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ABSTRACT

COMPUTER SIMULATION OF CEREBROVASCULAR RESPONSES DURING INDUCED HYPOTENSION

by

John Schalago

The purpose of this project was to develop a computer model of cerebrovascular hemodynamics interacting with a pharmacodynamic drug model to examine the effects of three commonly used anti-hypertensive drugs upon intracranial pressure and cerebral blood flow. The model is used to predict cerebrovascular response during the administration of commonly used anti-hypertensive agents.

The mathematical model of intracranial hemodynamics is a seven compartment constant volume system. A series of resistances relate blood and cerebrospinal fluxes to pressure gradients between compartments. Arterial, venous and tissues compliance are included. Autoregulation is modeled by transmural pressure-dependent arterial-arteriolar resistance. The effects of three drugs (Sodium Nitroprusside, Nitroglycerin and Esmolol) on cerebrovascular circulation was simulated by a variable arteriolar-capillary resistance and capillary-venous resistance. The three drugs are known to have a rapid on-set, a short half-life and are normally therapeutically administered using continuous infusion. A direct relationship between mean arterial pressure and arteriolar-capillary and capillary-venous resistance was developed. Comparing the simulation results with available experimental observations validated the model. The simulation program was written usingVisSim ® dynamic simulation language for an IBM-compatible PC.

The developed model was used to calculate intracranial pressure changes that occur with deliberate hypertension. Response to intravascular administration was predicted for simulated patients with elevated intracranial pressure and non-autoregulated cerebral circulation. The simulations demonstrated that Sodium Nitroprusside and Nitroglycerin reduce mean arterial pressure while simultaneously elevating intracranial pressure. The simulations demonstrated that intracranial pressure increases with reduction in mean arterial pressure until a maximum value is reached at which point a reduction in intracranial pressure occurs with additional decreases in mean arterial pressure. Esmolol reduces mean arterial pressure without a significant change in intracranial pressure.

The presented simulation compared the effect of commonly used anti-hypertensive drugs on cerebral hemodynamics. The simulation demonstrates that Sodium Nitroprusside and Nitroglycerin may increase intracranial pressure. This effect is more significant in non-autoregulated circulation. Only minor intracranial pressure changes have been predicted during Esmolol infusion. Esmolol is a preferable intra-operative hypotensive agent for patients with non-auto-regulated cerebral circulation (head trauma, brain tumor, etc.) The model developed in this project can be extended to analyze more complex intraoperative events by adding new submodels.

COMPUTER SIMULATION OF CEREBROVASCULAR RESPONSES DURING INDUCED HYPOTENSION

by
John A. Schalago

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To the three most important people in my life. My wife, Lynn, and my two daughters, Kaitlin, and Stephanie

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CHAPTER 1

INTRODUCTION

1.1 Overview of Induced Hypotension

Multiple factors combine to maintain normal systemic pressure. These factors include cardiac output, circulating blood volume, the peripheral resistance, blood viscosity and compliance of large vessels. Further, these factors are influenced and subject to control by numerous physiological factors such as the central nervous system, and hormones. Deliberate hypotension is an anesthetic technique used in a variety of surgical techniques to improve the surgical field, reduce blood loss, and reduce transfusion requirements [1-2]. The factors of most importance during deliberate hypotension are peripheral resistance, cardiac output and total circulating blood volume. When total blood volume is maintained constant, deliberate hypotension is induced by reducing cardiac output and/or decreasing peripheral resistance. Today, deliberate hypotension is induced intraoperatively through the administration of anti-hypertensive (hypotensive) agents [1]. These agents induce hypotension by dilating peripheral vessels or by reducing cardiac output [2].

The cerebral circulatory system is a constant volume system consisting of blood, cerebrospinal fluid and cerebral tissue. Complex multiple factors combine to maintain normal cerebral spinal fluid levels, cerebral blood flow (CBF), and intracranial pressure (ICP). Cerebral blood volumes are distributed between arteries, capillaries and veins, with the greatest volume (75%) in the veins. Administration of anti-hypertensive agents during induced hypotension are often associated with untoward events such as increased

intracranial pressure and increased cerebral blood flow depending on patient status [23]. Specifically, vasodilators are anti-hypertensive agents that reduce systemic pressure by dilating peripheral vessels and directly dilate the cerebral capacitance vessels increasing cerebral blood volume [18]. The increased cerebral blood volume may concomitantly increase intracranial pressure. In addition, in normal patients, autoregulatory response to decreased mean arterial pressure causes an increase in cerebral blood flow.

The complexity of the cerebral circulatory system and autoregulation make it difficult to predict the unanticipated complications and changes in intracranial pressure and cerebral blood flow during deliberate hypotension. Computer simulation may be a useful tool to access the complex interactions of the numerous hemodynamic variables affecting intracranial hemodynamics.

1.2 Intracranial Hemodynamic Models

Over the past fifteen years, various biophysical and mathematical models have been developed to simulate intracranial hemodynamics [5-12]. Hudetz, *et. al.*, developed a computer model of cerebral circulation to predicted changes in cerebral blood flow and tissue oxygenation with autoregulation intact during occlusion of the middle cerebral artery (MCA) [8]. The model design included the pial and intracerebral arteries and autoregulatory system. Several models have been developed to evaluate cerebrospinal fluid dynamics [3, 4, 7, 9]. These models were designed using known experimental data and were used to predict the effect of dynamic changes in cerebrospinal fluid on cerebrospinal fluid pressure. Sorek designed a lumped parameter compartmental model of the cerebrovascular system [5]. The model was used to predict changes in resistance

and compliance during non-steady cerebrospinal fluid flow. The model developed by Kadas, *et.al.*, was a four compartmental model of intracranial hemodynamics [3]. The model was used to predict cerebral autoregulatory induced changes in cerebral blood flow. Hoffman designed a mathematical model to predict changes in intracranial cerebrospinal fluid and intracranial hemodynamics [15]. The model includes cerebral circulatory and systemic circulatory components. This model was used to predict cerebral circulatory response to changes in mean arterial pressure.

The most extensive and complete model was developed by Ursino [10-12]. The model was designed to simulate the behavior of the intracranial arterial vascular bed, the intracranial venous vascular bed, cerebrospinal fluid absorption and production process and incorporates physiological and anatomical data. The model is a lumped parameter seven-compartment, constant volume system. The seven compartments represent cerebrovascular arterial and arteriolar beds, an intracranial capillary compartment, a venous vascular bed, venous sinuses, a cerebrospinal fluid compartment (brain tissue) and a central venous compartment. The unique aspect of the model is the inclusion of cerebral blood flow autoregulation, and cerebrospinal fluid formation. In addition, the model calculates model parameters using physiological and recent anatomical data.

Bekker, *et.al.*, recently reported the use of a model to predict changes in intracranial hemodynamics during administration of an anesthetic drug [31]. Specifically, the model consisted of a sub-model designed to simulate the pharmacokinetic and pharmacological effect of thiopental and a modified version of the intracranial hemodynamic model developed by Ursino.

1.3 Objective

During induced hypotension, the complex interaction of numerous hemodynamic variables affecting intracranical hemodynamics makes it difficult to predict changes in intracranial pressure and cerebral blood flow. A computer model consisting of a cerebrovascular hemodynamic subsystem interacting with a pharmacodynamic drug model may be a useful tool capable of predicting simulated patient response with varying physiological conditions.

The objectives of this research project are:

1. To develop a computer model of cerebrovascular hemodynamics interacting with a pharamcodynamic drug model to examine the cerebrovascular response during induced hypotension.
2. Predict the cerebrovascular response to three commonly used anti-hypertensive agents, two vasodilators and a beta-adrenergic.
3. Use the computed data to recommend an intraoperative hypotensive agent depending on patient status.

CHAPTER 2

MODEL

2.1 Overview

The overall structure of the three system models developed to simulate and predict the effects of three commonly used anti-hypertensive agents are presented in figures 1, 2, and 3. Each computer model consists of a sub-model of pharmacodynamic effects of a particular anti-hypertensive agent interfaced with a modified version of the intracranial hemodynamic model first developed by Ursino.

The intracranial hemodynamic sub-model is a lumped parameter seven-compartment constant volume system. The seven compartments represent cerebrovascular arterial and arteriolar beds, intracranial capillary compartment, venous vascular bed, venous sinuses, cerebrospinal fluid compartment (brain tissue) and a central venous compartment. The unique aspect of the model is the inclusion of cerebral blood flow autoregulation, cerebrospinal fluid formation and calculation of model parameters using physiological and recent anatomical data.

The three pharmacodynamic sub-models were developed from experimental data [13-30]. The pharmacodynamic sub-model for sodium nitroprusside was constructed with the assumption that sodium nitroprusside predominantly affects cerebral arteriolar-capillary vessels [14-19]. The sub-model is defined by an exponential relationship between the

conductance of the arteriolar-capillary bed and the percent change in mean arterial pressure during sodium nitroprusside induced hypotension.

The pharmacodynamic sub-model for nitroglycerin was constructed assuming that nitroglycerin predominantly affects cerebral venous vessels [20-25]. The sub-model is defined by an exponential relationship between conductance of the venous bed and percent change in mean arterial pressure during nitroglycerin induced hypotension. The pharmacodynamic sub-model for esmolol differs from the other sub-models in that we assume that esmolol effects mean arterial pressure without concomitant effect on cerebrovascular vessels [26-30]. The sub-model is an described by an exponential relationship between change in mean arterial pressure and drug concentration.

2.2 Intracranial Hemodynamic Model

The model of intracranial hemodynamics was chosen as the cerebral circulation submodel because the model includes cerebrospinal fluid formation rate as a function of transmural pressure, capable of simulating hemodynamic response with autoregulation intact and non-autoregulated conditions, and the system parameters and constants are based upon physiological and anatomical data [10-12]. The equations and system parameters that define the cerebral circulation model are provided in the Appendix. An overview of the sub-model design and the general principles and equations are described herein. In addition, the subsystem for each of the three anti-hypertensive agents investigated in this paper is described in detail.

The following assumptions were made to derive the cerebral circulatory system and pharmacodynamic model equations:

- The change in fluid in a compartment is equal to the sum of the net fluid influx through the compartmental boundaries, plus external sources.
- The change in volume is produced by the changes in pressure difference.
- Arteriolar-capillary and venous cerebrovascular resistance is controlled by chemical factors including pharmacological agents.
- The sum of all volumes does not change in time, *i.e.*, constant volume.
- Arterial-arteriolar and venous cerebrovascular resistance is a function of transmural pressure.

The mathematical model of intracranial hemodynamics is a seven-compartment constant volume system. The seven compartments represent 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 CSF fluxes to the pressure gradient between compartments:

$$dV_n/dt = \Sigma_m \; q_{mn} = \Sigma_m (P_m - P_n) / R_{mn} \qquad (1)$$

where Vn 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.

As described above a unique feature of the model is the incorporation of cerebrospinal fluid production and absorption processes. The CSF production rate is directly

proportional to the difference between capillary and intracranial pressures and inversely proportional to the resistance that the choroid plexus applies to CSF secretion. The CSF absorption rate is directly proportional to the difference between intracranial and dural sinus pressures and inversely proportional to the arachoid villi resistance to fluid flow.

Two lumped parameters are used to describe changes in cerebral arterial and venous blood volumes. The relationship between arterial blood volume and pressure is assumed to be monoexponential and is described by the following equation

$$P_a - P_{ic} = e^{Ka(Va - Va0)} \tag{2}$$

where V_{a0}, and Ka are constants. Compliance of the arterial compartment is defined by the equation

$$C_a = dV_a / d(P_a - P_{ic}) = 1/K_a(P_a - P_{ic}) \tag{3}$$

where C_a is the arterial compartment compliance, K_a denotes the arterial elastance coefficient and pressure in the arterial, and intracranial compartments are described by P_a, and P_{ic}. The relationship between venous blood volume and pressure is also assumed to be monoexponential and is described by the following equation

$$P_v - P_{ic} = e^{Kv(Vv - Vv0)} + P_{vi} \tag{4}$$

where V_{v0}, and Kv are constants. Compliance of the venous compartment is defined by the equation

$$C_a = dV_a / d(P_a - P_{ic}) = 1/K_a(P_a - P_{ic} - P_{vi}) \tag{5}$$

where C_v is the venous compartment, K_v denotes the venous elastance coefficient and pressure in the venous compartment, and intracranial tissue are described by P_v, P_{ic}. Parameter P_{vi} represents the transmural pressure value at which the large cerebral vessels collapse and therefore, venous compliance would become infinite.

An exponential pressure-volume relationship is also assumed for the cerebral tissue compartment. The cerebral tissue compliance is equal to the negative of the change in volume of the tissue compartment divided by the change in pressure which is inversely proportional to the product of intracranial pressure and the elastance coefficient, that is

$$C_{ic}=-(dV_{ic}-dP_{ic}) =1 / K_e [P_{ic}+(P_{ic}/ P_{01})]^2 \quad (6)$$

Rearranging, the compliance of cerebral tissue is described by

$$C_{ic}= 1 / [K_e * (P_{ic} + (P_{ic} / P_{ic})^2)] \quad (7)$$

where K denotes elastance coefficient of cerebral tissue, P_{01} is a constant and P_{iv} represents intracranial pressure. The equations indicate that at low intracranial pressure the cerebral tissue compliance is linear because the quadratic term becomes negligible. Conversely, when intracranial pressure rises the quadratic term becomes significant and cerebral tissue compliance decreases, *i.e.*, the compartment becomes more rigid.

The differential equations describing intracranial dynamics are written by imposing a mass balance on each compartment. The general equation for describing intracranial dynamics follows:

$$\Sigma_m \; C_{mn}(P_m , P_n) \, dP_n/dt \; + \Sigma_m (P_m - P_m) / R_{mn} = 0 \quad (8)$$

where $C_{m,n}(P_m, P_n)$ is the pressure dependent compliance of the nth compartment. The equation states that the flux into the n-th compartment is equal to the flux out of the n-th compartment. Accumulation within the n-th compartment is assumed to be zero.

The intracranial volume is a function of arterial and venous blood volume, cerebrospinal fluid volume, and cerebral volume. Since the model is a constant volume, the constancy of the total intracranial volume, in keeping with the Monro-Kelly principle, is expressed by the following equation:

$$\Sigma_n \, dV/dt + Q_n = 0 \qquad (9)$$

Where Q denotes the rate at which the CSF compartment can expand. This equation may be used to simulate the injection of fluid into the CSF space as well as pathologic conditions [11].

Cerebral autoregulation is represented by a table function of arterial-arteriolar conductances versus transmural pressures across the arterial wall. The autoregulatory curve generated from the data set correlates well with experimentally observed changes in autoregulatory resistance. During the computational simulation the program selects a conductance corresponding to the transmural pressure at the given time. Inhibition of the autoregulation response is simulated by setting arterial-arteriolar conductance to a fixed value of $(100 \text{ mm Hg})^{-1}$.

2.3 Overview of Pharmacodynamic Models

The effect of three antihypertensive agents (sodium nitroprusside, nitroglycerin, and esmolol) on cerebral circulation is simulated by a variable-arteriolar-capillary resistance relationship, a venous resistance relationship, and a drug concentration mean arterial pressure relationship. These three agents are known to have a rapid onset, a short half-life and are normally therapeutically administered using a continuous infusion rate. Sodium nitroprusside and nitroglycerin are vasodilators which means that mean arterial pressure is reduced by dilatation of peripheral vessels, including cerebral vascular vessels. Esmolol is a beta-adrenergic blocker. Beta-adrenergic blockers reduce systemic pressure primarily by reducing cardiac output.

Sodium nitroprusside is predominantly an arterial dilator that directly dilates the cerebral arteriolar-capillary bed [14]. The effect of sodium nitroprusside was simulated by a mean arterial pressure dependent arteriolar-capillary resistance relationship. This resistance is the predominant site of sodium nitroprusside action in the brain. In the model, the resistance of the arteriolar-capillary compartment is a function of a constant, $G_{ar\text{-}c}$. This resistance, $G_{ar\text{-}c}$, is not controlled by autoregulation, but rather $G_{ar\text{-}c}$ responds to secondary effects such as carbon dioxide concentration, metabolic changes and drug administration.

The model was used to determine $G_{ar\text{-}c}$ values by inputting a constant mean arterial pressure and varying $G_{ar\text{-}c}$ until the simulated change in intracranial pressure correlated with experimental data [14-19]. The percent change in mean arterial pressure, intracranial pressure, cerebral blood flow, and $G_{ar\text{-}c}$ values were recorded.

The calculated conductance values were regressed using the exponential equation:

$$G_{ar\text{-}c}(cm^3 sec^{-1} mmHg^{-1}) = 0.37*\exp(-x/0.173) \qquad (10)$$

where x is the percent change in mean arterial pressure induced by the administration of sodium nitroprusside. During model simulation, percent change in mean arterial pressure, variable x, is input into the pharmacodynamic model and the corresponding conductance value is determined. . Figure 1 shows the sodium nitroprusside sub-model interfacing with the intracranial hemodynamic model.

Nitroglycerin is predominantly a venodilator that directly dilates the cerebral venous bed [25]. The effect of nitroglycerin was simulated by a mean arterial pressure dependent venous vascular resistance relationship. This resistance is the only site of nitroglycerin action in the brain.

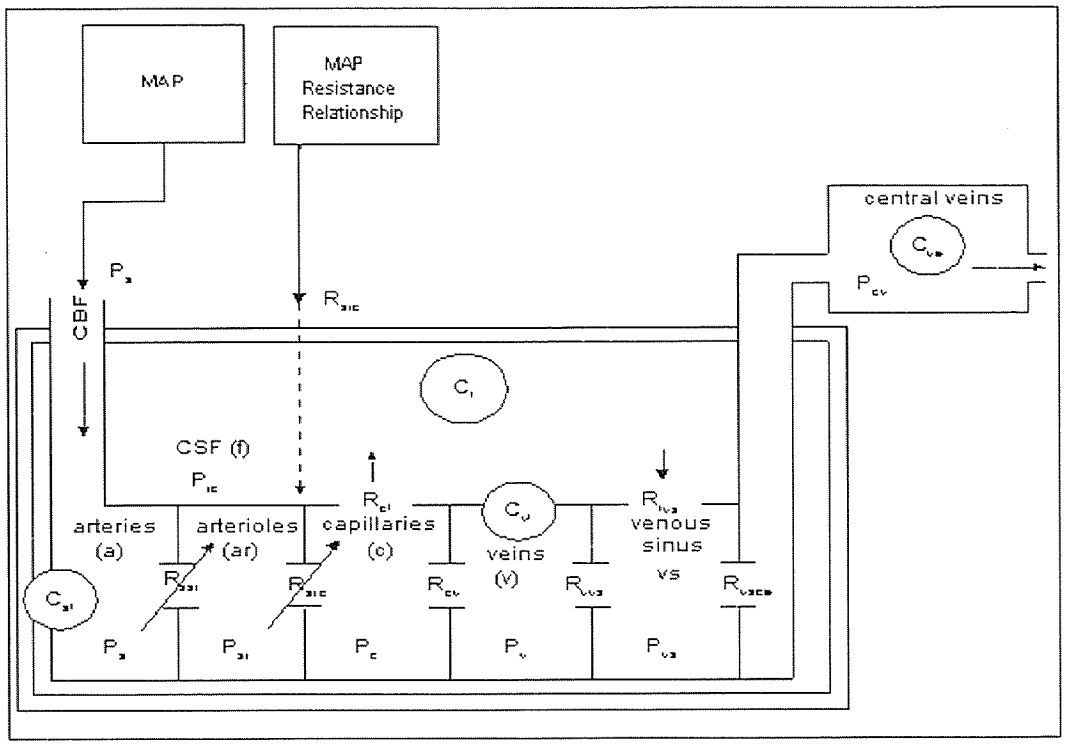

Figure 1 Overall structure of the model, the affected site P_a, P_{ar} = arterial and arteriolar pressures; P_c, P_v = capillary and cerebral venous pressures; P_{vs} = venous sinus pressure; P_{cv} = central venous pressure; C_{af}, C_{vf} = cerebral arterial and venous compliances; C_f = brain tissue compliance; C_{ve} = extracranial venous compliance; R_{aar} = variable arterial-arteriolar resistance (transmural pressure-dependent); R_{arc} = arteriolar-capillary resistance (thiopental concentration dependent); R_{ev}, R_{vvs} = capillary-venous system-venous sinuses resistance; R_{ef}, R_{fvs} = resistance to cerebrospinal fluid formation and cerebrospinal fluid outflow; R_{vsce} = resistance to the extracranial venous outflow.

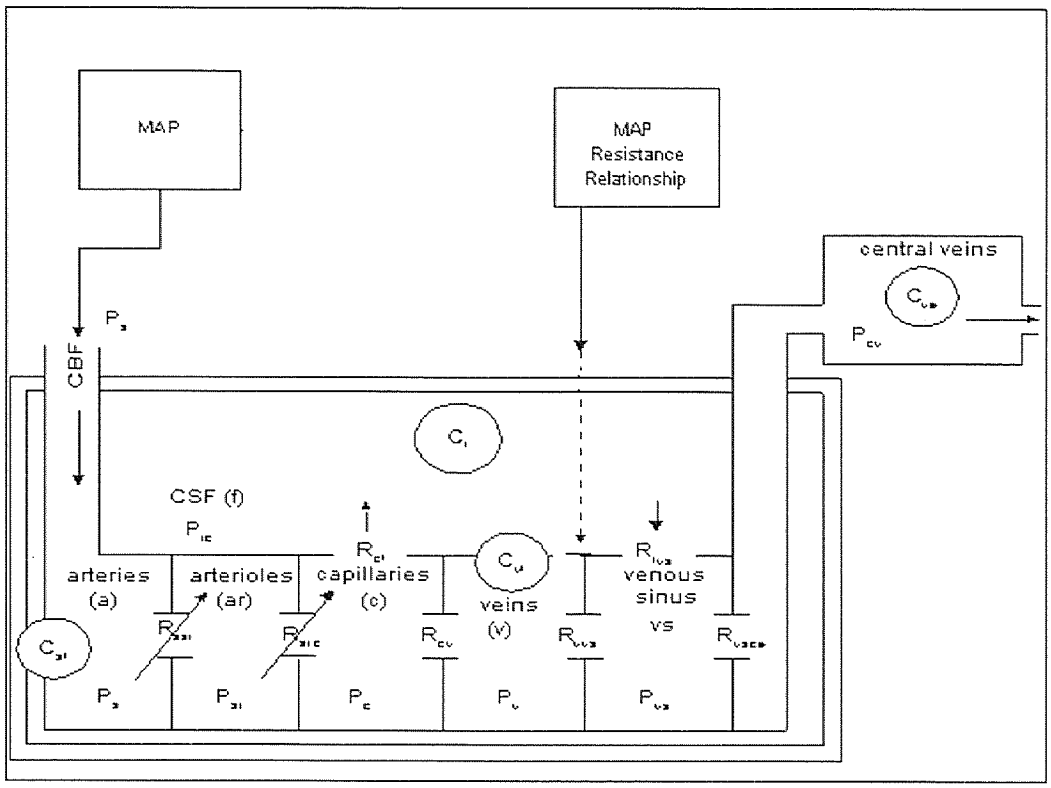

Figure 2: Overall structure of the model. P_a, P_{ar} = arterial and arteriolar pressures; P_c, P_v = capillary and cerebral venous pressures; the affected site P_{vs} = venous sinus pressure; P_{cv} = central venous pressure; C_{af}, C_{vf} = cerebral arterial and venous compliances; C_f = brain tissue compliance; C_{ve} = extracranial venous compliance; R_{aar} = variable arterial-arteriolar resistance (transmural pressure-dependent); R_{arc} = arteriolar-capillary resistance (thiopental concentration dependent); R_{ev}, R_{vvs} = capillary-venous system-venous sinuses resistance; R_{ef}, R_{fvs} = resistance to cerebrospinal fluid formation and cerebrospinal fluid outflow; R_{vsce} = resistance to the extracranial venous outflow.

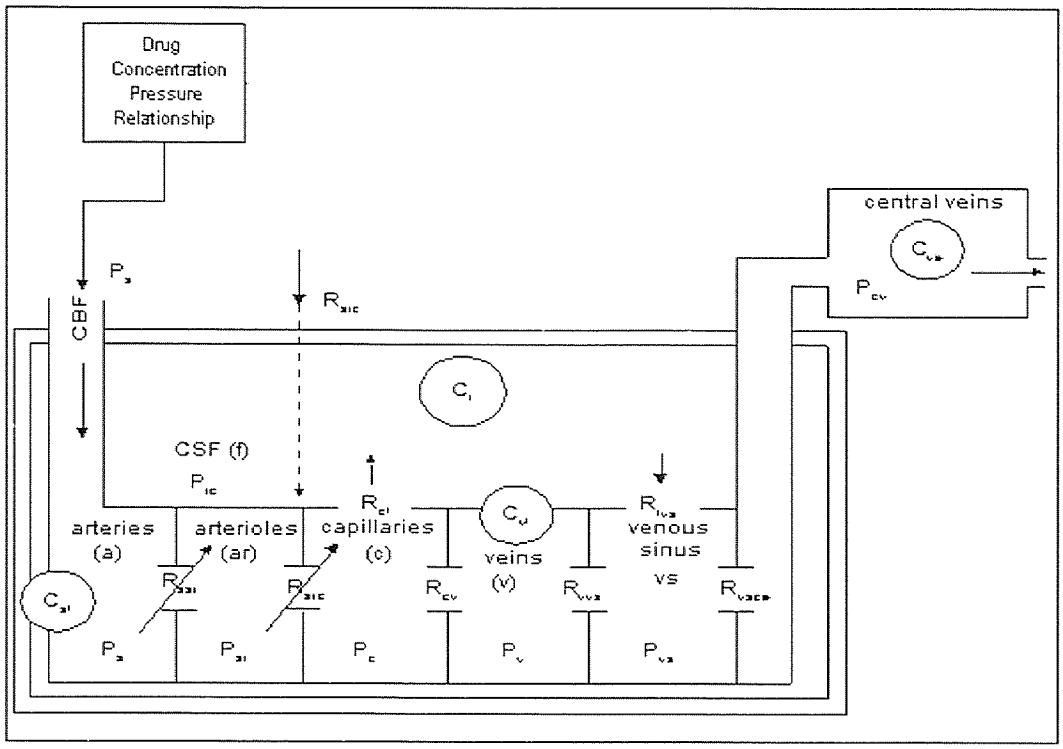

Figure 3: Overall structure of the model of Esmolol. P_a, P_{ar} = arterial and arteriolar pressures; P_c, P_v = capillary and cerebral venous pressures; P_{vs} = venous sinus pressure; P_{cv} = central venous pressure; C_{af}, C_{vf} = cerebral arterial and venous compliances; C_f = brain tissue compliance; 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_{ef}, R_{fvs} = resistance to cerebrospinal fluid formation and cerebrospinal fluid outflow; R_{vsce} = resistance to the extracranial venous outflow.

In the model, the resistance of the venous compartment is determined by the resistance constant, G_{ce}. This resistance, G_{ce}, is not controlled by autoregulation, but rather G_{ce} responds to secondary effects such as carbon dioxide concentration, metabolic changes and drug administration. The model was used to determine G_{ce} values by inputting a constant mean arterial pressure and varying G_{ce} until the simulated change in intracranial pressure correlated with the published experimental ICP [20-25]. The percent change in mean arterial pressure, intracranial pressure, cerebral blood flow, and $G_{ar\text{-}c}$ values were recorded.

The calculated conductance values were regressed using an exponential equation:

$$G_{ce}(cm^3 sec^{-1} mmHg^{-1}) = 6.25*\exp(-x/0.133) \qquad (11)$$

where x is a percent change in mean arterial pressure induced by the administration of nitroglycerin. During model simulation, percent change in mean arterial pressure, variable x, is input into the pharmacodynamic model and the corresponding conductance value is determined. Figure 2 shows the nitroglycerin pharmacodynamic sub-model interfacing with the intracranial hemodynamic model.

Esmolol directly affects systemic pressure by changing cardiac output and without effecting cerebral vessels [25-29]. The effect of esmolol on cerebrovascular circulation was simulated by a drug concentration dependent change in mean arterial pressure. Experimental data (drug concentration and mean arterial pressure) from several investigations studying the cardiovascular effects of esmolol were regressed to develop a relationship between esmolol drug concentration and mean arterial pressure [25-29]. The equation is presented below.

$$MAP(\%change)=100.0*\exp(-x/9.167) \qquad (12)$$

During model simulation, drug concentration, variable x, is input into the pharmacodynamic model and the percent change in mean arterial pressure is simulated.

2.4 Operation of the Computer Model

The simulation program was written in VisSim®, a simulation programming language for an IBM compatible PC. VisSim® is a Windows-based modeling program designed for programming simulations of complex dynamic systems, such as the cerebrovascular hemodynamic model described herein. In VisSim®, models are constructed in the form of block diagrams from function blocks and connecting wires. Each interconnected block represents and describes a portion of the system, *e.g.*, linear and nonlinear equations. Fourth-order Runge-Kutta integration blocks with a time interval of 50 msec were chosen for a solution of the model equations. A 50 msec time interval was chosen to provide optimal performance and precision. A larger time interval would decrease simulation time but reduce system precision, while smaller time intervals significantly increase simulation time without increasing system precision. A 32-bit PC microcomputer was used to realize real-time simulation. The Vissim® code is provided in Appendix B.

CHAPTER 3

RESULTS

The computer model developed was used to calculate intracranial pressure (ICP) and cerebral blow flow (CBF) changes that occur with deliberate induced hypotension. Simulation results include computation of ICP and CBF as a function of mean arterial pressure (MAP) with autoregulation intact and autoregulation impaired. In addition, cerebrovascular response was predicted for simulated patients with normal blood pressure (100 mm Hg) and increased blood pressure (150 mm Hg). The computed predictions were evaluated and the preferable intra-operative hypotensive agent was proposed.

3.1 Clinical Applications

The anti-hypertensive agents evaluated and discussed herein are known to have a rapid on-set and are typically administered using a constant infusion. Although these agents may be administered intraoperatively as a bolus to cause an immediate, rapid decrease in mean arterial pressure, for the purposes of this project cerebrovascular response is simulated assuming a constant infusion rate. For simulated response to sodium nitroprusside and nitroglycerin, the percent change in mean arterial pressure is varied. For esmolol, drug concentration is varied inducing a corresponding percent change in mean arterial pressure. The model predicted changes intracranial pressure and cerebral blood flow are recorded for each agent.

The computer simulation data are plots of changes in intracranial pressure and cerebral blood flow versus the percent change in mean arterial pressure. The plots can be

used to predict intracranial pressure and cerebral blood changes at a corresponding change in mean arterial pressure for each agent.

Standard clinical practice is to vary the infusion rate and/or drug concentration until the desire reduction in mean arterial blood pressure is achieved. The patient status is monitored for untoward changes and agent administration is adjusted accordingly. Thus, we have chosen the data plot technique described above to provide clinically relevant and useful simulated data.

3.2 Vasodilators: Sodium Nitroprusside

ICP and CBF changes during induced hypotension were computed for initial ICP values of 10, 30, and 50 mm Hg and mean arterial pressure of 150 mm Hg, simulating a hypertensive state, and 100 mm Hg, simulating a normal blood pressure. Induced hypotension was simulated as a percent reduction in mean arterial pressure from a ten percent (10%) reduction in mean arterial pressure to a forty percent (40%) reduction in mean arterial pressure.

Figure 4 simulated data plot shows that intracranial pressure increases during induced hypotension until a maximum pressure is reached, further reduction in mean arterial pressure reduces intracranial pressure. For an initial intracranial pressure of 10 mm Hg, intracranial pressure increases approximately (80%) of baseline at a (35%) reduction in mean arterial pressure. At higher initial intracranial pressures, 30 mm Hg and 50 mm Hg, the percent change in intracranial pressure is less, approximately thirty percent (30 %) and (10 %) respectively, than the percent ICP change observed at an initial ICP of 10 mmHg. Similarly, Figure 5 simulated data plot shows that a simulated hypertensive

patient with increased intracranial pressure will experienced marked increase in intracranial pressure. A simulated patient with an initial intracranial pressure of 30 mm Hg will experience approximately one hundred percent (100%) increase in ICP from baseline at a thirty percent (30%) reduction in mean arterial pressure. In addition, a simulated patient with an initial intracranial pressure of 50 mmHg will experience a sixty percent (60%) increase in intracranial pressure at a twenty percent (20 %) reduction in mean arterial pressure. Conversely, a hypertensive simulated patient with normal intracranial pressure (ICP = 10 mmHg) will experience only a fifty percent (50%) increasse at a forty percent (40%) reduction in mean arterial pressure.

Summarizing, the simulated results in figures 4 and 5 show that in simulated patients with autoregulation intact the administration of sodium nitroprusside, a vasodilator, induces hypotensive state and increases intracranial pressure. Direct dilation of the cerebral arterial vascular bed increase the cerebral blood volume therein with concomitant increased in ICP. This is consistent with observations of Cottrell, *et al*, who reported marked increases (200% of baseline) in intracranial pressure during the administration of sodium nitroprusside [19].

In addition, figures 4 and 5 show that at higher initial intracranial pressure the onset of increased intracranial pressure occurs with approximately five percent (5%) reduction in mean arterial pressure. Intracranial pressure maximum is achieved at approximately fifteen percent (15%) reduction in mean arterial pressure. Further reduction in mean arterial pressure reduces ICP and the most pronounced change in intracranial pressure occurs at an initial intracranial pressure of 30 mm Hg. At normal intracranial pressure (ICP=10 mm), intracranial pressure maximum is reached at a thirty percent (30%)

reduction in mean arterial pressure. The shape of the curve infers a linear relationship between percent change in mean arterial pressure and ICP similar to the clinical results reported by Cottrell who reported a linear relationship between ICP and percent change in blood pressure in patients with space occupying lesions.

Figures 6 and 7 show predicted changes in intracranial pressure computed by the simulation model during administration of sodium nitroprusside in a patient without autoregulation. A comparison of the predicted responses in simulated patients with autoregulation intact and with autoregulation impaired show that the change in intracranial pressure is more pronounced in a patient with autoregulation intact. Further, a patient with autoregulation impaired and normal intracranial pressure (ICP=10 mm Hg) will not experience the marked increase in intracranial pressure observed in the patient with autoregulation intact.

The results show that in simulated patients with autoregulation intact, the autoregulatory response may increase CBF in response to a reduction in mean arterial pressure increasing cerebral blood volume within the now more compliant compartment. In addition, computed intracranial pressure changes for a patient with autoregulation impaired shows that intracranial pressure is not significantly affected by a reduction in mean arterial pressure.

A plot of cerebral blood pressure versus percent change mean arterial pressure, (figure 8), shows that sodium nitroprusside does not significantly affect cerebral blood flow. These results are consistent with the reported experimental data that indicate that CBF is preserved during administration of sodium nitroprusside [15-18].

Sodium Nitroprusside Administration in a Simulation Patient with Autoregulation Intact and MAP = 100 mm Hg

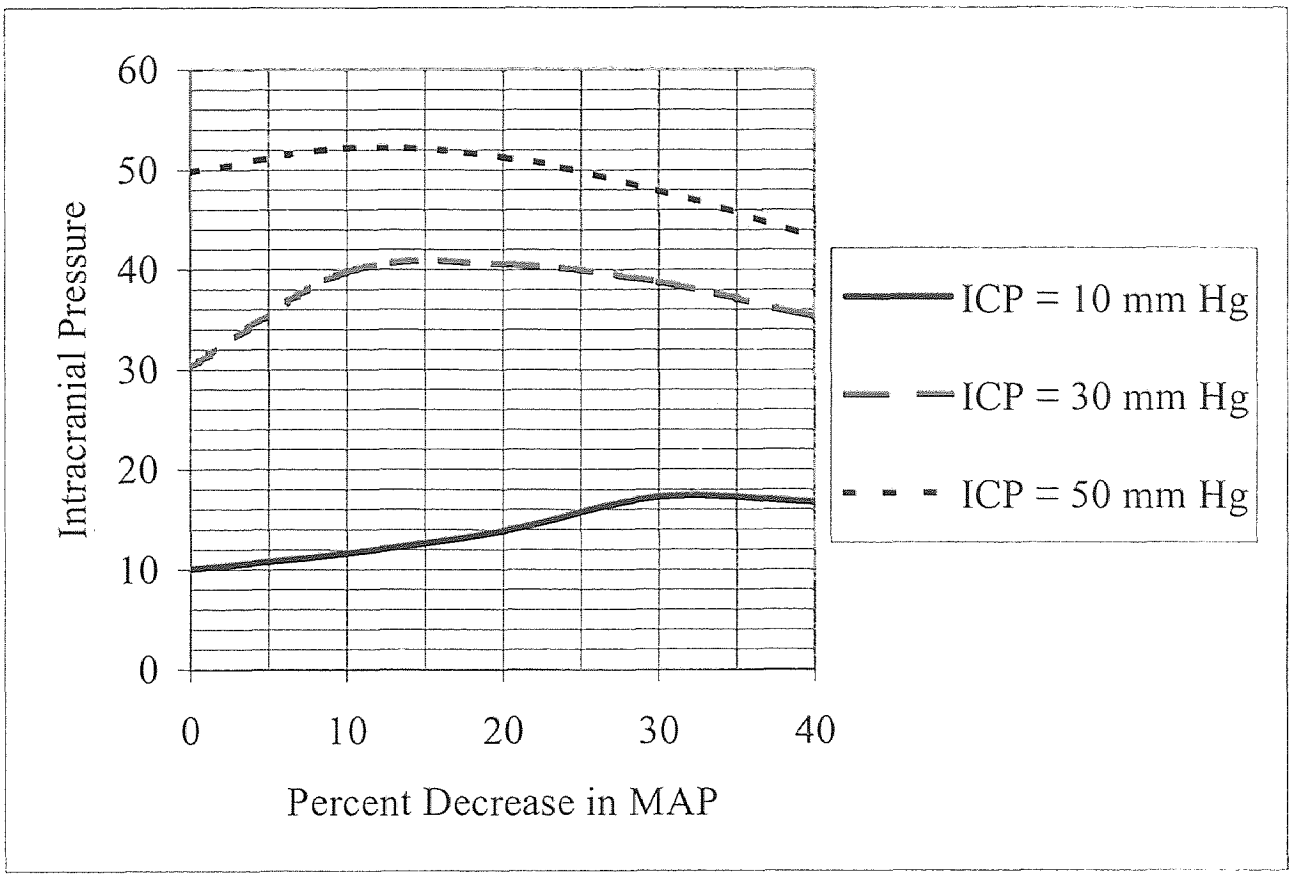

Figure 4: Effects of the administration of sodium nitroprusside on intracranial pressure in a simulated patient with autoregulatory system intact and an initial mean arterial pressure of 100 mm Hg.

Sodium Nitroprusside Administration in Simulated Patient with Autoregulation Intact and MAP = 150 mm Hg

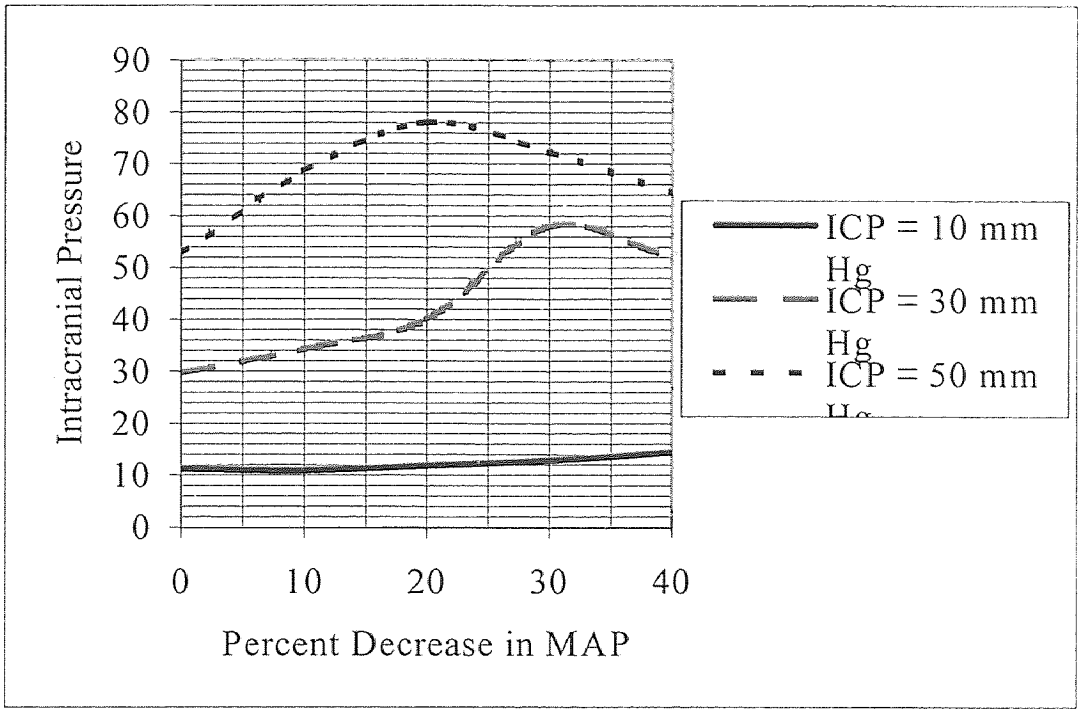

Figure 5: Effects of the administration of sodium nitroprusside on intracranial pressure in a simulated patient with autoregulatory system intact and an initial mean arterial pressure of 150 mm Hg.

Sodium Nitroprusside Administration in Simulated Patients with Autoregulation Impaired and MAP = 100 mm Hg

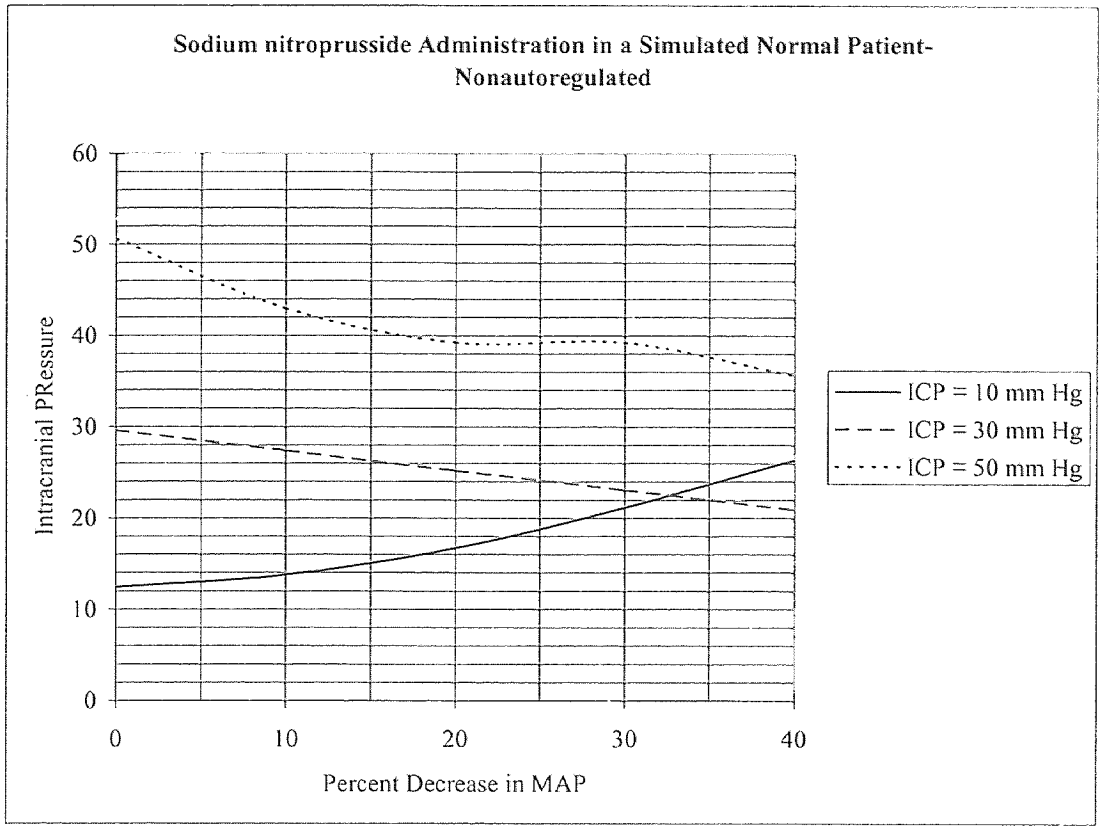

Figure 6: Effects of the administration of sodium nitroprusside on intracranial pressure in a simulated patient with autoregulatory system impaired and an initial mean arterial pressure of 100 mm Hg.

Sodium Nitropruside Administration in Simulated Patients with Autoregulation Impaired and MAP = 150 mm Hg

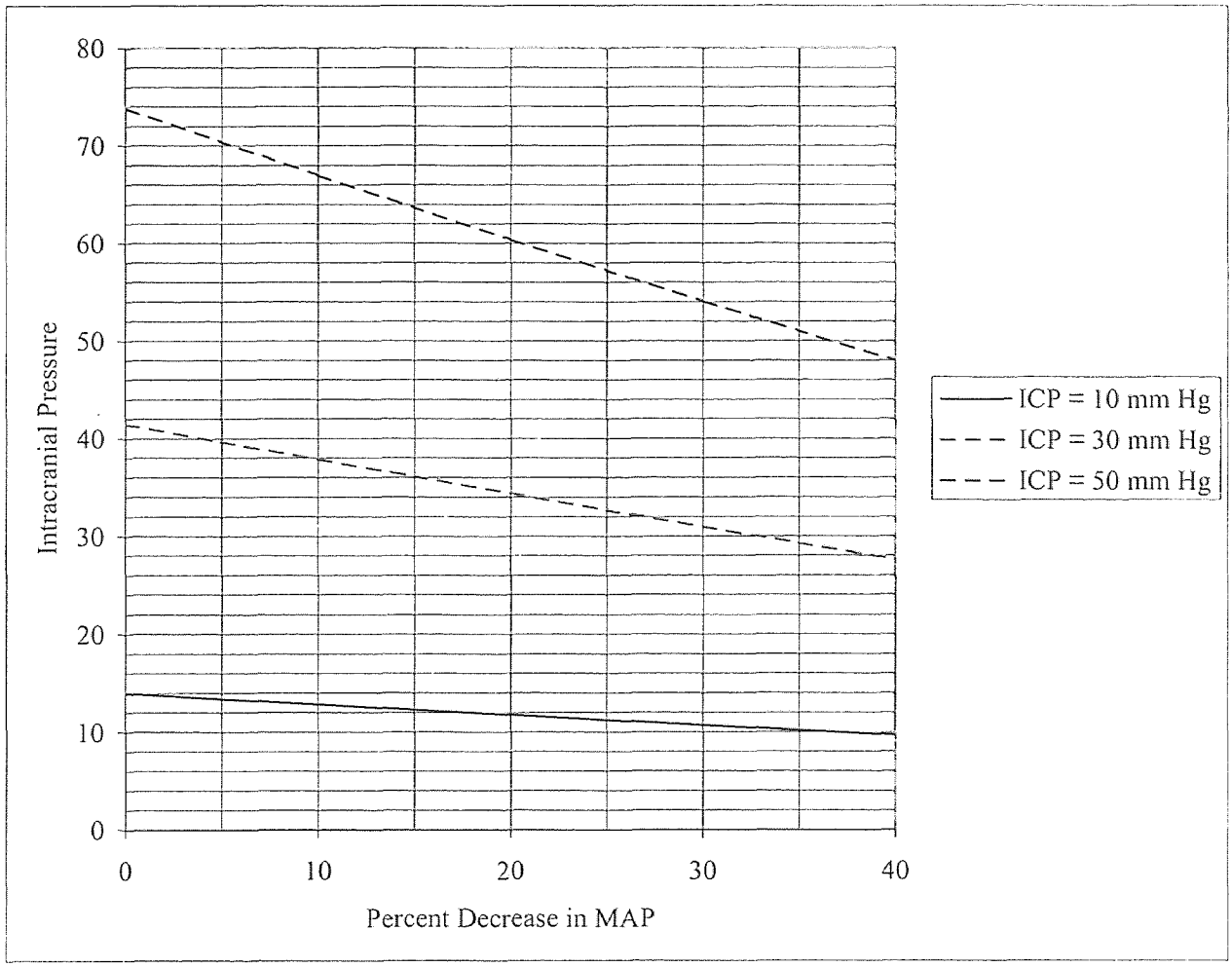

Figure 7: Effects of the administration of sodium nitroprusside on intracranial pressure in a simulated patient with autoregulatory system impaired and an initial mean arterial pressure of 150 mm Hg.

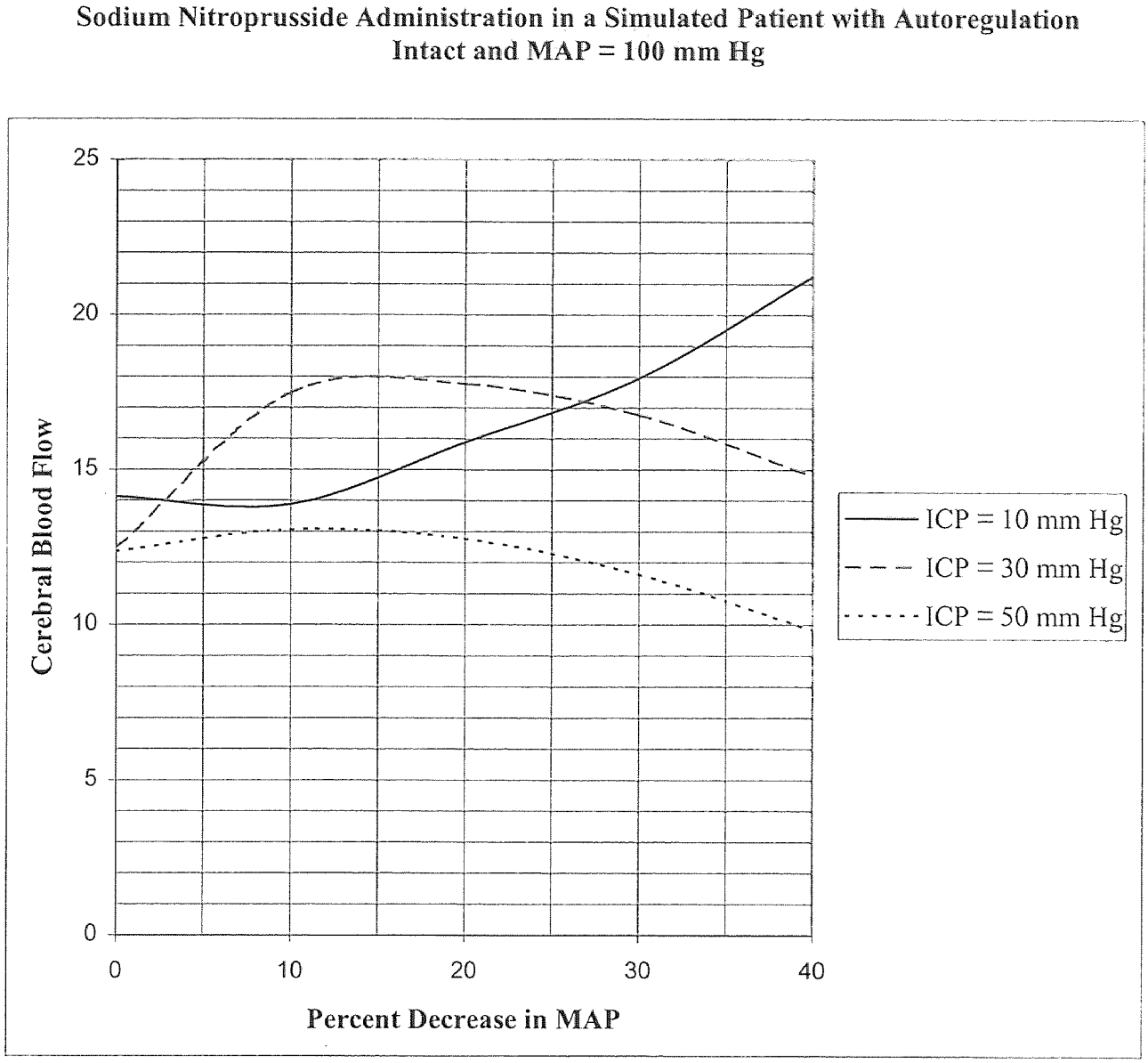

Figure 8: Effects of the administration of sodium nitroprusside on cerebral blood flow in a simulated patient with autoregulatory system intact and an initial mean arterial pressure of 100 mm Hg.

3.3 Vasodilators: Nitroglycerin

The effect of nitroglycerin, a venodilator, was simulated under the same conditions as the sodium nitroprusside model. ICP and CBF changes during induced hypotension were computed for initial ICP values of 10, 30, and 50 mm Hg and mean arterial pressure of 150 mm Hg, simulating hypertension, and 100 mm Hg, simulating normal blood pressure. Induced hypotension was simulated as a percent reduction in mean arterial pressure from a ten percent (10%) reduction to forty percent (40%) reduction.

Figures 9 and 10 show that administration of nitroglycerin to a simulated patient with autoregulation intact with normal or elevated intracranial pressure results in a marked increase in intracranial pressure in a simulated patients with normal initial intracranial pressure (10 mm Hg) at an induced hypotension of twenty percent reduction of mean arterial pressure and greater. The model predicts that dilation of the intracranial venous capacitance vessels increases the cerebral blood volume concomitantly increasing intracranial pressure. This is consistent with *in-vivo* observations presented elsewhere [20-25]. Further, Lagerkranser demonstrated an exponential relationship between intracranial pressure and intracranial volume [22].

Conversely, figures 9 and 10 show that simulated patients with elevated initial intracranial pressure (ICP equal to 30 mmHg and 50 mmHg) will experience a reduction in intracranial pressure. The intracranial pressure of a simulated patient with normal mean arterial pressure and an initial intracranial pressure of 30 mmHg decreases by approximately ten percent (10 %) at a forty percent (40%) reduction in mean arterial pressure. Similarly, the intracranial pressure of a simulated patient with normal mean arterial pressure and an initial intracranial pressure of 50 mmHg decreases by

approximately forty percent (40%) at a forty percent (40%) reduction in mean arterial pressure, respectively.

Figures 11 and 12 demonstrate that in simulated patients with autoregulation impaired the most pronounced change occurs at a normal initial intracranial pressure of 10 mm Hg. Further, the computer model predicts that direct dilation of cerebral venous vascular bed and reduced mean arterial pressure in a simulated hypertensive patient and a normal patient at increased intracranial pressure (30 mmHg and 50 mmHg) reduces intracranial pressure. These results indicate that at high intracranial pressure and low cerebral blood flow a significant reduction in mean arterial pressure and venodilation slightly decreases intracranial volume.

The model predicts that cerebral blood flow is directly related to intracranial pressure and mean arterial pressure. Figure 13 shows that cerebral blood flow during the administration of nitroglycerin varies within five percent of baseline until a twenty percent (20%) reduction in mean arterial pressure is achieved. Cerebral blood flow will then decrease with increased reduction in mean arterial pressure and increased intracranial pressure. These results are consistent with animal studies conducted by Traystman to evaluate the effect nitroglycerin on cerebral blood flow and cerebral spinal fluid [25].

Nitroglycerin Administration in a Simulated Patient with Autoregulation Intact and MAP = 100 mm Hg

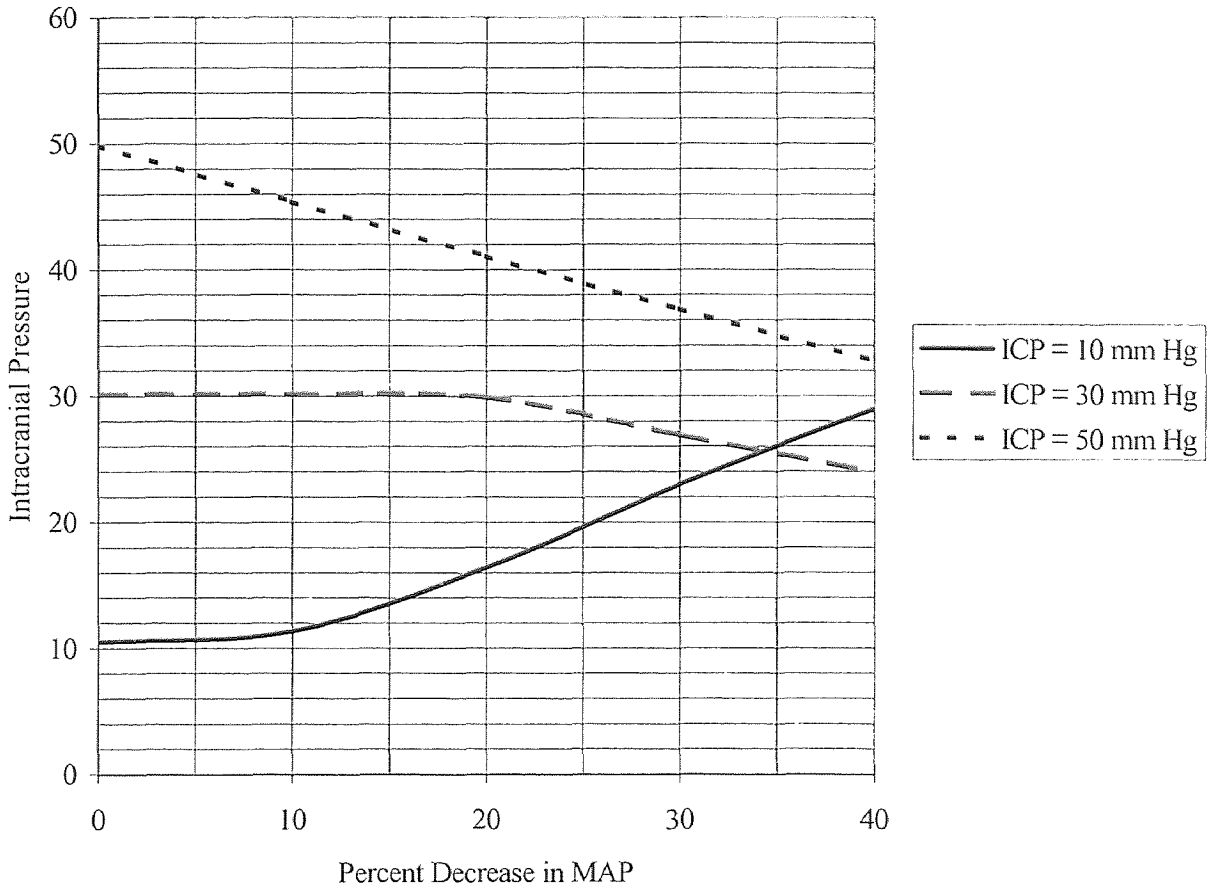

Figure 9: Effects of the administration of nitroglycerin on intracranial pressure in a simulated patient with autoregulatory system intact and an initial mean arterial pressure of 100 mm Hg.

Nitroglycerin Administration in a Simulated Patient with Autoregulation Intact and MAP = 150 mm Hg

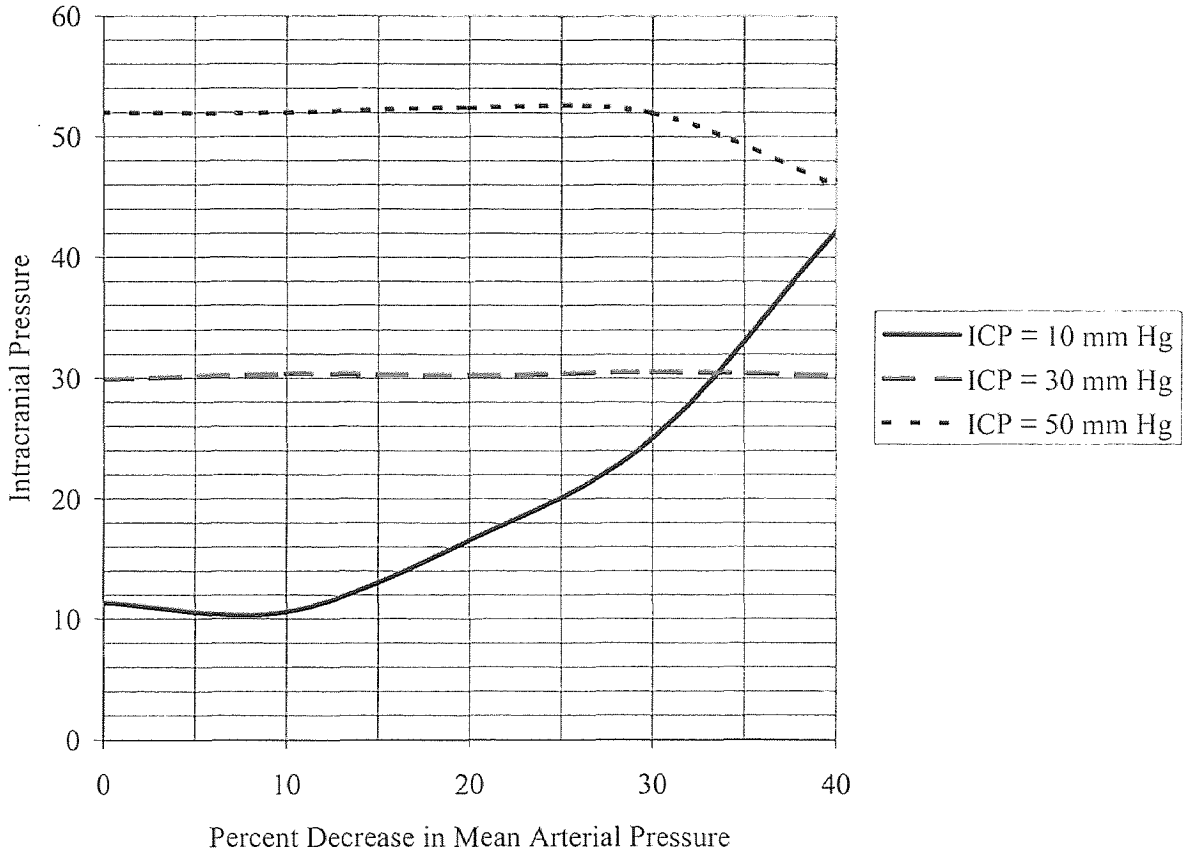

Figure 10: Effects of the administration of nitroglycerin on intracranial pressure in a simulated patient with autoregulatory system intact and an initial mean arterial pressure of 150 mm Hg.

Nitroglycerin Administration in a Simulated Patient with Autoregulation Impaired and MAP = 100 mm Hg

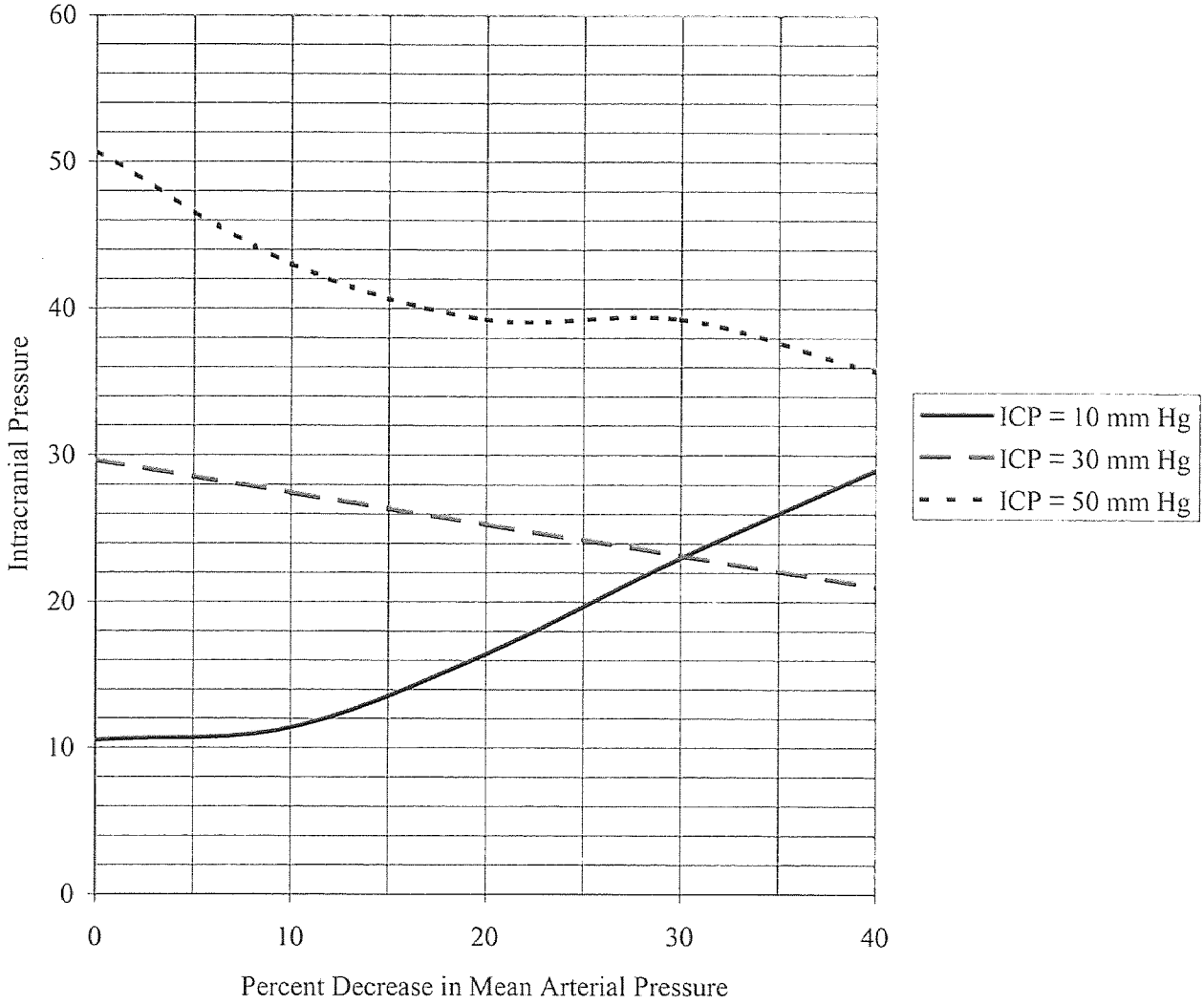

Figure 11: Effects of the administration of nitroglycerin on intracranial pressure in a simulated patient with autoregulatory system impaired and an initial mean arterial pressure of 100 mm Hg.

Nitroglycerin Administration in Simulated Patients with Autoregulation Impaired and MAP = 150

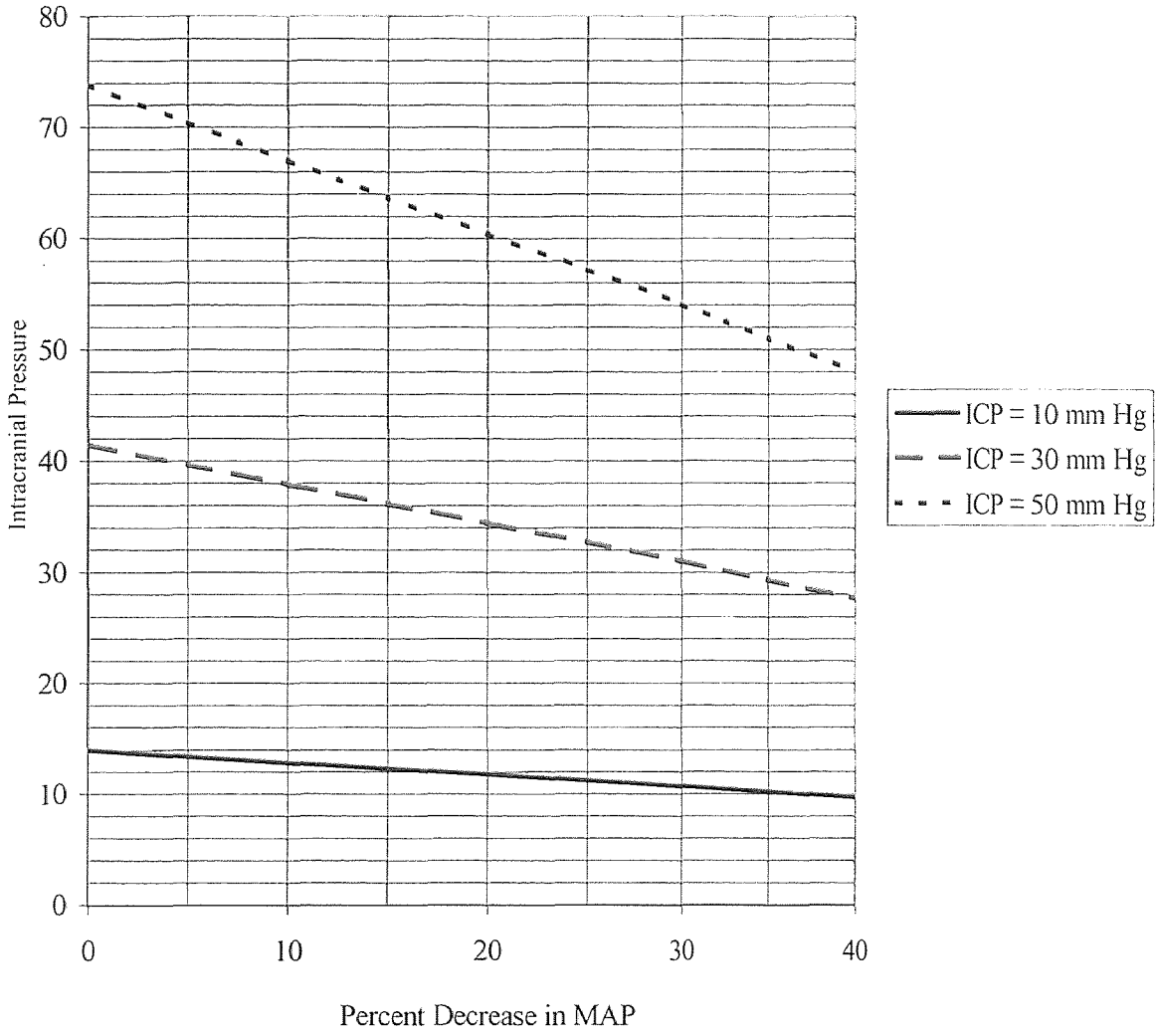

Figure 12: Effects of the administration of nitroglycerin on intracranial pressure in a simulated patient with autoregulatory system impaired and an initial mean arterial pressure of 150 mm Hg.

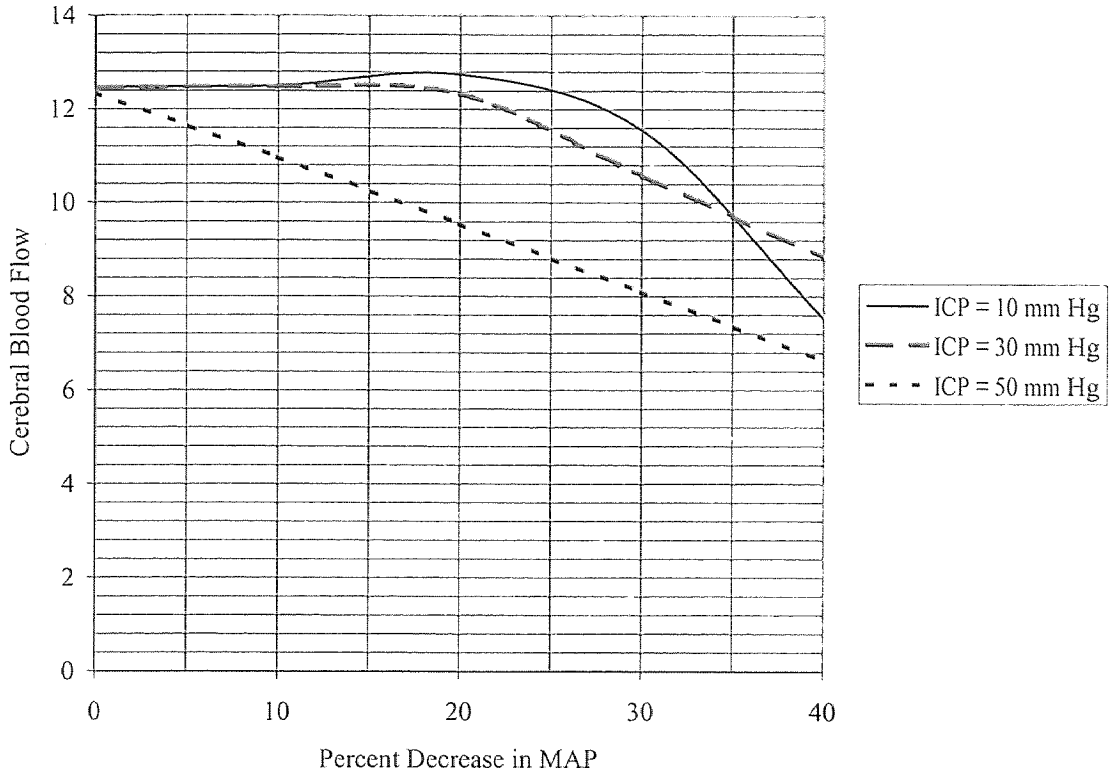

Figure 13: Effects of the administration of nitroglycerin on cerebral blood flow in a simulated patient with autoregulatory system intact and an initial mean arterial pressure of 100 mm Hg.

3.4 Beta-adrenergic Blockers: Esmolol

Similar to sodium nitroprusside and nitroglycerin, esmolol has a rapid onset, short half-life and is typically administered using a constant infusion rate. These hypotensive agents differ in that esmolol reduces mean arterial pressure by reducing cardiac output and does not dilate cerebral vessels whereas vasodilators such as sodium nitroprusside and nitroglycerin dilate cerebral vessels concurrent with dilatation of systemic vessels.

Assuming a constant infusion rate, ICP and CBF changes during induced hypotension were computed for initial ICP values of 10, 30, and 50 mm Hg and mean arterial pressure of 150 mm Hg, simulating hypertension, and 100 mm Hg, simulating normal blood pressure. Induced hypotension was simulated as a percent reduction in mean arterial pressure from a ten percent (10%) reduction to forty percent (40%) reduction.

Figures 14, and 15 show that administration of esmolol in simulation patients with autoregulation intact and initial intracranial pressure of 10 mm Hg does not significantly affect intracranial pressure. In a simulated normal patient with an initial intracranial pressure of 30 mmHg, intracranial pressure is preserved until a twenty percent reduction in mean arterial pressure is achieved; further reduction in mean arterial pressure reduces intracranial pressure. In a simulated hypertensive patient with initial intracranial pressure of 30 mmHg, intracranial pressure is preserved from ten percent to forty percent reductions in mean arterial pressure. These predicted results are consistent with clinically observed responses reported elsewhere [26-30]. In addition, Ornstein, *et.al.*, evaluated the effects of esmolol on intracranial pressure and mean arterial pressure during resection of intracranial arteriovenous malformation (AVM) and reported that esmolol rapidly

induces a twenty percent reduction in mean arterial pressure without causing large fluctuations in intracranial pressure [27].

Figure 18 shows that induced hypotension in simulated patients with elevated intracranial pressure reduces cerebral blood flow. Simulated patient with normal intracranial pressure will experience negligible changes in cerebral blood flow.

A comparison of computed response in simulated patients with autoregulation intact and autoregulation impaired demonstrates that both populations will experience similar changes in intracranial pressure and cerebral blood flow. Reference figures 16 and 17 for predicted cerebral vascular response in simulated patients with autoregulation impaired.

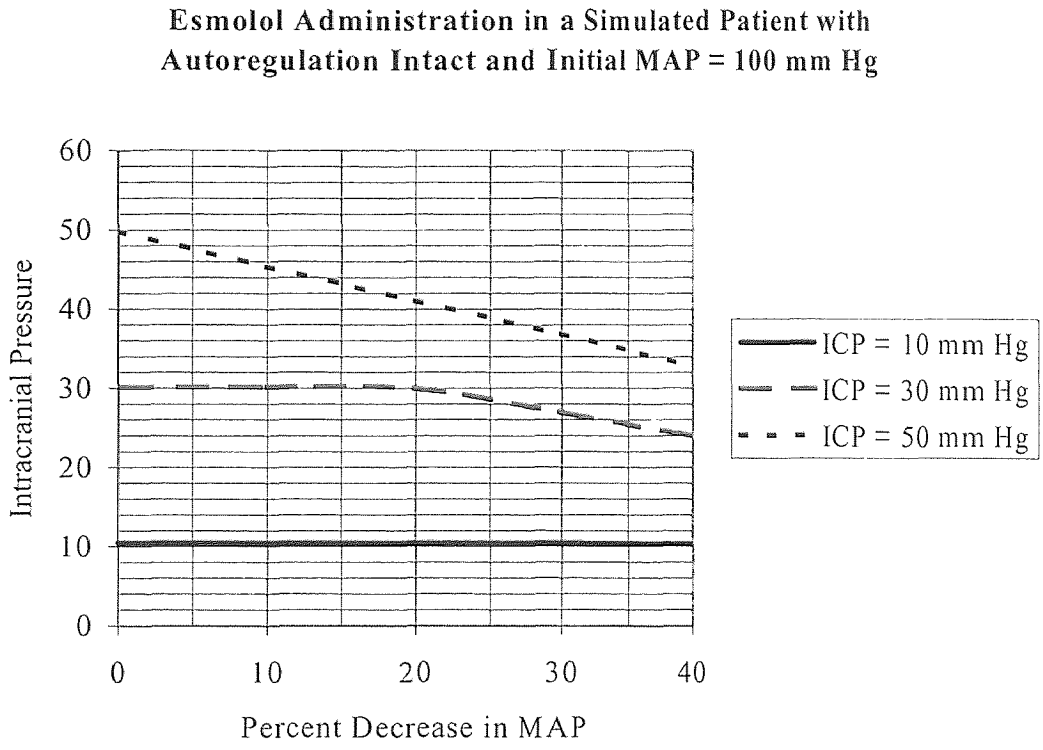

Figure 14: Effects of the administration of esmolol on intracranial pressure in a simulated patient with autoregulatory system intact and an initial mean arterial pressure of 100 mm Hg.

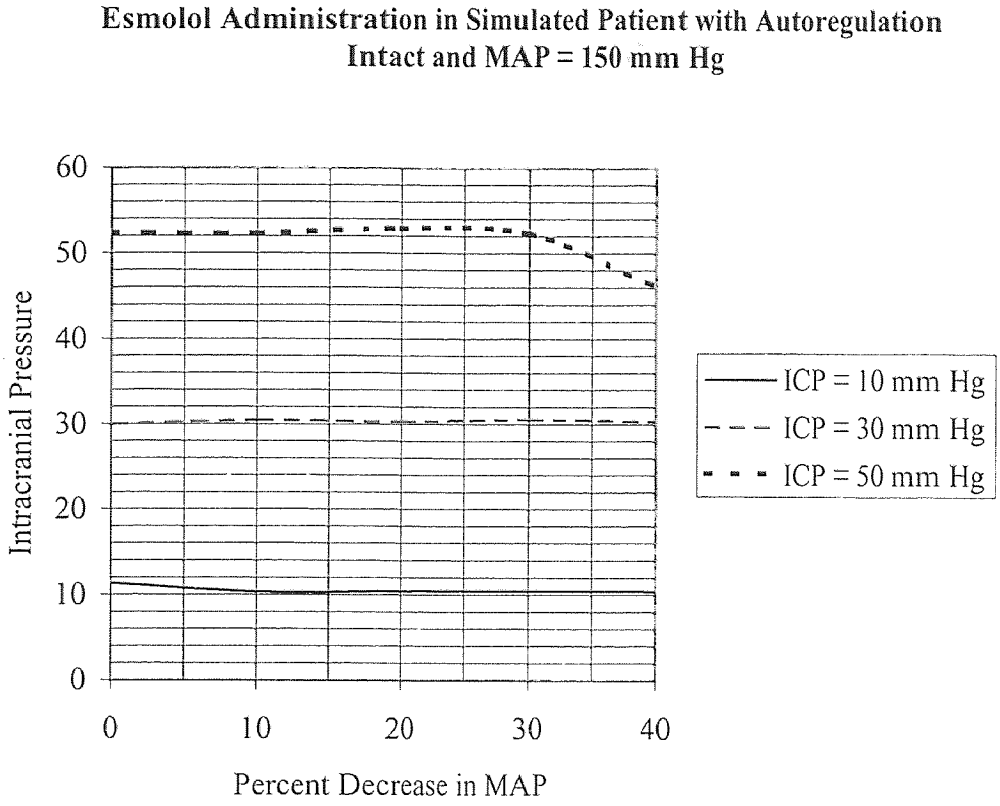

Figure 15: Effects of the administration of esmolol on intracranial pressure in a simulated patient with autoregulatory system intact and an initial mean arterial pressure of 150 mm Hg.

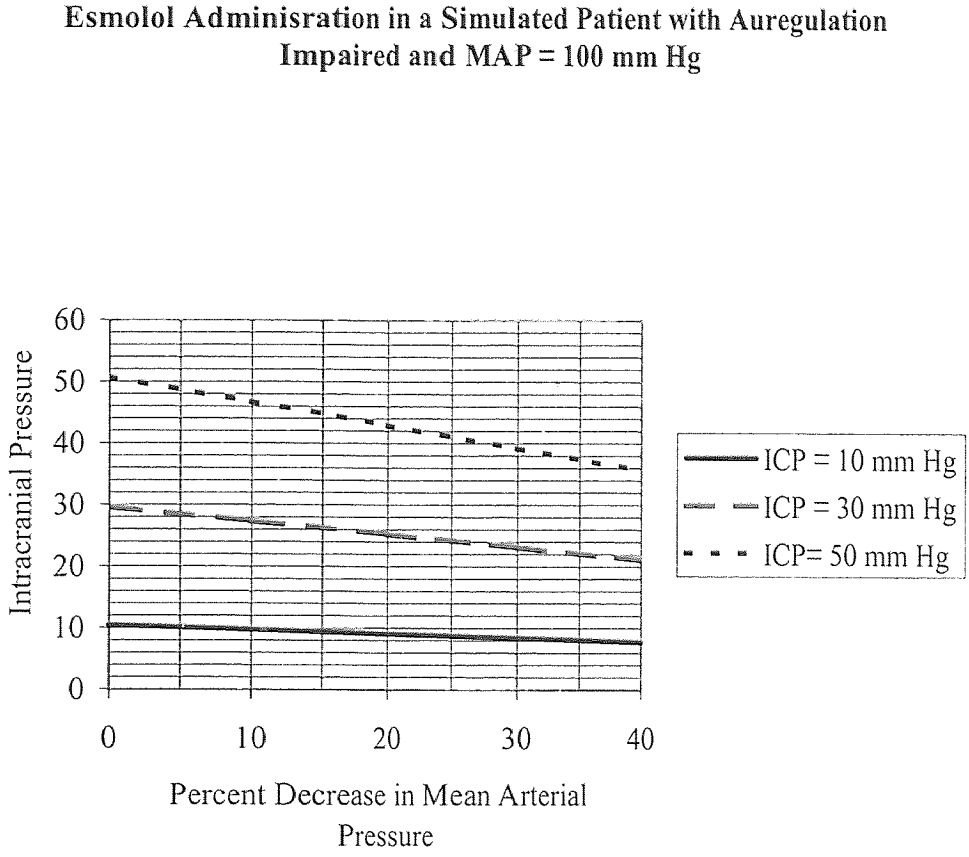

Figure 16: Effects of the administration of esmolol on intracranial pressure in a simulated patient with autoregulatory system impaired and an initial mean arterial pressure of 100 mm Hg.

Esmolol Administration in Simulated Patients with Autoregulation Impaired and MAP = 150 mm Hg

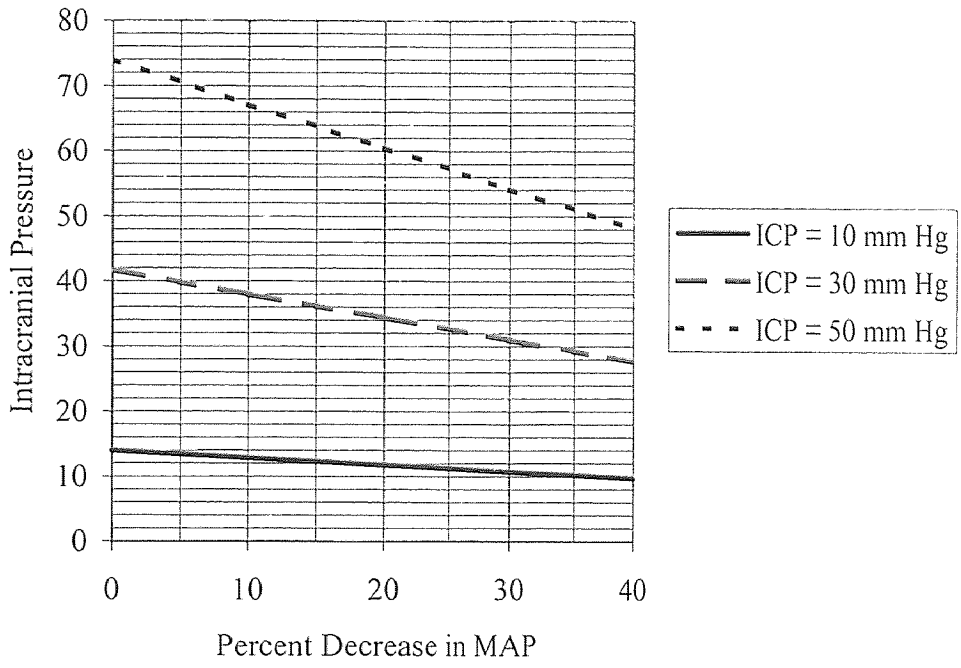

Figure 17: Effects of the administration of esmolol on intracranial pressure in a simulated patient with autoregulatory system impaired and an initial mean arterial pressure of 150 mm Hg.

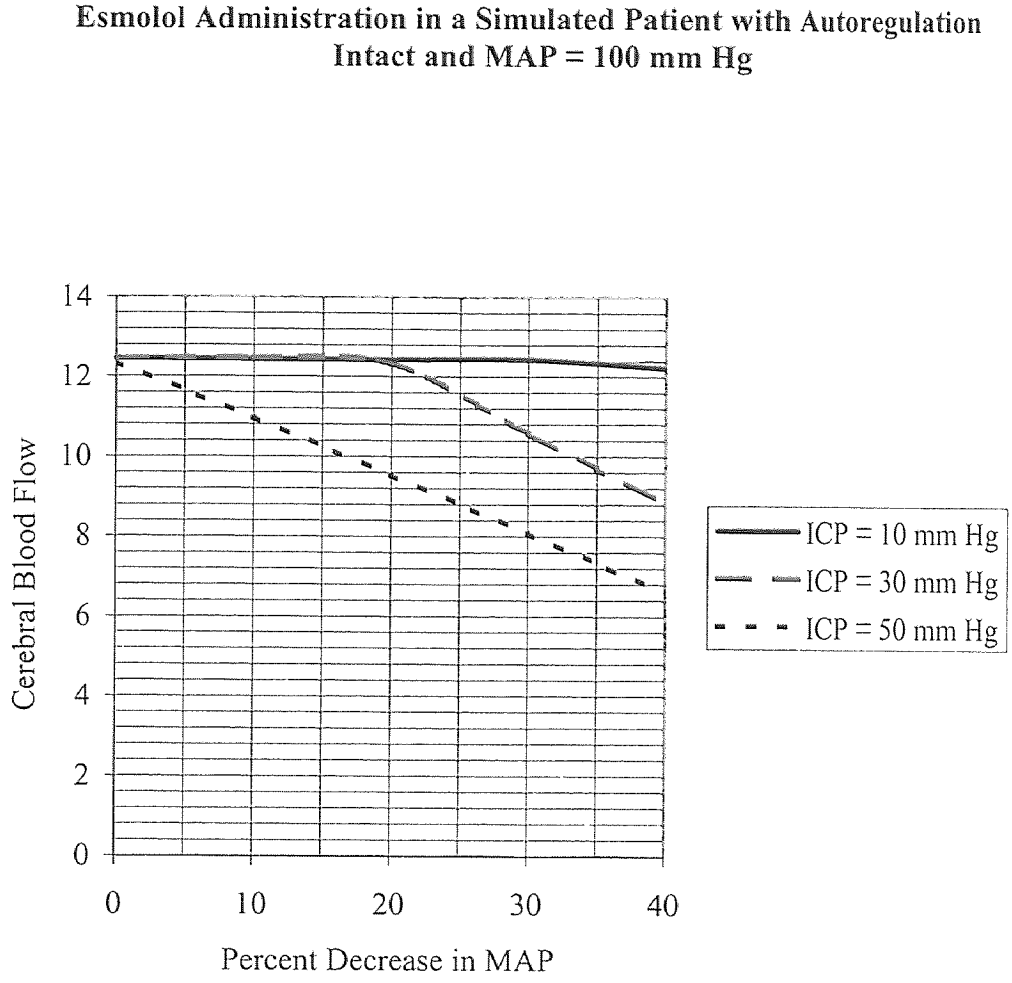

Figure 18: Effects of the administration of esmolol on cerebral blood flow in a simulated patient with autoregulatory system intact and an initial mean arterial pressure of 100 mm Hg.

CHAPTER 4

DISCUSSION

A variety of hypotensive techniques and anti-hypertensive agents are used to reduce neurosurgical blood loss and maintain a dry surgical field. Sodium nitroprusside is the most commonly used as a hypotensive agent in neurosurgery for the provision of deliberate hypotension. The prevalent use of the agent for this indication is in part attributed to its rapid onset and ease of administration. Sodium nitroprusside is a vasodilator that predominantly dilates arteriolar-capillary vessels. Further, clinical data in animal and human studies shows that administration of sodium nitroprusside decreases cerebral vascular resistance increasing cerebral blood volume concomitantly increasing intracranial pressure [15-20].

Another commonly used nitrovasodilator is nitroglycerin. Nitroglycerin has gained popularity over the past twenty years because of its similar characteristics to sodium nitroprusside. This agent has a rapid onset, easy to manage and reduces blood pressure by direct dilation of vascular vessels. In addition, nitroglycerin dilates the venous cerebral vascular bed increasing intracranial capacitance. Clinical data has shown that direct dilation of the venous vascular bed may concomitantly increase intracranial pressure in response to increased cerebral blood volume. This cerebrovascular result has been demonstrated in animal studies on dogs and baboons and in controlled clinical trials on human subjects [20-25].

Esmolol, a beta-adrenergic blocker, is an anti-hypertensive agent commonly used to induce hypotension in patients with intracranial arteriovenous malformations. Beta-

adrenergic blockers reduce mean arterial pressure by reducing cardiac output. Unlike vasodilators, these agents do not affect the capacitance of cerebral vessels.

Our computer simulations demonstrate that esmolol may be the preferable hypotensive agent. Esmolol does not significantly affect cerebral blood flow or intracranial pressure regardless of the initial simulated patient status. In both simulated patients with autoregulation intact and autoregulation impaired with normal and increased intracranial pressure, cerebral blood flow is preserved and no marked increase in intracranial pressure is observed. These results are consistent with reported cerebrovascular response in animal studies and controlled human studies [26-30]

Sodium nitroprusside causes marked increase in intracranial pressure in simulated patients with autoregulation intact. These effects may be attributed to two basic mechanisms: direct dilation of the cerebral arterial vessels and autoregulatory response to changes in mean arterial pressure. Direct dilation of cerebral arterial vessels increases the cerebral blood volume with concomitant increase in ICP. Further, a concurrent increase in cerebral blow flow was induced by the system simulated autoregulatory response to reduction in mean arterial pressure.

Computations of cerebrovascular response to the administration of sodium nitroprusside in simulated patients with autoregulation impaired demonstrate that intracranial pressure is maintained with increased reduction in mean arterial pressure. These effects may be attributed to changes in mean arterial pressure during impaired autoregulation and direct dilation of cerebral arterial vessels. Reduction of mean arterial pressure in a simulated patient with autoregulation impaired significantly decreases cerebral blood flow. These results indicate that the reduction in mean arterial pressure

and cerebral blood flow negate the effect arterial vessel dilation and increased capacitance of the compartment. Unlike the simulated patient with autoregulation intact that shows an increase in cerebral blood volume, the cerebral blood volume in the simulated patient with autoregulation impaired is maintained.

The computer model developed to determine cerebrovascular hemodynamic response to the administration of nitroglycerin demonstrated comparable results to sodium nitroprusside in simulated patients with autoregulation intact. Computation shows that the administration of nitroglycerin may cause marked increases in intracranial pressure while maintaining cerebral blood flow. These effects are attributed to two basic mechanisms: direct venodilation and reduction in systemic mean arterial pressure. Dilation of the intracranial venous capacitance vessels increases the cerebral blood volume concomitantly increasing intracranial pressure. In simulated patients with autoregulation impaired, computations show that intracranial pressure and cerebral blood flow decrease.

The computed results in simulated patients with autoregulation impaired during the administration of sodium nitroprusside may expose a limitation of the computer model. The presence of intracranial mass lesions inhibits the autoregulatory system, directly affecting cerebral vascular compliance and may block outflow [19, 20, 27]. The clinical data obtained in these patients indicate that at increased initial intracranial pressure direct dilation of cerebral arterial vessels and the presence of intracranial lesions cause a marked increase in intracranial pressure. Therefore, the computed data for sodium nitroprusside that shows a reduction in pressure would conflict with clinical observations in this population. Conversely, clinical data from patients with intracranial lesions that

are administered nitroglycerin show a reduction in mean arterial pressure and cerebral blood flow. These clinical observations are consistent with the computed results presented herein.

Figures 19, 20 and 21 are comparative plots of the computed cerebrovascular response to sodium nitroprusside, nitroglycerin and esmolol. Summarizing, the results of the simulated cerebrovascular response to these agents indicate that esmolol should be considered as the agent of choice during neurosurgery.

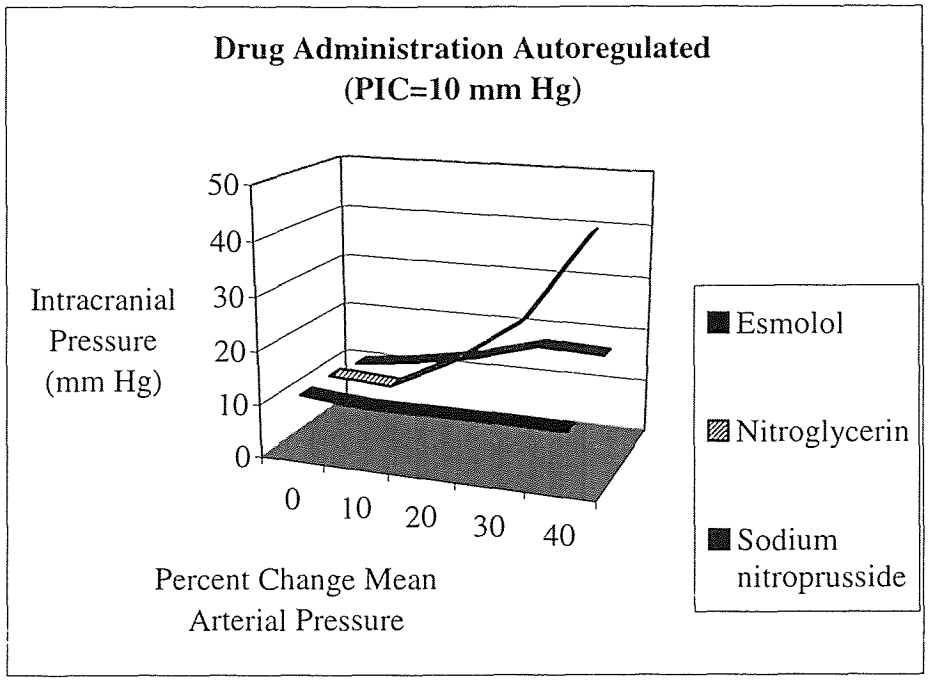

Figure 19: Effect of the administration of three antihypertensive agents on intracranial pressure in a simulated patient with autoregulatory system intact and an initial mean arterial pressure of 100 mm Hg.

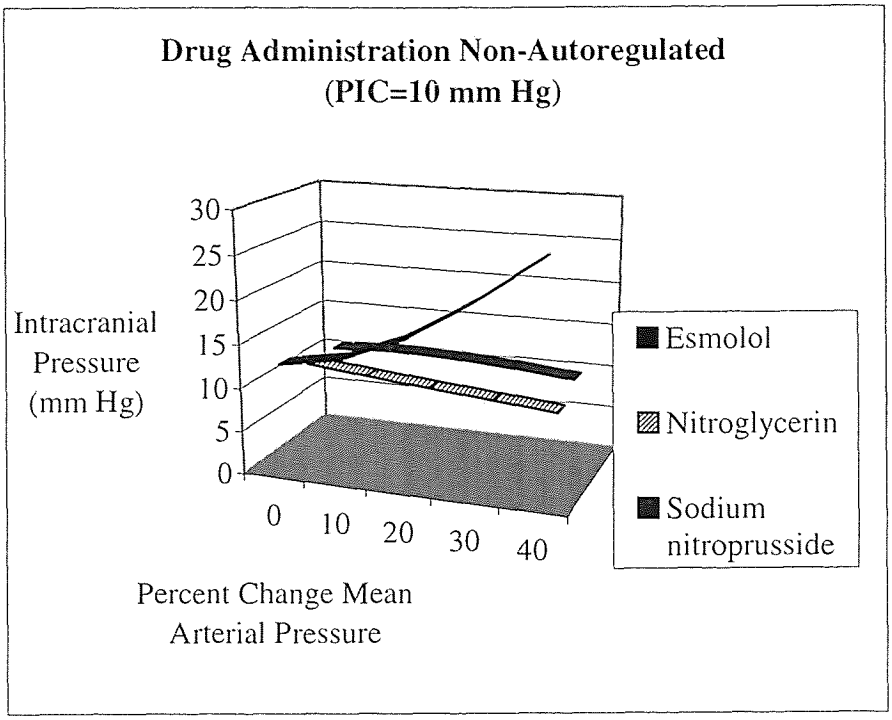

Figure 20: Effect of the administration of three antihypertensive agents on intracranial pressure in a simulated patient with autoregulatory system impaired and an initial mean arterial pressure of 100 mm Hg

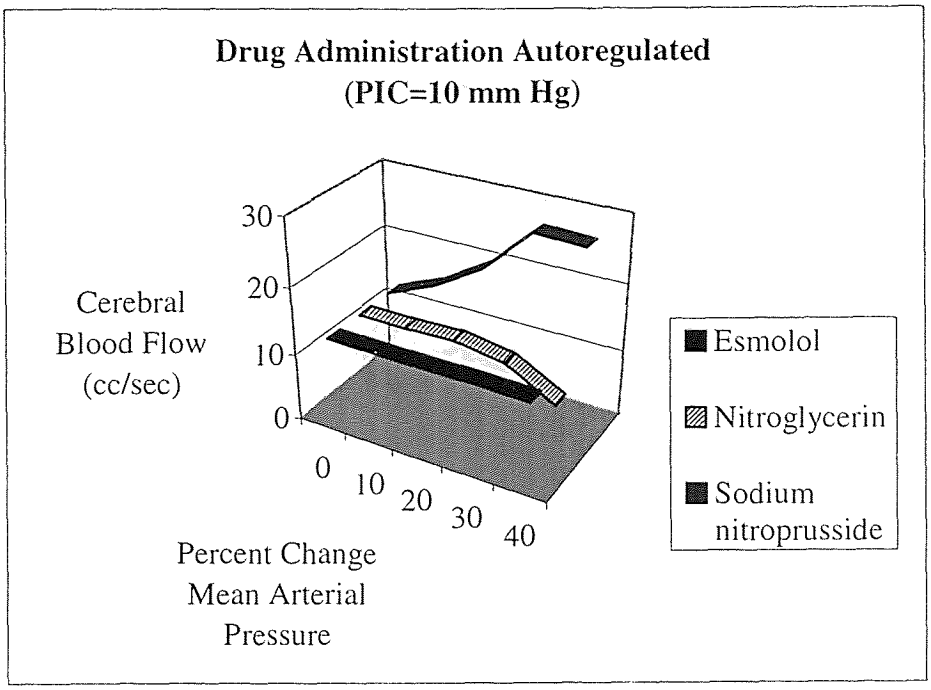

Figure 21: Effect of the administration of three antihypertensive agents on cerebral in a simulated patient with autoregulatory system intact and an initial mean arterial pressure of 100 mm Hg

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

The objective of this project was three-fold. The primary objective of this project was to develop a computer model of cerebrovascular hemodynamics interacting with a pharmacodynamic drug model to examine the effects of three commonly used anti-hypertensive agents upon intracranial pressure and cerebral blood flow. The second objective was to utilize the model to predict patient response under different physiological conditions. The final objective was to evaluate the computed intracranial hemodynamic response to three agents and postulate the agent that will induce hypotension with the least probability of untoward events.

The result of this research yielded following results and observations:

- Three individual cerebrovascular models were developed that predicted intracranial hemodynamic responses to the administration of three commonly used anti-hypertensive agents that correlate with reported experimental data.
- The computations predict that vasodilators such as sodium nitroprusside and nitroglycerin dilate cerebral vascular vessels increasing cerebral blood volume concomitantly increasing intracranial pressure.
- The model predicts that in simulated patients with an impaired autoregulatory system a reduction in mean arterial pressure does not significantly affect intracranial pressure and cerebral blood flow.
- The cerebrovascular model of intracranial hemodynamic response to the administration of esmolol also demonstrated results that correlate with reported

experimental data. The model predicts that beta-adrenergic hypotensive agents do not produce marked changes in intracranial pressure or cerebral blood flow.

- Esmolol effectively induces hypotension without significantly affecting intracranial pressure or cerebral blood flow.

Based on a comparison of computed intracranial pressure and cerebral blood flow response to two vasodilators and a beta-adrenergic agent, the author would recommend the use of beta-adrenergic agents such as esmolol as a anti-hypertensive agent in patients with autoregulatory system intact or non-autoregulated cerebral circulation and under normal or elevated mean arterial pressure.

5.2 Recommendations

Concern regarding the sodium nitroprusside toxicity has prompted anesthesiologists to supplement sodium nitroprusside infusion with beta-adrenergic receptor blockers, calcium channel blockers, and nitroglycerin. The model described herein was used to predict cerebrovascular response to the effects of sodium nitroprusside without supplemental administration. The results demonstrated that direct dilation of cerebral vessels increased cerebral blood volume and concomitantly increased intracranial pressure. The sodium nitroprusside model may be extended to combine multiple pharmacodynamic relationships to model concurrent administrations of multiple agents. In addition, hypertension has been reported to spike upon discontinuing administration of sodium nitroprusside [17]. Using experimental data a pharmacodynamic relationship may be developed to predict this phenomenon

.

In addition, presence of mass lesions proximal to the descending veins may cause a blockage to cerebral blood flow out of the compartment. Therefore, the presence of lesion proximal to the descending veins may contraindicate the administration of vasodilators. The intracranial hemodynamic sub-model may be extended to simulate a blockage within this compartment to predict the affects of vasodilators in the presence of mass lesions. An additional sub-model representing the presence of mass legions may be added to the overall model structure. The mass lesion sub-model may be an exponential relationship between mass lesion volume and resistance to extracranial outflow, R_{vsce}. The presence of a mass lesion would than increase resistance to extracranial venous outflow thus reducing cerebral blood flow out of the compartment and increasing intracranial pressure.

APPENDIX A

EQUATIONS

The cerebrovascular hemodynamic model equations presented below were programmed in Vissim language to simulate patient cerebrovascular response during anti-hypertensive agent administration. The Vissim block diagrams are provided in this appendix. Reference Table 1 for system parameters and table 2 for definition of system symbols.

The cerebrovascular hemodynamic model equations were derived using the following assumptions:

- The change in fluid in a compartment is equal to the sum of the net fluid influx through the compartmental boundaries, plus external sources.
- The change in volume is produced by the changes in pressure difference.
- Arteriolar-capillary and venous cerebrovascular resistance is controlled by chemical factors including pharmacological agents.
- The sum of all volumes does not change in time, *i.e.*, constant volume.
- Arterial-arteriolar and venous cerebrovascular resistance is a function of transmural pressure.

Constancy of the overall intracranial volume:

The constancy of the overall intracranial volume is defined as a function of the net fluxes between the arterial-arteriolar, capillary, veins, venous sinus and cerebral tissue compartment and additional volume added to the compartment.

$$C_{ic}\, dP_{ic}/dt = C_{ai}\,(dP_a/\,dt - dP_{ic}/dt) + G_f\,(P_c - P_{ic}) + C_{vi}\,(dP_v/\,dt - dP_{ic}/dt) - G_o(P_{ic} - P_{vs}) + I \quad (13)$$

Intracranial pressure is derived by rearranging the equation and solving for intracranial pressure as a function of time.

$$dP_{ic}/dt = [G_f (P_c - P_{ic}) + C_{vi} (dP_v/ dt) - G_o(P_{ic} - P_{vs}) + I_I] / [C_{ai} + C_{vi} + C_{ic}] \quad (14)$$

Cerebral Arterial-arteriolar Compartment:

Cerebral Blood Flow is defined as the net fluxes between the arterial-arteriolar, capillary bed, and cerebral tissue compartments.

$$Q = P_a * R = C_{ai} (dP_a/ dt - dP_{ic}/dt) + G_{ai}(P_a - P_c) \quad (15)$$

Rearranging the equation and solving for arterial-arteriolar pressure yields the following equation:

$$P_{ar} = [G_{ai} P_a - G_{ar}P_c] / [G_{ai} + G_a] \quad (16)$$

Capillary Compartment:

The volume of the capillary compartment is a function of the net fluxes between the arterial-arteriolar, capillary and veins compartments:

$$G_a (P_a - P_v) - G_{pv}(P_c - P_v) = G_f (P_c - P_{ic}) \quad (17)$$

Rearranging the equation and solving for pressure of the capillary yields the following:

$$P_c = [G_a P_a + G_{pv} P_v + G_f P_v] / [G_a + G_{pv} + G_f] \quad (18)$$

Cerebral venous compartment:

The following equation defines the volume of the cerebral vein compartment as a function of cerebral tissue compartment, capillary compartment and the veinus sinus compartment:

$$G_{pv}(P_c - P_v) - G_{vs}(P_v - P_{vs}) = C_{vi} (dP_v/ dt - dP_{ic}/dt) \quad (19)$$

Solving for the vein compartment pressure yields the following equation:

$$dP_v/ dt = [G_{pv}(P_c - P_v) - G_{vs}(P_v - P_{vs}) + C_{vi}dP_{ic}/dt] / Cvi \quad (20)$$

Venous sinus compartment:

The following equation defines the volume of the venous sinus compartment as a function of cerebral tissue compartment, veins compartment and the central venous compartment:

$$G_{vs}(P_v - P_{vs}) + G_o(P_{ic} - P_{vs}) = G_{ve}(P_{vs} - P_{cv}) + C_{ve}\, dP_{vs}/dt \quad (21)$$

Solving for the venous sinus pressure yields the following equation:

$$dP_{vs}/dt = [G_{vs}(P_v - P_{vs}) + G_o(P_{ic} - P_{vs}) - G_{ve}(P_{vs} - P_{cv})] / C_{ve} \quad (22)$$

Compliance equations of the arterial, venous and cerebral tissue compartments:
The derivation of the following compliance equations are described in detail in Section 2.2.

$$C_a = dV_a / d(P_a - P_{ic}) = 1/K_a(P_a - P_{ic}) \quad (23)$$

$$C_a = dV_a / d(P_a - P_{ic}) = 1/K_a(P_a - P_{ic} - P_{vi}) \quad (24)$$

$$C_{ic} = 1 / [K_e * (P_{ic} + (P_{ic} / P_{ic})^2)] \quad (25)$$

Table 1: Parameter values used during the simulation

$G_{ai} = 2.77\ cm^3\ sec^{-1}\ mm\ Hg^{-1}$	$G_{pv} = 1.136\ cm^3\ sec^{-1}\ mm\ Hg^{-1}$
$G_f = 0.42 * 10\ cm^3\ sec^{-1}\ mm\ Hg^{-1}$	$G_o = 1.90 * 10\ cm^3\ sec^{-1}\ mm\ Hg^{-1}$
$G_{vs} = 2.77\ cm^3\ sec^{-1}\ mm\ Hg^{-1}$	$G_{ve} = 6.25\ cm^3\ sec^{-1}\ mm\ Hg^{-1}$
$G_{ai} = 0.37\ cm^3\ sec^{-1}\ mm\ Hg^{-1}$	$K_a = 3.68\ cm^3$
$C_{ve} = 2.34$ cm mm Hg	$K_e = 0.26\ cm^3$
$P_{vi} = -2.5$ mm Hg	$K_v = 0.31\ cm^3$
Pa = 100 mm Hg	

Table 2: Description of Symbols

Pa:	Arterial pressure
Pc:	Cerebral capillary pressure
Pv:	Cerebral venous pressure
Pic:	Intracranial pressure
Pvs:	Venous sinus pressure
Pcv:	Central venous pressure
Gai:	Arterial-arteriolar conductance
Gpv:	Proximal venous conductance
Gvs:	Terminal venous conductance
Gve:	Extracranial venous conductance
Gf:	Conductance to CSF formation
Go:	Conductance to CSF outflow
Cai:	Intracranial arterial compliance
Cvi:	Intracranial venous compliance
Cic:	Intracranial compliance
Cve:	Extracranial venous compliance
Q:	Cerebral blood flow
Ka:	Arterial elastance coefficient
Kv:	Venous elastance coefficient
I:	Rate of liquid injection into subarachnoid space

APPENDIX B

CEREBROVASCULAR SYSTEM MODEL

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

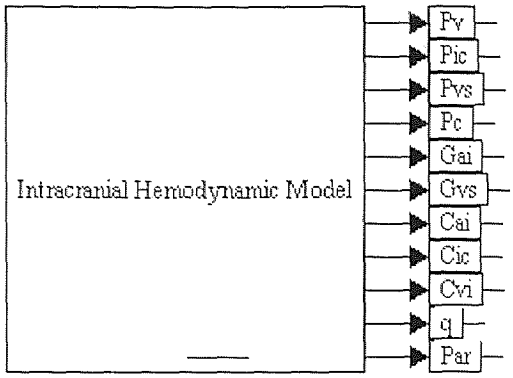

Figure 22 Intracranial hemodynamic compound block with outputs

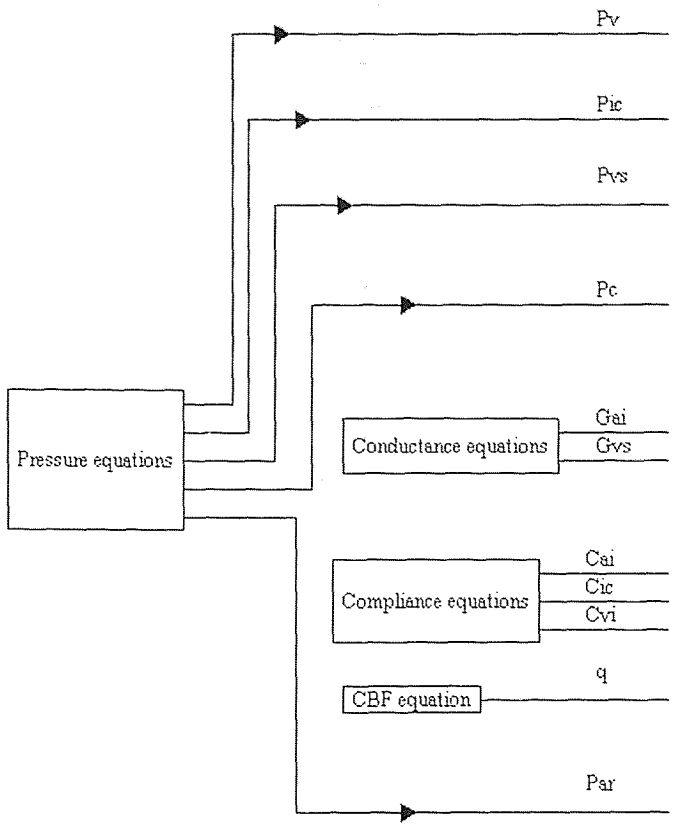

Figure 23 Intracranial hemodynamic compound block expanded

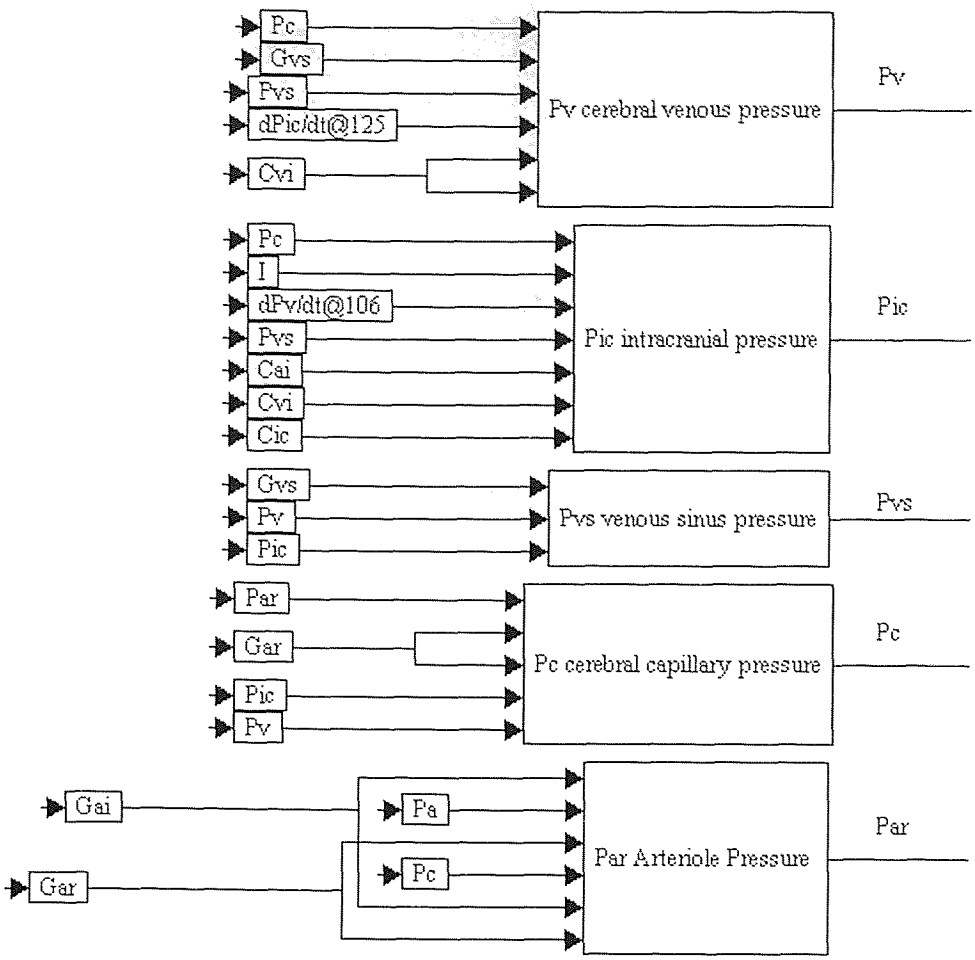

Figure 24 Pressure equations compound block expanded

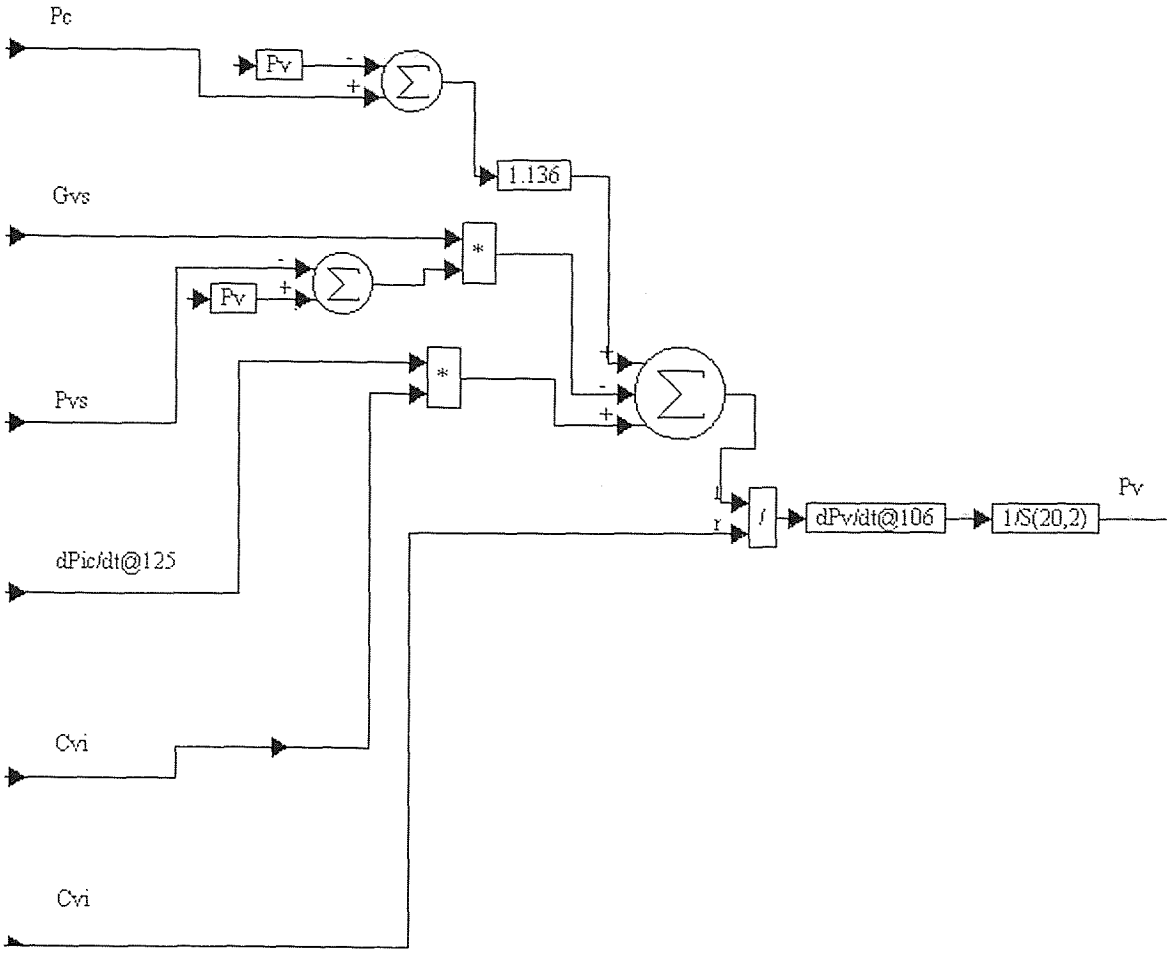

Figure 25 Pv cerebral venous pressure compound block expanded

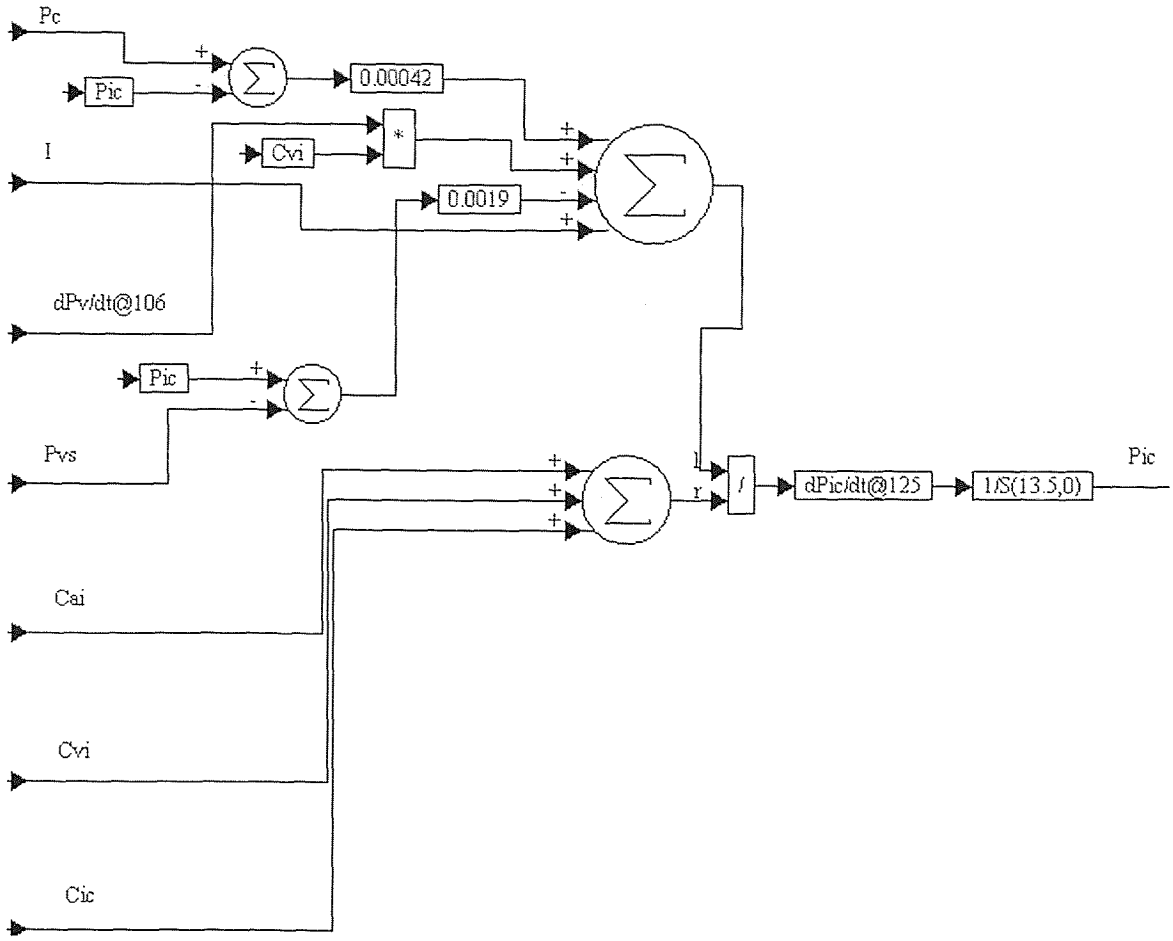

Figure 26 Pic intracranial pressure compound block expanded

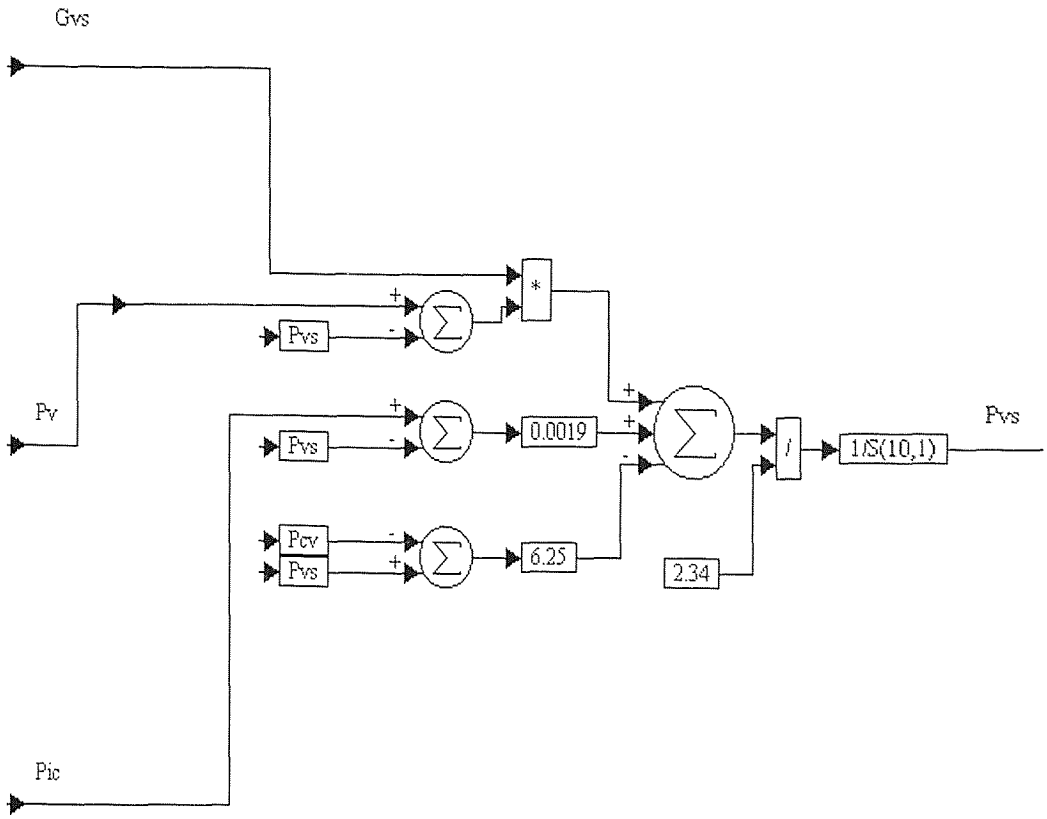

Figure 27 Pvs venous sinus pressure compound block expanded

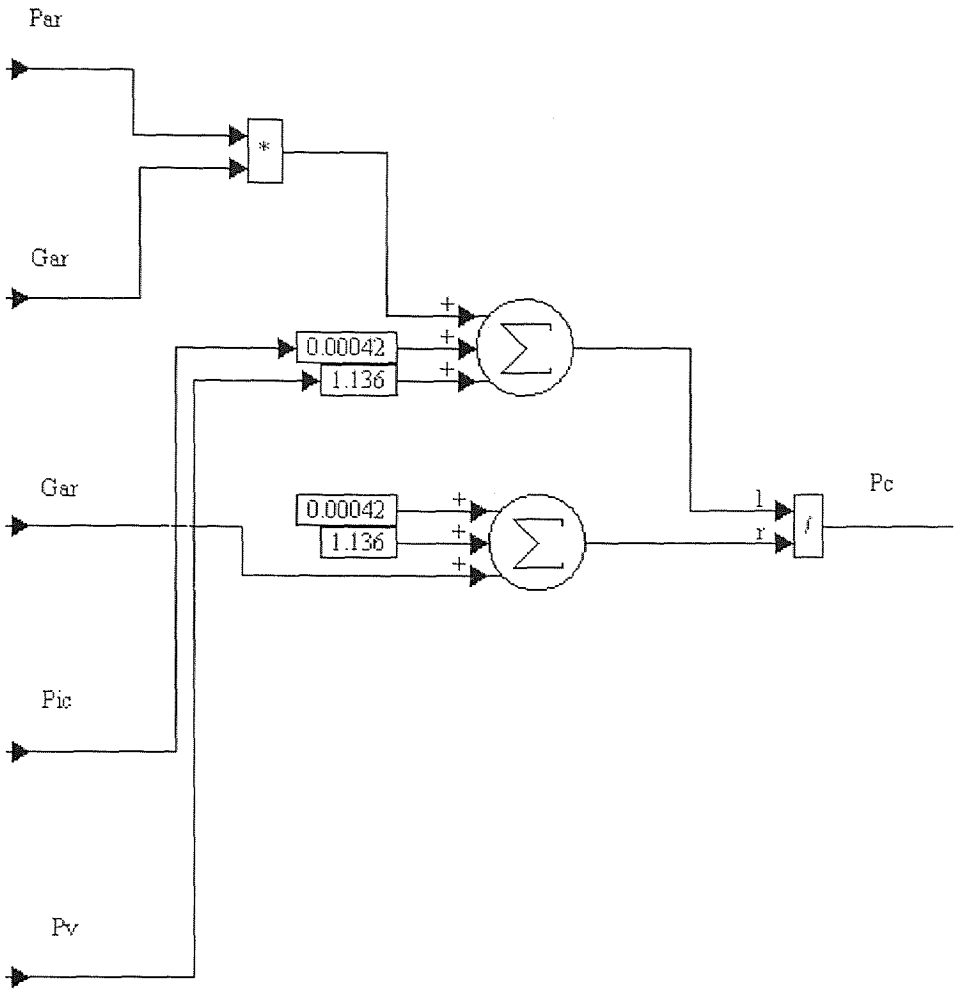

Figure 28 Pc cerebral capillary pressure compound block expanded

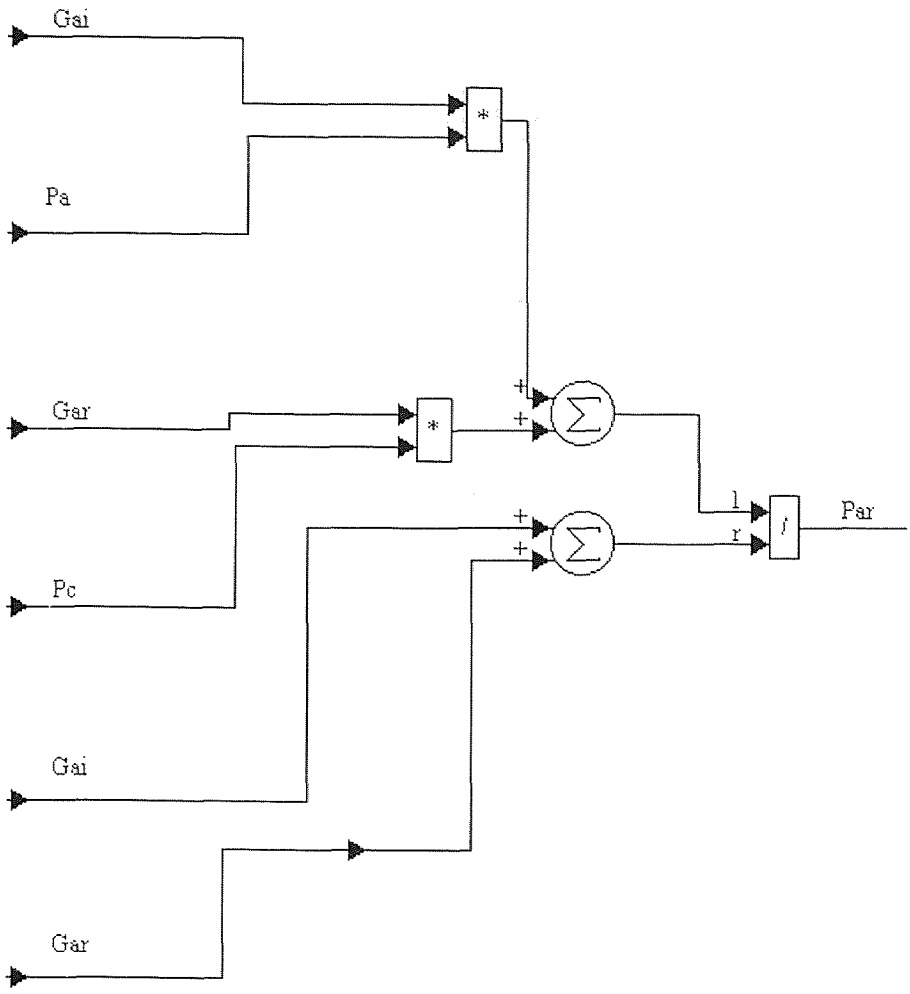

Figure 29 Par arteriole pressure compound block expanded

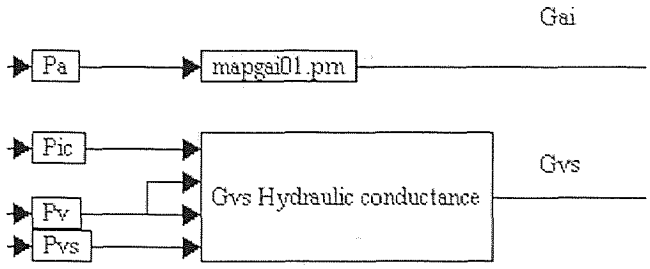

Figure 30 Conductance equations compound block expanded

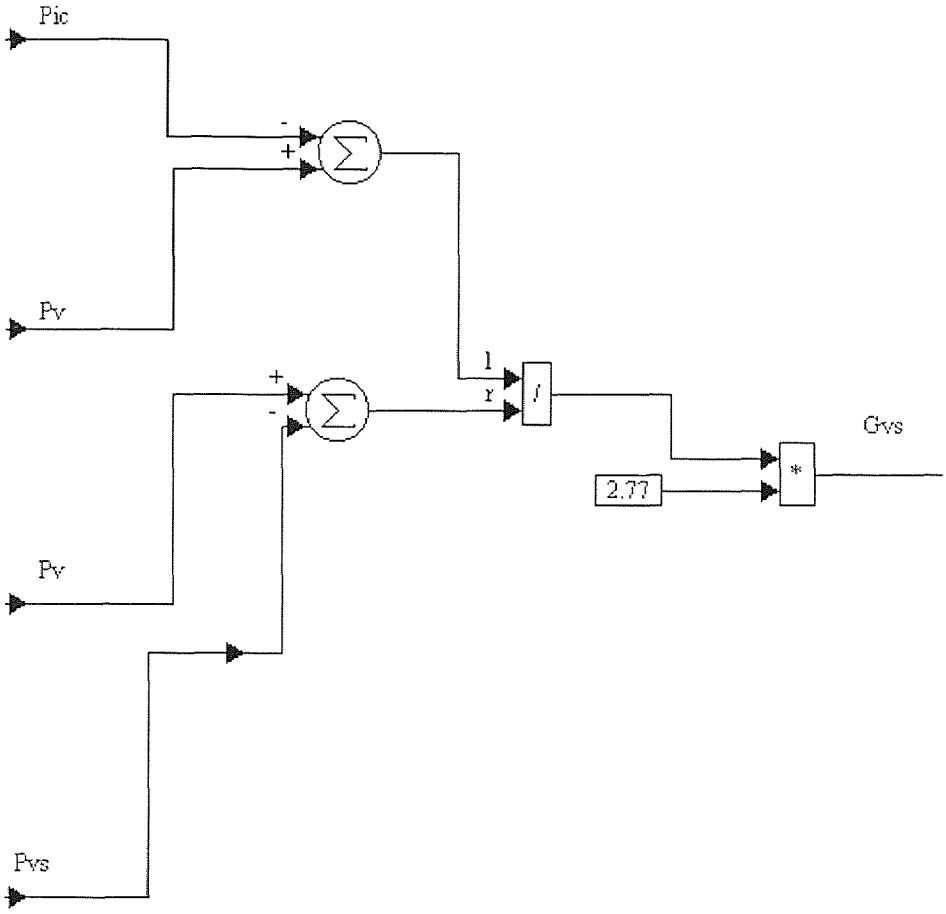

Figure 31 Gvs hydraulic conductance compound block expanded

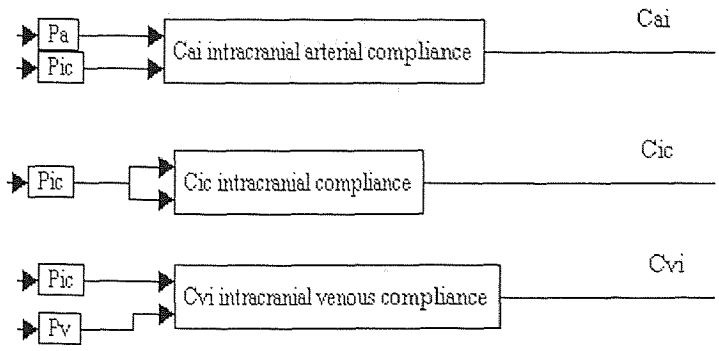

Figure 32 Compliance equations compound block expanded

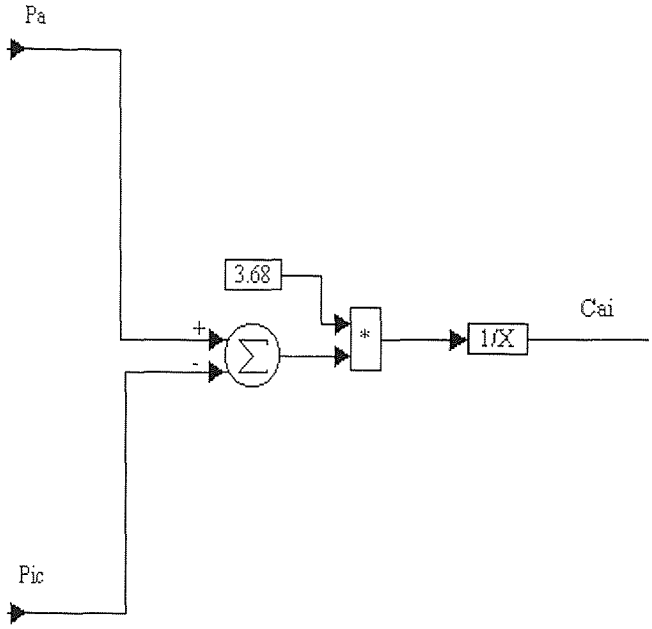

Figure 33 Cai arteriolar compliance compound block expanded

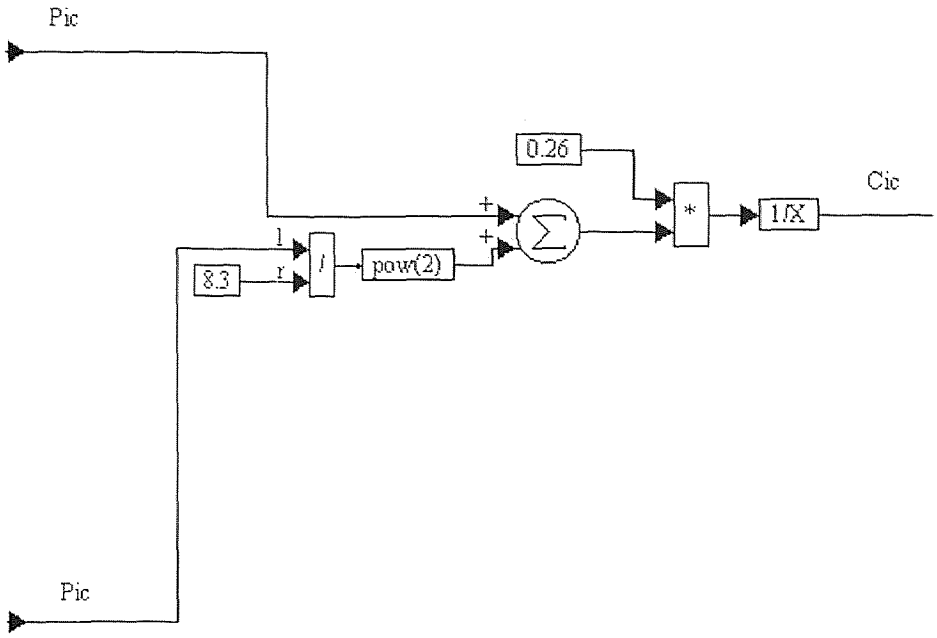

Figure 34 Cic intracranial compliance compound block expanded

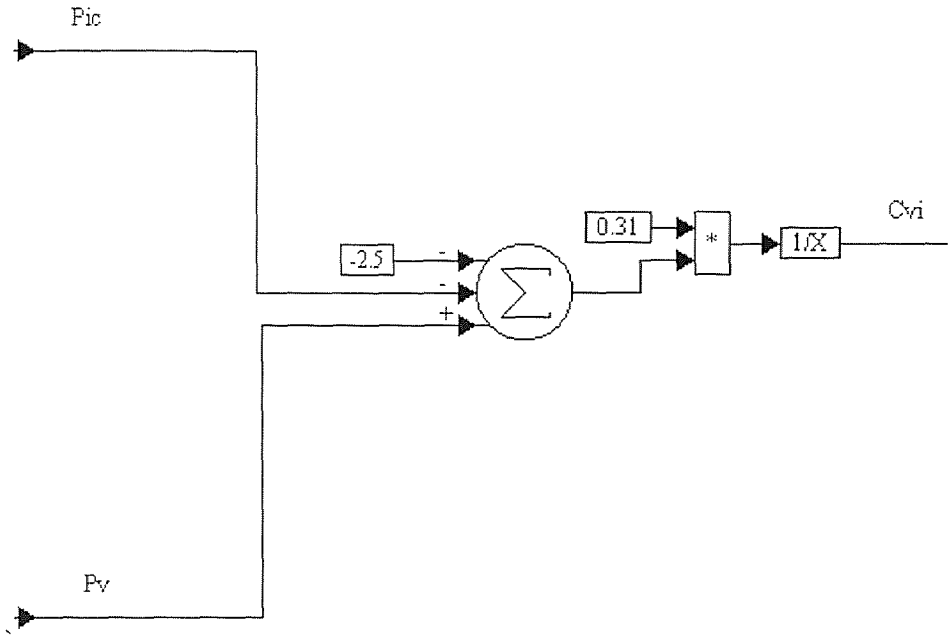

Figure 35 Cvi intracranial venous compliance compound block expanded

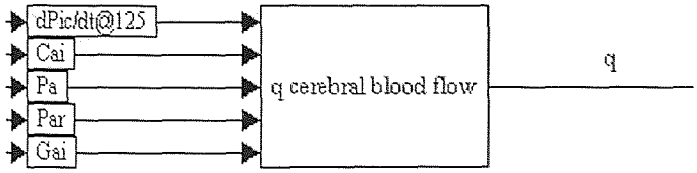

Figure 36 CBF equation compound block expanded

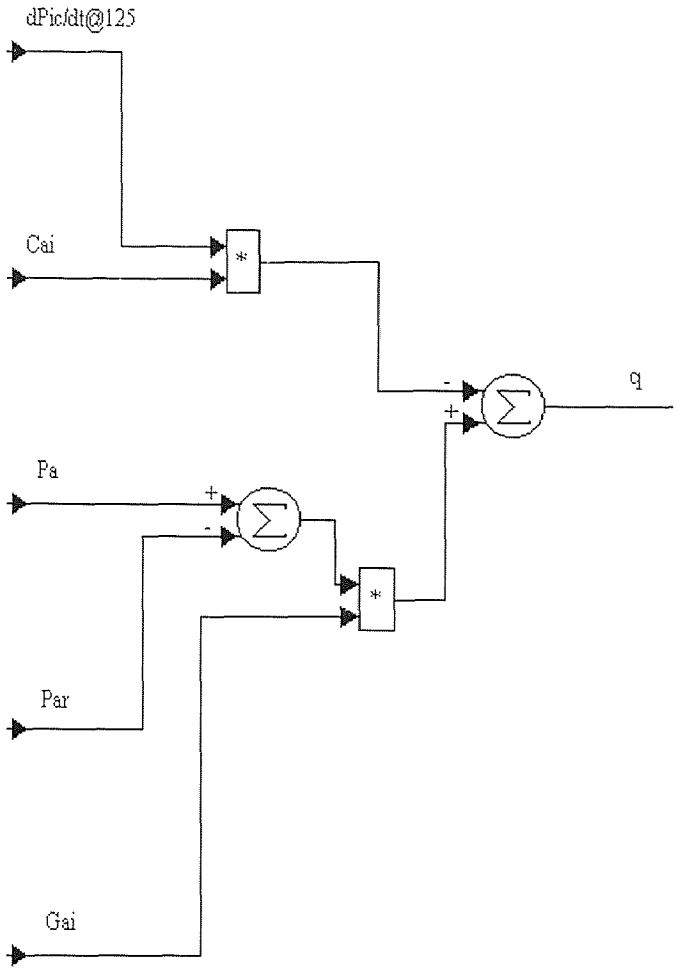

Figure 37 q cerebral blood flow compound block expanded

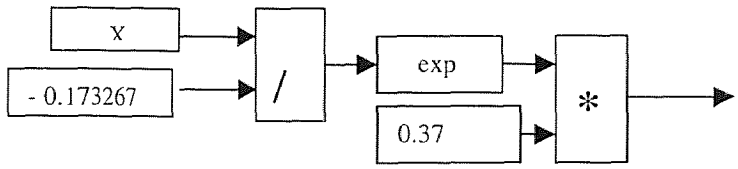

Figure 38 Sodium nitroprusside pharamcodynamic sub-model.

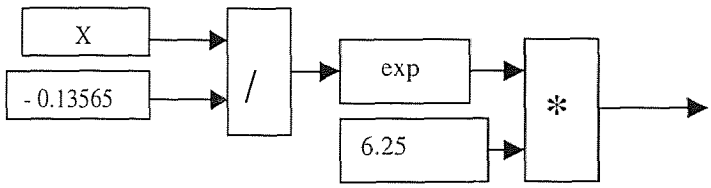

Figure 39 Nitroglycerin pharmacodynamic sub-model.

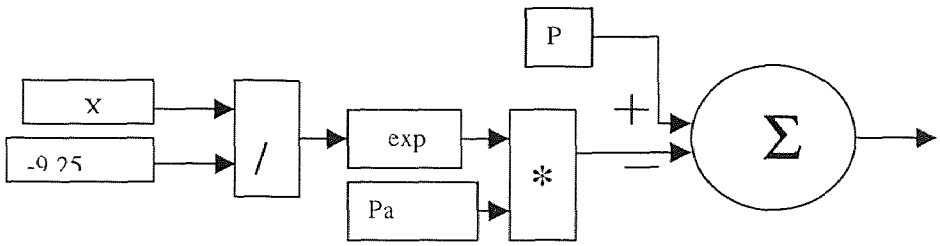

Figure 40 Esmolol pharmacodynamic sub-model.

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