Mathematical considerations for modeling cerebral blood flow autoregulation to systemic arterial pressure

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Gao, Erzhen, William L. Young, John Pile-Spellman, Eugene Ornstein, and Qiyuan Ma. Mathematical considerations for modeling cerebral blood flow autoregulation to systemic arterial pressure. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H1023–H1031, 1998.—The shape of the autoregulation curve for cerebral blood flow (CBF) vs. pressure is depicted in a variety of ways to fit experimentally derived data. However, there is no general empirical description to reproduce CBF changes resulting from systemic arterial pressure variations that is consistent with the reported data. We analyzed previously reported experimental data used to construct autoregulation curves. To improve on existing portrayals of the fitting of the observed data, a compartmental model was developed for synthesis of the autoregulation curve. The resistive arterial and arteriolar network was simplified as an autoregulation device (ARD), which consists of four compartments in series controlling CBF. Each compartment consists of a group of identical vessels in parallel. The response of each vessel category to changes in perfusion pressure was simulated using reported experimental data. The CBF-pressure curve was calculated from the resistance of the ARD. The predicted autoregulation curve was consistent with reported experimental data. The lower and upper limits of autoregulation (LLA and ULA) were predicted as 69 and 153 mmHg, respectively. The average value of the slope of the CBF-pressure curve below LLA and beyond ULA was predicted as 1.3 and 3.3% change in CBF per mmHg, respectively. Our four-compartment ARD model, which simulated small arteries and arterioles, predicted an autoregulation function similar to experimental data with respect to the LLA, ULA, and average slopes of the autoregulation curve below LLA and above ULA.

cerebrovascular autoregulation; compartmental flow model; simulation

autoregulation is the intrinsic ability of an organ or a vascular bed to maintain constant perfusion in the face of blood pressure changes. The precise molecular mechanisms of a cerebrovascular autoregulation bed are incompletely understood (5). Previous studies have shown that, besides the most important factor, arterial blood pressure, many other factors such as intracranial pressure (ICP) and cerebral venous pressure affect cerebral blood flow (CBF) autoregulation (2, 32, 41). The effects of changing arterial blood pressure have been experimentally investigated for humans (18, 27, 33) and a variety of animals (6, 16, 19, 20, 24). However, the data have not been well summarized. The effects of changing ICP and cerebral venous pressure on CBF autoregulation have been investigated experimentally (2, 32, 41) and theoretically (8). Some groups (41) have reported that the cerebral vascular bed responds to changes in the perfusion pressure gradient in a similar fashion, whether they result from decreasing mean arterial pressure, increasing jugular venous pressure, or increasing ICP. However, others (2) have reported that the effect of changing ICP on the vessel inner radius may be quite different from the effect of changing arterial blood pressure. Previously published modeling efforts have focused primarily on understanding mechanisms of autoregulation (4, 8, 39). However, the autoregulation curve itself has not been precisely described in these models by a simple formula (4, 8, 39).

This study was undertaken to develop an empirical formula of autoregulation modeled on basic hemodynamic principles and experimental data. The modeling was done for a normal circulation. In our model, with the assumption that cerebral venous pressure and ICP were zero, variations in perfusion pressure were induced solely by changes in systemic arterial pressure. A microvascular network served as an autoregulation device (ARD) to control CBF. A new compartmental model simulating the autoregulatory function of an ARD was constructed to synthesize the autoregulation curve. Our model was used to analyze the contribution of different hierarchical levels of vessel sizes to autoregulation. In addition to providing a mathematical description of the autoregulation curve, this study attempts to place into an interpretable framework experimental studies that describe hierarchies of vasoactive behavior in resistive vessels between 50 and 300 µm.

METHODS

Overview

After reviewing a number of previous studies of cerebral autoregulation, we summarized the autoregulation curves used by other authors into three general types. The disagreement between these curves and experimental data is discussed. On the basis of the reviewed experimental data, we constructed a compartmental model to simulate autoregulatory function. An ideal microvascular network served as an...
ARD to control CBF (Fig. 1). This model consists of four compartments in series (A, B, C, and D). Each compartment contains a group of identical vessels in parallel. It was assumed that these vessels determine autoregulation.

**Literature Review**

A number of representative studies of autoregulation were reviewed with attention to the lower and upper limits of autoregulation (LLA and ULA, respectively; Table 1). The description of autoregulation given by the various authors differs to some extent. Many are limited in scope, with the range of the experimental data (especially in humans) usually not exceeding the ULA. In addition, the values of “normal” CBF, LLA, and ULA given by the various authors differ in animal experiments (6, 16, 19, 20, 24) and human observations (18, 27, 33) because of species difference, CBF methodology (direct or indirect), and the presence of anesthetics. Agent. Another disagreement among previous reports is that some authors (18, 27, 33) describe the CBF-pressure curve below the ULA as a combination of two straight lines, whereas other groups (6, 16, 19, 20, 24, 43) indicate that the autoregulation curve near the LLA is curved rather than straight.

Using a cranial window preparation, Kontos et al. (16) studied the responses of cerebral arteries and arterioles in cats to acute hypotension and hypertension (40–200 mmHg pressure). They demonstrated that the vascular responses of cerebral arteries and arterioles to arterial pressure were caliber dependent; e.g., as blood pressure decreased, larger vessels (150–173 µm diameter) began to dilate at a higher pressure, whereas their maximum response, which occurred at a lower pressure, was smaller than that of the smaller vessels (37–59 µm). We utilized the data reported by Kontos et al. to construct a compartmental model for the purpose of this report.

**Synthesis of Reviewed Autoregulation Curves**

We summarized the previously described autoregulation curves into three types (1–3).

Types 1 and 2 (fixed and variable maximal vasoreactivity). The simplest type of autoregulation curve (type 1) is based on the premise that once the LLA or ULA is reached, either maximal vasodilation or vasoconstriction of the resistive bed has occurred; hence, flow becomes pressure passive (3, 9) (Fig. 2). The CBF-pressure curve is made up of three straight lines: one horizontal line between the LLA and the ULA and two sloped lines below the LLA and above the ULA, respectively. Importantly, this description of autoregulation implies that the slope of the line above the ULA (slope upper) is smaller than the slope of the line below the LLA (slope lower).

The second type of autoregulation (type 2) is similar to type 1, except the flow-pressure relationship above the ULA has the same slope as, and is thus parallel to, the relationship below the LLA (Fig. 3). Type 2 is based on the fact that the CBF autoregulation curve most frequently described in the experimental literature shows such a parallel pattern (13, 29).

Type 3 (third-order polynomial fit). Direct fitting of the observed autoregulation curve is one way to obtain a mathematical function to describe autoregulation. Dirnagl and Pulsinelli (6) used a third-order polynomial to fit the autoregulation data of rats, although the coefficients of their fitted function were not reported. In the present study, third-order polynomials were used to fit previously reported autoregulation curves from the rat reported by Dirnagl and Pulsinelli and human data reported by Olsen et al. (27) (see Results and Fig. 4). Because Olsen et al. presented only the autoregulation curves below the ULA, these curves were extended to the range above their ULA (assumed to be 150 mmHg) by assuming that each curve was center symmetrical (before fitting), with the center at a mean blood pressure of 100 mmHg and CBF of 50 ml·100 g⁻¹·min⁻¹.

**Construction of Compartmental Model**

We constructed a new compartmental model of autoregulation by assuming that the CBF is regulated by the response of resistive arteries and arterioles to the change in perfusion pressure. We further assumed that ICP and cerebral venous pressure were constant and set them at zero, so that the net perfusion pressure was equal to arterial pressure. The observed vascular diameters were used to calculate cerebrovascular resistance and CBF as follows

\[
Q = \frac{\pi (d/2)^4 P}{8 \eta L} \text{ or } R = \frac{8 \eta L}{\pi (d/2)^{4/3}}
\]

where \(Q\) signifies CBF, \(d\) is vessel diameter, \(P\) is perfusion pressure, \(\eta\) is blood viscosity (3.5 cP), \(L\) is vessel length, and \(R\) is vascular resistance.

An ARD as a compartmental structure was developed to control the CBF. The model of an ARD was constructed with four series compartments (A, B, C, and D in Fig. 1). The detailed structural parameters, such as numbers, diameters, and lengths of the vessels within each compartment of the ARD, are listed in Table 2. In each compartment the vessel diameter was selected to be similar to the classification of Kontos et al. (16) for pial arterioles found in their experiment, as shown in Table 2. The lengths of the vessels were based on the experimental data in a 20-kg dog (21). The numbers of the vessels in each compartment were based on Murray’s law (17)

\[
N_{f A} = N_{f B} = N_{f C} = N_{f D}
\]

where \(r_X\) and \(N_X\) are the radius and number of the vessel in compartment \(X\), respectively (\(X = A, B, C, \text{or} D\)).

The diameter of each of the four classes of vessels was the same as the experimental results of Kontos et al. (16). As assumed here, it is the responses of cerebral arterial and arteriolar vessels in these four compartments to changes in arterial blood pressure that regulate the CBF (see below). These data of Kontos et al. were limited and did not cover pressure below 40 mmHg. To predict the vessel diameters at <40 mmHg pressure, certain assumptions were necessary. According to the observations of Kontos et al. and Mackenzie et al. (19), small cerebral arteries and arterioles reach their maximum diameter at ∼40 mmHg. We used an empirical formula to fit the diameter

\[
d = a_0(1 - e^{-a_1p})(1 - a_2 e^{-0.5(p - a_3/p)})^2 + a_4 e^{-0.5(p - a_5/p)^2}
\]

where \(a_0\), \(a_1\), \(a_2\), \(a_3\), \(a_4\), and \(a_5\) are parameters fitted by using the data of Kontos et al.
From Eq. 1, the series resistance of an ARD (treated as an electrical circuit) is

\[ R = \sum \frac{8\eta L_i}{\pi N_i (d_i/2)^4} \]  

(4)

where \( i \) varies between 1 and 4 to account for the four compartments of an ARD (Fig. 1). The CBF through one ARD is

\[ \text{CBF} = \frac{P}{R} \]  

(5)

The equivalent diameter, \( d_e \), of an ARD was calculated by its resistance

\[ d_e = 2\left(\frac{8\eta L}{\pi} \right)^{1/4} \]  

(6)

where \( L = L_1 + L_2 + L_3 + L_4 \).

LLA, ULA, and the Two Slopes of the Autoregulation Curve

For comparison of our model with the experimental autoregulation curves, data were taken from the original studies (if the data were given in numeric form) or reconstructed by us from the experimental curves (if the data were given in graphical form). These data included the LLA, the ULA, and two slopes of the CBF-pressure curve in the ranges below LLA (slope_{lower}) and beyond ULA (slope_{upper}). For reconstructed data, the following rules were applied: 1) the data were taken from graphically represented curves for normal individuals (normotensive, normocapnia, and without vasodilator or vasoconstrictor) with the sole exception being the human data reported by Strandgaard et al. (37) (see DISCUSSION); 2) the data were mean values if more than one curve was reported; 3) the LLA was estimated at the point where CBF decreased by 10% of baseline, and ULA was estimated where CBF increased by 10% of baseline; 4) slope_{lower} was estimated as the average value over the pressure range between the point where CBF decreased by 50% from baseline and where pressure was equal to LLA; 5) slope_{upper} was estimated at the pressure where the autoregulation curve turns to a straight line right to ULA.

RESULTS

Literature Review

The reviewed articles are summarized in Table 1. For each study, two limits of autoregulation and two slopes of CBF-pressure curves in the range of pressure below LLA (slope_{lower}) and beyond ULA (slope_{upper}) were measured and listed in Table 1. The average calculated data are given in Table 4 for animals, humans, and animals and humans combined. The average values of LLA, ULA, slope_{lower}, and slope_{upper} were calculated over all experimental data listed. If experimental data were given as a range, such as \( x_1 - x_2 \), a mean value \( \frac{x_1 + x_2}{2} \) was used. *Estimated by authors of present study; †combinations of normotensive and hypertensive data.

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**Table 1. Summary of reviewed literature**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Species</th>
<th>CBF Method</th>
<th>Pressure Range, mmHg</th>
<th>Estimated LLA, mmHg</th>
<th>Estimated ULA, mmHg</th>
<th>Slope_{lower}</th>
<th>Slope_{upper}</th>
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<tr>
<td>3</td>
<td>Rat</td>
<td>(^{133})Xe</td>
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<td>70–89</td>
<td>&gt;200</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>11</td>
<td>Rat</td>
<td>avDO₂</td>
<td>30–220(^*)</td>
<td>70(^*)</td>
<td>150(^*)</td>
<td>1.1</td>
<td>1.8</td>
</tr>
<tr>
<td>31</td>
<td>Rat</td>
<td>H₂</td>
<td>105–180(^*)</td>
<td>70(^*)</td>
<td>142(^*)</td>
<td>1.4</td>
<td>1.9</td>
</tr>
<tr>
<td>42</td>
<td>Rat</td>
<td>(^{133})Xe</td>
<td>40–140(^*)</td>
<td>75(^*)</td>
<td>120(^*)</td>
<td>1.4</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
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<td>LDF</td>
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<td>180(^*)</td>
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<td>2.0</td>
</tr>
<tr>
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<td>35–120(^*)</td>
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<td></td>
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<td>7</td>
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<tr>
<td>40</td>
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<td>2.7</td>
</tr>
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<td>180(^*)</td>
<td></td>
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<td>7</td>
</tr>
<tr>
<td>19</td>
<td>Cat</td>
<td>dₚₚₜ , H₂</td>
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<td></td>
<td>1.8</td>
<td>7</td>
</tr>
<tr>
<td>16</td>
<td>Cat</td>
<td>dₚₚₜ</td>
<td>40–200(^*)</td>
<td>70(^*)</td>
<td></td>
<td>1.8</td>
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<td>160</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>44</td>
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<td>40–130(^*)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>10</td>
<td>Dog</td>
<td>(^{85})Kr</td>
<td>12.5–180(^*)</td>
<td>90(^*)</td>
<td></td>
<td>0.9</td>
<td></td>
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<tr>
<td>22</td>
<td>Dog</td>
<td>Microspheres</td>
<td>30–80</td>
<td>36(^*)</td>
<td></td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Dog</td>
<td>Microspheres</td>
<td>20–90</td>
<td>60</td>
<td></td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Dog</td>
<td>(^{85})Kr</td>
<td>45–113(^*)</td>
<td>59</td>
<td></td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Dog</td>
<td>Microspheres</td>
<td>0–85</td>
<td>62(^*)</td>
<td></td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>Baboon</td>
<td>(^{133})Xe</td>
<td>80–170</td>
<td>120–150</td>
<td>2.2–7.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>Human</td>
<td>avDO₂</td>
<td>50–220(^*)</td>
<td>70(^*)</td>
<td>161(^*)</td>
<td>1.27</td>
<td>3.7(^*)</td>
</tr>
<tr>
<td>34</td>
<td>Human</td>
<td>avDO₂</td>
<td>40–150(^*)</td>
<td>73</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Human</td>
<td>avDO₂</td>
<td>50–130(^*)</td>
<td>81</td>
<td></td>
<td>2.3(^*)</td>
<td></td>
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<tr>
<td>43</td>
<td>Human</td>
<td>avDO₂</td>
<td>50–140</td>
<td>93</td>
<td></td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>Human</td>
<td>avDO₂</td>
<td>60–160(^*)</td>
<td>85</td>
<td></td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Human</td>
<td>avDO₂</td>
<td>48–122</td>
<td>79</td>
<td></td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Human</td>
<td>avDO₂</td>
<td>50–120</td>
<td>88</td>
<td></td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>26</td>
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<td>avDO₂</td>
<td>65–130</td>
<td>73</td>
<td></td>
<td>2.6</td>
<td></td>
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</table>

Slope_{lower} and slope_{upper}, slopes of cerebral blood flow (CBF)-pressure curve in ranges of pressure below lower limit of autoregulation (LLA) and above upper limit of autoregulation (ULA), respectively, expressed as percent change in CBF per mmHg. \(^{133}\)Xe, \(^{133}\)Xe inhalation; avDO₂, arteriovenous O₂ content difference; H₂, H₂ clearance; LDF, laser-Doppler flowmetry; dₚₚₜ, cranial windows for direct observation of pial diameters; \(^{85}\)Kr, \(^{85}\)Kr inhalation. Average values of LLA, ULA, slope_{lower}, and slope_{upper} were calculated over all experimental data listed. If experimental data were given as a range, such as \( x_1 - x_2 \), a mean value \( \frac{x_1 + x_2}{2} \) was used. *Estimated by authors of present study; †combinations of normotensive and hypertensive data.
reviewed autoregulation curves and our model in Table 4 (see below).

Synthesis of Reviewed Autoregulation Curves

Our calculations revealed some limitations and disadvantages of three previously used descriptions of autoregulation curves.

Type 1. As shown in Fig. 2, the slopes, slope\(_{\text{lower}}\) and slope\(_{\text{upper}}\), predicted by this type of autoregulation curve are 2 and 0.7% change in CBF per mmHg, respectively. Slope\(_{\text{lower}}\) is larger and slope\(_{\text{upper}}\) is smaller than the mean calculated from experimental data. Type 1 is inconsistent with most experimental data, which demonstrate that the slope of the flow-pressure relationship in the range of pressure below the LLA is not smaller than that above the ULA and that resistance does not remain constant when pressure increases above the ULA (6, 14, 37).

Type 2. Although vascular diameter and resistance remain constant below the LLA, the pressure increases above the ULA are associated with a decrease in vascular resistance resulting from vasodilation (Fig. 3). Compared with type 1, the curve description of type 2 provides an improved description of pressure-induced changes in upper-range CBF. However, there are still discrepancies between this curve and experimental observations. As observed in the cat (19), maximum levels of vascular dilation and constriction do not necessarily occur at the LLA and the ULA, respectively. Thus LLA (\(\sim 65\) mmHg) occurred at a pressure significantly higher than that at which the vessels were

Table 2. Structural parameters of an ARD representing an element structure of cerebral artery and arteriole network to control CBF compared with related experimental data

<table>
<thead>
<tr>
<th>Compartment</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of vessels</td>
<td>1</td>
<td>3</td>
<td>8</td>
<td>216</td>
</tr>
<tr>
<td>Diameter in this model, (\mu m)</td>
<td>300</td>
<td>200</td>
<td>150</td>
<td>50</td>
</tr>
<tr>
<td>Length in this model, mm</td>
<td>20</td>
<td>8</td>
<td>4</td>
<td>1.2</td>
</tr>
<tr>
<td>(N_e r_e^2/N_A r_A^2)</td>
<td>1</td>
<td>0.89</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Control vessel diameter, (\mu m)</td>
<td>322 ± 10.4</td>
<td>202 ± 4.3</td>
<td>162 ± 1.9</td>
<td>42 ± 1.0</td>
</tr>
<tr>
<td>Normo- to hypotensive range</td>
<td>338 ± 10.8</td>
<td>223 ± 7.0</td>
<td>149 ± 5.7</td>
<td>46 ± 1.2</td>
</tr>
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</table>
| Normo- to hypertensive range | \(\pm SD\) reported by Kontos et al. (16) were defined as internal vessel diameter at mean arterial pressure of 120 mmHg. An autoregulation device (ARD) consists of 4 compartments: A, B, C, and D. In each compartment, there are a number of identical vessels. According to Murray’s law (17), \(N_e r_e^2/N_A r_A^2\) is approximately equal to 1.

Fig. 2. CBF, cerebrovascular resistance, and arteriolar diameter for fixed maximal vasoreactivity type of autoregulation. Between lower and upper limit of autoregulation (LLA and ULA), CBF is autoregulated by changing vessel diameter. Vessel dilates as pressure decreases and reaches its maximal size when pressure falls below LLA. Similarly, vessel constricts as pressure increases and maintains its minimal size when pressure rises above ULA. Two sloped lines are not in parallel with each other (cf. variable maximal vasoreactivity type in Fig. 3).

Fig. 3. CBF, cerebrovascular resistance, and arteriolar diameter for variable maximal vasoreactivity type of autoregulation. At pressure below ULA, this type of autoregulation is the same as fixed maximal vasoreactivity type of autoregulation. However, when pressure rises above ULA, CBF increases at same rate as when pressure is below LLA. This implies that arteriole dilates when pressure rises above ULA. Two sloped lines are in parallel with each other (cf. fixed maximal vasoreactivity type in Fig. 2).

Fig. 4. CBF of type 3 autoregulation curves. CBF curve was obtained by curve fitting to 3rd-order polynomial of data reported by Dirnagl and Pulsinelli (6) (dashed line) and Olsen et al. (27) (solid line). Prediction that blood flow ceases if pressure is \(< 30\) (dashed line) or \(20\) (solid line) mmHg conflicts with experimental observations.

onstrate that the slope of the flow-pressure relationship in the range of pressure below the LLA is not smaller than that above the ULA and that resistance does not remain constant when pressure increases above the ULA (6, 14, 37).
maximally dilated (~35 mmHg). The direct observation of vasodilation in resistive arteries and arterioles at a pressure below the LLA has also been described (16). Similarly, vasoconstriction continues as the arterial pressure rises above the ULA. In general, because the vascular resistance changes with the vascular diameter, the sections of the autoregulation curve below the LLA and above the ULA cannot be represented as simple straight lines.

The slopes, $slope_{lower}$ and $slope_{upper}$, predicted by this type of autoregulation curve are 2% change in CBF per mmHg. $slope_{lower}$ is larger and $slope_{upper}$ is smaller than the mean experimental data. The prediction that $slope_{lower}$ equals $slope_{upper}$ is not consistent with experimental data.

Type 3. A CBF-pressure curve was generated using an empirical third-order polynomial, which is obtained by fitting to the data reported by Dirnagl and Pulsinelli (6).

$$CBF = 6.11 \times 10^{-5} P^3 - 2.37 \times 10^{-2} P^2 + 3.00P - 75.0$$

Another CBF-pressure curve was calculated with a third-order polynomial by fitting to the data reported by Olsen et al. (26).

$$CBF = 4.79 \times 10^{-5} P^3 - 1.74 \times 10^{-2} P^2 + 2.51P - 38.8$$

Figure 4 shows the CBF calculated by using Eqs. 7 (dashed line), and 8 (solid line). From Fig. 4, one can see that Eqs. 7 and 8 cannot be used to predict autoregulation at <30 mmHg pressure, inasmuch as they predict that blood flow ceases at <30 mmHg pressure.

The slopes, $slope_{lower}$ and $slope_{upper}$, predicted by this type of autoregulation curve are 1.7 and 2.0% change in CBF per mmHg, respectively. $slope_{lower}$ is similar to the mean experimental data; $slope_{upper}$ is smaller.

Compartmental model. The results of the coefficients for Eq. 3 are listed in Table 3. Figure 5 shows the diameter-pressure relationships of the vessels in the four compartments compared with the data of Kontos et al. (16). The fitted curves for vessel diameters agree with the experimental data and provide reasonable predictive values for pressures outside the range of the experimental data. The vessels of three smaller compartments (50, 150, and 200 μm) begin to constrict if the pressure decreases below 40 mmHg, whereas this threshold pressure is 70 mmHg for the largest vessels.

Table 3. Coefficients used to calculate diameters of vessels in the four compartments of our compartmental ARD model

<table>
<thead>
<tr>
<th>Diameter, μm</th>
<th>$a_0$</th>
<th>$a_1$</th>
<th>$a_2$</th>
<th>$a_3$</th>
<th>$a_4$</th>
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<tr>
<td>50</td>
<td>319.4</td>
<td>0.0543</td>
<td>0.845</td>
<td>137.8</td>
<td>314.3</td>
<td>33.07</td>
<td>35.62</td>
</tr>
<tr>
<td>150</td>
<td>523.9</td>
<td>0.0432</td>
<td>0.717</td>
<td>151.6</td>
<td>217.9</td>
<td>74.24</td>
<td>34.00</td>
</tr>
<tr>
<td>200</td>
<td>956.9</td>
<td>0.0357</td>
<td>0.804</td>
<td>164.0</td>
<td>224.3</td>
<td>65.40</td>
<td>30.73</td>
</tr>
<tr>
<td>300</td>
<td>745.6</td>
<td>0.0188</td>
<td>0.619</td>
<td>179.4</td>
<td>118.9</td>
<td>19.16</td>
<td>49.80</td>
</tr>
</tbody>
</table>

Coefficients $a_0$–$a_7$ used in Eq. 3 for diameter were calculated by curve fitting of Eq. 3 to experimental data of vessel diameter reported by Kontos et al. (16).

The composite or equivalent resistance of an ARD was calculated using Eq. 4, and a regression was carried out for the calculated resistance, resulting in

$$R = 47.4 - 6.54 \times 10^{-2} P + 2.2 \times 10^7 P^{-4} + 18 \sin \left(\frac{2\pi P}{252.6} + 3.68\right) \quad (0 < P < 200)$$

Figure 6 shows the predicted curves of the vascular resistance and the resultant equivalent diameter and CBF of an ARD based on Eq. 9. The two limits, LLA and ULA, were calculated from the CBF-pressure curve, inasmuch as the LLA and ULA are defined as the pressure where the CBF changes 10% from the baseline (the mean value of the plateau). When the pressure decreases below the LLA, the equivalent diameter of an ARD increases until it reaches the maximum at a lower pressure of ~60 mmHg. As the pressure approaches...
zero, the vascular resistance approaches infinity, because the diameters of all vessels in the model are approaching zero. Some experimental data are also plotted in Fig. 6. These individual data points were obtained from hand-fitted curves of reported data, because the numerical values were not reported in the original reports. Some deviations in resistance between the experimental data and the regression curve occur at ~70 and >150 mmHg pressure. An attempt was made to reduce the deviation by using the best-fitted curve. However, the best-fitted curve resulted in a CBF-pressure curve that slightly underestimates the plateau at 100–150 mmHg pressure.

Our compartmental ARD model predicted LLA and ULA that were similar to those averaged over all reviewed articles (Table 4). The predicted LLA is 69 mmHg, which is between a most frequently cited value of 50 mmHg and an estimated experimental value from the reviewed articles of 73 mmHg. The predicted ULA is 153 mmHg, similar to a frequently cited value of 150 mmHg. It is, however, slightly lower than 157 mmHg, a value estimated from the reviewed experimental articles (Table 4). The mean values of slope$_{lower}$ and slope$_{upper}$ predicted by our model are 1.3 and 3.3% change in CBF per mmHg, respectively; these values compare favorably with the experimental data obtained from the literature review: 1.5 and 3.4% change in CBF per mmHg. Our model produces a 13 and 3% difference in slope$_{lower}$ and slope$_{upper}$, respectively, from the experimental data, being much smaller than those for the three types of autoregulation curves reviewed here: 33 and 79% for type 1, 33 and 41% for type 2, and 13 and 41% for type 3 (Table 4).

**DISCUSSION**

In this study the network of small arteries and arterioles was simplified as an ARD that controls CBF. A compartmental ARD model was constructed to simulate the autoregulation function of an ARD. The structural parameters of the model and the response of the vessel diameters to the changes in arterial pressure were based on reported experimental data. The blood flow through the ARD was calculated by Eqs. 4 and 5 and was represented as a function of pressure (autoregulation curve). The estimated values of LLA, ULA, and two slopes of the autoregulation curve of this model were consistent with previously reported experimental data. A summary of the comparison of our model with the previous curves is shown in Table 5.

Regarding the previously used curves, two simple types of autoregulation curves, i.e., fixed maximal vasoreactivity (type 1) and variable maximal vasoreactivity (type 2), are frequently used or implied by previous studies. However, the simplified assumptions used to generate these curves and their limitations have not been previously addressed. The common characteristic of these two curves is that the CBF-pressure curve is generated with three straight lines. The experimental data, however, demonstrate that in ranges of pressure below the LLA and above the ULA the diameter of small arteries or arterioles changes with arterial blood pressure. Thus in these two ranges the autoregulation curve cannot be represented by straight lines, as types 1 and 2 would necessitate. Furthermore, although type 3 is based on experimental data, it does not account for the behavior of different vascular hierarchies.

In this study, absolute CBF values were not discussed, because CBF is proportional to the weight of the tissue perfused. This model suggests that, in constructing an autoregulatory curve with a morphology consistent with observed data, vessels of different hierarchical levels, including small arteries and arterioles, must be taken into consideration. The traditionally used “diameter” of autoregulatory vessels, as embedded in the terminology “maximal vasodilation” or “maximal vasconstriction” (29), is simply a weighted average for an effective “composite” ARD, which has no clear biophysical or anatomic basis and is not supported by experimental observations.

The discrepancies between the experimental data and our simulated curve occur at ~70 and >150 mmHg pressure. Our model minimally underestimates the plateau at 100–150 mmHg pressure. This may be due to the omission of some hierarchy of circulation, the effects of which on autoregulation are not negligible. It may well be that the circulatory level not accounted for includes intraparenchymal vessels (38). Although the pial circulation is the most readily accessible for study of vascular behavior, there may be underlying differences from the intraparenchymal resistive bed, as suggested by experimental observations (9, 38).

Our proposed ARD compartmental model might be termed an instrumentalist approach to describing autoregulatory behavior. Such an instrumental approach in the present application is merely a mathematical tool for deducing one set of variables from another (30). We cannot claim that the ARD compartmental model that we have described is based on the essential mechanistic properties of the cerebral vascular network. The ARD model is simply a means for predicting the behavior of an autoregulating vasculature by knowledge of arterial

**Table 4. Principal autoregulatory parameters predicted by our compartmental ARD model compared with experimental data of reviewed literature**

<table>
<thead>
<tr>
<th>Study</th>
<th>Estimated LLA, mmHg</th>
<th>Estimated ULA, mmHg</th>
<th>Slope$_{lower}$, %baseline/ mmHg</th>
<th>Slope$_{upper}$, %baseline/ mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal average</td>
<td>69</td>
<td>157</td>
<td>1.5 (0.9–1.8)</td>
<td>3.4 (1.2–7.1)</td>
</tr>
<tr>
<td>Human average</td>
<td>80</td>
<td>161</td>
<td>1.5 (0.9–2.6)</td>
<td>3.7</td>
</tr>
<tr>
<td>Total average</td>
<td>73</td>
<td>157</td>
<td>1.5 (0.9–2.6)</td>
<td>3.4</td>
</tr>
<tr>
<td>Type 1: fixed maximal</td>
<td>50</td>
<td>150</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Type 2: variable</td>
<td>50</td>
<td>150</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Type 3: 3rd-order</td>
<td>83</td>
<td>180</td>
<td>1.7</td>
<td>2.0</td>
</tr>
<tr>
<td>Type 4: compartmental</td>
<td>69</td>
<td>153</td>
<td>1.3</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Values in parentheses represent ranges. See Table 1 for data from reviewed literature.
perfusion pressure. Our model (instrument) predicts observational or experimental data better than previously proposed systems, i.e., curves for types 1–3. Besides the three types of autoregulation curves reviewed, several mathematical models have been proposed to simulate CBF autoregulation (8, 28, 39) or regulation in other vascular beds (4). In general, they have been primarily focused on the time-dependent responses of the cerebral vessels. Borgstrom et al. (4) used the forces exerted on the vessel wall to determine the vessel radius and then used radius to determine flow. The forces used by Borgstrom et al. included passive pressure force, passive elastic force, passive wall viscosity, dynamic myogenic force, and control contractile force. Ursino and Di Giammarco (39) and Giuliani and Ursino (8) used three feedback mechanisms (myogenic, sympathetic, and cholinergic) to control the muscle tension of the vessel wall and used vessel tension (and pressure) to determine the vessel diameter and then determine CBF. Panerai (28) used fast Fourier transform methods to analyze the experimental data relating pressure, CBF velocity, and resistance-area product to obtain a spectrum of gain functions, which as an indicator of CBF was then used to determine resistance-area product in terms of CBF velocity, and then determined CBF. Our model directly applied experimental data to a new compartmental ARD model to simulate the CBF-arterial pressure curve.

In comparison to these previously proposed models, our approach is novel and offers some improvements over existing models for several reasons. First, the experimental data used in this model are based on direct observations of diameter responses of vessels to changes in arterial pressure (16). These vessels were selected from a relatively wide range of arterial and arteriolar sizes that are considered to be important in CBF autoregulation. Pressure-induced changes in vessel diameter were the controlling factor for CBF. Previously described models (4, 8, 28, 39) used indirect factors such as myogenic force, sympathetic feedback, or muscle tension of the vessel wall to determine diameter, then used diameter to determine blood flow. In these models, therefore, the assumptions of the relationship between indirect factors and diameters will affect the predicted CBF. The use of previously reported experimental data allowed our model to avoid using indirect factors and thus reduced the error associated with the assumed relationship between indirect factors and vascular diameters. Second, our compartmental ARD model is structurally different from the compartmental models used in other autoregulation modeling studies. In our model there are four compartments, each of which contains a number of identical vessels. The number of vessels inside a compartment was determined by Murray's law. In the other models the number of vessels in each compartment was not discussed in detail. Therefore, a compartment in our ARD model contains more information about the structure of the vascular network. This information could be used to investigate the hemodynamic properties of intracranial arterial vessels in different levels of cerebral circulation. Our ARD approach may also be used to improve our previously developed compartmental model of a complete cerebral blood circulation (7).

Third, one result of our ARD model is a simple formula that can easily predict a CBF response that is in reasonable agreement with experimental mean values (Table 4).

There are several important limitations to our approach. First, our model did not include mechanisms describing how pressure influences diameter. Second, of the many factors that influence CBF, only the most important one, arterial pressure, has been taken into account. Other factors, such as ICP or the effect of arterial PCO₂, have not been included. Third, in our model, time-averaged values were used for all parameters; therefore, the dynamic aspects of autoregulation were not considered. Although it is a “black-box” approach, the fit of observed data from a wide range of human and animal preparations supports the underlying mechanistic proposition that vascular hierarchies are of critical importance in flow regulation. In our model, physiological, biomechanical, and anatomic concepts, such as Murray's law, Poiseuille's law, and the structural parameters of vessels (diameter and length), are used.

Because capillaries and veins were not included in the present model, ICP and cerebral venous pressure were set at zero. The effects of changing ICP and cerebral venous pressure on CBF autoregulation have been investigated experimentally (2, 32, 41) and theoretically (8). Some groups (41) have reported that the
cerebral vascular bed responds to changes in the perfusion pressure gradient in a similar fashion, whether these changes are obtained by decreasing mean arterial pressure, increasing jugular venous pressure, or increasing cerebrospinal fluid pressure. However, others (2) have reported that the effect of changing ICP on inner radius may be quite different from the effect of changing arterial blood pressure. Further work on the current model needs to be done to take into consideration pathophysiological changes in ICP and cerebral venous pressure.

The contribution of postarteriolar resistance in the capillary and venous vascular beds was not included in this study. If we assume that postarteriolar resistance is constant, our model will overestimate CBF when the precapillary resistance is lower and underestimate CBF when the precapillary resistance is higher. If we further assume that postarteriolar resistance is ~20% of total cerebrovascular resistance at 120 mmHg pressure, then CBF is overestimated by 10% at minimal resistance (60 mmHg pressure) and underestimated by 6% at maximal resistance (170 mmHg pressure).

Because the experimental data for vessel diameters at profound hypotension (<40 mmHg) or severe hypertension (>200 mmHg) are not available, the fitted parameters (Table 3) of Eq. 3 are not necessarily able to reproduce correct diameters at these extremes of pressure. By use of reported data above 40 mmHg and with the assumption that CBF is zero at zero pressure and that the resistive vessels reach their maximal dilation at 40 mmHg pressure, the inner diameter-pressure curve was fixed at 0 and 40 mmHg pressure. Therefore, the shape of this curve at <40 mmHg pressure will not be significantly affected by changing the fitted parameters (Table 3). However, at >200 mmHg pressure, inner diameter will be affected by changing the parameters. Consequently, the morphology of the autoregulation curve above 200 mmHg cannot be predicted by this model. Our model is constructed with experimental data that are limited in pressure range and species (cat). Because of insufficient data, examination of the variability of parameter estimates is not possible here. Because Eq. 3 is empirical and provides no information about the physiological nature of the vessels, there is no indication of how the parameters may change as a consequence of external stimuli. Parameter sensitivity was estimated for Eq. 3 by increasing each of the parameters listed in Table 3 by 10%, resulting in <5.4% change in diameter, except for \( a_2 \) of the largest two vessels (compartments C and D). A 10% change in \( a_2 \) induces changes in diameter of 15 and 20% for the vessels in compartments C and D, respectively. We do not wish to attach physiological significance to each parameter in Eq. 3; we merely state that it is an empirical approach to better simulate autoregulation.

The true vascular network is a nonlinear, time-dependent system. For simplicity in our model, we assumed that the vessels were linearly combined in a compartment and that the compartments were linearly combined in the ARD. In our model, time-averaged values were used for all parameters.

Our compartmental ARD model provides a mathematical function to describe a CBF-pressure autoregulation curve that is based on observed data. This study supports the hypothesis that there are multiple sites of autoregulation in animal and human cerebral circulation. In future studies the model can be used to explore or predict responses to experimental interventions that preferentially affect different hierarchical levels of the cerebral circulation.

The authors thank Joyce Ouchi and Steven Marshall for assistance in preparation of the manuscript. The authors gratefully acknowledge the support and contributions of the other members of the Columbia University Arteriovenous Malformation Study Project. This work was supported in part by National Institute of Neurological Disorders and Stroke Grants RO1-NS-27713 and RO1-NS-34949 and in part by a Clinical Scholar Grant from the International Anesthesia Research Society.

Received 8 April 1997; accepted in final form 26 November 1997.

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