Cerebral autoregulation and gas exchange studied using a human cardiopulmonary model

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1Dynamical Systems Group, Rice University, Houston 77005; 2Baylor College of Medicine, Houston 77005; 3Department of Internal Medicine and Thoracic Surgery, University of Texas Medical Branch, Galveston 77555; and 4Department of Internal Medicine, University Texas Medical School, Houston, Texas 77030

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Lu, K., J. W. Clark, Jr., F. H. Ghorbel, C. S. Robertson, D. L. Ware, J. B. Zwischenberger, and A. Bidani. Cerebral autoregulation and gas exchange studied using a human cardiopulmonary model. Am J Physiol Heart Circ Physiol 286: H584–H601, 2004. First published August 28, 2003; 10.1152/ajpheart.00594.2003.—The goal of this work is to study the cerebral autoregulation, brain gas exchange, and their interaction by means of a mathematical model. We have previously developed a model of the human cardiopulmonary (CP) system, which included the whole body circulatory system, lung and peripheral tissue gas exchange, and the central nervous system control of arterial pressure and ventilation. In this study, we added a more detailed description of cerebral circulation, cerebrospinal fluid (CSF) dynamics, brain gas exchange, and cerebral blood flow (CBF) autoregulation. Two CBF regulatory mechanisms are included: autoregulation and CO2 reactivity. Central chemoreceptor control of ventilation is also included. We first established nominal operating conditions for the cerebral model in an open-loop configuration using data generated by the CP model as inputs. The cerebral model was then integrated into the larger CP model to form a new integrated CP model, which was subsequently used to study cerebral hemodynamic and gas exchange responses to test protocols commonly used in the assessment of CBF autoregulation (e.g., carotid artery compression and the thigh-cuff deflation test). The model can closely mimic the experimental findings and provide biophysically based insights into the dynamics of cerebral autoregulation and brain tissue gas exchange as well as the mechanisms of their interaction during test protocols, which are aimed at assessing the degree of autoregulation. With further refinement, our CP model may be used on measured data associated with the clinical evaluation of the cerebral autoregulation and brain oxygenation in patients.

physiological modeling; thigh-cuff test; carotid artery compression

NORMAL CEREBRAL AUTOREGULATION provides a constant cerebral blood flow (CBF) over a wide range of cerebral perfusion pressures (CPP) (1, 25). Because this regulatory mechanism is complex, several investigators have found that mathematical models can help guide experimental design and provide explanations of experimental results (8, 14–16, 18, 32, 36). These models have largely been directed at developing mechanistic descriptions of cerebral autoregulation or the dynamics of intracranial systems. None have considered the effect of CO2 on cerebral hemodynamics and autoregulation or described the gas exchange between cerebral vessels and brain tissue. Ursino et al. (37, 39) and Czosnyka et al. (5) included CO2 reactivity in their modeling studies of intracranial dynamics. However, their models did not include gas transport in brain tissue and thus can not simulate the impact of cerebral hemodynamic changes on brain tissue gas content.

We recently presented a modeling study of human whole body gas exchange (20), in which our previous human cardiopulmonary (CP) model (19) was significantly extended to include descriptions of gas transport to the peripheral tissue, hemodynamic effects of peripheral chemoreflex and pulmonary stretch reflex, and chemical control of ventilation as well as capillary filtration and lymph flow. However, this model describes the cerebral circulation only as a resistive pathway. In addition, the brain tissue was considered the same as other body tissues and hence could be lumped into a single tissue compartment. To better study cerebral hemodynamics and brain gas exchange using the CP model, we present another major extension wherein we add more detailed descriptions of cerebral hemodynamics, autoregulation of CBF, and gas exchange between brain capillaries and the extravascular space. The brain tissue compartment consists of two compartments, the interstitial (ISF) and intracellular (ICF) fluid spaces. Gas dynamics in the cerebrospinal fluid (CSF) are also included. Two CBF regulating mechanisms are considered, namely, cerebral autoregulation and CO2 reactivity. Cerebral autoregulation activates in response to changes in cerebral perfusion, whereas CO2 reactivity modulates CBF and the strength of autoregulation in response to a change in brain tissue PCO2. Both mechanisms affect CBF by adjusting the cerebrovascular resistance (CVR) and cerebrovascular compliances. An empirical relationship that describes the central chemoreceptor control of ventilation is also included and integrated with the previous peripheral chemoreflex model (20).

As a first step, parameters of the cerebral vascular and gas exchange model were adjusted to yield good nominal behavior by driving the cerebral model with inputs derived from our closed-loop CP model [e.g., arterial pressure waveforms, and arterial Po2 (PaO2) and Pco2 (Paco2)]. Several open-loop tests were performed (e.g., arterial hypotension) and the results compared with measured data reported in the literature. Once general agreement was achieved between model-generated and measured data, the circulatory loop was closed and the cerebral model was integrated into the larger human CP model. Subsequently, the integrated CP model was used to simulate the normal human response to routine clinical tests for cerebral autoregulation and brain gas exchange, such as carotid artery

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compression, a commonly used bedside test for autoregulation (9), and the “thigh-cuff” test of Aaslid et al. (1). The model-generated results provide a mechanistic picture of the transient hemodynamic and gas transport effects produced by these test procedures, as well as, an evaluation of indexes used to assess autoregulatory state and their sensitivity to brain tissue CO2 levels.

GLOSSARY

ABP arterial blood pressure
αi solubility coefficient of gas i, i = O2 or CO2, ml·mmHg⁻¹
[H+] concentration of hydrogen ion in CSF, mol/ml
\( [HCO_3^-] \) concentration of \( HCO_3^- \) in CSF, mol/ml
\( C_{sw} \) width of the sigmoidal curve, ml/mmHg
\( C_{i,j} \) concentration of gas i in the jth cerebral capillary segment, i = O2 or CO2, ml/ml
\( C_i \) concentration of gas i in cerebral arteries, ml/ml
\( C_a \) compliance of the cerebral arterial segment, ml/mmHg
\( C_c \) compliance of the cerebral capillary segment, ml/mmHg
\( C_v \) compliance of the cerebral venous segment, ml/mmHg
\( C_n \) midpoint of the sigmoidal curve, ml/mmHg
\( C_{ax} \) compliance of the neck artery segment, ml/mmHg
\( C_{nv} \) compliance of the neck vein segment, ml/mmHg
\( C_{ic} \) concentration of gas i in intracranial space, i = O2 or CO2, ml/ml
\( C_{ih} \) concentration of gas i in interstitial space, i = O2 or CO2, ml/ml
\( C_{CSF,i} \) concentration of gas i in CSF, i = O2 or CO2, ml/ml
\( CBF \) cerebral blood flow, ml/s
\( CBF_0 \) desired CBF, ml/s
\( CBF_n \) nominal CBF, ml/s
\( CVR \) cerebral vascular resistance (CVR = \( R_a + R_c + R_v \)) of arteries, capillaries, and veins, respectively, mmHg·s·ml⁻¹
\( D_{bi} \) diffusion capacity of gas i between blood and ISF, ml·STPD·mmHg⁻¹·s⁻¹
\( D_{bi} \) diffusion capacity of gas i between ISF and ICF, ml·STPD·mmHg⁻¹·s⁻¹
\( D_{bi} \) diffusion capacity of gas i between ISF and CSF, ml·STPD·mmHg⁻¹·s⁻¹
\( D_{nv} \) offset constant for collapsible neck veins, mmHg
\( ICP \) intracranial pressure
\( g_{cc} \) normalized central chemoreceptor discharge, dimensionless
\( k_{cc} \) gain, dimensionless
\( k_f \) inverse of the central slope of the sigmoidal curve
\( K_{aut} \) autoregulation gain, dimensionless
\( k_0 \) rigidity coefficient of cranium, 1/ml
\( K_r \) cerebral arterial resistance constant, mmHg·s·ml⁻¹
\( K_{is} \) dissociation constant for carbonic acid, mol/ml
\( K_{nv} \) constant for collapsible neck veins, ml/mmHg
\( K_{ven} \) constant for neck venous resistance, mmHg·s·ml⁻¹
\( M_i \) metabolic rate of gas i, i = O2, CO2, ml/s
\( N_{cap} \) number of capillary segments
\( \dot{P}_{o_2} \) arterial O2 tension, mmHg
\( \dot{P}_{co_2} \) arterial CO2 tension, mmHg
\( P_{i,j} \) tension of gas i in the jth cerebral capillary segment, i = O2 or CO2, mmHg
\( P_{o_2} \) pressure in the cerebral venous vascular segment, mmHg
\( P_{co_2} \) intracranial pressure, mmHg
\( P_{i,j} \) tension of gas i in intracranial space, i = O2 or CO2, mmHg
\( P_{o_2} \) tension of gas i in interstitial space, i = O2 or CO2, mmHg
\( P_{O_2} \) O2 tension in peripheral tissue, mmHg
\( P_{CO_2} \) CO2 tension in peripheral tissue, mmHg
\( P_{TM,a} \) transmural pressure of the cerebral arterial segment, mmHg
\( P_{TM,c} \) transmural pressure of the cerebral capillary segment, mmHg
\( P_{TM,v} \) transmural pressure of the cerebral venous segment, mmHg
\( P_{nv} \) pressure in neck veins, mmHg
\( q_f \) CSF formation rate, ml/s
\( q_a \) CSF absorption rate, ml/s
\( q_b \) cerebral blood flow in the cerebral arterial segment, ml/s
\( q_c \) cerebral blood flow in the cerebral capillary segment, ml/s
\( q_v \) cerebral blood flow in the cerebral venous segment, ml/s
\( R_e \) resistance of cerebral arterial segment, mmHg·s·ml⁻¹
\( R_c \) resistance of cerebral capillary segment, mmHg·s·ml⁻¹
\( R_v \) resistance of cerebral venous segment, mmHg·s·ml⁻¹
\( R_{nv} \) resistance of neck artery segment, mmHg·s·ml⁻¹
\( R_{nv} \) resistance of neck vein segment, mmHg·s·ml⁻¹
\( R_{mt0} \) constant parameter for the resistance of neck vein segment, mmHg·s·ml⁻¹
\( R_t \) CSF formation resistance, mmHg·s·ml⁻¹
\( R_r \) CSF absorption resistance, mmHg·s·ml⁻¹
\( ROR \) rate of regulation, 1/s
\( S_{o_2,CSF} \) cerebral venous O2 saturation, %
\( \tau_{aut} \) autoregulation time constant, s
\( \tau_{cc} \) time chemoreceptor constant, s
\( \tau_{aut} \) cerebral autoregulation variable, dimensionless
\( V_{a} \) blood volume in cerebral arterial segment, ml
\( V_{c} \) blood volume in cerebral capillary segment, ml
\( V_{v} \) blood volume in cerebral venous segment, ml
\( V_{nv} \) intracranial volume, ml
\( V_{nv} \) blood volume in neck vein, ml
\( V_{nv} \) unstressed volume in neck vein, ml
\( V_{nv,max} \) maximal volume in neck vein, ml
\( V_{ic} \) intracellular volume, ml
\( V_{is} \) interstitial volume, ml
\( V_{CSF} \) total CSF volume, ml
\( \dot{V}_{f} \) blood flow velocity in jth capillary segment, cm/s
\( W_{cc} \) weighting coefficient of central chemoreceptors
\( W_{pc} \) weighting coefficient of peripheral chemoreceptors
\( z \) capillary length coordinate

MODEL DEVELOPMENT

A lumped cerebral tissue compartment model was developed that included the following: 1) a model of the cerebral circulation, 2) a multicompartment tissue model consisting of ISF, ICF, and CSF compartments, 3) a gas transport model between the blood and tissue compartments, and 4) mechanisms for implementing CBF autoregulation and CO2 reactivity.

Cerebral Hemodynamics

Our cerebral hemodynamics model is similar to the previous models developed by Ursino et al. (36, 39). It consists of three lumped cerebral vascular segments: cerebral arteries, capillaries, and veins, as shown in Fig. 1. In our study, representations of the neck arteries and veins are also included as needed for the integration with the human circulatory loop model (19).
Cerebral venous resistance is as follows (33):

\[
R_v = \frac{P_v - ICP}{q_v} = R_{cv} + R_c
\]

The cerebral venous outflow then becomes

\[
q_v = \frac{P_v - ICP}{R_{cv}}
\]

which is independent of the extracranial venous pressure \( P_{nv} \) as far as ICP exceeds \( P_{nv} \) (2, 27).

The extracranial veins in the neck may also collapse (4, 7, 29). We used a piecewise approximation similar to that used for systemic veins (19) to describe the pressure-volume relationship of the collapsible neck veins

\[
\text{if } (V_{nv} \geq V_{nv0}) P_{nv} = -K_{nv} \times \log \left( \frac{V_{nv,\text{max}}}{V_{nv}} - 0.999 \right) - D_{nv}
\]

\[
\text{else } P_{nv} = -D_{nv}
\]

where \( K_{nv}, R_{nv} \), and \( D_{nv} \) are constants similar to those used in Ref. 19 but scaled to generate a nominal pressure of 6.0 mmHg in the neck veins (23). In addition, the valves present in neck veins (23) are characterized by a leaky valve representation similar to that employed by Snyder and Rideout (31)

\[
V_{ic} = V_i + V_c + V_{nv} + q_t - q_v
\]

The intracranial and extracranial fluid volumes are assumed constant.

Because the cranium is rigid, any change in the intracranial volume will cause significant variations in the intracranial pressure, which tend to counteract this volume change. Hence, an exponential formula is adopted to characterize the intracranial pressure-volume relationship (3)

\[
C_{ic} = \frac{1}{K_e \times ICP}
\]

where \( K_e \) is the rigidity coefficient of the cranium (3).

**CSF Dynamics**

CSF is continuously formed by the choroid plexus and removed by the arachnoid villi (23). In our model, we assume this process is...
Brain Gas Exchange

To model gas exchange in cerebral capillaries, we divided the intracranial space into ISF, ICF, and CSF compartments (Fig. 2). The first two are assumed to be well mixed and homogeneous and to have constant volumes, with the ICF enclosed by the ISF. On the other hand, CSF volume is subject to its formation and absorption rates as shown in Figs. 1 and 2. Figure 2 shows that the ISF interfaces with the cerebral capillary, where gas exchange primarily takes place. Additional exchange occurs between the ISF and the enclosed ICF compartment as well as the surrounding CSF. The gas exchange is assumed driven by the pressure gradient between the compartments, and CSF gas composition can also be affected by the bulk flow generated during CSF formation and absorption.

Blood gas variation in cerebral capillary. The lumped equivalent cerebral capillary is represented by a cylindrical tube, wherein perfect radial mixing of blood is assumed. Within the capillary, reactions between the gaseous species (O₂ and CO₂) and blood are assumed to reach equilibrium instantly. The tube is divided into \(N_{seg}\) equal segments (Fig. 2), and the temporal behavior of gas concentrations in each segment is evaluated using a molar balance for each gaseous species \(i\), according to the following partial differential equation

\[
\frac{dC_{i}^{(h)}}{dt} = - \frac{\partial}{\partial z} C_{i}^{(h)} + \frac{D_{i}(P_{IS} - P_{IC})}{V_{c}}
\]

The empirical dissociation curves developed in a previous study (17) can mimic the Bohr and Haldane effects. Diffusion capacity \(D_{i}\) indicates the ability of gas \(i\) to cross the blood-tissue barrier, and we assume the following values

\[
D_{i_{O2}} = 0.66 \text{ ml gas} \cdot \text{mmHg}^{-1} \cdot \text{s}^{-1}
\]

\[
D_{i_{CO2}} = 13.3 \text{ ml gas} \cdot \text{mmHg}^{-1} \cdot \text{s}^{-1}
\]

Gas variations in tissue compartments. The gas content in tissue (both interstitial and intracellular compartments) and its partial pressure are related according to the equations

\[
P_{IS} = C_{IS}/\alpha_{i}
\]

\[
P_{IC} = C_{IC}/\alpha_{i}
\]

where \(P\) represents gas partial pressure (in mmHg) and \(C\) represents gas concentration (in ml/ml). IS is ISF, IC is ICF, and \(i\) refers to O₂ or CO₂. \(\alpha_i\) refers to both tissue compartments.

By applying the mass conservation law, the variation in gas composition in each of the fluid compartment can be expressed as ISF, ICF, and CSF.

**ISF.** The ISF exchanges gases with capillary blood, ICF, and CSF, thus the time rate of change of ISF gas concentration \(dC_{IS}/dt\) is determined by

\[
\frac{dC_{IS}}{dt} = \frac{1}{V_{IS}} \left[ -D_{M}(P_{IS} - P_{IC}) - D_{N}(P_{IS} - P_{CSF}) + \sum_{j=1}^{N_{seg}} \frac{D_{i}(P_{IS} - P_{IC}^{(j)})}{V_{c}} \right]
\]

**ICF.** In the ICF, we assume that the metabolic consumption rate of O₂ and the production rate of CO₂ are constant, and denoted by \(M_i\), where \(i\) can be O₂ or CO₂. Hence, the time rate of change in gas concentration is

\[
\frac{dC_{IC}}{dt} = \frac{1}{V_{IC}} \left[ D_{M}(P_{IS} - P_{IC}) - M_{i} \right]
\]

**CSF.** Gas composition in the CSF is directly affected by gas partial pressure within the ISF and capillary blood as well as by the formation and drainage of CSF. Thus the time rate of change in gas concentration in CSF is

\[
\frac{dC_{CSF}}{dt} = \frac{1}{V_{CSF}} \left[ q_{t} \cdot C_{h}^{(n)} - q_{t} \cdot C_{CSF} + D_{N}(P_{IS} - P_{CSF}) \right]
\]

An important relationship exists between the concentration of dissolved CO₂ in the CSF and the CSF [H⁺]. According to the Henderson-Hasselbalch equation

\[
[H^+] = K_H \left( \frac{\alpha_{CO2} \times P_{CSF}}{[HCO_3^-]} \right)
\]

where [HCO₃⁻] in CSF is assumed to remain at a constant level of 24.5 mmol/l (10).

**CBF Regulation**

Autoregulation maintains CBF over a wide range of perfusion pressures (60–150 mmHg) (23). In our model, autoregulation occurs by making the compliance \(C_a\) and resistance \(R_a\) (Fig. 1) functions of CBF. Specifically, an increase in CBF causes \(C_a\) to decrease and \(R_a\) to increase, indicating vasocostriction, whereas a decrease in cerebral blood flow increases \(C_a\) and decreases \(R_a\), causing vasodilation. In characterizing autoregulation, we have adopted the following empirical transfer function developed by Ursino et al. (39)

\[
\dot{x}_{aut} = -x_{aut} + \frac{K_{aut} \left( CBF - CBF_0 \right)}{CBF_0}\]

where \(x_{aut}\) is the variable accounting for autoregulation, CBF₀ is the desired CBF. Subsequently, \(x_{aut}\) modifies \(C_a\) by means of the following sigmoidal relationship from Ursino et al. (39)
Here, $C_a$ and $C_w$ are parameters defining the midpoint and width of the sigmoidal curve, respectively, and $k_p$ is inversely proportional to the central slope of the curve (39). Thus

\[
C_a = \frac{(C_n - \frac{1}{2} C_u) + (C_n + \frac{1}{2} C_u)e^{-x_0/k_p}}{1 + e^{-x_0/k_p}} \tag{22}
\]

If $x_{\text{aut}} \leq 0$; $C_u = C_{u1}$, \( k_p = C_u/4 \) \tag{23}

If $x_{\text{aut}} > 0$; $C_u = C_{u2}$, \( k_p = C_u/4 \) \tag{24}

Previous studies (1, 25, 30) indicate that CO2 also has major effects on autoregulation and cerebral blood flow. Specifically, during hypocapnia, the CBF increases and autoregulation is impaired, whereas in hypocapnia, CBF decreases and autoregulation is improved. The effect of CO2 on CBF is implemented by making CBF0 in Eq. 21 a function of $P_{\text{IS,CO2}}$, i.e.

\[
\Delta \text{CBF}_0 = 1.8 \frac{1}{1 + e^{-0.06([H\text{CO}_3]_o - 57)10^{-3}}} - 0.6 \tag{25}
\]

\[
\text{CBF}_0 = \text{CBF}_0 \cdot (1 + \Delta \text{CBF}_0) \tag{26}
\]

where $\Delta \text{CBF}_0$ is the variation because of $P_{\text{IS,CO2}}$. The model parameters are chosen to mimic the experimental results of Harper and Glass (12).

Unlike the approach taken by Ursino et al. (39), which superimposes the effects of autoregulation and CO2 on CBF, we emphasize the modulating effect of CO2 on autoregulation and thus directly change $K_{\text{aut}}$ according to $P_{\text{IS,CO2}}$.

\[
K_{\text{aut}} = \frac{18.0}{1 + e^{0.06([H\text{CO}_3]_o - 57)10^{-3}}} \tag{27}
\]

where $P_{\text{IS,CO2},0}$ represents the control value of $P_{\text{IS,CO2}}$. The above equation generates a monotonically decreasing $K_{\text{aut}}$ with an increase of $P_{\text{IS,CO2}}$, indicating a continuously weakened autoregulation.

From Eq. 22, we have

\[
\dot{C}_a = -\frac{C_h}{k_p} \cdot \frac{e^{-x_0/k_p}}{1 + e^{-x_0/k_p}} \times (-\dot{x}_{\text{aut}}) \tag{28}
\]

Equation 4 then becomes

\[
\dot{P}_{\text{PaCO}} = \frac{V_a}{C_a} - \frac{V_a}{C_a} \times \dot{C}_a \tag{29}
\]

Because cerebral arterial resistance varies with vasoconstriction or dilation, we have used the following formula to account for these resistance changes (39)

\[
R_s = \frac{K_p \cdot C_u^2}{V_a^2} \tag{30}
\]

Central Chemoreflex Control of Ventilation

Our previous studies using the human CP model (19, 20) did not include the central chemoreflex control of ventilation. Central chemoreceptors are located in the ventral surface of the medulla and detect changes in CSF $[H^+]$ (13). We assumed a linear relationship (38) between central chemoreceptor discharge and CSF $[H^+]$ according to the following equation

\[
g_{\text{cc}}(t) = K_{\text{cc}}[H^+](t - d_{\text{cc}}) - [H^+]_o(t) - g_{\text{cc}}(t) \tag{31}
\]

where $g_{\text{cc}}(t)$ represents the normalized central chemoreceptor discharge, and $g_{\text{cc}}$ is its variation rate. $[H^+]_o$ represents the control value of $[H^+]$ in the CSF. The parameter $d_{\text{cc}}$ represents the delay from central chemoreceptor activation to the ventilatory response. $K_{\text{cc}}$ is chosen to generate the similar percentage change of ventilatory neural activity reported in (11). We implemented the central chemoreceptor control by adding it to our previously developed peripheral chemoreceptor control of ventilation model (20), which modifies the depth and frequency of pleural pressure variation (Eqs. 21–24 in Ref. 20). The drive signal to the ventilatory control center ($g_v$) is now the weighted sum of the central chemoreceptor discharge and the peripheral chemoreceptor discharge

\[
g_v = W_{\text{cc}} \cdot g_{\text{cc}} + W_{\text{cp}} \cdot g_{\text{cp}} \tag{32}
\]

$g_v$ replaces $g_c$ in Eqs. 21–24 found in Ref. 20. Here, $W_{\text{cc}}$ and $W_{\text{cp}}$ are weighting coefficients of $g_{\text{cc}}$ and the peripheral chemoreceptor frequency ($g_{\text{cp}}$), respectively. Because of a lack of experimental data on the relation between the peripheral and central chemoreflex control, we currently assigned a value 1.0 for both $W_{\text{cc}}$ and $W_{\text{cp}}$.

### Computational Aspects

In this study, we first established the nominal conditions of the cerebral model in an open loop configuration using model-generated data (ABP, venous blood pressure, $P_{\text{aCO}}$, and $P_{\text{aCO2}}$) from the human CP model (20) as inputs. Once these open-loop simulations were completed, we incorporated the cerebral model into our human CP model (20) and added the central chemoreceptor control. This more comprehensive closed-loop CP model is used to study human responses induced by carotid artery compression and the thigh-cuff test.

Our model contains many parameters, which are carefully assigned values to generate model predictions that are in agreement with normal physiological data reported in literature. In the cerebral hemodynamic model (Fig. 1), the resistances are chosen to generate steady-state pressures and flows that mimic typical measurements in human as shown in Table 1. The total cerebral blood volume is $\sim 100$ ml (23). We assume that blood distribution in brain is similar to that in the systemic circulation, thus the ratio of the blood volume contained in the arterial, capillary, and venous segments is 1:1:3 (23). The cerebral vascular capacitances are based on the normal values reported by Ursino et al. (33, 36, 39). Most of the parameters associated with CBF autoregulation algorithm are adopted from Ursino et al. (39), with the exception of Eq. 27, which describes the modulating effect of CO2 on autoregulation gain (discussed previously). Here, we use a sigmoidal shape to represent the saturation and threshold characteristics often observed in human neural control systems, and the parameters of this sigmoidal relationship are chosen so that the model can produce autoregulation indexes that are in agreement with clinical data reported in carotid artery compression (Table 2) and thigh-cuff tests (Table 3). In the brain gas exchange model, the diffusing capacity and solubility coefficients of O2 and CO2 are modeled using the parameters associated with CBF autoregulation algorithm.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Nominal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP</td>
<td>Mean arterial blood pressure, mmHg</td>
<td>100.0</td>
</tr>
<tr>
<td>ICP</td>
<td>Mean intracranial pressure, mmHg</td>
<td>9.7</td>
</tr>
<tr>
<td>CBF</td>
<td>Mean cerebral blood flow, ml/s</td>
<td>12.5</td>
</tr>
<tr>
<td>$g_{\text{cc}}$</td>
<td>CSF formation rate, ml/day</td>
<td>560</td>
</tr>
<tr>
<td>$g_{\text{cp}}$</td>
<td>CSF absorption rate, ml/day</td>
<td>560</td>
</tr>
<tr>
<td>$V_{\text{CSF}}$</td>
<td>CSF volume, ml</td>
<td>150</td>
</tr>
<tr>
<td>$[H^+]_o$</td>
<td>CSF hydrogen ion concentration, mol/ml</td>
<td>$4.4000 \times 10^{-5}$</td>
</tr>
<tr>
<td>$S_{\text{O}_2}$</td>
<td>Cerebral venous $O_2$ saturation, %</td>
<td>68%</td>
</tr>
</tbody>
</table>

### Table 1. Nominal variables predicted by human cerebral system model

- **$O_2$**
- **$CO_2$**

CSF, cerebrospinal fluid. The predictions are in general agreement with the typical values observed in the normal human subject (27).
are identical to those used in our previous models (17, 19, 20). Brain metabolic rates (MO and MCO2) are set to the average values reported for human (23). DM and DN in Eqs. 17–19 are calculated from the typical gaseous tensions observed in brain as shown in Table 1. The average brain volume for human is ~1,200 ml (40) and the interstitial fluid comprises one-fourth of the total tissue volume (23). Thus we use Vsh = 300 ml and Vic = 900 ml.

Tables 4 and 5 list the model parameters and initial conditions used in our study. The CP model is programmed in C programming language and solved by using the variable step-size Runge-Kutta-Merson algorithm with a maximum time step size of 2 × 10⁻⁴ s and an error tolerance of 1 × 10⁻⁶.

### RESULTS

As mentioned previously, we first performed open-loop simulations to establish the nominal conditions of the cerebral model. To test cerebral autoregulation, the PaCO2 input to the cerebral model is kept constant at a normal value of 40 mmHg and mean ABP is varied from 20 to 200 mmHg. Figure 3A shows the steady-state values of CBF obtained at different mean ABP. CBF is well maintained between 60 and 150 mmHg, but <60 mmHg, it decreases with ABP at a rate of 1.58% per mmHg. Above 150 mmHg, CBF increases at a rate of 1.24% per mmHg. Good agreement is obtained between the model prediction and the measured data from Refs. 21 and 22.

#### Hypotension

Episodic hypotension commonly occurs in head injured patients, and its effect on cerebral hemodynamics is of particular interest to investigators. Using our model of the normal human subject, we examined the hemodynamic effect of gradually decreasing ABP. Figure 4 illustrates the hemodynamic responses predicted by the cerebral circulatory model with (Fig. 4A) and without (Fig. 4B) the autoregulatory mechanism. Starting from 30 s, ABP is decreased linearly at 0.5 mmHg/s for 150 s. Figure 4A shows that mean CBF is well maintained by autoregulation until 100 s, after which it begins to decrease. There is a gradual increase in CBF pulse amplitude (the difference between systolic and diastolic CBF) before 100 s marked by increasing systolic flow and decreasing diastolic flow. After 100 s, CBF pulse amplitude remains large, whereas mean CBF decreases. ICP rises continuously during hypotension, reaching its peak right before the 100-s mark. Figure 4A shows that vasodilation occurs in response to the slowly decreasing perfusion pressure. Specifically, as soon as hypotension starts, Rª begins to decrease and Cª begins to slowly increase (Fig. 4A, bottom panels). Vasodilation reaches a maximum at 100 s, corresponding to the point where the mean ABP drops below the lower autoregulation limit (60 mmHg). As arterial pressure continues to decrease, both mean CBF and ICP decrease quickly.

There is an increase in both CBF and ICP pulse amplitude before the 100-s mark as indicated by Fig. 4. The increase in CBF pulsatility is due to vasodilation. Because the cerebral artery dilates in response to hypotension, its lumen pressure becomes less pulsatile and its mean value decreases. This translates to a larger systolic pressure difference and a smaller diastolic pressure difference, between the ABP and the cerebral arterial pressure. The increase in ICP pulse amplitude is due to the increased blood volume in cerebral arteries caused by the arterial vasodilation. Because the cranium has little tolerance for a volume increase, this causes an increase in ICP and hence a decrease in intracranial compliance (Eq. 11). When autoregulation is absent (Fig. 4B), cerebral arterial vasodilation does not occur, and both CBF and ICP and their pulse amplitudes decrease with decreasing ABP.

During these simulations, input arterial PO2 and PCO2 are maintained at control levels (100 and 40 mmHg, respectively).
Autoregulation and CO₂ Reactivity

<table>
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<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>$\tau_{aut}$</td>
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</tr>
<tr>
<td>$P_{R,CO_2}$</td>
<td>45.5 mmHg</td>
</tr>
<tr>
<td>$C_{w1}$</td>
<td>2.87 ml/mmHg</td>
</tr>
<tr>
<td>$K_{c}$</td>
<td>4.96 $\times$ 10$^{-4}$ mmHg$^{-1}$s$^{-1}$</td>
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</tbody>
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Central Chemoreflex

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>$W_{cc}$</td>
<td>1.0</td>
</tr>
<tr>
<td>$\tau_{cc}$</td>
<td>10.0 s</td>
</tr>
</tbody>
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However, $P_{bO_2}$ and $P_{bCO_2}$ vary (Fig. 5). They are assumed equal to the gas tensions in brain interstitial space. When autoregulation is present (Fig. 5A), the mean value of $P_{bO_2}$ is constant until the lower autoregulation limit is reached. Thereafter, it decreases because of the diminished CBF. $P_{bCO_2}$ decreases slightly and then increases quickly at the autoregulation limit. In the absence of autoregulation (Fig. 5B), $P_{bO_2}$ decreases and $P_{bCO_2}$ increases more quickly throughout the hypotensive episode. We are unaware of any measured data that confirms this model prediction.

We further examined the effect of ABP on CBF and ICP pulsatility using the isolated cerebral model. Keeping the ABP pulse amplitude constant, we changed the mean ABP from 30% to 200% of the nominal value (100 mmHg) and observed the changes in peak amplitudes of CBF and ICP (Fig. 6A). When mean ABP decreases from 100 mmHg, CBF pulse amplitude increases constantly and reaches a maximum (180%) just after the lower autoregulation limit (ABP = 60 mmHg). With further decreases, it saturates at 180% of its nominal value. On the other hand, when mean ABP becomes >100 mmHg, the CBF pulse amplitude increases only slightly (10% increase). The ICP pulse amplitude has a much larger response than CBF when mean ABP decreases <100 mmHg. Figure 6A shows that ICP pulse amplitude peaks at a mean ABP just <60% and then decreases as ABP decreases. In this region of decline, vasodilation cannot compensate the low ABP and cerebral blood volume begins to decrease. When mean ABP is increased beyond 100%, the ICP at first decreases due to vasocostriction. A minimum in pulse amplitude occurs at 125% of nominal mean ABP. As ABP is increased further, the autoregulation reserve is depleted (maximum vasocostriction), the cerebral vascular volume starts to increase, and the ICP pulse amplitude increases.

Figure 6B shows that when we change the pulse amplitude of ABP while maintaining the mean ABP at the nominal value, an approximately linear relationship exists between both the ICP and CBF pulse amplitudes and the pulse amplitude of the ABP.

Our open-loop simulation results closely mimic previous findings of various authors (see Discussion); thus they help to validate our cerebral model. In the following sections, we incorporated the cerebral model into the human CP model (20) and used this more comprehensive closed-loop CP model to study the responses induced by carotid artery compression and the thigh-cuff test.

Carotid Artery Compression

Carotid artery compression is widely used as a bedside test for cerebral autoregulation (9). An intact autoregulation is manifested by a transient hyperemia (increased cerebral perfusion) after the release of the compression (6, 9).

Hemodynamic Responses

To study the hemodynamic responses to this test using our closed-loop human CP model, we simulated 10 s of bilateral carotid artery compression by increasing the resistance of neck arteries threefold for the duration of the compression. Figure 7A shows that with the onset of compression, CBF drops abruptly because of the sudden reduction in cerebral perfusion. CBF starts to recover immediately when autoregulation is present (Fig. 7A) and at the end of the compression exhibits the attendant hyperemia. When autoregulation is absent (Fig. 7B), there is no initial recovery phase and hyperemia is missing. To better understand these phenomena, it is helpful to examine the changes in $R_a$ and $C_a$, both of which show fast responses to the compression test. Immediately after application of compression, $R_a$ decreases and $C_a$ increases (Fig. 7A). This strong
Fig. 3. Cerebral autoregulation predicted by the model. A: CBF (%) vs. ABP compared with the experimental data [× (21, 22)]. B: CBF (%) vs. arterial CO₂ tension (P_{aCO₂}) compared with the experimental data [× (12)].

Fig. 4. Model-predicted cerebral hemodynamic response to arterial hypotension in the presence (A) and absence (B) of CBF autoregulation. From top to bottom, ABP, CBF, ICP, cerebral arterial resistance (R_a), and cerebral arterial compliance (C_a). Dashed line indicates the start of the hypotensive episode.
vasodilatory response acts to compensate for the elevated carotid artery resistance, and produces a fast recovery of CBF (initial recovery phase). When compression is released, \( R_a \) and \( C_a \) do not return immediately to rest levels due to the delay in the autoregulatory response. Correspondingly, there is a transient surge in cerebral perfusion (hyperemia). In the severely disordered autoregulatory system, the vasodilatory response does not occur (Fig. 7B), and hence no transient hyperemia is seen.

Fig. 5. Model-predicted brain tissue \( \text{O}_2 \) and \( \text{CO}_2 \) tensions (\( \text{PbtO}_2 \) and \( \text{PbtCO}_2 \)) during arterial hypotension with the presence (A) and absence (B) of autoregulation. Dashed line indicates start of hypotension episode.

Fig. 6. Model-predicted CBF and ICP amplitude when different mean (A) and pulse (B) ABP amplitudes are used as inputs to the cerebral model.
Tissue Gas Responses

In brain tissue, PbtO₂ is reduced and PbtCO₂ is elevated during simulated carotid artery compression due to the reduced perfusion (Fig. 7). However, in the intact autoregulating system, the magnitude of these changes is smaller because of the partial recovery of CBF. When compression is released, hyperemia ensues causing PbtO₂ to overshoot and PbtCO₂ to undershoot. In the absence of autoregulation, both PbtO₂ and PbtCO₂ return gradually to their normal values after compression, and there is no overshoot or undershoot.

Figure 7 indicates that the dynamics of PbtCO₂ are slower than that of PbtO₂, e.g., it takes 5 s for PbtCO₂ to undershoot after the compression test but <2 s for PbtCO₂ to overshoot. Similarly, when autoregulation is absent, PbtO₂ returns to normal within 10 s after the test, whereas PbtCO₂ does not fully return until 30 s. Slower CO₂ dynamics are caused by the following: 1) the higher solubility of CO₂ in tissue fluids (20 times that of O₂) and 2) the smaller pressure gradient between blood and brain tissue (2–5 mmHg for CO₂ vs. 40–60 mmHg for O₂). Thus, although CO₂ tends to diffuse more easily (i.e., it has larger diffusion coefficient than O₂, see Eqs. 13 and 14), its partial pressure variations are generally milder and slower than those of O₂. Slower CO₂ dynamics are a consistent observation in our CP model predictions.

THRR

It is also interesting to study the hemodynamic and gas transport responses to carotid artery compression in different states of autoregulation. Because it is well known that hypercapnia impairs autoregulation, whereas hypocapnia improves it (1, 25, 30), we performed two additional tests, one with elevated CO₂ content in air (5%), and the other with hyperventilation. Figure 8 shows that in normocapnia and hypocapnia, CBF recovers after the initial decrease at the onset of the compression, whereas in hypercapnia, there is no recovery. Hyperemia is present in both normocapnia and hypocapnia. Because of the impaired autoregulation, there is no hyperemia in hypercapnia.
Smielewski et al. (30) defined the THRR as an autoregulation index

\[ \text{THRR} = \frac{\text{FVS}_{\text{hyperemia}}}{\text{FVS}_{\text{baseline}}} \]

where FVS represents systolic flow velocity in middle cerebral artery. To calculate THRR using our simulation results, we assumed that changes in velocity accurately reflect changes in cerebral flow (24). Thus FVS is replaced by CBF. The baseline systolic CBF is the average of 10-s data (~2 respiration cycles) before compression. The hyperemic CBF is calculated by averaging systolic CBF in two heart cycles after the first cycle after the release of compression. The first cycle is excluded because the sudden release of the compression causes a transient blood surge into the cerebral arteries, and the magnitude of the surge does not reflect the true state of cerebral vasodilation (30). On the basis of Smielewski et al.’s formula, our model predicts a THRR of 1.23 in normocapnia, 1.41 in hypocapnia, and 1.03 in hypercapnia. These simulation results agree well with the measured data of Smielewski et al. (30), as shown in Table 2, and indicate that the THRR index is a good indicator of the autoregulation state.

Figure 8 also shows that mean CBF is increased in hypercapnia, and decreased in hypocapnia. The reason is that high CO\(_2\) dilates cerebral arteries and decreases \(R_a\). On the other hand, low CO\(_2\) causes vasoconstriction and hence elevates \(R_a\). Similarly, mean ICP is elevated by hypercapnia because of the vasodilation, and is lowered by hypocapnia due to vasoconstriction. Different from the other two tests, ICP is reduced during the compression in hypercapnia. This is because the dilatory mechanism induced by the impaired autoregulation cannot fully compensate for the reduced cerebral perfusion caused by compression. This can be clearly seen in the mild responses of \(R_a\). The inadequate cerebral perfusion reduces the total intracranial blood volume and thus decreases ICP. In hypercapnia, the ICP waveform becomes more oscillatory. The reason is that the vasodilatory response to elevated CO\(_2\) tends to increase the overall cerebral blood volume, which not only increases the intracranial pressure, but also reduces the compliance of the intracranial space (Eq. 11).

**Thigh-Cuff Experiment**

In the bilateral thigh-cuff technique introduced by Aaslid et al. (1), pneumatic cuffs are applied to both thighs, and the cuffs are simultaneously inflated and deflated suddenly to induce a transient and abrupt fall in ABP. This change in ABP poses a challenge to the autoregulated cerebral circulation, and an analysis of the cerebrovascular responses to this maneuver can help yield insights into the mechanisms of cerebral autoregulation.

We simulated the thigh-cuff technique by assuming that thigh-cuff inflation can be mimicked by increasing peripheral...
arterial and venous resistance in the appropriate component of the circulatory system. Thus we added two additional lumped resistances to the small systemic arterial and venous segments to represent cuff inflation and reduced these resistances to zero for cuff deflation. Attention is focused on the deflation transient for analysis.

Figure 9A shows that on cuff deflation (at 0 s), ABP drops rapidly. The total decrease of mean ABP is 19 mmHg (20% of control). ABP recovers after 5 s due to baroreflex action and overshoots the control value at 15 s. The mean CBF drops initially but quickly recovers fully within 5 s. Overshoot occurs at 8 s. ICP peaks at 8 s and the total increase is 36%. Figure 9, D and E, shows that on cuff deflation, the cerebral arteries immediately dilate. Maximal dilation occurs a little after 5 s, coincident with the recovery of CBF. Figure 9E also shows that end-tidal $P_{CO_2}$ does not change significantly during the thigh cuff experiment. All of these model predictions agree with the results of Aaslid et al. (1).

**ROR**

Aaslid et al. (1) introduced an index called ROR as a measure of cerebral autoregulation. It is defined as $ROR = \frac{\Delta CVR/\Delta T}{\Delta CPP}$, where $\Delta CVR/\Delta T$ is the slope of the decrease in total CVR on cuff deflation, and $\Delta CPP$ is the change in CPP. Both the numerator and the denominator are normalized by the corresponding control values for the quantities. Thus ROR has units of s$^{-1}$. If one assumes that CPP is equal to ABP, full recovery of CBF occurs if $\Delta CVR$ equals to $\Delta ABP$ (1). Aaslid et al. observed that in normal human subjects with intact autoregulation, CBF recovers fully within 5 s. According to the definition of ROR, a $ROR = \Delta CVR/\Delta ABP = 0.2$ is necessary to fully compensate for the $\Delta ABP$. For the 20% $\Delta ABP$ predicted by our simulation, this implies a total $\Delta CVR$ of 20% after cuff deflation. Figure 9D shows that CVR (the sum of the cerebral arterial, capillary, and venous resistances) decreases almost linearly following cuff deflation, and the total percent change in the first 5 s is 23% (the CBF reaches full recovery at 5 s; Fig. 9B), a little higher than the calculated value. This is because the actual percent decrease in CPP (23%) is larger than that of ABP (20%) due to the increased ICP (Fig. 9C). Thus larger percent decreases in CVR are needed to compensate for the drop in CPP. In their study, Aaslid et al. (1) approximated CPP by subtracting a constant pressure offset from ABP.

![Fig. 9. Model-predicted cerebral hemodynamic responses to cuff deflation.](image-url)
Gas Transport

The model-generated variations in gas tensions are shown in Fig. 10. After the cuffs are deflated, the blood that pools in the legs during the test (high CO₂ and low O₂ concentrations) redistributes to the proximal vessels. Thus there is an initial drop in \( P_aO_2 \) and an increase in \( P_aCO_2 \). This redistribution is complete in \(~20\) s. Afterward, both \( P_CO_2 \) and \( P_aCO_2 \) recover toward their predeflation levels. In peripheral tissues, there is a sudden increase in \( P_TO_2 \) and a sudden decrease in \( P_TCO_2 \) when the cuffs are deflated. This is because the sudden deflation of the cuffs releases the arterial vessels and eases the blood flow through the cuff-affected area. Thus more O₂-rich blood is delivered to the peripheral tissues and more CO₂ in the tissue is removed. The overall changes are small (<7% for \( P_TO_2 \), and <3% for \( P_TCO_2 \)). In contrast, because CBF initially decreases due to the sudden drop of ABP, \( P_{btO_2} \) initially decreases and \( P_{btCO_2} \) increases. However, as CBF quickly recovers, so do \( P_{btO_2} \) and \( P_{btCO_2} \).

\[ CO_2 \text{ Effects on Autoregulation}\]

In the previous cuff simulation, \( P_aCO_2 \) varies but stays close to the control level of 40 mmHg. To examine the effect of CO₂ on cerebral autoregulation, we performed two additional cuff simulations, one in the presence of hypercapnia and the other in hypocapnia. Hypercapnia is produced by breathing 5% CO₂, whereas hypocapnia is produced by hyperventilation. Figure 11 compares the simulation results obtained during normocapnia, hypocapnia and hypercapnia (from left to right). To facilitate the comparison, all quantities except time are normalized by their corresponding control (predeflation) values.

ABP variations are similar in all three cases. Pressure drops quickly after the cuff deflation and stays low for \(~5\) s and then quickly recovers and overshoots the predeflation level. ABP decreases slightly more (~25%) in hypocapnia compared with the other two tests (20%). CBF decreases initially and then recovers. An overshoot is seen in all three cases, but in hypocapnia CBF recovers fastest and overshoots to the greatest extent. This is because hypocapnia improves autoregulation, which in turn compensates more strongly for the initial decrease in CBF. Improved autoregulation also causes a faster decrease in CVR after the cuff deflation (Fig. 11C). In contrast, hypercapnia impairs autoregulation, indicated by the slow recovery and minimal overshoot in CBF, and relatively small decrease in CVR. We observe that hypocapnia almost doubles the ROR index. The ROR index is lowest in hypercapnia (0.10/s).

![Fig. 10](image-url) Model-predicted variations of gas tensions in arterial blood (\( P_aO_2 \) and \( P_aCO_2 \); A and B), peripheral tissue (\( P_{TO_2} \) and \( P_{TCO_2} \); C and D) and brain tissue (\( P_{btO_2} \) and \( P_{btCO_2} \); E and F) during the thigh-cuff experiment. Dashed line indicates the cuff deflation time.
Table 3 lists the model-predicted variables of the thigh-cuff simulations, which compare favorably with measured data from Aaslid et al. (1).

**DISCUSSION**

Investigating human cerebral autoregulation is problematic because the regulatory mechanism is complex and experiments are difficult to design (1). We have developed a lumped model of the cerebrovascular and cerebral spinal fluid systems that includes a pressure- and CO$_2$-sensitive cerebral blood flow autoregulatory mechanism and a CSF formation and secretion system to describe pressure, volume, and flow characteristics of the vascular and extravascular compartments of the brain. We tested the model for its autoregulatory properties and then added it to our human CP model (20) to study the responses to carotid artery compression and the thigh-cuff experiment (1). The enlarged CP model can offer biophysically based explanations of the complex multisystem responses to conventional test protocols (hemodynamic, tissue and blood gas, and CO$_2$ reactivity responses) and can be used to design new tests for exploring the cerebrovascular autoregulatory mechanism.

**Open-Loop Testing**

During open-loop testing, the cerebrovascular model closely mimicked normal autoregulation. During hypotension simulation, arterial vasodilation causes an increase in CBF pulse amplitude. A characteristic feature of this increased pulsatility is an increased systolic and decreased diastolic CBF in mild hypotension. When ABP is extremely low, systolic CBF also starts to decrease and CBF pulse amplitude decreases. This prediction agrees well with the previously modeling study of Ursino et al. (35), which indicates that three characteristic zones exits in the cerebral blood velocity response to reduced perfusion pressure with intact autoregulation. As shown in Fig. 4A, zone 1 is marked by mean ABP between 70 and 100 mmHg, in which mean CBF does not change but CBF pulse amplitude increases. In zone 2, (ABP between 40 and 70 mmHg), when the lower autoregulation limit is reached, mean CBF starts to decrease as well as the systolic blood flow. However, the CBF pulse amplitude remains high. With a further decrease in ABP exceeding the autoregulatory range (ABP < 40 mmHg), zone 3 is characterized by quickly diminishing CBF and CBF pulsatility. In severely impaired autoregulation case (Fig. 4B), there is no distinction among the three zones. CBF and CBF pulse amplitude decreases monotonically with decrease of ABP.

The break point, which marks the transition of systolic CBF from increasing to decreasing, has been observed consistently in experimental studies when CPP falls < 55 mmHg (6). Our model predicts this break point is the same as the lower limit of cerebral autoregulation, which corresponds to a CPP of 50 mmHg. This agrees favorably with the experimental data (6). When autoregulation is absent (Fig. 4B), no break point occurs.

Additional studies of the open-loop model reveal that mean ABP significantly affects the pulse amplitude of CBF and ICP. Our simulations indicate that at low ABP levels, the maximum CBF pulse amplitude increase is 80% and that of ICP is 500% above those at normotensive levels. Our results are in general agreement with the more detailed studies on ICP pulsatility in Refs. 3 and 26.

**Closed-loop Integrated Model Testing**

The integrated CP model consists of the close-loop cardiovascular system, respiratory system, whole body gas exchange
(in the lungs, peripheral tissue, and brain), and local (autoregulation) and reflex control mechanisms (baroreflex, chemoreflex). The model describes multiple physiological systems and their interactions, which, once validated, can be used to help evaluate the response of human subjects to clinical protocols, such as carotid artery compression and the thigh-cuff test, which are commonly used to evaluate cerebral autoregulation.

**Carotid Artery Compression Analysis**

Our simulations of carotid artery compression confirm the widely held principle that an intact autoregulation is manifested by a transient increase in CBF (hyperemia) after release of compression (Fig. 7A). When autoregulation is severely disordered or absent, no hyperemia occurs (Fig. 7B). The CP model provides mechanistic explanations of the responses of several additional variables (some measurable, others not) to carotid compression, including ICP, and the cerebral tissue gas tensions. It also predicts pronounced changes in these responses in the presence of different levels of \( P_{\text{CO}_2} \). For example, hypocapnia induces cerebral artery vasoconstriction, which reduces overall cerebral perfusion. This leads to a decrease in \( \text{CO}_2 \) removal, which counteracts hypocapnia. Similarly, hypercapnia increases mean CBF, which tends to increase \( \text{CO}_2 \) exchange and enhance \( \text{CO}_2 \) removal. Mechanistically, \( \text{CO}_2 \) in the brain serves as an effective control variable that modulates cerebral perfusion. Our simulations also indicate activation of the chemoreflex at different \( \text{CO}_2 \) levels. In hypocapnia, the chemoreflex inhibits respiration by lengthening the respiratory cycle, whereas in hypercapnia, this cycle is shortened. These effects may be seen in Fig. 8, where the lower frequency component of CBF (corresponding to respiration) is decreased in hypocapnia and increased in hypercapnia.

Our study indicates a close correlation between THRR and \( \text{PaCO}_2 \). High \( \text{PaCO}_2 \) enhances autoregulation and increases THRR, whereas low \( \text{PaCO}_2 \) impairs autoregulation and decreases THRR (Fig. 8). Thus this index can be used to evaluate cerebral autoregulation. THRR is also affected by the length of the compression. We simulated carotid compression of 2, 3, 5, 7, 9, 10, 12, and 15 s and calculated THRR in each case. Figure 12 shows that the relationship between the duration of compression and THRR can be approximated by a saturation curve. Below 10 s, THRR increases monotonically with duration, whereas >10 s, THRR reaches saturation. Smielewski et al. (30) observed the similar effects in their experimental study in human and concluded that 5- to 7-s compression should be used for clinical applications. Our study, however, suggests that a 10-s compression can yield more accurate results.

In our simulations, we found that the rate of initial decrease in \( R_a \) is also a very good indicator of the strength of autoregulation. Hypocapnia improves autoregulation, and in the case illustrated, the rate of initial decrease of \( R_a \) was 0.83 mmHg·s⁻¹·ml⁻¹, double the value calculated in normocapnia (0.41 mmHg·s⁻¹·ml⁻¹). In the hypercapnic case, autoregulation is impaired and the rate of decrease in \( R_a \) is lowest (0.06 mmHg·s⁻¹·ml⁻¹). Thus another practical index can be derived for the carotid compression test, as has been done previously for the thigh-cuff test (1). The cerebrovascular model parameter most sensitive to the state of autoregulation is \( R_a \), especially its initial rate of decrease at the onset of compression. The new index should be proportional to \( \Delta (R_a / R_a) / \Delta t \), where \( R_a \) is the steady-state value of \( R_a \) before the test (these values can vary considerably as seen in Fig. 8), and should be easily calculated using data routinely obtained during carotid compression tests (e.g., transcranial Doppler blood flow and arterial pressure). These efforts would yield an index that could grade autoregulation much like the ROR index used in the thigh-cuff test and yet be easier to implement.

**Thigh-Cuff Analysis**

Unlike carotid artery compression, the thigh-cuff technique produces an abrupt drop in cerebral perfusion by suddenly changing ABP, while other physiological variables remain constant. It has been shown that the thigh-cuff test consistently detects the state of cerebral autoregulation (1).

Although the thigh-cuff test was designed specifically as a test of cerebral autoregulation, our simulations indicate that several other mechanisms are involved. The deflation of the thigh cuffs reduces the peripheral resistance (afterload) to the heart, thus there is a sudden drop of the ABP. The reduction in ABP triggers baroreflexes, which cause vasoconstriction and increase heart rate and ventricular contractility. Thus ABP starts to recover. At the same time, the lowered ABP decreases

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Fig. 12. Model-predicted relationship between transient hyperemic response ratio (THRR) and the duration of carotid artery compression.
the perfusion to the brain and reduces CBF. To conserve CBF, the local autoregulation mechanism immediately dilates cerebral arteries. Therefore, the CBF recovery phase of the thigh-cuff test contains both baroreflex and cerebral autoregulation components. CBF recovers fully within 5 s of cuff deflation under normal autoregulation. As ABP gradually returns to the predeflation level, the cerebral arteries are still dilated by the autoregulation, thus there is an overshoot of CBF. Our simulations also show that local CO2 reactivity affects the recovery and overshoot of CBF by changing the strength of cerebral autoregulation. The contributions of different regulatory mechanisms to the CBF response during the thigh-cuff test are summarized by Fig. 13.

Because of the release of the arterial and venous vessels by the deflation of the cuffs, resistance to blood flow in the cuff-affected area are decreased. More blood is delivered to the peripheral tissue, and thus PtO2 increases and PtCO2 decreases. In the brain, however, the perfusion is transiently decreased. Thus, PbtO2 decreases and PbtCO2 increases, but they are quickly restored by the recovering CBF. Cuff deflation also returns the deoxygenated blood that pools in the legs during cuff inflation to the lungs for gas exchange. This causes a slight decrease in PaO2, and an increase in PaCO2. However, these changes are too small to cause a significant activation of other reflex pathways, such as the chemoreflex and pulmonary stretch receptor reflex (20). Our subsequent simulations of thigh cuff test under hypocapnia and hypercapnia reveal the complicated interactions of these reflex pathways. In hypocapnia, low PaCO2 deactivates peripheral chemoreceptors and tends to cause vasodilation and tachycardia. At the same time, hyperventilation, which is used to induce hypocapnia, activates pulmonary stretch receptors and causes tachycardia and vasodilation. The result predicted by our model is a decreased ABP. In hypercapnia, increased PaCO2, activates peripheral chemoreceptors and leads to vasoconstriction and bradycardia. High PaCO2 also activates central chemoreceptors in the brain. Together with the peripheral chemoreceptors, they cause an increase in ventilation. This increase in ventilation triggers pulmonary stretch receptors, and leads to vasodilation and tachycardia. Our model predicts a slightly elevated ABP (Table 3).

In addition, we have demonstrated the effect of CO2 on autoregulation. Hypocapnia greatly improves autoregulation and the ROR index doubles that of normocapnia (Fig. 10), whereas hypercapnia impairs autoregulation and the ROR index is greatly reduced. The results agree closely with measured data (1) and indicate that the ROR index serves as a good measure of the rate and strength of autoregulation.

Our simulations show that ICP transiently increases due to vasodilation after the cuff deflation and that percentage CPP decrease is bigger than that of ABP. The decrease of CPP induces further vasodilation, which elevates ICP even more and causes further decrease in CPP. This positive feedback loop will continue until adequate cerebral perfusion can be reestablished [e.g., Cushing response: spontaneous increase of ABP in response to very low CPP (28)]. This mechanism is well known to be responsible for the generation of “plateau waves,” which are characterized by sustained high ICPs (28). Modeling studies by Ursino et al. (34, 36) have demonstrated that decreasing intracranial compliance and increasing CSF absorption resistance can easily lead to such an unstable condition. In our simulations of the thigh-cuff test, however, the quick recovery of ABP due to baroreceptor activation terminates the positive feedback loop and consequently only a small increase in ICP is observed (Fig. 9C). Thus the assumption used by Aaslid et al. (1) that ABP closely approximate CPP during the thigh-cuff test is valid. The use of either ABP or the model predicted CPP to calculate ROR yields similar results. This assumption, however, will overestimate ROR when ICP is greatly elevated under abnormal conditions. Although our model can follow the ICP changes and continue to calculate the ROR index, the current study considers only normal subjects.

Model Limitations

Like all models, ours has limitations. Some of the more important are discussed below.

First, in its present form, the cerebrovascular model cannot characterize regional differences, e.g., regional cerebral ischemia. In addition, it does not describe the interaction between the anterior, middle and posterior cerebral circulations (e.g., the circle of Willis), making it inappropriate for a detailed study of cerebrovascular disease. As a broad assessment model, it would suffice.

Second, in modeling cerebral autoregulation, we adopted the approach of Ursino et al. (39) to make the cerebral arterial resistance and compliance dependent on CPP and CO2 tension. Our simulations suggest that this closely approximates normal physiology over a wide range of CPP values. However, with extremely low CPP, or cerebral ischemia, the cerebral arteries may collapse, causing a sharp increase of in cerebral vascular resistance (8, 14). Our present model does not simulate such events, which are well outside the autoregulatory range.

Fig. 13. Contributions of different regulatory mechanisms to CBF response during the thigh-cuff experiment.
Third, acute elevation of ICP can induce a sharp increase in ABP above the ICP level. This is known as the “Cushing response,” which tends to restore the minimal blood flow to the brain (23, 28). The present study concerns only mild changes in ICP and hence does not include the Cushing response.

Finally, because of a lack of experimental data, the description of central nervous system control of the CP system is based on simple assumptions. However, the modular structure of the CP model permits a ready incorporation of new data as it becomes available. In its present form, it can only serve as an approximation to the control mechanism.

Despite these limitations, we have demonstrated that our human CP model can reproduce the cerebral hemodynamic and gas transport responses that occur with large transient cardiovascular perturbations. It provides indexes reflecting the state of cerebral autoregulation. In addition, it predicts the cardio-pulmonary interactions mediated by the central nervous system, which helps to elucidate the underlying mechanisms of these interactions. With incorporation of new measured data, e.g., O₂ and CO₂ tensions in the brain and peripheral tissue during carotid compression or thigh-cuff tests and cardiopulmonary changes that reflect central nervous activities, the model can be further refined to fit these data and to provide a more accurate description of the interactions among the cardiopulmonary systems. Such a model can then be easily modified to mimic human disease so that it can be used to provide biophysically based predictions, that may help to unravel the complex responses observed in clinical tests on head-injured patients.

REFERENCES


