



Control of Cerebral Blood Flow by Blood Gases

James Duffin^{1,2,3,4*}, David J. Mikulis⁵ and Joseph A. Fisher^{1,2,3,4,6}

¹ Department of Anesthesia and Pain Management, University of Toronto, Toronto, ON, Canada, ² Department of Physiology, University of Toronto, Toronto, ON, Canada, ³ Thornhill Research Inc., Toronto, ON, Canada, ⁴ University Health Network, Toronto, ON, Canada, ⁵ Division of Neuroradiology Imaging, Joint Department of Medical Imaging, University Health Network, Toronto, ON, Canada, ⁶ Faculty of Medicine, Institute of Medical Science, University of Toronto, Toronto, ON, Canada

Cerebrovascular reactivity can be measured as the cerebrovascular flow response to a hypercapnic challenge. The many faceted responses of cerebral blood flow to combinations of blood gas challenges are mediated by its vasculature's smooth muscle and can be comprehensively described by a simple mathematical model. The model accounts for the blood flow during hypoxia, anemia, hypocapnia, and hypercapnia. The main hypothetical basis of the model is that these various challenges, singly or in combination, act via a common regulatory pathway: the regulation of intracellular hydrogen ion concentration. This regulation is achieved by membrane transport of strongly dissociated ions to control their intracellular concentrations. The model assumes that smooth muscle vasoconstriction and vasodilation and hence cerebral blood flow, are proportional to the intracellular hydrogen ion concentration. Model predictions of the cerebral blood flow responses to hypoxia, anemia, hypocapnia, and hypercapnia match the form of observed responses, providing some confidence that the theories on which the model is based have some merit.

Keywords: cerebral blood flow, mathematical model, hypercapnia, hypoxia, anemia, hypocapnia

OPEN ACCESS

Edited by:

Antonio Colantuoni,
University of Naples Federico II, Italy

Reviewed by:

Romeo Martini,
University Hospital of Padua, Italy
Nancy Rusch,
University of Arkansas for Medical
Sciences, United States

*Correspondence:

James Duffin
j.duffin@utoronto.ca

Specialty section:

This article was submitted to
Vascular Physiology,
a section of the journal
Frontiers in Physiology

Received: 10 December 2020

Accepted: 25 January 2021

Published: 18 February 2021

Citation:

Duffin J, Mikulis DJ and Fisher JA
(2021) Control of Cerebral Blood Flow
by Blood Gases.
Front. Physiol. 12:640075.
doi: 10.3389/fphys.2021.640075

INTRODUCTION

The mathematical model proposed here is concerned with the physiological mechanisms regulating cerebral blood flow (CBF) in response to anemia, hypoxia, and hypercapnia and hypocapnia. Cerebral blood flow increases in anemia (Brown et al., 1985; Borzage et al., 2016; Zheng et al., 2016); as well as during acute alterations in arterial blood gases (Willie et al., 2012) such as hypoxia (Cohen et al., 1967; Mardimae et al., 2012), and hypercapnia (Battisti-Charbonney et al., 2011). The model is tested by comparing its predictions to observations.

Cerebral blood flow is largely controlled by changes in the vascular resistance in parenchymal arterioles. The large pial arteries on the surface of the cortex contain multiple layers of vascular smooth muscle cells (Wei et al., 1980). These pial vessels branch into penetrating arterioles containing a single layer of vascular smooth muscle cells (Nishimura et al., 2007), and enter the cortical parenchyma, where micro vessels covered by pericytes but do not control microregional CBF (Hill et al., 2015). Vascular smooth muscle is the final CBF control effector in: (i) *Autoregulation* which mitigates against variations in brain perfusion pressure (Tan and Taylor, 2014; Tzeng and Ainslie, 2014), and (ii) *Neurovascular Coupling* which increases local blood flow

in response to increased neuronal metabolic demand (Attwell et al., 2011, 2016; Phillips et al., 2016; Hosford and Gourine, 2019; Hoiland et al., 2020).

Acute changes in arterial blood gases also affect CBF, independently of these regulatory mechanisms (Willie et al., 2012). Hypoxia (Cohen et al., 1967; Mardimae et al., 2012) and hypercapnia (Battisti-Charbonney et al., 2011; Hoiland et al., 2019), as well as decreases in hemoglobin (anemia) (Borzage et al., 2016; Duffin et al., 2020) increase CBF, while hypocapnia decreases CBF (Battisti-Charbonney et al., 2011; Hoiland et al., 2019). It is the increase in CBF during hypercapnia that is the basis of cerebrovascular reactivity (CVR) testing.

In the presence of hypoxia and anemia, vascular tone decreases to increase CBF and maintain an adequate O₂ supply (Duffin, 2020). Long term changes in CBF occur in chronic anemia (Brown et al., 1985) including sickle cell anemia (Bush et al., 2016), altitude acclimatization (Wolff, 2000) and chronic hypoxia (Powell and Fu, 2008), and are accompanied by a multitude of adaptive changes orchestrated via the HIF 1 alpha pathway (Poellinger and Johnson, 2004). Over the long term the cerebral vasculature remodels to provide larger diameter vessels and accommodate higher CBF (Hulbert et al., 2017).

Vascular smooth muscle tone depends on intracellular [H⁺]; contracting in alkalosis and relaxing in acidosis (Austin and Wray, 1993; Aalkjaer and Peng, 1997) to consequently alter CBF. Changes in intracellular [H⁺] alter intracellular [Ca²⁺] (Swietach et al., 2013) and consequently smooth muscle tone (Boedtkjer, 2018), with the relaxation produced by hypercapnic acidosis, as in CVR testing, mediated by a reduction of [Ca²⁺] (Peng et al., 1998), although, rapid acute acidification can cause a transient increase in intracellular [Ca²⁺] that leads to contraction (Jensen et al., 1993).

Intracellular [H⁺] is the key intracellular regulated ion (Boedtkjer and Aalkjaer, 2012; Boedtkjer, 2018; Rasmussen and Boedtkjer, 2018); with a typical resting intracellular [H⁺] in vascular smooth muscle cells of about 50–80 nM/L (Boedtkjer et al., 2012). This regulation requires a net acid extrusion to maintain normal intracellular acid–base homeostasis, and it is this regulation that is challenged during CVR hypercapnia, producing a vasodilation and increased CBF (Kontos et al., 1977; Peng et al., 1998).

Stewart (Stewart, 1983; Hughes and Brain, 2013) has suggested an insightful approach to understanding acid–base changes in biological systems. In this system, intracellular [H⁺] is determined by CO₂ tension, the balance of concentrations of the strongly dissociated ions (the strong ion difference [SID]), and the requirement for electroneutrality. Consequently, the regulation of intracellular [H⁺] depends on cell membrane ion exchangers (Aalkjaer, 1990; Hughes and Brain, 2013; Boedtkjer, 2018; Garneau et al., 2020), to control intracellular [SID]. These membrane ion exchangers are energy dependent (Garneau et al., 2020) so that reductions in O₂ availability (Hoiland et al., 2016) (blood O₂ content, CaO₂) to the cerebral vasculature smooth muscles reduces the ability of these membrane ion exchangers to control intracellular [SID], and hence intracellular [H⁺], smooth muscle tone and CBF. Thus, changes in arterial CO₂ tension (PaCO₂) override intracellular [H⁺] regulation to

produce vasodilation and vasoconstriction. Similarly, decreases in CaO₂ caused by decreases in arterial O₂ tension (PaO₂, i.e., hypoxia) or hemoglobin concentration ([Hb] i.e., anemia) degrade the efficiency or capacity of membrane ion exchangers that control [SID] producing an increase in intracellular [H⁺], which causes vasodilation and results in an increase in CBF. This model is pictured in **Figure 1**.

MATERIALS AND METHODS

The model equations are presented in the following assumptions using these symbols:

[H⁺] = intracellular hydrogen ion concentration (nM/L).
 PCO₂ = intracellular CO₂ tension = arterial CO₂ tension (mmHg).
 [SID] = intracellular [strongly dissociated cations] – [strongly dissociated anions] (mM/L).
 CBF = cerebral blood flow (ml/min/100 ml).
 CaO₂ = arterial O₂ concentration/content (ml/ml).

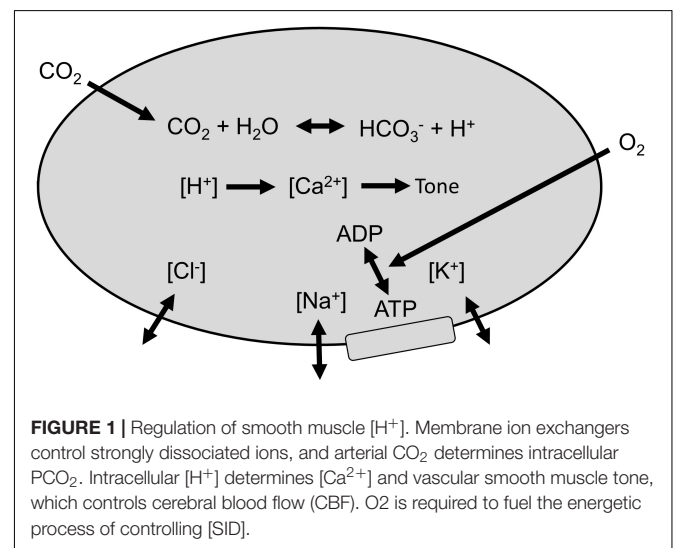
The equation parameters were empirically derived from observed responses to the various disturbances.

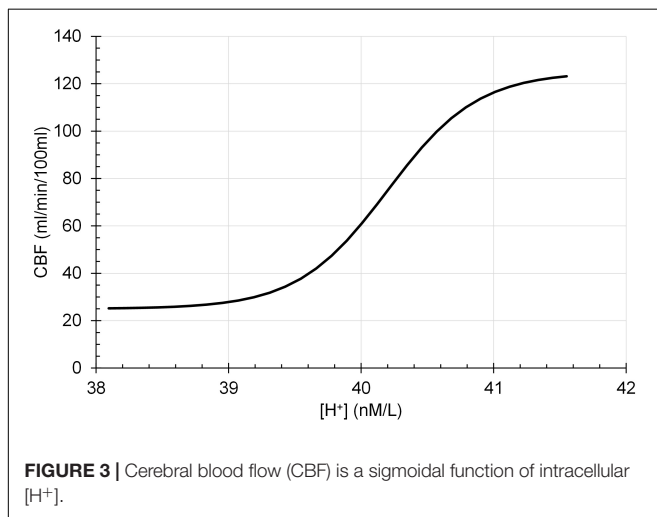
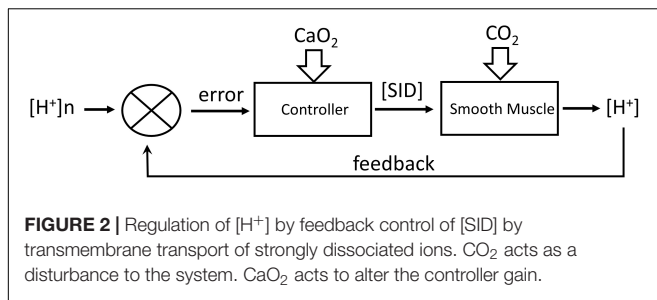
Assumption 1: Cerebrovascular smooth muscle intracellular [H⁺] is a function of PCO₂ and [SID] (Stewart, 1983) (see **Appendix**):

$$[H^+] \text{ (nM/L)} = \text{Function of } \{PCO_2, [SID]\} \quad (1)$$

Assumption 2: [H⁺] is regulated by a feedback alteration of [SID] proportional to the deviation of [H⁺] from its regulated value of [H⁺]_n = 40 nM/L according to the following eq. 2, which assumes that maximum vasoconstriction occurs at PCO₂ = 10 mmHg and [SID] = 5.5 mM/L. **Figure 2** outlines the operation of this regulator.

$$[SID] = 5.5 + \text{Gain} * (([H^+] - 40) + 2) \quad (2)$$





Assumption 3: Smooth muscle tone is assumed to be limited to a maximum vasoconstriction and vasodilation so that CBF is a sigmoid function of intracellular $[H^+]$ according to the following eq. 3, which is illustrated in **Figure 3**:

$$CBF = 25 + 100 / (1 + \exp(-([H^+] - 40.2) / 0.34)) \quad (3)$$

Assumption 4: The regulation of $[H^+]$ by $[SID]$ is oxygen dependent with the Gain of eq. 2 a function of arterial oxygen content, CaO_2 , according to eq. 4, as illustrated in **Figure 4**.

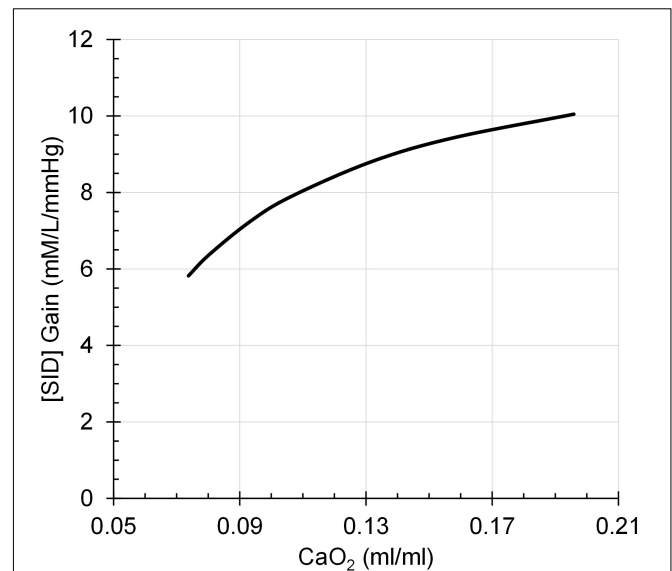
$$\text{Gain} = 12.6 - 0.5 / CaO_2; \quad (4)$$

CaO_2 is calculated from $PaCO_2$, PaO_2 , and $[Hb]$ using previously published equations (Duffin, 2005; Balaban et al., 2013).

The system equations are solved using an iterative approach (LabVIEW, National Instruments, Austin, TX, United States) outlined in the block diagram of **Figure 5**.

RESULTS

The model performance was assessed by its CBF responses to changes in PCO_2 , PO_2 and $[Hb]$ as shown in the following figures (**Figures 6–8**), which compare the model responses with examples of observed responses.



DISCUSSION

The model predictions for CBF responses match the form of the observed responses, providing some confidence that the theories on which the model was based are realistic. Of course, such a model does not prove the theories are correct, merely that they are feasible physiological mechanisms, and the interaction of the flow determinants are generally aligned to that of the model.

It must be emphasised that the model does not attempt to accurately predict the experimental examples provided but is a generic prediction of the form of the responses to test the hypotheses. For example, the midpoint of the sigmoidal response to CO_2 from a TCD experiment in **Figure 6** is lower than that of the model response. However, it is not beyond the bounds of observed midpoints in other experiment using different methods. For example, the midpoints in the TCD experiments (means of 35–36 mmHg) differ from those derived from the vascular resistance which varied over a range of 38–48 mmHg (Duffin et al., 2018). A similar observation may be made for the responses to $[Hb]$ in **Figure 8** where the model responses exhibit considerable curvature as $[Hb]$ decreases compared to the experimental observations. We note that there is considerable variability in the experimental observations, and while the authors chose to fit a linear response, the data indicates that curvature is present, as we showed in Duffin et al. (2020). Another confounding factor in the experimental observations is the variability of PCO_2 in the experiments where PCO_2 was uncontrolled compared to the model where isocapnia was maintained. In summary, there is no doubt that the model can be improved by adjusting the parameters and the relations used, such as the linear one between $[SID]$ and $[H^+]$ which is almost certainly a simplification and awaits experimental measurements.

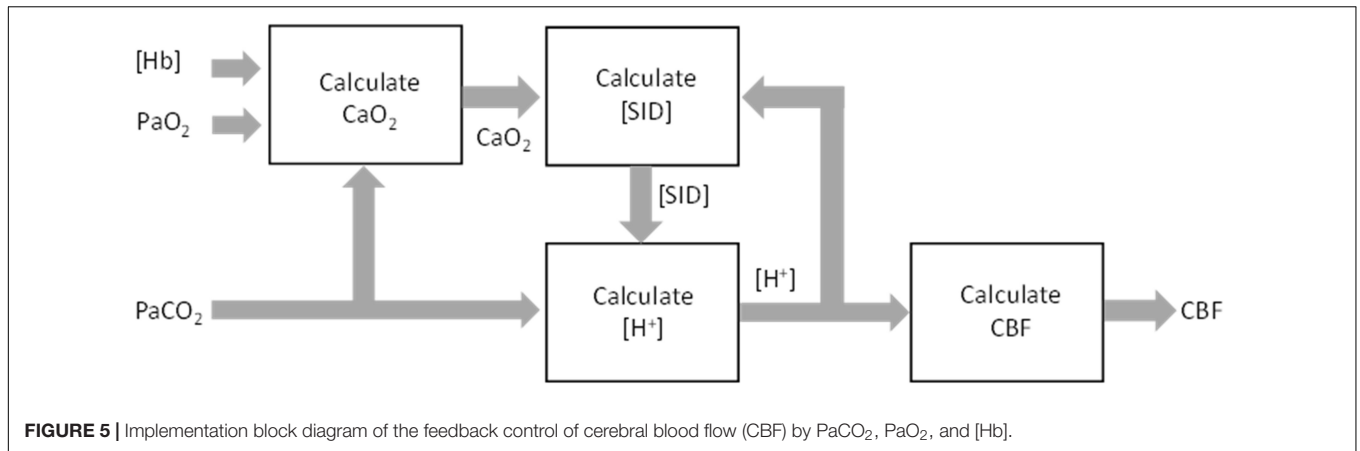


FIGURE 5 | Implementation block diagram of the feedback control of cerebral blood flow (CBF) by $PaCO_2$, PaO_2 , and $[Hb]$.

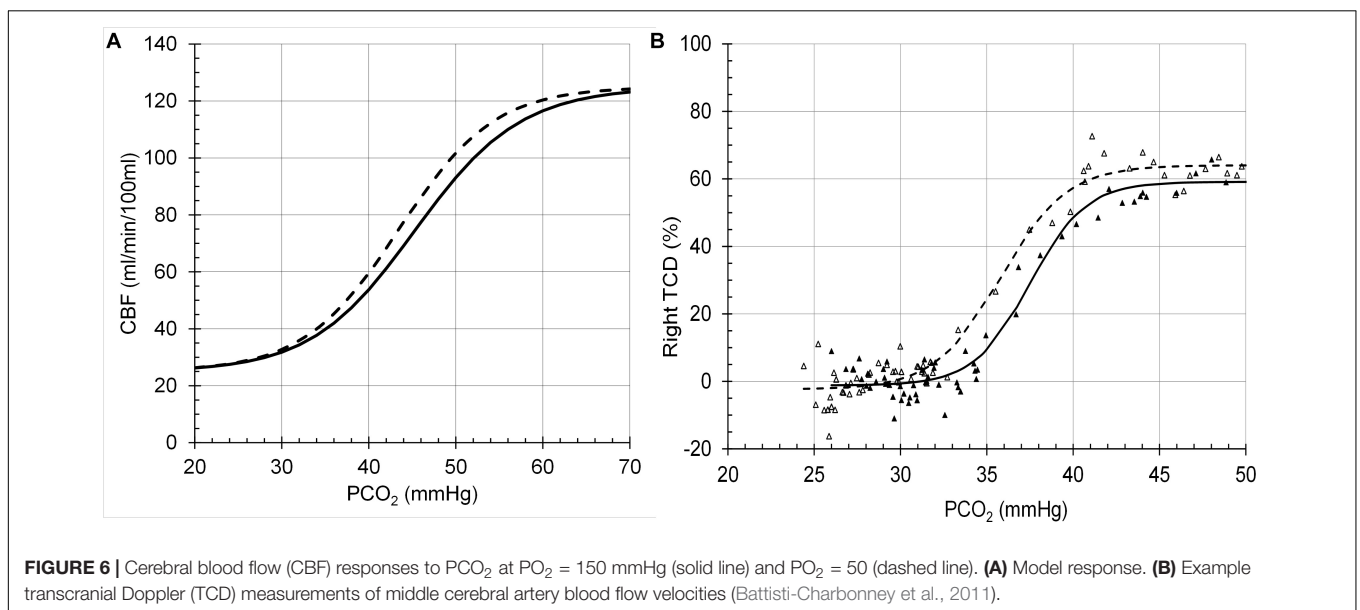


FIGURE 6 | Cerebral blood flow (CBF) responses to PCO_2 at $PO_2 = 150$ mmHg (solid line) and $PO_2 = 50$ (dashed line). **(A)** Model response. **(B)** Example transcranial Doppler (TCD) measurements of middle cerebral artery blood flow velocities (Battisti-Charbonney et al., 2011).

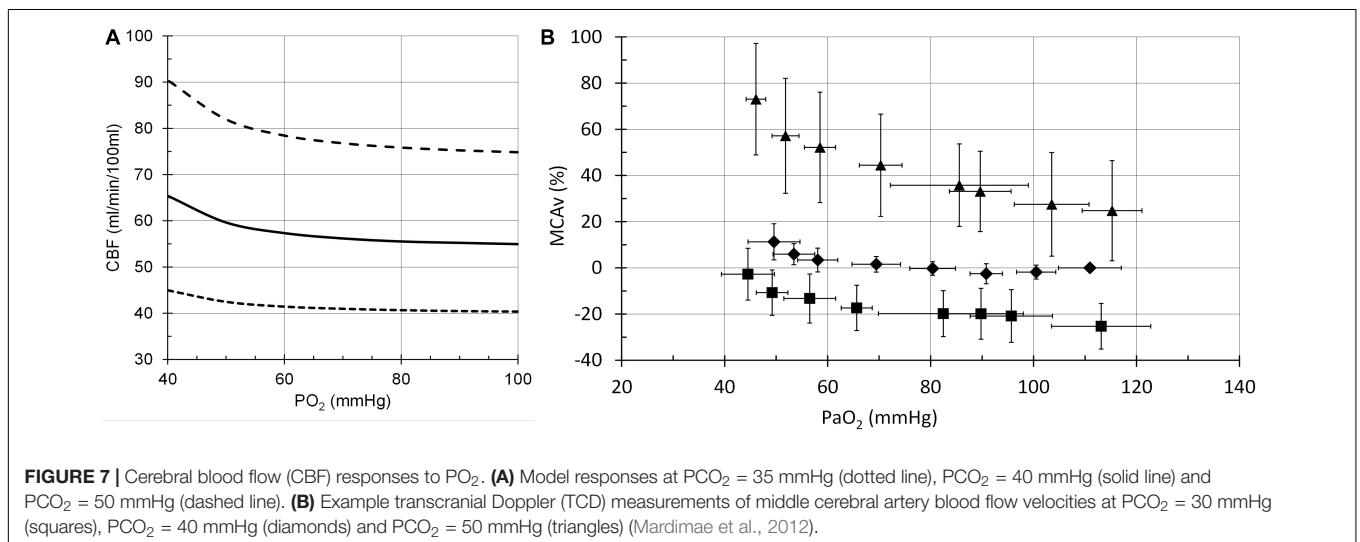
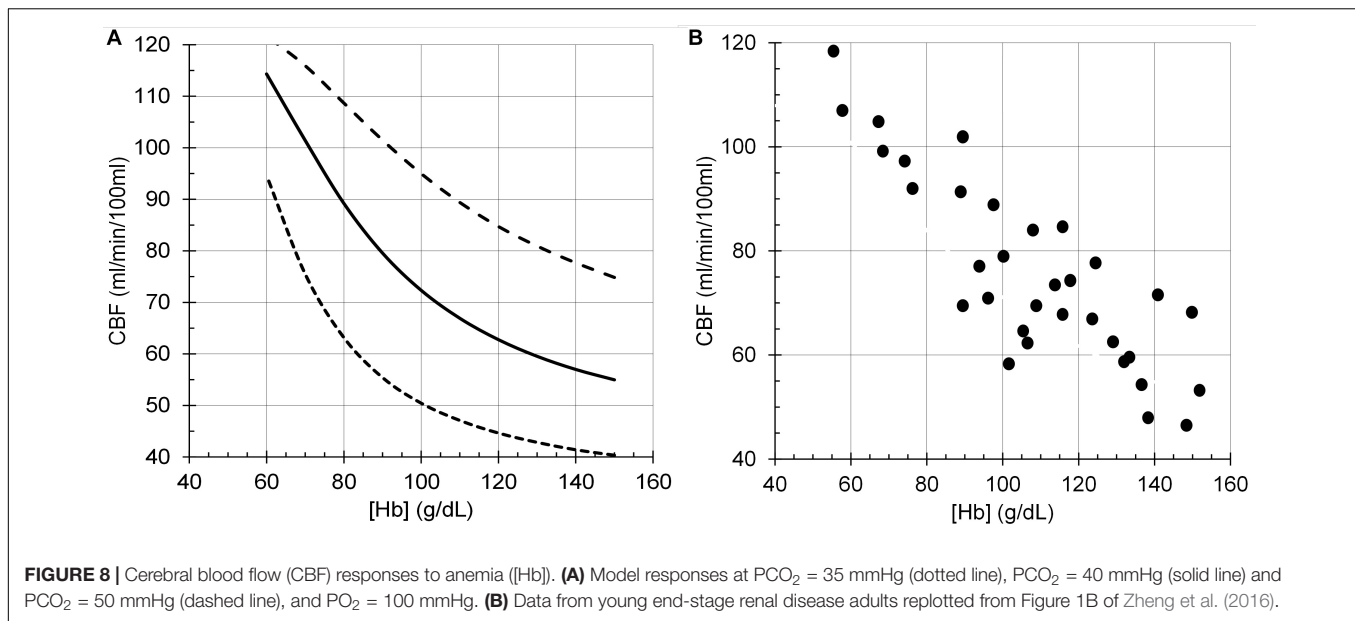


FIGURE 7 | Cerebral blood flow (CBF) responses to PO_2 . **(A)** Model responses at $PCO_2 = 35$ mmHg (dotted line), $PCO_2 = 40$ mmHg (solid line) and $PCO_2 = 50$ mmHg (dashed line). **(B)** Example transcranial Doppler (TCD) measurements of middle cerebral artery blood flow velocities at $PCO_2 = 30$ mmHg (squares), $PCO_2 = 40$ mmHg (diamonds) and $PCO_2 = 50$ mmHg (triangles) (Mardimae et al., 2012).



There are several assumptions underlying the model, and, as reviewed in the introduction, some are supported by experimental evidence. That cerebrovascular smooth muscle attempts to maintain a constant intracellular $[H^+]$ by some regulatory process appears to be supported (Boedtkjer, 2018). Furthermore, that $[H^+]$ acts via alterations in $[Ca^{2+}]$ to control vascular smooth muscle tone and consequently CBF also appears to be substantiated (Aalkjaer and Peng, 1997). The physico-chemical theory of acid-base described by Stewart (Stewart, 1981) and illustrated in Hughes and Brain (2013) dictates that intracellular $[H^+]$ and bicarbonate $[HCO_3^-]$ are dependent variables, with CO_2 and [SID] independent variables that determine them. Therefore, the model assumption that $[H^+]$ is regulated by controlling [SID] in the face of a CO_2 disturbance is an obvious conclusion. That [SID] must be adjusted by membrane transport processes is well known (Garneau et al., 2020).

The simple equation proposed to describe this regulation process is one of many that could be used to describe the relation between [SID] and the error signal, deviation of $[H^+]$ from a normal resting value. The equation form assumes that maximum vasoconstriction occurs at the hypocapnic limit of vasoconstriction ($PCO_2 = 10$ mmHg where $[SID] = 5.5$ mM/L attempting to restore $[H^+]$ to 40 nM/L). This assumption has the result that at a normal resting PCO_2 of 40 mmHg the regulation of [SID] is active and consequently subject to degradation by a lack of O_2 .

The assumption that a decrease of CaO_2 affects intracellular $[H^+]$ by degrading the [SID] regulation is a major hypothesis of the model and is testable. That CBF is related to CaO_2 , whether changed by anemia or hypoxia is well documented and the subject of a previous model (Duffin, 2020). Furthermore, it was previously demonstrated that brain tissue PO_2 was not a viable choice as a sensed variable controlling CBF (Duffin et al., 2020). Consequently, CaO_2 was the obvious choice of variable to

represent a decreased O_2 supply affecting the supply of energy to the membrane transporters of strongly dissociated ions thereby degrading the [SID] regulation of $[H^+]$. However, there does not currently appear to be supportive experimental evidence for this assumption, and it requires investigation.

Other mechanisms by which CaO_2 may change CBF involving nitric oxide (NO) have been proposed. Some (Hoiland et al., 2020) are linked to neurovascular coupling control of CBF (Attwell et al., 2011) rather than the control of blood O_2 supply. Others involve release of NO from red blood cells (Hoiland et al., 2016) or endothelial cells (Iadecola, 1992; Kisler et al., 2017). However, experiments show that NO does not appear to be involved in responses to changes in blood gases (White et al., 1998; Ide et al., 2007). Furthermore, these mechanisms for CBF control independent of CO_2 , whether involving NO or not, do not agree with the observations of the interaction of CaO_2 and CO_2 in the control of CBF. For example, in hypocapnia, where vasoconstriction lowers CBF, a decrease in CaO_2 would be expected to increase CBF at least as much as is observed in normocapnia, but does not (Mardimae et al., 2012). The model proposed does so, exhibiting the interaction between CaO_2 and CO_2 observed (Figure 5).

CONCLUSION

This model can be used to predict the effects of hypoxia, hypercapnia and anemia, alone and in combination, on CBF. It therefore has practical usefulness for intensive care and intra-operative management where these conditions apply, as well as for drugs that affect carbonic acid dissociation and elimination, and shift the oxyhemoglobin dissociation curve.

The hypothetical basis of the model is not only supported in part by the experimental evidence used in its formulation, but also by the success of the model predictions of experimental observations. Thus, the hypothesized mechanisms merit

consideration as realistic possibilities, deserving of experimental investigation to determine their correctness. We suggest that the physiological mechanism described in this model for the response to CO₂ has widespread application as a general principle. It has already been used to describe the responses of the carotid body glomus cells to CO₂ (Duffin, 2020) and may also be applicable to the central chemoreception of CO₂ (Guyenet et al., 2019). It is an aspect of a physioc-chemical view of acid-base control pioneered by Stewart (1981) that should enable a better understanding of the processes involved in sensing CO₂ and the effects of disturbances in energy supply and external CO₂ on the process. We believe that such an increased understanding will impact research in this field to further characterise the mechanisms involved which in turn may inspire intervention opportunities that apply to clinical care.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

REFERENCES

- Aalkjaer, C. (1990). Regulation of intracellular pH and its role in vascular smooth muscle function. *J. Hypertens.* 8, 197–206. doi: 10.1097/00004872-199003000-00001
- Aalkjaer, C., and Peng, H.-L. (1997). pH and smooth muscle. *Acta Physiol. Scand.* 161, 557–566.
- Attwell, D., Buchan, A. M., Charpak, S., Lauritzen, M., Macvicar, B. A., and Newman, E. A. (2011). Glial and neuronal control of brain blood flow. *Nature* 468, 232–243. doi: 10.1038/nature09613
- Attwell, D., Mishra, A., Hall, C. N., O'Farrell, F. M., and Dalkara, T. (2016). What is a pericyte? *J. Cereb. Blood Flow Metab.* 36, 451–455. doi: 10.1177/0271678x15610340
- Austin, C., and Wray, S. (1993). Extracellular pH signals affect rat vascular tone by rapid transduction into intracellular pH changes. *J. Physiol.* 466, 1–8.
- Balaban, D. Y., Duffin, J., Preiss, D., Mardimae, A., Vesely, A., Slessarev, M., et al. (2013). The in-vivo oxyhaemoglobin dissociation curve at sea level and high altitude. *Respir. Physiol. Neurobiol.* 186, 45–52. doi: 10.1016/j.resp.2012.12.011
- Battisti-Charbonney, A., Fisher, J., and Duffin, J. (2011). The cerebrovascular response to carbon dioxide in humans. *J. Physiol.* 589, 3039–3048. doi: 10.1113/jphysiol.2011.206052
- Boedtker, E. (2018). Acid-base regulation and sensing: accelerators and brakes in metabolic regulation of cerebrovascular tone. *J. Cereb. Blood Flow Metab.* 38, 588–602. doi: 10.1177/0271678x17733868
- Boedtker, E., and Aalkjaer, C. (2012). Intracellular pH in the resistance vasculature: regulation and functional implications. *J. Vasc. Res.* 49, 479–496. doi: 10.1159/000341235
- Boedtker, E., Damkier, H. H., and Aalkjaer, C. (2012). NHE1 knockout reduces blood pressure and arterial media/lumen ratio with no effect on resting pH(i) in the vascular wall. *J. Physiol.* 590, 1895–1906. doi: 10.1113/jphysiol.2011.227132
- Borzage, M. T., Bush, A. M., Choi, S., Nederveen, A. J., Václavů, L., Coates, T. D., et al. (2016). Predictors of cerebral blood flow in patients with and without anemia. *J. Appl. Physiol.* 120, 976–981. doi: 10.1152/jappphysiol.00994.2015
- Brown, M. M., Wade, J. P., and Marshall, J. (1985). Fundamental importance of arterial oxygen content in the regulation of cerebral blood flow in man. *Brain* 108(Pt 1), 81–93. doi: 10.1093/brain/108.1.81
- Bush, A. M., Borzage, M. T., Choi, S., Vaclavu, L., Tamrazi, B., Nederveen, A. J., et al. (2016). Determinants of resting cerebral blood flow in sickle cell disease. *Am. J. Hematol.* 91, 912–917. doi: 10.1002/ajh.24441

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the Local Legislation and Institutional Requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JD: conception and programming. JD, JF, and DM: drafting and revising of the article and final approval of the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors thank Thornhill Research Inc. for support.

- Cohen, P. J., Alexander, S. C., Smith, T. C., Reivich, M., and Wollman, H. (1967). Effects of hypoxia and normocarbina on cerebral blood flow and metabolism in conscious man. *J. Appl. Physiol.* 23, 183–189. doi: 10.1152/jappl.1967.23.2.183
- Duffin, J. (2005). Role of acid-base balance in the chemoreflex control of breathing. *J. Appl. Physiol.* 99, 2255–2265. doi: 10.1152/jappphysiol.00640.2005
- Duffin, J. (2020). Fail-safe aspects of oxygen supply. *J. Physiol.* 598, 4859–4867. doi: 10.1113/jp280301
- Duffin, J., Hare, G. M. T., and Fisher, J. A. (2020). A mathematical model of cerebral blood flow control in anaemia and hypoxia. *J. Physiol.* 598, 717–730. doi: 10.1113/jp279237
- Duffin, J., Sobczyk, O., Mcketton, L., Crawley, A., Poulblanc, J., Venkatraghavan, L., et al. (2018). Cerebrovascular Resistance: The Basis of Cerebrovascular Reactivity. *Front. Neurosci.* 12:409. doi: 10.3389/fnins.2018.00409
- Garneau, A. P., Slimani, S., Fiola, M. J., Tremblay, L. E., and Isenring, P. (2020). Multiple facets and roles of Na⁺-K⁺-Cl⁻ cotransport: mechanisms and therapeutic implications. *Physiology* 35, 415–429. doi: 10.1152/physiol.00012.2020
- Guyenet, P. G., Stornetta, R. L., Souza, G. M. P. R., Abbott, S. B. G., Shi, Y., and Bayliss, D. A. (2019). The retrotrapezoid nucleus: central chemoreceptor and regulator of breathing automaticity. *Trend. Neurosci.* 42, 807–824. doi: 10.1016/j.tins.2019.09.002
- Hill, R. A., Tong, L., Yuan, P., Murikinati, S., Gupta, S., and Grutzendler, J. (2015). Regional blood flow in the normal and ischemic brain is controlled by arteriolar smooth muscle cell contractility and not by capillary pericytes. *Neuron* 87, 95–110. doi: 10.1016/j.neuron.2015.06.001
- Hoiland, R. L., Bain, A. R., Rieger, M. G., Bailey, D. M., and Ainslie, P. N. (2016). Hypoxemia, oxygen content, and the regulation of cerebral blood flow. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 310, R398–R413.
- Hoiland, R. L., Caldwell, H. G., Howe, C. A., Nowak-Flück, D., Stacey, B. S., Bailey, D. M., et al. (2020). Nitric oxide is fundamental to neurovascular coupling in humans. *J. Physiol.* 598, 4927–4939. doi: 10.1113/jp280162
- Hoiland, R. L., Fisher, J. A., and Ainslie, P. N. (2019). Regulation of the cerebral circulation by arterial carbon dioxide. *Compr. Physiol.* 9, 1101–1154. doi: 10.1002/cphy.c180021
- Hosford, P. S., and Gourine, A. V. (2019). What is the key mediator of the neurovascular coupling response? *Neurosci. Biobehav. Rev.* 96, 174–181. doi: 10.1016/j.neubiorev.2018.11.011
- Hughes, R., and Brain, M. J. (2013). A simplified bedside approach to acid-base: fluid physiology utilizing classical and physicochemical approaches. *Anaesth. Intens. Care Med.* 14, 445–452. doi: 10.1016/j.mpaic.2013.07.013

- Hulbert, M. L., Guilliama, K. P., Fields, M. E., Bijlani, P., Ragan, D. K., Eldeniz, C., et al. (2017). Normalization of cerebral hemodynamics after hematopoietic stem cell transplant in children with sickle cell anemia. *Blood* 130, 2245–2245.
- Iadecola, C. (1992). Does nitric oxide mediate the increases in cerebral blood flow elicited by hypercapnia? *Proc. Natl. Acad. Sci. U.S.A.* 89, 3913–3916. doi: 10.1073/pnas.89.9.3913
- Ide, K., Worthley, M., Anderson, T., and Poulin, M. J. (2007). Effects of the nitric oxide synthase inhibitor L-NMMA on cerebrovascular and cardiovascular responses to hypoxia and Hypercapnia in humans. *J. Physiol.* 584, 321–332. doi: 10.1113/jphysiol.2007.138206
- Jensen, P. E., Hughes, A., Boonen, H. C., and Aalkjaer, C. (1993). Force, membrane potential, and $[Ca^{2+}]_i$ during activation of rat mesenteric small arteries with norepinephrine, potassium, aluminum fluoride, and Phorbol ester. Effects of changes in pHi. *Circ. Res.* 73, 314–324. doi: 10.1161/01.res.73.2.314
- Kisler, K., Nelson, A. R., Montagne, A., and Zlokovic, B. V. (2017). Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. *Nat. Rev. Neurosci.* 18, 419–434. doi: 10.1038/nrn.2017.48
- Kontos, H. A., Wei, E. P., Raper, A. J., and Patterson, J. L. Jr. (1977). Local mechanism of CO₂ action of cat pial arterioles. *Stroke* 8, 226–229. doi: 10.1161/01.str.8.2.226
- Mardimae, A., Balaban, D. Y., Machina, M. A., Han, J. S., Katznelson, R., Minkovich, L. L., et al. (2012). The interaction of carbon dioxide and hypoxia in the control of cerebral blood flow. *Pflugers Arch.* 464, 345–351.
- Nishimura, N., Schaffer, C. B., Friedman, B., Lyden, P. D., and Kleinfeld, D. (2007). Penetrating arterioles are a bottleneck in the perfusion of neocortex. *Proc. Natl. Acad. Sci. U.S.A.* 104, 365–370. doi: 10.1073/pnas.0609551104
- Peng, H. L., Ivarsen, A., Nilsson, H., and Aalkjaer, C. (1998). On the cellular mechanism for the effect of acidosis on vascular tone. *Acta Physiol. Scand.* 164, 517–525. doi: 10.1111/j.1365-201x.1998.tb10701.x
- Phillips, A. A., Chan, F. H., Zheng, M. M., Krassioukov, A. V., and Ainslie, P. N. (2016). Neurovascular coupling in humans: physiology, methodological advances and clinical implications. *J. Cereb. Blood Flow Metab.* 36, 647–664. doi: 10.1177/0271678x15617954
- Poellinger, L., and Johnson, R. S. (2004). HIF-1 and hypoxic response: the plot thickens. *Curr. Opin. Genet. Dev.* 14, 81–85. doi: 10.1016/j.gde.2003.12.006
- Powell, F. L., and Fu, Z. (2008). HIF-1 and ventilatory acclimatization to chronic hypoxia. *Respir. Physiol. Neurobiol.* 164, 282–287. doi: 10.1016/j.resp.2008.07.017
- Rasmussen, J. K., and Boedtker, E. (2018). Carbonic anhydrase inhibitors modify intracellular pH transients and contractions of rat middle cerebral arteries during CO₂/HCO₃⁻ fluctuations. *J. Cereb. Blood Flow Metab.* 38, 492–505. doi: 10.1177/0271678x17699224
- Stewart, P. A. (1981). *How to Understand Acid - Base: A Quantitative Acid - Base Primer for Biology and Medicine*. New York, NY: Elsevier.
- Stewart, P. A. (1983). Modern quantitative acid-base chemistry. *Can. J. Physiol. Pharmacol.* 61, 1444–1461. doi: 10.1139/y83-207
- Swietach, P., Youm, J. B., Saegusa, N., Leem, C. H., Spitzer, K. W., and Vaughan-Jones, R. D. (2013). Coupled Ca²⁺/H⁺ transport by cytoplasmic buffers regulates local Ca²⁺ and H⁺ ion signaling. *Proc. Natl. Acad. Sci. U.S.A.* 110, E2064–E2073.
- Tan, C. O., and Taylor, J. A. (2014). Integrative physiological and computational approaches to understand autonomic control of cerebral autoregulation. *Exper. Physiol.* 99, 3–15. doi: 10.1113/expphysiol.2013.072355
- Tzeng, Y. C., and Ainslie, P. N. (2014). Blood pressure regulation IX: cerebral autoregulation under blood pressure challenges. *Eur. J. Appl. Physiol.* 114, 545–559. doi: 10.1007/s00421-013-2667-y
- Wei, E. P., Kontos, H. A., and Patterson, J. L. Jr. (1980). Dependence of pial arteriolar response to hypercapnia on vessel size. *Am. J. Physiol.* 238, 697–703.
- White, R. P., Deane, C., Vallance, P., and Markus, H. S. (1998). Nitric oxide synthase inhibition in humans reduces cerebral blood flow but not the hyperemic response to hypercapnia. *Stroke* 29, 467–472. doi: 10.1161/01.str.29.2.467
- Willie, C. K., Macleod, D. B., Shaw, A. D., Smith, K. J., Tzeng, Y. C., Eves, N. D., et al. (2012). Regional brain blood flow in man during acute changes in arterial blood gases. *J. Physiol.* 590, 3261–3275. doi: 10.1113/jphysiol.2012.228551
- Wolff, C. B. (2000). Cerebral blood flow and oxygen delivery at high altitude. *High. Alt. Med. Biol.* 1, 33–38. doi: 10.1089/152702900320667
- Zheng, G., Wen, J., Yu, W., Li, X., Zhang, Z., Chen, H., et al. (2016). Anemia rather than hypertension contributes to cerebral hyperperfusion in young adults undergoing hemodialysis: a phase contrast MRI study. *Sci. Rep.* 6:22346.

Conflict of Interest: JF and DM have equity in Thornhill Medical Inc. JD receives salary support from Thornhill Medical Inc. Thornhill Medical Inc. provided no other support for the study.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Duffin, Mikulis and Fisher. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

APPENDIX

The acid-base control of intracellular $[H^+]$ was calculated using an iterative approach that solved eq. 1–4 to enforce electrical neutrality by minimizing R.

$$[HCO_3^-] = KC \cdot PCO_2 / [H^+] \quad (1)$$

$$[CO_3^{2-}] = K3 \cdot [HCO_3^-] / [H^+] \quad (2)$$

$$[OH^-] = K_w / [H^+] \quad (3)$$

$$R = [SID] + [H^+] - [HCO_3^-] - 2 \cdot [CO_3^{2-}] - [OH^-] \quad (4)$$

where:

PCO_2 (mmHg) is an input.

$[SID] = [\text{strongly dissociated cations}] - [\text{strongly dissociated anions}]$ (mM/L) is an input.

$[HCO_3^-]$ (mM/L)

$[CO_3^{2-}]$ (mM/L)

$[OH^-]$ (nM/L)

$KC = 2.45 \times 10^{-11}$

$K3 = 1.16 \times 10^{-10}$

$K_w = 2.39 \times 10^{-14}$