



Application

01962 - The GEM Challenge 2015

02115 - Patient-Specific Risk Assessment of Intraventricular Thrombus Formation Based on Blood Stasis Quantification

Collaborative awards with IEM

Status: Submitted

Submitted Date: 12/05/2014 8:43 AM

Primary Contact

First Name*

Andrew

Mitchell

Kahn

First Name

Middle Name

Last Name

Degree

MD/PhD

Faculty Rank*

Associate Professor

Faculty Rank - Other

Email:

akahn@ucsd.edu

eRA Commons Name

AMKAHN

Area of Specialty

Cardiology

(If you are not currently a CTRI member, please fill out a membership application by [clicking here.](#))

Are you a CTRI member?

No

Address:

UCSD Sulpizio Cardiovascular Center

9444 Medical Center Dr., # 7411

*

La Jolla

92037-7411

California

City

Postal Code/Zip

State/Province

Fax:

Phone:*

858-657-5378

Phone

Ext.

Organization Information

Name:

UCSD

Instructions for Individuals registering for WebGrants access: The organization name should be your affiliated organization, i.e. UCSD, SDSU, etc.

Organization Type:

University

Phone:

858-534-1222

Ext.

Fax:

Information

PI Name (Last Name, First Name)

Kahn, Andrew

CO-PI Name (Last name, First name)

Project Title

Patient-Specific Risk Assessment of Intraventricular
Thrombus Formation Based on Blood Stasis
Quantification

PI Contact information - include email and campus phone
number

UCSD Sulpizio Cardiovascular Center
9444 Medical Center Dr., # 7411
La Jolla, CA 92037-7411
email: akahn@ucsd.edu
phone: (858) 657-5378
fax: (858) 657-5028

PI Biosketch

File Name

Description

File Size

Kahn-biosketch-GEM-2014.pdf

Andrew Kahn Biosketch

Narrative

File Name

Description

File Size

GEM_Kahn.pdf

The GEM Challenge 2015 Phase I
Proposal

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Andrew M. Kahn, M.D., Ph.D.	POSITION TITLE		
eRA COMMONS USER NAME AMKAHN	Associate Professor of Medicine		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Weslyan University	B.A.	1981-1985	Physics
Harvard University	M.A., Ph.D.	1985-1991	Physics
University of California San Diego	M.D.	1996-2000	Medicine
University of California San Diego	Residency	2000-2003	Internal Medicine
University of California San Diego	Fellowship	2003-2006	Cardiology

Personal Statement

As a cardiologist specializing in cardiac imaging with a strong physics background Dr. Kahn is uniquely qualified to help lead the proposed research. His research and clinical interests are in the field of cardiovascular imaging, including echocardiography, magnetic resonance imaging (MRI), and computed tomography. He has extensive experience interpreting clinical and research echocardiograms at UCSD. In addition to his medical training, Dr. Kahn has a doctoral degree in physics from Harvard University and has specific training in imaging and analyzing complex patterns. His background that combines both technical and clinical training and experience will allow him to understand the technical issues and challenges facing the engineers, while also providing clinical input and imaging expertise. He has an established track record of successful collaboration with engineering colleagues at UCSD, having worked with Dr. Marsden and Dr. del Alamos on NIH-supported research.

A. Positions and Honors

Positions

1991-1995	Postdoctoral Fellow, Physics Department, University of California, Santa Barbara.
1995-1996	Lecturer, Physics Department, University of California, San Diego.
2006-2011	Assistant Professor of Medicine, University of California, San Diego
2011-present	Associate Professor of Medicine, University of California, San Diego

Honors

1984	Phi Beta Kappa Honor Society
1985	Bertman Research Prize, Department of Physics, Wesleyan University.
1985	Sigma Xi Scientific Honor Society.
1985	High Honors, Wesleyan University.
2006	Schulman Research Award, UCSD Cardiology Division.
2006-2007	Biosite Cardiovascular Fellow, UCSD Cardiovascular Center.

B. Selected peer-reviewed publications (selected from 33 peer-reviewed publications)

1. Ethan Kung, Kahn AM, Burns JC, Marsden AL, In Vitro Validation of Patient-Specific Hemodynamic Simulations in Coronary Aneurysms Caused by Kawasaki Disease, Cardiovascular Engineering and Technology, 2014 June; 5(2): 189-201.
-

2. Dibyendu Sengupta, Kahn AM, Shirinsky O, Burns JC, Marsden AL, Thrombotic risk stratification using computational modeling in patients with coronary artery aneurysms following Kawasaki disease, *Biomech Model Mechanobiol.* 2014 April 11, Epub ahead of print.
3. Jiang Du, Peterson M, Kansal N, Bydder GM, Kahn AM, Mineralization in calcified plaque is like that of cortical bone - Further evidence from ultrashort echo time (UTE) magnetic resonance imaging of carotid plaque calcification and cortical bone, *Medical Physics* 2013; 40: 102301.
4. Sankaran S, Esmaily Moghadam M, Kahn AM, Guccione J, Tseng E, Marsden AL, "Patient-specific multiscale modeling of blood flow for coronary artery bypass graft surgery," *Annals of Biomedical Engineering*, 2012 Oct; 40(10): 2228-42.
5. Daniels LB, Tjajadi MS, Walford HH, Jimenez-Fernandez S, Trofimenko V, Fick Jr DB, Phan HL, Linz PE, Nayak K, Kahn AM, Burns JC, Gordon JB. Prevalence of Kawasaki Disease in Young Adults with Suspected Myocardial Ischemia. *Circulation*, 2012 May 22; 125(20): 2447-53.
6. Sengupta, D, Kahn AM, Burns JC, Sankaran S, Shadden S and Marsden AL, "Image-based modeling of hemodynamics and coronary artery aneurysms caused by Kawasaki disease," *Biomechanics and Modeling in Mechanobiology*, 2012; 11: 915-932.
7. Kahn AM, Budoff MJ, Daniels LB, Jimenez-Fernandez S, Cox AS, Gordon JB, Burns JC. Calcium Scoring in Patients with a history of Kawasaki Disease. *J Am Coll Cardiol Img*, 2012; 5: 264-272.
8. Du J, Corbeil J, Znamirowski R, Angle N, Peterson M, Bydder GM, Kahn AM. Direct Imaging and Quantification of Carotid Plaque Calcification Using Ultrashort TE (UTE) Pulse Sequences. *Magnetic Resonance in Medicine*, 2011 Apr; 65(4):1013-20.
9. Wessman DE, Blanchard DG, Kahn AM. Elongated Eustachian Valve Dividing the Right Atrium. *Echocardiography*, 2011 Mar; 28(3): E53-5.
10. Olson N, Brown JP, Kahn AM, Auger WR, Madani M, Waltman TJ, Blanchard DG, Left Ventricular Strain and Strain Rate by 2D Speckle Tracking in Chronic Thromboembolic Pulmonary Hypertension before and after Pulmonary Thromboendarterectomy, *Cardiovasc Ultrasound*. 2010 Sep 27; 8: 43.
11. Bin Thani K, Khadivi B, Kahn AM, Cotter B, Blanchard DG. Ebstein's Anomaly with Left Ventricular Non-compaction and Bicuspid Aortic Valve. *J Am Coll Cardiol*. 2010 Sep 7; 56(11): 899.
12. Gordon JB, Kahn AM, Burns JC. When children with Kawasaki disease grow up: Myocardial and vascular complications in adulthood. *JACC* 2009; 54: 1911-1920.
13. Kahn AM, DeMaria AN. The Role of Cardiac Ultrasound in Stem Cell Therapy. *Journal of Cardiovascular Translational Research*. 2009 Mar; 2(1): 2-8.
14. Kahn AM, Weissman JS, Dalton ND, Blanchard DG Echocardiography of Unusual Cardiac Tumors: A Case Series. *Cardiac Ultrasound Today*, 2007; 13(2): 29-48.
15. Kahn AM, Krummen DE, Feld GK, Narayan SM. Localizing Circuits of Atrial Macro-Reentry Using ECG Planes of Coherent Atrial Activation. *Heart Rhythm Journal*, 2007 Apr; 4(4): 445-51.

C. Research Support

Ongoing Research Support

NIH NHLBI R01 grant 1R01HL123689-01 (Co-PI) 7/1/14-6/30/19

"Multiscale modeling for vein graft failure risk stratification in CABG patients"

Patient specific modeling of coronary artery bypass patients for assessment of risk of vein graft failure. The project will develop multiscale modeling and fluid structure interaction methods, will validate simulations against clinical data, and will virtually reverse graft stenosis to identify precursors of vein graft failure in post-CABG patients.

NIH NHLBI R01 grant R01HL098237 (Site-PI) 3/22/11-04/30/15

"Prospective Multicenter Imaging Study for Evaluation of Chest Pain"

A multicenter prospective randomized clinical trial to determine whether an initial non-invasive anatomic imaging strategy with coronary CT angiography will improve clinical outcomes in subjects with symptoms concerning for coronary artery disease relative to an initial functional testing strategy.

Recently Completed Research Support (within last 3 years)

R21HL108268-1 (co-PI)

5/15/11 – 3/31/14

“Characterization and synchronization of intraventricular filling vortices in the clinical setting”

This project used Doppler echocardiography to measure blood flow vortices in the left ventricle and evaluated the changes that occur in patients with cardiomyopathies.

Gordon Macklin Foundation (Co-I)

9/1/09 – 8/31/13

“The San Diego Adult KD Collaborative”

This project involved a cross-sectional analysis of 300 young adults with a history of KD in childhood who will undergo cardiovascular testing and imaging to determine the spectrum of abnormalities following KD.

Sotera Wireless Inc. (PI)

02/27/12 – 02/26/13

“Validation of a New Method for Measuring Stroke Volume: Cardiac Magnetic Resonance Imaging (cMRI) vs. Transbrachial Cardio-electric Velocimetry (TCEV)”

This project used cMRI to validate a novel non-invasive measure of cardiac output derived from electrical interrogation of the brachial artery.

R21 HL102596 (Co-I)

4/15/10 – 3/31/12

“Patient-specific simulations for thrombotic risk assessment in Kawasaki disease”

The goal of this project was to use cardiac imaging studies to create computer models of flow in the coronary artery aneurysms of patients following Kawasaki disease to assess shear stress and turbulence.

Challenge: Patient-Specific Risk Assessment of Intraventricular Thrombus Formation Based on Blood Stasis Quantification (PI Andrew Kahn)

Aim: The goal of this challenge is to test the hypothesis that personalized assessment of blood stasis in the left ventricle can predict the risk of intraventricular thrombus formation in patients with left-ventricular (LV) systolic dysfunction. In the US alone, it is estimated that LV thromboembolism is responsible for 70,000 cases of stroke in these patients every year (1,2). This challenge has translational importance because current management of embolic risk in patients with LV systolic dysfunction is not based on patient-specific data, and embolic events occur with increased frequency in these patients.

To achieve our goal, we will perform a case-control study of 15 subjects with LV systolic dysfunction and a history of LV thrombi that have resolved (with absence of thrombus at the time of the study), and a matched comparison group of 30 subjects with LV systolic dysfunction without a history of thrombi. All subjects will undergo full echocardiograms with additional images taken specifically for this protocol. We postulate that the patients with a history of thrombi that have resolved will have altered LV flow patterns leading to higher LV blood stasis compared to the patients without history of thrombi. Patients with existing thrombi will not be studied because the presence of an intramural thrombus disturbs LV flow patterns (3).

This study poses the following engineering challenge: to non-invasively quantify blood flow stasis in a patient-specific basis using non-invasive medical imaging. We have identified a group in the Jacobs School of Engineering (JSOE) with the necessary expertise to address this challenge: Prof. del Alamo's lab at the Mechanical and Aerospace Engineering Dept.

Significance: Intraventricular thrombosis is an important clinical problem that contributes to the incidence of stroke, peripheral arterial thrombosis and other embolic events (4). Additionally, some thrombi have been reported to grow inside the ventricle until they occupy a significant fraction of the chamber, leading to severe cardiac dysfunction (5). Several studies have shown that there is a significantly higher incidence of thrombosis and thromboembolic syndromes in patients with LV systolic dysfunction (2,6). Specifically, the incidence of stroke has been reported to be 5 times higher in these patients than in controls (7). However, the routine treatment with anticoagulation of LV systolic dysfunction patients is not supported by existing data. While anticoagulation treatment does reduce embolic events, it also increases the incidence of major bleeding and it does not improve 5-year patient survival rate (8). Consequently, the majority of patients are not treated, despite the knowledge that they are at increased risk of forming thrombi and having embolic events (9). Thus, there is a major clinical need for patient-specific risk assessment of intraventricular thrombus formation to identify those patients who are at highest risk and would benefit most from treatment.

Rationale: Thrombosis is precipitated by a combination of stasis, endothelial injury and hypercoagulability commonly known as "Virchow's triad" (9). Stasis of blood in regions of myocardial dysfunction can lead to thrombus formation by triggering activation of the coagulation system and leading to fibrin formation. Thus, understanding the role of blood stasis and blood flow in the genesis and evolution of intraventricular thrombi would significantly improve the identification and clinical management of patients at risk, for whom there is currently no evidence-based therapy. In recent years there has been a substantial increase in the sophistication and clinical applicability of computational tools for the patient-specific quantification of intraventricular blood flow (10). These tools involve clinical image acquisition, anatomic model construction and flow simulation to produce performance measures that are surrogates for known predictors of patient outcomes.

The rationale for studying patients with resolved thrombi is that the blood flow patterns associated with stasis that trigger thrombus formation are recovered once the thrombus disappears. This approach will allow us to recruit the required number of patients within the time scope of this project. The rationale for the proposed engineering challenge is that determining blood stasis in each patient by computational analysis of the patient's echocardiographic images will provide a patient-specific surrogate measure of thrombogenic risk. Successful completion of this challenge will address an important need for evidence-based clinical decision-making.

Innovation: Intraventricular blood stasis is recognized as one of the three key elements in the pathophysiology of thrombogenesis in patients with LV systolic dysfunction. However, blood stasis and its correlation with thrombus formation have not yet been quantified in the clinical setting, let alone on a patient-specific basis. It is generally agreed that intraventricular flow critically depends on several physiological factors such as heart rate, valve morphology and chamber geometry (11-13). Consequently, recent pilot studies with small numbers of subjects suggest that intraventricular blood stasis and transport can be significantly altered in cardiomyopathies (14,15). However, there is no information about how these changes correlate with patient outcomes. Novel indices of thrombogenesis based on blood stasis may permit the identification of patients at highest risk who are most likely to benefit from anticoagulation, and to subsequently determine the duration of such treatment through serial assessments. The proposed work may contribute to the development of new clinical practice guidelines for managing patients with decreased LV function, thus enabling a major translational innovation that may lead to decreased morbidity and mortality.

Feasibility: From a clinical perspective, the proposed study is feasible given the large number of patients with LV systolic dysfunction and patients with history of LV thrombi treated at UCSD Medical Center. The proposed case-control study design will permit the acquisition of preliminary data to demonstrate the utility of this technique. We envision subsequently using these pilot data to apply for extramural funding to carry out a larger prospective study.

From a technological standpoint, this project will leverage a novel echocardiographic modality developed by del Alamo's group at the UCSD JSOE: color-Doppler velocimetry. This modality provides two-dimensional bi-directional time-resolved flow maps in the LV (16,17). Compared with other existing noninvasive modalities such as phase contrast MRI, color-Doppler velocimetry is fast, clinically feasible in all patients (unlike MRI, for which many of these patients would have a contraindication due to the presence of implantable cardioverter defibrillators), and requires little training. Patients routinely undergo evaluations with echocardiograms as part of their standard care. Color-Doppler velocimetry only requires a few additional images, extending the duration of the study by approximately 5 minutes (16).

In addition to the necessity of reliably measuring blood flow velocity in the ventricle, a barrier to assessing thrombogenic risk is being able to comprehend how flow arrangement contributes to blood stasis within the LV. This can be achieved by tracking the evolution of blood transport and mixing inside the LV, using the patient-specific flow data obtained by color-Doppler velocimetry. The expected outcome of this multidisciplinary challenge is a quantitative index of blood stasis and mixing that will correlate positively with history of resolved thrombi in the study population.

Investigator Qualifications: Dr. Kahn is well-qualified to perform the proposed research in collaboration with engineering colleagues. In addition to his medical training Dr. Kahn has a doctorate degree in physics and specific expertise and board certification in echocardiography. He also has a track record of successful collaborations doing NIH-supported research with two members of the engineering faculty.

References

1. Dries DL, Rosenberg YD, Wacławski MA, Domanski MJ. Ejection fraction and risk of thromboembolic events in patients with systolic dysfunction and sinus rhythm: evidence for gender differences in the studies of left ventricular dysfunction trials. *Journal of the American College of Cardiology* 1997;29:1074-80.
2. Freudenberger RS, Hellkamp AS, Halperin JL et al. Risk of thromboembolism in heart failure: an analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation* 2007;115:2637-41.
3. Son JW, Park WJ, Choi JH et al. Abnormal left ventricular vortex flow patterns in association with left ventricular apical thrombus formation in patients with anterior myocardial infarction: a quantitative analysis by contrast echocardiography. *Circulation journal : official journal of the Japanese Circulation Society* 2012;76:2640-6.
4. Adams PC, Cohen M, Chesebro JH, Fuster V. Thrombosis and embolism from cardiac chambers and infected valves. *J Am Coll Cardiol* 1986;8:76B-87B.
5. Egolom UO, Stover DG, Anthony R, Wasserman AM, Lenihan D, Damp JB. Intracardiac thrombus: diagnosis, complications and management. *The American journal of the medical sciences* 2013;345:391-5.
6. Delewi R, Zijlstra F, Piek JJ. Left ventricular thrombus formation after acute myocardial infarction. *Heart* 2012;98:1743-9.
7. Hays AG, Sacco RL, Rundek T et al. Left ventricular systolic dysfunction and the risk of ischemic stroke in a multiethnic population. *Stroke; a journal of cerebral circulation* 2006;37:1715-9.
8. Homma S, Thompson JL, Pullicino PM et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. *The New England journal of medicine* 2012;366:1859-69.
9. Freudenberger RS, Schumacker MM, Homma S. What is the appropriate approach to prevention of thromboembolism in heart failure? *Thromb Haemostasis* 2010;103:489-495.
10. Bermejo J, Martinez-Legazpi P, Alamo JCd. The Clinical Assessment of Intracardiac Flows. *Ann Rev Fluid Mech* 2015;47.
11. Bermejo J, Benito Y, Alhama M et al. Intraventricular vortex properties in nonischemic dilated cardiomyopathy. *American journal of physiology Heart and circulatory physiology* 2014;306:H718-29.
12. Kim WY, Walker PG, Pedersen EM et al. Left ventricular blood flow patterns in normal subjects: a quantitative analysis by three-dimensional magnetic resonance velocity mapping. *Journal of the American College of Cardiology* 1995;26:224-38.
13. Shortland AP, Black RA, Jarvis JC et al. Formation and travel of vortices in model ventricles: application to the design of skeletal muscle ventricles. *Journal of biomechanics* 1996;29:503-11.
14. Eriksson J, Bolger AF, Ebberts T, Carlhall CJ. Four-dimensional blood flow-specific markers of LV dysfunction in dilated cardiomyopathy. *European heart journal cardiovascular Imaging* 2013;14:417-24.
15. Hendabadi S, Bermejo J, Benito Y et al. Topology of blood transport in the human left ventricle by novel processing of Doppler echocardiography. *Annals of biomedical engineering* 2013;41:2603-16.
16. Garcia D, Del Alamo JC, Tanne D et al. Two-dimensional intraventricular flow mapping by digital processing conventional color-Doppler echocardiography images. *IEEE transactions on medical imaging* 2010;29:1701-13.
17. P. Martinez-Legazpi, J. Bermejo, Y. Benito et al. Contribution of the diastolic vortex ring to left ventricular filling. *J Amer Coll Card* 2014;64:1711-1721.