**Summary of the doctoral dissertation**
**'Model studies of the dynamics of cerebral blood flow'**
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The most important parameters, that characterise the cerebral hemodynamics are cerebral blood flow (*CBF*) and cerebral blood volume (*CBV*). Changes of the *CBV*, occurring during a single cardiac cycle, are the results of the interplay between the pulsatile arterial inflow ($CBF_a$) and the venous outflow ($CBF_v$). Non-invasive monitoring of changes of the *CBV* is challenging due to the specific biomechanical properties of a closed skull in a human. Estimation of changes of the *CBV* is possible using medical imaging techniques: magnetic resonance imaging (*MRI*), computed tomography (*CT*) or positron emission tomography (*PET*) (Sakoh *et al*. 2000), (Alperin *et al*. 2005). However, those methods do not allow continuously monitoring the changes in the cerebral hemodynamic. The alternative method is transcranial Doppler ultrasonography (*TCD*)—a non-invasive, easy applicable technique, which allows continuous, near-bed monitoring of the cerebral blood flow velocity (*CBFV*) (Robba *et al.* 2018). The *CBFV* is applied as a substitute of the *CBF* in many cerebral hemodynamic studies (Panerai *et al.* 2007), (Kim *et al*. 2009), (Carrera, Kim, Castellani *et al*. 2011), (Varsos *et al*. 2013).

The estimation of pulse changes of the cerebral arterial blood volume ($\Delta C_aBV$) was proposed in the eighties of the twentieth century by Avezaat and van Eijndhoven (Avezaat *et* van Eijndhoven 1984a), (Avezaat *et* van Eijndhoven 1986). Their findings were based on the experiment, conducted with an invasive magnetoflowmetry. According to their research, $\Delta C_aBV$ during a cardiac cycle can be calculated as an integral of the difference between the pulsatile cerebral blood arterial inflow ($CBF_a$) and the venous outflow ($CBF_v$). Under the assumption that the $CBF_v$ is relatively low pulsatile in relation to the $CBF_a$, it can be approximated by the mean $CBF_a$. An alternative approach was presented by team of Czosnyka (Kim *et al*. 2009). They proposed a *TCD* -based, non-invasive methodology of the $\Delta C_aBV$ estimation and expressed the normalised $\Delta C_aBV$ ($n\Delta C_aBV$) as an integral of the difference between the *CBFV* and the mean *CBFV*. This model was termed in the more recent studies as the '*Continuous Flow Forward model'* (*CFF* model) (Uryga *et al.* 2017), (Uryga, Kasprowicz, Calviello *et al.* 2018). The *CFF* model assumes a relatively low pulsatile character of cerebral blood outflow. Hence, the *CFF* model is applicable for the distal part of cerebral arterial bed

(arterioles and capillaries). In order to fully describe the cerebral hemodynamics, there is a need to develop a new model of $n\Delta C_aBV$, which estimates the volume changes in the proximal part of the cerebral vascular bed (smaller arteries and arterioles).

In this PhD dissertation a modification of the mathematical model of $n\Delta C_aBV$ was proposed. The pulsatile character of the cerebral blood flow that forwards the proximal cerebral arterial bed was expressed as the ratio between the pulsatile changes in the arterial blood pressure (*ABP(t)*) and the normalised cerebrovascular resistance (*nCVR*). Thus, $n\Delta C_aBV$ was expressed in the new model as the integral of difference between *CBFV* and a ratio between *ABP(t)* and mean *nCVR*. In recent studies this new model was termed as the *'Pulsatile Flow Forward model'* (*PFF* model) (Uryga *et al.* 2017), (Uryga, Kasprowicz, Calviello *et al.* 2018). The estimation of $n\Delta C_aBV$ based on the *PFF* model induces new definitions of model cerebral hemodynamic parameters, such as:

a) the normalised compliance of the cerebral arterial bed ($nC_{aPFF}$), calculated as a ratio between amplitude of $n\Delta C_aBV$ estimated using *PFF* model and amplitude of pulsatile change in arterial blood pressure,

b) the time constant of the cerebral arterial bed ($\tau_{PFF}$), being a product of $nC_{aPFF}$ and *nCVR*,

c) the critical closing pressure ($CrCP_{PFF}$), being a function of $\tau_{PFF}$ and heart rate.

Furthermore, a new *PFF* model eliminates the impact of the time delay between pulse changes in *ABP* and *CBFV* on the amplitude of $n\Delta C_aBV$ calculation. This time delay resulted from the distance between a digital artery, where *ABP* is measured and the main cerebral arteries, where *CBFV* is monitored.

The changes in the model cerebral hemodynamic parameters, estimated based on both the *PFF* and the *CFF* models, during normal breathing, controlled breathing (6, 10, 15 [breaths/min]) and while controlled changing an arterial blood $CO_2$ concentration were analysed. The middle cerebral artery (*MCA*) and the posterior cerebral artery (*PCA*) were insonated using *TCD* (Doppler BoxX, DWL, Compumedics Germany GmbH, Singen, Germany). The $CO_2$ concentration was recorded with a capnograph (RespSense™, NONIN, Plymouth, MN, USA). The *ABP* signal was measured non – invasively using photoplethysmography (Finometer® MIDI, FMS Medical Systems, Amsterdam, The Netherlands). The measurements were conducted in a group of 53 young, healthy volunteers (31 females, 22 males, median age ± interquartile range: 22±13) in the Department of Biomedical Engineering, Wroclaw University of Science and Technology. The research was supported by the National Science Centre grant Sonata Bis (2013/10/E/ST7/00117). The study

was approved by the bioethical committee of the Wroclaw Medical University (Permission No. KB – 170/2014). This dissertation is comprised of three articles, published in the journals from *Master Journal List* (Uryga *et al.* 2017), (Uryga, Kasprowicz, Calviello *et al.* 2018), (Uryga, Kasprowicz, Burzyńska *et al.* 2018).

The aim of the first study was to compare the model cerebral hemodynamic parameters, estimated using the *PFF* and the *CFF* models, during normocapnia, hypercapnia, and hypocapnia (Uryga, Kasprowicz, Calviello *et al*. 2018). It was found that the changes in the *PFF* – based cerebral hemodynamic parameters were in accordance with physiological cerebrovascular reactivity, whereas the *CFF* – based ones did not demonstrate significant alterations during $CO_2$ concentration elevation or decrease. In comparison to normocapnia, the $CrCP_{PFF}$ and $\tau_{PFF}$ increased during a hypocapnia and decreased during a hypercapnia. No changes were found for $CrCP_{CFF}$ during hypercapnia or in $\tau_{CFF}$ during hypocapnia. The values of the *PFF* – based cerebral hemodynamic parameters were significantly lower than the *CFF* – based ones. This is due the fact that the *PFF* model describes a proximal part of cerebral arterial bed, whereas the *CFF* model characterises a distal part. These results confirmed the **first thesis of the doctoral dissertation that** *'modified mathematical model of the cerebral arterial blood volume changes, that accounts for the pulsatile blood flow forward the cerebral arterial bed, enables to determine the cerebral hemodynamic parameters, that reflect the physiological changes in the cerebral blood circulation after controlled alterations in carbon dioxide concentration in healthy volunteers'.*

In the second study the changes in the following parameters were analysed during controlled–frequency respiration: the time – frequency phase shifts (*TFPS*), between the breathing (0.10 [Hz] – 0.25 [Hz]) and slow (0.02 [Hz] – 0.07 [Hz]) oscillations in *ABP* and *CBFV*, as well as in $\tau_{PFF}$, describing mechano-elastic properties of brain arteries, and *Mxa* being a mean velocity correlation index used for cerebral autoregulation assessment (Uryga *et al*. 2017). It was found that an increase in the breathing frequency causes significant shortening of $\tau_{PFF}$, lower values of *Mxa* and lower values of the respiratory *TFPS*. An increase in slow wave *TFPS* with breathing frequency was also observable but this growth was statistically insignificant. The results showed a moderately strong correlation between respiratory *TFPS* and $\tau_{PFF.}$ There was no correlation between slow wave *TFPS* and $\tau_{PFF,}$ but the slow wave *TFPS* correlated significantly with *Mxa*. These results proved the **second thesis of the doctoral dissertation that** that *'the respiratory time – frequency phase shift between the arterial blood pressure and cerebral blood flow velocity in the frequency range of 0.10 [Hz] – 0.25 [Hz] reflects the mechano-elastic parameters of the cerebral arteries.*

The aim of the third study was to investigate the ability of the *CFF* and the *PFF* models to differentiate the characteristics of the cerebral vasculature, using the time constant of cerebral arterial bed ($\tau_{CFF}$ and $\tau_{PFF}$) (Uryga, Kasprowicz, Burzyńska *et al*. 2018). The results showed that $\tau_{PFF}$ from the *MCA* and $\tau_{PFF}$ from the *PCA* differed significantly. There was no difference in $\tau_{CFF}$ from the *MCA* and in $\tau_{CFF}$ from the *PCA*. $\tau_{PFF}$ was significantly shorter than $\tau_{CFF}$, both when calculated from the *MCA* as from the *PCA*. $\tau_{PFF}$ and $\tau_{CFF}$ should be interpreted as two physiologically different metrics, related to a proximal and a distal part of cerebral arterial bed, respectively. These results confirmed the **third thesis of the doctoral dissertation that**: '*applying the Pulsatile Flow Forward model (PFF model) for estimation of cerebral arterial blood volume changes, enables to reflect the differences in cerebral hemodynamic parameters, calculated from the cerebral arteries'*.

Obtained results confirmed the proposed theses. First, the ability of *PFF* model to describe the changes in cerebral hemodynamic parameters during controlled $CO_2$ concentration alterations was proven. Secondly, the phase shift between respiratory oscillation in *ABP* and *CBFV* was found as related with mechano-elastic parameters of cerebral vessels. Thirdly, the differences in time constant of the cerebral arteria bed were delineated using *PFF* model.

The outcomes of performed studies contribute to the interdisciplinary field of science, which is Biomedical Engineering, by developing knowledge in the field of biological signal processing and modelling of human physiology. Applying both the *CFF* and the *PFF* models allows for more complete characterisation of a cerebral arterial bed. Further work needs to be done to establish whether the *PFF* model could be successfully applied in clinical settings.

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