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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 opening pressure (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.



## 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 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, four large SPEs occurred with proton fluence energy above 30 MeV, exceeding $10^9$ protons/cm$^2$; during solar cycle 23, five 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.

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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 warningor 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 inhomogenous, 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. [1]).

## 2. Materials and 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 two 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° with every quarter dose. The desired dose rate was achieved by modulating the output of the LINAC to deliver the desired dose over 3 h. 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 $33 \times 25 \times 75\ cm^3$ (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