Application

01962 - The GEM Challenge 2015

02128 - Computational Analysis of Surface Electrocardiography to Detect and Localize Human Ventricular Fibrillation Rotors

Collaborative awards with IEM

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Primary Contact

First Name*	David First Name	Edward Middle Name	Krummen Last Name
Degree	MD		
Faculty Rank*	Associate Professor Faculty Rank - Other		
Email:	dkrummen@ucsd.edu		
eRA Commons Name	DKRUMMEN		
Area of Specialty	Cardiology		

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*	*San Diego* *City*	*92161* *Postal Code/Zip*	*California* *State/Province*
Fax:	*858-552-7490*		
Phone:*	*858-642-3889* *Phone*	*Ext.*	

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Ext.	
Fax:	

Information

PI Name (Last Name, First Name)	*Krummen, David*
CO-PI Name (Last name, First name)	*Ho, Gordon*
Project Title	*Computational Analysis of Surface Electrocardiography to Detect and Localize Human Ventricular Fibrillation Rotors*
PI Contact information - include email and campus phone number	*dkrummen@ucsd.edu* *858-642-3889*

PI Biosketch

File Name	Description	File Size
2014-12-05 Krummen NIH Biosketch.doc	*Krummen Biosketch*	

Narrative

File Name	Description	File Size
2014-12-05 Grant application- ECG localization of VF rotors DEK V2.docx	*KrummenGrantV2*	

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/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 **David E. Krummen**	POSITION TITLE **Associate Professor of Medicine, UCSD** **Director of Electrophysiology, VA San Diego Healthcare System**
eRA COMMONS USER NAME (credential, e.g., agency login) **DKRUMMEN**	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Notre Dame	B.S.	1995	Aerospace Engineering
The Ohio State University	M.D.	1999	Medicine
The Ohio State University	--	2002	Internal Medicine Residency
University of California San Diego	--	2005	Cardiology Fellowship
University of California San Diego	--	2007	Electrophysiology Fellowship

A. Personal Statement

My goals are to (1) address current shortcomings our understanding of arrhythmia mechanisms and (2) develop new therapies based upon this work to improve patients' lives. I have led several clinical studies incorporating detailed physiologic measurements, computational modeling, and signal processing to achieve such goals, and will apply these skills to the proposed studies. Notably, our laboratory has provided strong evidence for the central role of rotors to the initiation and maintenance of sustained ventricular fibrillation, and we have recently performed the first targeted ablation of VF rotors in animal models and patients. We now plan to test new methods to detect rotors from surface ECG recordings. I am board certified in internal medicine, cardiovascular disease, and clinical cardiac electrophysiology. I have clinical privileges at UCSD and VA San Diego Medical Centers to perform the proposed studies, and significant experience in performing the physiologic measurements and computational modeling outlined in this proposal. I have a talented team to address the study specific aims.

B. Positions and Honors

Positions and Employment

1999-2002 Residency, Internal Medicine, The Ohio State University
2002-2005 Fellowship, Cardiovascular Disease, University of California San Diego
2004-2005 Chief Cardiology Fellow, University of California San Diego
2005-2007 Fellowship, Clinical Cardiac Electrophysiology, University of California San Diego
2007-2011 Assistant Professor of Medicine, University of California San Diego
2011-present Associate Professor of Medicine, University of California San Diego
2014-present Director of Electrophysiology, VA San Diego Healthcare System

Other Experience and Professional Memberships

2002-2009 Member, American College of Cardiology
2009-present Fellow, American College of Cardiology
2002-present Member, American Heart Association
2004-2011 Member, Heart Rhythm Society
2011-present Fellow, Heart Rhythm Society
2008-present Code Blue Committee, VA San Diego Healthcare System
2014-present NASA Standing Review Panel, Human Health Countermeasures for Long-Duration Spaceflight

Honors and Awards

2001 Alpha Omega Alpha Medical Honor Society

2002 Ohio State University Housestaff Teaching Award
2006 Featured Poster Presentation, Heart Rhythm Society Scientific Sessions
2006 Schulman UCSD Cardiology Reasearch Award
2007 Schulman UCSD Cardiology Reasearch Award
2008 American College of Cardiology Young Investigator Award Finalist
2010 UCSD Schulman Research Award
2010 Nominated for the UCSD Kaiser Excellence in Teaching Award
2011 American Heart Association Levine Young Investigator Finalist
2013 Nominated for the UCSD Kaiser Excellence in Teaching Award

C. 20 Most Relevant Peer-reviewed Publications (from >40)

1. **Krummen DE**, Feld GK, Narayan SM. Diagnostic accuracy of irregularly irregular rr intervals in separating atrial fibrillation from atrial flutter. Am J Cardiol. 2006;98:209-214.
2. **Krummen DE**, Peng KA, Bullinga JR, Narayan SM. Centrifugal gradients of rate and organization in human atrial fibrillation. Pacing Clin Electrophysiol. 2009;32:1366-1378.
3. **Krummen DE**, Patel M, Nguyen H, Ho G, Kazi DS, Clopton P, Holland MC, Greenberg SL, Feld GK, Faddis MN, Narayan SM. Accurate ecg diagnosis of atrial tachyarrhythmias using quantitative analysis: A prospective diagnostic and cost-effectiveness study. Journal of cardiovascular electrophysiology. 2010;21:1251-1259.
4. Aguado-Sierra J, Krishnamurthy A, Villongco C, Chuang J, Howard E, Gonzales MJ, Omens J, **Krummen DE**, Narayan S, Kerckhoffs RC, McCulloch AD. Patient-specific modeling of dyssynchronous heart failure: A case study. Progress in biophysics and molecular biology. 2011;107:147-155.
5. **Krummen DE**, Bayer JD, Ho J, Ho G, Smetak MR, Clopton P, Trayanova NA, Narayan SM. Mechanisms of human atrial fibrillation initiation: Clinical and computational studies of repolarization restitution and activation latency. Circulation. Arrhythmia and electrophysiology. 2012;5:1149-1159.
6. Lalani GG, Schricker A, Gibson M, Rostamian A, **Krummen DE**, Narayan SM. Atrial conduction slows immediately before the onset of human atrial fibrillation: A bi-atrial contact mapping study of transitions to atrial fibrillation. Journal of the American College of Cardiology. 2012;59:595-606.
7. Narayan SM, **Krummen DE**, Enyeart MW, Rappel WJ. Computational mapping identifies localized mechanisms for ablation of atrial fibrillation. PLoS One. 2012;7:e46034.
8. Narayan SM, **Krummen DE**, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: Confirm (conventional ablation for atrial fibrillation with or without focal impulse and rotor modulation) trial. Journal of the American College of Cardiology. 2012;60:628-636.
9. Hayase J, Patel J, Narayan SM, **Krummen DE**. Percutaneous stellate ganglion block suppressing vt and vf in a patient refractory to vt ablation. Journal of cardiovascular electrophysiology. 2013;24:926-928.
10. Hayase J, Tung R, Narayan SM, **Krummen DE**. A case of a human ventricular fibrillation rotor localized to ablation sites for scar-mediated monomorphic ventricular tachycardia. Heart rhythm : the official journal of the Heart Rhythm Society. 2013;10:1913-1916.
11. Jones AR, **Krummen DE**, Narayan SM. Non-invasive identification of stable rotors and focal sources for human atrial fibrillation: Mechanistic classification of atrial fibrillation from the electrocardiogram. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2013;15:1249-1258.
12. Krishnamurthy A, Villongco CT, Chuang J, Frank LR, Nigam V, Belezzuoli E, Stark P, **Krummen DE**, Narayan S, Omens JH, McCulloch AD, Kerckhoffs RC. Patient-specific models of cardiac biomechanics. J Comput Phys. 2013;244:4-21.
13. Lalani GG, Schricker AA, Clopton P, **Krummen DE**, Narayan SM. Frequency analysis of atrial action potential alternans: A sensitive clinical index of individual propensity to atrial fibrillation. Circulation. Arrhythmia and electrophysiology. 2013;6:859-867.

14. Narayan SM, **Krummen DE**, Clopton P, Shivkumar K, Miller JM. Direct or coincidental elimination of stable rotors or focal sources may explain successful atrial fibrillation ablation: On-treatment analysis of the confirm trial (conventional ablation for af with or without focal impulse and rotor modulation). Journal of the American College of Cardiology. 2013;62:138-147.
15. Narayan SM, Shivkumar K, **Krummen DE**, Miller JM, Rappel WJ. Panoramic electrophysiological mapping but not electrogram morphology identifies stable sources for human atrial fibrillation: Stable atrial fibrillation rotors and focal sources relate poorly to fractionated electrograms. Circulation. Arrhythmia and electrophysiology. 2013;6:58-67.
16. **Krummen DE**, Hayase J, Morris DJ, Ho J, Smetak MR, Clopton P, Rappel WJ, Narayan SM. Rotor stability separates sustained ventricular fibrillation from self-terminating episodes in humans. Journal of the American College of Cardiology. 2014;63:2712-2721.
17. Miller JM, Kowal RC, Swarup V, Daubert JP, Daoud EG, Day JD, Ellenbogen KA, Hummel JD, Baykaner T, **Krummen DE**, Narayan SM, Reddy VY, Shivkumar K, Steinberg JS, Wheelan KR. Initial independent outcomes from focal impulse and rotor modulation ablation for atrial fibrillation: Multicenter firm registry. Journal of cardiovascular electrophysiology. 2014;25:921-929.
18. Narayan SM, Baykaner T, Clopton P, Schricker A, Lalani GG, **Krummen DE**, Shivkumar K, Miller JM. Ablation of rotor and focal sources reduces late recurrence of atrial fibrillation compared with trigger ablation alone: Extended follow-up of the confirm trial (conventional ablation for atrial fibrillation with or without focal impulse and rotor modulation). Journal of the American College of Cardiology. 2014;63:1761-1768.
19. Schricker AA, Lalani GG, **Krummen DE**, Rappel WJ, Narayan SM. Human atrial fibrillation initiates via organized rather than disorganized mechanisms. Circulation. Arrhythmia and electrophysiology. 2014
20. Villongco CT, **Krummen DE**, Stark P, Omens JH, McCulloch AD. Patient-specific modeling of ventricular activation pattern using surface ecg-derived vectorcardiogram in bundle branch block. Progress in biophysics and molecular biology. 2014

D. Research Support

Ongoing Research Support

1R01HL083359 (Narayan) 09/01/14 – 08/31/19
NIH
The Dynamics of Human Atrial Fibrillation
Role: Consultant
This project will compare the effectiveness of ablation of atrial fibrillation-sustaining sites versus trigger ablation in a clinical trial. The trial will also investigate the mechanisms of AF recurrence following unsuccessful ablation.

Completed Research Support

1 ACC/Merck 2004-2005 (Krummen) 07/01/04 – 06/30/05
American College of Cardiology / Merck Foundation
Prospective ECG Classfication and Characterization of Atrial Arrhythmias Using Temporal and Spatial Variability of Atrial Waveforms
Role: Principal Investigator
The goal of this study was to evaluate the accuracy of a novel computer diagnostic algorithm on the quality of life and cost of patient care for atrial tachyarrhythmias.

10 BGIA 3500045 (Krummen) 07/01/10 – 06/30/12, no cost extension to 6/30/13
American Heart Association
Ventricular Fibrillation Rotors Stereotypically Anchor at Myocardial Scar Borders
Role: Principle Investigator

This project used multi-electrode mapping catheters to record human ventricular fibrillation during electrophysiology study. The goal of the study is to localize ventricular fibrillation rotors and determine their relationship to myocardial scar.

1R01HL096544 (McCulloch) 07/01/09 – 06/30/14
NIH
Multi-Scale Modeling of the Failing Heart for Cardiac Resynchronization Therapy
Role: Co-Investigator
This project created patient-specific computational models of human left and right ventricles to test the hypothesis that reductions in regional wall stress or improvements in synchrony predict the remodeling response to cardiac resynchronization therapy at 3 months.

Computational Analysis of Surface Electrocardiography to Detect and Localize Human Ventricular Fibrillation Rotors

Gordon Ho, MD and David E. Krummen, MD, FACC, FHRS

A. Rationale / Clinical Need

Ventricular fibrillation (VF) is a life threatening arrhythmia and a leading cause of the 700,000 annual cases of sudden death in the United States and Europe. Presently, the only treatment modality available to terminate VF is defibrillation electrical shock by an implantable cardiac defibrillator (ICD) or external defibrillator. Although lifesaving, shock therapy is painful and traumatic, presenting a significant problem in patients with VF storm who receive frequent repeated ICD shocks. Currently, there are no targeted treatments for VF that address its underlying mechanisms.

Multiple mechanisms for sustaining human VF have been proposed and observed, but a growing body of animal[1, 2] and human data[3-5] suggests that electrical rotors (figure 1) may be important drivers of sustained VF. Electrical rotors are areas of rotating electrical activation located in different areas throughout the heart that create regions of re-entry to sustain fibrillation. Although the importance of rotors in human VF had previously been uncertain, recent work from our lab demonstrated that VF rotor sites are spatially conserved across VF episodes.[6] We have been the first to use biventricular, 128-electrode endocardial mapping, and found that sustained VF was associated with greater prevalence and stability of electrical rotors compared with self-limited VF.[6] In both a retrospective case report[7] and a prospective VF rotor ablation,[8] we have shown that VF rotor ablation decreases VF inducibility and clinical events in patients with VF. This potentially represents a novel treatment paradigm in patients with clinical VF, and parallels our work showing improved ablation outcomes in atrial fibrillation.[9]

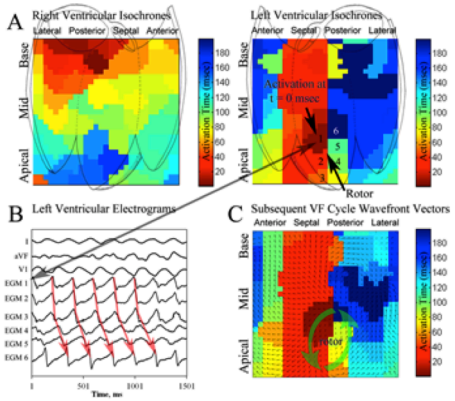

Figure 1.
(A) Isochronal map of the RV and LV obtained from endocardial 128 electrode basket catheter recordings showing a LV rotor (numbers 1-6) during induced ventricular fibrillation in a 73 year old patient with EF 25%.
(B) Simultaneous surface and endocardial lead recordings obtained during this rotor.
(C) This rotor is shown in a subsequent VF cycle (green arrow) in a stable location using vector analysis.

It would be clinically important to detect and localize VF rotors using noninvasive methods in order to identify candidates for targeted treatment and help guide the ablation of rotors, prior to invasive mapping. For many arrhythmias such as monomorphic ventricular tachycardia (VT), the standard 12 lead surface electrocardiogram (ECG) is routinely interpreted by physicians to diagnose and localize anatomical origins of the arrhythmia. Unfortunately, the surface ECG in VF appears disorganized to the human eye and currently there is no method to analyze the surface ECG to detect the presence or location of rotors. Because the ECG records the global electrical activation of the heart, it is conceivable that the spirals of electrical activity from a rotor can be constructed from the ECG waveforms by a computer either using signal processing techniques or graphically using spatiotemporal visual representation of electrical activation.

This grant proposal is based on our central hypothesis that that *global electrical activation patterns derived from the surface ECG during VF can be used to identify the presence of rotors versus alternate VF mechanisms and can predict the location and stability of such rotors.* If our hypothesis is correct, such information would be of critical importance to

improving our understanding of the mechanisms of VF, and planning invasive, targeted therapy of VF rotors prior to endocardial mapping.

B. Project Aims

Specific Aim 1: To develop computational tools to analyze the surface ECG obtained from an existing human data set of simultaneous 12-lead ECG and 128-electrode endocardial recordings of induced ventricular fibrillation to detect the presence and location of rotors.
Specific Aim 2: To derive diagnostic criteria, based on this data, to predict the presence and location of VF rotors.
Specific Aim 3: To prospectively test the diagnostic criteria in a second set of patient data in whom VF rotor and focal source locations have been mapped using 128-electrode endocardial recordings.

C. Feasibility

Several bioengineering labs, including at UCSD, have been investigating methods to analyze the electrical behavior of arrhythmias using signal processing and computer modeling techniques. For example, Dr. Andrew McCulloch's lab has studied the electrical activation of left bundle branch block using vectorcardiograms, which is a spatiotemporal graphical representation of electrical activation. Vectorcardiograms are created using a computer to plot the net vector of electrical activation of the heart through time. These visualizations may simplify the electrocardiogram and potentially help localize the anatomical origin of an electrical impulse. Vectorcardiograms may be one possible non-invasive technique to analyze the presence and localize VF rotors.

D. Innovation / Significance

The potential significance of this research to the scientific community and society is high. Identification of the type and location of VF sustaining mechanisms from noninvasive, widely available electrocardiograms would dramatically improve our mechanistic understanding of VF and greatly aid in the planning of a novel invasive electrophysiology intervention for a life-threatening disease currently lacking targeted treatment. For example, if a rotor can be detected and localized in a patient with VF, then this patient can be referred for invasive electrophysiology study using our novel endocardial basket mapping catheter technique and targeted ablation treatment. Prior to invasive mapping, knowing whether a rotor is in the right or left ventricle would greatly assist in planning invasive access, since left ventricular access is riskier and more difficult. If a patient is known to only have a rotor in the right ventricle, then left ventricular access can be avoided in this patient. In the same way that surface ECGs are used to help characterize and localize origins to help guide ablation of other arrhythmias, we hope this tool can be used to identify candidates and guide rotor ablation.

E. Investigator Qualifications

This innovative research will be conducted by a team of physician-scientists with engineering backgrounds with a focus in translational research, including David Krummen, MD, who is Associate Professor in Medicine at UCSD and an actively practicing clinical cardiac electrophysiologist as Director of the Clinical Electrophysiology Laboratory at San Diego VA Medical Center, and has a degree in Aerospace Engineering. Gordon Ho, MD, is a Clinical cardiology fellow at UCSD, and has an undergraduate degree in Biomedical Engineering. The unique background of both clinicians will help facilitate collaboration with engineers.

References

1. Davidenko JM, Kent PF, Chialvo DR, Michaels DC, Jalife J. Sustained vortex-like waves in normal isolated ventricular muscle. *Proceedings of the National Academy of Sciences of the United States of America*. 1990;87:8785-8789.
2. Gray RA, Jalife J, Panfilov AV, Baxter WT, Cabo C, Davidenko JM, Pertsov AM. Mechanisms of cardiac fibrillation. *Science*. 1995;270:1222-1223; author reply 1224-1225.
3. Masse S, Downar E, Chauhan V, Sevaptsidis E, Nanthakumar K. Ventricular fibrillation in myopathic human hearts: Mechanistic insights from in vivo global endocardial and epicardial mapping. *Am J Physiol Heart Circ Physiol*. 2007;292:H2589-2597.
4. Nair K, Umapathy K, Farid T, Masse S, Mueller E, Sivanandan RV, Poku K, Rao V, Nair V, Butany J, Ideker RE, Nanthakumar K. Intramural activation during early human ventricular fibrillation. *Circulation. Arrhythmia and electrophysiology*. 2011;4:692-703.
5. Nash MP, Mourad A, Clayton RH, Sutton PM, Bradley CP, Hayward M, Paterson DJ, Taggart P. Evidence for multiple mechanisms in human ventricular fibrillation. *Circulation*. 2006;114:536-542.
6. Krummen DE, Hayase J, Morris DJ, Ho J, Smetak MR, Clopton P, Rappel WJ, Narayan SM. Rotor stability separates sustained ventricular fibrillation from self-terminating episodes in humans. *Journal of the American College of Cardiology*. 2014;63:2712-2721.
7. Hayase J, Tung R, Narayan SM, Krummen DE. A case of a human ventricular fibrillation rotor localized to ablation sites for scar-mediated monomorphic ventricular tachycardia. *Heart rhythm : the official journal of the Heart Rhythm Society*. 2013;10:1913-1916.
8. Krummen DE, Hayase J, Vampola SP, Schricker AA, Lalani GG, Baykaner T, Coe TM, Clopton P, Rappel WJ, Omens JH, Narayan SM. Suppressing ventricular fibrillation by targeted rotor ablation: Proof-of-concept from the canine laboratory to the first human case. *in Review*. 2014
9. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: Confirm (conventional ablation for atrial fibrillation with or without focal impulse and rotor modulation) trial. *Journal of the American College of Cardiology*. 2012;60:628-636.