Fiscal Year:	FY 2014	**Task Last Updated:**	FY 10/14/2014
PI Name:	Levine, Benjamin D M.D.		
Project Title:	Cardiovascular Imaging and Strategies to Mitigate the Risk for Cardiac Events in Astronauts During Prolonged Spaceflight		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline-- Element/Subdiscipline:	NSBRI--Cardiovascular Alterations Team		
Joint Agency Name:		**TechPort:**	Yes
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **Cardiovascular**:Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes (2) **Medical Conditions**:Risk of Adverse Health Outcomes and Decrements in Performance Due to Medical Conditions that occur in Mission, as well as Long Term Health Outcomes Due to Mission Exposures		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	75231-5129	**Congressional District:**	5
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2009 Crew Health NNJ09ZSA002N
Start Date:	06/01/2010	**End Date:**	05/31/2014
No. of Post Docs:	3	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	1	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: Risk/Gap changes per IRP Rev E (Ed., 3/19/14)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Radford, Nina (Cooper Clinic) Khera, Amit (The University of Texas Southwestern Medical Center at Dallas)		
Grant/Contract No.:	NCC 9-58-CA02201		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	This project from the Cardiovascular Alterations Team was designed to enhance current NASA cardiovascular disease risk reduction strategies by partnering with investigators from the Aerobics Center Longitudinal Study (ACLS) and the Dallas Heart Study (DHS) to determine how to minimize the risk of a catastrophic cardiovascular event in asymptomatic astronauts. During an exploration class space mission, such as a mission to Mars, astronauts will not have access to comprehensive health care services for periods of 2 years, and possibly longer. Since the majority of experienced astronauts are middle aged (average age 46, range 33-58 years), they are at risk for developing serious cardiovascular events which are life-threatening for the astronaut, and mission threatening for NASA. The ability to identify 'at risk' individuals who are currently asymptomatic is a topic of intense research within the cardiovascular community that is relevant both for NASA and public health. The primary objective of this application was to determine the risk of coronary events associated with changes in coronary artery calcium (CAC) scores over time, and to determine whether this risk can be mitigated by increases in physical fitness, or use of lipid lowering therapy. Hypothesis 1: A change in coronary calcium score over time from <10 to >10, is associated with an increase in risk for coronary events; this risk is most prominent when the CAC score increases above a threshold level of 100.
	Hypothesis 2: The increased risk associated with increasing CAC scores is mitigated by increasing levels of physical fitness and/or the use of lipid lowering therapy (statins).
	To test these hypotheses, we will accomplish the following specific aims: Specific Aim 1: To identify ALL clinical events in the ACLS data base. We will identify and verify all myocardial infarctions, new onset angina, and revascularization procedures in ACLS patients who fit the astronaut demographics and who have had more than one CAC measurement. Specific Aim 2: To update the ACLS data base to include information about timing and dose of statin medications. This information will be linked with treadmill time and the clinical events from aim 1 to developed robust risk prediction models. The project was completed on time, and within budget. All analyses were completed as planned, and a number of papers have been published (JACC; Imaging) or submitted (JAMA, Mayo Clinic Proceedings). A few are still in preparation and will be completed without additional funding as the analyses are complete and preliminary figures are already finished.
	The key take home messages from this project are: 1). The definition of CAC progression -- specifically how to quantify and express it -- critically influences whether patients are classified as "progressors" or "non-progressors." The most common clinical definition of >15% per year, which to date has been used by NASA flight surgeons, is much too sensitive to the baseline CAC value and frequently gives erroneous information (for example and increase of 1 to 2, 10 to 11, or 100 to 101 reflect a 100%, 10%, and 1% change). Different methods can result in divergent classification in up to 30% of individuals. Although we could not define the "best" score, the Hokanson method, based on the square root of the change in CAC seemed to be the most robust, and will be utilized in other publications; 2). Perhaps the most important finding from the complete study, which has just been submitted to JAMA (Journal of the American Medical Association), is that when more than one CAC score is obtained, virtually all the clinically relevant information is obtained from the absolute value of the second CAC scan. Stated from a clinical perspective, these findings imply that if serial CAC scanning is performed, the latest scan should be used for risk assessment and that knowledge of the change in CAC leading to this subsequent score will provide no independent prognostic information. This important finding obviates the need for complex calculations regarding rate of progression, and further emphasizes that risk for future events depends predominantly on the overall atherosclerotic burden, not on how fast the patient gets there. 3). The second major aim involved assessing the mitigating effects of physical fitness on preventing cardiac events associated with CAC. Although this paper is still in preparation, the key figure is presented in detail in the final report section which shows a dose dependent reduction in cardiovascular events with increasing physical fitness and any age and any CAC level. 4). This study stimulated the development of the Astro-CHARM (Cardiovascular Health and Risk Modification) score which is the only scoring system available which quantifies global cardiovascular risk in a relatively young population like the astronaut corps, using routine clinical information plus a CAC score. The primary paper from the overall study confirms that we do NOT have to update this score to include the rate of change -- only the final score. 5). Lastly, a spin off study which derived from our event verification analysis was a study looking at the risk of developing diabetes in patients on statins. This problem has become increasingly recognized, and is of real importance to astronauts since many of them are on statins. We wanted to know whether being physically fit prevented the development of diabetes from statins. The results from the study showed that increased fitness clearly attenuated the risk of diabetes in statin users, but didn't prevent it entirely. This type of project reflects a transition for the Cardiovascular Team & for NASA.
	As the future of manned spaceflight transitions to longer durations of exposure, concerns about the intrinsic cardiovascular risks of flying middle aged men and women are superseding concerns about orthostatic tolerance, or even arrhythmias. Thus reassessment of cardiovascular (CV) risks in space is necessary.

Rationale for HRP Directed Research:	
	Since this was fundamentally an Earth based investigation with impact/benefits for astronauts, virtually all the findings are relevant for cardiovacular medicine on Earth. The focus of our studies was on the clinical question of how to track and interpret imaging data regarding progression of coronary artery disease. For our studies, we concentrated on coronary artery calcium (CAC) scoring, which gives reliable, clinically relevant information about the overall burden of atherosclerosis in the coronary arteries. Many doctors (including NASA flight surgeons) will get repeat scans to follow the progression of disease. However the clinical implications of such changes, particularly in a relatively young population are unknown. They key benefits from our studies are:
	1). DEFINED HOW TO QUANTIFY PROGRESSION OF CAC: Our publication: Paixao ARM...Levine BD et al. Disagreement Between Different Definitions of Coronary Artery Calcium (CAC) Progression. JACC: Imaging, 2014, in press, demonstrated that different methods of quantifying the "progression" of CAC can result in divergent classification in up to 30% of individuals. The most common clinical definition of >15% per year, which is used currently by NASA flight surgeons, is too sensitive to the baseline CAC value and frequently gives erroneous information, especially in patients with low baseline levels of CAC (for example an increase of 1 to 2, 10 to 11, or 100 to 101 reflect a 100%, 10%, and 1% change, but would still reflect the same absolute change in CAC). It is likely that this paper, along with the subsequent paper described in #2 will substantially change how physicians interpret repeat CAC scans.
	2). DETERMINED THAT THE FINAL CAC SCORE, RATHER THAN A MEASURE OF DISEASE

Research Impact/Earth Benefits:	PROGRESSION IS THE MOST IMPORTANT PIECE OF INFORMATION FOR PREDICTING CLINICAL EVENTS. So if serial CAC scanning is performed by any physician (including flight surgeons), the latest scan should be used for risk assessment; knowledge of the change in CAC leading to this subsequent score will provide no independent prognostic information. This new finding obviates the need for complex calculations regarding rate of progression, and emphasizes that risk for future events depends mainly on the overall atherosclerotic burden, not on how fast the disease progresses. Radford NB...Levine BD et al. Baseline Value, Follow-Up Value and Progression Rate of Coronary Artery Calcification Score and Risk of Incident Cardiovascular Disease Events. Submitted JAMA 08/2014. 3). HIGHER DEGREES OF FITNESS MITIGATE THE EFFECT OF CAC AT ANY AGE OR LEVEL OF CAC. This study shows that for patients with large amounts of CAC, being high fit reduces the risk of cardiovascular events. It also determines the amount of fitness that is required to afford the most protection at any given age, or amount of CAC. The information will be very important to health care providers to reduce the risk of CV events by prescribing specific levels of fitness. DeFina LF...Levine BD et al. Cardiorespiratory Fitness, Coronary Artery Calcium and Cardiovascular Disease Events. To be presented at American Heart Association meetings 2014. 4). DEVELOPED THE ASTRO-CHARM (Cardiovascular Health and Risk Modification). This score quantifies global cardiovascular risk in a relatively young population like the astronaut corps, using routine clinical information plus a CAC score. After final validation, this scoring system will be placed on-line and made available for all medical practitioners to get a more accurate assessment of cardiovascular risk in their patients. 5). DEMONSTRATED THAT INCREASED FITNESS PROTECTS AGAINST THE DEVELOPMENT OF DIABETES IN PATIENTS ON STATINS. This study provides a strategy (increasing fitness) to prevent diabetes in patients placed on statins. Radford NB...Levine BD et al Impact of Fitness on Incident Diabetes from Statin Use in Primary Prevention. Submitted Mayo Clinic Proceedings 07/2014.
Task Progress:	All aims have been accomplished. Because this section will be made publicly available, a modified selection from "main findings" is reproduced here. 1). DEFINED HOW TO QUANTIFY PROGRESSION OF CAC: The most common clinical definition of >15% per year, which is used by NASA flight surgeons, is too sensitive to the baseline CAC and frequently gives erroneous information, especially in patients with low baseline levels of CAC (for example an increase of 1 to 2, 10 to 11, or 100 to 101 reflect a 100%, 10%, and 1% change, but would still reflect the same absolute change in CAC). Different methods can result in divergent classification in up to 30% of individuals. Although we could not define the "best" score, the Hokanson method, based on the square root of the change in CAC, seemed to be the most robust, and will be utilized in other publications. This paper has been accepted in the Journal of the American College of Cardiology (JACC): Imaging; Paixao ARM...Levine BD et al. Disagreement Between Different Definitions of Coronary Artery Calcium Progression. JACC: Imaging, 2014, in press. 2). MADE THE NOVEL, CLINICALLY IMPORTANT OBSERVATION THAT THE FINAL CAC SCORE, RATHER THAN A MEASURE OF DISEASE PROGRESSION IS THE MOST IMPORTANT PIECE OF INFORMATION FOR PREDICTING CLINICAL EVENTS. So if serial CAC scanning is performed by flight surgeons, the latest scan should be used for risk assessment; knowledge of the change in CAC leading to this subsequent score will provide no independent prognostic information. This new finding obviates the need for complex calculations regarding rate of progression, and emphasizes that risk for future events depends mainly on the overall atherosclerotic burden, not on how fast the diseases progresses. Radford NB...Levine BD et al. Baseline Value, Follow-Up Value and Progression Rate of Coronary Artery Calcification Score and Risk of Incident Cardiovascular Disease Events. Submitted JAMA 08/2014 3). HIGHER DEGREES OF FITNESS MITIGATE THE EFFECT OF CAC AT ANY AGE OR LEVEL OF CAC. DeFina LF...Levine BD et al. Cardiorespiratory Fitness, Coronary Artery Calcium and Cardiovascular Disease Events. To be presented at American Heart Association meetings 2014; referenced as Circulation 2014; abstract in press. 4). DEVELOPED THE ASTRO-CHARM (Cardiovascular Health and Risk Modification). This score is the only system available which quantifies global cardiovascular risk in a relatively young population like the astronaut corps, using routine clinical information plus a CAC score. The final results from Astro-CHARM, including the functional calculator were delivered to NASA and the Human Research Program (HRP) in February 2014, and is actively being used by flight surgeons now. 5). DEMONSTRATED THAT INCREASED FITNESS PROTECTS AGAINST THE DEVELOPMENT OF DIABETES IN PATIENTS ON STATINS. Radford NB...Levine BD et al. Impact of Fitness on Incident Diabetes from Statin Use in Primary Prevention. Submitted Mayo Clinic Proceedings 07/2014.
Bibliography Type:	Description: (Last Updated: 05/20/2025)
Abstracts for Journals and Proceedings	DeFina LF, Leonard D, Willis B, Barlow CE, Radford NB, Khera A, Levine BD. "Cardiorespiratory Fitness, Coronary Artery Calcium and Cardiovascular Disease Events." American Heart Association Scientific Sessions 2014, Chicago, Illinois, November 15-19, 2014. Circulation. 2014 Nov 25;130(Suppl 2):A20477. http://circ.ahajournals.org/content/130/Suppl_2/A20477.abstract ; accessed 9/7/2020. , Nov-2014
Articles in Other Journals or Periodicals	Radford NB, DeFina LF, Barlow CE, Kerr A, Chakravorty R, Khera A, Levine BD. "Impact of Fitness on Incident Diabetes from Statin Use in Primary Prevention." Mayo Clinic Proceedings. In press, as of September 2014. , Sep-2014
Articles in Peer-reviewed Journals	Radford NB, DeFina LF, Barlow CE, Lakoski SG, Leonard D, Paixao AR, Khera A, Levine BD. "Progression of CAC score and risk of incident CVD." JACC Cardiovasc Imaging. 2016 Dec;9(12):1420-9. Epub 2016 Jun 29. http://dx.doi.org/10.1016/j.jcmg.2016.03.010 ; PubMed PMID: 27372023 (NOTE: previously reported in August 2014 as "submitted" and later in June 2016 as Epub) , Dec-2016

Articles in Peer-reviewed Journals	Radford NB, DeFina LF, Barlow CE, Kerr A, Chakravorty R, Khera A, Levine BD. "Effect of fitness on incident diabetes from statin use in primary prevention." Atherosclerosis. 2015 Mar;239(1):43-9. Epub 2014 Dec 23. http://dx.doi.org/10.1016/j.atherosclerosis.2014.12.051 ; PubMed PMID: 25568952 , Mar-2015
Articles in Peer-reviewed Journals	Radford NB, DeFina LF, Leonard D, Barlow CE, Willis BL, Gibbons LW, Gilchrist SC, Khera A, Levine BD. "Cardiorespiratory fitness, coronary artery calcium and cardiovascular disease events in a cohort of generally healthy, middle aged men: Results from the Cooper Center Longitudinal Study." Circulation. 2018 May 1;137(18):1888-95. Epub 2018 Jan 17. https://doi.org/10.1161/CIRCULATIONAHA.117.032708 ; PubMed PMID: 29343464 , May-2018
Articles in Peer-reviewed Journals	DeFina LF, Radford NB, Barlow CE, Willis BL, Leonard D, Haskell WL, Farrell SW, Pavlovic A, Abel K, Berry JD, Khera A, Levine BD. "Association of all-cause and cardiovascular mortality with high levels of physical activity and concurrent coronary artery calcification." JAMA Cardiol. 2019 Feb;4(2):174-81. https://doi.org/10.1001/jamacardio.2018.4628 ; PubMed PMID: 30698608 , Feb-2019
Articles in Peer-reviewed Journals	Hansen AB, Lawley JS, Rickards CA, Howden EJ, Sarma S, Cornwell WK 3rd, Amin SB, Mugele H, Marume K, Possnig C, Whitworth LA, Williams MA, Levine BD. "Reducing intracranial pressure by reducing central venous pressure: Assessment of potential countermeasures to spaceflight associated neuro-ocular syndrome." J Appl Physiol (1985). 2021 Feb 1;130(2):283-9. https://doi.org/10.1152/japplphysiol.00786.2020 ; PMID: 33270516 , Feb-2021
Articles in Peer-reviewed Journals	Paixao ARM, Chakravorty R, Khera A, LeonardD, DeFina LF, Barlow CE, Radford NB, Levine BD. "Disagreement between different definitions of coronary artery calcium progression." Journal of the American College of Cardiology: Cardiovascular Imaging. 2015 Jun;8(6):743-4. Epub 2014 Nov 12. http://dx.doi.org/10.1016/j.jcmg.2014.07.019 ; PubMed PMID: 25457766 , Jun-2015
Awards	Levine BD. "Dill Lecture at American College of Sports Medicine Meetings, May 2014." May-2014
Awards	Levine B. "Association of American Physicians, April 2014." Apr-2014
Awards	Levine B. "Best Doctors, Dallas, January 2014." Jan-2014
Awards	Levine B. "Fellow, American Physiological Society, Cardiovascular Section, December 2013." Dec-2013
Awards	Levine B. "Hermann Rahn Memorial Lecture, University of Buffalo, June 2013." Jun-2013