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Red solid line: Patterns of terminal loss of cerebrovascular reactivity at the bedside

Erta Beqiri [a,*], Marek Czosnyka [a], Michal M. Placek [a,b], Giada Cucciolini [a,c], Virginia Motroni [a,c], Claudia A. Smith [a], Peter Hutchinson [a], Peter Smielewski [a]

[a] Brain Physics Laboratory Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, UK
[b] Neurosurgery Department, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[c] Department of Surgical, Medical, Molecular Pathology and Critical Care Medicine, University of Pisa, Italy

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ABSTRACT

Introduction: Continuous monitoring of the pressure reactivity index (PRx) provides an estimation of dynamic cerebral autoregulation (CA) at the bedside in traumatic brain injury (TBI) patients. Visualising the time-trend of PRx with a risk bar chart in ICM + software at the bedside allows for better real-time interpretability of the autoregulation status. When PRx>0.3 is sustained for long periods, typically of at least half an hour, the bar shows a pattern called "red solid line" (RSL). RSL was previously described to precede refractory intracranial hypertension and brain death.
Research question: We aimed to describe pathophysiological changes in measured signals/parameters during RSL.
Material and methods: Observation of time-trends of PRx, intracranial pressure, cerebral perfusion pressure, brain oxygenation and compensatory reserve of TBI patients with RSL.
Results: Three pathophysiological patterns were identified: RSL precedes intracranial hypertension, RSL is preceded by intracranial hypertension, or RSL is preceded by brain hypoperfusion. In all cases, RSL was followed by death and the RSL onset was between 1 h and 1 day before the terminal event.
Discussion and conclusion: RSL precedes death in intensive care and could represent a marker for terminal clinical deterioration in TBI patients. These findings warrant further investigations in larger cohorts to characterise pathophysiological mechanisms underlying the RSL pattern and whether RSL has a significant relationship with outcome after TBI.

1. Introduction

Continuous monitoring of pressure reactivity index (PRx) provides an estimation of dynamic cerebral autoregulation (CA) at the bedside in severe traumatic brain injury (TBI) patients (Czosnyka et al., 1997). Visualising the time-trend of PRx with a risk bar chart in ICM + software (Smielewski et al., 2012; ICM+. https) at the bedside, allows for better real-time interpretability of the autoregulation status. The bar displays green colour for PRx<0 (intact CA) and red colour for PRx>0.3 (impaired CA). A yellow colour is displayed for PRx values between 0 and 0.3, a grey zone where CA functioning is not well defined (Sorrentino et al., 2012). When PRx>0.3 is sustained for long periods, typically longer than half an hour, the bar shows a pattern called "red solid line" (RSL). RSL was previously described to precede refractory intracranial hypertension and brain death (Czosnyka et al., 2016) in TBI and subarachnoid haemorrhage patients. However, the pathophysiological mechanisms associated with RSL are not always clear.

We aimed to investigate the possible pathophysiological changes related to a RSL pattern, describing the behaviour of collected signals/parameters during the observed RSL.

2. Material and Methods

De-identified minute-by-minute time-trends of PRx, intracranial pressure (ICP), arterial blood pressure, cerebral perfusion pressure (CPP), brain tissue oxygenation (PbtO2) and compensatory reserve index (RAP) (Czosnyka et al., 2007) of TBI patients admitted in the neurocritical care unit of the Addenbrookes Hospital (Cambridge, UK), and that required ICP directed therapy, were accessed from the Brain Physics Lab research database (REC 23/YH/0085).

Monitoring of brain modalities was conducted as a part of standard

* Corresponding author.
E-mail address: vb391@cam.ac.uk (E. Beqiri).

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Abbreviations

PRx	pressure reactivity index
TBI	traumatic brain injury
CA	cerebral autoregulation
CPP	cerebral perfusion pressure
ICP	intracranial pressure
ABP	arterial blood pressure
pbtO2	brain oxygenation
RSL	red solid line

patient care for severe TBI (Donnelly et al., 2019; Menon and Ercole, 2017). ICP (Codman ICP MicroSensor, Codman & Shurtleff, Raynham, Massachusetts) and $PbtO_2$ (Licox, Integra Neurosciences, Andover, UK), were monitored with intraparenchymal probes in the frontal lobe. ABP was monitored invasively from the radial or femoral artery (Baxter Healthcare, Deerfield, Illinois) with a zero calibration at the level of the foramen of Monro. Data of ICP and ABP from the patient monitor (GE, Carescape) B850) and $PbtO_2$ from Licox monitor, respectively, were streamed in real-time into the ICM + software (Cambridge Enterprise, University of Cambridge, UK) [https://icmplus.neurosurg.cam.ac.uk/] (Smielewski et al., 2012), which provided data integration and storage at sampling rate of 240 Hz. The ICM + based integrated neuromonitoring data, such as PRx, were available to the treating clinician, however the pattern of RSL was not used for clinical decision-making. The software ICM+ was also used for data processing, obtaining the minute-by-minute time trends of derived parameters, and de-identification for the Brain Physics Lab research database.

We performed visual inspection of neuromonitoring data acquired with ICM+ during the intensive care (ICU) management of the patients in 2022 and flagged records that presented the RSL of at least 30 min. These records were subsequently accessed from the Brain Physics research database and scrutinized manually using ICM+. Before storage the data were curated by an expert researcher (EB) according to the laboratory protocols. For each record, the following aspects were described: 1) time to onset of RSL from the recording start time and duration of RSL; 2) Occurrence of death after the RSL; 3) Occurrence of refractory intracranial hypertension; 4) Time profile of ICP, CPP, RAP and PbtO2 values, in relation with the onset of RSL; 5) Availability of PRx-based lower limit of reactivity (identified through the PRx/CPP error bar charts). Accordingly, patho-physiological patterns identification was attempted based on the behaviour of the variables listed above.

3. Results

Three different patho-physiological patterns that involve RSL were identified: RSL precedes intracranial hypertension (Fig. 1), RSL is preceded by intracranial hypertension (Fig. 2), or RSL is preceded by brain hypoperfusion (Figs. 3 and 4). Here we present and discuss one example for each of these.

3.1. - case 1 - red solid line precedes intracranial hypertension

Fig. 1 shows the neuromonitoring screenshot of the first type of patterns. The RSL is visible in the third chart of the neuromonitoring screenshot, where PRx is presented with a risk bar chart. The RSL started 9 h after the start of neuromonitoring with ICM+ (which is close to the time of admission of the patient in ICU) and was preceded by a period of highly variable PRx. At the onset of RSL, ICP was around 20 mmHg (denoted by the horizontal blue dashed line in the second chart). ICP increased above this threshold starting from 6 h after the onset of RSL and reached 30 mmHg after 1 day 5 h from the onset of the RSL. The compensatory reserve index presented in the bottom chart, was close to values indicating impaired compensatory reserve (or low intracranial compliance) through the whole period. CPP was on average 70 mmHg through the recording and never decreased below 50 mmHg (denoted by the horizontal blue dashed line in the first chart). The lower limit of reactivity could not be identified. The picture describes a case of cerebrovascular paralysis that lasted for a long period of time and preceded the refractory intracranial hypertension and brain death.

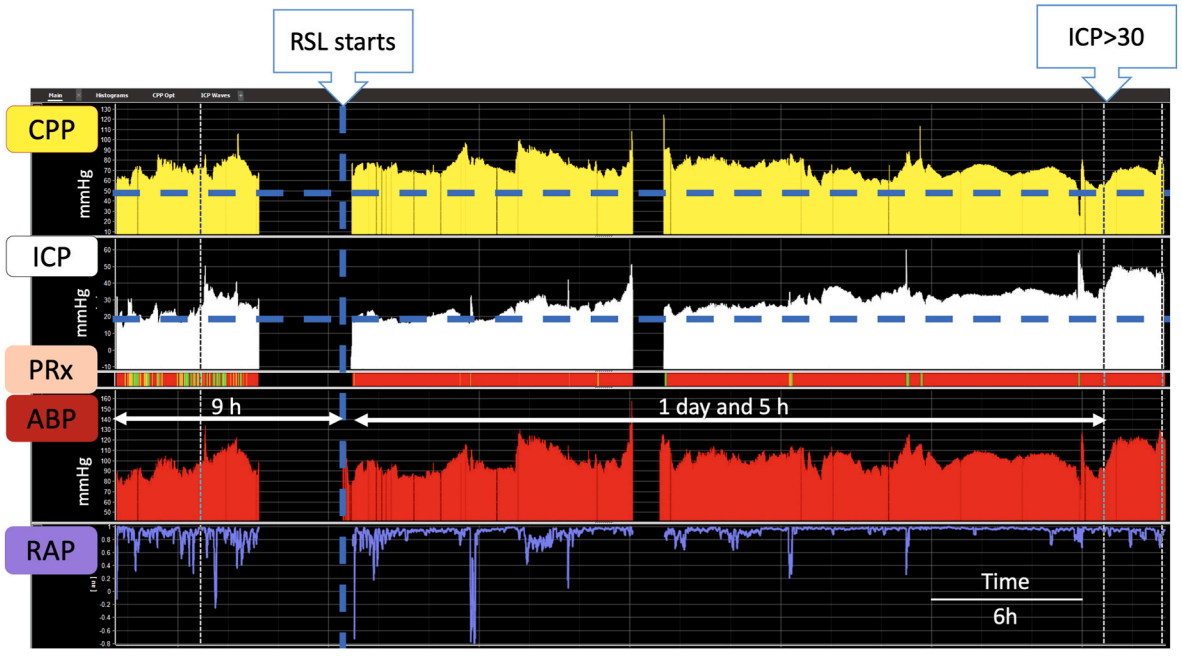

Fig. 1. Red solid line precedes intracranial hypertension. The screenshot presents time trends of CPP, ICP, ABP and RAP and the risk bar chart of PRx (third chart from the top). The horizontal blue lines mark a CPP threshold of 50 mmHg, and an ICP threshold of 20 mmHg, respectively. CPP: cerebral perfusion pressure; ICP: intracranial pressure; PRx: pressure reactivity index; ABP: arterial blood pressure; RAP: compensatory reserve index.

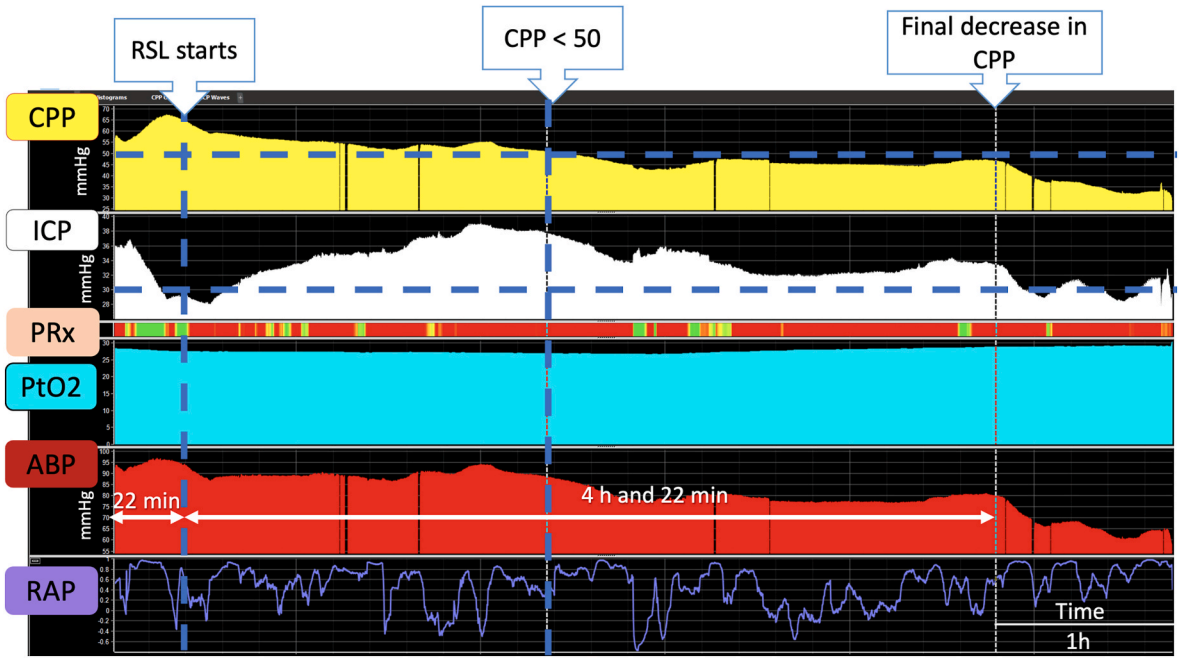

Fig. 2. – Intracranial hypertension precedes the red solid line. The screenshot presents time trends of CPP, ICP, PtO2, ABP and RAP and the risk bar chart of PRx (third chart from the top). The horizontal blue lines mark CPP threshold of 50 mmHg, high ICP threshold of 30 mmHg, and $PbtO_2$ threshold of 20 mmHg, respectively. CPP: cerebral perfusion pressure; ICP: intracranial pressure; PRx: pressure reactivity index; $PbtO_2$: brain tissue oxygenation; ABP: arterial blood pressure; RAP: compensatory reserve index.

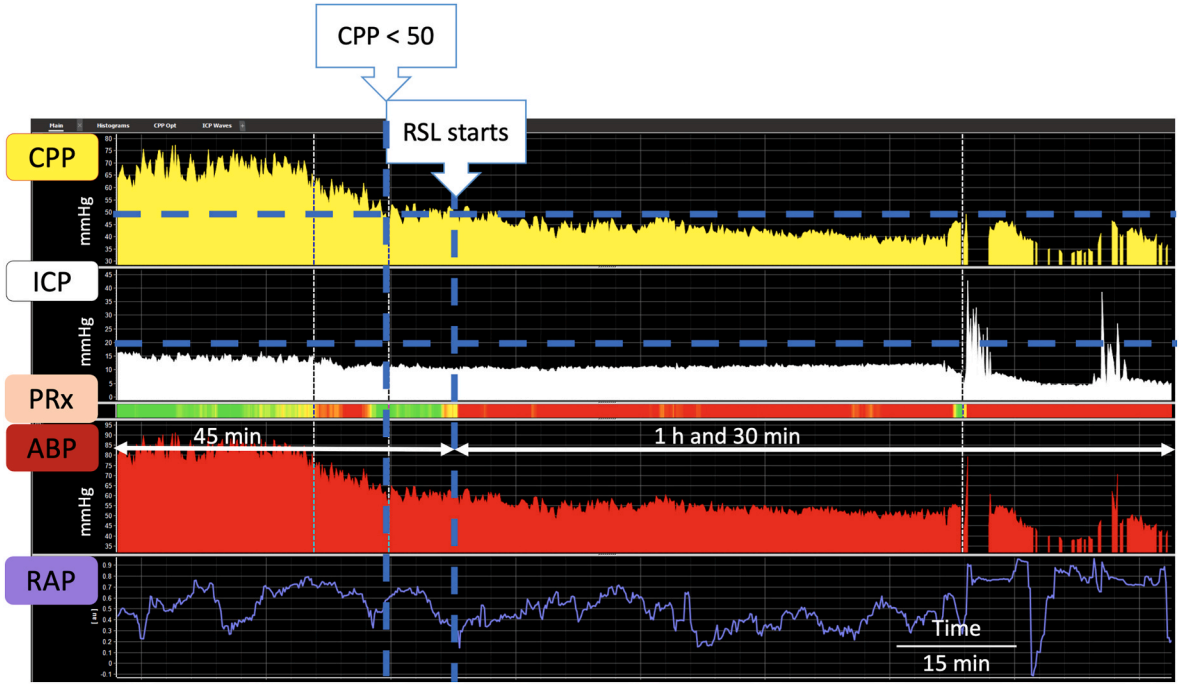

Fig. 3. Systemic hypoperfusion precedes the red solid line. The screenshot presents time trend of CPP, ICP, ABP and RAP and the risk bar chart of PRx (third chart from the top). The horizontal blue lines mark CPP threshold of 50 mmHg, and ICP threshold of 20 mmHg, respectively. CPP: cerebral perfusion pressure; ICP: intracranial pressure; PRx: pressure reactivity index; $PbtO_2$: brain tissue oxygenation; ABP: arterial blood pressure; RAP: compensatory reserve index.

3.2. - case 2 - intracranial hypertension precedes the red solid line

Fig. 2 shows the neuromonitoring screenshot of the second type of patterns. The RSL is visible in the third chart of the screenshot, where PRx is presented with a risk bar chart. The RSL started 22 min after the start of neuromonitoring with ICM+ (which is a proxy for the ICU admission time). In this case, the RSL is interrupted by brief periods of 'green' line, however, given the long periods of only red solid line one after the other, we considered the whole period as RSL. Isolated short 'green' areas are likely to be a representation of physiological variability of the mechanism, The compensatory reserve index RAP was below 0.8 on average.

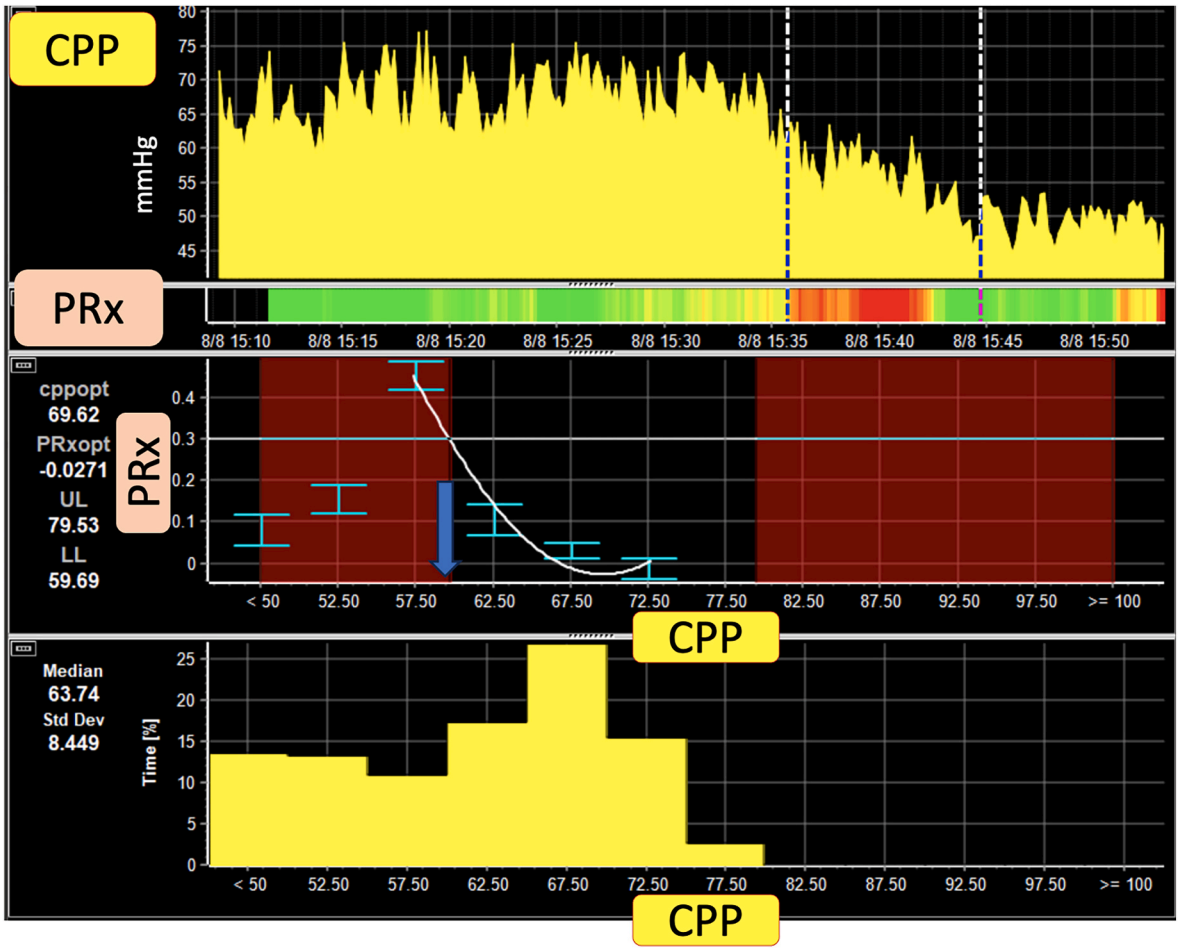

Fig. 4. The lower limit of reactivity before the onset of the red solid line. The screenshot presents the time trend of CPP (top chart), the risk bar chart of PRx (second chart), the error bar chart that describes the relationship between PRx and CPP (third chart) and the distribution of CPP values over the selected period (bottom chart). CPP: cerebral perfusion pressure; PRx: pressure reactivity index.

From the very beginning of this neuromonitoring session, ICP was high and above 30 mmHg (blue dashed horizontal line in the second chart) and CPP was low, around 60 mmHg. ICP remained at high levels, reaching 40 mmHg, and CPP dropped further and below 50 mmHg (blue dashed horizontal line in the first chart) after 2 h from the onset of RSL. The final drop in CPP, led by haemodynamic failure, happened more than 4 h after the onset of RSL. The lower limit of reactivity could not be identified. Interestingly, $PbtO_2$ was constantly above 20 mmHg (blue dashed horizontal line in the fourth chart). This is a case where intracranial hypertension preceded the onset of RSL and led to brain death.

3.3. - case 3 - Systemic hypoperfusion precedes the red solid line

Fig. 3 shows the neuromonitoring screenshot of the third type of patterns. Fig. 4 shows the PRx/CPP relationship for the period preceding the RSL. The RSL is visible in the third chart of the screenshot in Fig. 3, where PRx is presented with a risk bar chart. The RSL started 45 min after the start of neuromonitoring with ICM+. The compensatory reserve index RAP was on average below 0.8. ICP was constant and stable below 20 mmHg (dashed line in the second chart). CPP was above 60 mmHg at the beginning of the recording and dropped below 50 mmHg 7 min before the onset of RSL. Death occurred 1 h and a half after the onset of RSL. In the 45 min preceding the onset of RSL, the relationship PRx/CPP could identify a U-shape curve and a lower limit of reactivity (LLR) at 60 mmHg (Fig. 4). This is an example of haemodynamic failure that led to a drop of CPP below the limit of reactivity (hence the RSL was visible) and preceded the terminal event.

4. Discussion

We presented and discussed three examples of pathophysiological patterns based on the RSL in TBI patients. In all cases, the onset of RSL is followed by death. While it was previously described that RSL could precede refractory intracranial hypertension (Czosnyka et al., 2016) (as in case 1), RSL was not explored within other pathophysiological events. Here we did not seek to perform an exhaustive and systematic characterization of such conditions, but rather to highlight the relevance of the interplay between neuromonitoring variables and the loss of vascular reactivity highlighted by the onset of RSL.

Multimodality monitoring in TBI patients offers the opportunity to tailor the ICU treatment towards individualized management (Khellaf et al., 2019; Svedung Wettervik et al., 2021; Tas et al., 2022). In this context, continuous neuro-monitoring at the bedside, data integration and appropriate visualisation (as offered by ICM + software), provides a high granularity pathophysiological interpretation of clinical events (Smielewski et al., 2012; workshops, 2022). Within the ICM + platform, RSL is readily available in real-time at the bedside, and is therefore easily identifiable. The clinician can then relate this intracranial information to other physiological variables, and it can inform the clinical picture.

RSL can be treated as a warning marker of both clinical severity and poor intensive-care outcome. In the cases we presented, the onset of the RSL happened within minutes to hours from the beginning of the neuromonitoring session, which can be approximated to the admission time. This could suggest that RSL may be considered as an early digital marker

for grading the clinical severity of TBI patients, particularly for cases without an early rise in ICP (such as case 1 and 3). In addition, the terminal loss of vascular reactivity appeared with a time lag of around 1 h up to more than 1 day before death. While 1 h might be a very short time for taking any significant action, 1 day instead seems a reasonable amount of time that allows for clinical review of the patients, which could eventually lead to clinical interventions, provided this was appropriate and feasible. We advocate that future studies should characterise the short-term mortality predictive power of RSL in TBI patients and the optimal time frame at which RSL exhibits such feature.

The drop of cerebral perfusion pressure below the lower limit of reactivity (LLR) causes the impairment of pressure reactivity: the cerebral arteriola undergo passive constriction, and the cerebral blood flow decreases linearly with CPP (Brassard et al., 2021; Claassen et al., 2021; Klein et al., 2021). In Case 3, the relationship between PRx and CPP in the period preceding the loss of vascular reactivity as denoted by the RSL, could identify the patients' LLR. After this level was crossed, i.e. CPP dropped and maintained low values below LLR for a prolonged period of time, the RSL appeared. We could speculate that in this case, RSL could be prevented if CPP was kept above LLR. Obviously, whether this was at all feasible is a crucial point, but out of scope here. However, continuous monitoring of time trends of LLR might prove helpful in preventing brain hypoperfusion (Beqiri et al., 2023; Donnelly et al., 2017).

The current definition of RSL is based on pure visual observations and relies on long periods of loss of vascular reactivity displayed in red colour within the display in ICM+, of a duration of at least half an hour. In the cases we presented, there are short yellow and green components within the red bars, however we judged the RSL as the prevalent pattern in the periods explored. For future investigations it will be necessary to state a quantitative definition of RSL, with identifying a maximum duration considered or a tolerance for the above-mentioned transition periods. It might be that the physiological changes behind these transitions represent windows of physiological recovery or of clinical intervention opportunities. On the other side, these transitions might simply reflect noise in the data. A better quantitative definition of RSL will allow to perform the systematic analytical investigations that we advocate.

4.1. Limitations

We did not integrate the neuromonitoring findings with other clinical variables, such as demographic or presentation data, imaging data and clinical interventions. Hence the interpretation of the pattern presented is limited and firm conclusions should not be derived from it. In addition, our exploration was not systematic, but simply driven by daily observations.

5. Conclusion

RSL precedes death in ICU and could represent a marker for terminal clinical deterioration in TBI patients. These warrants further investigations in larger cohorts to characterise pathophysiological mechanisms underlying the RSL pattern.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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