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## ABSTRACT

### COMPUTER SIMULATION OF CEREBROVASCULAR CIRCULATION. ASSESSMENT OF INTRACRANIAL HEMODYNAMICS DURING INDUCTION OF ANESTHESIA.

by  
Steven D. Wolk

The purpose of this project was to develop a computer model of cerebrovascular hemodynamics interacting with a pharmacokinetic drug model to examine the effects of various stimuli during anesthesia on cerebral blood flow and intracranial pressure.

The mathematical model of intracranial hemodynamics is a seven compartment constant volume system. A series of resistances relate blood and cerebrospinal fluid fluxes to pressure gradients between compartments. Arterial, venous, and tissue compliance are also included. Autoregulation is modeled by transmural pressure dependent arterial-arteriolar resistance. The effect of a drug (thiopental) on cerebrovascular circulation was simulated by a variable arteriolar-capillary resistance. Thiopental concentration, in turn, was predicted by a three-compartment pharmacokinetic model. The effect site compartment was included to account for a disequilibrium between drug plasma and biophase concentrations. The model was validated by comparing simulation results with available experimental observations. The simulation program is written in VisSiM<sup>®</sup> dynamic simulation language for an IBM-compatible PC.

The model developed was used to calculate cerebral blood flow and intracranial pressure changes which occur during the induction phase of general anesthesia. Responses to laryngoscopy and intubation were predicted for simulated patients with elevated intracranial pressure and nonautoregulated cerebral circulation. Simulation shows that the induction dose of thiopental reduces intracranial pressure up to 15%. The duration of this effect is limited to less than three minutes by rapid redistribution of thiopental and cerebral autoregulation. Subsequent laryngoscopy causes acute intracranial hypertension exceeding the initial intracranial pressure. Further simulation predicts that this untoward effect can be minimized by an additional dose of thiopental administered immediately prior to intubation.

The presented simulation allows comparison of various drug administration schedules to control intracranial pressure and preserve cerebral blood flow during induction of anesthesia. The model developed can be extended to analyze more complex intraoperative events by adding new submodels.

**COMPUTER SIMULATION OF CEREBROVASCULAR CIRCULATION.  
ASSESSMENT OF INTRACRANIAL HEMODYNAMICS DURING  
INDUCTION OF ANESTHESIA.**

by  
Steven D. Wolk

**A Thesis  
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**COMPUTER SIMULATION OF CEREBROVASCULAR CIRCULATION.  
ASSESSMENT OF INTRACRANIAL HEMODYNAMICS DURING  
INDUCTION OF ANESTHESIA.**

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To my family

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# CHAPTER 1

## INTRODUCTION

Quantitative understanding of how hemodynamic changes influence cerebrovascular responses in neurosurgical patients is essential to prevent untoward changes in intracranial pressure (ICP) and cerebral perfusion pressure (CPP). This information is usually obtained from studies in which all variables except the one under investigation are controlled. During administration of anesthesia, however, multiple pharmacological and mechanical interventions may take place simultaneously. The resultant effect of these manipulations on cerebrovascular hemodynamics is difficult to predict despite an abundance of detailed information about mechanisms of drug actions. In other words, there are large number of analytical investigations but a scarcity of significant synthetic studies at present. A computer model of the cerebrovascular circulation combined with a pharmacokinetic and pharmacodynamic model of a particular drug is a method which potentially allows systematic examination of the whole system.

The aim of this study is to develop a model of cerebrovascular circulation which interfaces with a pharmacokinetic drug model. This objective requires linking of blood flow and drug distribution kinetics, and is used in anesthesia simulators and studies of the cardiovascular system [1-5]. The model developed can simulate the effects of drug(s) on intracranial hemodynamics. The changes in cerebral blood flow (CBF) and ICP were calculated during induction of general anesthesia. Hemodynamic responses to laryngoscopy and endotracheal intubation were predicted for simulated patients with

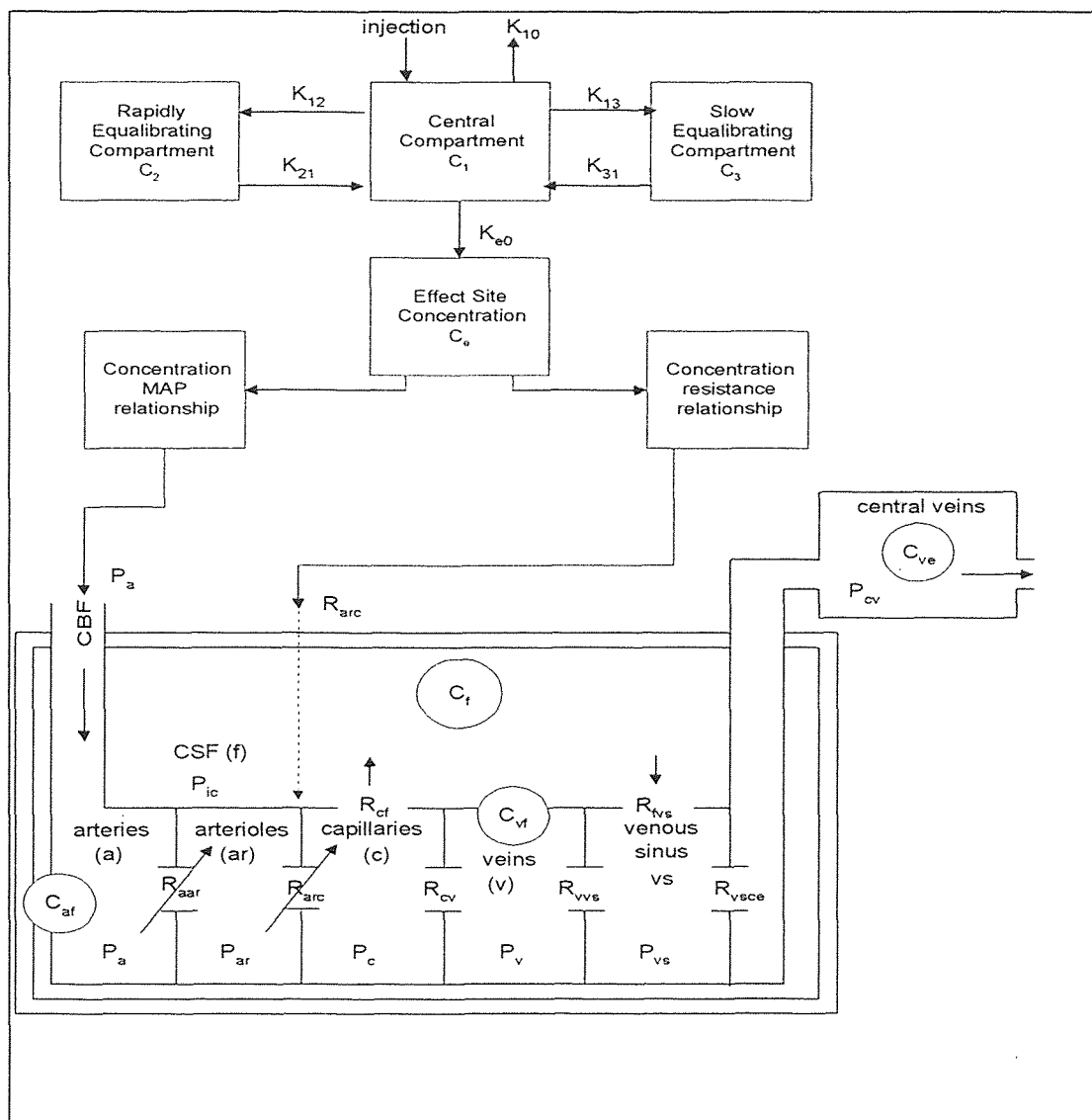
autoregulated and non-autoregulated cerebral circulations. Because thiopental is a widely used and extensively studied induction agent in neuroanesthesia, it was chosen as the sole induction agent in our analysis in order to validate the simulation. Computed results were then compared to available experimental data. The model was also used to suggest a drug administration regimen which minimized intracranial pressure increases associated with endotracheal stimulation.



## CHAPTER 2

### MODEL DEVELOPMENT

The overall simulation program structure is shown in Figure 1. The sub-model of the cerebrovascular system was constructed using a lumped-parameter method, in which the variables (e.g. pressure, flow, etc.) are assumed to be uniform within defined zones or control volumes. This approach is widely used in modeling physiological systems [6-9]. It enables prediction of average trends and responses of the system when subjected to pressure and flow perturbations. The other submodel is a three-compartment pharmacokinetic model of thiopental transport and metabolism linked to the biophase compartment by the first order rate process. Thiopental primarily affects mean systemic arterial pressure which secondarily influences CBF and ICP. This is used as an input parameter to the cerebrovascular circulation sub-model. Action of the pharmacokinetic model on hemodynamic model also occurs through regulation of the drug concentration dependent arteriolar-capillary resistance. The model developed does not include the effect of hemodynamic perturbations on pharmacokinetic parameters.



**Figure 1** Overall structure of the model.  $K_{12}$ ,  $K_{21}$ ,  $K_{13}$ ,  $K_{31}$  = first-order, inter-compartment rate constants;  $K_{10}$  = first-order elimination constant;  $K_{e0}$  = first-order equilibrium constant between central and effect site compartments;  $C_e$  = apparent thiopental concentration at the effect site;  $P_a$ ,  $P_{ar}$  = arterial and arteriolar pressures;  $P_c$ ,  $P_v$  = capillary and cerebral venous pressures;  $P_{vs}$  = venous sinus pressure;  $P_{cv}$  = central venous pressure;  $C_{af}$ ,  $C_{vf}$  = cerebral arterial and venous compliances;  $C_f$  = brain tissue compliance;  $C_{ve}$  = extracranial venous compliance;  $R_{aar}$  = variable arterial-arteriolar resistance (transmural pressure-dependent);  $R_{arc}$  = arteriolar-capillary resistance (thiopental concentration dependent);  $R_{cv}$ ,  $R_{vvs}$  = capillary-venous system-venous sinuses resistance;  $R_{cf}$ ,  $R_{fvs}$  = resistance to cerebrospinal fluid formation and cerebrospinal fluid outflow;  $R_{vsce}$  = resistance to the extracranial venous outflow.

## 2.1 Intracranial Hemodynamics Model

During the last decade various biophysical and mathematical models of intracranial hemodynamics have been developed [9-15]. Depending on the aim of the study, authors focused their attention on a particular aspect of CBF or CSF dynamics. The most complete model of cerebral circulation was formulated by Ursino [15,16]. The unique aspect of this model is its ability to combine many specific attributes of cerebral hemodynamics. In particular it includes CBF autoregulation, simulates CSF formation rate as a function of transmural pressure, and calculates model parameters using physiological and recent anatomical data. A modified version of this model was used in our simulation. Modification of the original model was required to introduce drug concentration dependent parameters to predict system behavior in clinical situation.

The equations and parameters for the intracranial hemodynamics model are presented in detail and are justified in the original articles [15,17]. Only general principles and our modifications will be discussed in this paper. In its present form the model is a constant volume system consisting of seven compartments: cerebrovascular arterial and arteriolar beds, intracranial capillary compartment, venous vascular bed, venous sinuses, cerebrospinal fluid compartment (brain tissue), and a central venous compartment. The behavior of each compartment is represented by a single pressure value and by values of mass flux exchanged with adjacent compartments. A series of resistances relate blood and CSF fluxes to the pressure gradient between compartments:

$$\frac{dV_n}{dt} = \sum_m q_{mn} = \sum_m \frac{P_m - P_n}{R_{mn}} \quad (1)$$

where  $V_n$  is the volume of compartment  $n$  surrounded by  $m$  compartments,  $q_{mn}$  denotes the flux between compartments  $m$  and  $n$ ,  $(P_m - P_n)$  is the pressure difference between the  $n$ -th and  $m$ -th compartment, and  $R_{mn}$  is the resistance of the compartmental boundary.

CSF production is directly proportional to capillary transmural pressure and inversely proportional to choroid plexus resistance to CSF secretion. CSF re-absorption depends on the difference between CSF and dural sinus pressure and is inversely related to arachnoid villi resistance to fluid flow. Temporal changes of cerebral arterial and venous blood volumes are taken into account with the two lumped parameters, arterial and venous compliance. An exponential pressure-volume relationship has been assumed. This implies that compliances of these compartments are inversely proportional to the corresponding value of distending pressure where  $C_{ai}$  and  $C_{vi}$  are arterial and venous compliances respectively,  $K_a$  and  $K_v$  arterial and venous elastance coefficients; values for these parameters were computed based on anatomical data on major human intracranial vessels.  $P_a$ ,  $P_{ic}$ ,  $P_v$  are pressures in arterial, intracranial, and venous compartments respectively.  $P_{vl}$  denotes the transmural pressure value at which the large cerebral veins would collapse.

$$C_{ai} = \frac{1}{K_a(P_a - P_{ic})} \quad (2)$$

$$C_{vi} = \frac{1}{K_v(P_v - P_{ic} - P_{vl})}$$

Compliance of cerebral tissue is described by the following equation:

$$C_{ic} = \frac{1}{K_e \left[ P_{ic} + \left( \frac{P_{ic}}{P_{0l}} \right)^2 \right]} \quad (3)$$

where  $K_e$  is an elastance of cerebral tissue and  $P_l$  is a constant. According to this equation tissue compliance is fairly linear at low ICP, but decreases dramatically as intracranial pressure increases (quadratic term in the equation become relevant). Detailed explanations and derivations describing the pressure dependency of arterial, venous, and cerebral tissue compartments are presented elsewhere [15].

Differential equations describing intracranial dynamics can be written by imposing a mass balance for each compartment. Compact form of these equations for all cells is:

$$\sum_m C_{mn}(P_m, P_n) \frac{dP_n}{dt} + \sum_m \frac{P_m - P_n}{R_{mn}} = 0 \quad (4)$$

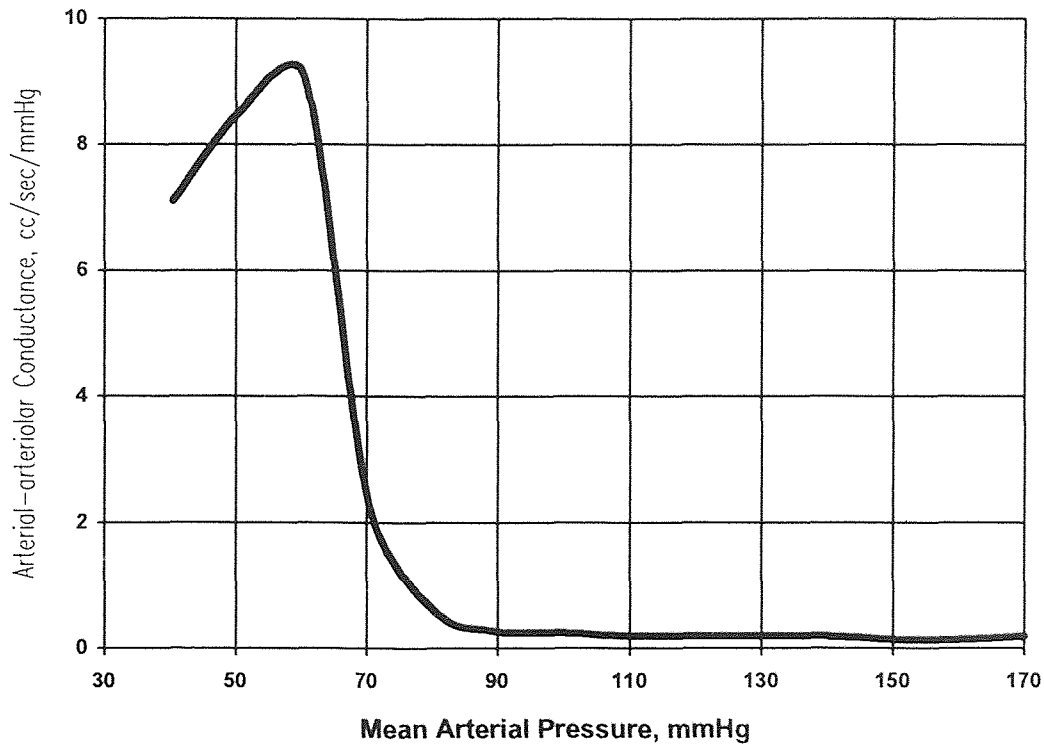
where  $C_{mn}(P_m, P_n)$  is the pressure dependent compliance of the nth compartment.

The constancy of intracranial volume (Monro-Kelly principle) is expressed by the following equation:

$$\sum_n \frac{dV_n}{dt} + Q_n = 0 \quad (5)$$

where  $Q$  denotes rate at which the CSF compartment can expand. This can be used to simulate the injection of liquid into the CSF space ( used clinically to test intracranial compliance in neurosurgical practice) as well as certain pathologic conditions (e.g. subarachnoid hemorrhage).

Cerebral autoregulation is represented by a transmural pressure dependent arterial-arteriolar cerebrovascular conductance. In the original model, an S-shaped autoregulatory curve was assumed and simulated using characteristics of the arctangent function. The regulatory mechanism gain is an argument in the equation. The gain, in turn, was determined by solution of a first order differential equation which includes a time constant and a perfusion pressure percent change. This allows study of the partially autoregulated circulation by changing equation parameters. Although satisfactory for theoretical analysis of cerebrovascular physiology, the resulting autoregulatory curve correlates poorly with the well described cerebral blood flow vs arterial pressure relationship based on experimental measurements in humans reported in numerous publications [18-20]. The data from [20] were used in our model to develop a table function of arterial-arteriolar conductances (inverse of resistance) vs transmural pressures across arterial wall. Figure 2 shows calculated conductances that were used in the present model. The shape of the curve is consistent with experimentally observed changes in autoregulatory resistance [19]. During the computational cycle the program chooses a conductance corresponding to the transmural pressure value at any given time. A six second time delay following a step change in arterial blood pressure was introduced to reflect the dynamic nature of the autoregulatory response, as was experimentally determined by Aaslid, et al.[21].

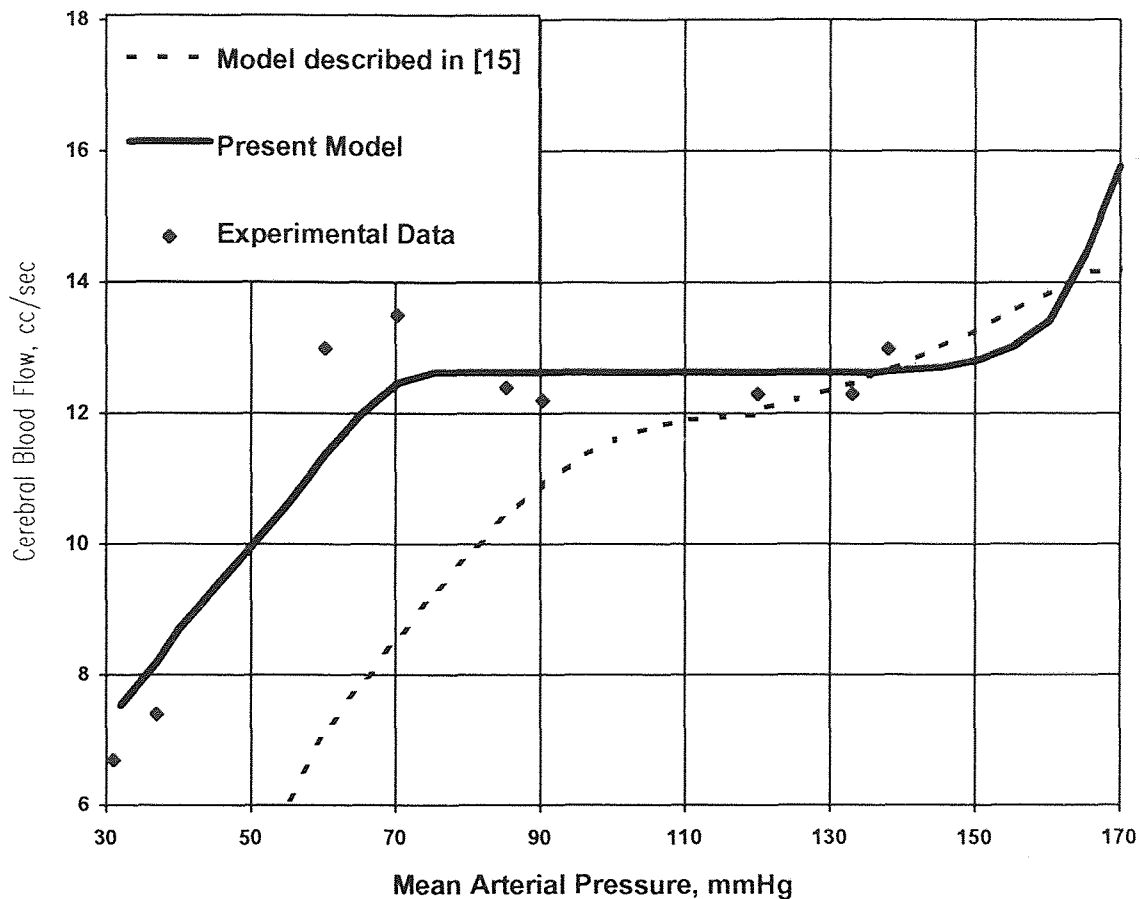


**Figure 2** Variations of arterial -arteriolar conductance ( $G_{a-ar}$ ) with blood pressure;  $G_{a-ar}$  is calculated from cerebral blood flow versus mean arterial pressure data reported by Harper and McCulloch [20]

Figure 3 compares autoregulatory curves generated by the original model, by our modification, and experimental points from several studies reported by Lassen [18].

A table function describes only one autoregulatory curve. It lacks the flexibility of differential equation in constructing a series of partially autoregulated curves offered by the original model. Our choice of a table function was dictated by poor correlation of the equation generated curve with experimental data and an inability to find an experimental verification of partial autoregulation. The absence of autoregulation in our model was

studied by assuming fixed arterial-arteriolar conductance (conductance at mean arterial pressure of 100 mmHg) at all pressures.



**Figure 3** Autoregulatory curves predicted by the present model and calculated using solution of differential equations as described by Ursino [15]. Experimental points are from Lassen [18]. Mean values of 9 groups of subjects have been plotted.

The effect of thiopental on cerebrovascular circulation was simulated by a concentration dependent arteriolar-capillary resistance. Postulating that this resistance is the only site of thiopental action in the brain, the model can be used to develop a conductance (reverse of resistance) versus concentration function from experimental data



relating thiopental concentration and CBF [22]. Calculated conductance values were regressed using exponential equation:

$$G_{ar-c}(cm^3sec^{-1}mmHg^{-1}) = 0.37 * \exp\left(\frac{-x}{57.1}\right) \quad (6)$$

where  $x$  is thiopental concentration in  $\mu g/mL$ . Product moment correlation coefficient for this equation,  $r$ , equals 0.95.

Following a bolus intravenous injection, thiopental decreases systemic arterial pressure by reducing cardiac output and by venodilation [23]. Experimental data from several investigations studying the cardiovascular effects of thiopental during induction of anesthesia, were regressed to develop a relationship between thiopental concentration and mean systemic arterial pressure:

$$MAP(\%change) = 100.0 * \exp\left(\frac{-x}{370}\right) \quad (7)$$

where  $x$  is thiopental concentration in  $\mu g/mL$  and MAP is mean arterial pressure in mmHg. There is good correlation between experimental data and the above equation ( $r = 0.96$ ).

## 2.2 Pharmacokinetic Model

The three compartment model was used to calculate plasma concentration of thiopental at various times. Pharmacokinetic parameters reported by Stanski et al. [25] were used in our simulation. Plasma concentration was linked to the apparent effect-site concentration

with a first-order rate constant,  $K_{e0}$ . Effect-compartment was introduced to account for temporal dissociation between serum (central compartment), thiopental concentration and EEG effect. Numeric integration of the system of three linear differential equations can predict plasma concentration of thiopental following bolus injection. However, the simulation language structure used to solve the model equations (VisSim<sup>®</sup>) does not permit interruption of the numerical integration when the additional drug boluses are studied. To simulate a clinical setting when two or more injections are required, an analytical solution of the system of three linear differential equations proposed by Hull et al. [26] was used in our model. The solution allows simulation of multiple injections as well as the continuous infusion of drug [27].

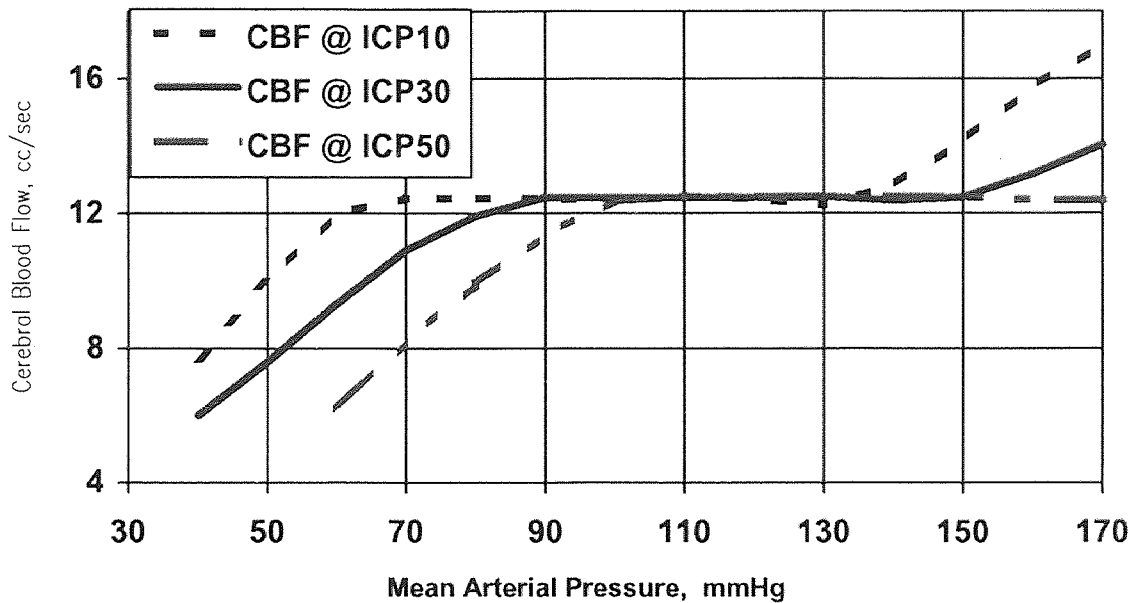
### **2.3 Operation of the Computer Model**

The simulation program was written in VisSim<sup>®</sup>, a simulation programming language for an IBM compatible PC. In VisSim<sup>®</sup>, models are constructed in the form of block diagrams. Each interconnected block represents and describes a portion of the system. The specifics of programming using block diagram languages are discussed by Karayanakis [28]. Fourth-order Runge-Kutta integration blocks with a time interval of 50 msec were chosen for a solution of the model equations. A 32-bit PC microcomputer was used to realize real-time simulation.

## CHAPTER 3

### RESULTS

Simulation results include computation of cerebral blood flow as a function of mean arterial pressure at different intracranial pressures and prediction of cerebrovascular responses during the induction phase of general anesthesia. Changes in cerebral blood flow and intracranial pressure are calculated for simulated patients with and without autoregulation. The predictions of the model are compared with available experimental data.



**Figure 4** Cerebral blood flow as a function of cerebral perfusion pressure and intracranial pressure (10, 30 and 50 mmHg); it is assumed that autoregulation is intact at all times.

### 3.1 Effect of ICP on CBF

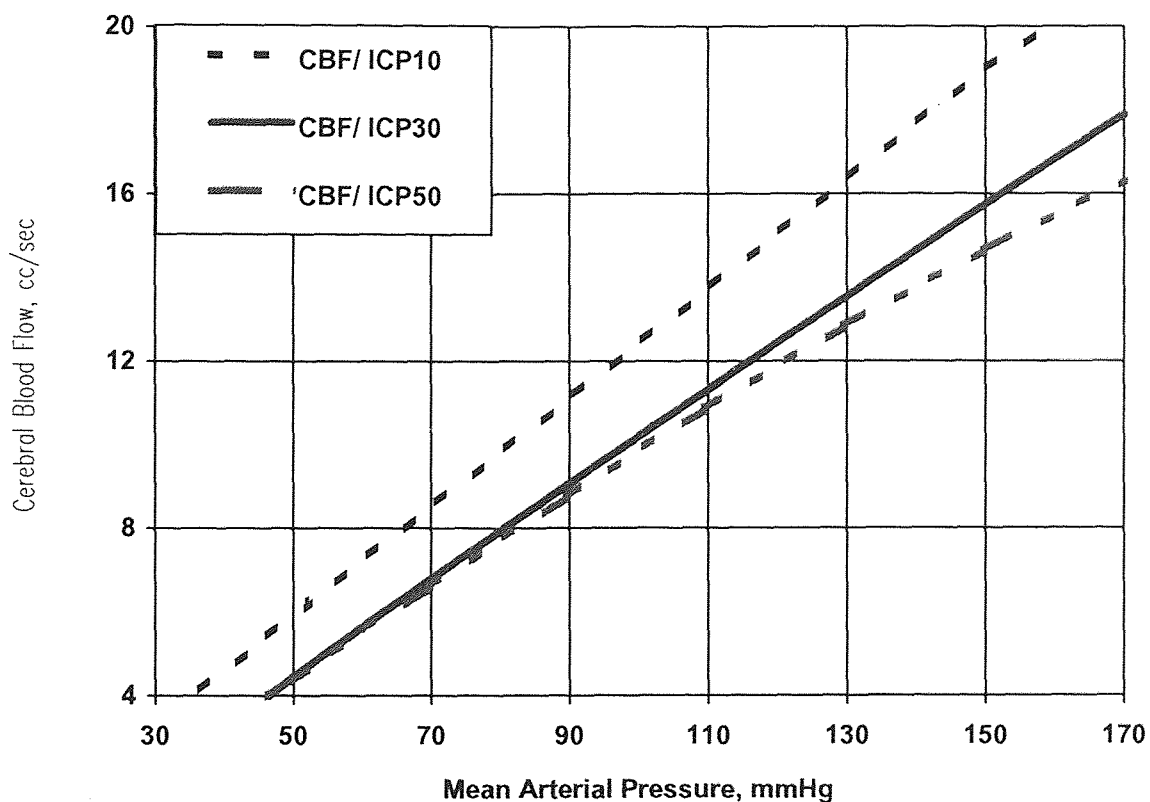
Figure 4 compares CBF calculated for MAP up to 170 mmHg for simulated patients with ICP of 10, 30, and 50 mmHg. The model predicts that an ICP increase shifts the autoregulatory curve to the right. A higher cerebral perfusion pressure is required to maintain cerebral blood flow in these patients. ICP elevation was accomplished by increasing resistance to CSF re-absorption. The original model used liquid bolus injected into the CSF space to simulate intracranial hypertension. This results in a transient response and could not be used for our simulation.

Autoregulation is modified or impaired in areas surrounding a space occupying, traumatic, or inflammatory lesion and may be completely lost in severe head injury [18,29]. Loss of autoregulation may leave surviving brain tissue unprotected against the potentially deleterious effects of significant blood pressure changes. Figure 5 shows that absence of autoregulation results in a passive CBF increase if systemic blood pressure is increased. Sengupta et al. [30] demonstrated a similar relationship between MAP and CBF in primates with compromised cerebral circulation. Intracranial hypertension reduces transmural pressure and increases vascular resistance. This is reflected in a decreased slope of CBF versus ICP with the elevation of ICP.

### 3.2 Clinical Applications

The induction of general anesthesia was modeled using a bolus thiopental injection followed by laryngoscopy and intubation. ICP and CBF changes were compared for cerebral circulation with intact and compromised autoregulation. Simulation is initiated by injecting a typical induction dose of thiopental (5 mg/kg). It is assumed that a

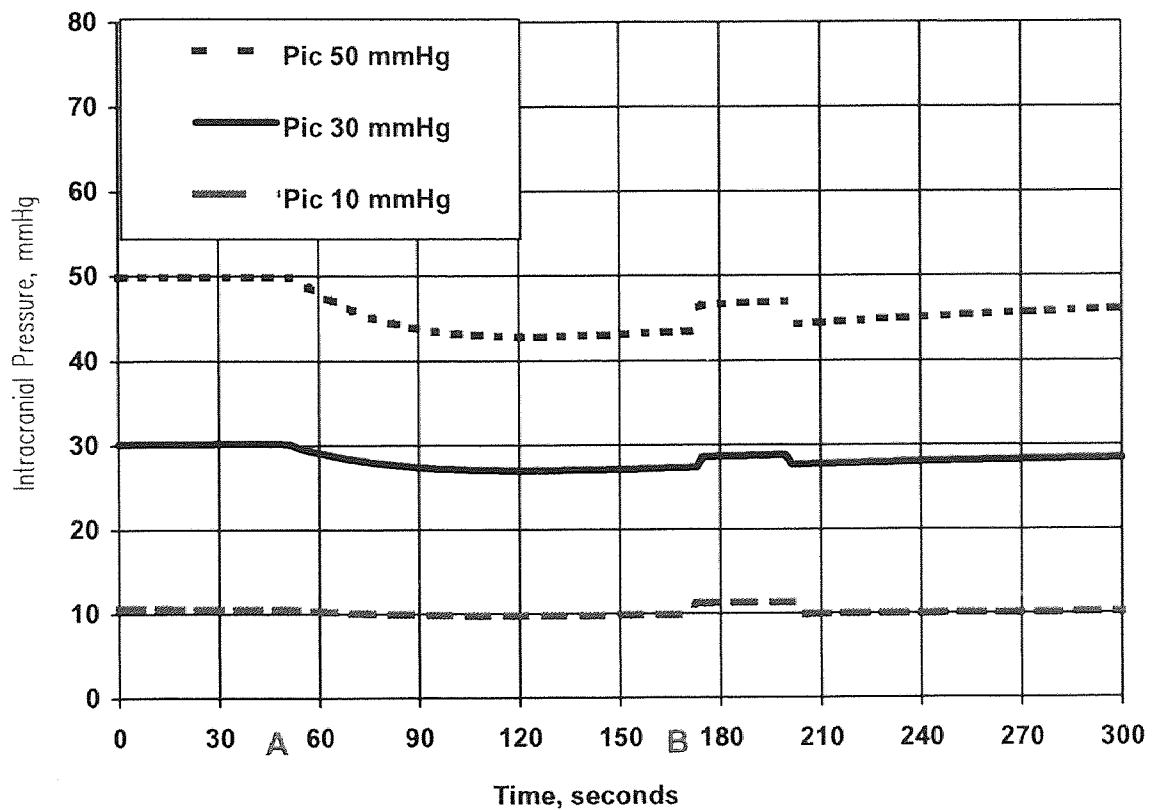
hemodynamically stable nondepolarizing neuromuscular agent is administered essentially at the same time (e.g. vecuronium). Under normal conditions hemodynamically stable relaxants do not alter CBF or ICP and their influence on intracranial hemodynamics is expressed primarily by determining a time for laryngoscopy and intubation (approximately two minutes).



**Figure 5** Cerebral blood flow as a function of cerebral perfusion pressure in non-autoregulated cerebral circulation.

Laryngoscopy and tracheal intubation are associated with sympathetic discharge which may lead to a hypertensive response [31,32]. If thiopental is used as the sole induction agent, endotracheal stimulation may increase MAP by  $35 \pm 10$  mmHg

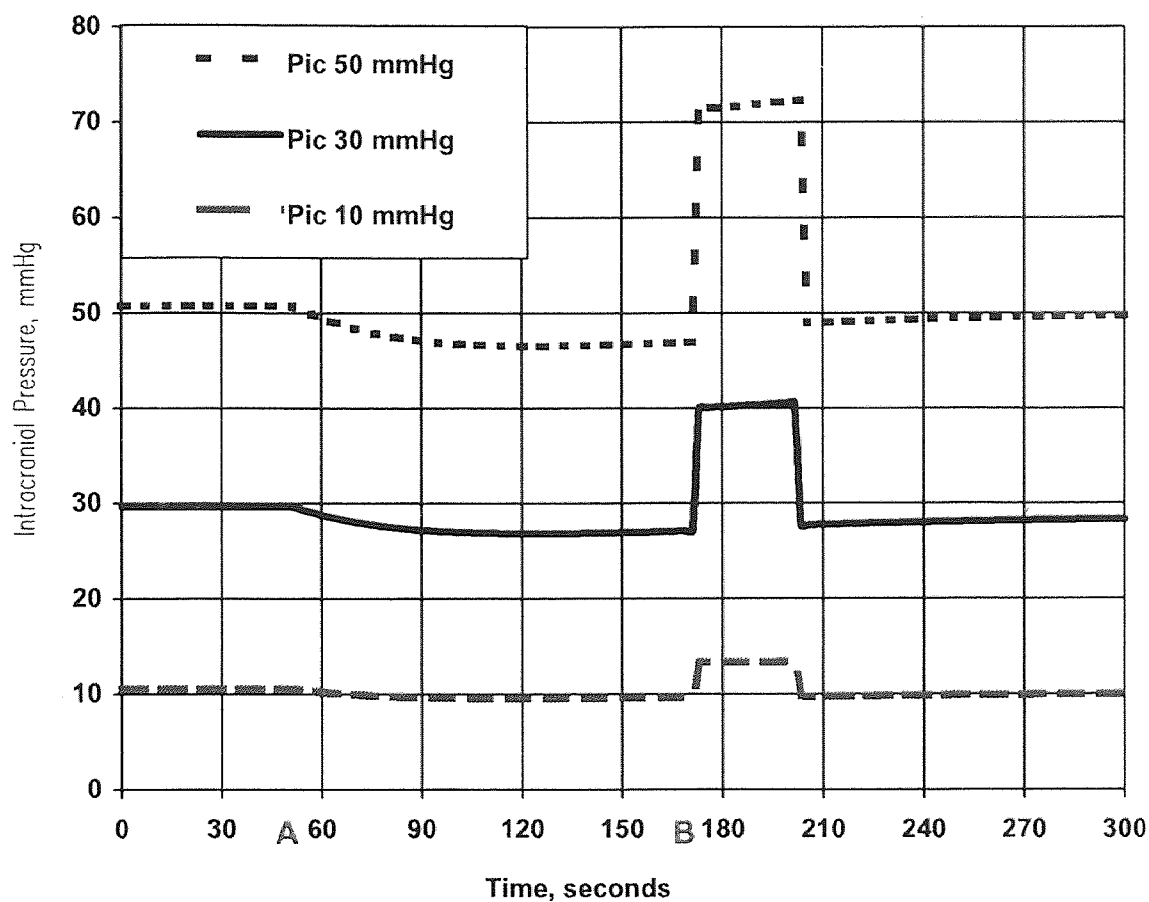
compared to preinduction values and by  $60 \pm 20$  mmHg compared to preintubation values [33,34]. In our model, systemic hypertension was simulated by adding 60 mmHg to the value of MAP 120 seconds following the induction dose of thiopental. Stimulation persisted for 30 seconds.



**Figure 6** Changes in intracranial pressure during induction of anesthesia in a simulated patient with intact autoregulation; A) thiopental, 5 mg/kg bolus is injected; B) laryngoscopy begins.

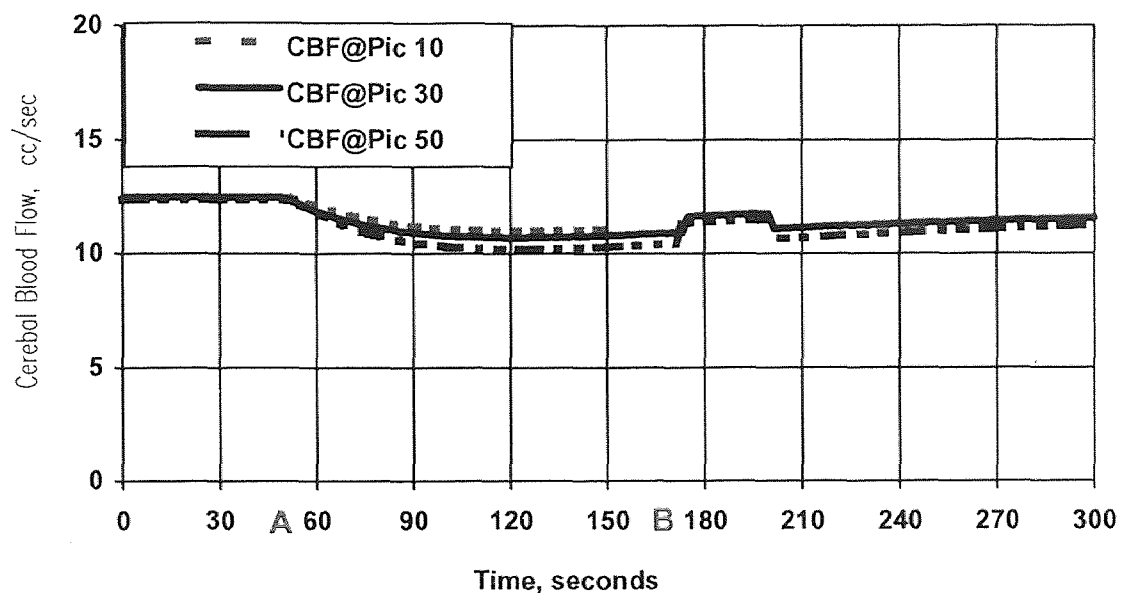
ICP and CBF changes during induction of anesthesia were computed for initial ICP values of 10, 30 and 50 mmHg. Figure 6 shows that an induction dose of thiopental

decreases ICP. The model predicts that ICP reduction is more pronounced in patients with increased intracranial pressure (7% for patients with ICP of 10 mmHg and 15% for patients with ICP of 50 mmHg). This effect, however, lasts less than three minutes. Autoregulation and rapid redistribution of thiopental resulting in systemic pressure rise lead to ICP elevation almost to preinduction level. Subsequent laryngeal stimulation raises ICP by 5 mmHg.



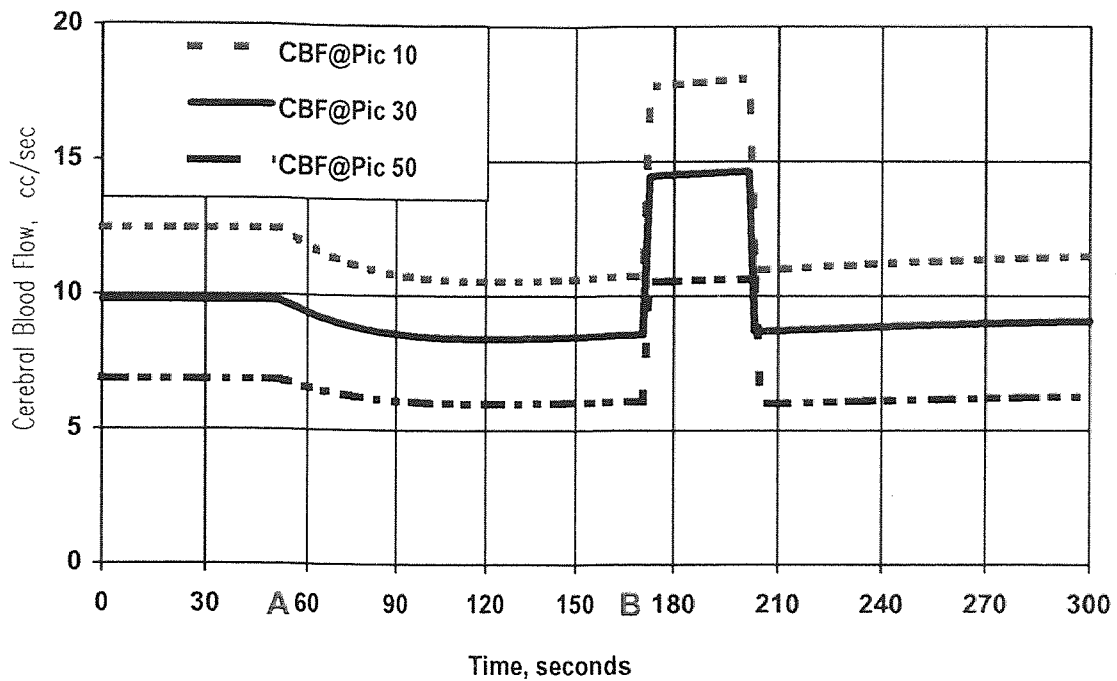
**Figure 7** Changes in intracranial pressure during induction of anesthesia in simulated patient without autoregulation: A) thiopental, 5 mg/kg bolus is injected; B) laryngoscopy begins.

Figure 7 shows simulated ICP changes after a thiopental bolus and endotracheal intubation in a patient without autoregulation. Simulation demonstrates that laryngoscopy and endotracheal intubation may dangerously increase ICP by an additional 14 and 26 mmHg in compromised patients whose intracranial pressure begins at 30 and 50 mmHg, respectively. The duration of ICP increase is determined by the length of laryngeal stimulation (30 seconds in our simulation).



**Figure 8** Changes in cerebral blood flow during induction of anesthesia in a simulated patient with intact autoregulation: A) thiopental, 5 mg/kg bolus is injected; B) laryngoscopy begins.





**Figure 9** Changes in cerebral blood flow during induction of anesthesia in a simulated patient without autoregulation; A) thiopental, 5 mg/kg bolus is injected; B) laryngoscopy begins.

Figures 8 and 9 show simulated CBF changes during induction of general anesthesia with thiopental for patients with and without cerebral autoregulation. Similar to ICP responses, CBF changes are exaggerated in simulated patients with increased ICP and no autoregulation.

## CHAPTER 4

### DISCUSSION

The mathematical model described in this paper is being developed to simulate clinical behavior of the cerebrovascular circulation. The model is constructed by connecting sub-models of intracranial hemodynamics and drug pharmacokinetics. The complexity of the model can be reduced by using a multiple modeling technique. Simplification is achieved by setting up and testing individual units separately and then combining them into a complete model [35,36]. The modular approach also allows addition of new units to the model as needed. The multiple modeling technique is used to study performance of systems with two or more kinds of transport (e.g. momentum, mass, etc.) taking place simultaneously [2,3,5,37].

In building a model a compromise must be made between model simplicity and accuracy of results. Approximations and assumptions are always involved. This model was developed to study the effect of pharmacologic and mechanical intervention on the cerebrovascular circulation during administration of anesthesia. Three sets of assumptions were used: assumptions related to development of the intracranial hemodynamic model, assumptions related to pharmacokinetics of thiopental, and assumptions concerning the simulated example - induction of anesthesia with thiopental. Limitations related to these assumptions should be evaluated in order to appreciate the results of the simulation.

#### 4.1 Circulation Model Limitations

The lumped parameter model of cerebral circulation was constructed by grouping cerebral vessels and brain parenchyma into distinct functional compartments. The equations that ensue are linear ordinary differential equations (as opposed to partial differential equations for distributed systems). This method does not allow evaluation of the relative role of different cerebral regions in regulation of blood flow. Consequently pathologic conditions which are associated with regional CBF differences (cerebral ischemia, steal phenomena, etc.) can not be studied with this model in its present form.

Including the arteriolar compartment and thiopental dependent resistance was necessary to study the effects of drug concentration on intracranial hemodynamics. A dose-dependent reduction of metabolism ( $CMRO_2$ ) with thiopental administration in humans and animal experiments is well documented [20,38,39]. Functional depression of brain activity leads to a corresponding CBF decrease. Although the exact mechanism linking flow and metabolism is unclear, it appears that coupling occurs at the level of small arterioles [40]. Thus, arteriolar-capillary resistance was chosen as the model site of thiopental action.

The goal of any particular study determines the degree of simplification necessary. Metabolic and respiratory factors have been omitted, although they can be added in modules as needed. The level of  $CO_2$ ,  $H^+$ , and  $O_2$  profoundly affect CBF and ICP, but it was assumed that these parameters were unchanged in order to compare the effects of thiopental administration and intubation under various simulated clinical situations. Simple "experimental" design was necessary at the initial stage of model development to validate simulated results with the available clinical observations.

Our model includes intracranial arterial, venous, and tissue compliances. Pressure difference between adjacent compartments and elastance coefficients determines their numerical values. Although it is very likely that elastance coefficients would be affected by thiopental concentration, there is no experimental verification of this relationship. Thus, only the effect of pressure changes on compliance is included in the model.

ICP elevation in our simulation was accomplished by increasing a resistance to CSF re-absorption. Intracranial hypertension can be produced also by increasing the brain tissue elastance coefficient. Comparison of the various ways of decreasing intracranial compliance and examination of compliance changes on cerebral blood flow and intracranial pressure was not part of this study, but will be addressed in the future.

#### **4.2 Limitations of Pharmacokinetic Model**

Rigorous determination of thiopental uptake by brain tissue requires knowledge of cerebral blood flow, volume, and blood-tissue partition and diffusion coefficients (assuming uniform thiopental concentration in various brain regions). To construct a complete physiological model of drug distribution this information should be also available for other organs. Perfusion-limited models of thiopental disposition have been developed by Price [41] and Saidman and Eger [42]. Although valuable in understanding the general principles of thiopental distribution, these models never gained widespread acceptance because of their complexity, arbitrary selection of organ volumes and flows, and inherent inability to determine partition and diffusion coefficients in humans.

An alternative analysis of drug disposition consists of formulating a model containing the minimum number of compartments that adequately fit the observed data. Although compartmental analysis gives little insight into the physiological determinants of pharmacokinetics, these models are widely used in clinical pharmacology and anesthesiology due to their simplicity and easy experimental verification. A three-compartmental model (e.g. tri-exponential equation) is commonly used to describe the thiopental concentration-time curve during the first 30 minutes following an intravenous bolus administration [23,43] and was used in our simulation. The degree of disequilibrium in drug concentration versus time and effect versus time was evaluated by adding an effect compartment (biophase) to the three-compartmental model [44]. The apparent drug concentration at the effect site was calculated using first order kinetics and plasma concentration predicted by the three-compartmental model. The rate constant of blood-brain equilibration used in our simulation ( $k=0.58 \text{ min}^{-1}$ ) was estimated by Stanski and Maitre [25] from EEG versus thiopental plasma concentration data. We assumed that cardiovascular and central nervous system effects are kinetically indistinguishable.

Limitations of compartmental analysis in describing early distribution of thiopental are well recognized [45]. Compartmental kinetics assumes instantaneous mixing of a drug in the central compartment following intravenous injection. Speed of injection, however, may influence the drug dose-concentration-effect relationship. Following intravenous drug administration, the injected bolus travels along the venous vasculature to the right heart. Using a sheep model, Upton and Huang [46] determined that the maximum concentration of indocyanine green injected into the inferior vena cava occurred 7 to 18 seconds after injection (injection time 1 to 10 seconds). Although it is possible

to study this delay by introducing an additional central compartment [47], it is unlikely that a delay of this magnitude will significantly alter model predictions.

There are several other factors that influence thiopental kinetics, which have not as yet been studied. The effects of disease states, can be simulated by changing inter-compartmental and elimination kinetic constants, but were not evaluated. Thiopental protein-binding and the extent of thiopental ionization are not included in this model.

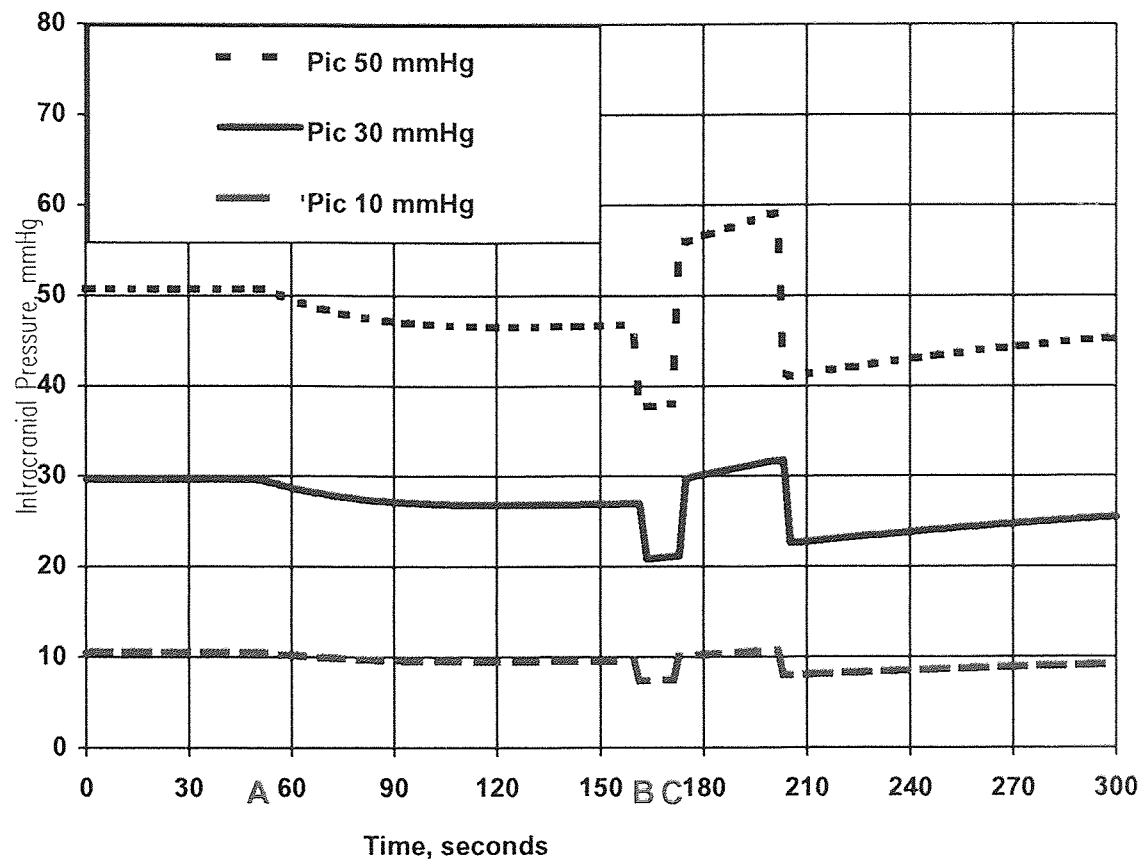
Thiopental pharmacokinetics determines hemodynamic changes in our model. The effects of altered hemodynamic parameters on drug distribution cannot be accounted for by the model in its present form. "Closing the loop" will be an important feature of future studies.

#### 4.3 Concerning Simulation

Laryngoscopy and endotracheal intubation may elevate systemic pressure and ICP [48, 49]. Although this transient increase is probably unimportant in patients with intact autoregulation, brain edema and trans-compartmental brain tissue shifts may occur in patients with already compromised intracranial hemodynamic [50,51]. Our computations show that a single bolus of thiopental is insufficient to prevent an ICP elevation associated with intubation carried out 3 min after thiopental administration. Cerebrovascular effects of thiopental may be attributed to two basic mechanisms; direct arteriolar vasoconstriction and reduction of systemic mean arterial pressure [52]. Both effects are dose-dependent. Rapid redistribution of thiopental decreases its plasma concentration from 65  $\mu\text{g/mL}$  to 20  $\mu\text{g/mL}$  in 2 minutes. Consequently, systemic arterial pressure and cerebrovascular conductance rise, negating the initial desirable action of this drug. If cerebral autoregulation is absent, exaggerated elevation of ICP occurs during laryngeal stimulation.

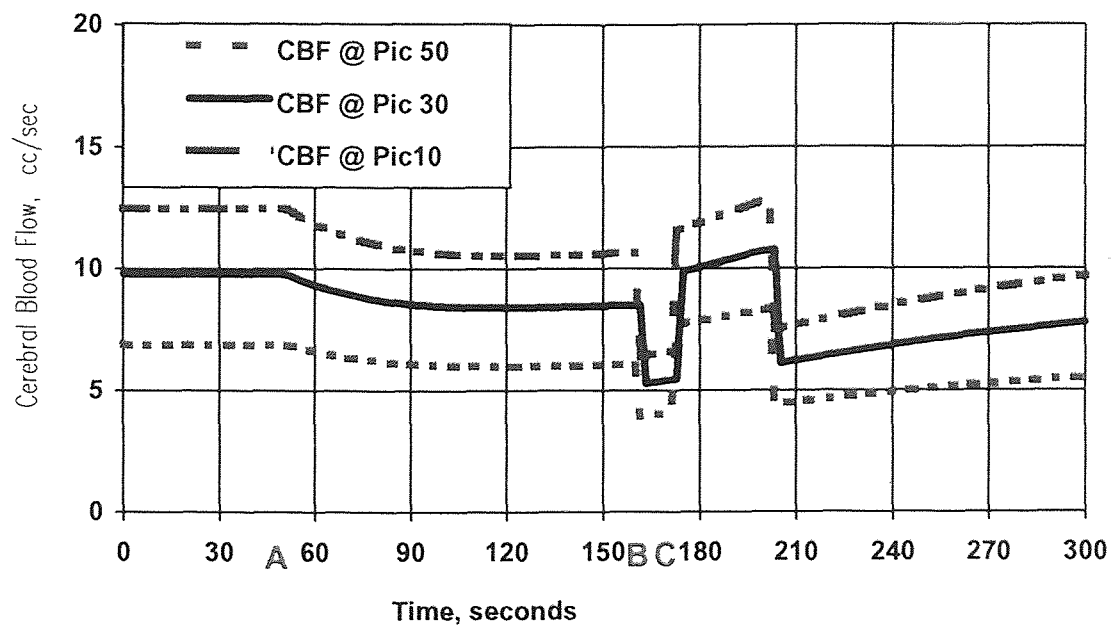
The pattern of ICP and CBF changes produced by our simulation closely resembles experimental *in vivo* observations. Shapiro et al. [53] and Greenbaum et al. [54] demonstrated that patients with preoperative signs of elevated ICP had a significant ICP increase (30 to 80 mmHg) during intubation using thiopental. Transcranial Doppler ultrasonography of middle cerebral artery blood flow velocity suggests that hypertensive responses during laryngoscopy and intubation increase CBF [55,56]. Due to variations in experimental conditions, the simulated and experimental results can only be compared qualitatively.

Prevention of hypertensive responses in neurosurgical patients is the subject of numerous investigations [57-59]. Our computer model looked at the effect of a second dose of thiopental (4.0 mg/kg) prior to intubation. The simulation shows that this will attenuate increased ICP and CBF in simulated patients with non-autoregulated cerebral circulation (Figures 10 and 11). The additional dose of thiopental reduces MAP and extends the time period of cerebral vasoconstriction.



**Figure 10** Changes in intracranial pressure during induction of anesthesia in a simulated patient without autoregulation and a second dose of thiopental administered prior to intubations; A) thiopental, 5 mg/kg bolus is injected; B) laryngoscopy begins; and C) thiopental 4 mg/kg is injected.





**Figure 11** Changes in cerebral blood flow during induction of anesthesia in a simulated patient without autoregulation and a second dose of thiopental administered prior to intubation; A) thiopental, 5 mg/kg bolus is injected; B) laryngoscopy begins; and C) thiopental, 4 mg/kg is injected.

## CHAPTER 5

### CONCLUSION

The primary purpose of this work is to synthesize cerebrovascular physiology and pharmacology to allow analysis of complex effects of drugs and mechanical interventions on CBF and ICP occurring during the administration of anesthetics. The overall model was constructed from two constituent sub-models: a lumped parameter compartmental model of intracranial hemodynamics and a pharmacokinetic model of thiopental distribution. Interaction of the two sub-models was accomplished through concentration dependent resistance and MAP (mean arterial pressure). The model was tested by comparing simulation results to available experimental data. Although many aspects of the mathematical formulation and the values assigned to the variables are controversial, the important consideration is whether this overall approach is useful to examine the behavior of the cerebrovascular circulation *in vivo*. Some merits of our approach are:

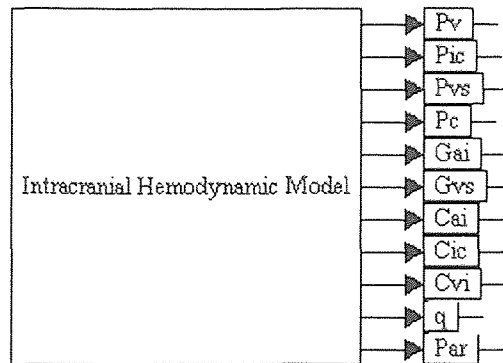
1. We analyzed the effect of autoregulation on intracranial hemodynamics; this can be extended to examine the effect of brain pathology on the cerebral circulation. For example, a brain tumor may be modeled by decreasing brain parenchyma compliance and/or increasing vascular resistance to CSF reabsorption.
2. The model was used to study responses of the cerebrovascular system to thiopental and endotracheal intubation. There is no limitation on the variety or

combination of drugs which can be studied using this model. The relationship between plasma drug concentration and at least one cerebrovascular parameter must be available (or derived from the experimental data).

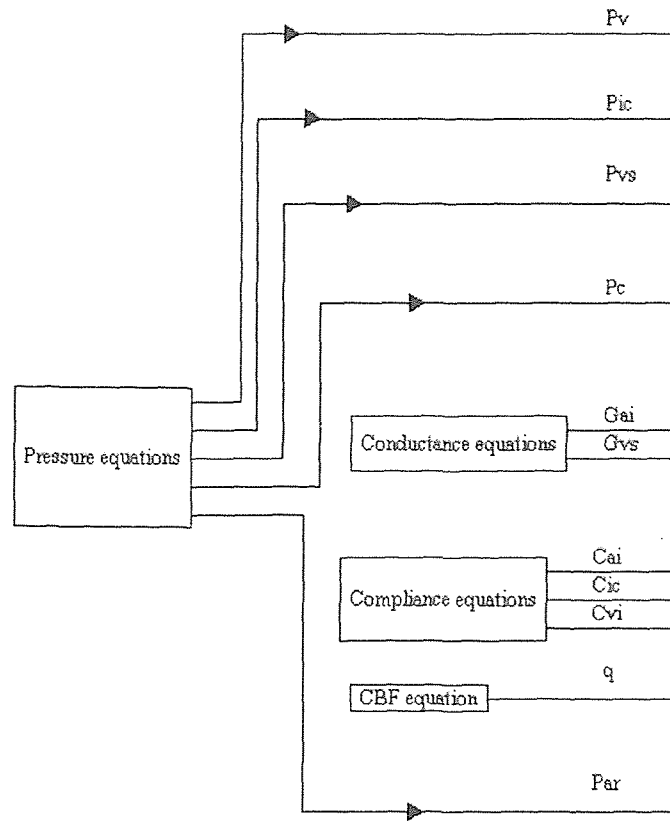
3. We have examined hemodynamic responses of an intact and compromised cerebral circulation during the induction of general anesthesia; with appropriate modifications the model can be used to analyze other clinical situations.
4. A drug administration regimen which prevents ICP increase associated with laryngoscopy and intubation was proposed using our model; this can be extended to develop optimum drug(s) therapy to achieve specific clinical goals. The model is also useful to conceptualize the problem and examine the interaction between various parts of the system. Areas that require further studies can be identified as well.

## Cerebrovascular System Model

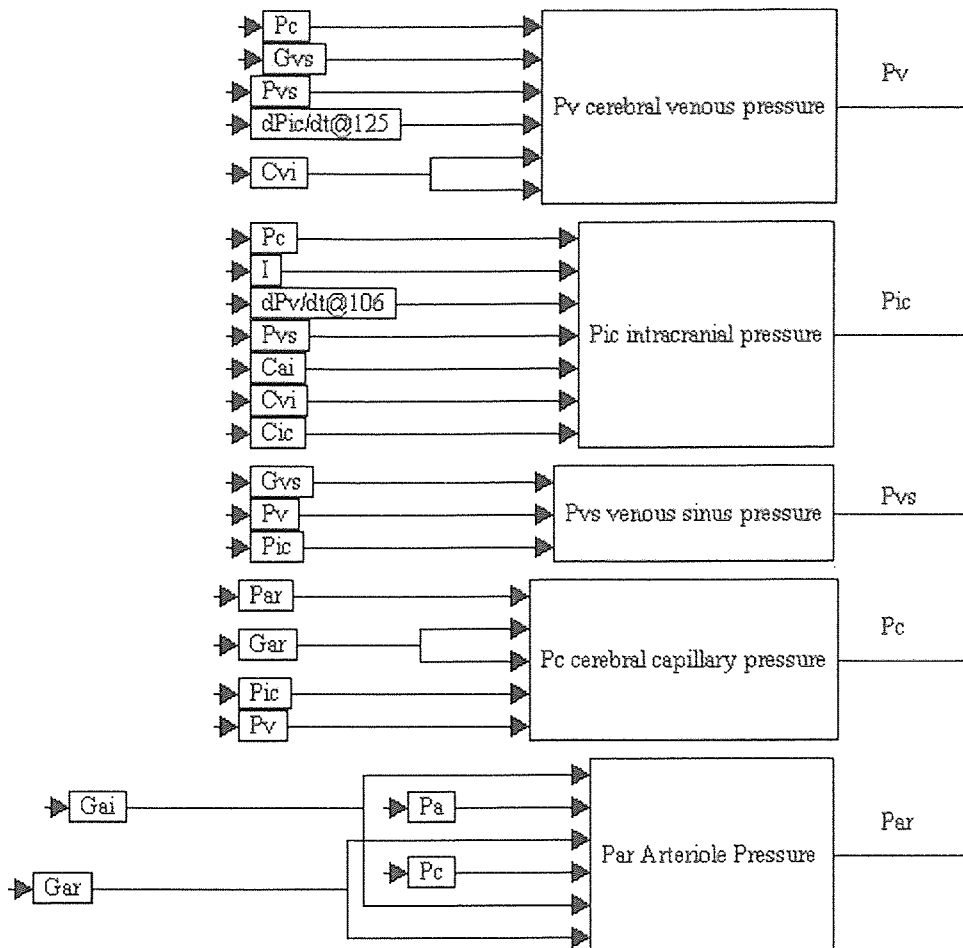
The appendix contains a listing of the VisSim<sup>®</sup> code for the Cerebrovascular System Model developed.



**Figure 12** Intracranial hemodynamic compound block with outputs



**Figure 13** Intracranial hemodynamic compound block expanded



**Figure 14** Pressure equations compound block expanded

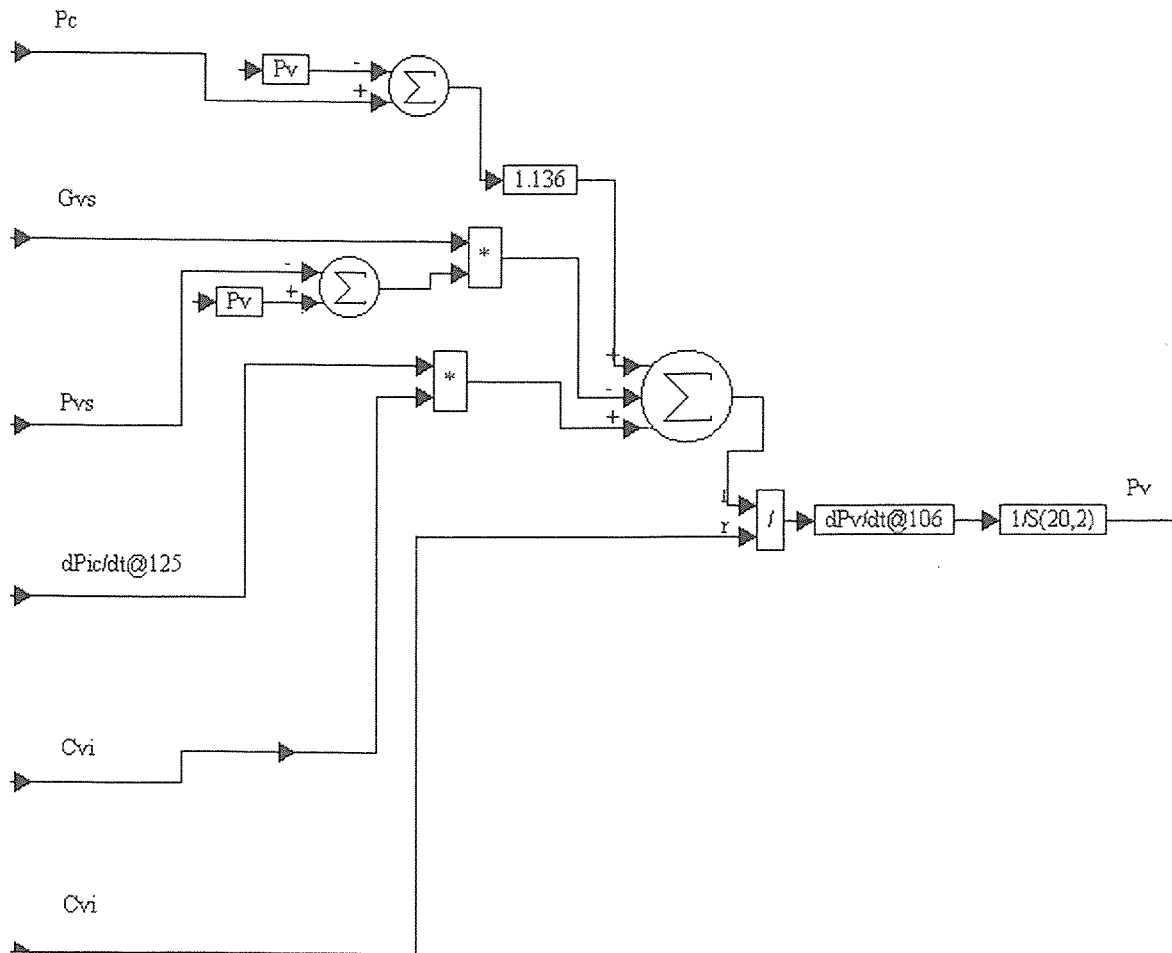
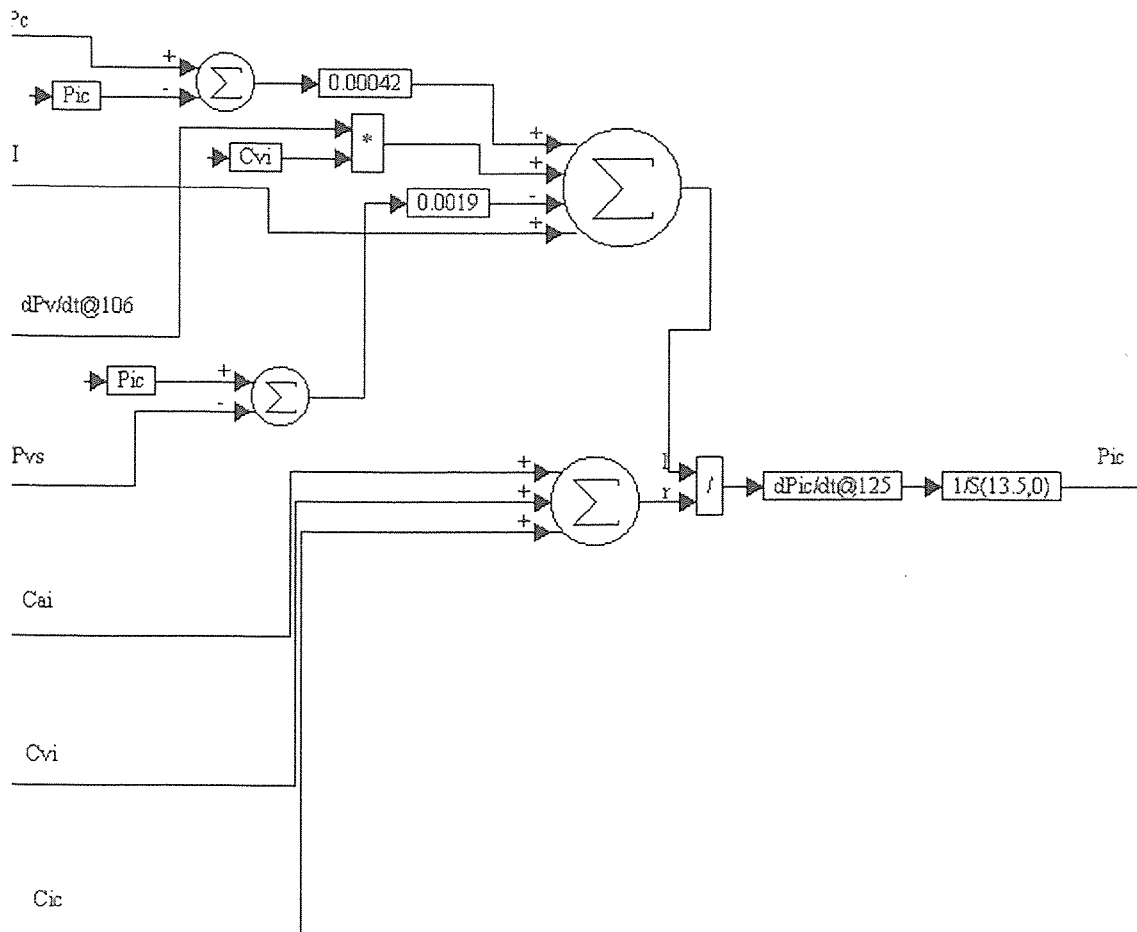


Figure 15  $P_v$  cerebral venous pressure compound block expanded



**Figure 16** Pic intracranial pressure compound block expanded



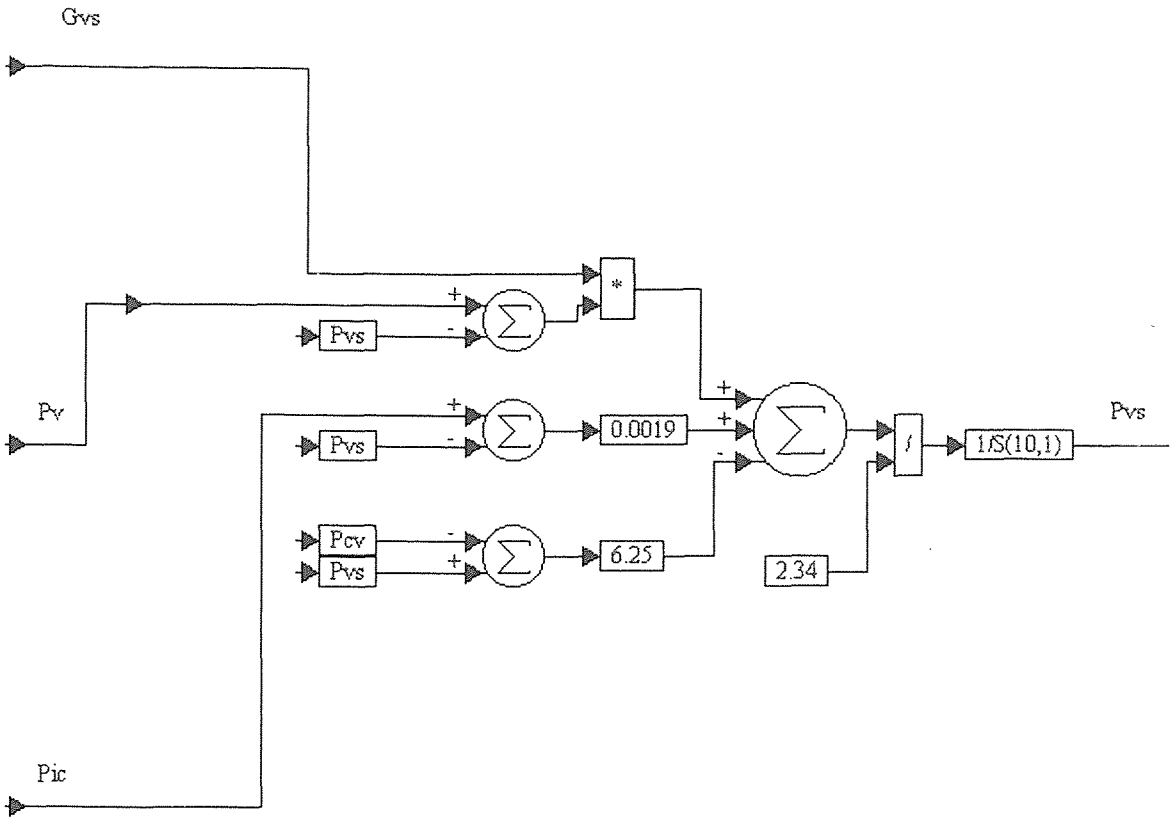
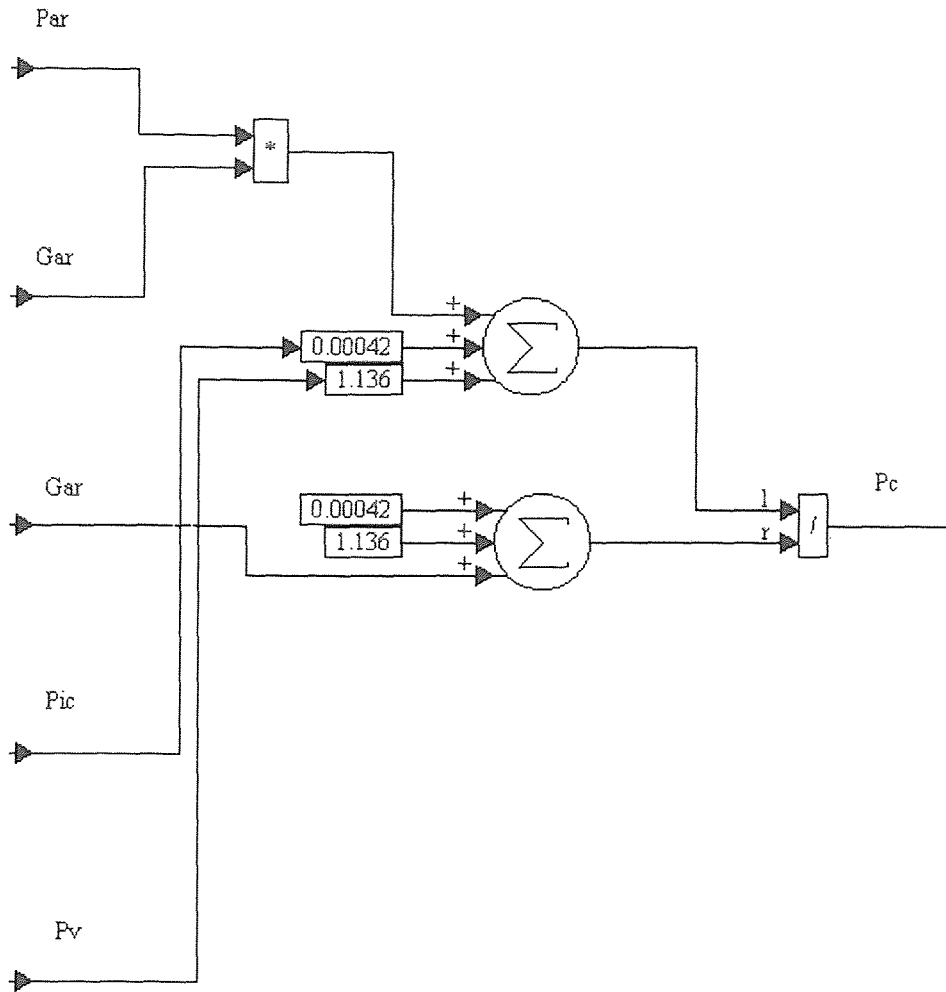
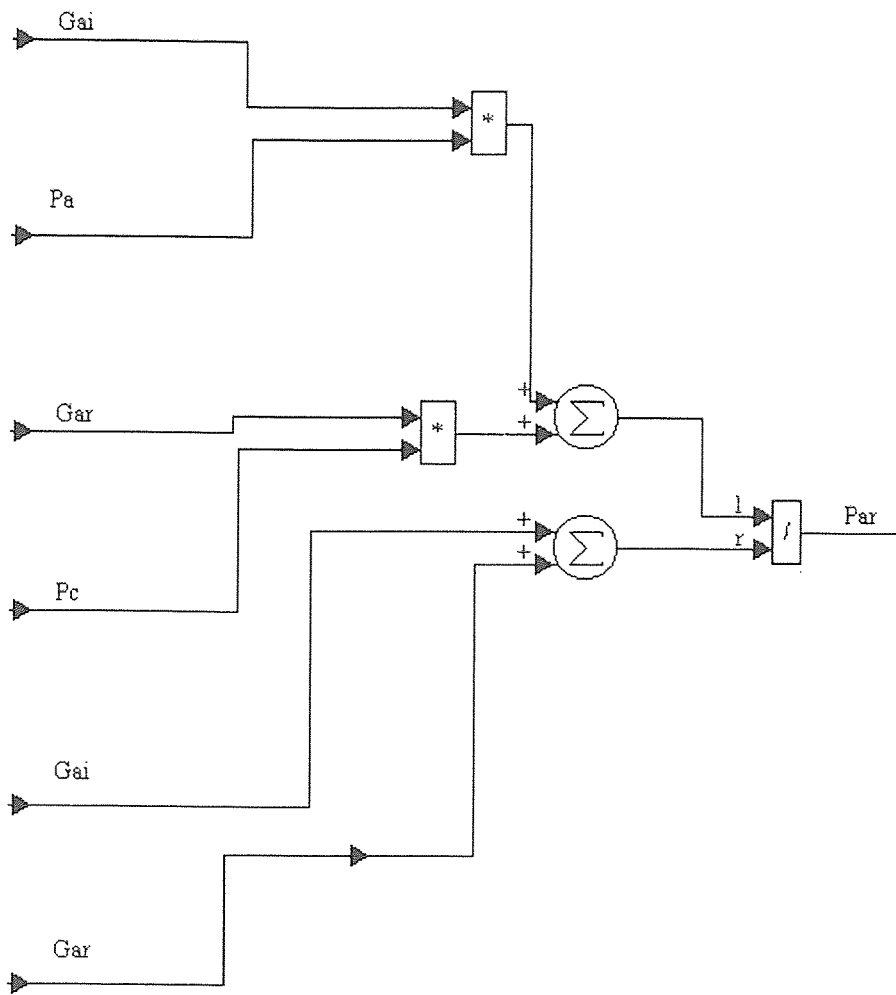


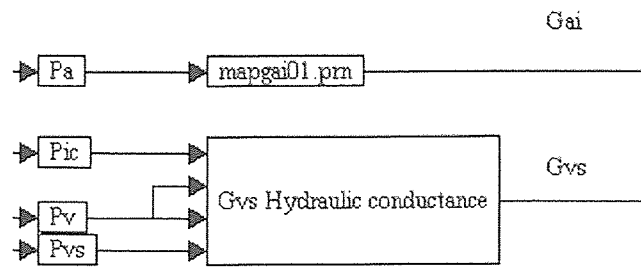
Figure 17 Pvs venous sinus pressure compound block expanded



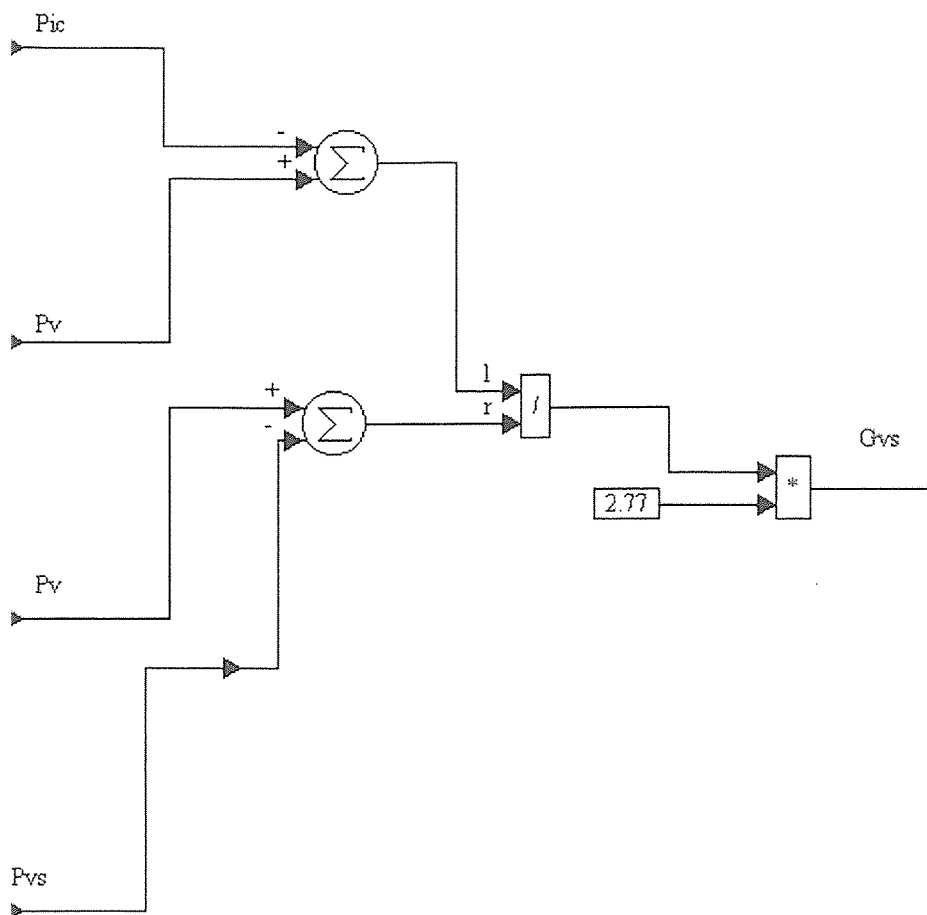
**Figure 18**  $P_c$  cerebral capillary pressure compound block expanded



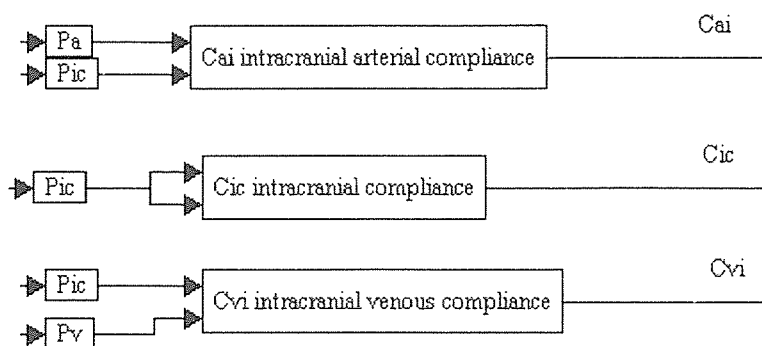
**Figure 19** Par arteriole pressure compound block expanded



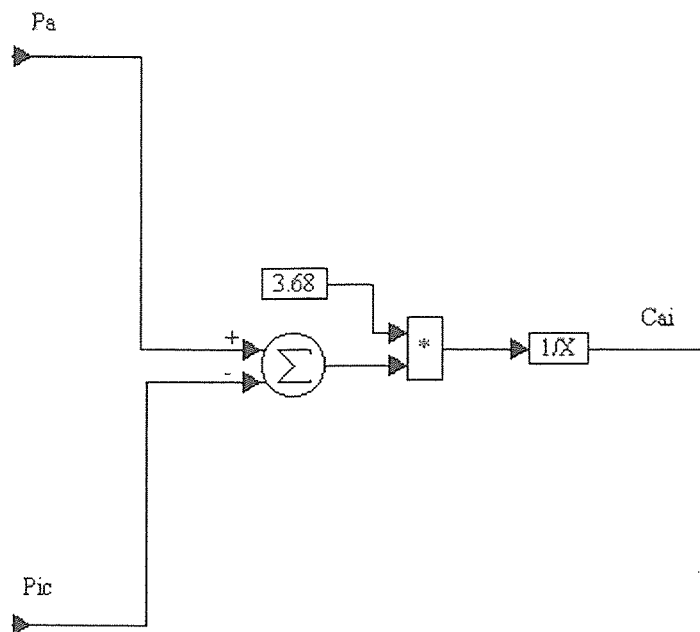
**Figure 20** Conductance equations compound block expanded



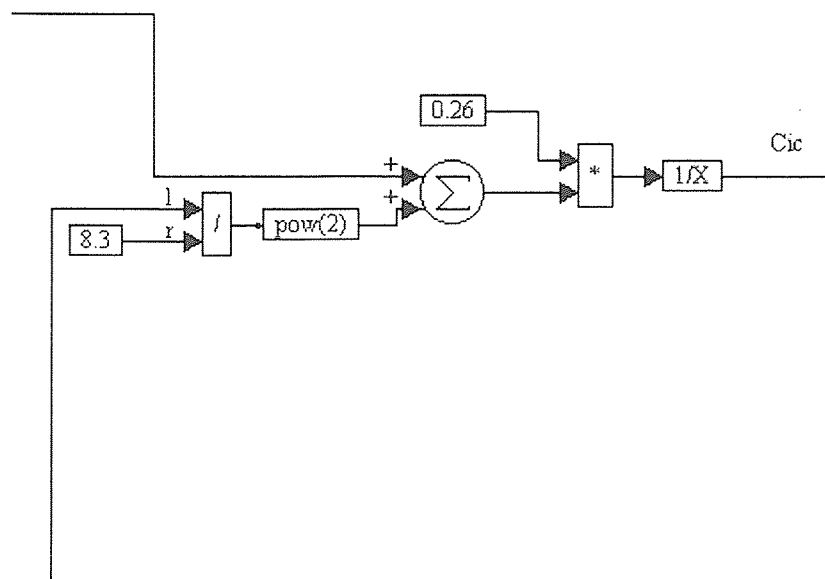
**Figure 21** Gvs hydraulic conductance compound block expanded



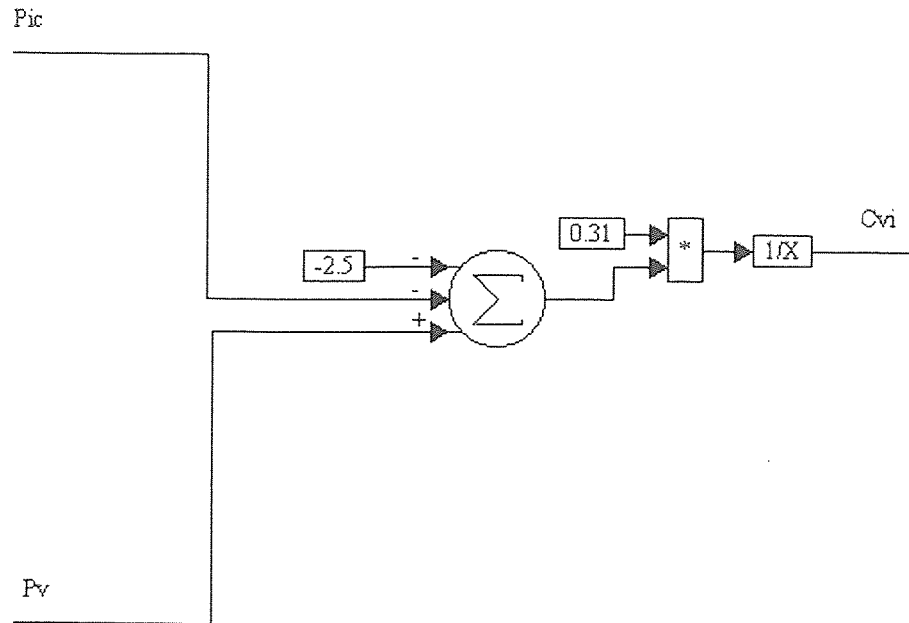
**Figure 22** Compliance equations compound block expanded



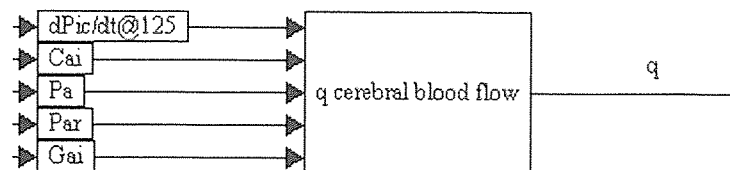
**Figure 23**  $C_{ai}$  arteriolar compliance compound block expanded



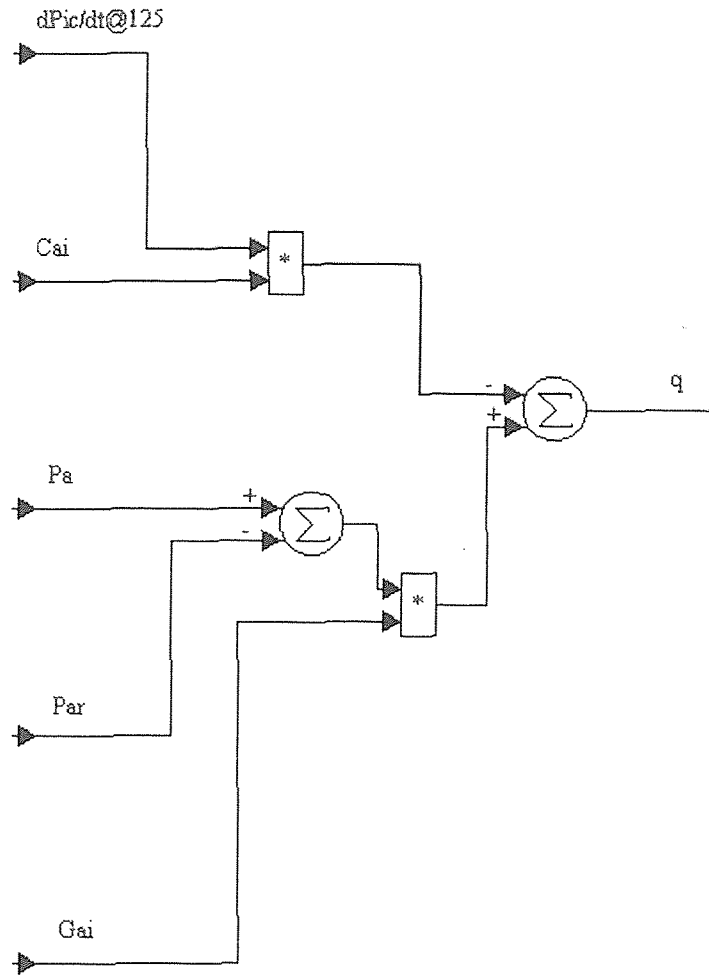
**Figure 24**  $C_{ic}$  intracranial compliance compound block expanded



**Figure 25** Cvi intracranial venous compliance compound block expanded



**Figure 26** CBF equation compound block expanded



**Figure 27**  $q$  cerebral blood flow compound block expanded



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