Fiscal Year:	FY 2013	**Task Last Updated:**	FY 02/19/2013
PI Name:	Sa, Rui Carlos Ph.D.		
Project Title:	Variability in Flow Distribution within the Lung and Its Effects on Deposition and Clearance of Inhaled Particles in Normal and Reduced Gravity		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Human Factors and Performance Team		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **SHFH**:Space Human Factors & Habitability (archival in 2017)		
Human Research Program Risks:	(1) **Dust**:Risk of Adverse In-Mission Health and Performance Effects and Long-Term Health Effects Due to Celestial Dust Exposure		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	rcsa@ucsd.edu	**Fax:**	FY 858-534-6046
PI Organization Type:	UNIVERSITY	**Phone:**	858-822-5081
Organization Name:	University of California, San Diego		
PI Address 1:	Department of Medicine		
PI Address 2:	9500 Gilman Drive, MC 0852		
PI Web Page:			
City:	La Jolla	**State:**	CA
Zip Code:	92093-0852	**Congressional District:**	53
Comments:	Last name ometimes seen as “Pereira de Sa” "		
Project Type:	Ground	**Solicitation / Funding Source:**	2009 NSBRI-RFA-09-01 Postdoctoral Fellowships
Start Date:	11/01/2009	**End Date:**	10/31/2012
No. of Post Docs:	1	**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:	0	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Prisk, G. Kim (MENTOR/University of California, San Diego)		
Grant/Contract No.:	NCC 9-58-PF02103		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	POSTDOCTORAL FELLOWSHIP 1) Original project aims/objectives: Our goal is to provide a better understanding of how variability in convective flow patterns in the lung affects aerosol deposition, and thus subsequent clearance between individuals. Such an understanding will allow better characterization of the normal variability in deposition and clearance rates both in 1G, and in low-gravity such as on the lunar surface. Three key factors define the toxicological risk to the lung of exposure to airborne lunar dust which is believed to be highly reactive: 1) the degree of deposition, 2) the toxicological properties of the material itself, and 3) the residence time within the lung of the particles once they have been deposited. The distribution of ventilation within the lung determines deposition. Studies by us using computational fluid dynamics (CFD) in realistic central airway trees show that ventilation varies widely at the lobar level. However, typical boundary conditions for deposition simulations assume that lung expansion is uniform, which we know to be incorrect. We have developed a Magnetic Resonance Imaging (MRI) technique that allows the quantification of regional specific ventilation in the human lung, providing realistic boundary conditions. In this proposal we will: a) map the spatial pattern of specific ventilation; b) map deposition in the supine position at 1G; and combine these with data on the spatial pattern of deposition of inhaled particles collected in low-gravity as part of our parallel NSBRI studies; c) The measured pattern of aerosol deposition will be compared with the CFD predictions, using uniform and the more realistic boundary conditions. By comparing across a number of subjects, the mechanisms underlying the observed variability in deposition and regional ventilation can be elucidated. By comparing 1G and low-gravity deposition, the magnitude of the gravitational effect can be assessed. 2) Key findings of the project: We have successfully developed, applied, and validated a Magnetic Resonance Imaging technique for quantifying specific ventilation in the human lung- Specific Ventilation Imaging - completing aim a). We are able to routinely map the spatial pattern of specific ventilation in humans, with a technique that requires no ionizing radiation, and thus allows for repeated, horizontal studies. We have used this technique to quantify the vertical, gravitational induced, gradient in specific ventilation that is present in the human lung on Earth. Our findings are in accordance with previous radiation based techniques for quantifying specific ventilation. An article describing the technique was published during the second year of the project (Journal of Applied Physiology). A patent, protecting the intellectual property of this and two other MRI methods developed at our lab is being pursued. We have mapped particle deposition for 5µm particles, when inhalation occurs in the supine position on Earth (10 subjects) and in low-gravity (5 subjects). A paper describing the low gravity results has been recently submitted to the Journal of Applied Physiology. The completion of aim c has been hampered by the missing 1µm particles deposition maps. Despite our efforts, a second parabolic flight campaign opportunity to measure 1µm particle deposition never materialized. We expect the analysis of 5µm data to lead to a publication, to be submitted in the first half of 2013. 3) Impact of key findings on original project: The successful completion of aim a) was essential to completion of the project. A paper describing deposition of coarse particles (5µm) in low-gravity and subsequent clearance has been recently submitted for publication. The analysis of the spatial distribution of ventilation and deposition in the supine posture is ongoing. The absence of 1µm particle deposition data complicates the analysis. 4) Future plans: A paper linking regional ventilation and particle deposition for 5µm particles is in preparation.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The overall goal of this project is to better understand how variability in convective flow patterns in the lung affects aerosol deposition and subsequent clearance between individuals. Such knowledge will help better characterize the normal variability, both on the ground and in low gravity (the lunar surface), and thus better characterize the risks of exposure to potentially toxic, aggressive dust. This improved risk assessment is important both for future lunar exploration (lunar dust is aggressive, highly reactive, and in low gravity, dust particles are likely to deposit further down in the lung, increasing residence time), as well as in Earth's gravity, where many people are exposed to airborne dust. From a different and more long-term perspective, a better understanding of the individual variability in deposition might also help optimize aerosols drug delivery, aerosols that will more accurately target specific portions of the lung. In the framework of this project, we have developed a novel MRI technique for the quantification of specific ventilation in the human lung. The technique requires a standard proton MRI machine with a 1.5 Tesla field, machines that are widely available in clinical setting. The technique does not require the use of radiation, and is therefore suitable for repeated measures. At a first stage, we are using the technique as a novel research tool, but its repercussions can be extended to the clinical setting. The recent effort to validate this MRI technique by comparing the distribution of specific ventilation obtained using our MRI technique and the identical distribution obtained using Multiple Breath Washouts (a technique that provides no spatial information) will certainly leverage its applicability. The fact that MRI does not involve radiation opens a novel diagnostic window, for it can be applied repetitively. This can be of particular importance in patient populations suffering from chronic respiratory diseases, such as asthma, cystic fibrosis, and chronic obstructive pulmonary disease (COPD). Patients with chronic respiratory disease could benefit from a non invasive, zero radiation dose assessment of their lung function, that can thus be repeated time and again, allowing for a more regular follow up than the existing techniques. A patent protecting this MRI technique as well as two additional MR-sequences developed by our group is currently being pursued (provisional patent application: New method for imaging ventilation and perfusion in the lung using MRI - SD2010-320, provisional application number 61420554, PCT/US2011/063854 - R.B. Buxton, G.K. Prisk, S.R. Hopkins, R.C. Pereira de Sa, R.J. Theilmann, M.V. Cronin).
	The goal of this project is to provide a better understanding of how variability in convective flow patterns in the lung affects aerosol deposition, and thus subsequent clearance between individuals. In order to achieve the goal, three specific aims need to be addressed: a) Map the spatial pattern of specific ventilation; b) Map deposition in the supine position at 1G; combine these with data on the spatial pattern of deposition of inhaled particles collected in low-gravity (µG) as part of our existing NSBRI studies; c) The measured pattern of aerosol deposition will be compared with the Computational Fluid Dynamics (CFD) predictions, using uniform and the realistic boundary conditions. By comparing across a number of subjects, and different particles sizes, the mechanisms underlying the variability in deposition and regional ventilation can be elucidated. By comparing the data collected in 1G with data from µG, the magnitude of the gravitational effect can be assessed. In the first two years of the project we have successfully developed a Magnetic Resonance Imaging technique for quantifying specific ventilation in the human lung - Specific Ventilation Imaging (SVI), completing point a) of the initial project aims. We have used SVI to quantify the vertical, gravitational induced, gradient in specific ventilation that is present in the human lung on Earth. An article describing the technique was published in the Journal of Applied Physiology, and a patent application is pursued.

Task Progress:	Aim 2 was completed by quantifying specific ventilation in 10 subjects, thus determining realistic boundary conditions required for addressing aim c) in an individualized subject by subject basis. We have mapped the supine deposition of 5µm particles (1G supine) in the same 10 subjects. A subset of these (N=5) participated in a NASA parabolic flight campaign, where the first maps of particle deposition in low gravity were obtained, thus completing data acquisition for 5µm particles. A second parabolic flight opportunity to acquire the µG deposition maps for 1µm particles did not materialize, despite our continuous efforts. In this project year we have completed the optimization of the analysis software and applied it to the µG and supine data. A paper describing the µG results for 5µm particle deposition and clearance was recently submitted (Journal of Applied Physiology). We have completed a validation and reliability analysis of the MR-imaging technique, by comparing heterogeneity estimated using SVI and the spatial-insensitive Multiple Breath Nitrogen Washout technique. A paper describing the validation of the SVI method will be submitted to the Journal of Applied Physiology. The analysis linking ventilation and deposition (aim c) is hampered by the missing 1µm particle deposition data; additional data analysis is ongoing. We expect a publication linking ventilation and peripheral deposition for 5µm particles to be submitted in the next ~3-4 months.
Bibliography Type:	Description: (Last Updated: 01/11/2021)
Abstracts for Journals and Proceedings	Arai TJ, Sa RC, Tedjasaputra V, Prisk GK, Hopkins SR. "Ventilation-Perfusion Heterogeneity in the Lung: insights from the underlying distributions of ventilation and perfusion." American Thoracic Society 2012 International Conference, San Francisco, California, May 18-23, 2012. Am J Respir Crit Care Med. 2012 May;185(1, Meeting Abstracts):A2684. , May-2012
Abstracts for Journals and Proceedings	Darquenne C, Borja MG, Oakes JM, Breen EB, Olfert IM, Sa RC, Scadeng M, Prisk GK. "Microgravity reduces the central-to-peripheral deposition ratio of inhaled aerosols: implications for particle clearance rates." 2012 NASA Human Research Program Investigators' Workshop, Houston, TX, February 14-16, 2012. 2012 NASA Human Research Program Investigators' Workshop, Houston, TX, February 14-16, 2012. , Feb-2012
Abstracts for Journals and Proceedings	Darquenne C, Zeman KL, Sa RC, Cooper TK, Fine JM, Bennett WD, Prisk GK. "Effect of gravity on the regional distribution of particles deposited in the human lung." 19th World Congress of the International Society for Aerosols in Medicine, Chapel Hill, NC, April 6-10, 2013. 19th World Congress of the International Society for Aerosols in Medicine, Chapel Hill, NC, April 6-10, 2013. Abstract book, P-007. , Apr-2013
Abstracts for Journals and Proceedings	Darquenne C, Zeman KL, Sa RC, Cooper TK, Fine JM, Bennett WD, Prisk GK. "Removal of sedimentation decreases deposition of coarse particles in the lung periphery, reducing retention." 2013 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-14, 2013. 2013 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-14, 2013. , Feb-2013
Abstracts for Journals and Proceedings	Darquenne C, Zeman KL, Sa RC, Cooper TK, Fine JM, Bennett WD, Prisk GK. "Effect of Gravity on Retention of Inhaled Particles in the Human Lung." American Thoracic Society 2013 International Conference, Philadelphia, PA, May 17-22, 2013. Am J Respir Crit Care Med supplement. In press, as of February 2013. , Feb-2013
Abstracts for Journals and Proceedings	Henderson AC, Sa RC, Cook FR, Arai TJ, Wagner HE, Theilmann RJ, Darquenne C, Ramsdell JW, Friedman PJ, Wagner PD. "Identification of the gas exchange defects present in Chronic Obstructive Pulmonary Disease patients noninvasively using Magnetic Resonance Imaging." American Thoracic Society 2012 International Conference, San Francisco, California, May 18-23, 2012. Am J Respir Crit Care Med. 2012 May;185(1, Meeting Abstracts):A2039. , May-2012
Abstracts for Journals and Proceedings	Henderson AC, Sa RC, Theilmann TJ, Buxton RB, Prisk GK, Hopkins SR. "The gravitational distribution of ventilation-perfusion ratio in the normal human lung is more uniform in prone than supine posture." American Thoracic Society 2013 International Conference, Philadelphia, PA, May 17-22, 2013. Am J Respir Crit Care Med supplement. In press, as of February 2013. , Feb-2013
Abstracts for Journals and Proceedings	Prisk GK, Darquenne C, Sa RC. "Human life sciences studies in sub-orbital flight: insights from parabolic flight." Next-Generation Suborbital Researchers Conference 2012, Palo Alto, California, February 27-29, 2012. Next-Generation Suborbital Researchers Conference 2012, Palo Alto, California, February 27-29, 2012. Abstract Book. http://www.boulder.swri.edu/NSRC2012/Site1//PDF/Prisk-PSRP.pdf , Feb-2012
Abstracts for Journals and Proceedings	Sa RC, Hopkins SR, Prisk GK, Darquenne C. "Validation of the distribution of specific ventilation obtained by proton MR imaging." American Thoracic Society 2012 International Conference, San Francisco, California, May 18-23, 2012. Am J Respir Crit Care Med. 2012 May;185(1, Meeting Abstracts):A2035. , May-2012
Abstracts for Journals and Proceedings	Sa RC, Prisk GK, Darquenne C. "Mapping the regional distribution of ventilation within the lung: validation of specific ventilation imaging against multiple breath nitrogen washout." 2012 NASA Human Research Program Investigators' Workshop, Houston, TX, February 14-16, 2012. 2012 NASA Human Research Program Investigators' Workshop, Houston, TX, February 14-16, 2012. , Feb-2012
Articles in Peer-reviewed Journals	Asadi AK, Cronin MV, Sa RC, Theilmann RJ, Holverda S, Hopkins SR, Buxton RB, Prisk GK. "Spatial-temporal dynamics of pulmonary blood flow in the healthy human lung in response to altered FI(O2)." J Appl Physiol. 2013 Jan 1;114(1):107-18. Epub 2012 Oct 25. PMID: 23104691 , Jan-2013
Articles in Peer-reviewed Journals	Henderson AC, Sa RC, Barash IA, Holverda S, Buxton RB, Hopkins SR, Prisk GK. "Rapid intravenous infusion of 20 mL/kg saline alters the distribution of perfusion in healthy supine humans." Respiratory Physiology and Neurobiology. 2012 Mar 15;180(2-3):331-41. Epub 2011 Dec 31. PubMed PMID: 22227320 , Mar-2012
Articles in Peer-reviewed Journals	Prisk GK, Sa RC, Darquenne C. "Cardiogenic mixing increases aerosol deposition in the human lung in the absence of gravity." Acta Astronautica. 2013 Nov;92(1):15-20. (originally reported in Feb. 2013 as "In Press, Corrected Proof, Available online 12 June 2012") http://dx.doi.org/10.1016/j.actaastro.2012.05.022 , Nov-2013

Articles in Peer-reviewed Journals	Tedjasaputra V, Sa RC, Arai TJ, Holverda S,Theilmann RJ, Chen WT, Wagner PD, Davis CK, Prisk CK, Hopkins SR. "The heterogeneity of regional specific ventilation is unchanged following heavy exercise in athletes." J Appl Physiol (1985). 2013 Jul 1;115(1):126-35. http://dx.doi.org/10.1152/japplphysiol.00778.2012 ; PubMed PMID: 23640585; PubMed Central PMCID: PMC3727009 , Jul-2013
Articles in Peer-reviewed Journals	Sá RC, Henderson AC, Simonson TS, Arai TJ, Wagner H, Theilmann RJ, Wagner PD, Prisk GK, Hopkins SR. "Measurement of the distribution of ventilation-perfusion ratios in the human lung with proton MRI: Comparison with the multiple inert gas elimination technique." J Appl Physiol (1985). 2017 Jul;123(1):136-46. http://dx.doi.org/10.1152/japplphysiol.00804.2016 ; PubMed PMID: 28280105 , Jul-2017
Articles in Peer-reviewed Journals	Hall ET, Sá RC, Holverda S, Arai TJ, Dubowitz DJ, Theilmann RJ, Prisk GK, Hopkins SR. "The effect of supine exercise on the distribution of regional pulmonary blood flow measured using proton MRI." J Appl Physiol (1985). 2014 Feb 15;116(4):451-61. Epub 2013 Dec 19. https://doi.org/10.1152/japplphysiol.00659.2013 ; PubMed PMID: 24356515; PubMed Central PMCID: PMC3921353 , Feb-2014
Articles in Peer-reviewed Journals	Sá RC, Asadi AK, Theilmann RJ, Hopkins SR, Prisk GK, Darquenne C. "Validating the distribution of specific ventilation in healthy humans measured using proton MR imaging." J Appl Physiol (1985). 2014 Apr 15;116(8):1048-56. Epub 2014 Feb 6. https://doi.org/10.1152/japplphysiol.00982.2013 ; PubMed PMID: 24505099; PubMed Central PMCID: PMC4035784 , Apr-2014
Articles in Peer-reviewed Journals	Asadi AK, Sá RC, Kim NH, Theilmann RJ, Hopkins SR, Buxton RB, Prisk GK. "Inhaled nitric oxide alters the distribution of blood flow in the healthy human lung, suggesting active hypoxic pulmonary vasoconstriction in normoxia." J Appl Physiol (1985). 2015 Feb 1;118(3):331-43. Epub 2014 Nov 26. https://doi.org/10.1152/japplphysiol.01354.2013 ; PubMed PMID: 25429099; PubMed Central PMCID: PMC4312852 , Feb-2015
Articles in Peer-reviewed Journals	Sá RC, Zeman KL, Bennett WD, Prisk GK, Darquenne C. "Effect of posture on regional deposition of coarse particles in the healthy human lung." J Aerosol Med Pulm Drug Deliv. 2015 Dec;28(6):423-31. Epub 2015 Mar 31. https://doi.org/10.1089/jamp.2014.1189 ; PMID: 25826480 , Dec-2015
Articles in Peer-reviewed Journals	Geier ET, Theilmann RJ, Darquenne C, Prisk GK, Sá RC. "Quantitative mapping of specific ventilation in the human lung using proton magnetic resonance imaging and oxygen as a contrast agent." J Vis Exp. 2019 Jun 5(148):e59579. https://doi.org/10.3791/59579 ; PMID: 31233033; PMCID: PMC6743506 , Jun-2019