REVIEW

Impaired cerebral autoregulation: measurement and application to stroke

Li Xiong,[1] Xiuyun Liu,[2] Ty Shang,[3] Peter Smielewski,[2] Joseph Donnelly,[2] Zhen-ni Guo,[4] Yi Yang,[5] Thomas Leung,[1] Marek Czosnyka,[2] Rong Zhang,[3] Jia Liu,[5] Ka Sing Wong[1]

[1]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China
[2]Department of Clinical Neurosciences, Brain Physics Laboratory, Division of Neurosurgery, University of Cambridge, Cambridge, UK
[3]Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, Texas, USA
[4]Department of Neurology, Neuroscience Center, The First Norman Bethune Hospital of Jilin University, Changchun, China
[5]Chinese Academy of Sciences, Shenzhen Institutes of Advanced Technology, Shenzhen, China

Correspondence to
Jia Liu, Chinese Academy of Sciences, Shenzhen Institutes of Advanced Technology; jia.liu@siat.ac.cn and
Dr Ka Sing Wong, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China; ks-wong@cuhk.edu.hk

JL and KSW contributed equally.,

LX, XL and TS contributed equally.

Received 31 August 2016
Revised 5 January 2017
Accepted 9 January 2017
Published Online First
22 February 2016

To cite: Xiong L, Liu X, Shang T, *et al*. *J Neurol Neurosurg Psychiatry* 2017;**88**:520–531.

ABSTRACT

Cerebral autoregulation (CA) is a protective mechanism that maintains cerebral blood flow at a relatively constant level despite fluctuations of cerebral perfusion pressure or arterial blood pressure. It is a universal physiological mechanism that may involve myogenic, neural control as well as metabolic regulations of cerebral vasculature in response to changes in pressure or cerebral blood flow. Traditionally, CA has been represented by a sigmoid curve with a wide plateau between about 50 mm Hg and 170 mm Hg of steady-state changes in mean arterial pressure, defined as static CA. With the advent of transcranial Doppler, measurement of cerebral blood flow in response to transient changes in arterial pressure has been used to assess dynamic CA. However, a gold standard for measuring CA is not currently available. Stroke has been the leading cause of long-term adult disability throughout the world. A better understanding of CA and its response to pathological derangements can help assess the severity of stroke, guide management decisions, assess response to interventions and provide prognostic information. The objective of this review is to provide a comprehensive insight about physiology of autoregulation, measurement methodologies and clinical applications in stroke to help build a consensus for what should be included in an internationally agreed protocol for CA testing and monitoring, and to promote its translation into clinical bedside practice for stroke management.

INTRODUCTION

The ability of the brain to regulate its own blood supply is termed cerebral autoregulation (CA), which maintains an adequate and stable cerebral blood flow (CBF) despite changes in cerebral perfusion pressure (CPP).[1] CA is a universal physiological mechanism, depicted by the Lassen curve (Figure 1), with arterial blood pressure (ABP) or CPP along the x-axis and CBF along the y-axis. A decrease in CBF to ischaemic levels may be tolerated for a short period, depending on the severity of the ischaemia. If CBF ceases completely, brain cell death occurs within minutes. A variety of conditions are encountered clinically, such as in stroke or traumatic brain injury, an actual or potential alteration in CBF puts the brain at risk for ischaemia and infarction. Stroke has been the leading cause of long-term adult disability throughout the world.[2] Therefore, a better understanding of CA and its response to pathological derangements can help assess the severity of stroke, guide management decisions, assess response to interventions and provide prognostic information.

However, a gold standard for measuring CA is not currently available. Research is also ongoing to assess and validate the impact of CA measures on clinical outcomes under a variety of conditions.[3–6] In this paper, we provide a comprehensive and educational review from physiology of autoregulation, measurement methodologies and clinical applications in stroke to help build a consensus for what should be included in an internationally agreed protocol for CA testing and monitoring, and to promote its translation into clinical bedside practice for stroke management. It consists of two parts. The first part contains technical description of methodologies. The second shows the most important evidenced clinical applications of CA testing in stroke.

BASIC PHYSIOLOGY OF CA

The underlying physiological mechanisms of CA may involve myogenic, neural control as well as metabolic regulations in response to changes in CPP or CBF.[1] However, relative contributions of each of these mechanisms to CA under specific physiological or pathophysiological conditions are complex and poorly understood. Furthermore, with poorly delineated border between the conductive and the resistive part of the cerebral arterial tree, CA may involve both large and small cerebral arteries and arterioles, and it has been shown that large extracranial arteries and intracranial pial blood vessels may contribute about 50% of cerebrovascular resistance, and the rest are from the penetrating parenchymal arteries and arterioles.[7 8] In addition, the arteries and arterioles embedded in the brain parenchyma may possess unique and distinct properties from that of pial arteries in regulating cerebrovascular resistance. Finally, CA is likely to be heterogeneous segmentally, regionally and temporally in the regulation of CBF to meet brain metabolic demand.

It has been well recognised that neurogenic and myogenic mechanisms play important roles in CA. Neurogenic regulation includes sympathetic and cholinergic mechanisms.[9] Using pharmacological blockage methods, studies have shown that sympathetic, cholinergic and myogenic mechanisms in pial arteries accounted for about 62% of changes in total cerebrovascular resistance in response to moderate changes in arterial pressure.[10] However,

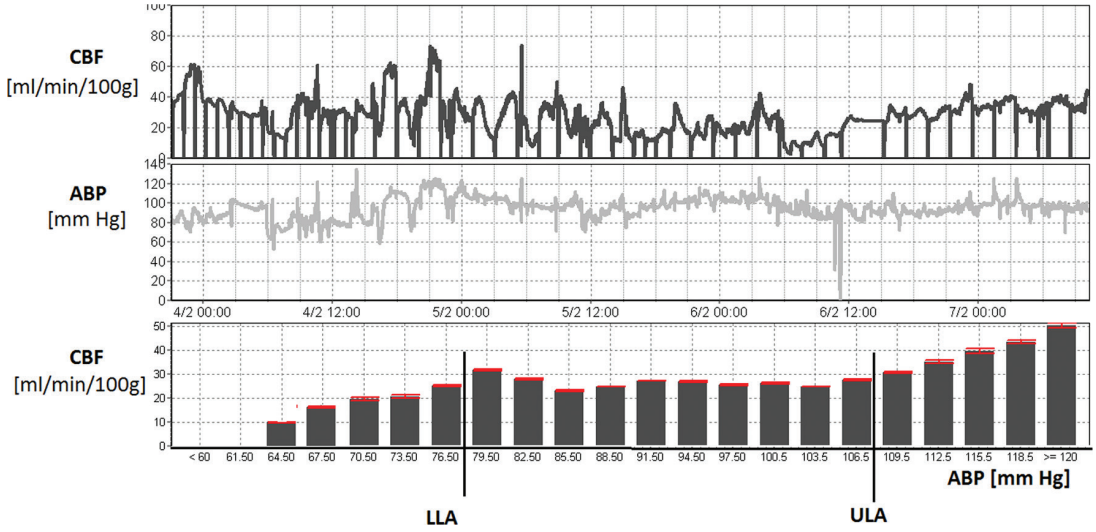

Figure 1 Lassen autoregulatory curve. It has been obtained from 3.5 days of recording of thermodilution CBF and radial artery blood pressure in a patient after poor-grade haemorrhagic stroke. Natural variations of ABP from 60 mm Hg to 120 mm Hg provoked changes in CBF, which enabled plotting of curve and visualising the upper (ULA) and lower (LLA) limit of autoregulation. ABP, arterial blood pressure; CBF, cerebral blood flow.

the relative contribution from neurogenic and myogenic mechanism to CA may vary in different regions of autoregulation curve. The neurogenic mechanism may be responsible for CA during moderate changes in arterial pressure, whereas myogenic mechanism may be predominant during large changes in arterial pressure, which may lead to hypoperfusion or hyperperfusion injury out of the range of effective CA.[10]

There is also segmental heterogeneity in neurogenic regulation. One of the manifestations of the complexity in CA is that the neurogenic reactivity varies as cerebral blood vessel branches down from the pial arteries into parenchymal arteries and arterioles.[9 11] Both the pial and parenchymal arteries and arterioles are likely to contribute equally to the total cerebrovascular resistance and thus CA. However, differences exist between the pial and parenchymal arteries and arterioles in terms of anatomy, physiology and neurogenic reactivity. The pial artery receives perivascular innervation from the peripheral autonomic nervous system originated from the superior cervical ganglion, sphenopalatine ganglion, otic ganglion and trigeminal ganglion (extrinsic innervation).[9 11] On the other hand, the parenchymal arteries and arterioles are innervated mainly by the intrinsic nerves originated from the subcortical neurons, such as those located in the locus coeruleus, raphe nucleus, basal forebrain or local cortical interneurons, that project to the perivascular space surrounding the parenchymal arteries and arterioles (intrinsic innervation).[9 11] Parenthetically, it should be highlighted that parenchymal arterioles are a crucial part of neurovascular unit that control local perfusion to meet brain metabolic demands, linking CA with the brain neuronal activity.[12] The heterogeneity in neurogenic reactivity in the pial and parenchymal artery is manifested also by the different expression levels of neurotransmitter receptors and different functional responses to similar stimuli. For example, the α-adrenoceptor reactivity is absent in the parenchymal artery due to a shift from α-adrenoceptor to β-adrenoceptor.[13] Similar heterogeneity has been shown with serotonin receptor.[13] As the consequence of these changes, the marked vasoconstrictive effects of the pial arteries to serotonin and norepinephrine are absent in the parenchymal arteries or arterioles or even cause parenchymal artery dilation.[14] This segmental heterogeneity in neurogenic regulation may provide the brain with the capability to efficiently change CBF locally to meet the metabolic demand.

CA also possesses segmental heterogeneity in myogenic regulation in the pial and parenchymal arteries and arterioles. The smooth muscle cells (SMC) in the cerebral resistance vessels are responsible for the myogenic tone and regulation. For example, the important role of SMC in myogenic regulation is seen in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) disease,[15] showing a degree of diffuse SMC degeneration in small cerebral arteries. In animal model of and human with CADASIL, myogenic regulation is impaired, which leads to impaired CA.[16 17] Notably, the myogenic tone and regulation are not homogeneous along the resistance vessels. An interesting characteristic of cerebral parenchymal artery is that the parenchymal artery possesses greater basal tone compared with the pial arteries.[14] Under this basal tone, pressure-induced myogenic reactivity in the parenchymal artery is reduced compared with that observed in the pial arteries.[14] This mechanism may buffer effects of upstream rapid changes in ABP on CBF and attenuate the transmission of pulsatile mechanical stress into the brain microcirculation.

CA was also demonstrated to have regional heterogeneity. Differences in regional sympathetic innervation and CA measured in the anterior and posterior circulation were observed. Specifically, sympathetic nerve fibre endings were denser in the anterior circulation arteries than those in the posterior circulation arteries originated from the vertebrobasilar arteries.[18] In addition, CA was found to be more effective in the brainstem than in the anterior circulation during severe hypertension.[19] For example, CBF was increased markedly in the anterior circulation in contrast to an only modest increase in the brainstem during severe hypertension. This has been attributed to the observation that the resistance of small vessels in the anterior circulation was decreased, whereas that in the brainstem was increased during severe hypertension, indicating regional CA heterogeneity.[19] It is interesting to note that this regional heterogeneity in sympathetic neurogenic mechanism may play a role in developing posterior reversible encephalopathy syndrome (PRES).[20] PRES is characterised radiographically by transient bilateral subcortical vasogenic oedema mostly common in the posterior circulation territory.

METHODOLOGIES OF THE ASSESSMENT OF CA

Table 1 contains a brief description of the methods used in patients with stroke and patients with carotid stenotic disease. Selected methods of assessment of CA listed in table 1 are illustrated in Figure 2. According to the definition of autoregulation, the principle of assessing CA is to examine changes in CBF in response to changes in ABP assuming other confounding factors such as arterial CO_2 or PaO2 (pCO_2) remains unchanged. Intuitively, changes of ABP 'must' be induced so as to examine the corresponding dynamics of CBF and then determine the status of autoregulation. In the early study, the pressure change was often induced by vasoactive drug infusion, for example, phenylephrine.[21] At different pressure levels, the corresponding blood flow was measured to produce a CA curve showing that within a certain pressure range (normally 50–170 mm Hg in a healthy subject) CBF may remain relatively constant. This pressure–flow relationship is referred to as 'static' autoregulation.[1]

With the advent of continuous measurements of blood flow (ie, transcranial Doppler for CBF velocity) and blood pressure (vascular unloading techniques in the fingers), allowing for recordings of instantaneous response of CBF velocity to changes of ABP, the concept of 'dynamic' autoregulation was coined.[22] A number of approaches for manipulation of ABP have been proposed to investigate dynamic autoregulation, including thigh-cuff release, body tilt, handgrip, lower-body negative pressure, squat-stand manoeuvres, paced breathing, transient compression of carotid artery, and others.[23] However, these approaches of ABP might not be acceptable in the assessment of CA in patients with stroke. For example, a thigh-cuff test can result in a sudden drop of blood pressure up to 30 mm Hg.[24] This may potentially impose risks of secondary injury of the brain for patients with ischaemic stroke, especially with autoregulation compromised. Moreover, alterations in ABP using these methods may induce responses from other physiological systems (eg, sympathetic activation or vagal withdrawal) or changes in arterial pCO_2, which can profoundly affect blood flow independent of changes in ABP. It is therefore more desirable, for patients with stroke, to have alternative methods that avoid these problems.[23] Recently, a series of studies reported external counterpulsation (ECP) may benefit patients with acute ischaemic stroke, which is a non-invasive method to augment CBF by elevation of blood pressure.[25 26] Cerebral augmentation index, the increase in the percentage of the middle cerebral artery (MCA) mean flow velocity during ECP compared with baseline using transcranial Doppler monitoring method, is calculated to evaluate the augmentation effects of ECP. The relationship between the cerebral augmentation index and blood pressure changes induced by ECP may reflect the status of dynamic CA in ischaemic stroke.[27] However, this speculation should be further validated as ECP has never been previously used for assessment of CA.

With a number of mathematical methods proposed, induced changes of ABP may not necessarily be a 'must'. Instead, the use of spontaneous fluctuations of blood pressure for dynamic CA assessment has been increasingly employed.[23] Although it is clinically appealing to record spontaneous changes in ABP and CBF velocity, assessment of CA at rest may not reveal full capacity of autoregulation because of relatively low variations in spontaneous ABP. In addition to the transcranial Doppler methods, other neuroimaging techniques, such as MRI or positron emission tomography (PET), that measure regional CBF or blood oxygen level-dependent signal have also been explored in assessing autoregulation. Understanding the advantages as well as the limitations of these methods will be helpful for clinicians to choose appropriate methods for their studies of CA in stroke diagnosis or management.

Most studies of CA in stroke relied on linear (cross-spectral or correlation-based) methods to assess the integrity of autoregulation. If the pressure–flow relation displays a low coherence (ie, if it lacks linear dependence), the relation between pressure and CBF cannot be quantified via linear analyses. In other words, the method itself creates uncertainty in its linear estimates. This is a problem of the analytical technique, not the input signal (spontaneous oscillations vs induced blood pressure manipulation). Limitation can be overcome by using a non-linear approach.

Autoregulation index

Autoregulation index (ARI) is a gauging system to quantify the status of CA.[22] The index consists of 10 levels (0–9) of autoregulatory status from damaged to intact. A second-order differential equation simulates 10 possible CBF velocity responses to an ideal step change of ABP by giving 10 sets of predefined parameters including damping factor, time constant and gain parameter. By comparing the recorded CBF velocity with the 10 simulated CBF velocities, the index number is determined by finding the best match. This grading method is simple and easy to implement and interpret. However, this method presumes a predefined linear and stationary relationship between ABP and CBF velocity, which is generally not true. The actual responses of CBF velocity are more diverse and dispersed. Therefore, the 10 predefined cases are not enough to explain all situations, resulting in inappropriate assignments of the index number in some cases and have large individual variability.

Transfer function analysis

Transfer function analysis (TFA) is based on a linear and stationary model with no preconstraint levels on the status of autoregulation. The principle is that autoregulation is supposed to attenuate the influence of ABP on CBF velocity by preventing a direct transfer of the waveform at a low frequency range (normally <0.2 Hz). Two parameters, gain and phase-shift, can be derived from the transfer function at each frequency. Gain quantifies the compression of the relative changes in amplitude of CBF velocity to ABP, whereas phase-shift indicates the time lag (given a specific frequency) between ABP and CBF velocity. Gain is a continuous value. For example, a value of 0.5 suggests that 50% of the relative amplitude of CBF velocity is attenuated with respect to a unit of changes in ABP. Phase-shift is denoted in degree or radian. The larger the phase of CBF velocity is shifted from ABP, the better the autoregulation is taking effect.[23] It is important to note that TFA can only explain linear relationship between ABP and CBF velocity. Coherence is thus normally accompanied to test the linearity of the two variables. A value above 0.5 is considered acceptable if TFA is considered to apply, as it can explain at least 50% of the linear relationship. A series of studies of the performance and implementation of TFA by multicentres was recently published by the Society of Cerebral Autoregulation Research Network.[23] Please refer to these works for more comprehensive details concerning the method of TFA.

Time correlation

Time correlation method allows continuous estimation of CA through a moving linear correlation between slow waves of ABP and ICP (PRx), or CBF velocity and ABP (Mxa) or near-infrared spectroscopy (NIRS)-derived tissue oxygenation index (TOI) and ABP (TOxa).[28] These parameters can reflect the compliant ability of cerebral vessels in response to changes in ABP or CPP.

Table 1 Methods for CA assessment and monitoring in patients with stroke

Method	Monitors	Component of CA	Principle	Limitations	Clinical applications
Pharmacological increase or decrease in mean arterial pressure	TCD, PET, MRI, perfusion CT or radionuclide CBF compared with CPP or ABP	Static	Test involves measurement of CBF at baseline and after rise in ABP induced by a vasopressor. The static rate of autoregulation is calculated as the ratio of relative rise in CVR divided by relative rise in CPP or ABP. 1 or 100%, as it is sometimes expressed as percentage ratio, denotes ideal autoregulation, 0 denotes absolutely non-functioning autoregulation (see Figure 2A).	If autoregulation is not working, pharmacological increases in ABP may cause rise in ICP, leaving CPP unchanged. In such a situation CBF remains unchanged, giving a false impression of autoregulation staying functional. Such a situation is named in literature as 'false autoregulation'.	Both ischaemic and haemorrhagic stroke
Thigh-cuff test	TCD or NIRS, compared with ABP	Dynamic	It involves inducing a temporary decrease in ABP after deflation of thigh cuffs, previously inflated above systolic ABP, and measuring the response in CBF using the parameter RoR (rate of autoregulation). This response describes the change in CVR in time, which characterises autoregulation (Figure 2B). Alternatively, the response in CBF can be modelled as the step-response of a high-pass filter. Autoregulation is described as the filter parameter ARI.	Signal-to-noise ratio may be low as response to thigh-cuff test may be weak. Therefore it is advised to repeat test three times. In conscious patients, inflating cuffs may be painful. In patients with depleted pressure-volume compensatory reserve, sudden decrease in ABP may lead to a rise in ICP, disturbing the assessment of autoregulation if ICP is not monitored.	Ischaemic stroke, carotid artery stenosis
Transient hyperaemic response test	TCD	Dynamic	Doppler sonography flow velocity recording of response to release of 6–9 s compression of carotid artery. A positive hyperaemic response, indicated by CBFV during hyperaemia divided by baseline CBFV being greater than 1.1 denotes working autoregulation. Otherwise autoregulation is judged as depleted (see Figure 2C).	Carotid arteries need to be screened to eliminate cases with carotid plaque, in which carotid artery compression may pose a risk of embolisation. Compressions producing baroreceptor activation of ABP regulation may produce false response; ABP monitoring is advised.	Haemorrhagic stroke
Valsalva manoeuvre	TCD	Dynamic plus component of CO_2 reactivity	The Valsalva manoeuvre produces phasic variations in ABP.	During Valsalva, changes in ICP are possible.	Ischaemic stroke
Lower body negative pressure	Radionuclide methods or TCD compared with ABP monitoring	Mixture of static and dynamic	Lower body negative pressure produces arterial hypotension provoked by strong autonomic activation. Pulsatile lower body negative pressure can be also used to induce slow changes in ABP and assess phase-shift between CBF and ABP slow rate waveforms. Zero phase-shift indicates autoregulation is not working properly.	It is very difficult to resolve information regarding pressure autoregulation and responses (ABP, heart rate and $PaCO_2$) observed during alteration of autonomic haemodynamic control.	Ischaemic stroke, carotid artery diseases
Time correlation between CBF/CBV and CPP/ABP	TCD compared with CPP or ABP	Dynamic	Mx, Correlation between 30 consecutive 10 s averages of TCD mean CBF velocity and ABP. Alternative indices for systolic and diastolic flow velocity (Sx and Dx) can be calculated.	Long-term monitoring of TCD signal is difficult, as position of ultrasound probes cannot be always maintained.	Haemorrhagic and ischaemic stroke
	NIRS compared with CPP or ABP	Dynamic	COx or TOx, Pearson correlation between 30 consecutive 10 s means of ABP and tissue oxygenation index. They have been also demonstrated (as PRx or PAx) to aid monitoring of individual target of CPPopt or ABPopt, which preserves cerebrovascular autoregulation: during cardiopulmonary bypass, after traumatic brain injury and in haemorrhagic stroke.	Shows good affinity to gold standard assessment of lower limit of autoregulation. NIRS signals, however, look like noise, and even if they are easier for long-term monitoring than TCD one can never know when monitoring is valid or not.	Ischaemic and haemorrhagic stroke
	PbtiO2 compared with CPP or ABP	Dynamic	ORx, Pearson correlation coefficient between intraparenchymal brain tissue oxygenation and CPP or ABP, calculated over longer (60 or 20 min) time window	After years of reporting, still there is no convincing proof that ORx is an index of autoregulation.	Haemorrhagic stroke
	DCS compared with ABP	Dynamic	A novel software correlator optimised for continuous, high-speed monitoring of deep tissue blood flow based on DCS.	This is a new, emerging methodology able to monitor instant CBF from NIRS changes. Clinical applications remain to be documented.	Experiment in healthy people—planned to be applied in stroke
Transfer function analysis	TCD or NIRS, or (DCS) compared with ABP	Dynamic	Assuming that the cerebral circulation acts as a high-pass filter (high-frequency fluctuations in ABP pass through to FV unimpeded, whereas lower frequencies are dampened), transfer function phase, gain and coherence can be studied.	Phase-shift is the most promising variable, but it can be evaluated only if frequency of slow waves is stable. Therefore methods involving slow respirations or slow modulations of PEEP are most promising in this area.	Ischaemic stroke, carotid artery stenotic disease

Continued

Table 1 Continued

Method	Monitors	Component of CA	Principle	Limitations	Clinical applications
MMPF analysis	ABP and TCD	Dynamic	Any complex signal S(t) can be represented as the superimposition of more basic (simpler) components: $S(t) = \Sigma Sk(t)$, where Sk are empirical modes that fulfil certain criteria of the original signal. The results indicate that the MMPF phase measure of autoregulation has much better repeatability/reproducibility than the traditional Fourier TFA.	Mathematically advanced; so far not replicated.	Stroke
Brain imaging techniques: MRI, perfusion CT, MRI	CBF, CBV, OEF and oxygen consumption rate ($CMRO_2$)	Static	The depression of $CMRO_2$ in the ischaemic cortex was associated with a trend for CBV to return towards normal values, compared with the maximally elevated CBV found in oligaemic but metabolically normal areas. This suggests that a process of metabolic vasoconstriction may participate, among other factors, in the vascular collapse that occurs, and would serve to regenerate some haemodynamic reserve, at very low CPP levels.	Cortical blood volume was reduced in proportion to the matched reduction in CBF and $CMRO_2$, suggesting that the metabolic depression increases the resting tone of pial vessels.	Ischaemic stroke
	MRI	Static	Dynamic CA was assessed by the rate of return of CBFV (R_{Return}) following a sudden drop induced by the thigh-cuff manoeuvre.	1. No significant between-hemisphere differences were seen in controls using either the TCD or MRI technique. 2. R_{Return} for both TCD and MRI was impaired in patients with acute ischaemic stroke compared with controls in both unaffected and affected hemispheres.	Ischaemic stroke
	Perfusion CT	Static	Measurement of Xe-CBF using CT method, before and after alteration of ABP (pharmacologically) or vasodilation by acetazolamide.	If ICP is not measured, real changes in CPP cannot be assessed. CPP may not follow changes in ABP or may be decreased in response to xenon or acetozalamide (both are vasodilators, able to rise ICP).	Ischaemic and haemorrhagic stroke

ABP,arterial blood pressure; ARI, autoregulatory index; CA, cerebral autoregulation; CBF, cerebral blood flow; CVR, cerebral vascular reactivity; CBV, cerebral blood volume; CBFV, cerebral blood flow velocity; TFA, transfer function analysis; $CMRO_2$, oxygen consumption rate; COx (also TOx), cerebral oximetry reactivity index; CPP, cerebral perfusion pressure; DCS, diffuse correlation spectrometry; Dx, diastolic flow index; FV, flow velocity; HR, heart rate; HVx, haemoglobin volume reactivity index; ICP, intracranial pressure; MMPF, multimodal pressure flow; Mx, mean flow reactivity index; OEF, oxygen extraction fraction; ORx, oxygen reactivity index; PAx, pressure amplitude reactivity index; $PbtiO_2$, pressure of brain tissue oxygen; PEEP, positive end expiratory pressure; PET, positron emission tomography; PRx, pressure reactivity index; Sx, systolic flow index; NIRS, near-infrared spectroscopy; TFA, transfer function analysis; TCD, transcranial Doppler; THx, total haemoglobin reactivity index; TOx, tissue oxygenation reactivity index; THRT, transient hyperaemic response test .

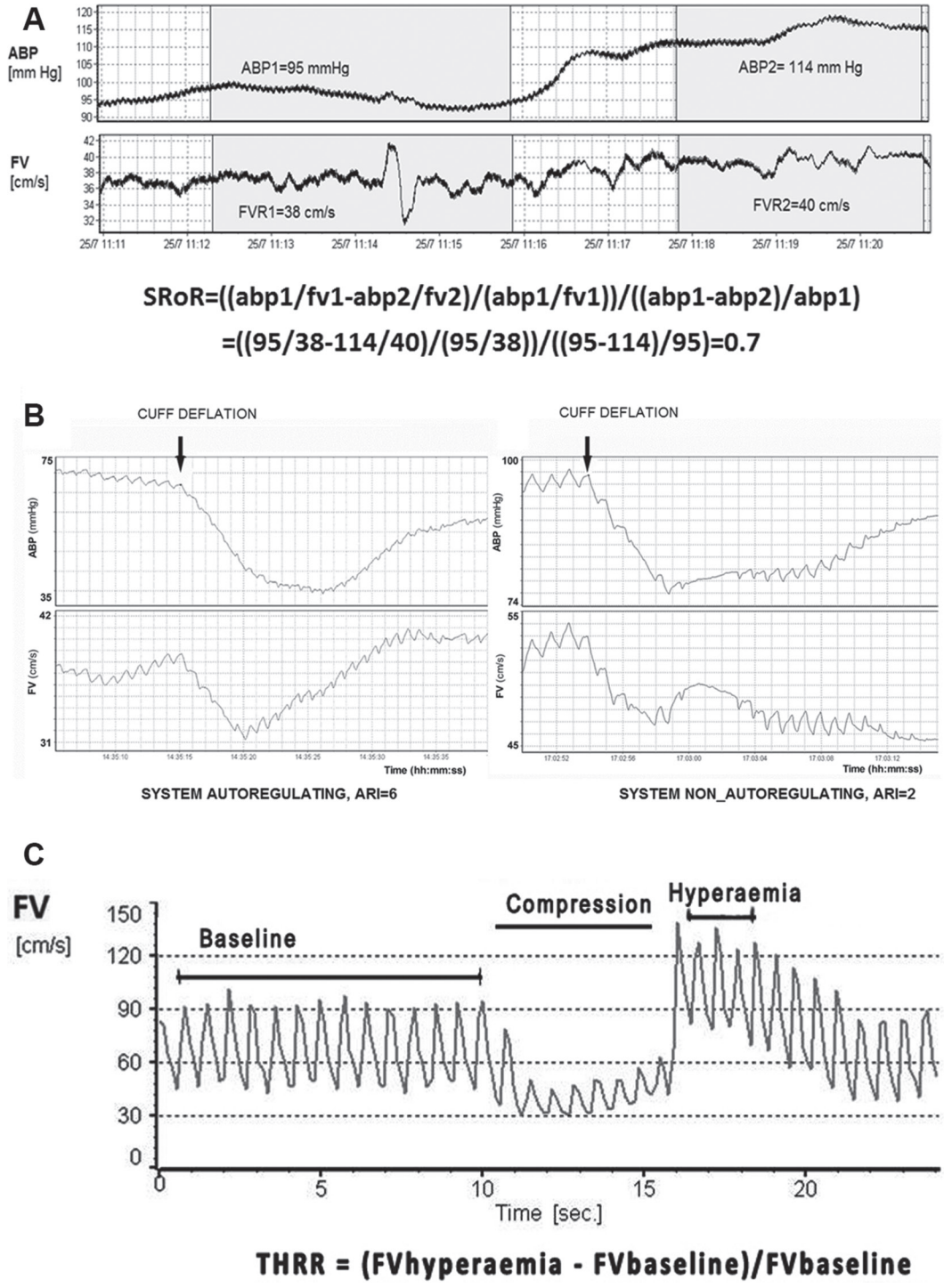

Figure 2 Examples of different methods of assessment of autoregulation. (A) Example of evaluation of static rate of autoregulation. Arterial blood pressure has been increased from 95 mm Hg to 114 mm Hg with vasopressor. Changes in CBF were recorded using transcranial Doppler ultrasonography (FV). (B) Example of deflation of leg cuffs to test cerebral autoregulation. On left: pattern specific for working autoregulation: In response to deflation, blood pressure (ABP) drops and so does blood flow velocity in MCA. With working autoregulation FV starts to recover before ABP increases back to baseline (left panel). With autoregulation disturbed- FV stays decreased, as long as ABP remains decreased. (C) Example of transient hyperemic response test. Following 6 second compression of common carotid artery, after release hyperaemia is observed. Transient hyperemic response ration is a useful index of cerebral autoregulation.

The parameters are always calculated as the correlation coefficient between 30 consecutive, 10 s averaged values of input (ABP, CBF velocity) and corresponding output signals (ICP, ABP or TOI). Averages over 10 s were used to suppress the influence of the pulse and respiratory frequency wave components. A positive correlation is indicative of passive cerebral vasculature and impaired autoregulation. Zero or negative correlation is indicative of reactive vasculature and intact autoregulation. They have been widely used for continuous monitoring CA in patients requiring neurointensive care predominantly after haemorrhagic stroke.[29 30] One of the limitations of this method is that calculation of the correlation coefficient may be influenced by the time scales used. Another is

that the method assumes intact autoregulation if there is lack of correlation. However, poor data quality also leads to poor correlation and may be misinterpreted as intact autoregulation.

Multimodal pressure flow (MMPF) or wavelet analysis

It is a model based on Hilbert Huang transform.[31] The principle is to calculate the phase-shift between ABP and CBF velocity without assuming a linear relationship a priori. The ABP and CBF velocity are empirically decomposed into a series of modes from fast to slow waves, respectively. The mode that is considered the most relevant to autoregulation is then identified, and the instantaneous phase of ABP and CBF velocity is computed by Hilbert transform. The phase difference between the variables can then be calculated readily. A number of studies have shown that it is capable of dealing with non-linear relationship of ABP and CBF velocity. Wavelet analysis is a time frequency approach that can be used to quantify dynamic CA under non-stationary conditions. Both time-varying coherence and phase at different time scales between changes in ABP and CBF velocity or brain tissue oxygenation using NIRS can be obtained.[32] However, the validity and effectiveness of these methods need to be further tested or replicated in multicentre studies.

Advanced mathematical models

There is increasing evidence showing that the variation of blood flow is a non-linear, non-stationary (changing over time) and multivariate (eg, the influence of CO_2) process. A number of advanced mathematical models have therefore been proposed to deal with these characteristics. Several groups have attempted to apply the Laguerre-Volterra expansion of kernels to model the dynamics of CA with non-linearity considered.[33] Additionally, multivariate models were designed to model the influence of covariates, for example, CO_2, on CBF velocity, and more recently non-stationary property was investigated by using moving windows or adaptive methods.[34] Analytical techniques to measure CA should include projection pursuit regression. This approach has been shown to predict delayed cerebral ischaemia after subarachnoid haemorrhage (SAH) on an individual patient basis.[35 36]Given more degrees of freedom, it is not surprising that these advanced models may significantly reduce estimation error of CBF velocity. For example, higher order models can always achieve better (at least the same) estimation than the ones with lower order. This does not necessarily mean that the complex models are always better than the simple ones, as the advanced models may be overfitting the data, which may result in a worse prediction. We therefore suggest that in the future study one should have a clear and proper justification before choosing one of these models. For example, a multivariate model can help in assessing autoregulation when significant CO_2 reactivity also presents.[34]

Advanced neuroimaging techniques

Of the greater potential imaging techniques, MRI, PET and CT perfusion (CTP), appear suitable because of their availability in acute care situations, high-spatial resolution and excellent safety record. Through these techniques, CBF, blood volume, oxygen extraction fraction and oxygen consumption rate ($CMRO_2$) can be measured in multiple regions. The relationship between changes in blood volume and changes in CBF velocity or changes in $CMRO_2$ was analysed. Studies showed that the result of using advanced neuroimaging techniques to assess CA matched with traditional methods (such as transcranial Doppler).[37 38] However, these methods in general are expensive and have poor temporal resolution (approximately in minutes) and can be challenging to be used in bedside studies. Advanced neuroimaging techniques may be useful and are available in acute care situations, but it is important to recognise that they may not be generally applicable and there are disadvantages in the assessment of a critically ill patient in this way.

CLINICAL APPLICATIONS OF CA STUDIES IN STROKE

The presence or absence of CA in acute stroke is critical for the maintenance of stable blood flow in the ischaemic penumbra and for avoidance of excessive hyperperfusion. A widely applicable method of measuring CA in patients with acute stroke is needed to allow detailed investigation of the relation between altered CA following stroke and clinical outcome, and may ultimately be relevant in the treatment of blood pressure in the acute period following stroke. Therefore, in this section, we identified and reviewed articles applying different methods of measuring CA in the stroke-related clinical studies during the past two decades. These original articles were searched by the keywords ‘cerebral autoregulation’ and ‘stroke’ in PubMed (provided by the National Center for Biotechnology Information, USA), with additional criteria of date from 1996 and studies of humans. We then chose the studies of stroke or cerebrovascular diseases with autoregulatory assessment. This results in more than 40 articles as listed from 950 searched items (table 2), which revealed that there is inconsistency in the application of autoregulatory methods, with altered CA over the infarcted ipsilateral, contralateral or bilateral side and its time course effects after stroke onset.

Global or focal impairment of CA?

CA may become impaired after ischaemic stroke. Focal impairment of static autoregulation in the reperfused ischaemic area itself has been demonstrated.[1] Moreover, some studies indicated a more global impairment of static autoregulation in the affected and also in the unaffected hemisphere,[39 40] whereas another study found static autoregulation in the unaffected hemisphere to be generally preserved.[41] Because assessment of static autoregulation requires considerable manipulation of ABP, it is not routinely applicable in acute stroke treatment. Therefore, the so-called dynamic CA approach has evolved. It has been postulated that dynamic CA may be more sensitive to cerebral haemodynamic impairment.[22]

Using the method of ARI estimated from thigh-cuff test or spontaneous transient pressor and depressor blood pressure stimuli, a global bihemispheric impairment of dynamic CA in acute stroke within 24–72 hours of symptom onset with preserved static autoregulation has been found,[42–44] which is not related to stroke subtype classified as total/partial anterior circulation syndrome, lacunar syndrome and posterior circulation syndrome.[42 44] Dawson *et al* also found dynamic CA, as assessed by ARI with thigh-cuff test, is globally impaired within 96 hours of ischaemic stroke onset and remains abnormal for at least 1–2 weeks post-ictus.[45] However, using TFA approach to derive the autoregulatory parameters of gain and phase, Immink *et al* reported dynamic CA is impaired ipsilaterally in the MCA territory ischaemic stroke but bilaterally in lacunar ischaemic stroke.[46] With the same measurement method, a recent study further demonstrated the similar findings that dynamic CA is impaired ipsilaterally in stroke of large artery atherosclerosis but bilaterally in stroke of small artery occlusion,[47] which might be attributed to the varied pathological changes of cerebral blood vessels. Assessing dynamic CA on days 0–2, 3–6 and ≥7 days after acute large vessel ischaemic stroke in the MCA territory, one recent study showed that dynamic CA is impaired in the affected hemisphere throughout the first week, and then normalises by week 2.[48]

Table 2 Summary of studies using different methods to measure CA in patients with stroke

Method	Autoregulatory parameter	Study design	Timing measurement	Main findings
TFA (Immink *et al*, 2005)[46]	Gain and phase	Lacunar ischaemic stroke (n=10; NIHSS, 9±1; age, 63±3 years) MCA ischaemic stroke (n=10; NIHSS, 17±2; age, 59±5 years) Reference subjects (n=10; age, 57±2 years)	More than 24 hours of symptom onset	Autoregulation is impaired ipsilaterally in MCA stroke but bilaterally in lacunar stroke.
TFA (Guo *et al*, 2014)[47]	Gain, phase and slope of step response	Unilateral MCA territory stroke of large artery atherosclerosis (n=15; NIHSS, 7.1±4.7; age, 44.7±13.1 years) and small artery occlusion (n=26; NIHSS, 3.8±2.8; age, 54.1±9.7 years) Healthy volunteers (n=20; age, 42.2±13.7 years)	Within 5–10 days of symptom onset	Autoregulation is impaired ipsilaterally in stroke of large artery atherosclerosis but bilaterally in stroke of small artery occlusion.
ARI (Eames *et al*, 2002)[43]	ARI	Acute ischaemic stroke (n=56; Barthel index, 60; age, 70±9 years) Normal controls (n=56; age, 69±7 years)	Within 72 hours of ictus	Autoregulation is globally impaired after acute ischaemic stroke.
ARI based on thigh-cuff test (Saeed *et al*, 2013)[44]	ARI	Acute ischaemic stroke including lacunar clinical syndrome (n=11; age, 60±18 years) Total anterior circulation stroke/partial anterior circulation syndrome) (n=11; age, 65±19 years) Healthy controls (n=10; age, 59±15 years)	Within 48 hours of symptom onset	Autoregulation is impaired in the affected and non-affected sides with no difference in different stroke subtype.
ARI based on thigh-cuff test (Dawson *et al*, 2000)[42]	ARI	Acute ischaemic stroke with different subtypes (n=54; NIHSS, 8±4; age, 69±12 years, including total/partial anterior circulation syndrome, lacunar syndrome and posterior circulation syndrome) Control subjects (n=61; age, 67±10 years)	Within 96 hours of ictus	Dynamic but not static CA appears to be globally impaired in acute ischaemic stroke, which is not related to stroke subtypes.
PET (Powers *et al*, 2009)[40]	Static autoregulation	Ischaemic stroke (n=9)	Within 1–11 days after ischaemic stroke	Two out of nine patients had impaired autoregulation bilaterally.
ARI (Atkins *et al*, 2010)[69]	ARI	Mild ischaemic stroke (n=19; NIHSS <8; age, 67±11 years) Transient ischaemic attack (n=17; age, 62±11 years) Controls (n=22; age, 65±8 years)	At a median of 36 hours from onset and again a median of 96 hours from onset	Autoregulation is compromised acutely following mild ischaemic stroke but not transient ischaemic attack.
TFA and time correlation (Reinhard *et al*, 2008)[52]	Mx and phase	Acute MCA occlusion after rtPA thrombolysis (n=16; NIHSS, 14±3; age, 67±12 years) Minor stroke not receiving rtPA (n=11; NIHSS, 5±4; age, 62±7 years) Healthy adults (n=71; age, 64±9 years)	Within the first 5 days (120 hours) after stroke onset (study 1 at 12–24 hours, study 2 at 60±12 hours and study 3 at 108±12 hours)	CA is increasingly impaired in major ischaemic stroke after unsuccessful rtPA thrombolysis. It is bilaterally preserved in minor stroke after successful rtPA thrombolysis.
TFA (Petersen *et al*, 2015)[48]	Gain and phase	Acute large vessel ischaemic stroke in the MCA territory (n=28; NIHSS, 12±7; age, 68±17 years) Healthy controls (n=29; age, 55±9 years)	At days 0–2, 3–6 and ≥7 days after stroke	Dynamic CA is impaired in the affected hemisphere throughout the first week after large vessel ischaemic stroke, and then normalises by week 2.
TFA (Kwan *et al*, 2004)[49]	Gain and phase	Ischaemic stroke in the MCA territory (n=10)	At <7 days, 6 weeks and 3 months after stroke	The bilateral impairment of dynamic CA might improve up to 3 months after ischaemic stroke
Modified MMPF (Hu *et al*, 2012)[70]	Phase	Chronic ischaemic stroke (n=39; NIHSS, 2.6±0.4; age, 65±1 years) Non-stroke subjects (n=40; age, 68±1 years)	At 0.5–30.9 years (mean=6.1 years) after stroke	CA is impaired in chronic ischaemic stroke (≥6 months after stroke).
Time correlation (Dohmen *et al*, 2007)[53]	COx	Ischaemic stroke in the MCA territory including malignant and benign course groups (n=15)	At 24 and 72 hours after stroke	Early impairment of cerebrovascular autoregulation in peri-infarct tissue of patients who developed malignant brain oedema, whereas autoregulation was preserved in patients with a benign course.
Time correlation and TFA (Reinhard *et al*, 2005)[51]	Dx and Mx, gain and phase	Acute ischaemic stroke in the MCA territory (n=40; NIHSS, 6±4)	Within 22±11 hours and 134±25 hours of ictus	Dynamic CA might not be disturbed in minor MCA stroke but slightly impaired at the subacute stage.

Continued

Table 2 Continued

Method	Autoregulatory parameter	Study design	Timing measurement	Main findings
ARI based on thigh-cuff test and static autoregulation (Dawson *et al*, 2003)[45]	ARI and static autoregulation	Acute ischaemic stroke including total anterior/partial anterior circulation, lacunar and posterior circulation strokes (n=54; NIHSS, ≤10; age, 69±11 years) Controls (n=51; age, 67±10 years)	Within 96 hours of ischaemic stroke and again 7–14 days later	Dynamic, but not static, CA is impaired after acute ischaemic stroke and remains abnormal for at least 1–2 weeks post-ictus.
MMPF (Aoi *et al*, 2012)[3]	Phase	Chronic ischaemic stroke in the MCA territory (n=33; NIHSS, 2.5±2.6; age, 63.4±1.4 years) Controls (n=109; age, 65.3±0.8 years)	More than 6 months poststroke	Better dynamic CA is associated with less atrophy and better long-term functional status in chronic ischaemic infarctions.
Time correlation (Reinhard *et al*, 2012)[4]	Mx	Acute ischaemic stroke in the MCA territory (n=45)	Within 48 hours from onset) and again days 5–7	Impairment of dynamic CA ipsilateral to acute ischaemic stroke is associated with larger infarction. Dysautoregulation tends to worsen and spread to the contralateral side over the first days poststroke and is associated with poor clinical outcome.
TFA (Ma *et al*, 2016)[6]	Gain and phase	Acute intracerebral haemorrhage (n=43; age, 53.7±10.0 years)	On days 1–2, 4–6 10–12 and 30 days after ictus	Dynamic CA is bilaterally impaired lasting at least 10–12 days and recovers within a month. Phase is associated with clinical status at acute stage and phase on affected side on days 4–6, which can be an independent predictor for outcomes.
TFA (Otite *et al*, 2014)[55]	Gain and phase	Subarachnoid haemorrhage (n=68; age, 54±13 years)	On days 2–4 post-SAH	Dynamic CA is impaired in the early days after subarachnoid haemorrhage.
TFA (Oeinck *et al*, 2013)[5]	Gain and phase	Acute intracerebral haemorrhage (n=26; NIHSS, 12±7; age, 65±11 years) Controls (n=55; age, 64±8 years)	On days 1, 3 and 5 after ictus	PooreThe mThe mr individual phase values are associated with larger intracerebral haemorrhage volume, lower blood pressure and worsened outcome.
Linear regression (Gould *et al*, 2013)[54]	Correlation coefficient (between systolic blood pressure and relative CBF measured by CTP)	Acute intracerebral haemorrhage (n=20; NIHSS, 9; age, 73±11 years)	At a median time from onset of 20.2 hours and reimaged 2.1 hours later	CA is preserved within 72 hours of intracerebral haemorrhage.
Time correlation (Budohoski *et al*, 2012)[29]	Sxa (TCD based) and TOxa (NIRS based)	Subarachnoid haemorrhage (n=98)	Less than 5 days of onset	Disturbed autoregulation in the first 5 days after subarachnoid haemorrhage increases the risk of delayed cerebral ischaemia.
Time correlation (Jaeger *et al*, 2012)[56]	ORx	Severe subarachnoid haemorrhage (n=80)	At 7.9 days (range, 1.9–14.9 days) of onset	Impaired autoregulation was independently associated with an unfavourable outcome.
TFA (Gommer *et al*, 2008)[66]	Gain and phase	Lacunar ischaemic stroke (n=29)	NA	Dynamic CA and cerebrovascular reactivity are different mechanisms. TFA needs no provocation and adverse patient effects are minimal.
MMPF (Hu *et al*, 2008)[50]	Phase	Subjects (n=32; mean age 46.7 years) including 12 control, 10 hypertensive and 10 stroke subjects	NA	MMPF is better than ARI in terms of reproducibility.
Time correlation (Reinhard *et al*, 2003)[65]	Dx and Mx	Severe unilateral carotid stenosis (> or =70%) or occlusion (n=150; age, 67±8 years)	NA	Time correlation and TFA is comparable in assessing autoregulation.
Time correlation (Schmidt *et al*, 2003)[67]	Mx and PRx	Severe head injuries or stroke (n=145; age, 35±18 years)	NA	The Mx and PRx provide a non-invasive and continuous assessment of autoregulation.
ARI based on TFA (Elting *et al*, 2014)[68]	ARI	Patients with acute ischaemic stroke (n=27; NIHSS, 10.2±6.3; age, 59.1±16.9 years) Healthy subjects (n=16; age, 54.5±17.3 years)	NA	A transfer function filter may reduce ARI variability in controls, resulting in more pronounced group differences between patients with stroke and healthy subjects.

ARI, autoregulation index; CA, cerebral autoregulation; CBF, cerebral blood flow; COx, COx (also TOx), cerebral oximetry reactivity index; CTP, computed tomography perfusion; Dx, diastolic flow index; MCA, middle cerebral artery; MMPF, multimodal pressure flow; Mx, mean flow reactivity index; NA, not applicable; NIRS, near-infrared spectroscopy; ORx, oxygen reactivity index; PET, positron emission tomography; PRx, pressure reactivity index; rtPA, recombinant tissue plasminogen activator; TCD, transcranial Doppler; TFA, transfer function analysis; NIHSS, National Institutes of Health Stroke Scale.

Changes in CA over time after stroke

Kwan *et al* assessed dynamic CA in acute MCA territory patients with ischaemic stroke at <7 days, 6 weeks and 3 months after stroke, and found that bilateral impairment of dynamic CA might improve up to 3 months after ischaemic stroke.[49] However, using a different modified MMPF method, Hu *et al* reported that the impaired dynamic CA may persist up to 6 months after ischaemic stroke.[50] In contrast to what were found in these studies, Reinhard *et al* found dynamic CA, as assessed by both time correlation and TFA methods, might not be disturbed in minor MCA stroke within 22 hours of symptom onset but slightly impaired at the subacute stage within 134 hours of ictus.[51] In one study to investigate the effect of recombinant tissue plasminogen activator (rtPA) on dysautoregulation in 16 patients with acute ischaemic stroke based on both TFA and time correlation methods, dynamic CA is found to be increasingly impaired, mainly on the affected side, over the first 5 days of major ischaemic stroke after unsuccessful rtPA thrombolysis and bilaterally preserved in minor stroke after successful rtPA thrombolysis.[52] These suggest that development of cerebral dysautoregulation may be particularly critical during the early stage of reperfusion in acute ischaemic stroke. This is probably also the most interesting time period with regard to functional brain reorganisation. Cerebral dysautoregulation may therefore play a significant role within the detrimental effect of reperfusion and hyperperfusion. As supposed for malignant MCA infarction,[53] a vicious circle may start in the peri-infarct area by spreading local acidosis with consequent dysautoregulation, hypoperfusion or hyperperfusion, oedema, and further infarction. Studies with large sample size emphasising the role of reperfusion in the evolution of autoregulatory failure are needed.

CA and clinical outcome

There are two studies to investigate the relationship between dynamic CA and clinical outcome after ischaemic stroke using MMPF and combined time correlation and TFA method, respectively. One study indicated that better bilateral dynamic CA is associated with less atrophy and better long-term functional status in older adults with chronic ischaemic infarctions.[3] The other showed that impairment of dynamic CA ipsilateral to acute ischaemic stroke is associated with larger infarction, and dysautoregulation tends to worsen and spread to the contralateral side over the first days poststroke and is associated with poor clinical outcome.[4] However, these observations were obtained from relatively small sample size studies. It remains largely unclear whether impairment of dynamic CA is related to the long-term clinical outcome in stroke survivors. Multicentre studies with greater statistical powers are needed to address the prognostic significance of perturbations in CA, which may benefit patients with stroke in the future.

CA in intracerebral haemorrhage

So far, management of hypertension during acute intracerebral haemorrhage (ICH) is controversial. Haematoma expansion may be attenuated by acute blood pressure reduction, but concern persists that dynamic CA may be impaired after ICH, making perfusion of the brain passively dependent on blood pressure.[6] Perihaematoma tissue is moderately hypoperfused and therefore may be vulnerable to blood pressure reduction. However, in contrast, a CTP study in 20 patients within 72 hours of ICH indicated that CBF remained stable after acute blood pressure reduction, suggesting some preservation of CA which was assessed by linear regression analysis between systolic blood pressure and relative CBF measured by CTP.[54] Using the TFA method, 26 patients with ICH were studied on days 1, 3 and 5 after ictus to evaluate the time course of dynamic CA in acute ICH and its relationship with clinical outcome.[5] Dynamic temporal characteristics of CA are not generally altered in acute ICH, but poorer individual phase values are associated with larger ICH volume, lower blood pressure and worsened outcome.[5] Blood pressure reductions in acute ICH should thus be viewed with caution.

CA after SAH

In SAH studies using TFA or time correlation method, impaired dynamic CA is observed in the first 5 days post-SAH, before evidence of vasospasm can be found, is strongly predictive of delayed cerebral ischaemia[29 55] and is independently associated with an unfavourable outcome after 6 months of SAH onset.[56] Including autoregulation as part of the initial clinical and radiographic assessment may enhance our ability to identify patients at a high risk for developing secondary complications after SAH.

CA and blood pressure management after stroke

Considering the complexity of CA, it is not surprising that significant controversies exist in blood pressure management in patients suffering from acute stroke. It is believed that both very high and very low blood pressure after acute stroke are harmful and are associated with worsening outcome. The ideal blood pressure range after acute stroke is unknown. Current guideline recommended permissive hypertension after acute ischaemic stroke. In patients who do not receive thrombolysis, it is recommended that blood pressure treatment should be on hold unless systolic blood pressure is >220 mm Hg or diastolic blood pressure is >120 mm Hg within the initial 24 hours after stroke.[57] In patients who receive intravenous thrombolysis, the systolic blood pressure should be below 185 mm Hg and the diastolic blood pressure should be below 110 mm Hg before initiating thrombolysis. After initiating thrombolysis, the systolic blood pressure should be below 180 mm Hg and the diastolic blood pressure should be below 105 mm Hg within 24 hours after intravenous thrombolysis.[58] In patients with spontaneous ICH and elevated blood pressure, the 2010 American Heart Association (AHA) guideline recommends keeping systolic blood pressure below 160 mm Hg if no other contraindication.[59] Overall, an optimal ABP range likely exists during acute stroke but probably depends on an individual CA variability, temporal and spatial heterogeneity of stroke pathophysiology, and stroke subtype. Unfortunately, such an ideal blood pressure range has not yet been determined based on randomised, controlled trials. Recently, several large randomised clinical trials were performed to address the controversies in acute blood pressure management after acute stroke, including ICH and ischaemic stroke. Most trials suggested that lowered blood pressure in acute stroke has acceptable safety profile but did not improve functional outcome. For example, INTERACT2 is the first large randomised trial of rapid blood pressure lowering in acute ICH, which suggests that aggressive lowering of blood pressure <140 mm Hg within 1 hour is safe in acute ICH within 6 hours from symptom onset.[60] Accordingly, the 2015 AHA guideline states that for patients with ICH presenting with systolic blood pressure between 150 mm Hg and 220 mm Hg and without contraindication to acute blood pressure treatment, acute lowering of systolic blood pressure to 140 mm Hg is safe.[61] However, harmful effects (renal adverse events) of aggressive blood pressure were reported in another trial (ATACH-2).[62] The ongoing ENCHANTED trial will evaluate whether early intensive blood pressure lowering (systolic blood pressure target to 130–140 mm Hg) is superior to guideline-recommended systolic blood pressure target of <180 mm Hg) in patients with ischaemic

stroke who receive intravenous thrombolysis in terms of efficacy and safety.[63] It should be noted that CA study was not performed or even considered in these trials; thus, its potential effects on clinical outcome measures are not known. Furthermore, hypertension is one of the major risk factors for stroke. De novo hypertension is common in patients with acute stroke. It is unclear whether de novo hypertension should be treated or prestroke antihypertensive medications should be continued or stopped in acute stroke. The recent ENOS trial did not show any benefit to continue prestroke antihypertensive treatment in patients with acute stroke.[64] It is possible that a subpopulation of patients with acute stroke with relative intact CA may benefit from aggressive blood pressure treatment to improve clinical outcome and decrease harmful side effects. It is also not known if similar to acute stroke, an 'optimal ABP' which assures best CA exists and can be assessed using continuous monitoring.[30] This critical knowledge gap further supports the need to understand the complex mechanisms of CA on an individual basis and apply to patient care in an era of precision medicine.

Comparison of different methodologies

Several studies have investigated the comparisons among the current methods of measuring dynamic CA. Time correlation and TFA are comparable in assessing autoregulation in carotid artery occlusive disease.[65] For patients with stroke, TFA needs no provocation and adverse patient effects are minimal,[66] and time correlation provides a non-invasive and continuous assessment of autoregulation.[67] A transfer function filter may reduce ARI variability in controls, resulting in more pronounced group differences between patients with stroke and healthy subjects.[68] Moreover, MMPF might be better than ARI in terms of reproducibility estimated in controls, traumatic brain injury and patients with stroke.[50] It should be kept in mind that the results from a single episode of induced hypotension, for example, a thigh-cuff based ARI, may represent distinct processes from spontaneous fluctuation of ABP, and their impairment and recovery after stroke may be dissociated. This issue is also addressed in our methodology section with more explanation.

Currently, there is no widely accepted 'best choice' for the autoregulatory assessment. The decision should be made according to the status of the targeted patients and the research questions to be answered. For example, for patients with stroke at acute stage, TFA might be a good option, as it requires minimal cooperation with no stimulus of blood pressure and the procedure of data recording can be performed at bedside; for patients with stroke at chronic stage, paced breathing or thigh-cuff tests might become acceptable to provide visual inspections of blood flow responses after passive ABP challenges and for patients in the intensive care unit, a long-term monitoring of CPP and CBF velocity is possible, and therefore time correlation method is more suitable to understand the temporal course of autoregulation, which can be helpful in predicting outcomes.

Clinical trials are needed. Although 'autoregulation-oriented therapy' has been addressed in traumatic brain injury (although there is still no evidence that it is able to improve outcome), in stroke there is very little room for manoeuvre. Statins proved to improve autoregulation and short-term outcome in haemorrhagic stroke in a phase II study, but a phase III multicentre trial did not show any benefit.

CONCLUSION

This review shows that TFA and time correlation are the most frequently used assessments across multicentres. These methods can differentiate patients with disturbed haemodynamics due to stroke or cerebrovascular diseases from healthy controls by the phase-shift derived from TFA and (or) correlation coefficient indices. It is generally accepted that CA is disturbed both in ischaemic and haemorrhagic stroke, and in ICH or severe cerebrovascular diseases. CA may change with pathological progression. The status of autoregulation at a certain temporal stage might be associated with the outcome.[6 29] Further investigation on autoregulation follow-ups with large sample size is required to confirm this. Moreover, it shows that the individual status of autoregulation cannot always be determined by the current methods accurately.[40] Although a few attempts have been made to improve the current assessments by including non-linear and multivariate properties in the mathematical models, these studies are still limited to single centres. Clinical study across multi-centres of advanced mathematical models and the neuroimaging techniques is desirable to improve assessment of individuals.

Contributors LX, XL and TS performed the literature search and wrote the manuscript. JL and KSW conceived and designed the review outlines. JL, MC and RZ helped revise the manuscript. PS and JD proposed professional advice on the methodologies of the assessment of cerebral autoregulation. ZG, YY and TL proposed professional advice on the clinical research related to cerebral autoregulation in ischaemic stroke.

Funding This work was supported by the Health and Medical Research Fund (HMRF, Project No 02130836) and the General Research Fund from Research Grants Council (GRF, Reference No. 14100215) in Hong Kong.

Competing interests None declared.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES

1 Paulson OB, Strandgaard S, Edvinsson L, *et al*. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990;2:161–92.
2 Liu L, Wang D, Wong KS, *et al*. Stroke and stroke care in China: huge burden, significant workload, and a national priority. *Stroke* 2011;42:3651–4.
3 Aoi MC, Hu K, Mt L, *et al*. Impaired cerebral autoregulation is associated with brain atrophy and worse functional status in chronic ischemic stroke. *PLoS One* 2012;7:e46794.
4 Reinhard M, Rutsch S, Lambeck J, *et al*. Dynamic cerebral autoregulation associates with infarct size and outcome after ischemic stroke. *Acta Neurol Scand* 2012;125:156–62.
5 Oeinck M, Neunhoeffer F, Buttler KJ, *et al*. Dynamic cerebral autoregulation in acute intracerebral hemorrhage. *Stroke* 2013;44:2722–8.
6 Ma H, Guo ZN, Liu J, *et al*. Temporal course of dynamic cerebral autoregulation in patients with intracerebral hemorrhage. *Stroke* 2016;47:674–81.
7 Faraci FM, Heistad DD. Regulation of large cerebral arteries and cerebral microvascular pressure. *Circ Res* 1990;66:8–17.
8 Liu J, Zhu YS, Hill C, *et al*. Cerebral autoregulation of blood velocity and volumetric flow during steady-state changes in arterial pressure. *Hypertension* 2013;62:973–9.
9 Hamel E. Perivascular nerves and the regulation of cerebrovascular tone. *J Appl Physiol* 2006;100:1059–64.
10 Hamner JW, Tan CO. Relative contributions of sympathetic, cholinergic, and myogenic mechanisms to cerebral autoregulation. *Stroke* 2014;45:1771–7.
11 Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci* 2004;5:347–60.
12 Rosengarten B, Huwendiek O, Kaps M. Neurovascular coupling and cerebral autoregulation can be described in terms of a control system. *Ultrasound Med Biol* 2001;27:189–93.
13 Lincoln J. Innervation of cerebral arteries by nerves containing 5-hydroxytryptamine and noradrenaline. *Pharmacol Ther* 1995;68:473–501.
14 Cipolla MJ, Li R, Vitullo L. Perivascular innervation of penetrating brain parenchymal arterioles. *J Cardiovasc Pharmacol* 2004;44:1–8.
15 Chabriat H, Joutel A, Dichgans M, *et al*. Cadasil. *Lancet Neurol* 2009;8:643–53.
16 Joutel A, Monet-Lepretre M, Gosele C, *et al*. Cerebrovascular dysfunction and microcirculation rarefaction precede white matter lesions in a mouse genetic model of cerebral ischemic small vessel disease. *J Clin Invest* 2010;120:433–45.
17 Lacombe P, Oligo C, Domenga V, *et al*. Impaired cerebral vasoreactivity in a transgenic mouse model of cerebral autosomal dominant arteriopathy

with subcortical infarcts and leukoencephalopathy arteriopathy. *Stroke* 2005;36:1053–8.
18 Edvinsson L, Owman C, Sjoberg NO, *et al*. Mast cells, and Amine receptors in human brain vessels. A histochemical and pharmacological study. *Brain Res* 1976;115:377–93.
19 Faraci FM, Mayhan WG, Heistad DD. Segmental vascular responses to acute hypertension in cerebrum and brain stem. *Am J Physiol* 1987;252:H738–42.
20 Roth C, Ferbert A. The posterior reversible encephalopathy syndrome: what's certain, what's new? *Pract Neurol* 2011;11:136–44.
21 Aaslid R, Lindegaard KF, Sorteberg W, *et al*. Cerebral autoregulation dynamics in humans. *Stroke* 1989;20:45–52.
22 Tiecks FP, Lam AM, Aaslid R, *et al*. Comparison of static and dynamic cerebral autoregulation measurements. *Stroke* 1995;26:1014–9.
23 Claassen JA, Meel-van den Abeelen AS, Simpson DM, *et al*. Transfer function analysis of dynamic cerebral autoregulation: a white paper from the international cerebral autoregulation research network. *J Cereb Blood Flow Metab* 2016;36:665–80.
24 Mahony PJ, Panerai RB, Deverson ST, *et al*. Assessment of the thigh cuff technique for measurement of dynamic cerebral autoregulation. *Stroke* 2000;31:476–80.
25 Lin W, Xiong L, Han J, *et al*. External counterpulsation augments blood pressure and cerebral flow velocities in ischemic stroke patients with cerebral intracranial large artery occlusive disease. *Stroke* 2012;43:3007–11.
26 Xiong L, Lin W, Han J, *et al*. Enhancing cerebral perfusion with external counterpulsation after ischaemic stroke: how long does it last? *J Neurol Neurosurg Psychiatry* 2016;87:531–6.
27 Lin W, Xiong L, Han J, *et al*. Hemodynamic effect of external counterpulsation is a different measure of impaired cerebral autoregulation from vasoreactivity to breath-holding. *Eur J Neurol* 2014;21:326–31.
28 Zweifel C, Castellani G, Czosnyka M, *et al*. Continuous assessment of cerebral autoregulation with near-infrared spectroscopy in adults after subarachnoid hemorrhage. *Stroke* 2010;41:1963–8.
29 Budohoski KP, Czosnyka M, Smielewski P, *et al*. Impairment of cerebral autoregulation predicts delayed cerebral ischemia after subarachnoid hemorrhage: a prospective observational study. *Stroke* 2012;43:3230–7.
30 Rasulo FA, Girardini A, Lavinio A, *et al*. Are optimal cerebral perfusion pressure and cerebrovascular autoregulation related to long-term outcome in patients with aneurysmal subarachnoid hemorrhage? *J Neurosurg Anesthesiol* 2012;24:3–8.
31 Novak V, Yang AC, Lepicovsky L, *et al*. Multimodal pressure-flow method to assess dynamics of cerebral autoregulation in stroke and hypertension. *Biomed Eng Online* 2004;3:39.
32 Tian F, Tarumi T, Liu H, *et al*. Wavelet coherence analysis of dynamic cerebral autoregulation in neonatal hypoxic-ischemic encephalopathy. *Neuroimage Clin* 2016;11:124–32.
33 Mitsis GD, Marmarelis VZ. Modeling of nonlinear physiological systems with fast and slow dynamics. I. methodology. *Ann Biomed Eng* 2002;30:272–81.
34 Liu J, Simpson DM, Kouchakpour H, *et al*. Rapid pressure-to-flow dynamics of cerebral autoregulation induced by instantaneous changes of arterial CO2. *Med Eng Phys* 2014;36:1636–43.
35 Santos GA, Petersen N, Zamani AA, *et al*. Pathophysiologic differences in cerebral autoregulation after subarachnoid hemorrhage. *Neurology* 2016;86:1950–6.
36 Tan CO. Defining the characteristic relationship between arterial pressure and cerebral flow. *J Appl Physiol* 2012;113:1194–200.
37 Shin HK, Nishimura M, Jones PB, *et al*. Mild induced hypertension improves blood flow and oxygen metabolism in transient focal cerebral ischemia. *Stroke* 2008;39:1548–55.
38 Panerai RB, Jara JL, Saeed NP, *et al*. Dynamic cerebral autoregulation following acute ischaemic stroke: comparison of transcranial doppler and magnetic resonance imaging techniques *J Cereb Blood Flow Metab*. Online First: 5th Nov 2015.
39 Paulson OB, Olesen J, Christensen MS. Restoration of autoregulation of cerebral blood flow by hypocapnia. *Neurology* 1972;22:286–93.
40 Powers WJ, Videen TO, Diringer MN, *et al*. Autoregulation after ischaemic stroke. *J Hypertens* 2009;27:2218–22.
41 Georgiadis D, Schwarz S, Evans DH, *et al*. Cerebral autoregulation under moderate hypothermia in patients with acute stroke. *Stroke* 2002;33:3026–9.
42 Dawson SL, Blake MJ, Panerai RB, *et al*. Dynamic but not static cerebral autoregulation is impaired in acute ischaemic stroke. *Cerebrovasc Dis* 2000;10:126–32.
43 Eames PJ, Blake MJ, Dawson SL, *et al*. Dynamic cerebral autoregulation and beat to beat blood pressure control are impaired in acute ischaemic stroke. *J Neurol Neurosurg Psychiatry* 2002;72:467–72.
44 Saeed NP, Panerai RB, Horsfield MA, *et al*. Does stroke subtype and measurement technique influence estimation of cerebral autoregulation in acute ischaemic stroke? *Cerebrovasc Dis* 2013;35:257–61.
45 Dawson SL, Panerai RB, Potter JF. Serial changes in static and dynamic cerebral autoregulation after acute ischaemic stroke. *Cerebrovasc Dis* 2003;16:69–75.
46 Immink RV, van Montfrans GA, Stam J, *et al*. Dynamic cerebral autoregulation in acute lacunar and middle cerebral artery territory ischemic stroke. *Stroke* 2005;36:2595–600.
47 Guo ZN, Liu J, Xing Y, *et al*. Dynamic cerebral autoregulation is heterogeneous in different subtypes of acute ischemic stroke. *PLoS One* 2014;9:e93213.
48 Petersen NH, Ortega-Gutierrez S, Reccius A, *et al*. Dynamic cerebral autoregulation is transiently impaired for one week after large-vessel acute ischemic stroke. *Cerebrovasc Dis* 2015;39:144–50.
49 Kwan J, Lunt M, Jenkinson D. Assessing dynamic cerebral autoregulation after stroke using a novel technique of combining transcranial Doppler ultrasonography and rhythmic handgrip. *Blood Press Monit* 2004;9:3–8.
50 Hu K, Peng CK, Czosnyka M, *et al*. Nonlinear assessment of cerebral autoregulation from spontaneous blood pressure and cerebral blood flow fluctuations. *Cardiovasc Eng* 2008;8:60–71.
51 Reinhard M, Roth M, Guschlbauer B, *et al*. Dynamic cerebral autoregulation in acute ischemic stroke assessed from spontaneous blood pressure fluctuations. *Stroke* 2005;36:1684–9.
52 Reinhard M, Wihler C, Roth M, *et al*. Cerebral autoregulation dynamics in acute ischemic stroke after rtpa thrombolysis. *Cerebrovasc Dis* 2008;26:147–55.
53 Dohmen C, Bosche B, Graf R, *et al*. Identification and clinical impact of impaired cerebrovascular autoregulation in patients with malignant middle cerebral artery infarction. *Stroke* 2007;38:56–61.
54 Gould B, McCourt R, Asdaghi N, *et al*. Autoregulation of cerebral blood flow is preserved in primary intracerebral hemorrhage. *Stroke* 2013;44:1726–8.
55 Otite F, Mink S, Tan CO, *et al*. Impaired cerebral autoregulation is associated with vasospasm and delayed cerebral ischemia in subarachnoid hemorrhage. *Stroke* 2014;45:677–82.
56 Jaeger M, Soehle M, Schuhmann MU, *et al*. Clinical significance of impaired cerebrovascular autoregulation after severe aneurysmal subarachnoid hemorrhage. *Stroke* 2012;43:2097–101.
57 Jauch EC, Saver JL, Adams HP, *et al*; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44:870–947.
58 Demaerschalk BM, Kleindorfer DO, Adeoye OM, *et al*. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2016;47:581–641.
59 Morgenstern LB, Hemphill JC, Anderson C, *et al*; American Heart Association Stroke Council and Council on Cardiovascular Nursing. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2010;41:2108–29.
60 Anderson CS, Heeley E, Huang Y, *et al*. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med* 2013;368:2355–65.
61 Hemphill JC, Greenberg SM, Anderson CS, *et al*. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2015;46:2032–60.
62 Qureshi AI, Palesch YY, Barsan WG, *et al*. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med* 2016;375:1033–43.
63 Huang Y, Sharma VK, Robinson T, *et al*. Rationale, design, and progress of the enhanced control of hypertension and thrombolysis stroke study (ENCHANTED) trial: an international multicenter 2 x 2 quasi-factorial randomized controlled trial of low- vs. Standard-dose rt-PA and early intensive vs. Guideline-recommended blood pressure lowering in patients with acute ischaemic stroke eligible for thrombolysis treatment. *Int J Stroke* 2015;10:778–88.
64 Bath PM, Woodhouse L, Scutt P, *et al*. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOs): A partial-factorial randomised controlled trial. *Lancet* 2015;385:617–28.
65 Reinhard M, Roth M, Muller T, *et al*. Cerebral autoregulation in carotid artery occlusive disease assessed from spontaneous blood pressure fluctuations by the correlation coefficient index. *Stroke* 2003;34:2138–44.
66 Gommer ED, Staals J, van Oostenbrugge RJ, *et al*. Dynamic cerebral autoregulation and cerebrovascular reactivity: a comparative study in lacunar infarct patients. *Physiol Meas* 2008;29:1293–303.
67 Schmidt B, Czosnyka M, Raabe A, *et al*. Adaptive noninvasive assessment of intracranial pressure and cerebral autoregulation. *Stroke* 2003;34:84–9.
68 Elting JW, Maurits NM, Aries MJ. Variability of the autoregulation index decreases after removing the effect of the very low frequency band. *Med Eng Phys* 2014;36:601–6.
69 Atkins ER, Brodie FG, Rafelt SE, *et al*. Dynamic cerebral autoregulation is compromised acutely following mild ischaemic stroke but not transient ischaemic attack. *Cerebrovasc Dis* 2010;29:228–35.
70 Hu K, Mt L, Peng CK, *et al*. A nonlinear dynamic approach reveals a long-term stroke effect on cerebral blood flow regulation at multiple time scales. *PLoS Comput Biol* 2012;8:e1002601.

Impaired cerebral autoregulation: measurement and application to stroke

Li Xiong, Xiuyun Liu, Ty Shang, Peter Smielewski, Joseph Donnelly, Zhen-ni Guo, Yi Yang, Thomas Leung, Marek Czosnyka, Rong Zhang, Jia Liu and Ka Sing Wong

*J Neurol Neurosurg Psychiatry*2017 88: 520-531
doi: 10.1136/jnnp-2016-314385