Title

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Journal

physiological measurement, 40(1)

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Publication Date

2019-01-22

Data Availability

The data associated with this publication are available upon request.

Peer reviewed

IOP Publishing Physiol. Meas. 40 (2019) 01LT01 (9pp) https://doi.org/10.1088/1361-6579/aafab1

Physiological Measurement

IPEM Institute of Physics and Engineering in Medicine

RECEIVED
20 September 2018

REVISED
13 December 2018

ACCEPTED FOR PUBLICATION
21 December 2018

PUBLISHED
22 January 2019

LETTER

Continuous monitoring of cerebrovascular reactivity through pulse transit time and intracranial pressure

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Keywords: cerebrovascular reactivity, intracranial pressure, pulse transit time, non-invasive arterial blood pressure

Supplementary material for this article is available online

Abstract

Objective: Cerebrovascular reactivity (CR) is a mechanism that maintains stable blood flow supply to the brain. Pressure reactivity index (PRx), the correlation coefficient between slow waves of invasive arterial blood pressure (ABP) and intracranial pressure (ICP) has been validated for CR assessment. However, in clinical ward, not every subarachnoid hemorrhage (SAH) patient has invasive ABP monitoring. Pulse transit time (PTT), the propagation time of a pulse wave travelling from the heart to peripheral arteries, has been suggested as a surrogate measure of ABP. In this study, we proposed to use PTT instead of invasive ABP to monitor CR. *Approach*: Forty-five SAH patients with simultaneous recordings of invasive ABP, ICP, oxygen saturation level (SpO2) and electrocardiograph (ECG) were included. PTT was calculated as the time from the ECG R-wave peak to the onset of SpO2. PTT based pressure reactivity index (tPRx) was calculated as the correlation coefficient between slow waves of PTT and ICP. Wavelet tPRx (wtRx) was calculated as the cosine of wavelet phase shift between PTT and ICP. Meanwhile, PRx and wPRx were also calculated using invasive ABP and ICP as input. *Main results*: The result showed a negative relationship between PTT and ABP ($r = -0.58, p < 0.001$). tPRx negatively correlated with PRx ($r = -0.51$, $p = 0.003$). Wavelet method correlated well with correlation method demonstrated through positive relationship between wPRx and PRx ($r = 0.82, p < 0.001$) as well as wtPRx and tPRx ($r = 0.84$, $p < 0.001$). *Significance*: PTT demonstrates great potential as a useful tool for CR assessment when invasive ABP is unavailable.

Key points

- Pulse transit time (PTT), defined as the propagation time of a pulse wave travelling from the heart to the peripheral arteries, has been proposed as a surrogate measure of ABP. The relationship between PTT and ABP in SAH patients remains unknown.
- Cerebrovascular reactivity (CR) assessment through PTT has advantages over invasive ABP, as it avoids bleeding and infection risk, and can be used outside of the ICU.
- We introduced a new method to assess CR using PTT and ICP through correlation based method and wavelet based method.

- We found that beat-to-beat PTT was negatively related with invasive ABP in SAH patients. A significant linear relationship exists between PTT-based CR parameter and a well validated method, PRx. PTT demonstrates great potential as a useful tool for CR assessment when invasive ABP is unavailable in SAH patients.

Introduction

Cerebrovascular reactivity (CR) is an important mechanism to maintain stable oxygen and nutrition supply to the brain through regulation of cerebral blood flow (CBF) over a wide range of arterial blood pressure (ABP) (Addison 2015, Caldas *et al* 2018). Currently, there is no gold standard to assess dynamic CR, neither for the experimental protocol nor for how to process the recorded clinical signals including ABP, intracranial pressure (ICP) or CBF (Claassen *et al* 2016). Methods for CR assessment are still controversial: on the one hand, some studies suggest that spontaneous fluctuations should be used to assess the relationship between ABP and CBF whenever possible (Tzeng and Panerai 2018); on the other hand, other investigators suggest that more robust results can be obtained using manoeuvers that induce larger changes in ABP than normally observed at rest (Simpson and Claassen 2018). However, on a practical level, the spontaneous fluctuations are favored due to its convenience, ease of operation, high availability and continuity in intensive care units (ICU).

Over the past two decades, considerable progress has been made in assessing CR through spontaneous waves, including correlation methods (Lee *et al* 2011, Da Costa *et al* 2015, Highton *et al* 2015, Czosnyka *et al* 1997), frequency domain methods (e.g. transfer function method) (Blaber *et al* 1997, Panerai *et al* 2002, Meel-van den Abeelen *et al* 2014) and time-frequency domain methods (e.g. wavelet methodology) (Highton *et al* 2014, Addison 2015, Tian *et al* 2016, Liu *et al* 2017). Among all these methods, pressure reactivity index (PRx), calculated as the correlation coefficient between slow waves of invasive ABP and ICP, has been widely used in different cohorts of patients (Czosnyka *et al* 1997, Steiner *et al* 2003, Tseng *et al* 2006, Brady *et al* 2009, Lewis *et al* 2015), and proved to be related to patient outcome after head injury (Balestreri *et al* 2006). PRx has also been used to determine optimal cerebral perfusion pressure value for traumatic brain injury patients (Steiner *et al* 2002, Aries *et al* 2012).

However, not every patient in clinical ward has invasive ABP monitoring. Standard monitoring in ICU includes electrocardiograph (ECG, for heart rate and rhythm monitoring) and pulse oximetry (for oxygen saturation level (SpO2) measurement) (Perkins *et al* 2003, Van Oostrom and Melker 2004). Invasive ABP is normally measured in ventilated patients or moderate- to high-risk patients by inserting an arterial line, most often in the radial or femoral artery (Svensen *et al* 2018). An alternative method to invasive ABP measurement is pulse transit time (PTT) (Singham *et al* 2003, Sugo *et al* 2010), defined as the propagation time of a pulse wave from the heart to the peripheral arteries (e.g. a finger or a toe) and is generally calculated as the time between the R-peak of the ECG and the onset of the corresponding pulse wave at the given peripheral site (figure 1) (Foo *et al* 2005, Vlahandonis *et al* 2014, van Velzen *et al* 2017). Because a portion of PTT is determined by peripheral arterial stiffness that is also under influence of systemic blood pressure, a large body of research has been carried out to develop noninvasive beat-to-beat estimation of blood pressure from PTT (Pitson and Stradling 1998, Galland *et al* 2007, Xu *et al* 2011). While challenges still exist in obtaining accurate estimation of absolute ABP from PTT due to various reasons, e.g. motion artifacts, the assumption that the component of pre-ejection period (PEP) in PTT is not related to ABP (Payne 2006, Zhang *et al* 2011, Buxi *et al* 2015), it is possible that relative changes in PTT can substitute changes in ABP as input to assess CR. CR assessment through PTT has advantages over invasive ABP, as it avoids bleeding and infection risk, and can be used outside of the ICU (Lehman *et al* 2013). However, to our knowledge, no study has used PTT to assess CR previously. Moreover, while the relationship between ABP and PTT has been studied in normal subjects and in patients with sleep disorders, hypertension (Drinnan *et al* 2001, Kim *et al* 2013, Vlahandonis *et al* 2014), it has not been studied for patients with aneurysmal subarachnoid hemorrhage (SAH). In addition to hydrocephalus, SAH patients are at risk to develop cerebral vasospasm and infarction in the days and weeks following aneurysm rupture (Jun *et al* 2010). Having a noninvasive method to identify SAH patients with cerebral vasospasm—such as through the measurement of CR—would improve triage of ICU patients to be taken to the angiography suite where endovascular therapies can reverse cerebral vasospasm and prevent infarction.

Hence, we conducted the present study with the following objectives: (1) to test if changes in invasive ABP are correlated with changes in noninvasive PTT in SAH patients; (2) to evaluate the potential of using PTT to estimate CR.

Materials and methods

A total of 181 nontraumatic aneurysmal SAH patients admitted to University of California, San Francisco Medical Center (San Francisco, CA, USA) between March 2013 and September 2016 were studied retrospectively.

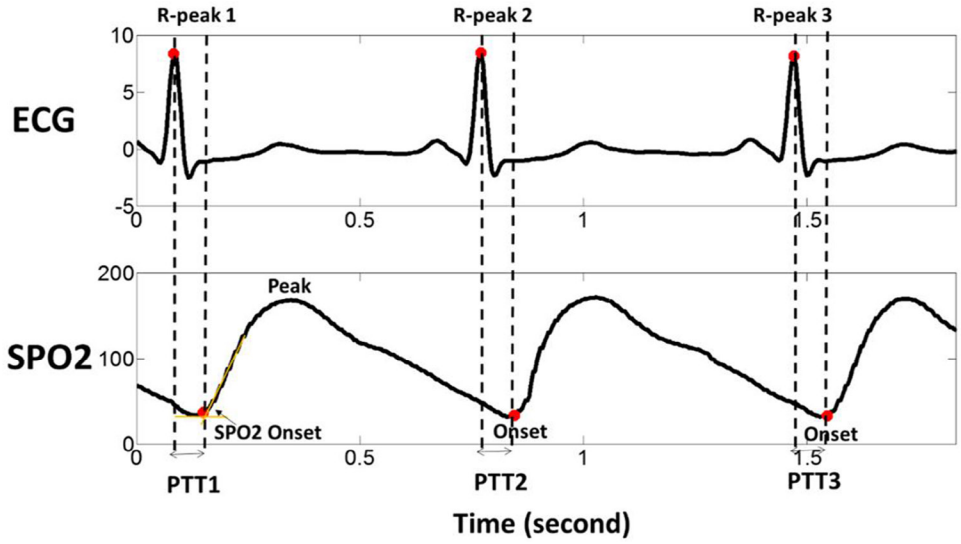

Figure 1. Graphical explanation of PTT calculation when using the pulse wave onset as the landmark that indicates arrival of the pulse wave. ECG: electrocardiogram, SpO2: blood oxygen saturation.

To be included in the study, subjects must have continuous monitoring of ICP, SpO2, ECG and ABP. 45 of 181 SAH patients met the inclusion and exclusion criteria and were selected for this study. The data were collected during external ventricular drain (EVD) clamping trials.

Continuous ICP was monitored through EVD (LimiTorr 20 or 30 ml, Integra, New Jersey, USA) while it is closed to cerebral spinal fluid drainage; SpO2 was monitored through a pulse oximeter (PILSOX-1, Konica Minolta Sensing, Osaka, Japan); ECG was recorded using 5-lead configuration for all patients (Drew *et al* 2014); ABP was monitored invasively through the radial or femoral artery using a standard pressure monitoring kit (Baxter Healthcare, CardioVascular Group, Irvine, CA). All data were recorded through BedMasterEx software (Excel Medical Electronics, Inc., Jupiter, FL) at a sampling rate of 240 Hz (Drew *et al* 2014). Artifacts due to patient movement or bedside interventions were removed manually through ICM + software (University of Cambridge, Cambridge Enterprise, Cambridge, UK, www.neurosurg.cam.ac.uk/icmplus). The data were retrieved from a continuous archival of patient monitoring data under an approved institutional review board (IRB) protocol. Each patient provided written informed consent. The result of the clamping test was solely clinically based without any influence from this study.

Calculation of PTT, beat-to-beat mean ICP and ABP

As shown in figure 1, PTT was calculated as the time from the ECG R-wave peak to the onset point of the pulse oximeter wave (SpO2). The onset point of SpO2 was determined using an algorithm as described previously for finding onset of ICP pulses (Hu *et al* 2008). This algorithm is robust to the presence of missed or spurious ECG beat detections, which is a critical feature for handling signals recorded in clinical settings. Parameters in the original algorithm were tweaked to match the range of SpO2 PTT because these parameters were designed for ICP pulse. In our data set, beat-to-beat mean value of ICP and ABP was calculated by one beat ahead of PTT calculation to synchronize the data, which means the average value of ICP, ABP between R-peak 1 and R-peak 2, was aligned with PTT2 rather than PTT1 in figure 1.

Cerebrovascular reactivity (CR)

PRx and transit PRx (tPRx)

PRx was calculated as a moving Pearson correlation coefficient between 10 s averages of ABP and ICP, using a 300 s data window (Czosnyka *et al* 1997). tPRx was calculated as a moving Pearson correlation coefficient between 10 s averages of PTT and ICP, using a 300 s window.

Wavelet PRx and wavelet tPRx (wtRx)

We used the wavelet transform method to assess CR (Addison 2002), as it has recently been proved to show more stable result than PRx in a cohort of TBI patients (Liu *et al* 2017) and also in animal experiments (Liu *et al* 2018). In this study, the wavelet transform phase shift (WTP) between ABP and ICP was calculated in the frequency of 0.0067 Hz–0.05 Hz by using Morlet mother wave (Liu *et al* 2017). An 800 s window was used to calculate WTP, in order to allow enough data points to be calculated after removing the edge effect. More details about the criteria of selecting frequency band and about the edge effect can be found in our previous publication (Liu *et al* 2017).

The calculation of WTP was updated every 10 s. The cosine of the WTP angle was calculated afterwards, termed wPRx. The same calculation was also done by using PTT and ICP as input, rendering wtPRx. More details about the algorithm were described in our previous publications (Liu *et al* 2017, 2018).

Statistical analysis

Statistical analyses were performed using Matlab software (ver. R2012A, MathWorks, Inc.) and SPSS (version 25.0, IBM, NY, USA). To analyze the inter-individual correlation between different parameters, the averaged values of PTT, ABP, PRx and tPRx were calculated across the whole monitoring period for each patient (one value per patient). Spearman's correlation coefficient (R) between the mean values was calculated. A simple linear regression was used to describe the relationship between the mean values of the tested parameters. $p < 0.05$ was considered to be significant relationship.

In order to analyze the intra-individual correlation between these parameters, 5 min averaged data were calculated, resulting in multiple measurements for each patient. Then the linear mixed-effects models with random intercepts and slopes were conducted to assess the intra-individual correlations of repeated measurements between PTT and ABP, and between PRx and tPRx (Twisk 2006, Magezi 2015, Zhang *et al* 2017, Curran *et al* 2011, Van Der Leeden *et al* 1998, Minalu *et al* 2011). In a linear mixed-effects model, $Y_{ij} = \beta_0 + \beta_1 X_{ij} + \mu_{i0} + \mu_{i1} X_{ij} + \varepsilon_{ij}$, where Y_{ij} (PTT or tPRx) is the response of jth measurement of ith subject; β_0 is the fixed intercept for the regression model; β_1 is the fixed slope for the regression model; X_{ij} (ABP or PRx) is the predictor for jth measurement of ith subject; $\mu_{i0} \overset{iid}{\sim} N(0,\ \sigma_0^2)$ is the random intercept for the ith subject, *iid* means independent and identically distributed and σ is standard deviation; $\mu_{i1} \overset{iid}{\sim} N(0,\ \sigma_1^2)$ is the random slope for the ith subject, $\varepsilon_{ij} \overset{iid}{\sim} N\ (0,\ \sigma_1^2)$ is a Gaussian error term. The correlation coefficient was calculated through the formula below:

$$\text{Correlation} = \frac{\text{Covariance}}{\sqrt{\text{variance of intercepts}} \times \sqrt{\text{variance of fixed effects}}}.$$

Here, the covariance refers to the covariance of the intercepts and the fixed effects.

Standard deviation (SD) of each parameter was calculated across the whole monitoring period (one value per patient) to assess the variability of the parameters. Student t test was applied to compare whether there is significant difference in the variability of the tested parameters.

Results

The group of patients included 27 females and 18 males. Their mean age was 59.3 ± 16.3 (mean ± SD) years old. The mean recording time per patient after artifact removal was 73 min (range from 17 min to 233 min). The average ABP and ICP of this cohort was 79.8 ± 20.5 mmHg and 10.9 ± 9.9 mmHg, respectively. The average PTT was 193.7 ± 124.9 milliseconds (ms). An example of time trends of ABP, ICP, PTT, PRx, and tPRx is shown in figure 2.

The inter-individual correlation between the tested parameters

The average value of each tested parameter was calculated across the whole recording of each patient (one value one patient), and the correlation was studied using Spearman's correlation coefficient (R) as shown in figure 3 ($n = 45$). There was a statistically significant, negative, correlation between PTT and ABP, which can be described through a linear regression: $\text{PTT} = 477.0 - 3.55 \times \text{ABP}$ (figure 3(A), $R = -0.58, p < 0.001, n = 45$); PRx negatively correlated with tPRx (figure 3(B), $\text{tPRx} = 0.03 - 0.36 \times \text{PRx}$, $R = -0.51$, $p = 0.003$, $n = 45$). Wavelet method correlated well with correlation method demonstrated through linear, positive relationship between wPRx and PRx (figure 3(C), $R = 0.82$, $p < 0.001$, $n = 45$) as well as wtPRx and tPRx (figure 3(D), $R = 0.84, p < 0.001, n = 45$).

The intra-individual association between PRx and tPRx

The linear mixed-effects models analysis showed a significant, negative relationship between ABP and PTT (figure 4(A), $p < 0.001$). A unit increase in ABP was associated with 2.36 unit decrease in PTT (95% CI: −3.56 to −1.13). The correlation coefficient between ABP and PTT calculated through the linear mixed-effects models was −0.94 (covariance of intercept and ABP was −781.3 [−1269.4 to −293.3], the variance of intercept and ABP was 76 430.4 [42 663–136 924] and 9 [4.82–16.83] respectively).

There was a significant, negative relationship between PRx and tPRx (figure 4(B), $p = 0.001$). A unit increase in PRx was associated with 0.21 unit decrease in tPRx (95% CI: −0.32 to −0.09). The correlation coefficient between PRx and tPRx calculated through the linear mixed-effects models was −0.24 (covariance of intercept and ABP was −0.007 [−0.025–0.01], the variance of intercept and ABP was 0.014 [0.007–0.028] and 0.06 [0.02–0.17] respectively).

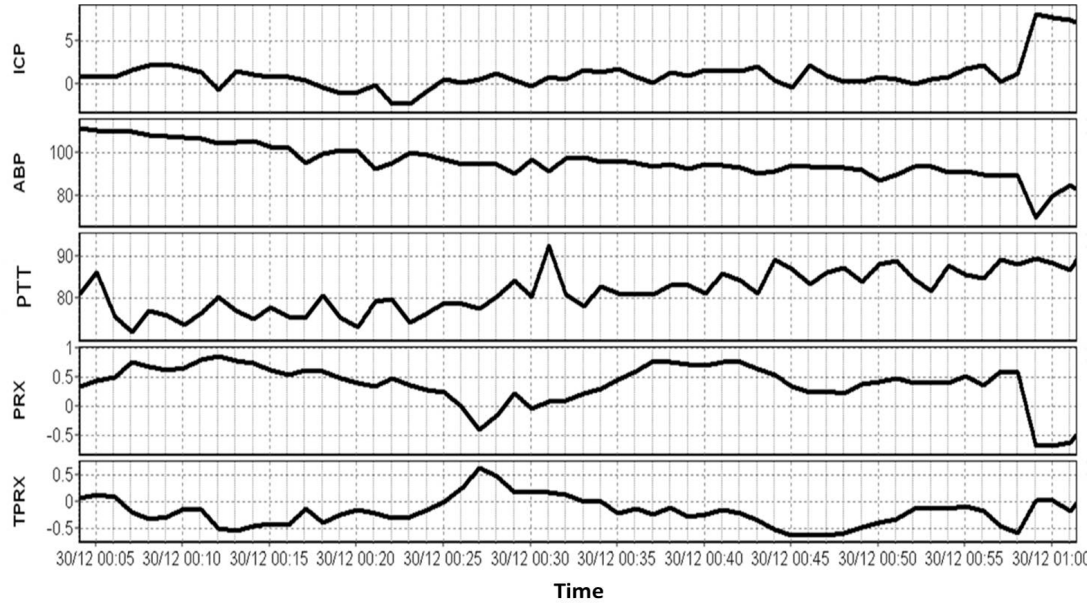

Figure 2. An example of time trends of ABP, ICP, PTT, PRx, and tPRx. ABP: arterial blood pressure; ICP: intracranial pressure; PTT: pulse transit time; PRx: pressure reactivity index; tPRx: transit PRx.

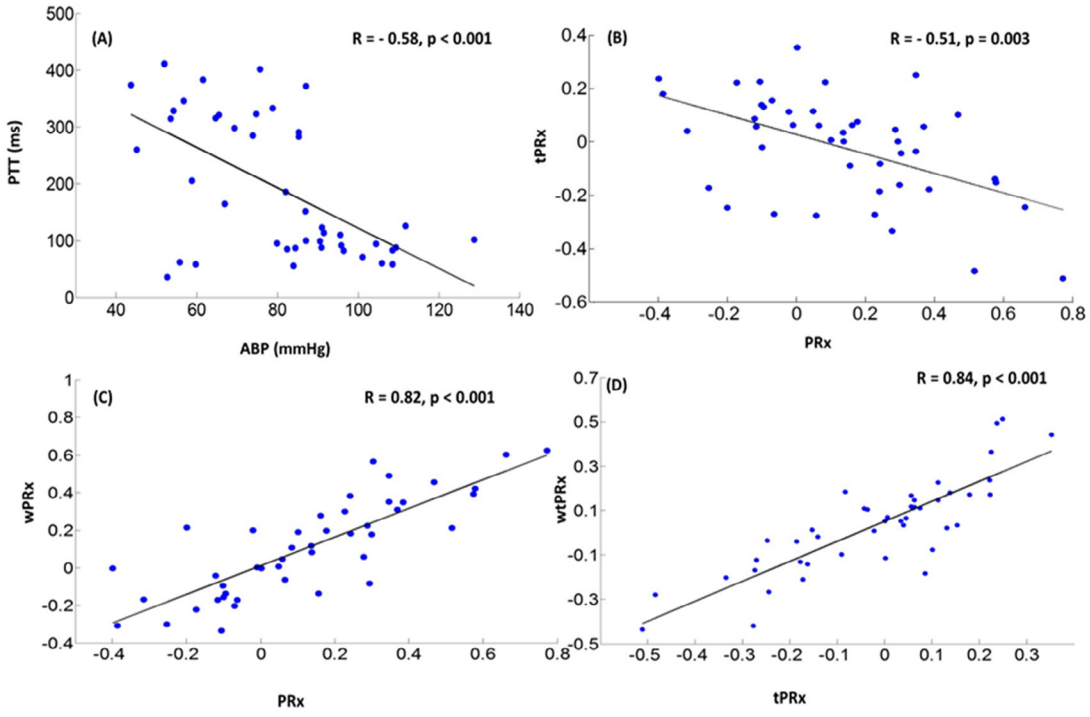

Figure 3. Inter -individual relationship between the tested parameters. (A) A statistically significant, negative correlation exists between PTT and ABP; (B) a statistically significant, negative correlation exists between PRx and tPRx; (C) there is a linear relationship between wPRx and PRx; (D) a linear relationship exists between wtPRx and tPRx ($n = 45$). ABP: arterial blood pressure; PTT: pulse transit time; ICP: intracranial pressure; PRx: pressure reactivity index, correlation coefficient between slow waves of ABP and ICP; tPRx: transit PRx, correlation coefficient between slow waves of PTT and ICP; wPRx: wavelet phase shift between ABP and ICP; wtPRx: wavelet phase shift between PTT and ICP.

Variability of wavelet method and correlation method

In order to compare the variability of wavelet method and correlation method, we compared the standard deviation of the tested parameters of each patient across the whole monitoring time using student t test. The result showed wPRx was more stable than PRx (mean SD of wPRx was 0.22 versus mean SD of PRx was 0.33, $p < 0.001$). Similar conclusion can also be drawn for wtPRx and tPRx (mean SD of wtPRx was 0.23 versus mean SD of tPRx was 0.31, $p < 0.001$).

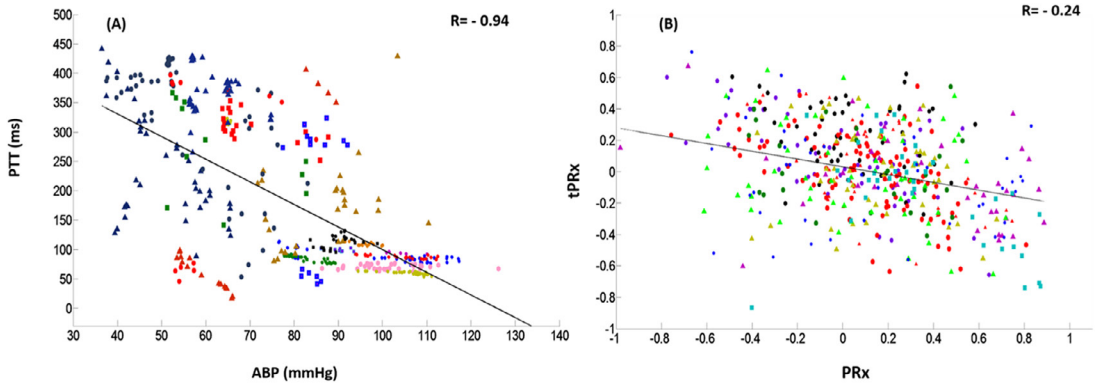

Figure 4. Intra-individual association between PTT and ABP, as well as between PRx and tPRx. (A) A negative correlation exists between PTT and ABP. (B) A negative correlation exists between tPRx and PRx. ABP: arterial blood pressure; PTT: pulse transit time; PRx: pressure reactivity index, correlation coefficient between slow waves of ABP and ICP; tPRx: transit PRx, correlation coefficient between slow waves of PTT and ICP. One color marker represents one patient.

Discussion

Noninvasive and cuffless measurement ABP is desirable for patient monitoring. Various methods have been developed to measure ABP noninvasively and continuously, which include arterial tonometry (e.g. Colin® tonometer), volume clamp method (e.g. Finapres) and PPT-based method (Teng and Zhang 2006). However, the arterial tonometer suffers from relatively high cost, and its accuracy decreased by wrist movement (Teng and Zhang 2006); and the volume clamp method needs a small inflatable cuff to measure beat-to-beat noninvasive ABP (Aitken *et al* 1991). Derived from routinely bedside signals (ECG and photoplethysmography, PPG), the PPT-based noninvasive ABP avoids the danger of cessation of perfusion to finger that might be caused by volume clamp method (Teng and Zhang 2006). However, the use of PTT as a surrogate measurement of ABP is still controversial. Some studies have shown a direct relationship between ABP and PTT in healthy patients and hypertensive patients (Pitson *et al* 1994, Foo *et al* 2005, Kim *et al* 2013); while others concluded inverse results (Payne 2006, Zhang *et al* 2011). Our study demonstrated a significant negative correlation between beat-to-beat PTT and invasive ABP in SAH patients. An increase in ABP causes a change in the geometric and mechanical properties of the arterial wall (e.g. vascular constriction), leading to increased stiffness (Foo and Wilson 2009, Vlahandonis *et al* 2014). This, in turn, causes pulse waves to travel faster, and consequently leads to a reduction in PTT (Galland *et al* 2007, Foo and Wilson 2009). On the contrary, a decrease in ABP leads to increase in PTT.

However, as measured at the peripheral arteries, PTT is also influenced by many other factors such as individual differences in vascular compliance, PEP, arm length, etc (Vlahandonis *et al* 2014), the PTT-based noninvasive ABP might be different from the invasive ABP measured from intravascular catheter in terms of waveforms and also systolic and diastolic values (Chin and Panerai 2013). In the calculation of CR, we care more about the relative changes of PTT rather than the absolute value, where peripheral measurements of ABP are not very problematic (Sammons *et al* 2007). Our results showed that PTT can replace direct ABP measurement in continuous monitoring of CR through the significant negative relationship between PRx and tPRx ($p = -0.51$). For PRx, a negative value indicates a pressure-active vascular bed with preserved CR, whereas a positive value indicates a pressure-passive vascular bed with impaired reactivity (Kvandal *et al* 2013). While for tPRx, high tPRx means high ICP is related with high PTT, which is normally due to low ABP; thus, high tPRx actually reflects close relationship between high ICP and low ABP and it refers to good CR; and vice versa. This study suggests a potential method of using PTT for CR measurement in SAH patients. Because of its ease of use, portability and applicability in a wide range of clinical settings of pulse oximeters (Lipnick *et al* 2016), PTT might bring benefits for future CR assessment.

Moreover, this study compared PRx with tPRx using data collected from 45 SAH patients. Although a significant negative correlation was found, both PRx and tPRx make use of the same ICP data and are not therefore completely independent. This may lead to a spurious correlation. Therefore, in order to clear this suspect, we randomly shuffled each patient's ICP, and used the original ABP and shuffled ICP to calculate 'artificial' PRx and used the original PTT and shuffled ICP to calculate 'artificial' tPRx. There is no significant relationship between the 'artificial' PRx and tPRx. The mean value of the PRx and tPRx using shuffled ICP was obtained for each patient, and the inter-individual correlation between the mean values of PRx and tPRx was 0.04 ($n = 45$, $p = 0.81$, supplementary figure 1 (stacks.iop.org/PM/40/01LT01/mmedia)). Therefore, the relationship between PRx and tPRx using real ABP or PTT and real ICP is not spurious. However, we still need larger numbers of patients to support the conclusion that the tPRx is a good surrogate for PRx.

The study also utilized a recently validated method, wavelet method for CR calculation. The wavelet method has shown more stable results than correlation-based method in TBI patients and it was more strongly associated with patient outcome. This study validated the wavelet method in SAH patients. Big wPRx values reflect small phase shifts between fluctuations in ABP and ICP, indicating direct changes in ICP following ABP because of impaired cerebrovascular function. The good correlation between PRx and wPRx matched our previous findings in a TBI cohort (Liu *et al* 2017). Moreover, we compared the standard deviation (SD) of the tested parameters in this SAH cohort, the result showed smaller SD of wPRx than the SD of PRx ($p < 0.001$), and smaller SD of wtPRx than the SD of tPRx ($p < 0.001$). The improved precision of wavelet method versus correlation method may be explained by the robustness of the wavelet method for determining phase shift from nonstationary signals (Keissar *et al* 2009). While correlation measurement takes all the information into calculation without removing any uncertain noise, wavelet method by using wavelet coherence as a filter, guarantees a reliable relationship between input and output. By removing points that represent noise, wavelet method produces a more stable estimation of pressure reactivity than traditional correlation method.

Limitation

In this study, we only collected data from 45 SAH patients, which is a rather small cohort. Further analysis needs to be carried out on a larger cohort of patients than in this study and on patients with other conditions. Calculation of PTT in this study does not take cardiac PEP into account, which represents the total duration of the electrical and mechanical events prior to the ejection of blood from the left ventricle (i.e. the electrical mechanical delay) defined by the opening of the aortic valve (Newlin and Levenson 1979). Payne *et al* demonstrated that PEP accounts for 12% to 35% of PTT variation (Payne 2006), but there were also other studies showing that the PEP variations can be considered negligible (Masè *et al* 2011). PEP during a resting state, such as SAH patients in our study, should have a rather low contribution (Vlahandonis *et al* 2014) to PTT demonstrated by the significant, negative relationship between PTT and ABP in our results. The method is a step toward non-invasive continuous monitoring of CR. If ICP measurement can be substituted with total hemoglobin NIRS measurement, this objective may be achieved.

Conclusion

In summary, beat-to-beat PTT showed good correlation with invasive ABP in SAH patients. Beat-to-beat PTT may be useful for CR assessment when invasive ABP is unavailable in SAH patients.

Acknowledgment

We sincerely thank Dr Bruce Cooper (School of Nursing, University of California, San Francisco, CA, United States of America) for his great help with our statistical analysis. We acknowledge the support from the National Institutes of Health (NIH) NS106905-01A1 and R01NS076738. We also acknowledge the support from Institute for Computational Health Sciences, University of California, San Francisco for the Middle Career Scientist Award.

Competing interests

ICM + Software is licensed by Cambridge Enterprise, Cambridge, UK (http://icmplus.neurosurg.cam.ac.uk). MC and PS have a financial interest in a fraction of the licensing fee.

Author contributions

The concept and study design were formed by XH and XYL. Data acquisition and data analysis were conducted by NT and XYL. Data interpretation was conducted by KG, RX, PS, MC, SH, and NK. Drafting of the manuscript and figures was contributed by XYL and XH. XYL, KG, RX, NT, PS, MC, SH, NK and XH revised the manuscript and approved the submission.

References

Addison P S 2002 *The Illustrated Wavelet Transform Handbook: Introductory Theory and Applications in Science, Engineering, Medicine and Finance 1st Edition* (Boca Raton, FL: CRC Press)

Addison P S 2015 A review of wavelet transform time-frequency methods for NIRS-based analysis of cerebral autoregulation *IEEE Rev. Biomed. Eng.* **8** 78–85

Aitken H A, Todd J G and Kenny G N C 1991 Comparison of the finapres and direct arterial pressure monitoring during profound hypotensive anaesthesia *Br. J. Anaesth.* **67** 36–40
Aries M J H *et al* 2012 Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury *Crit. Care Med.* **40** 2456–63
Balestreri M, Czosnyka M, Hutchinson P, Steiner L A, Hiler M, Smielewski P and Pickard J D 2006 Impact of intracranial pressure and cerebral perfusion pressure on severe disability and mortality after head injury *Neurocrit. Care* **4** 8–13
Blaber A P, Bondar R L, Stein F, Dunphy P T, Moradshahi P, Kassam M S and Freeman R 1997 Transfer function analysis of cerebral autoregulation dynamics in autonomic failure patients *Stroke.* **28** 1686–92
Brady K M, Shaffner D H, Lee J K, Easley R B, Smielewski P, Czosnyka M, Jallo G I and Guerguerian A-M 2009 Continuous monitoring of cerebrovascular pressure reactivity after traumatic brain injury in children *Pediatrics* **124** e1205–12
Buxi D, Redouté J-M and Yuce M R 2015 A survey on signals and systems in ambulatory blood pressure monitoring using pulse transit time *Physiol. Meas.* **36** 1–26
Caldas J R, Haunton V J, Panerai R B, Hajjar L A and Robinson T G 2018 Cerebral autoregulation in cardiopulmonary bypass surgery: a systematic review *Interact. Cardiovasc. Thorac. Surg.* **26** 494–503
Chin K Y and Panerai R B 2013 A new noninvasive device for continuous arterial blood pressure monitoring in the superficial temporal artery *Physiol. Meas.* **34** 407–21
Claassen J A, Meel-van den Abeelen A S, Simpson D M, Panerai R B and International Cerebral Autoregulation Research Network (CARNet) 2016 Transfer function analysis of dynamic cerebral autoregulation: a white paper from the International Cerebral Autoregulation Research Network *J. Cereb. Blood Flow Metab.* **36** 665–80
Curran P J and Bauer D J 2011 The disaggregation of within-person and between-person effects in longitudinal models of change *Annu Rev Psychol.* **62** 583–619
Czosnyka M, Czosnyka Z and Smielewski P 2017 Pressure reactivity index: journey through the past 20 years *Acta Neurochir.* **159** 2063–5
Czosnyka M, Smielewski P, Kirkpatrick P, Laing R J, Menon D and Pickard J D 1997 Continuous assessment of the cerebral vasomotor reactivity in head injury *Neurosurgery* **41** 11–9
Da Costa C S, Czosnyka M, Smielewski P, Mitra S, Stevenson G N and Austin T 2015 Monitoring of cerebrovascular reactivity for determination of optimal blood pressure in preterm infants *J. Pediatr.* **167** 86–91
Drew B J, Harris P, Zègre-Hemsey J K, Mammone T, Schindler D, Salas-Boni R, Bai Y, Tinoco A, Ding Q and Hu X 2014 Insights into the problem of alarm fatigue with physiologic monitor devices: a comprehensive observational study of consecutive intensive care unit patients *PLoS One* **9** e110274
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
Foo J Y A and Wilson S J 2009 Clinical applications of pulse transit time in paediatric critical care *J. Med. Eng. Technol.* **33** 79–86
Foo J Y A, Wilson S J, Dakin C, Williams G, Harris M A and Cooper D 2005 Variability in time delay between two models of pulse oximeters for deriving the photoplethysmographic signals *Physiol. Meas.* **26** 531–44
Galland B C, Tan E and Taylor B J 2007 Pulse transit time and blood pressure changes following auditory-evoked subcortical arousal and waking of infants *Sleep* **30** 891–7
Highton D, Ghosh A, Tachtsidis I, Elwell C and Smith M 2014 Analysis of slow wave oscillations in cerebral haemodynamics and metabolism following subarachnoid haemorrhage *Adv. Exp. Med. Biol.* **812** 195–201
Highton D, Ghosh A, Tachtsidis I, Panovska-Griffiths J, Elwell C E and Smith M 2015 Monitoring cerebral autoregulation after brain injury: multimodal assessment of cerebral slow-wave oscillations using near-infrared spectroscopy *Anesth. Analg.* **121** 198–205
Hu X, Xu P, Lee D J, Vespa P, Baldwin K and Bergsneider M 2008 An algorithm for extracting intracranial pressure latency relative to electrocardiogram *R* wave *Physiol. Meas.* **29** 459–71
Jun P, Ko N U, English J D, Dowd C F, Halbach V V, Higashida R T, Lawton M T and Hetts S W 2010 Endovascular treatment of medically refractory cerebral vasospasm following aneurysmal subarachnoid hemorrhage *AJNR. Am. J. Neuroradiol.* **10** 1911–6
Keissar K, Davrath L R and Akselrod S 2009 Coherence analysis between respiration and heart rate variability using continuous wavelet transform *Phil. Trans.* A **367** 1393–406
Kim S H, Song J G, Park J H, Kim J W, Park Y S and Hwang G S 2013 Beat-to-beat tracking of systolic blood pressure using noninvasive pulse transit time during anesthesia induction in hypertensive patients *Anesth. Analg.* **116** 94–100
Kvandal P, Sheppard L, Landsverk S A, Stefanovska A and Kirkeboen K A 2013 Impaired cerebrovascular reactivity after acute traumatic brain injury can be detected by wavelet phase coherence analysis of the intracranial and arterial blood pressure signals *J. Clin. Monit. Comput.* **27** 375–83
Lee J K *et al* 2011 Cerebral blood flow and cerebrovascular autoregulation in a swine model of pediatric cardiac arrest and hypothermia *Crit. Care Med.* **39** 2337–45
Lehman L W H, Saeed M, Talmor D, Mark R and Malhotra A 2013 Methods of blood pressure measurement in the ICU *Crit. Care Med.* **41** 34–40
Lewis P M, Czosnyka M, Carter B G, Rosenfeld J V, Paul E, Singhal N and Butt W 2015 Cerebrovascular pressure reactivity in children with traumatic brain injury *Pediatr. Crit. Care Med.* **16** 739–49
Lipnick M S, Feiner J R, Au P, Bernstein M and Bickler P E 2016 The accuracy of 6 inexpensive pulse oximeters not cleared by the food and drug administration: the possible global public health implications *Anesth. Analg.* **123** 338–45
Liu X, Czosnyka M, Donnelly J, Cardim D, Cabeleira M, Hutchinson P J, Hu X, Smielewski P and Brady K 2018 Wavelet pressure reactivity index: a validation study *J. Physiol.* **596** 2797–809
Liu X *et al* 2017 Cerebrovascular pressure reactivity monitoring using wavelet analysis in traumatic brain injury patients: a retrospective study *PLoS Med.* **14** 7
Magezi D A 2015 Linear mixed-effects models for within-participant psychology experiments: an introductory tutorial and free, graphical user interface (LMMgui) *Frontiers Psychol.* **6** 2
Masè 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
Meel-van den Abeelen A S S *et al* 2014 Between-centre variability in transfer function analysis, a widely used method for linear quantification of the dynamic pressure-flow relation: the CARNet study *Med. Eng. Phys.* **36** 620–7
Minalu G, Aerts M, Coenen S, Versporten A, Muller A, Adriaenssens N, Beutels P, Molenberghs G, Goossens H and Hens N 2011 Application of mixed-effects models to study the country-specific outpatient antibiotic use in Europe: a tutorial on longitudinal data analysis *J. Antimicrob. Chemother.* **66** 79–87
Newlin D B and Levenson R W 1979 Pre-ejection period: measuring beta-adrenergic influences upon the heart *Psychophysiology* **16** 546–52

Panerai R B, Hudson V, Fan L, Mahony P, Yeoman P M, Hope T and Evans D H 2002 Assessment of dynamic cerebral autoregulation based on spontaneous fluctuations in arterial blood pressure and intracranial pressure *Physiol Meas* **23** 59–72
Payne R A 2006 Pulse transit time measured from the ECG: an unreliable marker of beat-to-beat blood pressure *J. Appl. Physiol.* **100** 136–41
Perkins G D, McAuley D F, Giles S, Routledge H and Gao F 2003 Do changes in pulse oximeter oxygen saturation predict equivalent changes in arterial oxygen saturation? *Crit. Care* **7** R67
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
Pitson D, Chhina N, Knijn S and Stradling J 1994 Changes in pulse transit time and pulse rate as markers of arousal from sleep in normal subjects *Clin. Sci.* **87** 269–73
Sammons E L, Samani N J, Smith S M, Rathbone W E, Bentley S, Potter J F and Panerai R B 2007 Influence of noninvasive peripheral arterial blood pressure measurements on assessment of dynamic cerebral autoregulation *J. Appl. Physiol.* **103** 369–75
Simpson D and Claassen J 2018 CrossTalk opposing view: dynamic cerebral autoregulation should be quantified using induced (rather than spontaneous) blood pressure fluctuations *J. Physiol.* **596** 7–9
Singham S, Voss L, Barnard J and Sleigh J 2003 Nociceptive and anaesthetic-induced changes in pulse transit time during general anaesthesia *Br. J. Anaesth.* **91** 662–6
Steiner L A *et al* 2003 Assessment of cerebrovascular autoregulation in head-injured patients: a validation study *Stroke* **34** 2404–9
Steiner L A, Czosnyka M, Piechnik S K, Smielewski P, Chatfield D, Menon D K and Pickard J D 2002 Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury *Crit. Care Med.* **30** 733–8
Sugo Y, Ukawa T, Takeda S, Ishihara H, Kazama T and Takeda J 2010 A novel continuous cardiac output monitor based on pulse wave transit time *IEEE Eng. Med. Biol. Soc.* **2010** 2853–6
Svensen C H, Prough D S, Feldman L S and Gan T J 2018 *Fluid Therapy for the Surgical Patient* (Boca Raton, FL: CRC Press)
Teng X F and Zhang Y T 2006 An evaluation of a PTT-based method for noninvasive and cuffless estimation of arterial blood pressure *Annual Int. Conf. of the IEEE Engineering in Medicine and Biology—Proc.*
Tian F, Tarumi T, Liu H, Zhang R and Chalak L 2016 Wavelet coherence analysis of dynamic cerebral autoregulation in neonatal hypoxic-ischemic encephalopathy *NeuroImage Clin.* **11** 124–32
Tseng M Y, Czosnyka M, Richards H, Pickard J D and Kirkpatrick P J 2006 Effects of acute treatment with statins on cerebral autoregulation in patients after aneurysmal subarachnoid hemorrhage *Neurosurg Focus* **21** E10
Twisk J W R 2006 *Applied Multilevel Analysis: a Practical Guide for Medical Researchers* (Cambridge, UK: Cambridge University Press)
Tzeng Y C and Panerai R B 2018 CrossTalk proposal: dynamic cerebral autoregulation should be quantified using spontaneous blood pressure fluctuations *J. Physiol.* **596** 3–5
Van Der Leeden R 1998 Multilevel analysis of repeated measures data *Qual. Quant.* **32** 15–29
Van Oostrom J H and Melker R J 2004 Comparative testing of pulse oximeter probes *Anesth. Analg.* **98** 1354–8
van Velzen M H N, 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
Vlahandonis A, Biggs S N, Nixon G M, Davey M J, Walter L M and Horne R S C 2014 Pulse transit time as a surrogate measure of changes in systolic arterial pressure in children during sleep *J. Sleep Res.* **23** 406–13
Xu D, Ryan K L, Rickards C A, Zhang G, Convertino V A and Mukkamala R 2011 Improved pulse transit time estimation by system identification analysis of proximal and distal arterial waveforms *AJP Hear. Circ. Physiol.* **301** 1389–95
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
Zhang J, Cavallari J M, Fang S C, Weisskopf M G, Lin X, Mittleman M A and Christiani D C 2017 Application of linear mixed-effects model with LASSO to identify metal components associated with cardiac autonomic responses among welders: a repeated measures study *Occup. Environ. Med.* **74** 810–5