

# Modeling the Causes of Variation in Brain Tissue Oxygenation

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**BACKGROUND:** Clinical markers of the adequacy of cerebral perfusion may be misleading. The effects of isolated changes in systemic blood pressure,  $P_{aCO_2}$ ,  $P_{aO_2}$ , and cerebral edema on cerebral blood flow and oxygenation are relatively well known, but the quantitative effects of interactions between these factors are not easily calculated. We aimed to investigate the relationship between these factors using a computational model.

**METHODS:** Using a validated, quantitative, computational model of cerebral blood flow, the simulated effects of changes in systemic blood pressure (50–180 mm Hg),  $P_{aCO_2}$  (33–55 mm Hg [4.3–7.3 kPa]),  $S_{aO_2}$  (0.8–1.0), and cerebral edema (0%–10% increase in intercapillary distance) on middle cerebral artery flow velocity (MCAFV), brain tissue oxygenation ( $P_{bO_2}$ ), and jugular venous oxygen saturation ( $S_{jO_2}$ ) were recorded.

**RESULTS:** Individual markers of adequacy of cerebral perfusion (MCAFV,  $S_{jO_2}$ , and  $P_{bO_2}$ ) behave in accordance with clinical data with single changes in the parameters studied: the lower limit of autoregulation for MCAFV and  $S_{jO_2}$  lies around 60 mm Hg mean arterial blood pressure. In our model, the upper limit of autoregulation lies around 170 mm Hg, but is much less distinct for  $S_{jO_2}$  and  $P_{bO_2}$  than for MCAFV. Significant cerebral ischemia appears unlikely to occur with isolated physiological changes according to our simulation. However, the combination of hypotension, hypoxia, and edema makes ischemia much more likely in this model. Edema increases the  $S_{jO_2}$ : $P_{bO_2}$  gradient, confirming that diffusion-limited oxygen delivery may make  $S_{jO_2}$  values falsely reassuring.

**CONCLUSION:** The simulated effects of pathophysiological changes on cerebral oxygenation and perfusion have been quantitatively described. Significant cerebral ischemia is predicted in the presence of two or more physiological derangements. Cerebral edema is associated with an increased gradient between  $S_{jO_2}$  and  $P_{bO_2}$ .

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Computational modeling of cerebral oxygenation has been performed previously. This modeling has largely investigated single issues in isolation, with much work done on mathematical derivation of formulae to describe the dependence of brain tissue oxygen tension ( $P_{bO_2}$ ) on capillary radius, intercapillary distance, oxygen diffusibility and solubility, and oxygen extraction rates. *In vivo*, factors such as mean arterial blood pressure (MAP), cerebral perfusion pressure (CPP),  $P_{aCO_2}$ , and the presence or absence of autoregulation will all affect  $P_{bO_2}$  (1). The development of an integrated, computational model of cerebral vascular and metabolic behavior allows investigation of factors that provoke or protect against cerebral

tissue hypoxia, and also the circumstances where surrogate measures, such as jugular venous oxygen saturation ( $S_{jO_2}$ ), may be misleading. The aim of this study was to investigate the effects of changes in MAP,  $P_{aO_2}$ ,  $P_{aCO_2}$ , tissue edema, and autoregulatory capacity on  $S_{jO_2}$ ,  $P_{bO_2}$ , and middle cerebral artery flow velocity (MCAFV) using a computational simulation of cerebral blood flow (CBF) and oxygenation.

## METHODS

### Nottingham Cerebral Simulator

The construction of the Nottingham Cerebral Simulator (NCS) has been described in detail in an accompanying article (2). In brief, the NCS is a computational simulation of CBF and metabolism; it uses an iterative, lumped-parameter approach. Numerous compartments are simulated, representing the vascular bed from common carotid arteries to internal jugular veins. All intracranial vessels are subject to the effects of intracranial pressure. Arterioles are under active regulatory control in response to changes in CPP, CBF, cerebral spinal fluid (CSF) pH, (responsive to changes in  $P_{aCO_2}$ ), and  $S_{aO_2}$ . The cranium is relatively noncompliant and

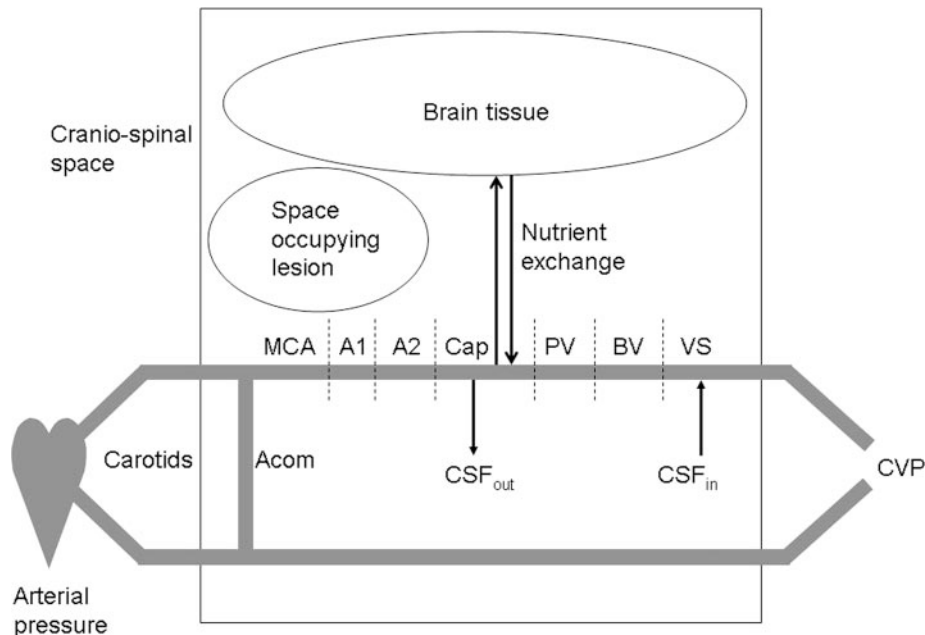
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**Figure 1.** Schematic representation of the model. Blood is modeled as flowing under pressure from the heart through carotid arteries, then the middle cerebral arteries (MCA), with collateral flow through an anterior communicating artery (ACOM). Flow then passes through the proximal (A1) and distal (A2) arterioles to the capillaries (Cap). At this point cerebrospinal fluid (CSF) is produced via a one-way pressure-dependent mechanism ( $CSF_{out}$ ). Nutrient exchange with the metabolically active brain tissue also occurs at the capillary level. Venous blood then flows through proximal veins (PV), bridging veins (BV), and venous sinuses (VS) back to the great veins opposed by central venous pressure (CVP). CSF is absorbed by a one-way process at the level of the VS. The proximal and distal arterioles are under active regulatory control, responding to cerebral blood flow (CBF), CSF pH, arterial oxygen content, and transmural pressure as well as being pressure-passive. All other vessels are pressure-passive. The bridging veins behave as a Starling resistor. Each “vessel” represents a bed of vessels (the number of which can be defined by the user) running in parallel, each one of which can have characteristics independent of the others. This allows creation of areas of abnormality. Each vessel bed has its own mid-point pressure, hydraulic conductance and compliance. The craniospinal space is of low, but variable compliance and contains incompressible brain tissue, CSF, and if necessary an additional volume of space-occupying lesion. CSF is under pressure and has its own independently calculated volume, pressure and pH (dependent upon arterial  $Paco_2$  and pH).

contains CSF formed at the capillaries and absorbed into the venous sinuses. Nutrient and metabolite exchange occurs at the capillaries. Two hemispheres are modeled connected by an anterior communicating artery and joining at the level of the superior vena cava. Individual vessel beds have independently modifiable behavior. For the purposes of this study, each hemisphere was treated as a homogenous unit. Thus, different patterns of behavior can be modeled during the same experiment, which simulates the effect of localized sampling of brain tissue as occurs in clinical practice. A schematic representation of the model is given in Figure 1. The simulations are run as an executable file (Microsoft Windows™). The executable file is available from the following URL: [www.nottingham.ac.uk/sms/school/anesthesia/models/NCS/NCS\\_AandA\\_13Mar07.exe](http://www.nottingham.ac.uk/sms/school/anesthesia/models/NCS/NCS_AandA_13Mar07.exe).

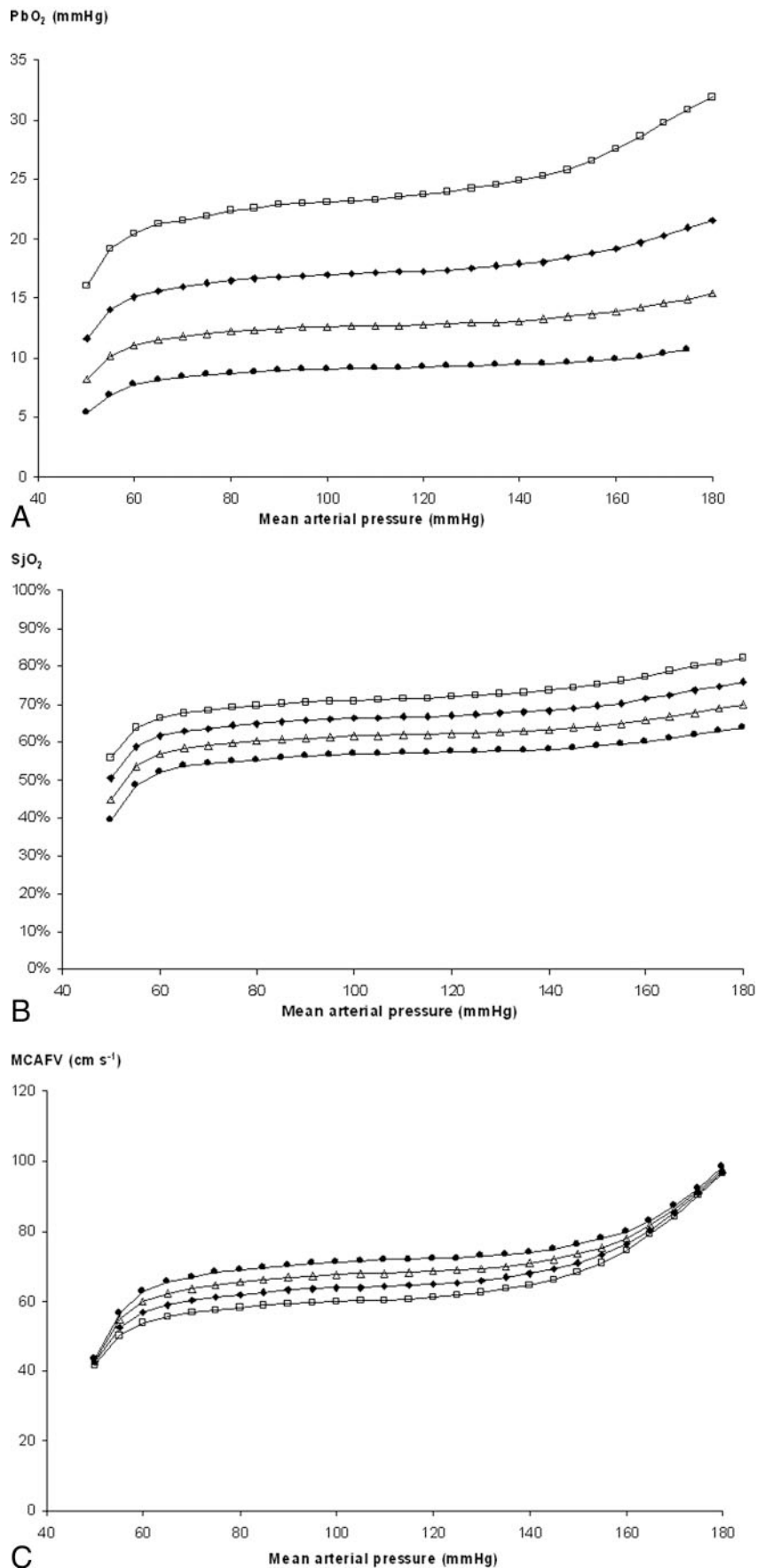
### Experimental Simulations

The NCS was run using standard values, which have been shown to simulate normal human cerebral physiology (2).

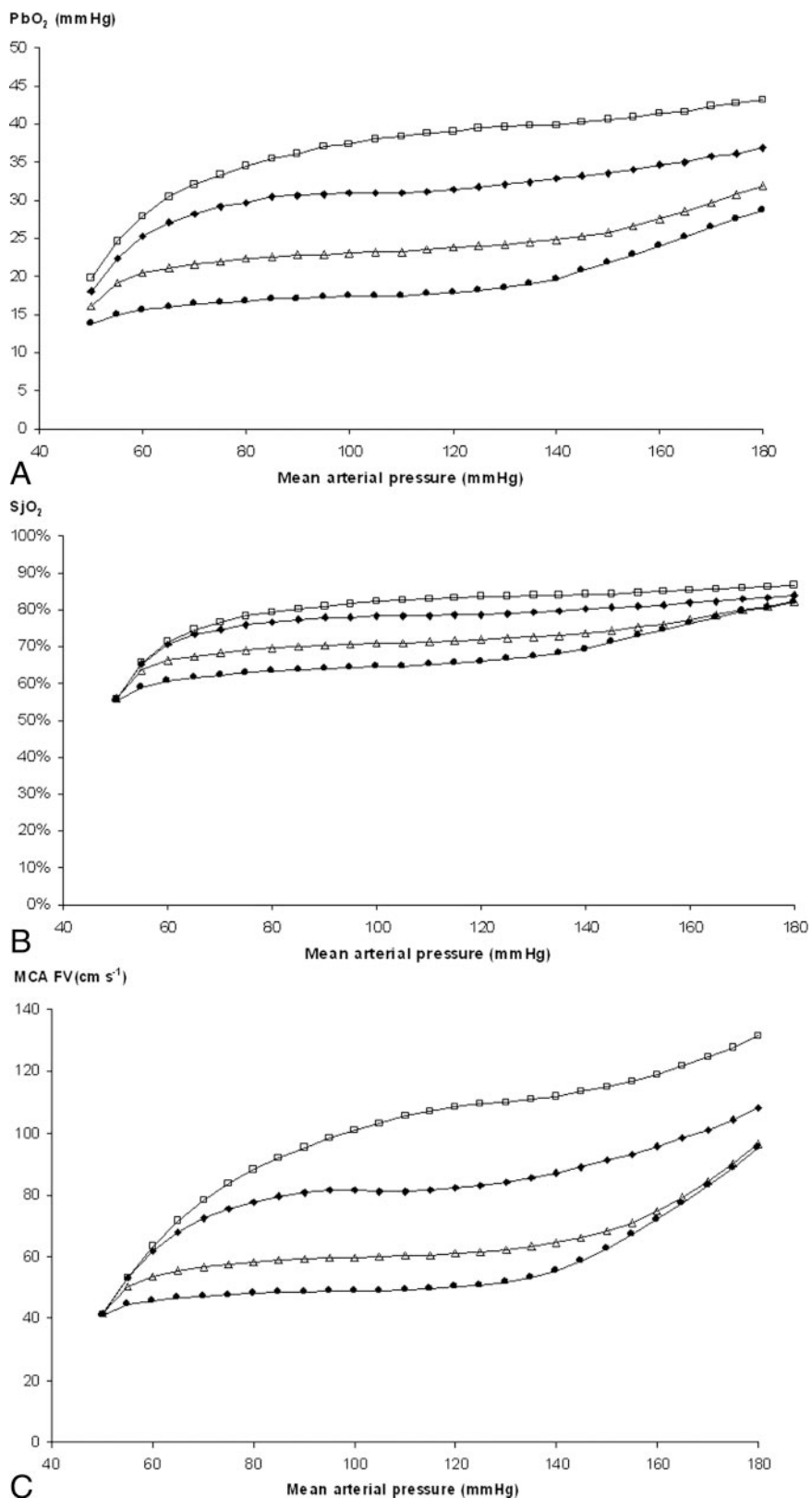
Jugular venous oxygen saturation  $SjO_2$ ,  $Pbo_2$ , and MCA<sub>AV</sub> were calculated while MAP was varied between 50 and 180 mm Hg. This was repeated while  $Paco_2$  was varied between 33 and 55 mm Hg (4.3 and

7.3 kPa), and  $Sao_2$  was varied between 80% and 100%. This testing matrix was repeated with altered vascular reactivity where the gain on one or both sides was reduced to 75%, 50%, or 25% of normal (vascular reactivity 0.75, 0.5, or 0.25) or absent (VR 0). Reduced vascular reactivity, combined with moderate resting vasodilatation or vasoconstriction were also modeled. All simulations were run for 10 min physiological time between each change.  $SjO_2$  was calculated as the saturation of completely mixed jugular blood.

Tissue edema was simulated by reducing the constant for diffusion for oxygen across brain tissue, which is mathematically equivalent to increasing the intercapillary distance. Thus, a notional scale for degree of edema was created, where edema percentage approximates to the relative increase in intercapillary distance (e.g., 10% edema represents the value of diffusion constant, which approximates to a 10% increase in intercapillary distance, which is consistent with ultrastructural changes seen in injured tissue). Static autoregulation curves were modeled for 0%, 5%, 10%, and 15% edema with  $Paco_2$  40 mm Hg and 33 mm Hg. These simulations were repeated with the effects of a space-occupying lesion of 40 mL, which represents a significant intracranial mass.



**Figure 2.** (A–C) The effects of mean arterial blood pressure (MAP) and  $SaO_2$ : normal vascular reactivity. A, The effect of arterial oxygen saturation on brain tissue oxygenation ( $PbO_2$ ).  $SaO_2$ : 0.98 ( $\square$ ), 0.92 ( $\blacklozenge$ ), 0.86 ( $\triangle$ ), 0.80 ( $\bullet$ ). B, The effect of arterial oxygen saturation on jugular venous oxygen saturation ( $SjO_2$ ).  $SaO_2$ : 0.98 ( $\square$ ), 0.92 ( $\blacklozenge$ ), 0.86 ( $\triangle$ ), 0.80 ( $\bullet$ ). C, The effect of arterial oxygen saturation on middle cerebral artery flow velocity (MCAFV).  $SaO_2$ : 0.98 ( $\square$ ), 0.92 ( $\blacklozenge$ ), 0.86 ( $\triangle$ ), 0.80 ( $\bullet$ ).

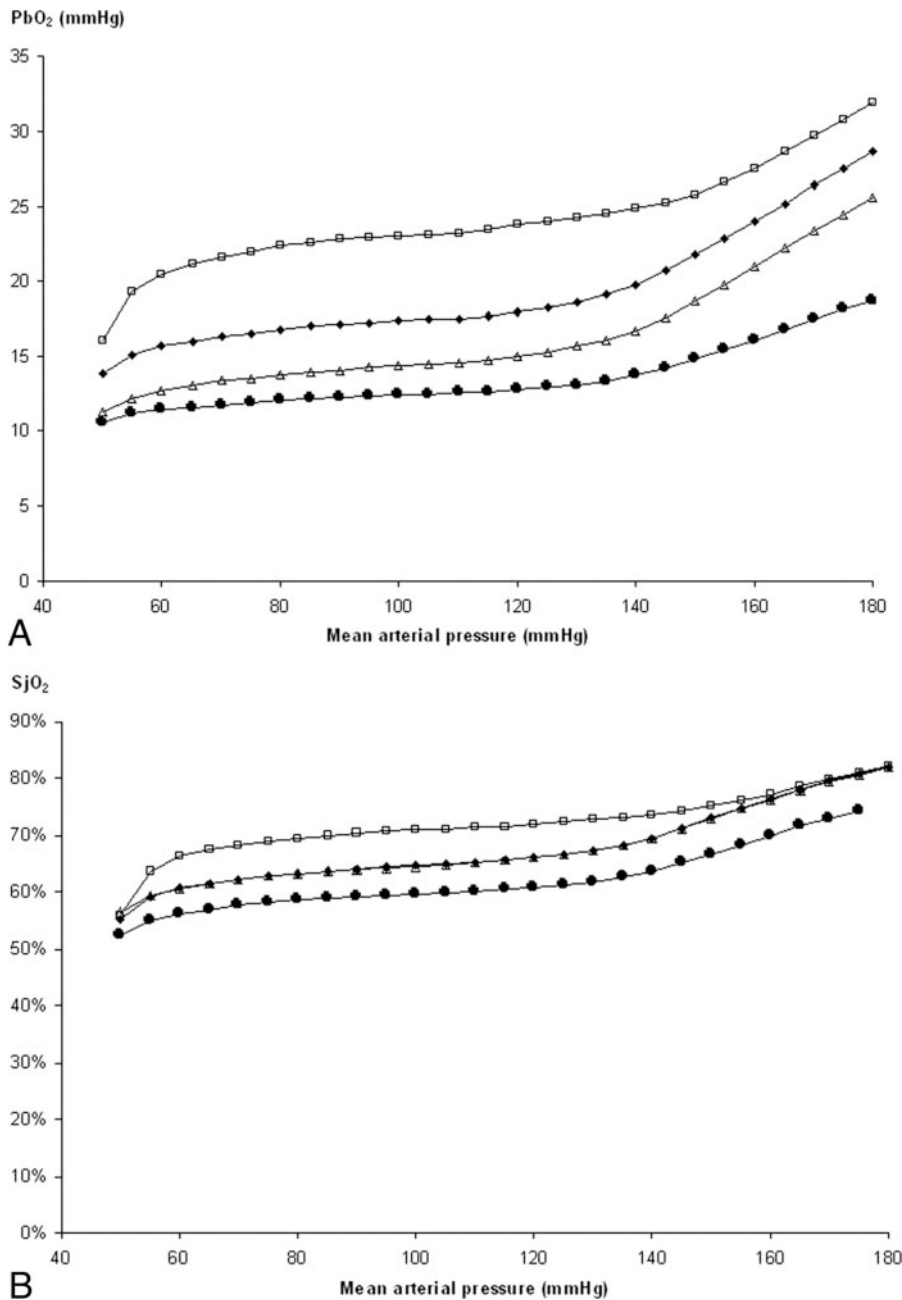


**Figure 3.** (A–C) The effect of mean arterial blood pressure (MAP) and PaCO<sub>2</sub>: normal vascular reactivity. A, The effect of arterial partial pressure of carbon dioxide on brain tissue oxygenation (Pbo<sub>2</sub>). Paco<sub>2</sub> mm Hg (kPa): 55 (7.3) (□), 48 (6.3) (◆), 40 (5.3) (△), 33 (4.3) (●). B, The effect of arterial partial pressure of carbon dioxide on jugular venous oxygen saturation (Sjo<sub>2</sub>). Paco<sub>2</sub> mm Hg (kPa): 55 (7.3) (□), 48 (6.3) (◆), 40 (5.3) (△), 33 (4.3) (●). C, The effect of arterial partial pressure of carbon dioxide on middle cerebral artery flow velocity (MCA FV). Paco<sub>2</sub> mm Hg (kPa): 55 (7.3) (□), 48 (6.3) (◆), 40 (5.3) (△), 33 (4.3) (●).

## RESULTS

Results of the testing matrices are given in the figures below. The effects of varying arterial oxygen saturation are shown in Figure 1. Despite the vasodilation caused by hypoxemia (Fig. 1C), Pbo<sub>2</sub> and Sjo<sub>2</sub> decrease with hypoxemia, though within this range, never to hypoxic

levels (c. 10 mm Hg) (3). The effects of varying PaCO<sub>2</sub> are shown in Figure 2. As expected, the vasodilatory effects of carbon dioxide cause increased flow, increased oxygen delivery, and increased Pbo<sub>2</sub>. Conversely, hypocapnia results in consistently lower Pbo<sub>2</sub>, though again, not to hypoxic levels. The effects of edema are shown in



**Figure 4.** The effect of mean arterial blood pressure (MAP),  $P_{aCO_2}$ , and edema. A, The effect of MAP,  $P_{aCO_2}$ , and edema on brain tissue oxygenation ( $P_{bO_2}$ ).  $S_{aO_2}$  0.98,  $P_{aCO_2}$  40 mm Hg, no edema ( $\square$ ).  $S_{aO_2}$  0.98,  $P_{aCO_2}$  33 mm Hg, no edema ( $\blacklozenge$ ).  $S_{aO_2}$  0.98,  $P_{aCO_2}$  33 mm Hg, 10% edema ( $\triangle$ ).  $S_{aO_2}$  0.92,  $P_{aCO_2}$  33 mm Hg, no edema ( $\bullet$ ). B, The effect of MAP,  $P_{aCO_2}$ , and edema on jugular venous oxygen saturation ( $S_{jO_2}$ ).  $S_{aO_2}$  0.98,  $P_{aCO_2}$  40 mm Hg, no edema ( $\square$ ).  $S_{aO_2}$  0.98,  $P_{aCO_2}$  33 mm Hg, no edema ( $\blacklozenge$ ).  $S_{aO_2}$  0.98,  $P_{aCO_2}$  33 mm Hg, 10% edema ( $\triangle$ ).  $S_{aO_2}$  0.92,  $P_{aCO_2}$  33 mm Hg, no edema ( $\bullet$ ). The values of  $S_{jO_2}$  for  $P_{aCO_2}$  33 mm Hg with and without edema are virtually identical.

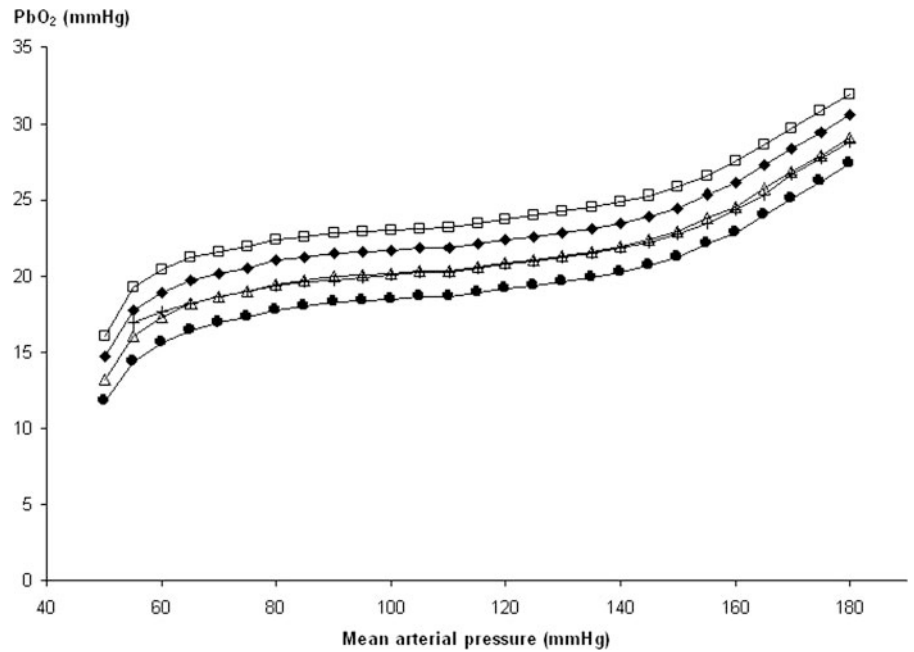
Figures 3–5. Isolated, significant edema causes a reduction in  $P_{bO_2}$ , which, when combined with hypocapnia, and particularly hypotension, may result in hypoxic levels of tissue oxygenation. Values in the presence of a space-occupying lesion are virtually identical. The data for 10% edema are shown in Figure 4. Edema *per se* has little effect on  $S_{jO_2}$  (Figs. 3B and 4). Reduced vascular reactivity has a proportionally larger effect on local  $P_{bO_2}$  than on  $S_{jO_2}$  (Fig. 6). Increasing impairment of vascular reactivity causes oligemia, leading to relative tissue hypoxia at low MAP and hyperemia with high  $S_{jO_2}$  and  $P_{bO_2}$  at high MAP (Fig. 6). Modeling-impaired vascular reactivity with a vasodilated or vasoconstricted component is shown in Figure 7, leading to hyperemia and oligemia, respectively, throughout the MAP range modeled.

## DISCUSSION

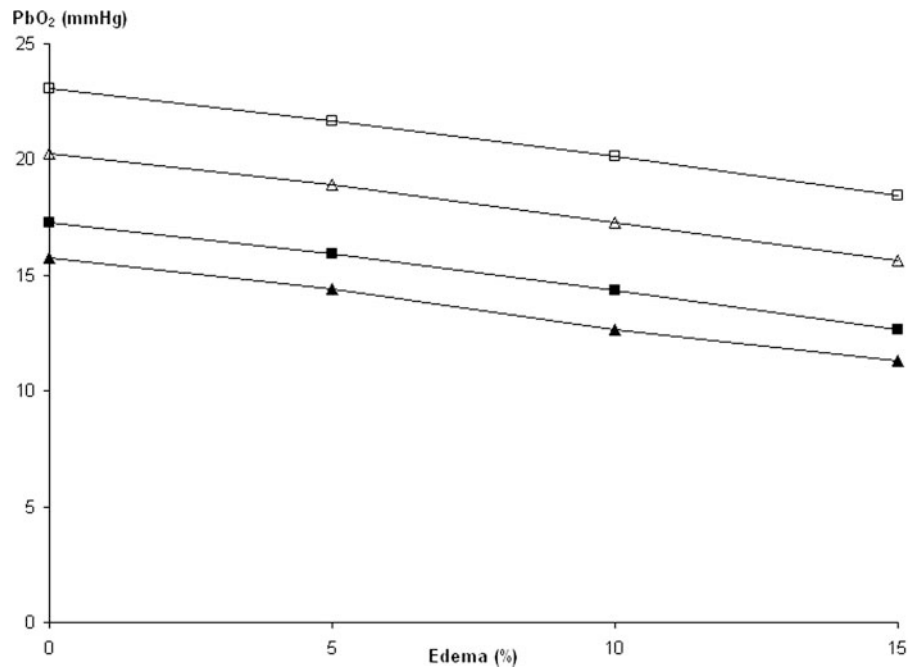
These simulation results provide some quantitative data for the effects of physiological changes on markers of cerebral oxygenation using a validated model of cerebral pathophysiology. Under normal conditions, moderate changes in  $P_{aCO_2}$  and  $S_{aO_2}$  have measurable, but modest, effects on brain tissue oxygenation, as measured by  $P_{bO_2}$  and  $S_{jO_2}$ . Severe hypoxia is associated with borderline cerebral oxygenation, worsened by hypotension or hypocapnia.

Using this model, abnormal vascular reactivity, without vasodilation or vasoconstriction is associated with relative under-perfusion with systemic hypotension and over-perfusion during systemic hypertension. The effect is more marked for  $P_{bO_2}$  than for  $S_{jO_2}$ ,

**Figure 5.** The effect of mean arterial blood pressure (MAP), space occupying lesion, and edema on  $PbO_2$ .  $Paco_2$  is 40 mm Hg,  $Sao_2$  0.98. Edema is a notional scale, where the value for oxygen diffusing capacity has been adjusted within the model to match the effect of increasing intercapillary distance. Ten percent edema is, therefore, equivalent to an intercapillary distance of 1.1 times normal. Edema: None ( $\square$ ), 5% ( $\blacklozenge$ ), 10% ( $\triangle$ ), 15% ( $\bullet$ ). Edema 10%, 40 mL space-occupying lesion: +.  $SjO_2$  values for each of the edema levels are essentially identical; thus, the cerebral venous:brain tissue  $PO_2$  gradient increased with increasing degrees of edema.



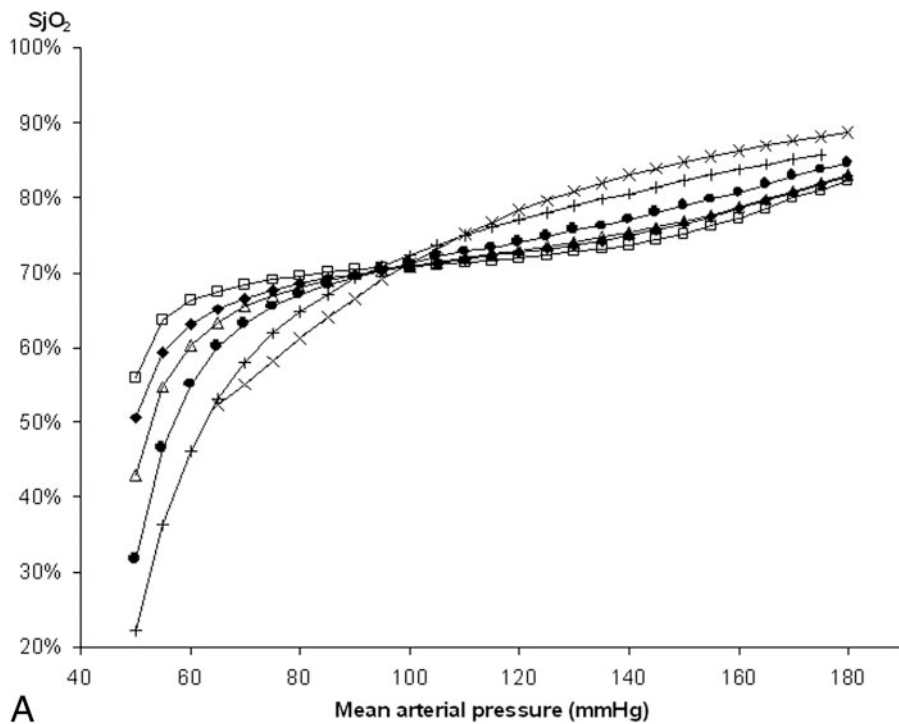
**Figure 6.** The effect of varying degrees of edema and  $Paco_2$  on modeled  $PbO_2$ .  $Paco_2$  40 mm Hg, MAP 100 mm Hg:  $\square$ .  $Paco_2$  40 mm Hg, MAP 60 mm Hg:  $\triangle$ .  $Paco_2$  33 mm Hg, MAP 100 mm Hg:  $\blacksquare$ .  $Paco_2$  33 mm Hg, MAP 60 mm Hg:  $\blacktriangle$ .



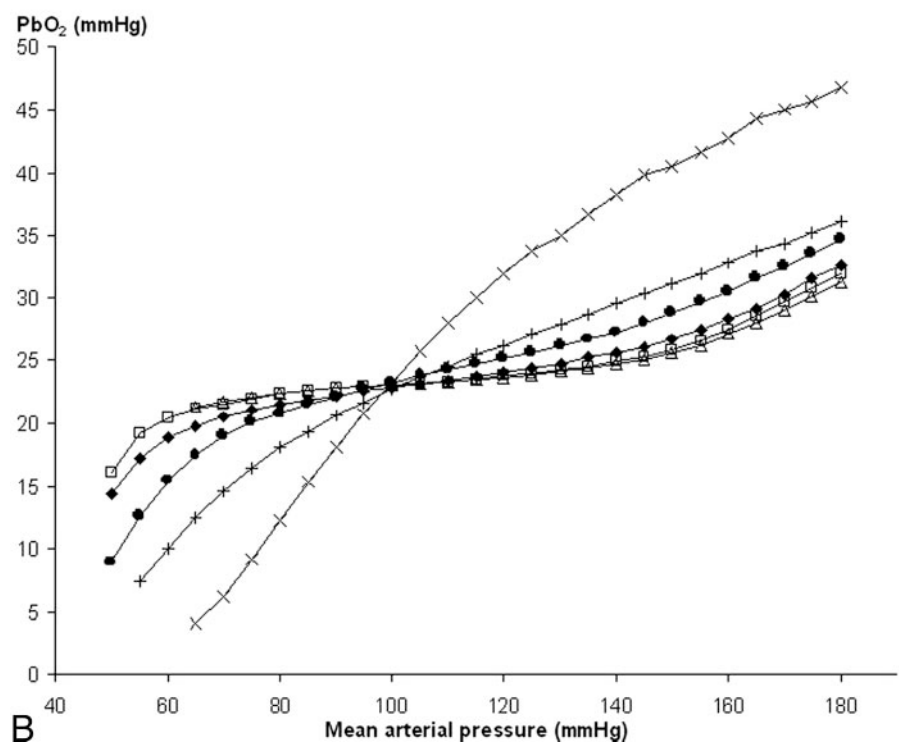
particularly at higher MAPs, which is analogous to the effects of extra-pulmonary shunt on arterial oxygenation. The modeled size of the effect is proportional to the degree of impairment of vascular reactivity. Given the relatively small changes simulated by hemispheric abnormalities in vascular reactivity, this would imply that jugular venous hyperoxia (4) is associated with very high proportions of luxury flow or poor oxygen extraction. This model of abnormal vascular reactivity used assumes that affected vessels assume (on average) an intermediate radius. If a vasodilated vasoparesis is modeled, then higher flows (and therefore higher  $PbO_2$  and  $SjO_2$ ) are seen; conversely, vasospastic vasoparesis has the opposite effect (Fig. 8). Clinical data do not clarify which effect predominates in brain

injury. The vasodilated and nondilated models of impaired vascular reactivity are consistent with clinical situations of increased edema formation (and worsening intracranial pressure) with increased CPP. The vasoconstrictive modeling provides a theoretical basis for the findings of Coles et al. (5), where increasing MAP reduced the amount of brain tissue with ischemic levels of oxygen supply.

The combination of moderate hypocapnia and either moderate hypoxia or intracranial edema leads to significantly reduced  $PbO_2$  (Fig. 4) in the simulation. This is consistent with some of the clinical data from patients with severe head injury, where hyperventilation was associated with significant reduction in  $PbO_2$  (6) and CBF (7), though not with others (8).

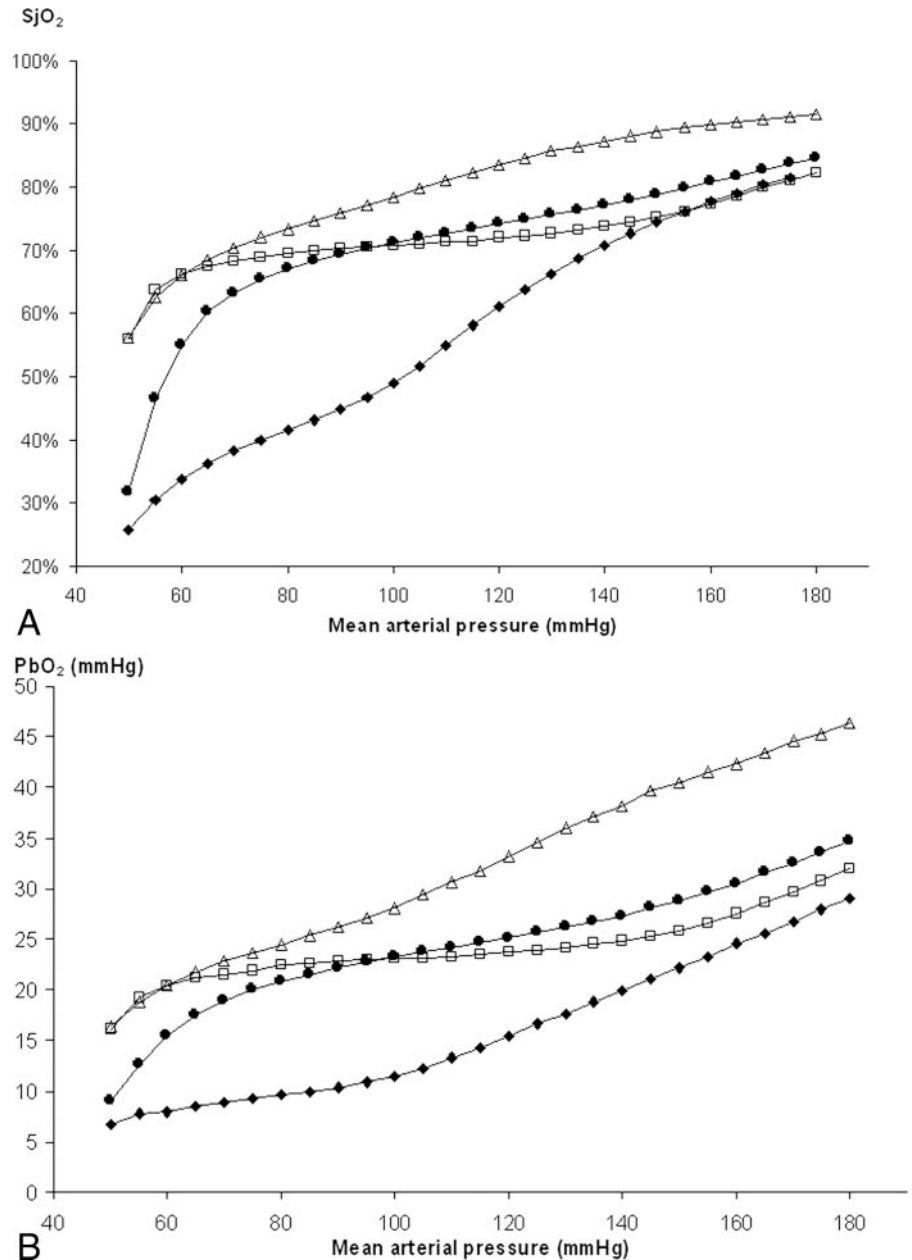


**Figure 7.** A, The effect of mean arterial blood pressure (MAP) and increasingly impaired vascular reactivity on modeled jugular venous oxygen saturation. Vascular reactivity is altered independently within the two hemispheres. Vascular reactivity normal ( $\square$ ). Vascular reactivity 75% bilaterally ( $\blacklozenge$ ). Normal vascular reactivity one side, 50% other side ( $\triangle$ ). Vascular reactivity 50% bilaterally ( $\bullet$ ). Vascular reactivity 25% bilaterally  $+$ . Normal vascular reactivity one side, complete vasoparesis other side  $\times$ . B, The effect of MAP and increasingly impaired vascular reactivity on modeled brain tissue oxygenation. Vascular reactivity is altered independently within the two hemispheres. Vascular reactivity normal ( $\square$ ). Vascular reactivity 75% bilaterally ( $\blacklozenge$ ). Normal vascular reactivity one side, 50% other side ( $\triangle$ ). Vascular reactivity 50% bilaterally ( $\bullet$ ). Vascular reactivity 25% bilaterally  $+$ . Normal vascular reactivity one side, complete vasoparesis other side,  $PbO_2$  from abnormal side  $\times$ .



Several assumptions have to be made as part of this modeling and these need to be considered when assessing the results. The model treats each hemisphere as a homogeneous unit with no difference in oxygen use or relative CBF. Although heterogeneity within the hemisphere would influence the absolute values seen, it is unlikely to alter the patterns of behavior noted here. The 25%–75% reduction in autoregulation gain used is necessarily arbitrary, and is not meant to imply a particular clinical scenario; rather it is used as an illustration of principle. Other workers

have used complete vasoparesis and vascular relaxation as a model. However, this is unlikely to occur in clinical practice, except with complete vasodilation due to volatile anesthetics or very high  $Paco_2$ . The NCS was set up with normal intracranial compliance and CSF dynamics. This was done to facilitate examination of a limited number of factors. Furthermore, greatly reduced CSF absorption and intracranial compliance, as is seen in some, but not all, acute brain injury, results in a temporally unstable system, which makes creation of meaningful static autoregulation curves difficult.



**Figure 8.** A, The effect of mean arterial blood pressure (MAP) and different models of impaired vascular reactivity on modeled jugular venous oxygen saturation. Vascular reactivity normal (□). Vascular reactivity 50% bilaterally, normal tone (●). Vascular reactivity 50% bilaterally, moderate vasoconstriction (◆). Vascular reactivity 50% bilaterally, moderate vasodilatation (△). B, The effect of MAP and impaired vascular reactivity on modeled brain tissue oxygenation. Vascular reactivity normal (□). Vascular reactivity 50% bilaterally, normal tone (●). Vascular reactivity 50% bilaterally, moderate vasoconstriction (◆). Vascular reactivity 50% bilaterally, moderate vasodilatation (△).

The edema effect used in the model is relatively simplistic, but effectively creates an increased distance between capillary and intracellular compartments. This, and the lack of change of CSF dynamics, is consistent with some forms of cerebral edema. Menon et al. (9) found microvascular collapse, endothelial swelling and perivascular edema in pericontusional tissue and interpreted this as creating an increase in tissue path length for oxygen. Thus, increased intercapillary distance can be used as a summary measure for the effective capillary density, which may be altered to varying degrees by edema or loss of open capillaries through blockage or upstream regulation. Quantitative values for this increase in tissue length are not available. Given that the model used accounts for both increased volume, secondary to edema, and loss of functioning capillaries, due to collapse or blockage, the 5%–15% increments used seem to be

reasonable estimates. Of note,  $SjO_2$  is not significantly affected by the presence of cellular edema, and thus the  $SjO_2$ – $PbO_2$  gradient increases, consistent with clinical data (10), suggesting that diffusion-limited oxygen delivery may occur in head injury. This will create clinical situations where  $SjO_2$  and MCA<sub>FFV</sub> may be near normal, despite brain tissue hypoxia.

Abnormal oxygen and glucose metabolism is found in the presence of brain injury and tumor and will influence local and global oxygen values. The model of intracellular metabolism used in the NCS is designed to be disease-free, and so does not reflect this behavior. However, Menon et al. (9) found that oxygen extraction fraction had a smaller increase in pericontusional tissue than in normal tissue in situations of low perfusion, which is consistent with the NCS oxygen model. The individual effects of  $Paco_2$  and  $Sao_2$  on CBF fit with experimental data, and Aubert and Costalat (11) have

reasonable data fitting the intracellular metabolism model to magnetic resonance imaging blood oxygenation level dependent results. Some caution needs to be exercised, as the magnetic resonance imaging blood oxygenation level dependent signals represent the effects of cerebral activation in normal brain, not the situation of reduced perfusion. The interaction between arterial oxygenation and carbon dioxide reactivity is not as complex as it needs to be to match some of the experimental data (12), though the interaction is relatively small and is unlikely to alter the results in a clinically significant manner. The effect of CPP on  $SjO_2$  and  $PbO_2$  has relatively few supporting human data, though as detailed in the accompanying article, there is good qualitative agreement between the NCS and clinical data (13). Significant decreases in CPP are associated with decreases in  $PbO_2$  in nonlesional tissue in subjects with acute traumatic brain injury (13).

Although the NCS does not attempt to reproduce gross anatomical volume effects such as transtentorial herniation, it does model some spatial effects.  $SjO_2$  is the flow-weighted average of all vessel beds and thus a global measure, whereas  $PbO_2$  is a local measure. For the purposes of these experiments, the differences were made to apply to a whole hemisphere, but the difference in  $PbO_2$  between "normal" and "abnormal" would apply wherever the local measurements were made. With smaller volumes of abnormality, a smaller change in global measures would be seen. Similarly, the data shown in Figure 5 can be interpreted as the effect of positioning a tissue oxygen sensor in different areas of perilesional tissue with varying degrees of edema.

Does this simulation add anything to what is already known: that hypoxia and hypotension are bad for the traumatized brain? If the NCS had produced results contradictory to that, then the NCS itself would be suspect. Importantly, the NCS has quantitatively demonstrated that  $SjO_2$  and MCA<sub>FV</sub> (and by implication regional CBF), on their own, are insensitive markers of tissue hypoxia in the presence of impaired vascular reactivity. Conversely, the presence of two or more markers of poor cerebral perfusion is a strong indicator of inadequate cerebral oxygenation. In addition, this theoretical demonstration of increased

$SjO_2$ - $PbO_2$  gradients when edema is present, in combination with the clinical findings of Menon et al. (9), should alert clinicians to the possibility of falsely reassuring global monitoring variables in patients with intracranial pathology.

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