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Between-centre variability in transfer function analysis, a widely used method for linear quantification of the dynamic pressure–flow relation: The CARNet study

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Conflict of interest

None declared.

Abstract

Transfer function analysis (TFA) is a frequently used method to assess dynamic cerebral autoregulation (CA) using spontaneous oscillations in blood pressure (BP) and cerebral blood flow velocity (CBFV). However, controversies and variations exist in how research groups utilise TFA, causing high variability in interpretation. The objective of this study was to evaluate between-centre variability in TFA outcome metrics. 15 centres analysed the same 70 BP and CBFV datasets from healthy subjects ($n = 50$ rest; $n = 20$ during hypercapnia); 10 additional datasets were computer-generated. Each centre used their in-house TFA methods; however, certain parameters were specified to reduce a priori between-centre variability. Hypercapnia was used to assess discriminatory performance and synthetic data to evaluate effects of parameter settings. Results were analysed using the Mann–Whitney test and logistic regression. A large non-homogeneous variation was found in TFA outcome metrics between the centres. Logistic regression demonstrated that 11 centres were able to distinguish between normal and impaired CA with an AUC > 0.85 . Further analysis identified TFA settings that are associated with large variation in outcome measures. These results indicate the need for standardisation of TFA settings in order to reduce between-centre variability and to allow accurate comparison between studies. Suggestions on optimal signal processing methods are proposed.

Keywords

Cerebral autoregulation; Transfer function analysis; Method comparison; Standardisation

1. Introduction

Oscillations in arterial blood pressure (BP) and cerebral blood flow velocity (CBFV) can be used for non-invasive assessment of the dynamic pressure–flow relationship of the cerebral circulation. Dynamic cerebral autoregulation (CA) is an important determinant of this pressure–flow relationship, and transfer function analysis (TFA) is a widely used linear approach to quantify CA.

The transfer function method was first carried out to quantify dynamic CA by Giller et al. [1] analysing the relationship between oscillations in BP and CBFV in the frequency domain. Evaluation of CA by TFA is based on the concept that CA minimises the effect of dynamic BP fluctuations on CBFV, which is reflected by reduced low-frequency gain and phase-lead of CBFV over BP. Without CA, CBFV would passively follow BP, and TFA would show constant gain and zero phase across the low-frequency band.

TFA has been employed to obtain quantification of CA during spontaneous oscillations in BP and CBFV. Using spontaneous oscillations to assess CA is often preferable to interventions which induce (larger) BP fluctuations [2], since these interventions require patient cooperation and/or can be uncomfortable; making them unsuitable in cases of severe illness or illness that reduces mobility. As a consequence, TFA is currently a widely used method in literature to quantify CA, both in basic physiological research and in clinical studies. However, there are large differences in TFA outcomes between studies. These

differences may be due to large inter-subject variation in CA, even for healthy controls, but may also be due to methodological differences between centres.

A systematic review on TFA found that most studies have used relatively small sample sizes, and were all done under different experimental conditions and for diverse research purposes [3]. Furthermore, this review showed a marked diversity in the signal processing methods used for TFA. This makes it difficult, if not impossible, to replicate or compare the results of the different studies or obtain normal values for healthy subjects.

The objective of this multi-centre study was to evaluate the differences in transfer function gain, phase, and coherence outcomes when the same datasets are analysed by different centres using their corresponding routine signal processing methods for TFA. Our study also investigated the effects of different parameter settings for the analysis on transfer function outcomes. Furthermore, our study evaluated the ability of TFA to identify the effects of hypercapnia [4].

2. Materials and methods

2.1. Multi-centre database

Five different centres from the UK (authors DS, RB, and MC), USA (author VN), and the Netherlands (author JC), provided datasets containing simultaneously recorded BP and CBFV of subjects during rest, to create a multi-centre database. Two centres also provided datasets recorded during 5% CO₂ breathing, a model known to alter transfer function outcome measures. One centre provided artificial datasets, using synthetic CBFV signals obtained by applying the models proposed by Tiecks et al. [5] to BP signals randomly selected from the available dataset. This Tiecks model provides the autoregulatory index (ARI), ranging from 0 to 9; in normal subjects ARI is approximately 5 with a standard deviation of 1. Ten signals were generated, one for each autoregulation index (ARI), covering the full range from 'absent' (ARI = 0) to 'fastest' (ARI = 9) autoregulation. Since most centres use beat-to-beat data to analyse transfer function gain, phase, and coherence, in this study we chose to use beat-to-beat data only. The beat-to-beat data were created using peak detection to identify subsequent beats, obtaining average values for BP and CBFV (unilateral) for each heart beat, and storing this information together with the beat-to-beat interval. The consecutive beat-to-beat intervals were used to reconstruct a time series of 5 min. The time-series data were linearly interpolated and resampled at 10 Hz to create equidistant data sampling over time. In some datasets an alternative procedure, with low-pass filtering of the original data (cut-off frequency of 0.5 Hz, third order Butterworth filter applied in the forward and reverse direction for a zero-phase response) was used to generate the mean BP and CBFV signals.

In total, the database contained 80 datasets ('subjects'), 50 beat-to-beat baseline datasets (normal resting baseline conditions); 20 5% CO₂-breathing datasets (from 20 subjects who were also included in the baseline dataset); and 10 synthetic datasets. Data files were blinded to the analysing centres and presented in a randomised order.

2.2. Participating centres

15 centres analysed the database and returned their transfer function results to a central collecting site (AM, JC). These centres are included in the author affiliation section.

3. Methods

3.1. Centre routine

All centres were first asked to report their normal routine settings for TFA in a predefined spreadsheet, including sampling rate, filtering or other pre-processing steps, and details on how the TFA was performed (e.g., type of window, window length, number of windows).

3.2. Pre-specified settings for analysis

Centres were asked to analyse the data using their own normal routine, however with some restrictions. This decision was made based on *Submitted review* [3] as well as a pilot study that had revealed such profound between-centre differences in TFA settings (for example different frequency band definitions, different units) that comparison between centres was impossible. Therefore, centres were requested to analyse the datasets using the following pre-specified settings: mean value beat-to-beat data as input data, no detrending, no prefiltering, number of windows set at 5, window length ranging between 90 s and 100 s with 50% superposition, Hanning window as anti-leakage window, no spectral smoothing, and no phase unwrapping. Centres were asked to report TFA parameter results as mean values, using standardised units for phase (radians) and gain (cm/s/mmHg) and apply pre-specified frequency band definitions (very low frequency (VLF): 0.02–0.07 Hz; low frequency (LF): 0.07–0.15 Hz; high frequency (HF): 0.15–0.4 Hz).

Every centre reported their TFA gain, phase, and coherence values for each of the frequency bands for every dataset.

To compare the transfer function data across the entire frequency spectrum, all centres were also asked to provide data to reconstruct frequency plots for gain, phase and coherence for ten specified subjects in the database.

3.3. Assessment of between-centre variability and comparison

As descriptors of between-centre variability, the median, quartile, and min-max values for the TFA parameters generated by the 15 centres were listed, and clustering between centres for parameter outcomes was tested using three-dimensional plots for phase, gain and coherence for each frequency band.

Discriminatory power was assessed for each centre's method by comparing TFA parameter differences between normocapnia and hypercapnia.

Finally, phase and gain values for each frequency band in the generated datasets were used as the reference standards to allow between-centre comparison; deviation from these reference values was used to create a ranking of the centres' method.

3.4. Effect of different transfer function settings

The usual routine, as reported by the different centres, contained different transfer function settings, such as sample frequency, interpolation, detrending, number of windows, window length, choice of anti-leakage window, percentage of superposition, and the definition of the frequency bands were then evaluated.

3.5. Explanation of these settings

The sample frequency defines the number of samples per second in which the continuous signals are stored. Interpolation can be used to create equidistant time intervals (in case of beat-to-beat data), by constructing new data points within the range of a discrete set of known data points. Most signal processing methods, including TFA, require equidistant data points. Detrending reduces the contribution of signal trends to the low-frequency power by removing any linear or non-linear trends from the input data. Pre-filtering can be used to delete frequencies that are of no interest, such as very high frequencies or extremely low frequencies. Data segments are usually windowed to reduce a particular kind of distortion called spectral leakage [6]. There are different kinds of anti-leakage windows, such as the cosine-tapered or Hanning window [7]. The window length defines the frequency resolution of the transfer function estimates. Averaging of spectral estimates over consecutive overlapped windows (Welch method) is used to reduce estimation errors (variance) in TFA estimates. As an alternative (or in addition), spectral smoothing can be achieved by applying a low-pass filter to spectral estimates, before calculating the transfer function. Triangular moving average filters are typically used for this purpose. Phase unwrapping is the inference of absolute phase from modulo- 2π phase [8]. A cut-off value for the coherence can be used to assure statistical reliability of the transfer function. This cut-off value is influenced by the number of windows (the value is lower for a higher number of windows) and smoothing of the frequency spectra using for example triangular moving averaging [9].

To evaluate how differences in usual routine settings of the centres might influence the outcome of the TFA, the following settings were compared using the artificial (generated) datasets: sample frequency (1, 5, 10, 20, and 50 Hz), type of interpolation (linear and spline), type of detrending (none, removal of the mean, linear, and third order polynomial detrending), number of windows (1, 3, 5, 10), window length (25, 50, 100, 300 s), type of anti-leakage window (Hanning, Hamming, rectangular, and Tukey), and percentage window superposition (25, 50, 75%). Furthermore, different frequency bands were evaluated. For the VLF, the following two sets were evaluated: 0.01–0.04 Hz and 0.02–0.07 Hz. The LF was defined as 0.04–0.15 Hz, 0.07–0.15 Hz, and 0.07–0.2 Hz and the HF as 0.15–0.4 Hz and 0.2–0.3 Hz. Since research has shown that some studies do not use three separate frequency bands [3], the outcomes for CA were also evaluated for 0.02–0.5 Hz.

For these comparisons, the actual values of gain and phase of the 10 ARI models were used as criterion standard. Next, using this same software, the effect of changing one of the settings as described above was investigated. The transfer function outcomes for VLF and LF gain and VLF and LF phase obtained for these different transfer function settings were compared by ranking the absolute deviation of the outcomes from the criterion standard values.

3.6. Statistics

Results are presented as median, min/max, and 1st and 3rd quartiles. Results were compared with the Mann–Whitney test. Logistic regression was used to construct a receiver operating characteristic (ROC) curve, in which the optimal sensitivity and specificity combination is visualised. The area under the curve (AUC) was quantified as a measure of quality of the classification model. A p -value < 0.05 was considered statistically significant.

4. Results

4.1. Centre routine

4.1.1. Participating centres—15 centres participated in this study. The approach of centre 3 is distinct (Laguerre expansions [10]) from other frequency-domain approaches. Centre 14 did not report results for coherence. Table 1 gives an overview of the normal routine settings of each centre and the settings used for this study. The centres differ in their signal processing methods for TFA in the following parameter settings: sample frequency, type of interpolation used, number of windows, window length, frequency resolution, type of spectral smoothing, and phase unwrapping. Furthermore, centre 15 reported to normalise the BP and CBFV data by the mean value during the 5-min period and subtracted by 1 before applying TFA. Table 1 shows that not all centres were able to report all their settings (not reported, NR) used for the TFA.

4.1.2. Transfer function plots—All centres were asked to present frequency plots, analysed using the pre-specified settings, for certain datasets. Fig. 1 represents the average transfer function plots generated by the 15 centres for a single subject under normocapnic baseline condition. These 15 plots are summarised as median (black line), 1st/3rd quartile (grey solid lines), and min/max (grey dashed lines).

The transfer function plots for gain and phase of two generated datasets at the ends of the CA spectrum (ARI = 0 and ARI = 9), generated when analysed using one set of parameter settings for TFA, are shown in Fig. 2. The specified parameter settings were: sample frequency = 10 Hz, window length = 95 s, anti-leakage window = Hanning, number of windows = 5, percentage of superposition = 50%, frequency bands were VLF: 0.02–0.07 Hz; LF: 0.07–0.15 Hz; HF: 0.15–0.4 Hz.

4.1.3. Differences between centre outcomes—The relation between the data generated by the 15 centres for the 50 healthy subjects is presented in Fig. 3. For all frequency bands, a cluster is formed by the following 9 centres: 1, 2, 4, 7, 8, 10, 11, 12 and 13.

4.1.4. Hypercapnia—Fig. 4 shows results for phase in VLF (top), LF (middle), and HF (bottom) for each centre (represented on the x -axis) obtained in the 20 subjects under normal resting conditions (normocapnia) and for these same 20 subjects during 5% CO₂ breathing (hypercapnia), using multiple box plots.

Logistic regression was performed using the two conditions of CA (normal = baseline, modified = hypercapnia) as outcome value, and as predictor variables the phase VLF, phase

LF, phase HF, gain VLF, gain LF, gain HF, coherence VLF, coherence LF, and coherence HF.

Fig. 5 shows the receiver operating curves (ROC) that were generated for all centres, describing their performance in separating normal from modified. The graph shows ROC curves for the best (Centre 3 AUC: 0.927), the worst (Centre 14 AUC: 0.68), and the median of all centres.

4.1.5. Artificial datasets—Gain (top), phase (middle), and coherence (bottom) results (y-axis) for ARI 0, 2, 4, and 6 are shown in Fig. 6. Results are shown as median, 1st and 3rd quartile, minimum, and maximum values of the results of all centres for the VLF, LF, and HF bands. The model for fully impaired autoregulation, ARI = 0, showed (as expected) a phase of nearly zero and a high gain (≈ 1 cm/s/mmHg). The model for intact CA, ARI = 6, shows a high phase (1.1 ± 0.4 rad) and a low gain (0.6 ± 0.2 cm/s/mmHg) in the very low frequency.

4.2. Effect of different transfer function settings

The effect of three different parameter settings on transfer function gain and phase results for the ARI = 6 generated data are shown in Fig. 7; sample frequency (1, 5, 10, 20, and 50 Hz), window length (25, 50, 75, and 95 s), and different frequency bands.

The best results are found for a sample frequency of 10 Hz (the sample frequency used to generate the data). The farther the sample frequency deviates from 10 Hz, the more the results deviate from the criterion value. Decimating the data produces larger deviations than up-sampling of the data.

No differences were found in gain and phase estimates when different methods of interpolation were used (including spline versus linear interpolation), detrending versus no detrending (including removal of the mean, linear trend removal, and third order polynomial detrending). Comparing the number of windows showed that using less than three windows resulted in less optimal results.

Also using window lengths smaller than 75 s resulted in larger deviations from the criterion value, particularly in the VLF. Using the Hamming or Hanning anti-leakage window did not result in different outcomes, but rectangular and Tukey window showed different results compared to the Hamming and Hanning windows. The rectangular window yields inferior results in LF gain and VLF phase and the Tukey window distorts the gain and the phase in the VLF. Varying the percentage of superposition, using percentages of 25%, 50%, and 75%, did not affect the outcomes. The use of different frequency bands affected outcomes for phase in VLF and in LF in all frequency bands. Using a frequency band of 0.02–0.5 Hz led to the strongest deviation from the criterion value.

5. Discussion

Strong diversity exists in the signal processing methods for TFA used by the international research community in quantifying CA. The objective of this multi-centre study was to evaluate how this diversity in methods affects transfer function outcomes for CA. An

important underlying question was whether these between-centre differences in how to perform TFA may contribute to the large variability in TFA outcomes in the literature. This objective was achieved by asking different centres that use different methodological approaches for TFA, to analyse the same dataset. Our main finding is that TFA analysis – of the same dataset – by these centres led to a large variability in metric outcomes. This large variability could in part be explained by the use of different parameter settings for TFA by these centres, however part of the variability remains unexplained. Below we will further discuss potential causes of this variability and recommendations to reduce it. This finding of large between-centre variability is in agreement with the results of a systematic review of published TFA studies [3]. Our study adds to this review by directly comparing multiple centres that analyse the same set of data. Furthermore, we systematically evaluated how different choices for the signal processing methods will affect outcomes.

Non-invasive monitoring of CA is important, since disorders of CA may lead to adverse clinical outcomes such as cerebral hypo-perfusion [11]. Currently, no gold standard test for the assessment of dynamic CA exists. TFA is the most widely used and reported method for non-invasive quantification of CA. However, no standardised form for the implementation of the transfer function exists, resulting in high diversity among studies [3]. Our study showed that the inter-centre variability is quite high, particularly for a procedure that is deemed rather straightforward and places restrictions on the choice of implementation parameters. Even though instructions were given to the centres that should have reduced variability, the observed high spread in CA outcomes was still due to diversity in TFA signal processing choices. Parameter settings that differed between the centres were: sampling frequency, type of interpolation, number of windows, window length, type of anti-leakage window, frequency resolution, type of spectral smoothing, and phase unwrapping. Based on our analyses discussed below, we can conclude that these differences in settings are in part responsible for the high diversity in results from the different centres. Not all variance could however be fully explained by these settings. Nevertheless, despite the large variance, most centres showed good ability to distinguish between normal CA and modified CA (using hypercapnia). Even the poorest performing centre had a ROC AUC higher than 0.75.

5.1. Effect of different parameter settings on TFA outcome

To further investigate how different settings may affect TFA analysis, in a sub-study we used the artificially generated datasets to systematically evaluate how different parameter settings affect transfer function outcome. These analyses were performed in a single centre. We did this by running repeated analyses of these artificial datasets, using analysis software written in Matlab® (by author DMS), each time changing a single parameter setting. These analyses showed that particularly the sampling frequency, number of windows, window length, type of anti-leakage window, and the definition of frequency bands influenced the results. Regarding the sampling frequency, we found that both decimating and up-sampling the data altered the results. A reduction of sample frequency resulted in a VLF phase decrease for the artificial data. When we compared the clustered centre data (1, 2, 4, 7, 8, 10, 11, 12, and 13) this VLF phase decrease was confirmed by the results of centre 4 that used a sample frequency of 1 Hz. Also the centres 3, 9, and 14 used low sample frequencies and showed lower VLF phase. In the present study a sampling frequency of 10 Hz resulted in the

best results. However, this could be due to the fact that the artificial datasets were created at 10 Hz. Therefore, a different sampling frequency may be optimal for biological signals of BP and CBFV; this awaits further investigation. Lowering the number of windows or the length of the window mainly affected the VLF outcomes, but this effect of increased VLF gain and decreased VLF phase with decreasing window length could not be confirmed by comparing the results in healthy subjects. However, since the pre-specified settings instructed the centres to use a window length of 90–100 s little between-centre variation in window length was present. Concerning the type of anti-leakage window, we found that the Hanning and Hamming window did not differ in outcome values. However, the use of a rectangular or Tukey window yielded inferior results. This can be explained by the fact that the rectangular window has excellent spectral resolution characteristics for sinusoids of comparable strength, but it is a poor choice for sinusoids of disparate amplitudes [7] and the Tukey window, also known as the tapered cosine window, has also relatively poor leakage protection. It should be pointed out that the analysis of synthetic data can only provide partial guidance into the optimal choices for estimator settings. For example, in the synthetic data, the input-output relationship was purely linear, and there was no noise present in the data. Thus the benefits of detrending or increased window-length present in signals recorded from human volunteers cannot be observed.

5.2. Implications

These results imply that standardisation of the parameter settings used to calculate the transfer function could substantially lower the inter-centre variability in transfer function outcomes.

However, some methodological issues need to be considered.

TFA is a linear method, while, in general, CA is considered to be a non-linear phenomenon. Therefore it is possible that other methods, i.e., non-linear approaches, may provide better estimates of CA although it is likely that variations in parameter settings may also influence metric outputs as observed here for TFA. We suggest that resolving the lack of methodological standardisation must take priority when new methods are proposed and implemented. Future studies should implement the approach taken in this study, with multiple centres analysing a central database, for a prospective study comparing different methods to analyse CA, to investigate whether non-linear methods are superior to TFA, while at the same time optimising standardisation of such methods. Another methodological issue is whether it is accurate to assume that TFA wholly reflects dynamic CA. Although the relationship between cerebral perfusion pressure and flow are influenced by dynamic CA, it is important to recognise that other physiological factors such as baseline BP, pCO₂ [12,13], brain metabolic activity, and sympathetic tone are also influential. Because TFA considers only the BP (input) and CBF (output) relationship, the approach is clearly a simplification of a highly complex physiological system. In this context, the contribution of pCO₂ as an additional input has been investigated by for example in [13,14]. However, the exclusion of this (and other) inputs does not mean that the transfer function analysis has no clinical utility. Indeed, the medical literature is replete with examples of simplified measures that have been successfully applied as metrics for risk stratification and monitoring. A good

example is the use of gait speed (measuring the time taken to walk 4 m) as a measure of the highly complex concept frailty, and even as a prediction of survival [15].

In conclusion, this study shows that there is an urgent need for detailed standardisation of the signal processing methods used for TFA. Without such standardisation, additional uncertainty is added to any comparison between studies of autoregulation carried out at different centres.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.medengphy.2014.02.002>.

Fig. 1.

Average transfer function results (gain (A), phase (B), and coherence (C)) of the centres found for one subject during normocapnia. Results are represented as median (black line), min/max (grey dashed lines), and 1st/3rd quartile (grey solid lines) for the gain in cm/s/mmHg (top), phase in radians (middle), and coherence (bottom).

Fig. 2.

Transfer function gain (A) and phase (B) of the artificial datasets ARI 0, 2, 4 and 6, analysed using one set of parameter settings for TFA. The specified parameter settings were: sample frequency = 10 Hz, window length = 95 s, anti-leakage window = Hanning, number of windows = 5, percentage of superposition = 50%, frequency bands were VLF: 0.02–0.07 Hz; LF: 0.07–0.15 Hz; HF: 0.15–0.4 Hz.

Fig. 3.

Relation between the average outcomes for phase (y-axis), gain (z-axis), and coherence (x-axis) of the centres for the very low frequency (A), low frequency (B), and high frequency (C). Vertical dashed lines indicate the projection of each point on the x - y plane. Centre 14 is excluded from the graph, because this centre did not report any values for the coherence.

Fig. 4.

Phase results in radians (y-axis; A–C) and gain results in cm/s/mmHg (y-axis; D–F) for each centre (x-axis) showing the differences found between normocapnia (dark boxes) and hypercapnia (light boxes). The spread between the results is represented using multiple box plots. On each box, the central mark is the median value, the edges of the box are the 25th and 75th percentiles, and the whiskers extend to the most extreme data points. Asterisks (*) indicate that the centre found a significant difference between normocapnia and hypercapnia ($p < 0.05$). The graphs show the phase results for the very low frequency (A and D), low frequency (B and E), and high frequency (C and F).

Fig. 5.

Receiver operating characteristics (ROC) curves of the centre with the best ability to distinguish (centre 3) between normocapnia and hypercapnia and the centre which is least able to distinguish (centre 14). ROC curves are derived using logistic regression. Logistic regression was performed using the state of CA (normal = baseline, impaired = hypercapnia) as the outcome value and as predictor variables the phase VLF, phase LF, phase HF, gain VLF, gain LF, gain HF, coherence VLF, coherence LF, and coherence HF.

Fig. 6.

Gain (A), phase (B), and coherence (C) results (y-axis) for ARI 0, 2, 4, and 6. The spread between the centres is represented using multiple box plots. On each box, the central mark is the median value of the centres of the specific subject, the edges of the box are the 25th and 75th percentiles, and the whiskers extend to the most extreme data points. Results are shown for the very low frequency (VLF), low frequency (LF), and high frequency (HF). Asterisks (*) indicate the values for transfer function phase and gain that were obtained by the software (written in Matlab by DS) that was used to generate the datasets.

Fig. 7.

The transfer function results expressed in VLF gain, LF gain, VLF phase, and LF phase of ARI = 6 for three different parameter settings: sample frequency (1, 5, 10, 20, and 50 Hz) (A), window length (25, 50, 75, and 95 s) (B), and different frequency bands (C). Standard indicates the actual values of gain and phase of the 10 ARI models were used as criterion standard which were used as criterion standard value.