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CENTER HEARTBEAT

NEWSLETTER OF THE CARDIAC BIOELECTRICITY AND ARRHYTHMIA CENTER (CBAC)

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

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

Washington University in St. Louis

http://cbac.wustl.edu

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.***

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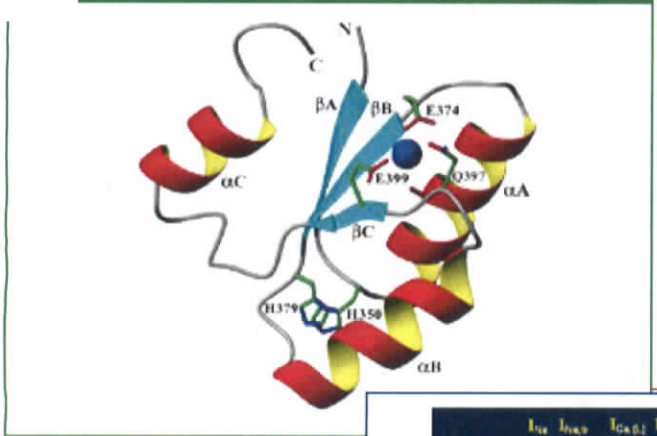
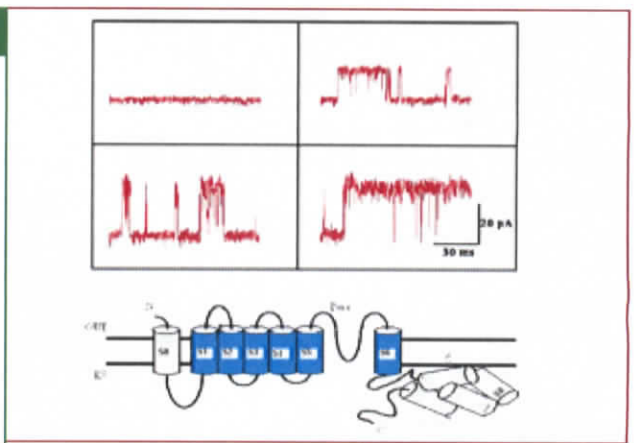
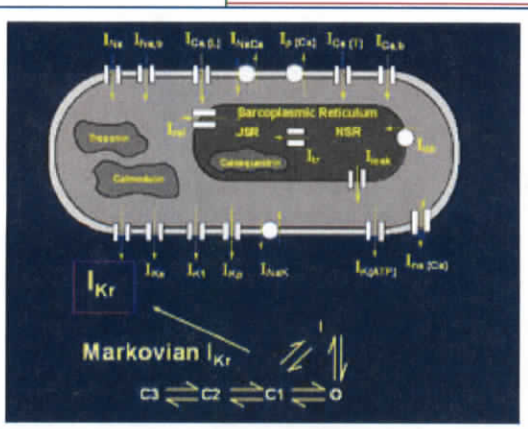
Molecular Structure of Cardiac Ion Channels





Structure/Function of Cardiac Ion Channels



Mathematical Modeling of Cardiac Cells and Tissue

Washington University in St.Louis

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

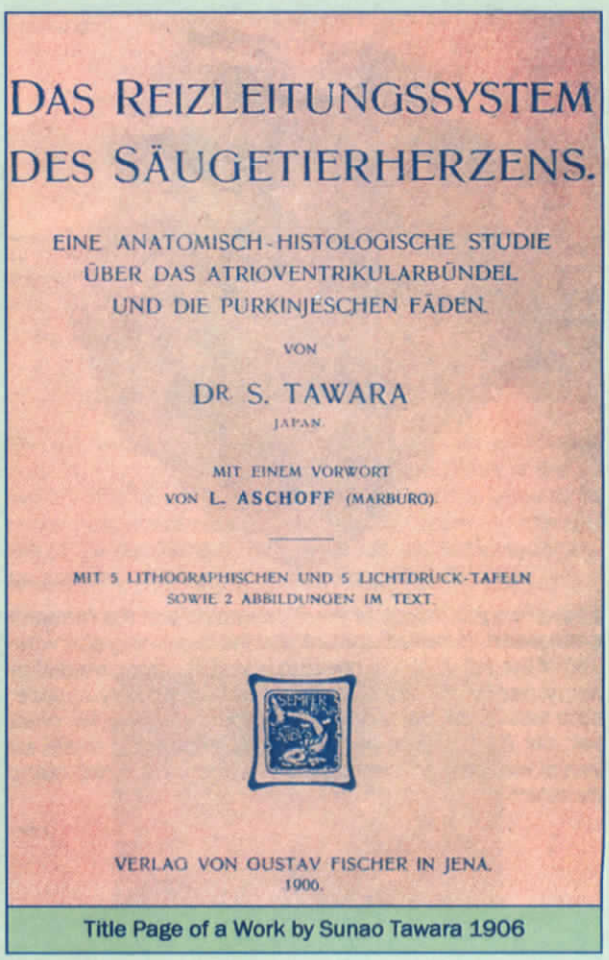
FROM THE DIRECTOR'S DESK……

A Historical Perspective On Cardiac Research

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

In the previous issue of the "Center Heartbeat" I discussed the importance of the long-term, basic discovery process that is not driven by an application. The study of cardiac anatomy and structure is an example of such a process. Structural studies are continuously being refined, as new methods provide data with increasingly higher spatial resolution and greater sensitivity and specificity. It is important, however, to maintain a historical perspective as new discoveries are being made. The "nodes" of the heart, the Sinus node and Atrioventricular node, are being studied extensively at the cellular and molecular levels. These studies, at the microscopic scale, rely on anatomic and histologic descriptions at the macroscopic scale, pioneered during the early 1900's. In 1907 Arthur Berridale Keith (1866-1955) and Martin William Flack (1882-1931) reported in "The Form and Nature of the Muscular Connections Between the Primary Divisions of the Vertebrate Heart" (J Ana Physiol 41:172-189) an annular sinoatrial muscular structure where the superior vena cava opens to the right atrium, which they termed the "sinuauricular node" (W. Koch referred to it in 1909 as the "Sinusknoten" or "Sinus node", the term that has been used since). In 1906, Ludwig Aschoff (1866-1942 and Sunao Tawara (1873-1952) described the AV node. The 1906 book by Tawara "The Conduction System of the Mammalian Heart. An Anatomic-Histologic study of the Atrioventricular node and the Purkinje Fibers" is a true masterpiece containing accurate descriptions and detailed illustrations (bottom of this page). As our field progresses and we add new blocks to the building, we should not lose sight of the pioneering work by those who laid the foundations and ensure that our students and trainees are familiar with their seminal contributions.

Sunao Tawara (1873-1952)



DAS REIZLEITUNGSSYSTEM DES SÄUGETIERHERZENS.

EINE ANATOMISCH-HISTOLOGISCHE STUDIE ÜBER DAS ATRIOVENTRIKULARBÜNDEL UND DIE PURKINJESCHEN FÄDEN.

VON

DR. S. TAWARA

JAPAN.

MIT EINEM VORWORT VON L. ASCHOFF (MARBURG).

MIT 5 LITHOGRAPHISCHEN UND 5 LICHTDRUCK-TAFELN SOWIE 2 ABBILDUNGEN IM TEXT.

VERLAG VON GUSTAV FISCHER IN JENA. 1906.

Title Page of a Work by Sunao Tawara 1906

SUMMER'S END

Pictured in the posed photo, Top Left: Back Row L-R: Dr. Ali Nekouzadeh; Namit Gaur; Dr. Pan Li; visiting scholar from Maastricht University, Jordi Heijman; Dr. K. Alan Desouza; Fu-Chiang Young, visiting scholar from National Cheng Kung University, Tainan, Taiwan. Front Row L-R: Dr. Leonid Livshitz; Jiajing Xu; Smiruthi Ramasubramanian and Tom O'Hara.

Top Right: CBAC members attend the first of the Fall Seminars in Whitaker Hall.

Bottom Left: A day of summer research in the CBAC laboratories.

INSIDE THIS ISSUE:

In this issue we will pay homage to some of the research pioneers whose contributions have made it possible to chart new and innovative pathways to future discoveries, diagnosis, and treatment of cardiac arrhythmias.

This issue features articles written by CBAC members John Boineau, MD, Professor of Surgery, Medicine and Biomedical Engineering who describes his "Adventures in Cardiac Electrophysiology: The Origin of Arrhythmia Ablation" and Igor Efimov, Ph.d. , Distinguished Professor of Biomedical Engineering who writes about "Naum Lazarevich Gurvich (1905-1981) and his Contribution to the History of Defibrillation" a profile of the work on the defibrillator by Naum Gurvich.

We hope that these accounts will help evaluating present day research from a historical perspective.

ADVENTURES IN CARDIAC ELECTROPHYSIOLOGY: THE ORIGIN OF ARRHYTHMIA ABLATION

John P. Boineau, MD

I am pleased and honored to present this report and share my thoughts on an earlier period during the development and progress in the field of cardiac electrophysiology (EP). The work illustrates the power of observation then recognition to shape thought and methodology, ultimately resulting in a breakthrough; in this case a systematic and direct approach to the control of arrhythmias.

In 1957, when I became interested in the electrocardiogram (ECG), very little was known regarding the mechanisms of the abnormal patterns or the bases of arrhythmias. At that time, there were no pacemakers, defibrillators, or CCUs. Cardiac diagnosis, patient care, and cardiac surgery were in their infancy. There was no clinical electrophysiology and although there were many questions, there were few answers. My introduction to cardiac EP was reading ECGs as a student with E. Harvey Estes in adults, and with Madison (Maddy) Spach in the pediatric patients. Both Maddy and I were very dubious of the conventional explanations for the ECG abnormalities and began to look for methods to get better answers to our questions. We read much of the work of the early investigators publishing at the turn of the century. These included Thomas Lewis, Drury, Mines, Eyster and Meek, Schmitt and Erlanger, and Wilson. We were also intrigued by the activation studies of Sodi-Pallares and argued vigorously over his concept of a septal barrier to conduction.

The publication of the proceedings of the New York Academy of Sciences on cardiac electrophysiology (1) became an enlightening introduction, further invigorating a burgeoning interest in the cardiac electrical events. The symposium featured the work of Allen Scher and Dirk Durrer who, in contrast to the majority of investigators at the time, had developed and were using methods to record potentials directly from the heart. Maddy and I visited the laboratories of both Scher and Durrer and learned to construct their electrodes and electronic systems for recording the cardiac electrograms from the epicardium and intramurally with multipoint needle electrodes. Initially, we began to investigate and publish on the mechanisms of the ECG, VCG, and body surface potential distributions in various forms of heart disease in adults and children.

MYOCARDIAL INFARCTION AND DELAYED CONDUCTION

After this early experience in student research at Duke, I joined the housestaff at Georgetown University Hospital, and it was during this period between 1959 to 1961 that I became frustrated with attempts to control serious arrhythmias with the few drugs available at the time. The pharmacologic effects were inconsistent and all too often detrimental (proarrhythmic). I became preoccupied by the idea that if one could really understand the mechanisms of an arrhythmia, that perhaps it could be surgically cut out or cauterized (ablated).

In 1961, Durrer et al had demonstrated that activation became fragmented and desynchronized after experimental myocardial infarction in canines (2). They demonstrated delays in conduction between 50 to 100 msec after the initial local activation. I toyed with the idea that if the local delays could last as long as 250 to 300 msec, then there was the potential for reentry of delayed activation to pass into adjacent earlier activated and recovered regions, resulting in ventricular arrhythmias. I proposed this idea to Durrer and he invited me to Amsterdam to work on the project with him. In 1963, after arriving in Amsterdam in the early AM, I proceeded to Durrer's lab which was already set up and waiting to begin the study that morning. After 24 hours with no sleep, Freud, Durrer's EP fellow, and I produced acute MI in a dog after recording control potentials from multiple needle electrodes. In that very first experiment, we demonstrated fragmentation with delays progressing beyond the local T-waves, causing VPDs and ventricular arrhythmias. Returning to Duke, I developed our mapping system and continued these studies, establishing that acute MI did indeed cause fragmented, delayed conduction beyond local repolarization intervals, resulting in reentry, VPDs, tachycardias, and Vfib (Fig. 1) (3, 4). These results later led to the surgical ablation of ventricular arrhythmias in five of six patients successfully (1974-5) (Fig. 2) (5, 6).

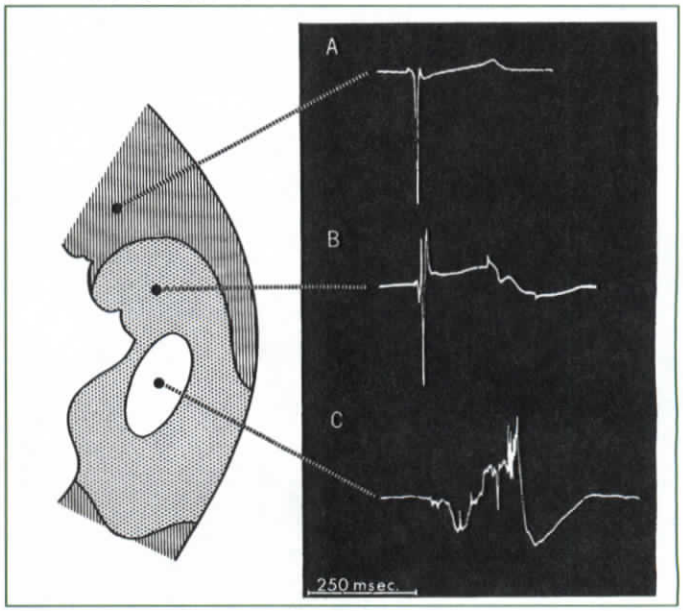


Fig. 1. Slow desynchronized conduction resulting in late potentials. Normal zone (A), late potentials (B), slow conduction zone (C) (1965).

ADVENTURES IN CARDIAC ELECTROPHYSIOLOGY: THE ORIGIN OF ARRHYTHMIA ABLATION CONT'D.

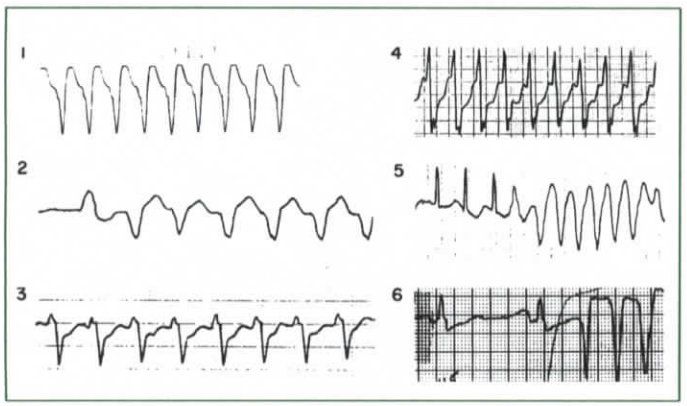


Figure 2. Arrhythmias of the first six patients to undergo surgical ablation of V. tach (1975).

WPW-PRE-EXCITATION

In the early 1960s, Neil Moore and I had been mapping the cardiac and body surface potentials in dogs with congenital heart disease to explain the abnormal ECG patterns in those conditions (7, 8). The experience gained from these studies were later applied to similar investigations in human subjects with both acquired and congenital heart disease, the combined studies giving us new understanding of the genesis of the abnormal ECG patterns (9, 10). During this period, Neil discovered a dog with congenital WPW (pre-excitation). We performed both epicardial and intramural mapping studies in this animal, localizing the site of pre-excitation to the inferior paraseptal area. Using vagal stimulation, we induced atrial fibrillation which immediately propagated to the ventricles. Using a new technique of 7 μm continuous film cross-section developed by Pickett and Summer at Duke, we were able to demonstrate an accessory AV connection crossing the inferior limbus of the coronary sinus in association with a coronary sinus diverticulum (Fig. 3). Anatomically, the pathway was composed of ordinary atrioventricular muscle and the propagation velocity confirmed a standard myocardial conduction velocity (11).

Later, we were able to obtain a squirrel monkey with bilateral, right and left, accessory AV connections and perform similar electrophysiologic anatomic correlations. The dual sites of pre-excitation in the monkey corresponded to very different morphologic connections on the two sides (12).

I returned to Amsterdam for two additional summers to learn as much as possible about patient mapping in the OR. On one of these occasions, they mapped a patient undergoing surgical closure of a secundum atrial septal defect. However, the ECG demonstrated WPW and mapping identified a site of pre-excitation at the lateral margin of the anterior RV. No attempt was made to ablate the pre-excitation (13).

Because of the work on the arrhythmias of myocardial infarction, I received support from one of the first SCOR grants (MIRU then) to expand the work to patients in the OR. Using this, we were able to develop another recording system above one of the Duke ORs which could be viewed from above through a glass observation tower. During the mapping, I was able to communicate with the technicians above who were recording data.

Prior to the completion of the studies on pre-excitation in the dog, we were presented with a patient with WPW and a paroxysmal-almost incessant supraventricular tachycardia (SVT), resulting in a hypertrophic cardiomyopathy. The surgeon and the other cardiologists involved wanted to cut the His bundle to stop the SVT. However, because of the map of WPW in the ASD patient in Amsterdam and our preliminary observations on WPW in the dog, it seemed most appropriate to identify and attack the actual anomalous substrate since I assumed we would be able to define the location by mapping.

Because we had not used map data to direct any procedures prior to this patient and anticipating inefficiencies, potential errors, and insufficient time, we electronically simulated pre-excitation in several dog studies to ensure that we would be able to accurately and rapidly record, measure, and reproduce the activation time data and maps online. This turned out to be fortuitous because of the diverting excitement occurring in the OR. We mapped both ventricles epicardially and completely from base to apex to establish a coherent pattern of expanding wavefront propagation from its earliest site of entry into the ventricles to its latest sites; we performed this three times for insurance. We were also able to map the SVT and the site of earliest atrial activation during the arrhythmia which coincided with the site of ventricular pre-excitation during normal sinus rhythm on the other side of the AV groove.

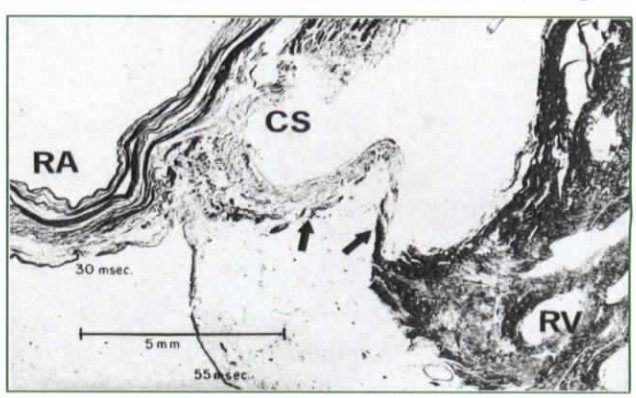


Figure 3. EP and anatomy of a posteroseptal accessory connection in the inferior coronary sinus limbus in the dog with pre-excitation (1968).

ADVENTURES IN CARDIAC ELECTROPHYSIOLOGY: THE ORIGIN OF ARRHYTHMIA ABLATION CONT'D.

Thus, it was clear where the localized incision should be directed. During the mapping, we also recorded an accessory A-V (Kent) potential from the anterior AV groove. The incision by Sealy separated the atrium from the ventricle at the site of pre-excitation and ablated both the SVT and the ECG pattern of WPW during sinus rhythm and atrial pacing (Fig. 4) (14, 15).

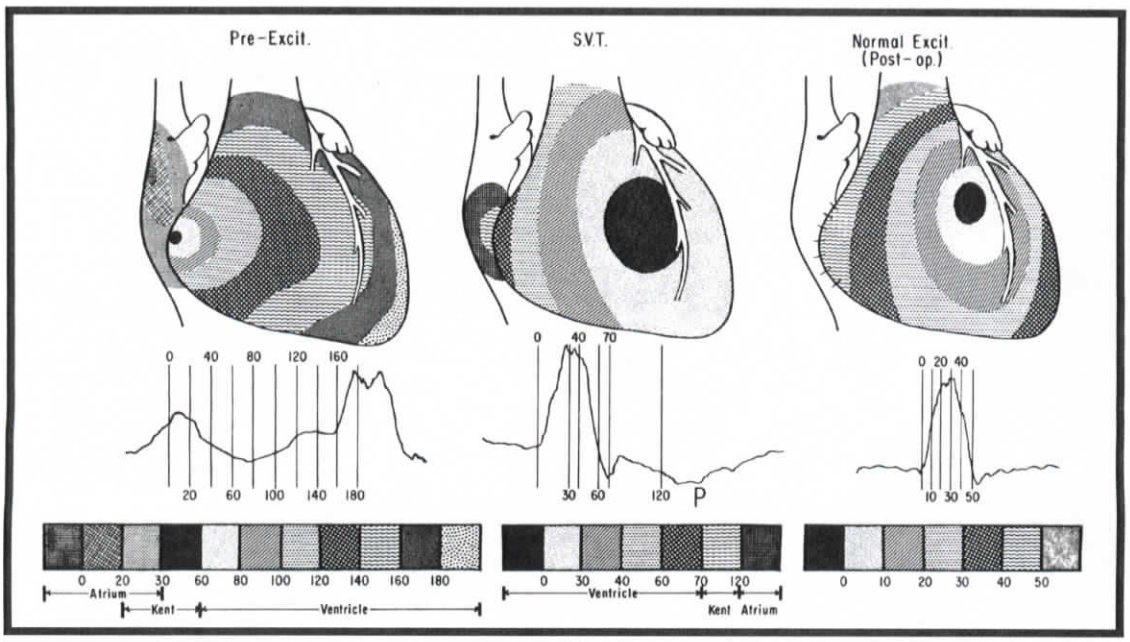


Figure 4. The first patient with successful surgical ablation of an accessory connection: A) pre-excitation, B) SVT, C) normal activation postoperatively (1968).

This result led to similar procedures in 14 other patients with pre-excitation. Some of these were successful and others with LV pre-excitation were failures. As a result of the failure of left sided ablation, I began a detailed examination of the left AV groove anatomy, including the atrial and ventricular insertions into the mitral annulus, the coronary arteries and veins, and encompassing fatty tissue within this space. As a result of these dissections, it became obvious that a new method for endocardial AV mapping of the LV and LA followed by an endocardial surgical approach was needed. Sealy liked the plan and thereafter LV endocardial surgical approach was needed. Sealy liked the plan and thereafter LV endocardial mapping and surgical approaches were used following extensive epicardial mapping to first approximate the location of the accessory connection (16).

In the beginning, mapping procedures were carried out with a single hand-held probe which was moved to different epicardial locations according to a predetermined grid. Activation times were placed on this grid and in addition, color Polaroid photographs were used to designate local activation times in relation to the specific cardiac structures for the surgeons. Sometime later, and after moving to California, we discovered and used an elastic netting containing 56 electrodes and a multichannel analog mapping system to record more potentials simultaneously. However, the activation time maps still had to be processed manually. In the mid '70s, we developed the first all digital mapping system in which data could be rapidly processed online, dramatically shortening the time needed for the procedure. These systems were used to map the arrhythmias in patients with both pre-excitation and previous myocardial infarction.

ESTABLISHMENT OF SUBSTRATES AND A BASIS FOR ARRHYTHMIA ABLATION

In retrospect, and as a result of the mapping studies in both the animal models and patients with myocardial infarction and pre-excitation, we had: 1) identified the substrates for two different reentrant arrhythmias in animals and then in patients. 2) Worked out the methods for rapid identification and localization of the abnormal substrates. 3) Demonstrated that the arrhythmias could be terminated by ablating the substrates. It is with the perspective of hindsight that I suggest that these results (1963-1971) launched the thought and technical evolution that led eventually to catheter ablation and clinical electrophysiology. Both the animal and human studies, mapping, and the surgical approaches in the exposed heart were a necessary first step, establishing the directions for future advances which have so rapidly evolved in this field.

COMPUTER SIMULATION OF VENTRICULAR FIBRILLATION

Because of the limitation of the physiologic studies to explain completely the mechanisms resulting in complex ventricular arrhythmias, in 1971 we developed a computer model of ventricular fibrillation (17), patterned after the two dimensional model of atrial fibrillation of Moe et al (18). This model was three dimensional and included a Purkinje system. From these computer simulations of ventricular fibrillation, we became aware of the importance of multiparameter interactions that were critical to the development of

ADVENTURES IN CARDIAC ELECTROPHYSIOLOGY: THE ORIGIN OF ARRHYTHMIA ABLATION CONT'D.

the arrhythmia which were not predictable based on the physiologic studies alone. We were able to simulate the effects of varying degrees of heterogeneous repolarization as well as changes in activation velocity in the vulnerability for arrhythmogenesis. We also learned how chance and variable distribution of heterogeneity modeled by a random number generator could result in an arrhythmia in one computer run and not in the other, even though both were at the vfib threshold. This explained why a patient with the substrate for a malignant arrhythmia might die on Wednesday but not on Tuesday, having little to do with disease progression and also emphasized the importance of varying autonomic inputs. Using this model, we gained insights into parameter interactions required for arrhythmogenesis that we could not have obtained through physiologic studies alone where the parameters identified and controlled were limited.

ATRIAL RHYTHMS AND THE MAZE

In 1974, I moved to Augusta, Georgia, and our group began to focus on impulse origin and arrhythmias in the atrium. As so often occurs when chasing one idea, we encountered totally unexpected event which ultimately changed our concepts regarding the mechanisms of atrial arrhythmias. By this time, we had developed a multi-electrode digital mapping system designed and fabricated by our engineer, Carey Miller. We were recording from 96 electrodes simultaneously and producing maps online. Purely by accident, we discovered a dog with naturally occurring atrial flutter of two types (19). One was identical to that seen in most patients and the other was different, both in rate and in ECG morphology. However, both were due to reentrant circus motion in the dog's right atrium. One was anti-clockwise and the other clockwise and we termed them type 1, or common flutter, and type 2, uncommon flutter. Both demonstrated an area of slow conduction with fragmented electrograms which were also present during normal sinus rhythm in the same region. Anatomic studies revealed that the area of slow conduction resulted from hypoplasia of the crista terminalis and adjoining pectinate muscles. The right atrium was not enlarged, but the slowing permitted a large excitable gap which established and sustained the circus motion.

Although these findings explained the sustainability of the arrhythmia, they did not account for its initiation. The findings in this unique animal were the motivation for subsequent studies to unravel the process of initiation of atrial flutter and serendipitously gain insight into certain aspects of afib. From our previous work, we assumed that all reentry involved a substrate of some form, either slow conduction orpossibly nonuniform repolarization, as well as a provocateur in the form of premature repolarization inhomogeneity (dispersion). Subsequent studies in canines demonstrated how large nonuniform repolarization gradients interacted with the sites and timing of APDs to locally block and mold circuitous premature wavefronts and route them back to the sites of origin, producing repetition (reentry) (19). We concluded that atrial flutter necessitated at least two substrates: 1) a nonuniform gradient of repolarization requiring a perfectly timed and located APD for initiation, and 2) either an area of slow conduction or a large enough circuit to create a critically lengthened excitable gap. Later, we demonstrated the importance of natural atrial orifices consisting of both the anterior discontinuity of the tricuspid annulus and the posterior discontinuities of the SVC and IVC which, when linked by intercaval functional block, converted the right atrium into a large cylindrical pathway where the combined anterior and posterior orifices prevented short circuiting and interruption of the repetition (20). During these studies complex and changing activation patterns characteristic of atrial fibrillation were frequently recorded. This seemed to agree with the prevailing theory of afib, that of numerous small independent reentrant circuits or wavelets (18), "too many to count". This was an intellectual barrier to any direct method to ablate this complexity, as with the single circuit substrate of pre-excitation related arrhythmias. In several studies, we observed irregular right atrial activation and ventricular responses due to a single repeating atrial flutter circuit in the left atrium (Fig. 5) (21). Because of its shorter repolarization interval and smaller pulmonary venous discontinuities, the left atrium permitted very rapid and regular atrial flutter-like reentry, with cycle times between 90 to 120 msec.

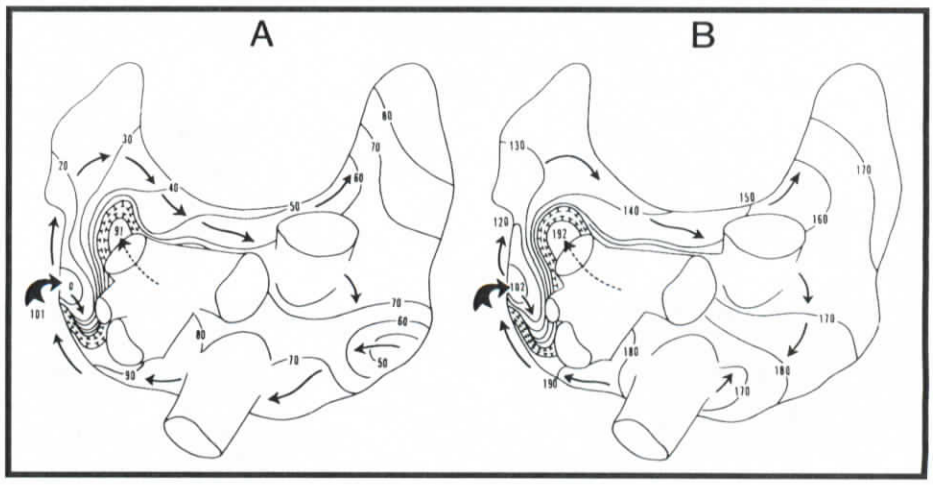


Figure 5. First example of a single left atrial reentrant "driver of atrial fibrillation" in a dog (1980). Note the single repeating reentry in the LA and changing multiple wavefront complexities in the RA and in these two consecutive cycles.

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However, the activation time of wavefronts departing the left atrial circuits required 160 to 170 msec to reach the lateral right atrium. This temporal disparity between the short left atrial repetition interval and the prolonged right atrial conduction resulted in multiple coexisting wavefronts beyond the single reentrant circuit, with each successive cycle. This effect interacted with the longer and nonuniform right atrial repolarization times resulting in irregular but passive dissociation of distant wavefronts resulting in the appearance of atrial fibrillation. However, the atrial irregularity was entirely passive. Thus, it was clear that not all atrial fibrillation was due to multiple active reentrant circuits and that much of the complexity was passive and driven by one active, and occasionally two interactive, changing sites of reentry (22). Now, many years later, these arrhythmias are referred to as atrial fibrillation with a single LA "driver". Other experiments revealed a greater complexity in which no consistently repeating reentrant source could be identified. However, even in these, it seemed that a major component of the multiple wavelet complexity was passive.

This was the experience of the group when we arrived in St. Louis to work with Jim Cox. Jim had been a fellow in the lab at Duke during the 1960s when we were involved in pre-excitation and ventricular arrhythmias. Many hours were spent deliberating the move and I believed that we would have to do something original to justify moving the lab and my coworkers and generally live up to expectations. Jim's mother had recently died after an embolic stroke due to atrial fibrillation. The prior experiences with MI, WPW, and the maps of atrial flutter and fibrillation had greatly influenced my thoughts on how to approach arrhythmias (i.e., ablation rather than drugs). These concepts were now focused on atrial fibrillation. I began to use "thought experiments", listened to a lot of Vivaldi, and pored over my stepson's books on mazes. I then proposed to Jim that we attempt to divide the atria into segments which might prevent atrial fibrillation due to the less complex forms of reentry encountered in some of our previous canine studies. The ideas which evolved were the Maze and Radial procedures. It was very theoretical at the beginning. Jim and I discussed the various specific approaches which might prevent atrial fibrillation reentry and still route the impulses from the atrial pacemaker complex to the AV node and right and left atria.

As with all previous work, we began with animal models and tried to create atrial fibrillation by producing mitral regurgitation with chordae cuts, etc. Too many animals died in congestive heart failure before developing the arrhythmia. I then decided to use a pharmacologic approach. This consisted of acetylcholine infusion to shorten atrial refractory period and possibly cause increasing atrial repolarization inhomogeneity. We then induced atrial fibrillation with rapid atrial stimulation. Although this would not exactly simulate the patient condition, it could represent a worst case scenario resembling primary AF and, because of the short repolarization duration and a potentially very complex arrhythmia with multiple circuits, ablation under these conditions might warrant further exploration in patients. In the initial experimental studies with Jim and Rick Schuessler, we attempted to isolate the pulmonary veins, since Jim's prior experience suggested that this might work. However, we quickly found that even if the atrial fibrillation was terminated, we produced a large left atrial reentrant circuit, resulting in sustained atrial flutter.

We reported the Maze as an experimental procedure and continued to work in the animal lab to perfect it (23). We had no intention of offering it to patients at that time. However, the reports were widely read and we were contacted by an airline pilot from Cyprus who had been taken off flying status because of atrial fibrillation. He tried to persuade Jim to perform the Maze on him. Jim refused, but the pilot kept pestering us and actually flew to St. Louis to discuss the possibility. Well, the rest you know; the procedure was successful. Out of the animal studies and early patient results, three stages of the surgical Maze evolved (24, 25, 26). Later, the Radial procedure was developed in our lab in conjunction with Takashi Nitta (Fig. 6) (33). As with WPW and V-tach ablation, atrial fibrillation took on a life of its own. An arrhythmia that was so common and yet "wallowed in the doldrums" for years without much new interest, became the arrhythmia of the new age (age of enlightenment).

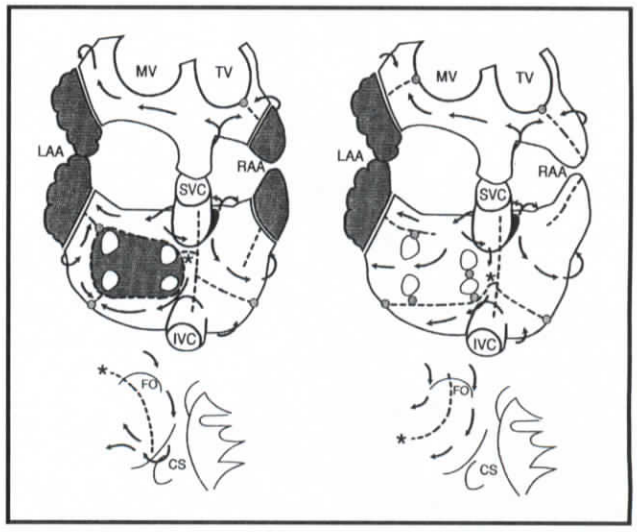

Figure 6. Schematic of the Maze and Radial procedures to ablate atrial fibrillation and atrial flutter (1986-1999).

Much of this earlier work was concerned with mechanisms and interventions at the macroscopic and microscopic (histologic) level. It seemed at the time that broad sweeping ideas and approaches were needed. Appropriately, these approaches have been succeeded by those at

ADVENTURES IN CARDIAC ELECTROPHYSIOLOGY: THE ORIGIN OF ARRHYTHMIA ABLATION CONT'D.

the basic cellular and molecular levels which should have even greater impact over the longer term. The journey has been fun, often amusing, occasionally hilarious, and sometimes disappointing. Altogether, it has been a privilege to be part of this era of arrhythmology and to be able to make some contributions to it. It all began as an obsession with the ECG as a medical student more than 50 years ago.

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Dr. Boineau is the Professor of Surgery, Medicine, & Biomedical Engineering and Director of Cardiothoracic Surgery Research Lab at Washinton University School of Medicine

CBAC Student Profiles

The Heartbeat sat down with Tom to chat about his past and future in research. When I asked Tom to start from the beginning, he did just that. "My family certainly influenced my career choice. My mother, a high school foreign language teacher, and my father, a battery chemist, both value education. Two of my three siblings are starting careers as teachers (high school math and biology). The love of teaching and learning my family instilled in me made graduate school a natural choice. I had my sights set on a graduate degree as far back as middle school. I remember making a "life goals" brochure for class and listing "PhD" as a goal."

So how did Tom become interested in research? Tom says, "I attended Rhodes College in Memphis, where I studied physics. My undergraduate mentor, Brent Hoffmeister, set me up with a research project after my first year. In collaboration with Robert Malkin and Semahat Demir at the University of Tennessee Biomedical Engineering Department, I studied the *in vivo* response of the canine heart to a variety of low amplitude alternating current waveforms. The problem motivating our research was the "leakage current" emitted from biomedical devices which can alter the heart rhythms of ICU patients. We discovered that standards for maximum leakage currents allowed from devices may be too high in some instances, especially when patients have low impendence pacemaker or ICD leads to guide currents into their hearts. I enjoyed my undergraduate research on the heart, and I made computational models to help explain mechanisms behind some aspects of the findings. I used one of Dr. Rudy's models in my work, and I chose to join his lab in graduate school."

Math, science, necessity and a bit of intrigue have always been the foundations of research and for Tom that was certainly the case. Tom states, "I always excelled in science and art. Anne Mowery, my dedicated and thoughtful high school physics teacher, inspired me to study physics in college. After college, most of the graduate programs to which I applied were in physics. I realized, however, the research in the physics departments that most appealed to me was biomedical/biophysics related, and so I decided to do BME with Dr. Rudy."

In terms of his most important accomplishment to date, Tom had this to say, "In my graduate research, I have strived to foster lively extra-institutional collaborations. To do good computational physiology, one needs good experimental data. For my project, the best data comes from András Varró in Szeged, Hungary, David Van Wagoner at the Cleveland Clinic, and Igor Efimov and Jianmin Cui here at Washington University BME. I have spent significant time in each of these places, learning and performing experiments. I understand that managing different experiments in different labs at different institutions is an important part of contemporary research. I am fortunate to have these research connections, and I think establishing them has been a critically important achievement."

Tom shared his thoughts on being a part of the CBAC; he states "CBAC seminars are world-class affairs. I am lucky to have seen so many outstanding presentations of cutting edge research that directly relates to my own research. The video archive of the seminars is a treasure. The seminars provide a forum to meet and discuss with the outstanding local scientists whom I would not necessarily see otherwise. I benefit greatly from one-on-one meetings with the visiting lectors with whom I share my research and receive valuable feedback. CBAC has enriched my graduate experience profoundly."

For the future, "I look forward to continuing cardiac bioelectricity research as a post-doctoral scientist. At this point, I am not sure where I will do this work, but I have an interest in combining experimental and theoretical modeling to examine new issues in the field and to, hopefully, help explain new and interesting findings."

New CBAC Members Cont'd.

George Van Hare, M.D.
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

Dr. Van Hare has a long-standing interest in using electrophysiology as a tool to diagnose and treat irregular heartbeats, arrhythmias, in children.
Dr. Van Hare's primary research focus is on children with heart rhythm disorders.
Dr. Van Hare is the Louis Larrick Ward Chair in Pediatric Cardiology at St. Louis Children's Hospital (SLCH) and Washington University School of Medicine (WUSM).
He is a fellow of the Heart Rhythm Society, the American Academy of Pediatrics and the American College of Cardiology. He is president of the Pediatric & Congenital Electrophysiology Society.

Announcements & News

Leonid Shmuylovich MSTP, graduate student in Dr. Sandor J. Kovacs' Cardiovascular Biophysics Research Group has been awarded a 3rd year of predoctoral fellowship support by the AHA, achieving a Percentile Rank of 2.31%. His research topic concerns theoretical and applied cardiovascular physiology regarding an echocardiographic, load independent index of diastolic function (LIIDF). {SEE: Shmuylovich L, Kovács SJ. A load-independent index of diastolic filling: model-based derivation with in-vivo validation in control and diastolic dysfunction subjects. Journal of Applied Physiology, 101:92-101, 2006}

Dr. Yoram Rudy delivered the Tawara Lecture *"Cardiac Excitation and Arrhythmia in the Human Heart: Insights from Noninvasive ECG Imaging (ECGI)* at the International Congress of Physiological Sciences (IUPS) in Kyoto, Japan, on July 30th, 2009. From August 2nd – 13th, Professor Rudy presented a series of invited lectures in Taiwan at the following universities: National Taiwan University in Taipei, National Cheng Kung University in Tainan, Providence University and National Chung Hsing Universities in Taichung. On August 2nd a National Symposium at National Cheng Kung University celebrated the 18 year anniversary of the publication of the Luo-Rudy model of the cardiac cell. (photo right, Dr. Ching-Hsing Luo presents to Dr. Yoram Rudy a commemorative piece of artwork in recognition of the Luo-Rudy model anniversary)

Subham Ghosh, Ph.D., a member of the Rudy Lab, defended his thesis "Electrocardiographic Imaging: Development of a Non-smooth Regularization Method and Clinical Application in Patients with Wolff-Parkinson-White Syndrome and Heart Failure" on May 19, 2009 and graduated with his PhD. in Biomedical Engineering. Subham is now a post-doctoral Research Associate in the Rudy Lab.

Yong Wang, Ph.D., also a member of the Rudy Lab, defended his thesis, "Contributions to the Methodology Of Electrocardiographic Imaging (ECGI) and Application of ECGI To Study Mechanisms Of Atrial Arrhythmia, Post Myocardial Infarction Electrophysiological Substrate and Ventricular Tachycardia In Patients" on June 11, 2009 and graduated with his PhD in Biomedical Engineering. He is now a Research Associate in the Radiology Department at Washington University School of Medicine.

Announcements & News Cont'd.

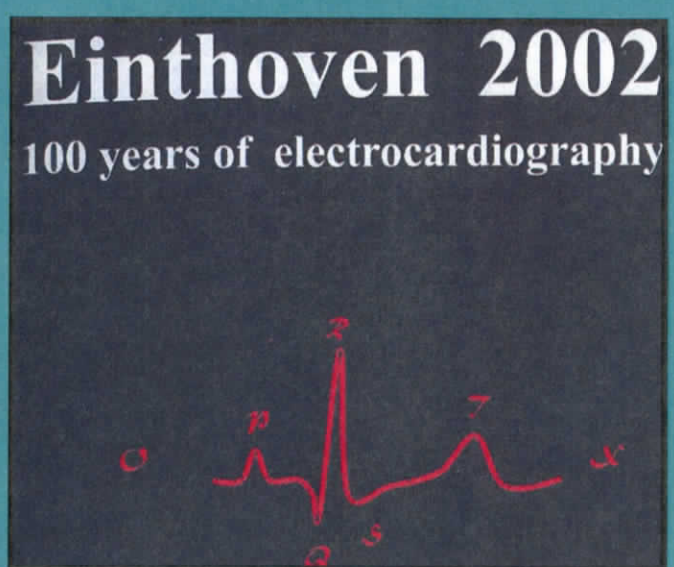
Thomas Hund, an alum of the Rudylab (Ph.D. 2004) won the 2008 Early Career Authors Prize, designed to recognize outstanding papers published by early-career authors in the *Journal of Molecular and Cellular Cardiology*. The award publication is: T.J. Hund, K.F. Decker, E. Kanter, P.J. Mohler, P.A. Boyden, R.B. Schuessler, K. A. Yamada, Y. Rudy, "Role of activated CaMKII in abnormal calcium homeostasis and I_{Na} remodeling after myocardial infarction: Insights from mathematical modeling", *J of Molecular and Cellular Cardiology* 2008;45:420-428.

GRANTS

Yoram Rudy, Ph.D.:

* *Cardiac Excitation and Arrhythmias*. Yoram Rudy, PI, $1,898,718, 04/01/2009-03/31/2013 from the NIH-National Heart, Lung and Blood Institute.
* *Alliance for CAMKII Signaling In Heart Disease, $271,356, 10/01/08–09/30/13 from the Fondation Leducq.*The mission of FLQ is to improve human health through international efforts to combat cardiovascular disease. The Fondation Leducq supports integrative research networks in cardiovascular disease under the Transatlantic Networks of Excellence in Cardiovascular Research Program.
* *Modeling Spatial Organization of Cardiac Cell Function:Application to Calcium Waves and Arrhythmia.* Yoram Rudy, PI, $294,621, 08/15/09-07/31/12 from The National Science Foundation.

Willem Einthoven (1860-1927)



Announcement of the anniversary congress "Einthoven 2002, 100 years of electrocardiography," on the occasion of the first ECG registration with Einthoven's string galvanometer.

CBAC Faculty Members

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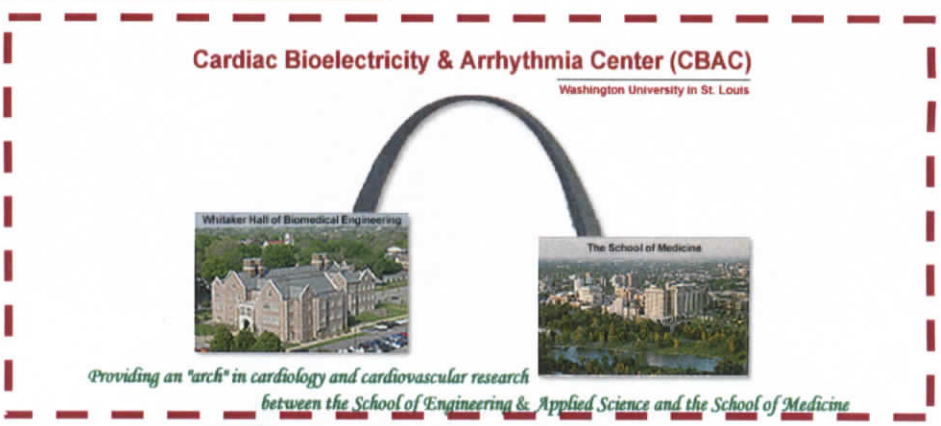
Michael Cain, M.D.
Daniel P. Kelly, M.D.
Bruce Lindsay, Ph.D.
Achi Ludomirsky, M.D.
Vladimir P. Nikolski, Ph.D.
Edward Rhee, Ph.D.
Jeffrey E. Saffitz , M.D

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

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



CARDIAC BIOELECTRICITY AND ARRHYTHMIA CENTER (CBAC)

http://cbac.wustl.edu

Seminar Schedule

Yoram Rudy, Director

Cardiac Bioelectricity & Arrhythmia Center (CBAC)
Fall 2009 Seminar Schedule

Mondays, 5:30 PM – 6:30 PM except where indicated in red
[Hors d'oeuvres Reception from 5:00PM - 5:30PM]
Room 218, Whitaker Hall, Washington University Danforth Campus
** Please contact <cbac@biomed.wustl.edu> for more information **

Date		Name of Speaker, Affiliation, Title of Talk
August 31, 2009		**W. Jonathan Lederer, MD, PhD** *Professor and Director* *Medical Biotechnology Center, University of Maryland Biotechnology Institute* **"Losing the Spark: Calcium Sparks and Calcium Leak in Heart"**
September 10, 2009 **Thursday**		**Douglas L. Mann, MD** *Tobias and Hortense Lewin Professor and Chief* *Cardiovascular Division, Department of Medicine, WUMS* **"Determinants of Cardiac Remodeling and Myocardial Recovery"**
October 6, 2009		**Anthony Muslin, MD, FAHA** *Oliver M. Langenberg Distinguished Professor of the Science and Practice of Medicine* *Professor of Cell Biology and Physiology* *Director, Center for Cardiovascular Research (CCR), Director, Cardiology Research Fellowship Program,* *Washington University School of Medicine, St. Louis, MO* **"New Insights in Pathological Cardiac Remodeling"**
October 19, 2009		**Jose Jalife, MD** *Cyrus and Jane Farrehi Professor of Cardiovascular Research,* *Professor of Internal Medicine and Molecular and Integrative Physiology, University of Michigan Medical School* *Co-director of the U-M Center for Arrhythmia Research, University of Michigan, Ann Arbor, MI* **"Arrhythmogenic Mechanisms in Inherited Catecholaminergic Polymorphic Ventricular Tachycardia"**
November 2, 2009		***Heather S. Duffy, PhD*** *Instructor in Medicine* *Cardiovascular Research, Cardiovascular Division* *Beth Israel Deaconess Medical Center, Harvard School of Medicine, Boston, MA* **"Forming the Arrhythmogenic Substrate: Molecular Mechanisms of Gap Junction Remodeling"**
November 9, 2009 **Begins at 4:00pm**		***Victor G. Davila-Roman, MD*** *Associate Professor, Medicine* *Division of Cardiovascular Diseases* *Associate Professor, Anesthesiolgy* *Associate Professor, Radiology* *Division of Cardiovascular Diseases, Washington University School of Medicine, St. Louis, MO* **"TBD"**

Washington University in St.Louis

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

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

CBAC Faculty Publications

Jane Chen, MD

* Gleva MJ, Chen J, Cooper J, Faddis M, Smith T, Lindsay B. The effect of venous access technique and body surface area on transvenous defibrillator lead failure. *Heart Rhythm* 2008; 5 (5S): S290 (abstract).
* Cooper JA, Latacha MP, Soto GE, Garmany RG, Chen J, Gleva MJ, Smith TW. Efficacy and stability of azygos defibrillation leads in patients with elevated defibrillation thresholds. *Heart Rhythm* 2008; 5 (5S): S243 (abstract).
* Chen J, Wilkoff BL, Choucair W, Cohen TJ, Crossley GH, Johnson WB, Mongeon LR, Serwer GA, Sherfesee L. Design of the Pacemaker Remote Follow-up Evaluation and Review (PREFER) trial to assess the clinical value of the remote pacemaker interrogation in the management of pacemaker patients. *Trials* 2008; 9:18.
* Cooper JA, Latacha MP, Soto GE, Garmany RG, Gleva MJ, Chen J, Faddis MN, Smith TW. The azygos defibrillator lead for elevated defibrillation thresholds: implant technique, lead stability, and patient series. *PACE* 2008; 31:1405-1410.
* Eckart R, Chen J, Epstein LM. Defibrillator Function and Implantation, Chapter 8. In Kusumoto F, Goldschlager N (Eds), *Cardiac Pacing for the Clinician*, 2nd Edition, Springer, New York, NY, 2008.

Ralph J. Damiano, Jr., MD

* Lall SC, Foyil KV, Sakamoto S-I, Voeller RK, Boineau JP, Damiano RJ Jr, Schuessler RP: Pulmonary vein isolation and Cox-Maze procedure only partially denervate the atrium. J Thorac Cardiovasc Surg 2008;135:894-900
* Voeller RK, Bailey MS, Zierer A, Lall SC, Sakamoto S, Aubuchon K, Lawton JS, Moazami N, Huddleston CB, Munfakh NA, Moon MR, Schuessler RB, Damiano RJ: Isolating the entire posterior left atrium improves surgical outcomes following the Cox-Maze procedure. J Thorac Cardiovasc Surg 2008;135:870-877.
* Olsen MA, Krauss M, Agniel D, Schootman M, Gentry CN, Yan Y, Damiano RJ Jr, Fraser VJ: Mortality associated with bloodstream infection following coronary artery bypass graft. Clin Infect Dis 2008;46:1537-1546
* Crabtree TD, Bailey MS, Moon MR, Munfakh N, Pasque MK, Lawton JS, Moazami N, Aubuchon KA, Al-Dadah AS, Damiano RJ Jr: Recurrent mitral regurgitation and risk factors for early and late mortality after mitral valve repair for functional ischemic mitral regurgitation. Ann Thorac Surg 2008;85:1537-1543
* Ishii Y, Sakamoto S, Kronengold RT, Virmani R, Rivera EA, Goldman SM, Prechtel EJ, Hill JG, Damiano RJ Jr: A novel bio-engineered small caliber vascular graft incorporating heparin and sirolimus: excellent 6 month patency. J Thorac Cardiovasc Surg 2008;135:1237-1246
* Damiano RJ Jr: What is the best way to surgically eliminate the left atrial appendage? (comment) J Am Coll Cardiol 2008; 52:930-931
* Melby SJ, Lee AM, Zierer A, Kaiser SP, Livhits MJ, Boineau JP, Schuessler RB, Damiano RJ Jr: Atrial fibrillation propagates through gaps in ablation lines: Implications for ablative treatment of atrial fibrillation. Heart Rhythm 2008; 5:1296-1301
* Melby SJ, Zierer A, Lubahn JG, Bailey MS, Cox JL, Schuessler RB, Damiano RJ Jr: Normal quality of life after the Cox-Maze procedure for atrial fibrillation. Innovations 2008; 3:142-146
* Voeller RK, Zierer A, Lall SC, Sakamoto S, Chang N, Schuessler RB, Moon MR, Damiano RJ Jr: The effects of the Cox-maze procedure on atrial fibrillation. J Thoracic Cardiovasc Surg 2008;136:1257-1264
* Sakamoto S-I, Voeller RK, Melby SJ, Lall SC, Chang N-L, Schuessler RB, Damiano RJ Jr: Surgical ablation for atrial fibrillation: The efficacy of a novel bipolar pen device in the cardioplegically arrested and beating heart. J Thorac Cardiovasc Surg 2008;136:1295-1301.
* Moraca RJ, Moon MR, Lawton JS, Guthrie TJ, Aubuchon KA, Moazami N, Pasque MK, Damiano RJ Jr: Outcomes of tricuspid valve repair and replacement: A propensity analysis. Ann Thorac Surg 2009;87:83-89.
* Moon MR, Lawton JS, Moazami N, Munfakh NA, Pasque MK, Damiano RJ Jr: Prosthesis-patient mismatch does not affect survival for patients greater than 70 years of age undergoing bioprosthetic aortic valve replacement. J Thorac Cardiovasc Surg 2009;137:248-283.
* Lee AM, Aziz A, Sakamoto S, Schuessler RB, Damiano RJ Jr: Epicardial ablation on the beating heart: Efficacy of a novel, cooled radiofrequency ablation device. Innovations 2009;4:86-92.Lawton JS, Moazami N, Pasque MK, Moon MR, Damiano RJ Jr: Early stenosis of Medtronic porcine mosaic valves in the aortic position. J Thoracic Cardiovasc Surg 2009;137:1556-1557.

Publications Cont'd.

Ralph Damiano, Cont'd.

* Damiano RJ Jr., Ishii Y, Schuessler RB: Surgery for atrial fibrillation: Is pulmonary vein isolation alone sufficient? Expert Review of Cardiovascular Therapy. In press.
* Sakamoto S, Melby SJ, Bailey MS, Schuessler RB, Damiano RJ Jr: Surgical treatment for inappropriate sinus tachycardia: operative results and late outcomes. In press. J Thorac Cardiovasc Surg
* 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 procine study. In press. J Thorac Cardiovasc Surg
* Moraca RJ, Bailey MS, Damiano RJ Jr: Current surgical techniques for ischemic ventricular tachycardia. In: Ventricular Arrhythmias and Sudden Cardiac Death. Wang PJ, Al-Ahmad A, Hsia HH, Zei PC (eds) Blackwell Futura Publishing, Malden, Massachusetts. In Press.
* Shen J, Bailey MS, Damiano RJ Jr: The surgical treatment of atrial fibrillation. In press.

Richard W. Gross, M.D., Ph.D.

* Malik, I, Turk, J, Mancuso, DJ, Montier, L, Wohltmann, M, Wozniak, DF, Schmidt, RE, Gross, RW, and Kotzbauer, PT. Disrupted membrane homeostasis and accumulation of ubiquitinated proteins in a mouse model of infantile neuroaxonal dystrophy due to PLA2G6 mutations. *Am. J. Pathol.* 2008, 172:406-416. PMID:18202189.
* Cheng H, Mancuso DJ, Jiang X, Guan S, Yang J, Yang K, Sun G, Gross RW, and Han X. Shotgun lipidomics reveals the temporally dependent, highly diversified cardiolipin profile in the mammalian brain: temporally coordinated postnatal diversification of cardiolipin molecular species with neuronal remodeling. *Biochemistry* 2008, 47:5869-80. PMID:18454555.
* Lehman JJ, Boudina S, Banke NH, Sambandam N, Han X, Young DM, Leone TC, Gross RW, Lewandowski ED, Abel ED, and Kelly DP. The transcriptional coactivator pgc-1{alpha} is essential for maximal and efficient cardiac mitochondrial fatty acid oxidation and lipid homeostasis. *Am J Physiol Heart Circ Physiol.* 2008, 295:H185-196. PMID:18487436.
* Han X, Yang K, and Gross RW. Microfluidics-based electrospray ionization enhances the intrasource separation of lipid classes and extends identification of individual molecular species through multi-dimensional mass spectrometry: development of an automated high-throughput platform for shotgun lipidomics. *Rapid Commun Mass Spectrom.* 2008, 22:2115-2124. PMID:8523984.
* Moon, SH, Jenkins, CM, Mancuso, DJ, Turk, J, and Gross, RW. Smooth muscle cell arachidonic acid release, migration, and proliferation are markedly attenuated in mice null for calcium-independent phospholipase A_2b. *J. Biol. Chem.* 2008, 283:33975-33987. PMID:18927078.
* Sun, G, Yang, K, Zhao, Z, Guan, S, Han, X, and Gross, RW. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometric analysis of cellular glycerophospholipids enabled by multiplexed solvent dependent analyte-matrix interactions. *Anal. Chem.* 2008, 80:7576-7585. PMID:18767869.
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