

# Passive leg raising in brain injury patients within the neurointensive care unit. A prospective trial

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## Abstract

**Background:** In critically ill brain-injured patients maintaining balanced fluid management is a crucial part of critical care. Many factors influence the relationship between fluid management, cerebral blood flow and cerebral oxygenation. Passive leg raising (PLR)-induced changes predict fluid responsiveness in the majority of non-neurological ICU patients. In patients with intracranial lesions, PLR testing has been hypothesized to increase intracranial pressure (ICP), although data are lacking. We wanted to investigate the feasibility of PLR with expected intracranial pressure increase, according to the higher cerebral blood volume. This should be self-limiting in patients with intact cerebral autoregulation.

**Methods:** We prospectively included patients with traumatic brain injury (TBI) or aneurysmal subarachnoid hemorrhage (aSAH) in this pilot trial. PLR was performed within 48 hours after the initial diagnosis and on days 5-8. All patients had ICP monitoring. Absence of intracranial hypertension (defined as ICP < 25 mm Hg) was considered a positive test result.

**Results:** Ten patients were recruited for this study. The cohort consisted of 6 male patients with TBI and 4 female patients with aSAH. Mean patient age was 55.6 years (range 35–76). Overall, 18 tests could be performed, of which only one had to be terminated due to temporarily elevated ICP. 9 out of 10 patients had no intracranial hypertension during the acute (mean ICP increase 8.45 mm Hg, range 4–16) or during the subacute phase (mean ICP increase 9.12 mm Hg, range 3–18).

**Conclusions:** PLR is feasible in patients with intracranial pathology to assess fluid responsiveness and provide optimized patient volume management without increasing the risk of persistent intracranial hypertension.

**Key words:** traumatic brain injury, subarachnoid hemorrhage, intracranial hypertension, passive leg raise, fluid administration, neurointensive care.

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Neurocritical care has substantially evolved over the past years, leading to invasive monitoring of intracranial pressure (ICP), brain tissue oxygenation (PbtO<sub>2</sub>), cerebral blood flow (CBF) (Hemedex), brain function and brain metabolism (microdialysis). It provides an early warning of secondary cerebral deterioration and offers the opportunity to deliver targeted therapy before neuronal damage occurs [1].

Volume management and its influence on outcome in neurocritical care patients, however, have been particularly elusive. Volume status is a major determinant of CBF and PbtO<sub>2</sub>, and a well-considered fluid management strategy is essential

for patients with critical neurological illness [2]. Current guidelines on fluid management in brain-injured patients recommend using fluid balances or central venous pressure (CVP) to guide volume status [3]. Fluid administration aims to increase cardiac output (CO). Considering that only about 50% of all patients are fluid responders, it seems desirable to predict the effect prior to its administration to avoid deleterious effects [4].

Passive leg raising (PLR) induces a rapid increase in preload through an increase in venous return, mimicking fluid administration, yet avoiding unnecessary volume administration [5].

Traumatic brain injury (TBI) and aneurysmal subarachnoid hemorrhage (aSAH) are associated with high morbidity and mortality [6, 7]. Primary injury and a subsequently induced cascade of pathophysiological sequelae determine the outcome in both pathologies [8, 9].

Unfortunately, the use of PLR in patients with acute brain injury has not been assessed based on the belief that intracranial hypertension may be aggravated [5]. This led to the hypothesis that the temporary PLR maneuver might increase ICP due to the increase of cerebral blood volume, but this effect should be self-limiting at the same time. The purpose of our study was to assess the feasibility of PLR in patients with intracranial pathologies in a neurocritical care setting.

## METHODS

This prospective non-randomized pilot trial was conducted in our neurosurgical intensive care unit (NICU) and was approved by the local ethics committee (AN2015-0260 355/4.11). Written informed consent was obtained according to legal regulations in all patients. For all patients who were eligible for participation (presence of intracranial pathology, ventilation, age 18–75, ICP and PbtO<sub>2</sub> monitoring), the protocol included pre-interventional echocardiography to determine the cardiac function. In order to prevent cardiac adverse events, the ejection fraction had to be greater than 35%. We enrolled 10 patients with either aneurysmal subarachnoid hemorrhage or TBI between January and September 2016. All patients were routinely equipped with an intraparenchymal probe for continuous ICP monitoring (Neurovent-P-Temp, Raumedic, Helmbrecht, Germany) and brain tissue oxygen monitoring (PbtO<sub>2</sub>, Licox, Integra NeuroSciences Implants, Sophia Antipolis, France). All TBI patients were scored with the IMPACT prognostic model for estimation of severity. After inclusion, PLR tests were performed, regardless of the fluid treatment of patients, in two stages: (1) within the first 48 hours after admission (acute phase) and (2) on days 5 to 8 (subacute phase). Due to the natural course of TBI and aSAH, we chose the two time points during the phase of primary brain injury when the mechanical damage or bleeding occurs [10–12] and in the

phase of the following cascade of secondary brain damage with the highest likelihood of cerebral dysfunction and vasospasm [13, 14]. All tests were performed by one physician (MB) and data were collected within our patient data management system (PDMS, Centricity Critical Care 8.1, GE Healthcare, Solingen, Germany). Continuously recorded data included intracranial pressure, PbtO<sub>2</sub>, mean arterial pressure (MAP), and cerebral perfusion pressure (CPP). Additionally, peripheral venous blood samples for S100β were obtained prior to PLR and 120 minutes after testing, according to its half-life [15].

During the study period all patients were kept sedated following our institutional standard protocol using midazolam and sufentanil accordingly (aiming for a RASS score of –5 [16]) and with continuous positive pressure ventilation (Infinity V500, Draeger, Lübeck, Germany). All TBI patients were treated in accordance with the Brain Trauma Foundation guidelines [17]. Following guidelines and our institutional practice, they were put in a head-elevated position with their upper body elevated at 30°. The PLR was performed by an immediate change in the position towards a 0° position of the head and elevation of the lower limbs to 45°; that position was maintained for 60 seconds, according to previously published PLR investigations [4, 18] (Figure 1). As a safety measure and according to the study protocol, ICP below 20 mm Hg had to be present for a period of 30 minutes prior to the intervention. If so, PLR was carried out. PLR testing was immediately terminated if the ICP increased above 25 mm Hg [19].

All data were processed using SPSS Statistics (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Standard descriptive analysis was performed and the results are reported as a mean with range. The Shapiro-Wilk test was used to assess the normality of data distribution. The paired samples *t*-test was used to examine changes in CPP and the Wilcoxon signed-rank test was used to compare S100β and PbtO<sub>2</sub> values prior to and after the PLR testing. A *P*-value < 0.05 was considered statistically significant.

## RESULTS

The patient population consisted of 10 patients with either TBI (all male, *n* = 6) or aSAH (all female, *n* = 4). The IMPACT prognostic calculator showed

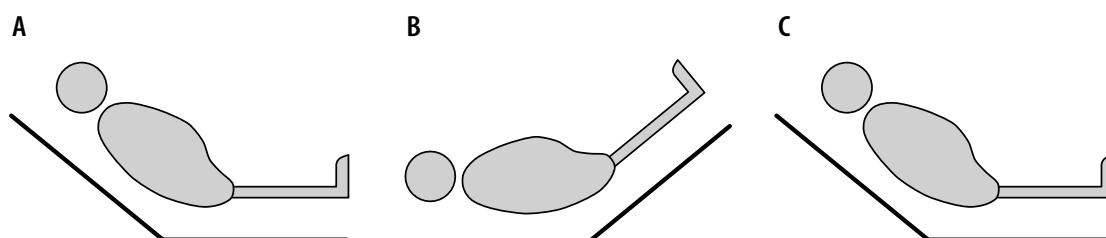


FIGURE 1. Patient's position before (A), during (B) and after (C) passive leg raise

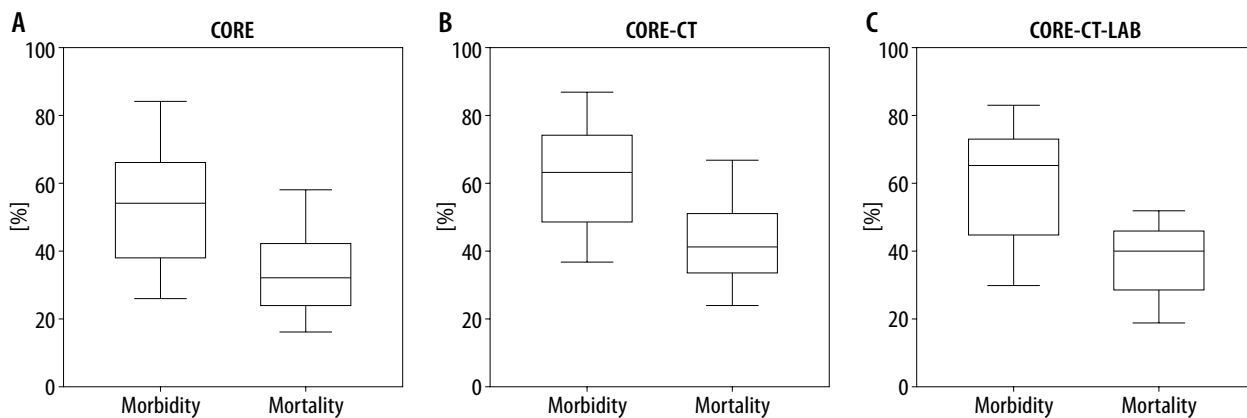


FIGURE 2. Traumatic brain injury patients' predicted probability of 6-month mortality and morbidity at admission. Values are mean (min/max)

TABLE 1. Demographics of patients included in the study

Patient	Age	Gender	Pathology	GCS/ H&H	PLR 1	PLR 2
1	43	Male	TBI	10	Yes	Yes
2	60	Male	TBI	3	Yes	Yes
3	53	Female	aSAH	3	Yes	Yes
4	56	Male	TBI	6	Yes	Yes
5	75	Female	aSAH	3	Yes	No
6	60	Male	TBI	3	Yes	Yes
7	65	Male	TBI	7	Yes	Yes
8	35	Female	aSAH	3	Yes	No
9	61	Male	TBI	12	Yes	Yes
10	47	Female	aSAH	2	Yes	Yes

aSAH – aneurysmatic subarachnoid hemorrhage, GCS – Glasgow Coma Scale, H&H – Hunt and Hess grade, PLR – passive leg raise during acute stage (1) and subacute stage (2), TBI – traumatic brain injury

a mean probability of 53.3% for 6-month morbidity and 33.8% mortality (CORE). The CORE-CT (mean 62.3% morbidity and 42.8% mortality) and CORE-CT-LAB (mean 60.7% morbidity and 37.8% mortality) showed the severity of TBI accordingly [20] (Figure 2). Mean patient age was 55.6 years (range 35–76). All but two patients were tested in both stages (Table 1). One patient was repatriated, and one died as a consequence of cerebral infarction. Overall, 18 PLR tests were performed. One test (5.6%) was terminated according to the safety protocol due to an increase of ICP over 25 mm Hg (baseline values: ICP 14 mm Hg, CPP 89 mm Hg, PbtO<sub>2</sub> 49 mm Hg, maximum values: ICP 26 mm Hg, CPP 72 mm Hg, PbtO<sub>2</sub> 52 mm Hg). During the 17 completed tests, there was no hazardous increase of ICP during the maneuver, in the acute phase or within the following 48 hours (mean 8.45 mm Hg, range 4–16), or in the subacute phase (mean 9.12 mm Hg, range 3–18). No statistically significant increase of ICP after intervention was observed ( $P = 0.447$ ) (Figure 3). CPP decreased statistically significantly in the acute phase ( $P = 0.013$ ) but not in the subacute phase ( $P = 0.234$ ) (Figure 4).

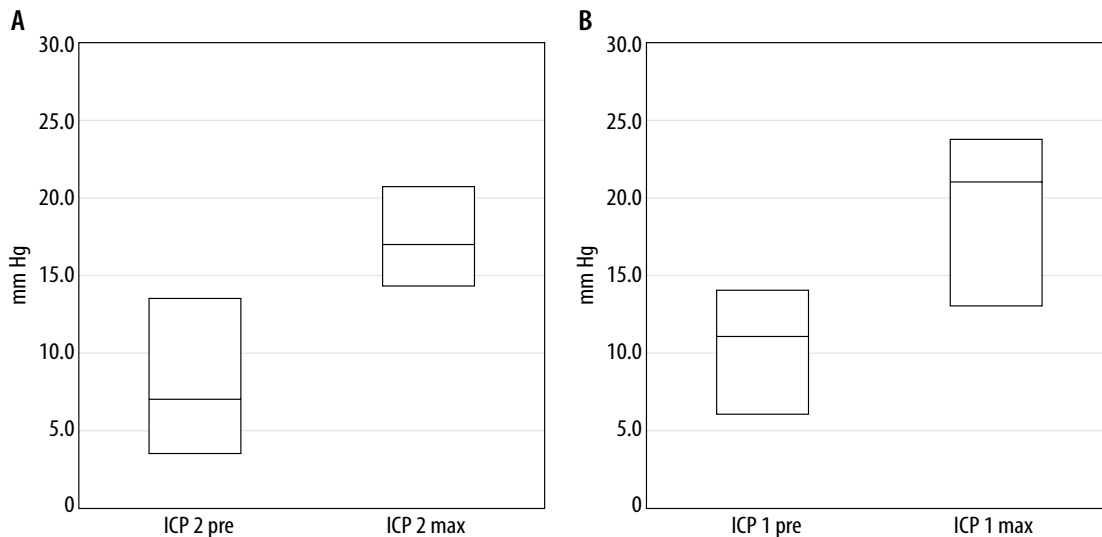
PbtO<sub>2</sub> was recorded continuously for 45 minutes. Measurement failed in one patient due to unintended detachment of the probe during PLR. In 17 tests a mean difference of 1.2 mm Hg (range –5.2 mm Hg to 5.2 mm Hg) was observed within the following 45 minutes ( $P = 0.102$ ).

S100β serum levels prior and 1–2 hours after the PLR test showed no significant increase in the acute or subacute phase (overall,  $P = 0.651$ ). Absolute values of ICP, CPP, PbtO<sub>2</sub> and S100β are depicted in Figure 5.

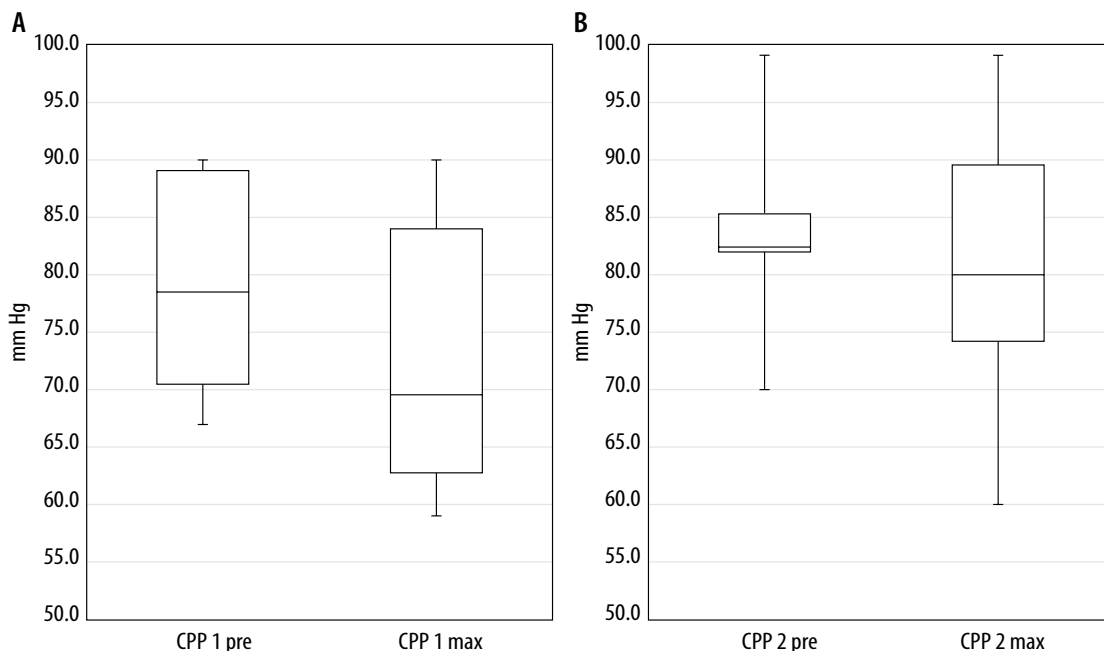
## DISCUSSION

Our pilot trial showed that PLR can be used for patients with severe intracranial pathology. The ICP increase was self-limiting throughout the PLR. The trial was designed to challenge the current opinion that patients suffering acute intracranial pathology have to be withheld from passive leg raising tests [5, 21]. A lack of large animal models for TBI warranted the present first-in-human study [22].

Maintaining normovolemia is a crucial step in the management of patients with intracranial pathologies [9, 23, 24]. Evaluation of individualized fluid therapy in critically ill brain-injured patients and its influence on cerebral blood flow and oxygenation requires a complex understanding of pathomechanisms and patterns of tissue damage [25]. Patients with brain injury are particularly susceptible to imbalanced volume management due to changes in intravascular volume and central neuroendocrine impingement leading to electrolyte and osmotic disturbances [4]. Particularly, fluid overload should be avoided in order to prevent intracranial hypertension and to maintain constant cerebral perfusion to minimize the risk of delayed cerebral ischemia [26]. Also, neurocritical care patients are prone to develop adverse effects related to fluid overload, such as acute lung injury and cerebral edema [27].



**FIGURE 3.** Intracranial pressure (ICP) during both stages (1, 2) of passive leg raise (PLR) test. ICP pre – intracranial pressure prior to PLR, ICP max – highest value of ICP during PLR



**FIGURE 4.** Decrease of cerebral perfusion pressure during both stages (1, 2) of passive leg raise (PLR) test. CPP pre – cerebral perfusion pressure prior to PLR, CPP max – cerebral perfusion pressure during maximal increased intracranial pressure

Current management guidelines recommend using measures of fluid balance to guide fluid administration in NICU patients [25]. Numerous methods have been described to obtain guidance in fluid treatment in critical care patients (e.g. central venous pressure, fluid balance). However, there has not been a reliable association with individual circulating blood volume or fluid responsiveness [9, 23, 28]. Due to its effectiveness in critically ill patients, the PLR represents the key examination for fluid responsiveness [29–31], based on the virtual fluid challenge leading to a hydrostatic increase of the mean systemic pressure. Severely head-injured

patients have been kept in the head-up position to ameliorate the effects of increased ICP [32, 33]. Due to the anticipated increased risk of intracranial hypertension during the maneuver and thereafter, PLR testing has not yet been implemented in NICUs [21, 34].

The aim of our study was to obtain safety information in crucial phases of TBI or aSAH. Measurements were done during the acute phase and within days 5–8, with elevated risk for cerebral vasospasm and elevated ICP [6, 35]. The autotransfusion of blood leads to increase in cerebral blood volume and therefore to an increase in ICP. Yet, we found no hazardous increase of ICP in our study population.

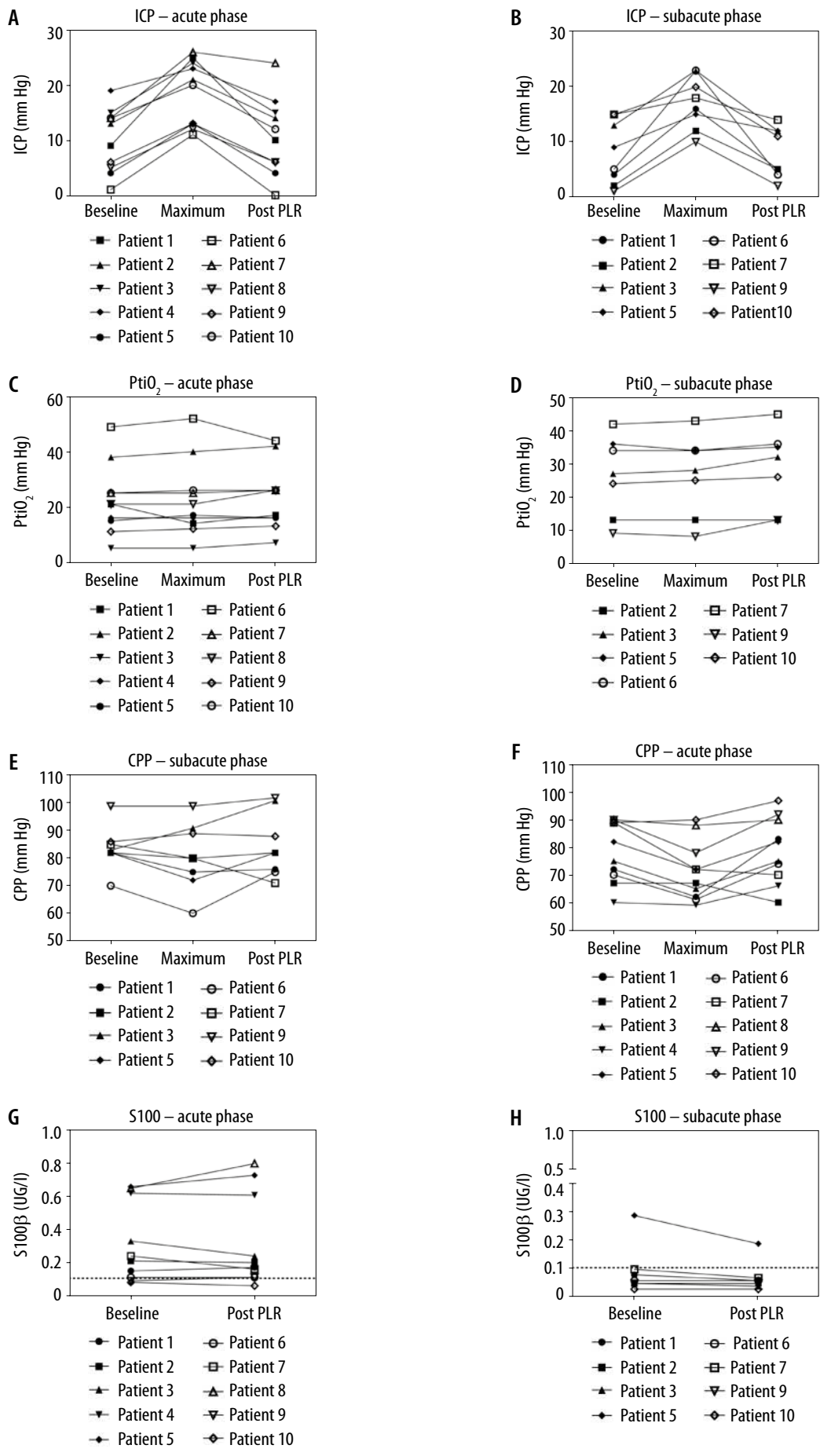


FIGURE 5. Trends of ICP, PbtO<sub>2</sub>, CPP and S100β prior (baseline), during (maximum) and after passive leg raise (post PLR) in both stages (acute and subacute)

Although one PLR had to be terminated prematurely, the intracranial hypertension was brief and self-limiting. Nevertheless, the general safety of PLR should be investigated in a larger cohort.

Additionally, we observed increased  $PbtO_2$ , though not significant, for 45 minutes after the PLR test. The lack of statistical significance in the improvement of brain tissue oxygenation might be explained by the limited sample size. Furthermore, the highly brain-specific subunit of S100 (S100 $\beta$ ), which was found to show elevated concentrations in patients with brain damage (traumatic brain injury, acute stroke or secondary insults after TBI) [36–39], was not significantly increased after the PLR test in either phase. Thus, we conclude that the PLR maneuver did not add substantial tissue damage to patients participating in our study.

This was a pilot proof-of-concept study with the aim of evaluating the safety of PLR in neurocritical care patients, showing that PLR does not cause prolonged intracranial hypertension. The limitations of the study are based on the fact that this pilot study was limited to 10 patients who had to be in a state of normal intracranial pressure (safety measure, < 20 mm Hg) prior to testing. For the feasibility concept of PLR in patients with intracranial pathology, we did not include fluid administration and assessment data and we did not include the results of the PLR maneuvers. Further, we did not gather data on  $PbtO_2$  changes after PLR, as this might be due to CPP decrease during the PLR. The fact that this study included a mixed population of patients reduces the generalizability of the results.

Based on these findings and considering the limitations of the present study, we are convinced that a large cohort study including randomized evaluation of the beneficial effects of PLR-guided goal-directed therapy on patients' outcomes is strongly needed. The impact of goal-directed therapy and its evaluation using PLR in patients with intracranial pathologies on the outcome and potentially severe adverse effects (such as cerebral edema or lung injury) are the subject of prospective studies.

## CONCLUSIONS

The passive leg raise test was feasible in our cohort of patients with TBI and SAH in both the acute and subacute stage and did not lead to persistent ICP elevation. Our results offer the possibility to use PLR in patients with intracranial pathologies and tendencies towards increased ICP.

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3. Conflicts of interests: none.

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