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PAPER

# A comparison of the time constant of the cerebral arterial bed using invasive and non-invasive arterial blood pressure measurements

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## Abstract

*Objective*: The time constant of the cerebral arterial bed ($\tau$), which is an index of brain haemodynamics, can be estimated in patients using continuous monitoring of arterial blood pressure (ABP), transcranial Doppler cerebral blood flow velocity (CBFV) and intracranial pressure (ICP) if these measures are available. But, in some clinical scenarios invasive measurement of ABP is not feasible. Therefore, in this study we aimed to investigate whether invasive ABP can be replaced with non-invasive ABP, monitored using the Finapres photoplethysmograph (fABP). *Approach*: Forty-six recordings of ICP, ABP, fABP, and CBFV in the right and left middle cerebral arteries were performed daily for approximately 30 min in 10 head injury patients. Two modelling approaches (constant flow forward [CFF, pulsatile blood inflow and steady blood outflow] and pulsatile flow forward [PFF, where both blood inflow and outflow are pulsatile]) were applied to estimate $\tau$ using either invasive ABP ($\tau_{CFF}$, $\tau_{PFF}$) or non-invasive ABP ($f\tau_{CFF}$, $f\tau_{PFF}$). *Main results*: Bland–Altman analysis showed quite poor agreement between the $f\tau$ and $\tau$ methods of estimation. The $f\tau$ method produced significantly higher values than the $\tau$ method when calculated using both the CFF and PFF models ($p < .001$ for both). The correlation between $f\tau_{CFF}$ and $\tau_{CFF}$ was moderately high ($r_s = 0.63$; $p < .001$), whereas that between $f\tau_{PFF}$ and $\tau_{PFF}$ was weaker ($r_s = 0.40$; $p = .009$). *Significance*: Our results suggest that using non-invasive ABP for estimation of $\tau$ is inaccurate in head injury patients.

## 1. Introduction

The time constant of the cerebral arterial bed ($\tau$) is an ultrasound–based index which estimates the time needed to fill the cerebral arterial bed with blood after heart constriction. The $\tau$ index reflects the interplay between cerebrovascular resistance (CVR) and compliance of the cerebral arterial bed ($C_a$), and is independent of the unknown cross-sectional area of the insonated cerebral artery (Kasprowicz *et al* 2012a, 2012c). An estimate of the amplitude of pulsatile changes in cerebral arterial blood volume (Amp ($\Delta C_aBV$)) is needed to calculate $C_a$. Currently, two mathematical models for continuous $\Delta C_aBV$ assessment have been proposed (Kim *et al* 2009, Uryga *et al* 2019b). The first presumes that cerebral blood outflow has lower pulsatility than cerebral blood inflow, and therefore that cerebral blood outflow may be approximated by average cerebral arterial inflow. This approach is referred to as the continuous flow forward (CFF) model. The second model, known as the pulsatile flow forward (PFF) model, recognizes that cerebral blood outflow is dependent on the impedance of the afferent part of the vascular system. The PFF model therefore expresses

cerebral blood outflow as the ratio of arterial blood pressure (ABP) to CVR. Thus, two alternative estimation methods of (a product of $C_a$ and CVR) are possible ($\tau_{CFF}$, $\tau_{PFF}$).

The $\tau$ index (estimated using either the CFF model or PFF model) has been widely applied in studying cerebral haemodynamics in the presence of head injuries (Calviello *et al* 2019, Puppo *et al* 2019), hydrocephalus (Capel *et al* 2014), severe carotid occlusive disease (Kasprowicz *et al* 2012b), and subarachnoid haemorrhages (Kasprowicz *et al* 2012a), as well as in both healthy volunteers (Kasprowicz *et al* 2012c, Uryga *et al* 2019a) and experimental studies (Czosnyka *et al* 2012). It has also been found that $\tau$ is correlated with severity of artery derangement in carotid stenosis (Kasprowicz *et al* 2012b) and that it becomes shorter during vasospasm in patients after a subarachnoid haemorrhage (Kasprowicz *et al* 2012a).

Ragland and Lee (2016) note that, in situations such as acute brain injury, stroke or intracerebral haemorrhage, where expansion in intracranial volume is observed, $\tau$ can be estimated in patients by continuously monitoring ABP, cerebral blood flow velocity (CBFV) and intracranial pressure (ICP). In clinical practice, ABP is assessed using a radial or brachial artery catheter and ICP is tracked via a parenchymal or ventricular intracranial probe, thus both signals are measured in an invasive manner. However, in some clinical scenarios where characterization of cerebral haemodynamics can be beneficial, invasive ABP measurements are not required. Such scenarios include infusion testing (Czosnyka *et al* 2016) and overnight monitoring of ICP (Liew *et al* 2019) in patients suffering from hydrocephalus. Moreover, difficulties in placing arterial lines and the possibility of infection during invasive monitoring make non-invasive ABP monitoring a promising alternative for critical care and anaesthesia scenarios (Chatterjee *et al* 2010).

Non-invasive measurement of ABP using the Finapres device has been compared with invasive ABP when making resting measurements and has indicated that the accuracy and precision of the device is adequate for tracking changes in blood pressure (Stokes *et al* 1991, Silke *et al* 1994, Imholz *et al* 1998). Also, a study of the possibility of assessing dynamic cerebral autoregulation using slow waves of ABP derived using the Finapres device has shown good agreement between non-invasive and invasive autoregulation indices (Lavinio *et al* 2007, Petersen *et al* 2014). Additionally, a cerebrovascular reactivity index has been shown to be sensitive enough to distinguish between passive and active reactivity (Kasprowicz *et al* 2010).

Despite the above work, there have been no tests of whether invasive ABP measurement can be replaced by non-invasive ABP measurement in assessing pulsatile changes in cerebral blood volume. The present study therefore aimed to investigate whether non-invasive ABP, measured by the Finapres photoplethysmograph, can achieve results comparable to those of invasive ABP in the estimation of $\tau$.

## 2. Material and methods

### 2.1. Subjects

Data for 10 patients hospitalized due to severe head injury in 1992 and managed in the Neurosurgical Critical Care Annexe of Addenbrooke's Hospital, Cambridge, UK were retrospectively analysed. The same set of data was previously used for a comparison of autoregulation assessment and cerebrovascular pressure reactivity in the low frequency range between invasive and non–invasive ABP (Lavinio *et al* 2007, Kasprowicz *et al* 2010). All subjects were adults (age $\geqslant$ 18 years). The patients were treated following the cerebral perfusion pressure/intracranial pressure (CPP/ICP) methodology later formalized as a set protocol (Menon 1999). Data were anonymized and computer–recorded during standard daily assessment of autoregulation after head injury. Blood pressure (direct continuous), ICP (direct, continuous) and transcranial Doppler (daily intermittent monitoring) were routine clinical methods for monitoring of traumatic brain injury (TBI) patients in the Annexe. The Neurosurgical Intensive Care User's Committee accepted the use of intermittent non-invasive Finapres blood pressure monitoring without the necessity of obtaining individual consent from patients' next of kin.

### 2.2. Data acquisition

Forty-six ABP, ICP and CBFV recordings in both brain hemispheres were analysed. ABP was monitored invasively using an arterial line positioned in the radial artery and a pressure transducer (Baxter Healthcare Cardiovascular Group). The average number of recordings per patient (calculated as a weighted average) was 5. Non-invasive ABP (fABP) was measured using the Finapres device (Finapres 2300, Ohmeda, Englewood, CO), which is a servo-controlled photoplethysmograph. The measurement principle is based on 'volume–clamping' a finger with a cuff, adjusting its pressure to maintain a signal of infrared amplitude at a constant level (Stokes *et al* 1991). Patients' hands were placed at heart level during monitoring. ICP was monitored invasively using a Codman parenchymal probe (Johnson & Johnson Medical, Raynham, Massachusetts). CBFV measurements were obtained continuously in the left ($CBFV_L$) and right ($CBFV_R$) middle cerebral arteries (MCA) by transcranial Doppler ultrasonography (TCD) (DWL-MultiDop, DWL,

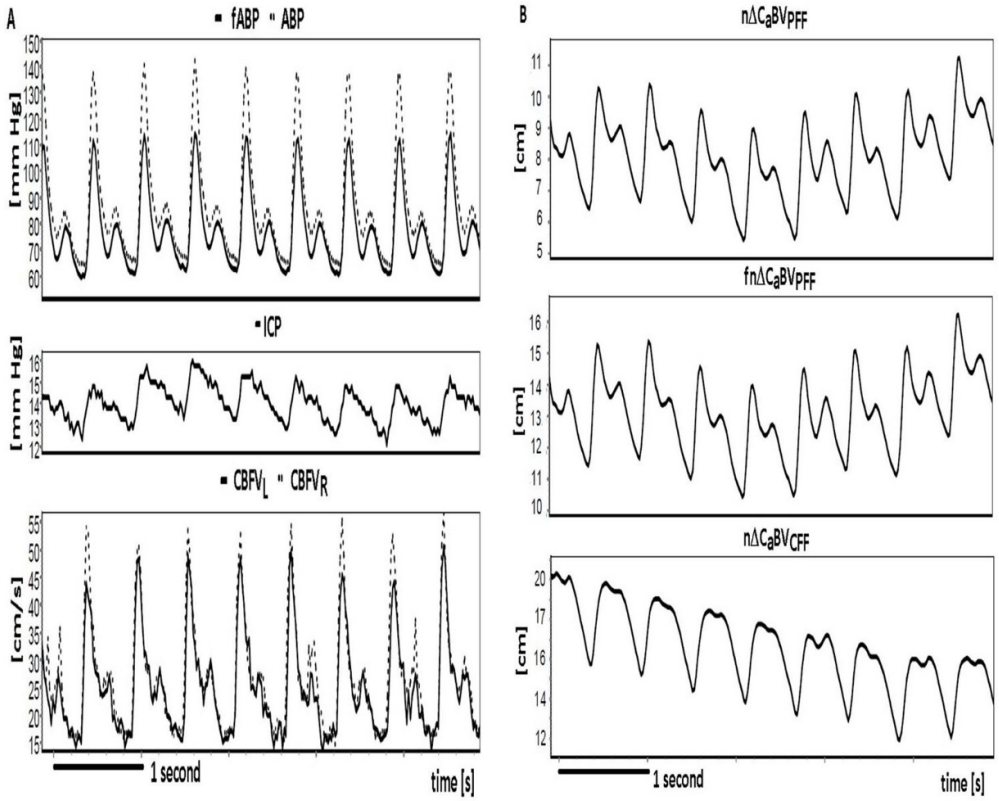


**Figure 1.** (A) Time trends of pulsatile changes in intracranial pressure (ICP), invasive arterial blood pressure (ABP), non-invasive arterial blood pressure (fABP), and cerebral blood flow velocity in the left and right middle cerebral arteries ($CBFV_L$ and $CBFV_R$). (B) Normalised pulsatile changes in cerebral arterial blood volume, calculated using the continuous flow forward model ($n\Delta C_aBV_{CFF}$) and the pulsatile flow forward model using invasive ABP ($n\Delta C_aBV_{PFF}$) and non-invasive ABP ($fn\Delta C_aBV_{PFF}$) in a severe head injury patient.

Compumedics Germany GmbH, Singen, Germany) using 2 MHz probes. CPP was calculated as the difference between ABP and ICP. Sequential measurements for the same patients were taken with a minimum 24-hour gap, thus recordings could be analysed as independent monitoring sessions. Data were recorded with a sampling frequency of 50 Hz using the Intensive Care Monitor (ICM+) system (Cambridge Enterprise Ltd, Cambridge, UK). Examples of time trends of the monitored physiological signals are presented in figure 1(A).

### 2.3. Signal analysis

The signals recorded were analysed using algorithms embedded in the ICM+ system and with a custom written program in MATLAB® (MathWorks®, Natick, USA). Artefacts, including self–calibration intervals in fABP signals, were identified by visual inspection, marked manually and ultimately removed. Further analysis was performed on the representative parts of signals. ABP, fABP, ICP, $CBFV_L$, and $CBFV_R$ samples were averaged over a 10 s window to calculate their mean values.

Linear systems theory was applied to determine whether pulse changes in ABP signals could be detected by Finapres monitoring. We calculated spectral mean coherence and mean values of the transfer gain function between ABP and fABP in the high-frequency range, corresponding to pulse pressure changes (40–140 beats $min^{-1}$; 0.67–2.33 [Hz]). The coherence function assesses how much invasive and non-invasive pressure pulse changes resemble each other (1 = perfect resemblance, 0 = no resemblance). A transfer function gain between ABP and fABP close to 1 reflects similarity in their amplitudes.

The cerebrovascular indices were estimated using a simplified cerebral circulation model (Czosnyka *et al* 1997) and averaged in a 10-second window. Parameters which, by definition, depended on unknown cross-sectional areas of arteries ($S_a$ [$cm^2$]) were normalized and given an 'n' prefix (nCVR, $nC_a$, $n\Delta C_aBV$). Formulas used to calculate the cerebrovascular parameters are discussed in detail elsewhere (Varsos *et al* 2014, Uryga *et al* 2019b). Here, we restrict ourselves to a brief description of previously mentioned parameters.

CVR is the resistance of small cerebral arteries and arterioles, and is defined as the ratio of mean cerebral perfusion pressure (CPP = ABP − ICP) to mean cerebral blood flow (CBF), approximated here by mean CBFV (Czosnyka *et al* 1994):

$$\mathrm{nCVR} = \frac{\mathrm{mean(CPP)}}{\mathrm{mean(CBFV)}} \left[\frac{\mathrm{mmHg}}{\mathrm{cm\ s^{-1}}}\right]. \tag{1}$$

$C_a$ is the compliance of the main cerebral arteries and can be estimated as the ratio of amplitude of normalised cerebral arterial blood volume changes to amplitude of ABP (Carrera *et al* 2011):

$$\mathrm{nC_a} = \frac{\mathrm{Amp}(n\Delta \mathrm{C_aBV})}{\mathrm{Amp(ABP)}} \left[\frac{\mathrm{cm}}{\mathrm{mmHg}}\right]. \tag{2}$$

The CFF model (Kim *et al* 2009) and the PFF model (Uryga *et al* 2019b) can be used to estimate $\mathrm{n\Delta C_aBV}$ during a single cardiac cycle using the following formulas::

$$\mathrm{n\Delta C_aBV}(m)_{\mathrm{CFF}} = \sum_{\mathrm{i}=1}^{\mathrm{m}} (\mathrm{CBFV(i)} - \mathrm{mean(CBFV)})\Delta t[\mathrm{cm}] \tag{3}$$

$$\mathrm{n\Delta C_aBV}(m)_{\mathrm{PFF}} = \sum_{\mathrm{i}=1}^{\mathrm{m}} (\mathrm{CBFV(i)} - \frac{\mathrm{CPP(i)}}{\mathrm{nCVR}})\Delta t[\mathrm{cm}] \tag{4}$$

where $m$ is the number of samples, $t$ is the time interval between two samples, CPP(i) is a sample's cerebral perfusion pressure, CBFV(i) is a sample's CBFV, and mean(CBFV) is the moving-average of CBFV calculated from a window including several previous cardiac cycles (Czosnyka *et al* 2012). Examples of time trends for $\mathrm{n\Delta C_aBV_{CFF}}$ and $\mathrm{n\Delta C_aBV_{PFF}}$ calculated using fABP and ABP in the left hemisphere are presented in figure 1(B).

There are two possible equations for calculating $\mathrm{Amp(n\Delta C_aBV)}$. In the CFF model the pulsatile amplitude of $\mathrm{n\Delta C_aBV}$ is determined using a Fourier transform as the amplitude of the fundamental components of $\mathrm{n\Delta C_aBV_{CFF}}$: $(\mathrm{Amp(n\Delta C_aBV_{CFF}}))$, whereas in the PFF model, in order to account for time delay between CBFV recorded from the cerebral arteries and ABP from a finger, the pulsatile amplitude of $\mathrm{n\Delta C_aBV}$ $(\mathrm{Amp(n\Delta C_aBV_{PFF}}))$ is determined using a formula proposed by Uryga *et al* (2019b): where

$$\mathrm{Amp}(n\Delta \mathrm{C_aBV_{PFF}}) = (\mathrm{Amp(CBFV)} - \frac{\mathrm{Amp(CPP)}}{\mathrm{nCVR}})/2\pi \cdot \mathrm{HR}[\mathrm{cm}] \tag{5}$$

Amp(CBFV) and Amp(CPP) are determined using a Fourier transform as the amplitude of the fundamental components of CBFV and CPP respectively, and HR is heart rate in Hz, calculated as the frequency of the fundamental component of the ABP signal using a Fourier transform.

To test the influence of the time window length used to average CBFV on the pulsatile amplitude of $\mathrm{n\Delta C_aBV_{CFF}}$ the following time periods were used: 3 s, 6 s, 9 s, and 12 s. The optimal time window was chosen based on the highest correlation coefficient between $\tau_{\mathrm{CFF}}$ values calculated using invasive and non-invasive ABP (see table 3).

The $\tau$ index is the time needed to stabilize cerebral blood volume after a change in ABP during a cardiac cycle (Kasprowicz *et al* 2012a) and is defined as the product of $C_a$ and CVR:

$$\tau = n\mathrm{C_a} \cdot \mathrm{nCVR}[\mathrm{s}]. \tag{6}$$

In a scenario where ABP can be monitored invasively and non-invasively, using both the CFF and PFF models, four possible formulas can be used to estimate $\tau$:

$$\tau_{\mathrm{CFF}} = \frac{\mathrm{Amp}(n\Delta \mathrm{C_aBV_{CFF}})}{\mathrm{Amp(ABP)}} \cdot \frac{\mathrm{mean(CPP)}}{\mathrm{mean(CBFV)}}[\mathrm{s}] \tag{7}$$

$$\mathrm{f}\tau_{\mathrm{CFF}} = \frac{\mathrm{Amp}(n\Delta \mathrm{C_aBV_{CFF}})}{\mathrm{Amp(fABP)}} \cdot \frac{\mathrm{mean(fCPP)}}{\mathrm{mean(CBFV)}}[\mathrm{s}] \tag{8}$$

$$\tau_{\mathrm{PFF}} = \frac{(\mathrm{Amp(CBFV)} - \frac{\mathrm{Amp(CPP)}}{\mathrm{mean(CPP)/mean(CBFV)}})/2\pi \cdot \mathrm{HR}}{\mathrm{Amp(ABP)}} \cdot \frac{\mathrm{mean(CPP)}}{\mathrm{mean(CBFV)}}[\mathrm{s}] \tag{9}$$

$$\mathrm{f}\tau_{\mathrm{PFF}} = \frac{(\mathrm{Amp(CBFV)} - \frac{\mathrm{Amp(fCPP)}}{\mathrm{mean(fCPP)/mean(CBFV)}})/2\pi \cdot \mathrm{fHR}}{\mathrm{Amp(fABP)}} \cdot \frac{\mathrm{mean(fCPP)}}{\mathrm{mean(CBFV)}}[\mathrm{s}] \tag{10}$$

**Table 1.** Median values and interquartile ranges ($Q_1$–$Q_3$) of physiological parameters for 46 recordings performed in severe head injury patients.

| Parameter | Median (Q1–Q3) |
|---|---|
| ABP [mm Hg] | 91.76 (87.09–100.85) |
| fABP [mm Hg] | 86.33 (74.07–92.00) |
| Amp(ABP) [mm Hg] | 17.63 (16.06–19.47) |
| Amp(fABP) [mm Hg] | 11.42 (9.51–13.24) |
| $CBFV_L$ [cm $s^{-1}$] | 46.67 (38.64–56.13) |
| $CBFV_R$ [cm $s^{-1}$] | 44.66 (38.57–57.44) |
| Amp($CBFV_L$) [cm $s^{-1}$] | 10.95 (9.64–14.35) |
| Amp($CBFV_R$) [cm $s^{-1}$] | 11.36 (9.80–14.01) |
| HR [beats $min^{-1}$] | 81.56 (68.10–95.03) |
| fHR [beats $min^{-1}$] | 77.84 (68.60–92.31) |
| ICP [mm Hg] | 15.16 (11.50–18.48) |
| CPP [mm Hg] | 77.38 (74.73–82.10) |
| fCPP [mm Hg] | 66.79 (61.57–77.20) |

ABP—invasive arterial blood pressure; fABP—non-invasive arterial blood pressure; Amp(ABP)—amplitude of ABP pulse changes; Amp(fABP)—amplitude of fABP pulse changes; $CBFV_L$—cerebral blood flow velocity in the left middle cerebral artery; $CBFV_R$–cerebral blood flow velocity in the right middle cerebral artery; Amp($CBFV_L$)-amplitude of $CBFV_L$ pulse changes; Amp($CBFV_R$)—amplitude of $CBFV_R$ pulse changes; HR—heart rate, calculated from ABP signals; fHR—heart rate calculated from fABP signals; ICP—intracranial pressure; CPP—cerebral perfusion pressure, calculated using invasive ABP: CPP = ABP–ICP; fCPP—cerebral perfusion pressure, calculated using non-invasive ABP: CPP = fABP–ICP.

where fHR is heart rate in Hz, calculated as the frequency of the fundamental component of the fABP signal using a Fourier transform, fCPP is cerebral perfusion pressure (defined as fCPP = fABP − ICP), and Amp(fCPP) is the amplitude of the fundamental component of the fCPP, determined using a Fourier transform.

### 2.4. Statistical methods

Normality of data distributions was tested using Shapiro–Wilk tests. The hypothesis of normality was rejected for most of the analysed variables and therefore non-parametric methods were used. The criterion for significance was set at $\alpha = .05$. Descriptive statistics are presented as medians (lower quartile–upper quartile). Relationships between pairs of physiological and haemodynamic parameters were assessed using (non-parametric) Spearman's rho correlation coefficients ($r_s$). Bland–Altman assessments of agreement were used to compare the two methods of calculating cerebral hemodynamic indices (using fABP and ABP), non-invasive vs. invasive measurement of arterial blood pressure, and amplitude of arterial blood pressure (fABP vs. ABP, and Amp(fABP) vs. Amp(ABP)). To assess bias and the limits of agreement between methods, approach proposed by Bland and Altman were used whereby a logarithmic transformation is applied for non–normally distributed differences between methods (Bland and Altman 1986, 1999). Mann–Whitney U tests were used to test differences between two physiological variables or cerebral hemodynamic indices. Effect sizes for tests are reported in terms of eta squared ($\eta^2$) values (Fritz *et al* 2012).

## 3. Results

### 3.1. Physiological signals

The median values of physiological parameters are presented in table 1. No significant differences were found between $CBFV_L$ and $CBFV_R$: $z = -0.13$, $p = .897$, or between their amplitudes: Amp($CBFV_L$) vs. Amp($CBFV_R$): $z = 0.33$, $p = .740$. Thus, cerebral haemodynamic parameters were averaged within the left and right hemispheres for further analyses.

### 3.2. Comparison of the fABP and ABP

Mean ABP and its pulse amplitude measured with Finapres were lower than values obtained by direct pressure measurement (see table 1): $z = -3.50$, $p < .001$, and $z = -7.75$, $p < .001$, respectively. The effect size for the difference between the non-invasive and invasive methods of measuring ABP was small ($\eta^2 = 0.14$), whereas for AmpABP the effect size was moderate ($\eta^2 = 0.67$). ABP was strongly correlated with fABP (see figure 2(A)) whereas the correlation between Amp(ABP) and Amp(fABP) was moderate (see figure 2(C)). Statistics resulting from Bland–Altman analyses of agreement between fABP vs. ABP and between Amp(fABP) vs. Amp(ABP) are shown in table 2. The results indicated that, on average, ABP derived from the Finapres was 10.36 mm Hg less than that measured with an invasive arterial line. The difference between the two methods tended to be positive, thus for greater average values of blood pressure the non-invasive method

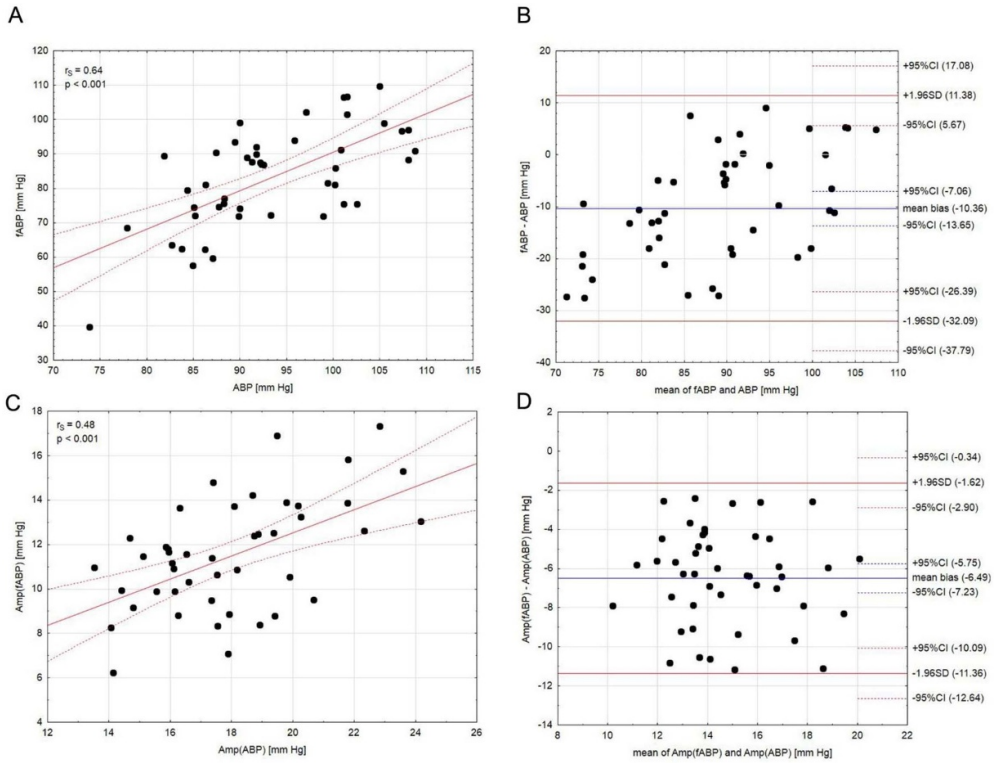


**Figure 2.** Correlations and Bland–Altman plots for arterial blood pressure and amplitude of arterial blood pressure measured non-invasively and invasively: fABP vs. ABP (A) and (B), and Amp(fABP) vs. Amp(ABP) (C) and (D). Regression lines (solid lines) and 95% prediction intervals (dashed lines) are shown in (A) and (C); $r_s$—non-parametric Spearman's rho correlation coefficients. The solid lines in (B) and (D) show bias (upper and lower limits of agreement), whereas dashed lines show 95% confidence intervals for these limits; CI—confidence interval, SD—standard deviation.

produced slightly higher measurements than the invasive method (see figure 2(B)). Amp(fABP) was on average 6.49 mm Hg lower than Amp(ABP). The difference between Amp(fABP) and Amp(ABP) fluctuated around the mean bias but the range between the limits of agreement was wide (see figure 2(D)). Median coherence and the transfer function gain between fABP and ABP calculated within a range of 40–140 beats $min^{-1}$ were 0.90 (0.85–0.96) [a.u.] and 0.78 (0.67–.90) [a.u.] respectively, which implies good linear coupling between fABP and ABP and moderate amplitude attenuation in the frequency range corresponding to pulse pressure changes (see figure 3(A)). The median phase shift (± the interquartile range) between fABP and ABP calculated in the high-frequency range, corresponding to pulse pressure changes (40–140 beats $min^{-1}$; 0.67–2.33 [Hz]), was −1.90° (±10.63°), and the mean (±*SD*) was 0.80° (±8.93°). The observed phase shift was negligible in comparison with no phase shift (0°), which indicates consistency in phases for fABP and ABP. The time delay between pulse waves of these two signals was approximately 4 ms on average (see figure 3(B)).

### 3.3. nCVR calculated using fABP and ABP

The nCVR estimated using non-invasive ABP (fnCVR) was significantly lower than that calculated with invasive ABP (nCVR): 1.41 (1.18–1.76) mm Hg $cm^{-1}$ $s^{-1}$ vs. 1.79 (1.31–2.06) mm Hg $cm^{-1}$ $s^{-1}$; $z = -2.53$, $p = .011$. A small effect size was found for this difference ($\eta^2 = 0.07$). The correlation between fnCVR and nCVR was very strong (see table 2). The mean bias was −0.27 mm Hg $cm^{-1}$ $s^{-1}$) and the range between the limits of agreement was moderate (see table 2). A negative tendency was found for the difference between the fnCVR and CVR methods, with increasing averages for these two methods.

### 3.4. Selection of the optimal moving–average window for $n\Delta C_aBV_{CFF}$ calculation

The results of the method used to select the optimal moving–average window applied to calculate mean CBFV and then used in estimation of the pulsatile amplitude of $n\Delta C_aBV_{CFF}$, are presented in table 3. Based on the mean bias, upper and lower limits of agreement and the $r_s$ between $f\tau_{CFF}$ and $\tau_{CFF}$, a 3 s window was chosen. Given that the median invasive HR was 81.56 (68.10–95.03) [beats $min^{-1}$], the 3 s window involved approximately four previous cardiac cycles.

**Table 2.** Mean values of bias, lower limits of agreement and upper limits of agreement with 95% confidence intervals for non-invasive and invasive methods of arterial blood pressure monitoring and cerebral haemodynamics, according to Bland–Altman statistics, and non-parametric Spearman's rho correlation coefficients ($r_s$).

| Methods | Bias | Lower limit of agreement | Upper limit of agreement | $r_S$ |
|---|---|---|---|---|
| fABP vs. ABP [mm Hg] | −10.36 (−13.65 to −7.06) | −32.09 (−37.79 to −26.39) | 11.38 (5.67–17.09) | 0.64 $p < .001$ |
| Amp(fABP) vs. Amp(ABP) [mm Hg] | −6.49 (−7.23 to −5.75) | −11.36 (−12.64 to −10.09) | −1.62 (−2.90 to −0.34) | 0.48 $p < .001$ |
| fnCVR vs. nCVR [mm Hg/cm/s] | −0.27 (−0.36 to −0.18) | −0.84 (−0.99 to −0.69) | 0.30 (0.15–0.45) | 0.82 $p < .001$ |
| Amp($fn\Delta C_aBV_{PFF}$) vs. Amp($n\Delta C_aBV_{PFF}$) [cm] | 0.08 (0.03–0.13) | −0.24 (−0.33 to −0.15) | 0.41 (0.32–0.50) | 0.91 $p < .001$ |
| ln($fnC_{aCFF}$) vs. ln($nC_{aCFF}$) [a.u.] | 0.51 (0.44–0.58) | 0.07 (−0.05 to 0.18) | 0.95 (0.83–1.07) | 0.81 $p < .001$ |
| ln($fnC_{aPFF}$) vs. ln($nC_{aPFF}$) [a.u.] | 0.91 (0.62–1.20) | −0.92 (−1.43 to −0.42) | 2.75 (2.24–3.25) | 0.45 $p = .003$ |
| $f\tau_{CFF}$ vs. $\tau_{CFF}$ [ms] | 55.72 (40.05–71.40) | −46.55 (−73.70 to −19.39) | 158.00 (130.84–185.15) | 0.63 $p < .001$ |
| ln($f\tau_{PFF}$) vs. ln($\tau_{PFF}$) [a.u.] | 0.85 (0.60–1.10) | −0.72 (−1.16 to −0.29) | 2.42 (1.99–2.86) | 0.40 $p = .009$ |

CFF–continuous flow forward model; PFF—pulsatile flow forward model; fABP and ABP—non-invasive and invasive arterial blood pressure; Amp(fABP) and Amp(ABP)—amplitude of fABP and ABP pulse changes; fnCVR and nCVR—normalised cerebrovascular resistance, calculated using fABP and ABP; Amp($fn\Delta C_aBV_{PFF}$) and Amp($n\Delta C_aBV_{PFF}$)—amplitude of normalised pulse changes in cerebral arterial blood volume, estimated using the PFF model and either fABP or ABP; ln($fnC_{aCFF}$) and ln($nC_{aCFF}$)—natural logarithm of normalised compliance of the cerebral arterial bed, estimated using the CFF model and either fABP or ABP; ln($fnC_{aPFF}$) and ln($nC_{aPFF}$)—natural logarithm of normalised compliance of the cerebral arterial bed, estimated using the PFF model and either fABP or ABP; $f\tau_{CFF}$ and $\tau_{CFF}$—time constant of the cerebral arterial bed, estimated using the CFF model and either fABP or ABP; ln($f\tau_{PFF}$) and ln($\tau_{PFF}$)—natural logarithm of the time constant of the cerebral arterial bed, estimated using the PFF model and either fABP or ABP.

### 3.5. Amp($n\Delta C_aBV_{PFF}$) calculated using fABP and ABP

No significant difference was found between Amp($n\Delta C_aBV_{PFF}$) calculated using fABP: 0.40 ± 0.29 [cm] and ABP 0.35 ± 0.34 [cm]; $z = 1.08$, $p = .282$. Amp($n\Delta C_aBV_{PFF}$) calculated using fABP was very strongly correlated with ABP and the mean bias between methods was negligible (see table 2). Since the ABP signal is not used to calculate Amp($n\Delta C_aBV_{CFF}$; see equation (3)), such a comparison was not performed for the CFF model.

### 3.6. $nC_a$ calculated using fABP and ABP

#### *3.6.1. The CFF model.*

A significant difference was found between $nC_{aCFF}$ estimated using non-invasive ABP and $nC_{aCFF}$ estimated using invasive ABP: ($fnC_{aCFF}$: 0.14 (0.11–0.18) [cm/mm Hg] vs. $nC_{aCFF}$: 0.08 (0.07–0.11) [cm/mm Hg]; $z = 5.49$, $p < .001$). This difference had a moderate effect size: $\eta^2 = 0.33$, and $fnC_{aCFF}$ correlated strongly with $nC_{aCFF}$ (see figure 4(A)). The range of agreement was moderately wide and $fnC_{aCFF}$ was on average 1.66 times greater than $nC_{aCFF}$ (see table 2 and figure 4(B)).

#### *3.6.2. The PFF model.*

For the PFF model, $nC_{aPFF}$ estimated using non-invasive ABP was significantly higher than its equivalent calculated using invasive ABP: ($fnC_{aPFF}$: 0.06 (0.04–0.09) [cm/mm Hg] vs. $nC_{aPFF}$: 0.02 (0.01–0.04) [cm/mm Hg]; $z = 5.70$, $p < .001$). A large effect size was observed for this difference: $\eta^2 = 0.36$. The correlation between $fnC_{aPFF}$ and $nC_{aPFF}$ was moderate (see figure 4(C)). The mean ratio of $fnC_{aPFF}$ to $nC_{aPFF}$ was 2.49, as shown in table 2 and figure 4(D).

### 3.7. Comparison of fτ and τ

Median values of fτ and τ calculated using the CFF and PFF models are shown in table 4.

#### *3.7.1. The CFF model.*

Calculation of $f\tau_{CFF}$ using non-invasive ABP was significantly higher than $\tau_{CFF}$ estimated using invasive ABP (see table 4), a large effect size being observed for this difference: $\eta^2 = 0.41$. Also, $f\tau_{CFF}$ and $\tau_{CFF}$ were

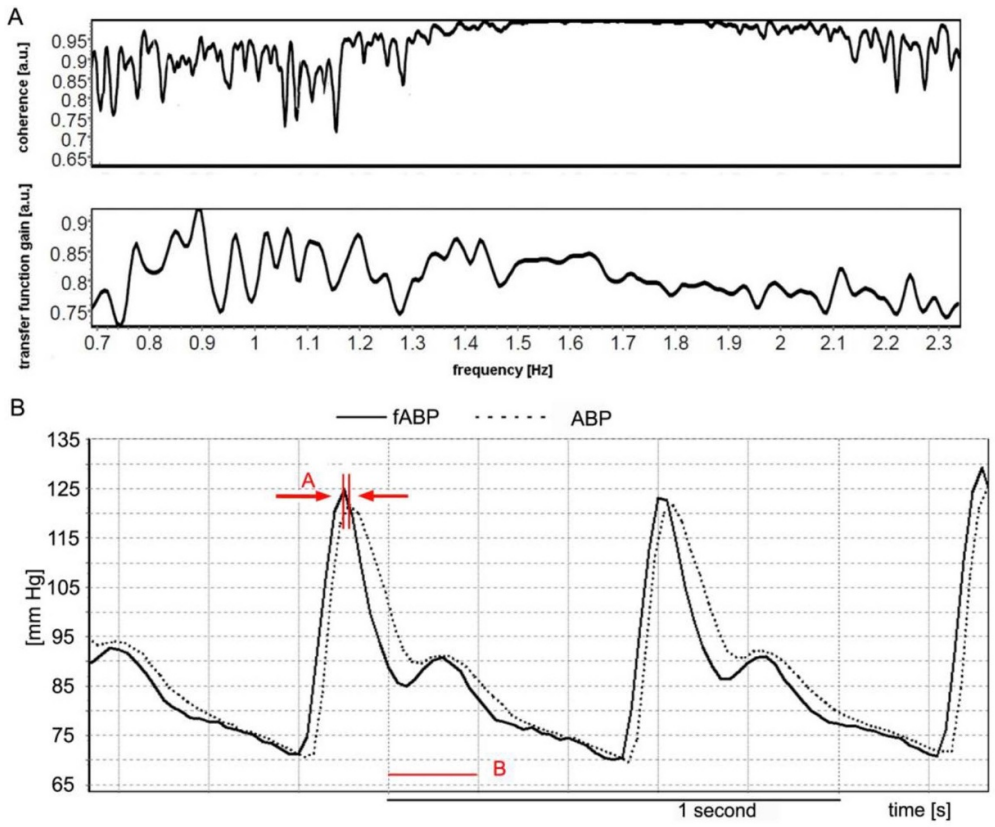


**Figure 3.** (A) Examples of mean coherence and mean transfer function gain calculated between invasive arterial blood pressure (ABP, input) and non-invasive arterial blood pressure (fABP, output) in the high-frequency range (40–140 beats per minute; 0.67–2.33 Hz). (B) An example of the time delay between pulse waves of ABP and fABP: A—time lag between ABP and fABP equals 10 ms; B—a single unit on the axis scale equals 200 ms.

**Table 3.** Bland–Altman statistics for the difference between the time constant of the cerebral arterial bed estimated using the continuous flow forward model (CFF) and either non-invasive arterial blood pressure ($f\tau_{CFF}$) or invasive blood pressure ($\tau_{CFF}$). Results are presented as means with 95% confidence intervals and expressed in ms; $r_s$ non-parametric Spearman's rho correlation coefficients for relationships between $f\tau_{CFF}$ and $\tau_{CFF}$.

| Moving–average time window [s] | Bias | Lower limit of agreement | Upper limit of agreement | $r_S$ |
|---|---|---|---|---|
| 3 | 55.72 (40.05–71.40) | −46.55 (−73.70 to −19.39) | 158.00 (130.84–185.15) | 0.63 $p < .001$ |
| 6 | 56.42 (39.88–72.97) | −50.22 (−78.87 to −21.57) | 163.07 (134.42–191.72) | 0.58 $p < .001$ |
| 9 | 56.13 (38.45–71.80) | −51.08 (−79.97 to −22.20) | 161.34 (132.45–190.23) | 0.54 $p < .001$ |
| 12 | 54.78 (38.10–71.45) | −51.44 (−80.33 to −22.55) | 161.00 (132.11–189.88) | 0.59 $p < .001$ |

strongly correlated (see figure 5(A)). There was a substantial difference in bias between $f\tau_{CFF}$ and $\tau_{CFF}$, Bland–Altman analysis showing that on average $f\tau_{CFF}$ was 55.72 [ms] greater than $\tau_{CFF}$ (see figure 5(B)).

*3.7.2. The PFF model.*

A significant difference was found between $f\tau_{PFF}$ and $\tau_{PFF}$ (see table 3), and the effect size for this difference was large: $\eta^2 = 0.46$. There was a moderate but significant correlation between $f\tau_{PFF}$ and $\tau_{PFF}$ (see figure 5(C)). The range between the lower and upper limits of agreement was wide. The mean ratio of $f\tau_{PFF}$ to $\tau_{PFF}$ was 2.34, as shown in figure 5(D).

*3.7.3. The CFF model vs. the PFF model.*

Comparison of the CFF and PFF models showed that $\tau_{CFF}$ was significantly higher than $\tau_{PFF}$, and that $f\tau_{CFF}$ was significantly higher than $f\tau_{PFF}$, see table 4. The effect size for the difference between $\tau_{CFF}$ and $\tau_{PFF}$ was

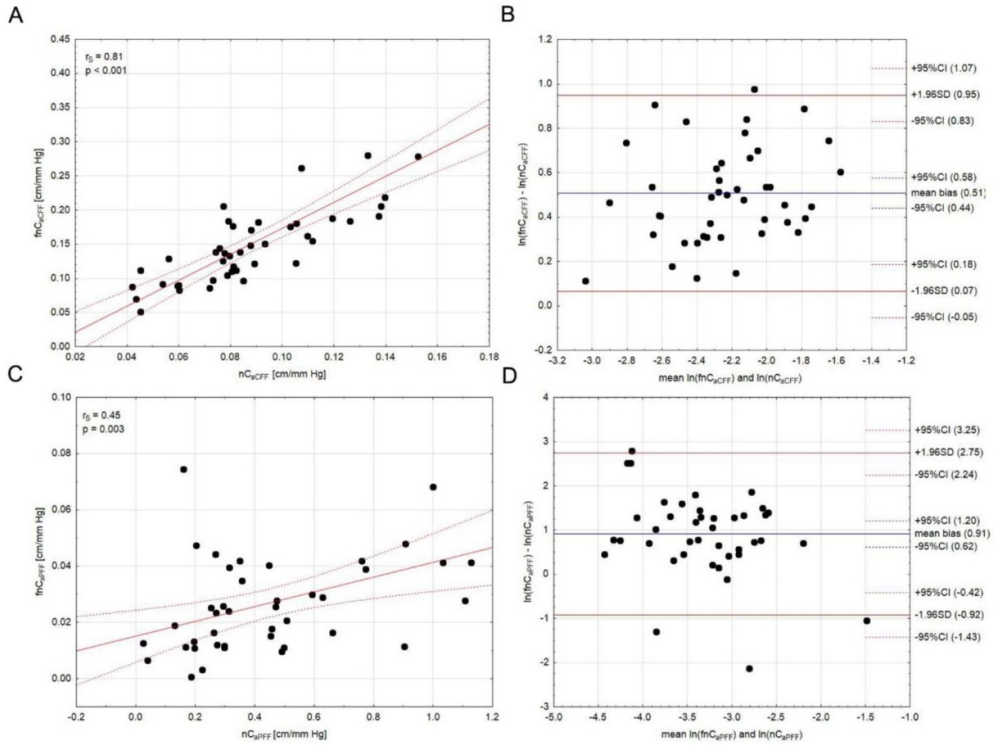


**Figure 4.** Correlations and Bland–Altman plots for normalised compliance of the cerebral arterial bed assessed using non-invasive and invasive ABP and the continuous flow forward model: $fnC_{aCFF}$ vs. $nC_{aCFF}$ (A) and (B), and the pulsatile flow forward model: $fnC_{aPFF}$ vs. $nC_{aPFF}$ (C) and (D). Regression lines (solid lines) and 95% prediction intervals (dashed lines) are shown in (A) and (C); $r_s$—non-parametric Spearman's rho correlation coefficients. The solid lines in (B) and (D) show bias (upper and lower limits of agreement), whereas dashed lines show 95% confidence intervals for these limits; CI—confidence interval, SD—standard deviation.

**Table 4.** Median values (lower quartile—upper quartile) of the time constant of the cerebral arterial bed, calculated using either the continuous flow forward (CFF) model or the pulsatile flow forward (PFF) model and non-invasive ABP ($f\tau_{CFF}$, $f\tau_{PFF}$) or invasive ABP ($\tau_{CFF}$, $\tau_{PFF}$).

| | Parameter | | *z*; *p*–value |
|---|---|---|---|
| | $f\tau_{CFF}$ [ms] | $\tau_{CFF}$ [ms] | |
| | 197.96 (151.08–238.15) | 145.40 (104.52–182.63) | $z = 3.92$; $p < .001$ |
| | $f\tau_{PFF}$ [ms] | $\tau_{PFF}$ [ms] | |
| | 93.30 (58.25–112.75) | 43.48 (10.45–18.26) | $z = 4.33$; $p < .001$ |
| *z*; *p*-value | $z = 6.07$; $p < .001$ | $z = 7.65$; $p < .001$ | |

*z* – non-parametric Mann–Whitney test statistic.

very large ($\eta^2 = 0.68$), whereas that for the difference between $f\tau_{CFF}$ and $f\tau_{PFF}$ was smaller but still large ($\eta^2 = 0.40$).

## 4. Discussion

Our results demonstrated significant differences in τ calculated using fABP and ABP regardless of the model used for estimation. Although a moderately strong, positive relationship was found between $f\tau_{CFF}$ and $\tau_{CFF}$ ($r_s = 0.63$), a Bland–Altman analysis showed a significant discrepancy between these two methods. Based on limits of agreement, $f\tau_{CFF}$ was lower than $\tau_{CFF}$ by 47 ms (lower limit) and exceeded $\tau_{CFF}$ by 158 ms (upper limit) for most measurements. The scatter around the observed bias was substantial, thus the agreement between the two methods was rather poor. Correlational analysis indicated a moderate association between $f\tau_{PFF}$ and $\tau_{PFF}$ ($r_s = 0.40$). Moreover, Bland–Altman analysis showed that, on average, $f\tau_{PFF}$ was 2.34 times greater than $\tau_{PFF}$. When expressed as a mean ratio, there was a wide range between the upper and lower limits of agreement for $f\tau_{PFF}$ and $\tau_{PFF}$, illustrating weak agreement between the two methods.

The τ index represents the joint dependency of $C_a$ and CVR (Czosnyka *et al* 2012). While fnCVR was lower than nCVR, the size of this effect was trivial. On the other hand, fnCa was significantly higher than $nC_a$

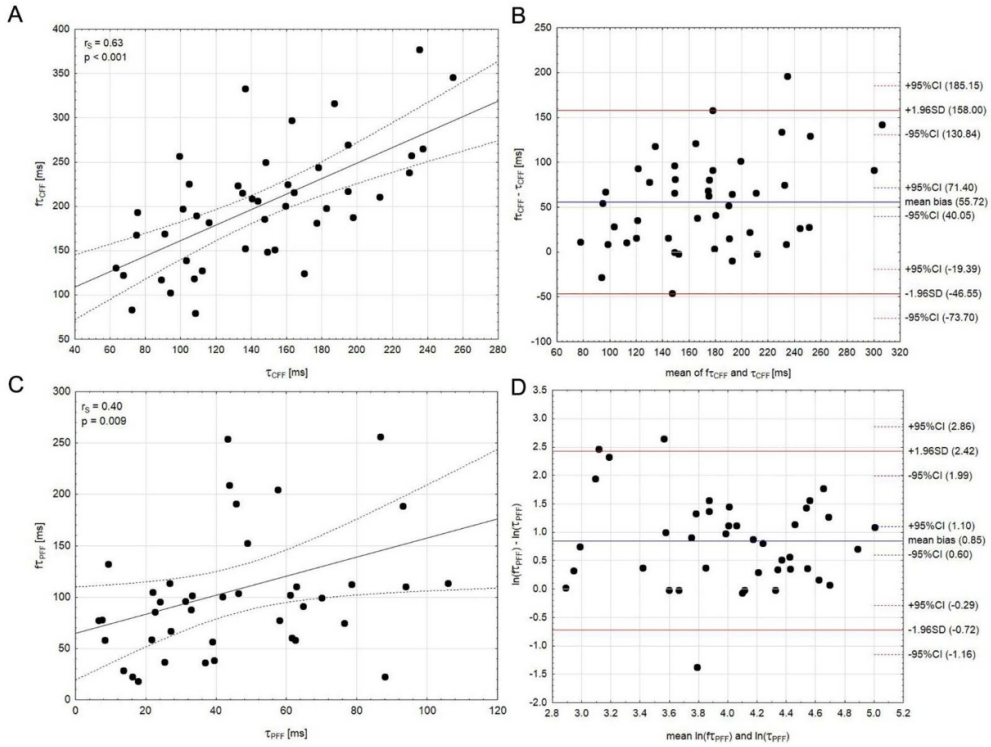


**Figure 5.** Correlations and Bland–Altman plots for the time constant of the cerebral arterial bed assessed using non-invasive and invasive ABP and the continuous flow forward model: $f\tau_{CFF}$ vs. $\tau_{CFF}$ (A) and (B), and the pulsatile flow forward model: $f\tau_{PFF}$ vs. $\tau_{PFF}$ (C) and (D). Regression lines (solid lines) and 95% prediction intervals (dashed lines) are shown in (A) and (C); $r_s$—non-parametric Spearman's rho correlation coefficients. The solid lines in (B) and (D) show bias (upper and lower limits of agreement), whereas dashed lines show 95% confidence intervals for these limits; CI—confidence interval, SD—standard deviation.

when calculated using either the CFF model or the PFF model. Similarly, fτ was significantly higher than τ for both the CFF and PFF models.

Looking more deeply into the definition of $nC_a$, this is estimated as the ratio between the pulse amplitude of changes in normalized cerebral arterial blood volume and the amplitude of arterial blood pressure. When the PFF model was applied, we found no significant difference between $Amp(n\Delta C_aBV_{PFF})$ estimated using fABP and ABP. In the case of the CFF model, the ABP signal does not influence $Amp(n\Delta C_aBV_{CFF})$ as it is not used in its calculation (see equation (3)). Thus, the differences in τ and fτ are mainly due to differences in Amp(fABP) and Amp(ABP), regardless of the model used to estimate $nC_a$ and then τ. A coherence function demonstrated good linear resemblance between ABP and fABP calculated in the frequency range corresponding to pulse pressure changes with moderate attenuation of the pulse amplitudes of the fABP signal. Bland–Altman analysis indicated that the average difference between Amp(fABP) and Amp(ABP) was significant, the range between the limits of agreement was rather wide, and there was a moderate correlation between the invasive and non-invasive methods of pressure pulse amplitude assessment. This latter observation is in line with a previous study of (Panerai *et al* 2006) in which it was concluded that the first harmonic of ABP measured by Finapres is smaller than that of ABP monitored invasively, and that this may significantly influence estimation of the cerebral haemodynamic critical closing pressure parameter.

The accuracy of non-invasive ABP measurements using Finapres has been widely described for both resting conditions and for different clinical scenarios using a variety of measurement conditions (Imholz *et al* 1991, 1998, Stokes *et al* 1991, Maestri *et al* 2005). The pressure gradient in the circulatory system along the arterial tree results in lower mean pressure in fingers than in the radial artery (Bos *et al* 1995). Within individuals, differences between non-invasive ABP measured from a finger and invasive ABP monitored in the brachial or radial arteries have been reported to change from −13 [mm Hg] (fABP lower than ABP) to 25 [mmHg] (fABP higher than ABP; (Imholz *et al* 1998). In our study, the mean bias between the fABP and ABP methods was −10.36 [mm Hg]. This discrepancy between non-invasive and invasive methods could result from several interdependent factors: cuff size and application, the finger involved (middle or annular; (Jones *et al* 1993), temperature of the hand (Hildebrandt *et al* 1991), or the finger's level in relation to the heart (Gizdulich *et al* 1995).

This study is the first to examine how the calculation of window length used to average CBFV in the CFF model influences the pulsatile amplitude of normalized changes in cerebral arterial blood volume. In previous work, the minimum time for CBFV averaging was arbitrarily chosen to be equal to at least one full period of a cardiac cycle (Kim *et al* 2009) or several previous heart evolutions (Czosnyka *et al* 2012). Our results showed that a good choice for mean CBFV calculation is a 3 s window.

The study's results confirmed our previous finding that $\tau_{PFF}$ is shorter than $\tau_{CFF}$, regardless of whether invasive or non-invasive ABP is used (Uryga *et al* 2019b). This is because the physiological interpretations of these time–related cerebral blood flow indices differ. The $\tau_{PFF}$ index, which includes the influence of pulsatile ABP characteristics, indexes filling of the arteries after a heart constriction, whereas the $\tau_{CFF}$ index, which assumes a steady blood outflow, characterises the time in which blood reaches the arterioles (Uryga *et al* 2019a). Therefore, $\tau_{PFF}$ and $\tau_{CFF}$ should be used in a complementary manner to characterise the proximal and distal parts of the cerebral arterial bed.

Despite the fact that there was poor agreement between the $f\tau$ and $\tau$ methods, the non-invasive approach could be beneficial in patients suffering from hydrocephalus or stroke. Cerebrovascular disorders are a common problem in chronic adult hydrocephalus patients, and these may cause further problems with shunt placement (Boon *et al* 1999, Israelsson *et al* 2017). Severe cerebrovascular disease may lead to reduced cerebral autoregulation, which impairs the ability to reperfuse the deep white matter after shunt placement (Bateman 2000, Czosnyka *et al* 2002). Additionally, cerebrovascular disorders can cause a reduction in cerebral blood flow, which can lead to a cerebral infarction, cerebral atrophy and a reduction in cerebrospinal fluid outflow resistance. As a result, chronic hydrocephalus may be unresponsive to shunt implantation and cause clinical symptoms similar to arteriosclerotic encephalopathy (Bateman 2004). Therefore, estimation of $f\tau$, which represents the relationship between compliance and resistance and is independent of a blood vessel's cross-sectional area, could be used to characterise cerebral haemodynamics in chronic adult hydrocephalus patients during overnight ICP monitoring and infusion tests.

Invasive ABP monitoring might be impossible to perform in other neurocritical care patients because of various contraindications such as local infections, coagulopathy, Raynaud syndrome, Buerger's disease and surgical considerations (Kaplan 2017). Invasive arterial blood pressure monitoring also carries some risks: cannulation of an artery needs to be performed by a trained clinician, it is time-consuming, and can cause the lesioning of nerves and vessels or even ischemia, although this rarely happens (Scheer *et al* 2002). Hence, the estimation of $\tau$ using non-invasive ABP could be used to assess the mechano-elastic properties of the cerebrovascular bed in patients for whom invasive ABP measurement is impossible or in whom it is likely to have adverse consequences.

## 5. Limitations

Although 46 independent signal recordings were analysed, only a small number of TBI patients (10) were included in the study. Also, certain factors which were not considered may have influenced our findings: patients' BMIs and their general health, the severity of brain injuries and their outcomes, treatments given, and other clinical circumstances (body position, temperature, sedation and analgesia, drugs administered, use of mechanical respiration, respiratory strategy used, etc). Thus, further research needs to be performed using a larger, homogenous cohort of TBI subjects to examine whether there is any correlation between $\tau$ and patients' clinical states. This said, several studies of $\tau$ in TBI patients have been published previously. The results of research on 161 TBI patients (Trofimov *et al* 2016) suggested that autoregulation of cerebral capillary blood flow fails in patients with severe TBI and that the total volume of capacitive vessels is reduced as an effect of brain oedema, which results in a significantly shorter $\tau$ in such patients compared to normal subjects. Another study showed that hypocapnia performed in 27 TBI patients caused a prolongation of $\tau$ as a result of increased cerebrovascular resistance which was greater than the decrease in compliance of the cerebral arterial bed (Puppo *et al* 2019). Also, Sheludyakov *et al* (2020) found that $\tau$ for 43 TBI patients who had ipsilateral haematoma and cerebral vasospasm was shorter than for 41 TBI patients without haematoma. All these previous findings suggest the potential utility of $\tau$ in describing cerebral haemodynamics in TBI patients.

The presently analysed data were digitally recorded almost 30 years ago. However, since then little, has changed in ICP, invasive blood pressure, TCD and Finapres monitoring. The signals analysed were technically sound, signal to noise ratios were within the limits of contemporary recordings, and sampling frequencies were satisfactory. We therefore used retrospective data to minimize the burden of performing new monitoring in a busy NCCU environment.

An updated version of the Finapres 2300 (the Finometer Midi) and the latest non-invasive continuous blood pressure monitor (the Finapres NOVA) provide a significant improvement in measurement accuracy by using several methods to correct for physiological radial or brachial to finger differences, including

waveform filtering, level correction, and continuous calibration (Guelen *et al* 2003). Further studies are needed to investigate agreement between cerebral haemodynamic indices estimated measuring ABP invasively and non-invasively by using this latest generation of non-invasive continuous blood pressure devices.

## 6. Conclusions

Differences between fτ and τ are significant. For head injury patients, estimation of τ using non-invasive ABP monitoring is inaccurate when using both the CFF and PFF modelling approaches.

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## Disclosure

The ICM+ software (www.neurosurg.cam.acuk/icmplus) is licensed by the University of Cambridge, Cambridge, UK, and Professor M. Czosnyka has a financial interest in part of the licensing fee.

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