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Increased intracranial pressure in mini-pigs exposed to simulated solar particle event radiation

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Abstract

Changes in intracranial pressure (ICP) during space flight have stimulated an area of research in space medicine. It is widely speculated that elevations in ICP contribute to structural and functional ocular changes, including deterioration in vision, which is also observed during space flight. The aim of this study was to investigate changes in OP occurring as a result of ionizing radiation exposure (at doses and dose-rates relevant to solar particle event radiation). We used a large animal model, the Yucatan mini-pig, and were able to obtain measurements over a 90 day period. This is the first investigation to show long term recordings of ICP in a large animal model without an invasive craniotomy procedure. Further, this is the first investigation reporting increased ICP after radiation exposure.

Keywords

Intracranial pressure; ionizing radiation; minipig

1. Introduction

Physiologic and pathologic changes associated with space flight have been studied extensively. A current focus in space medicine is the occurrence of intracranial hypertension induced by space flight, which when left untreated could lead to optical abnormalities. Recently, ophthalmic anatomical changes including disc edema, globe flattening, and choroidal folds in long duration astronauts have been associated with increased intracranial pressure, presumably as a result of fluid shifts induced by microgravity [1]. Approximately 30% of short-duration and 60% of long-duration mission crew members have experienced degradation in vision. Ultrasonography is routinely used to detect ophthalmic changes in-flight, while on Earth, ultrasonography confirmed increased optic nerve sheath diameter as a result of increased intracranial pressure (ICP) in a porcine model [2]. Other technological

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modalities utilized to assess post-space flight ocular changes, including changes in the optic nerve, include optical coherence tomography (OCT) and magnetic resonance imaging (MRI) post-flight [1]

Solar particle event (SPE) radiation largely consists of a flux of protons with energies greater than 10 MeV, lasting over a period of several hours to several days [3]. SPEs occur more often near the solar maximum (characterized as 7 active years of an 11-year solar cycle), but the correlation between event frequency and solar conditions is not entirely accurate. The energy spectra and total proton fluence vary from SPE to SPE. For example, during solar cycle 22, 4 large SPEs occurred with proton fluence energy above 30 MeV, exceeding 10^9 protons/cm²; during solar cycle 23, 5 large SPEs occurred as recently as 2005. Short term and career dose exposure limits are recommended by the National Council on Radiation Protection & Measurements (NCRP), and accepted by NASA, to prevent health consequences, including mission performance. The 30 day limit to the skin is approximately 1.5 Gy and to the lens is 1.0 Gy [4].

For long duration space missions, e.g., the Mars mission, not all SPEs will be observable from Earth because of the solar conjunction, when the sun is directly between Earth and Mars, which occurs approximately every 26 months. During this time interplanetary radio communications are silenced. Currently, the only SPE warning or alert system is activated at the onset of proton exposure. Appropriate forecasting with lead times are necessary not only for shielding requirements but for decision making on when to perform extravehicular activities [5].

The dose distribution of SPE radiation is inhomogeneous, with a larger superficial absorbed dose and a lower absorbed dose to internal organs [6]. Given the known occurrence of solar particle events (SPEs) and the inability to predict when they might occur, there is a large probability of the crew suffering from the symptoms of the acute radiation syndrome (ARS); the doses expected from SPE radiation could result in the development of the prodromal and hematopoietic syndromes. SPE radiation exposure may also lead to acute damage to organs and systems such as the hematopoietic system or the skin. Long term effects of radiation can include CNS effects [7, 8], circulatory disease [9, 10], and the induction of cancer [11–13].

Our current experiments utilize the Yucatan mini-pig model system exposed to simulated proton or electron SPE radiation to investigate multi-systemic changes induced by SPE radiation, including radiation effects on the skin and hematopoietic systems [14–16]. The prescribed skin doses used in these experiments range from 2.5–20 Gy (estimated range of doses received during an SPE, in the spacecraft, as well as during extravehicular activity [6]). We have reported the use of electron radiation as the conventional radiation to compare the biological effects of SPE (proton) radiation. Cengel et al. [14] describe the energy beam of 80% 6 MeV electrons and 20% 12 MeV electrons, which closely mimics the September 1989 SPE dose distribution, determined by clinical treatment planning software, Varian Eclipse, and the Varian Monte Carlo algorithm. More recent experiments utilizing 45% 6 MeV electrons and 55% 12 MeV electrons have been designed to mimic a “harder” SPE, such as the August 1972 SPE, with a slightly larger absorbed internal dose.

In a clinical setting there are three standard ways to monitor ICP: a catheter is inserted through a drilled burr hole in the skull and into the lateral ventricle; a subdural screw or bolt is inserted through a drilled hole in the skull and a pressure transducer is placed through the dura mater; or the transducer is guided through a burr hole drilled in the skull and inserted between the skull and dural tissue [17, 18]. Unfortunately, these methodologies are only applicable for a limited time period [19]. Telemetry systems were introduced in the last half century for long-term recording of ICP measurements [20] and only in the last decade have these systems proven reliable in small animal (rodent) model systems for recordings up to several days [21]. A standardized model is needed for continuous, reliable, and feasible ICP measurements in large animal model systems over extended time periods. Some advantages in establishing a monitoring system in a large animal model includes a longer lifespan and a more human-like neuro-architecture. Further, although rodent genetics are approximately 85% similar to its human homolog, cerebrospinal fluid (CSF) total volume is renewed at more than two times the rate in young adult rats, compared to the control humans [22]. Changes in CSF circulation can cause increased ICP [23].

Here, we report ICP measurements obtained by lumbar puncture procedures in anesthetized min-pigs. The ICP measurements were compared prior to and up to 90 days post-radiation exposure. Although the lumbar puncture is considered invasive, the technique is reasonably safe and justifiable in cases of intracranial hypertension [24]. We hypothesize that changes in ICP induced by SPE radiation could contribute to the vision alterations reported in astronauts; vision alterations have previously been observed in- and post-space flight, as described in detail elsewhere (Mader et al. 2011).

2. Materials & Methods

2.1. Animals

Yucatan minipigs aged 3–4 months old were purchased from Sinclair Bio Resources, LLC (Auxvasse, MO). Animals were acclimated for 7 days and were housed individually with ad lib access to water and fed standard mini-piglet chow twice daily. The animal care and treatment procedures were approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania.

Upon acclimation, the animals were randomly assigned to groups exposed to electron radiation at skin doses of 0 (sham-irradiation control), 2.5, 5.0, or 7.5 Gy. Animals were fed the appropriate chow 2 times a day with *ad libitum* access to water. Animals were evaluated once daily for at least 90 days after irradiation.

2.2 Irradiation

For the electron radiation exposure, the setup has been previously described [14, 15]. Briefly, a Clinac iX linear accelerator (LINAC) (Varian Medical Systems, Palo Alto, CA) was used to deliver 6 MeV and 12 MeV electrons in alternating intervals at a source to skin distance of 5 m, delivered to one side of the long axis of the animal's body. The entire radiation chamber was rotated 180 degrees with every quarter dose. The desired dose rate was achieved by modulating the output of the LINAC to deliver the desired dose over 3 hours. The entire set of electron fields produced in this study was measured using an IBA

Dosimetry PPC40 parallel plate ionization chamber and PTW electrometer. The PPC40 response was calibrated at nominal electron energies of 6 and 12 MeV with 1.5 cm and 2.5 cm buildup, respectively. The calibrations were performed using a 10 cm × 10 cm electron cone with an SSD of 100 cm. In these configurations, the LINAC was calibrated to output 1 cGy/MU.

At the time of exposure, animals were placed in custom Plexiglas chambers measuring 33 × 25 × 75 cm (height × depth × width), limiting mobility to allow homogeneous irradiation. The chambers were constructed with 5-mm-thick chamber walls with multiple 9-mm holes for air exchange. Animals were provided NapaNectar hydrogel and were not anesthetized for the irradiation procedures, allowing normal postural movements including standing and/or lying down.

2.3 Opening pressure measurements

Lumbar punctures were performed under general anesthesia (isoflurane inhalant) to measure the opening pressure of the CSF. The animal was placed in lateral recumbency, with the spine horizontal and perpendicular to the table throughout its entire length. The pig does not have the ability to flex the spine as much as other species, giving them a more stiff posture. Therefore, full flexion of the spine is achieved by holding the hindlegs toward the head.

An imaginary line was drawn between the most cranial aspects of the bilateral tuber coxae (iliac crest or wings of ileum), which are readily palpable. The intervertebral space cranial to this line was L6-7. The number of lumbar vertebrae varies from pig to pig and there is no prediction as to whether the lumbar region will terminate at L6 or L7 continuing down the sacral vertebrae. Making landmarks with a skin marker, a pediatric spinal needle (22 g, 1.5 in.) was inserted between either L6-S1 or L7-S1. The spinal cord terminates with the conus medullaris at S2-3. The needle was placed between the palpable dorsal spinous processes and was advanced slowly through the intervertebral space until a lack of resistance occurred/was detected/was felt (?). After entry into the site, the stylet was removed from the needle to ensure that CSF was flowing through the needle hub. Once the CSF flow is observed in the needle hub, the stylet was removed and the stopcock/manometer was attached to the needle. The reference point was the midline of the spinal cord and the highest stabilized measurement that the CSF achieved in the manometer was recorded as the opening pressure (OP). The OP was based on the CSF height within the manometer and recorded when respiratory fluctuation began, at the bottom of the concave meniscus. The accuracy of the positioning of the subject and the manner in which the OP was recorded agrees with previously documented protocols, which have been reviewed by Abel et al. [25].

2.4 Statistical analyses

In the first experiment, the 5.0 Gy dose group consisted of 6 animals and in the second experiment, the 2.5 Gy, 5.0 Gy, and 7.5 Gy dose groups each consisted of 3 animals. The sham-irradiation groups from the first and second experiment were combined and consisted of 6 animals. The average OP value at each time point and in each dose group was determined and is shown as the average ± SD. For example, in the first experiment, since there were 6 animals, there were 6 OP readings at each time point, and for the second

experiment, consisting of 3 animals per dose group, there were 3 OP readings at each time point. The designated time points that OP readings were recorded were pre-irradiation (baseline value), 30 days post-, 60 days post- and 90 days post-irradiation and they were all measured at a consistent time of day within a 4 hour window. To determine whether the changes in OP values were statistically significant, data were analyzed using the Student's t-test, in which the results from each time point were compared to the corresponding baseline value, or the pre-irradiation value, in each dose group. Values were considered statistically significant when $p < 0.05$, and of borderline statistical significance when $p < 0.1$. Using the data from the second experiment, the OP values from each dose group were grouped according to the time point at which the values were obtained (pre-, 30 day, 60 day or 90 day post-irradiation, $n = 9$ at each time point) and a non-parametric linear regression analysis was performed.

3. Results

The mean baseline OP value in the anesthetized Yucatan mini-pig was 109.4 ± 4.8 mmH₂O (average $\pm$ SEM, $n=21$). There were 6 animals that were not exposed to ionizing radiation, but were exposed to the containment apparatus that the animals were kept in during and after radiation; the total amount of time the animals were maintained in the containment apparatus was the same for sham-irradiated and irradiated pigs (approx. 3 hours). These animals were exposed to 0 Gy electron radiation and were designated as sham-irradiated controls. The OP measurements in the sham-irradiated group did not change in a statistically significant manner throughout the 90 day time period during which the animals were monitored (Fig. 1).

In the first experiment, animals were exposed to whole body electron radiation (80% 6 MeV + 20% 12 MeV electrons, mimicking the September 1989 SPE [14]) with a prescribed 5 Gy skin dose. The skin dose should be considered as 100% of the 5 Gy dose deposited at approximately 7mm deep, with a steep decline in dose deposition at > 7 mm depth. OP measurements were recorded prior to irradiation (0 day) and at 30 days, 60 days, and 90 days post-irradiation exposure. The average increase in OP measurements was 20% at the 3 time points, compared to 0 day (d). It was determined, using the Student's t-test, that the changes in OP were of borderline statistical significance at the 30 d and 90 d time points and they were statistically significant at the 60 d time point (Table 1).

In the second experiment, animals were exposed to skin doses of 2.5, 5.0, or 7.5 Gy of electron radiation. The dosimetry profile for the second experiment was different than that of the September 1989 SPE, and was intended to mimic the August 1972 SPE. To simulate this SPE, a mixed energy of 45% 6 MeV electrons + 55% 12 MeV electrons was utilized, and this resulted in a deeper dose penetration, which may be referred to as a "hard" SPE. The animals ($n=3$ for each dose group) were anesthetized and in similar fashion, the OP was recorded prior to and at 3 points post-radiation exposure. The results of the averaged OP readings are shown in Figure 2. The 2.5 Gy dose resulted in a significantly increased average OP value at all time points examined, compared to the pre-irradiation average OP value (Fig. 2A). The results were not as consistent in the 5 Gy and 7.5 Gy dose groups, although a similar trend is observed in the 7.5 Gy dose group (Fig. 2C). By 90 days post-

irradiation, in all dose groups, the average OP values were increased, in a statistically significant or a borderline statistically significant manner, compared to the corresponding average pre-irradiation OP value. The lowest skin dose group of 2.5 Gy, resulted in an increasing trend in the average OP value by 90 days post-irradiation (Fig. 2A) and the highest skin dose group (that received a skin dose of 7.5 Gy) displayed a similar trend (Fig. 2C). Interestingly, the intermediate dose group of 5.0 Gy, resulted in an increased average OP value by the 60 day post-irradiation time point, but only by approximately 12%, compared to the average value determined for the corresponding pre-irradiation time point. By the 60 day time point, the average increases in OP values were 22% and 39% for the 2.5 Gy and 7.5 Gy dose groups, respectively, compared to the corresponding pre-irradiation values. A non-parametric linear aggression analysis was performed on this dataset, in which the dose groups were grouped by time point; this analysis resulted in a p value < 0.0001 , indicating that the linear trend of the slope was significantly different from a slope of zero (Fig. 3).

4. Discussion

The current studies demonstrate that lumbar punctures can be adapted to measure OP routinely over the course of several months in a large animal model system. Our studies also indicate that ionizing radiation, specifically electron simulated SPE radiation, induces elevations in ICP. We report that the trend in radiation-induced increases in ICP may not be dose-dependent, but in most cases, the increases occurred within 60 days of radiation exposure. There are recent reports on the continuous monitoring of ICP measurements [17, 21, 26], with a higher count of reproducible results in small animals [27, 28], but there are no described methods for measuring ICP in large animals over the course of several months, without the performance of a craniotomy.

The lumbar puncture procedure is routinely performed at the bedside. However, there are no established comprehensive lumbar puncture protocols with OP measurement for the large animal model. Alternative procedures for OP measurement would be needle placement below the occipital bone in the back of the skull, which is guided by fluoroscopy because of the close proximity to the brain stem or ventricular puncture directly into one of the brain's ventricles. When evaluating brain versus lumbar puncture measurements for OP, one disadvantage is from an economic standpoint, considering the guidance by fluoroscopy or the surgical details of drilling a hole in the skull for admittance to a brain ventricle. A direct brain measurement may be advantageous, versus the measurement taken in the lumbar region, given that radiation treatment could affect spinal structures and functions. Although in this study, it has been determined by Monte Carlo based simulations using computed tomography images of the pig model used in this study that the spinal cord received less than 4% of the prescribed dose (Personal communication, Dr. Eric Diffenderfer). The design of the beam was to mimic historical SPEs with an inhomogenous dose distribution, so this is not surprising. However, one might consider comparing opening pressure measurements taken directly from the brain versus the lumbar region to confirm variability, if any.

There is speculation regarding the measurement of OP in an anesthetized animal because of the different effects on cerebral hemodynamics [29]; however, the only method of recording

OP without the induction of anesthesia is to perform a craniotomy. The implantation of a catheter connected to an external transducer is not feasible for the experiments reported here because of the unknown effects to the system from the radiation exposure. It should also be noted that the surgical procedure entails difficulties with accurate placement of the catheter into small ventricles and increased risk of infection, which could be exacerbated by radiation exposure. Lastly, lead damage, as a result of the placed sensor in the brain connecting to the external telemetry unit, is a reported problem in unrestrained pigs [30].

In these studies, we were able to obtain OP readings in mini-pigs over a 90 day period, without cranial surgical procedures. There were no significant changes in OP measurements in non-treated (non-irradiated or sham-irradiated) animals over the 90 day period. By 90 days post-radiation, all irradiated animals exhibited marked increases in OP values, with an average increase of 44% compared to the pre-irradiation average value. There was some variability between animals in their CSF opening pressures when obtained via lumbar puncture, which may contribute to the inconsistency in the increasing trend of ICP measurements over time (after radiation exposure) and/or with increasing dose. For example, readings from one animal may not have increased over time in a steady trend, but may have been increased at one time point, but not at a later time point, whereas a separate animal may have shown an increasing trend over time. In other words, the observation that OP readings were increased after radiation exposure was not an “all or nothing” effect, and the level of increased readings did differ from animal to animal, but this is expected using a large animal model that is not an inbred strain. It is noteworthy that, even with the small sample sizes in these experiments, statistically significant increases in OP after radiation exposure were observed.

With the pursuit for long-duration human explorations, a better understanding of the effects of SPE radiation is required. SPE radiation is a natural source of radiation that poses risks to astronauts and machinery/equipment during space travel. The rationale for the large animal model is a multi-systems approach for studying the biological effects of SPE radiation. Other parameters, including simulated SPE radiation-induced skin and hematopoietic cell changes are reported elsewhere [15, 31]. It is reasonable that changes in ICP be studied in a large animal model system (like the porcine model) versus a small animal model (rodent) system, because the phylogeny of humans is closer to pigs than that of rodents. Further, it is established that the overall structure of the eye of pigs is more comparable to humans than rodents, which is of great interest to study concurrently with changes in ICP because of the hypothesis that increased ICP may contribute to ophthalmic changes [1, 19]. At this time, there are no reports available on radiation-induced changes in ICP measured in small animal systems, like rodents, to compare the results in this report.

While the mechanisms involved in radiation-induced ICP increases are unknown, we hypothesize that increased CSF production and/or decreased absorption brought about by radiation exposure may be a contributing factor to the increased ICP observed in mini-pigs after radiation exposure. CSF flows between the brain and meninges, the subarachnoid space, and surrounds the optic nerve. Increased ICP has been associated with papilledema during long-duration space flight, which presumably is caused by postural movements and the cephalad shift of body fluids induced by microgravity [1]. The results reported here

suggest that exposure to SPE-like radiation doses can also cause increases in ICP. It is conceivable that lower doses of radiation, produced by natural background cosmic radiation, could have similar effects leading to increased ICP. Cosmic radiation includes HZE particles (high atomic number/mass, highly energetic charged particles) and high linear energy transfer (LET) radiation is associated with these HZE particles. Thus, higher relative biological effectiveness values are often observed for biological endpoints produced by HZE particle radiation compared to those observed for SPE radiation, as used in studies reported here. During a long duration space mission, astronauts are expected to have greater exposure to cosmic radiation at a steady, but low, dose rate, compared to SPE radiation that delivers a high dose in shorter time periods [32]. Other space flight conditions/stressors, such as elevated cabin carbon dioxide concentrations, may also be a confounding contributor to changes in cerebral blood flow and ICP [33, 34].

Increases in ICP are well-known in radiation oncology patients. It is conceivable that current therapies aimed at reducing ICP in the clinic could be applied to the radiation-induced changes reported here in the porcine model.

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Highlights

- Intracranial pressure measurements were recorded in a large animal model without an invasive craniotomy procedure.
- Intracranial pressure was measured in the minipig model over an extended period of 90 days.
- Solar particle event like radiation induces increased intracranial pressure.

Figure 1.

OP measurements recorded in sham-irradiated (non-irradiated) animals over time. Yucatan mini-pigs were restrained for approximately 3 hours in irradiation chambers, but were not exposed to ionizing radiation. These sham-irradiated animals served as a control group (n=6) and OP measurements were recorded at pre-sham-irradiation (Pre), 30 days (d), 60 d, and 90 d post-sham-irradiation. The average OP values at each time point were not changed in a statistically significant manner. Data are presented as the mean $\pm$ SD.

Figure 2.

OP measurements recorded in electron simulated SPE radiation exposed animals. Animals were exposed to either 2.5 Gy (A), 5.0 Gy (B), or 7.5 Gy (C) electron simulated SPE radiation. Data are presented as the mean $\pm$ SD, n=3. The average OP value at each time point was compared to the average OP value at the pre-irradiation time point (Pre). P values were determined by the Student's t test.

Figure 3.

OP increases in a time-dependent manner after mini-pig exposure to electron simulated SPE radiation. A linear regression analysis was performed to determine whether the increased ICP in animals exposed to SPE radiation was time-dependent. The slope of the line is significantly different from a slope of zero, with $p < 0.0001$. Data are presented as the mean $\pm$ SD, $n=3$ (using the same data set from Figure 2).

Table 1

Recorded ICP values in mini-pigs exposed to a 5 Gy dose of electron simulated SPE (September 1989 SPE dosimetry profile, n=6)

Time point (day post-radiation)	Average ICP value $\pm$ SEM (mm H ₂ O)	% change	p value
0	102.8 $\pm$ 10.2	NA	NA
30	130 $\pm$ 9.5	21%	0.08
60	153.3 $\pm$ 18.5	21%	0.04
90	127.3 $\pm$ 9.3	19%	0.1