*Point-Counterpoint*: Transfer function analysis of dynamic cerebral autoregulation: To band or not to band?

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**Abstract**

Transfer function analysis (TFA) is the most frequently adopted method for assessing dynamic cerebral autoregulation (CA) with continuously recorded arterial blood pressure (ABP) and cerebral blood flow velocity (CBFV). Conventionally, values of autoregulatory metrics (e.g., gain and phase) derived from TFA are averaged within three frequency bands separated by cut-off frequencies at 0.07 Hz and 0.20 Hz, respectively, to represent the efficiency of dynamic CA. However, this is of increasing concerns, as there remains no solid evidence for choosing these specific cut-off frequencies, and the rigid adoption of these bands can stifle further developments in TFA of dynamic CA. In this ‘Point-Counterpoint’ mini-review, we provide evidence against the fixed banding, indicate possible alternatives, and call for awareness of the risk of the ‘one-size-fits-all’ banding becoming dogmatic. We conclude that we need to remain open to the multiple possibilities offered by TFA to realize its full potential in studies of human dynamic CA.

The dynamic nature of cerebral autoregulation (CA) was initially described from the transient response of cerebral blood flow velocity (CBFV) to a sudden drop in arterial blood pressure (BP). In 1990, Giller applied transfer function analysis (TFA) to the BP (input)-CBFV (output) relationship, thus describing CA as a frequency-dependent phenomenon 1. In healthy subjects, the amplitude (or gain) of the input-output relationship shows a continuous increase with frequency, whilst the phase, reflecting the temporal dependence between BP and CBFV, is elevated at lower frequencies (<0.1 Hz), gradually falling to near zero for frequencies around 0.2 Hz 2, 3. Zhang et al 3 thus proposed aggregating parameters into three distinct frequency intervals: very low (VLF: 0.02-0.07 Hz); low (LF: 0.07-0.20 Hz) and high (HF:0.20-0.50 Hz) frequency bands. Their proposal was rapidly adopted by the CA research community, leading to a large number of reports in the literature based on values of gain and phase averaged for these three frequency bands. This practice was acknowledged in the CARNet White Paper (recommendation #17), with the proviso that not enough evidence was available to recommend these distinct frequency bands as optimal4. Fixed, standardized frequency bands are useful to report and facilitate statistical analysis of averaged values of gain and phase in physiological and clinical studies and compare results between studies and research centres. However, it is a major concern that the rigid adoption of these bands might stifle further developments in TFA of dynamic CA, and also result in sub-optimal sensitivity to detect pathological changes in CA. The main points of contention are the choice of the frequency cut-off values, that separate the different frequency bands, and the assumption that these values should be fixed and independent of phenotype, physiological or pathological conditions. In particular, the choice of 0.07 Hz, to separate the VLF and LF bands, is highly contentious as it was established as the frequency where the coherence function reached a value of 0.5, based on data from only 10 healthy subjects 3. More recent evidence indicates that the threshold for statistical significance of the coherence function is well under 0.5 4, 5, for the TFA settings usually adopted. More importantly, values below this threshold should not necessarily be considered as pertaining to a distinct frequency band and dismissed or as requiring different treatment and interpretation. In healthy subjects, coherence at very low frequencies tends to be low, not due to the lack of a reliable relationship between BP and CBFV, but due to the contribution of other parameters, such as PaCO2 or cerebrovascular resistance influencing the CBFV output 6. Similar considerations apply to the choice of 0.2 Hz to separate the LF and HF bands. It has been noted that impaired autoregulation also reduces the upper frequency range of the control function, with indicative upper frequency limits of dynamic CA ranging from 0.094±0.040 Hz during hypercapnia, to 0.167±0.036 Hz during hypocapnia 2. These multiple studies indicate that dynamic CA is not active in the HF band and may be weak or absent even in large parts of the LF band (and may thus impair the power to discriminate between lower levels of autoregulation). Other frequency cut-off values may also be appropriate, based on physiological or experimental considerations 7, 8. Tzeng et al also proposed different cut-off frequencies, in the attempt to improve correlation between different metrics of CA but did not find strong evidence for other choices either 9. Finally, in a large number of healthy subjects, the behaviour of the coherence function did not show any clear evidence that could suggest the need for segmentation of the frequency spectrum 5.

Given the concerns above, we argue against the risk of the ‘one-size-fits-all’ approach becoming dogmatic, as the evidence does not support such an approach. The averaged phase and gain calculated over the ‘standard’ bands is likely not to be optimal. Whilst the use of specific frequency bands might be advantageous in many circumstances (e.g., to facilitate comparison of results between studies), it is also important to acknowledge the existence of alternatives that may provide better insight into physiology and lead to improved diagnostic and prognostic performance in patients. While much effort has been put into modelling the relationship between CBFV and ABP, less effort has been put into optimally extracting information from this relationship, with relatively few exceptions. For example, a recent study showed that the performance of TFA can be further improved over the band-averaging method by machine learning approaches, suggesting that the current choice of the cut-off values for banding might not be optimal 10. It is possible to use the entire spectral values of gain and phase, to obtain estimates of the CBFV step response and derive metrics such as the autoregulation index (ARI), or other indices of CA 4­­­,10. It is also important to appreciate that at each frequency obtained from TFA , gain and phase provide potentially independent variables that allow for more powerful analyses using advanced statistical or machine learning methods than can be achieved with simple band-averaging. Nevertheless, there is currently little robust evidence to recommend a specific choice among the many alternative approaches described in the literature, and there is a great need for further research on which frequencies best contribute to distinguishing functional from impaired CA. In contrast, the choice of frequency (or frequencies) is clearly justified for ‘non-TFA’ frequency-domain methods, as they are mainly based on single-frequency physiological challenges, e.g., phase shift between oscillations of ABP and CBFV induced by lower body negative pressure using a vacuum box, paced breathing, or repeated squat-stand manoeuvres, usually at 0.05 or 0.10 Hz.

Although standardisation of dynamic CA metrics is important to facilitate comparison of clinical studies, it is premature for our field to permanently settle on the currently recommended 4 bands and associated analysis methods. We do not have solid evidence to support these, and their rigid adoption could stifle future research. We need to remain open to the multiple possibilities offered by TFA to realise its full potential in studies of human dynamic CA. At the current stage, it would be more reasonable to allow for the ‘coexistence’ of the band-averaging methods and alternatives.

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