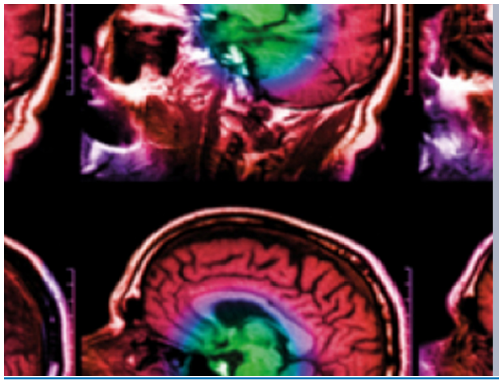
PAPER • **OPEN ACCESS**

Blood pressure wave propagation—a multisensor setup for cerebral autoregulation studies



Physiological Measurement

IPEM Institute of Physics and Engineering in Medicine

OPEN ACCESS

RECEIVED
27 May 2021

REVISED
29 October 2021

ACCEPTED FOR PUBLICATION
3 November 2021

PUBLISHED
28 December 2021

PAPER

Blood pressure wave propagation—a multisensor setup for cerebral autoregulation studies

Aleksandra Zienkiewicz[1], **Michelle Favre**[2], **Hany Ferdinando**[3], **Stephanie Iring**[2], **Jorge Serrador**[2] and **Teemu Myllylä**[1,3]

[1] Optoelectronics and Measurement Techniques Research Unit, University of Oulu, Oulu, Finland
[2] Department of Pharmacology, Physiology and Neuroscience, Rutgers New Jersey Medical School, Newark, United States of America
[3] Research Unit of Medical Imaging, Physics and Technology, University of Oulu, Oulu, Finland

E-mail: aleksandra.zienkiewicz@oulu.fi

Keywords: blood pressure, cerebral autoregulation, pulse transit time

Abstract

Objective. Cerebral autoregulation is critically important to maintain proper brain perfusion and supply the brain with oxygenated blood. Non-invasive measures of blood pressure (BP) are critical in assessing cerebral autoregulation. Wave propagation velocity may be a useful technique to estimate BP but the effect of the location of the sensors on the readings has not been thoroughly examined. In this paper, we were interested in studying whether the propagation velocity of a pressure wave in the direction from the heart to the brain may differ compared with propagation from the heart to the periphery, as well as across different physiological tasks and/or health conditions. Using non-invasive sensors simultaneously placed at different locations of the human body allows for the study of how the propagation velocity of the pressure wave, based on pulse transit time (PTT), varies across different directions. *Approach.* We present a multi-sensor BP wave propagation measurement setup intended for cerebral autoregulation studies. The presented sensor setup consists of three sensors, one placed on each of the neck, chest and finger, allowing simultaneous measurement of changes in BP propagation velocity towards the brain and to the periphery. We show how commonly tested physiological tasks affect the relative changes of PTT and correlations with BP. *Main results.* We observed that during maximal blow, valsalva and breath hold breathing tasks, the relative changes of PTT were higher when PTT was measured in the direction from the heart to the brain than from the heart to the peripherals. In contrast, during a deep breathing task, the relative change in PTT from the heart to the brain was lower. In addition, we present a short literature review of the PTT methods used in brain research. *Significance.* These preliminary data suggest that the physiological task and direction of PTT measurement may affect relative PTT changes. The presented three-sensor setup provides an easy and neuroimaging compatible method for cerebral autoregulation studies by allowing measurement of BP wave propagation velocity towards the brain versus towards the periphery.

1. Introduction

Autoregulation of cerebral blood flow is a critical mechanism of the brain to maintain a relatively constant supply of blood flow in the face of changing perfusion pressure (Madsen *et al* 1990). In this mechanism, the cerebral arterioles adjust vascular resistance in response to reductions and elevations in blood pressure (BP), thereby preventing damaging hypoperfusion and hyperperfusion of the brain, respectively (Paulson *et al* 1990). Cerebral autoregulation is affected in clinical populations such as patients with stroke (Eames *et al* 2002, Reinhard *et al* 2012, Castro *et al* 2017) and traumatic brain injury (Czosnyka *et al* 1996, Freeman *et al* 2008). Impairments in autoregulation are associated with worse functional outcomes in both of these patient groups (Freeman *et al* 2008, Reinhard *et al* 2012, Castro *et al* 2017, Rivera-Lara *et al* 2017). Thus, cerebral autoregulation

assessment is important in patient care settings and is commonly done by monitoring slow fluctuations of arterial BP (ABP) (Pham *et al* 2019).

ABP in cerebral autoregulation studies is commonly measured using an invasive catheter or non-invasive monitoring based on the volume-clamp method, such as Finapres. Catheterization is uncomfortable for the patient and requires the auspices of skilled medical staff. The invasive nature of measurement involves risk of haematoma formation (mean incidence 14.4%), bleeding (mean incidence 0.5%) and local infection (mean incidence 0.7%) (Scheer *et al* 2002). On the other hand, volume-clamp methods rely solely on peripheral BP reading, which differs from central BP because of wave reflections and arterial stiffness (Agabiti-Rosei *et al* 2007). Furthermore, the method requires use of a finger cuff which many subjects find uncomfortable. Thus, finding a non-invasive alternative method of measuring BP for cerebral autoregulation studies is of high interest.

In this article, we compare BP wave propagation properties when recorded simultaneously at different body sites, in particular the propagation from the heart towards the brain versus towards the periphery. We were interested in studying whether the placement of the sensors might affect the quality of blood flow monitoring in the context of cerebral autoregulation. Blood pulsation was recorded using three non-invasive sensors, one on each of the neck, chest and finger, and was then used to obtain the pulse transit time (PTT) in different directions from the heart. The sensor on the neck is placed above the carotid artery, and because of this, it is assumed that the PTT between the chest and neck reflects BP pressure propagation velocity and blood flow dynamics towards the brain. Consequently, the presented sensor placement may provide a robust and relatively simple method to study cerebral autoregulation.

2. Importance of BP and PTT measurements in brain research

PTT refers to pulse propagation time through the length of the arterial tree during the same cardiac cycle. This commonly known parameter, which reflects BP wave propagation, is affected by cardiac output and arterial compliance, but also by other factors, such as respiration (Drinnan *et al* 2001) or body position (Foo *et al* 2005). PTT has an inverse relationship with pulse wave velocity (PWV), which represents how fast a pulse propagates through arteries, and has been widely used as the indicator of arterial stiffness (Wentland *et al* 2014, Hudson *et al* 2015, Obeid *et al* 2017).

PTT has been of great interest among the research community for estimating ABP, due to the possibility of using it in a non-invasive and easy-to-use manner. However, there is a complex relationship between the cardiovascular system and BP (Ding and Zhang 2019). In a study highlighting the complexity, Xu *et al* (2018) introduced heart rate (HR)-related arterial baroreflex (ABR) to analyse the failure of PTT in low-frequency BP estimation before and after exercise. It was found that the correlations between ABR sensitivity and BP estimation error at low frequency were higher than those at high frequency. This might be an important factor influencing the usability of PTT-based methods in cerebral autoregulation assessment, since the low-frequency changes are the ones of interest (Pham *et al* 2019).

It must be noted that in PTT-based methods, it is also important to know how the characteristic points of the pulse are identified, which must be defined clearly in the publication prior to using them. Generally, the measured value is the time delay between two important events/points within the same cardiac cycle. However, researchers are testing various combinations of such points, e.g. R-wave peak to peak of the first derivative of PPG (Gesche *et al* 2012), R-wave peak to PPG peak, or a combination of several characteristic points (Esmaili *et al* 2017). In our analysis, we have decided to use the ECG R-peak and highest PPG peak.

The reliability of PTT in beat-to-beat BP estimation is still being investigated. The exact relation between BP and PTT is individual-specific and depends on the physical properties of the vessels and blood of each person (Esmaili *et al* 2017). Mukkamala *et al* (2015) suggested that PTT can be used to monitor BP as long as smooth muscle contraction and viscous effects are very small, aging and diseases have no impact on the arterial elasticity, and there is no pulse wave reflection. Considering these limitations, Zhang *et al* (2011) and Payne *et al* (2006) concluded that PTT was unreliable for estimating BP. Although we can assume that the smooth muscle contraction and viscous effect is small, the aging and disease impact on arterial stiffness and the presence of pulse wave reflection cannot be neglected. On the other hand, Gesche *et al* (2012) and Masé *et al* (2011) demonstrated that PTT was good enough to estimate BP, achieving average correlation of about 0.83 and 0.8, respectively.

2.1. Effect of sensor placement on PTT

Studies on PTT often include testing of multiple sensor combinations in simultaneous measurement. To the best of our knowledge, the multi-sensor approach is not yet used simultaneously with neuroimaging, despite the fact that it could give valuable input to the knowledge of cerebral and systemic haemodynamics.

Commonly, BP wave propagation is determined as PTT between the ECG R-peak and PPG measured at a peripheral site on the body, e.g. finger, ear, toe, forehead. However, the BP wave propagation can also be

measured using other sensors and sensor placements (Myllylä *et al* 2012). A variety of sensors and equipment developments is used in order to provide better signal quality (e.g. in wearable applications), as well as better compatibility with other modalities.

There are significant differences in PTTs measured at separate body sites at the same time. The quality of the result is commonly presented in reference to BP values; however, there is no agreement on which endpoints are the best choice. On one hand, PTT estimation along the central arteries seems to be promising, because of the central arterial wall properties and little interference caused by wave reflection (Mukkamala *et al* 2015). On the other hand, distal waveforms are often measured with satisfactory results, with measurement from the heart to the toes and fingers showing better correlation with cuff-based BP than from the heart to the earlobes (Budidha and Kyriacou 2014, Block *et al* 2020).

Various multi-sensor setups have been proposed, including those without using ECG measurement. For instance, smart glasses measure a user's pulse wave at three sites on the head using optical sensors (Holz and Wang 2017). The authors observed variations in correlations to reference BP, as well as differences in signal quality. Interestingly, discrepancies were noted even with small differences in sensor distances. Other examples are using two PPG measurements to define the PTT, e.g. between the earlobe and finger (Block *et al* 2020, Kao *et al* 2020), or utilizing a high-speed camera to capture PPG signals from the face and palm of the hand (Jeong and Finkelstein 2016).

Additional factors should be taken into account when choosing sensor placement for PTT measurement. For instance, the age of the subject can influence measured PTT, especially in toes (Allen and Murray 2002). The reason for this is an age-dependent increase in arterial stiffness, resulting in a decreased amount of time taken for the pulse to propagate to the periphery. The effect of PTT reduction in elderly patients is more profound when measured to the toe than to the finger or ear, due to a relatively longer artery. Peripheral arterial readings are also subject to vasomotion-induced inaccuracies, particularly in those patients who have long-term BP problems and need accurate measurements the most (Heydari *et al* 2020).

2.2. PTT in brain research

Combining the measurement of PTT with brain monitoring modalities, such as magnetic resonance imaging (MRI) and transcranial Doppler ultrasound (TCD), can provide complementary information on the relationship between systemic blood wave propagation and cerebral haemodynamics. In particular, simultaneous measurement of different physiological signals with neuroimaging enables analysis of their dynamics in relation to each other and to brain function (Korhonen *et al* 2014).

The study of PTT from the heart to various sites of the body together with brain images obtained in an MRI chamber can bring significant difficulties, as the ECG device will be highly obstructed by noise and artifacts (Oster and Clifford 2017). It is possible to use the QRS complex as a trigger to begin the data acquisition by MRI. However, the delays caused by such a setting can result in missing portions of the flow waveform, limiting the use of this solution on propagation time (Wentland *et al* 2014). In the study presented by Fabiani *et al* (2014), a sample of middle-aged and older adults was performing cognitive tests while being simultaneously recorded with ECG, oximeters and MRI. The problem of compatibility was solved by recording cardiovascular responses and MRI images during separate sessions, and later combining the data. Analysis of PTT was just one element of the study, in which cerebral pulsatile waveforms were taken from the scalp using six oximeters and compared to ECG. The authors observed differences in regional PTT associated with performance in distinct cognitive tasks. However, they acknowledged that the utility of extracting regional estimates of arterial compliance on cognition remained largely unknown.

Another approach to the analysis of BP propagation during MRI imaging might be the use of MRI-compatible equipment, which allows simultaneous recording by all modalities, such as fibre-optic accelerometers (Myllylä *et al* 2011). In the study presented by Raitamaa *et al* (2019), measurements conducted with such sensors were performed together with ultra-fast MRI, namely magnetic resonance encephalography (MREG), during a breath hold task (BH). PTT was used for estimation of continuous, relative BP values which were compared with brain oxygenation level and arterial MREG signal pulse amplitude. The authors observed that estimated BP dropped at the BH onset and end, and was highly correlated to arterial MREG signal pulse amplitude. Similar sensors were used by Myllylä *et al* (2017), when the measurement setup consisted of various optics-based modalities combined with magnetoencephalography (MEG). The study supported the potential for using the method in brain research, demonstrating the effects of BH in particular. MRI-compatible fibre-optic accelerometers placed on the chest and neck were also used in the present study, although it must be noted that any pulse-detecting sensors might be used in their place, as no magnetic imaging was used in the presented measurements.

Combining PTT measurement with TCD was presented e.g. in a study by Furtner *et al* (2009), in which cerebral blood flow velocity changes and vascular compliance were investigated in patients with severe obstructive sleep apnoea syndrome. Interestingly, unlike earlier studies that measured peripheral PTT, the endpoints for PTT measurement in this study were the ECG R-peak and the onset of the pulse wave at the middle

Table 1. Subject characteristics.

Number of participants (M/F)	12 (9/3)
Age	25 ± 5
Height (cm)	170 ± 20
Weight (kg)	75 ± 20

cerebral artery measured using TCD. Observed PTT decreased in all kinds of registered respiratory events, which is in contrast to earlier works that found increased peripheral PTT (Argod *et al* 1998, Pitson and Stradling 1998). According to the letter published by Liu *et al* (2019), PTT demonstrates great potential in cerebrovascular reactivity assessment. Liu calculated PTT as the time from the ECG R-wave peak to the onset of oxygen saturation level (SpO_2). It was then correlated with the values of intracranial pressure (ICP) and compared with a well-validated method based on invasive ABP measurement. Pressure reactivity indices obtained using both ABP and PTT measurements showed significant correlation. Since PTT has advantages over invasive ABP, as it avoids bleeding and infection risk, the authors concluded that PTT can be a useful tool for cerebrovascular reactivity assessment when invasive ABP is unavailable.

Shahsavari *et al* (2010) utilized ECG and ICP signals to measure PTT between the heart and cranial cavity among head-injured patients, with different levels of cerebrovascular pressure reactivity response. It was observed that in patients with intact cerebrovascular pressure-reactivity, gain of normalized transfer function at the fundamental cardiac component was highly correlated with pulse wave transit time. The authors concluded that although further assessment with a larger population of patients, including patients with impaired pressure-reactivity mechanism, is needed, PWV/PTT can be used continuously in head-injured patients and may reveal more information on the autoregulatory mechanism of cerebrovascular systems and its impact on the cerebrospinal compensatory reserve.

PTT has also been combined with near-infrared spectroscopy (NIRS). Mol *et al* (2020) proposed utilizing PPG, ECG and NIRS in the assessment of baroreflex and cerebral autoregulation. Mol tested the aforementioned sensor combination during different postural changes. Reference BP was measured continuously using the non-invasive haemodynamics monitor Finapres. PTT/PWV in this study correlated well with the reference BP during rapid supine to standing movement, but not during other postural changes. Näsi *et al* (2011) studied the haemodynamic responses evoked by transcranial magnetic stimulation using NIRS. Additional systemic recordings were made to measure HR and PTT. Stimulation affected all the circulatory parameters, causing a decrease in HR, PPG amplitude and PTT.

In the following, we present a multisensory setup intended to be used in cerebral autoregulation studies. We observe the relative changes of BP wave propagation when PTT is measured in the direction from the heart to the brain (towards the brain) versus from the heart to the periphery (towards the limbs). We also show PTT correlations with BP values measured using Finometer across different physiological tasks. The setup is fully compatible with commonly used brain imaging techniques, such as MRI, MEG, TCD and NIRS. Thus, we discuss the feasibility of the proposed technique for cerebral autoregulation studies in the future.

3. Materials and methods

This research was conducted in accordance with the guidelines established by the Declaration of Helsinki. Part of the study was conducted at Oulu University Hospital, and the other part was conducted at Rutgers University, with the approval of The Rutgers Health Sciences Institutional Review Board Newark, NJ. Subjects were given detailed written and verbal explanations of the study procedures prior to giving their written informed consent.

The recruited subjects in Oulu were university students who voluntarily choose to participate. The regional Ethical Committee of Northern Ostrobothnia Hospital District in Oulu University Hospital approved the study protocols. Subjects at Rutgers were recruited from the local campus community in Newark, NJ via flyers posted throughout campus. Subjects included in this study were excluded if they had any history of disease including cardiovascular disease (with the exception of hypertension), neuromuscular disorders, renal/electrolyte disorders, chronic infections, chemotherapy/radiation therapy, and history of psychiatric or substance abuse disorders within the past six months.

The subject characteristics are shown in table 1:

Subjects were asked to refrain from cold or headache medication for 24 h prior to testing, caffeine and exercise for 12 h prior to testing, and food and drink (except water) for 2 h prior to arriving in the laboratory.

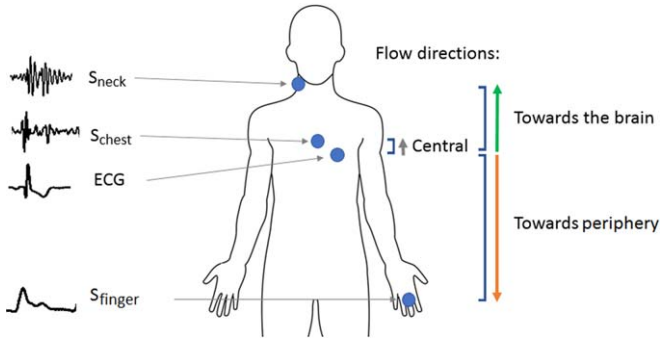


Figure 1. Sensor placement for the presented measurements and corresponding biosignals. ECG was measured with three leads.

Table 2. Protocols used in the study.

PROTOCOLS USED IN THE STUDY

Task	Duration (s)
SIT	120
REST	120
MAX. COMP.	200
MAX. BLOW	180
DEEP BREATHING	240
VALSALVA	210
BH	390
ISOMETRIC	180
STS	360
CVRT	480

Sitting, Resting state, Pressing sensor with max. force, Blowing with max. force, Deep breathing, Blowing, Holding breath, Pressing sensor, Standing, CO_2 administration, Fast breathing

3.1. Measurement setup

In the experiments, we used two MRI-compatible opto-mechanical sensors (Myllylä *et al* 2011) that were placed on the chest and neck and strapped in place throughout testing. These sensors provide signals similar to a seismocardiogram (SCG) and phonocardiogram (PCG).

Figure 1 displays sensor instrumentation on the subject. The sensor on the chest (S_{chest}) measured motions caused by cardiac activities and the sensor on the neck (S_{neck}) measured motions caused by the carotid artery. Simultaneously, a finger cuff BP monitoring device, Finometer (S_{finger}), provided continuous signals for PPG and BP, while ECG was measured using a three-lead ECG. Sensor placements were chosen in order to observe the differences between pressure wave propagation from the heart towards the periphery (towards S_{finger}) and from the heart in the direction of the brain (towards S_{neck}).

S_{neck} and S_{chest} in figure 1 show one cardiac cycle with S1 and S2. Similarly to in PCG, S1 refers to the first normal heartbeat sound and S2 the second normal heart sound. The sounds are the result of mechanical activity of the heart due to its physical movement.

3.2. Data acquisition and experiment protocol

Subjects were instructed to perform various tests aimed to measure feasibility of the tested setup for assessing cerebral autoregulation. Static tasks were used for establishing baseline values, while breathing manoeuvres, isometric and sit-to-stand exercises were chosen in order to induce sudden changes in BP. The task protocols are presented in table 2.

During the sitting test (SIT) and resting state test (REST), subjects were asked to breathe normally while staying in the sitting and supine positions respectively for 2 min.

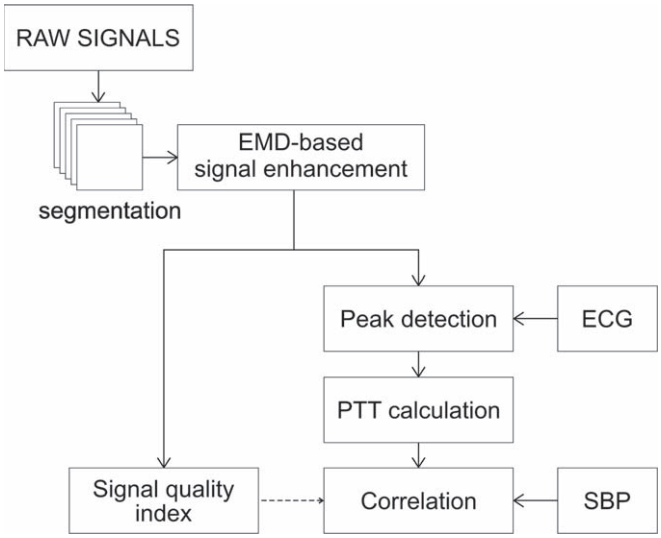


Figure 2. Signal processing diagram.

During the maximum compression test (MAX.COMP.) subjects were in the supine position for 1 min, followed by three repetitions of squeezing a compression sensor with maximal force. After this, subjects rested for 2 min.

During the maximum blowing test (MAX.BLOW.), subjects were in the supine position for 1 min, followed by a strong blow into a breathing sensing tube. Afterwards, subjects rested for 2 min while breathing normally.

The deep breathing test (DEEP BREATHING) started with 1 min of rest, followed by a 1 min section of slow inhales (5 s) and equally slow exhales (5 s). Then, subjects breathed normally for 1 min, followed by a second sequence of deep breathing, and ending with 1 min of rest.

The valsalva test (VALSALVA) was conducted as three repetitions of 30 s rest and 30 s blowing into a breathing tube. Finally, subjects were asked to rest for 30 s.

During the BH test, subjects were instructed to hold their breath for 32 s after 88 s of normal breathing. This sequence was repeated three times and ended with 30 s of rest.

The isometric test (ISOMETRIC) started with 1 min of rest, followed by squeezing the pressure sensor for 2 min.

During the sit-to-stand test (STS), subjects sat in a chair resting quietly for a 5 min baseline followed by standing up for 1 min and sitting down for 1 min. The sit-to-stand manoeuvres were repeated two times, totalling three sit-to-stand manoeuvres. During the cerebrovascular reactivity test (CVRT), subjects rested quietly sitting in a chair while breathing normally for 2 min. Then subjects were given a gas mixture containing 5% CO_2, 21% O_2, and balanced nitrogen with an oxygen mask for 2 min. Subjects were instructed to breathe normally again for 2 min, before ending the test with 2 min of mild hyperventilation.

Data from ECG, S_{chest}, S_{neck}, S_{finger} and end-tidal CO_2 were acquired simultaneously at 1 kHz using Powerlab (AD Instruments) and converted to MATLAB (MathWorks) for signal processing and analysis.

3.3. Signal processing

Signals measured by ECG, S_{chest}, S_{neck} and S_{finger} were processed segment by segment. The algorithm for S_{chest} and S_{neck} is shown in figure 2. Empirical mode decomposition (EMD) was applied to decompose S_{chest} and S_{neck} signals into their intrinsic mode functions (IMFs).

As mentioned in the previous section, S_{neck} and S_{chest} signals have similar structure to PCG. This means that in each cardiac cycle it is possible to observe two heartbeat sounds, here named S1 and S2. A preliminary experiment showed that subtracting IMF #2 from its original signal enhanced the signal quality by giving a clear separation between S2 from the current beat and S1 from the next beat.

All sensors were affected by body movements, mainly during the transition phase of the task, e.g. in the STS task, and because of this, some parts of the signals were corrupted. On the other hand, when subjects moved their head during measurement, only the sensor at the neck was affected. For these reasons, a method to evaluate the quality of the signal was developed ('Signal quality index'; see figure 2). The method is capable of real-time signal quality estimation so that low-quality signal is excluded before further signal analysis.

It began with squaring the enhanced S_{chest}/S_{neck} signal. Further, we convolved it with a rectangular window of 25% of its sampling frequency in hertz to combine all oscillations within the same cardiac cycle as a

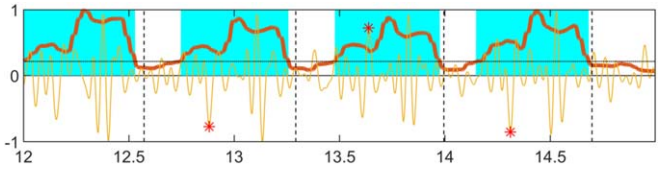


Figure 3. Example of the raw signal recorded using a neck sensor (thin line) with detected peaks (asterisk) and R- peaks (asterisk). Convolution between the squared enhanced signal and a rectangular window joins all oscillations within the same cardiac cycle as a one-shot-like signal (thick line). Using the adaptive threshold (dotted horizontal line slightly above zero), the one-shot-like signal is converted into a perfect rectangular signal (shaded block). Since these peaks are searched based on the R-peak prior to the rectangle window, there is no such peak on the first rectangle window.

one-shot-like signal; see the thick line in figure 3. This 25% of its sampling frequency was determined empirically. Using half of its median as a threshold (see the horizontal dotted line above zero in figure 3), we transformed it into pure rectangular pulses; see the colored block in figure 3

Since the widths of these blocks depend on the heartbeat, HR variability (HRV) was used to determine the maximum width of each block that contains S1 and S2 using robust statistics, which utilised the median and median absolute deviation (mad), as suggested by Lanata *et al* (2015):

$$width_{\max} = median(HRV) + 1.4286*mad(HRV) \tag{1}$$

Rectangular pulses with width larger than the maximum threshold as in (1) were marked as unaccepted. The signal quality index (Q) was calculated based on the following formula:

$$Q = \frac{sum\ of\ all\ accepted\ pulse\ widths}{sum\ of\ all\ pulse\ widths} \tag{2}$$

This value represents the quality of the signal within a segment as a single number within a range [0,1]. We applied a threshold from 0.5 to 0.9 to decide whether we should exclude the whole segment from analysis or not. We were interested to know the minimum value of Q to deliver good correlation between PTT and BP.

To calculate PTT, we needed to have the R-wave and S1 peaks. There were many algorithms to find the R-wave peak, e.g. the Pan–Tompkins algorithm employed various filter and certain threshold values (Pan and Tompkins 1985), and Lanata *et al* used the energy of the second derivative (Lanata *et al* 2015).

Detecting the S1 peak was done based on the R-wave peak position. The search area after the R-wave peak is defined based on the following formula:

$$width_{search} = \frac{median(HRV) - 1.4286*mad(HRV)}{2} \tag{3}$$

The highest peak of S1 is located within that search area, starting from the R-wave peak.

S_{finger} did not require a specific signal processing procedure, because the signal quality was good. The search for peaks from S_{finger} also utilises corresponding R-wave peaks as the starting point with the same width as in (3). It always aims to get the highest peak within the search window.

With all peaks found for all signals within each segment, three PTT values were derived:

1. Central: PTT between ECG R-peak and S_{chest}
2. Towards the brain: PTT between ECG R-peak and S_{neck}
3. Towards the periphery: PTT between ECG R-peak and S_{finger}

Instead of using PTT beat by beat, we calculated its median over a certain segment, as van Velzen *et al* averaged them over a certain length (van Velzen *et al* 2017) to minimize the measurement error, noise, motion and physiological artefacts such as respiration (Mukkamala *et al* 2015).

The pulse pressure signal shape measured from the finger using Finometer is similar to the PPG signal. The peak of each pulse represents SBP, while its trough represents DBP. We also averaged the upper envelope to get values for the corresponding segment.

4. Results

Figure 4 presents the detection results of accepted and unaccepted blocks based on (1) in a certain data segment from S_{chest} and S_{neck}.

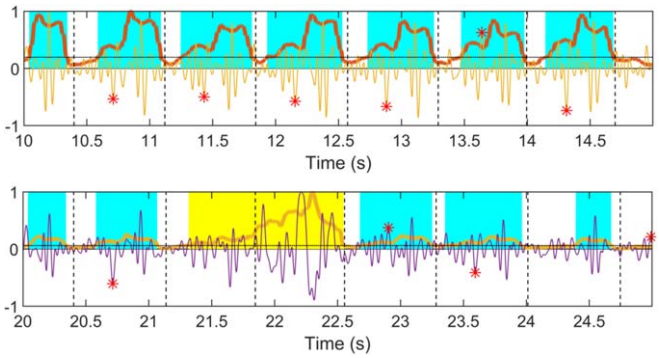


Figure 4. Detection results of accepted (top) and unaccepted (bottom) blocks in a segment of 5 s from S_{chest} and S_{neck}. The unaccepted block (yellow) contains indistinguishable S1 and S2 in one cardiac cycle. This block was discarded from further analysis. Dashed lines represent the positions of R-wave peaks.

Table 3. Correlation of BP propagation time (PTT) between different sensors with Finapres systolic BP signals in various tasks.

Task	Central	Towards the brain	Towards the periphery
SIT	−0.68	−0.69	−0.52
REST	−0.67	−0.78	−0.33
MAX. COMP.	−0.67	−0.81	−0.58
MAX. BLOW	−0.78	−0.86	−0.20
DEEP BREATHING	−0.85	−0.91	−0.31
VALSALVA	−0.72	−0.71	−0.11
BH	−0.92	−0.79	−0.25
ISOMETRIC	−0.91	−0.94	−0.26
STS	−0.64	−0.24	−0.33
CVRT	−0.76	−0.45	−0.24
Mean	−0.76	−0.72	−0.31

It was shown that the unaccepted block, marked with yellow, occupied almost two cardiac cycles. Within this block, it was hard to determine the S1 peak correctly, even with the human eye. For the accepted blocks, however, the algorithm could find these peaks easily. Figure 4 also revealed an important finding about the missing S1 peak as shown in the bottom plot between 24 s and 25 s. Consequently, the number of detected peaks from ECG and S_{chest}/S_{neck} signals might be different. Therefore, R-wave peaks without corresponding S1 peaks must be removed. We segmented the whole signals into segments of 60 s for PTT and BP averaging. Thus, the correlation value is based on the averaging value in each segment. The threshold for signal quality was chosen between 0.5 and 0.9; a segment with a signal quality index less than the threshold was discarded.

In the following, table 3 shows correlations between PTT and SBP measured by Finapres for each task. Correlations were calculated for 60 s segments, since using longer segments makes the system less sensitive to noise and abrupt changes due to the complexity of the cardiovascular control system.

Central PTT did not always provide the best results in all tasks, although on average it was the most accurate. PTT towards the periphery delivered the lowest correlation coefficient, with a mean value of only –0.31. PTT measured towards the brain had results comparable with central PTT, and achieved even higher accuracy in some of the tasks.

We measured signals from different locations simultaneously, because we were interested to know how sensor sites affect the sensitivity of PTT during different tasks. In order to assess this sensitivity, we calculated the relative change in PTT compared to PTT measured at rest, using the following formula:

$$Relative\ change = \left| \frac{PTT - PTT_{rest}}{PTT_{rest}} \right| * 100\% \quad (4)$$

Using relative values excludes the effect of different distances between the sensors. Figure 5 presents how various tasks affect the relative change in PTT.

It can be clearly seen that PTT measured towards the brain was more influenced by tasks than PTT towards the periphery. In fact, only the ISOMETRIC condition showed large changes in the peripheral PTT as well as the

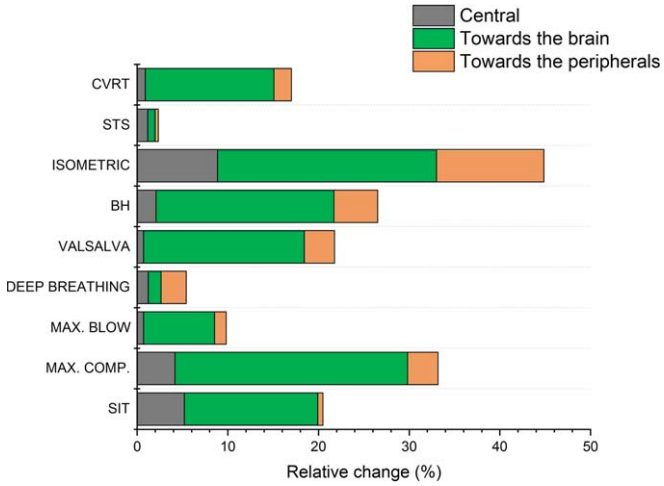


Figure 5. PTT response during various tasks in relation to PTT during rest task.

brain. This is consistent with previous data, which demonstrate that ISOMETRIC contractions are known to cause large increases in BP (Martin *et al* 1974). The value measured at the central site is most stable.

5. Discussion

We demonstrated that the BP wave propagation time measured from the chest to the brain and from the chest to the periphery differs strongly depending on the physiological task, as well as correlating differently when compared with BP values measured using Finometer. We acknowledge that BP regulation in humans is a complex mechanism. For this reason, we restrict the discussion to the correlation of PTT values to BP measured by Finometer. We discuss how BP propagation towards the brain and towards the periphery was affected by different tasks, noting that further work is needed to determine the cause of these differences.

Respiration has a profound effect on cardiovascular system control, e.g. through baroreflex. Respiration modulates RR interval via respiratory sinus arrhythmia and BP. Thus, respiration will also affect PTT, as confirmed e.g. by Drinnan *et al* (2001). Moreover, they found that RR interval changes affect PTT.

PTT measured towards the brain was highly correlated with BP for the respiratory protocols, with Pearson's coefficient values exceeding −0.7. Interestingly, for MAX. BLOW, VALSALVA and BH, the relative changes of PTT were higher when measured from the heart towards the brain than from the heart towards the periphery. BH is known to cause a strong response in cardiovascular signals. In the study conducted by Raitamaa *et al* (2019), where subjects were following the protocol of repeated BHs, central BP was dropping at the onset of the BH segment, followed by a gradual decrease during the whole segment duration. At the same time, oxygenation levels in the brain increased, which suggests that as a priority the oxygen was provided to the brain.

Our results indicate that respiration modulates PTT when measured towards the brain, which is an interesting finding. This may be due to the changes in cerebral blood flow and cerebrovascular resistance known to occur with changes in respiration (Eames *et al* 2004, Uryga *et al* 2017). Further work is needed to understand these changes, but a direct non-invasive measure of cerebral vascular state would be of significant benefit for research on cerebral autoregulation.

Examining the ISOMETRIC exercise, a large change in PTT was noted, both when measured towards the brain and towards the peripherals. This may be related to the overall large increase in BP known to occur during this manoeuvre (Martin *et al* 1974) which would affect PTT measured in both directions. In contrast, DEEP BREATHING resulted in minimal changes in BP or brain blood flow and the PTT also demonstrated few changes (Favre *et al* 2020). These findings support the ability of the PTT to detect changes in cardiovascular and cerebrovascular state.

Based on the studies discussed by Mukkamala *et al* (2015), measuring PTT through the central arteries is recommended. Interestingly, on average, central PTT in our experiments had the best correlation with BP. However, if we define PTT as a propagation time of pulse pressure along the artery within the same cardiac cycle, then the term 'central PTT' is a problematic expression in terms of BP propagation. Nevertheless, heart motions generate corresponding vibrations on the chest in a delay, and this time delay between the ECG and the corresponding chest motion, measured by S_{chest}, seems to have a high correlation with BP. Somewhat surprisingly, PTT measured towards the periphery delivered the lowest correlation values with BP Finometer. It

scored slightly higher in tasks requiring prolonged supine position with no breathing restrictions, namely rest and maximal compression tasks. In previous studies (Budidha and Kyriacou 2014, Block *et al* 2020), peripheral PTT was compared to the PTT measured to the earlobe (which can be considered analogical to our measurement towards the brain, since our sensor was placed on the neck). The aforementioned experiments were conducted in the reclined position. It was observed that during the cold pressor test, the change in PTT was much larger in the finger when compared to the other measurement sites, which likely reflects the effect of profound peripheral vasoconstriction seen at the peripheral site. Since tasks may evolve easily, finding a good BP estimation model for each task is difficult. It inhibits cuffless BP measurement based on a PTT-like index, because new models must be developed for new tasks.

As for signal processing part, an EMD-based algorithm was used in the analysis of S_{chest}/S_{neck} signals. Although EMD can enhance the signal well, its computational load depends on the signal length and oscillation complexity; longer signals and signals corrupted with noise require longer computational time. In our study, signals were under control except for several tasks when subjects made sudden movements. On average, the whole signal processing task from signal enhancement until peak detection required less than 5 s for 60 s segments, which indicates that the algorithm can be used in real-time application.

For IMF #2 as the subtractor signal enhancement, detailed analysis showed that this particular IMF provided the highest correlation with the original signal, but with a lower amplitude. This suggests that for general cases, it is better to use that criterion to select an appropriate IMF. SQI-based HRV worked well to provide a quality index of the signal. However, it highly depends on the ECG signal. When ECG was absent from the measurement, we needed other methods for this purpose. During SQI calculation, we used half of the median of the pulse-like shape signal to create a block of individual cardiac beats. We found that its percentile also offered similar results.

The R-peak of each cardiac beat guided peak detection from the chest, neck and finger sensors only from the accepted blocks, making the peak detection process relatively straightforward. This eases the process dramatically compared to using raw signals alone as in (Zienkiewicz 2017).

6. Conclusion

PTT between a sensor on chest and a sensor on the neck above the carotid artery measures BP pressure propagation velocity and reflects blood flow dynamics towards the brain. A third sensor placed on the finger measures BP pressure propagation velocity simultaneously towards the periphery. This three-sensor approach may provide an interesting tool for cerebral autoregulation studies by allowing an easy method to measure distinct BP wave propagation velocity towards the brain versus towards the periphery. Preliminary data suggest that physiological tasks affect relative PTT changes and, importantly, the direction of the BP propagation also seems to play a role. At a technical level this study tests the feasibility of EMD-based signal processing in SCG/PCG-like signals. In addition, our setup is fully compatible with various neuroimaging methods.

When compared to previous PTT studies, the main novelty of this study is that we show the placement of sensors in PTT measurements play a role and this can be of high interest in cerebral autoregulation studies. In addition, pulse wave propagation to the brain and to the periphery can be easily measured using wearable sensors, allowing long measurement periods. Nevertheless, we emphasize that the presented method is an indirect method to measure cerebral autoregulation-related dynamics, and thus requires further studies to verify its potential. As a next step, it is our intention to study the relation of these PTT signals with TCD signals.

Acknowledgments

This work was partly supported by the Academy of Finland (grants 318347 and 335723).

References

Agabiti-Rosei E, Mancia G, O'Rourke M F, Roman M J, Safar M E, Smulyan H, Wang J G, Wilkinson I B, Williams B and Vlachopoulos C 2007 Central blood pressure measurements and antihypertensive therapy: a consensus document *Hypertension* **50** 154–60

Allen J and Murray A 2002 Age-related changes in peripheral pulse timing characteristics at the ears, fingers and toes *J. Hum. Hypertens.* **16** 711–7

Argod J, Pepin J and Levy P 1998 Differentiating obstructive and central sleep respiratory events through pulse transit time *Am. J. Respir. Crit. Care Med.* **158** 1778–83

Block R C, Yavarimanesh M, Natarajan K, Carek A, Mousavi A, Chandrasekhar A, Kim C, Zhu J, Schifitto G and Mestha L K 2020 Conventional pulse transit times as markers of blood pressure changes in humans *Sci. Rep.* **10** 1–9

Budidha K and Kyriacou P A 2014 Investigation of pulse transit times utilizing multisite reflectance photoplethysmography under conditions of artificially induced peripheral vasoconstriction *2014 36th Annual Int. Conf. of the IEEE Engineering in Medicine and Biology Society (Piscataway, NJ)* (IEEE) pp 1965

Castro P, Serrador J M, Rocha I, Sorond F and Azevedo E 2017 Efficacy of cerebral autoregulation in early ischemic stroke predicts smaller infarcts and better outcome *Frontiers Neurol.* **8** 113
Czosnyka M, Smielewski P, Kirkpatrick P, Menon D K and Pickard J D 1996 Monitoring of cerebral autoregulation in head-injured patients *Stroke* **27** 1829–34
Ding X and Zhang Y 2019 Pulse transit time technique for cuffless unobtrusive blood pressure measurement: from theory to algorithm *Biomed. Eng. Lett.* **9** 37–52
Drinnan M J, Allen J and Murray A 2001 Relation between heart rate and pulse transit time during paced respiration *Physiol. Meas.* **22** 425-32
Eames P J, Blake M J, Dawson S L, Panerai R B and Potter J F 2002 Dynamic cerebral autoregulation and beat to beat blood pressure control are impaired in acute ischaemic stroke *J. Neurol. Neurosurg. Psychiatry* **72** 467–72
Eames P J, Potter J F and Panerai R B 2004 Influence of controlled breathing patterns on cerebrovascular autoregulation and cardiac baroreceptor sensitivity *Clin. Sci.* **106** 155–62
Esmaili A, Kachuee M and Shabany M 2017 Nonlinear cuffless blood pressure estimation of healthy subjects using pulse transit time and arrival time *IEEE Trans. Instrum. Meas.* **66** 3299–308
Fabiani M, Low K A, Tan C, Zimmerman B, Fletcher M A, Schneider-Garces N, Maclin E L, Chiarelli A M, Sutton B P and Gratton G 2014 Taking the pulse of aging: mapping pulse pressure and elasticity in cerebral arteries with optical methods *Psychophysiology* **51** 1072–88
Favre M E, Lim V, Falvo M J and Serrador J M 2020 Cerebrovascular reactivity and cerebral autoregulation are improved in the supine posture compared to upright in healthy men and women *PLoS One* **15** e0229049
Foo J Y A, Wilson S J, Williams G R, Harris M and Cooper D M 2005 Pulse transit time changes observed with different limb positions *Physiol. Meas.* **26** 1093
Freeman S S, Udomphorn Y, Armstead W M, Fisk D M and Vavilala M S 2008 Young age as a risk factor for impaired cerebral autoregulation after moderate to severe pediatric traumatic brain injury *J. Am. Soc. Anesthesiologists* **108** 588–95
Furtner M, Staudacher M, Frauscher B, Brandauer E, Esnaola y Rojas M M, Gschliesser V, Poewe W, Schmidauer C, Ritsch-Marte M and Högl B 2009 Cerebral vasoreactivity decreases overnight in severe obstructive sleep apnea syndrome: a study of cerebral hemodynamics *Sleep Med.* **10** 875–81
Gesche H, Grosskurth D, Küchler G and Patzak A 2012 Continuous blood pressure measurement by using the pulse transit time: comparison to a cuff-based method *Eur. J. Appl. Physiol.* **112** 309–15
Heydari F, Ebrahim M P, Redoute J, Joe K, Walker K and Yuce M R 2020 A chest-based continuous cuffless blood pressure method: estimation and evaluation using multiple body sensors *Inf. Fusion* **54** 119–27
Holz C and Wang E J 2017 Glabella: Continuously sensing blood pressure behavior using an unobtrusive wearable device *Proc. of the ACM on Interactive, Mobile, Wearable and Ubiquitous Technologies* 1, 1–23
Hudson L D, Rapala A, Khan T, Williams B and Viner R M 2015 Evidence for contemporary arterial stiffening in obese children and adolescents using pulse wave velocity: a systematic review and meta-analysis *Atherosclerosis* **241** 376–86
Jeong I C and Finkelstein J 2016 Introducing contactless blood pressure assessment using a high speed video camera *J. Med. Syst.* **40** 77
Kao Y, Wang C, Lee S, Wu W and Lee C 2020 Blood pressure measurement based on pulse transit time from different positioned photoplethysmography signals *Proceeding SPIE* 11363 (*Tissue Optics and Photonics*) (Society of Photo-Optical Instrumentation Engineers (SPIE)) pp 113631H
Korhonen V, Hiltunen T, Myllylä T, Wang X, Kantola J, Nikkinen J, Zang Y, LeVan P and Kiviniemi V 2014 Synchronous multiscale neuroimaging environment for critically sampled physiological analysis of brain function: hepta-scan concept *Brain Connectivity* **4** 677–89
Lanata A, Guidi A, Baragli P, Valenza G and Scilingo E P 2015 A novel algorithm for movement artifact removal in ecg signals acquired from wearable systems applied to horses *PLoS One* **10** e0140783
Liu X, Gadhoumi K, Xiao R, Tran N, Smielewski P, Czosnyka M, Hetts S W, Ko N and Hu X 2019 Continuous monitoring of cerebrovascular reactivity through pulse transit time and intracranial pressure *Physiol. Meas.* **40** 01LT01
Madsen P L, Vorstrup S, Schmidt J and Paulson O 1990 Effect of acute and prolonged treatment with propranolol on cerebral blood flow and cerebral oxygen metabolism in healthy volunteers *Eur. J. Clin. Pharmacol.* **39** 295–7
Martin C E, Shaver J A, Leon D F, Thompson M E, Reddy P S and Leonard J J 1974 Autonomic mechanisms in hemodynamic responses to isometric exercise *J. Clin. Invest.* **54** 104–15
Mase M, Mattei W, Cucino R, Faes L and Nollo G 2011 Feasibility of cuff-free measurement of systolic and diastolic arterial blood pressure *J. Electrocardiol.* **44** 201–7
Mol A, Maier A B, van Wezel R J and Meskers C G 2020 Multimodal monitoring of cardiovascular responses to postural changes *Frontiers Physiol.* **11** 168
Mukkamala R, Hahn J, Inan O T, Mestha L K, Kim C, Töreyin H and Kyal S 2015 Toward ubiquitous blood pressure monitoring via pulse transit time: theory and practice *IEEE Trans. Biomed. Eng.* **62** 1879–901
Myllylä T, Korhonen V, Vihriälä E, Sorvoja H, Hiltunen T, Tervonen O and Kiviniemi V 2012 Human heart pulse wave responses measured simultaneously at several sensor placements by two MR-compatible fibre optic methods *J. Sensors* **2012**
Myllylä T, Zacharias N, Korhonen V, Zienkiewicz A, Hinrichs H, Kiviniemi V and Walter M 2017 Multimodal brain imaging with magnetoencephalography: a method for measuring blood pressure and cardiorespiratory oscillations *Sci. Rep.* **7** 172
Myllylä T S, Elseoud A A, Sorvoja H S, Myllylä R A, Harja J M, Nikkinen J, Tervonen O and Kiviniemi V 2011 Fibre optic sensor for non-invasive monitoring of blood pressure during MRI scanning *J. Biophotonics* **4** 98–107
Näsi T, Mäki H, Kotilahti K, Nissilä I, Haapalahti P and Ilmoniemi R J 2011 Magnetic-stimulation-related physiological artifacts in hemodynamic near-infrared spectroscopy signals *PLoS One* **6** e24002
Obeid H, Khettab H, Marais L, Hallab M, Laurent S and Boutouyrie P 2017 Evaluation of arterial stiffness by finger–toe pulse wave velocity: optimization of signal processing and clinical validation *J. Hypertens.* **35** 1618–25
Oster J and Clifford G D 2017 Acquisition of electrocardiogram signals during magnetic resonance imaging *Physiol. Meas.* **38** R119
Pan J and Tompkins W J 1985 A real-time QRS detection algorithm *IEEE Trans. Biomed. Eng.* **BME-32** 230–6
Paulson O B, Strandgaard S and Edvinsson L 1990 Cerebral autoregulation *Cerebrovasc. Brain Metabol. Rev.* **2** 161–92 PMID:2201348
Payne R, Symeonides C, Webb D and Maxwell S 2006 Pulse transit time measured from the ECG: an unreliable marker of beat-to-beat blood pressure *J. Appl. Physiol.* **100** 136–41
Pham P, Bindra J, Aneman A, Chuan A, Worthington J M and Jaeger M 2019 Noninvasive monitoring of dynamic cerebrovascular autoregulation and 'optimal blood pressure'in normal adult subjects *Neurocrit. Care* **30** 201–6
Pitson D J and Stradling J R 1998 Value of beat-to-beat blood pressure changes, detected by pulse transit time, in the management of the obstructive sleep apnoea/hypopnoea syndrome *Eur. Respir. J.* **12** 685–92

Raitamaa L *et al* 2019 Breath hold effect on cardiovascular brain pulsations–a multimodal magnetic resonance encephalography study *J. Cerebr. Blood Flow Metabol.* **39** 2471–85

Reinhard M, Rutsch S, Lambeck J, Wihler C, Czosnyka M, Weiller C and Hetzel A 2012 Dynamic cerebral autoregulation associates with infarct size and outcome after ischemic stroke *Acta Neurol. Scand.* **125** 156–62

Rivera-Lara L, Zorrilla-Vaca A, Geocadin R, Ziai W, Healy R, Thompson R, Smielewski P, Czosnyka M and Hogue C W 2017 Predictors of outcome with cerebral autoregulation monitoring: a systematic review and meta-analysis *Crit. Care Med.* **45** 695–704

Scheer B V, Perel A and Pfeiffer U J 2002 Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine *Crit. Care* **6** 1–7

Shahsavari S, McKelvey T, Rydenhag B and Ritzén C E 2010 Pulse wave velocity in patients with severe head injury a pilot study *2010 Annual Int. Conf. of the IEEE Engineering in Medicine and Biology (Piscataway, NJ)* (IEEE) pp 5277

Uryga A, Placek M M, Wachel P, Szczepański T, Czosnyka M and Kasprowicz M 2017 Phase shift between respiratory oscillations in cerebral blood flow velocity and arterial blood pressure *Physiol. Meas.* **38** 310

van Velzen M H, Loeve A J, Niehof S P and Mik E G 2017 Increasing accuracy of pulse transit time measurements by automated elimination of distorted photoplethysmography waves *Med. Biol. Eng. Comput.* **55** 1989–2000

Wentland A L, Grist T M and Wieben O 2014 Review of MRI-based measurements of pulse wave velocity: a biomarker of arterial stiffness *Cardiovasc. Diagn. Ther.* **4** 193–206

Xu Y, Ping P, Wang D and Zhang W 2018 Analysis for the influence of abr sensitivity on PTT-based cuff-less blood pressure estimation before and after exercise *J. Healthcare Eng.* **2018**

Zhang G, Gao M, Xu D, Olivier N B and Mukkamala R 2011 Pulse arrival time is not an adequate surrogate for pulse transit time as a marker of blood pressure *J. Appl. Physiol.* **111** 1681–6

Zienkiewicz A 2017 Blood pressure estimation using pulse transit time models *Master's Thesis* University of Oulu (http://urn.fi/URN:NBN:fi:oulu-201712063289)