PAPER

Critical thresholds of intracranial pressure and cerebral perfusion pressure related to age in paediatric head injury

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Background: The principal strategy for managing head injury is to reduce the frequency and severity of secondary brain insults from intracranial pressure (ICP) and cerebral perfusion pressure (CPP), and hence improve outcome. Precise critical threshold levels have not been determined in head injured children.
Objective: To create a novel pressure–time index (PTI) measuring both duration and amplitude of insult, and then employ it to determine critical insult thresholds of ICP and CPP in children.
Methods: Prospective, observational, physiologically based study from Edinburgh and Newcastle, using patient monitored blood pressure, ICP, and CPP time series data. The PTI for ICP and CPP for 81 children, using theoretical values derived from physiological norms, was varied systematically to derive critical insult thresholds which delineate Glasgow outcome scale categories.
Results: The PTI for CPP had a very high predictive value for outcome (receiver operating characteristic analyses: area under curve = 0.957 and 0.890 for mortality and favourable outcome, respectively) and was more predictive than for ICP. Initial physiological values most accurately predicted favourable outcome. The CPP critical threshold values determined for children aged 2–6, 7–10, and 11–15 years were 48, 54, and 58 mm Hg. respectively.
Conclusions: The PTI is the first substantive paediatric index of total ICP and CPP following head injury. The insult thresholds generated are identical to age related physiological values. Management guidelines for paediatric head injuries should take account of these CPP thresholds to titrate appropriate pressor therapy.

Despite advances in resuscitation and trauma care the mortality and morbidity associated with head injury remains high.[1] If improvements are to be made in outcome from childhood head injury then a key challenge to neurointensive care is to minimise secondary ischaemic brain insults. Thresholds for intracranial pressure (ICP) and cerebral perfusion pressure (CPP) have become generally accepted in adult practice, although they have not been formally validated.[2–9] There remains a pressing need to define critical thresholds in children that can be used to define levels for treatment intervention and insult detection in the intensive care environment. That these clinically important thresholds have not yet been established in children reflects the ever changing cardiovascular physiology during growth and development, which will alter thresholds with age until they approach adult values. There has also been a reluctance to define normal CPP values for different childhood age groups because of the lack of normative ICP data in growing children resulting from the changing intracranial dynamics.

The rationale for attempting to define critical thresholds of CPP was based on the findings of Jones *et al*[10] who, using age specific norms, showed that the duration of age specific abnormal CPP predicted outcome (unfavourable/favourable) (p = 0.004) and mortality (p = 0.003) in a series of 71 children aged under 15 years. Similarly, Chambers *et al*[11] found important age related differences in CPP over the first six hours of monitoring, which were related to outcome.

Chambers *et al*[4] have suggested a minimum target CPP value of 45 mm Hg in children, based on a single point from a receiver operating characteristic (ROC) curve that had been created using a minimum of a rolling mean CPP value in 84 children aged three months to 16 years. In a pilot study addressing the same issue, Jackson *et al*[12] calculated the CPP insults determined for different arbitrary CPP thresholds (70, 60, and 50 mm Hg). For nine children aged less than 16 years, these median CPP thresholds were associated with median ICP values of 12, 14, and 24 mm Hg, and median blood pressure values were 77, 71, and 71 mm Hg, respectively.

All preceding studies that relate ICP/CPP to outcome in traumatic and non-traumatic encephalopathies in children have measured individual excursions of pressure, or the duration of derangement. Such approaches, which use a single summary measurement and do not combine severity and duration of derangement, may not capture the total insult burden. A measure that incorporates both degree and duration would theoretically be a better reflection of the total potential insult.

The sequential objectives of this study were, first, to create a novel index quantifying the secondary ischaemic brain insult, which combines both duration and intensity of derangement (for ICP and CPP), using detailed (one minute time resolution) physiological data; second, to derive age related physiological thresholds for ICP and CPP; and third, after establishing the sensitivity and specificity of the index in relation to outcome, to use it to define age related critical thresholds.

METHODS

This was a prospective observational study of 99 head injured children aged less than 16 years, admitted to two regional
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Table 1 Criteria for enrolment

- Traumatic brain injury
- Post-resuscitation Glasgow coma score[13] [14] $\leqslant$ 12 or $\leqslant$ 15, with injury severity score $\geqslant$ 16 or more
- Minute to minute computer data recording equipment available
- Physiological monitoring began within 24 hours of injury
- No previous head injury

Table 2 Causes of head injury in the 81 paediatric patients

Cause	Number
Pedestrian	38
Motor vehicle	11
Bicycle	10
Low fall	5
High fall	7
Struck on head	4
Assaults	3
Sport related	2
Penetrating injury	1

Table 3 Outcome dichotomies

1. **Favourable** outcome (good recovery or moderate disability) v **unfavourable** outcome (severe disability or death)
2. **Mortality** (death) v **survival** (good recovery, moderately disabled, or severely disabled)
3. **Morbidity** (good recovery) v **others** (moderately disabled, severely disabled, or dead)

Table 4 Predefined threshold values of intracranial pressure (ICP) and cerebral perfusion pressure (CPP)

Age	Mean MAP or CPP threshold
2–6 years	$\leqslant$ 48 mm Hg
7–10 years	$\leqslant$ 54 mm Hg
11–15 years	$\leqslant$ 58 mm Hg

centres in Edinburgh (n = 69) and Newcastle upon Tyne (n = 30) in 62 non-consecutive months up to July 2003. The study had local ethics committee and management approval in both centres and informed consent was obtained before enrolment in the study. The criteria for enrolment for entry to the study are given in table 1.

In all, 81 children (22 girls, 59 boys) aged two years or over (median 10.3 years, range 2 to <16) who fulfilled the criteria for entry into the study had ICP and arterial blood pressure monitoring. ICP and CPP treatment goals and general management guidelines were previously reported.[10] These were as follows: age 0–13 years: CPP >50 mm Hg; ICP <15 mm Hg; age 14–15 years: CPP >60 mm Hg, ICP <20 mm Hg. The causes of injury are listed in table 2. There were 37 cases that had a surgical evacuation and 44 cases managed conservatively. The numbers of diffuse and focal injuries were 65 and 35, respectively, based on a Marshall computed tomography classification.

Outcome for all 81 children was recorded at six months post-injury using a questionnaire completed by parents, carers, or general practitioner. This was based upon the model of Adelson *et al*[15] and allowed a modified Glasgow outcome scale (GOS) score to be assigned. In our analysis we used three different outcome dichotomies (table 3).

Monitoring of physiological variables

Intracranial pressure was monitored using an intraparenchymal transducer tipped catheter (Camino Laboratories, San Diego, California, USA) and continued for as long as was clinically indicated. Arterial blood pressure (systolic, diastolic, and mean) was monitored continuously using an intra-arterial line referenced to the right atrium. The bedside physiological monitors derived cerebral perfusion pressure. Oxygen saturation, heart rate, and body temperature (core and peripheral) were also recorded continuously.

Data acquisition and validation

Continuous recordings of variables at one minute time resolution were made from a networked paediatric intensive care unit in Newcastle and a mobile data collection system in Edinburgh. Both types of data recording were then transferred into the Edinburgh Browser[©] computer software system[16] for later off-line validation, review, and analysis.

Invalid data were identified and discarded for various artefactual reasons such as detached probes, line flushing etc. Abnormal but valid data (e.g. during chest physiotherapy) were retained. Agonal data were retrospectively excluded for the final four hours and terminal readings were noted from the last available simultaneous measurement of ICP and CPP.

Because of the limited number of patients at each year age and the obvious physiological differences between the ages of 2 and 15 it was necessary to group children into clearly defined age bands. The age bands chosen were based upon physiological tables of blood pressure[17] and by determining at what age the greatest incremental changes in blood pressure normally occurred. The age bands chosen were 2–6, 7–10, 11–15 years, and the lower limit means of mean arterial pressure (MAP) calculated for these age bands. These were considered to be the lowest acceptable value of MAP[10] and are shown in Table 4.

Given the relatively small contribution of ICP to the normal CPP value in young children, we chose the lowest acceptable CPP value to be the same as the lowest normal mean MAP value. This is likely to be numerically as accurate as formally estimating the true mean ICP level, even if data existed to allow such a calculation, and is described in detail in a previous study by Jones *et al*.[10]

Employing these values for each age band, the Edinburgh Browser system was then used to identify when the validated CPP value fell below or the ICP above these age related thresholds. Derangements were defined as abnormal values persisting for $\geqslant$ 5 minutes.[18] The commencement, number, and duration of all derangements were identified.

Derivation of index

For each patient recording the duration of each CPP or ICP insult was detected by the Edinburgh Browser program, the difference between the specific age threshold and the recorded pressure value was calculated for each minute value. These were then summed to produce what we have termed the pressure–time index for CPP (PTIc) and for ICP (PTIi), which can be mathematically described by

$$\text{PTIc} = \sum (\text{CPP}_{\text{threshold}} - \text{CPP}_{\text{value}}) * t_{\text{sample interval}} / 60$$

$$\text{PTIi} = \sum (\text{ICP}_{\text{value}} - \text{ICP}_{\text{threshold}}) * t_{\text{sample interval}} / 60$$

A PTIc value of 40 mm Hg hours could represent a single insult of two hours' duration at a constant level of 20 mm Hg

below the threshold level. It could equally represent an insult lasting four hours where the CPP was 10 mm Hg below the threshold. In practice, insults are likely to vary considerably in both duration and depth, and the index will be a cumulative total of all such insults. Clearly the PTI will provide a valid comparison of total secondary insult between different patients only when either the data acquisition is limited to the point where the ICP values have been consistently stable or within the normal range, or when data acquisition is continued up to the point of death. Varying a cut off point between 0 and the maximum PTI value, we calculated the sensitivity and specificity of the index for PTIi and PTIc for each of the three outcome divisions.

The sensitivity of PTIc will fall as the cut off point rises (fewer favourable outcomes with greater insult severity), while the specificity will rise with an increasing level of PTIc (greater number of unfavourable outcomes with increasing insult severity). Using the values of specificity and sensitivity calculated at each cut off point, ROC curves were plotted for each of the three outcome measures.

In order to investigate the effect of different threshold levels for insult detection and whether these might better differentiate outcome, each age band threshold was reduced first by 10% and then by 20%, and the PTIc recalculated. The age thresholds were then increased by 10% and the PTIc calculated again. Using the favourable versus unfavourable outcome dichotomy, ROC curves were plotted for each of the new threshold test levels and the area under each curve determined. For ICP the effect of altering the thresholds was also investigated by reducing the thresholds by 10% and then increasing them by 10% and then 20% (table 5).

The ICP monitoring was discontinued by the attending clinician when considered normal and no longer clinically appropriate. In order to ensure that the duration of monitoring did not significantly affect the PTI we have considered whether different durations or the severity of the primary injury would have influenced the PTI.

RESULTS

Based upon a post-resuscitation Glasgow coma score (GCS), 63 of the 81 children were considered to have suffered a severe head injury (GCS 3–8, E1, V = <2, and M = <5) and 16 children suffered a moderate head injury (GCS 9–12). There were two with a mild head injury (GCS13–15, with injury severity score (ISS) ≥16). The mean ISS was 20 (range 9–38).

Of the 81 children, 35 made a good recovery, 30 were moderately disabled (65 favourable outcome), five were severely disabled at six months post-injury, and 11 died (16 unfavourable outcome). None remained in a vegetative state.

Cerebral perfusion pressure

Using the initial age specific physiologically based threshold values, the PTIc ranged from 0 to 1959 mm Hg hours. The median PTIc values varied significantly with GOS (good recovery 4.2; moderate disability 16.5; severe disability 73.6; dead 769.1 mm Hg hours, Kruskall–Wallis p<0.001). There

was no significant difference in the mean values of PTIc between the three age groups taken as a whole (not subdivided by outcome)—that is, comparable amounts of insult were found in all childhood age groups.

Separately, within both favourable and unfavourable outcome, there were no significant differences in the magnitude of PTIc across the three age bands (fig 1A, p = 0.3). However, there was a very significant difference between the PTIc values in the unfavourable v favourable outcome categories (p<0.001).

The PTIc value associated with an 80% sensitivity for a favourable outcome was 73.1 mm Hg hours. The corresponding values for mortality and morbidity were 331 and 1.4 mm Hg hours, respectively (fig 2A).
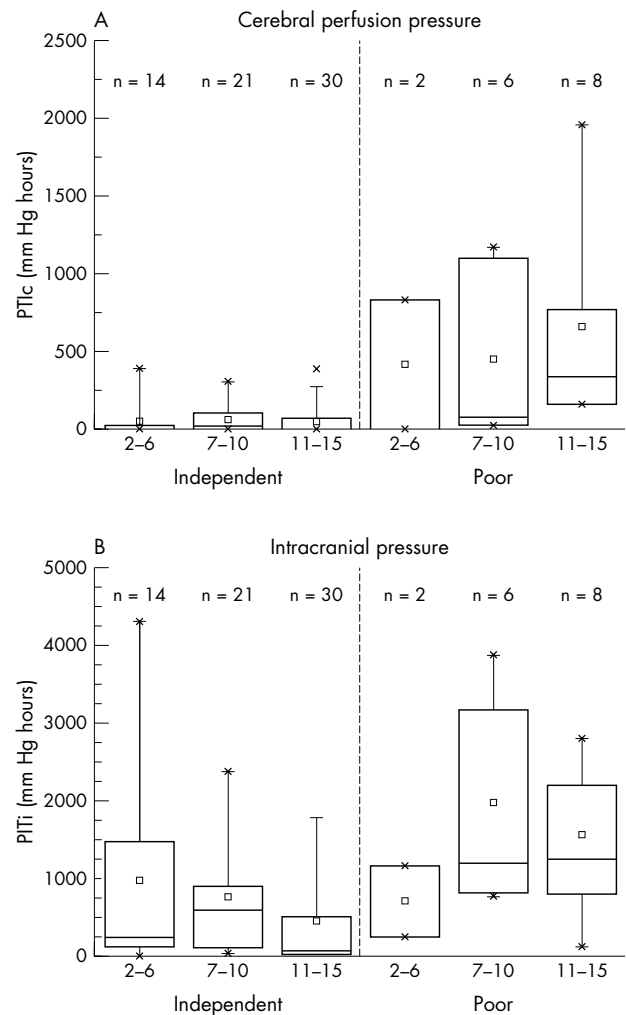

Figure 1 Box and Whisker plots of pressure–time index for (A) cerebral perfusion pressure (PTIc) and (B) intracranial pressure (PTIi) for the three age bands against outcome (favourable and unfavourable).

Table 5	Calculated ICP and CPP insult threshold values							
	CPP				**ICP**			
Age (years)	**−20%**	**−10%**	**Threshold**	**+10%**	**−10%**	**Threshold**	**+10%**	**+20%**
2–6	38	43	48	53	5.8	6.4	7.0	7.7
7–10	43	49	54	59	7.9	8.7	9.6	10.5
11–15	46	52	58	64	11.7	13	14.3	15.6
CPP, cerebral perfusion pressure; ICP, intracerebral pressure.								

When the threshold levels were changed (increased by 10% and lowered by 10% and 20%), the sensitivity fell more rapidly with lower threshold values, but there remained a clear delineation between each of the curves of sensitivity (fig 3A and B). For a specificity of 80% the PTIc values for each of the outcome groups were poorly separated, at 99.5, 96.9, and 101.4 mm Hg hours for mortality, independence, and morbidity, respectively, and with reduction in threshold values, the patterns were almost identical.

The ROC curves for PTIc created using the initial CPP threshold values for the three different outcome dichotomies are shown in fig 4A and the areas under the curves (AUCs) for all the ROC curves, along with their standard errors, are shown in table 6. The PTIc index had a very high predictive value for mortality (AUC = 0.957), and for a favourable outcome it was only slightly lower (AUC = 0.890). The predictive power was the lowest for separating the good outcome group from all the remaining outcome categories (AUC = 0.681).

When the threshold levels were altered by the previously described amounts, the resultant ROC curves for each of the three different outcome comparisons had smaller AUC values
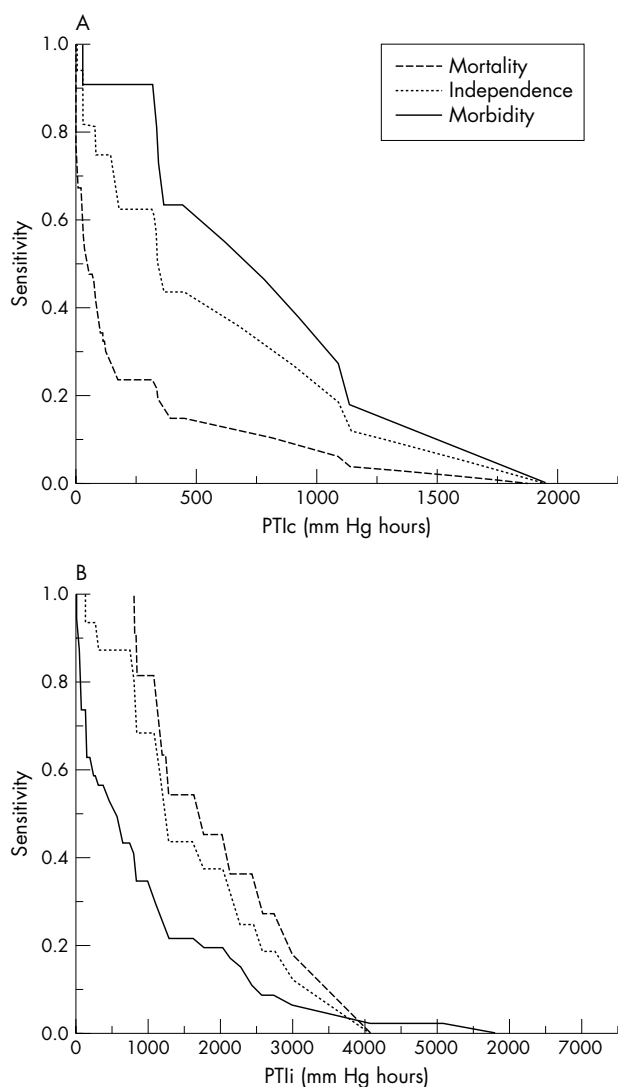

A

B

Figure 2 The sensitivities from the receiver operating characteristic (ROC) curve plotted against the pressure–time index for (A) cerebral perfusion pressure (PTIc) and (B) intracranial pressure (PTIi) in relation to mortality, favourable outcome, and morbidity.
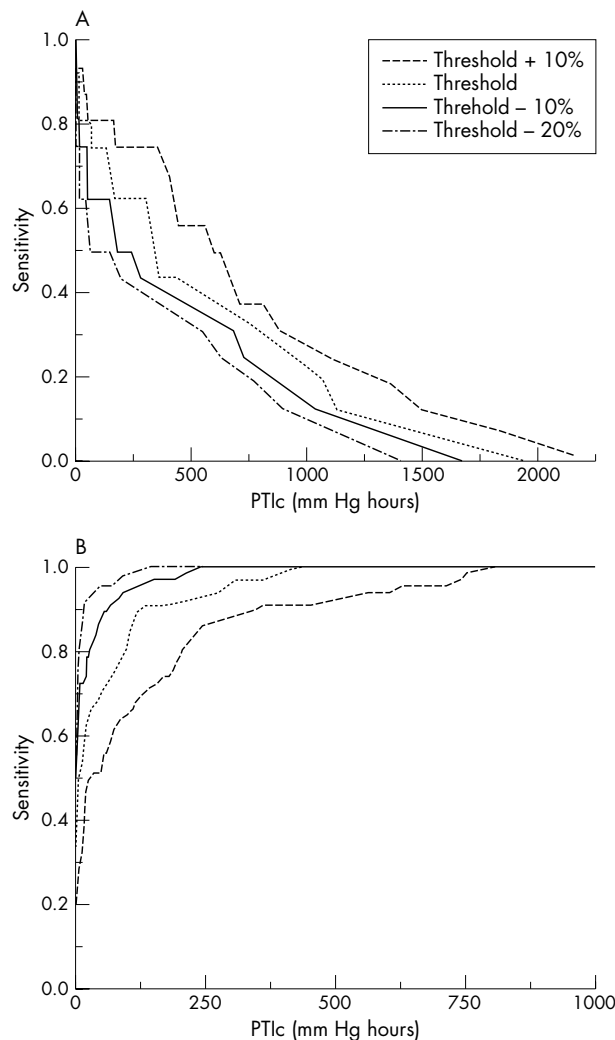

A

B

Figure 3 Sensitivity and specificity curves for the pressure–time index for cerebral perfusion pressure (PTIc) in relation to the tested threshold levels.

than that of our original threshold, indicating that our original thresholds were better predictive values.

For both favourable outcome and morbidity the original CPP threshold remained the best predictor of outcome, but for mortality the predictive value increased very slightly as the threshold level was decreased (table 6).

Intracranial pressure

The results for PTIi were similar but not identical to those for PTIc. The range of PTIi values was 0 to 5887 mm Hg hours, with a significant difference in median values of 232.8, 134.1, 776.3, and 1763.6 mm Hg hours in those who had good recovery, were moderately disabled, severely disabled, or died, respectively (Kruskall–Wallis, p<0.001). There was a greater variation in the index across the two older age groups for both favourable and unfavourable outcome than for PTIc (p = 0.026 and p<0.001) (fig 1B). There was a significant difference in the mean PTIi for favourable v unfavourable outcome (p<0.001).

The rate of change in specificity was very similar to that of the CPP index for the three outcome comparisons. Although the shapes of the sensitivity curves were similar to those of PTIc, they were spread over a much wider range of values (fig 2B). For each of the three outcome dichotomies, the
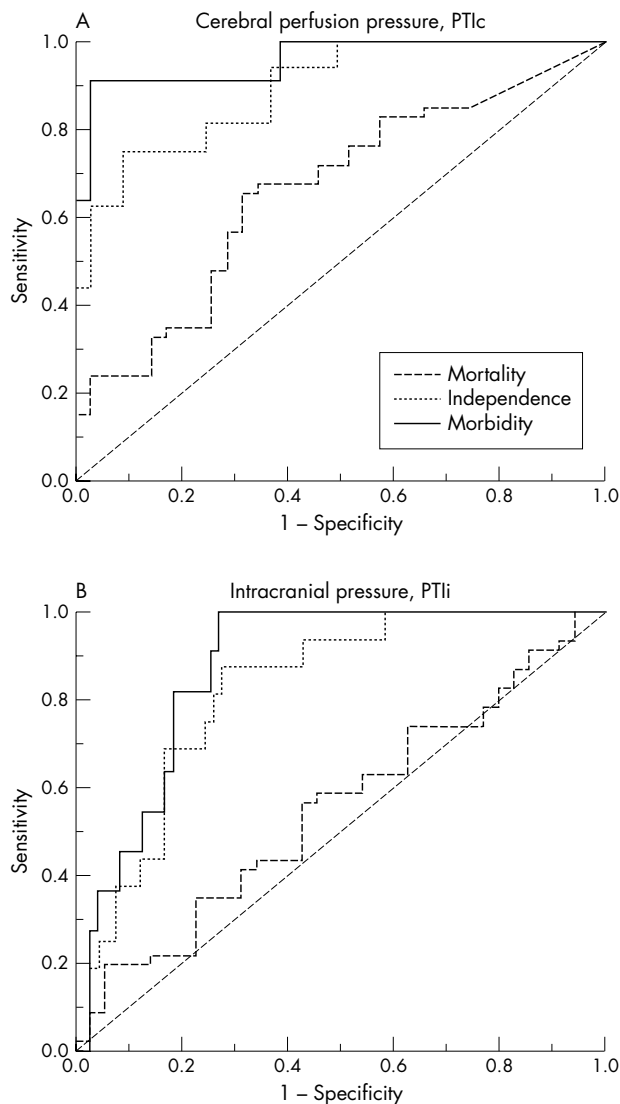
Figure 4 Receiver operating characteristic (ROC) curves for pressure–time index for (A) cerebral perfusion pressure (PTIc) and (B) intracranial pressure (PTIi) in relation to mortality, favourable outcome, and morbidity.

different threshold levels produced very similar sensitivity and specificity curves, with little difference between mortality, independence, and morbidity values—unlike those for CPP.

The areas under the ROC curves for the PTIi for mortality, favourable outcome, and morbidity were smaller than the respective PTIc values (fig 4 and table 6). The PTIi index had a very high predictive value for mortality (AUC = 0.871) and a slightly lower value for favourable outcome (AUC = 0.819). For morbidity, the ROC curve stayed near to the diagonal, indicating that the predictive value was always close to 50%.

The terminal ICP values for children aged 2–6 years were 12 mm Hg, for 7–10, 18 mm Hg, and for 11–15, 16 mm Hg, corresponding to terminal CPP values of 78, 74, and 79 mm Hg, respectively. Although 42 children had terminal ICP values that were a mean of 11 mm Hg above their age specific thresholds, this was obviously compensated because there was a negligible amount of corresponding terminal CPP insult, with only five children having had terminal CPP values of a mean of 3 mm Hg below threshold levels. Even if this level of insult in these five patients continued for the

next hour, the PTI would still have estimated 98.6% of all CPP insult. It can be seen, therefore, that the pressure recordings had been discontinued only when there was virtually no ongoing CPP derangement.

The duration of ICP monitoring bore no relation to the severity of the primary injury, as assessed by the initial GCS motor score level (p = 0.572), nor to the ISS (p = 0.237). In addition, there was no significant difference between the two participating children's head injury units in the duration of ICP monitoring (p = 0.749).

DISCUSSION

For the clinician managing head injured patients, cerebral perfusion pressure is a crucially important variable for determining management decisions. We have developed a novel pressure–time index that, for cerebral perfusion pressure, is independent of age and has similar values across our three different age bands for a favourable outcome (p<0.02) and survival (p<0.001)—that is, insult occurs in all age groups and is always predictive of outcome, thus allowing comparability of CPP insults at any age. The PTI was therefore a measure solely of secondary brain insult and was independent of the duration of ICP monitoring and highly comparable between the two centres in this study.

This cohort of head injured children is similar with respect to the type, cause, and severity of injury and their outcome to other reported British and European case series of head injured children.[19–23] Previous studies have focused on the relation between CPP and outcome in children's head injury, using a single measurement of derangement of CPP values (either mean, minimum, absolute, or percentage duration), but all failed to incorporate both duration and severity in the total burden of CPP insults.

Within the childhood population there are major differences between the blood pressure (and other physiological variables) of a 2 year old and a 10 year old, for example, unlike the adult population which recognises a single standard CPP value. However, the numbers of children in our study at each year from 2 to 15 are necessarily small and require banding for predictive statistics. The three age bands that we have used in determining insult thresholds have been described previously.[11] Although these bands could be refined, in practice the rate of development of the physiology of children can vary quite markedly and therefore the banding provides a measure of spread. We are conscious that we have not addressed ages between 0 and 2 years, because the rapidly changing physiology at this stage of development would require a larger cohort of patients and may only be possibly with a large multicentre study.

Cerebral perfusion pressure

The values of PTIc are significantly related to each of the GOS outcome categories or the combinations we have used (favourable v unfavourable, mortality, morbidity). Other studies cited above have shown a similar relation of ''single dimension'' CPP derangement to outcome. However, and uniquely, the PTIc is independent of age and was a very sensitive predictor of outcome, demonstrating a higher insult burden with worsened outcome on all three outcome measurers, although the specificity proved to be less discriminating (that is, some children made a relatively good recovery with a high PTIc value).

The threshold levels that were chosen were based on physiological norms (2–6 years, 48 mm Hg; 7–10 years, 54 mm Hg; 11–16 years, 58 mm Hg) and were not known at the outset to be insult thresholds or treatment thresholds. We reduced the CPP thresholds arbitrarily by a factor of 10% and 20%, and similarly increased it by 10% (theoretical

Table 6 Areas under the receiver operating characteristic (ROC) curves for the pressure–time index of intracranial pressure and cerebral perfusion pressure at each of the threshold levels

Outcome dichotomy	Threshold level	ROC area	SE
Favourable v unfavourable	CPP+10%	0.858	0.054
	CPP	0.890	0.044
	CPP−10%	0.883	0.053
	CPP−20%	0.886	0.051
	ICP−10%	0.816	0.050
	ICP	0.819	0.050
	ICP+10%	0.823	0.050
	ICP+20%	0.825	0.052
Good recovery v the rest	CPP+10%	0.652	0.062
	CPP	0.662	0.061
	CPP−10%	0.645	0.061
	CPP−20%	0.667	0.060
	ICP−10%	0.555	0.065
	ICP	0.550	0.065
	ICP+10%	0.548	0.064
	ICP+20%	0.545	0.064
Mortality v the rest	CPP+10%	0.931	0.046
	CPP	0.957	0.034
	CPP−10%	0.968	0.027
	CPP−20%	0.966	0.026
	ICP−10%	0.864	0.042
	ICP	0.871	0.041
	ICP+10%	0.882	0.039
	ICP+20%	0.887	0.038

values), and our analysis showed that the performance of PTIc was robust.

ROC curves are a very suitable method for analysing a process that has a binary outcome. The area under the curve gives a measure of the predictive value of a test and can be used to compare different variables.[24] Our ROC analysis has clearly shown that the PTI value for CPP, using our original CPP threshold values (at different ages), most accurately separated the outcome categories. Theoretical threshold levels above or below were less predictive than the original physiologically based thresholds.

Intracranial pressure
It is generally accepted that raised intracranial pressure is a secondary insult that adversely effects outcome.[4 25 26] For ICP our new index has an ROC area under the curve of 0.871 (for mortality), and 0.819 (favourable v unfavourable), and although this is lower than the CPP value it clearly has a considerable relation to outcome.

The children who were severely disabled or died had progressively larger amounts of ICP insult, as would be expected, but there was an apparently anomalous finding of median PTIi values in those children who made a good recovery (232.8 mm Hg hours) compared with those who were moderately disabled, who had less insult (134.1 mm Hg hours). However, this represents only a 6% difference in the total PTIi, and may be a reflection of several outliers. Investigating this, we found there was no significant difference in the duration of monitoring between those with a good recovery and those with moderate disability, but the significant differences in the mean values of PTIi between the three age groups (p = 0.017) might suggest that the a priori ICP threshold levels do not equate to the insult thresholds as they are too low.

Increasing or decreasing the ICP thresholds by 10% or 20% (of a relatively small numerical ICP value) did not significantly change the sensitivity or specificity and hence did not improve the predictive value in relation to outcome—that is,

it is the CPP at our age specific thresholds that is the more influential factor in the outcome of paediatric head injury.

Critical thresholds
Using this new index (PTI), which combines the degree and duration of derangement, to quantitate the totality of brain insult from pressure derangement, and when applied to predefined insult threshold values for ICP and CPP, we have shown that the index is robust and relates extremely well to both morbidity and favourable outcome. We have tested limits of these physiological thresholds by both increasing and decreasing them, and have shown clearly by calculating sensitivity and specificity of PTI that our initial physiological thresholds best separated children with head injuries for both mortality and favourable outcome using CPP. These critical threshold values for children aged 2–6, 7–10, and 11–<16 years were 48, 54, and 58 mm Hg, respectively. In relation to ICP, the predictive value of the PTI index improved slightly as the threshold level was increased. This may have been because the initial values, although developed from normal age related values, were at a relatively low level, but even a 20% change did not bring about a large absolute difference.

This is the first study that includes more than one dimension in the analysis of ICP and CPP data collected from head injured children. We consider that the PTI will therefore be needed for future studies that determine the totality of cerebral perfusion pressure insults. Further work is required to establish whether the shorter more severe insults have comparable effects to longer but less severe derangements.

There may, in theory, be three different types of threshold: physiological thresholds, treatment thresholds, and brain insult thresholds. Each of these would need to be precisely defined and understood, but we believe that for children the physiological thresholds (of CPP) are identical to the insult thresholds. Treatment thresholds are likely to be more arbitrary and individual, and what is defined here are absolute CPP values below which secondary brain injury

has a significant impact of the injured child's outcome. Critical care guidelines emphasise the value of ICP monitoring, and a more exact knowledge of the level of damaging thresholds of ICP and CPP should enhance the ability of the clinician to recognise abnormal pressures and to take therapeutic steps to avoid the insult extending beyond these thresholds.

ACKNOWLEDGEMENTS

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