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The effect of blood pressure calibrations and transcranial Doppler signal loss on transfer function estimates of cerebral autoregulation

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Abstract

There are methodological concerns with combined use of transcranial Doppler (TCD) and Finapres to measure dynamic cerebral autoregulation. The Finapres calibration mechanism (“physiocal”) causes interruptions to blood pressure recordings. Also, TCD is subject to signal loss due to probe movement. We assessed the effects of “physiocal” and TCD signal loss on transfer function estimates in recordings of 45 healthy subjects. We added artificial “physiocal” and removed sections of TCD signal from 5 min Finapres and TCD recordings. We also compared transfer function results from 5 min time series with time series as short as 1 min. Accurate transfer function estimates can be achieved in the 0.03–0.07 Hz band using beat-by-beat data with linear interpolation, while data loss is less than 10 s. At frequencies between 0.07 and 0.5 Hz, transfer function estimates become unreliable with 5 s of data loss every 50 s. 2 s data loss only affects frequency bands above 0.15 Hz. Finally, accurate transfer function assessment of autoregulatory function can be achieved from time series as short as 1 min, although gain and coherence tend to be overestimated at higher frequencies.

Keywords

Cerebral autoregulation; Transfer function; Physiocal; Data loss; Blood pressure; Cerebral blood flow

1. Introduction

Cerebral autoregulation is an intrinsic mechanism of the cerebrovasculature that maintains a relatively constant blood flow despite changes in mean arterial pressure, in the range of approximately 60–150 mm Hg [1]. Early investigations of cerebral autoregulation in humans relied on indicator-dilution techniques, including clearance of Xenon-133 or nitric oxide [2]. These approaches took mean values of blood pressure and cerebral blood flow over several minutes, to produce a single value of autoregulation. As these techniques relied on steady state values, they are generally referred to as ‘static’ measures of cerebral autoregulation. Static autoregulation assessment required the use of drugs to maintain constant blood pressure levels over several minutes, and were prone to technical and methodological problems [3].

The introduction of transcranial Doppler ultrasound (TCD) by Aaslid et al. [4] in 1982, and the simultaneous development of continuous blood pressure monitoring via the finger (Finapres) represented a major breakthrough in the assessment of cerebral autoregulation, as it enabled non-invasive measures of blood pressure and cerebral blood flow velocity on a beat-by-beat basis. The combined use of TCD and Finapres created the new field of ‘dynamic cerebral autoregulation’ assessment (a phrase first coined by Aaslid et al. [5] in 1989), as it provided the ability to characterise the autoregulatory response of the cerebrovasculature to sudden changes in arterial pressure on a beat-by-beat basis. Since then, a number of techniques have been developed to characterise the dynamic autoregulatory response to sudden pressure change, including the rate of regulation [5], and the Autoregulatory Index (ARI) [2]. These techniques are based on manoeuvres that elicit a sudden drop in blood pressure, such as sudden deflation of thigh cuffs, lower body negative pressure, sit-to-stand tests, or valsalva manoeuvres. However, in a clinical setting, there are several patient groups including those with stroke, traumatic brain injury or heart failure, where causing a sudden drop in blood pressure is not desirable. Instead, transfer function analysis has been used as an alternative technique to analyse spontaneous fluctuations in arterial blood pressure to assess dynamic autoregulation [6–11].

Transfer function analysis provides the capability to assess the beat-by-beat changes in cerebral blood flow velocity in response to spontaneous oscillations in blood pressure. By examining these changes in the frequency domain we can examine the autoregulation response not only during rapid changes in pressure (i.e. 0.2–1 Hz) but also during much slower changes (e.g. <0.2 Hz). Transfer function analysis provides information about the gain, phase difference and coherence of the relationship between blood pressure and cerebral blood flow. Gain represents the amplitude ratio between the input (arterial blood pressure) and output (cerebral blood flow velocity) at each frequency. If autoregulation is intact, changes in arterial blood pressure (ABP) will cause minimal changes in cerebral blood flow velocity (CBFV), and thus transfer function gains will be low. If cerebral autoregulation is impaired, however, changes in ABP cause large changes in flow and thus gains will be high [7,12]. Several studies have examined the phase difference between ABP and CBFV at frequencies below 1 Hz. With intact autoregulation, there is a phase lead between CBFV and ABP, due to the response time of the smooth muscle in the arteriolar vessel walls to modify the vessel diameter, and hence modulate cerebrovascular resistance [13,14]. Since the phase

lead is a result of intact autoregulation, loss of phase lead is associated with impaired autoregulation [15–17]. The coherence function is similar to a correlation coefficient, and will approach 1.0 when the output is entirely and linearly dependent on the input. Coherence will be low if there is a non-linear relationship between the input and output signals, if the output is dependent on more than one input or if there is a low signal to noise ratio [18]. Coherence has been used as an indicator of dynamic cerebral autoregulation [19]. If autoregulation is intact, changes in ABP would be attenuated by compensatory changes in cerebrovascular resistance, and thus coherence would be low. Conversely, if autoregulation is impaired, changes in ABP would directly affect the CBFV and coherence would be high.

There are a number of methodological concerns with the equipment used to measure ABP and CBFV for transfer function analysis. Continuous measures of ABP for transfer function analysis can be acquired by an invasive placement of an intra-arterial catheter in the radial, brachial or femoral artery, or non-invasively via a pressure cuff on the finger, using the volume clamp method [20] as implemented in the Finapres (Ohmeda Monitoring Systems). Intra-arterial catheters are not popular for cerebral autoregulation assessment, as they can cause local infection, arterial dissection, and pseudoaneurysm formation. In contrast, the Finapres, and its successors, Portapres and Finometer (Finapres Medical Systems), are non-invasive and relatively easy to use, and have become the most commonly used method of continuous ABP measurement. The Finapres is not considered accurate enough for measurement of absolute blood pressure. However, the accuracy of Finapres in measuring the changes in blood pressure have been validated in several studies [21].

These devices have an automatic calibration mechanism called a “physiocal” (abbreviation for physiologic calibration). During the Finapres start-up procedure, a dynamic servo set-point adjuster establishes arterial unloading at zero transmural pressure, and therefore full transmission of arterial blood pressure to cuff pressure. After the start-up procedure, the set-point is checked and adjusted if necessary during interruptions of blood pressure recordings (i.e. to enable “physiocal” servo calibrations to be carried out) [21]. Arteriolar vasoconstriction can interfere with measurement of the plethysmogram [21–24]. This can be caused by low ambient temperature, sympathetic activity or vascular abnormalities. Effects of these phenomena are reduced by the built-in “physiocal” algorithm [21]. Despite this, several authors have reported switching this servo calibration system off during measurements. This is because these calibrations temporarily disrupt blood pressure recordings (usually for 3 beats) and leave a characteristic step function in the blood pressure recording (Fig. 1). However, switching the “physiocal” servo calibration off may lead to inaccurate ABP measurements, particularly during protocols that involve changes in temperature (cold pressor test) or sympathetic tone (head up tilt, lower body negative pressure).

Another methodological challenge for transfer function analysis is maintaining adequate signal quality during TCD ultrasound measurements. The TCD probes are placed over the temporal window and held in place with a variety of probe holders, some of which are of custom design. Subject and/or probe movement can cause the probes to slip away from the temporal window, resulting in signal loss, which is often eliminated by readjustment of the

probe, resulting in short periods of unusable data. Missing data points are usually replaced by linear interpolation.

A review of the literature also reveals inconsistent methodologies for transfer function analysis. Most studies have used 5 min time series for transfer function analysis. However, various studies have also performed transfer function analysis on differing durations of data, from as high as 15 min [17] to as short as 1 min [25]. A wide range of other data lengths have been reported [7,12,14,26–28]. This makes inter-study comparisons difficult, as it is not clear how using different time series lengths affects transfer function estimates.

As far as the authors are aware, no studies have investigated the effect of “physiocal” episodes and TCD signal loss on transfer function estimates. To address this issue we analysed 45 blood pressure and cerebral blood flow recordings from a previous study [25]. Each recording contained 5 min of middle cerebral artery (MCA) CBFV and arterial blood pressure (Finapres) data. The “physiocal” calibration mechanism was turned off for all blood pressure recordings.

To investigate the effects of “physiocal” calibrations on transfer function estimates, we added artificial “physiocal” episodes to the blood pressure signals, and then compared transfer function estimates with the results from the original signal. We also examined the effect of TCD signal loss on transfer function estimates by removing sections of TCD signals at random intervals. We compared transfer function estimates from mean beat-by-beat values with transfer function estimates from complete waveforms. Finally, we compared transfer function estimates from 5 min, 3 min, 2 min and 1 min data recordings. We hypothesised that accurate transfer function estimates could still be achieved despite the presence of “physiocal” episodes in blood pressure signals, and loss of TCD signal. We also hypothesised that accurate transfer function estimates can be achieved using shorter data recordings.

2. Methods

2.1. Subject recruitment

Subjects were recruited as part of a previous study assessing autoregulation in the posterior circulation [25]. In total, 45 healthy subjects (25 male) aged 62 ± 3 years (mean $\pm$ SD) took part. All subjects were carefully screened with a medical history, physical examination, and ECG to exclude any acute or chronic medical conditions. Subjects were asked to refrain from alcohol or nicotine use for at least 12 h before the study. Subjects had mean systolic blood pressure = 129 ± 3 mm Hg, diastolic blood pressure = 63 ± 2 mm Hg, mean arterial pressure = 84 ± 2 mm Hg, heart rate = 66 ± 2 beats/min and end-tidal CO_2 = 36 ± 1 mm Hg. The study was approved by the Hebrew Rehabilitation Center for Aged and Brigham and Women’s Hospital Institutional Review Boards, and followed institutional guidelines.

2.2. Experimental setup

All data were recorded during a 5 min period of quiet sitting. Each subject was instrumented with a three lead ECG (Collins, TX) to obtain heart rate. Continuous arterial blood pressure measurements were obtained using a Finapres photoplethysmographic system placed on a

finger and held at heart level with a sling. CBFV was measured continuously in the MCA using transcranial Doppler ultrasonography while sitting in a chair. The MCA was insonated by placing a 2MHz pulsed flat TCD probe (MultiDop, DWL) over the right or left temporal bone, and held in place during recordings using the Spencer headband. The envelope of the velocity waveform was derived from fast Fourier transformation of the Doppler signal. All physiological signals were digitized at 500 Hz by using a commercially available digitizer (Windaq, Dataq Instruments, Columbus, OH) and stored on a computer for offline analysis.

2.3. Data processing and analysis

Postprocessing was carried out using custom-written MATLAB scripts. All time series were decimated to 100 Hz. Flow velocities were normalized in percent to mean baseline flow. All analyses were performed on measurements taken during 5 min of quiet sitting.

2.3.1. Beat-by-beat analysis—Beat-to-beat R–R intervals were determined from the R wave of the ECG. MAP and mean CBFV were determined from the integrals of each waveform, and systolic and diastolic values for ABP and CBFV were determined from the peak and nadir of the associated waveforms. Beat-to-beat values were interpolated at 10 Hz to obtain a uniform time basis.

2.3.2. Transfer function analysis—Transfer function gain, phase and coherence were calculated from the complete ABP and CBFV time series signals, and from beat-by-beat time series. The power spectrum density, based on Welch's algorithm of averaging periodograms was calculated for the filtered signals using a sliding window with a width of 100 s and a 2/3 overlap with application of a Hanning window. To preserve low frequency power, signal detrending was not employed. A summary of the Welch algorithm transfer function parameters used in this study is given in Table 1.

Coherence (C) of the frequency content (f) between the MAP and CBFV time series was calculated from the power spectra (P) in the sitting position using Eq. (1):

$$C_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)} \quad (1)$$

where x is the input signal (ABP) and y is the output (CBFV). The transfer function (T) is calculated as the quotient of the cross power spectral density (P_{xy}) of x and y and the power spectral density (P_{xx}) of x (Eq. (2)):

$$T_{xy}(f) = \frac{P_{xy}(f)}{P_{xx}(f)} \quad (2)$$

Gain is calculated as the absolute value of the transfer function $T_{xy}(f)$, and phase as the arc tan of the ratio of the real and imaginary parts of $T_{xy}(f)$.

Because different frequency bands have been examined in the literature, we examined the effects of data loss in a number of frequency bands: 0.03–0.07 Hz, 0.7–0.15 Hz, 0.15–0.3 Hz, and 0.3–0.5 Hz.

2.4. Effect of “physiocal” episodes on transfer function estimates

To assess the effect of “physiocal” episodes on transfer function estimates, we replaced sections of the blood pressure waveforms with artificial “physiocal” episodes. These artificial “physiocal” episodes were designed to mimic real calibrations as accurately as possible. An example of an artificial “physiocal” episode is shown in Fig. 1. Three beats of blood pressure recordings are replaced by a step function. The first step is equal to the mean of the three beats replaced, and step 2 and step 3 are the mean ± 5 mm Hg, respectively.

Initially we calculated transfer function estimates for the 5 min blood pressure and CBFV signals for each subject. Then we added artificial “physiocal” episodes at regular time intervals throughout each 5 min blood pressure recording, and recalculated the transfer function estimates. For the first analysis, “physiocal” episodes were added to the blood pressure recordings for each subject at 70 s intervals. For the second analysis, “physiocal” episodes were added every 50 s. Finally, “physiocal” episodes were added at 30 s intervals. A criterion for acceptance of Finapres output is that the signal should be stable, i.e. the period between “physiocal” adjustments should be 30 beats or more [21]. Transfer function estimates for each round of analysis were then compared with the transfer function estimate with no added “physiocal” episodes. Analyses were performed on both complete time series waveform data and beat-by-beat data. We also repeated transfer function analyses with “physiocal” episodes removed from beat-by-beat data, and replaced using linear interpolation. Fig. 2 shows an example of artificial “physiocal” episodes added to the complete waveform data, and its effect on beat-by-beat mean data.

2.5. Modelling the effect of “physiocal” and linear interpolation on transfer function estimates

The blood pressure signal can be modeled by the following equation:

$$y(t) = w(t)x(t) + v(t) \quad (3)$$

where $x(t)$ is the input blood pressure signal (with no “physiocal”), $y(t)$ is the output blood pressure signal (with “physiocal” added), $w(t)$ is a windowing function that is 0 during “physiocal”, and 1 otherwise, and $v(t)$ represents either the “physiocal” signal itself, or linear interpolation where this is used, and 0 otherwise. Where the “physiocal” signal is present, the spectrum $Y(\omega)$ is the sum of the true spectrum $X(\omega)$ convolved with the square window function and the distortion caused by $V(\omega)$. A similar principle can be applied to the replacement of sections of TCD data replaced by linear interpolation, except that linear interpolation can be represented by a filter.

2.6. Transcranial Doppler signal loss

To assess the effects of transcranial Doppler (TCD) signal loss, we removed sections of CBFV, and replaced the removed sections using linear interpolation. Data loss segments were 5 s, 10 s and 20 s in length and were introduced every 300, 70, 50, 30 and 15 s. Again, transfer functions were calculated both from complete time series waveform data and from beat-by-beat data.

2.7. Transfer function estimates on shorter data recordings

To compare transfer function estimates from shorter data recordings, we divided the 5 min data recordings into 3, 2 and 1 min data recordings. The 5 min datasets were divided into two 3 min time series (0–180 s, 120–300 s), four 2 min time series (0–120 s, 60–180 s, 120–240 s, 180–300 s) and five 1 min time series (0–60 s, 60–120 s, 120–180 s, 180–240 s, 240–300 s). Data window lengths of 100, 60, 45 and 30 s were used for time series length of 5 min, 3 min, 2 min and 1 min, respectively. An overlap ratio of 2/3 was used for all transfer function estimates. All Welch algorithm parameters for transfer function estimates are described in Table 1. The mean of the gain, phase and coherence for the 3, 2 and 1 min time series were then compared with the values from the 5 min time series.

2.8. Statistical analysis

The effects of adding “physiocal” episodes and segments of CBFV data loss on transfer function gain, phase and coherence were assessed by using both Pearson linear regression analysis and a repeated-measures two-way ANOVA, with a post hoc Bonferroni test for multiple comparisons. Paired Student *t*-tests were used to compare transfer function estimates from continuous waveforms and beat-by-beat mean data and from different time series lengths. Data are presented as means $\pm$ standard deviations, and levels of $P < 0.05$ are considered statistically significant.

3. Results

3.1. Frequency response of “physiocal” and linear interpolation

The time signals and the magnitudes of the corresponding Fourier transforms (FT) for the “physiocal” signal and the linear interpolation function are given in Fig. 3. The duration of the “physiocal” and linear interpolation was 3 s, and the amplitude was set to 1 (arbitrary units) for convenience. The “physiocal” is quite similar to a square wave, with a delay of 1 s. The spectrum of the “physiocal” is therefore essentially that of a square wave.

Linear interpolation corresponds to convolution with a triangle function, $\Lambda(x)$, which is defined as:

$$\Lambda = \begin{cases} 1 - \frac{|x|}{T} & \text{if } |x| < T \\ 0 & \text{otherwise} \end{cases} \quad (4)$$

The frequency response of the triangle function, shown in Fig. 3 is defined as:

$$\Lambda(x)T^2\text{sinc}^2(x) \quad (5)$$

3.2. Continuous waveform versus beat-by-beat waveform baseline transfer function estimates

Table 2 shows the transfer function gain, phase and coherence calculated from the entire waveform and from beat-by-beat mean signals. The transfer function variables calculated from the beat-by-beat signals match very closely with those calculated from the complete

waveform in the lower frequency bands. Coherence was significantly lower when calculated from beat-by-beat signals in the 0.03–0.07 Hz ($p = 0.011$) and 0.07–0.15 Hz bands ($p < 0.001$), but these differences were quite small and likely not of clinical significance. Gain ($p = 0.025$) and phase ($p = 0.003$) calculated from the beat-by-beat mean signal analysis were significantly lower in the 0.3–0.5 Hz band.

3.3. Effect of “physiocal” in blood pressure signal

Fig. 4 shows the effect of “physiocal” on transfer function gain, phase and coherences estimates for all frequencies below 0.5 Hz, for both continuous and beat-by-beat waveforms mean waveforms with “physiocal” replaced using linear interpolation. Also, Fig. 5 shows the effect of “physiocal” episodes on transfer function estimates for each of the frequency bands outlined previously. Data are presented as the mean differences between the data set with no physiocal and datasets with “physiocal” episodes added. In transfer function estimates from continuous waveforms (Fig. 5, left), gain and coherence were significantly lower after the addition of 4 or more physiocal in all frequency bands below 0.5 Hz ($p < 0.05$). Phase was not significantly different in all frequency bands below 0.5 Hz. However, the standard deviations of the difference in phase, before and after the addition of “physiocal” episodes, are quite large. This would suggest that transfer function estimations of continuous waveform signals containing “physiocal” episodes are unreliable.

Unlike transfer function estimates from continuous waveform data, transfer function estimates from beat-by-beat mean data with physiocal removed by linear interpolation (Fig. 4, right) agree very closely with the original transfer function estimates without the physiocal. Gain measurements were not significantly different in any frequency band after the addition of “physiocal” episodes. Similarly, beat-by-beat phase estimations are unaffected by the addition of “physiocal”. However, coherence is significantly lower in all frequency bands between 0.07 and 0.5 Hz but this difference is not as great as when the continuous waveform was used. The correlation coefficients are also much higher for gain, phase and coherence for beat-by-beat interpolated data than for waveform data (Table 3). These results demonstrate that transfer function estimates are more accurate when linear interpolation is used to remove “physiocal” episodes from beat-by-beat data.

3.4. Effect of loss of transcranial Doppler signal on transfer function estimation

To simulate the effects of loss of TCD signal, we removed sections of TCD cerebral blood flow velocity data and replaced the missing data with linear interpolations. We examined the effects of different lengths of data loss segments (2, 5, 10, and 20 s) and the effect of multiple sections of data loss (1, 4, 6, 10, 20 segments per 5 min time series). As expected, missing data had a major effect on complete waveform transfer function estimates, similar to the results from adding “physiocal” episodes to blood pressure signals. Therefore, we used beat-by-beat mean data for transfer function estimates.

3.4.1. Beat-by-beat transfer function results—Fig. 6 shows the results of inserting 2 s and 5 s of missing TCD data with linear interpolation. Examining the data from 2 s of data loss, coherence was not significantly affected in the 0.03–0.07 Hz band. The 0.07–0.15 Hz band demonstrated significantly lower coherence after 6 ($p = 0.026$) and 20 ($p = 0.017$)

sections of lost data. Coherence was significantly lower in both the 0.15–0.3 Hz and 0.3–0.5 Hz bands after just one 2 s section of lost data was replaced. Gain was not significantly affected in the 0.03–0.07 Hz and 0.07–0.15 Hz bands. However, in the 0.15–0.3 Hz and 0.3–0.5 Hz bands, gain was significantly lower after 4 or more sections of missing data were added. Phase was not significantly affected in any frequency band, and correlation coefficients were high in all frequency bands until 10 or more sections of data loss were added.

Examining the data from 5 s of data loss, coherence was only significantly lower in the 0.03–0.07 Hz band after 20 sections of missing data were added ($p = 0.025$). In the 0.07–0.15 Hz band, coherence was significantly lower after 6 or more sections of data loss were added. The 0.15–0.3 Hz and 0.3–0.5 Hz band coherence was significantly lower after 1 or more sections of data loss. Transfer function gain was not significantly affected by 5 s data loss in the 0.03–0.07 Hz band. Gain was significantly reduced after 6 or more sections of data loss in the 0.07–0.15 Hz band, and after 1 or more sections of data loss in the 0.15–0.3 Hz and 0.3–0.5 Hz bands. Phase was not significantly affected in any frequency band, and correlation coefficients were high in all frequency bands until 10 or more sections of data loss were added.

From Fig. 6 it is clear that 2 and 5 s sections of data loss affect the frequency bands between 0.07 and 0.5 Hz, while the 0.03–0.07 Hz band is largely unaffected. However, the question remains as to what length of data loss will affect the lowest frequency band. Fig. 7 shows the effect of 10 and 20 s of data loss on transfer function estimates in the 0.03–0.07 Hz band. Gain ($p = 0.001$) and coherence ($p = 0.02$) are significantly affected after six 10 s segments are replaced. While phase is not significantly different, the R^2 correlation drops to 0.80 after four 10 s segments of interpolation, and 0.55 after six 10 s segments. However, gain is significantly different with just one 20 s section of missing data, and coherence is significantly affected with 4 segments of missing data. Again, phase does not differ significantly after 20 s segments of linear interpolation are introduced.

3.5. Comparison of transfer function estimates from different time lengths

Table 3 shows the comparison of continuous waveform transfer functions estimated from the original 5 min time series and the means of the three, 2 and 1 min time series (beat-by-beat analysis showed the same pattern as shown in Table 3).

Transfer functions from 3 min and 2 min time series agree very closely with the 5 min data in all frequency bands. Transfer function gain was overestimated in all frequency bands from 1 min time series. Gain was significantly higher in the 0.15–0.3 Hz band ($p = 0.007$), and the 0.3–0.5 Hz band ($p < 0.001$). Coherence was significantly higher in the 0.15–0.3 Hz band ($p < 0.026$). Phase was not significantly different in any frequency band.

4. Discussion

There are three major findings in this study. First, accurate transfer function estimates can be achieved despite the presence of “physiocals” in ABP signals, when beat-by-beat data is used and “physiocal” episodes are replaced using linear interpolation. Second, the effect of

lost TCD data, particularly in the lower frequencies, is significantly reduced when using beat-by-beat data with linear interpolation. Finally, accurate transfer function estimate can be achieved from 3 or 2 min sections of data. Transfer function estimates from 1 min sections tend to overestimate gain and coherence.

Transfer function analysis has been performed during a wide variety of interventions, including quiet resting [12,17,29], standing [30] head upright tilt [27,28], repeated squatting [15] and lower body negative pressure [7,27]. Arteriolar vasoconstriction can interfere with measurement of the plethysmogram [21–24] and can be caused by low ambient temperature, sympathetic activity or vascular abnormalities. Cold fingers can interfere with the measurement and can even result in no outcome [31,32]. When graded vasoconstriction with phenylephrine is performed, accurate measurement is possible with the “physiocal” mechanism [23,24]. However, some groups report switching off the “physiocal” calibrations before recording time series for transfer function analysis [7,29,33], to permit uninterrupted data collection. Other groups have reported turning off the “physiocal” calibration when calibrations occur at intervals greater than 30 s [5,34] for the same reason. Some groups do not report whether or not calibrations were turned off [6,8,11,35]. Based on the results of the studies described above, it would appear that to ensure accurate transfer function estimates, the experimenters should ensure that the subjects hands are sufficiently warm, that the subject has no vascular abnormalities, and that the physiocal calibration mechanism should remain on if the protocol involves interventions that elicit a strong sympathetic response (e.g. vasopressor agents such as phenylephrine and epinephrine, cold pressor testing, lower body negative pressure, etc.)

Although “physiocal” episodes have a very detrimental effect on transfer function estimates using continuous waveform analysis, the effects are minimal when beat-by-beat mean waveforms are used, and “physiocal” episodes replaced with linear interpolation. Therefore, the most effective way to minimise the effect of “physiocal” episodes is to use the transfer function of the beat-by-beat mean of blood pressure and cerebral blood flow and to replace “physiocal” episodes with linear interpolation, rather than using continuous BP and TCD waveforms.

Similarly, loss of TCD signal can also have a major effect of transfer function accuracy. As with “physiocal” episodes, the best approach is to use beat-by-beat mean signals for transfer function estimates, and replace lost data using interpolation, rather than using continuous waveform signals. All frequency bands above 0.07 Hz were significantly affected by even relatively short segments of data loss, whereas the 0.03–0.07 Hz band was relatively unaffected even by 10 s segments of data loss. This is because the 0.03–0.07 Hz band relates to periods of 14.3–33.3 s, therefore shorter data loss segments will have a lesser effect.

In a similar study by Eames et al. [36], the authors examined the effect of ectopic heart beats on cerebral autoregulation measures. The results showed that removal of ectopic heart beats by linear interpolation reduced gain and coherence in all frequency bands, when compared with transfer function estimates with ectopic beats included. This happened because ectopic heart beats cause spikes in both MAP and CBFV signals, which would increase power in all frequency bands. In contrast, our results showed that gain and coherence were reduced by

adding “physiocal”, because “physiocal” only affect the blood pressure signal. The same is true of replacing segments of CBFV data with linear interpolation. In either case, estimates of gain and phase from data with segments replaced by linear interpolation should not be trusted unless the value of squared coherence remains high, as this indicates that a large fraction of CBFV variability is still related to fluctuations in MAP. Squared coherence cut-offs of 0.4 [37] and 0.5 [29,38] have been used in previous studies.

The averaged results from 3 and 2 min data recordings correlate well with 5 min transfer function estimates. Gain and coherence estimates from 1 min averaged recordings did not significantly differ in the 0.03–0.07 Hz and 0.07–0.15 Hz frequency bands, but were significantly higher in the 0.15–0.3 Hz and 0.3–0.5 Hz bands. Also, phase was not significantly different in any frequency band. The use of shorter time series with Welch’s method results in a reduction in frequency resolution, while permitting a higher degree of averaging and a reduction in variance, i.e. there is a trade-off between variance reduction and resolution. With shorter time series, greater frequency resolution can be achieved by using zero-padding. However, this was not used here. For assessment of cerebral autoregulation, a degree of reduced frequency resolution is acceptable, because most researchers have analysed gain, phase and coherence in relatively wide frequency bands, e.g. 0.03–0.07 Hz, 0.07–0.15 Hz, etc. For shorter time series, alternative techniques such as autoregressive moving average (ARMA) modelling or cross-correlation methods should also be considered for assessment of cerebral autoregulation.

A limitation of this study is that we analysed only the effect of the “physiocal” signal interruptions on transfer function accuracy. The artificial “physiocal” episodes we used in this study did not affect the mean ABP levels, whereas real “physiocal” episodes alter the ABP set-point [39]. This limitation may be overcome in future work by the simultaneous use of two Finapres devices, one with “physiocal” turned on, and one with “physiocal” turned off. This would allow for analysis of the effect of set-point adjustment on transfer function analysis. Also, the artificial “physiocal” episodes in this study were all 3 beats long. Actual “physiocal” episodes can vary in length and number of steps. We chose to mimic a 3 beat duration “physiocal” as this would be the typical length “physiocal” during normal measurement procedures. Longer duration “physiocal” episodes only occur when the signal quality is deteriorating, and transfer function estimates would not be reliable in any case.

5. Conclusion

In conclusion, the presence of “physiocal” episodes and/or TCD signal loss have a detrimental effect on transfer function analysis when estimated from complete time series waveforms, particularly in frequency bands greater than 0.07 Hz. By estimating transfer function from beat-by-beat ABP and CBFV values and replacing “physiocal” episodes or data loss by linear interpolation, significantly more reliable results are achieved. The “physiocal” calibration system should only be switched off if the subjects’ fingers are sufficiently warm, and if the testing protocol does not elicit a sympathetic response. Otherwise, only beat-by-beat data should be used when the interval between “physiocal” episodes is greater than 30 s. Accurate transfer function estimates can be achieved in the 0.03–0.07 Hz band using beat-by-beat data, as long as sections of data loss are less than 10

s. At frequencies between 0.07–0.5 Hz, transfer function estimates become unreliable with 5 s of data loss every 40 s. 2 s data loss only affects frequency bands above 0.15 Hz. Finally, accurate transfer function assessment of autoregulatory function can be achieved from time series as short as 1 min, although gain and coherence tend to be overestimated at higher frequencies.

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Conflict of interest

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Artificial servo correction

Fig. 1. Example artificial “physioical” servo calibration. Step 1 is the mean of the three replaced beats, and step 2 and step 3 are mean ± 5 mm Hg, respectively.

Fig. 2.

The effect of “physiocal” episodes on beat-by-beat mean calculations. The presence of “physiocal” episodes creates a swing of approximately 10 mm Hg over 4 beats in the beat-by-beat mean arterial pressure (MAP) signal. Removing the “physiocal” data in the beat-by-beat signal using linear interpolation is much more representative of the true signal.

Fig. 3.
Frequency response of “physiocal” and linear interpolation.

Fig. 4. Effect of “physiocal” episodes on transfer function analysis of continuous waveforms (left), and transfer function estimates of beat-by-beat mean waveforms, with “physiocal” episodes replaced by linear interpolation. Data are presented as the group mean values.

Fig. 5. Effect of "physiocal" episodes on transfer function analysis of continuous waveforms (left), and transfer function estimates of beat-by-beat mean waveforms, with "physiocal" episodes replaced by linear interpolation. Data are presented as the mean difference $\pm$ standard deviations of transfer function estimates before and after "physiocal" episodes are added. * $p < 0.05$.

Fig. 6.

Transfer function estimates of beat-by-beat data with 2 and 5 s of data removed from CBFV time series by linear interpolation. Data are presented as mean individual difference $\pm$ standard deviation of individual difference. *Significant difference (repeated measures). Missing data has little effect below 0.07 Hz.

Fig. 7.

Transfer function estimates of beat-by-beat data with 20 s of data removed by from CBFV time series linear interpolation. Data are presented as mean individual difference $\pm$ standard deviation of individual difference. *Significant difference (repeated measures).

Table 1

Summary of Welch algorithm parameters used for transfer function analysis.

Time series length (s)	Window length (s)	Data points per window	Overlap	Spectral resolution (Hz)
Complete waveform				
300	100	100,000	66.67	0.01
180	60	60,000	66.67	0.017
120	45	45,000	66.67	0.022
60	30	30,000	66.67	0.033
Beat-by-beat waveform				
300	100	1000	66.67	0.01

Table 2

Baseline transfer function estimates from continuous and beat-by-beat waveforms in all frequency bands. mm Hg = millimeters of mercury. Data are presented as mean individual difference $\pm$ standard deviation of individual difference.

	Continuous waveform	Beat-by-beat waveform	R^2
Gain (%/mm Hg)			
0.03–0.07 Hz	1.32 $\pm$ 0.58	1.32 $\pm$ 0.58	0.99
0.07–0.15 Hz	1.94 $\pm$ 0.67	1.91 $\pm$ 0.67	0.99
0.15–0.3 Hz	2.14 $\pm$ 0.71	2.12 $\pm$ 0.66	0.95
0.3–0.5 Hz	2.05 $\pm$ 0.71	2.14 $\pm$ 0.66*	0.85
Phase (°)			
0.03–0.07 Hz	41.6 $\pm$ 30.7	42.1 $\pm$ 31.2	0.99
0.07–0.15 Hz	34.5 $\pm$ 24.0	34.1 $\pm$ 22.2	0.91
0.15–0.3 Hz	13.5 $\pm$ 20.3	13.0 $\pm$ 20.2	0.84
0.3–0.5 Hz	5.7 $\pm$ 24.0	–1.25 $\pm$ 14.6*	0.66
Coherence			
0.03–0.07 Hz	0.53 $\pm$ 0.16	0.52 $\pm$ 0.16*	0.99
0.07–0.15 Hz	0.64 $\pm$ 0.19	0.62 $\pm$ 0.19*	0.99
0.15–0.3 Hz	0.66 $\pm$ 0.19	0.65 $\pm$ 0.19	0.95
0.3–0.5 Hz	0.60 $\pm$ 0.21	0.60 $\pm$ 0.21	0.89

* Significant difference (repeated measures).

Table 3

Transfer function estimates from 5 min, 3 min, 2 min and 1 min sections of data in all frequency bands. mm Hg= millimeters of mercury. Data are presented as mean individual difference $\pm$ standard deviation of individual difference.

	5 min	3 min means	R^2	2 min means	R^2	1 min means	R^2
Gain (%/mm Hg)							
0.03–0.07 Hz	1.32 $\pm$ 0.58	1.34 $\pm$ 0.57	0.86	1.37 $\pm$ 0.57	0.84	1.43 $\pm$ 0.71	0.66
0.07–0.15 Hz	1.94 $\pm$ 0.67	1.94 $\pm$ 0.66	0.94	1.93 $\pm$ 0.66	0.91	2.1 $\pm$ 0.70	0.72
0.15–0.3 Hz	2.15 $\pm$ 0.71	2.17 $\pm$ 0.70	0.96	2.18 $\pm$ 0.70	0.93	2.36 $\pm$ 0.83*	0.75
0.3–0.5 Hz	2.05 $\pm$ 0.71	2.07 $\pm$ 0.66	0.97	2.10 $\pm$ 0.66	0.92	2.30 $\pm$ 0.78*	0.79
Phase ($^{\circ}$)							
0.03–0.07 Hz	41.6 $\pm$ 30.7	42.5 $\pm$ 27.1	0.60	43.0 $\pm$ 21.5	0.67	37.5 $\pm$ 26.1	0.45
0.07–0.15 Hz	34.5 $\pm$ 24.0	33.2 $\pm$ 19.0	0.72	37.0 $\pm$ 19.9	0.75	36.8 $\pm$ 20.4	0.61
0.15–0.3 Hz	13.5 $\pm$ 20.3	15.3 $\pm$ 17.9	0.82	16.0 $\pm$ 18.1	0.78	15.3 $\pm$ 18.2	0.73
0.3–0.5 Hz	5.7 $\pm$ 24.0	5.0 $\pm$ 23.0	0.80	5.1 $\pm$ 25.0	0.87	6.0 $\pm$ 20.23	0.76
Coherence							
0.03–0.07 Hz	0.53 $\pm$ 0.16	0.53 $\pm$ 0.15	0.74	0.55 $\pm$ 0.15	0.70	0.57 $\pm$ 0.14	0.38
0.07–0.15 Hz	0.64 $\pm$ 0.19	0.64 $\pm$ 0.19	0.93	0.64 $\pm$ 0.19	0.92	0.67 $\pm$ 0.15	0.78
0.15–0.3 Hz	0.67 $\pm$ 0.19	0.67 $\pm$ 0.17	0.94	0.67 $\pm$ 0.16	0.92	0.70 $\pm$ 0.14*	0.82
0.3–0.5 Hz	0.60 $\pm$ 0.21	0.59 $\pm$ 0.19	0.94	0.59 $\pm$ 0.17	0.86	0.63 $\pm$ 0.14	0.76

* Significant difference (repeated measures).