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How can integrative physiology advance stroke research and stroke care?

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Despite clear recent advances in stroke research and stroke care, many important questions remain unanswered. For example, what is optimal blood pressure treatment in stroke? This one question will likely receive many new questions in return. Do we mean optimal blood pressure treatment in the acute phase of stroke, or in the context of secondary prevention of stroke? Do we mean ischemic stroke, ICH, or SAB? Does it concern blood pressure treatment around thrombolysis or thrombectomy? Is the goal of treatment to prevent bleeding (through hyperperfusion or increased intracranial pressure), or is it to prevent ischemia (hypoperfusion)?

When we think of optimal blood pressure control in such different settings, even other questions may come to mind. Blood pressure is acutely elevated in acute stroke. What is the mechanism behind this, and does it perhaps serve a purpose? Does the brain initiate this rise in blood pressure to maintain perfusion, and will blood pressure lowering treatment lead to hypoperfusion?

We cannot, and should not, answer these questions without integrative physiology.[1,2]

Integrative physiology in stroke

Just as an example, to begin to answer the question whether the brain may purposefully initiate hypertension in acute stroke, we have to understand the baroreflex function.[2] This system senses systemic blood pressure and uses feedback loops to adapt heart rate and peripheral vascular resistance to control it.[3] There is no input from a 'brain blood flow sensor' into the baroreflex loop: even though its existence may seem logical, there is no known physiological mechanism by which the brain can sense a reduction in cerebral blood flow (CBF) and respond by increasing blood pressure. However, recent work has indicated that astrocytes that lie adjacent to the brain stem centers involved in the autonomic nervous system, are responding to increased intracranial pressure, and can initiate transient hypertension through stimulation of these brain stem centers (for more context and discussion, see Claassen et al.[4]). This means that the acute hypertension in stroke could be a response to an increase in intracranial pressure,[1,2] although several other candidate mechanisms may be involved.

To answer the question if this increase in blood pressure may serve the purpose of maintaining CBF, we need to understand cerebral autoregulation.[4] If autoregulation works properly, the rise in blood pressure in acute stroke should not be necessary to maintain CBF. Similarly, if autoregulation is preserved, treatment of high blood pressure in acute stroke should have little effect on CBF. The question here of course is how autoregulation is affected by stroke, a question that has received an in depth discussion in our recent comprehensive review on autoregulation.[4] Meanwhile, several clinical trials have investigated the effects of acute (<48 h) blood pressure lowering on stroke outcome, reviewed in Robinson et al.[5] There was no evidence of adverse effects of blood pressure lowering, but equally no evidence for a benefit.[5] Autoregulation however was not assessed in these trials, and it is theoretically possible that beneficial effects in patients with preserved autoregulation were cancelled out by patients with impaired autoregulation, and vice versa.[4]

In this Special Issue, Nogueira et al. provide an excellent overview of clinical studies on autoregulation in acute stroke.[1] Their review covers acute ischemic stroke, intracranial haemorrhage, and subarachnoid haemorrhage, all <48 h after onset, and investigates the relationship between measurements of autoregulation with stroke severity, and with clinical outcome. Their review covers 30 studies with 1700 patients. In acute stroke, autoregulation is impaired to a varying

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degree in the affected hemisphere, and the degree of impairment correlates with longer term outcome.[1]

A special issue on cerebral hemodynamic regulation in stroke in JCBFM

The examples above serve to illustrate how insights from physiology may be applied to improve stroke research and stroke care.

This Special Issue is dedicated to this topic. It deals with the complexity of cerebral hemodynamic regulation during different stages of ischemic stroke and ischemic stroke treatment.

The vessel occlusion in acute ischemic stroke has obvious consequences for regional CBF in the infarct core and penumbra. Most of the research on stroke is devoted to this, with its own complexity including how hypoperfusion and reperfusion affect ischemia in different neurons, the role of inflammation, and optimal timing for clot removal/thrombolysis.[6]

However, in stroke, much more happens than a regional disruption of CBF.

Acute stroke affects blood pressure and $PaCO_2$ levels, which are the two most important determinants of CBF.[4] Cerebral autoregulation is the mechanism that aims to stabilize CBF.[4] It does so not only to maintain perfusion and delivery of oxygen and nutrients, but also to prevent increases in intracranial pressure. A common misperception is that autoregulation can keep CBF fully stable within a wide range of blood pressure levels. As a simple rule of thumb, the faster a change in blood pressure occurs, the more unstable CBF becomes.[4] Even if cerebral autoregulation functions normally, an acute change in blood pressure, occurring over seconds to minutes, will have large effects on CBF before autoregulation is able to restore CBF towards baseline. Acute stroke is associated with an acute rise in blood pressure, which may lead to transient increases in CBF, which in turn may increase intracranial pressure. On the other hand, acute drops in blood pressure, during postural changes with postural hypotension, due to medication with hypotensive side-effects,[7] or due to complicating illnesses (e.g. aspiration pneumonia with sepsis) may cause transient reductions in CBF.

Regarding the changes in $PaCO_2$ in stroke, small changes already have strong effects on CBF, with approximately 3–8% change in CBF for each mmHg change in $PaCO_2$, such that acute hyperventilation may reduce CBF by 30%.[8]

Pharmacotherapy is an important aspect of stroke care. However, some of the drugs used in stroke management may directly affect blood pressure or CBF, as summarized by Mueller et al.[7]

Monitoring of autoregulation during therapeutic interventions, such as thrombolysis, or mechanical thrombectomy, may help improve patient outcome.[1]

Fan and colleagues provide a comprehensive overview of these and many other examples showing how integrative physiology can be applied in the context of stroke.[2] In a closely related review, they subsequently illustrate how these concepts may be applied in clinical practice and clinical research.[9]

For this Special Issue, we have selected four original research papers that illustrate the wide range of research applications of these concepts.

The paper by Wang and colleagues reports an optimized mouse model to study middle cerebral artery occlusion as a model for human stroke.[10] This model allows more precise control of the occlusion combined with close monitoring of its effects on regional CBF. These parameters can then be linked to infarct size, and stroke outcome. Such a model, offering good control of vessel occlusion and reperfusion, and its effects on infarct size, could be applied in experiments wherein other parameters, such as blood pressure or $PaCO_2$, are manipulated.

Stadlbauer and colleagues elegantly show how neurovascular uncoupling can lead to reduced BOLD-responses to neural activation in fMRI.[11] While their results were obtained mainly in patients with brain tumors, where vascular dysfunction was explained by tumor infiltration, it is possible that their technique can be applied in stroke patients. Their study, when we translate it to stroke, indicates that fMRI studies may incorrectly suggest regional neuronal dysfunction based on impaired BOLD responses, when in fact neural function is preserved, but the vascular responses are impaired, explaining the reduced BOLD signal.[11] While this caveat of fMRI is theoretically well known, it is often ignored in fMRI research. Another possible application of their technique is to provide insights in the vascular 'mismatch' that occurs under these conditions, which may cause relative hypoxia during neural activation. In the longer term, persistent mismatch is expected to lead to neuronal dysfunction. This then could be an interesting mechanism to explain post-stroke cognitive decline and dementia.

Neurovascular coupling is explored further by Sencan et al. who demonstrate observations in awake animals, avoiding the confounding effects of anaesthesia, to study laminar differences (i.e. in different cortical layers) in neurovascular coupling.[12]

Horiuchi et al.'s study is an example of how one of various methods to assess dynamic cerebral autoregulation can be applied to test an intervention.[13] In this example, dietary NO supplementation was hypothesized to ameliorate the impairment in dynamic autoregulation caused by hypoxia. Such a design could easily

be translated to stroke. Their discussion includes the limitations of the method that was chosen to estimate autoregulation.

The review by Nogueira et al. makes clear that autoregulation research in stroke is still in its infancy however.[1] The available studies have a high heterogeneity in population and in methodology, and often have small sample sizes. Together, far too often this leads to inconclusive or even contradictory findings. How then should we move forward?

The small sample sizes may be overcome by retrospective, and prospective, pooling of data, with analyses of individual patient data. However, to do this, consistency in methodology and reporting is essential.

For this, the paper by Simpson et al. is essential reading, and should even be required reading for everyone thinking of performing an autoregulation study in stroke.[14] This paper clearly explains the concept of autoregulation, how it can be measured, and how measurements can be analyzed. This will aid in improving study design.[14]

Harmonizing methodology and reporting of outcomes will be the next step to advance research. This is not easy when there is no accepted single gold standard method to measure autoregulation in the field. But we do not have to wait for this gold standard to be chosen or developed. In fact, several gold standards are already available. A gold standard has to be no more or no less than a universally applied method that allows comparison. It does not have to be perfect or beyond scrutiny, it just has to be applied according to the same standards in different settings.[15]

For example, each new study on autoregulation in stroke could collect 10 min of supine baseline data, free of artefacts, with continuous beat-to-beat blood pressure, end-tidal CO_2, and Transcranial Doppler blood velocity in the middle cerebral artery, and store these data for future exchange. This will make it possible to combine datasets from various studies, where data have been collected according to the same, strict protocol. In the next step, all these data can be analyzed with a rigorously applied single method. In this way, data from different centers and patient populations can be directly compared. This process can be repeated for several different methods.[16] As a next step, in addition to the supine, resting data, a universally accepted protocol to challenge autoregulation (e.g. to induce blood pressure changes, or $PaCO_2$ changes) can be adopted in the same fashion.

We have previously shown that a consensus paper outlining methodology and analysis can help to harmonize study protocols, and reporting of results in journals,[17] thus reducing heterogeneity.[18] Efforts are underway to update and expand this consensus paper. Hopefully, this will improve the quality of autoregulation research in stroke and translate to better quality of care.

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