A SIMPLE FEEDBACK CONTROL MODEL TO CHARACTERIZE CEREBRAL AUTOREGULATION

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Abstract: **The traditional description of cerebral autoregulation (CA) states that cerebral blood flow (CBF) is held constant over a certain range of mean arterial blood pressure (MABP). Addressing this notion we developed a feedback control model for CA and fitted it to experimental canine data from the literature. Model parameters include the pressure at the lower limit of autoregulation (LLA) and the slope of the linear relationship between CBF and MABP below the LLA. Optimization results were compared with those obtained by fitting classical CA behavior to the data. The feedback control model conforms more to the data than the classical model, and yields lower pressures for the LLA. Our results suggest that constancy of CBF in the autoregulatory range cannot be assumed. Moreover, they underline the importance of considering individual data sets rather than averaged or aggregate data from multiple individuals.**

Introduction

CA has been defined as the intrinsic capacity of cerebral vasculature to maintain constant CBF [1]. Within a certain range of MABP (autoregulatory range), a drop in pressure is compensated by arteriolar vasodilation and a rise in pressure by vasoconstriction. At much lower pressures, however, the cerebral vessels are under maximal vasodilation and the CBF drops with decreasing MABP. In contrast, when subject to higher pressures, the vasoconstrictive effect is overcome and CBF increases with increasing MABP. It has been observed that the LLA and the upper limit of autoregulation (ULA) occur at pressures of about 60 mmHg and 150 mmHg in humans [2]. Similar values have been noted in animal data [3].

A literature review of the various mathematical descriptions of the autoregulatory relationship between CBF and MABP has previously been conducted [3]. Most of these models comply with the traditional description of CA by fitting two [4] or three straight lines to experimental CBF-MABP data. The first and third lines have identical or different slopes, and simulate the behavior of the data below the LLA and above the ULA, respectively. The second line models the CBF plateau phase in the autoregulatory range as a horizontal line. Polynomial fits on aggregate data from many individuals [5] or on individual data sets [6] have also been used in an attempt to describe the CBF-MABP behavior. Several other types of mathematical descriptions, such as those that employ compartmental models simulating vascular networks, fast Fourier transform methods, or calculate myogenic forces to determine the response of cerebral vessel diameters have also been reported [3].

These models, however, do not provide a concise description that captures the salient behavior of the CA system as represented by CBF-MABP data. We have developed a simple mathematical model, which takes advantage of the concept that autoregulation is a feedback mechanism by employing a negative feedback control loop.

Materials and Methods

Classical CA behavior may be characterized by a simple feedback control model as shown in Figure 1 and described by Eqn. (1).

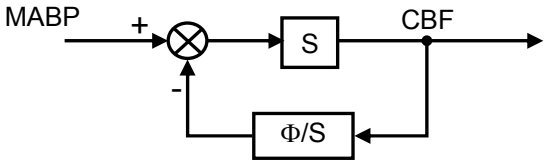

Figure 1: Feedback control loop characterizing CA. MABP: mean arterial blood pressure, CBF: cerebral blood flow, S: slope of the CBF vs MABP line below the lower limit of autoregulation, Φ: feedback function.

If no autoregulation was present, CBF would vary linearly with MABP with slope S. The classical notion of CA posits that within the autoregulatory range, CBF is held constant (Figure 2, dashed line). From the point of view of feedback theory, this implies that a negative feedback causes the CBF value in the autoregulatory

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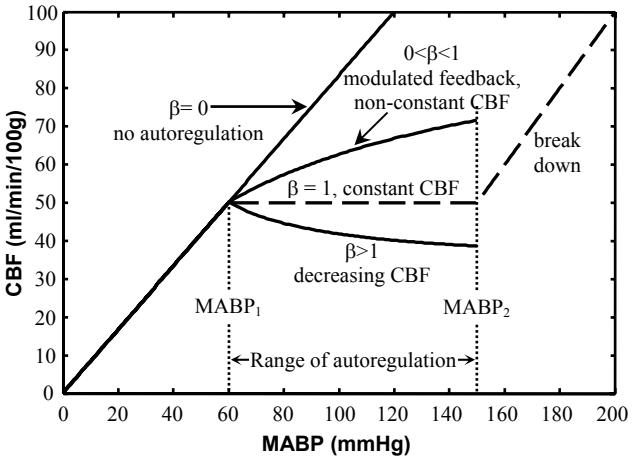

Figure 2. The effect of modulation factor β. Classical CA (dashed line), with constant CBF in the autoregulatory range is represented by $\beta = 1$. The feedback model is not applicable to pressures above the upper limit of autoregulation ($MABP_2$) where the autoregulatory effect breaks down.

range to be diminished by a function that is proportional to MABP. Denoting this feedback function by Φ, the quantity to be subtracted is Φ·CBF. The resulting equation is

$$CBF = S \cdot MABP - \Phi \cdot CBF \qquad (1)$$

where, Φ and CBF are both functions of MABP. If the LLA occurs at a pressure value of $MABP_1$, then the value of CBF at this point on the autoregulatory curve is $S \cdot MABP_1$. Using this boundary value and Eqn. (1), the feedback function may be defined as

$$\Phi = \begin{cases} 0 & 0 \le MABP \le MABP_1 \\ \left(\dfrac{MABP}{MABP_1} - 1 \right) & MABP_1 < MABP \le MABP_2 \end{cases} \qquad (2)$$

where, $MABP_2$ is the pressure value at the ULA. The variation of Φ with MABP is shown in Figure 3 (dotted line) for a single case.

To investigate deviations from this classical model, we introduced a constant β that serves to modulate the feedback. Eqn (1) may then be expressed in terms of CBF as

$$CBF = \frac{S \cdot MABP}{1 + \beta \cdot \Phi} \qquad (3)$$

Eqn. (3) represents the model that was used to fit the data by optimizing the variables S, $MABP_1$ and β. The effect of the factor β on the variation of CBF within the autoregulatory range is shown in Figure 2. When β is 0, CBF continues to increase linearly with MABP, representing the case where there is no autoregulation. For values of β between 0 and 1, the model allows for pressure-dependent changes in flow in contrast to the classical notion of CA, which requires CBF to be pressure-passive ($\beta = 1$). A more constant CBF value through the autoregulatory range is achieved as β approaches 1. For $\beta > 1$, the model suggests a decrease in CBF with increasing pressure. It is noted from the definition of the feedback function in Eqn. (2) that the model is applicable only for pressures that are below the ULA.

The data subjected to modeling were obtained from the literature [5]. CBF was measured in 12 dogs over a wide range of MABP by recording Krypton^{85} clearance curves. The minimum and maximum pressure measurements for the entire data were 12.5 and 180 mmHg, respectively. Data from eight cases were obtained under normocapnic conditions by maintaining the partial carbon dioxide pressure ($PaCO_2$) between 30 and 40 mmHg. Hypercapnia was induced in the remaining four animals by adding carbon dioxide to the anesthetia. Mean $PaCO_2$ under hypercapnia ranged from 68 to 86 mmHg [5]. Because there would be no flow if the perfusion pressure were zero, the origin (CBF = 0, MABP = 0) was added as a data point to the data sets before modeling. The intracranial pressure was assumed to be zero.

The model was fit to the data in the least-squares sense using optimization functions in Matlab® (The Mathworks, Natick, MA) that employ the Nelder-Mead simplex method. To facilitate comparison with the classical CA model, only the parameters S and $MABP_1$ were optimized initially while β was kept constant at 1. No constraints were imposed. The modulated feedback model with all three parameters S, $MABP_1$, and β was then fit to the data while constraining the $MABP_1$ value between 30 and 100 mmHg. Based on data from five studies, the LLA has previously been estimated to range from 40 to 90 mmHg in dogs [3]. The constraints were imposed in line with this observation. Comparison with classical CA was based on the sum of the difference squares between the optimized model and data (residual). A wide range of initial values were chosen for the parameters and the global residual minimum from all these optimizations was selected as the final result.

Results

Tables 1 and 2 show the optimized variables obtained by fitting the model to the normocapnic and hypercapnic dogs, respectively. In all hypercapnic cases, the model converged to a β value of 0, indicating a linear relationship. The $MABP_1$ values obtained in these cases were discarded. Figure 3 shows the model fit to the data recorded for one normocapnic case along with the resulting feedback function Φ as defined in Eqn. (2). Also depicted is the fit obtained from the classical CA model. Figure 4 shows the model-fit for one hypercapnic case.

In three normocapnic cases (Dogs B3, B5, and B7), the global minimum either settled on a $MABP_1$ value

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Table 1. Optimized parameters for normocapnic dogs. Slopes obtained for the classical CA model were very similar to the modulated feedback model and are not listed. The mean and standard deviation (SD) for these slope values were 1.12 and 0.3, respectively. P_1 (mmHg) is $MABP_1$, S (ml/min/100g/mmHg) is the initial slope, β is the feedback modulation factor, and Res. represents the residual obtained after optimization.

Dog	Classical CA (β=1)		Modulated Feedback			
	P_1	Res.	S	P_1	β	Res.
B1	66.2	354	1.35	51.12	0.62	216.8
B2	90.56	373.5	0.82	80.86	0.61	299.8
B3	98.62	464.4	0.8*	98.62*	1.09	448
B4	54.07	439.5	1.2	35.03	0.44	68.8
B5	64.74	871.5	0.95*	64.74*	0.87	783.2
B6	62.19	793.9	1.41	66.32	1.16	767.2
B7	100.2	230.9	0.86*	100.2*	1.03	226.4
B8	59.48	1211	1.81	40.81	0.67	1080
Mean	74.5	592.4	1.15	67.21	0.81	486.2
SD	18.74	333.1	0.36	24.67	0.26	352.5

* Values obtained from the classical CA model. Due to sparsity of data, only β was optimized in these cases.

Table 2. Optimized parameters for four hypercapnic dogs. Abbreviations as in Table 1.

Dog	B9	B10	B11	B12	Mean±SD
S	0.78	1.2	1.06	0.96	1±0.17
Res.	173.9	1189	128	643	533.5±495.1

that was lower than the least pressure recording or on a narrow range of $MABP_1$ values between two recorded data points. In these cases with sparse data, the global minimum result was rejected. The optimized slope S and $MABP_1$ value obtained from the classical CA model were then used to optimize only the modulation factor β.

Discussion

The average pressure at the LLA and average linear slope of the CBF–MABP relationship below the LLA in canines have previously been found to be about 61 mmHg and 1.6% change in CBF/mmHg, respectively [3]. We obtained an average $MABP_1$ value of 67 mmHg. If the CBF value at the intial MABP recording were considered the resting value in the data modeled here, the average slope is about 1.5% change in CBF/mmHg. Our results are thus consistent with this previous observation.

A comparison of the residuals showed that the modulated feedback model provided a significantly better fit to the data than the classical CA model (two-tailed paired Student's t test p value = 0.039). The LLA was consistently lower in the feedback model as

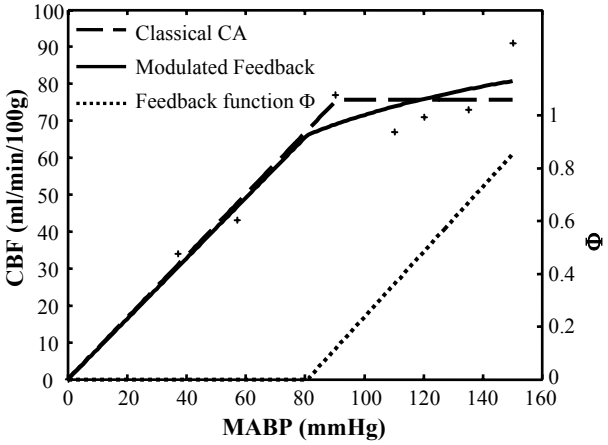

Figure 3. Model-fit for the data from a single normocapnic case (Dog B2). Originial data (+); the pressure at the lower limit of autoregulation ($MABP_1$) was 80.9 mmHg for the modulated feedback model and 90.6 mmHg for the classical CA model (see Table 1).

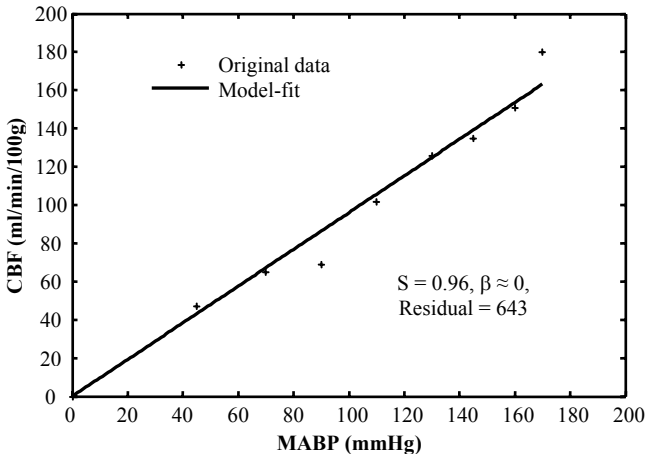

Figure 4. Model-fit for the data recorded from a single animal (Dog B12) under hypercapnia.

compared with classical CA. Although a two-tailed paired Student's t test suggested that the $MABP_1$ values of the two groups were not significantly different ($p = 0.065$), the sparsity of data forced us to opt identical $MABP_1$ values in three of the eight cases as described above.

The publication from which these data were obtained [5] is invaluable because it presents individual data sets, while most publications present only aggregate or average data collected from many individuals. The data from this study [5] are, however, sparse and the number of data points collected per dog ranges from 5 to 17 points only. Needless to say, a greater sampling rate would facilitate more concrete results from the modeling. It may be expected, for example, that better data in the three cases mentioned above would have resulted in significantly lower $MABP_1$ values for the modulated feedback model as compared with the classical CA model. Also, no

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measurements seem to have been made of the CBF-MABP curve above the ULA in these data sets. If such data points were available, our model could be extended by the addition of a linear equation with a second slope to describe the autoregulation curve over a wider range.

In three cases (Dogs B3, B6, and B7), Dog B6 in particular, the optimized β value is larger than 1 implying a decrease in flow with increasing pressure in the autoregulatory range. To our knowledge, this excess feedback effect has not been described previously. Whether it is an artifact of the data collection or modeling process, or a genuine physiological phenomenon, requires further investigation. The autoregulatory effect vanishes under hypercapnic conditions and CBF continues to increase linearly with MABP, suggesting that CA is dependent on arterial $PaCO_2$. The cerebral resistance vessels are dilated under hypercapnia leading to an increase in CBF, which results in narrowing of the CBF plateau phase or even abolishment of autoregulation [2] as is evidenced in these four cases. This phenomenon is captured by the modeling as it settles on β values approaching zero. A more robust model of CA, however, might include $PaCO_2$ as an additional parameter to be optimized.

The autoregulatory curve is known to be altered in definite ways under pathological or abnormal conditions [2]. Pharmacological vasodilators may achieve the same effect as hypercapnia by narrowing the plateau phase or even abolishing it. In contrast, the cerebral vessels are constricted under hypocapnia and the CBF plateau phase is elongated. The LLA and ULA are shifted towards higher pressures under both hypertension and activation of the sympathetic nervous system. Blocking of the renin-angiotensin system shifts the limits towards lower pressures. Our model provides a more refined characterization of CA under normal conditions and also captures CA behavior under hypercapnia. It would be interesting to evaluate its response to data obtained under these various abnormal conditions.

Our results suggest that there is considerable variability in the modulation factor when individual data sets are considered. Moreover, the mean β value is close to 1 and points to the traditional inference that CBF is held constant over the autoregulatory range. The analysis of individual data, as opposed to averaged or pooled data sets, may thus provide a more discriminating conceptualization of the process of CA.

Clinically, the quantification of individual variations in CA such as that allowed by our model is relevant to the interpretation of neuroimaging assays, as an example. Perfusion and blood flow are critical parameters in neuroimaging measurements such as functional magnetic resonance imaging (fMRI), in which minute variations in vessel diameter evoke large changes in perfusion values. Investigators who use fMRI rely on CA when they measure and index different aspects of CBF in subjects lying supine and motionless inside narrow enclosures. CA is implicitly thought to make up for the hemodynamic changes that are associated with the postural and psychological constraints of recumbent fMRI. This notion has been questioned of late and it has been suggested, for example, that hydrostatic factors and potential tube collapse in supine subjects may augment resistance to blood flow and significantly skew cerebral hemodynamics [7]. Our results indicate that neuroimagers may be overextending the concept of autoregulation of global perfusion by promoting a simplified notion of CA. Personalized, expressly-tailored models will likely contribute to better characterization of experimental groups in fMRI assays and permit a more discerning examination of the mechanisms involved in CA.

Conclusions

The goal of mathematical modeling is to yield an empirical relationship that is consistent with experimental recordings. Although such models have been constructed before to define the variation of CBF with MABP, a succinct description of CA that is physiologically appropriate has not yet been reported. A simple mathematical model that characterizes CA as a feedback mechanism has been developed here. The model competently captures varied experimental data.

The classical notion that global perfusion remains constant over a physiological range of MABP may hold true only for aggregate data. Variation in autoregulation may be a critical factor in individual measurements. Characterizing such variations could also be useful in making more accurate assessments from fMRI data. Better and larger individual data sets are required for a comprehensive analysis of the model. Given such data, it is plausible that the modulation factor β may, in the future, serve as an index to evaluate deviations from the normal physiological state. Evaluation of the model under abnormal conditions is the subject of further study.

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