Cerebral autoregulation in children with traumatic brain injury:

Comparing the autoregulatory index (ARI) to pressure reactivity index (PRx) and their associations with cerebral physiological parameters

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DECLARATION

I, MARYAM PATEL, hereby declare that the work on which this dissertation/thesis is based, is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

As an important hemodynamic mechanism, pressure autoregulation protects the brain against inappropriate fluctuations in cerebral blood flow subject to changing cerebral perfusion pressures. In acute neurological illnesses, including traumatic brain injury in children, impaired autoregulation is associated with a worse prognosis. It also has important clinical implications for managing blood pressure and intracranial pressure. Two common methods of measuring pressure autoregulation reported in the adult literature have been rarely reported in children. This pilot study aimed to examine the relationship between two autoregulatory indices, namely PRx (pressure reactivity index) and ARI (autoregulatory index) in children with severe TBI. The study also examined their relationship with the response of clinically relevant variables such as intracranial pressure (ICP), brain oxygenation (PbtO2) and local cerebral blood flow (loCBF) to dynamic testing.

The study is a retrospective cohort study of prospectively collected data conducted at the Red Cross Children Hospital. We analyzed the results of 18 patients in 28 tests of autoregulation to determine the static state of autoregulation by calculating the autoregulatory index (ARI). These tests were done by controlled elevation of blood pressure to evaluate changes in transcranial Doppler-derived flow velocity of the middle cerebral artery. Concomitant recordings were made of ICP, PbtO2, and loCBF. Secondly, we also calculated the PRx as a moving correlation co-efficient between slow changes in blood pressure and ICP. Two time epochs of PRx were examined in relation to the static tests: 1 hour before and after the test, and 12 hours before and after the test.

The results included 28 tests done for ARI and 27 calculations for PRx epochs; all tests had ICP and PbtO2 data and 23 had loCBF. PRx and ARI showed no significant relationship between them. However, there was a significant relationship between ARI and ΔICP ($p=0.04$), i.e. when autoregulation was weak the change in ICP with a change in blood pressure was greater; and between PRx and ΔPbtO2 ($p=0.04$). There was a trend in correlation analysis between loCBF and PRx but not in the linear mixed effects model

In conclusion, the study showed no correlation between the two autoregulatory indices, PRx and ARI, probably because they assess different aspects of autoregulation. However, significant relationships exist between ARI and ΔICP as well as PRx and ΔPbtO2, which generate interesting hypotheses about autoregulation and have clinical implications. Both autoregulatory indices have benefits and limitations. Further studies on such relationships, taking into consideration a larger sample group, inclusion of unstable patients, and utilization of the same range in BP for calculating the indices, are recommended.

INTRODUCTION

By the year 2020, it is estimated that traumatic brain injury (TBI) will exceed many diseases as the major cause of mortality and morbidity worldwide. (1) Affecting both developed (2) and developing (3) countries, its physical, long term cognitive effects, and economic strains are well documented. (4-7) TBI is common in young men and children (8) and is the leading cause of paediatric injury deaths in developed countries. (9, 10) The main goal in managing TBI patients is treatment of the primary insult whenever possible and prevention of secondary insults to achieve the best possible outcome. However, according to the Brain Trauma Foundation Committee there is "insufficient high quality evidence" to produce specific treatment plans in children with severe TBI. (10) Therefore, most of the evidence used in managing such children has been extrapolated from adult research. (11)

TBI is dynamic in nature. Significant variability exists between individuals and within the same individual over a period. (12) This creates a complex set of clinical circumstances where decision-making is challenging. In paediatric TBI, decision making is further complicated by variations in age and mechanism of injury (7, 13-18) and the significant differences between adults and children. (12) In dealing with this complexity, it seems that a guidelines-based approach increases the survival rate without increasing disabled survivors. (19) Aggressive and early optimal management in TBI patients may have substantial benefits for outcome. (12-14, 20-22)

Secondary injuries in TBI include both systemic and local events such as hypoxemia, raised intracranial pressure (ICP), hypotension, seizures, hyper- and hypoglycemia, hyperthermia, acidosis, infection and vasospasm. (23) Various monitoring strategies have been developed in recent years to detect impending injury so that it can be avoided or at least ameliorated. These include mean arterial blood pressure (MAP), ICP, brain oxygenation (PBtO2), EEG and brain chemistry. (24-28) Many centers pursue a multimodal approach in the expectation that a combined interpretation of such results may enable the clinician to tailor management to benefit individual patients. (26-29)

Blood pressure management in TBI is particularly difficult. On one hand, hypotension is associated with poor outcomes, exacerbating the effects of low cerebral blood flow after head injury and raised ICP. On the other hand, hypertension may exacerbate raised ICP via vasogenic edema or increased cerebral blood volume. Cerebral perfusion pressure (CPP) is commonly defined as the difference between MABP and ICP. The optimal CPP remains controversial - CPP thresholds at both lower and higher levels have been recommended in adult patients (30, 31). In children, this is even more challenging because of the changing normative blood pressure profiles with age and uncertainty about the variability in the cerebral autoregulatory function after TBI.

Cerebral autoregulation (AR) is the physiological capacity of the cerebral arterioles to maintain relatively constant blood flow despite changes in arterial blood pressure (pressure autoregulation) or the adjustment of blood flow through the brain in accordance with its metabolic needs (metabolic regulation). It is not an all or nothing phenomenon but rather a continuous spectrum of the strength of AR. The exact mechanism is still not well understood. It is believed to be governed by metabolic, neurogenic and myogenic regulation.

Cerebral pressure AR normally maintains cerebral blood flow within a blood pressure range of about 50 to 150mmHg (32) In myogenic regulation, the vascular smooth muscles in small arteries and arterioles detect and are directly affected by transmural blood pressure changes. Therefore, changes in vessel caliber allows for a constant blood flow. (23) The pressure AR response usually occurs within seconds. (33) This response is important in maintaining constant and adequate blood supply to the brain, important because the brain has a high metabolic demand, consuming almost 20 percent of the total body energy (34) and brain perfusion is essential for life. Several variables affect blood flow to the brain and these influence decisions in neurocritical care, including ICP, arterial blood pressure (ABP), arterial CO2 levels, and many others.

Numerous studies have been conducted on AR in TBI, mostly in adults. (34-38) Methods of determining AR have prognostic value. (18, 39-42) Impaired AR in children with TBI has been shown to be an independent

risk factor for poor outcome, particularly shortly after TBI. (7, 20, 21, 43, 44) This is more common after severe TBI and non-accidental injury. (7, 45) AR in TBI children demonstrates both hemispheric (44, 46) and gender (47) differences. Gender differences have also been shown in animal studies for TBI AR. (48) In the 2012 TBI guidelines for children, currently applicable, there has been no consideration of AR status when recommending cerebral perfusion pressure (CPP) (42, 49).

Autoregulation has been assessed in the literature in several different ways. One way is to use a transcranial Doppler (TCD) ultrasound, a non -invasive, non -radiation method that can be done at the bedside. Tests are usually done by either increasing BP (static AR) (50) or decreasing the BP (dynamic) while observing the cerebral blood flow (CBF) or flow velocity (FV) responses to a change of blood pressure. These variables can then be used to calculate the change in cerebral vascular resistance when blood pressure is increased or decreased. TCD enables measurement of CBFV at the basal cerebral arteries, the most commonly used of which is the middle cerebral artery. Although TCD does not measure CBF directly, changes in both CBFV and CBF usually correlates well in absence of confounding circumstances such as vasospasm. (44)

When examining CBF or FV in children, it is important to note that CBF varies by gender and age; therefore, it is the change in values rather than absolute values themselves that are most informative. (44, 47) The cerebral blood flow velocity (CBFV) in health newborns is around 24cm/sec and increases with age, peaking at 6-9 years with values of about 97cm/sec. (44) Children above 10 years of age show a decline in CBFV, until they reach adult values (+/- 50cm/sec).

Dynamic ARI is defined as (ΔCVR/ΔT)/ΔMABP i.e. Δ: change, CVR: cerebrovascular resistance, T: time) (42). Most investigations of cerebral AR have not considered the time course of change in flow following changes in pressure, thus looking only at the steady state relationship between CBF and MABP or CPP. (51) Therefore, static ARI is defined as %ΔeCVR /%ΔCPP or %ΔMABP. The changes in eCVR (estimated CVR) is calculated as MABP/FV. These changes are calculated as the differences between values at baseline and after elevation of MABP. (50) Thus, the autoregulatory index (ARI) quantifies the strength and capacity for AR. Both tests are limited by the availability of staff to perform the various tests, and are valid only for the period of testing. Many studies have been conducted to determine the relationship between static AR and outcome using the Glascow Outcome Score. (21, 45, 46, 50, 52-55) A systematic review of these studies concluded that there are inconsistencies regarding the outcome which is due to various issues including a small sample size, variability in the timing of measurements and outcome assessments. (56)

AR is known to change over time, and in response to physiological factors, and so continuous assessment also has value. The pressure reactivity index (PRx) was introduced several years ago as a continuous assessment of AR capacity by using a moving correlation of ABP and ICP (the latter being used as a surrogate of cerebral blood volume, which varies with vascular diameter). This method has been validated in many experiments. (42) As such, it has been used to assess AR in clinical studies. (57, 58) PRx has been used to determine the strength of AR and for prognosis. However, most studies have evaluated adult patients. (14, 57, 59). Also, the value of PRx is subject to noise within the recorded ICP and blood pressure signals, the representivity of the blood pressure range over which spontaneous fluctuations occur, and the degree to which ICP is an adequate proxy of ICP.

To date, only three studies using PRx has been performed in children (60-62) in small samples, each of which concluded that PRx quantifies AR and that it correlates with survival in paediatric TBI.

Determining the AR status is useful in paediatric TBI management because it reveals the expected changes in CBF and ICP with spontaneous or induced changes in BP. This is important because daily decisions must be made about what blood pressure to target, in the face of changing ICP and CPP values. There is also no agreement on what an optimal CPP in children is, possibly because of the significant inter-individual variation that occurs in this, subject to the status of autoregulation in those individual patients. It may also assist, therefore, in identifying an optimal CPP in TBI management of individual patients, which may differ from standard thresholds. A continuous assessment of PRx is attractive because it minimizes the resources

required for autoregulation tests and can be used on a continuous basis. However, PRx is not without its limitations and has not been compared to the static ARI in children to date, or indeed any other measure of autoregulation.

Our pilot study aims to compare the static ARI and PRx in paediatric TBI, and examine each of these indices with clinically important physiological variables in children with severe TBI who have undergone advanced brain monitoring.

OBJECTIVES

In this study, we aimed to:

1) Compare the static state of autoregulation (ARI) with PRx. PRx was calculated over two time epochs around the time of the test used to calculate ARI, namely for a period of 1 hour before and 1 hour after the test, and over a 12-hour period before and after the test. Because PRx is influenced by the prevailing ICP, we also calculated PRx over a shorter period at ICP values that were the same as during the ARI calculation within a window of 6 hours of the test.
2) Examine the relationships between measures of autoregulation (ARI and PRx) and the response of baseline variables to an induced change in blood pressure (intracranial pressure, brain oxygenation and local cerebral blood flow) that was performed for the ARI test.
3) Examine the correlation between both autoregulatory measures and clinical outcome.

STUDY DESIGN

This is a retrospective, analytic cohort study with prospectively collected data. Data for clinical characteristics, autoregulation testing (ARI tests), and outcome were collected prospectively. These were retrospectively analyzed from PRx calculated from high frequency continuous data collection of ICP and MAP.

SETTING

Paediatric intensive care unit at Red Cross War Memorial Children's Hospital (RCWMCH).

PATIENT SELECTION

We selected patients in our prospectively collected database of children (<14 years old) who had severe TBI (post resuscitation GCS ≤8), who had ICP monitoring and continuous physiological data collection (ICMPlus, Cambridge University, U.K.), and who underwent tests to calculate the static state of autoregulation (ARI). All patients also had PbtO2 monitoring; some patients also had local cerebral blood flow monitoring (see below).

Based on the need for additional information regarding the relationship between ICP and BP, ARI was calculated as part of routine clinical management of patients to determine the status of autoregulation to guide clinical decisions. The tests were conducted when expertise for testing was available and therefore it was not possible to perform AR testing in all consecutive patients. Tests were also only performed in stable patients, excluding patients who had ICP greater than 20 mmHg or where hemodynamically unstable. Because of a change in intracranial dynamics, we also excluded tests in patients who had undergone decompressive craniectomy.

OVERVIEW OF PATIENT MANAGEMENT

In general, TBI patients who are admitted to the paediatric ICU are initially resuscitated, intubated and mechanically ventilated in accordance with standard paediatric TBI guidelines. Care is provided at the discretion of the health care providers, with respect to current protocols based on Brain Trauma Foundation Guidelines but adapted based on additional monitoring tools. Management is aimed at preventing secondary insults such as hypotension and systemic hypoxia. The initial ICP target for treatment is 20mmHg. If brain tissue oxygenation is monitored (PbtO2), the initial treatment threshold for this is 20mmHg. The initial CPP target is set at 50mmHg (45 mmHg for children aged 2 or younger). These targets are subsequently modified based on interaction with all variables, the clinical examination and radiological features, as well as the balance between risks and benefits for each intervention to maintain those thresholds. Basic measures at the start of treatment include head elevation of 15-20 degrees, sedation (midazolam +/- diazepam), analgesia (morphine), maintenance of serum sodium greater than 140mmol/L, normothermia, and ventilation with a PaCO2 target of 4-4.5kPa. Targets are adjusted according to clinical response.

Mean arterial pressure (MAP) was maintained independently in keeping with normative ranges for age and in response to other parameters such as CPP and PbtO2 with the use of isotonic saline and vasopressor agents (most commonly noradrenaline). Hypertonic saline was used where needed to reach and maintain serum sodium targets. Mannitol was not used.

DATA RECORDING

Physiological data collection:
Codman ICP Express (Codman, Johnson and Johnson) or Camino (Integra Neurosciences) monitors were used to monitor ICP. LICOX (Integra Neurosciences) was used to monitor brain tissue oxygenation (PBtO2). Both ICP and PBtO2 monitors were inserted into 'normal-appearing' white frontal matter on the right side in cases of diffuse injury, or in the hemisphere with the focal pathology or greater swelling but not in the penumbral region. Head CT scan confirmed position of monitors. ABP was monitored via a radial or femoral artery catheter zeroed at the level of the heart.

Some patients also underwent local cerebral blood flow monitoring with the Hemedex Bowman perfusion monitor (LoCBF). The Hemedex monitor is an intraparenchymal catheter that measures local tissue blood flow in ml/100g/min using a thermal diffusion principle, and is described elsewhere. (63, 64) Based on clinical experience, the monitor provides stable data within a short calibration time epoch (over 20-30 minutes). Calibration of the monitor according to the manufacturer's manual was performed prior to each test. To evaluate a similar area of the brain, the Hemedex catheter was placed near the PBtO2 catheter, without interference.

ARI tests: (50)
ARI was calculated by raising the BP in a controlled fashion over 3-4 minutes while monitoring flow velocity in the middle cerebral artery with transcranial Doppler (TCD). All TCD recordings (Smart-lite, Rimed) were performed on the MCA insonated ipsilateral to the parenchymal monitors (FVmca). All TCD recordings were performed by the same operator. Tests were only conducted if patients were stable and the TCD recordings were stable. A titrated infusion of phenylephrine was used to raise the MAP by 20% of its baseline value in a controlled fashion as previously described. (50) Recordings at baseline, peak MAP, and return to baseline post-test were made for MAP, ICP, PBtO2, loCBF, and FVmca. All tests were performed at stable CO2 values within our target range.

PRx:
Continuous data from ICP, ABP, PBtO2, and loCBF from the individual monitors were converted via an analogue-digital converter (Datatranslation DT8904) and transferred to a bedside computer running ICMPlus software (Cambridge University, UK). The ICMPlus software was used to collect and analyze data at 50Hz. (65) Raw data files were manually cleaned of artefacts that included disconnections or monitor faults. Monitoring and recording were carried out over the entire duration of ICP monitor use.

The Paediatric Glasgow Outcome Score Extended (GOS-E Peds) was recorded from clinical notes at 6 months post injury. This is an 8-point scale in which a score of 1 represents a functionally normal outcome and 8 represents death. Outcome was dichotomized as 1-4 for good outcome, and 5-8 for poor outcome (death, vegetative state, lower and upper severe disability). The association between continuous ARI and PRx indices with dichotomized outcome was assessed with linear mixed effects models, and the relationships between binary ARI and PRx indices with outcome were analyzed using generalized linear mixed models. The level of significance was set at $p=0.05$.

SIGNAL SAMPLING AND CALCULATION OF:

ARI (50)

ARI was calculated based on the FVmca response to increased MAP as follows:
ARI = %ΔeCVR / %ΔMAP or %ΔCPP
eCVR (Estimated cerebrovascular resistance) =MAP/FV.

The difference between the values baseline and peak BP are used to calculate the change (Δ) in eCVR and CPP. A change in BP as compared to the absolute change in FV is more accurate to calculate the change in CVR, as even when AR is intact, the slope of CBF in response to BP is not zero. CVR is the active output of AR, thus producing a more reliable approximation of how the vascular bed reacts to changes in BP. (33)

ARI values reflect autoregulatory strength: a value of 1 implies maximal strength, or intact AR, and 0 implies absent or impaired AR. The value of ARI 0.4 has been used previously used as a threshold and as such any value less than 0.4 have been considered as impaired AR and the ARI of 0.4 and above has been associated with intact AR. (44, 66) However, it must be remembered that autoregulation capacity is best appreciated as a continuum of strength rather than a binary intact or impaired physiological response.

PRx (60, 65)

Before PRx is calculated, the ICM+ files were cleaned of artefactual data. Artefacts were manually identified as an electronic deviation from baseline unexplained by clinical or physiological events or when notes have been made in the clinical record to identify monitor disconnections, poor calibration and monitor malfunction. Physiological reactions to clinical events, such as suctioning and patient movement were retained. Data cleaning was performed blinded to clinical outcome. CPP was calculated as MAP minus ICP.

Physiological data were recorded as described above. Low frequency waves from ICP and ABP are preserved using a low pass filter, whilst respiration and pulse waveforms were removed. Variables were averaged over 10 seconds for display. By configuring ICMPlus, a moving Pearson's coefficient of correlation is used over 30 paired ICP and BP samples (300 seconds). (60) The signal for each PRx calculation is from spontaneous slow waves with periods from 20 to 300 seconds. Thus, each PRx value can be obtained by analyzing overlapping 300 second epochs, every 60 seconds. PRx is defined as a slow frequency specific analysis of linear correlation between ICP and ABP waveforms. With respect to slow ABP waveforms, ICP and cerebral blood volume have slow waves that are phase shifted (from 90 degrees to 180 degrees) when pressure reactivity is intact. In such instances, PRx is negative or close to 0. However,

with impaired pressure reactivity, the correlation between ICP and ABP is positive due to the alignment of both waveforms (i.e. phase shift near 0 degrees).

Values close to 0 or negative values of PRx indicate preserved pressure AR, whereas PRx values that are positive and approaching 1 indicate impaired pressure AR.

PRx was calculated over 3 different periods to explore several possible relationships with the ARI calculated from the static tests. These included PRx 1 hour before and 1 hour after the test (expressed as a mean value $PRx_{1\ hour}$) and PRx calculated for 12 hours before and 12 hours after the test ($PRx_{12\ hours}$). Finally, because PRx is affected by the prevailing ICP, PRx was also calculated at a similar ICP in a 6-hour window around the test (PRx_{ICP}).

STATISTICAL ANALYSIS

ARI and PRx calculations are described above. Depending on the distribution of the characteristics, reporting of results are as median and interquartile ranges or means +/- standard deviation. The Shapiro dWilk test was used to test for normality of variables. Significance was set at p=0.05. Spearman and Pearson correlation coefficients were used to test correlations between ARI and baseline physiological factors (ICP, CPP, MABP, PBtO2) prior to testing and the change in physiological factors with testing.

We explored the relationship with other physiological variables, in addition to analyzing the relationship between PRx and ARI. The variables included ICP, PbtO2, CBF. Only patients that were stable at the time, were tested. During the autoregulation testing, the baseline and peak of the included variables, were recorded. Prior to the test, averaging for a period of 5 minutes was completed to obtain the baseline values. When BP was at its maximum during the test, peak values were recorded. A change in a specific parameter, was recorded as the difference between the baseline values and peak values (Δ). Both percentage changes (%Δ) and absolute values (Δ) were recorded. These variables were then analyzed to search for a relationship between each other, PRx and ARI.

The association between the various indices of ARI and PRx were analyzed using Spearman's correlation as well as linear mixed effects models where necessary (to account for repeated measurements and intra-individual variability). Similarly, the associations between indices of ARI or PRx and the physiological variables (ΔPbtO2, %ΔPbtO2, ΔICP, %ΔICP, ΔCBF and %ΔCBF) were examined using the same statistical tools. Dichotomized ARI and ARI_CPP were generated at the threshold of 0.4 and 0.6 as the threshold for impaired autoregulation has not been definitively established, and dichotomized PRx and PRx_12 were generated at the threshold of 0. The associations between this binary ARI and PRx indices with physiological variables were examined using generalized linear mixed effect models.

RESULTS

There were 18 patients in whom 28 ARI tests were performed. Clinical and demographic data are shown in Table 1. Most patients had a favourable outcome (78%), one patient died (6%), 2 had severe disability (11%), and one patient did not have a 6-month outcome score recorded. All 28 tests performed had ARI calculated, 27 of which also had P

Rx data. All patients had ICP and PBtO2 recordings; 23 patients also had loCBF recorded. Table 2 shows the individual test data for the ARI values, PRx, baseline and change (Δ) values for physiological parameters, and GOS-E Peds. Table 3 shows median values (with minimum, maximum and quartiles) for changes in ICP, PbtO2, and loCBF and the p-values for ARI and PRx calculations for each of these.

As expected there were significant relationships between absolute changes and percentage changes for each specific parameter, such as ΔICP and %ΔICP. Based on clinical experience ICP and CBF values tend to be less stable and more fluctuant than PbtO2, so we considered a change of 2 points clinically relevant. ICP decreased by 2 or more mmHg in 8 tests (28%), increased by 2 or more mmHg in 5 tests (18%), and remained within less than 2 mmHg of baseline in 15 tests (54%). CBF decreased by more than 2 in 1 test (4%, 1 of 24), stayed within 2 in 5 tests (21%), and increased by more than 2 in 18 tests (75%). Because PbtO2 is generally more stable, we considered a change of 1mmHg to be clinically significant. PbtO2 stayed within 1mmHg of baseline in 5 patients (18%), decreased by 1 or more in 3 patients (11%), and increased by 1 or more in 20 patients (71%).

Notably, PRx and ARI showed no correlation (r=-0.02, p=0.9) and there was no relationship in the linear mixed effects model (p=0.84). Trends were noted in the following variables in the correlation analysis: PRx and ΔPbtO2 (r=0.34, p=0.08) and %ΔPbtO2 (r=0.38, p=0.05); PRx and ΔCBF (r=0.37, p=0.08) and %ΔCBF (r=0.36, p=0.09); ARI and ΔICP (r=-0.35, p=0.07) and %ΔICP (r=0.36, p=0.06). In the linear mixed effects model, the relationship between PRx and PbtO2 was significant (p=0.04) but not between PRx and CBF (p=0.15-0.75) Figure 1 shows the difference in the change in ICP when blood pressure was increased between 2 groups: one where autoregulation was weaker and one where autoregulation was stronger (ARI dichotomized at 0.4). This was true also when ARI was calculated using CPP rather than MAP and dichotomized at 0.6 (Figure 2). Figure 3 shows the separation of CBF changes for the tests when dichotomized to groups defined by PRx stronger (PRx negative) or weaker (PRx positive). In the linear mixed effects model the relationship between ARI and ΔICP was also significant (p=0.036) as was the relationship between PRx and ΔPbtO2 (p=0.046) and %ΔPbtO2 (p=0.01 for PRx12hr). There was no relationship between autoregulatory indices and GOS-E Peds.

Table 1

GENDER	MALES:13 (72%); FEMALES: 5 (28%)
MECHANISM OF INJURY	MVA PASSENGER: 4 (22%); MVA PEDESTRIAN :12 (67%); MVA CYCLIST:1 (5.5%); FALL FROM HEIGHT: 1 (5.5%)
POST-RESUS GCS	7 (6-7)
TIME TO MONITORS	18.5 HOURS (9-22 HOURS)
POLYTRAUMA	PRESENT: 10 (56%); ABSENT: 8 (44%)
OUTCOME	SURVIVORS:17 (94%); NON-SURVIVORS: 1 (6%)
GOS-E SCORE	2 (2-3)
AGE	6 YEARS (4-9 YEARS)

Test number	ARI (MAP)	ARI 0.4	ARI CPP	ARI CPP 0.4	PRx 1 hr	PRx 12hrs	ΔPbtO2	%ΔPbtO2	ΔICP	%ΔICP	ΔCBF	%ΔCBF	FV Mean	PbtO2	CBF	ICP	MAP	CPP	GOSE Peds
1	1,00	0	1,00	0	0,18	-0,03	-0,99	-2,04	-1,00	-8,14	6,92	22,39	113	48,54	30,91	12	71	59	2
2	0,62	0	0,71	0	-0,14	-0,13	3,24	6,61	-1,30	-7,14	6,98	21,36	86	48,98	32,68	18	75	57	2
3	1,00	0	1,00	0	x	x	1,83	6,05	-4,31	-30,31	32,84	58,09	137	30,25	56,53	14	68	54	x
4	0,65	0	0,58	0	0,96	0,65	1,73	8,99	5,92	34,99	10,57	27,78	173	19,25	38,05	17	82	65	2
5	0,32	1	-0,05	1	0,04	-0,31	0,77	2,43	7,58	60,69	17,11	66,68	127	31,66	25,66	12	93	80	2
6	1,00	0	1,00	0	0,14	0,09	-0,90	-5,06	0,03	1,17	-1,54	-6,24	97	17,78	24,66	3	83	81	2
7	0,45	0	0,58	0	-0,50	-0,49	-0,10	-0,43	-1,09	-7,00	3,83	9,95	92	23,20	38,50	16	68	52	2
8	1,00	0	1,00	0	0,29	0,18	6,17	33,77	-0,63	-4,55	x	x	103	18,27	x	14	66	52	3
9	0,81	0	0,83	0	0,01	-0,21	2,17	5,38	-0,15	-1,52	x	x	70	40,36	x	10	72	62	3
10	0,71	0	0,73	0	-0,35	-0,46	9,17	33,69	0,16	1,79	x	x	90	27,22	x	9	71	62	2
11	0,68	0	0,67	0	-0,54	-0,42	-11,20	-26,85	1,44	28,80	x	x	68	41,71	x	5	85	80	2
12	0,73	0	0,80	0	0,30	0,48	1,90	7,73	-3,12	-21,40	2,73	4,36	104	24,59	62,65	15	75	60	3
13	0,74	0	0,79	0	0,55	0,30	9,91	26,78	-0,45	-3,70	17,12	20,19	120	37,01	84,78	12	59	47	3
14	0,62	0	0,65	0	0,00	0,11	7,08	14,67	0,57	7,97	13,24	23,01	120	48,25	57,55	7	66	59	3
15	0,80	0	0,85	0	0,03	0,22	7,20	23,14	-3,15	-20,30	28,75	56,61	101	31,12	50,79	16	67	51	3
16	0,44	0	0,48	0	0,68	0,63	8,00	30,69	2,26	16,98	0,03	0,08	100	26,07	36,27	13	68	55	2
17	1,00	0	1,00	0	-0,14	0,52	4,66	48,90	-2,33	-19,29	4,35	10,57	70	9,53	41,14	12	59	47	6
18	0,82	0	0,85	0	-0,13	-0,08	1,17	12,55	-3,52	-32,20	0,98	11,09	92	9,35	8,81	11	75	64	6
19	1,00	0	1,00	0	-0,44	-0,22	-3,45	-10,89	2,32	60,06	-0,92	-5,59	97	31,67	16,45	4	80	76	2
20	0,59	0	0,72	0	0,53	0,36	5,34	13,07	-5,12	-27,15	10,09	45,15	104	40,85	22,35	19	80	61	8
21	0,33	1	0,34	1	0,35	0,56	3,74	16,28	3,55	26,32	19,97	75,47	147	22,98	26,46	13	80	66	8
22	0,63	0	0,71	0	0,15	-0,22	0,44	2,18	-3,39	-19,07	8,00	17,69	88	20,18	45,23	18	78	60	2
23	0,77	0	0,79	0	-0,11	-0,22	1,12	4,19	-0,16	-2,05	1,22	4,19	117	26,75	29,11	8	83	75	6
24	0,71	0	0,75	0	-0,33	-0,09	2,11	5,38	-0,46	-5,04	3,26	11,24	103	39,24	29,00	9	64	55	3

25	0,82	0	0,83	0	-0,02	x	4,75	26,87	0,94	8,42	-4,97	-17,15	77	17,68	28,98	11	88	76	2
26	0,88	0	0,90	0	-0,31	-0,14	3,74	7,80	-2,20	-16,44	2,40	12,40	79	47,93	19,35	13	78	64	2
27	0,42	0	0,46	0	-0,55	-0,46	0,14	0,39	-0,03	-0,41	2,74	7,57	117	36,03	36,19	7	91	84	2
28	0,18	1	0,22	1	-0,16	-0,12	3,76	5,13	1,68	14,26	2,60	12,16	115	73,26	21,39	12	79	67	2

TABLE 2 Table of values for ARI, PRx, baseline clinical variables before test, and change from baseline variables to peak of test (Δ). **ARI**, Autoregulatory index; **ARI 0.4**, ARI dichotomized to less than 0.4 (1) or ≥0.4 (0); **ARI CPP** (ARI calculated with CPP as blood pressure variable; **PRx 1hr**, mean value for PRx calculated over 1 hour before the test and 1 hour after the test; **PRx 12 hrs;** mean value of PRx calculated for 12 hours preceding the test and 12 hours after the test; **FV mean**, transcranial Doppler flow velocity of the middle cerebral artery at baseline; all other variables recorded as baseline variables before test, or the difference between baseline and peak values (Δ) as an absolute number or % change. **GOS-E Peds**, Paediatric Glasgow Outcome Score- Extended for Paediatrics, where 8=death and 1=normal.

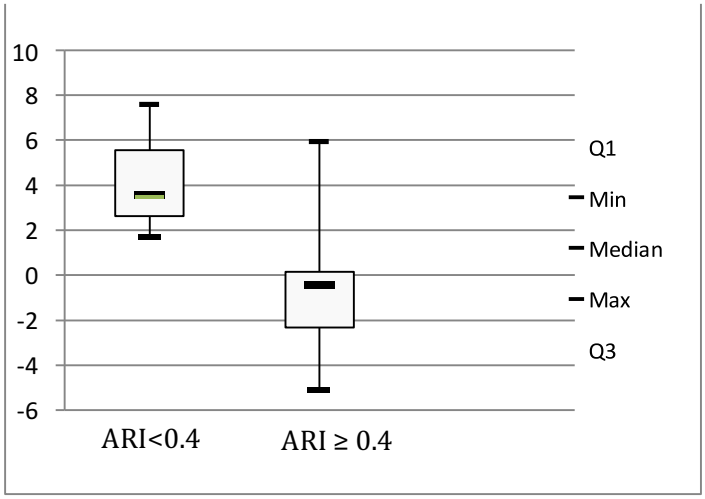

Figure 1: Box and whisker plot showing the change in ICP (vertical axis, in mmHg) from baseline (point zero, vertical axis) to peak of test for 2 groups of ARI dichotomized to <0.4 and ≥0.4. ICP tended to remain stable or decrease when autoregulation was stronger (greater ARI) and increase when autoregulation was weaker.

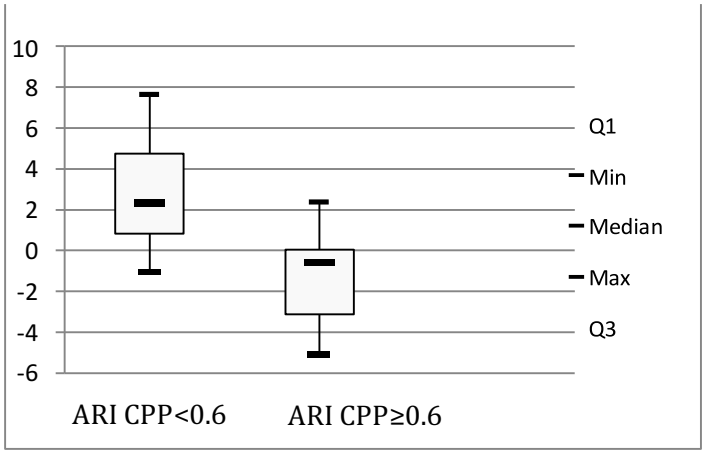

Figure 2: Box and whisker plot showing the change in ICP (vertical axis, in mmHg) from baseline (point zero, vertical axis) to peak of test for 2 groups of ARI calculated from CPP (ARI CPP) and dichotomized to <0.6 and ≥0.6. ICP tended to remain stable or decrease when autoregulation was stronger (greater ARI) and increase when autoregulation was weaker.

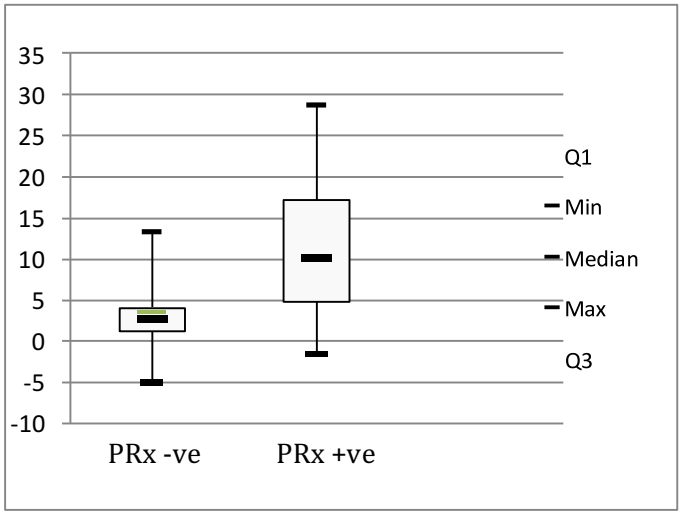

Figure 3: Box and whisker plot showing change in loCBF (vertical axis, in ml/100g/min) from baseline (point zero, vertical axis) for groups dichotomized based on PRx negative (stronger autoregulation) and PRx positive. Most CBF values increased during the test, whether ARI was low or high. The change in loCBF when blood pressure was increased was greater when autoregulation was weaker.

	Min	Q1	Median	Q3	Max	ARI (p value)	PRx 1 hour (p-value)	PRx 12 hour (p-value)
Baseline ICP	3	9	12	14	18			
Baseline PbtO2	9,35	22,28	30,69	40,48	73,26			
Baseline loCBF	8,81	25,41	31,80	42,16	84,78			
ΔPbtO2	-11,20	0,69	2,14	4,90	9,91	0.68	0.04*	0.04*
%ΔPbtO2	-26,85	2,37	7,17	17,99	48,90	0.60	0.08	0.01*
ΔICP	-5,12	-2,23	-0,31	1,07	7,58	0.04*	0.46*	0.75
%ΔICP	-32,20	-17,10	-2,87	9,88	60,69	0.09	0.99	0.79
ΔCBF	-4,97	2,11	4,09	11,24	32,84	0.84	0.15	0.75
%ΔCBF	-17,15	6,77	12,28	24,20	75,47	0.20	0.19	0.25
ARI	0,18	0,61	0,72	0,84	1,00	x	0.84	0.35
PRx 1 hour	-0,55	-0,24	0,00	0,24	0,96	0.84	x	x
PRx 12 hour	-0,49	-0,22	-0,08	0,28	0,65	0.49	x	x

TABLE 3 Table showing the minimum (min), 1st quartile (Q1), median, 3rd quartile (Q3) and maximum (max) values for baseline variables and the difference between baseline and peak values (Δ) and absolute numbers or % change. The columns for ARI, PRx 1 hour, and PRx 12 hours denote the p-value for the relationships between these variables and the test variables in the linear mixed effects model. * denotes significant values

DISCUSSION

This study of 18 children with severe TBI examined two autoregulatory measures, both of which are under-reported in the pediatric population. The study is also unique in that several additional physiological measures are reported, in conjunction with the results of autoregulation assessment, to better understand the actual changes in clinically relevant physiological measures in relation to these calculated autoregulatory indices. This is important because the autoregulatory status in severe TBI patients clearly impacts CPP management and has been associated with prognosis. Currently, there exists no gold standard for cerebral autoregulation testing or how this should influence clinical management of patients, especially in children, largely because autoregulatory testing is seldom performed and our knowledge of the effect of autoregulatory status on clinical parameters is poor.

PRx and ARI showed no clear relationship between the two indices. This may suggest that both measures reflect different aspects of autoregulation in children. There may be differences in the examined BP ranges as well as differences in the steady state of cerebrovascular changes in response to slow wave changes in blood pressure compared with induced blood pressure changes. As per definition, a wider range of blood pressure above baseline was used to calculate ARI, whereas PRx was calculated over smaller spontaneous blood pressure changes, in a steady state. Therefore, different parts of the autoregulation curve may have been examined.

The relationships between the autoregulatory indices and the other monitored physiological variables create interesting hypotheses to explore. ARI and ΔICP and %ΔICP showed a trend in correlation and were significantly related in the mixed effects model. The inverse correlation implies that when ARI was higher (stronger autoregulation), ICP was stable or decreased when blood pressure was raised (Figure 1 and 2). When ARI was lower (weaker autoregulation), ICP increased with an increase in blood pressure. This is in keeping with our understanding of macrovascular autoregulatory control. When autoregulation is intact, an increase in BP results in a decrease in cerebral blood volume (at least on the arterial side), due to vasoconstriction. When autoregulation is weak, there is little vascular resistance change and the increase in BP passively distends the cerebrovascular bed, increasing cerebral blood volume and, therefore, ICP. The changes in cerebral blood volume are thus manifest as changes in ICP. The graphs comparing changes in ICP for ARI, dichotomized at 0.4, which has previously been suggested as an autoregulatory cutoff (45), suggest a separation of ICP values i.e. ICP changes are greater when autoregulation is impaired (ARI <0.4). Unfortunately, only a few cases had ARI < 0.4. Dichotomization of ARI at 0.6, showed a less pronounced separation when MAP was used as calculation, but stronger when CPP was used instead of MAP to calculate ARI, as some have described, (67) this separation between ICP changes increased, even when ARI was dichotomized at the higher threshold of 0.6. This is in keeping with a rule of thumb: if ICP is increased during induced increase in BP, autoregulation is more likely to be impaired or weaker. There is little change in ICP, or a decrease in most cases, when autoregulation is intact. In this, the calculated ARI reflects an important aspect of the relationship between ICP and blood pressure in patients and is a useful measure.

Similarly, PRx showed correlation trends with PbtO2 and loCBF. The relationship was significant for ΔPbtO2 in the mixed effects model. This implies that higher values of PRx (weaker autoregulation) were more likely associated with an increase in both parameters during the tests, i.e. when autoregulation was impaired, there were greater increases in PbtO2 and CBF when BP was increased. However, for static autoregulation tests, PbtO2 (71%) and loCBF (75%) increased in most cases, even if autoregulation was strong by measures of ARI or PRx, suggesting that autoregulation is not absolute and may reflect macrovascular phenomenon, whereas PbtO2 and loCBF measure changes at a microvascular level. This is also consistent with why the ARI had a stronger relationship with ICP, which reflects larger changes in blood volume, whereas even small changes in flow are likely to influence PbtO2 and loCBF. At the same time, ICP has an impact on PbtO2 and loCBF, so the observed changes in the latter two variables may be explained not only by the direct vasoactive changes in vessels but also the secondary change in ICP, i.e. an increase in PbtO2 in these tests could be due to the small increase in flow even when autoregulation is intact

or because of the slight reduction in ICP when autoregulation is strong, which occurred in 28% of the tests (where ICP decreased to 2 or more mmHg below baseline).

The graphs comparing changes in CBF at dichotomized PRx values show a separation between negative (autoregulation intact) and positive PRx values for CBF changes. This separation is less clear for PbtO2 at dichotomized PRx, possibly because PbtO2 depends on more than just CBF changes and the attendant change in ICP and CPP may affect diffusion of oxygen due to reduced or increased tissue pressure.

LIMITATIONS

In this study, we compared two different measures of autoregulation across different blood pressure ranges (active and passive) and in different conditions. ARI was calculated from an induced change in blood pressure; PRx was calculated from passive observation of spontaneous fluctuations in blood pressure and the relationship between this and ICP, a proxy for cerebral blood volume. These are inherently different; however, both are measures of autoregulation that have been published and used clinically. It is presumed that PRx can be derived from passive observation of physiological data and has implications for induced changes in blood pressure management. Although both measures appear to have clinical relevance, they may reflect different physiological processes.

This study was conducted with a small cohort of patients, with some cases undergoing more than one test, although inter-individual variation was controlled for. This limits the generalization of the data. However, this is a unique set of patients with multiple parameters simultaneously evaluated. It is the most comprehensive set of physiological parameters related to autoregulation that have been examined in a paediatric cohort.

Since tests were performed only on stable patients, the study may therefore not reflect hemodynamic relationships in unstable patients. Stable patients were selected because we did not intend to place unstable patients at risk of acute changes in blood pressure or ICP, even if for a short time. Unstable patients with high ICP are more likely to have impaired autoregulation. Therefore, our figures, likely underestimate the frequency of impaired autoregulation. However, the aim was not to describe the central measures of autoregulation in an unselected population, but rather to compare two different measures of autoregulation and their association with clinically relevant variables. Thus, we are limited in the selection of patients who could undergo testing.

CONCLUSION

This study is unique in that it analyzes two autoregulatory measures (PRx and ARI), as well as assesses the relationship of clinically relevant variables to both indices. This analysis is the first of its kind in children. No clear relationship was demonstrated between PRx and ARI, probably because they reflect slightly different aspects of autoregulation, as well as inherent methodological difficulties in measuring a biological phenomenon such as autoregulation. However, each measure yielded interesting relationships with physiological variables that should be explored further. In aggregate, the data are clear that the status of autoregulation in TBI has clinically important relevance for how changes in blood pressure effect brain oxygenation, CBF and ICP, and how these potentially inter-relate.

Both ARI and PRx testing of autoregulation have their advantages and drawbacks. Due to the uncertain relationship between the ARI and PRx, as well as the above-mentioned limitations of the study, continuation of multimodality monitoring is advised until more conclusive studies are conducted.

ETHICAL CONSIDERATIONS:

Patient consent from the nearest relative was obtained for inclusion in the study. The institutional review boards of the university of Cape Town and Red Cross War Memorial Children's Hospital approved the study.

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