Automated Infrared Pupillometer Use in Assessing the Neurological Status in Pediatric Neurocritical Care Patients: Case Reports and Literature Review

Molly E. McGetrick1, Nathan Schneider2,3, DaiWai M. Olson3,4, Venkatesh Aiyagari3,4, Darryl Miles1

Introduction

An estimated 16% of all pediatric intensive care unit (PICU) admissions are secondary to acute neurologic illness and while technological advances have improved medical care leading to lower mortality rates, adverse outcomes due to neurocritical illnesses remain high. Pediatric patients with neurologic diagnoses have significantly higher mortality rates and percentages of severe long-term neurologic morbidities than the general PICU population.1 For instance, the age-adjusted mortality rate is more than doubled (5.7 per 100,000) in children with traumatic brain injury (TBI) compared with those with childhood cancer (2.0 per 100,000).2,3 Despite the seriousness of these conditions, neurological monitoring remains largely dependent on serial clinical neurologic exams. The pupillary light reflex (PLR), which involves constriction and relaxation of the iris sphincter muscle in response to an external light stimulus, is an essential component of the neurologic examination and is particularly consequential in states of coma or altered sensorium where other components of the neurological exam are less discernible. Loss of the PLR can indicate increased intracranial pressure (ICP), midbrain dysfunction, or horizontal or vertical shifts in brain parenchyma due to mass effect. Until recently, only manual methods for assessing pupillary reactivity were available that used imprecise descriptors such as “brisk,” “sluggish” or “absent” to describe the PLR.
introducing a potential for bias and error. A study of manual bedside pupil assessments found remarkable variation from provider to provider with interexaminer discrepancies occurring in >40% of assessments and a 50% failure rate for detecting clinically significant anisocoria.4

Automated infrared pupillometry (AIP) was developed to decrease interobserver variability and create objective output measured variables of the PLR in responses to a calibrated standard light source.5 This advance greatly improved upon traditional methods for assessing PLR by removing the subjective components of pupillary size, reactivity to variable light stimuli.5 The pupillometer is a hand-held computer-based infrared digital video camera device that measures pupil size to within 0.01 mm and quantifies components of PLR including the percent change and velocity of constriction from baseline following light stimulus, the latency or time of onset of the constriction response, and dilation velocity or the speed of dilation recovery after the constriction response. The Neurological Pupil index (NPI) is an algorithmic score combining the AIP features of the PLR into a numerical value ranging from 0 to 5, where 0 indicates a nonreactive pupil, a value less than 3 indicates an abnormal response, and a value of 3 or greater is considered normal. The automated pupillometry exam takes approximately 3 seconds to perform and has been studied in children of all ages without any adverse events, although it may be limited by patient cooperation in awake children.7 Studies in adult patients support a potential role of the NPI assessed by AIP for prognostication after cardiac arrest and subarachnoid hemorrhage,8–12 detection of significant intracranial events,13–15 and elevated ICP,16–20 and for detecting nonconvulsive status epilepticus.21,22 Published literature established normative data PLR reference values in healthy children, but investigations of AIP use in neurocritically ill pediatric patients are limited to a single study on its use for detection of increased ICP.7,23 This report highlights four cases where trend changes in NPI values served as a valuable objective measure for detection of neurological worsening and acute neurological events in pediatric neurocritical illness (Table 1).

Case 1: In-Hospital Cardiac Arrest
A previously healthy 2-year-old presented to the emergency department (ED) unresponsive in shock secondary to acute vomiting, diarrhea, and sepsis. Despite resuscitative efforts in the ED the patient became pulseless and cardiopulmonary resuscitation (CPR) was initiated. Return of spontaneous circulation (ROSC) was achieved after 20 minutes of CPR and inotropic medications were started for hemodynamic support. In the PICU, the patient remained hemodynamically unstable despite increasing inotropic support and was cannulated to venaocordial extracorporeal membrane oxygenation. After cannulation, AIP was ordered to coincide with her neurologic assessments. Throughout the first 22 hours spontaneous movement of all extremities was noted with intact brainstem reflexes and bilateral NPI values greater than 4 (Fig. 1, Case 1). Between hours 22 and 29, intermittent drops in her NPI from a baseline of 4.8 bilaterally to a minimum of 3.2 on the right and 3.4 on the left were observed without significant anisocoria.

Changes in the NPI were correlated with onset of seizure activity on electroencephalogram (EEG) and the NPI returned to baseline once seizures were controlled with antiepileptic medications. An increase in pupil size was also observed over this time period. Between hours 40 and 45 after PICU admission, a downward trend in the right NPI to an abnormal value of 2.6 was noted, while the left NPI remained at 4.7. Her neurological exam performed after anisocoria was noted at hour 45 revealed absence of withdrawal response to painful stimuli and loss of corneal, cough, and gag reflexes. Mannitol was administered followed by a brief return of the right NPI to a baseline value of 4.7, although the remainder of the clinical neurological exam was otherwise unchanged. The pupils rapidly thereafter became less reactive as indicated by the fall in the NPI (right then left) and by hour 56, bilateral values were 0. A head computed tomography (CT) revealed diffuse cerebral edema, basal cistern effacement, and uncal herniation (Fig. 2A). Given her poor neurologic prognosis, mechanical circulatory support was withdrawn, and the patient expired.

Case 2: Out-of-Hospital Cardiac Arrest
A previously healthy 17-year-old was found unresponsive at home. At the scene emergency medical services noted agonal breathing and a palpable pulse. The patient subsequently became pulseless with a pulseless electrical activity rhythm and CPR was started. After 25 minutes of CPR, ROSC was obtained. The initial blood gas in the ED demonstrated a significant metabolic acidosis with a pH of 6.9, a pCO2 of 43, and a base deficit of 24. Other notable laboratory values were a blood glucose of greater than 700 mg/dL, elevated hepatic transaminases, and acute kidney injury. Further history revealed a 2-week history of weight loss, polydipsia, polyuria, and fatigue consistent with new-onset diabetic ketoacidosis. Upon arrival to the PICU, hourly AIP was ordered with his neurological assessments. Notably, he had anisocoria—the right pupil measured 6.5 mm and left measured 4.6 mm with bilateral normal NPI values of 4.5 (Fig. 1, Case 2). A head CT was obtained shortly after PICU admission which did not show any acute intracranial abnormality (Fig. 2B). Despite receiving no sedative or paralytic medications, the patient lacked spontaneous eye opening or response to painful stimuli for the initial 24 hours, although cough and gag reflexes were present. The course was complicated by idioventricular rhythm requiring lidocaine infusion and hypotension requiring three continuous vasoactive infusions (epinephrine, norepinephrine, and vasopressin). The NPI readings remained stable and above 4.0 bilaterally during the admission, consistent with normally reactive pupils (Fig. 1, Case 2). Insulin was titrated to correct the hyperglycemia with an improving neurologic exam improved, and vasoactive infusions were discontinued. On hospital day (HD) 7 the patient was transferred out of the PICU and a brain magnetic resonance imaging (MRI) study on HD 10 was normal. The patient was discharged home without any residual neurological deficit.

Case 3: Vertebral Artery Dissection and Cerebellar Stroke
A previously healthy 14-year-old presented with 2 weeks of morning headache which on the day of presentation was
unrelenting. Initial vital signs showed hypertension with a systolic blood pressures above 150 mm Hg and bradycardia with a heart rate less than 50 beats per minute. On neurological examination, a left-sided dysmetria, decreased tone in the left-upper and left-lower extremities, and a wide-based gait were found. Neuroimaging revealed a left vertebral artery dissection with associated nonocclusive thrombus and an acute left posterior–inferior cerebellar artery territory infarction. The patient was admitted to the PICU for close neurological monitoring and initiation of systemic anticoagulation with heparin. Pupillometry was ordered on admission, which established a normal baseline NPI of 4.2 to 4.9. Although headaches persisted, no new neurologic symptoms developed in the first 18 hours of PICU admission. Between hours 18 and 20, there was an acute drop in the bilateral NPI values by 0.8 (\( \downarrow \text{Fig. 1, Case 3} \)). By hour 22, the patient became confused with incomprensible speech, and a new left-sided facial droop was found.

**Fig. 1** A graphic representation of Neurological Pupil index (NPI) and pupil size reported over time for cases 1–4. Case 1: NPI values immediately following emergent cannulation to venoarterial (VA) ECMO established a baseline of 4.8. Between hours 22 and 29 electrographic seizure activity is associated with decreases in NPI values to 3.4, which return to baseline following treatment of seizures by hour 32. At hour 45, a significant fall in the right pupil NPI to 2.6 occurs with loss of cough and gag reflexes and absence of withdrawal to painful stimulus. Mannitol (1 g/kg) is administered followed by brief improvement in NPI. Between hours 50 and 55, bilateral NPI values (right then left) show a rapid decline to zero with increase in pupil size. The patient continues to show poor neurological function and a CT scan at hour 56 reveals diffuse cerebral edema and uncal herniation. Case 2: admission PICU NPI values of 4.8 in a comatose state. There is a brief fall in the left NPI that occurs after admission, which remains above 3 and quickly returns to baseline values and remain above 4.5. At hour 12 the patient exhibits withdrawal response to painful stimuli but otherwise remained unresponsive. By hour 24 the patient begins to make purposeful movements and follow simple commands. Case 3: baseline NPI values upon PICU admission of 4.7. Between hours 18 and 20 the NPI drops by 0.8 points bilaterally to 3.9 over 2 hours that persists. The patient then began exhibiting speech difficulties followed by facial droop prompting imaging and emergent occipital decompressive craniotomy and extraventricular drain (EVD) placement. Patient returns to PICU from operating room with improvement in NPI values to previous baseline of 4.5–4.7. Case 4: baseline NPI values upon PICU admission of 3.9–4.7. At hour 48, the patient experiences clinical seizure activity, associated with an intracranial pressure spike to 25 mm Hg and a drop in the NPI to 2.2 bilaterally. By hour 50, clinical seizure activity resolved, and EEG was consistent with absence of electrographic seizures. Again, at hour 71, there was a decline in the NPI to 3.2 on the right and 1.0 on the left associated with subclinical seizures localized to the right frontal region. These abnormal discharges resolved by hour 74 and the NPI returned to baseline of 4.7. CT, computed tomography; EEG, electroencephalogram; PICU, pediatric intensive care unit.
Case 4: A Traumatic Subdural Hematoma
A 9-month-old female with no significant past medical history presented to the ED after a fall from a bed at home. The initial Glasgow Coma Score was 4 with extensor posturing and no spontaneous eye opening. She was emergently intubated and presumed intracranial hypertension was treated with 3% hypertonic saline and 60 mg/kg of intravenous (IV) levetiracetam for seizure prophylaxis. A head CT demonstrated a large right-sided subdural hemorrhage and a nondepressed occipital skull fracture. In the PICU, an ICP monitor was placed with an opening pressure of 6 mm Hg. Initially, the pupils measured 2.6 mm on the right and 2.9 mm on the left by AIP with an NPi of 3.9 and 4.5, respectively. Over the first 48 hours, the patient was sedated on fentanyl and midazolam infusions with an ICP below 20 mm Hg. At hour 48 she developed acute tachycardia and upper extremity twitching associated with elevated ICP to 25 mm Hg. Simultaneously, her bilateral NPi dropped from 4.5 to 2.2 bilaterally and her pupil size increased from 2.4 to 6 mm (► Fig. 1, Case 4). Electrographic seizures were confirmed on bedside EEG and treated with increasing midazolam infusion. Brain MRI revealed diffuse signal changes consistent with cytotoxic edema from hypoxic-ischemic injury (► Fig. 2F).
At hour 71 the patient exhibited another acute drop from a baseline NPi of 4–4.5 to 3.2 on the right and 1 on the left eye, which was associated with an elevated ICP spike to 34 mm Hg. The patient was paralyzed at this time, and seizure activity was noted on the EEG. IV lacosamide was administered and by hour 74, all seizure activity stopped and the subsequent NPi values remained stable (>4.0) for the duration of the monitoring period. ICP remained low, and the patient was extubated on HD 10 and later discharged to inpatient rehabilitation with residual left-sided motor impairments and paroxysmal sympathetic hyperreactivity.

Discussion
In January 2020, our institution changed the method of assessing pupil size and reaction to include objective assessments of the PLR with a NeurOptics NPi-200 pupillometer (Laguna Hills, California, United States) in all children admitted to the PICU following a TBI, cardiac arrest, stroke, intracranial hemorrhage, or with any neurocritical illness at risk for neurological decline. The cases described in this report illustrate potential advantages of using AIP as a noninvasive neuro-monitoring tool in the neurological assessment of critically ill pediatric patients (► Table 1). The NPi as a quantifiable measurement of the PLR provides an objective trend to detect changes in the PLR compared with traditional standard manual assessments limited to subjective descriptions such as “brisk,” “reactive,” or “sluggish.” Similar to findings published in adult populations, we found that changes in the NPi may be a useful marker for early detection of significant neurologic events including brain herniation, convulsive and nonconvulsive seizures, and hydrocephalus.5,9,10,13,21,24

In cases 1 and 2, we demonstrate that pupillometry may provide valuable information regarding the development of significant brain swelling and herniation during the post-arrest phase of care. In case 1, we present a young child who...
<table>
<thead>
<tr>
<th>Clinical events</th>
<th>Hours of stay</th>
<th>GCS</th>
<th>NPI R</th>
<th>NPI L</th>
<th>Imaging or EEG finding</th>
<th>Intervention</th>
<th>Hours of stay</th>
<th>GCS</th>
<th>NPI R</th>
<th>NPI L</th>
</tr>
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<tbody>
<tr>
<td>Case 1</td>
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<td></td>
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<tr>
<td>Admitted after cardiac arrest, hypotensive, and unresponsive</td>
<td>0</td>
<td>8</td>
<td>4.8</td>
<td>4.8</td>
<td>None</td>
<td>ECMO cannulation</td>
<td>4</td>
<td>8</td>
<td>4.8</td>
<td>4.8</td>
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<tr>
<td>Rhythmic movement of bilateral lower extremities</td>
<td>21</td>
<td>6</td>
<td>4.3</td>
<td>3.8</td>
<td>EEG: periodic lateral discharges primarily over left hemisphere</td>
<td>Levetiracetam 60 mg/kg</td>
<td>22</td>
<td>6</td>
<td>4.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Lip smacking and left lower extremity movement</td>
<td>29</td>
<td>6</td>
<td>3.2</td>
<td>3.4</td>
<td>EEG: periodic lateral discharges bilateral hemispheres</td>
<td>Phenobarbital 20 mg/kg</td>
<td>30</td>
<td>6</td>
<td>4.8</td>
<td>4.8</td>
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<tr>
<td>Loss of cough, gag, and pain reflex</td>
<td>45</td>
<td>6</td>
<td>2.6</td>
<td>4.7</td>
<td>CT: diffuse hypoxic-ischemic injury, diffuse cerebral edema, bilateral uncal herniation</td>
<td>Mannitol 1 g/kg given; epinephrine infusion initiated</td>
<td>46</td>
<td>6</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Continued absence of cough, gag, and pain reflex</td>
<td>52</td>
<td>5</td>
<td>0.9</td>
<td>3.7</td>
<td>None</td>
<td>Escalation of epinephrine and norepinephrine infusions; hydrocortisone 25 mg/m² administered</td>
<td>54</td>
<td>4</td>
<td>0</td>
<td>2.9</td>
</tr>
<tr>
<td>Absent of all brain stem reflexes, hypotension refractory to vaspressors</td>
<td>56</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>None</td>
<td>Withdrawal of mechanical support</td>
<td>60</td>
<td>3</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Case 2</td>
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<tr>
<td>Admitted to the ICU in comatose state, hypotensive, with idioventricular rhythm</td>
<td>1</td>
<td>6</td>
<td>4.5</td>
<td>4.5</td>
<td>CT: no acute intracranial abnormality</td>
<td>Therapeutic insulin, lidocaine, vasopressin, and norepinephrine infusions started</td>
<td>3</td>
<td>6</td>
<td>4.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Patient begins withdrawing from painful stimulus; idioventricular rhythm resolved</td>
<td>7</td>
<td>6</td>
<td>4.6</td>
<td>4.7</td>
<td>EEG: generalized slowing, without seizures</td>
<td>Epinephrine infusion weaned off</td>
<td>7</td>
<td>9</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Begins to open eyes, follow some commands; hyperglycemia and acidosis corrected</td>
<td>24</td>
<td>11</td>
<td>4.7</td>
<td>4.7</td>
<td>None</td>
<td>Weaned off epinephrine and norepinephrine infusions. Insulin infusion converted to a subcutaneous regimen.</td>
<td>30</td>
<td>11</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Case 3</td>
<td></td>
<td></td>
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<tr>
<td>Admitted to the ICU for heparin infusion and neurological monitoring</td>
<td>0</td>
<td>15</td>
<td>4.6</td>
<td>4.4</td>
<td>CT/CTA: left-sided vertebral artery dissection, left-sided posterior-inferior cerebellar infarction</td>
<td>Heparin infusion started for thrombosis prophylaxis</td>
<td>8</td>
<td>15</td>
<td>4.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Acute development of incomprehensible speech and left-sided facial droop on exam</td>
<td>20</td>
<td>11</td>
<td>4</td>
<td>3.9</td>
<td>MRI: left-sided cerebellar infarction with obstructive hydrocephalus</td>
<td>Ventriculostomy placed</td>
<td>30</td>
<td>3</td>
<td>4.3</td>
<td>4.0</td>
</tr>
<tr>
<td>Prolonged coughing spell, intracranial pressure elevation for greater than 5 minutes</td>
<td>43</td>
<td>9</td>
<td>4.2</td>
<td>4.5</td>
<td>None</td>
<td>Sedation provided with morphine</td>
<td>45</td>
<td>11</td>
<td>4.7</td>
<td>4.6</td>
</tr>
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</table>

(Continued)
experienced an in-hospital cardiac arrest and despite reported normal pupillary reactivity (NPI > 3) for much of the course, downward trends in the patient’s NPI preceded documented clinical neurological changes. The continued decline in the patient’s NPI to 0 ultimately correlated with progressive cerebral edema and herniation with complete loss of the PLR and neurological function. Although in-hospital cardiac arrests are associated with higher likelihood of survival compared with those that occur outside the hospital, mortality is still high. Recent evidence from the Get With The Guidelines-Resuscitation registry, a United States-based in-hospital cardiac arrest registry, reported that 62% of children who arrest within the hospital will die, with brain death accounting for greater than half of these deaths. Despite implementation of evidence-based neuroprotective strategies in the critical hours after cardiac arrest, neurological injury from anoxic insults may progress leading to cerebral swelling, neuronal cell death, and brainstem herniation, as seen in the unfortunate demise of case 1. Although the patient suffered a more abrupt fall in the NPI and rapid clinical deterioration, changes in the PLR detected by AIP may occur prior to changes in the clinical exam when significant intracranial events occur. In one report, changes in NPI occurred at a median of 7.4 hours before transtentorial herniation occurred. This is demonstrated in case 3 where we see a fall in NPI hours before a clinical change was observed. In herniation events with a more insidious onset, AIP may uncover subtle changes in pupillary reactivity much earlier than a standard clinical examination would allow, providing opportunity for life-saving intervention. In case 2 the patient suffered an out-of-hospital cardiac arrest of similar duration to case 1 and presenting physical and laboratory examinations might suggest a poor neurologic prognosis. In contrast to case 1 where the patient had a declining NPI within 48, the patient in our second case had bilateral NPI values that remained normal despite an initial comatose state, and as his neurological status gradually improved in the following days. Because the clinical exam was limited by coma, the PLR and NPI values were important clinical markers used at the bedside to assess this patient’s neurological status. Recent adult studies have suggested that AIP may serve as a prognostication tool after cardiac arrest, with reasonable associations between abnormal NPI and mortality or unfavorable neurologic outcome. Although there may be stark differences in the etiologies for cardiac arrest in children compared with adults, our experiences suggest that AIP could potentially play a role in prognostication after cardiac arrest in children as well.

In cases 3 and 4, a pupillometry NPI decline trend was associated with evolving neurological changes in the patient’s condition. In case 4 a decline in the NPI was associated with an increase in ICP levels above 20, coinciding with onset of seizures. The relationships between the NPI and invasive ICP values have been explored in adult patients as a noninvasive method for detecting elevated ICP. In a pediatric prospective observational study by Freeman et al, 1,130 paired measurements of invasive ICP and NPI values were analyzed in 28 children with invasive ICP monitors placed secondary to either TBI or encephalopathy. The
authors found a modest but significant inverse correlation (−0.31 [95% confidence interval: −0.53 to −0.1], p = 0.004) between the NPI and ICP values. The reliability of using NPI for noninvasively detecting intracranial hypertension is still being elucidated with a need for more robust datasets investigating this relationship in children of all ages. In case 3 the downward trend in NPI which persisted below the patient’s previously established baseline was associated with developing hydrocephalus and raised ICP that was ultimately amendable surgical or medical intervention resulting in a good outcome.

Interestingly, in cases 1 and 4 declining NPI was associated with convulsive and electrographic seizure activity, which improved with appropriate antiepileptic therapy. The association between seizures and changes in the NPI has until recently not been well described, and to our knowledge the existing literature is limited to adults. A recent study conducted in adult patients demonstrated that nonconvulsive status epilepticus was associated with significant reductions in NPI from baseline, and discrepancies between right and left NPI during an event.21 Our findings suggest that exploration of changes in AIP in patients with epileptic events could pose an additional area of investigation.

It is worth noting that although the manufacturer suggests an NPI threshold of 3 to distinguish between normal and abnormal pupillary reactivity, serially trend values over time in patients may also provide important information for evolving neurologic injury. In the study by Freeman et al, a significant difference in mean NPI values (4.4 versus 3.4) was found when the ICP was less than or greater than 20 respectively (p < 0.001), although in both cohorts a value greater than 3 would be considered normal. In case 3 a persistent change in bilateral NPI values occurred by 0.8 from a baseline of 4.7 to 3.9, which was associated with clinical worsening and developing hydrocephalus. In case 1 declines in NPI which still remained above 3 were associated with seizure activity. Therefore, a single NPI value might represent a clinically relevant change which could be interpreted as normal (above the 3 threshold) without establishing baseline AIP values. In our PICU pupillometry policy, medical staff are to be notified if the NPI falls to less than 3 or if there is a change of >1 that does not return to baseline within 30 minutes, recognizing that a fall from 4.5 to 3.1 may be clinically meaningful even though the absolute value is still above 3.

There is a growing body of literature supporting AIP use in adult patients for applications described in these cases, nevertheless literature in pediatrics is scarce. This series where AIP provided noninvasive detection of neurologic changes in the clinical status of pediatric patients with acute brain injury. Given this small sample size, as well as single-center design, our experiences may not be shared by all pediatric centers using this device for patients with brain injury. Although these cases suggest that pupillometry trends may provide valuable detection of significant neurologic events in the setting of known or suspected brain injury, further investigations are needed to elucidate situations in which measurements from this device may be limited. Combining the experience of multiple institutions would certainly add awareness about the benefits of AIP and may help elucidate sources of error.

Conclusion
Automated pupillometry can provide valuable clinical information as a noninvasive neurologic monitoring tool in pediatric patients with acute neurological injury who are at risk for neurologic events. This technology may detect changes in the PLR not observable with manual pupil assessments providing earlier detection allowing for more timely intervention to reduce secondary brain injury. The use of automated pupillometry for the detection of subclinical seizures, increased ICP, and injury prognostication in children are interesting potential applications of this technology and deserve further study in children.

Conflict of Interest
None declared.

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