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

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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 HI Glass, 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 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 cerebral partial pressure of CO2 (PaCO2) on the cerebral circulation in conditions of normal arterial blood pressure, moderate hypotension and severe hypotension. To this end, the authors applied in anaesthetised 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.

The strong effects of changes in PaCO2 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 by means of jugular vein PO2 measurements, and then directly by Kety and Schmidt in 1946 using their whole-brain cerebral blood flow (CBF) technique that used inhaled N2O. These studies established that hypercapnia is the most potent brain vasodilator, and conversely hypocapnia a very potent vasoconstrictor. In 1964, Reivich documented in monkeys that hypercapnic vasodilatation, and hence the CBF increase, reached a plateau around 150 mm Hg PaCO2 and conversely that vasoconstriction was maximal for PaCO2 levels around 18 mm Hg. In parallel, Fog, Forbes and others, using the glass window approach, showed in the 1930s that reductions in mean arterial blood pressure induced pial artery vasodilatation, and conversely, that is, the cerebral auto-regulation.

In their seminal 1965 JNNP article, Harper and Glass aimed to assess whether the vasodilation induced by hypotension affected the cerebral vascular response to changes in PaCO2. They indeed found that, as compared with the normotensive condition, the slope of the CBF response to PaCO2 changes was shallower at moderate arterial hypotension, and completely flat at severe hypotension (figure 1), documenting that the same resistive pial vessels were involved in the two regulations, and that maximal vasodilatation/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-anesthesia, neuro-intensive care and, of course, cerebrovascular diseases—specifically, that, on top of PaO2, both blood pressure and PaCO2 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 intracranial pressure (ICP)—which causes maximal vasodilatation, further increasing the ICP in a vicious cycle—brief hypocapnia can be life-saving by rapidly reducing the cerebral blood volume.

In clinical neurology and stroke medicine, the implications of the concept of maximal vasodilatation has had to this day major impact in the understanding and management of cerebrovascular diseases including transient ischaemic attacks (TIAs) and acute ischaemic stroke. Indeed, thanks to the development of non-invasive techniques to measure regional CBF and oxygen metabolism in man using positron emission tomography, 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 haemodynamic—as opposed to embolic—basis. Subsequently, Lassen and co-workers developed a pharmacological vasodilatation challenge using acetazolamide (Diamox) to test the cerebral vasodilatory reserve, also called cerebrovascular reactivity (CVR), an approach still in use today using single-photon emission computed tomography and perfusion radiotracers such as 99mTc-HMPAO (hexamethylpropylene amine oxime). Transcranial Doppler ultrasound using the breath holding test is also routinely used worldwide to assess the CVR distal to, and hence the haemodynamic effects of, carotid stenosis or occlusion. More recently, MRI-based 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, 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 CO₂ challenge using blood oxygen level dependent MRI or arterial spin labelling.

Regarding acute ischaemic stroke (AIS), the concept of maximal vasodilatation non-hazardous, because inducing vasodilation in ischaemic areas— but unfortunately this approach failed to show clinical benefit.

The relationship between cerebral blood flow and PaCO₂ (range: ~10–100 mm Hg) in mongrel dogs (reprinted from Harper and Glass). PaCO₂, arterial partial pressure of CO₂.

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.

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REFERENCES