Pupillary changes after clinically asymptomatic high-acceleration head impacts in high school football athletes

Jacob R. Joseph, MD; Jennylee S. Swallow, MS; Kylene Willsey, MD; Andrea A. Almeida, MD; Matthew T. Lorincz, MD, PhD; Robert K. Fraumann, JD, MD; Mark E. Oppenlander, MD; Nicholas J. Szerlip, MD; and Steven P. Broglio, PhD

OBJECTIVE Previous studies have shown that clinically asymptomatic high-acceleration head impacts (HHIs) may be associated with neuronal and axonal injury, as measured by advanced imaging and biomarkers. Unfortunately, these methods of measurement are time-consuming, invasive, and costly. A quick noninvasive measurement tool is needed to aid studies of head injury and its biological impact. Quantitative pupillometry is a potential objective, rapid, noninvasive measurement tool that may be used to assess the neurological effects of HHIs. In this study, the authors investigated the effect of HHIs on pupillary metrics, as measured using a pupillometer, in the absence of a diagnosed concussion.

METHODS A prospective observational cohort study involving 18 high school football athletes was performed. These athletes were monitored for both the frequency and magnitude of head impacts that they sustained throughout a playing season by using the Head Impact Telemetry System. An HHI was defined as an impact exceeding 95g linear acceleration and 3760 rad/sec² rotational acceleration. Pupillary assessments were performed at baseline, midseason, after occurrence of an HHI, and at the end of the season by using the NeurOptics NPI-200 pupillometer. The Sport Concussion Assessment Tool, 5th Edition (SCAT5), was also used at each time point. Comparisons of data obtained at the various time points were calculated using a repeated-measures analysis of variance and a t-test.

RESULTS Seven athletes sustained HHIs without a related diagnosed concussion. Following these HHIs, the athletes demonstrated decreases in pupil dilation velocity (mean difference 0.139 mm/sec; p = 0.048), percent change in pupil diameter (mean difference 3.643%; p = 0.002), and maximum constriction velocity (mean difference 0.744 mm/sec; p = 0.010), compared to measurements obtained at the athletes’ own midseason evaluations. No significant changes occurred between the SCAT5 subtest scores calculated at midseason and those after a high impact, although the effect sizes (Cohen’s d) on individual components ranged from 0.41 to 0.65.

CONCLUSIONS Measurable changes in pupil response were demonstrated following an HHI. These results suggest that clinically asymptomatic HHIs may affect brain reflex pathways, reflecting a biological injury previously seen when more invasive methods were applied.

https://thejns.org/doi/abs/10.3171/2019.7.JNS191272

KEYWORDS pupillometry; traumatic brain injury; concussion; accelerometry; pediatrics; trauma

SPORTS-RELATED concussion (SRC) is a topic of concern for many athletes, parents, and coaches, but diagnosing a concussion continues to be problematic. In addition to a concussion’s complex pathophysiology, which results in a variety of clinical presentations, the diagnosis relies primarily on self-reporting of symptoms. This results in a conflict of interest on the part of the athlete with a possible brain injury, who may desire to continue playing, and depends on the athlete being adequately educated about the symptoms and repercussions

ABBREVIATIONS ANOVA = analysis of variance; CISG = Concussion in Sports Group; CTE = chronic traumatic encephalopathy; HHI = high-acceleration head impact; HITS = Head Impact Telemetry System; mTBI = mild traumatic brain injury; NPI = Neurological Pupil index; QP = quantitative pupillometry; RHI = repetitive head impact; SCAT5 = Sport Concussion Assessment Tool, 5th Edition; SRC = sports-related concussion.


INCLUDE WHEN CITING Published online November 26, 2019; DOI: 10.3171/2019.7.JNS191272.
of SRC.4 Underreporting of symptoms has been highlight-
ed as a major issue in SRC, with research indicating that
50% of concussions are unreported.4,11 The limitations of
self-reporting of symptoms underscore the importance of
developing an objective method to diagnose those athletes
at risk for SRC or other brain injury.

Numerous studies have recently shown that changes in
biomarkers that occur with SRC may be useful for both
diagnosis determination and return-to-play decisions.1,31,32
However, biomarker analysis typically requires invasive
methods of collection, advanced laboratory processing, or
advanced imaging, which limits its utility in most athletic
settings (e.g., high schools). Furthermore, there is now
evidence of brain injury in athletes who are asympto-
matic or do not otherwise seek immediate clinical atten-
tion.2,13,22 A rapid, objective, noninvasive method to iden-
tify athletes at risk and diagnose concussion would be a
major advance.

The pupillary light reflex has long been a critical por-
tion of the neurological examination.16 However, a pupi-
lar examination typically involves use of a penlight and
may involve subjective interpretation, particularly in cases
in which there are subtle findings.23 More recently, use
of quantitative pupillometry (QP) has become common-
place, particularly in the neurointensive care setting.8 QP
provides the advantage of being an objective and quantifi-
able biometric test, and has previously been evaluated in
patients with subacute and chronic mild traumatic brain
injury (mTBI). In a study in which military personnel
were evaluated 15–45 days following blast-induced mTBI,
clinicians found evidence of decreased dilation velocity,
decreased average constriction velocity, and increased
constriction latency.7 A separate study of patients who had
suffered an mTBI longer than 1 year previously revealed
decreases in maximum constriction velocity, average con-
striction velocity, average dilation velocity, maximum
diameter, and constriction amplitude.30 However, QP has
not been meaningfully evaluated in athletes who sustain
significant head impacts. In the present study, we sought
to determine if clinically asymptomatic high-acceleration
head impacts (HHIs) resulted in measurable changes in
neurological function, specifically changes in the pupi-
lar light reflex as determined using QP, in the absence of
other neurocognitive findings.

Methods

Patient Population and Study Design

A prospective cohort study of varsity high school foot-
ball athletes was performed from July through October
2017. After approval of the study protocol had been granted
by the University of Michigan Institutional Review Board
(IRB), assent and written consent were obtained from all
athletes and parents. The athletes and their parents were
given an opportunity to provide assent and consent a sec-
time following an IRB amendment near midseason.
Any athlete who was undergoing active treatment for an
mTBI, had a history of moderate or severe TBI, or had un-
dergone neurosurgery in the past was excluded. Eighteen
athletes volunteered for participation. Demographic in-
formation was collected, including each athlete’s age, height,
weight, concussion history, and sports participation his-
tory. All athletes underwent a preseason neurocognitive
evaluation (see below) and QP. The initial assessment was
performed during a period of rest, and not after an athletic
event.

Each athlete’s helmet was fitted with the encoder for the
Head Impact Telemetry System (HITS; Riddell) to mea-
sure and record head impact data during all practices and
games. All athletes were monitored for concussion symp-
toms by the athletic training staff, and diagnoses of SRC
were made by independent physicians. Any athlete who re-
ceived a diagnosis of SRC at some time during the season
was excluded from the study thereafter. Repeated neuro-
cognitive evaluation and QP were performed immediately
after the athletic event during which an athlete suffered an
HHI (defined as an impact that simultaneously achieved
a linear acceleration of > 95 g and a rotational accelera-
tion of > 3760 rad/sec2). This definition was based on data
from a previous investigation in which a correction had
been made to the resultant rotational acceleration value.5,13
All athletes also underwent a midseason assessment that
included a neurocognitive evaluation and QP immediately
after an athletic event during which the athlete did not sus-
tain an HHI. This midseason assessment was performed
approximately 2–2.5 months after the baseline assessment
and took place within a 10-day period. Both the midsea-
son and HHI assessments were performed within 1 hour
of the end of a game. Finally, 1 week after the final game
of the season, all athletes again underwent an additional
assessment that included a neurocognitive evaluation and
QP. This end-of-season evaluation was performed during
a period of rest, and not after an athletic event.

Neurocognitive Evaluation

Neurocognitive evaluations were performed using the
The SCAT5 is a concussion assessment tool that was
designed by the Concussion in Sports Group (CISG) in
2016.6 The SCAT5 allows medical personnel to assess an
athlete and report potential signs and symptoms that may
help diagnose a concussion. In the current study, symptom
evaluation, cognitive screening, balance examination, and
delayed recall were utilized.9

Quantitative Pupillometry

Quantitative pupillometry was performed using the
NPi-200 Pupillometer System (NeurOptics, Inc.). The
system is used to evaluate eight parameters of the pupil. The
Neurological Pupil index (NPi; NeurOptics, Inc.) value,
range from 0 to 4.9, determines the reactivity of the pu-

pil. Lower values represent decreased pupillary reactivity
detected by the device. The maximum size metric is def-
in as the maximum diameter (mm) of the pupil, and the
minimum size metric is defined as the minimum diameter
(mm) of the pupil. The percent change metric is defined
by the following formula: [maximum pupil diameter (mm) –
minimum pupil diameter (mm)]/maximum pupil diam-
eter (mm) × 100. Constriction velocity is the rate (mm/
sec) at which the pupil constricts after exposure to light.
Latency to constriction is the amount of time (seconds)
between the eye’s exposure to a light stimulus and initiation of pupil constriction. Maximum constriction velocity is the top rate (mm/sec) at which the pupil constricts. Dilation velocity is the rate (mm/sec) at which the pupil dilates after constriction. Testing takes less than 2 minutes and was conducted in similar ambient lighting throughout the study.

Statistical Methods

Means and standard deviations of values representing the athletes’ demographic information, including age, height, weight, years participating in football, and previous concussion, were calculated using descriptive statistics. Comparisons were made between the baseline, midpoint, and end-of-season measurements obtained for athletes who completed all time points, so that we could evaluate changes in QP and neurocognitive assessments over the course of the season. Additionally, comparisons were made between changes in the results of the neurocognitive and QP assessments after HHI and at the midpoint evaluation by using a within-subject control group. The midpoint evaluation was used as a comparator to minimize the effect of game play itself. A repeated-measures analysis was used to evaluate the F-statistic and the significance of neurocognitive scores across the season in all athletes at the baseline, midpoint, and end-of-season evaluations. Neurocognitive scores at the midpoint evaluation were compared with those obtained immediately after HHI when compared to values at the athletes’ own midpoint evaluations (Table 1). There was no significant difference in the NPi, maximum size metric (maximum diameter), minimum size metric (minimum diameter), latency to constriction, or constriction velocity (all p > 0.05) at the same time point. An evaluation of the SCAT5 components did not reveal any differences between values obtained at the HHI evaluation and those obtained at the midpoint evaluation (p > 0.05). The associated data are summarized in Table 2.

When we compared differences in the QP over the course of the season, there was a significant change in both constriction velocity (p = 0.019) and maximum constriction velocity (p = 0.043; Table 3). Neurocognitive testing performed using the SCAT5 did not show any significant differences over the course of the season. The associated data are summarized in Table 4.

Discussion

Concussion was first defined by the Congress of Neurological Surgeons in 1966 as a clinical syndrome characterized by immediate and transient impairment of neural function, such as alteration of consciousness, disturbance of vision, equilibrium, etc., due to mechanical forces.11

TABLE 1. Comparison of QP results obtained following HHIs and at midseason

<table>
<thead>
<tr>
<th></th>
<th>HHI Evaluation</th>
<th>Midseason Evaluation</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPi value</td>
<td>3.721 ± 0.423</td>
<td>3.936 ± 0.308</td>
<td>0.069</td>
</tr>
<tr>
<td>Max diameter, mm</td>
<td>5.163 ± 0.698</td>
<td>5.504 ± 0.716</td>
<td>0.178</td>
</tr>
<tr>
<td>Min diameter, mm</td>
<td>3.599 ± 0.554</td>
<td>3.648 ± 0.520</td>
<td>0.775</td>
</tr>
<tr>
<td>% change in pupil diameter</td>
<td>30.286 ± 2.701</td>
<td>33.929 ± 2.269</td>
<td>0.002</td>
</tr>
<tr>
<td>Max constriction velocity, mm/sec</td>
<td>4.382 ± 0.854</td>
<td>5.126 ± 0.534</td>
<td>0.010</td>
</tr>
<tr>
<td>Latency to constriction, sec</td>
<td>0.228 ± 0.032</td>
<td>0.213 ± 0.019</td>
<td>0.166</td>
</tr>
<tr>
<td>Constriction velocity, mm/sec</td>
<td>3.121 ± 0.573</td>
<td>3.429 ± 0.378</td>
<td>0.082</td>
</tr>
<tr>
<td>Dilation velocity, mm/sec</td>
<td>1.359 ± 0.290</td>
<td>1.498 ± 0.261</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SDs. Boldface type indicates statistical significance.
Since that time the definition of SRC has become more varied and complex. A recent systematic review identified 14 articles that provided definitions of concussion by six different organizations. The authors of the review recommended that the clinical definition of concussion include elements of biomechanics, physiology, clinical findings, neuroimaging, and fluid biomarkers/genetics. These recommendations culminated in a definition of SRC provided by the CISG in 2016 as a traumatic brain injury induced by biomechanical forces... [that] typically results in the rapid onset of short-lived impairment of neurological function... [and] results in a range of clinical signs and symptoms. Because of the ambiguity in reporting and identifying the subjective clinical symptoms of SRC, the definition would be improved by an objective measure for diagnosis.

In the present study, there was evidence of biometric changes, as measured by the pupillary light reflex assessed after clinically asymptomatic HHI. Relative to values obtained at the participant’s own evaluation following an uneventful (no HHI) athletic event, there were significant decreases in dilation velocity, percent change of pupil diameter, and maximum constriction velocity. No significant differences were seen in the results of neurocognitive assessments that were performed after the HHI and non-HHI evaluations. These results indicate that the forces experienced by these athletes were sufficient to alter intrinsic brain reflex pathways, even when the effects of the HHI were otherwise clinically silent. Clinically asymptomatic HHIs have already been associated with increases in serum tau and UCH-L1, both biomarkers of TBI. Coupled with the QP data, an otherwise asymptomatic HHI potentially meets the criteria proposed for concussion by the CISG based on an objective biomechanical, physiological, and biomarker evaluation. Previous literature has suggested that there is a wide spectrum of mTBIs. The results reported in the present study indicate that an HHI may be another grade on the concussion spectrum that cannot be captured by standard clinical testing.

Concussions, as clinically defined, have remained in the spotlight over the last 10 years due to ongoing concern about their relationship to chronic traumatic encephalopathy (CTE). While the prevailing theories are that CTE develops as a result of repetitive head impacts (RHIs), the exact cause and mechanism of CTE is still under investigation. In fact, there is evidence against the prevailing understanding of RHIs as the sole mechanism of CTE. In the present study, HHI was associated with pupillary changes that were not seen during evaluations made following events during which there were no HHIs. These results suggest that HHIs may have a more profound impact on the health of athletes than a typical collision. RHIs, which by definition entail 100% of head impacts, constitute a nearly impossible entity to avoid short of abandoning all collision sports. However, an HHI accounts for only 0.01% of all head impacts experienced by high school athletes. Given this low incidence, an HHI

**TABLE 2. Neurocognitive performance following HHI and at midseason**

<table>
<thead>
<tr>
<th>Neurocognitive Testing*</th>
<th>HHI Evaluation</th>
<th>Midseason Evaluation</th>
<th>p Value</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-report: symptom severity</td>
<td>10 ± 18.64</td>
<td>6 ± 8.39</td>
<td>0.767</td>
<td>–0.127</td>
</tr>
<tr>
<td>Self-report: no. of symptoms</td>
<td>3.67 ± 5.61</td>
<td>3.67 ± 4.13</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Self-report: % of normal</td>
<td>87.5 ± 11.73</td>
<td>95.83 ± 8.01</td>
<td>0.175</td>
<td>0.645</td>
</tr>
<tr>
<td>Orientation</td>
<td>4.33 ± 1.21</td>
<td>4.86 ± 0.378</td>
<td>0.203</td>
<td>0.598</td>
</tr>
<tr>
<td>Immediate recall</td>
<td>14.5 ± 1.22</td>
<td>14.71 ± 0.488</td>
<td>0.363</td>
<td>0.408</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>2.67 ± 1.21</td>
<td>3.57 ± 1.51</td>
<td>0.363</td>
<td>0.408</td>
</tr>
<tr>
<td>Concentration</td>
<td>3.17 ± 1.33</td>
<td>3.43 ± 0.786</td>
<td>0.465</td>
<td>0.323</td>
</tr>
<tr>
<td>Balance</td>
<td>12 ± 5.37</td>
<td>10.43 ± 3.87</td>
<td>0.605</td>
<td>–0.225</td>
</tr>
</tbody>
</table>

* Neurocognitive testing was performed using the SCAT5.*

**TABLE 3. Comparison of QP results over the course of the season**

<table>
<thead>
<tr>
<th>NPI value</th>
<th>Max diameter, mm</th>
<th>Min diameter, mm</th>
<th>% change</th>
<th>Max constriction velocity, mm/sec</th>
<th>Latency to constriction, sec</th>
<th>Constriction velocity, mm/sec</th>
<th>Dilation velocity, mm/sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.808 ± 0.401</td>
<td>5.258 ± 0.931</td>
<td>3.580 ± 0.558</td>
<td>31.231 ± 6.849</td>
<td>4.576 ± 1.247</td>
<td>0.215 ± 0.031</td>
<td>2.874 ± 0.923</td>
<td>1.170 ± 0.470</td>
</tr>
<tr>
<td>3.981 ± 0.343</td>
<td>5.341 ± 0.658</td>
<td>3.513 ± 0.513</td>
<td>34.385 ± 3.499</td>
<td>5.165 ± 0.796</td>
<td>0.220 ± 0.026</td>
<td>3.467 ± 0.457</td>
<td>1.477 ± 0.219</td>
</tr>
<tr>
<td>3.919 ± 0.290</td>
<td>5.290 ± 0.290</td>
<td>3.550 ± 0.493</td>
<td>32.769 ± 3.861</td>
<td>4.744 ± 0.712</td>
<td>0.232 ± 0.031</td>
<td>3.222 ± 0.481</td>
<td>1.284 ± 0.309</td>
</tr>
</tbody>
</table>

* Values are expressed as means ± SDs. Boldface type indicates statistical significance.
appears to be an actionable entity. Previous studies have suggested that the frequency of high-speed collisions can be regulated out of football and, perhaps, other sports. Potential interventions include an increased football field width to decrease the likelihood of collisions, fewer practices involving contact, rule changes such as targeting penalties, and coaching interventions into improper tackling techniques.\textsuperscript{6,10,12,29}

A clear causal relationship between chronic neurodegenerative disease and collision sports has yet to be established, in part due to the difficulty of defining and documenting all head impact and head injury events. Future studies of head impacts and their sequelae would be improved by the development of a reproducible definition of head injury that does not rely on clinical acumen. Helmet accelerometry is one method by which these impacts can be quantified, although it is limited in its ability to correlate impact with injury.\textsuperscript{24} Based on the results seen here, QP may be a rapid noninvasive method of measuring brain injury in conjunction with or without helmet accelerometry. With tools such as QP, as well as others such as eye-tracking devices, a better objective understanding of the relationship between impact and injury (both short-term and long-term) is possible.\textsuperscript{5,25,26} Furthermore, simple devices such as these can enhance the detection of head injury on a larger scale, benefitting the many youth sports that do not have access to athletic trainers.\textsuperscript{15} These objective measures will allow more rigorous studies to be performed on the relationship between head impacts and their sequelae.

There were a number of limitations in this study. The sample size was low, increasing the effect of outliers. The multiplicity of hypotheses tested here further worsened the effect of the low sample size and could potentially have altered the results. A significantly larger cohort is needed to elucidate the changes that occur following an HHI. In addition, the results may have been affected by the use of within-subject controls rather than a separate cohort. The clinical implications of the subtle pupillary change seen with QP are also unclear.

Conclusions

Measurable changes in pupil response were demonstrated following HHIs. Based on these results, we can infer that nonconcussive HHIs may affect intrinsic brain reflex pathways and may reflect biological injuries that previously were found using more invasive methods.

Table 4. Neurocognitive Performance in all Athletes over the Course of the Season

<table>
<thead>
<tr>
<th>Neurocognitive Testing*</th>
<th>Baseline Evaluation</th>
<th>Midseason Evaluation</th>
<th>End-of-Season Evaluation</th>
<th>F-Test</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-report: symptom severity</td>
<td>5.23 ± 5.42</td>
<td>5.38 ± 7.65</td>
<td>2.0 ± 2.89</td>
<td>3.149</td>
<td>0.083</td>
</tr>
<tr>
<td>Self-report: no. of symptoms</td>
<td>3.23 ± 3.24</td>
<td>2.77 ± 3.56</td>
<td>1.54 ± 2.18</td>
<td>3.069</td>
<td>0.087</td>
</tr>
<tr>
<td>Self-report: % of normal</td>
<td>92.31 ± 9.61</td>
<td>96.77 ± 6.57</td>
<td>95.77 ± 7.32</td>
<td>0.733</td>
<td>0.502</td>
</tr>
<tr>
<td>Orientation</td>
<td>4.69 ± 0.48</td>
<td>4.69 ± 0.48</td>
<td>4.92 ± 0.28</td>
<td>2.912</td>
<td>0.097</td>
</tr>
<tr>
<td>Immediate recall</td>
<td>14.08 ± 1.8</td>
<td>14.77 ± 0.44</td>
<td>14.62 ± 0.77</td>
<td>0.992</td>
<td>0.402</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>3.08 ± 1.49</td>
<td>3.54 ± 1.33</td>
<td>3.15 ± 1.63</td>
<td>1.413</td>
<td>0.284</td>
</tr>
<tr>
<td>Concentration</td>
<td>3.31 ± 1.32</td>
<td>3.31 ± 0.75</td>
<td>3.15 ± 1.57</td>
<td>0.183</td>
<td>0.835</td>
</tr>
<tr>
<td>Balance</td>
<td>12.69 ± 6.86</td>
<td>10.69 ± 3.3</td>
<td>10.77 ± 5.97</td>
<td>0.83</td>
<td>0.462</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SDs.
* Neurocognitive testing was performed using the SCAT5.\textsuperscript{9}

References

as a result of clinically asymptomatic high-acceleration head impacts in high-school football athletes. J Neurosurg 130:1409–1788, 2019


Disclosures
Dr. Joseph reports having received support for the study from NeurOptics, Inc., and the Blue Cross Blue Shield Foundation of Michigan. Dr. Oppenlander is a consultant for Globus Medical, DePuy Synthes, and LifeNet Health.

Author Contributions
Conception and design: Joseph, Swallow, Szerlip, Broglio. Acquisition of data: Joseph, Swallow, Willsey, Almeida, Lorincz. Analysis and interpretation of data: Joseph, Swallow, Willsey, Szerlip, Broglio. Drafting the article: Joseph, Swallow, Willsey, Szerlip, Broglio. Critically revising the article: Joseph, Swallow, Almeida, Lorincz, Fraumann, Oppenlander, Szerlip, Broglio. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Joseph. Statistical analysis: Joseph, Swallow, Broglio. Administrative/technical/material support: Joseph, Broglio. Study supervision: Joseph, Szerlip, Broglio.

Correspondence
Jacob R. Joseph: University of Michigan, Ann Arbor, MI. jrjosephmd1@gmail.com.