# Ocular Hemorrhages in Neonatal Porcine Eyes from Single, Rapid Rotational Events

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**Purpose.** To characterize ocular hemorrhages from single, rapid head rotations in the neonatal pig.

**Methods.** Three- to 5-day-old anesthetized piglets ($n$ = 51) underwent a single, rapid (117-266 rad/s) head rotation in the sagittal ($n$ = 13), coronal ($n$ = 7), or axial ($n$ = 31) planes. Six hours after injury, the animals were euthanatized and perfusion fixed, and the brain and eyes were harvested for gross and histopathologic examination by masked neuro- and ocular pathologists.

**Results.** Ocular hemorrhage was found in 73% of animals (51% bilateral). Intraocular hemorrhage was primarily located near the vitreous base (70% of injured animals had ciliary body hemorrhage, and 11% had peripheral retinal hemorrhage). Hemorrhages were also found in the anterior chamber (11%), vitreous (5%), and optic nerve (disc, 8%; nerve sheath, 57%). Rapid axial head rotations resulted in a higher incidence of intraocular hemorrhage than coronal or sagittal head rotations, but the difference did not reach statistical significance ($P$ = 0.06). Control eyes had no injuries.

**Conclusions.** Optic nerve sheath and ciliary body hemorrhages were common in piglets that experienced a single, rapid head rotation. Retinal hemorrhage was present in a smaller number of animals. Most intraocular hemorrhages were located in regions of strong vitreous attachment, suggesting that this animal model will be useful in investigating the effect of vitreoretinal adhesion on ocular hemorrhage caused by inertial head rotations. Extrapolation of this model to the human infant should not be made until the effect of anatomic differences between the human and pig on the occurrence and patterns of ocular injuries is further investigated. (*Invest Ophthalmol Vis Sci.* 2010;51:4792–4797) DOI:10.1167/iovs.10-5211

Abusive head trauma (AHT) is the leading cause of death and disability from child abuse[1,2] and is characterized by intracranial hemorrhage and/or intraocular hemorrhage (primarily retinal), with or without additional systemic injuries. In cases of AHT with less severe signs and symptoms, AHT is often misdiagnosed.[3] An increased understanding of the mechanisms of the injuries associated with AHT may assist in the evaluation of difficult cases. Careful in vitro and animal studies[4–10] have aided in elucidating the mechanisms of pediatric traumatic brain injury and have provided clinicians with empirical data to help identify the inconsistent histories associated with brain injury. However, few controlled experimental studies to date have investigated mechanisms of retinal hemorrhages in pediatric head trauma, and an animal model has yet to be clearly established.

There is a lack of agreement about the mechanisms by which retinal hemorrhages develop in AHT. Theories include vitreous traction, acute increases in retinal arterial or venous pressure from raised intracranial or intrathoracic pressure, and tracking of intracranial blood. A viable animal model must be developed to experimentally test mechanistic theories and investigate the effect of repetitive back-and-forth head rotations (often reported in AHT) on ocular hemorrhages. The neonatal piglet is an established large animal model for pediatric brain injury,[4,9,11] and several similarities of the piglet retina to the human retina make it a promising model for studying traumatic retinal hemorrhages.

To evaluate the potential of the piglet as an immature animal model for retinal hemorrhages and other ocular injuries resulting from inertial head trauma, we retrospectively examined the eyes of 3- to 5-day-old piglets involved in multiple studies of traumatic brain injury. We sought to characterize ocular hemorrhages in animals undergoing single, rapid head rotation.

## Methods

### Inertial Head Rotation

In a protocol approved by the Animal Care and Use Committee at the University of Pennsylvania and in accordance with the animal research guidelines set forth in the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, 51 neonatal (3–5-day-old) piglets were anesthetized via an endotracheal tube with 2% to 4% isofluorane. Once the piglet was fully anesthetized, its head was secured by a padded snout clamp to the linkage assembly of a pneumatic actuator (HYGE device; Bendix Corp., South Bend, IN). The device did not hinder or compress the chest cavity of the animal. The actuator and linkage assembly created a purely inertial, nonimpact rotation of the head around the C3 to C5 segment of the spine. The rotational velocity of the head was measured with an angular rate transducer (ARS-06; ATA Sensors, Albuquerque, NM) and acquired at a 10-kHz sampling rate onto a computer. Each animal underwent a single, rapid unidirectional head rotation in one of three planes: sagittal ($n$ = 13), coronal ($n$ = 7), or axial ($n$ = 31). Heart rate, respiratory rate, body temperature, end-tidal $CO_2$, and oxygen saturation were recorded before the injury and at 30-minute intervals after the injury. Five uninjured control

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animals underwent identical procedures, but no head rotation was induced.

### Ocular Examination and Histology

In a subset of animals (subset 1: 10 injured, 2 control), a pediatric ophthalmologist (BJF) performed a dilated ophthalmic fundus examination with indirect ophthalmoscopy before injury, immediately after injury, and between 4 and 6 hours after injury. All animals were euthanatized and perfusion fixed 6 hours after injury. Both eyes in each animal were harvested by removing the orbital roof, transecting the optic nerve just anterior to the optic chiasm, and removing the eye anteriorly. The brain and eyes of each animal were stored in 10% formalin in preparation for histologic analysis. Each eye was sectioned with one cross-sectional cut through the transected end of the optic nerve, one cut through the pupil–optic nerve–macular plane, and one cut through a plane either superior or inferior to the optic nerve. All slices were stained with hematoxylin and eosin (H&E).

In a second subset of animals (subset 2: 41 injured, 3 control), no ophthalmic examination was performed, but eyes were extracted and stored in 10% formalin in the same manner as those in subset 1. In lieu of the ophthalmic examination, the eyes were examined grossly before histologic analysis, and three additional cuts were made for histology. Briefly, the eyes were removed en bloc, and the extraocular muscles and surrounding soft tissues were examined for hemorrhages or abnormalities and photographed in color. The muscles and surrounding soft tissue were subsequently removed, and the anatomic dimensions were measured, including horizontal, vertical, and anterior–posterior dimensions of the globe; horizontal and vertical dimensions of the cornea; and the diameter of the pupil. The optic nerve was examined for hemorrhages and the length recorded. After external inspection, a horizontal cut was made in each eye starting at a point just above the superior corneoscleral limbus and passing through a point just above the superior optic disc margin. The resulting superior and inferior calottes were examined in 70% alcohol under a dissecting microscope and photographed in color. Five thin (5 $\mu$m) sections of each eye (one section through the pupil–optic nerve–head plane, two sections slightly superior and inferior to that plane, and two sections through the retinal periphery superior and inferior to this plane) were stained with H&E (Fig. 1).

H&E slides from both animal subsets were examined microscopically by an ocular pathologist (RLP). The pathologist, who was masked to the mechanical loading experienced by the animal, evaluated each eye for the presence and location of ocular abnormalities, including retinal hemorrhages, optic nerve head swelling, optic nerve sheath hemorrhage, and other ocular hemorrhage (e.g., ciliary body, hyphema, subconjunctival, or extraocular muscle) or injury (e.g., retinal detachment). Brain pathology for both subsets was performed by a neuropathologist. Pearson's $\chi^2$ test was used to assess the effect of head rotation direction (sagittal, axial, or coronal) on the incidence of ocular hemorrhage, bilateral ocular hemorrhage, optic nerve sheath hemorrhage, retinal hemorrhage, and ciliary body hemorrhage. $P < 0.05$ was considered significant (JMP Statistical Software; SAS Institute, Cary, NC).

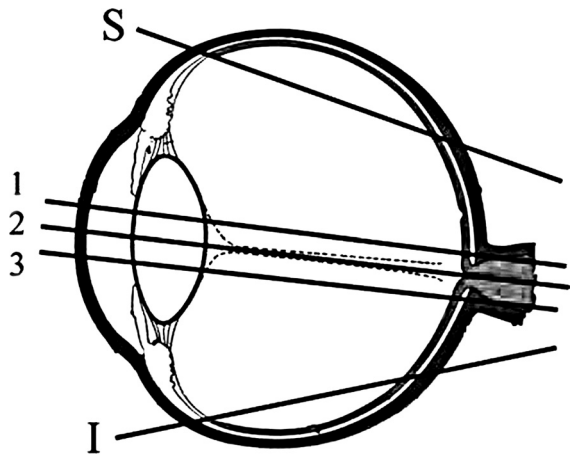


**Figure 1.** Five microsections were made in each eye from the second animal subset. Three sections were cut through the pupil–optic nerve plane (1, 2, 3). Two sections were cut inferior (I) and superior (S) to that plane. All sections were stained with H&E for microscopic analysis.

## Results

The average ocular dimensions (±SD) after removal of extraocular tissues from 44 piglets (3–5 days old) were 16.6 ± 0.6, 15.0 ± 0.1, and 14.1 ± 0.8 mm for the horizontal, vertical, and anterior–posterior axes, respectively. Average corneal width and height were 10.8 ± 0.6 and 9.1 ± 1.0 mm, respectively; pupil diameter was 7.2 ± 0.6 mm; and mass (measured in 6 of the 44 animals) was 2.1 ± 0.1 g. The ranges of measured angular velocities and accelerations of the head rotations were 117 to 266 rad/s and 30.6–101 krad/s$^2$. By design, sagittal head rotations occurred at slightly lower loads (mean ± SD, 185 ± 17 rad/s) compared with axial and coronal head rotations (207 ± 31 and 208 ± 11 rad/s, respectively) because piglets have limited range of motion in the neck in this direction.

Ocular hemorrhage was found in 73% of all animals undergoing a single, rapid head rotation and was bilateral in 51% of the animals with ocular hemorrhage. Intraocular hemorrhage was primarily located near the vitreous base (70% of the animals with eye injury had ciliary body hemorrhage, 11% had peripheral retinal hemorrhage), but hemorrhages were also found in the anterior chamber (11%) and optic nerve (disc 8%, nerve sheath 57%).

Overall, animals that experienced a rapid head rotation in the axial direction had a higher incidence of ocular hemorrhage (81%) than did those with a rapid head rotation in the sagittal (62%) or coronal plane (57%), but these differences did not reach statistical significance ($P = 0.06$; Fig. 2), possibly because of limited statistical power ($\beta = 0.54$). In addition, there was no significant effect of head rotation direction on the incidence of bilateral injury ($P = 0.32$), optic nerve disc or sheath hemorrhage ($P = 0.21$), ciliary body hemorrhage ($P = 0.12$), and retinal hemorrhage ($P = 0.53$). Three animals died at 1 to 2 hours after injury due to cardiac or respiratory complications, but the ocular findings in these animals were not unique from those in the remaining 48 animals surviving 6 hours.

### Subset 1

In the first subset of eyes ($n = 10$), no signs of ocular injury were found during indirect ophthalmic examination. However, histologic staining revealed three (30%) animals with optic nerve sheath hemorrhage (subdural or intradural), five (50%) with hemorrhage located in the stroma of the ciliary body, two (20%) with hyphema, and one (10%) with a unilateral preretinal hemorrhage (Fig. 3) located near the ora ciliaris retinae (akin to the ora serrata in humans). It is possible that this retinal hemorrhage was not seen on ophthalmic examination because of the inherent difficulty in systematically examining the ora in the neonatal piglet.

### Subset 2

Gross examination in the second subset of animals revealed six (15%) with optic nerve sheath hemorrhages confined to focal regions on the optic nerve and eight (20%) with extraocular hemorrhage in either the muscle or fat tissue. H&E staining revealed 11 additional animals with optic nerve sheath hemor-

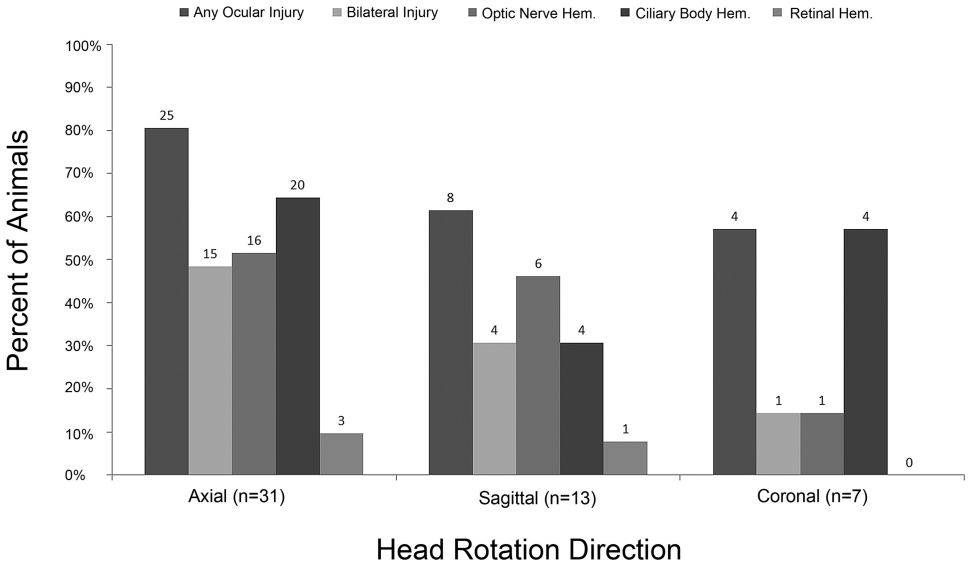


**FIGURE 2.** The incidence of ocular injuries observed from single, rapid head rotations, grouped by the plane of head rotation. The numbers at the top of the bars are the number of animals. In subsets 1 and 2, combining axial head rotations resulted in a slightly higher occurrence of ocular injury than with the sagittal or coronal rotations, but this finding was not statistically significant with a Pearson's $\chi^2$ test ($P = 0.06$). The incidence of various types of ocular hemorrhage (i.e., optic nerve, ciliary body, and retinal) was also not significantly different among the groups.

rhage, increasing the total occurrence of optic nerve sheath hemorrhages in this subset to 17 (41%) animals. Optic nerve sheath hemorrhages were mostly subdural (Fig. 4A) or intradural (Fig. 4B). Twenty-three (56%) animals had other signs of ocular trauma, including hemorrhage in the stroma of the ciliary body (56%), hyphema (5%), persistent hyaloid vessel hemorrhage (2%), vitreous hemorrhage (5%), optic disc hemorrhage located either over the disc or in the parenchyma (7%), and three animals had subretinal (5%) or preretinal (7%) hemorrhage (Fig. 5). All these hemorrhages (with the exception of the hyaloid vessel hemorrhage, hyphema, and optic disc hemorrhage) were located near the ora. In total, 28 (68%) animals in the second subset had some form of ocular hemorrhage, which was bilateral in 14 animals. Pathology of the five control animals revealed no ocular injuries.

### Brain Pathology

Gross brain examination was completed in 46 of the 51 animals in the experimental group. Thirty-eight (83%) of these animals had bilateral subdural hemorrhages, five (11%) had unilateral subdural hemorrhages, and the remaining three (6%) had little or no blood found on examination. Microscopic evaluation was performed on the brains of 31 experimental animals. H&E staining confirmed the distribution of subdural and subarachnoid hemorrhage, as identified on gross examination, and further revealed 15 (48%) animals with white matter hemorrhage. Staining with NF-68 ($n = 10$) or βAPP ($n = 21$) revealed 23 (74%) animals with axonal injury, which was diffuse in 15 and focal in 8. Sagittal and axial head rotations resulted more often in bilateral subdural hemorrhage, white matter hemorrhage, and diffuse axonal injury than did coronal head rotations (Table 1).

Twenty-six (68%) of the animals with bilateral subdural hemorrhages had ocular hemorrhages, but only one of the animals with unilateral subdural hemorrhage had ocular injury (ciliary body hemorrhage). Conversely, all animals with ocular hemorrhages had associated brain injury, except two that had small ciliary body hemorrhages and no intracranial findings.

Gross examination and microscopic pathology were performed on all control brain specimens, and no abnormalities were reported.

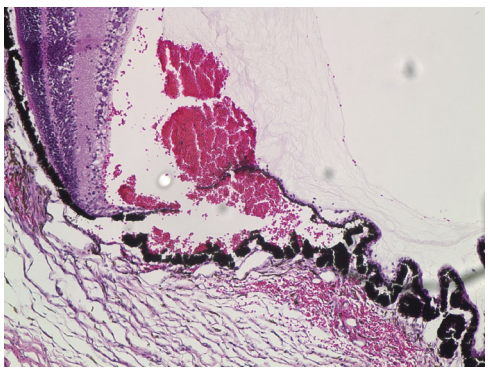

**FIGURE 3.** Peripheral preretinal and ciliary body hemorrhage in a 3- to 5-day-old piglet after a single high-velocity rotational head acceleration. The hemorrhage was not detected during indirect ophthalmic examination. H&E. Magnification, ×10.

## DISCUSSION

For better differentiation between patterns of ocular hemorrhage from accidental and AHT in children, it is important to understand the mechanisms and loading conditions that can cause these injuries. We sought to evaluate an immature animal model for its potential to study mechanisms of traumatic hemorrhage associated with head accelerations. We found that approximately three-fourths of the animals in this preliminary model developed ocular hemorrhage as the result of a single, high-velocity head rotation, even though the limited number of histologic cuts may have led to an underestimation of findings. Seventy percent of hemorrhages were located in a region of strong vitreoretinal attachment in the pig. Thus, this animal model will be useful for evaluating the role of the vitreoretinal interface in the development of hemorrhage from rotational head accelerations. However, to assess the clinical relevance of this model, one must consider the pattern and severity of ocular injuries, the similarities and differences between pig and human ocular and orbital anatomy, and the nature and magnitude of the loads applied.

Retinal hemorrhages have been reported to occur in 0% to 20% of cases of pediatric accidental head trauma, depending on the cause of injury. The higher reported incidences are from case series investigating crush head injuries or fatal motor vehicle accidents. When present, the retinal hemorrhages in young children with accidental head trauma are typically in-

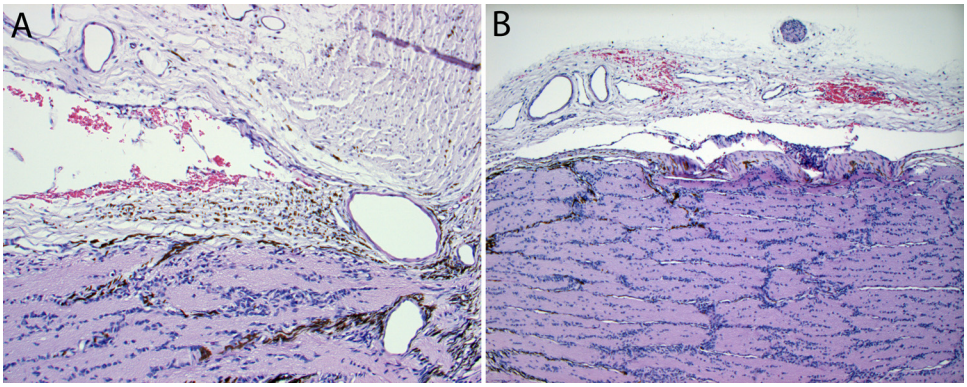


**FIGURE 4.** Histology of eyes from 3- to 5-day-old piglets undergoing a single rapid angular head acceleration. Of all the animals, 64% had optic nerve sheath hemorrhage. Optic nerve hemorrhages were subdural (**A**), intradural (**B**), and epidural (not shown). H&E. Magnification: (**A**) ×20; (**B**) ×10.

traretinal, few in number, and confined to the posterior pole, even in complex falls with multiple impacts.[12–16] Rarely, in cases of severe trauma, such as fatal motor vehicle accidents or crush head injuries, more extensive hemorrhages can be seen.[17] In contrast, retinal hemorrhages in children with AHT can range from a few, isolated intraretinal hemorrhages, as seen in accidental trauma, to numerous hemorrhages that may be multilayered and extend into and throughout the retinal periphery and can include macular folds and hemorrhagic macular cysts.[18–22] The distribution and types of hemorrhages reported in abusive and accidental head trauma may be informative with regard to mechanistic etiology. The overlap in findings at the mild end of the injury spectrum and occasionally at the severe end of the injury spectrum (e.g., fatal car accidents) suggests that there may be some common mechanism(s) underlying the retinal hemorrhages in accidental and AHT. However, the additional patterns of injury in AHT (e.g., macular cysts) suggest that additional mechanisms may be involved in those cases.

A favored theory in the literature is that acceleration–deceleration forces cause the vitreous to pull on the retina, possibly damaging retinal vessels, with subsequent hemorrhaging, or causing changes in vascular autoregulation.[23] In our study, most of the intraocular hemorrhages were located near the vitreous base in the form of ciliary body hemorrhage or less frequently as peripheral retinal hemorrhage. It is not clear how this pattern of injury relates clinically to pediatric head trauma, as the vitreous base is not typically visualized on clinical examination in the awake child without scleral depression, and ophthalmologists are unlikely to perform scleral depression in awake children in the absence of posterior pole findings. However, the location of the hemorrhages is coincident with areas of strong vitreoretinal attachment in the pig,[24] suggesting a possible role for traction in the model. In fact, ciliary body and optic nerve sheath hemorrhages have been described on postmortem examination in AHT.[20,21]

Another mechanistic theory involves the direct tracking of blood from the brain along the optic nerve and into the eye. Most of the animals in our study had an optic nerve sheath subdural hemorrhage and a few animals had microscopic optic disc hemorrhages. However, the nerve sheath hemorrhages were focal rather than spread over the length of the nerve, and no retinal hemorrhage was observed pos-

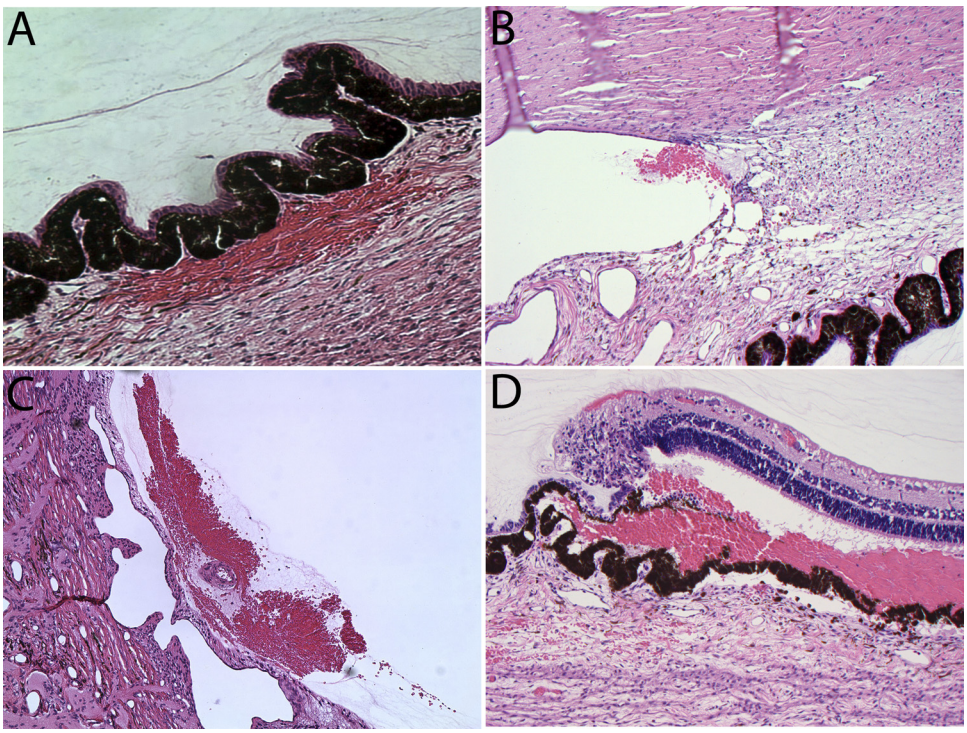


**FIGURE 5.** Histology of eyes from 3- to 5-day-old piglets undergoing a single rapid angular head acceleration found ocular hemorrhages in 84% of the eyes. Nonoptic nerve sheath hemorrhages included (**A**) ciliary body hemorrhage, (**B**) hyphema, (**C**) hemorrhage from a persistent hyaloid vessel, and (**D**) subretinal and preretinal hemorrhages. H&E. Magnification: (**A**) ×20; (**B–D**) ×10.

**Table 1.** Summary of Brain Pathology Findings from Gross and Microscopic Examination

| | Subdural Hemorrhage | | Axonal Injury | | |
|---|---|---|---|---|---|
| **Direction** | **Bilateral** | **Unilateral** | **Diffuse** | **Focal** | **White Matter Hemorrhage** |
| Sagittal ($n$ = 13, 7)* | 13 (100) | 0 (0) | 5 (71) | 1 (14) | 4 (57) |
| Axial ($n$ = 26, 19)* | 25 (96) | 0 (0) | 10 (53) | 6 (32) | 11 (58) |
| Coronal ($n$ = 7, 5)* | 0 (0) | 5 (71) | 0 (0) | 1 (20) | 0 (0) |

Data are the number of animals (% of total). Subdural hemorrhage, $n$ = 46; axonal injury and white matter hemorrhage, $n$ = 31.

* Animal sample size for gross and microscopic examination, respectively.

teriorly in the eye; on the contrary, most of the intraocular hemorrhages were found anteriorly.

A third theory involves increased intracranial or intravenous pressure. The pattern of ocular hemorrhage observed in this preliminary model matches neither the peripapillary hemorrhages associated with papilledema nor the distinctive retinal hemorrhage pattern of retinal venous occlusion, but we did not measure intracranial or intravenous pressure in this study.

We selected the immature piglet as a potential model for the study of retinal hemorrhages, as the porcine retina is more similar to the human retina than other domestic animals.[25,26] Specifically, the porcine retina does not have a tapetum and contains a well-developed vascular arcade, with the major retinal vessels lying within the nerve fiber layer and capillaries present throughout multiple layers of the retina. The vitreous base of the pig is comparable to the human vitreous base and straddles the ora. However, the piglet eye does not contain a fovea or a macula, and there is debate in the literature over whether it has a macula-like region devoid of major retinal vessels.[25,26] We found one persistent hyaloid vessel hemorrhage in our study, but piglet hyaloid vessels typically regress before birth, with hyaloid remnants persisting for 1 week after birth.[27] Since completion of this study, we have examined the eyes of several additional 3- to 5-day-old piglets and noted many with clear hyaloid stalks, but none with hyaloid arteries containing blood.

Vitreoretinal attachments in the pig have been reported to occur throughout the retina, but one plasmin-assisted vitrectomy study demonstrated that the attachments at the vitreous base are stronger compared to other regions.[24] In humans, vitreoretinal attachments occur across the entire retina, as they do in the pig, but locations of stronger attachment are at the vitreous base, optic nerve head, macula, and along major retinal vessels.[28,29] Should vitreoretinal traction play a significant role in the development of retinal hemorrhages, these ocular anatomic differences may influence the patterns of hemorrhage seen experimentally.

Contrasts in human and porcine orbital anatomy may also affect the patterns of observed injury. The pig has an open orbit, and instead of a bony closure, a strong fibrous ligament stretches from the frontal bone to the zygomatic bone, effectively enclosing the orbit but with slightly less rigidity than in humans.[25] Although this relative laxity may allow more freedom of movement for the orbital contents, the pig's extraocular muscles may inhibit the globe's motion. The annulus of Zinn is absent, and the origins of the muscles are on bone and are characterized as extremely strong.[25] In addition, the pig, like most domestic animals, has an additional muscle called the retractor bulbi, which inserts circumferentially on the globe and retracts it into the orbit, allowing the nictitating membrane, or third eyelid, of the animal to close and further inhibit movement of the globe within the orbit.[25] Future studies are necessary to evaluate whether movement within the orbit is an important factor in the pathogenesis of ocular hemorrhage in pediatric head trauma.

A final anatomic consideration is the orientation of the porcine eye. We observed that animals with axial head rotations appeared to have more ocular hemorrhages than did animals with sagittal or coronal rotations, although the differences were not statistically significant. The visual axis of the pig is oriented approximately 30° outward from that of the human. This 30° offset causes a 50% decrease in the force being applied along the optic nerve during sagittal head rotation and an 87% increase in the force along the optic nerve during coronal head rotation. The offset would not cause any difference in the forces applied to the eye during axial head rotation. Assuming that there is a relationship between the inertial load applied along the optic nerve and the development of ocular hemorrhage, these calculations suggest that for a given load, our porcine animal studies may underestimate the incidence of ocular hemorrhage from sagittal rotations and overestimate the incidence from coronal rotations in comparison with that expected in a human.

It is important to recognize that the load applied in this study was a single, high-velocity rotation of the head and not a low-velocity, repetitive, back-and-forth motion often reported in cases of AHT. We selected a single, high-velocity head rotation to establish the ability of the model to produce ocular hemorrhages from angular head acceleration and to serve as a baseline for future studies investigating the effect of cyclic back-and-forth head rotations on eye injury. To date, the only controlled animal experiment investigating retinal hemorrhages from repetitive, cyclic head rotations has been in mice.[30] The mouse eye is extremely small in mass compared with the human infant eye, and to achieve an equivalent scaled load, a shaking frequency five times greater than that found physically possible in investigations of loads from shaking infant surrogate dolls (2–3 Hz) is necessary.[31] Investigations of cyclic loading that can better approximate real-world forces and are more similar to human retinal and vasculature structure would be of greater value in a large animal model such as the pig.

The single, high-velocity head rotations applied in this animal model were of sufficient magnitude to result in severe brain injury in almost all the animals. When scaled to the brain mass of a human infant (420 g), the applied head rotations are greater than those measured for low-height falls (1–2 feet) onto concrete,[32] but less than would occur during an inflicted impact onto a hard surface.[31,33] Because the mass of the immature porcine eye is similar to the mass of the human infant eye (2.29 g),[34] scaling is less important. The axial length of the piglet eye measured postmortem is smaller (14 mm) than the axial length measured in vivo in the human infant (17 mm).[35] Postmortem shrinkage may account for some shortening, but it is unclear whether the remaining difference is primarily attributable to vitreous chamber size or anterior chamber depth or how changes in axial length may affect ocular hemorrhage from rapid, nonimpact rotations of the head. Clinical conclu-

sions regarding ocular injuries cannot be made from these animal studies until we know how anatomic differences between the human and porcine orbit affect the way mechanical loads applied to the head are translated to mechanical loads experienced by the eye.

To date, there is no experimental model that can be used to investigate the mechanisms and loading conditions that cause retinal hemorrhages in pediatric head injuries. The development of such a model may have important clinical, legal, and social implications related to accurately identifying and protecting children who are suffering child abuse, while correctly differentiating accidental injuries. We investigated the potential of the neonatal piglet as such a model. Optic nerve sheath and ciliary body hemorrhages were common in piglets that experienced a single, nonimpact head rotation, with some retinal hemorrhage, which was less common but all of which was located near the ciliary body at the vitreous base. Although this pattern differs from the severe, diffuse retinal hemorrhages often seen in cases of AHT, we are encouraged by the high percentage of animals demonstrating a rather consistent pattern of ocular injuries, the localization of injuries to regions of strong vitreoretinal attachment in the pig, and the common finding of optic sheath nerve hemorrhages. Future studies will include evaluation of lower velocity cyclic loading conditions and manipulations of the vitreoretinal interface and extraocular muscle anatomy. Anatomic differences between the species may affect the observed injury patterns in the model, and such differences must be investigated before experimental results can be safely extrapolated to head injuries in infants.

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