Shock Cardiogenic 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*	*3*	*2*	*3*	*3*	*3*

***N/A's in Table 4 need to be a number. They should be 0 instead of N/A.

Comments and limitations:

1. **General comments.** This CLiFF characterizes cardiogenic shock (CS) that could occur during spaceflight. CS is a condition in which low cardiac output leads to lack of tissue profusion and subsequent organ dysfunction. CS can be diagnosed by clinical signs and symptoms. Despite significant advances in stabilizing patients with CS until they recover cardiac function or receive a heart transplant, the mortality remains high. The mainstay of treatment is percutaneous coronary intervention (PCI) which will not be available during spaceflight. The most common cause of CS is acute myocardial infarction (AMI), but any etiology leading to congestive heart failure (CHF) could be the origin. It is a reasonable assumption to make that AMI will be the etiology of CS during spaceflight since all astronauts will have been well-screened for signs of underlying CHF prior to launch. It is difficult to use terrestrial studies for CS to estimate the incidence during spaceflight because the studies use unscreened populations and often the groups in which CS occurs are much older. The incidence can be derived by a two step-process. First, determining the risk of MI in active

astronauts and secondly, estimating the risk of developing CS once MI has occurred. ICL 3 calculated the risk of acute coronary syndrome (ACS) in astronauts. ACS refers to a condition in which there is a suspicion or confirmation of acute myocardial ischemia or infarction. In the past ACS has been categorized as non-ST-elevation myocardial infarction (NSTEMI), ST-elevation MI (STEMI), or unstable angina (UA). It is now possible to classify more patients who would formerly have been diagnosed with UA as having an NSTEMI through the use of high sensitivity troponin blood testing. Troponin testing has not been available during previous spaceflights, and it is unclear whether this will be an onboard diagnostic tool in the near future. Since most cases of ACS can now be classified as either an NSTEMI or STEMI, it is reasonable to assume that the risk of ACS that was calculated in ICL 3 can approximate the risk of MI in astronauts. There was no best case best definition for this CLiFF. All cases were considered worst case which is life-threatening circulatory collapse requiring extensive support measures. This condition is presumed to be post-myocardial infarction unrelated to other conditions such as toxic ingestion, sepsis, etc.

2. **Incidence.** Since there are no spaceflight reports of CS, the incidence calculation was based on ICL 3 data which computed the risk of ACS in active duty astronauts. This estimation utilized a tool called the Astro-CHARM calculator is based on large terrestrial studies and uses cardiac risk factors and coronary artery calcium scores to estimate the overall 10-year risk in this healthy population. The authors were able to obtain the Astro-CHARM scores for all active duty astronauts. This was felt to be a much better predictor of ACS risk in astronauts than using terrestrial studies that survey the general population. An assumption was made that the risk for ACS is the same as the risk for MI. Since almost all cases of ACS can now be classified as NSTEMI or STEMI, this was felt to be a reasonable assumption. Using this analysis as a basis, terrestrial studies were used to determine the risk of CS once an MI has occurred. These studies revealed a 2-3% risk for NSTEMI and a 7-8% risk for STEMI. A factor of 5% was used since most NSTEMI is more common than STEMI and astronauts are less likely to have a STEMI given fewer risk factors than the general population. This factor was applied to the baseline ACS risk to calculate the overall incidence of CS. There is no best case definition for CS, so the BC/WC split is 0/100%. The clinical phase durations, RTDC and Loss of crew life probabilities are supported by terrestrial evidence, and I am in agreement with their calculation. RTDC was determined to be 100% in all cases by the clinical science team. 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 although underlying coronary heart disease may become symptomatic or unmasked during heavy exertion and lead to cardiogenic shock..

6. **Limitations**

- The assumption was made that all cases of CS are caused by MI. This is a reasonable assumption for astronauts who presumably have normal cardiac function at launch, but there could be other causes such as toxins, metabolic causes, electrical shock, worsening congestive heart failure from idiopathic cardiomyopathy, myocarditis.

- The assumption was made that the ACS risk for astronauts that was estimated in ICL 3 ACS is equivalent to the risk for MI. This is a reasonable assumption since nearly all ACS can be classified as either NSTEMI or STEMI.
- The case definition did not include a best case. This was based on the fact that there will be inadequate treatment available onboard the spacecraft to treat cardiogenic shock.
- The "treated worst case" is a misnomer as ICU level are, PCI, pressors, etc. will not available onboard. In reality, treated and untreated cases will have very similar outcomes.
- There were no papers found that provided specific duration of untreated cases although it can be assumed that the duration would last between 1-24 hours if left untreated.

Reviewed by:

David C. Hilmers