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Cerebral Autoregulation: From Models to Clinical Applications

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Abstract Short-term regulation of cerebral blood flow (CBF) is controlled by myogenic, metabolic and neurogenic mechanisms, which maintain flow within narrow limits, despite large changes in arterial blood pressure (ABP). *Static* cerebral autoregulation (CA) represents the steady-state relationship between CBF and ABP, characterized by a plateau of nearly constant CBF for ABP changes in the interval 60–150 mmHg. The transient response of the CBF–ABP relationship is usually referred to as *dynamic* CA and can be observed during spontaneous fluctuations in ABP or from sudden changes in ABP induced by thigh cuff deflation, changes in posture and other manoeuvres. Modelling the dynamic ABP–CBFV relationship is an essential step to gain better insight into the physiology of CA and to obtain clinically relevant information from model parameters. This paper reviews the literature on the application of CA models to different clinical conditions. Although mathematical models have been proposed and should be pursued, most studies have adopted linear input–output ('black-box') models, despite the inherently non-linear nature of CA. The most common of these have been transfer function analysis (TFA) and a second-order differential equation model, which have been the main focus of the review. An index of CA (ARI), and frequency-domain parameters derived from TFA, have been shown to be sensitive to pathophysiological changes in patients with carotid artery disease, stroke, severe head injury, subarachnoid haemorrhage and other conditions. Non-linear dynamic models have also been proposed, but more work is required to establish their superiority and applicability in the clinical environment. Of particular importance is the development of multivariate models that can cope with time-varying parameters, and protocols to validate the reproducibility and ranges of normality of dynamic CA parameters extracted from these models.

Keywords Cerebral blood flow · Mathematical model · Diagnostic tests · Arterial blood pressure

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Introduction

Quantitative modelling is an essential tool for research on complex physiological systems. In general, mathematical models can be regarded as 'knowledge organizers', synthesizing data and information derived from diverse sources, as a single entity which can then be put to different uses, such as identifying gaps in knowledge, testing hypotheses, or simulating conditions which cannot be tested experimentally. Typical examples are models of the entire cardiovascular system, which have been evolving continuously during the last four decades (Beneken 1965; Fink et al. 2004; Grodins 1959; Guyton and Coleman 1967; Lanzarone et al. 2007). In models of this kind, most variables of interest, like arterial and venous pressures, blood flow, blood gas concentrations, or blood volumes, are measurable physical quantities and, as such, it is possible, at least theoretically, to assess model performance by comparing real values with model predictions.

A very different situation exists though, when a complex physiological phenomenon is reduced to a single concept. There are many examples of this reductionist approach in

medicine and physiology, such as the concepts of 'cardiac contractility', 'CO_2 reactivity', 'baroreceptor sensitivity', 'depth of anaesthesia', and so on. What is common to all these concepts, is that the main aspect of interest, exactly what is being 'conceptualized' cannot be directly measured. In this context, 'modelling' takes an entirely different meaning, because it becomes the only approach that can be used to define, describe, and quantify the phenomenon of interest.

'Cerebral autoregulation' is a typical single concept that simplifies the complex interplay of a large number of different physiological mechanisms (Lassen 1959; Paulson et al. 1990). A sudden change in mean arterial blood pressure (ABP) leads to a simultaneous change in cerebral blood flow (CBF), in the first instance, but also triggers a number of other responses (Aaslid et al. 1989). The change in ABP produces dilatation of the elastic cerebral arteries, and the smooth muscle surrounding these arteries is stretched. As a result of the combination of changes in smooth muscle ionic permeability, the muscle will contract, the diameter of the vessels will be reduced, and the cerebral vascular resistance will increase. This chain of events is what has been called the *myogenic* mechanism (Faraci et al. 1989; Golding and Golding 2001; Ngai and Winn 1995; Schubert and Mulvany 1999; Thorin-Trescases et al. 1997). On the other hand, the transient increase in CBF will promote increases in O_2 availability and reduction in products of cerebral metabolism, such as CO_2. In the absence of greater demand for O_2, a complex chain of events will take place to restore the balance between O_2 supply and demand, leading to vasoconstriction. Again, a large number of different phenomena, in this case involving the activation of nitric oxide and several other metabolites in the arterial endothelium, are simply labelled as the *metabolic* mechanism (Buxton et al. 2004; Faraci and Brian 1994; Faraci and Heistad 1998; Hyder et al. 1998; Kuschinsky 1991; Moody et al. 2005; Payne 2006; Zonta et al. 2003).

Despite the overwhelming complexity of the two main mechanisms involved, and the possibility that sympathetic neural control might also play a role (Branston 1995; Busija and Heistad 1984; Faraci and Heistad 1990; Hamel 2006; Micieli et al. 1994; Paulson et al. 1990; Purves 1978; Roatta et al. 1998; Zhang et al. 2002), the basic concept of cerebral autoregulation usually focuses on either the static or dynamic relationship between ABP (or cerebral perfusion pressure, CPP) and CBF (Aaslid et al. 1989; Lassen 1959; Panerai 1998; Paulson et al. 1990; Tiecks et al. 1995). Different models have been applied to each of these modalities. In the static definition, mean CBF is assumed to remain constant for changes in ABP (or CPP), in the range 60–150 mmHg (Lassen 1959; Panerai 1998; Paulson et al. 1990; Rosenblum 1995; Strandgaard 1976), when these variables are measured and averaged during 30 s or longer. The simplest model in this case is a linear regression (Czosnyka et al. 1996; Panerai et al. 1995). If the slope is below a certain threshold, it can be assumed that CA is normal, otherwise it is considered to be impaired. The dynamic concept of CA is based on the observation that when CBF is disturbed by a sudden change in ABP, its temporal response shows a relatively fast return to its original value, usually lasting 2–10s (Aaslid et al. 1989). As presented below, a diversity of models have been proposed for dynamic CA, for example using linear differential equations to represent the transient relationship between ABP and CBF (Tiecks et al. 1995). Most work performed on dynamic CA have benefited from the excellent temporal resolution of transcranial Doppler ultrasound to record CBF velocity (CBFV) in the middle cerebral artery (MCA) or other large cerebral arteries. Changes in CBFV will reflect changes in CBF, as long as the diameter of the insonated artery remains constant (Giller et al. 1993; Newell et al. 1994; Serrador et al. 2000).

Because modelling is essential to quantify the phenomenon of CA, the main objective of this review is to trace the evolution of models and their utilization in clinical conditions where the regulation of CBF might be disturbed. To reflect the most recent trends of research in this area, only models involving dynamic CA will be considered, but this should not be interpreted as an indictment on the clinical usefulness of models of static CA. Another bias of the review will be towards input–output (black-box) models, for the simple reason that these have dominated clinical applications of dynamic CA.

Linear Models of Dynamic Cerebral Autoregulation

Linear systems analysis is the simplest approach to generate models that can quantify the dynamic relationship between ABP and CBF/CBFV. A major problem in this case though, is that CA is clearly a non-linear phenomenon, because key parameters, like cerebrovascular resistance (CVR) are not time-invariant. This problem will be addressed in the section, which follows. In general, the linear approximation has been justified by the relatively small changes in ABP and CBF/CBFV around a point of equilibrium (Panerai 1998; Panerai et al. 2006). The most common linear approach has been transfer function analysis (TFA), involving the relationship between ABP and CBF(V) in the frequency domain. The cross-spectrum is defined as:

$$G_{pv}(f) = E[P(f)^* \cdot V(f)] \quad (1)$$

where $P(f)$ and $V(f)$ are the discrete Fourier transforms of ABP and CBF(V) beat-to-beat time series, usually obtained

via the FFT algorithm (Bendat and Piersol 1986). The expected value of the complex product, $E[\ ]$ is usually obtained by smoothing the spectra with a triangular moving average window and by averaging multiple segments of data (Bendat and Piersol 1986). Similarly, the auto-spectra of *ABP* is computed as:

$$G_{pp}(f) = E[P(f)^* \cdot P(f)] \tag{2}$$

The squared coherence function represents the fraction of output power (that is CBFV) that can be linearly explained by the input power (that is ABP), at each frequency:

$$\gamma^2(f) = \frac{|G_{pv}(f)|^2}{G_{vv}(f)G_{pp}(f)} \tag{3}$$

The squared coherence varies between 0 and 1, covering the range from absence of any linear relationship, to expressing a perfect linear dependence between input and output. In real life, most values of coherence will be <1 due to the presence of noise (Bendat and Piersol 1986). Values of $\gamma^2(f) = 0.5$ have been used by many investigators as the lower threshold to regard the relationship between ABP and CBFV as linear, but this cannot be generalized because the 95% confidence limit for coherence is a complex function of the degrees of freedom of the cross- and auto-spectral estimates and of the expected mean value of coherence (Bendat and Piersol 1986; Panerai et al. 1998, 2006). Low values of coherence can be the consequence of noise, lack of a relationship between input and output, multivariate influences on the output, or an input–output relationship that is non-linear. For this reason, it is not possible to assume that the relationship is non-linear, by simply looking at the absolute value of coherence (Panerai et al. 2006). Examples of coherence functions are shown in Fig. 1.

From the cross- and auto-spectra, the transfer function is calculated as:

$$H(f) = \frac{G_{pv}(f)}{G_{pp}(f)} \tag{4}$$

From the real and imaginary parts of *H(f)*, the amplitude and phase of the frequency response are calculated as

$$|H(f)| = \left[H_R(f)^2 + H_I(f)^2\right]^{\frac{1}{2}} \tag{5}$$

$$\varphi(f) = \tan^{-1}\left[\frac{H_I(f)}{H_R(f)}\right] \tag{6}$$

The first frequency-domain model proposed for CA already dealt with a clinical condition. Giller (Giller 1990) showed that the coherence function between ABP and CBFV was relatively low in subjects with normal CA, but increased significantly in patients with subarachnoid haemorrhage (SAH) and other cerebrovascular conditions. Giller explained these changes in coherence, based on the non-linear changes in CVR with a working CA, which would then buffer changes in CBF, thus reducing coherence. On the other extreme, when CA is impaired, CVR will not change. This leads to a more linear system and consequently to higher values of coherence.

The pioneering contribution of Giller (1990) was followed by several studies demonstrating the potential of transfer function analysis (TFA) to model the ABP–CBFV relationship (Blaber et al. 1997; Hu et al. 1999; Panerai et al. 1996, 1998; Schondorf et al. 2001; Zhang et al. 1998). Figure 1 shows the main frequency- and time-domain functions that are usually obtained by TFA (Panerai 2004). For the two patients represented, clear differences can be observed in the coherence function, amplitude (gain) and phase frequency responses, and CBFV step response, suggesting that CA is normal in one case but severely impaired in the other. The step response is particularly useful to interpret the dynamic CA response since it shows both the speed and the extent to which CBFV recovers to the original level.

Impulse/step responses like the ones shown in Fig. 1 can also be estimated directly in the time domain, using MA or ARMA models (moving average/autoregressive) (Edwards et al. 2001; Liu et al. 2003; Panerai et al. 2000, 2001; Simpson et al. 2000, 2001) or linear differential equation models, like the one proposed by Tiecks et al. (1995). The Aaslid–Tiecks model uses a 2nd order ODE whose gain (K), damping factor (D) and time constant (T) are combined to produce 10 template CBFV step response curves. Initially, the pressure change is normalized as:

$$dP(t) = \frac{P(t)}{1 - CCP_r} \tag{7}$$

where CCP_r is a parameter introduced by Tiecks et al. (1995) to represent the critical closing pressure as a fraction of the baseline pressure. The relative velocity change estimated by the model is given by

$$\hat{V}(t) = 1 + dP(t) - K \times x_2(t) \tag{8}$$

where K represents a gain parameter in the second order equation, and $x_2(t)$ is a state variable obtained from the following state equation system representing a second-order equation:

$$x_1(t) = x_1(t-1) + \frac{dP(t-1) - x_2(t-1)}{f \times T} \tag{9}$$

$$x_2(t) = x_2(t-1) + \frac{x_1(t-1) - 2 \times D \times x_2(t-1)}{f \times T} \tag{10}$$

where f is the sampling frequency, T is the time constant, and D is the damping factor. Tiecks et al., introduced a dynamic autoregulation index (ARI), ranging from 0

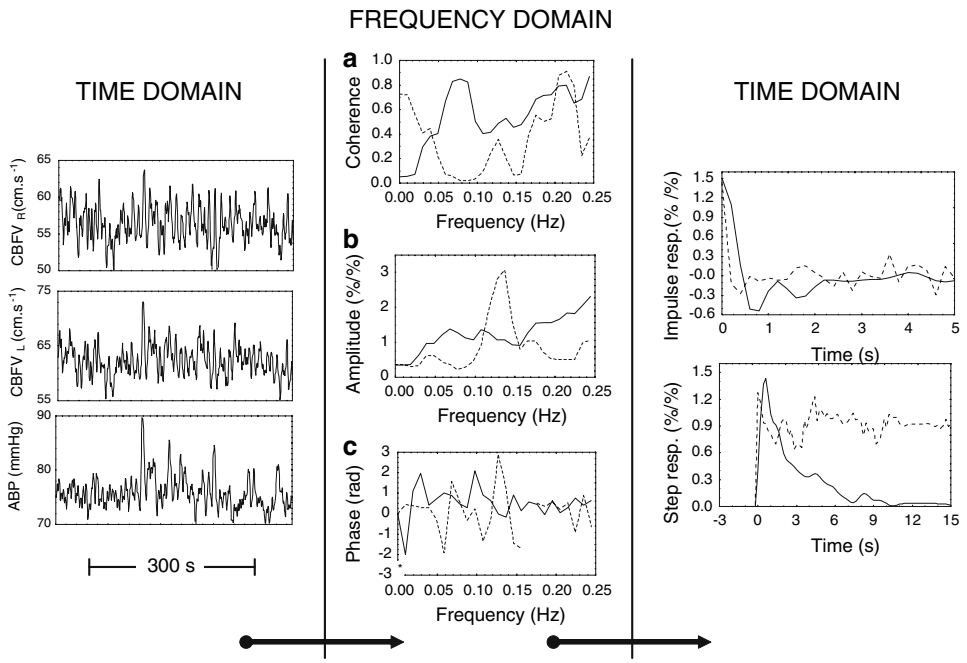

Fig. 1 Main parameters extracted by transfer function analysis (TFA) from beat-to-beat values of mean arterial blood pressure and cerebral blood flow velocity from the right and left middle cerebral artery (left panel). In the frequency-domain (central panel), the coherence function (**a**), amplitude (**b**) and phase (**c**) frequency responses indicate significant differences between two subjects with severe head injury. The inverse discrete Fourier transform of amplitude and phase give an estimate of the CBFV impulse and step responses (right panel). From the latter it can be suggested that dynamic CA is relatively normal in one subject (continuous line), but severely impaired in the other (dashed line)

(absence of CA) to 9 (best CA) by choosing 10 diffferent combinations of the *K*, *D*, *T* parameters (Tiecks et al. 1995). For ARI = 0, a theroretical step change in ABP is followed by a corresponding step change in CBF(V), as it would be expected in the absence of CA (Fig. 2). As the efficacy of CA increases, the CBF(V) step response gradually shows the capacity to return to its original level, and for the most efficient responses (ARI > 6), an undershoot is observed (Fig. 2). For any pair of ABP–CBFV measurements, the standard curve that best fits the data is selected by minimizing the quadratic error or maximizing the correlation coefficient, and the corresponding value of ARI is taken as the parameter of clinical interest, as shown by the example in Fig. 2. Tiecks et al. (1995) developed and validated the model for changes in ABP induced by the sudden release of inflated thigh cuffs. Other investigators have shown that the model can be applied to other maneuvers that change ABP or even to spontaneous fluctuations in ABP and CBFV, as represented in Fig. 2 (Panerai et al. 1998, 2001, 2003a; Simpson et al. 2004).

Multivariate, Non-linear and Time-variant Models

Before presenting the clinical applications of simple, univariate linear models, it would be useful to discuss their limitations and the potential advantages of more advanced models. The term *model performance* reflects the extent to which model predicted responses match experimental data. This is usually assessed using the time-domain, normalized quadratic error (NMSE) or the correlation coefficient (r^2). For obvious reasons, any model validation should use a different set of data from that used for model development, for example when finding basic model parameters, or training an artificial neural network.

Hitherto, most univariate linear models of dynamic CA have shown limited performance, as reflected by their NMSE or r^2. Before jumping to the conclusion that a better performance would necessarily be obtained with a non-linear model, it is important to remember that fitting the experimental data would also be influenced by: (i) co-variates that were not accounted for (e.g. $PaCO_2$, posture, cerebrovascular resistance, neural activation); (ii) time-varying system parameters; (iii) noise. Previous studies have shown that including other co-variates, like $PaCO_2$ (Edwards et al. 2001; Panerai et al. 2000; Simpson et al. 2005) or changes in resistance-area product (Panerai et al. 2006), led to significant improvements in model performance. It is possible that similar results could be obtained by including other determinants of CBF, like ICP (Panerai et al. 2002), PaO_2, or mental activation (Panerai et al. 2005). If the characteristics of dynamic CA change over

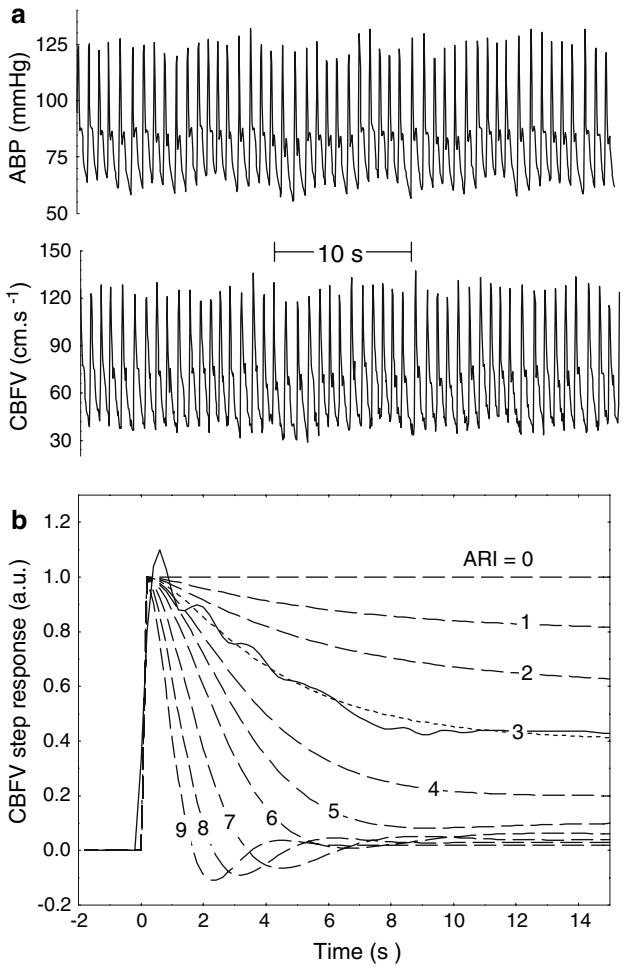

Fig. 2 Estimation of the dynamic index of CA (ARI), from spontaneous fluctuations in ABP and CBFV: (**a**) Continuous recording of ABP and CBFV showing spontaneous fluctuations; (**b**) Resulting CBFV step response, calculated by TFA (solid line) is compared to 10 hypothetical model responses generated by the Aaslid-Tiecks model. The best fit corresponds to a value of ARI = 3

time, this too will lead to poor model performance when model validation is performed with a different set of data collected either before or after the development dataset (Latka et al. 2005; Panerai et al. 2003a, c). Although the term 'noise' is often assumed to mean 'white noise', and hence amenable to be significantly reduced by low-pass filtering, this is not generally the case in dynamic CA modelling. The main problem here is that the most likely sources of noise can distort CBFV and ABP measurements in the very low frequency band (<0.1 Hz), which is exactly the frequency region where dynamic CA is more active. This happens because of slow changes in ultrasound probe position, or loss of signal quality for a sequence of heart beats. Most studies of dynamic CA have used the Finapres or other devices to measure ABP in the finger using arterial volume clampling controlled by photoplethysmography. In this case, changes in blood flow to the hand, for example due to thermoregulation, can lead to significant transient differences between peripheral and central arterial pressure, which is likely to be a better representation of the true ABP in the MCA (Panerai et al. 2007).

To improve the performance of linear models, by addressing the role of missing co-variates, time-varying properties and noise, several attempts have been made to test the significance of non-linear models of the dynamic ABP–CBF(V) relationship (Mitsis et al. 2002; Panerai et al. 1999a, 2003b). The artificial neural network (ANN) approach has been instrumental in the implementation of these models, in some cases being combined with the Laguerre–Volterra expansion of kernels (Marmarelis 1993; Mitsis et al. 2002; Panerai et al. 1999a). Neither univariate nor multivariate non-linear models of dynamic CA have been able to demonstrate a significant contribution of non-linear terms to the influence of ABP on CBF(V) (Mitsis et al. 2002; Panerai et al. 1999a). On the other hand, Mitsis et al. (2002) concluded that the contribution of CO_2 is non-linear, mainly due to its interaction with ABP. Applying the same model to orthostatic stress, as simulated by increasing levels of lower body negative pressure (LBNP), the authors concluded that CA and CO_2 reactivity were both gradually impaired as the level of LBNP increased (Mitsis et al. 2006). Future studies are needed to assess the clinical performance of non-linear models, for example by comparing their sensitivity and specificity to detect deterioration of CA, in comparison with more simple linear models. Furthermore, innovative approaches are also needed to address the problem of time-varying properties of CA, regarding model validation, assessment of reproducibility, and clinical protocols.

From Time to Frequency and Back

The finding that the ABP–CBF(V) relationship does not show a significant departure from the linear hypothesis is reassuring, since most clinical applications of CA have been based on linear models (Blaber et al. 1997; Carey et al. 2000; Dawson et al. 2000; Eames et al. 2003; Edwards et al. 2001; Giller 1990; Hlatky et al. 2002; Hu et al. 1999; Liu et al. 2003; Panerai et al. 1996, 2001, 2002; Reinhard et al. 2001; Serrador et al. 2005; Simpson et al. 2005; Zhang et al. 1998). Of these, two main approaches have dominated: the estimation of ARI (autoregulation index), using the Aaslid–Tiecks model (Tiecks et al. 1995), and TFA. Before describing the main findings of clinical studies though, it is useful to discuss whether the two approaches lead to consistent results when reflecting a deterioration of CA. One possible, and simple way to do this, is to perform a TFA on data generated with the Aaslid–Tiecks model, whilst gradually changing the values

of ARI from 0 to 9. Once the data is generated, it is possible to use standard procedures, e.g. with Welch's method (Bendat and Piersol 1986) to obtain the amplitude and phase frequency responses. From these, it is possible to select characteristic feature points in the frequency region where CA is most active (<0.1 Hz), as shown in Fig. 3 for the minimum gain (amplitude) and maximum phase difference between CBFV and ABP.

Figure 3 shows that worsening of dynamic CA, as reflected by values of ARI changing from 9 to 0, leads to increases in minimum gain and a reduction of the maximum phase for frequencies below 0.1 Hz. This result is in very good agreement with experimental observations which showed decreases of very-low-frequency phase with conditions which are expected to impair CA, such as hypercapnia (Birch et al. 1995; Panerai et al. 1999b), carotid artery disease (Hu et al. 1999; Reinhard et al. 2004), MCA stenosis (Haubrich et al. 2003), and neonatal prematurity (Panerai et al. 1998). The increases in gain with worsening CA, which would be a reasonable expectation, is less consistently reported in the literature. One problem of using gain, as a parameter to assess the efficiency of dynamic CA, is that CBFV cannot provide a measure of absolute flow. For this reason, most investigators prefer to express gain using relative changes in CBFV, such as in %/mmHg or %/%. Noteworthy, most clinical studies have not been able to show simultaneous significant changes in both gain and phase, as expected from the curves in Fig. 3. In most cases, significant differences in phase were observed, but not in gain. In a smaller number of studies though, significant differences were only observed in gain, but not in phase (Blaber et al. 1997; Tutaj et al. 2004; Zhang et al. 1998). Also, Fig. 3a shows that the relationship between the minimum gain and ARI is highly non-linear. To a lesser extent, the same is observed for the maximum phase curve (Fig. 3b).

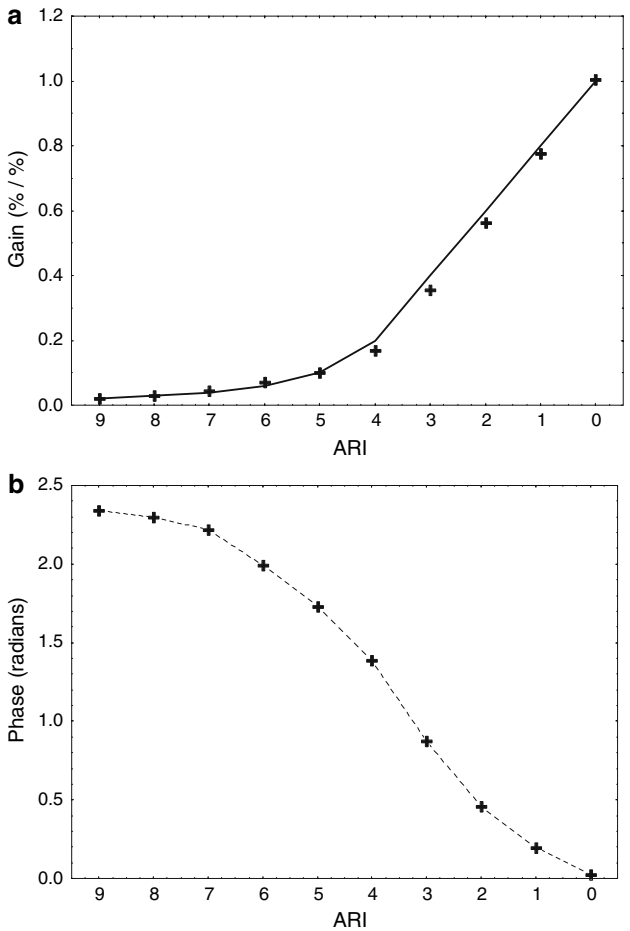

Fig. 3 Changes in gain and phase with reducing values of ARI: (**a**) Minimum gain in the frequency range <0.1 Hz. The crosses represent values estimated by transfer function analysis (TFA). The solid line is the theoretical DC gain of Aaslid–Tiecks model; (**b**) Maximum phase in the frequency range <0.1 Hz. The dashed line is the linear interpolation for values obtained by TFA (crosses)

Noise could be one possible explanation of why gain and phase do not always show consistent changes due to worsening CA. In this case, one relevant question is: which one, gain or phase, is more robust to reflect changes in dynamic CA efficacy? Although a more definitive answer will probably have to wait for further experimental studies, it is possible to shed some light on this problem by performing 'spectral swapping'. This is an approach that has been used in many other areas, to identify whether the gain or the phase are responsible for the dominant characteristics of a given set of data. If the temporal pattern of a signal, for example the ECG, remains approximately the same when different amplitude spectra are used with the same phase spectrum, there is a suggestion that its features are more due to the phase than to the amplitude spectra.

Assume that $H_i(f)$ and $\varphi_i(f)$ represent the gain and phase frequency responses (Eqs. 5 and 6) of the data generated with Aaslid–Tiecks model, for values of ARI_i ranging from 0 to 9, as expressed by the index $i = 0, 1, 2, ...9$. By swapping the amplitude and phase spectra, four different situations can be contemplated:

A: $H_i(f)|_{i=0}$; $\varphi_j(f)|_{j=0,\ 1,\ 2,\ ...9}$
B: $H_i(f)|_{i=9}$; $\varphi_j(f)|_{j=0,\ 1,\ 2,\ ...9}$
C: $\varphi_i(f)|_{i=0}$; $H_j(f)|_{j=0,\ 1,\ 2,\ ...9}$
D: $\varphi_i(f)|_{i=9}$; $H_j(f)|_{j=0,\ 1,\ 2,\ ...9}$

When transformed back to the time–domain, these four distinct conditions lead to the step responses presented in Fig. 4. These results indicate that phase is a much more sensitive component of the ABP–CBFV relationship than the gain. When the gain was kept constant (cases A and B), the corresponding CBFV step responses had their patterns dominated by the phase spectra, depending on whether it corresponded to a poor (ARI = 0) or excellent

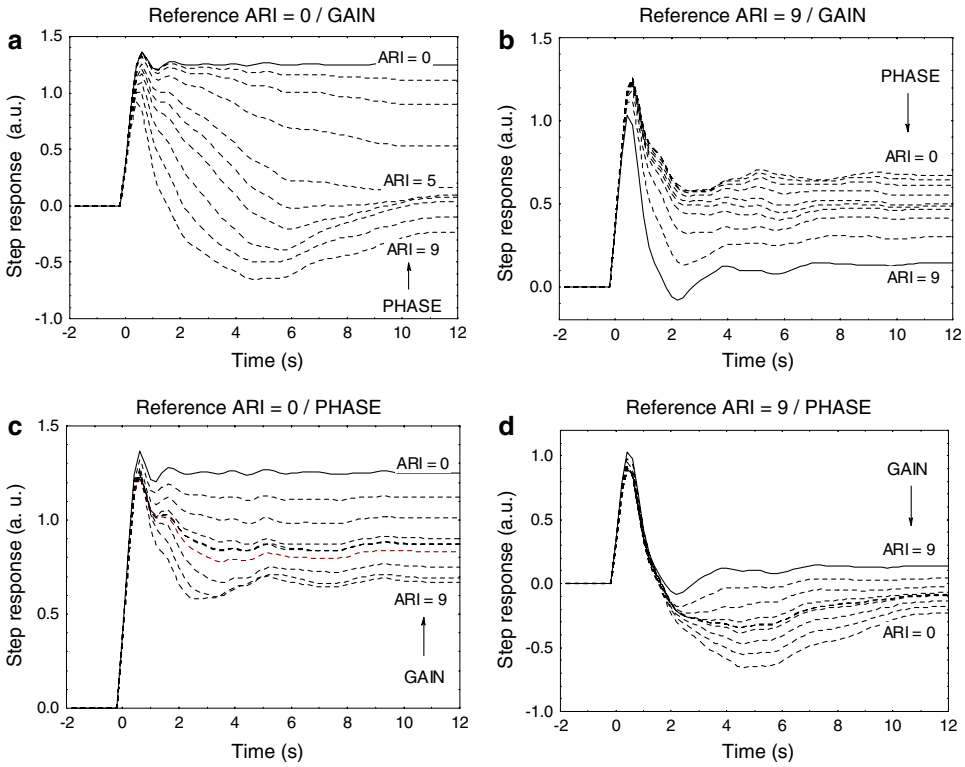

Fig. 4 Step responses for Aaslid–Tiecks model after swapping amplitude and phase frequency responses. In each case, the reference situation maintained a constant gain (amplitude) or phase, for extreme values of ARI, and the phase/gain was then varied for values of ARI ranging from 0 to 9 (see text)

(ARI = 9) CA. The reverse situations (C and D) when the phase spectra were kept constant, the gain had only limited effect in changing the step response pattern when the ARI varied from 0 to 9 (Fig. 4c, d). The overall conclusion is that phase is dominant and that a high value of gain should not be accepted as an indication of impaired autoregulation in the presence of higher values of phase. Unfortunately, there are several instances in the literature where investigators concluded that dynamic CA was impaired, based only on changes in gain, despite normal values of phase (Blaber et al. 1997; Tutaj et al. 2004; Zhang et al. 1998).

The reasons for a greater sensitivity of phase as an indicator of autoregulatory performance, in comparison with gain, are not clear, but have also been observed in many other physiological systems, such as the temporal pattern of auditory evoked potentials (Sayers et al. 1974). In the case of the Aaslid–Tiecks model, this tendency of phase to dominate in the characterization of the step response pattern might have been accentuated by the strong non-linearity between gain and the ARI index (Fig. 3a).

Clinical Applications of Dynamic CA Models

For the reasons mentioned previously, the review of clinical applications of dynamic CA models will be limited to those based on TFA or the Aaslid–Tiecks model.

Validation Studies

One inherent difficulty in clinical applications of dynamic CA is the lack of a 'gold standard' to allow direct validation of model parameters. Due to its many limitations, static CA cannot be regarded as a reliable reference and it is yet to be established if it reflects the same regulatory pathways as dynamic CA (Panerai 1998). As a consequence, the process of validating model parameters that could be of clinical value is one that could be seen as a 'bootstrap'. Models are applied to different physiological and pathological conditions, and the resulting behaviour of a given model parameter gradually forms a pattern of its potential usefulness to reflect different clinical manifestations. In the case of human cerebrovascular diseases, this process is made even more empirical, tentative, and potentially misleading, due to the lack of suitable animal models that could underpin validation studies.

With TFA, Giller (1990) showed that the coherence function was increased in subjects with subarachnoid haemorrhage. Diehl et al. (1995) and Birch et al. (1995) demonstrated that the phase lead of CBFV was reduced in patients with arterio-venous malformations and subjects breathing 5% CO_2, respectively. Both studies performed measurements of phase directly, from induced oscillations in ABP and CBFV, but provided useful evidence to support the use of phase as an indicator of dynamic CA in estimates obtained by formal TFA. A few years later, 3 studies

reported large reductions in the phase frequency response in premature newborns (Menke et al. 1997; Panerai et al. 1996, 1998). Likewise, Hu et al. (1999) showed that the CBFV phase lead was almost abolished in patients with carotid artery occlusions, and Cencetti et al. (1999) reported a mean reduction in phase of 34% in patients with insulin-dependent diabetes.

When proposing their second-order differential equation model, Tiecks et al. (1995) showed that the ARI index was progressively reduced during isoflurane anaesthesia, and also correlated well with an index of static autoregulation. Subsequent clinical studies by White and Markus (1997) and Dawson et al. (2000) showed that the ARI was significantly reduced in patients with carotid artery disease and stroke, respectively.

Despite these early encouraging results, around the same time, other studies did not find alterations in phase or ARI index in a number of other clinical conditions and this will be discussed later.

Attempts to validate the concept of cerebral perfusion pressure as the difference between ABP and ICP, in the context of TFA were disappointing due to the finding that oscillations in ICP are strongly linked to fluctuations in CBFV (Panerai et al. 2002).

The Leap of Faith

As knowledge accumulates on the properties of model parameters and their sensitivity to reflect different clinical conditions, new research questions are likely to be raised and further validation studies will be needed. For this reason, it is impossible to tell when the stage of validation ends and routine clinical use of CA models starts. Nevertheless, an analysis of the literature shows a surprising change in the confidence placed on models and extracted parameters, shortly after a handful of preliminary studies appeared in the literature. What is most surprising in these studies is that models are not used in applications involving the same or similar conditions in which they were initially tested. Instead, based on the premise that these models/parameters are valid indicators of dynamic CA, they are then used to generate entirely new knowledge on the pathophysiology of the cerebral circulation. Starting with the ARI, Doering et al. (1999) concluded that dynamic CA was worsened by hypothermia, but was better than average during hyperthermia. Carey et al. (2000) also suggested that in adults dynamic CA was not affected by ageing, based on the ARI index. (More recently this finding has been confirmed by several other studies based on other models/parameters of CA). Despite the findings of Carey et al. and others, Vavilava et al. (2002), also using the ARI, suggested that dynamic CA was worse in adolescents (3.8 ± 2.1) as compared to young adults (5.8 ± 0.8). Interesting findings were also reported by Leftheriotis et al. (2000), indicating that dynamic CA was impaired in patients with carotid sinus syndrome, but not in atrioventricular block, despite both conditions presenting potentially similar risks to asystolic syncope.

The trust placed in models of dynamic CA, allowing investigators to suggest new facets of the mechanisms regulating CBF, was not limited to the ARI, but also involved the use of gain and phase, obtained by TFA. This is nowhere as clear as in the ongoing controversy surrounding the involvement of CA in different forms of syncope. Although the majority of studies did not find significant changes in gain or phase, this was mainly used to reinforce the view that CA is not the primary cause or a major determinant of syncope (Cencetti et al. 1999; Diehl et al. 1999; Schondorf et al. 2001). Finally, Zhang et al. (2002) observed significant reductions in phase and increases in gain following ganglion blockade and concluded that dynamic CA is mediated by the autonomic nervous system. With this caveat in mind, other clinical studies, involving more recent and widespread applications of the ARI and TFA, will be discussed below.

Studies Based on ARI

Clinical studies adopting the ARI are summarized in Table 1. The table does not capture all the subtle differences between studies, but the main aspects listed in Table 1 are enough to give an idea of the methodological diversity and scope of these studies. The condition, which received the most attention was ischaemic stroke, with the majority of studies showing reductions in ARI. This persisted over several weeks and was not improved by at least one particular hypotensive drug. Severe head injury (SHI) was another condition where the ARI was found to be consistently depressed. The ARI was the main predictor of outcome in two studies, one involving SHI patients (Panerai et al. 2004) and the other acute mountain sickness (van Osta et al. 2005). On the other hand, the ARI was not altered in vasovagal syncope (except presyncope), arterial hypertension, minor head injury, or intracranial tumours (Table 1). It is not clear if these studies had the appropriate statistical power to detect differences in ARI given its considerable variability (Simpson et al. 2004).

Lack of standardization is of concern as well. Most studies induced changes in ABP using the thigh cuff maneuver (THC), but in other cases spontaneous fluctuations in ABP or head-up tilt were employed. Even in the case of THC, there were considerable differences with the number of maneuvers performed ranging from 1 to 8.

Table 1 Clinical applications of ARI index

Study	Clinical condition	Age [number]	ABP manoeuvre (number)	ARI values	Main results and conclusions
White and Markus (1997)	Carotid artery disease (CAD)	63 ± 11 [27 (CAD)] 68 ± 7 [21(Co)]	THC (5)	3.3 ± 2.2 (CAD) 6.3 ± 1.1 (Co)	ARI reduced in severe carotid stenosis/occlusion.
Junger et al. (1997)	Minor head injury (mHI) (GCS > 12)	38 ± 16 [29 (mHI)] 38 ± 16 [29 (Co)]	THC (3–8)	4.0 ± 2.1 (mHI) 4.7 ± 1.0 (Co)	ARI < 2.5 in 8 patients, but not in the controls.
Leftheriotis et al. (2000)	Carotid sinus syndrome(CSS) and AVB	75 ± 8 [14 (CSS)] 69 ± 1 [8 (AVB)]	70° HUT + carotid sinus massage	4.8 ± 1.3 (CSS) 8.5 ± 1.1 (AVB)	ARI significantly worse in CSS than in AVB.
Dawson et al. (2000)	Acute stroke (AS)	69 ± 11.7 [54 (AS)] 67 ± 9.7 [61 (Co)]	THC (1)	4.09 ± 3.32 (AS) 6.18 ± 2.34 (Co)	ARI depressed in relation to Co for both aH and naH.
Schmieder et al. (2000)	Intracranial tumors	49.8 (range 15–73) [50]	THC (5)	5.5 ± 1.9 (before surgery) 5.4 ± 1.2 (after surgery)	ARI not influenced by surgery, or artery territory. Lower values in patients with co-morbidity.
Carey et al. (2001)	Recurrent vasovagal syncope (VVS)	48 ± 22 [17 (VVS)] 49 ± 20 [17 (Co)]	70° HUT	baseline: 4.4 ± 2.7 (VVS) 4.2 ± 2.7 (Co) return supine: 2.3 ± 1.8 (VVS) 4.9 ± 2.3 (Co)	ARI decreases in late pre-syncope and early post-syncope period.
Eames et al. (2002)	Acute stroke (AS)	69 ± 7 [56 (AS)] 70 ± 9 [56 (Co)]	spontaneous transients	3.8 ± 2.2 (AS) 4.7 ± 2.2 (Co)	ARI reduced in patients with stroke. NS difference between hemispheres.
Hlatky et al. (2002)	Severe head injury (SHI)(GCS ≤ 8)	35.7 ± 15.2 [122]	THC (>2)	2.8 ± 1.9 (12 h) 1.7 ± 1.1 (36–48 h) 2.5 ± 1.4 (day 5) 2.8 ± 1.2 (day 10)	ARI abnormal in relation to values for healthy subjects. Deteriorates during first 36–48 h but returns to initial value by day 10 after injury.

Table 1 continued

Study	Clinical condition	Age [number]	ABP manoeuvre (number)	ARI values	Main results and conclusions
Dawson et al. (2003)	Stroke (S)	69 ± 11 [54 (S)] 67 ± 10 [51 (Co)]	THC (1)	6.2 ± 2.3 (Co) Acute: 3.9 ± 3.1 (aH) 5.0 ± 2.9 (naH) 10-d follow up: 3.9 ± 2.8 (aH) 4.6 ± 3.2(naH)	aH significantly depressed in relation to Co. No significant improvement 10 days after ictus.
Eames et al. (2003)	Arterialhypertension (H)	67 ± 6 [46 (H)] 68 ± 6 [35 (Co)]	THC (1) + spontaneous transients	6.7 [5.2–7.3] (H) 6.5 [5.5–8.1] (Co)	ARI not influenced by hypertension in middle age/older people.
Panerai et al. (2004)	Severe head injury(GCS ≤ 8)	30.3 ± 12.0 [17 (Sv)] 29.7 ± 13.7 [12 (nSv)]	spontaneous fluctuations	6.9 [5.9–7.4] (Sv) 4.8 [0.0–5.9] (nSv)	ARI main independent predictor of mortality.
Eames et al. (2004)	Hypertensive stroke (S)	74 ± 9 [36 (S)] 55 ± 18 [12 (Co)]	THC (2) + spontaneous transients	6.0 [2.1–7.1] (S) 6.6 [6.2–7.7] (Co)	ARI not influenced by bendrofluazide, 4 weeks after ischaemic stroke.
Hlatky et al. (2005)	Severe head injury(GCS ≤ 8)	31 ± 11.8 [21]	THC (3)	2.4 ± 1.6 (before) 3.0 ± 1.1 (after PHE)	Increases in MAP induced by PHE led to increase in ARI.
van Osta et al. (2005)	Acute mountain sickness (AMS)	40 (range 26–58) [35]	THC (3)	4.44 ± 0.86 (sea level) 4.55 ± 1.16	ARI only independent predictor of AMS score. Tadalafil or dexamethasone had no influence on ARI.

Values are indicated as mean ± SD or median [IQR]

Co: control subjects; THC: Thigh cuff test; HUT: head up tilt; PHE: phenylephrine MAP: mean arterial pressure; CSS: carotid sinus syndrome; AVB: atrio-ventricular block aH: affected hemisphere; naH: non-affected hemisphere Sv: survivors; nSv: non-survivors

Studies Based on TFA

Considerably more work has been done using TFA as shown by the studies listed in Table 2. As mentioned previously, the main parameter considered has been the phase frequency response, followed by the gain and the coherence. Similarly to the ARI, there are considerable methodological differences between studies. One example is the frequency range used for calculating estimates of phase and gain. From the diversity of values listed in Table 2, we should expect an equally wide range of values for parameter estimates in controls and patients as is indeed observed in Table 2. Some authors have used terms like VLF (very-low frequency), LF (low frequency), or M-waves, to refer to different frequency ranges, but due to the lack of standardization, these terms will be ignored here, and whenever 'gain' or 'phase' is referred to below, it will apply to the corresponding frequency range indicated in Table 2.

What Table 2 does not show is several other methodological aspects of TFA that can have a bearing on estimated parameters, mainly because these are often omitted in most communications. Some of these would be: total duration of recordings, number of segments used for spectral estimation, degree of superposition between segments of data (Welch's method), number of samples in each segment (256, 512, etc.), type of tapering window applied, degree of smoothing of the cross- and auto-spectra, whether there was an attempt to unwrap the phase spectra or not (Panerai 2004), and the number of harmonics used to calculate mean values of gain and/or phase. It is unlikely that a standard procedure will ever be agreed upon to control for the influence of these choices, but an important first step would be to encourage authors to improve reporting of these data analysis details. This would allow better insight into potential sources of variability and would facilitate inter-study comparisons. One important aspect is also to inform the reader about the degrees of freedom of TFA estimates, which have a bearing on related statistical analyses (Bendat and Piersol 1986).

The condition, which received the most attention in TFA studies was carotid artery disease (CAD). The majority of studies showed that the phase was reduced in these patients and, in some cases, correlated negatively with the degree of occlusion. One important finding, reported by Reinhard et al. (2004), was that the phase returned to approximately normal values following carotid endarterectomy or stenting of the carotid artery. It is still not clear if other conditions, like stroke for example (Kwan et al. 2004), can show similar recovery of dynamic CA. Nevertheless, the results of Reinhard et al. (2004) demonstrate the potential of dynamic CA modelling for patient monitoring and follow-up. In addition to CAD, some of the studies listed in Table 2 helped to reinforce the conclusions of investigations based on the ARI (Table 1). This is certainly the case of ischaemic stroke where the phase was shown to be affected, except for minor stroke (Reinhard et al. 2005). On the other hand, the phase values were not altered in arterial hypertension, again in agreement with was found with the ARI, except for malignant hypertension where the phase was found to be significantly reduced (Immink et al. 2004).

From combined analysis of Tables 1 and 2, a picture starts to emerge, indicating some associations between model parameters and severity of disease. This is more obvious for CAD where both the ARI and phase where shown to be correlated with degree of stenosis. This might also be the case for other conditions, like hypertension, stroke and head injury since the ARI and phase were altered in more severe states but not in milder cases.

Discussion and Conclusions

The lack of a 'gold standard' for assessment of CA in humans, together with the absence of well-established protocols for data measurement, pre-processing and analysis, creates major difficulties for introducing these techniques into clinical practice. Despite this inherent problem, initial studies, using parameters derived from relatively simple input–output models, have shown promising results with selected parameters showing sensitivity to pathophysiological conditions where one would expect CA to be impaired, such as stroke, CAD, severe head injury, and others. In the absence of alternative animal models, these clinical studies were invaluable for advancing knowledge about the potential clinical usefulness of different models and derived parameters. On the other hand, it could be argued that it was premature to bring models that have not been properly standardized and validated to the clinical arena due to the risk of generating confusion and disappointment. Unfortunately, this is part of the process of 'bootstrapping' mentioned previously, and it is important to keep in mind that a 'long and winding road' still lies ahead. Without this frame of mind, there will always be the risk of potentially useful techniques being hastily discarded. Despite these considerations, a review of the current knowledge-base shows many gaps involving models of dynamic CA that should be addressed as a matter of urgency to allow better design of clinical studies. To list only a few examples, more information is needed about the influence of methods of measurement on model parameters and their statistical properties. The Aaslid–Tiecks model was formulated for data acquired during thigh cuff maneuvers. The ARI index shows considerable intra- and inter-subject variability (Mahony et al. 2000) and this could be, at least partially, due to its statistical properties

Table 2 Representative clinical studies of dynamic cerebral autoregulation based on transfer function analysis

Study	Condition	Age [number]	Frequency (Hz)	Coherence	Gain	Phase	Main conclusions
Giller (1990)	Subarachnoid haemorrhage (SAH)	– [18]	0.005	0.18 ± 0.05 (Co) 0.43 ± 0.24 (SAH)	–	–	Coherence elevated in patients with SAH
Menke et al. (1997)	Ventilated preterm infants	Newborn [15]	0.02–0.2	>0.59	–	0° at 24 h 55° at 96 h	dCA lost during first days of life
Blaber et al. (1997)	Autonomic failure (ANSF)	– [8 (ANSF)] [8 (Co)]	0.03–0.14	–	11.3 ± 0.6 mm.s^{-1} · mmHg^{-1} (ANSF) 6.8 ± 0.6 mm.s^{-1} · mmHg^{-1} (Co)	31° ± 5 (ANSF) 30° ± 5 (Co)	Worse dCA in ANSF due to higher gain.
Panerai et al. (1998)	Prematurity of newborn	Newborn [83]	0.08	0.48 ± 0.18 (better CA) 0.64 ± 0.22 (worse CA)	0.56 cm · s^{-1} · mmHg^{-1} (better CA) 0.70 cm · s^{-1} · mmHg^{-1} (worse CA)	Slope of phase spectrum 9.3 ± 1.05 rad/Hz (better CA) 1.80 ± 1.2 rad/Hz (worse CA)	Coherence elevated and phase slope reduced in impaired CA
Diehl et al. (1999)	Neurocardiogenic syncope (NCS)	28.5 ± 10 [16 (NCS)] 29.5 ± 7.1 [20(Co)]	0.05–0.15	>0.4	–	52.6 ± 18° (Co) 45.7 ± 19.2° (NCS) 72.0 ± 27.1° (NCS + POTS)	dCA not affected in patients with NCS
Hu et al. (1999)	Carotid artery disease (CAD)	69.7 ± 7.4 [83(CAD)] 60.9 ± 8.7 [37(Co)]	0.04–0.15	–	–	58.7 ± 20.9° (Co) 6.6 ± 38.5° (CAD- 90–99% occlusion) 0.2 ± 25.2° (CAD-occlusion)	Phase negatively correlated with degree of stenosis
Cencetti et al. (1999)	Diabetes (IDDS) and vasovagal syncope (VVS)	51.1 ± 5.3 [12(IDDS)] 31.2 ± 4.5 [10(VVS)] 46.3 ± 5.8 [13(Co)]	0.03–0.15	>0.5	–	1.38 ± 0.3 rad (Co) 1.36 ± 0.2 rad (VVS) 0.91 ± 0.1 rad (IDDS)	dCA preserved in VVS but impaired in IDDS
Lipsitz et al. (2000)	Hypertension (HT)and elderly normotensive (NTe)	72 ± 2 [10 (HT)] 72 ± 3 [10(NTe)] 24 ± 1 [10(Co)]	0.05–0.15	0.76 ± 0.04 (Co) 0.78 ± 0.02 (NTe) 0.67 ± 0.05 (HT)	0.78 ± 0.09 (Co) 0.83 ± 0.07 (NTe) 0.53 ± 0.13 (HT) cm · s^{-1} · mmHg^{-1}	55.5 ± 6.4° (Co) 46.2 ± 8.3° (NTe) 50.3 ± 7.5° (HT)	Elderly NT and HT retain capacity to autoregulate
Schondorf et al. (2001)	Neurocardiogenic syncope (NCS)	32.7 ± 1.2 [37 (NCS)] 30.7 ± 1.7 [15 (Co)]	0.02–0.04	–	0.72 ± 0.08 (NCS) 0.85 ± 0.13 (Co)	0.71 ± 0.07 rads (NCS) 0.62 ± 0.10 rads (Co)	CA remains intact in NCS with recurrent syncope

Table 2 continued

Study	Condition	Age [number]	Frequency (Hz)	Coherence	Gain	Phase	Main conclusions
Reinhard et al. (2001)	carotid artery disease (CAD)	61 ± 8 [19(CAD)] 58 ± 4 [17(Co)]	0.1	0.97 ± 0.04 (CAD) 0.98 ± 0.02 (Co)		26.95 ± 21.14° (CAD) 65.56 ± 21.48° (Co-right MCA)	CA impaired in CAD
Zhang et al. (2002)	ganglion blockade	29 ± 6 [12]	0.02–0.07	0.46 ± 0.05 (before) 0.32 ± 0.03 (after)	0.62 ± 0.07 (before) 1.12 ± 0.12 (after) $cm \cdot s^{-1} \cdot mmHg^{-1}$	1.08 ± 0.14 rads (before) −0.14 ± 0.33 rads (after)	autonomic blockade causes deterioration of CA
Panerai et al. (2002)	Intracranial hypertension (ICH)	29.5 ± 11.4 [18(normal ICP)] 33.5 ± 11.4 [14(ICH)]	0.02–0.5	>0.4	CBFV step response at t = 3s 0.25 ± 3.0 (normal ICP) 0.6 ± 2.5 (ICH) %/mmHg	–	CA less effective in ICH in comparison with normal ICP
Haubrich et al. (2003)	MCA stenosis (Sn)	61.7 ± 10.5 [22(Sn)] – [24 (Co)]	0.05–0.15	>0.4	1.6 ± 0.7 (Co) 1.3 ± 0.4 (low Sn) 1.5 ± 0.8 (moderate Sn) 1.3 ± 0.8 (high Sn) %/%	44.6 ± 21.1° (Co) 43.5 ± 34.4° (low Sn) 24.0 ± 25.5° (moderate Sn) 16.7 ± 19.5° (high Sn)	CA gradually impaired with degree of MCA stenosis.
Reinhard et al. (2004)	endarterectomy (CEA) or stenting (SPAC) on CAD	– [41 (CEA)] [17 (SPAC)]	0.06–0.12 (phase) 0.20–0.30 (gain)	>0.49	Before: 0.52 ± 0.22 (CEA) 0.61 ± 0.40 (SPAC) After: 0.96 ± 0.51 (CEA) 1.31 ± 0.38 (SPAC) $cm \cdot s^{-1} \cdot mmHg^{-1}$	Before: 25.7 ± 21.3° (CEA) 25.6 ± 33.7° (SPAC) After: 47.6 ± 22.0° (CEA) 57.1 ± 27.0° (SPAC)	CEA and SPAC lead to improvements in dCA in CAD patients.
Kwan et al. (2004)	Ischaemic stroke (S)	72.5 ± 11.4 [10]	0.025	–	Visit: 1: 1.43 ± 0.49 2: 0.94 ± 0.21 3: 0.81 ± 0.2%/ %	Visit: 1: −26.5 ± 22.6° 2: −10.3 ± 14.4° 3: +33.8 ± 14.6°	dCA might improve 3 months after stroke.
Immink et al. (2004)	Malignant hypertension (MH)	46 (25–64) [8 (MH)] 44 (24–54) [8 (Co)]	0.1	0.75 (0.54–0.84) (Co) 0.64 (0.49–0.76) (MH)	1.02 (0.48–1.37) (Co) 1.32 (0.93–1.87) (MH) %/%	58° (41–82) (Co) 30° (6–67) (MH)	dCA impaired in MH

Table 2 continued

Study	Condition	Age [number]	Frequency (Hz)	Coherence	Gain	Phase	Main conclusions
Tutaj et al. (2004)	Glaucoma (NPG)	57 ± 18 [10 (NPG)] 52 ± 11 [11(POAG)] 51 ± 19 [11(Co)]	0.1	0.94 ± 0.1 (Co) 0.96 ± 0.1 (NPG) 0.93 ± 0.1 (POAG)	1.21 ± 0.1 (Co) 2.44 ± 0.5 (NPG) 1.99 ± 0.2 (POAG)(a.u.)	–	dCA compromised in NPG and POAG
Haubrich et al. (2005)	Bilateral vertebral arterial disease (VAD)	63.4 ± 7.9 [20(VAD)] 58.2 ± 11.1 [22(Co)]	0.05–0.15	0.64 ± 0.16 (VAD) 0.57 ± 0.13 (Co) Right MCA	–	23.1 ± 13.2° (VAD) 52.1 ± 18.8° (Co) right MCA	dCA impaired in PCA territory in VAD
Reinhard et al. (2005)	Minor MCA stroke (S)	61 ± 12 [33 (S)] 61 ± 13 [25 (Co)]	0.06–0.12	>0.49	0.57 ± 0.24 (S,aH) 0.58 ± 0.20 (S,naH) $cm \cdot s^{-1} \cdot mmHg^{-1}$	48 ± 15° (Co) 44 ± 20° (S,aH) 49 ± 20° (S,naH)	dCA not disturbed in minor stroke
Immink et al. (2005)	Ischemic stroke(MCAS) vs lacunar stroke (LS)	59 ± 5 [10(MCAS)] 63 ± 3 (LS) [10 (LS)] 57 ± 2 (Co) [10 (Co)]	0.07–0.15	–	–	56 ± 5° (Co-Left) 59 ± 5° (Co-Right) 26 ± 6° (MCAS,aH) 61 ± 6° (MCAS,naH) 32 ± 6° (LS,aH) 33 ± 5° (LS,aH)	dCA affected both sides with LS, but only on aH for MCAS.
Serrador et al. (2005)	Hypertension	72 ± 4 [60]	0.03–0.07	0.38–0.44	0.22–0.39 dB	38–77°	dCA maintained in both controlled and uncontrolled hypertensives
Haubrich et al. (2006)	Bilateral vertebral artery disease (VAD)	63.3 ± 8.4 [19]	0.05–0.15	>0.4	–	44.8 ± 20.7° (Co) right MCA 20.9 ± 11.5° (VAD) right MCA	dCA impaired in VAD both supine and upright positions.

Co: control subjects; POTS: Postural orthostatic tachycardia syndrome; IDDS: insulin dependent diabetes; NTe: elderly normotensives ICP: intracranial pressure; ICH: intracranial hypertension CEA: carotid endarterectomy; SPAC: stent-protected angioplasty of the carotid artery NPG: normal pressure glaucoma; POAG: Open-angle glaucoma; MCAS: MCA territory stroke; LS: lacunar stroke aH: affected hemisphere; naH: non-affected hemisphere

(Simpson et al. 2004). It would be important to have more indepth information about the physiological variability of the ARI (Panerai et al. 2003c) and its sensitivity to physiological co-variates like $PaCO_2$, posture, intra-thoracic pressure, temperature, and so on. The same obviously also applies to TFA, and some preliminary results seem to indicate that there is a high risk of blurring TFA estimates, unless rigid controls are imposed during measurement protocols, (Panerai et al. 1999b, 2002, 2005). The conditions under which it is possible to obtain reliable estimates of model parameters during spontaneous fluctuations in ABP and CBFV also need further attention since it might depend on standardizing a minimum spectral distribution of ABP power that should be acceptable (Bendat and Piersol 1986; Liu et al. 2005; Ramos et al. 2006; Zhang et al. 1998). Finally, refinements should also be introduced in future clinical studies, by giving more emphasis to staging of disease, this following from preliminary results suggesting a close association between CA model parameters and severity of illness.

The problems faced with the development of simple, univariate linear models of dynamic CA, and the gaps left behind by their somewhat premature application to clinical studies, can be seen as a forewarning for the introduction of more complex, multivariate, adaptive and, possibly, nonlinear models. First of all, it would be important to try to advance knowledge about the *dimensionality* of CA. Hitherto, most studies, like those listed in Tables 1 and 2, have assumed that CA operates along an unidimensional scale, even when different parameters like coherence, gain and phase are simultaneously extracted by TFA and each harmonic could be treated as a statistically independent estimate. The time domain CBFV step response combines all the information contained in the gain and phase into a single curve, but this has also been used within an unidimensional framework, for example to yield estimates of ARI (Panerai et al. 2003c, 2004). In the near future, it is likely that MRI studies will shed light on the spatial heterogeneity of dynamic CA, which would be one way to expand its dimensionality. Alternatively, with current techniques relying on TCD, NIRS or laser Doppler, increased dimensionality could unravel the different mechanisms which contribute to CBF regulation like CO_2 reactivity, neurovascular coupling, myogenic, metabolic, and, possibly, neurogenic control, accepting that there might be considerable functional overlap in what is usually described by these terms. The main conclusion here is that priority should be given to multivariate models, both as a way to widen the information that could be extracted about the regulation of CBF, and also to take into account physiological co-variates that might be difficult to control during data acquisition. It is important to appreciate though, that progress in this direction will depend on substantial improvements in our ability to measure key variables like central/carotid ABP, $PaCO_2$, PaO_2, ICP, cerebrovascular resistance, critical closing pressure, venous blood flow, intra-thoracic pressure, mental activation, intracranial vessel diameters, and others.

When considering more advanced models, the second priority is to address the question of time-varying parameters as suggested by a few studies (Latka et al. 2005; Novak et al. 2004; Panerai et al. 2003a, c). This will require innovative modelling techniques (Latka et al. 2005; Novak et al. 2004), and, even more important, a new paradigm for the concept of 'reproducibility'.

In summary, most clinical applications of the concept of dynamic CA have been based on relatively simple input–output linear models. Although more prior knowledge of the properties of these models, and their behaviour under different physiological conditions, would have been desirable, their application to different clinical conditions was important to demonstrate the sensitivity of some of their parameters to pathologies where abnormal CA could be expected. The introduction of more complex models should give priority to a multivariate approach to take into account the contribution of other variables that can influence CBF regulation. In addition to their predictive value, these models should be assessed by their potential to improve diagnosis, prognosis and management of patients with cerebrovascular diseases.

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