Cerebrovascular Accident CLIFF Peer Review

1. *Strength of evidence presented in CLIFF in modeling the characteristics and mission impact of this medical condition within the spaceflight environment?*

   Score: 3

   Grading Scale:

   4 - Confident

   3 - Somewhat confident

   2 – Neutral

   1 – Somewhat unconfident

   0 – Not confident

2. How confident are you that these data accurately represent the spaceflight environment?	*Tables 1, 2* *Composite Incidence and Level of Confidence*	*Table 3, 4 BC/WC* *Loss of Crew and probability*	*Table 4 - Clinical Phase 1, 2 durations* *Table 5 – CP 2 Loss of Crew*	*Table 4 – RTDC %* *Table 6 – RTDC Loss of Crew*	*Table 4 – Loss of Crew Life %* *Table 7 – Loss of Crew Life, Loss of Crew*	*Table 8 – TI*
Score	*3*	*2*	*3*	*3*	*3*	*3*

Comments and limitations:

1. **General comments.** A cerebrovascular accident (CVA) represents the temporary or permanent loss of perfusion to a portion of the brain that is caused by obstruction or rupture of a blood vessel. The spectrum of disease is broad, ranging from a transient ischemic attack (TIA) lasting less than 24 hours to severe disability to death. Most strokes are ischemic with the remainder hemorrhagic. The same conditions that predispose an individual to coronary heart disease (e.g. diabetes, hypertension, smoking, and hyperlipidemia) also are risk factors for CVA. There have been no recorded cases of CVA during spaceflight, but very mild TIA's would be very difficult to detect or diagnose. It is unclear whether microgravity with its associated cephalad fluid shift puts astronauts at increased for CVA. Similar to ACS, astronauts would be expected to be at lower risk than the general population. The best case is a TIA, or mild stroke, with no significant neurologic impairment while the worst case is a stroke that causes significant permanent neurologic impairment, negatively affecting mission objectives.

2. **Incidence.** Since there have been spaceflight events, LSAH data using active astronauts only reveals 1 event over 4430 person-years. This was felt to be the best data available since it represents the astronaut population that is eligible for spaceflight. Terrestrial papers reporting epidemiologic data for large populations were not felt to be representative of the risk of CVA in astronauts. Other data sets include retired astronauts who would be at higher risk than active astronauts because of their age. It is possible that very minor TIA's may not have been reported or detected, whether or the ground or during spaceflight, and might have gone unreported. This could lead to a small underestimate of the true incidence value. The best case/worst case probabilities used data from a study of 338 NASA astronauts over their lifetimes. There were a total of 9 CVA events in the cohort. Of these, 3 were TIAs, 3 were ischemic strokes, and 3 were life-ending strokes of unknown origin, giving a best case/worst case probability of 33%/67%. The clinical phase durations and Loss of crew life probabilities are supported by terrestrial evidence, and I am in agreement with their calculation. RTDC was pre-determined to be 100% for all cases by the CST. The probability density curve that was derived appears to be a reasonable representation of the data presented.

3. **Clinical phase data**. I am in agreement with the clinical phase 1 duration entered in this CLIFF. This data was compiled by a team of expert clinicians, and I was involved in the discussions leading to the calculation of the clinical phase duration. CP2 was supported by terrestrial evidence.

4. **Task impairment**. The analysis was performed and reviewed by a separate team of expert clinicians. I am aware of the methods that were used but did not directly participate in the discussions.

5. **Dependence on mission phase or duration of mission**. This medical condition is not dependent on mission phase as CVA could occur during any flight phase with equal probability.

6. **Limitations**

- Under-reporting for this condition could have occurred during past space missions due to subtle TIA's that were not of clinical consequence. This may result in underestimation of the incidence.
- There is a paucity of data regarding untreated scenarios of stroke as even placebo groups in these studies still receive some kind of treatment, always clearly defined. (Duca, 2016) and (Easton, 2009) predominately focus on the pathophysiology of TIAs, by definition, <24 hours.
- No search was done for RTDC for BC and WC as it was pre-determined to be 100% by the clinical science team. Therefore, no LOE has been given for RTDC. There may be some TIA's that could be mild enough to be treated with medical assets onboard the spacecraft. The diagnosis can be easily missed without adequate imaging.
- Outcomes from strokes vary widely, and the wide margins of CP2 durations reflect this uncertainty. While the baseline health of the astronaut corps would pre-dispose for a shorter convalescence, the anatomy of a CVA (e.g., ischemic penumbra) would be the driving factor in task impairment-- nevertheless, the necessity of a wide range of functional outcomes remains a significant limitation in this risk assessment.

Reviewed by:

David C. Hilmers