The effect of changing arterial blood pressure and carbon dioxide on cerebral blood flow.

Jean Claude Baron

Journal of
Neurology, Neurosurgery
& Psychiatry

The effect of changing arterial blood pressure and carbon dioxide on cerebral blood flow

Journal:	*Journal of Neurology, Neurosurgery, and Psychiatry*
Manuscript ID	jnnp-2019-322432.R1
Article Type:	Editorial commentary
Date Submitted by the Author:	n/a
Complete List of Authors:	Baron, J-C; Hopital sainte-anne, neurology
Keywords:	CEREBROVASCULAR DISEASE
Specialty:	Stroke

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Editorial Commentary: The effect of changing arterial blood pressure and carbon dioxide on cerebral blood flow

Jean-Claude Baron

Dept of Neurology, Sainte-Anne Hospital, Université de Paris, INSRM U1266, Paris, France,

and Stroke Research Group, Dept of Clinical Neurosciences, University of Cambridge, Cambridge, UK.

JC. Baron@ghu-paris.fr or jean-claude.baron@inserm.fr or jcb54am.ac.uk

The short article entitled «Effect of alterations in the arterial carbon dioxide tension on the blood flow through the cerebral cortex at normal and low arterial blood pressures», published in 1965 in the JNNP by A. Murray Harper and H.I. Glass[1], is among the most cited articles ever published in the journal (429 citations as of 21 January 2020). Interestingly, the same first author published the subsequent year in the JNNP another highly cited article[2] on a closely related subject (372 citations as of 2020).

The Harper and Glass 1965 article was the first to assess the effects of changes in the arterial partial pressure of CO_2 ($PaCO_2$) on the cerebral circulation in conditions of normal arterial blood pressure, moderate hypotension and severe hypotension. To this end, the authors applied in anaesthetized mongrel dogs the technique that Lassen and Ingvar had just developed to measure quantitative regional blood flow of the exposed cerebral cortex using radioactive krypton injected in the internal carotid artery[3].

The strong effects of changes in $PaCO_2$ on the cerebral vasculature, first discovered in 1928 by Forbes and Wolff via direct observation of the pial arteries through a glass window in animals, was subsequently confirmed in humans, first indirectly by Lennox and Gibbs in 1932[4] by means of jugular vein PO_2 measurements, and then directly by Kety and Schmidt[5] in 1946 using their whole-brain cerebral blood flow (CBF) technique that used inhaled N_2O. These studies established that hypercapnia is the most potent brain vasodilator, and conversely hypocapnia a very potent vasoconstrictor. In 1964, Reivich[6] documented in monkeys that hypercapnic vasodilation, and hence the CBF increase, reached a plateau around 150 mmHg $PaCO_2$, and conversely that vasoconstriction was maximal for $PaCO_2$ levels around 18 mmHg. In parallel, Fog, Forbes and others, using the glass window approach, showed in the 1930's that reductions in mean arterial blood pressure (MABP) induced pial artery vasodilatation, and conversely, i.e., the cerebral auto-regulation[2].

In their seminal 1965 JNNP article, Harper and Glass[1] aimed to assess whether the vasodilation induced by hypotension affected the cerebrovascular response to changes in $PaCO_2$. They indeed found that, as compared to the normotensive condition, the slope of the

CBF response to $PaCO_2$ changes was shallower at moderate arterial hypotension, and completely flat at severe hypotension levels (**Figure**), documenting that the same resistive pial vessels were involved in the two regulations, and that maximal vasodilation/vasoconstriction in response to changes in one physiological variable abolished the response to the other physiological variable.

Why has this paper been, and still is - 28 citations since 2016 - so widely cited? First of all, it describes a key physiological phenomenon that has wide implications in animal and human cardiovascular and respiratory physiology and pharmacology. Second, Harper and Glass' observations have major clinical implications in numerous medical disciplines, particularly neuro-anaesthesia, neuro-intensive care and, of course, cerebrovascular diseases - specifically, that, on top of PaO_2, both BP and $PaCO_2$ have to be closely monitored and controlled to avoid worsening of the already present brain damage. For instance, in acute traumatic brain injury with threateningly elevated intra-cranial pressure (ICP) - which causes maximal vasodilation, further increasing the ICP in a vicious cycle -, brief hypocapnia can be life-saving by rapidly reducing the cerebral blood volume[7].

In clinical neurology and stroke medicine, the implications of the concept of maximal vasodilation has had to this day major impact in the understanding and management of cerebrovascular diseases including transient ischemic attacks (TIAs) and acute ischemic stroke. Indeed, thanks to the development of non-invasive techniques to measure regional CBF and oxygen metabolism in man using positron emission tomography (PET), it was shown that in a subset of patients with repeated TIAs affecting the territory of an occluded or severely stenotic internal carotid artery, there was permanent hypoperfusion in the distal cortical areas associated with increased oxygen extraction fraction, documenting exhausted vasodilatory reserve in turn causing clinical symptoms on a hemodynamic – as opposed to embolic - basis[8]. Subsequently, Lassen and co-workers developed a pharmacological vasodilatation challenge using acetazolamide (Diamox®) to test the cerebral vasodilatory reserve, also called cerebrovascular reactivity (CVR)[9], an approach still in use today using single-photon emission computed tomography (SPECT) and perfusion radiotracers such as ^{99m}Tc-HMPAO. Transcranial Doppler ultrasound using the breath holding test is also routinely used worldwide to assess the CVR distal to, and hence the hemodynamic effects of, carotid stenosis or occlusion[10]. More recently, MRI- or CT-based perfusion imaging has been used to map impaired CVR across the whole brain in the form of prolonged arterial mean transit time under physiological conditions[11], currently the most widely used approach to determine optimal medical and/or surgical management of such patients. Novel, completely non-invasive MR-based approaches, not as yet fully implemented in routine, involve inhaled CO_2 challenge using BOLD MRI or arterial spin labelling (ASL)[12].

Regarding acute ischemic stroke (AIS), the concept of maximal vasodilatation also had important implications. First of all, it made the old idea of treating AIS patients with pharmacological vasodilators not only obsolete, but also potentially hazardous, because inducing vasodilation in the non-maximally vasodilated territories involves a risk of diverting blood flow away from the ischemic areas (so-called 'Robin Hood syndrome', or 'hemodynamic steal')[13], an effect also well documented in chronic carotid occlusion[14].

Lassen's group subsequently tested 'inverse steal' - i.e., they assumed that reducing perfusion in unaffected areas by means of hyperventilation would elevate perfusion in ischemic areas -, but unfortunately this approach failed to show clinical benefit[15]. Second, the concept of maximal vasodilation pointed to the potential risk of worsened ischemia associated with drops in systemic blood pressure, a variable now closely monitored and controlled in AIS[16].

To sum up, Harper and Glass' widely cited physiology paper reporting results from animal experiments 55 years ago in the JNNP has contributed to major advances in understanding the disorders of the cerebral circulation involved in numerous neurological and neurosurgical conditions, and in turn has impacted to the present day the management of the afflicted patients.

References

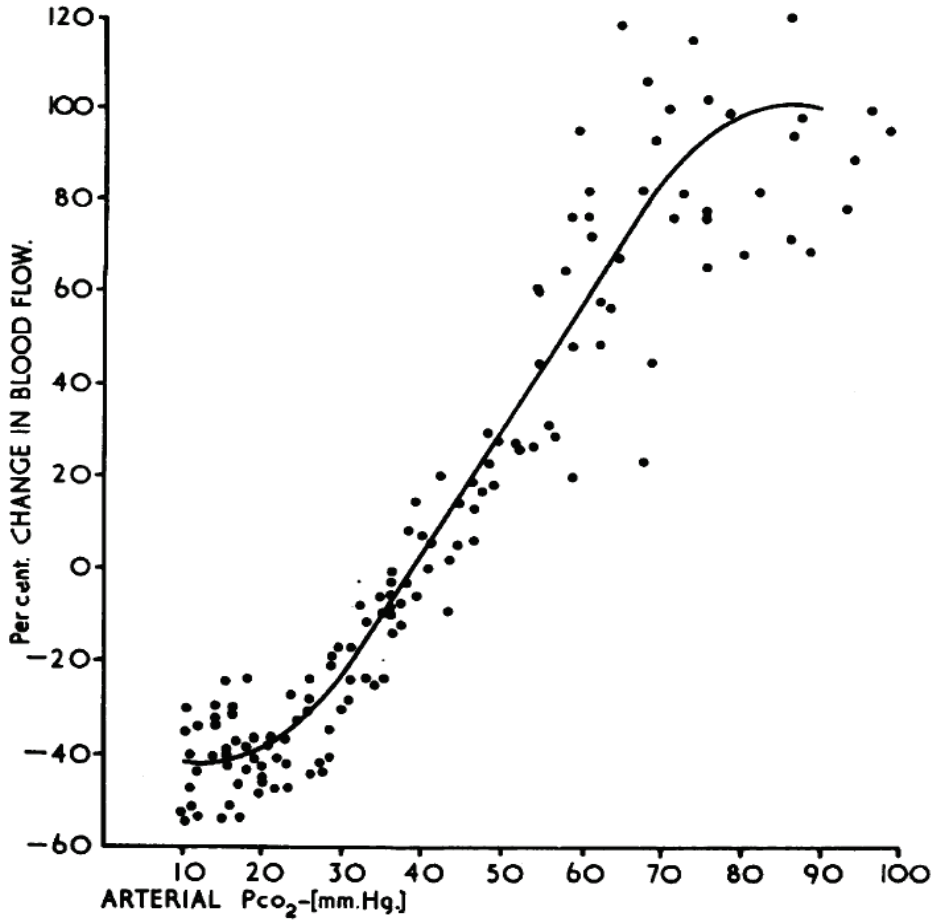
1. Harper AM and Glass HI. Effect of alterations in the arterial carbon dioxide tension on the blood flow through the cerebral cortex at normal and low arterial blood pressures. *J Neurol Neurosurg Psychiatry*. 1965; 28: 449-52.
2. Harper AM. Autoregulation of cerebral blood flow: influence of the arterial blood pressure on the blood flow through the cerebral cortex. *J Neurol Neurosurg Psychiatry*. 1966; 29: 398-403.
3. Lassen NA and Ingvar DH. The blood flow of the cerebral cortex determined by radioactive krypton. *Experientia*. 1961; 17: 42-3.
4. Lennox WG and Gibbs EL. The Blood Flow in the Brain and the Leg of Man, and the Changes Induced by Alteration of Blood Gases. *J Clin Invest*. 1932; 11: 1155-77.
5. Kety SS, Schmidt, C.F. The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output and blood pressure of normal young men. *Journal of Clinical Investigation*. 1946; 25: 107-19.
6. Reivich M. Arterial Pco2 and Cerebral Hemodynamics. *Am J Physiol*. 1964; 206: 25-35.
7. Curley G, Kavanagh BP and Laffey JG. Hypocapnia and the injured brain: more harm than benefit. *Crit Care Med*. 2010; 38: 1348-59.
8. Baron JC, Bousser MG, Rey A, Guillard A, Comar D and Castaigne P. Reversal of focal "misery-perfusion syndrome" by extra-intracranial arterial bypass in hemodynamic cerebral ischemia. A case study with ^{15}O positron emission tomography. *Stroke*. 1981; 12: 454-9.
9. Vorstrup S, Brun B and Lassen NA. Evaluation of the cerebral vasodilatory capacity by the acetazolamide test before EC-IC bypass surgery in patients with occlusion of the internal carotid artery. *Stroke*. 1986; 17: 1291-8.
10. Ratnatunga C and Adiseshiah M. Increase in middle cerebral artery velocity on breath holding: a simplified test of cerebral perfusion reserve. *Eur J Vasc Surg*. 1990; 4: 519-23.
11. Maeda M, Yuh WT, Ueda T, et al. Severe occlusive carotid artery disease: hemodynamic assessment by MR perfusion imaging in symptomatic patients. *AJNR Am J Neuroradiol*. 1999; 20: 43-51.
12. Liu P, De Vis JB and Lu H. Cerebrovascular reactivity (CVR) MRI with CO2 challenge: A technical review. *Neuroimage*. 2019; 187: 104-15.
13. Olesen J and Paulson OB. The effect of intra-arterial papaverine on the regional cerebral blood flow in patients with stroke or intracranial tumor. *Stroke*. 1971; 2: 148-59.

14. Kuwabara Y, Ichiya Y, Sasaki M, Yoshida T and Masuda K. Time dependency of the acetazolamide effect on cerebral hemodynamics in patients with chronic occlusive cerebral arteries. Early steal phenomenon demonstrated by [15O]H2O positron emission tomography. *Stroke*. 1995; 26: 1825-9.
15. Christensen MS and Paulson OB. Prolonged artificial hyperventilation in severe cerebral apoplexy. Clinical results and cerebrospinal fluid findings in a controlled study. *Eur Neurol*. 1972; 8: 137-41.
16. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2019; 50: e344-e418.

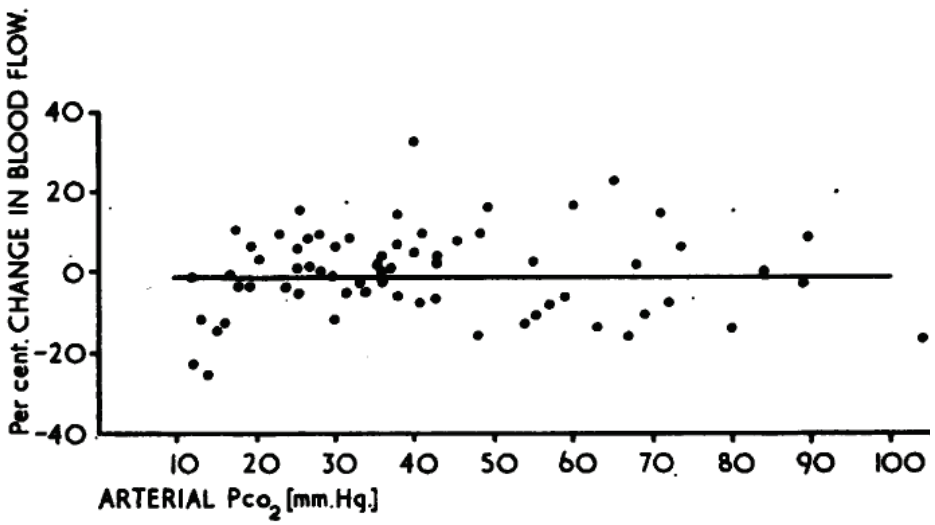
Figure Legend

The relationship between cerebral blood flow and $PaCO_2$ (range: ~10 - 100 mmHg) at normotension (A; mean arterial blood pressure = 150 mmHg) and at marked hypotension (B; mean arterial blood pressure = 50 mmHg) in mongrel dogs (from Harper and Glass[1])

A


Per cent. CHANGE IN BLOOD FLOW.
120
100
80
60
40
20
0
-20
-40
-60
10 20 30 40 50 60 70 80 90 100
ARTERIAL Pco2-[mm.Hg.]

B


Per cent. CHANGE IN BLOOD FLOW.
40
20
0
-20
-40
10 20 30 40 50 60 70 80 90 100
ARTERIAL Pco2 [mm.Hg.]