RESEARCH ARTICLE

Estimating Outcomes of Astronauts with Myocardial Infarction in Exploration Class Space Missions

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Introduction: We estimate likelihood of presenting rhythms and survival to hospital discharge outcome after acute cardiac ischemia with arrhythmia and/or myocardial infarction (AMI) during long-duration space missions (LDSM) using selected terrestrial cohorts in medical literature. Medical scenarios were risk-stratified by coronary artery calcium score (CAC) and Framingham risk factors (FRF). ***Methods:*** AMI with and without sudden cardiac arrest (SCA) likelihoods and clinically significant rhythm scenarios and associated outcomes in "astronaut-like" cohorts were derived from two prospective trials identified by an evidence-based literature review. Results are presented using an event sequence diagram and event time line. The association of increasing CAC scores and FRF with AMI and SCA outcomes was calculated. ***Results:*** Low AMI likelihoods are estimated in individuals with CAC scores of zero or < 100 and a low number of FRF. Survival rate to hospital discharge after out of hospital SCA in a large urban environment study was 5.2%. EMS-witnessed ventricular tachycardia and/or ventricular fibrillation survival rate of 37.5% represents < 1% of all urban out of hospital AMI, and these patients have a high proportion of known ischemic cardiovascular and pulmonary disease "disqualifying for spaceflight." ***Discussion:*** Multiple factors may be expected to delay or defeat rapid access to "chain of survival" resources during LDSM, lowering survival rates below urban levels of 5.2%. Low CAC and FRF reflect lower risk for AMI events. Zero CAC was associated with the lowest risk of AMI after 3.5 yr of follow-up. Quantifiable incidence and outcome characterization suggests AMI in LDSM outcomes will be relatively independent of in-flight medical resources.

Keywords: coronary artery calcium score, Framingham risk factors, risk quantification, sudden cardiac death, ventricular arrhythmia, acute myocardial infarction, spaceflight, risk mitigation.

MANNED LONG-DURATION space missions (LDSM) require effective and efficient preventive approaches to minimize medical disorders posing hazards to mission success and long-term crew health. This requires identifying medical disorder likelihoods, resource specifications, and outcome predictions for future novel missions launching to remote, isolated, austere, and constrained alien environments. Analyses are program-mandated by NASA for minimizing predicted mission performance losses and adverse long-term health impacts using quantified probabilistic risk assessment and matching risk mitigation resources across all NASA program systems, including the human system.

Our study illustrates the utility of quantitative risk characterization in identifying estimated clinical scenario likelihoods and outcomes for acute myocardial infarction (AMI), including out of hospital sudden cardiac arrest (OOH SCA) and, for AMI without OOH SCA (non-OOH SCA), the likelihood of ventricular tachycardia (VT) and/or ventricular fibrillation (VF) during hospitalization. Survival to hospital discharge (after OOH SCA) and to 30 d post-hospitalization (for non-OOH SCA) in the robust urban environment is used to make inferences in the LDSM environment. Historical Earth analog outcomes have been used to establish a reasonable "best-case" potential for post-AMI treatment success during LDSM and suggest methodology for estimating the risk mitigation effectiveness of potential pre-mission crew selection (including waiver considerations), pre-mission health maintenance, and onboard mission medical resources for these disorders. Quantitative likelihood and outcome estimates, event sequence diagrams (ESD), and timelines for time-critical outcome analysis produce risk characterizations directly compatible with both NASA medical and engineering procedures and mission medical planning needs.

We compare and contrast the implications of the relative effectiveness of primary, secondary, and tertiary cardiovascular prevention strategies for LDSM. Coronary artery disease (CAD) is a mission medical hazard and the leading cause of death in developed nations (4,21). CAD accounts for 1 in every 2.5 deaths in the U.S (15), where approximately 50% of AMI initially present as OOH SCA (24) with an associated high mortality. Cardiovascular health is especially significant for astronauts, where incapacitation presents a high consequent mission risk and a long-term health and performance risk. Due to limited treatment capabilities and the delayed (if even possible) evacuation from exploration reference missions, prevention of acute CAD events during missions is essential to mission success and the long-term health of astronauts (9,10).

Determining the onboard medical capability required to minimize degraded mission performance and maximize long-term crew health can be done using Monte Carlo techniques utilizing event likelihoods and outcomes. The utility of these techniques for NASA lies in

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improved forecasting based on available medical evidence, better definition of medical hazards to missions, and recognition and exploitation of opportunities to mitigate the risks to mission success. This method helps NASA space medicine personnel make informed decisions regarding the optimal constrained medical footprint tailored to specific mission risk profiles. "Optimal" means identifying the most effective and efficient medical capability giving the minimal loss of performance during a mission while minimizing long-term health effects.

The launch weight constraints of any medical care system increase markedly for lunar and planetary missions because the payload mass fraction is progressively lower as rocket structure and propellant requirements increase. This emphasizes the importance of using primary and secondary medical preventive strategies before and during missions versus manifesting tertiary prevention (treatment) as a hazard control for exploration class missions. Reducing medical event likelihoods may be more feasible than salvaging catastrophic events in the severely constrained environment of LDSM.

While there are a number of root causes of ventricular tachycardia and fibrillation (VT/VF), historically AMI and OOH SCA have been viewed as the most likely for space missions, particularly for astronauts of increasing age. Our study focuses on life-threatening arrhythmias secondary to 'hard' CAD events (e.g., AMI) during missions, which have been a continuing concern of NASA medical researchers, risk managers, and operational flight medical personnel for many years.

Providing even minimal essential initial care for AMI and OOH SCA requires a substantial portion of preflight medical training and medical resources (crew medical skills, equipment, supplies, and communication resources) available on the International Space Station (ISS). The astronaut designated Crew Medical Officer (CMO) receives 30-40 h of general preflight medical training. Current on-orbit medical treatment resources in the ISS include a defibrillator, a transport ventilator, and various advanced life support supplies and pharmaceuticals. The medical effectiveness of this tertiary prevention strategy has not been completely validated. Essential follow-on care after AMI initial emergency care will be necessarily delayed and constrained, probably lowering the chance of survival for AMI below that achieved in a robust urban environment. The patient astronaut cannot return to full duty during or after the mission and will require an early emergency evacuation to Earth, if possible, with its attendant transport constraints of care (2). Tertiary prevention is thus less likely to be an effective hazard control for AMI or OOH SCA, resulting in either a fatal or surviving outcome that cannot restore full functionality to the patient, and requires extended close, continuous care by at least one other crewmember for an extended period of time.

Preventing mission losses from AMI by more effective risk screening and better astronaut health maintenance processes that reduce the incidence of mission AMI effectively reduces the AMI risk to mission success while shifting some of the mitigation footprint from in-flight to preflight ground resources not burdened by the adverse launch payload mass fraction of LDSM. NASA has implemented coronary artery calcium (CAC) scoring criteria for screening LDSM astronauts, anticipating that this will improve risk stratification of AMI when used in conjunction with Framingham risk factor (FRF) criteria (9). Documented AMI outcomes in the robust urban environment can serve as a benchmark for best potentially achievable outcomes for AMI and OOH SCA treatments during space missions.

METHODS

Evidence-Based Literature Review

To identify important clinical and mission scenarios following an acute ischemic initiating event (AMI with or without OOH SCA), published, peer-reviewed medical literature was reviewed using PubMed and Google text searches with multiple text strings, identifying 2200 potentially relevant articles. Title, publication date, and abstract review further identified approximately 200 articles for more complete review, with focus on AMI, OOH SCA, and associated VT/VF arrhythmias. Current critical care textbooks, American Heart Association guidelines, and germane NASA reports were also reviewed. Methodological quality, relevance to an astronaut analog cohort, study subgroup sample size, and clinically relevant medical outcomes determined selected studies for use.

Selection of an Analog Astronaut Cohort for Incidence Analysis

There have been no diagnosed acute myocardial infarctions during spaceflight missions. Therefore, analysis was performed using analog cohorts to predict incidence and outcome severity. A cohort was identified which provided several suitable subgroups for AMI incidence, characterized by somewhat greater known risk factors than the actual astronaut population possesses, providing a more conservative estimate of incidence.

LaMonte (11) reported a sex-adjusted subgroup (with CAC scores of 0) and an age stratum of 40–65 yr, representing approximately 60% of a 10,746 total population with hard event rates (fatal or nonfatal AMI) during a 3.5-yr follow-up. CAC scores (with hard event rates per 1000 person-years) in their total population were: 0 (0.03), > 0 (0.2), ≥ 100 (6.7), and ≥ 400 (10.6). This suggests a significant increase in AMI risk for CAC ≥ 100. We calculated AMI rates for the CAC $= 0$ subgroup and included these with clinical scenarios and outcome likelihoods as Subgroup I. Prevalence of FRF for the CAC $= 0$ subgroup are presented in **Table I**.

Church (3) analyzed the same population of 10,746 by CAC < 100 or CAC ≥ 100, and stratified them by the number of FRF present (hypercholesterolemia, diabetes, hypertension, and history of current or past smoking). These individuals reported their risk factors (yes/no) by

TABLE I. PREVALENCE OF FRAMINGHAM RISK FACTORS IN 2692 MEN AND 2780 WOMEN WITH CORONARY ARTERY CALCIUM SCORE (CAC) = 0.*

Risk Factor Presence	Men (% of 2692)	Women (% of 2780)
High cholesterol	23.3	26.5
High blood pressure	12.4	11.6
Diabetes	1.6	2.4
Current smoker	10.9	6.1

* From LaMonte (11).

questionnaire. A subgroup of 3619 men and women had clinical values determined that validated the questionnaire responses. We integrated AMI rates of this group with clinical scenarios and outcome likelihoods as Subgroups II (CAC < 100) and III (CAC ≥ 100). The prevalence of FRF in this analog cohort is somewhat higher than currently selected long-duration astronauts, representing a reasonable "ceiling" for AMI incidence for a long-duration astronaut cohort, and may be a conservative estimate for AMI rates in LDSM astronauts selected under recent criteria (3,11). Evidence has not been identified which would suggest the likelihood of AMI is increased by space mission exposure itself.

Clinically Significant AMI and OOH SCA Scenarios and Outcomes

Zipes (24) and others have noted that AMI of CAD origin presents as OOH SCA in approximately 50% of events. We assumed that among all potential AMIs in space 50% would present as OOH SCA and 50% would present with ischemic chest pain or dyspnea and clinically confirmed findings of AMI. This scenario proportion was used for percentage and probability calculations for all AMI scenarios.

AMI with OOH SCA outcomes: Using the American Heart Association recommended Utstein Style reporting (4), Stiell et al. (18) studied OOH SCA within 1 h of onset of AMI symptoms. These were two-phased (before-after), controlled studies in urban general population environments, with incremental introduction of prehospital interventions. These studies documented out of hospital emergency medical services' (EMS) responses and percentage of survivors in 11,969 OOH SCA secondary to CAD. Outcomes from the Ontario Prehospital Advanced Life Support (OPALS) Phase II study (18) of 1641 CAD OOH SCA cases assessed the impact of rapid-response defibrillation in a large, multicenter EMS system. Their Phase I control period included 4690 OOH SCA. Their Phase II introduced a rapid defibrillation intervention by a well-trained, experienced EMS service with a defibrillator on scene in less than 8 min in 92.5% of cases (vs. 76.7% in Phase I). Experienced and extensively trained EMS teams, firefighters, and police were equipped with automated external defibrillators (AEDs). Extensive data collection in this carefully conducted Phase II study provided a robust data set for analysis of multiple parameters affecting outcomes (5,6,11,18). We used Phase II scenarios and survival outcomes to populate a likelihood-enhanced ESD for OOH SCA after AMI scenarios.

AMI Without OOH SCA outcomes (non-OOH SCA): AMI patients not presenting as SCA may experience VT/VF during their hospital stay, associated with increased mortality at 30 d and 1 yr post-AMI. Delineation of these non-OOH SCA scenarios, their incidences, probabilities, and outcomes, were derived from the GUSTO-III study (1) with 15,042 AMI patient hospital admissions. These AMI patients presented with ischemic chest pain of 0.5 to 6 h duration. Their hospitalized incidence of VT/VF and 30 d survival represent robust resource references for comparison of space mission outcomes.

Scenario Probabilities and Outcomes, Stratified by CAC Score and Framingham Risk Factors

Microsoft Excel 2003® worksheets were constructed for each SCA and non-SCA AMI annual rate groups for calculating probabilities of resulting clinically significant scenarios following AMI. The age- and CAC-stratified, sex-adjusted subgroup AMI incidence rates of LaMonte (11) (Subgroup 1) and the initial rhythms and outcomes of Stiell (17,18) allowed calculation of probabilities of fatal and permanently impaired (for astronaut duties and long term health) survivor outcomes by initial SCA rhythm. These Earth outcomes were achieved by an optimized EMS response with early defibrillation, rapid transport to an urban level of care hospital emergency department with appropriate follow-on procedures (diagnostic and therapeutic) for AMI and OOH SCA in a general population cohort of Stiel (18). These 18 scenarios and their outcomes are a benchmark for estimating the relative effectiveness of current primary, secondary, and tertiary preventive mitigations of AMI with OOH SCA. This benchmark can be used to help estimate the effectiveness of AMI prevention strategies for ISS and exploration class mission.

Similarly, probabilities for Utstein clinically significant scenarios and their outcomes, grouped as either CAC < 100 (Subgroup 2) or ≥ 100 (Subgroup 3) from Church (3), were analyzed utilizing their respective event rates, stratified by number of FRF, after OOH SCA. For each subgroup worksheets were constructed for the non-OOH SCA VT/VF scenarios and 30 d probabilities of survival and fatal outcomes, given the identified standard treatments in robust urban hospital environments as reported by Al-Khatib (1). Worksheet likelihoods (per person-year) for the nine event scenarios and eighteen outcomes, representing all AMIs, were calculated (assuming 50% OOH SCA) and summarized.

Likelihood Enhanced ESD and Event Timeline Example for ISS AMI and OOH SCA

Subgroup 1 likelihoods, expressed both as a percentage of all predicted AMIs and as an estimated probability (per person-year) for clinically significant scenarios and their outcomes, were used to construct a likelihood enhanced (ESD) with AMI as the root cause. ESDs are used in engineering risk analysis to identify scenarios resulting from an initial failure event (in this case, an AMI) and offer a common format, with the addition of scenario likelihoods, for medical and engineering risk characterization and communication. An event timeline (4) for recognition, alarm, rescue, and treatment of an AMI with SCA on the ISS was constructed to indicate likely events, clinically significant intervals and critical delays, task conflicts and unavailable medical resources, and information essential to care and survival of an AMI during a mission.

Three-phase model of post OOH SCA timeline: Although cardio-pulmonary resuscitation (CPR) has been applied in OOH SCA settings for more than 40 yr, overall survival remains poor. Recently, Weisfeldt et al. (21) proposed a 3-phase model of cardiac arrest which reflects the time-sensitive progression of resuscitation physiology. The insidious progression of these phases requires appropriate time-critical interventions given a presenting rhythm of VT or VF without pulse:

1. Electrical Phase: Survival is improved when defibrillation shock is applied within 4 min or less after onset of SCA.
2. Circulatory Phase: 4 to 10 min of VF – the myocardium now needs oxygen delivery through effective CPR followed by defibrillation.
3. Metabolic Phase: After 10 min of arrest tissue injury from myocardial and whole body ischemia may not be reversible.

RESULTS

OOH SCA: Surviving and Fatal Outcomes

Initial rhythms after OOH SCA are asystole and pulseless electrical activity (PEA), which are not treatable with defibrillation, and VT/VF (pulseless ventricular tachycardia/ventricular fibrillation), which are treated with defibrillation. By definition, VT as an initial rhythm in SCA is unstable, given the SCA definition includes losses of consciousness, spontaneous respiration, and circulation. VT/VF outcomes are grouped for reporting in the Utstein Style (4) and outcomes are categorized as Emergency Medical System (EMS) witnessed, bystander witnessed, or unwitnessed OOH SCA. Because the interval from SCA to first shock is a major determinant of survival to hospital discharge, if this interval exceeds 2-3 min there is decreasing likelihood of survival to hospital discharge, even with otherwise similar chains of survival (6). Circumstances of remote, isolated, confined, and austere environments are associated with markedly increased interval to defibrillation and lower survival rates (19).

Stiell et al. (17,18), during the four phases of their OPAL studies of 11,969 OOH SCAs, reported initial rhythms, likelihoods, and survival to hospital discharge outcomes. The Phase II survival to hospital discharge outcomes (18), highest among the four phases of these two publications, were used for estimating scenario likelihoods and outcomes. **Table II** summarizes the variation in initial rhythm percentages and survival among the four study phases reported by Stiell, suggesting event likelihoods are relatively stable.

OOH SCA witnessed by EMS personnel provided the opportunity for most rapid defibrillation of VT/VF and is associated with the highest percentage of survivors to hospital discharge. In the robust urban environment, this rapid, initial treatment is followed by rapid transport (some EMS-witnessed SCAs occurred during this transport), with EMS care enroute, to an emergency department, further care, and specialty procedures. However, this EMS-witnessed SCA scenario represented only 2.4% of all OOH SCA (estimated 1.2% of all AMI) in this urban cohort (**Fig. 1** and **Fig. 2**). The larger cohorts of asystole and PEA scenarios had very poor survival and these rhythms are not candidates for defibrillation. Bystander witnessed OOH SCA VT/VF contributed the largest numbers of survivors of any scenario and a 12.0% survival proportion.

Non-OOH SCA AMI: Surviving and Fatal Outcomes

The 30-d incidence and survival percentages for the non-OOH SCA AMI group were similarly analyzed to obtain a percentage of an all-AMI group. Scenario likelihoods, and survival and fatal outcome likelihoods are shown in **Tables III–V**. These survival proportions represent benchmark proportions since these patients received thrombolytic drugs, aspirin, and other anti-ischemic drugs as indicated. Of the total 7.5% non-OOH SCA AMI (3.75% of all AMIs) occurrences of VT/VF during hospitalization, 5.7% (2.9%) occurred within 48 h after AMI and 1.2% (0.6%) occurred more than 48 h after AMI. The most commonly prescribed drugs after VT/VF, both in hospital and after discharge, were oral beta-blockers and ACE inhibitors. Amiodarone or sotalol was the most frequently prescribed antiarrhythmic drug in both arrhythmias (1).

TABLE II. INITIAL RHYTHMS, RANGES, AND SURVIVAL PERCENTAGES IN 11,969 OOH SCA OF CHD ORIGIN.*

Initial Rhythm	Phase II %	Range (%) in all Phases	Phase II % Survival	Range (%) Survival in all Phases
PEA	21.0	19.0-25.2	2.5	1.1-2.5
Asystole	37.4	37.4-40.5	0.3	0.2-0.3
All VT/VF	36.7	31.5-36.7	11.9	10.0-13.2
All Witnessed VT/VF	25.8	21.1-25.8	14.4	12.2-15.5
Bystander Witnessed VT/VF	22.3	19.0-23.3	12.0	10.2-13.7
EMS Witnessed VT/VF	2.4	1.9-2.4	37.5	28.1-45.3

* From Stiell (17,18). Legend: OOH SCA = Out of hospital sudden cardiac arrest; CHD = coronary heart disease; PEA = pulseless electrical activity; VT/VF = Ventricular tachycardia and fibrillation; EMS = emergency medical services.

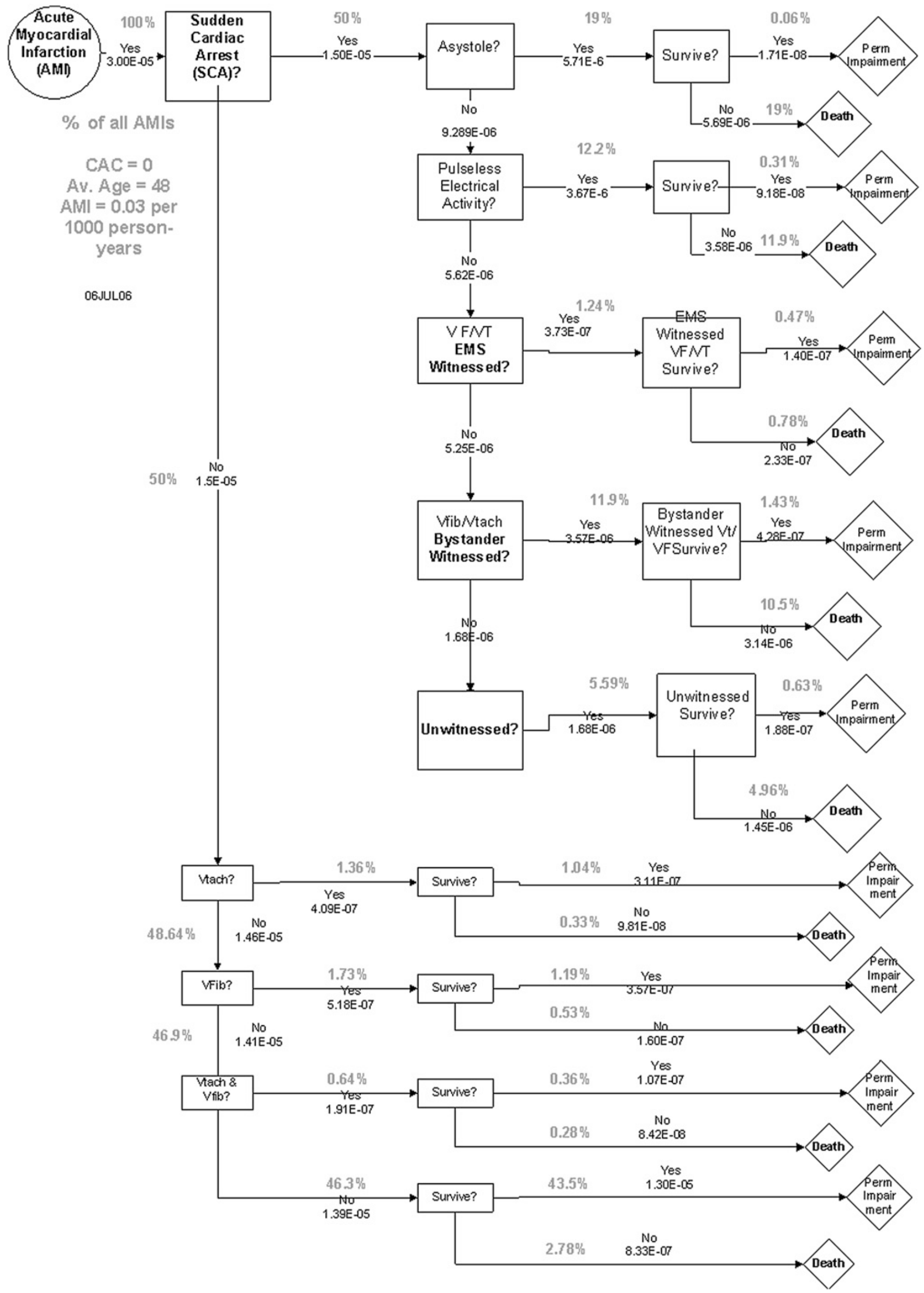

Fig. 1. ESD for AMI root cause with scenarios and outcomes. Likelihoods for Subgroup 1. Assumptions: Sex-adjusted AMI rate of 0.03 per 1,000 person-yrs; Age stratum, 40-65 yrs; 50% of AMI present as out-of-hospital sudden cardiac arrests (OOH SCA); $N = 1641$ OOH SCA for outcomes (18); n ~6450 for hard event rate (3,11).

Scenario Likelihoods and Outcomes, Stratified by CAC Score and Framingham Risk Factors

Worksheets were constructed for the three subgroups (by CAC score and number of FRFs) identified previously for calculating probabilities of clinically significant scenarios and their outcomes following AMI, assuming 50% of AMIs present with OOH SCA. The age-stratified and CAC score-stratified, sex-adjusted subgroup of LaMonte (11) (Subgroup 1) allowed calculation of probabilities of fatal and permanently impaired (for astronaut duties and long-term health) outcomes by initial SCA rhythms.

Similarly, probabilities for clinically significant scenarios, grouped as either CAC < 100 (Subgroup 2) or ≥ 100 (Subgroup 3) from Church (3) were analyzed, utilizing their respective event rates, stratified by number of FRFs.

For each subgroup, worksheets were constructed for the non-OOH SCA scenarios and the 30 d probabilities of survival (and permanently impaired for astronaut duty) and fatal outcomes, given the identified standard

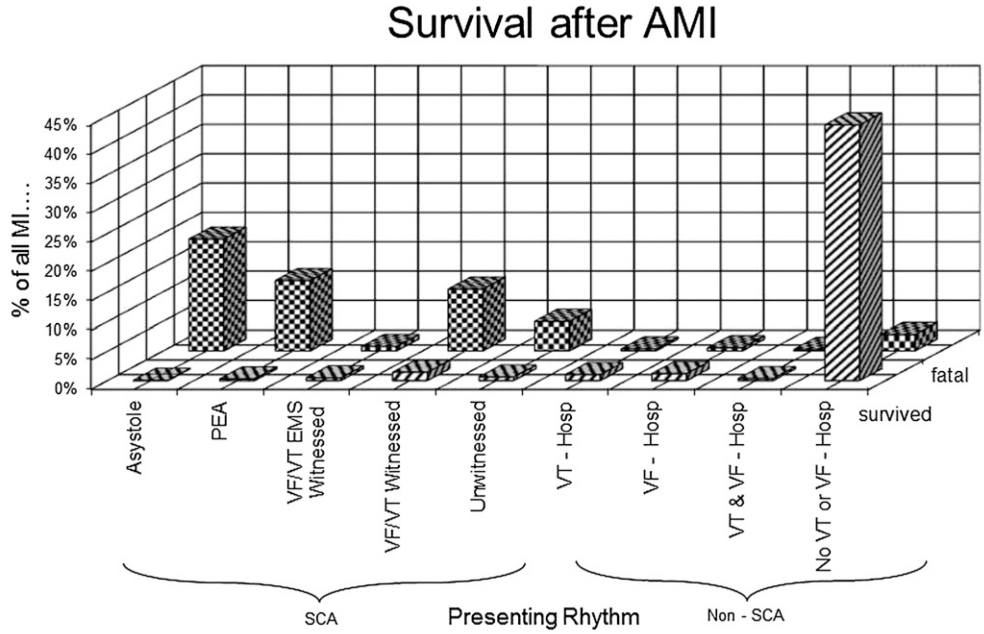

Fig. 2. Fatal and survival to hospital discharge outcomes. Estimated percentages of fatal and surviving to hospital discharge outcome scenarios after acute myocardial infarction (AMI) in a robust urban environment, adapted from Phase II (18).

treatments in robust urban hospital environments as reported by Al-Khatib (1). Outcome likelihoods were tabulated for Subgroup 1 (Table III), Subgroup 2 (Table IV) and Subgroup 3 (Table V).

Event Sequence Diagram, Subgroup 1, OOH SCA and Non-SCA AMIs

The ESD of Fig. 1 identifies three clinically significant initial rhythms in five clinically significant scenarios for OOH SCA and four clinically significant VT/VF scenarios in non-OOH SCA AMI and related 30 d mortality. These nine scenarios terminate in either permanent impairment of physical capabilities required to perform critical astronaut duties during current and future missions, or death. There are a total of 18 terminating states, none of which are trivial and all of which present major consequences for mission performance and long term health. The relative potential mission impact is not only apparent, but can be understood by engineers, managers, and others who must determine rational trade-offs of mitigation resources to optimize mission success across various mission disciplines and risks.

Cardiac Arrest Events Timeline on ISS

In sequenced critical events, delays are cumulative in their compromise of good outcomes. Cumulative interval to defibrillation after SCA must be minimized in the 19% of all AMIs which are candidates for rapid defibrillation after OOH SCA. There is no effective initial treatment in the astronaut cohort for CAD OOH SCA other than rapid defibrillation for the VT/VF scenarios. First shock, when administered more than 2-3 min after cardiac arrest, is associated with a progressive reduction in the likelihood of survival (6,19,22). In the ISS, with a 6-person crew in a vehicle the size of a Jumbo aircraft, daily activities will strongly influence the interval to recognition of an SCA event and the rescue interval. Importantly, in microgravity there is no collapsing fall with SCA to alert nearby potential responders. **Fig. 3** illustrates the cardiac arrest event timeline on ISS.

EKG is monitored during extravehicular activities (EVA) and during periodic exercise testing, when metabolic workload is elevated. SCA during an EVA would be immediately recognized, but would require rescue by the second EVA crewman, probably requiring more than 30 min for return to the airlock, followed by recompression of the airlock, doffing of the space suit and liquid cooling garment from the unconscious crewmember, followed by moving the patient to the single electrically isolated crewmember restraint system (CMRS), located adjacent to the defibrillator in the Destiny Lab module. Safely securing the EVA activities, unsuiting of the second EVA crewman, deploying the defibrillator, and communications tasks all generate conflicts with time critical medical tasks and reduce the probability of timely first shock and initial restoration of spontaneous circulation and respiration. Delays in first shock beyond 2-3 min after SCA increase the proportion of asystole, fatal outcomes, and, among survivors, neurological damage.

Successful initial outcomes in urban hospitals are achieved with responsive, experienced EMS teams, rapid transport to hospital Emergency Departments with robust care resources, and thrombolysis, percutaneous, or open coronary revascularization, as indicated. The longer term successful outcomes are continued with critical care in well-staffed coronary care units. Higher rates of VT/VF may occur on the ISS in the non-SCA AMI subgroup during the following 30 d, as was the case prior to current advanced interventions in urban centers. Survival after successful defibrillation will be

TABLE III. SUMMARY PERCENT AMI AND OUTCOME LIKELIHOOD BY CAC SCORE (AGE 48-65, SEX-ADJUSTED, WITHOUT FRAMINGHAM RISKS).

CAC Score		**0**	**>0**	**≥100**	**≥400**
AMI Likelihood per Person-yr		**3.00E-05**	**2.00E-04**	**6.70E-03**	**1.06E-02**
Relative Risk		**1.0**	**6.7**	**223.3**	**353.3**
Initial Rhythm	**% of All AMI**	**Likelihood / person-yr**	**Likelihood / person-yr**	**Likelihood / person-yr**	**Likelihood / person-yr**
SCA Asystole	19.04%	5.71E-06	3.81E-05	1.28E-03	2.02E-03
Survived	0.06%	1.71E-08	1.14E-07	3.83E-06	6.05E-06
Fatal	18.98%	5.69E-06	3.80E-05	1.27E-03	2.01E-03
SCA PEA	12.24%	3.67E-06	2.45E-05	8.20E-04	1.30E-03
Survived	0.31%	9.18E-08	6.12E-07	2.05E-05	3.24E-05
Fatal	11.93%	3.58E-06	2.39E-05	7.99E-04	1.26E-03
SCA VF/VT EMS Witnessed	1.24%	3.73E-07	2.48E-06	8.32E-05	1.32E-04
Survived	0.47%	1.40E-07	9.32E-07	3.12E-05	4.94E-05
Fatal	0.78%	2.33E-07	1.55E-06	5.20E-05	8.23E-05
SCA VF/VT Bystander Witnessed	11.89%	3.57E-06	2.38E-05	7.97E-04	1.26E-03
Survived	1.43%	4.28E-07	2.85E-06	9.56E-05	1.51E-04
Fatal	10.47%	3.14E-06	2.09E-05	7.01E-04	1.11E-03
SCA Unwitnessed	5.59%	1.68E-06	1.12E-05	3.75E-04	5.93E-04
Survived	0.63%	1.88E-07	1.26E-06	4.21E-05	6.65E-05
Fatal	4.96%	1.49E-06	9.92E-06	3.32E-04	5.26E-04
VT during Hospitalization	1.36%	4.09E-07	2.73E-06	9.13E-05	1.44E-04
Survived	1.04%	3.11E-07	2.07E-06	6.94E-05	1.10E-04
Fatal	0.33%	9.81E-08	6.54E-07	2.19E-05	3.47E-05
VF during Hospitalization	1.73%	5.18E-07	3.45E-06	1.16E-04	1.83E-04
Survived	1.19%	3.57E-07	2.38E-06	7.98E-05	1.26E-04
Fatal	0.53%	1.60E-07	1.07E-06	3.58E-05	5.67E-05
VT & VF during Hospitalization	0.64%	1.91E-07	1.28E-06	4.28E-05	6.77E-05
Survived	0.36%	1.07E-07	7.15E-07	2.39E-05	3.79E-05
Fatal	0.28%	8.42E-08	5.62E-07	1.88E-05	2.98E-05
No VT or VF During Hospitalization	46.27%	1.39E-05	9.25E-05	3.10E-03	4.91E-03
Survived	43.50%	1.30E-05	8.70E-05	2.91E-03	4.61E-03
Fatal	2.78%	8.33E-07	5.55E-06	1.86E-04	2.94E-04

Legend: CAC = coronary artery calcium score; SCA = sudden cardiac arrest; PEA = pulseless electrical activity; VT/VF = Ventricular tachycardia and fibrillation; EMS = emergency medical services.

impaired by lack of the above mentioned treatment resources in the chain of survival.

Limited advanced life support is available on the ISS for patients with return of spontaneous circulation after defibrillation (2). These interventions will usually not be conducted by experienced EMS personnel nor will rapid transport to a robust urban facility follow. Stiell (17) did not find any improvement in survival to hospital discharge when OOH SCA advanced life support was administered even by experienced, well-trained EMS personnel (Phase IV). These advanced interventions on the ISS can be expected to experience delays and to be degraded by incomplete resources and by task conflicts after the initial resuscitation to spontaneous circulation and respiration.

DISCUSSION

This study identified a terrestrial analog cohort, somewhat similar to astronauts qualified for long-duration space exploration missions, to estimate the probability of AMI in person-years during missions. Three subgroups of the analog cohort were used to stratify AMI and OOH SCA likelihoods by CAC score and by number of conventional Framingham risk factors. Clinically significant scenarios after OOH SCA and non-OOH SCA presentations of AMI were then used to estimate the probability of each scenario and its outcomes. Survival after OOH SCA, even in the robust urban environment, is unlikely (overall less than 5.2%). There is no expectation that space mission environments will meet or improve these outcomes after OOH SCA. Survival rates of 45.1% of the 50% of AMIs potentially presenting as non-OOH SCA are likely to be reduced during space missions. Nonetheless, preventing AMI during space missions appears to be achievable by using currently available primary and secondary prevention strategies, which will make the probability of AMI acceptable for long duration missions.

In Subgroup 1, the sex-adjusted hard event rate for the age stratum of 40-65 yr was 3.0E-05 per person year for CAC = 0. This event rate has more uncertainty secondary to smaller numbers of events in younger persons. However, Maron (13) reports SCA in competitive athletes < 35 yr of age are most often secondary to hypertrophic cardiomyopathy (48%), idiopathic left ventricular hypertrophy (18%), and coronary artery anomalies (14%). SCA etiology in older athletes (> 35 yr of age) is

TABLE IV. SUMMARY PERCENT AMI AND OUTCOME LIKELIHOOD BY FRAMINGHAM RISKS FOR CAC SCORE < 100.

# Framingham Risks		0	1	2	3-4
CAC Score		<100	<100	<100	<100
AMI Likelihood per Person-yr		**4.00E-04**	**1.00E-03**	**3.00E-04**	**2.40E-03**
Relative Risk		**1.0**	**2.5**	**0.8**	**6.0**
Initial Rhythm	**%of All AMI**	**Likelihood / person-yr**	**Likelihood / person-yr**	**Likelihood / person-yr**	**Likelihood / person-yr**
SCA Asystole	19.04%	7.61E-05	1.90E-04	5.71E-05	4.57E-04
Survived	0.06%	2.28E-07	5.71E-07	1.71E-07	1.37E-06
Fatal	18.98%	7.59E-05	1.90E-04	5.69E-05	4.56E-04
SCA PEA	12.24%	4.89E-05	1.22E-04	3.67E-05	2.94E-04
Survived	0.31%	1.22E-06	3.06E-06	9.18E-07	7.34E-06
Fatal	11.93%	4.77E-05	1.19E-04	3.58E-05	2.86E-04
SCA VF/VT EMS Witnessed	1.24%	4.97E-06	1.24E-05	3.73E-06	2.98E-05
Survived	0.47%	1.86E-06	4.66E-06	1.40E-06	1.12E-05
Fatal	0.78%	3.11E-06	7.76E-06	2.33E-06	1.86E-05
SCA VF/VT Bystander Witnessed	11.89%	4.76E-05	1.19E-04	3.57E-05	2.85E-04
Survived	1.43%	5.71E-06	1.43E-05	4.28E-06	3.43E-05
Fatal	10.47%	4.19E-05	1.05E-04	3.14E-05	2.51E-04
SCA Unwitnessed	5.59%	2.24E-05	5.59E-05	1.68E-05	1.34E-04
Survived	0.63%	2.51E-06	6.28E-06	1.88E-06	1.51E-05
Fatal	4.96%	1.98E-05	4.96E-05	1.49E-05	1.19E-04
VT during Hospitalization	1.36%	5.45E-06	1.36E-05	4.09E-06	3.27E-05
Survived	1.04%	4.14E-06	1.04E-05	3.11E-06	2.49E-05
Fatal	0.33%	1.31E-06	3.27E-06	9.81E-07	7.85E-06
VF during Hospitalization	1.73%	6.90E-06	1.73E-05	5.18E-06	4.14E-05
Survived	1.19%	4.76E-06	1.19E-05	3.57E-06	2.86E-05
Fatal	0.53%	2.14E-06	5.35E-06	1.60E-06	1.28E-05
VT & VF during Hospitalization	0.64%	2.55E-06	6.38E-06	1.91E-06	1.53E-05
Survived	0.36%	1.43E-06	3.57E-06	1.07E-06	8.58E-06
Fatal	0.28%	1.12E-06	2.81E-06	8.42E-07	6.74E-06
No VT or VF During Hospitalization	46.27%	1.85E-04	4.63E-04	1.39E-04	1.11E-03
Survived	43.50%	1.74E-04	4.35E-04	1.30E-04	1.04E-03
Fatal	2.78%	1.11E-05	2.78E-05	8.33E-06	6.66E-05

Legend: AMI = acute myocardial infarction; CAC = coronary artery calcium score; SCA = sudden cardiac arrest; PEA = pulseless electrical activity; VT/VF = Ventricular tachycardia and fibrillation; EMS = emergency medical services.

predominately secondary to coronary heart disease (80%). CAD is strongly related to age and CAC score, even after adjusting for CAD risk factors (3). The very low incidence in Subgroup 1 may represent a risk nadir resulting from exhaustion of the primary mechanisms in younger individuals and the nascent risk of CAD in the fourth decade of life for persons with no CAC or low CAC scores and minimal conventional cardiac risk factors.

This middle-aged risk nadir is seen in some other disease states, for instance, spontaneous pneumothorax (SP). In the general population the risk of SP requiring hospital admission or physician consultation was published by Gupta et al. (8) with an incidence of about 20 per 100,000 person years in the typical age group of the astronaut corps (30 to 50 yr).

SCA Subgroup 1 scenarios are illustrated in an ESD (Fig. 1). ESDs are widely used in engineering to develop relevant scenarios, consisting of a sequence of events occurring after an initial failure and progressing to an outcome state. The scenario probabilities are useful in better understanding, for instance, the small impact on total outcomes EMS-witnessed OOH SCA have, given the full spectrum of potential outcomes after AMI. ESDs also aid in identifying where effective mitigation may be applied to significantly improve outcomes. Quantification of end states in an ESD facilitates consideration of not only the probability of a given scenario, but its impact or consequence to the mission. Probability (and related incidence) and outcome consequence (severity) are the two essential elements of risk characterization and mitigation, particularly when faced with multiple root causes (risk factors or hazards) which require mitigation. Likelihood enhanced ESDs facilitate probabilistic analysis, which is useful in medical decision making under uncertainty. Required medical resource planning, novel exploration and spaceflight missions, small numbers of participants, deliberate minimization of events of consequence, and mission-dependent launch mass penalties all contribute to the level of uncertainty and argue for analytic approaches which are most informative when data are incomplete.

In Subgroup 2, with CAC score < 100, rates of AMI increased sixfold as FRF increased from 0 to 3–4. Most striking FRF effect was a 10.2 (3.8–27.6) relative rate (age, sex, and smoking history adjusted) for diabetes mellitus. Diabetes exclusion criteria for astronauts thus further

TABLE V. SUMMARY PERCENT AMI AND OUTCOME LIKELIHOOD BY FRAMINGHAM RISKS FOR CAC SCORE ≥ 100.

# Framingham Risks		**0**	**1**	**2**	**3-4**
CAC Score		**≥100**	**≥100**	**≥100**	**≥100**
AMI Likelihood perPerson-yr		**6.40E-03**	**4.80E-03**	**7.40E-03**	**8.40E-03**
Relative Risk		**16**	**12**	**18.5**	**21**
Initial Rhythm	**% of All AMI**	**Likelihood / person-yr**	**Likelihood / person-yr**	**Likelihood / person-yr**	**Likelihood / person-yr**
SCA Asystole	19.04%	1.22E-03	9.14E-04	1.41E-03	1.60E-03
Survived	0.06%	3.66E-06	2.74E-06	4.23E-06	4.80E-06
Fatal	18.98%	1.21E-03	9.11E-04	1.40E-03	1.59E-03
SCA PEA	12.24%	7.83E-04	5.87E-04	9.05E-04	1.03E-03
Survived	0.31%	1.96E-05	1.47E-05	2.26E-05	2.57E-05
Fatal	11.93%	7.64E-04	5.73E-04	8.83E-04	1.00E-03
SCA VF/VT EMS Witnessed	1.24%	7.95E-05	5.96E-05	9.19E-05	1.04E-04
Survived	0.47%	2.98E-05	2.24E-05	3.45E-05	3.91E-05
Fatal	0.78%	4.97E-05	3.73E-05	5.75E-05	6.52E-05
SCA VF/VT Bystander Witnessed	11.89%	7.61E-04	5.71E-04	8.80E-04	9.99E-04
Survived	1.43%	9.13E-05	6.85E-05	1.06E-04	1.20E-04
Fatal	10.47%	6.70E-04	5.02E-04	7.75E-04	8.79E-04
SCA Unwitnessed	5.59%	3.58E-04	2.68E-04	4.14E-04	4.70E-04
Survived	1.43%	4.02E-05	3.01E-05	4.64E-05	5.27E-05
Fatal	4.96%	3.18E-04	2.38E-04	3.67E-04	4.17E-04
VT during Hospitalization	1.36%	8.72E-05	6.54E-05	1.01E-04	1.14E-04
Survived	1.04%	6.63E-05	4.97E-05	7.66E-05	8.70E-05
Fatal	0.33%	2.09E-05	1.57E-05	2.42E-05	2.75E-05
VF during Hospitalization	1.73%	1.10E-04	8.28E-05	1.28E-04	1.45E-04
Survived	1.19%	7.62E-05	5.71E-05	8.81E-05	1.00E-04
Fatal	0.53%	3.42E-05	2.57E-05	3.96E-05	4.49E-05
VT & VF during Hospitalization	0.64%	4.08E-05	3.06E-05	4.72E-05	5.36E-05
Survived	0.36%	2.29E-05	1.72E-05	2.64E-05	3.00E-05
Fatal	0.28%	1.80E-05	1.35E-05	2.08E-05	2.36E-05
No VT or VF During Hospitalization	46.27%	2.96E-03	2.22E-03	3.42E-03	3.89E-03
Survived	43.50%	2.78E-03	2.09E-03	3.22E-03	3.65E-03
Fatal	2.78%	1.78E-04	1.33E-04	2.05E-04	2.33E-04

Legend: AMI = acute myocardial infarction; CAC = coronary artery calcium score; SCA = sudden cardiac arrest; PEA = pulseless electrical activity; VT/VF = Ventricular tachycardia and fibrillation; EMS = emergency medical services.

reduce the CAC < 100 and zero-FRF expected rates. In Subgroup 3, with CAC ≥ 100, the zero-FRF rate was 16 times the corresponding CAC < 100 rate. The relative rate with diabetes mellitus (age, sex, and smoking history adjusted) was 21.3 (9.0-50.3). For all levels of FRFs, individuals with CAC ≥ 100 "were at substantially greater age- and gender-adjusted risk of a primary CAD event" relative to those with CAC < 100. Church's Receiver Operator Characteristic (ROC) analysis resulted in a C-index for AMI of 0.87 for FRF and CAC score and suggests CAC ≥ 100 was a useful decision point for selection criteria (9).

Scenarios derived from Stiell's studies, with 11,969 OOH SCAs, (Table II–V) show there are dismal salvage probabilities for asystole (0.2–0.3%) and PEA (1.1–2.5%) and these were initial rhythms in 58.4% of SCA in Phase II. Initial return of spontaneous circulation after VT/VF is highly dependent upon rapid defibrillation after arrest, with progressively lower survival for longer intervals (6,21). Survival to hospital discharge was 11.9% for Phase II witnessed VT/VF OOH SCA, reflecting the benefit of the early defibrillation EMS service and 92.5% EMS response in less than 8 min. In a study with 9273 patients with OOH SCA from the OPALS studies, De Maio (5,6) found the 95% confidence interval (CI) of the actual survival percentage versus cumulative response interval was 5–6% for 5 min, 6–9% for 4 min, and 8–18% for 2 min response. An 8-min response interval was "well into the plateau phase" of poor outcome on the survival curve.

Survival rates were 36.7% for patients with VT/VF initial rhythms which were EMS-witnessed and shocked rapidly. Unfortunately, the rapid-defibrillation-attempt, EMS-witnessed cohort in urban environments is an unlikely space mission scenario (≤ 1.2% of all AMI and ≤ 2.4% of all OOH SCA) and is composed mostly of patients with known cardio-respiratory disease with prodromal symptoms preceding their OOH SCA. De Maio (5) describes 610 OOH cardiac arrests witnessed by EMS personnel during the OPALs study. Of these, 81.5% had pre-existing cardiac or respiratory disease and 91.4% had experienced prodromal symptoms prior to the arrival of EMS. This resulted in short intervals to attempted defibrillation in those cardiac arrests initially in VT/VF and

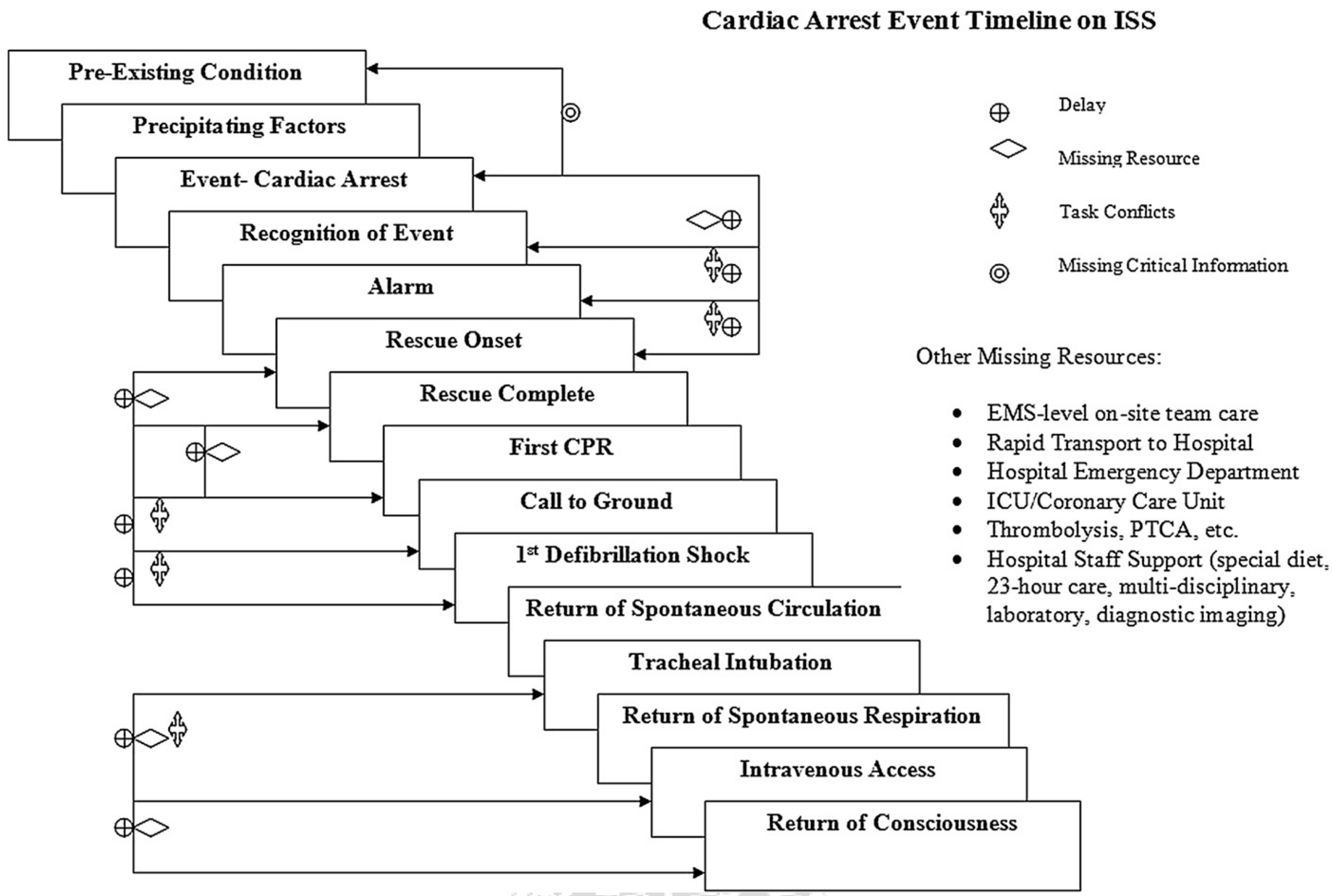

Fig. 3. Cardiac Arrest Events Timeline for ISS modified from Cummins (4).

explains how the SCA came to be witnessed by EMS personnel, the essential precursor to their high survival rate. Astronauts are not selected to fly long-duration space missions with known cardiac and respiratory disease, which could reduce the 2.4% likelihood of this scenario (4.97E-06 per person-year for CAC < 100, 0 FRF) to a 0.4% likelihood (8.28E-07 per person-year for CAC < 100, 0 FRF).

It is not established whether the percent survival of EMS-witnessed VT-VF after immediate defibrillation is related solely to early defibrillation, or also to previous recurrent episodes of ischemia and increased collateral circulation in the myocardium, or to cardiac medications increasing the efficacy of defibrillation (56% of De Maio's cases had taken nitroglycerin prior to EMS arrival). It could be that healthy astronauts who have not induced collateral circulation secondary to chronic ischemia have a lower likelihood of surviving an SCA secondary to AMI. In the De Maio study, when SCA occurred, 125 of 605 patients were enroute to the hospital and 25 had arrived at the hospital. These circumstances collectively reduce the probability of this scenario contributing to a high survival rate on the ISS.

During the OPALS initial control Phase I, with 4690 OOH SCA patients, 3.9% survived to hospital discharge. With the addition of a Phase II rapid defibrillation program (defibrillator on scene in 8 min or less in 92.5% of cases) and 1641 patients, 5.2% survived to hospital discharge. During a subsequent control period (17) with rapid defibrillation and 1391 OOH SCA patients, 5.0% survived to hospital discharge. Addition of EMS advanced life support to this early defibrillation program with 4247 OOH SCA patients produced 5.1% survival to hospital discharge. Thus, addition of an early defibrillation program improved the percentage of patients surviving to hospital discharge by only 1.3% absolute. Addition of advanced life support by EMS teams did not further improve outcomes when the endpoint was survival to hospital discharge. These upper limits on outcome may be expected during any long duration space mission.

Non-OOH SCA, post-AMI 30-d scenario likelihoods are included in Tables III–V. VT/VF likelihood is much less in non-OOH SCA AMI than life-threatening arrhythmias after OOH SCA. ISS and other space missions are likely to experience a greater incidence of VT and VF than reported in GUSTO-III and a lower likelihood of scenario survival since space missions lack the skill level, medical manning level, and facility resources (limited supply for advanced life support, thrombolysis, IV beta-blocker, PTCA, diagnostic radiology, suitable respiratory support and continuous monitoring) of robust urban hospitals. An increased incidence of VT and VF will likely reduce survival likelihood. We did not further estimate these likelihoods.

Tables IV and V suggest the current long-duration mission CAC criteria, used in conjunction with FRF evaluation, offer a feasible approach to limiting the likelihood of AMI during space missions. The likelihood of AMI can be further reduced with age limits. The analog cohort includes a significant number of older persons and age is a known driver of AMI risk. Establishing a lower CAC score limit can further reduce the risk for LDSMs. Therefore, employing specific selection criteria such as the exclusion of diabetes mellitus, setting a maximum CAC score at or below 100 or, optimally, zero, and using FRF and age stratification in addition to vigorous health maintenance practices for long duration missions could lower an individual crewmember cardiac risk below a credible risk threshold within the context of an overall 3-yr Mars mission. Other risk mitigation strategies such as genetic screening for congenital channelopathies could also be considered to reduce noncoronary artery risks.

Not reflected in Stiell's studies are the consequences of OOH SCA survival during a space mission. There is little capability to effectively sustain a crewmember after initial resuscitation from an SCA until evacuation from the ISS. Evacuation interval can be prolonged awaiting a nadir-risk status for a Soyuz return. Early return by Soyuz entails a lack of access to the patient, a 180 min (2 orbits) loiter in a very small capsule with no medical care capability, a stressful re-entry with 3 to 8 g_x for more than 5 min deceleration with a high impact landing into an austere, remote environment, and a potentially extended interval of 24 h before rescue and transport to a distant hospital. It is a given that having an SCA during launch or re-entry would have a dismal outcome. All of these factors will predictably reduce the likelihood of survival compared to the usual SCA in a robust U.S. urban environment. Evacuation will not be an option for foreseeable Mars missions. The 'residential scenario' and space vehicles/habitats share some characteristics of isolated, confined, and medically austere environments. Space vehicles and habitats are also remote during missions, as are some residences, with resulting decreases in survival after AMI. Stapczynski (16), using stepwise logistic regression models of rural SCA data, concluded "survival to hospital discharge was best predicted by an initial rhythm of VF/VT and population density greater than 100 persons per square mile" and that basic life support services in areas with lesser population density obtained "little benefit from the addition of AEDs to their treatment of patients who had out of hospital cardiac arrests."

Given initial survival after an OOH SCA or AMI, early consequences include confining the patient to the Destiny Lab module (where monitoring and immediate defibrillation can be conducted), then a risky, graded program of exercise rehabilitation pending emergency evacuation, a high level of temporary impairment, permanent disqualification for further spaceflight and astronaut duties, and a variable degree of lifetime functional and occupational impairment. Prior to evacuation, the patient-crewmember requires an interval of 24-hour-a-day care and monitoring for treatable arrhythmias, pain control, respiratory difficulty, anxiety control, and potentially congestive heart failure. This postevent care is limited by constrained medical resources and is provided by other crewmembers whose nominal duties are interrupted by these medical responsibilities, increasing the total crew duty impairment burden of AMI during a mission.

Continuous visual or ECG monitoring of all crewmembers could potentially increase survival for the ~37% of OOH SCAs (18.5% of all AMIs) presenting with VT/VF if immediate defibrillation were available on the ISS. During the approximately 8-h daily sleep period, when crew usually wear sound protection and blinders, the average time to recognition of an SCA in another crewmember may be as long as 4 h. If crew have assigned tasks for 6 h daily and are out of visual contact with other crewmembers (working in different compartments, etc.) 50% of that time, event recognition will be significantly delayed. In microgravity a SCA will not be accompanied by a fall, which is a strong alerting signal, so recognition may be generally delayed unless incidental close contact is established early.

During an EVA, an astronaut experiencing an SCA is unlikely to be successfully rescued and defibrillated. Risk of AMI may be accentuated during EVA because of increased sympathetic nervous system activity with vigorous exercise (23), or increased catecholamine release (14). Strenuous exercise may also increase risk of AMI due to effects on platelet adhesion (20). These potential aggravating factors may be somewhat mitigated by regular moderate exercise countermeasure prescriptions.

The Utstein-style event timeline is a useful tool for identifying sources of delay, task conflicts, missing resources and/or critical information in remote, confined, isolated, austere environments such as the ISS and exploration missions. The interval from SCA to event recognition, alarm, resource recruitment, rescue, movement to the CMRS, and provision of CPR and defibrillation, if indicated, is critical. Visual and aural isolation impairs augmenting the initial witness and response resources. The chain of survival is further impaired as no fully trained and experienced EMS team is available to respond, and there is no rapid transport to an appropriate hospital.

Valenzuela (19) reported survival to hospital discharge of up to 74% after cardiac arrest in several casinos. However, there are more differences than similarities among critical characteristics of casinos and space vehicles. Casino scenarios are characterized by both floor-level and in-ceiling personnel who continuously monitor customer activity, including collapse and fall. Responsive EMS care and rapid transport was available to urban-level hospital care. Casino customers, when compared to astronauts, represent a high risk for AMI secondary to life style prevalence, including sedentary activities, smoking, alcohol consumption, obesity, prior ischemic episodes, age, and FRF. The 74% survival reported includes only witnessed arrests (not all necessarily CAD OOH SCA), an AED immediately at hand, VT/VF initial rhythm, and first defibrillation no later than 3 min after collapse. Data collection was not consistent with the Utstein protocol, the CAD origin of the SCA was not documented, and the number of patients in the 74% survival cohort was not specified. There were a total of 90 witnessed collapses treated at varying intervals with various survival rates. "The security officers completed a one-page data form and an incident report specific to the casino," and applied age and weight exclusion criteria "estimated visually by security officers." No information is available as to the percent with prodromal symptoms, history of known cardiopulmonary disease, cardiac medications taken, or confirming CAD etiology of the collapse. This single high-survival scenario and its patient population have little in common with the astronaut cohort, environment, or likelihood of OOH SCA of CAD origin in a space mission environment.

A fundamental limitation of our analysis is the absence of any recognized AMI during previous space missions. This requires the use of an analog cohort and identification of operative processes that determine incidence, clinically significant scenarios, and outcomes. Postulated influences and effects of the identified processes must be determined in the context of missing data and uncertainty and analyzed using techniques appropriate for risk analysis and decision support under uncertainty in this "game against nature" decision problem. Given the absence of evidence that exposure to spaceflight increases the risk of AMI, we used Earth analog data, a valid precursor analysis to establishing any attributable risk to space mission exposure as a root cause (such as microgravity effects) in the future.

While we would have preferred analog cohorts exactly matched to the astronaut cohort, no such robust data were available. However, Hamilton et al. (9) present evidence that the average age of U.S. astronauts in 2002 was 44 ± 6.7 for men and 44.5 ± 5.6 for women, and that their 10-yr risk of AMI was approximately half that of the general population. This suggests that our analog cohort is a conservative cohort for purposes of this analysis. Our Subgroup 1 is an age-stratified, gender-adjusted group analysis and LaMonte's age strata is 40-65 yr, which extends beyond the range astronauts would be participating in spaceflight, again, giving us a conservative estimate of AMI rates.

This manuscript was written to specifically address the predictive value of using CAC scores for astronaut selection for future space missions (7). There are many cardiovascular conditions for which CAD is not a root cause of SCA (e.g., reentrant arrhythmias, channelopathies); however, many of them are "ruled out" in the astronaut selection process. The astronauts selected for missions are fit but the vast majority of them are not super fit like competitive athletes. The astronaut selection process is reviewed and approved by an international panel of experts who consider the predictive power of every test and criteria that is used. SCA is one of many catastrophic root causes to crew illness which can impact mission success. This manuscript was written to draw attention to the usefulness of primary and secondary prevention instead of tertiary prevention to control cardiac risk for long duration missions. It is clear that SCA may occur during spaceflight, nonetheless, the risk of not using CAC for selection is greater than the risk of using CAC from a mission success perspective.

CONCLUSIONS

While astronaut space mission AMI data would avoid the need for analog cohort analysis, avoiding such AMI events is a program goal. Prospective analysis is required as an alternate pathway to effective AMI risk characterization and mitigation while avoiding the catastrophic impacts of both fatal and survivable AMI in space. As mission duration and the number of crewmembers increases, the likelihood of an AMI event increases and progressively more effective screening, selection criteria, and health maintenance programs become necessary to avoid these AMI events.

The incidence of AMI can be lowered with feasible selection standards and vigorous cardiac health maintenance programs supported by available testing modalities to reduce the likelihood of AMI below a credible risk threshold. Survival after OOH AMI in the robust urban environment is dismal and there is no evidence such outcomes can be improved within the constraints of space mission medical resources, activities, isolation, remoteness, and inherent delays in return to terrestrial hospital facilities. That is to say, given feasible astronaut selection criteria and continuing health maintenance, the root cause event probability is sufficiently small, and outcomes that improve on dismal Earth urban outcomes sufficiently unlikely, that AMI and OOH SCA outcomes are essentially independent of medical resources aboard the ISS and future vehicles and habitats. A single scenario, EMS-witnessed immediate defibrillation has high survival potential, but a very small likelihood of occurring and a consequently small likelihood of contributing to a final successful conclusion in space. Non-OOH SCA AMI outcomes will be compromised by constrained medical resources, prolonged evacuation intervals, and austere transport facilities. Post-AMI survival becomes progressively constrained in more remote, long duration exploration missions to the Moon and Mars. It does, however, appear feasible to lower the incidence of AMI in space sufficiently, using currently available primary and secondary strategies to simultaneously avoid the significant tertiary prevention (treatment) logistical burden *and* the high cost to mission performance and long-term health associated with both fatal and survival outcomes after AMI in space. Current ISS mission selection criteria of CAC $<$ 100 and vigorous cardiac health maintenance programs should be effective in avoiding the high mission consequence of AMI in low Earth orbit.

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