterial baroreceptors.** The parameters that describe the afferent pathway from arterial baroreceptors have been given the same values used in a previous work (46). These were assigned to reproduce experimental results by Chapleau and Abboud (9) and Kubota et al. (31) in dogs. Model dependence of baroreceptor afferent activity (spikes/s) on mean arterial pressure is shown in Fig. 4 and compared with experimental data.

**Peripheral chemoreceptors.** The parameters that describe the afferent activity from peripheral chemoreceptors in static

---

**Figure 3.** Response of the cerebral vascular bed to hypoxia. Normalized cerebral blood flow vs. \( P_{O_2} \) is shown in steady-state conditions. ▲, Experimental data of McPherson et al. (36); ■, experimental data of McPherson et al. (37); ●, experimental data of Ulatowski et al. (45); continuous line, pattern of normalized model blood flow in segment b of Fig. 2.
conditions (see Eq. 17) have been given to reproduce experimental results by Biscoe et al. (5) (Fig. 5). These data suggest that afferent activity remains quite constant as long as \( P_{aO_2} \) is higher than \( 100 \text{ mmHg} \); then it increases. The chemoreceptor time constant has been given the value 2 s, which reflects the time required for early cardiovascular adjustments to appear after chemoreceptor stimulation by cyanide or nicotine (42).

**Lung stretch receptors.** In the model the activity of lung stretch receptors is a function of changes in \( V_T \). Most experimental data, however, relate the activity in vagal afferents to pulmonary inflation pressure (26, 38). To permit assignment of model parameters starting from these in vivo data, we assumed that the relationship between \( V_T \) and inflation pressure is rather linear at moderate levels of lung inflation. Parameters in the static relationship (Fig. 6) have been assigned by considering the response of the so-called “slowly adapting receptors with myelinated A-fibers,” since these are responsible for cardiovascular adjustments (tachycardia and vasodilation) at moderate levels of lung inflation.

The time constant has been given on the basis of data by Hainsworth (23), who observed that the maximum change in heart rate occurs within 5 s from the onset of lung inflation. Because vagal control of heart rate occurs with a time constant of \( \approx 2 \text{ s} \) (46), lung stretch receptor dynamics should also be characterized by a time constant \( \leq 1–2 \text{ s} \). This assumption agrees with data by Rutherford and Vatner (42) as well. They observed that maximal vasodilation in the iliac vascular bed occurs at \( \approx 12 \text{ s} \) from inflation of the lungs. Because reflex resistance control exhibits a time constant of \( \approx 5 \text{ s} \) (46) and considering that at least two time constants are necessary for the response to realize its action, we further obtain a time constant of lung stretch receptors of \( \approx 1–2 \text{ s} \).

**Efferent Neural Pathways**

**Sympathetic fibers to blood vessels.** To characterize the activity of efferent sympathetic nerves directed to vessels, we need to assign four parameters: the synaptic weights (excitatory or inhibitory) connecting baroreceptors, chemoreceptors, and lung stretch receptors to sympathetic neurons and the offset term. Of course, baroreceptor and lung stretch receptor weights are inhibitory, since activation of these fibers causes vasodilation, whereas the chemoreceptor weight is excitatory. The weight connecting baroreceptors to sympathetic neurons was given the same value as in the previous work (46). The weight connecting chemoreceptors to sympathetic neurons was assigned starting from data reported in Daly and Scott (15, 16) and Karim et al. (25). Experiments with cholinergic blockade or vagotomy suggest that the primary
bradycardic response to carotid chemoreceptor stimulation is predominantly mediated by the vagus (15, 16, 34). Moreover, Karim et al. observed that stimulation of aortic chemoreceptors results in an average increase in heart rate of 11 beats/min due to activation of cardiac efferent sympathetic nerves. Starting from these data, we assumed that chemoreceptor activation increases heart sympathetic activity, mainly through activation of aortic chemoreceptors. Hence, the weight was given a positive value, assigned according to the results of Karim et al.

Several authors state that the action of lung stretch receptors on heart is mainly mediated by the vagus (1); hence, the weight from lung stretch receptors to cardiac sympathetic activity was set to zero.

**Efferent vagal activity.** The positive weight from baroreceptor activity to the efferent vagal response was the same as in the previous study (46). The weight connecting chemoreceptor activity to the vagus was assigned a positive value on the basis of experimental results by Karim et al. (25) and Daly and Scott (16). These authors state that activation of carotid chemoreceptors by hypoxic (venous) blood causes a 20–30% vagally mediated reduction in heart rate. Finally, the tachycardic effect of lung stretch receptors was mimicked by assigning a negative weight, thus reducing vagal activity during lung inflation; the weight value was assigned to reproduce the progressive increase in heart rate measured by Hainsworth (23) at a moderate level of lung inflation. A comparison between model and in vivo data concerning the effect of lung inflation on heart rate is shown in Fig. 8.

**Hypoxia of the CNS**

The offset terms in the sympathetic response to the heart and peripheral vessels depend on \( P_{O_2} \) via a static function and a time constant. Parameters in the static relationships have been given to simulate the heart rate and systemic resistance changes observed by Koehler et al. (27) at deep levels of isocapnic hypoxia. The time constant of the hypoxic response has been taken from data reported elsewhere (35).

**Pulmonary Ventilation**

Parameters describing the \( V_T \) response include a pure delay, a gain, and a time constant. The delay has been assigned starting from data reported by Clement and Rob-
parameters that characterize the response of the various effectors (i.e., gains, time constants, and pure delays) have been given the same values assigned in the previous work (46). A difference is that, in the present model, the extraplenchic circulation has been divided into the coronary, brain, skeletal muscle, and other extraplenchic vascular beds, and only the last two compartments are under reflex control. Hence, parameters that characterize the gains of the sympathetic control on resistances, $R_{mp}$ and $R_{ep}$, and venous unstressed volumes, $V_{u,mv}$ and $V_{u,ev}$, have been given so that during normoxia the parallel arrangement of segments e, m, h, and b in Fig. 2 provides the same overall response to sympathetic activation obtained in the previous work for the entire extraplenchic circulation.

The model was simulated on Pentium-based personal computers by using the Runge-Kutta-Fehlberg 4/5 algorithm with adjustable step length for the numerical integration of differential equations.

RESULTS

Here we present a few simulation results, performed to validate the model during deep hypoxia, as to its steady-state and dynamic characteristics. In the conditions simulated below, we assumed that all mechanisms are present and superimpose their action in a dynamic nonlinear way.

Figure 11 shows the time patterns of SAP, heart rate, blood flow in the peripheral vascular beds with higher metabolic need (brain, skeletal muscle, and heart), and blood flow in all the remaining peripheral systemic vascular beds in response to a severe protracted hypoxia. PaO$_2$ is decreased from 95 to 28 mmHg between 50 and 60 s, when the model is in steady-state pulsating conditions, and is maintained throughout the remaining simulation period. As clearly shown in Fig. 11, hypoxia in the model evokes the classic well-defined cardiovascular changes: mean SAP and heart rate increase within 1 min from the beginning of the perturbation. Furthermore, hypoxia causes a significant redistribution of the available blood flow: blood flow increases dramatically in the organs with higher metabolic need, whereas it initially decreases in the remaining systemic vascular beds, mainly as a consequence of chemoreflex vasoconstriction. As a consequence, cardiac output remains quite constant during the first 10–20 s after the perturbation. The subse-

Fig. 11. Time pattern of systemic arterial pressure (A), heart rate (B), blood flow in the metabolically autoregulated vascular beds (C; parallel arrangement of branches m, h, and b in Fig. 2), and blood flow in all the remaining systemic vascular beds (D; parallel arrangement of splanchnic (s) and extraplenchic (e) branches in Fig. 2) simulated with the model after an isocapnic decrease in PaO$_2$. PaO$_2$ was decreased from 95 to 28 mmHg between 50 and 60 s and maintained throughout the remaining simulation period.
sequent gradual blood flow recovery in the “nonautoregulated” vascular bed is a consequence of the response of the lung inflation reflex and the CNS hypoxia, which increase heart rate and cardiac output, and of the vasodilatory action of the baroreflex and the lung inflation reflex, which reduce splanchnic and extrasplanchnic resistances.

Figure 12 shows a quantitative comparison between the steady-state percent changes in the main cardiovascular quantities obtained with the present model and the experimental results by Koehler et al. (27) in the dog during isocapnic hypoxia. The agreement between model and in vivo data is satisfactory, apart from a slight underestimation of cardiac output changes by the model.

To test the model’s capacity to reproduce not only steady-state values during hypoxia but also the dynamic aspects of the response, we performed a subsequent simulation in which deep hypoxia is protracted for a few seconds only, and then PO_2 is restored to its basal level. The aim of this simulation is to verify whether the model’s response to transient chemoreceptor activation exhibits the temporal pattern noticed by Rutherford and Vatner (42). These authors observed a biphasic response after intracarotid injection of cyanide or nicotine in dogs. The early phase occurred after \( \approx 6-7 \) s and was characterized by bradycardia, a decrease in regional (iliac) blood flow, and an increase in mean SAP. The later phase occurred after \( \approx 12-13 \) s and was characterized by an increase in heart rate, a relevant increase in regional (iliac) blood flow, and a return of mean SAP at the initial level. Figure 13 shows that the model provides a quite similar biphasic response after transient chemoreceptor stimulation, with time delays close to those observed in vivo. The model ascribes the early phase to the primary action of chemoreceptors, whereas the delayed phase is mainly attributed to secondary activation of lung stretch receptors.

DISCUSSION

The aim of this work was to develop a mathematical model of the cardiovascular regulatory response to isocapnic hypoxia by incorporating the multitude of physiological factors that are known. In our opinion,
the development of such a model is needed for several reasons. First, the enormous amount of experimental data that has been gathered in the past decades might be only superficially utilized and their mutual relationships poorly perceived, if they are not summarized into a comprehensive theoretical structure. Second, simulation of the cardiovascular behavior in response to different stimuli (including hypoxia) may be of great didactic value. Ultimately, knowledge of the interplay among the different mechanisms in pathophysiological conditions may help in the analysis and management of critical patients, in whom hypoxia is the primary perturbation or is added to other cardiovascular stresses (e.g., pulmonary embolism, heart failure, and myocardial infarction).

When the mathematical model was developed, the single portions of the overall system were first recognized; then each part was individually described according to physiological data to characterize its specific input-output static relationship and the situation. The ultimate system behavior was then obtained as the result of the nonlinear superimposition and mutual interactions among all these different constituents. Hence, physiological knowledge was included at two different levels in the model: the behavior of the individual portions and the way the different portions are mutually linked and interact to generate the overall response.

In the present study we analyzed the whole model response to deep hypoxia, when all parameters have a basal value assigned on the basis of physiological data. The results are in satisfactory agreement with those arising from classic physiological experiments (1, 24, 27, 30, 34): isocapnic hypoxia causes an increase in heart rate, mean SAP, and cardiac output, a decrease in venous capacity and total systemic resistance, and a significant blood flow redistribution toward the organs with higher metabolic demand. The model ascribes these well-defined cardiovascular adjustments to a complex “compromise” between various excitatory and inhibitory influences, which superimpose at different time intervals after the hypoxic perturbation.

Because the various control mechanisms exhibit a variety of temporal lags, i.e., temporal heterogeneity, the complexity of their superimposition can be better appreciated by looking at the time pattern of the hemodynamic quantities. In this regard, an important model result is that the temporal response to hypoxia displays two subsequent phases: an early phase, dominated by the activation of the peripheral chemoreflex, and a later phase, characterized by the participation of other regulatory actions. Looking at the time behavior of the different quantities (Figs. 11 and 13), we can speculate that the two phases have a different physiological meaning and respond to different protective requirements.

In the early phase (lasting ~10–20 s after a step change in PaO2), one can observe significant vasoconstriction and blood flow reduction in the organs subjected only to reflex control, with a moderate increase in mean SAP. In the same period, cardiac output remains rather constant; hence, a significant amount of blood flow is diverted to the organs with higher metabolic demand. This blood flow redistribution is further favored by the progressive vasodilation in the coronary, brain, and skeletal muscle circulation. Because of the moderate arterial hypertension, joined with reduced vascular resistance, blood flow to these organs increases two- or threefold above the basal value during a deep hypoxia.

The later phase of the response is characterized by various regulatory actions, which develop with a greater time constant. They include the increase in ventilation, triggered by the peripheral chemoreceptor activation, a progressive increase in heart rate, a reduction of the vasoconstriction in the reflexly regulated organs, and a further increase in mean SAP. During the later phase of the response, the main regulatory mechanisms responsible for the hemodynamic changes are the lung stretch receptors and the hypoxia of the CNS. Moreover, the baroreflex system also significantly participates in vasodilation during the later phase, responding to the gradual increase in mean SAP. As a consequence of these adjustments, blood flow in the reflexly regulated organs progressively returns toward a value close to the basal one.

The chain of events described above has a functional significance. The early response aims at maintaining adequate O2 delivery in the organs with higher metabolic rate, despite the dramatic reduction in the O2 content of blood, at the same time avoiding excessive work for the heart. Indeed, during the early phase, not only cardiac output remains quite constant, but also heart rate is reduced. We hypothesize that this kind of response has a protective function for the heart; an excessive increase in cardiac output and heart rate, in fact, joined with increased mean SAP, would imply a dramatic increase in power generation by the cardiac pump, with a consequent dramatic increase in its metabolic requirement. It is thus natural that cardiac output and heart rate do not increase in this phase and that arterial pressure exhibits only a moderate increase.

Significant augmentation of heart rate, cardiac output, and mean SAP (hence, a strong increase in cardiac power) occurs in the later phase only, when pulmonary ventilation has already risen; hence, O2 delivery to the organism is ameliorated. At this time, a certain O2 delivery can be ensured also to the organs with lower autoregulation, enforcing greater activity and power generation for the heart.

The difference between the early and late response is evident in several experimental works performed on animals (including dogs and primates). Various authors in recent years observed that the response to chemoreceptor stimulation in spontaneously breathing animals is time variable: the skeletal muscle displays short-lasting vasoconstriction followed by later vasodilation (14, 16); heart rate consistently shows initial bradycardia followed by tachycardia. The delayed response is abolished or significantly attenuated if che-
moreceptor stimulation is performed with controlled ventilation or after denervation of the lungs (42).

Even though the present model is able to account for the amplitude and time pattern of the main phenomena involved in the cardiovascular response to isocapnic hypoxia, it also exhibits some simplifications and limitations, which may become the target of future extensions.

A first limitation of the model is the absence of equations for gas exchange at the lung and in the tissue. Inclusion of these aspects will be necessary in future work to simulate conditions of real clinical relevance, such as asphyxia, respiratory diseases, or altitude hypoxia. In all these conditions, PaO₂ is not an input quantity (as in the present work) but a controlled quantity that varies according to a mass balance in the lung and tissue. O₂ mass balance, in turn, depends on various factors, such as the O₂ fraction in the inspired air, changes in ventilation and in local blood flow, and tissue metabolism.

A second limitation in the model is the absence of a role for PCO₂ changes; i.e., we simulated isocapnic hypoxia only. By contrast, in most clinical conditions a fall in PaCO₂ is accompanied by large changes in arterial CO₂ content. For instance, during lung disease, the fall in PaCO₂ occurs along with a rise in Pco₂; conversely, at high altitude the fall in PaCO₂ is followed by a decrease in PaCO₂, consequent to the rise in ventilation. Inclusion of the cardioventilatory effect of Pco₂ changes will require analysis of many additional phenomena that are not included in this work: especially the nonlinear interaction between O₂ and CO₂ at the peripheral chemoreceptors (20), the effect of central chemoreceptors on ventilation (39), and the local CO₂ effect on the autoregulated peripheral vessels. The complexity of these aspects justifies the choice to consider only O₂ in the present preliminary report to achieve progressive and step-by-step validation of the individual aspects.

Another limitation is that sympathetic outflow in the model depends on the additive combination of the three reflexes, with different weighting factors (see Eqs. 21 and 22). This is a drastic simplification, since data in the literature suggest the existence of a more complex interaction at the central neural level (8). The introduction of more reliable equations for central processing might be the subject of future studies, perhaps by use of neural network modeling techniques. Nevertheless, it is interesting to observe that even the simple central interaction proposed in this work (Eqs. 21 and 22) permits the net final cardiovascular response to be simulated quite well, without the need for a more sophisticated neural approach.

Another aspect to be underlined is that the model was designed to simulate the cardiovascular response in large mammals. Simulation of different animals may be carried out by simply scaling all parameters per unit weight (or by considering the percent changes of hemodynamic quantities). However, the model is probably inadequate to simulate the response in small mammals (such as rodents), for which different scaling factors are necessary. For instance, rats do not exhibit an increase in arterial pressure during hypoxia, whereas they often show a decrease.

Finally, in the present model, we did not include the role of cardiopulmonary (or low-pressure) baroreceptors. The latter might be responsible for a reflex increase in heart rate with an increase in filling pressure (Bainbridge reflex). Because an increase in filling pressure occurs during hypoxia, as a consequence of venoconstriction, it is possible that the absence of the Bainbridge reflex in this work might have led us to an underestimation of the heart rate increase.

In conclusion, the present model allows a quantitative study of the cardiovascular response to isocapnic hypoxia, with particular emphasis on the temporal superimposition among the different control mechanisms at different levels of the cardiovascular system. However, to better clarify the specific role of each mechanism and the effect of its possible alterations, it will be of value to simulate the regulatory system at different levels of PaO₂ and to test its sensitivity to parameter changes. These aspects are investigated in depth in the companion study (48).

APPENDIX

Quantitative Model Description

Equations describing the heart are unchanged compared with the previous study (46). Hence, only equations for blood vessels and control mechanisms are presented.

Vascular System

The extrasplanchnic circulation (which was a single compartment in the previous model) has been subdivided into a parallel arrangement of four distinct compartments: circulation in the brain (b), circulation in the skeletal muscle (m), coronary circulation (h), and circulation in all the remaining extrasplanchnic vascular beds (e). This choice is justified, since each compartment exhibits a specific regulatory response during hypoxia. The equations express the mass balance at the capacities and the force equilibrium at the interfaces. P is intravascular pressure in the jth compartment, V is the corresponding unstressed volume (defined as the volume at zero pressure), F is blood flow, and C, L, and R are compliances, inertances, and hydraulic resistances. Finally, F and F are cardiac output from the right and left ventricles.

Conservation of Mass at Pulmonary Arteries (Cpa)

\[ \frac{dP_{pa}}{dt} = \frac{1}{C_{pa}} \cdot (F_{o,r} - F_{pa}) \]  

(1)

where P and F are pulmonary arterial pressure and flow, respectively.

Balance of Forces at Pulmonary Arteries (Lpa)

\[ \frac{dF_{pa}}{dt} = \frac{1}{L_{pa}} \cdot (P_{pa} - P_{pp} - R_{pa} \cdot F_{pa}) \]  

(2)

where P is pulmonary peripheral pressure and R is pulmonary arterial resistance.
Conservation of Mass at Pulmonary Peripheral Circulation (C_{pp})
\[
\frac{dP_{pp}}{dt} = \frac{1}{C_{pp}} \left( P_{pa} - \frac{P_{pp} - P_{pa}}{R_{pp}} \right)
\]
(3)
where \( C_{pp} \) is pulmonary peripheral compliance, \( P_{pp} \) is pulmonary venous pressure, and \( R_{pp} \) is pulmonary peripheral resistance.

Conservation of Mass at Pulmonary Veins (C_{pv})
\[
\frac{dP_{pv}}{dt} = \frac{1}{C_{pv}} \left( \frac{P_{pp} - P_{pv}}{R_{pp}} - \frac{P_{pv} - P_{la}}{R_{pv}} \right)
\]
(4)
where \( R_{pv} \) is pulmonary venous resistance and \( P_{la} \) is left atrial pressure.

Conservation of Mass at Systemic Arteries (C_{sa})
\[
\frac{dP_{sa}}{dt} = \frac{1}{C_{sa}} \cdot (P_{sa} - P_{sp} - R_{sa} \cdot F_{sa})
\]
(5)
where \( P_{sa} \) is systemic arterial pressure and \( F_{sa} \) is systemic arterial flow.

Balance of Forces at Systemic Arteries (L_{sa})
\[
\frac{dF_{sa}}{dt} = \frac{1}{L_{sa}} \cdot (P_{sa} - P_{ap} - R_{sa} \cdot F_{sa})
\]
(6)
where \( P_{sp} \) is systemic peripheral pressure and \( R_{sa} \) is systemic arterial resistance.

Conservation of Mass at Systemic Peripheral Circulation (C_{sp}, C_{mp}, C_{bp}, and C_{hp})
\[
\frac{dP_{sp}}{dt} = \frac{1}{C_{sp} + C_{mp} + C_{bp} + C_{hp}} \cdot \left( F_{sa} - \frac{P_{sp} - P_{sv}}{R_{sp}} - \frac{P_{sp} - P_{mv}}{R_{mp}} - \frac{P_{sp} - P_{bv}}{R_{hp}} - \frac{P_{sp} - P_{lv}}{R_{lp}} \right)
\]
(7)
where \( C_{sp}, C_{mp}, C_{bp}, \) and \( C_{hp} \) are splanchnic, extrasplanchnic, skeletal muscle, brain, and coronary peripheral compliance; \( R_{sp}, R_{mp}, R_{bp}, \) and \( R_{hp} \) are splanchnic, extrasplanchnic, muscle, brain, and coronary peripheral resistance; and \( P_{sv}, P_{mv}, P_{bv}, \) and \( P_{hv} \) are splanchnic, extrasplanchnic, skeletal muscle, brain, and coronary venous pressure.

Conservation of Mass at Splanchnic Veins (C_{sv})
\[
\frac{dP_{sv}}{dt} = \frac{1}{C_{sv}} \left( P_{sv} - \frac{P_{sp} - P_{sv} - P_{ra} - dV_{u,sv}}{R_{sv}} \right)
\]
(8)
where \( R_{sv} \) and \( R_{sp} \) are splanchnic venous and peripheral resistance, \( P_{ra} \) is right atrial pressure, and \( V_{u,sv} \) is unstressed splanchnic venous volume.

Conservation of Mass at Skeletal Muscle Veins (C_{mv})
\[
\frac{dP_{mv}}{dt} = \frac{1}{C_{mv}} \left( P_{mv} - \frac{P_{sp} - P_{mv} - P_{ra} - dV_{u,mv}}{R_{mv}} \right)
\]
(9)
where \( R_{mv} \) is skeletal muscle resistance and \( V_{u,mv} \) is unstressed skeletal muscle volume.

Conservation of Mass at Pulmonary Venous Pressure (P_{pv})
\[
\frac{dP_{pv}}{dt} = \frac{1}{C_{pv}} \left( \frac{P_{pp} - P_{pv}}{R_{pp}} - \frac{P_{pv} - P_{la}}{R_{pv}} \right)
\]
(10)
where \( R_{pv} \) is pulmonary venous resistance.

Conservation of Mass at Coronary Veins (C_{cv})
\[
\frac{dP_{cv}}{dt} = \frac{1}{C_{cv}} \left( \frac{P_{sp} - P_{cv} - P_{la}}{R_{sp}} - \frac{P_{cv} - P_{la}}{R_{cv}} \right)
\]
(11)
where \( R_{cv} \) is coronary venous resistance.

In writing Eqs. 8–11, active changes in venous unstressed volume \( dV_{u}/dt \) have been included only in the compartments subject to reflex regulation (i.e., skeletal muscle and splanchnic compartments).

Finally, venous pressure in the extrasplanchnic compartment \( P_{cv} \) is computed by assuming that the total amount of blood volume contained in the circulatory system \( V_{tot} \) is known. Hence
\[
P_{cv} = \frac{1}{C_{cv}} \left[ V_{tot} - C_{sp} \cdot P_{sa} - (C_{sp} + C_{mp} + C_{bp} + C_{hp}) \cdot \frac{P_{sp} - C_{sp} \cdot P_{sv} - C_{mv} \cdot P_{mv} - C_{bp} \cdot P_{bv} - C_{hp} \cdot P_{hv}}{R_{sp}} \cdot \frac{P_{sp} - C_{sp} \cdot P_{sv} - C_{mp} \cdot P_{mv} - C_{bp} \cdot P_{bv} - C_{hp} \cdot P_{hv}}{R_{mp}} \cdot \frac{P_{sp} - C_{sp} \cdot P_{sv} - C_{bp} \cdot P_{bv} - C_{hp} \cdot P_{hv}}{R_{hp}} \right]
\]
(12)
where \( V_{cv}, V_{cv} \) are the volumes contained in the right and left ventricles, respectively, and \( V_{u} \) is equal to the sum of the unstressed volumes of the different compartments, i.e.
\[
V_{u} = V_{u,sp} + V_{u,sv} + V_{u,as} + V_{u,mp} + V_{u,bp} + V_{u,hp} + V_{u,hv} + V_{u,la}
\]
(13)
Afferent Neural Pathways

Afferent baroreflex pathway. According to experimental results, the afferent baroreflex pathway is described as the series arrangement of a linear derivative first-order dynamic block and a sigmoidal static characteristic
\[
\tau_{p,b} \frac{d\hat{P}}{dt} = \tau_{a,b} \frac{dP_{b}}{dt} - \hat{P}
\]
(14)
\[
f_{ab,min} + f_{ab,max} \cdot \exp \left( \frac{\hat{P} - P_{n}}{k_{ab}} \right)
\]
(15)
where \( \tau_{p,b} \) and \( \tau_{a,b} \) are the time constants for the real pole and the real zero in the linear dynamic block (usually with \( \tau_{a,b} > 1 \)), \( P_{b} \) is the pressure at arterial baroreceptors, \( \hat{P} \) is the output variable of the linear dynamic block (having the dimension of a pressure), \( f_{ab,min} \) is the frequency of spikes in the afferent fibers, \( f_{ab,max} \) and \( f_{ab,min} \) are the upper and lower saturation of the frequency discharge, respectively, \( P_{n} \) is the value of baroreceptor pressure at the central point of the sigmoidal function, and \( k_{ab} \) is a parameter, with the dimension of pressure, related to the slope of the static function at the central point. By denoting with \( G_{b} \) the maximum baroreceptor gain, i.e., the gain at the central point, the following expression holds
\[
G_{b} = \frac{\partial f_{ab}}{\partial P} \bigg|_{P = P_{n}} k_{ab} = \frac{f_{ab,max} - f_{ab,min}}{4 \cdot G_{b}}
\]
(16)
In closed-loop conditions, pressure at arterial baroreceptors is equal to SAP, i.e., \( P_b = P_{sa} \). By contrast, during open-loop simulations \( P_b \) is considered a model input.

**Afferent chemoreflex pathway.** The chemoreceptor response to changes in \( P_{ao} \) also includes a static function and first-order linear dynamics. We assume that the chemoreceptor frequency discharge is a sigmoidal function of \( P_{ao} \) at constant levels of \( P_{aco2} \). Hence

\[
\varphi_{ac}(P_{ao}) = \frac{f_{ac,max} + f_{ac,min} \cdot \exp \left( \frac{P_{ao} - P_{ao2} \cdot k_{ac}}{k_{ac}} \right)}{1 + \exp \left( \frac{P_{ao} - P_{ao2} \cdot k_{ac}}{k_{ac}} \right)}
\]

(17)

where \( f_{ac} \) represents the frequency spikes of the afferent fibers, \( f_{ac,max} \) and \( f_{ac,min} \) are the upper and lower saturation of frequency discharge, respectively, \( k_{ac} \) is a parameter with the dimension of pressure, related to the slope of the sigmoid at the central point, \( P_{ao2} \) is \( P_{o2} \) at the central point of the sigmoidal function, and \( \tau_c \) is the time constant of the chemoreceptor dynamics.

**Afferent activity from pulmonary stretch receptors.** We assume that at moderate levels of lung inflation the afferent activity of pulmonary stretch receptors is a linear function of the VT. Moreover, the response includes first-order dynamics. Hence, the relation between the pulmonary receptor frequency discharge \( f_{sp} \) and VT is described by the following equations

\[
\varphi_{sp}(VT) = G_{sp} \cdot VT
\]

(19)

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

(20)

where \( G_{sp} \) is a constant gain factor and \( \tau_p \) is the time constant of the lung inflation afferent response. The expression for \( VT \) is computed as a function of peripheral chemoreflex activation (see Ventilatory Response).

**Efferent Neural Pathways**

**Efferent sympathetic pathway.** Compared with the previous work (46), the present study distinguishes between the sympathetic fibers to the vessels and those to the heart. The former work on the peripheral resistances and unstressed venous volumes of the splanchnic, skeletal muscle, and other extraplanchnic beds; the latter work on the heart period and contractility.

The function that relates the activity in the afferent pathways to the efferent sympathetic activities has been given an exponential trend. The input to the exponential is the weighted sum of the afferent activities from baroreceptors, chemoreceptors, and lung stretch receptors. However, we assumed that sympathetic activity cannot increase above a saturation level. Hence

\[
f_{sp} = \begin{cases} 
    f_{es,n} + (f_{es,0} - f_{es,n}) \cdot \exp[k_{es} \cdot (-W_{b,sp} \cdot f_{ab} + W_{c,sp} \cdot f_{ac} - W_{p,sp} \cdot f_{sp} - \theta_{sp})] & \text{if } f_{sp} < f_{es,max} \\
    f_{es,max} & \text{if } f_{sp} \geq f_{es,max}
\end{cases}
\]

(21)

\[
f_{sh} = \begin{cases} 
    f_{es,n} + (f_{es,0} - f_{es,n}) \cdot \exp[k_{es} \cdot (-W_{b,sh} \cdot f_{ah} + W_{c,sh} \cdot f_{ac} - \theta_{sh})] & \text{if } f_{sh} < f_{es,max} \\
    f_{es,max} & \text{if } f_{sh} \geq f_{es,max}
\end{cases}
\]

(22)

where \( f_{sp} \) and \( f_{sh} \) represent the frequency of spikes in the sympathetic efferent fibers to the vessels and to the heart, respectively, \( k_{es}, f_{es,max}, f_{es,n} \) and \( f_{es,0} \) are constants (with \( f_{es,max} > f_{es,n} > f_{es,0} \)), and \( W_{b,sp}, W_{b,sh}, W_{c,sp}, W_{c,sh}, \) and \( W_{p,sp} \) are synaptic weights, tuned to reproduce physiological results. Finally, \( \theta_{sp} \) and \( \theta_{sh} \) are offset terms for sympathetic neural activation.

**Efferent vagal pathway.** The efferent vagal activity increases with the activity in the afferent baroreceptor fibers until an upper saturation is reached. To reproduce this relationship, we have used the sigmoidal function used in the previous study (46). The physiological literature documents a bradycardic response to carotid chemoreflex stimulation and a tachycardic response to pulmonary receptor stimulation; we take account of this by assuming that the vagal activity increases linearly with chemoreceptor activity and decreases linearly with stretch receptor activity. Hence

\[
f_e = \begin{cases} 
    f_{ev,0} + f_{ev,n} \cdot \exp \left( \frac{f_{sh} - f_{sh,0}}{k_{ev}} \right) \frac{1}{1 + \exp \left( \frac{f_{sh} - f_{sh,0}}{k_{ev}} \right)} + W_{ev} \cdot f_{ac} - W_{p,v} \cdot f_{sp} - \theta_v & \text{if } f_{ev,0} > f_{ev,n} \cdot \exp \left( \frac{f_{sh} - f_{sh,0}}{k_{ev}} \right) \frac{1}{1 + \exp \left( \frac{f_{sh} - f_{sh,0}}{k_{ev}} \right)}, f_{sh,0} \text{ is the central value in Eq. 15, } W_{ev} \text{ and } W_{p,v} \text{ are constant synaptic weights, tuned to reproduce experimental data, and } \theta_v \text{ is the offset term.}
\end{cases}
\]

**CNS Hypoxic Response**

The CNS response to lack of \( O_2 \) is mimicked by modifying the threshold of the sympathetic efferent activity to the heart and vessels. To reproduce experimental data, we assumed that \( \theta_{sp} \) and \( \theta_{sh} \) in Eqs. 21 and 22 depend on \( P_{ao3} \) through a static characteristic and first-order low-pass linear dynamics. The static characteristic is a sigmoidal function that remains equal to zero until \( P_{ao3} \) is higher than a certain threshold; then it rises rapidly until an upper saturation is reached. This is consistent with experimental evidence, which shows that CNS hypoxia plays a primary role only during severe hypoxia. According to experimental data, the threshold for the response of cardiac sympathetic nerves (50–60 mmHg) is higher than the response of peripheral sympathetic nerves (35–40 mmHg). The following equations have been used

\[
\chi_{sp}(P_{ao}) = \frac{\chi_{min,sp} + \chi_{max,sp} \cdot \exp \left( \frac{P_{ao} - P_{ao2,sp}}{k_{isc,sp}} \right)}{1 + \exp \left( \frac{P_{ao} - P_{ao2,sp}}{k_{isc,sp}} \right)}
\]

(24)

where

\[
\begin{align*}
\chi_{sp}(P_{ao}) = & \quad \frac{\chi_{min,sp} + \chi_{max,sp} \cdot \exp \left( \frac{P_{ao} - P_{ao2,sp}}{k_{isc,sp}} \right)}{1 + \exp \left( \frac{P_{ao} - P_{ao2,sp}}{k_{isc,sp}} \right)} \\
\end{align*}
\]
where \( \chi_{\text{min}} \) and \( \chi_{\text{max}} \) represent the upper and lower saturation of the hypoxic response, \( P_{O_2,\text{a}} \) is the \( P_{O_2} \) at the central point of the sigmoidal function, and \( k_{\text{ic}} \) is a parameter with the dimension of pressure, related to the slope of the static function at the central point. Finally, \( \tau_{\text{ic}} \) is the time constant; its value is higher than all the other time constants used in the model.

**Ventilatory Response**

The respiratory muscles respond to the peripheral chemoreceptor stimulation by changing ventilation. For the sake of simplicity, we assume that the controller acts only by modifying \( V_T \). \( V_T \) is described as follows

\[
V_T = V_{T0} + \Delta V_T \tag{28}
\]

where \( V_{T0} \) and \( \Delta V_T \) represent basal \( V_T \) and its changes due to the peripheral chemoreceptor activation. As in most clinical studies, we assume that, in steady-state conditions, \( V_T \) is a linear function of chemoreceptor activity. The time pattern of the ventilation response includes a pure delay (\( D_V \)) and first-order dynamics with time constant \( \tau_V \). Hence

\[
\frac{d\Delta V_T}{dt} = \frac{1}{\tau_V} \cdot [\Delta V_T + G_V \cdot [|f_a(t-D_V)-f_{a,c,n}]] \tag{29}
\]

where \( G_V \) is a constant gain factor, tuned to reproduce experimental data, and \( f_{a,c,n} \) is the value of chemoreceptor afferent activity in basal conditions.

**Effectors for Reflex Regulation**

The effectors for reflex regulation include the peripheral resistance and venous unstressed volume in the skeletal muscle (\( m \)), splanchic (\( s \)), and nonautoregulated extra-splanchnic (\( e \)) vascular beds, end-systolic elastances in the left and right heart, and heart period. The response of the resistances, venous unstressed volumes, and cardiac elastances to the sympathetic drive includes a pure latency, a monotonic logarithmic static function, and low-pass first-order dynamics. For the resistances and unstressed volumes

\[
\sigma_s = \begin{cases} G_s \cdot \ln [f_a(t-D_s)-f_{s,\text{min}}+1] & \text{if } f_a \geq f_{s,\text{min}} \\ 0 & \text{if } f_a < f_{s,\text{min}} \end{cases} \tag{30}
\]

\[
\frac{d\theta}{dt} = \frac{1}{\tau_s} \cdot (-\Delta \theta + \sigma_s) \tag{31}
\]

\[
\theta(t) = \Delta \theta(t) + \theta_0 \tag{32}
\]

and for the cardiac elastances

\[
\sigma_s = \begin{cases} G_s \cdot \ln [f_a(t-D_s)-f_{s,\text{min}}+1] & \text{if } f_a \geq f_{s,\text{min}} \\ 0 & \text{if } f_a < f_{s,\text{min}} \end{cases} \tag{33}
\]

\[
\frac{d\theta}{dt} = \frac{1}{\tau_s} \cdot (-\Delta \theta + \sigma_s) \tag{34}
\]

\[
\theta(t) = \Delta \theta(t) + \theta_0 \tag{35}
\]

where \( \theta \) denotes the generic controlled parameter (\( R_{mp}, R_{sp}, R_{ep}, V_{a,\text{mv},v}, V_{a,\text{ev},v}, E_{max,\text{ev}}, \) or \( E_{max,\text{mv}} \)), \( \sigma_s \) is the output of the static characteristic, \( \tau_s \) and \( D_s \) are the time constant and the pure latency of the mechanism, \( f_{s,\text{min}} \) is a threshold for sympathetic stimulation, and \( \Delta \theta \) is the parameter change caused by sympathetic stimulation. Finally, \( G_s \) is a constant gain factor, positive for mechanisms working on \( E_{max,\text{ev}}, E_{max,\text{mv}}, R_{mp}, R_{sp}, \) and \( R_{ep} \) but negative for \( V_{a,\text{mv},v}, V_{a,\text{ev},v} \) and \( V_{a,\text{mv}} \). However, with reference to skeletal muscle (\( \theta = R_{mp} \)), Eq. 32 does not furnish the true value of peripheral resistance, since skeletal muscle is further controlled by local \( O_2 \) mechanisms. Hence, for skeletal muscle only, we adopted a different symbol on the left-hand side of Eq. 32 (i.e., \( R_{mp,n} \)) to remind us that the true value of \( R_{mp} \) is obtained in the model only after inclusion of the \( O_2 \) effect (see below).

The response of the heart period includes a balance between the vagal and sympathetic activities. The changes in heart period induced by sympathetic stimulation (i.e., \( \Delta T_p \)) are obtained through equations analogous to Eqs. 33–35. The response to vagal activity differs from the others, since heart period increases linearly with the efferent frequency in the vagus. Finally, the heart period is obtained by assuming a linear interaction between the sympathetic and parasympathetic responses. Hence

\[
\sigma_{T_p}(t) = \begin{cases} G_{T_p} \cdot \ln [f_a(t-D_{T_p})-f_{s,\text{min}}+1] & \text{if } f_a \geq f_{s,\text{min}} \\ 0 & \text{if } f_a < f_{s,\text{min}} \end{cases} \tag{36}
\]

\[
\frac{d\Delta T_p}{dt} = \frac{1}{\tau_{T_p}} \cdot [-\Delta T_p(t) + \sigma_{T_p}(t)] \tag{37}
\]

\[
\sigma_{T_p}(t) = G_{T_p} \cdot f_a(t-D_{T_p}) \tag{38}
\]

\[
\frac{d\Delta T_p}{dt} = \frac{1}{\tau_{T_p}} \cdot [-\Delta T_p(t) + \sigma_{T_p}(t)] \tag{39}
\]

\[
T_p = T_{0} + \Delta T_p + T_0 \tag{40}
\]

where the symbols are as defined for Eqs. 30–35. In particular, \( T_0 \) denotes heart period in the absence of cardiac innervation.

**Local Effect of \( O_2 \)**

In the model the cerebral, skeletal muscle, and coronary peripheral conductances are directly regulated by local changes in \( O_2 \). This represents the sole regulation mechanisms acting on brain and coronary compartments, since these vascular beds are not under reflex control. By contrast, as described above, skeletal muscle circulation is controlled not only by the local effect of \( O_2 \) but also by the efferent sympathetic activity.

The stimulus for local regulation is assumed to be the change in \( O_2 \) concentration in the venous blood leaving the compartment (\( C_{j,o_2} \), with \( j = b, h, \) or \( m \)), since this quantity reflects \( O_2 \) content in the tissue. The mechanism includes a static gain (\( G_{i,j,o_2} \)) and first-order low-pass dynamics with time constant \( \tau_j \). This behavior is summarized as follows

\[
\frac{dx_j}{dt} = \frac{1}{\tau_j} \cdot [-x_j - C_{j,o_2} \cdot (C_{j,o_2} - C_{j,f,o_2})] \tag{41}
\]

\[
R_{j,p,n} = \frac{R_{j,p,n}}{1 + x_j} \tag{42}
\]

where \( C_{j,f,o_2} \) and \( R_{j,p,n} \) represent venous \( O_2 \) concentration and peripheral resistance in the \( j \)th compartment (\( j = b, h, \) or \( m \)) in normal conditions (i.e., when blood flow, \( P_{a,V_o} \), and tissue metabolism are at their basal value). According to the previous equations, a decrease in \( C_{j,f,o_2} \) below the basal
value causes an increase in the variable $x_i$ above zero, resulting in a linear increase in peripheral conductance and a decrease in peripheral resistance. The “normal” peripheral resistance in Eq. 42, $R_{P,p}$, is a constant parameter in the coronary and brain compartments because of the absence of significant reflex mechanisms in these vascular beds. By contrast, the same quantity is not constant in the skeletal muscle compartment, since it is dependent on the action of sympathetic nerves through Eq. 32.

An expression for venous $O_2$ concentration (see Eq. 41) is computed by imposing a mass balance between $O_2$ extraction and $O_2$ consumption rate

$$C_{V,O_2} = C_{A,O_2} - \frac{M_j}{F_j}$$

(43)

where $C_{A,O_2}$ is $O_2$ concentration in the arterial blood, $F_j$ is blood flow in the $j$th compartment (computed according to the hydraulic analog of Fig. 2), and $M_j$ is $O_2$ consumption rate in the same compartment.

$C_{A,O_2}$ is computed, as a function of $P_{A,O_2}$ (which is an input for the model), by means of the equations proposed by Spencer et al. (44) to reproduce the $O_2$ dissociation curve in blood

$$C_{A,O_2} = \frac{P_{O_2}^{1/4} \cdot \frac{F_{O_2}}{1 + \frac{P_{O_2}}{F_{O_2}}}}{\frac{F_{O_2}}{1 + \frac{P_{O_2}}{F_{O_2}}}}$$

(44)

$$P_{O_2} = P_{A,O_2} \cdot \frac{1 + \beta \cdot P_{CO_2}}{K(1 + \alpha \cdot P_{CO_2})}$$

(45)

where $C$, $\alpha$, $\beta$, and $K$ are constant parameters.

The $O_2$ consumption rates in the brain and skeletal muscle compartments ($M_b$ and $M_m$) are assumed to remain constant throughout the simulations. By contrast, $O_2$ consumption rate in the heart ($M_h$) depends on the average power of the cardiac pump ($W_h$)

$$M_h = W_h \cdot M_{hn}$$

(46)

where the subscript $hn$ is used to denote the value of the corresponding quantity in the basal condition.

The average $W_h$ is computed by low-pass filtering the instantaneous power produced by the left and right ventricle ($W_v$)

$$\dot{W}_h = -P_r \cdot \frac{dV_r}{dt} - P_v \cdot \frac{dV_v}{dt}$$

(47)

$$\frac{dW}{dt} = \frac{1}{\tau_w}(w_h - W_h)$$

(48)

where $\tau_w$ is the time constant of the filter.

This work was supported by a grant from the Italian Ministry of Scientific Research.

REFERENCES


