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Reliability and variability of pressure reactivity index (prx) during oscillatory pattern in arterial blood pressure and intracranial pressure in traumatic brain injured patients

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ABSTRACT

Introduction: Pressure reactivity index (PRx) is used for continuous monitoring of cerebrovascular reactivity in traumatic brain injury (TBI). However, PRx has a noisy character. Oscillations in arterial blood pressure (ABP) introduced by cyclic positive end-expiratory pressure adjustment, can make PRx more reliable. However, if oscillations are introduced by the cycling process of an anti-decubitus-mattress the effect on PRx is confounding, as they affect directly also intracranial pressure (ICP). In our routine monitoring in TBI patients we noticed periods of highly regular, slow, spontaneous oscillations in ABP and ICP signals.
Research question: We set out to explore the nature of these oscillations and establish if PRx remains reliable during the oscillations.
Materials and methods: 10 TBI patients' recordings with oscillations in ICP and ABP were analysed. We computed PRx, PRx variability (hourly-average of standard-deviation, SD), phase-shift and coherence between ABP and ICP in the slow frequency range. Metrics were compared between oscillation and peri-oscillation periods.
Results: During oscillations (frequency 0.006± 0.002Hz), a significantly lower variability of PRx (SD 0.185vs0.242) and higher coherence ABP-ICP (0.618±0.09 vs 0.534 ±0.09) were observed. No external oscillations sources could be identified. 34 out of 48 events showed signs of 'active' transmission associated with negative PRx, indicating a potential positive impact on PRx reliability.
Discussion and conclusions: Spontaneous oscillations observed in ABP and ICP signals were found to enhance rather than confound PRx reliability. Further research is warranted to elucidate the nature of these oscillations and develop strategies to leverage them for enhancing PRx reliability in TBI monitoring.

1. Introduction

Autoregulation of cerebral blood flow (CBF) is an important homeostatic mechanism that allows CBF to remain constant despite changes in cerebral perfusion pressure (CPP). Following traumatic brain injury (TBI), autoregulation can be impaired, and this can be monitored continuously at the bedside, using the pressure reactivity index (PRx) (Czosnyka et al., 1997a). PRx is a simple correlation coefficient between slow vasogenic waves seen in arterial blood pressure (ABP) and intracranial pressure (ICP). There are two main aspects that make PRx the most widely spread autoregulation index. Firstly, PRx is strongly associated with outcome, where high PRx (denoting lost vascular reactivity) is associated with higher mortality in severe TBI (Czosnyka et al., 2017). Secondly, PRx allows for individualising CPP targets, by identifying the optimal cerebral perfusion pressure (CPPopt) (Tas et al., 2021; Steiner et al., 2002).

In addition to its strengths, PRx suffers from some weaknesses, which should be considered when interpreting this index. It relies on the assumption that the only determinant of ICP vasogenic variability is an extracranial source (ABP). However, there could be intracranial factors

Abbreviations: ABP, arterial blood pressure; CBF, cerebral blood flow; CPP, cerebral perfusion pressure; SD, standard deviation; ICP, intracranial pressure; PEEP, positive end expiratory pressure; PRx, pressure reactivity index; PS, Phase shift; TBI, traumatic brain injury.

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that might affect ICP and therefore reduce the reliability of PRx. It has been demonstrated that the oscillations introduced in ABP by cyclic positive end-expiratory pressure (PEEP) waves, lower the variability of PRx (Brady et al., 2012). Conversely, it has also been reported that periodic adjustments of an anti-decubitus-mattress may have a confounding effect on the metric, as they seem to affect directly also ICP (Jeanette et al., 2021).

During our neuromonitoring practice, we noticed in one TBI patient a sudden onset of slow, regular, in sync, oscillations in ABP and ICP signals, which we suspected to be of an external origin. PRx values in the periods covered by the oscillations were negative (preserved autoregulation). Examination of data from previously monitored TBI patients revealed a similar pattern, but the patients showed different relationships between ABP and ICP waves, resulting in different values of PRx (both impaired and preserved autoregulation). In this work, we set out to explore the nature of these oscillations and to establish if PRx can be considered reliable during the oscillatory period.

We also speculated that these unknown oscillations might be caused by the cycling induced by external devices, for example the anti-decubitus mattress, Artemis I®, Sidhil. We hypothesised that the anti-decubitus mattress could cause hydrostatic changes, due to the squeezing of lymphatic and venous vessels, and may affect ABP directly, but not ICP. Thus, we aimed to scrutinize our recordings to explore the nature of the waves in patients managed with different types of devices and to establish whether there is a causal relationship between the cycling induced by the device and the oscillatory pattern.

2. Materials and methods

We performed an observational study where we inspected retrospectively and prospectively neuromonitoring recordings from April to October 2022 and selected those presenting very slow, regular and synchronised oscillations in both ABP and ICP signals of unknown origin. Therefore, de-identified high-resolution arterial blood pressure (ABP), intracranial pressure (ICP) recordings of TBI patients admitted in the neurocritical care unit of the Addenbrookes Hospital (Cambridge, UK) between April and October 2022, were accessed from the Brain Physics Lab research database (REC 23/YH/0085). In addition, he following clinical descriptors were retrieved: age, sex, Glasgow Coma Scale (GCS) at the scene.

All patients were sedated and mechanically ventilated and had both continuous and invasive ICP and ABP monitoring (Carney et al., 2016), as recommended by the international TBI guidelines (Hawryluk et al., 2019; Carney et al., 2017; Donnelly et al., 2019). ABP was monitored through radial or femoral arterial lines connected to pressure transduces (Edward Lifesciences, Irvine, CA). ICP was acquired via an intraparenchymal strain gauge probe (Codman ICP MicroSensor, Codman & Shurtleff Inc., Raynham, MA). Continuous high-resolution raw signals of ABP and ICP were streamed in real-time from the vital monitor into the ICM + software (ICM+® Cambridge Enterprise Ltd., Cambridge, United Kingdom) [https://icmplus.neurosurg.cam.ac.uk], which provided data integration and storage at sampling rate 240 Hz.

The number and type of external devices applied on patients were systematically collected for all prospective records, in order to highlight any relationship with the onset of the oscillations. Similar annotations were available in the retrospective cases, although this was not performed systematically for all available devices. In addition, the cycling frequence of external devices such as ventilators variables (for example PEEP), anti-decubitus mattresses or leg cuff machines was recorded and compared with the frequency of the oscillations present in the recordings. Additional trials were made variating the frequence of external devices cycling and observing the behaviour of the recorded oscillations.

3. Data processing

All signals' waveforms were visually inspected for artefacts and manually cleaned before further processing. Data cleaning and processing were conducted using the ICM + software.

Oscillations periods were defined as periods with regular and synchronised waves in both ABP and ICP within the frequencies less than 0.01 and lasting at least 10 min, and that did not exhibit a wide oscillatory band (i.e the power of the frequency was concentrated on a peak rather than distributed on all frequencies). All the periods with the oscillations were labelled. Peri-oscillations periods were defined as a 1 h before and after the oscillation period, or the maximum period available in the recording when recordings started or ended less than 1h before/after the oscillations.

For each recording, separately for the oscillations and peri-oscillations periods, we computed the following metrics: minute-by-minute values of PRx; the frequency of the fundamental harmonic of the oscillations; the oscillations' amplitude of ABP and ICP; the SD of ABP, ICP and PRx (for assessment of variability – in particular PRx variability was computed as hourly average of the SD of PRx); Transfer function analysis metrics (coherence between ABP and ICP) at the frequency of maximum cross-spectral amplitude (the most pronounced common oscillations spectral peak).

PRx was calculated as a moving correlation coefficient between 30 consecutive 10-s mean values of ICP and ABP and updated every minute (Czosnyka et al., 1997b). Impaired vascular reactivity was defined as PRx$>$ 0. Transfer function analysis (TFA) coherence was computed for a period of 300s, updated every 10s. Coherence estimates the strength of linear association between the two signals at the frequency of oscillations. In our case, the higher the coherence the more accurate PRx should be (Claassen et al., 2015).

4. Statistical analysis

Statistical analysis was conducted using MedCalc® Statistical Software version 20.104 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022). Normality of continuous variables was tested with the Shapiro-Wilk test. We described all the computed metrics within the oscillations period as mean ± SD or median (IQR) when not normally distributed. For each metric, we compared oscillation periods with peri-oscillations periods with the Wilcoxon signed rank test.

5. Results

81 recordings were visually inspected and 30 recordings presented with periods of oscillatory pattern. These recordings were further screened and 20 were excluded because they exhibited a wide frequency band of oscillations. The 10 remaining recordings presented with very regular and consistent slow waves with a frequency below 0.01 Hz (Fig. 1).

The study population included 10 patients (70% male), with mean age of 35.50 (±14.30 SD) years. The mean GCS was 7.89 ± 4.91. The average duration of neuromonitoring was 13.86 ± 6.41 days. Patients with oscillations presented from none to a variable number of external devices (such as different types of anti-decubitus mattress, pneumatic leg-cuffs and cooling systems); 5 out of 10 patients presented with no external devices. Moreover, the cycling frequency of external devices was always different from the frequency of the recorded oscillations, and modification of the cycling frequency did not modify the frequence of recorded oscillations. Thus, no clear relationship was found between the presence of a particular device and appearance of oscillations.

Each recording presented more than one oscillation period (10 ± 4.9 on average) and the total number of oscillatory events was 48. The mean duration of the oscillation periods was 227min (±124min). The average time between the oscillation periods was 8.8 h (±4.7h).

Summary statistics of the variables analysed during the oscillation periods are illustrated in Table 1; the oscillations in ABP signals showed a very low mean frequency of the fundamental harmonic 0.006Hz ± 0.003 with a normal distribution. The mean amplitude of ABP and ICP

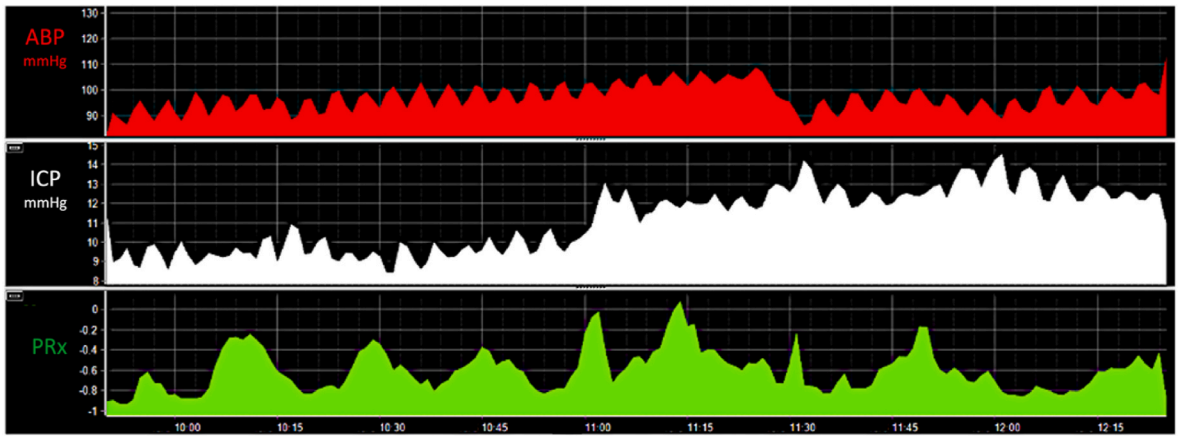

Fig. 1. ILLUSTRATIVE TIME COURSES OF A CONSISTENT PATTERN OF SLOW WAVES IN ABP AND ICP. The figure shows an example of regular slow waves in both ABP and ICP signals with a very low frequency in the lower range of B waves (0.05–0.005hz) lasting for more than 2 h. The corresponding PRx time trend is also shown in the bottom chart. ABP, arterial blood pressure; ICP, intracranial pressure; PRx, pressure reactivity index.

Table 1
Comparison between the oscillation periods with the peri-oscillation periods. ABP: Arterial blood pressure, ICP: Intracranial pressure, PRX: Pressure reactivity index.

	Oscillation periods Median (IQR)	Peri-oscillations period Median (IQR)	Wilcoxon test, *p*
ABP Oscillations Fundamental amplitude (mmHg)	2.52 (1.6–4.1)	2.14 (1.26–2.58)	0.2324
ICP Oscillations Fundamental amplitude (mmHg)	0.76 (0.40; 0.91)	0.73 (0.51; 0.94)	1.000
ABP (mmHg)	83.91 (81.63–88.34)	82.64 (82.40–88.16)	0.4316
ICP (mmHg)	11.23 (7.41–14.96)	11.81 (6.57–14.51)	0.2324
PRx	−0.07 (−0.28 to 0.12)	−0.09 (−0.21; −0.048)	0.6953
PRx variability	0.18 (0.15; 0.22)	0.25 (0.23; 0.27)	***0.002***
Coherence ABP-ICP	0.65 (0.516; 0.668)	0.53 (0.442; 0.641)	***0.004***

were respectively 3.39 ± 2.75 and 0.79 ± 0.36. PRx variability (hourly average of SD) was 0.18 ± 0.04. The mean coherence was 0.65.

The vascular reactivity was preserved in 34 oscillatory periods (out of 48) and was impaired in 14 oscillatory periods.

Most of the variables failed the normality test and thus non-parametric tests were subsequently used for data exploration.

Table 1 shows comparison between oscillation and peri-oscillation periods (1h before and after) for the metrics considered in the analysis. Evidence of reduced variability of PRx during the oscillations period was found (0.18 vs 0.25, Wilcoxon test, p = 0.002, Fig. 2). The coherence was higher during the oscillations period (0.65 vs 0.53 Wilcoxon test, p = 0.004).

To investigate whether the status of vascular reactivity influenced the metrics described above, we compared oscillations periods with preserved vs impaired autoregulation as denoted by PRx. Patients presented alternatively only periods with intact autoregulation, or only impaired autoregulation, or a mix of the two. No differences in ABP, ICP, oscillations fundamental frequency of ABP and ICP were found. Coherence was higher during oscillations with impaired autoregulation (Table 2).

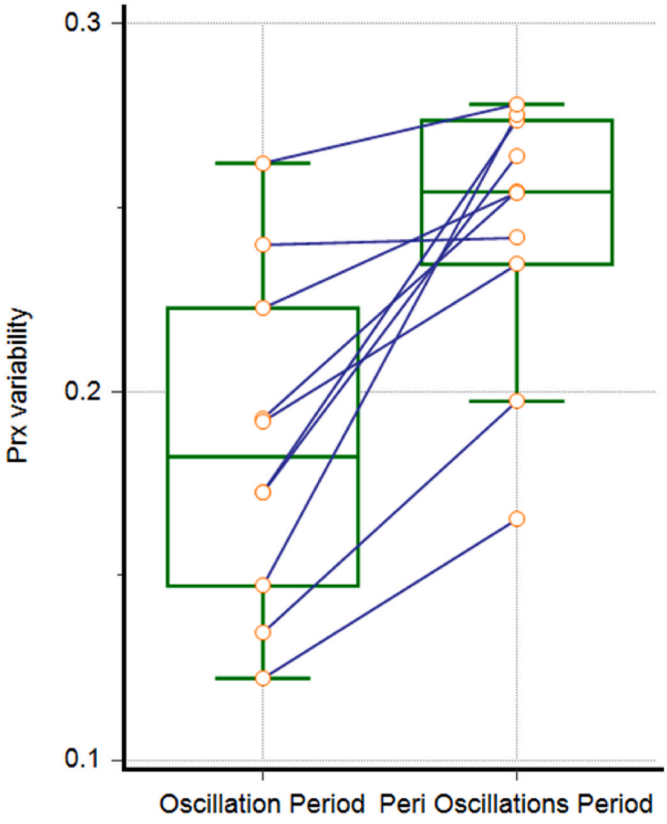

Fig. 2. Comparison of PRx variability between the oscillatory pattern periods and the peri-oscillations periods. The data are presented with box-plots for the two groups and each pair of pattern/peri-patter is linked with a line. The Wilcoxon-test showed that PRx variability is significantly lower during the oscillatory pattern period ($p < 0.05$).

6. Discussion

In this observational study, we explored the nature of slow, highly regular, oscillations of unknown origin recurring in ABP and ICP signals in TBI patients, and we established the influence of these oscillations on the variability of PRx. We confirmed a reduced variability of PRx during the oscillations periods when compared with the peri-oscillations periods. In addition, we found a higher coherence between ABP and ICP during the oscillatory pattern and we excluded that external devices may

Table 2
Differences between oscillation periods with preserved and impaired PRX. ABP: Arterial blood pressure, ICP: Intracranial pressure, PRX: Pressure reactivity index.

Variable	Preserved Autoregulation N = 34	Impaired Autoregulation N = 14	Mann-Whitney test
	Median (IQR)	Median (IQR)	P[a]
ABP Oscillations Fundamental amplitude (mmHg)	2.63 (1.91–3.69)	2.22 (1.43–5.128)	0.9097
ABP Oscillations Fundamental frequency (Hz)	0.005 (0.004–0.006)	0.007 (0.004–0.011)	0.0999
ABP (mmHg)	86.2 (81.4–90.2)	85.6 (79.2–89.5)	0.6178
Coherence ABP-ICP	0.59 (0.47–0.69)	0.73 (0.60–0.84)	**0.0057**
ICP Oscillations Fundamental amplitude (mmHg)	0.84 (0.65–1.11)	0.53 (0.23–0.91)	0.0390
ICP Oscillations Fundamental frequency (Hz)	0.010 (0.007–0.014)	0.012 (0.010–0.018)	0.1844
ICP (mmHg)	11.3 (5.5–15.5)	13.0 (11.9–15.1)	0.1960
PRx	−0.3 (−0.5 to −0.2)	0.3 (0.1–0.7)	–
PRx variability	0.18 (0.16–0.22)	0.13 (0.10–0.22)	**0.0247**

be involved in the generation of the oscillations.

PRx is a very noisy index as its main assumptions are likely to be often violated. In particular, PRx calculations assume that the only determinant of ICP variability is an extracranial source (ABP), while in reality this is not the case as there could be other, intracranial factors, that could affect the variability of ICP. Regular oscillations within the slow vasogenic frequency range, that are visible, and coherent, in ICP and ABP, increase the signal-to-noise ratio as they strongly suggest their extracranial origin.

An experimental study conducted by Brady et al. (2012) demonstrated that oscillations introduced by regular 1 min positive end-expiratory pressure (PEEP) waves in ABP, make the computation of PRx more reliable by reducing noise. In this case, stable low-frequency ABP oscillations are transmitted to ICP via modulation by the mechanism of cerebral autoregulation. Similarly, we found that in our oscillatory patterns, PRx variability was lower when compared to periods without such pattern (PRx SD 0.18 vs 0.25). Tas et al. showed that the PEEP approach experimented by Brady could be used to increase the reliability of PRx time series in TBI patients, by using the sigh function of the ventilator(Tas et al., 2022). The advantage of implementing this kind of procedure is that the waves in ABP would be induced in a controlled fashion, making sure that the assumption is met (provided PEEP does not influence directly ICP) (Beqiri et al., 2023). Instead, the oscillations that we observed were spontaneous, or at least of unknown source. Hence it was crucial to determine whether the direction here was ABP-to-ICP or whether both ABP and ICP were affected simultaneously by an (internal or external) oscillator.

In a different study, Tas et al. (Jeanette et al., 2021) described how oscillations introduced by cyclic inflation/deflation of an anti-decubitus mattress influence PRx. In this case, both ABP and ICP are affected directly and independently by the mattress cycling, and there isn't any autoregulatory mediated transmission of ABP waves to ICP, so the PRx assumption is violated and PRx shows erroneously impaired vascular reactivity. In our data, we could appreciate that PRx average values over the oscillation patterns were in either preserved (34 periods) or not preserved (14 periods) autoregulation range. This is important as in the case of direct transmission from an external device PRx the ABP and ICP oscillations would be always in phase, that it PRx would have been close to +1, which was not the case in our data. Hence, in contrast to Tas et al., we could confirm that the oscillator did not influence both ABP and ICP at the same time, but rather that what we observed was the result of the transmission ABP-to-ICP as modulated by vascular reactivity. At the same time a higher coherence within the oscillations periods, meant that more of the variability of ICP could be attributed to variability in ABP. Thus, we postulate that periods with such oscillations are to be considered reliable and beneficial for PRx assessments.

Slow waves (or B waves) are long-lasting waves within the frequency range of 0.005–0.05Hz (20s-3min) that occur with irregular periodicity and amplitude (Spiegelberg et al., 2016). Conversely, our oscillation periods showed a longer duration and were regular (low variability of the fundamental frequency of oscillations) and consistent, with a very low mean dominant frequency in the lower range of B waves (0.005 Hz, 3.3min period), a constant amplitude of 2.52 (1.6–4.1) and an average duration of 227.38 min ± 123.62 (Fig. 1).

The frequency and recurrence of our oscillations didn't reflect the cycling of any devices used on our patients. In particular, we excluded that the waves were generated by the anti-decubitus mattress Artemis I®, Sidhil, used in our unit. Not all the patients were managed with the anti-decubitus mattress during the appearance of the oscillations, and the cycling of the mattress was about 5 min periods, incompatible with our findings. Our results therefore seem to exclude the external device as a source. As far as we can tell these oscillations seem to be spontaneous. We still don't know the nature of these alterations; however, it is recognised that different mechanisms may be involved in the occurrence of slow oscillations below the respiratory rate. (Hawryluk et al., 2019), (Martinez-Tejada et al., 2019)(Martinez-Tejada et al., 2019). These haemodynamic oscillations are transmitted from ABP to CBF, with accompanying changes in ICP. As already known both intrinsic and extrinsic mechanisms regulate the cardiovascular system to maintain the delivery of oxygen and nutrients to metabolically active tissues and to remove waste products. Recent evidence points to a possible role of these spontaneous oscillations in ABP in the distribution of blood flow protection of tissue oxygenation and in the clearance of interstitial fluid (Anderson and Rickards, 2022). Therefore, these spontaneous oscillations in ABP transmitted to ICP (through oscillations in cerebral blood volume - CBV) may have a role in the distribution of cerebral blood flow to protect tissue oxygenation and allow the clearance of interstitial fluid. Hence, it could be possible that haemodynamic oscillations might be beneficial in TBI patients, aiding to reduce secondary brain injury (Castellani et al., 2009). Further investigations are necessary to shed light in the role of such spontaneous oscillations in maintaining the brain homeostasis and cerebral oxygen delivery.

7. Limitations

This observational study was conducted on the basis of an observation; therefore, the sample size was a sample of convenience as no power analysis was performed ahead. This might have caused a bias in the severity of the cases analysed (generally low ICP, although autoregulation was found both preserved and impaired).

Further systematic investigations should be conducted to corroborate our results. In addition, the recordings were visually scrutinized by the authors in order to find and extract the oscillatory patterns periods. An automated method to detect those patterns would vastly increase the number of those patients for analysis, thus potentially strengthening the important messages in this paper on PRx variability. Furthermore, our database did not have enough information about the external devices used for each patient, and about events that may trigger the oscillations. There is merit in analyzing signals other than ABP and ICP, such as transcranial doppler derived cerebral blood flow velocity, near infrared spectroscopy, brain oxygenation and EEG, when available, to try to explain the origin of the patterns better, along with the physiological interactions behind them. We did not pursue such analysis at this stage.

8. Conclusions

In this study, we described the occurrence of spontaneous, highly regular, oscillations in patients with TBI, affecting both ABP and ICP. We

demonstrated that in our cohort, these oscillations influence PRx calculations by reducing noise, hence they increase the reliability of PRx. The development of automated algorithms for detection and classification of those oscillations, alerting clinicians about the possible unreliability of PRx, is warranted, particularly in the context of autoregulation guided management of CPP.

Declarations of competing interest

Peter Smielewski and Marek Czosnyka receive part of licensing fees for ICM + software, licensed by Cambridge Enterprise Ltd, University of Cambridge, Cambridge.

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Authors contributions

Authors PS, GC and VM contributed to the conception and design of the study. GC,MV,EB, CS and PS contributed to data collection and curation. GC and PS performed the data analysis. All the authors participated to interpretation of data results. VM drafted the article. All the authors revised the article, contributed to its intellectual content, and approved the final version of the article.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Peter Smielewski reports financial support was provided by ERDF (European Regional Development Fund), Interreg France (Channel) England Programme. Peter Smielewski reports a relationship with Cambridge Enterprise Ltd, Cambridge, U.K. that includes: consulting or advisory. Peter Smielewski has patent with royalties paid to Cambridge Enterprise Ltd, Cambridge, U.K. Marek Czosnyka reports a relationship with Cambridge Enterprise Ltd, Cambridge, U.K. that includes: consulting or advisory. Marek Czosnyka has patent with royalties paid to Cambridge Enterprise Ltd, Cambridge, U.K.

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Peter Smielewski, Marek Czosnyka has patent with royalties paid to Cambridge enterprise ltd, University of Cambridge, Cambridge.

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