



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)

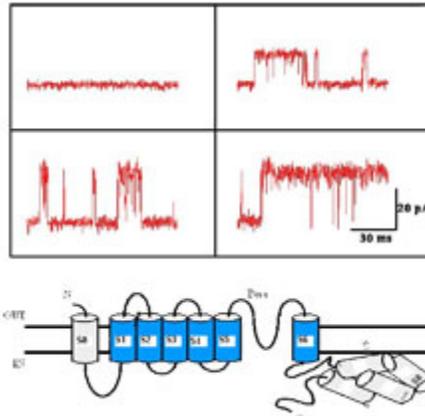
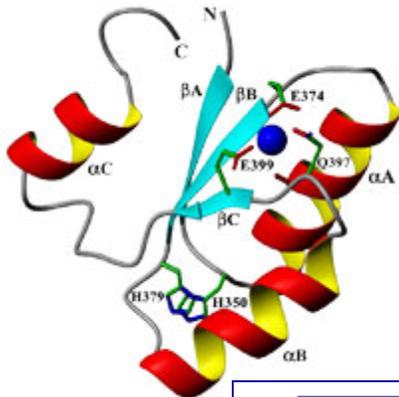


The **Cardiac Bioelectricity and Arrhythmia Center, CBAC**, is an interdisciplinary center whose goals are to study the mechanisms of rhythm disorders of the heart (cardiac arrhythmias) and to develop new tools for their diagnosis and treatment. Cardiac arrhythmias are a major cause of death (over 300,000 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.

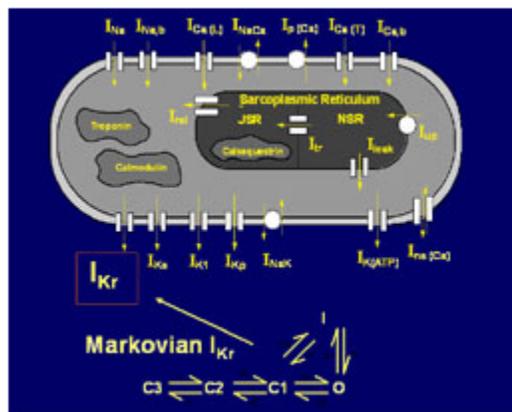
Our mission is **to battle cardiac arrhythmias and sudden cardiac death through scientific discovery and its application in the development of mechanism-based therapy.**

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



FROM THE DIRECTOR'S DESK.....

Thanks to Kimberly Smith who produced yet another interesting issue of the *Center Heartbeat*, and to the CBAC members who contributed to the issue. While preparing a lecture for the Cardiac Physiome Workshop, held at **Merton College** of Oxford University in July, I discovered that **William Harvey** (1578-1657) was made a "Doctor of Physic" at Oxford in 1642 and later Warden of Merton College in 1645 "by the king's mandate" (Merton College was established in 1264).



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

William Harvey was the first person to describe the circulation of blood. Based on many experimental observations and quantitative arguments, he rejected the accepted concept at the time, based on the teachings of Claudius Galen, that blood was formed in the liver and absorbed by the body, and that it flowed through the septum of the heart. From examination of the heartbeat, Harvey argued that blood was being re-circulated in a closed system and pumped by the heart into two separate loops, the pulmonary circulation and systemic circulation. He provided a detailed analysis of the structure of the heart and determined that the two ventricles contracted together, almost simultaneously. Harvey announced his discovery of the circulatory system in 1616 and in 1628 published (in Frankfurt) his treatise *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (an Anatomical Exercise on the Motion of the Heart and Blood in Animals). Harvey's radical ideas about the blood circulation hurt his medical practice. However, he was appointed as court physician to King James I in 1618 and later to Charles I in 1625. The English Civil War led King Charles to Oxford, with Harvey attending.

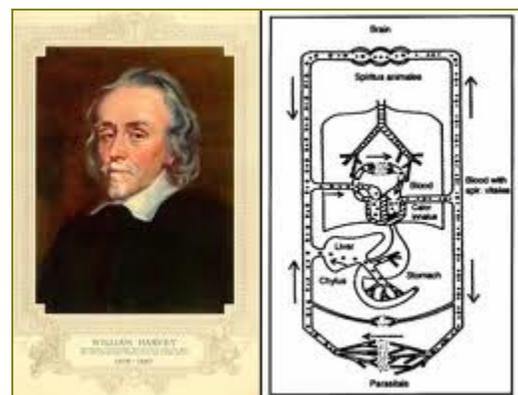
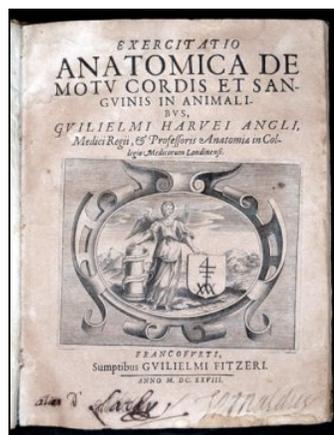
Harvey made profound statements about the heart and other subjects; here are a few quotes:

"The heart of animals is the foundation of their life, the sovereign of everything within them, the sun of their microcosm, that upon which all growth depends, from which all power proceeds."

"[The heart] is the household divinity which, discharging its function, nourishes, cherishes, quickens the whole body, and is indeed the foundation of life, the source of all action."

"There is a lust in man no charm can tame: Of loudly publishing his neighbor's shame: On eagles wings immortal scandals fly, while virtuous actions are born and die."

"I just start singing, and it all comes back."



CBAC PEOPLE & EVENTS



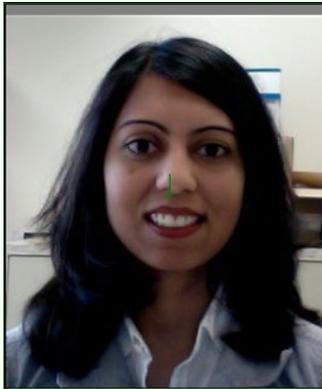
INSIDE THIS ISSUE:

- 2...CBAC Mission
- 3...From the Director's Desk
- 5...CBAC Profiles...Urvi Lee
- 6...*"The Evolution of Surgical Treatment of Atrial Fibrillation"* by Dr. Richard Schuessler
- 9...*"Finding There"*, Dr. Daniel Cooper
- 10..Lectures & Presentations
- 14...*Spotlight On, Dr. Patrick Jay*
- 16...Announcements & News
- 17...*"Friends from Abroad"*
- 19...CBAC Faculty Members
- 22...Publications
- 25...CBAC Fall 2011 Seminar Schedule
- 30...CBAC Contact Information

Each year the CBAC strives to provide academics and clinicians the opportunity to network and possibly develop collaborations that will further the discovery of new and innovative ways to save the lives of individuals with cardiac illnesses. The CBAC Seminar Series for Fall and Spring featured speakers from both worlds who came from far and near to share their expertise. Top left, Drs. Yoram Rudy and guest speaker, Dr. Stanley Nattel, Chair of Cardiovascular Electrophysiology, Professor of Medicine University of Montreal, Director, Electrophysiology Research Program at the Montreal Heart Institute Research Center in Canada. Top right, Philip Cuculich, M.D., Assistant Professor of Medicine at Washington University is both a clinician and research scientist. Lower left, Dr. Peng-Sheng Chen is the Chair of Cardiology, and Director of the Krannert Institute of Cardiology and the Chief of Cardiology at Indiana University School of Medicine. Lower right, Dr. Bernard Attali is a professor in the Department of Physiology & Pharmacology at the Sackler Medical School, Tel Aviv University. As you see from the two middle photos, attendees enjoy refreshments, the presentation and Q&A that follows. The seminars are always open to the public and free.



CBAC Profiles....



Urvi Lee

The CBAC is comprised of not only a superb group of faculty, there is a budding group of researchers that are being trained by these faculty who are looking to blaze further trails in the field of cardiology. Urvi Lee is a Ph.D. fellow who is currently working in Dr. Schuessler's lab. Urvi shares some of her story with the *Center Heartbeat*. I have always enjoyed math and science classes. When deciding on a career in college, I came across bioengineering, which was a perfect combination of these two interests. I was very excited, as this was exactly what I wanted. I did not know that I wanted to do in research until I began working with Dr. Sangeeta Bhatia at UCSD, whose interest includes understanding liver physiology. In her laboratory, I utilized microfabrication tools, commonly used in manufacturing computer chips, as a scaffold to culture hepatocytes to study their function and received a scholarship for this work. It was this exciting experience that led me to consider a PhD. My interest in cardiac physiology and pathophysiology stems primarily from the numerous engineering and physiology courses focused on the cardiac system while in undergraduate school. However, I would not be able to pursue my current research topic in the Cardiothoracic Surgery Research Laboratory if not for my doctoral work in Dr. Jianmin Cui's laboratory where I learned to become an independent scientist. After receiving my BS in Bioengineering from UCSD in 2001, I spent a year working as a research associate at Aurora Biosciences. It was during this time that I decided to pursue a doctorate degree and matriculated in Washington University's Biomedical Engineering Department. I did my doctoral thesis under Dr. Jianmin Cui and graduated in May 2010. Soon after, I began working as a postdoctoral fellow in the Cardiothoracic Surgery Research Laboratory under Dr. Richard Schuessler. My project focuses on examining the ionic remodeling in right atrial myocytes in a canine inflammation model of postoperative atrial fibrillation. I would not call it a personal achievement, but am tremendously grateful that throughout my short career I have had the support of my best friend, my husband. I am having a wonderful time working in the CT surgery lab where I have had the opportunity to assist and watch the surgical fellows with their projects, discuss complications in cardiac function with the fellows, and attend in-house clinical conferences to understand different surgical problems. In the CT Surgery Research laboratory, the right atrial tissue from the canine inflammation model was used to examine changes in ion channels, gap junction proteins and inflammatory cytokines gene expression using quantitative PCR. Now, we are interested in quantifying the ion channel protein expressed in right atrial myocytes from the canine inflammation model by using a whole cell recording technique. These studies are being conducted in collaboration with Drs. Jeanne Nerbonne and Kathryn Yamada. Currently, we have successfully isolated right atrial myocytes and have been able to do whole cell recordings, but do not have complete results, as this project is still ongoing. I hope in the next few years to have some results for publication. I have been participating in CBAC activities since its inception and have been impressed with the speakers from our own institution and those visiting. It is a great forum to hear about exciting work that is going on in understanding the electrical activity of the heart from microscopic cellular level to the organ as a whole. This type of perspective has been very beneficial in my understanding of arrhythmia.



The Evolution of Surgical Treatment of Atrial Fibrillation, by Richard B. Schuessler, Ph.D.

In a previous issue of this newsletter (Issue # 5, Fall 2009), John Boineau presented an excellent review of the early development of the surgical treatment of cardiac arrhythmias. His pioneering work established the paradigm and set the stage for development of surgical treatment of atrial fibrillation (AF). In that review he summarized the animal and human studies that resulted in the development of the Maze procedure with Dr. James Cox. The first Maze procedure was performed by Dr. Cox in a patient with persistent lone AF in September 1987. The operation involved the creation of a series of incisions in the left and right atria (Figure 1) that isolated some regions of the atria and subdivided other regions. The incisions were designed to terminate the AF and permit normal sinus rhythm activation of the atria and ventricles. A human study trial involving long term follow-up of patients who had failed numerous other therapies and undergone the Maze procedure showed that over 90% were in NSR at 8 years. Between 1987 and 1999, only 198 patients had undergone the Cox Maze(CM) procedure at Washington University. The number of CM procedures performed worldwide only numbered a few hundred over this 12 year period. Why were so few procedures performed when the results were so positive?

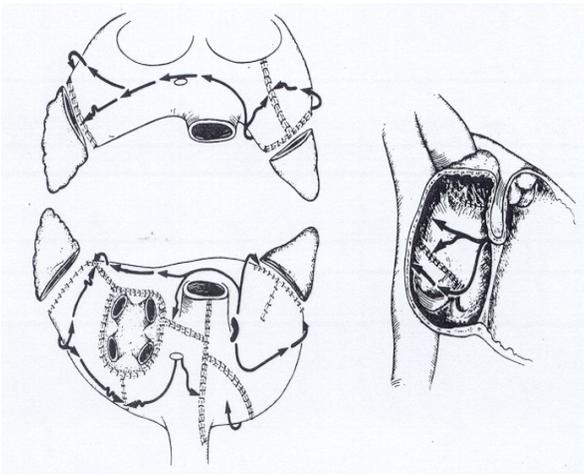


Figure 1 The Cox Maze III Procedure-The final cut and sew version of the Cox Maze procedure.

A major problem with the CM procedure is that it is a very complex and difficult procedure to perform. The extensive nature of the incisions requires a long period of suturing to close all of the incisions. Even in the hands of an experienced surgeon, it adds 90 minutes to the time the patient is on cardiopulmonary bypass and the heart is arrested. In addition, the procedure is often performed with a concomitant procedure, such as a valve repair or coronary bypass procedure. Even at Washington University only 5 CM procedures were performed in 1998. Prior to 1998, only 198 CM procedures were performed at our institution.

In 2000, Dr. Ralph Damiano, Jr. became chief of Cardiac Surgery at Barnes-Jewish Hospital and Washington University. As a student of Dr. Cox, he set out to address the issue of the complexity of the CM procedure and make it more accessible to cardiac surgeons. He realized that if the “cut and sew” lesions could be replaced by a line of block created by a device that made a transmural lesion without having to cut the tissue, the operation could be simplified. The technology would have to be reliable, because the success of the CM procedure depended on the creation of a transmural lesion that completely blocked the spread of activation. Cutting the tissue with surgical scissors makes it easy to verify that the lesion is transmural, because the tissue separation can be visually verified. When the tissue is sewn back together, it creates a scar that does not allow propagation of activation across the scar. A technology was needed that would create these linear lesions and have a feedback mechanism that would verify that the lesion was transmural through the tissue and blocked activation. In addition, the lesion would have to be permanent. In other words, rather than stunning the tissue so that it temporarily blocked conduction, the lesion had to be permanent so that the tissue would not recover over time.

During this period, a number of both large medical device companies and small start up companies began working on the development of ablation devices and we worked with them to test their ideas in our laboratory in animal models. All of the companies took one of two basic approaches. They either heated the tissue or froze the tissue to kill it. A number of energy sources to heat the tissue were tested. The challenge was to create a lesion by heating the tissue to approximately 50°C to kill it, but keep it below 100°C so that it did not create a hole or cut through the tissue. A number of technologies were tried. These included radio frequency (RF), microwave, high frequency ultrasound, and laser energies. The most successful technology was RF. This type of energy historically has been used in a variety of surgical procedures. Electrocautery devices, which use RF energy, are routinely used to cut and coagulate tissue. The energy is applied by a unipolar probe that serves as one pole of the electric circuit and a common large grounding plate is placed on the back of the patient to complete the circuit. The focused

The Evolution of Surgical Treatment of Atrial Fibrillation (Cont'd.)

RF energy from the probe creates a current density that heats the tissue and cuts or coagulates it. The current density on the grounding plate is too low to heat the tissue above it. These electrocautery devices were also equipped with a thermistor to control the temperature. Once the temperature of the tissue was above 50°C, a controller modulated the energy delivery to maintain the temperature above 50°, but below 100° for a fixed period of time. We performed extensive testing of these RF devices, as well as laser and microwave devices, in laboratory animals. None of the devices reliably created the lines of transmural block required for the CM procedure. However, a number of manufacturers made bipolar RF clamps that had an electrode on each jaw of the clamp.

By clamping the tissue between the two jaws, all of the RF energy was focused between the jaws. With a bipolar device, impedance between the two electrodes could be measured. The impedance would suddenly increase when all the water was removed from the tissue between the jaws. We were able to show that the change

in impedance was a reliable surrogate for cell death and permanent transmural ablation of all the tissue between the jaws of the clamp. Both acute and long term animal studies demonstrated that these clamps could be used to create the lesion set of the CM III procedure reliably and safely. We also tested cryoablation devices. Instead of heating the tissue, these devices froze the tissue to kill it. Cryoablation has a long history of use in cardiac arrhythmia surgery and other surgical procedures, appears to do minimal damage to sensitive cardiac structures such as the valves and coronary arteries, and has few safety concerns. However, cryoprobes are more difficult and time consuming to use and create much wider lesions. But because of their safety record, we used the cryoprobes to create the lesions near the mitral and tricuspid annuli, which are near the circumflex and right coronary arteries respectively.

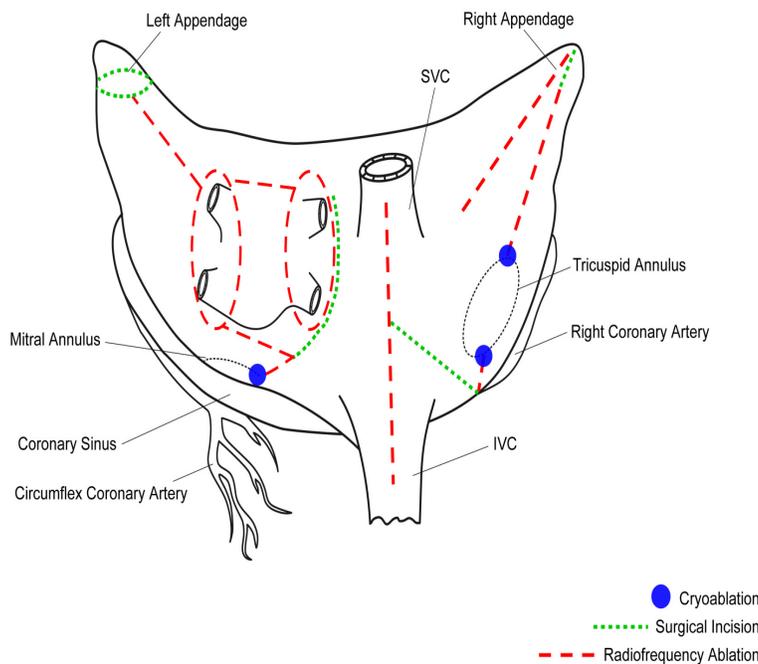


Figure 2 The Cox Maze IV

Based on our animal studies, Dr. Damiano designed a procedure, based on the CM III procedure, that used both the new RF bipolar clamps and a cryoprobe. The lesion set is shown in Figure 2. Many of the original CM incisions were replaced with ablation lines created with RF ablation or cryoablation. The new procedure was designated the Cox Maze IV (or CM IV) and was used in patients with AF. We performed a propensity analysis to compare 58 matched patients who had the CM III with 58 patients who had the CM IV. All the outcomes except the cross clamp time, including the freedom from AF, were equivalent. The cross clamp time of the CM III was two hours, whereas the cross clamp time of the CM IV was only one hour. The use of these ablation devices made the procedure much easier to perform and reduced the risk to the patient.

The next step was to determine if the procedure could be simplified. A number of reports have suggested that isolating only the pulmonary veins can terminate AF. However, when we isolated only the pulmonary veins, only 60% of those patients were free of AF at one year, compared to over 90% free from AF at one year in an equivalent group of patients who received the full CM IV procedure.

Even though pulmonary vein isolation was inadequate in our patient population, we still questioned whether it was necessary to do the complete CM IV procedure. In particular, the CM IV isolates the entire posterior left atrium, including the pulmonary veins and the region between them. We tested whether or not complete atrial isolation was necessary. In a cohort of patients, all the lesions of the CM IV were created, except for the lesion connecting the superior pulmonary veins. This allowed the region between the pulmonary veins to be activated during normal sinus rhythm. We felt that this area could contribute to the atrial contraction if it were activated. When compared to patients who had the full CM IV, the group without the full lesion set was 80% free of AF at one year compared to 90% in patients who underwent the complete CM IV procedure. In addition, more patients with the reduced lesion set required anti-arrhythmic drug therapy to remain free of AF.

The Evolution of Surgical Treatment of Atrial Fibrillation (Cont'd.)

In a recent paper, we evaluated 100 patients who underwent the CM IV. At two years, the rate of freedom from AF in these patients was 90%. However, some patients required anti-arrhythmic drugs to remain free of AF. The rate of freedom from AF without the use of anti-arrhythmic drugs was 82%. So why did some patients fail to be free of AF? One of the principal risk factors for failure is preoperative left atrial size. As the left atrial size goes from a normal size to grossly enlarged, a common occurrence in mitral valve disease, the failure rate of the CM IV goes from less than 10% to over 50%. We are presently doing research in our laboratory to understand how atrial sizes affect the heart's ability to sustain AF. It is clear from the clinical data that the CM IV is inadequate for some patients with AF. On the other hand, a significant number of patients can be cured of AF with a more limited procedure. The CM IV is too extensive a procedure for some patients and not extensive enough for other patients. How can the optimal procedure for each patient be determined? A patient-specific approach to the treatment of each AF patient which accounts for the individual patient's anatomy and electrophysiology needs to be developed. In the future, we hope to use ECGI as developed by Dr. Yoram Rudy to characterize the anatomy and electrophysiology of individual AF patients.

What does the future hold? In addition to developing a patient-specific approach for surgical treatment of AF, we are trying to make the procedure less invasive. Presently, the CM IV requires cardiopulmonary bypass and a median sternotomy. This is a major cardiac operation with all its associated risk. For patients who are already undergoing a cardiac operation, adding the CM IV procedure does not significantly increase the risk in most patients. In 2010, 930 open heart operations were performed at Barnes-Jewish Hospital. Approximately, 15% of these patients had preexisting AF along with their primary disease. All of these patients are potential candidates for the CM IV procedure. By making the operation easier to perform, Dr. Damiano has increased the number of patients who receive the CM IV procedure from 5 in 1998 before he came to Washington University, to 93 in 2010. (Figure 3) Nationally, the Society of Thoracic Surgeons, which maintains a database of surgeries performed at most major medical centers in the United States, reported that during the period between 2004 and 2006 over 25,000 patients underwent a procedure for the treatment of AF. This only represents about 60% of the patients undergoing cardiac surgery who had AF in addition to their primary disease, so there is room to increase the number of cardiac surgery patients who could benefit from the CM IV. This still only represents a small fraction of the 2-3 million people in the US who have AF. To expand treatment to these patients, a procedure that is less invasive and that does not require cardiopulmonary bypass is needed.

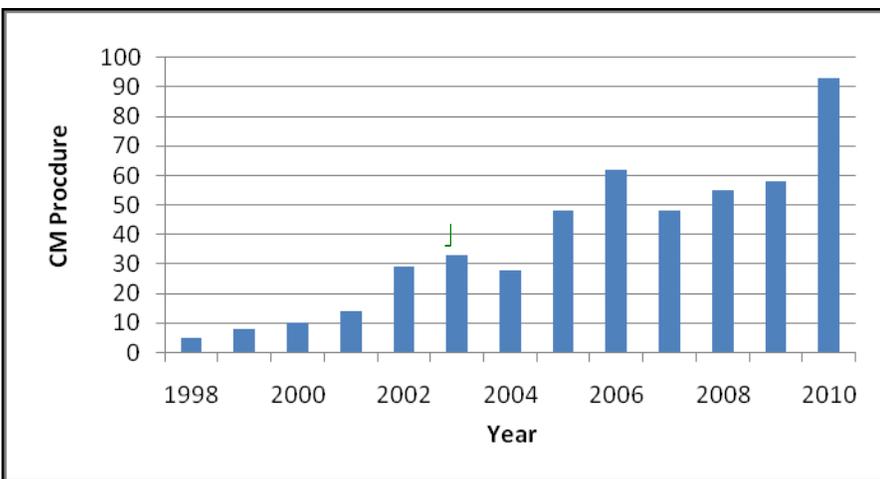


Figure 3 The number of patients who have had the CM IV procedure at Washington University from 1998 through 2010 by year.

Dr. Damiano and Dr. Hersh Maniar are currently working with Dr. Philip Cuculich, a Washington University cardiologist, to develop a hybrid procedure in which the cardiologist places catheters transvenously into the heart while at the same time the surgeon introduces ablation devices through the chest wall using minimally invasive ports. This approach is in its infancy and will require improvements in the technology. We are testing new devices in our laboratory in animal models to develop more effective ablation technology along with techniques for better access to the heart. As we make progress, we increase the number of patients who can benefit from these new treatment modalities.

I have been fortunate to have been involved in the development of the original Maze procedure with Drs. Cox and Boineau. I am now privileged to work with Dr. Damiano, as well as Drs. Maniar and Cuculich, helping to improve and expand the treatment of the most common cardiac arrhythmia, atrial fibrillation.

The Journey to M.D.



Daniel H. Cooper, M.D.

Honestly, I thought I was going to be an orthopedic surgeon. However, once you are immersed in a particular field of study, you start to get a feel for the nuances unique to each specialty. I tell every medical student I come across who is struggling with career choices that we all have to be critical and honest with ourselves and choose a field that suits our personality and skill sets. A poor choice made for the wrong reasons could leave you in a career that you have little passion for and you'll find yourself with little opportunity to advance the field. Cardiology, for me, was the choice that I thought would get me out of bed in the morning for the decades to come.

Like most students, I tended to gravitate towards those teachers who were passionate and effective at communicating the interesting subtleties to their trade. There was one cardiologist in medical school who taught us ECGs, whose enthusiasm was particularly contagious and started me down this path. At that time, I was completely unaware of the subspecialty of electrophysiology and he encouraged me to do an away rotation at Washington University on the "arrhythmia service". During this month, I had the opportunity to work with Drs. Jane Chen, Timothy Smith, Mitchell Faddis, Marye Gleva and Lindsay and was exposed for the first time to EP. I loved it... but it felt very much like being dropped into a foreign country. I quickly learned the basic vocabulary I needed to survive and have spent the subsequent 9 years working towards fluency.

My undergraduate studies were at Washington University-St. Louis, medical degree from Loyola University Chicago, and residency, chief residency, cardiology and EP fellowships have been at Barnes Jewish Hospital/Washington University School of Medicine. Now that I have run out of opportunities to prolong my training any further, I will become an assistant professor in the EP section at Wash U starting in July.

My current collaboration with Dr. Rudy's lab looking at the differences in electrophysiologic substrate in ischemic cardiomyopathy patients with and without clinical ventricular arrhythmias is particularly exciting. We are utilizing ECGi to noninvasively characterize patients who have required ICD therapy to terminate VT and comparing them to patients who have never received ICD therapy despite being > 4 years since implant and having, on the surface, similar clinical characteristics. Preliminary results suggest patients with VT tend to have larger areas of abnormal electrophysiologic substrate and have a greater prevalence of electrogram characteristics reflective of scar heterogeneity. A better understanding of what makes these patients different will aid in our ability to risk stratify our patients and could contribute to decisions regarding ablative therapies in the future. In the next few years, I hope to quickly build a successful, busy clinical practice. I hope to offer my patients the opportunity to participate in research that will be geared towards advancing our understanding of their ailment. Through my collaboration with scientists in CBAC I hope to contribute to cutting edge research that will push the science forward and provide us the insight and/or technology not yet available to improve outcomes for our patients.

My family is, by far, my most important personal achievement. My wife, Amber, and my two daughters, Ashley and Alexis, remind me everyday of what is most important in life and how fortunate I am to have them.

CBAC offers the unique opportunity to meet and discuss our research with thought leaders across the globe. In addition to the valuable insight it provides for our own projects, the conferences help us realize how others are approaching the difficult questions of our day where the knowledge gaps remain wide. It helps foster collaboration between centers and it provides the audience, especially those of us at the beginning of our careers, with weekly examples of success in academic medicine to emulate.



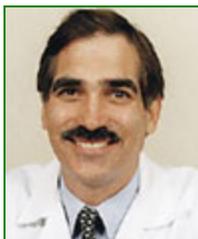
LECTURES & PRESENTATIONS



Phillip S. Cuculich, M.D., Assistant Professor of Medicine, Cardiovascular Division, Washington University School of Medicine

- * “Noninvasive ECG Imaging (ECGI)”, CBAC Spring 2011 Seminar, April 4, 2011.
- * Invited Speaker at Stanford BioDesign in Electrophysiology Symposium, Palo Alto, CA.

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Ralph J. Damiano, Jr., M.D., John M. Shoenberg Professor of Surgery; Chief of Cardiac Surgery, Washington University School of Medicine

- * Melby SJ, Damiano RJ Jr: Surgical treatment of arrhythmias. In: Sabiston & Spencer: Surgery of the chest (8th edition). Selke FW, del Nido PJ, Swanson SJ (eds) Saunders Elsevier, Philadelphia; 2010 pp 1345-1365
- * Lawton JS, Damiano RJ Jr: Off pump coronary artery bypass. A valuable technique but not for everyone (Editorial). Innovations 2010;5:1-2.
- * Sakamoto S, Schuessler RB, Lee AM, Aziz A, Lall SC, Damiano RJ Jr: Vagal denervation and reinnervation after ablation of ganglionated plexi. J Thorac Cardiovasc Surg 2010; 139:444-452.
- * Voeller RK, Zierer A, Lall SC, Sakamoto S, Schuessler RB, Damiano RJ Jr: Efficacy of a novel bipolar radiofrequency ablation device on the beating heart for atrial fibrillation ablation: A chronic porcine study. J Thorac Cardiovasc Surg 2010;140:203-208.
- * Cuculich PS, Wang Y, Lindsay BD, Faddis MN, Schuessler RB, Damiano RJ, Li L, Rudy Y: Noninvasive characterization of epicardial activation in humans with diverse atrial fibrillation patterns. Circulation 2010;122:1364-1372.
- * Aziz A, Lawton JS, Moazami N, Pasque MK, Damiano RJ Jr., Moon MR: Factors affecting survival following mitral valve replacement in patients with prosthesis-patient mismatch. Ann Thorac Surg 2010;90:1202-1211.
- * Lee AM, Clark K, Bailey MS, Aziz A, Schuessler RB, Damiano RJ Jr: A minimally invasive Cox-Maze procedure. Operative technique and results. Innovations 2010;5:281-286.
- * Damiano RJ Jr, Schwartz FH, Bailey MS, Maniar HS, Munfakh NA, Moon MR, Schuessler RB: The Cox maze IV procedure: Predictors of late recurrence. J Thorac Cardiovasc Surg 2011;141:113-121.
- * Shen J, Lall S, Zheng V, Buckley P, Damiano RJ, Schuessler RB: The persistent problem of new-onset postoperative atrial fibrillation: A single-institution experience over two decades. J Thorac Cardiovasc Surg 2011;141:559-570.
- * Voeller RK, Zierer A, Schuessler RB, Damiano RJ Jr: Performance of a novel dual electrode bipolar radiofrequency ablation device. A chronic porcine study. Innovations 2011;6:17-22.

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Igor R. Efimov, Ph.D., F.A.H.A., F.H.R.S., Lucy and Stanley Lopata Distinguished Professor of Biomedical Engineering, Washington University

- * “Functional Remodeling in Heart Failure”, Heart Rhythm Society, San Francisco, CA, 5/6/11
- * “Biophotonic Imaging of the Human Heart”, Heart Rhythm Society, San Francisco, CA, 4/5/11
- * “Dual Pathways and Connexin 43 in the Human AV Node”, Andrew L. Wit Symposium, Columbia University, New York City, NY, 2/5/11
- * “Structural and functional evidence for discrete exit pathways”, International Society for Computerized Electrocardiography, San Jose, CA, 4/14/11
- * “Towards a Pain-free Implantable Atrial Cardioverter”, Visiting Professor, Cleveland Clinic Foundation, 04/11./2011
- * “Painless defibrillation”, Old Dominion University, Norfolk, VA, 03/18./2011
- * “Electrophysiology of Failing Human Heart”, Gordon Research Conference on Cardiac Arrhythmia Mechanisms, Galveston, TX, 02/15./2011
- * “Low voltage atrial defibrillation”, Boston Scientific, Minneapolis, MN, 02/04./2011
- * “The Sinus and AV Nodes of the Heart: from Mouse to Man”, New York University, New York, NY, 12/17/2010.
- * “Low Voltage Atrial Defibrillation”, Medtronic, Minneapolis, MN, 2010/11/09.



LECTURES & PRESENTATIONS CONT'D.

Igor R. Efimov, Ph.D., F.A.H.A., F.H.R.S., cont'd.:

- * "History of Progress Towards Painless Defibrillation", Department of Biomedical Engineering, University of Michigan at Ann Arbor, MI, 2010/11/04.
- * "Electrophysiological Remodeling of Failing Human Heart", Department of Molecular and Integrative Physiology, University of Michigan at Ann Arbor, MI, 2010/11/03.
- * "Biophysics and Bioengineering of the Heart", State University of Nizhny Novgorod, Russia, 2010/10/15.
- * "Low voltage defibrillation", Institute of Applied Physics, Russian Academy of Sciences, Nizhny Novgorod, Russia, 2010/10/12.
- * "History of Progress Towards Painless Defibrillation", Department of Cardiology, Rhode Island Hospital, Cardiology Grand Rounds, 2010/10/01.
- * "Imaging Electrophysiological Remodeling in Failing Human Heart", Cardiovascular Research Center, Rhode Island Hospital and Brown Medical School, 2010/09/30.
- * "Electrophysiological Remodeling in Human Cardiomyopathy", Grand Rounds, Department of Anesthesiology, Washington University School of Medicine, 2010/09/08
- * "Cardiac electrotherapy", Nizhny Novgorod State University, Nizhny Novgorod, Russia, 2010/06/29
- * "Quantitative cardiac physiology", Nizhny Novgorod State University, Nizhny Novgorod, Russia, 2010/06/28
- * "Molecular basis of human heart physiology", Ioffe Physico-technical Institute, Sankt Peterburg, Russia, 2010/06/23
- * "Sinoatrial excitation", Cardiostim, Nice, France, 2010/06/17

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Douglas L. Mann, M.D., 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

- * 2010 "Heart Failure is Dead, Long Live the Heart Failure Society of America," Presidential Address at the 14th Annual Scientific Session of the Heart Failure Society of America, San Diego, CA (9/13/10)
- * 2010 "Innate Immunity and the Failing Heart, for Whom the Cell Tolls," 8th Annual Center for Heart Failure Research Symposium. Oslo, Norway (9/30/10)
- * 2010 Guest Speaker at the Course Transcending Frontiers in Internal Medicine "Inflammatory Mediators in Heart Failure: Past, Present and Future", "Patho-physiologic Basis for Therapeutic Strategies in Congestive Heart Failure" and "Optimization in the Management of Heart Failure" Quito, Ecuador (10/18-20/10)
- * 2010 American Heart Association Scientific Sessions Moderator, Session "MicroRNAs in Heart Failure: Novel Diagnostic Markers and Treatment Targets" Chicago, IL (11/13/10)
- * 2010 University of Missouri – Columbia, Division of Cardiovascular Medicine Give Cardiovascular Medicine Grand Rounds, "Cardiac Remodeling as a Therapeutic Target in Heart Failure" Columbia, MO (12/2/10)
- * 2011 12th Hellenic National Heart Failure Congress "Role of Inflammation in Diabetic Cardiomyopathy" Chair of session, "Regenerative Medicine and Advanced HF" Athens, Greece (2/5/11)

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Jeanne M. Nerbonne, Ph.D., Alumni Endowed Professor of Molecular Biology and Pharmacology, Department of Developmental Biology, Washington University School of Medicine

- * "Targeting miRNAs: Can miRNAs be Potential targets?" 31st Annual Scientific Sessions of the Heart Rhythm Society, Special Session on Basic/Translational Science Forum: Novel Targets to Cure Cardiac Arrhythmias. Denver, CO, May 2010.
- * "Ion Channels in Atrial Fibrillation." Cardiostim 2010; 10th Biennial World Congress on Cardiac Arrhythmias and 17th World Congress on Cardiac Electrophysiology and Cardiac Techniques. Symposium entitled: Mechanisms of Fibrillation. Nice, France, June 2010.
- * "Ion Channel Remodeling in Cardiac Hypertrophy and Failure." 33rd Meeting of the North American Section of the International Society for Heart Research (ISHR). Philadelphia, PA, May 2011.



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 Bio-medical Engineering, Cell Biology & Physiology, Medicine, Radiology and Pediatrics, Director, Cardiac Bioelectricity & Arrhythmia Center

- * 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.
- * Heart Rhythm Society 31st Scientific Sessions. ECG-Imaging to Identify Scar. Denver, May 2010.
- * Heart Rhythm Society 31st Scientific Sessions. Linking Ion-Channel Molecular Dynamics and Electrostatics to the Cardiac Action Potential. Denver, May 2010.
- * University of Milan, Department of Biology. Modeling and Imaging Cardiac Repolarization. Milan, Italy, May 26, 2010.
- * University of Parma, Department of Physiology. Modeling and Imaging Cardiac Repolarization. Parma, Italy, May 28, 2010.
- * University of Parma, Department of Physiology. Noninvasive ECG Imaging (ECGI) of Human Cardiac Arrhythmias. Parma, Italy, May 28, 2010.
- * University of Florence, Center for Molecular Medicine. Modeling and Imaging Cardiac Repolarization. Florence, Italy, June 1, 2010.
- * Cardiostim 2010 -10th World Congress on Cardiac Arrhythmias. Perspectives on Mathematical Modeling of Cardiac Electrophysiology. Nice, France, June 2010.
- * Cardiostim 2010 -10th World Congress on Cardiac Arrhythmias. Noninvasive ECG Imaging (ECGI) of Human Atrial Fibrillation. Nice, France, June 2010.
- * Workshop on Cardiac Arrhythmias, “The molecular basis of cardiac repolarization” University of Bern, Switzerland, June 20-22, 2010.
- * Cleveland Clinic Foundation, Visiting Professor Lecture Series. “ECG Imaging”. Cleveland, Ohio, July 27, 2010.
- * University of Missouri, Department of Biological engineering and Dalton Cardiovascular Research Center. “Modeling and Imaging Cardiac Repolarization and Arrhythmias” Columbia, Missouri, September 1, 2010.
- * 8th Annual Heart Failure Research Symposium, “The molecular basis of cardiac action potential repolarization”. Center for Heart Failure Research, University of Oslo, Norway, September 30 – October 1, 2010.
- * American Heart Association Scientific Sessions 2010, “Computational Modeling with Real Human Experimental Data”. Chicago, Nov. 13-17, 2010.
- * Second European VT/VF Meeting “Noninvasive ECG Imaging [ECGI]”, Berlin, Germany, November 20, 2010.
- * Gordon Research Conference on Cardiac Arrhythmia Mechanisms. “Molecular Dynamics of LQT1 Syndrome”, Galveston, Feb. 13-18, 2011.
- * Heart Rhythm Society 32nd Scientific Sessions. “Novel Imaging Techniques – ECG Imaging”, San Francisco, May 2011.
- * Heart Rhythm Society 32nd Scientific Sessions. “Imaging Modalities in Electrophysiology - Electrocardiographic Imaging”, San Francisco, May 2011.
- * Heart Rhythm Society 32nd Scientific Sessions. “In-Silico Prediction of Drug Responses”, San Francisco, May 2011.
- * Heart Rhythm Society 32nd Scientific Sessions. “Molecular Dynamics and Channel Structure-Function”, San Francisco, May 2011.
- * Fields Institute Conference on Mathematics of Medical Imaging, Keynote Presentation “Noninvasive ECG Imaging (ECGI) of Cardiac Arrhythmia”, University of Toronto, Canada, June 2011.



Jeane E. Schaffer, M.D., Virginia Minnich Distinguished Professor in Medicine, Director, Diabetic Cardiovascular Disease Center and Diabetes Research Training Center, Washington University School of Medicine

- * “Targeting miRNAs: Can miRNAs be Potential targets?” 31st Annual Scientific Sessions of the Heart Rhythm Society, Special Session on Basic/Translational Science Forum: Novel Targets to Cure Cardiac Arrhythmias. Denver, CO, May 2010.
- * “Ion Channels in Atrial Fibrillation.” Cardiostim 2010; 10th Biennial World Congress on Cardiac Arrhythmias and 17th World Congress on Cardiac Electrophysiology and Cardiac Techniques. Symposium entitled: Mechanisms of Fibrillation. Nice, France, June 2010.
- * “Ion Channel Remodeling in Cardiac Hypertrophy and Failure.” 33rd Meeting of the North American Section of the International Society for Heart Research (ISHR). Philadelphia, PA, May 2011.

LECTURES & PRESENTATIONS CONT'D.



Gautam Singh, MD, Associate Professor of Pediatrics, Director of Noninvasive Imaging Research, Co-Director Echocardiography Laboratory, Washington University School of Medicine

- * University of Cork, Cork, Ireland - Clinical Investigational Unit, Department of Paediatrics and Child Health: "Obesity and Alteration in Cardiac Structure and Function In children and Adolescents" on October 11, 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

- * Meet the Experts Session: Using Multicenter Databases and Registries to Direct Pediatric and Adult Congenital Electrophysiology Care (discussant) Heart Rhythm 2011 Annual Scientific Sessions, San Francisco, May 5.
- * 2011 Mincourse: Extrapolating Large Randomized Clinical Trials in Adults to Pediatrics and CHD. Heart Rhythm 2011 Annual Scientific Sessions. (presenter) May 4.



Lihong Wang, Ph.D., the Gene K. Beare Distinguished Professor, Optical Imaging Laboratory, Department of Biomedical Engineering, and Professor of Radiology, Mallinckrodt Institute of Radiology, Washington University

- * 04/04/2011, Photoacoustic tomography: Breaking through the optical diffusion limit. OSA Optics and Photonics Congress on Optics in the Life Sciences, Monterey, CA.
- * 04/09/2011, Photoacoustic tomography: Breaking through the optical diffusion limit. IEEE International Conference on Computational Photography, Carnegie Mellon, Pittsburg, PA. Keynote.
- * 04/15/2011, Photoacoustic tomography: Breaking through the optical diffusion limit. Department of Biomedical Engineering, University of Virginia, Charlottesville, VA.
- * 04/20/2011, Photoacoustic tomography: Breaking through the optical diffusion limit. IEEE Photonics Society, MIT Lincoln Laboratory, Lexington, MA.
- * 04/21/2011, Photoacoustic tomography: Breaking through the optical diffusion limit. Bioengineering Graduate Program, Northeastern University, Boston, MA.
- * 04/29/2011, Photoacoustic tomography: Breaking through the optical diffusion limit. Blaustein Pain Lecture Series, Department of Anesthesiology, Johns Hopkins University, Baltimore, MD.

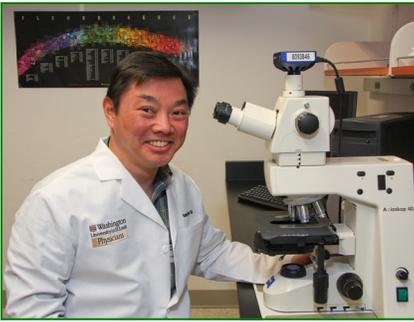


Kathryn Yamada, Ph.D., Research Professor of Medicine; Director, Mouse Cardiovascular Phenotyping Core, Center for Cardiovascular Research, Washinton University School of Medicine :

- * "Regulation of Connexins in the Post-Infarct Heart" at Experimental Biology 2011 in Washington, D.C. on 12 April 11, and "Cx43 and Remodeling in the Infarcted Heart" at Heart Rhythm 2011 in San Francisco, CA on May 5, 2011.



“Spotlight on Dr. Patrick Jay”



Dr. Patrick Jay

The CBAC is comprised of some of the most dynamic yet charmingly down to earth practitioners and scientists in the Midwest. Dr. Patrick Jay was mentored by some of the greatest researchers right here at Washington University. Fortunately for us, he chose to continue on and now works to make a difference in the hearts of children.

My graduate student training in Elliot Elson’s lab in the Department of Biochemistry launched my career. As a first-year medical student, after a cell biology lecture, I asked the professor, John Cooper, about the physical chemistry of actin polymerization. He suggested that I talk to Elliot. That led to a summer spent in the cold room where I tried to purify filamin, an actin-crosslinking protein, from chicken breasts and a series of fluorescence photobleaching experiments, a technique that Elliot invented. The experience convinced me to apply to the MD-PhD program. I spent the next few years studying why various *Dictyostelium* amoeba mutants crawled slowly. More important than the thesis research was the example set by Elliot, the other graduate students in his lab like Hong Qian, and biochemistry professors like Carl Frieden and George Drysdale. Every Saturday we would have lunch in the Barnes Hospital cafeteria where I listened to their conversations ranging from science to music and history. They are scholars and gentlemen who have a fine appreciation for elegant ideas of all kinds. I thought that it would be great to follow in their footsteps.

Area of specialization

I was an intern at Boston Children’s Hospital and had to pick a subspecialty to pursue within a few months of starting. Cardiology seemed to offer the best opportunity to make a unique scientific contribution. I also thought that the competition would be less intense. The jury is still out about the former. I was definitely wrong about the latter. I started pediatrics residency in 1995, cardiology fellowship in 1997, and postdoctoral research in 1999. I started looking for a postdoc lab shortly before my clinical training was finished. Little did I know that postdoc positions are given long in advance. I was lucky to find a spot in Seigo Izumo’s lab. His lab had discovered *Nkx2-5*, a cardiac transcription factor homologous to *tinman* in *Drosophila*. A complete loss of *tinman* function causes the fly not to develop a heart. The gene is hence named after the Wizard of Oz character. *Tinman* raised the possibility of a similar master regulator of mammalian cardiac development. The mouse *Nkx2-5* knockout forms a heart, but it arrests early in development. Research on the mutant mouse might have stopped had it not been for the subsequent discovery that heterozygous *Nkx2-5* mutations in man cause congenital heart disease and conduction defects. I came at an opportune time. An initial characterization of the heterozygous knockout mouse had been done. Some small atrial septal defects were found, as was first-degree atrioventricular block. After seeing so many children with heart defects I thought that there must be more to the mouse, but I knew nothing about mice or molecular biology. So I learned about mice the same way that I did patients. I “rounded” on them every day just as we do on patients and examined the heart of every mouse even if it was not for a specific experiment. I even listened to a mouse heart with a stethoscope. I thought I could hear a murmur in one. I owe a lot to Tom Schultheiss, who discovered the role of BMP signaling in the embryonic induction of the cardiac lineage, for teaching me developmental biology. My postdoc project determined the mechanistic basis of the conduction defect in *Nkx2-5* mutation. We have been working on the structural heart defects ever since. I don’t think there has ever been a pivotal moment that cemented my confidence in my chosen field. I just keep plugging, trying to ask questions that interest me but not other people yet. Otherwise, there would be too much competition from the start. The hope is that others will find them fascinating later. There have been critical moments when I know that a project is on the right track. For example, one day Colin Maguire in Charlie Berul’s lab, which pioneered invasive cardiac electrophysiology in the mouse, told me that he could not detect a good His bundle signal in some mice. I was giving him mice for experiments without telling him the *Nkx2-5* genotype. Colin could identify the mutants with 100% accuracy by the His signal. The His signal was tiny because the His bundle is a thin thread in the mutant. This led us to realize that the mutant’s entire atrioventricular conduction system had many fewer cells than the wild-type.

Important personal achievement

Despite all my years of training and demands of work, I have somehow managed to build a big and delightful family. This is my most important personal achievement. My wife Kathleen is incredibly supportive. I met her in Boston and used to call her a prairie girl because she has the can-do spirit of the American pioneers. She had never worked in a lab, but she once came to help me do some chick embryo experiments. Little did I know that a few years later we would likewise venture westward. Her pioneer skills have come in handy in herding our four children. We have three boys, ages 4, 6 and 8, and a girl, who is almost 2. The Jay household is crazy and rambunctious. In lieu of a covered wagon we have a minivan.

Continued on p. 16

“Spotlight on Dr. Patrick Jay” Cont’d.

Activities in the lab

When I started my lab, I decided to tackle a project that many thought was impossible. I wanted to study why individuals who carry the same genetic mutation that can cause a congenital heart defect present with highly variable phenotypes. Consider a baby who has a serious heart defect. A detailed family history not uncommonly raises the suspicion for an inherited mutation. Several relatives, say, some cousins or an aunt and uncle have milder heart defects, but the parent does not. The parent and the affected relatives all carry the same mutation as the baby, but they somehow have escaped more serious disease. What scientists know so far does not explain why. Doctors currently manage heart defects much as a plumber would. Would it instead be possible to steer the embryonic development of the heart away from a defect with a drug? The problem is that the known cardiac developmental genes are not feasibly “druggable”. The genes are usually transcription factors, whereas drugs target proteins such as receptors, enzymes and ion channels. Genes that modify the mutant phenotype might be attractive alternative targets to prevent congenital heart disease. The modifier genes might even relate to things that cardiologists understand well and can manipulate pharmacologically, such as ventricular load, because hemodynamics plays a fundamental role in cardiac development.

We sought to map genes that modify the mutant phenotype in a mouse model. Inbred strains of mice have genetic polymorphisms that commonly influence phenotype. So, investigators typically study their favorite mutation in an inbred strain, which has a homogeneous genetic background. We turned the problem on its head, doing inbred strain crosses to increase genetic heterogeneity. We set up the infrastructure to collect and catalog a massive number of hearts and mouse DNA. Since 2005, we have collected about 15,000 mice and mapped genes that influence the risk of specific heart defects caused by *Nkx2-5* mutation.

Known cardiac developmental genes seem unlikely to underlie the mapped loci. Perhaps this work will inspire a pill that mimics the activity of a protective gene. The pill could be prescribed to expectant mothers to prevent congenital heart disease in their babies, just as folic acid is now to prevent neural tube defects.

You may ask whether there was a key moment that led me to believe this project was on the right track. Early on I wanted to know that I was not venturing into a quagmire. We had some very preliminary evidence that strain-specific modifier genes existed but nothing more concrete. A back-of-the-envelope calculation suggested that after a few dozen hearts we should find at least one with a defect. If not, I was going to ditch the project. A day later my first lab tech showed me a big hole in heart #60. Reality checking is an important test of sanity. Many people thought this project would be impossible, but enough people had enough faith to keep me going. I have been fortunate to have a fabulously supportive family, chairman and faculty colleagues as well as, a great team of students and techs. I think we are just beginning to see the return on their investment.

Most important research achievement

It is hard for me to know what achievement is important. Only history (i.e., the future looking back upon our present) will tell. I like to judge experiments by their aesthetic appeal. In the best cases they can be described with a catchy phrase. For example, I am fond of the “sticky coverslip” experiment. When various myosin knockout mutant amoebas were first made, everyone could see that they crawled more slowly than the wildtype, but no one knew why. I thought about a cell crawling forward as a series of mechanical steps - protrusion of its front, traction to move its body forward, and retraction of its tail. I devised simple assays to show where the block might lie. Onemyosin mutant became stuck in place when placed on a very sticky coverslip. The wildtype could exert enough force to pull its tail off the surface, but the force was so hard as to pull the top of its rear end down to the bottom, forming an ultrathin lamella. Therefore, one could see that the knocked out myosin exerts a retraction force. The workings of retraction still keep cell biologists busy. A recent paper in *Nature Immunology* said that T cells use the same mechanism described in *Dictyostelium* years ago.

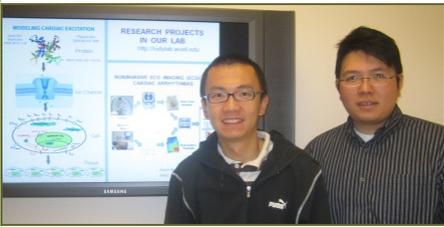
Future goals

My long term goal is to make discoveries that will have a significant practical impact or be recognized as something truly original. Hopefully I will know what the outcome is by the time I retire. We have cast a wide net. There are projects ranging from the analysis of insulin resistance in pediatric heart failure patients to heart defects in mice to novel genes involved in adipocyte and cardiac function.

Beginning with the Barnes Hospital lunches years ago, I enjoy being with people who think deeply about interesting ideas. Wash U has some of the world’s leading scholars of cardiac electrophysiology. Even though I am not currently working on the conduction system, I know that the heart is an integrated system. Biology has a limited tool kit that it redeploys in unlimited ways. Work on the AV node led me to holes in the heart. I would not be surprised if I come full circle someday. It pays to listen to elegant thinkers.



Announcements & News



Pan Li and Junjie Zhang, both trainees in the laboratory of Professor Yoram Rudy, received awards for best poster presentations in the 2011 Gordon Conference on Cardiac Arrhythmia Mechanisms (Galveston, February 13-18). Pan Li received first prize for his project *“A Model of the Cardiac Purkinje Action Potential and Calcium Cycling”*. Junjie Zhang received second prize for the project *“Characterization of Electrophysiologic Substrate in Post- Myocardial Infarction Patients using Noninvasive Electrocardiographic Imaging (ECGI)”*.



George Van Hare was featured in the article, *“Taking Kids to Heart”*, January 14, 2011 in *The Record*. Dr. Van Hare is the Pediatric Chair for the new IBHRE Exam Electrophysiology-MD certification exam which will be available in 2011. George Van Hare, MD (right) and Jennifer A. Silva, MD (left).



Lihong Wang , Ph.D., the Gene K. Beare Distinguished Professor, Optical Imaging Laboratory, Department of Biomedical Engineering, and Professor of Radiology, Mallinckrodt Institute of Radiology, Washington University

Honors:

- * Induction into the GRC Hall of Fame, Gordon Research Conferences.
- * C. E. K. Mees Medal, OSA. For seminal contributions to photoacoustic tomography and Monte Carlo modeling of photon transport in biological tissues and for leadership in the international biophotonics community (\$3,000).

Grants:

- * NIH, High Frequency Ultrasonic and Photoacoustic Imaging System, 04/01/2011-03/31/2012, \$598,910

Patents:

- * L. V. Wang, L. Song, K. Maslov, and B. Rao, "Multi-focus optical-resolution photoacoustic microscopy with ultrasonic array detection," United States Patent, pending (Filed on Feb. 11, 2011). Supported by NIH grants R01 EB000712 and U54 CA136398. OTM Tech #: 10922.



Friends From Abroad

The CBAC is an interdisciplinary group of scientists and practitioners from all over the world who collaborate to the end of improving the quality of life for everyone. Last Fall, Dr. Hsiang-Chun Lee, attending physician in the Cardiology Division of Kaohsiung Medical University, Chung-Ho Medical Hospital in Kaohsiung, Taiwan travelled to St. Louis to conduct research at Washington University. The Center Heartbeat spoke to Dr. Lee about her journey to medicine and Washington University.



Dr. Hsiang-Chun Lee

I grew up in a traditional family in northern Taiwan. My father was a traditional Chinese physician whose clinic was next door to our home. Therefore, I had many chances to observe his clinical practice from a very young age. My father believed that after a girl grew up, she would be happy to marry an ideal husband because he didn't believe that girls would study and work hard academically. However, I enjoyed studying very much and was very interested in biology and science. When I was a junior high school student, I began to dream of being a modern medical doctor rather than the traditional physician. I believed that modern medical doctors could help patients as well as, conduct scientific research. I started to be



Kaohsiung Medical University Hospital

interested in the cardiovascular system as a medical student. At one time, I thought I would like to be a cardiac surgeon. However, I observed that surgeons spent a lot of time performing operations and could not pay as much attention to diagnosis and pharmacological treatment. I decided to train in the Internal Medicine Department and the Cardiology Division. Five years later, I became a cardiologist and an attending physician at the hospital of my alma mater, Kaohsiung Medical University. Taiwan's national health insurance system has facilitated convenient and inexpensive medical care for all Taiwanese people. While I was an intern, the fifth year's implementation of the national health insurance system, I began to experience an excess in clinical work. For example, while I was a junior resident, I had 10 night shifts per month and worked a normal shift the next day. While I was a cardiology fellow I had on-call duty for 15 nights per month. After I became an attending physician in the Cardiology division, the work load did not reduce. At my 5th year as an attending physician in the cardiology department, a single day's job could include seeing fifty out-patients, and two to three cardiac catheterizations or fifteen echocardiography exams. I also had to take care of patients at the coronary care unit every other month as well as, teach medical students and residents. Moreover, I had on-call duty for emergency cardiac catheterization and also had to handle emergency situations at night and weekends whenever I was in charge of the coronary care unit. Under this background, I became a well-trained clinician and could practice medicine skillfully and efficiently. But I did not have enough time for science research. This is not the physician that I wanted to be. In 2007, I decided to study for a Ph.D. and learned genetics under the supervision of Professor Jan-Gowth Chang. I am confident in my medical training in terms of making differential diagnosis of clinical problems and decision making for clinical strategies, and I am capable of providing accurate management for patients in the Internal Medicine and Cardiology fields. I have earned the trust of my patients based on professionalism and good doctor-patient relationships. After becoming a Ph.D. student, I began to explore the area of my interest - ion channels. I believe that any biological phenomenon, including electrophysiology, is related to some degree to genetic regulation. (continued)

experience an excess in clinical work. For example, while I was a junior resident, I had 10 night shifts per month and worked a normal shift the next day. While I was a cardiology fellow I had on-call duty for 15 nights per month. After I became an attending physician in the Cardiology division, the work load did not reduce. At my 5th year as an attending physician in the cardiology department, a single day's job could include seeing fifty out-patients, and two to three cardiac catheterizations or fifteen echocardiography exams. I also had to take care of patients at the coronary care unit every other month as well as, teach medical students and residents. Moreover, I had on-call duty for emergency cardiac catheterization and also had to handle emergency situations at night and weekends whenever I was in charge of the coronary care unit. Under this background, I became a well-trained clinician and could practice medicine skillfully and efficiently. But I did not have enough time for science research. This is not the physician that I wanted to be. In 2007, I decided to study for a Ph.D. and learned genetics under the supervision of Professor Jan-Gowth Chang. I am confident in my medical training in terms of making differential diagnosis of clinical problems and decision making for clinical strategies, and I am capable of providing accurate management for patients in the Internal Medicine and Cardiology fields. I have earned the trust of my patients based on professionalism and good doctor-patient relationships. After becoming a Ph.D. student, I began to explore the area of my interest - ion channels. I believe that any biological phenomenon, including electrophysiology, is related to some degree to genetic regulation. (continued)

Friends from Abroad



Kaohsiung Medical University Campus

I conducted experiments regarding the genetic regulation genes. At that time, I realized that I must receive advanced training for electrophysiological studies of ion channels in order to complete my project. I started to search for information about academic institutions around the world involved in basic electrophysiological study. In August 2009, Dr. Ching-Hsing Luo, a distinguished professor at the National Cheng-Kung University in Taiwan, held a symposium in collaboration with the Taiwan society of Cardiology. Dr. Rudy gave a talk in that symposium. I was very impressed by his talk and two weeks after that symposium, I visited Professor Luo and told him of my intention to travel to the United States. Because of his recommendation, I was lucky to get this great opportunity to learn in Dr. Rudy and Dr. Cui's labs.

At the CBAC, I have learned some basic concepts about computational simulation models of cardiac myocytes and electrocardiogram imaging by attending weekly lab meetings. For my research project, I conducted experiments in Dr. Cui's Lab since September 2010. I have learned dual-electrode voltage clamp, inside-out patch clamps on *Xenopus* oocytes, and sub-cloning of mutant ion channel genes. Since January 2011, I started to do canine cardiomyocyte patch clamp experiments. During the first half year, I received a lot of professional assistance from Dr. Rudy and Dr. Cui. Dr. Colin Nichols kindly offered COS-m6 cells, this cell culture facilities and gave comments for my transfection experiments. Dr. Kai-Chien Yang and Dr. Jeannne M. Nerbonne taught me important knowledge and technique of the patch clamp for cardiomyocytes. Dr. Urvi Lee and Dr. Richard Schuessler not only kindly offered isolated canine cardiomyocytes but also paid for efforts to incorporate several labs to improve canine cardiomyocyte experiments. I really enjoy the great academic atmosphere of both the main campus and the medical school. I did not pay much attention to living life before. I rarely went to shops, museums, galleries, and concerts after being a cardiologist. It's very convenient to buy meals around-the-clock in Taiwan so I almost never cooked. After being in Saint Louis, I began to learn how to use the microwave, cook Chinese food, and to contemplate life. Compared to the intense work in my hospital, I can now do research at a much slower pace in Saint Louis. Thus, I have time to experience life and enjoy the people who surround me. Most people here are polite and the streets are very clean. Public transportation is always on time. I love this city and I feel that it is my second home. I hope I can prove some of my hypotheses in genetic regulation of ion channel function. I want to do my best to learning while at the CBAC. I'll keep working on ion channel research in the future after returning to Taiwan. I plan to establish an electrophysiological research lab in my institution, Kaohsiung Medical University and also collaborate with the Engineering Department of National Cheng-Kung University for computational simulation. It will serve as a platform for both research and teaching in southern Taiwan. I enjoyed every CBAC seminar. I was impressed that researchers other than cardiologists can recognize and study the very important clinical questions in the field of cardiology. I've raised similar questions in my mind for many years during my clinical practice. Dr. Yoram Rudy, the chief of the CBAC, is my role model. I admire his determination and persistence in cardiac electrophysiological research. His enthusiasm and knowledge in cardiac electrophysiology is much more than any cardiologist I've ever met.



CBAC Faculty Members

<p>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</p>	<p>Patrick Y. Jay, M.D., Ph.D., jay_p@wustl.edu Assistant Professor of Pediatrics and Genetics</p>
<p>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</p>	<p>R. Gilbert Jost, M.D., jostg@wustl.edu Elizabeth Mallinckrodt Professor of Radiology; Chairman, Department of Radiology; Director, Mallinckrodt Institute of Radiology</p>
<p>Philip V. Bayly, Ph.D., pvb@wustl.edu Professor of Mechanical Engineering, and Chair of the Department of Mechanical, Aerospace, and Structural Engineering.</p>	<p>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</p>
<p>Sanjeev Bhalla, M.D., bhallas@wustl.edu Associate Professor of Radiology; Assistant Radiology Residence Program Director, Mallinckrodt Institute of Radiology</p>	<p>Leonid Livshitz, Ph.D., lmivshitz@biomed.wustl.edu, Research Assistant Professor, CBAC, Biomedical Engineering, Washington University</p>
<p>John P. Boineau, M.D., schuesslerd@wustl.edu Professor of Surgery, Medicine, and Biomedical Engineering</p>	<p>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</p>
<p>Jane Chen, M.D., janechen@wustl.edu Assistant Professor of Medicine</p>	<p>Ali Nekouzadeh, Ph.D., ali@biomed.wustl.edu Research Assistant Professor, CBAC, Biomedical Engineering, Washington University</p>
<p>Philip S. Cuculich, M.D., pcuculich@wustl.edu, Assistant Professor of Medicine, Clinical Cardiac Electrophysiologist, Department of Medicine at Washington University School of Medicine</p>	<p>Arye Nehorai, Ph.D., nehorai@wustl.edu Chairman and Professor of the Department of Electrical & Systems Engineering</p>
<p>Jianmin Cui, Ph.D., jcui@wustl.edu Associate Professor of Biomedical Engineering on the Spencer T. Olin Endowment</p>	<p>Jeanne M. Nerbonne, Ph.D., jnerbonne@wustl.edu Alumni Endowed Professor of Molecular Biology and Pharmacology, Department of Developmental Biology, Washington University School of Medicine</p>
<p>Ralph J. Damiano, Jr., M.D., damianor@wustl.edu John M. Shoenberg Professor of Surgery; Chief of Cardiac Surgery</p>	<p>Colin G. Nichols, Ph.D., cnichols@wustl.edu Carl Cori Professor of Cell Biology and Physiology, Washington University School of Medicine</p>
<p>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</p>	<p>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</p>
<p>Igor R. Efimov, Ph.D., igor@wustl.edu Professor of Biomedical Engineering</p>	<p>Jean E. Schaffer, M.D., jschaff@wustl.edu Virginia Minnich Distinguished Professor in Medicine, Director, Diabetic Cardiovascular Disease Center and Diabetes Research Training Center, Washington University School of Medicine</p>
<p>Mitchell N. Faddis, M.D., Ph.D., mfaddis@wustl.edu Assistant Professor of Medicine, Radiology; Clinical Cardiac Electrophysiologist, Barnes Hospital</p>	<p>Richard B. Schuessler, Ph.D., schuesslerr@wustl.edu Associate Research Professor of Surgery; Associate Research Professor of Biomedical Engineering; Director, Cardiothoracic Surgery Research Laboratory</p>
<p>Richard W. Gross, M.D., Ph.D., rgross@wustl.edu Professor of Biological, Biophysical and Bioorganic Chemistry, Departments of Medicine, Molecular Biology and Pharmacology and Chemistry, Washington University School of Medicine</p>	

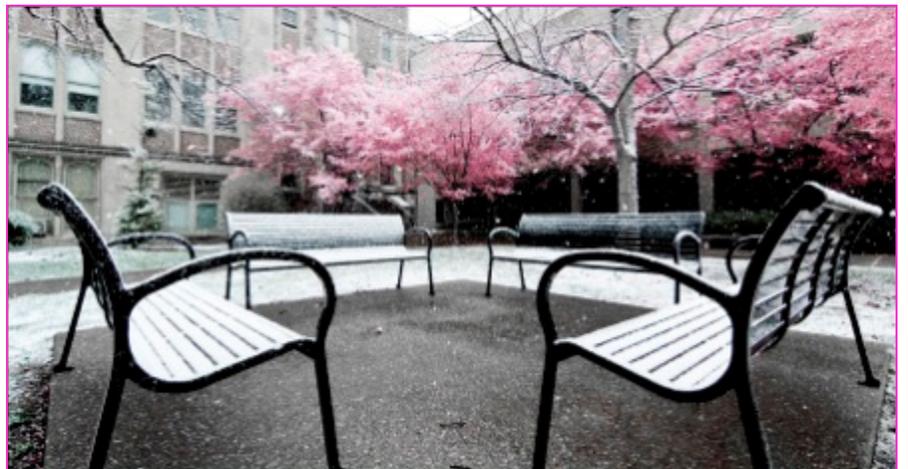
CBAC Faculty Members

<p>Jingyi Shi, Ph.D., jshi22@wustl.edu Research Faculty, Biomedical Engineering</p>
<p>Jennifer N. A. Silva, M.D., silva_j@kids.wustl.edu Instructor in Pediatrics, Director of Pediatric Electrophysiology, Washington University School of Medicine, Division of Pediatric Cardiology</p>
<p>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</p>
<p>Timothy W. Smith, D.Phil., M.D., tsmith@wustl.edu Assistant Professor of Medicine</p>
<p>Jason W. Trobaugh, D.Sc., jason@wustl.edu Research Instructor in Medicine, Electrical and Systems Engineering</p>
<p>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</p>
<p>Lihong Wang, Ph.D., lhwang@wustl.edu Gene K. Beare Distinguished Professor; Department of Biomedical Engineering; Director, Optical Imaging Laboratory</p>
<p>Samuel A. Wickline, M.D., saw@wustl.edu Professor of Medicine; Adjunct Professor of Physics and Biomedical Engineering; Co-Director of Cardiology</p>
<p>Pamela K. Woodard, M.D., woodardp@wustl.edu Professor, Diagnostic Radiology, Cardiovascular Imaging Laboratory, Mallinckrodt Institute of Radiology</p>
<p>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</p>

- CBAC Faculty Alumni:**
 Amir A. Amini, Ph.D.
 Kyongtae T. Bae, M.D., Ph.D.
 Michael Cain, M.D.
 Jonas Cooper, M.D.
 Vadim Fedorov, Ph.D.
 Daniel P. Kelly, M.D.
 Bruce Lindsay, Ph.D.
 Achi Ludomirsky, M.D.
 Tony J. Muslin, M.D., F.A.H.A.
 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>.

Late Winter on the Danforth Campus



For the first time in decades, the Washington University Danforth Campus closed due to inclement weather. St. Louis, MO experienced unusually cold temperatures and a hefty dose of snow in late March. The pictures above were taken by the Rudy Lab's Junjie Zhang on March 26th on the Danforth campus. Snowy Cherry Blossoms is an amazingly beautiful sight. Thank you for the photos Junjie!

R. Martin Arthur, Ph.D., Newton R. and Sarah Louisa Glasgow Wilson Professor of Engineering :

- * R. M. Arthur, W. D. Richard, and J. W. Trobaugh, "A Modular Synthetic-Aperture System for In Vitro Tissue Characterization", Ultrasonic Imaging, in review. <abstract>
- * R. M. Arthur, "Temperature Imaging Using Ultrasound", in Physics Of Thermal Therapy, Fundamentals and Clinical Applications, Editor: E. G. Moros, Series: Imaging In Medical Diagnosis And Therapy (William R. Hendee, Series Editor), Taylor & Francis, in press, 2011. <abstract>
- * R. M. Arthur, S Wang, and JW Trobaugh, "Changes in Body-Surface Electrocardiograms from Geometric Remodeling due to Obesity", IEEE Transactions on Biomedical Engineering, in press, 2011.

Preben Bjerregaard, M.D., D.M.Sc., Professor of Medicine, Cardiovascular Division, Washington University School of Medicine, Section Head, Cardiac Electrophysiology, John Cochran VA Medical Center, St. Louis:

- * Shah RR, Bjerregaard P, Gussak I. Drug-induced QT interval shortening: an emerging component in integrated assessment of cardiac safety of drugs. *J Electrocardiol* 2010;43:386-389
- * Bjerregaard P, Nallapaneni H, Gussak I. Short QT interval in clinical practice. *J Electrocardiol* 2010;43:390-395

Phillip S. Cuculich, M.D.:

- * Wang Y, Cuculich PS, Zhang J, Desouza KA, Vijayakumar R, Chen J, Faddis MN, Lindsay BD,
- * Smith TW, Rudy Y. Noninvasive Electroanatomic Mapping of Human Ventricular Arrhythmias Using ECG Imaging (ECGI). *Science Translational Medicine*, in press.
- * Cuculich PS, Zhang J, Wang Y, Desouza KA, Vijayakumar R, Woodard PK, Rudy Y. The
- * Electrophysiologic Cardiac Ventricular Substrate in Patients after Myocardial Infarction: Noninvasive Characterization with ECG Imaging (ECGI). *J Am Coll Cardiol*, in press.

Igor R. Efimov, Ph.D.:

- * Kurian T, Ambrosi C, Hucker W, Fedorov VV, Efimov IR, Anatomy and Electrophysiology of the Human AV Node, *Pacing Clin. Electrophysiol. Review.* 2010, 33(6): 754-62. PMID: 20180918
- * Glukhov AV, Fedorov VV, Lou Q, Ravikumar VK, Kalish PW, Schuessler RB, Moazami N, Efimov IR, Transmural Dispersion Of Repolarization In Failing And Non Failing Human Ventricle. *Circ Res.* 2010; 106(5): 981-91. PMID: 20093630.
- * Fedorov VV, Chang R, Glukhov AV, Kostecki G, Janks D, Schuessler RB, Efimov IR, Complex interactions between the sinoatrial node and atrium during reentrant arrhythmias in the canine heart. *Circulation.* 2010; 122(8): 782-9. PMID: 20697021
- * Fedorov VV, Glukhov AV, Chang R, Kostecki G, Aferol1 H, Hucker WJ, Wuskell J, Loew LM, Schuessler RB; Moazami N, Efimov IR. Optical mapping of the isolated coronary-perfused human sinus node, *JACC*, 2010; 56 (17), 1386-1394. PMID: 20946995.
- * Kurian TK, Efimov IR. Mechanisms of fibrillation: neurogenic or myogenic? Reentrant or focal? Multiple or single? Still puzzling after 160 years of inquiry. *J Cardiovasc Electrophysiol.* 2010, 21(11): 1274-5. PMID: 20550608
- * Glukhov AV, Fedorov VV, Anderson ME, Mohler PJ, Efimov IR, Functional Anatomy Of The Murine Sinus Node: High-Resolution Optical Mapping Of Ankyrin-B Heterozygous Mice, *AJP*, 2010 Aug; 299(2): H482-91. PMID: 20525877.
- * Ambrosi CM, Ripplinger CM, Efimov IR, Fedorov VV. Termination of sustained atrial flutter and fibrillation using low energy multiple shock therapy. *Heart Rhythm.* 2011 Jan; 8(1): 101-8. PMID: 20969974.
- * Greener I, Monfredi O, Inada I, Chandler N, Tellez J, Atkinson A, Taube MA, Billeter R, Anderson R; Efimov IR, Molenaar P, Sigg D, Sharma V, Boyett M, Dobrzynski H, Molecular architecture of the human specialized atrioventricular conduction axis. *JMCC*, 2011, 50(4): 642-51. PMID: 21256850.
- * Lou Q, Fedorov VV, Glukhov AV, Fast VG, Moazami N, Efimov IR, Heterogeneity and Remodeling of Transmural Ventricular Excitation-Contraction Coupling in Human Heart Failure. *Circulation*, 2011, in press, PMID: 21502574.



Publications Cont'd.

May 2010—June 2011

Igor R. Efimov, Ph.D. (cont'd):

- * Fedorov VV, Glukhov AV, KostECKI G, Chang R, Janks D, Schuessler RB, Moazami N, Nichols CG, Efimov IR. Effects of KATP channel openers diazoxide and pinacidil in coronary-perfused atria and ventricles from failing and non-failing human hearts. *JMCC*, 2011, in press.
- * Lou Q, Li W, Efimov IR. Multiparametric Optical Mapping of the Langendorff-perfused Rabbit Heart, *JOVE*, 2011, in press
- * Lang D, Sulkin M, Lou Q, Efimov IR, Optical Mapping of Action Potentials and Calcium Transients in the Mouse Heart, *JOVE*, 2011, in press
- * Fedorov VV, Ambrosi CM, KostECKI G, Hucker WJ, Glukhov AV, Wuskell J, Loew LM, Moazami N, Efimov IR, Anatomic Localization and Autonomic Modulation of AV Junctional Rhythm in Failing Human Hearts, *Circulation: Electrophysiology and Arrhythmia*, 2011, subm.
- * Lang D, Glukhov AV, Efimova T, Efimov IR. Cardiac Arrhythmia in Calcium-dependent Tyrosine Kinase Pyk2 Knock-out Mice, *AJP: Heart*, 2011, subm.
- * Swaminathan PD, Purohit A, Soni S, Voigt N, Singh MV, Glukhov AV, Gao Z, He JB, Luczak ED, Joiner M, Kutschke W, Yang J, Donahue JK, Weiss RM, Grumbach IM, Chen PS, Efimov IR, Dobrev D, Mohler PJ, Hund TJ, Anderson ME. Oxidized CaMKII causes cardiac sinus node dysfunction, *JCI*, 2011, under revision.
- * Glukhov AV, Fedorov VV, Kalish PW, Ravikumar VK, Lou Q, Janks D, Schuessler RB, Moazami N, Efimov IR, Arrhythmogenic remodeling in human end-stage non-ischemic left ventricular cardiomyopathy, *Circ.* 2011, subm.
- * Bordas R, Gillow K, Lou Q, Efimov IR, Gavaghan D, Kohl P, Grau V, Rodriguez B,
- * Full Rabbit-Specific Ventricular Model of Cardiac Electrophysiological Function including Specialized Conduction System, *Progress in Biophysics and Molecular Biology*, 2011, in press.



"The Sick Woman" Jan Steen, c.1665



"The Lovesick Woman", Jan Steen c. 1660



Publications Contol.

May 2010—June 2011

Richard Gross, Ph.D.:

- * Chen, M., Su, X., Yang, J., Jenkins, C.M., Cedars, A.M., and Gross, R.W. Facile identification and quantitation of protein phosphorylation via α -elimination and Michael Addition with natural abundance and stable isotope labeled thiocholine. *Anal. Chem.* 2010, 82:163-171. PMID: 2813211.
- * Dietrich, H.H., Abendschein, D.R., Moon, S.H., Nayeb-Hashemi, N., Mancuso, D.J., Jenkins, C.M., Kaltenbronn, K.M., Blumer, K.J., Turk, J., and Gross, R.W. Genetic ablation of calcium-independent phospholipase A(2)beta causes hypercontractility and markedly attenuates endothelium-dependent relaxation to acetylcholine. *Am. J. Physiol. Heart Circ. Physiol.* 2010, 298:H2208-2220. PMID: 2886658.
- * Kiebish, M.A., Bell, R., Yang, K., Phan, T., Zhao, Z., Ames, W., Seyfried, T.N., Gross, R.W., Chuang, J.H., Han, X. Dynamic simulation of cardiolipin remodeling: Greasing the wheels for an interpretative approach to lipidomics. *J. Lipid Res.* 2010, 51:2153-2170. PMID: 2903823.
- * Cheng, H., Sun, G., Yang, K., Gross, R.W., Han, X. Selective desorption/ionization of sulfatides by MALDI-MS facilitated using 9-aminoacridine as matrix. *J. Lipid Res.* 2010, 51:1599-1609. PMID: 3035524.
- * Mancuso, D.J., Sims, H.F., Yang, K., Kiebish, M.A., Su, X., Jenkins, C.M., Guan, S., Moon, S.H., Pietka, T., Nassir, F., Schappe, T., Moore, K., Han, X., Abumrad, N.A., and Gross, R.W. Genetic ablation of calcium-independent phospholipase A2 prevents obesity and insulin resistance during high fat feeding by mitochondrial uncoupling and increased adipocyte fatty acid oxidation. *J. Biol. Chem.* 2010, 285:36495-36510. PMID: 2978578.
- * Basantani, M.K., Sitnick, M.T., Cai, L., Brenner, D.S., Gardner, N.P., Li, J.Z., Schoiswohl, G., Yang, K., Kumari, M., Gross, R.W., Zechner, R., Kershaw, E.E. Pnpla3/Adiponutrin deficiency in mice does not contribute to fatty liver disease or metabolic syndrome. *J. Lipid Res.* 2010, 52:318-329. PMID: 3023552.
- * Sharma, J., Turk, J., Mancuso, D.J., Sims, H.F., Gross, R.W., and McHowat, J. Activation of Group VI phospholipase A2 isoforms in cardiac endothelial cells of wild type and knockout mice. *Am. J. Physiol. Cell Physiol.* 2010, 300:C825-C832. PMID: "PMC Journal-In Process".
- * Jenkins, C.M., Yang, J., Sims, H.F., and Gross, R.W. Reversible high affinity inhibition of phosphofructokinase-1 by acyl-CoA: A mechanism integrating glycolytic flux with lipid metabolism. *J. Biol. Chem.* 2011, 286:11937-11950. PMID: 3069396.
- * Harris, C.A., Haas, J.T., Streeper, R.S., Stone, S.J., Kumari, M. Yang, K., Han, X., Brownell, N., Gross, R.W., Zechner, R., and Farese, R.V. Jr. DGAT enzymes are required for triacylglycerol synthesis and lipid droplets in adipocytes. *J. Lipid Res.* 2011, 52:657-667. PMID: "PMC Journal-In Process".
- * Kuda, O., Jenkins, C.M., Skinner, J.R., Moon, S.H., Su, X., Gross, R.W. and Abumrad, N.A. CD36 is involved in store operated calcium flux, phospholipase A2 activation and production of prostaglandin E2. *J. Biol. Chem.* 2011, 286:17785-17795. PMID: "PMC Journal-In Process".
- * Gross, R.W., and Han, X. Lipidomics at the interface of structure and function in systems biology. *Chem. Biol.* 2011, 18:284-291. PMID: "PMC Journal-In Process".
- * Yang, K., Zhao, Z., Gross, R.W., Han, X. Identification and quantitation of unsaturated fatty acid isomers by electrospray ionization tandem mass spectrometry: A shotgun lipidomics approach. *Anal. Chem.* May 2, 2011. [Epub ahead of print]. PMID: "PMC Journal-In Process".



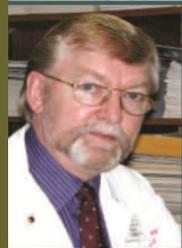
Cardiac Bioelectricity & Arrhythmia Center (CBAC)

DR. YORAM RUDY, DIRECTOR



<http://cbac.wustl.edu>

FALL 2011 SEMINAR SCHEDULE

<p>No Image Available</p>	<p style="text-align: center;">OCTOBER 10</p> <p>Brian O'Rourke, MD, Professor of Medicine, Director, Multiphoton Laser Scanning Microscope Facility, Johns Hopkins Hospital, Baltimore, MD</p> <p style="text-align: center;"><i>"TBA"</i></p>
	<p style="text-align: center;">OCTOBER 31</p> <p>David Rosenbaum, MD, Chief, Division of Cardiology and Director, Heart and Vascular Center for the MetroHealth System, Professor of Medicine, Biomedical Engineering, Physiology & Biophysics, Case Western Reserve University School of Medicine, Cleveland, OH</p> <p style="text-align: center;"><i>"TBA"</i></p>
	<p style="text-align: center;">NOVEMBER 7</p> <p>Randall Rasmusson, PhD., Professor of Physiology & Biophysics, School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, Buffalo, NY</p> <p style="text-align: center;"><i>"TBA"</i></p>
	<p style="text-align: center;">NOVEMBER 28</p> <p>Preben Bjerregaard, MD, DM.Sc., Professor of Medicine, Cardiovascular Division, Washington University School of Medicine; Section Head, Cardiac Electrophysiology, John Cochran VA Medical Center, St. Louis, MO</p> <p style="text-align: center;"><i>"The Development of a Short QT Syndrome"</i></p>
	<p style="text-align: center;">DECEMBER 5</p> <p>Kenneth Laurita, PhD, Assistant Professor of Medicine and Biomedical Engineering, Senior Scientist, Heart and Vascular Research Center MetroHealth Campus, Case Western Reserve University, Cleveland, OH</p> <p style="text-align: center;"><i>"TBA"</i></p>
	<p style="text-align: center;">DECEMBER 12</p> <p>Alfred George, Professor of Medicine and Pharmacology; Chief, Division of Genetic Medicine, Director, Vanderbilt Institute for Integrative Genomics, Associate Chair for Science Education, Dept of Medicine; Director, Physician-Scientist Training Program, Vanderbilt University, Nashville, TN</p> <p style="text-align: center;"><i>"TBA"</i></p>

 Washington University in St. Louis

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

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

Publications Control

Jeanne Nerbonne, Ph.D.:

- * Nerbonne, J.M. Molecular determinants and regulation of excitability in the mouse heart, submitted (2010).

Ali Nekouzadeh, Ph.D., Research Associate Professor, Biomedical Engineering, Washington University

- * Nekouzadeh A., Rudy Y. “Three Residue Loop Closure in Proteins: A New Kinetic Method Reveals a Locus of Connected Loop Conformations” Accepted, *Journal of Computational Chemistry*, 2011.
- * Nekouzadeh A., Rudy Y. “Continuum Molecular Simulation of Large Conformational Changes During Ion-Channel Gating” Accepted, *PLoS ONE*, 2011.
- * Wu D., Delaloye K., Zaydman M.A., Nekouzadeh A., Rudy Y., Cui J. “State dependent electrostatic interactions of S4 arginines with E1 in S2 during Kv7.1 activation” *Journal of General Physiology* 135(6): 595-606, 2010.

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

- * 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;7:1316-1317.
- * 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;7:705-707.
- * N. Varma, P. Jia, C. Ramanathan, Y. Rudy, “Right Ventricular Electrical Activation in Heart Failure during Right, Left and Biventricular Pacing” *JACC: Cardiovascular Imaging* 2010;3:567-575.
- * D. W, K. Delaloye, M. Zaydman, A. Nekouzadeh, Y. Rudy, J. Cui, “State-dependent electrostatic interactions of S4 arginines with E1 in S2 during Kv7.1 activation” *J. Gen. Physiol.* 2010;135:595-606.
- * J. R. Silva, Y. Rudy, “Multi-scale electrophysiology modeling: from atom to organ” *J. Gen. Physiol.* 2010;135:575-581.
- * P.S. Cuculich, Y. Wang, B.D. Lindsay, M.N. Faddis, R.B. Schuessler, R.D. Damiano, L. Li, Y. Rudy, “Noninvasive Characterization of Epicardial Activation in Humans with Diverse Atrial Fibrillation Patterns” *Circulation* 2010;122:1364-1372.
- * K.F. Decker, Y. Rudy, “Ionic Mechanisms of Electrophysiological Heterogeneity and Conduction Block in the Infarct Border Zone” *Am J Physiol Heart Circ Physiol* 2010; 299: H1588–H1597.
- * R.J. van Oort, A. Garbino, W. Wang, S.S. Dixit, A.P. Landstrom, N. Gaur, A.C. De Almeida, D.G. Skapura, Y. Rudy, A.R. Burns, M.J. Ackerman, X.H.T. Wehrens, “Disrupted Junctional Membrane Complexes and Hyperactive Ryanodine Receptors Following Acute Junctophilin Knockdown in Mice” *Circulation* 2011;123:979-988.
- * J. Heijman, P.G.A. Volders, R.L. Westra, Y. Rudy, “Local control of β -adrenergic stimulation: Effects on ventricular myocyte electrophysiology and Ca^{2+} -transient” *J Mol Cell Cardiol* 2011;50:863-871.
- S. Ghosh, J.N.A. Silva, R.M. Canham, T.M. Bowman, J. Zhang, E.K. Rhee, P.K. Woodard, Y. Rudy, “Electrophysiological Substrate and Intraventricular LV Dyssynchrony in Non-ischemic Heart Failure Patients Undergoing Cardiac Resynchronization Therapy” *Heart Rhythm* 2011;8:692-699.
- * K. Acsai, G. Antoons, L. Livshitz, Y. Rudy, K. R. Sipido, “Microdomain $[Ca^{2+}]$ near ryanodine receptors as reported by L-type Ca^{2+} and Na/Ca exchange currents” *J Physiol* 2011;589:2569-2583.
- * A. Nekouzadeh, Y. Rudy, “Three Residue Loop Closure in Proteins: A New Kinematic Method Reveals a Locus of Connected Loop Conformations” *J Comp Chemistry* 2011; 32: 2515–2525.
- * Nekouzadeh, Y. Rudy, Continuum Molecular Simulation of Large Conformational Changes during Ion-Channel Gating” *PLoS ONE* 2011; 6(5): e20186. doi:10.1371/journal.pone.0020186
- * T.J. O’Hara, L. Virág, A. Varró, Y. Rudy, “Simulation of the undiseased human cardiac ventricular action potential: Model formulation experimental validation” *PLoS Computational Biology* 2011; 7(5): e1002061.doi:10.1371/journal.pcbi.1002061
- * 100:2904-2912.



Publications Cont'd.

May 2010—June 2011

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

- * P. Li, Y. Rudy, "A Model of Canine Purkinje Cell Electrophysiology and Ca²⁺ Cycling: Rate Dependence, Triggered Activity and Comparison to Ventricular Myocyte" *Circ Res* 2011; 109:71-79
- * N. Gaur, Y. Rudy, "Multiscale modeling of Ca cycling in cardiac ventricular myocyte: Macroscopic consequences of microscopic dyadic function" *Biophys J* 2011; 100:2904-2912.

Book Chapters:

- * 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.
- * J. Silva, Y. Rudy, "Voltage-Gated Channels and the Heart" In: *Molecular Machines*, Benoit Roux Editor. World Scientific Publishers, 2011, Chapter 13.

Mark E. Josephson, M.D., Chief Division of Cardiovascular Medicine, Cardiovascular Institute, Beth Israel Deaconess Medical Center; Professor of Medicine, Harvard Medical School was the CBAC guest speaker on October 18 for the Fall 2010 seminar series. Dr. Josephson, (front left) is pictured with Dr. Jane Chen, Director of the Electrophysiology Fellowship Program (rear left), Dr. Timothy Smith, Associate Professor of Medicine (front right) and the Cardiology Electrophysiology Fellows from the Washington University School of Medicine.



Drs. Mark Levin, left and Patrick Jay are paying close attention to guest speaker, Dr. Colleen Clancy at the October 11th CBAC Seminar.

Publications Cont'd.

May 2010—June 2011

Jean E. Schaffer, M.D.:

- * "Targeting miRNAs: Can miRNAs be Potential targets?" 31st Annual Scientific Sessions of the Heart Rhythm Society, Special Session on Basic/Translational Science Forum: Novel Targets to Cure Cardiac Arrhythmias. Denver, CO, May 2010.
- * "Ion Channels in Atrial Fibrillation." *Cardiostim 2010*; 10th Biennial World Congress on Cardiac Arrhythmias and 17th World Congress on Cardiac Electrophysiology and Cardiac Techniques. Symposium entitled: Mechanisms of Fibrillation. Nice, France, June 2010.
- * "Ion Channel Remodeling in Cardiac Hypertrophy and Failure." 33rd Meeting of the North American Section of the International Society for Heart Research (ISHR). Philadelphia, PA, May 2011.

Richard B. Schuessler, Ph.D.:

- * Federov VV, Glukhov AV, Ambrosi CM, Kostecky G, Chang R, Janks D, Schuessler RB, Moazami N, Nichols CG, Efimov IR: Effects of K(ATP) channel openers diazoxide and pinacidil in coronary-perfused atria and ventricles from failing and non-failing human hearts. *J Mol Cell Cardiol* 2011 May 7 [Epub ahead of print]. PMID 21586291
- * Shen J, Lall S, Zheng V, Buckley P, Damiano RJ Jr, Schuessler RB: The persistent problem of new-onset Postoperative atrial fibrillation: A single-institution experience over two decades. *J Thorac Cardiovasc Surg* 141(2):559-70, 2011. PMID: PMC 2917532

Gautam Singh, MD, DCH, MRCP, FACC:

- * Johnson BL, Hoffman JJ, Singh GK, Holland MR, Miller JG. Development of Myocardial Tissue-Mimicking Phantoms Exhibiting a Range of Lipid Concentrations Comparable to that Observed in Obese Diabetic Subjects. *IEEE*; 2010:
- * Singh GK, Cupps B, Woodard PK, Pasque M, Holland MR, Ludomirsky A. Altered cardiac mechanics of the univentricular heart - myocardial strain characteristics of single ventricle in pediatric Fontan patients: a MRI and speckle tracking echocardiography correlative study. *J Am Soc Echocardiogr* 2010;23:1143-52.
- * Muyskens S, Holt B, Ludomirsky A, Pilgram T, Foerster S, Balzer D, Woodard PK, Singh GK. A novel approach to non-invasive assessment of homograft form and function: a cardiac catheterization, Doppler echocardiography and CT angiography correlative study. *Eur J Echocardiogr* 2011 (Under Review).
- * Balzer DT, Johnson MC, Singh GK, Huddleston C. Transcatheter Ventricular Septal Defect Creation for Restrictive VSD in Double Outlet Right Ventricle. *Catheterization and Cardiovascular Interventions*. 2011 (in press).
- * Goldstein BS, Holland MR, Klein S, Singh GK. Altered Cardiac Function in Overweight Children and Adolescents: Does Obesity Cardiomyopathy Evolve in Pediatric Age? 60th Annual Scientific Session of American College of Cardiology, New Orleans, LA. April 2-5, 2011.

Jennifer N. A. Silva, MD, Instructor in Pediatric Electrophysiology, Washington University School of Medicine, Division of Pediatric Cardiology

- * Silver ES, Silva JNA, Ceresnak SR, Chiesa NA, Rhee EK, Dubin AM, Avasarala K, Van Hare GF, 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* 2010;33:681-6.
- * Collins KK, Silva JNA, Rhee EK, Schaffer MS. Use of wearable automatic defibrillator in children compared to young adults. *Pacing Clin Electrophysiol* 2010;33:1119-24.
- * Silva JNA, Canter CE, Singh TP, Gauvreau K, Piercey GE, Berul CI, Blume ED, Smoot LB, Almond CS. *Heart transplantation using donor hearts from infants with sudden infant death syndrome*. *J Heart Lung Transplant* 2010;29:1226-30. Epub 2010 Aug 5.
- * Ghosh S*, Silva JNA*, Canham R, Woodard PK, Rhee EK, Rudy Y (*contributed equally). *Characterization of Electrophysiologic Substrate and Left Ventricular Dyssynchrony in Non-ischemic Patients Undergoing Cardiac Resynchronization Therapy: A Retrospective Study using Noninvasive Electrocardiographic Imaging (ECGI) and Tissue Strain Imaging*. In Press *Heart Rhythm* (1/2011).

Publications Cont'd.

May 2010—June 2011

George F. Van Hare, III, M.D.:

Book Chapters:

- * Van Hare GF. Arrhythmias. In Rudolph's Pediatrics, Twenty-second Edition. Rudolph C, Lister G, Gershon A, First L, Rudolph A, editors. New York: McGraw-Hill; 2010 (in press)
- * Van Hare GF. Electrocardiogram. In Rudolph's Pediatrics, Twenty-second Edition. Rudolph C, Lister G, Gershon A, First L, Rudolph A, editors. New York: McGraw-Hill; 2010 (in press)
- * Van Hare GF. Neonatal Arrhythmias. in Neonatal-Perinatal Medicine. Diseases of the Fetus and Infant. RJ Martin, AA Fanaroff, MC Walsh, eds. St Louis: Elsevier Mosby. pp 1278-89. 2010
- * Van Hare GF. Ablation of ventricular tachycardia with congenital heart disease. (Chapter 32) in SKS Huang, MA Wood, eds. Catheter Ablation of Cardiac Arrhythmias. 2nd Edition. Philadelphia: Elsevier Saunders; 2011: pp 574-580.

Lihong Wang, Ph.D.

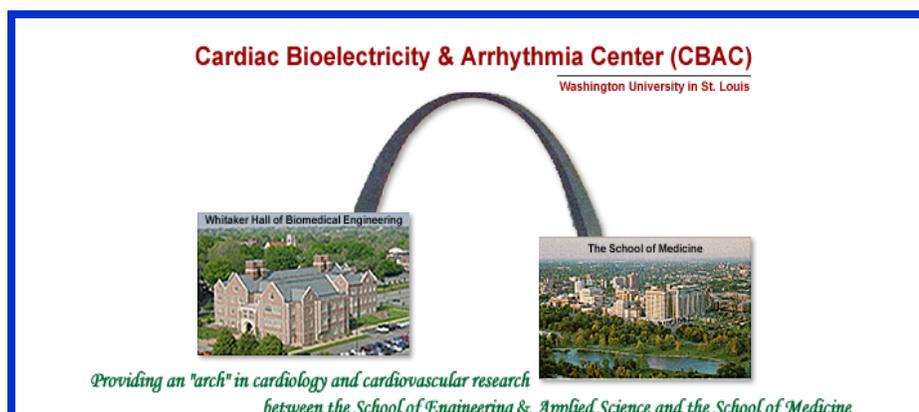
- * G. L. Coté, L. V. Wang, and S. Rastegar, "Biomedical Optics and Lasers," *Introduction to Biomedical Engineering*, J. Enderle and J. Bronzino, eds. 3rd ed. (Academic Press, 2011), pp. 1111-1173.

Pamela K. Woodard, M.D., Professor, Diagnostic Radiology, Cardiovascular Imaging Laboratory, Mallinckrodt Institute of Radiology, Biomedical Engineering

- * Hundley WG, Bluemke DA, Finn JP, Flamm SD, Fogel MA, Friedrich MG, Ho VB, Jerosch-Herold M, Kramer CM, Manning WJ, Patel M, Pohost GM, Stillman AE, White RD, **Woodard PK**. ACCF/ACR/AHA/NASCI/SCMR 2010 Expert Consensus Document on Cardiovascular Magnetic Resonance. A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation*. 2010 May 17. [Epub ahead of print] No abstract available.
- * McCommis KS, O'Connor R, Lesniak D, Lyons M, **Woodard PK**, Gropler RJ, Zheng J. Quantification of global myocardial oxygenation in humans: initial experience. *J Cardiovasc Magn Reson*. 2010 Jun 2;12(1):34.
- * Khan M, Cummings KW, Gutierrez FR, Bhalla S, **Woodard PK**, Saeed IM. Contraindications and side effects of commonly used medications in coronary CT angiography. *Int J Cardiovasc Imaging*. 2010 Jun 23. [Epub ahead of print]

Kathryn Yamada, Ph.D., Research Professor of Medicine; Director, Mouse Cardiovascular Phenotyping Core, Center for Cardiovascular Research, Washington University School of Medicine :

- * Huang RY-C, Laing JG, Kanter EM, Berthoud VM, Bao M, Rohrs HW, Townsend RR, Yamada KA. Identification of CaM-KII phosphorylation sites in connexin43 by high-resolution mass spectrometry. *J Proteome Res* 2011;10:1098-1109.



Contacts

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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.