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## **INTRA-AURAL PULSE PRESSURE WAVES IN AFRICAN CHILDREN WITH ACUTE NON-TRAUMATIC COMA**

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## **ABSTRACT**

### **Background**

Standard tools for measuring Intra-cranial pressure (ICP) are invasive and require technical proficiency. Intra-aural pulse pressure waves, measured using the tympanic membrane displacement (TMD) analyser, may be of value in monitoring ICP. We explored the relationship between TMD pulse pressure measurements, and clinical features and mortality, in children with acute coma in Kilifi, Kenya.

### **Methods**

Between November 2007 and September 2009, we made serial TMD and clinical observations on children with acute coma (Blantyre coma score  $\leq 2$ ) at the paediatric high dependency unit of Kilifi District Hospital. We examined middle ear function using tympanometry and measured cardiac pulse (CPA) and respiratory pulse pressure amplitudes (RPA) using the TMD analyser. When a child was stable, we made lumbar puncture (LP) manometry measurements alongside TMD pulse pressure measurements. We compared differences in TMD measurements between two or more groups using the Student's t-test and Kruskal-Wallis test as appropriate.

### **Results**

We recruited 75 children [median age 3.3 (Inter-quartile range (IQR) 2.0, 4.3) years]. Thirty (40%) children were observed to have clinical features of raised ICP at least once during the period of observation. Children with clinical features of raised ICP had higher maximum CPA [median 248 (IQR 198,350) nl] and RPA [median 487 (IQR 295,836) nl] measurements in the

semi-recumbent position compared to those without; [CPA median 158 (IQR 123,288) nl; P=0.02, and RPA median 292 (IQR 183,365) nl P<0.01]. Twenty-one (28%) children died. Children who died had significantly higher cardiac pulse amplitudes in both the semi-recumbent and recumbent positions, and higher semi-recumbent respiratory pulse amplitudes, compared to those who survived. Only 8 children underwent LP manometry. We did not observe significant correlation between TMD pulse pressure and LP manometry measurements. Abnormal tympanometry was associated with greater mortality compared to normal tympanometry (OR 16.3 95% C.I. 1.7-158.5; P<0.01).

### **Conclusion**

TMD pulse pressure measurements may be useful in detecting and monitoring altered ICP dynamics and may help predict clinical outcome in childhood coma. Abnormal tympanometry appears to predict outcome and may be related to ICP or other intracranial pathology. Studies incorporating invasive ICP monitoring and neuro-imaging may help clarify the utility of the TMD analyser and tympanometry in monitoring children with acute coma.

### *Keywords*

Intracranial Pressure, Tympanic Membrane Displacement Analyser, Intra-aural Pulse Pressure Amplitude, Coma, Child

## BACKGROUND

Acute coma is a common presentation of infectious diseases in children. In sub-Saharan Africa (SSA), it is most frequently caused by cerebral malaria (CM), acute bacterial meningitis (ABM), and viral encephalitides [1, 2]. These diseases are associated with high mortality and neuro-cognitive sequelae among survivors [3-5]. The risk of such poor outcome is associated with deep coma, repeated seizures, shock and raised intracranial pressure (ICP)[6]. Raised ICP is common in all these encephalopathies [2, 5, 7]. It impairs cerebral perfusion, leading to ischaemic brain injury, and may result in death due to herniation of brain tissue[8].

Intensive monitoring and management of ICP dynamics may improve outcome [9, 10]. However, tools for monitoring ICP are invasive and require technical proficiency to maintain accuracy. Their use may be complicated by probe displacement, haemorrhage and infection, particularly pertinent limitations in resource poor SSA [8]. Non-invasive tools for monitoring ICP could circumvent these limitations, provide insights on the pathophysiology of these encephalopathies, and allow for development of appropriate interventions to improve outcome.

Intra-aural pressure measurements using the Tympanic Membrane Displacement (TMD) analyser may be of value in non-invasive monitoring of ICP. The TMD analyser makes use of the communication between the subarachnoid space and the inner ear through the cochlear aqueduct which allows for transmission of ICP to the perilymphatic space[11]. The resultant change in perilymphatic pressure causes alteration in the dynamics of the middle ear ossicles causing volume displacements of the tympanic membrane [12, 13]. These nanolitre ( $10^{-9}$ L)

displacements can be detected by the TMD analyser through an air displacement sensor probe sealed onto the external auditory meatus. Previous studies have indicated significant correlation between baseline TMD measurements, derived through stimulation of the stapedial reflex, and direct ICP measurements[14, 15]. Normal variations in ICP caused by systemic pressure changes due to the cardiac and respiratory cycles can also be perceived by the TMD analyser[16]. Raised ICP may increase these pulsatile variations due to reduced intracranial compliance. Thus, TMD analyser measurements of these variations (cardiac pulse and respiratory pulse amplitudes) may provide an indirect measure of ICP. These TMD pulse pressure measurements have been little studied.

We conducted this study to explore the relationship between TMD cardiac and respiratory pulse pressure amplitude measurements and, lumbar puncture (LP) manometry measurements, other clinical parameters and mortality, in children presenting with acute non-traumatic coma in a rural hospital in Kilifi, Kenya.

## **METHODS**

We carried out this study at the paediatric high dependency unit (HDU) of Kilifi District Hospital at the rural coast of Kenya. We made observations on children aged between 6 months and 13 years presenting in coma (Blantyre Coma Score (BCS)  $\leq 2$ , persisting for more than 30 minutes after correction of hypoglycaemia or treatment of a seizure)[17]. The BCS is a simple score of coma status, similarly based on assessment of motor, verbal and eye opening as the modified Glasgow Coma Scale, but preferred in malaria endemic areas because of its simplicity and better inter-observer agreement among health workers in this setting[17]. We excluded

children known to have sickle cell disease, epilepsy, or developmental delay, being co-morbid conditions which may alter ICP dynamics and clinical outcome. The study was approved by the Kenya Medical Research Institute Ethics Review Committee (SSC 1249) and was conducted between November 2007 and September 2009.

### *Standard Care*

At admission, we provided emergency care based on standard guidelines[18]. Initial investigations included blood glucose, full blood count, sodium and potassium levels, venous blood gas analysis, and blood culture. We performed lumbar puncture when the children were stable and examined the cerebrospinal fluid (CSF) for evidence of infection. We could not consistently perform lumbar puncture opening pressure measurements because often when the children were stable, they were agitated and would not tolerate the procedure, or they remained severely ill and a lumbar puncture was contra-indicated. We considered post-mortem lumbar puncture for children who died to determine the aetiology of the encephalopathy, but not for pressure measurements, if the parents gave consent. All children received first-line parenteral anti-malarial (intravenous quinine or artesunate) and antibiotics (benzyl-penicillin and chloramphenicol) therapy until otherwise guided by the results of three initial 8 hourly malaria slide microscopy and bacterial culture. We classified children as having CM based on the WHO definition; coma in a child with malaria parasitaemia in the absence of evidence for an alternative explanation for cause of illness [19]. We considered a diagnosis of ABM when bacteria were detected through CSF culture, gram staining or bacterial antigen testing, or when there was a CSF leucocyte count of at least 10 per  $\mu\text{L}$  and the CSF to blood glucose ratio was

less than 0.67 [20]. Children who had blood culture confirmed bacteraemia in the absence of any indication of ABM were assumed to have sepsis. We classified children who did not have any history of trauma and no indication of CM, ABM, or bacteraemia, as unknown encephalopathy. During care, we assessed for clinical features of raised ICP, defined as at least two of the following features: dysconjugate eye gaze, dilated un-reactive pupils, decerebrate or opisthotonic posturing, papilloedema as confirmed by two clinicians, irregular and shallow respiration, and evident Cushing's reflex (bradycardia associated with hypertension).

### *Study procedure*

Upon obtaining consent from the parents or guardians, we examined the children's ears using an otoscope and a handheld Kamplex™ tympanometer (Interacoustics A/S, Assens). We classified tympanometry measurements as either normal or abnormal using the Liden and Jerger criteria[21]. This classification is based on a plot of the compliance of the tympanic membrane and the middle ear pressure. We used the right ear for TMD measurements to maintain consistency unless tympanometry was abnormal on that side and normal on the left. When possible, we took measurements in both semi-recumbent (at an angle of approximately 45 degrees) and recumbent positions. Peak-to-peak amplitude measurements of the TMD cardiac (Cardiac Pulse Amplitude; CPA) and respiratory (Respiratory Pulse Amplitude; RPA) pulses were made by two raters (SG and ED). All the complete cardiac waveforms along a respiratory cycle were measured and the readings averaged to give a single measurement. We made retinal fundi observations through indirect fundoscopy and assessed neurological status alongside the TMD measurements. We carried out observations at 0, 4, 12, 24, 48 and 72 hours



or until the child regained consciousness or died. When the child was stable and was not agitated or could stay calm, we carried out LP manometry alongside TMD pulse pressure measurements.

### *Analysis*

We entered the data onto a Filemaker (Filemaker Pro 10 v1) database system. We analysed the data using STATA software version 11.0 (StataCorp LP, Texas USA). We explored continuous data for any violations of the normality assumption both graphically using histograms and formally using the Shapiro-Wilk test, and transformed the data where appropriate. For continuous data, we applied the Student's t-test and Kruskal-Wallis (KW) test to examine the differences in TMD measurements as appropriate. We applied the Chi-square and Fishers exact tests to test for associations between categorical data as appropriate. All statistical significance testing was assessed at the conventional 5% significance level and where appropriate, results were reported in odds ratio (OR) with 95% confidence intervals (95%CI). To examine for the relationship between TMD pulse pressure and lumbar puncture manometry measurements, we carried out spearman's pair-wise correlations between the two sets of measurements.

## **RESULTS**

### *Admission clinical characteristics and outcome*

We recruited 75 children out of an eligible 113 (Fig. 1). They were of median age 3.3 (IQR 2.0-4.3) years and 32 (43%) were female. Forty children (53%) had CM, 23 (31%) unknown encephalopathy, 8 (11%) ABM, and 4 (5%) sepsis. There was no difference in median age, gender, depth of coma at admission, diagnosis, and mortality, between those who were

recruited and those who were not (Supplementary Table 1). Twenty-one (28%) children died.

The clinical characteristics of those who died and those who survived are compared in table 1.

Table 1: Comparison between clinical characteristics of study patients who died and those who survived

Characteristic	Alive (n=54)	Died (n=21)	P-value
Age (Years)	3.6 [2.2,4.3]	2.4 [1.3,3.4]	0.81
Sex			
Male	30 (56%)	13 (62%)	
Female	24 (44%)	8 (38%)	0.62
Duration of Coma at Presentation	4 [1,8]	2 [1,5]	0.09
History of Seizures at Admission	40 (74%)	13 (62%)	0.44
Agitation at Admission	2 (4%)	1 (5%)	0.80
Cough	13 (24%)	7 (35%)	0.35
Blantyre Coma Score			
0	6 (11%)	4 (19%)	
1	15 (28%)	3 (14%)	
2	33 (62%)	14 (67%)	0.38
Irregular Respiration	7 (13%)	16 (76%)	<0.01
Respiratory Rate	38 [30,49]	48 [33,57]	0.10
Deep Breathing	20 (39%)	10 (48%)	0.16
Capillary Refill >2 seconds	8 (15%)	6 (29%)	0.17
Systolic Blood Pressure	98 [91,106]	99 [89,106]	0.96
Diastolic Blood Pressure	60 [52,68]	59 [54,70]	0.94
Heart Rate	142 [128,161]	164 [129,186]	0.07
Axillary Temperature	37.9 [36.9, 38.9]	37.8 [37.1, 39.4]	0.35*
Mid Upper Arm Circumference	15 [14,15]	14 [12,15]	0.42
Abnormal Motor Posturing			
Opisthotonus	3 (5.6%)	3 (14%)	
Decerebrate	8 (15%)	3 (14%)	
Decorticate	7 (13%)	0	0.24
Retinal Hemorrhage	8 (15%)	1 (2%)	0.23
Papilloedema	1 (2%)	2 (10%)	0.13
PH	7.40 [7.29,7.44]	7.36 [7.28,7.41]	0.21
Partial Pressure of CO <sub>2</sub> (kPa)	4.0 [3.4,4.5]	3.7 [2.0,4.5]	0.25
Partial Pressure of O <sub>2</sub> (kPa)	6.7 [5,11.9]	9.5 [6.7,18.7]	0.02
Bicarbonate (mmol/L)	17.2 [14.6, 19.7]	16.2 [8.7,17.7]	0.04
White Blood Cell Count (Count x 10 <sup>9</sup> /L)	11.1 [8.6,18.5]	15.8 [11.8, 24.7]	0.08
Haemoglobin (g/dL)	8.7 [(6.9,10.4]	8.8 [6.8,9.7]	0.59
Platelets Count (Count x 10 <sup>9</sup> /L)	159 [55,380]	271 [167, 365]	0.17
Sodium (mmol/L)	133 [131,137]	134 [130,136]	0.52
Potassium (mmol/L)	3.8 [3.5,4.3]	3.5 [2.6,4.3]	0.20
Diagnosis			
Cerebral Malaria	33 (83%)	7 (17%)	
Acute Bacterial Meningitis	3 (38%)	5 (63%)	<0.01
Sepsis	1 (25%)	3 (75%)	<0.01
Unknown Encephalopathy	17 (74%)	6 (26%)	0.42

Continuous data presented as median [IQR]. Analysis of continuous data made using Kruskal Wallis equality of population test apart from temperature\* (student T-test). Categorical data analysed using chi square and Fisher's exact tests.

Admission clinical characteristics of irregular respiration, partial pressure of oxygen, bicarbonate levels, and invasive bacterial infections were associated with death.

Children with ABM and sepsis were more likely to die compared to children with CM [OR 7.9 (95% C.I. 1.3, 47.8;  $P < 0.01$ ) and OR 14.1 (95% C.I. 1.0, 199.8;  $P < 0.01$ ) respectively]. Admission tympanometry was normal in only 25 (33%) of the children recruited. Children with abnormal tympanometry had a greater risk of death compared to those with normal tympanometry (OR 16.3 95% C.I. 1.7, 158.5;  $P < 0.01$ ). Specifically, children who died were more likely to have a lower tympanic membrane compliance (median 0.3 [inter-quartile range (IQR) 0.1, 0.3]  $\text{cm}^3$ ) compared to those who survived (median 0.5 [IQR 0.3, 0.7]  $\text{cm}^3$ ) ( $P < 0.01$ ; KW test).

#### *TMD measurements, clinical features of raised ICP, and mortality*

Admission (0 hour) TMD measurements were successful in 63 (84%) children in the semi-recumbent position, and in 60 (80%) in the recumbent position. Thereafter, TMD measurements were not consistently made because many children were regaining consciousness or being resuscitated and therefore could not be sufficiently still for the measurements, or died within the first few hours of admission. Therefore, analysis of the TMD measurements was focussed on the admission (0 hour) measurements. There was good agreement between the two raters ( $\kappa = 0.70$ ,  $P < 0.01$ ). There were no differences in the initial TMD measurements between the different diagnoses (Table 2). Thirty children (40%) were classified as having raised ICP based on clinical features observed during the whole period of observation. These children were more likely to die compared to those who did not have

clinical features of raised ICP (OR 9.14, 95% C.I. 2.41-34.63; P<0.01). The maximal TMD measurements in the semi-recumbent position observed for each individual over the period of observations were higher for children with clinical features of raised ICP compared to those without (Table 3). Children who died had significantly higher admission semi-recumbent TMD measurements compared to those who survived (Table 4). In the recumbent posture, only CPA measurements were significantly higher in those who died than in those who survived.

Table 2: Admission TMD measurements by diagnosis

	Cerebral Malaria	Meningitis	Unknown Encephalopathy	Sepsis	P*
CPA - (Semi R.)	172 (90,298)	241 (157,290)	118 (95,153)	233 (214,388)	0.09
CPA - (R.)	157 (106,260)	271 (104,666)	132 (98,246)	185 (142,267)	0.52
RPA- (Semi R.)	271 (115,383)	727 (308,1455)	248 (182,343)	295 (208,489)	0.19
RPA- (R.)	340 (143,487)	314 (222,836)	332 (209,494)	312	0.88

\*Kruskal-Wallis equality of population tests. (CPA-cardiovascular pulse amplitude, RPA – Respiratory pulse amplitude, Semi. R. – Semi-recumbent, R-Recumbent). RPA-(R) measurement for sepsis is for only one individual. Data presented as median (IQR). TMD measurements are in nanolitres

There were no significant differences in TMD measurements between the different diagnoses.

Table 3: Relationship between TMD measurements and clinical features of raised ICP.

TMD parameter	Features of raised ICP§		P*
	Present	Absent	
CPA - (Semi. R.)	248 (198,350)	158 (123,288)	0.02
CPA - (R.)	260 (142,326)	209 (143,304)	0.56
RPA- (Semi. R.)	487 (295,836)	292 (183,365)	<0.01
RPA- (R.)	352 (276,685)	361 (213,573)	0.30

§At least two clinical features of raised ICP, \* Kruskal-Willis equality of populations test. Data presented in median (Inter-quartile Range). R – Recumbent, Semi-R – Semi-recumbent CPA-cardiovascular pulse amplitude, RPA – Respiratory pulse amplitude. TMD measurements are in nanolitres.

The maximal TMD measurements in the recumbent position observed for each individual during the period of observations were higher for children who had clinical features of raised ICP at any one time during the duration of observation compared to those without.

Table 4: Comparison of admission TMD measurements by outcome

TMD Parameter	Survived	Died	P*
n	46	17	
Semi. R. CPA	142 (118,172)	224 (156,323)	0.01
n	43	17	
Rec. CPA	147 (124,176)	245 (164,366)	<0.01
n	23	10	
Semi. R. RPA	238 (181,312)	415 (248,694)	0.03
n	31	9	
Rec. RPA	285 (218,372)	381 (241,603)	0.28

Data represents geometric mean with 95% confidence interval in brackets. \*Comparison made using student T test of natural log transformed values. n- Number of individuals in each group, CPA-Cardiovascular pulse amplitude, RPA – Respiratory pulse amplitude, Semi. R. – Semi-recumbent, R-Recumbent. TMD measurements are in nanolitres.

Apart from recumbent RPA measurements, children who died had significantly greater TMD measurements compared to those who survived.

#### TMD and Lumbar Puncture Pressure Measurements

We only succeeded in conducting concurrent LP manometry and TMD measurements in 8 children because most children were either too sick to undergo lumbar puncture or were already fully conscious and unable to stay calm to facilitate accurate LP manometry and TMD measurements. The eight children had a median LP opening pressures of 12.8 (IQR 11.4, 17.8) cm of water. We did not observe any significant correlation between LP and TMD measurements (Table 5).

Table 5: Correlation between LP Manometry measurements and TMD pulse pressure measurements

	Spearman's Rho	n	P*
CPA - (Semi R.)	-0.60	8	0.12
CPA - (R.)	-0.43	6	0.40
RPA- (Semi R.)	0.20	5	0.75
RPA- (R.)	-	0	-

\* Spearman's pair-wise correlation

There was no significant correlation between the TMD pressure and LP manometry measurements

### *Qualitative assessment of TMD measurements*

We observed three main morphological patterns of TMD pulses. The most common (70%; n=193) type was characterized by a clear cardiac pulse with or without an underlying respiratory pulse (Figure 2a). Twenty nine percent (n=80) of the pulse waveforms appeared to have prominent respiratory component with effaced overlying cardiac pulses that varied in amplitude in different phases of the respiratory pulse (Figure 2b). The third form of pulsatile waveforms was characterized by sharp clefts on the apices of the cardiovascular waveforms (Figure 2c). Only four such waveforms were observed. There appeared to be no apparent association between the morphology of the pulses and systemic respiratory patterns, cardiovascular status, clinical features of raised ICP or mortality.

## **DISCUSSION**

One of the greatest research priorities in the management of children with severe illnesses in sub-Saharan Africa is that of developing simple and inexpensive tools for diagnosis, and monitoring physiological parameters. In children with acute coma, such tools could be used to detect important risk factors for poor neurological outcomes, potentially advance understanding of the pathophysiology of non-traumatic encephalopathies, and facilitate the development of effective life-saving interventions. Raised ICP is a common complication of childhood non-traumatic encephalopathies in SSA and is associated with poor outcome. The need to develop non-invasive tools for monitoring ICP is of priority.

In this study, we explored the relationship between TMD pulse amplitude measurements, and LP manometry measurements, clinical features of raised ICP and mortality, in children presenting to our hospital with acute non-traumatic coma. We demonstrated greater semi-recumbent CPA and RPA in children with clinical features of raised ICP compared to those without. We also showed that children who died had greater semi-recumbent CPA and RPA, and recumbent CPA, than those who survived. We however did not observe any significant correlation between LP manometry and TMD measurements.

Previous studies using the TMD analyser have been on baseline pressure measurements in individuals with chronic derangements in ICP dynamics like IIH and hydrocephalus [14, 15, 22]. They have indicated significant correlation between LP manometry and TMD baseline pressure measurements. These studies have been on children with chronic disturbances of ICP dynamics and some of them have demonstrated significant inter-subject variability in TMD baseline pressure measurements, albeit in subjects with varied aetiology[22]. Our study was on little studied TMD pulse pressure measurements in children with acute encephalopathies in a resource-poor setting. We intended to make comparisons between pulse pressure measurements and LP manometry measurements. However, we only managed to conduct concurrent measurements in 8 children. Lumbar puncture manometry is not an optimal method for monitoring ICP in an intensive care setting. The assumption made is that ICP is uniformly distributed in the CSF compartment which is not always the case in infectious encephalopathies. Decent monitoring should be conducted for at least 30 minutes over which period a measure of pulse pressure is preferred[8]. Clearly, LP manometry was not optimally

conducted in our study on children who were not sedated and for which significant compliance was needed to facilitate measurement. This significant methodological flaw reflects the practicalities of our resource-poor setting and makes us unable to validate or invalidate the utility of the TMD pulse pressure measurements in monitoring ICP.

Systemic variations in pressure and flow cause fluctuations in ICP and intracranial fluid flow[16]. Thus, blood pressure variations due to the cardiac cycle cause concurrent variations in ICP and fluid flow. To a lesser extent, respiratory and vasomotor induced oscillations also affect ICP and flow. This pressure pulsatility can be changed by altered intracranial compliance, defined by an exponential pressure and volume relationship in the cranium[23, 24]. Accordingly, reduced intracranial compliance due to increased ICP causes greater pulsatile variations for which measure is therefore an indirect gauge of ICP. The TMD pulse amplitude measurements could be a measure of the variations in ICP due to the cardiac (CPA) and respiratory (RPA) cycles through a window communication between the intracranial compartment and the inner ear. In a study on individuals with idiopathic intracranial hypertension (IIH), mean ICP was found to be normal in 50% of the patients but ICP pulse amplitude was raised in all the patients[25]. Shunt implantation resulted in improved symptoms and reduced ICP wave amplitude but no significant change in mean ICP. Thus, ICP pulse amplitude measurements may even be more relevant than static ICP in monitoring ICP dynamics. If TMD pulse pressure measurements are indeed a measure of ICP pulse amplitudes, they may provide an attractive opportunity to better understand the pathophysiology of childhood encephalopathies and improve management.



It is possible that TMD measurements provide more information on intracranial dynamics than that derived from measuring pulsatile pressure variations alone, manifest as the different morphological types of TMD pulse waveforms observed. Suppression of the cardiac pulse in TMD measurements that had large respiratory components (Figure 2b) is explained by the fact that both the cardiac and respiratory pulses are registered on the same scale of the TMD output and when the respiratory waveform is large, the cardiac pulse appears attenuated. Studies incorporating neuro-imaging, invasive ICP monitoring and fluid flow studies may provide further insights and explain the different morphological types observed.

A surprise finding in our study was the fact that children with low tympanic membrane compliance as measured by tympanometry were more likely to die compared to those with higher compliance. This relationship with death was more remarkable than that between TMD measurements and death. Abnormal middle ear function in children with encephalopathy could be indicative of the point of onset of fatal intracranial pathology, widespread pathology, or window information on intracranial pathology and/or ICP. The implication of this finding needs to be investigated prospectively, incorporating imaging studies of the cranium and the auricular system. Potentially, the tympanometer, being a cheaper and simpler tool to use, may greatly aid in monitoring and prognosticating children with raised ICP.

Our study sample was small and a larger study could help confirm our findings. Being in a resource poor environment, the management of the comatose children was not optimal in that we were not able to ventilate the patients, facilitate consistent direct ICP monitoring, and

perform magnetic resonance imaging studies. Thus, the amount of information that we could derive from our study was limited.

Nonetheless, high intra-aural pulsatile pressure variations as measured by the TMD analyser appear to represent increased risk of mortality, either as a result of raised ICP or altered biomechanical properties that confer a greater risk of adverse neurological outcome in the event of an intracranial insult. Thus, intra-aural pulse pressure measurements may be useful for detecting and monitoring altered ICP dynamics in children with acute coma. Such utility needs to be clarified with studies that involve direct ICP monitoring in intensive care settings where other physiological parameters can be monitored, and incorporates intracranial imaging. The role of tympanometry in childhood non-traumatic coma can also be investigated with such studies. A non-invasive tool for monitoring ICP may provide an opportunity to better understand the pathophysiology of childhood encephalopathies and investigate effective interventions to improve outcome.

### **List of Abbreviations**

ABM – Acute Bacterial Meningitis

CI – Confidence Interval

CM – Cerebral Malaria

CPA – Cardiac Pulse Amplitude

IQR – Inter-Quartile Range

ICP – Intra-Cranial Pressure

RPA – Respiratory Pulse Amplitude

TMD – Tympanic Membrane Displacement

### **Competing Interests**

RM is a majority shareholder in Marchbanks Measurement Systems Ltd, a non-profit making company and spin-out from Southampton University that manufactures the TMD Analyser for clinical evaluation purposes. The rest of the authors declare no conflict of interest.

### **Authorship Contribution**

SG contributed in designing and conducting the study, analysed the data and drafted the manuscript. MK, EC and CN assisted in designing and conducting the study, analyzing the data and reviewing the manuscript. EO ,TB, RM and FK assisted in designing the study, analyzing the data and reviewing the manuscript.

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## FIGURES

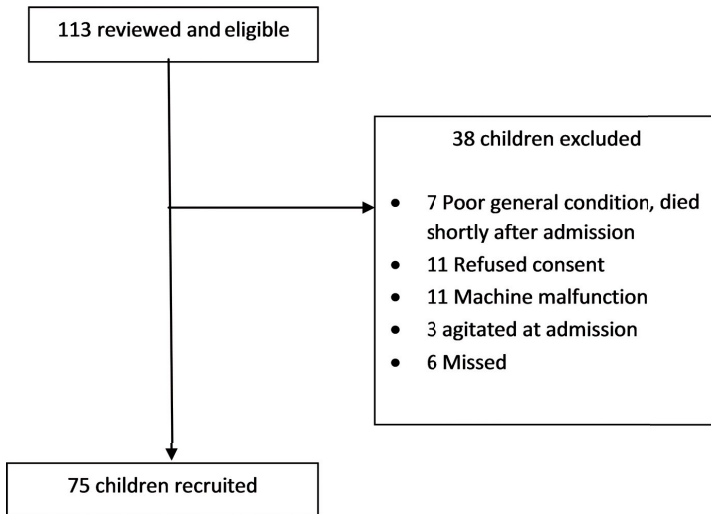
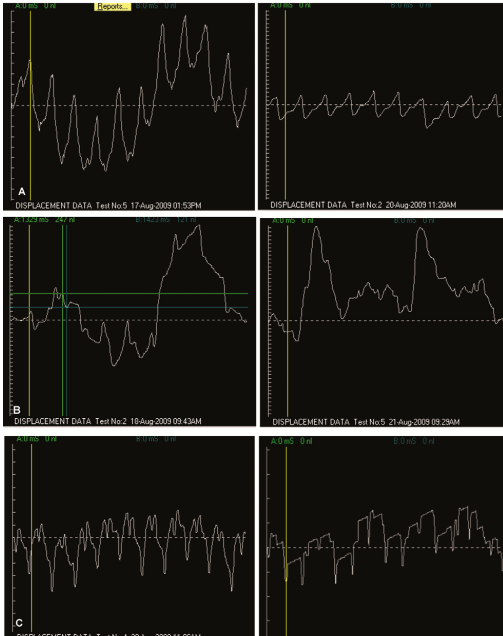


Figure 1: Study Flow Chart for HDU children. Study clinician was not aware of 6 children eligible for recruitment (Missed).



Each unit graduation on the Y axis represents 40 nanolitres. The waveforms are recorded over a duration of 6 seconds (X axis = time).

Figure 2: TMD pressure pulse types

Figure 2a: TMD waveforms with clear cardiac pulses, sometimes superimposed on a respiratory component. These made up 70% of all the measurements.

Figure 2b: Spontaneous waveforms with prominent respiratory components and irregular and/or effaced cardiac pulses. Twenty nine percent of all the measurements were of this form.

Figure 2c: A unique pattern with cardiovascular waveforms characterized by sharp clefts at the apex. Only four such waveforms were observed.