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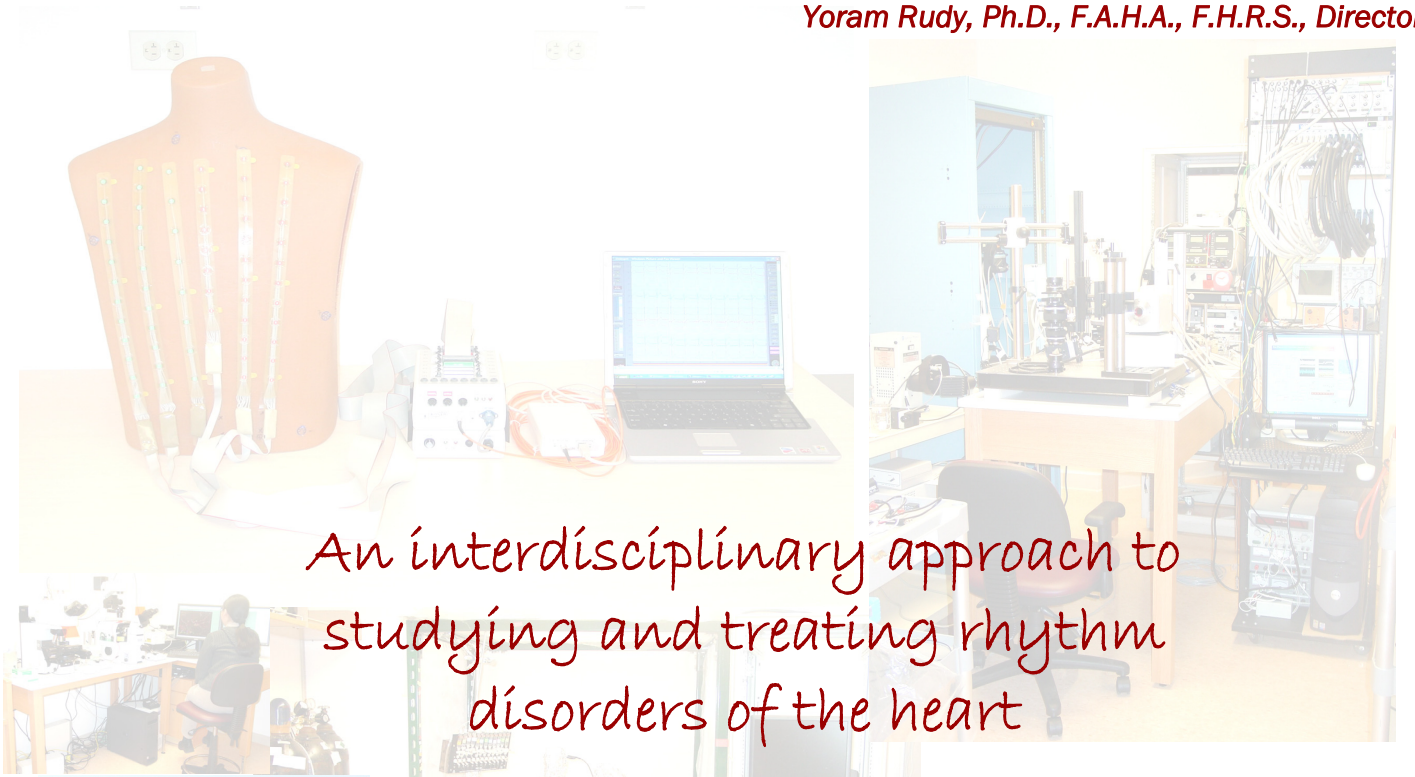
CENTER HEARTBEAT

NEWSLETTER OF THE CARDIAC BIOELECTRICITY AND ARRHYTHMIA CENTER (CBAC)

Yoram Rudy, Ph.D., F.A.H.A., F.H.R.S., Director



An interdisciplinary approach to studying and treating rhythm disorders of the heart

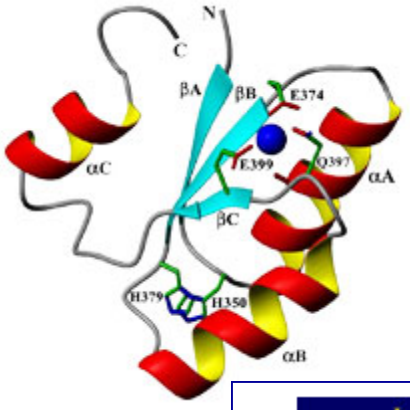
Cardiac Bioelectricity and Arrhythmia Center (CBAC)

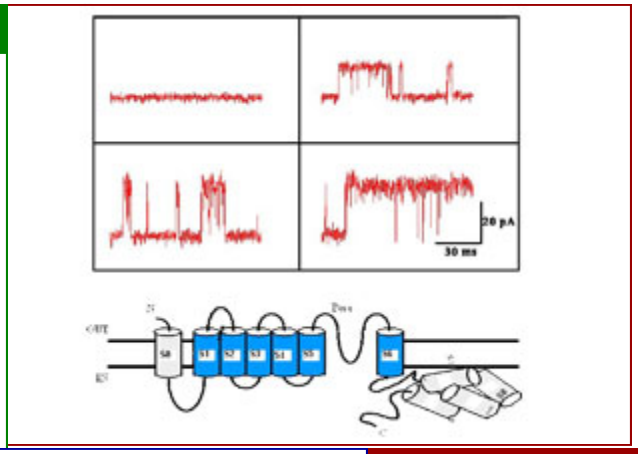
The **Cardiac Bioelectricity and Arrhythmia Center, CBAC**, is an interdisciplinary center whose goals are to study the mechanisms of rhythm disorders of the heart (cardiac arrhythmias) and to develop new tools for their diagnosis and treatment. Cardiac arrhythmias are a major cause of death (over 300,000 deaths annually in the US alone; estimated 7 million worldwide) and disability, yet mechanisms are poorly understood and treatment is mostly empirical. Through an interdisciplinary effort, CBAC investigators apply molecular biology, ion-channel and cell electrophysiology, optical mapping of membrane potential and cell calcium, multi-electrode cardiac electrophysiological mapping, Electrocardiographic Imaging (ECGI) and other noninvasive imaging modalities, and computational biology (mathematical modeling) to study mechanisms of arrhythmias at all levels of the cardiac system.

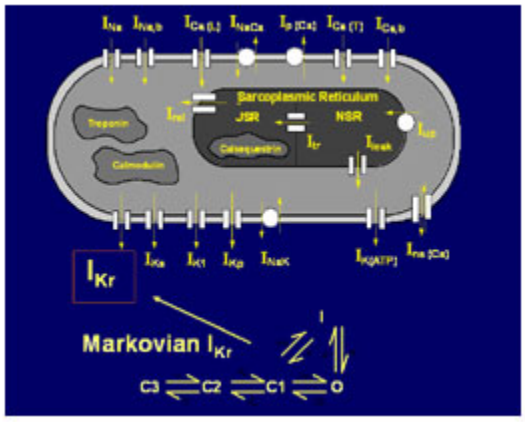
Our mission is ***to battle cardiac arrhythmias and sudden cardiac death through scientific discovery and its application in the development of mechanism-based therapy.***

Visit the CBAC website at http://cbac.wustl.edu/ to get more information about the research, CBAC members and seminars. There is also a video archive from past seminars that is updated following each season of seminars that is available for viewing.

Molecular Structure of Cardiac Ion Channels







Structure/Function of Cardiac Ion Channels

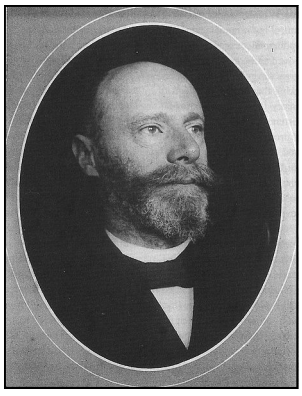
Mathematical Modeling of Cardiac Cells and Tissue

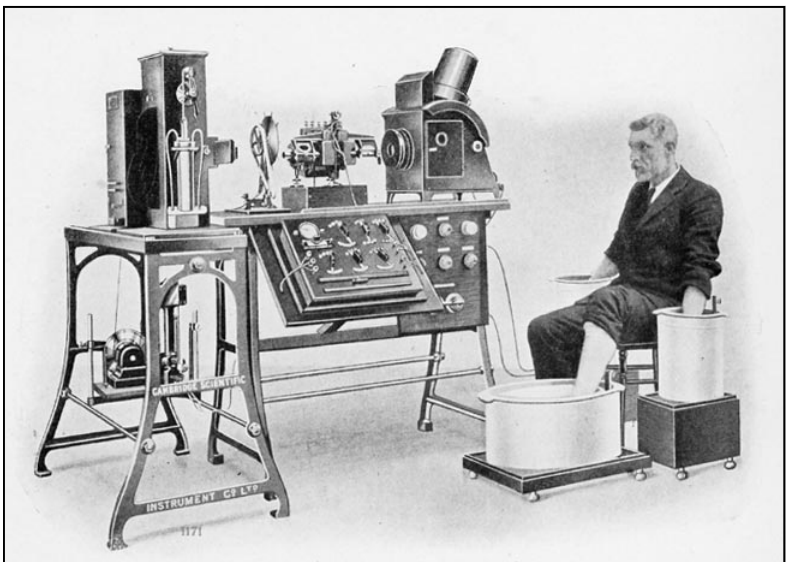
Washington University in St. Louis

FROM THE DIRECTOR'S DESK……...

Yoram Rudy, Ph.D., F.A.H.A., F.H.R.S.

Thanks to Kimberly Smith for producing yet another issue of the "Center Heartbeat". In the previous issue I stressed the importance of maintaining a historical perspective as new technologies are being developed and new discoveries are being made. I brought as an example the pioneering work of Arthur Berridale Keith and Martin William Flack on the Sinus node, and of Ludwig Aschoff and Sunao Tawara on the AV node. These discoveries were made in 1906-1907. The development of electrocardiography is another early milestone in the progression of cardiac electrophysiology as a field of research and a clinical discipline. Augustus Desire Waller recorded the first human body-surface ECG as early as 1887. He used a capillary electrometer to do so. The clinical significance of the ECG became clear only later, after Willem Einthoven adopted and refined the use of the string galvanometer for recording electrocardiograms in 1902 (in 2002 we celebrated 100 years of electrocardiography and honored Einthoven's legacy in Leiden, the Netherlands). This is another example of research driven by curiosity, translated into clinical application fifteen years later. 100 years later, the ECG is still a cornerstone of clinical practice and although the technology for its recording has advanced greatly, its underlying principles remain the same.





PHOTOGRAPH OF A COMPLETE ELECTROCARDIOGRAPH, SHOWING THE MANNER IN WHICH THE ELECTRODES ARE ATTACHED TO THE PATIENT, IN THIS CASE THE HANDS AND ONE FOOT BEING IMMERSED IN JARS OF SALT SOLUTION

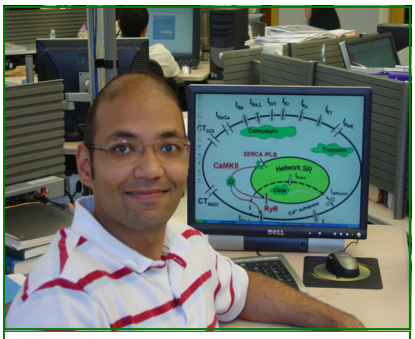
CBAC PEOPLE & EVENTS

The CBAC Seminar Series is hosted every semester throughout the year. These gatherings allow scientists and clinicians to engage in what often proves to be very fascinating dialogue and networking. Above all, the seminars bring in world renowned scientists and clinicians who are doing pivotal work in the field of cardiology and electrophysiology. Above, far right, Jose Jalife, MD was a guest speaker in the Fall seminar series and, Lower Center, Robert Kass, Ph.D. was a guest speaker during the Spring 2010 seminar series.

INSIDE THIS ISSUE:

More attendees preparing for the CBAC seminar to begin.

CBAC Profiles....



Namit Gaur

The Rudy Lab has been and still is home to many aspiring scientist who through their work hope to impact the field of cardiology. One doctoral student, Namit Gaur talks about his journey to the Rudy Lab and his hopes for the future.

"My family and early upbringing has been quite influential in enabling me to choose my career. My father is a Professor of Anatomy and we were surrounded by his friends and acquaintances in the medical and engineering professions since my early childhood. I was born in Libya and at my youth I had plenty of opportunities to interact with engineers who worked in the Petroleum industry and other professional careers. Both of my elder brothers chose medicine as their profession; one is an Ophthalmologist and the other a Hematologist/Oncologist. However, I opted to choose engineering as a career.

The choice of engineering became obvious to me between middle and high school. I detested memorization of facts and preferred mathematics and physical sciences over life sciences. The creative opportunities offered in the engineering profession appealed to me far more than what I believed medicine or life sciences could offer me at that time.

I pursued a Bachelors in Technology in Chemical Engineering from Indian Institute of Technology, Bombay. During my final year, while working on a B-Tech project, "Optimization of Batch Distillation Columns," I had a great opportunity to work with Dr. Madhavan, my B-Tech advisor who is known widely in the field of Process Control and Optimization and Dr. Diwekar, the president and founder of The Center for Uncertain Systems: Tools for Optimization and Management at the University of Chicago, Illinois. The experience and encouragement from my mentors led me to pursue an MS in Chemical Engineering at Texas Tech University. There, I came in contact with Dr. Gyorke, whose group at that time was working on pioneering work exploring the role of luminal SR Ca on Ryanodine Receptor openings. During that period, I learned a lot about computational electrophysiology of ventricular myocytes and for the first time discovered the joy of creativity and scientific discovery in cardiac physiology. This experience during my MS studies was the key moment that led me to pursue a Ph.D. in Biomedical Engineering here in Dr. Rudy's world renowned cardiac electrophysiology theoretical modeling group.

A major highlight of my time here in Dr. Rudy's lab has been the successful outcome of a collaborative project with Dr. Livia Hool from the University of Western Australia. We explored electrophysiological changes during acute hypoxia using the computer model of ventricular myocytes. A major result of the study is that increased sensitivity of L-type Ca channel to beta-adrenergic stimulation during hypoxia leads to arrhythmogenic Early Afterdepolarizations (EADs). Beta-adrenergic stimulation is necessary to induce EADs, as EADs are not observed during hypoxia in the absence of Beta-adrenergic stimulation. For more details please see Circ Res. 2009; 105:1196-1203. Continued interaction in group and individual meetings with current faculty and students in the laboratory has proved invaluable in my scientific education and I feel quite indebted for it.

The Cardiac Bioelectricity and Arrhythmia Center (CBAC) seminars provide a wonderful opportunity to attend talks held by world-class visiting scientists. Having the opportunity to have one on one Interaction and even further, present my work to them been quite an enriching and stimulating experience for me.

After my graduation, I plan to continue pursuing research in cardiac bioelectricity combining both an experimental approach and theoretical modeling. The experience gained through CBAC and the opportunity to network with some of the most important scientist of this day has and will continue to prove invaluable as I embark upon a successful, satisfying and worthy scientific career."

The Mouse Cardiovascular Phenotyping Core (MCPC)

The **Mouse Cardiovascular Phenotyping Core** (**MCPC**) was established on the Medical School campus of Washington University in 1998 to provide phenotyping support to a growing number of investigators interested in utilizing murine models to gain insights into the pathogenesis of cardiac arrhythmias, ventricular hypertrophy, myocardial ischemia or infarct remodeling. At that time, cardiac phenotyping was often purely descriptive, and investigators were just learning how to interpret data obtained from a mammalian heart that weighs 3 orders of magnitude less than a human heart and that beats 10 times faster. Also at that time, development and utilization of state-of-the-art equipment and methods for assessing cardiovascular function were being championed by a relatively small number of specialists, such as Drs. Howard Rockman, Michael Entman and Charles Berul to name a few, who had adapted methods used to assess cardiac function in larger mammals for interrogation of mice. These pioneers were instrumental in helping the **MCPC** establish its own protocols and procedures that have been in use for the past 12 years. The **MCPC** has expanded its service function substantially since those early days, and is open to discussions with anyone interested in pursuing cardiovascular phenotyping in mice.

The **MCPC** was established with 4 working staff members—Drs. Carrie Gierasch, Attila Kovacs, Carla Weinheimer, and Kathryn Yamada—and continues to operate with the same founding members today, bringing over 80 years of collective experience in their pursuit of applying a systematic approach to studying basal physiology and pathophysiology of the mouse cardiovascular system.

MCPC staff members Left to Right: Drs. Attila Kovacs, Carrie Gierasch, Carla Weinheimer and Kathryn Yamada

The expertise of the **MCPC** lies within three major overlapping spheres: (1) in vivo and in vitro phenotyping, (2) specialized micro-surgical services and (3) innovative, mouse-specific echocardiographic imaging. Members of the **MCPC** share their expertise by performing fee-for-service and/or collaborative studies; development and validation of new disease models; and consultative, educational, and training sessions. In the latter, the **MCPC** serves as a resource for those investigators who request guidance or information pertaining to animal studies protocol approval processes, strain variability in basal and stressed states, influence of various anesthetic agents on mouse cardiovascular physiology, quantification of in vivo and in vitro imaging data, and interpretation of complex structural and functional remodeling during disease progression.

The Mouse Cardiovascular Phenotyping Core (MCPC), cont'd.

The **MCPC** has worked with over 50 different principal investigators/users representing 13 different departments on both Danforth and Medical School campuses, as well as investigators at outside universities and pharmaceutical companies. The backbone of the **MCPC** is the superb surgical skills of surgeons, Carla Weinheimer and Carrie Gierasch. They have experience in a wide variety of surgical models including, for example, transverse aortic constriction-induced ventricular hypertrophy or coronary artery ligation-induced myocardial infarction. **MCPC** surgeons also perform diagnostic interventions such as cardiac catheterization, therapeutic interventions, pharmacological treatments and combined surgical and phenotyping procedures. Recently, the **MCPC** has acquired a new Scisense ADVantage pressure-volume system for acquiring reliable, consistent hemodynamics data. One of the greatest advances of the Scisense system is its "admittance" technology for monitoring optimal catheter positioning for measurement of intraventricular pressure and acquisition of robust pressure-volume loop data in the intact mouse.

Surgeons Carla Weinheimer and Carrie Gierasch in delicate operations

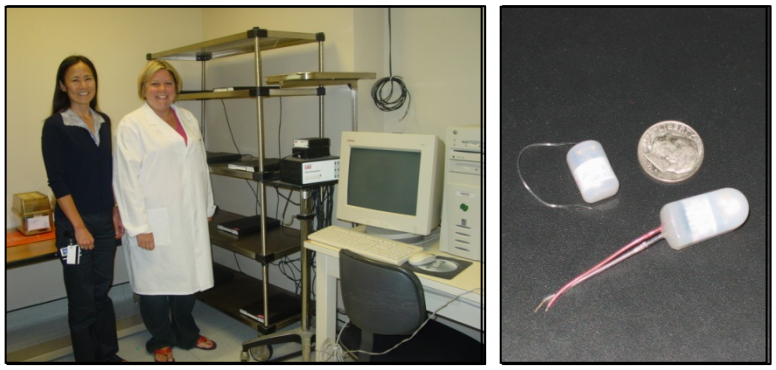
Typically, each new genetic or surgical model is subjected to structural and functional phenotyping by Dr. Attila Kovacs, a trained cardiologist who specializes in ultrasound imaging, and who has recently been successful in acquiring an NIH Shared Instrumentation Grant for upgrading the **MCPC's** current Vevo 770 system to VisualSonics newest Vevo 2100 high-frequency, high-resolution digital imaging platform with color Doppler. Dr. Kovacs is assisted in image acquisition and analysis by Carrie Gierasch.

"The Ultrasound Imaging Team"

Dr. Kovacs has developed a number of analytical tools to assess both cardiac and vascular pathology. He is also in the process of developing novel, exciting protocols for implementing contrast-enhanced echocardiography, and for using nanoparticles and gene therapy as potential treatment paradigms in murine models of cardiovascular disease.

The Mouse Cardiovascular Phenotyping Core (MCPC), cont'd.

In addition to the surgical and imaging services, the **MCPC** offers ambulatory ECG or blood pressure monitoring using surgically implanted radiofrequency transmitters that allow for recording ECGs in awake, unanesthetized mice.



Left panel: Kathryn Yamada (left) and Carrie Gierasch (right) record ambulatory ECGs in a dedicated telemetry and exercise suite outfitted with Transoma/Data Sciences receivers and acquisition system. Right panel: blood pressure (left) and ECG (right) transmitters used for ambulatory recordings.

Dr. Kathryn Yamada and Carrie Gierasch perform continuous or scheduled data acquisition and subsequent off-line analysis of data recorded from transgenic mice models with or without surgical intervention, with or without pharmacological treatment, and with or without exercise stress. Although mouse hearts are only 5-7 mm in their longest dimension, they are able to initiate and sustain reentrant ventricular tachycardia and fibrillation. Additional in vivo and in vitro electrophysiology studies can be performed in conjunction with the **MCPC** and our CBAC colleagues using miniature bipolar or octapolar pacing catheters to investigate the mechanisms underlying arrhythmogenesis during progression of heart disease and cardiac injury in mammals.

Bipolar (left) and octapolar (right) pacing catheters that can be placed transvenously for intracardiac pacing and/or recording in mice.

Importantly, the goals of the **MCPC** are not only to facilitate the research endeavors of colleagues and collaborators, but also to develop novel diagnostic, imaging and analysis tools that will advance translational research, with the ultimate goal of facilitating advancement of mechanistic insights that will help prevent arrhythmias and heart disease in humans.

Additional information, request forms, images and videos, publications, and contact information can be found at the **MCPC** website: http://mcpc.wustl.edu/.

The Road to Research

Christina Ambrosi

The CBAC is comprised of many dedicated and dynamic members who are faculty and also those who are on their way to becoming dynamic research scientists. One of those travelling the road to making a difference is doctoral student, Christina Ambrosi. Christina is a member of Dr. Igor Efimov's lab where the primary focus is on the use of Optical Imaging to better understand the mechanisms of cardiac arrhythmias and the improvement of anti-arrhythmic therapies. The Heartbeat wanted to chat with Christina to see where she has been and where she is going. "I have always had a special interest in the math and sciences. My parents, both being in the medical professions themselves, have always supported my education and been a crucial part of my journey thus far. My beloved high school physics teacher, Mrs. Ricci, however instilled in me a curiosity for both the known and unknown. My experiences in her class and subsequent self-reflections solidified my desire to study biomedical engineering in college. It is a choice I have never regretted.

I attended Wash U for both my BS and MS degrees in biomedical engineering. During that time I became involved in research under Dr. Frank Yin studying the responses of human aortic endothelial cells to various types of mechanical stresses. I not only gained a great deal of knowledge regarding cellular mechanics and tissue culture, but I also gained valuable experience in conducting myself as an independent scientist both in the lab and at national conferences. My education at Wash U both in and out of the classroom was a truly unique experience.

After graduation, I made the decision to pursue a career in the medical device industry. I subsequently worked for two years as a Technical Service Specialist with St. Jude Medical. My primary responsibilities included providing technical support to physicians during the implantation and follow-up of pacemakers, ICDs, and biventricular pacing and defibrillation systems. In this position, I really gained an appreciation for and saw firsthand the advances in medicine and engineering which have greatly improved the quality of life for so many people. However, it was through these experiences that I also came to the conclusion that my heart and true interests lie in research. Consequently, I returned to Wash U in the Fall of 2006 to pursue my Ph.D. in biomedical engineering in the laboratory of Dr. Igor Efimov.

In order to achieve balance in my life, I have taken up endurance running in the last 5 years. I have completed seven half marathons to date and look forward to completing my first full marathon this spring.

During my time in the Efimov lab, I have been fortunate to have had the opportunity to travel to several national and international conferences. My interactions with professors, cardiologists, and other trainees have allowed me to receive critical feedback on my own research, as well as establish both professional and personal connections.

My research in Dr. Efimov's lab is focused on understanding the structural components that are involved in supraventricular arrhythmias specifically atrial fibrillation and AV nodal reentrant tachycardia. We use a variety of imaging methods, such as optical mapping, optical coherence tomography, and confocal microscopy. Our ongoing collaboration with the cardiac transplant program at Barnes-Jewish Hospital has allowed us the unique opportunity to study explanted human hearts from transplant recipients. These experiments always prove to be exciting and novel, however tiresome, especially when the calls from the transplant team come in the middle of the night!

The CBAC and its activities has only served to enrich my graduate experience. Attending seminars delivered by world-class scientists has exposed me to outstanding research and broadened my own research experience by having the chance to interact with many of these visiting scientists to both learn about their work and receive feedback critical to my own research.`

Once I receive my degree, I initially look forward to continuing my study of cardiac bioelectricity as a post-doctoral scientist. After that I am open to either remaining in academia or returning to industry to pursue a position in research and development." The Heartbeat wishes Christina the best in all of her endeavors and we look forward to hearing more from you about your research.

Lectures & Presentations

Leonid Livshitz, Ph.D., Research Assistant Professor, Biomedical Engineering, Cardiac Bioelectricity and Arrbythmia Center

"Calcium and Action Potential Alternans" Cardiovascular Seminar, Calcium-Dependent Arrhythmias, American Heart Association 2010 Conference, Orlando, FL

Colin Nichols, Ph.D., Professor, Cell Biology and Physiology, Washington University School of Medicine

"Cardiac K_{ATP} Channels", University of Michigan, February 2009

Sandor Kovacs, Ph.D., M.D., Professor of Internal Medicine, Physics and Biomedical Engineering, Director and Founder, Cardiovascular Biophysics Laboratory

* May 13-15, Visiting Professor at Cornell University,
* May 3-7 Visiting Professor, Lund University, Sweden
* May 6, ISMRM International Meeting, Stockholm, Sweden, "Assessment of LV Function Via Cardiac MRI"

Left: CBAC seminar with guest speaker Dr. Robert Kass (bottom of picture)

Top: Drs. Vadim Fedorov and Kathryn Yamada chat briefly before the start of the seminar.

Lectures & Presentations Cont'd.

Yoram Rudy, Ph.D., F.A..H.A., F.H.R.S., The Fred Saigh Distinguished Professor of Engineering, Professor of Biomedical Engineering, Cell Biology & Physiology, Medicine, Radiology and Pediatrics, Director, Cardiac Bioelectricity & Arrhythmia Center (Lectures from September 2009 to April 2010)

* Safety in Pharmacology Society 9th Annual Meeting, "Noninvasive ECG Imaging (ECGI) for Cardiac Electrophysiology and Arrhythmia", Strasbourg, France, September 15-18, 2009.
* Catholic University of Leuven, Department of Cardiovascular Medicine, "Modeling and Imaging Cardiac Repolarization", Leuven, Belgium, September 22, 2009.
* Maastricht University and Academic Hospital, Grand Rounds in Cardiology, "Noninvasive ECG Imaging (ECGI) of Cardiac Arrhythmias", Maastricht, The Netherlands, September 24, 2009.
* Maastricht University and Academic Medical Center, Hein Wellens Distinguished Professorship Presentation, "Theoretical Concepts in Cardiac Conduction and Imaging Abnormal Electrophysiological Substrate", Maastricht, The Netherlands, September 28, 2009.
* Maastricht University and Academic Medical Center, Frontiers in Computational Electrocardiology Workshop, "Modeling Electrophysiological Drug Effects and Imaging Arrhythmogenic Substrate", Maastricht, The Netherlands, October 1, 2009.
* Washington University, Cardiology Grand Rounds, November 4, 2009.
* American Heart Association Scientific Sessions 2009, Cardiovascular Seminar "From Molecular Structure to Ion Channel Function in Repolarization", Orlando, Florida, November 15, 2009.
* First European VT/VF Meeting "Noninvasive ECG Imaging [ECGI] of VT and Electrophysiological Substrate", Berlin, Germany, November 20, 2009.
* Washington University, Grand Rounds in Medicine, January 28, 2010.
* Washington University, Anesthesiology Grand Rounds, March 10, 2010.
* Harvard Medical School, the 11th Paul Zoll Memorial Lecture at Beth Israel Deaconess Medical Center "Non-invasive Electrocardiographic Imaging for Cardiac Arrhythmias", Boston, April 16, 2010.

George Van Hare, III, MD, Director of the Division of Pediatric Cardiology at Washington University School of Medicine in St. Louis and the Louis Larrick Ward Chair in Pediatric Cardiology at St. Louis Children's Hospital

* "State of the Art in Pediatric and CHD Patients: Difficult ablation techniques" Heart Rhythm Society Annual Scientific Sessions, 5/13/09, Boston, MA (invited lecture)
* "Catheter or Surgical Ablation of Ventricular Tachycardia is a Safe Substitute for an Implantable Defibrillator in Repaired Tetralogy of Fallot (proponent)" Heart Rhythm Society Annual Scientific Sessions, Boston, MA 5/15/09 (debate)

"Spotlight On...."

Amir Toib, M.D.

Another interesting CBAC member is Amir Toib, M.D. Amir is a post-doctoral fellow at the Washington University School of medicine where he works in the lab of Dr. Colin Nichols, in the Department of Cell Biology and Physiology. Dr. Nichols' research group is focused on the molecular and cellular regulation of potassium channels, and their role in linking cellular metabolism to electrical activity in cardiac and other tissues. Amir has an interesting story of how he came to be in Dr. Nichols lab.

"I chose medical studies because of a deep interest and passion to explore, research and learn. My first research mentor was a scientist who was both a wonderful person and a great scientist perusing a question. He was a real role model. The other mentor who had a big impact on me was the first pediatric cardiologist I worked with. He was "in love" with his profession and enjoyed his patients and work. The combination of genuine exploration with a fulfilling and enjoyable profession appeared to me as the right career choice. I will always have these two people in my mind.

I always loved working with kids and going into pediatrics was an obvious choice. The fascinating physiology of the heart and dynamic and developing field of pediatric cardiology caught my interest. I attended medical school in Haifa, Israel (Technion), and came to the US to pursue pediatric cardiology and research training. Being a physician who is also interested in basic research is challenging, trying to balance both worlds: medicine and science. However, being a physician enables me to bring the clinical perspective and questions into research. In spite of the difficulties, I hope to keep both worlds alive.

I received my M.D. 12 years ago. During medical school I also obtained an MSc in physiology, studying cellular electrophysiology. I then completed four years of obligatory army service as a physician in the Israeli Defense Forces. I started pediatric residency in Israel and repeated pediatric training after moving to the US. I am now completing my pediatric cardiology fellowship and will stay for another year of basic research, studying the role of KATP channels in cardiac development.

My family is my greatest personal achievement. I have a wonderful wife who is a true partner and two precious kids (10 year old daughter and 11 year old son).

I am studying the role of KATP channels in cardiac development. After breeding and careful dating of the gestational stage in wild type and transgenically KATP over expressing mice, the embryos are dissected and cardiac morphology is delineated. The research also involves isolating embryonic cardiomycytes in different pregnancy stages and studying the cellular electrophysiology properties, using whole cell and excised patch recordings.

On a previous research project studying Hypertrophic Cardiomyopathy, I came up with an original hypothesis that arrhythmogenesis in this condition stems from cell autonomous electrophysiological remodeling. Preliminary experiments supported the hypothesis. I remember the excitement of getting these results. It was the joy of discovery.
My future goals are to combine clinical pediatric heart failure practice with basic science research focusing on cellular electrophsiolgy, cardiac development and cardiomyopathies.

CBAC is a great resource for collaboration, enrichment and sharing ideas. During my three years at Washington University I have met and discussed numerous topics with the CBAC PI's and research staff. The seminars are superb and serve as an excellent opportunity to get exposed to internationally renowned leaders in the field of cardiovascular research.

"Welcome New Rudy Lab & CBAC Faculty Members"

Christopher Andrews is a new Ph.D. student in the Rudy Lab. His research will focus on using Electrocardiographic Imaging (ECGI) to study the mechanisms of arrhythmia and electrical remodeling in the human heart.

Aswhin Mohan, Ph.D. is a Post-Doctoral Fellow in the Rudy Lab. Ashwin comes to Washington University from the University of Missouri at Columbia where he received his Ph.D. in Electrical and Computer Engineering. Ashwin is focusing his work on altered rate-dependence of action potential (AP) repolarization and its role in post-infarction arrhythmias in the 5-day old canine epicardial border zone. The study will focus on the spatio-temporal properties and underlying mechanisms of abnormal repolarization, and how they lead to arrhythmogenesis

Smiruthi Ramasubramanian is a Ph.D. student in the Rudy Lab. Smiruthi's research interest is how the molecular structure of proteins (ion channels in the heart) correlates to their function. She is interested to see how structural changes (eg. Mutations) can affect the function of the ion channel from the perspective of the whole cardiac cell behavior.

Vadim Fedorov, Ph.D.

Research Assistant Professor, Department of Biomedical Engineering, Washington University, member of the Efimov lab.

Mark Levin, M.D.

Instructor in Pediatrics, Attending Cardiologist, Arrhythmia Service, Division of Pediatric Cardiology, St. Louis Children's Hospital, Washington University School of Medicine

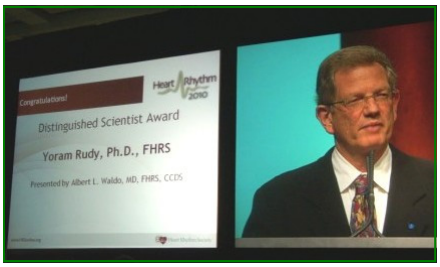
Jennifer N. A. Silva, M.D.

Instructor in Pediatrics, Director of Pediatric Electrophysiology, Washington University School of Medicine, Division of Pediatric Cardiology, St. Louis, MO

Announcements & News

Keith F. Decker, Ph.D., is a graduated member of the Rudy Lab. He defended his thesis "Ionic Mechanisms of Action Potential Rate Dependence, Conduction and Block in Normal Epicardium and in Remodeled Epicardium Post-Infarction" on May 19, 2010 and graduated with his Ph.D. in Biomedical Engineering. Keith is now a Post-Doctoral Research Associate in the laboratory of Dr. John Edwards at the Washington University School of Medicine, Center for Pharmacogenomics. Keith is using computational methods to study the role of epigenetic changes in cancer.

Subham Ghosh, Ph.D., is now a Senior Scientist in the Tachyarrhythmia and Sensors Group at Medtronic. Congratulations Subham and best wishes for a long and prosperous career.



Dr. Yoram Rudy was awarded the 2010 Heart Rhythm Society Distinguished Scientist Award. The award ceremony took place on May 14th at the Annual Heart Rhythm Society Scientific Sessions in Denver, CO. : ABOVE: Dr. Rudy accepting this award.

Lihong Wang , Ph.D., the Gene K. Beare Distinguished Professor, Optical Imaging Laboratory, Department of Biomedical Engineering, Radiology and Electrical and Systems Engineering, Washington University in St. Louis and Hsin-I are the recipients of the 2010 Joseph W. Goodman Book Writing Award for their book Biomedical Optics: Principles and Imaging,. This award is co-sponsored by SPIE, the international society for optics and photonics and The Optical Society of Light (OSA) on March 11, 2010 in Bellingham, WA

Dr. George Van Hare, III *is the Pediatric Chair for the new IBHRE Exam Electrophysiology-MD certification exam which will be available in 2011.*

Announcements & News Cont'd.

Pamela K. Woodard, M.D., *Associate Professor, Diagnostic Radiology, Cardiovascular Imaging Laboratory, Mallinckrodt Institute of Radiology, Washington University School of Medicine has been made a Fellow of the American College of Radiology.*

GRANTS

Jeanne Nerbonne, Ph.D.:

New NIH Grant – R21-HL098781-01 – **Novel Mechanisms Linking SCNIB to Cardiac Excitability**; Jeanne M. Nerbonne, P.I.

SPECIAL PROJECTS

Colin Nichols, Ph.D.:

A major project in the lab is to understand the roles of ATP-sensitive K (KATP) channels in the pathophysiology of the heart and other organs. We demonstrated a dramatic diabetic phenotype as a consequence of KATP channel overactivity in beta-cells (Koster et al., 2000; 2006). This work predicted a correlate human disease, and it has since been shown that similar gain-of-function mutations in KATP indeed underlie human neonatal diabetes. We are now focused on multiple translational efforts to diagnose, explain, and improve therapy for this rare disease, and for the involvement of KATP in the epidemic of type 2 diabetes (Remedi et al., 2002; 2004; 2006; 2008; Koster et al., 2007; 2008). By contrast, the heart shows a remarkable tolerance for reduced sensitivity of KATP channel activity (Koster et al., 2001; Rajashree et al., 2002), a feature that we are now examining the underlying mechanism of (Masia et al., 2005; Flagg et al., 2004; 2005; 2008). We have recently discovered that the make-up of the cardiac KATP channel is different in distinct regions of the heart (Elrod et al., 2007; Flagg et al., 2008), opening the way for understanding and manipulating differential pharmacology of the channel. We are currently developing novel inducible transgenic strategies, as well as utilizing alternative viral-mediated approaches, which promise insight to mechanisms of ischemic protection and preconditioning, as well as to membrane lipid regulation of cardiac and pancreatic function.

CBAC ELECTROCARDIOGRAPHIC IMAGING (ECGI) RETREAT

On Saturday, January 30, 2010, the ECGI group from the Rudy Lab hosted a retreat on the Danforth Campus of Washington University. The retreat was an opportunity for the collaboration of scientists and clinicians who comprise the CBAC to hear and discuss the challenges and progress of their research and treatment. Dr. Rudy gave an overview of ECGI and its' results to date. Other participant speakers were: Subham Ghosh, Ph.D. (WPW and CRT in non-ischemic cardiomyopathy), Jennifer Silva, M.D. (ECGI in congenital heart disease), Phil Cucullich, M.D. (Atrial fibrillation). Among the other participants were: George Van Hare, M.D., Sudhir Vashist, M.D. (Pediatric Cardiology), Ralph Damiano, M.D. and Richard Schuessler, Ph.D. (Cardio-thoracic Surgery), Mitchell Faddis, Ph.D., M.D., Scott Marrus, Ph.D., M.D., Dan Cooper, M.D. (Adult Cardiology), and Pamela Woodard, M.D. (Radiology) who discussed applications of imaging modalities in the context of ECGI.

CBAC Faculty Members

Director - Yoram Rudy, Ph.D., F.A.H.A., F.H.R.S.
The Fred Saigh Distinguished Professor of Engineering; Professor of Biomedical Engineering, Cell Biology & Physiology, Medicine, Radiology, and Pediatrics; Director of the Cardiac Bioelectricity and Arrhythmia Center (CBAC), rudy@wustl.edu, 314.935.8160 Ph, 314.935.8168 Fax

R. Martin Arthur, Ph.D. , rma@wustl.edu
Newton R. and Sarah Louisa Glasgow Wilson Professor of Engineering; Professor of Electrical and Systems Engineering; Professor of Biomedical Engineering

Philip V. Bayly, Ph.D. , pvb@wustl.edu
Professor of Mechanical Engineering, and Chair of the Department of Mechanical, Aerospace, and Structural Engineering.

Sanjeev Bhalla, M.D., bhallas@wustl.edu
Associate Professor of Radiology; Assistant Radiology Residence Program Director, Mallinckrodt Institute of Radiology

John P. Boineau, M.D., schuesslerd@wustl.edu
Professor of Surgery, Medicine, and Biomedical Engineering

Jane Chen, M.D., janechen@wustl.edu
Assistant Professor of Medicine

Jonas Cooper, M.D., M.P.H., JCOOP-ER987623610@wustl.edu
(Washington University School of Medicine, 2001, MD; Harvard University, 2008, MPH)

Philip S. Cuculich, M.D., pcuculic@wustl.edu, Assistant Professor of Medicine, Clinical Cardiac Electrophysiologist, Department of Medicine at Washington University School of Medicine

Jianmin Cui, Ph.D., jcui@wustl.edu
Associate Professor of Biomedical Engineering on the Spencer T. Olin Endowment

Ralph J. Damiano, Jr., M.D., damianor@wustl.edu
John M. Shoenberg Professor of Surgery; Chief of Cardiac Surgery

Victor G. Davila-Roman, M.D., vdavila@wustl.edu
Associate Professor of Medicine, Anesthesiology, and Radiology; Medical Director, Cardiovascular Imaging and Clinical Research Core Laboratory

Igor R. Efimov, Ph.D., igor@wustl.edu
Professor of Biomedical Engineering

Mitchell N. Faddis, M.D., Ph.D., mfaddis@wustl.edu
Assistant Professor of Medicine, Radiology; Clinical Cardiac Electrophysiologist, Barnes Hospital

Vadim Fedorov, Ph.D., vfedorov@biomed.wustl.edu
Research Assistant Professor, BME Department

Richard W. Gross, M.D., Ph.D., rgross@wustl.edu
(Joint Appointment with the School of Medicine), Professor of Biological, Biophysical and Bioorganic Chemistry, Departments of Medicine, Molecular Biology and Pharmacology and Chemistry, Washington University School of Medicine

Patrick Y. Jay, M.D., Ph.D., jay_p@wustl.edu
Assistant Professor of Pediatrics and Genetics

R. Gilbert Jost, M.D., jostg@wustl.edu
Elizabeth Mallinckrodt Professor of Radiology; Chairman, Department of Radiology; Director, Mallinckrodt Institute of Radiology

Sándor J Kovács, Ph.D., M.D., sjk@wustl.edu
Professor of Medicine and Physiology, Adjunct Professor of Physics and Biomedical Engineering, Director, Cardiovascular Biophysics Laboratory

Leonid Livshitz, Ph.D., lmlivshitz@biomed.wustl.edu, Research Assistant Professor, CBAC, Biomedical Engineering, Washington University

Douglas L. Mann , M.D., dmann@wustl.edu
Tobias and Hortense Lewin Professor and Chief, Cardiovascular Division, Department of Medicine at Washington University School of Medicine, Cardiologist-in-Chief, Barnes Jewish Hospital, St. Louis, MO

Tony J. Muslin, M.D., F.A.H.A., amuslin@wustl.edu
Oliver M. Langenberg Distinguished Professor of the Science and Practice of Medicine; Professor of Cell Biology and Physiology; Director, Center for Cardiovascular Research (CCR); Director, Cardiology Research Fellowship Program

Ali Nekouzadeh, Ph.D., ali@biomed.wustl.edu
Research Assistant Professor, CBAC, Biomedical Engineering, Washington University

Arye Nehorai, Ph.D., nehorai@wustl.edu
Chairman and Professor of the Department of Electrical & Systems Engineering

Jeanne M. Nerbonne, Ph.D., jnerbonne@wustl.edu
Alumni Endowed Professor of Molecular Biology and Pharmacology

Colin G. Nichols, Ph.D., cnichols@wustl.edu
Professor of Cell Biology and Physiology

Joseph A. O'Sullivan, Ph.D., jao@wustl.edu
Professor of Electrical and Systems Engineering, Associate Professor of Radiology, Professor of Biomedical Engineering, Director of Electronic Systems and Signals Research Laboratory, Associate Director, Center for Security Technologies

CBAC Faculty Members

Jean E. Schaffer, M.D., jschaff@wustl.edu
Professor Internal Medicine, Developmental Biology

Richard B. Schuessler, Ph.D., schuesslerr@wustl.edu
Associate Research Professor of Surgery; Associate Research Professor of Biomedical Engineering; Director, Cardiothoracic Surgery Research Laboratory

Jingyi Shi, Ph.D., jshi22@wustl.edu
Research Faculty, Biomedical Engineering

Gautam K. Singh, M.D., M.R.C.P., singh_g@wustl.edu
Associate Professor, Department of Pediatrics, Director of Non-invasive Cardiac Imaging Research; Co-Director, Echocardiography Laboratory

Timothy W. Smith, D.Phil., M.D., tsmith@wustl.edu
Assistant Professor of Medicine

Jason W. Trobaugh, D.Sc., jasont@wustl.edu
Research Instructor in Medicine, Electrical and Systems Engineering

George F. Van Hare, M.D., vanhare_g@wustl.edu, Director, Pediatric Cardiology and Louis Larrick Ward Chair in Pediatric Cardiology at St. Louis Children's Hospital

Lihong Wang, Ph.D., lhwang@wustl.edu
Gene K. Beare Distinguished Professor; Department of Biomedical Engineering; Director, Optical Imaging Laboratory

Samuel A. Wickline, M.D., saw@wustl.edu
Professor of Medicine; Adjunct Professor of Physics and Biomedical Engineering; Co-Director of Cardiology

Pamela K. Woodard, M.D., woodardp@wustl.edu
Associate Professor, Diagnostic Radiology, Cardiovascular Imaging Laboratory, Mallinckrodt Institute of Radiology

Kathryn A. Yamada, Ph.D., F.A.H.A., kyamada@wustl.edu
Research Professor of Medicine; Director, Mouse Cardiovascular Phenotyping Core, Center for Cardiovascular Research, Cardiovascular Division

CBAC Faculty Alumni:

Amir A. Amini, Ph.D.
Kyongtae T. Bae , M.D., Ph.D.
Michael Cain, M.D.
Jonas Cooper, M.D.
Daniel P. Kelly, M.D.
Bruce Lindsay, Ph.D.
Achi Ludomirsky, M.D.
Vladimir P. Nikolski, Ph.D.
Edward Rhee, Ph.D.
Jeffrey E. Saffitz , M.D

Learn more information about the CBAC Faculty members at the CBAC website located at

http://cbac.wustl.edu/pageFaculty.asp.

Cardiac Bioelectricity & Arrhythmia Center (CBAC)

DR. YORAM RUDY, DIRECTOR

http://cbac.wustl.edu

FALL 2010 SEMINAR SCHEDULE

OCTOBER 11

Colleen Clancy, PhD, Associate Professor, Department of Pharmacology, University of California at Davis, Davis, California

"Computational Approaches to Reveal Mechanisms of Excitability in the Heart and Brain "

OCTOBER 18

Mark E. Josephson, MD, Chief, Division of Cardiovascular Medicine, CardioVascular Institute, Beth Israel Deaconess Medical Center. Professor of Medicine, Harvard Medical School, Director, Harvard-Thorndike Electrophysiology Institute and Arrhythmia Service, Boston, MA 02215

"Role of Substrate Mapping in Ablation of No-Tolerated VT in CAD"

OCTOBER 25

Gautam K. Singh, M.D., M.R.C.P., Pediatric Cardiologist, Director, The Preventive Cardiology Clinic, St. Louis Children's Hospital, and Associate Professor, Washington University School of Medicine

" Application of Tissue Doppler and Speckle Tracking Echocardiography in Clinical Cardiac Practice and Cardiac Resynchronization Therapy"

NOVEMBER 1

Mark Levin, M.D., Instructor in Pediatrics, Attending Cardiologist, Arrhythmia Service, Division of Pediatric Cardiology, St. Louis Children's Hospital, Washington University School of Medicine

"A Novel Model of Pulmonary Vein Triggers for Atrial Fibrillation "

NOVEMBER 8

Kalyanam Shivkumar, M.D., Ph.D., Professor of Medicine & Radiological Sciences, Director UCLA Cardiac Arrhythmia Center & EP Programs, David Geffen School of Medicine at UCLA, Los Angeles, CA

"Ventricular Tachycardia: Catheter Ablation and Beyond"

NOVEMBER 29

Barry London, M.D., Ph.D., Director, Cardiovascular Institute at the University of Pittsburgh Medical Center and Chief, Division of Cardiology and Professor of Medicine, Cell Biology & Physiology, University of Pittsburgh School of Medicine, Pittsburgh, PA.

"The Genetic Basis of Sudden Cardiac Death: From Inherited Arrhythmia Syndromes to Heart Failure

Washington University in St. Louis

Time: 5:30pm, Reception at 5:00pm
Location: Whitaker Hall, Room 218, Danforth Campus

CBAC Faculty Publications

November 2009—April 2010

Jeanne Nerbonne, Ph.D.:

* Ye, B. and Nerbonne, J.M. Proteolytic processing of HCN2 and heteromeric assembly with HCN4 in the generation of cardiac pacemaker channels. Journal of Biological Chemistry 284: 25553-25559 (2009).
* Marionneau, C., LeDuc, R.D., Rohrs, H.W., Link, A.J., Townsend, R.R., and Nerbonne, J.M. Proteomic analysis of native brain Kv4.2 channel complexes. Channels 3:284-294 (2009).
* Lorenzetto, E., Caselli, L., Feng, G., Yuan, W., Nerbonne, J.M., Sanes, J.R., and Buffelli, M. Genetic perturbation of postsynaptic activity regulates synapse elimination in developing cerebellum. Proceedings of the National Academy of Sciences, USA 106:16475-16480 (2009).
* Niwa, N., and Nerbonne, J.M. Molecular determinants of cardiac transient outward K^+ current (I_{to}): Expression and regulation. Journal of Molecular and Cellular Cardiology 48: 12-25 (2010).
* Matkovich, S.J., Wang, W., Tu, Y., Eschenbacher, W.H., Dorn, L.E., Diwan, A., Nerbonne, J.M., and Dorn, G.W. II. MicroRNA-133a decreases interstitial fibrosis and increases electrical remodeling without altering normal or pathological myocardial growth. Circulation Research 106: 165-175 (2010).
* Haim, T.E., Wang, W., Flagg, T.P., Tones, M.A., Bahinski, T., Numann, R., Nichols, C.G., and Nerbonne, J.M. Palmitate attenuates myocardial contractility through augmentation of repolarizing K^+ currents. Journal of Molecular and Cellular Cardiology, 48: 395-405 (2010).

Yoram Rudy, Ph.D.:

* J. R. Silva, H. Pan, D. Wu, A. Nekouzadeh, K. Decker, J. Cui, N. A. Baker, D. Sept, **Y. Rudy**, "A Multiscale Model Linking Ion-Channel Molecular Dynamics and Electrostatics to the Cardiac Action Potential" *Proc Natl Acad Sci USA (PNAS)* 2009;106:11102-11106.
* J. N. Silva, S. Ghosh, T. M. Bowman, E. K. Rhee, P. M. Woodard, **Y. Rudy**, "Cardiac Resynchronization Therapy in Pediatric Congenital Heart Disease: Insights from Noninvasive Electrocardiographic Imaging" *Heart Rhythm* 2009;6:1178-1185.
* L. Livshitz, **Y. Rudy,** "Uniqueness and Stability of Action Potential Models during Rest, Pacing, and Conduction Using Problem-Solving Environment" *Biophysical Journal* 2009;97:1265-1276.
* N. Gaur, **Y. Rudy**, L. Hool, "Contributions of ion-channel currents to ventricular action potential changes and induction of early afterdepolarizations during acute hypoxia" *Circulation Research* 2009;105:1196-1203.
* **Y. Rudy,** "Cardiac repolarization: Insights from mathematical modeling and electrocardiographic imaging (ECGI)" *Heart Rhythm* 2009;6(11):49-55.
* **Y. Rudy,** "Noninvasive imaging of cardiac electrophysiology and arrhythmia" *Annals N.Y. Academy of Sciences* 2010;1188:214-221.
* P.S. Cuculich, Y. Wang, B.D. Lindsay, R. Vijayakumar, **Y. Rudy**, "Noninvasive real-time mapping of an incomplete pulmonary vein isolation using Electrocardiographic Imaging (ECGI)" *Heart Rhythm* 2010, in press.
* S. Ghosh, D.H. Cooper, R. Vijayakumar, J. Zhang, S. Pollak, M. Haissaguerre, **Y. Rudy**, "Early repolarization associated with sudden death: Insights from noninvasive Electrocardiographic Imaging (ECGI)" *Heart Rhythm* 2010;7(4):534-537. M.P.
* Latacha, N.B. Memon, P.S. Cuculich, J. Hertel, Y. Wang, **Y. Rudy**, T.W. Smith, "Pathologic Examination after Epicardial Ablation of VT in Cardiac Sarcoidosis" *Heart Rhythm* 2010, in press.

Publications Cont'd.

November 2009—April 2010

Yoram Rudy, Ph.D. Continued:

* **Y. Rudy**, C. Ramanathan, S. Ghosh, "Noninvasive Electrocardiographic Imaging (ECGI): Methodology and Excitation of the Normal Human Heart" In: *Cardiac Electrophysiology: From Cell to Bedside*, 5th edition, Eds. D.P. Zipes and J. Jalife. Elsevier Science Publisher, 2009, pp. 467-472.
* **Y. Rudy**, Y. Wang, P. Cuculich, "Noninvasive Electrocardiographic Imaging (ECGI): Examples of Clinical Applications" In: *Cardiac Electrophysiology: From Cell to Bedside*, 5th edition, Eds. D.P. Zipes and J. Jalife. Elsevier Science Publisher, 2009, pp. 905-912.
* J Silva and Y. Rudy, "Ionic Mechanisms of Ventricular Action Potential Excitation" In: *Cardiac Electrophysiology: From Cell to Bedside*, 5th edition, Eds. D.P. Zipes and J. Jalife. Elsevier Science Publisher, 2009, pp. 317-328.
* N. Varma, P. Jia, **Y. Rudy**, "Electrocardiographic Imaging of Heart Failure Patients with Left Bundle Branch Block. Effects of Right Ventricular Pacing and Cardiac Resynchronization Therapy" In: *Cardiac Mapping*, 3rd edition, Eds. M. Shenasa, G. Hindricks, M. Borggrefe, G. Breithardt. Wiley - Blackwell Publishing, 2009, pp. 492-501.
* N. Varma, P. Jia, **Y. Rudy,** "The Role of Electrocardiographic Imaging in Cardiac Resynchronization Therapy" In: Cardiac Resynchronization Therapy in Heart Failure" Eds. W. T. Abraham and R.R. Baliga. Lippincott Williams & Wilkins, 2010, pp. 165-174.

George Van Hare, III:

* Silver ES, Silva JN, Ceresnak SR, Chiesa NA, Rhee EK, Dubin AM, Avasarala K, GF VANH, Collins KK. Cryoablation with an 8 -mm Tip Catheter for Pediatric Atrioventricular Nodal Reentrant Tachycardia Is Safe and Efficacious with a Low Incidence of Recurrence. *Pacing Clin Electrophysiol.(in press)*
* Anand RG, Rosenthal GL, Van Hare GF, Snyder CS. Is the mechanism of supraventricular tachycardia in pediatrics influenced by age, gender or ethnicity? *Congenit Heart Dis.* 2009;4(6):464-468.
* Silva JN, Van Hare G. Management of postoperative pediatric cardiac arrhythmias: current state of the art. *Curr Treat Options Cardiovasc Med.* 2009;11(5):410-416.
* Friedberg MK, Dubin AM, Van Hare GF, McDaniel G, Niksch A, Rosenthal DN. Acute effects of single-site pacing from the left and right ventricle on ventricular function and ventricular-ventricular interactions in children with normal hearts. *Congenit Heart Dis.* 2009;4(5):356-361.
* Van Hare GF. Pediatric electrophysiology series--catheter ablation in children. *Heart Rhythm.* 2009;6(3):423-425.
* Collins KK, Van Hare GF, Kertesz NJ, Law IH, Bar-Cohen Y, Dubin AM, Etheridge SP, Berul CI, Avari JN, Tuzcu V, Sreeram N, Schaffer MS, Fournier A, Sanatani S, Snyder CS, Smith RT, Jr., Arabia L, Hamilton R, Chun T, Liberman L, Kakavand B, Paul T, Tanel RE. Pediatric nonpost-operative junctional ectopic tachycardia medical management and interventional therapies. *J Am Coll Cardiol.* 2009;53(8):690-697.
* Khairy P, Van Hare GF. Catheter ablation in transposition of the great arteries with Mustard or Senning baffles. *Heart Rhythm.* 2009;6(2):283-289.
* Friedberg MK, Dubin AM, Van Hare GF, McDaniel GM, Niksch A, Rosenthal DN. Pacing-induced electromechanical ventricular dyssynchrony does not acutely influence right ventricular function and global hemodynamics in children with normal hearts. *J Cardiovasc Electrophysiol.* 2009;20(5):539-544.

Washington University in St. Louis

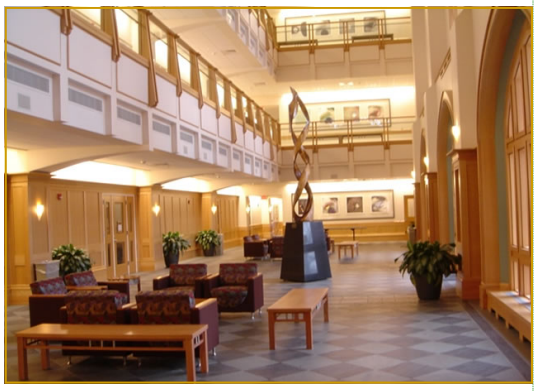
School of Engineering, Department of Biomedical Engineering

Contacts

If you would like to be added to the CBAC email list to receive information on upcoming seminars, events, and news, or to be added to the CBAC mailing list to receive future newsletters, email cbac@biomed.wustl.edu or call 314.935.7887.

Contact Information:

Cardiac Bioelectricity and Arrhythmia Center (CBAC)
Washington University in St. Louis
Whitaker Hall, Room 290A
1 Brookings Drive, Campus Box 1097
St. Louis, MO 63130-4899, USA
Phone: 314.935.7887
Fax: 314.935.8168
www.cbac.edu
www.rudylab.edu



Whitaker Hall Atrium, home to the Department of Biomedical Engineering and the CBAC.

The *"Center Heartbeat"* is a publication of the Cardiac Bioelectricity and Arrhythmia Center @ Washington University in St. Louis, MO.
Created, Designed and Edited by Kimberly M. Smith, CBAC Administrator and Webmaster