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Cardiac Arrhythmias: Investigating Mechanisms of Action

Contributing faculty: **David J. Christini, PhD**


Dr. David J. Christini

Sudden cardiac death, primarily caused by ventricular arrhythmias, is one of the leading causes of mortality in the United States. In the Cardiac Electrodynamics Laboratory directed by David J. Christini, PhD, Vice Chair for Basic Research and Professor of Medicine in the Division of Cardiology at Weill Cornell Medical College, an integrated, multiscale approach is underway to better understand cardiac electrophysiological dynamics. From the cellular to the organ level, Dr. Christini and his colleagues are interested in revealing the mechanisms underlying arrhythmia initiation and utilizing this knowledge to develop new arrhythmia therapies.

"Because of the complexity of electrophysiological dynamics we use a hybrid approach that combines computational, experimental, and clinical methods to bridge the gap between physics and biology," says Dr. Christini. "Computational modeling and experimental approaches – primarily patch clamping and calcium imaging of isolated cardiac myocytes – have provided novel insights into the ionic factors that cause instabilities in the cardiac action potential and how these channel level instabilities trigger cardiac arrhythmias in the whole heart."

Cardiac Arrhythmias, continued on page 3

Bedside to Bench…and Back Again: A Case Study on Controlling Symptoms of Long QT Syndrome

Contributing faculty: **Wendy K. Chung, MD, PhD**

Four years ago, a newborn was transferred to NewYork-Presbyterian/Morgan Stanley Children's Hospital for treatment of a severe arrhythmia. The full-term infant boy had normal heart structure but a prenatal history significant for fetal bradycardia of unclear etiology. There was no family history of arrhythmias, long QT syndrome, or sudden death. "The baby was having multiple episodes of ventricular tachycardia daily," recalls Wendy K. Chung, MD, PhD, Director of the Division of Clinical Genetics at NewYork-Presbyterian/Columbia. "He was arresting at least once a day, and had such a malignant type of arrhythmia that within the first month of life he had a defibrillator implanted and required defibrillation several times a month."

The infant was diagnosed with congenital long QT (LQT-3) causing extreme QT prolongation. The condition resulted from a *de novo* mutation in the heart's sodium channel and possibly a common polymorphism in a critical heart potassium channel. This particular form of the syndrome, while less common, is more lethal. Evidence has shown that mutations in ion channels may contribute to sudden infant death syndrome and other cardiac arrhythmias in newborns. "It is very unusual to see symptomatic long QT syndrome in a newborn," notes Dr. Chung. "It generally presents in children or in adults."

There are at least 12 genes associated with long QT syndrome and hundreds of mutations within these genes have been identified. Mutations in three of these genes account for about 70 to 75 percent of long QT syndrome cases. LQT-3 is caused by mutations in *SCN5A*, the gene coding for the sodium (Na+) ion channel protein, NaV1.5. Evidence has shown that frequency, severity, and

Long QT Syndrome, continued on page 4

Weill Cornell Establishes Chest Pain Program for Kids

Contributing faculty: **Patrick A. Flynn, MD**

Chest pain is the second leading reason for referral to pediatric cardiologists and accounts for more than half a million visits to emergency rooms or unscheduled visits to pediatrician offices over the course of a year in the United States. "Pediatric chest pain is very, very common but infrequently a sign of serious cardiac pathology," says Patrick A. Flynn, MD, Co-Director, Pediatric Chest Pain Program at the Phyllis and David Komansky Center for Children's Health at NewYork-Presbyterian/Weill Cornell.

Dr. Patrick A. Flynn

According to Dr. Flynn, the most common cause of chest pain is idiopathic, but in the rare cases when pediatric chest pain is a sign of cardiac pathology, that pathology is significant. "We hear about cases of sudden cardiac death in a young athlete in this country because it gets a lot of attention," notes Dr. Flynn. "Each time we all privately say that it's such a shame that there wasn't a warning sign that it was going to happen. Chest pain, in certain cases, can be a warning sign for those kinds of events."

Though chest pain is more frequently a sign of true pathology in adults than it is in the pediatric population, it still causes much anxiety among patients and their family members. "And it creates anxiety around the other elements surrounding the lives of children and adolescents – the schools, the coaches, the camps, and so on," says Dr. Flynn. "When you add that all together – it's common, it's usually benign, it's not necessarily benign, and it causes so much disruption in people's lives – the diagnosis of chest pain is important, not only to find out the pathology that can be lifesaving, but also to get these kids back in school and back to their normal activities."

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Enter the Pediatric Chest Pain Program at Weill Cornell, opening in early 2013, where an evaluation of a child's chest pain begins with a thorough medical and family questionnaire sent to the patient ahead of time. Responses are carefully reviewed by pediatric cardiologists who decide, based on the answers provided, which other subspecialties the patient might need to see during their visit. In addition to pediatric cardiologists, the integrated care team includes pediatric digestive disease specialists and pediatric pulmonary specialists – and has input from child psychiatrists – all with a unique focus on evaluation and diagnosis of chest pain in children. Cardiology testing includes an EKG, an echocardiogram if necessary, and possibly an exercise stress test. The pulmonologist is prepared not only to see the patient, but also perform pulmonary function tests, if required, on the date of the initial visit.

"Our goal is to provide a workup that demonstrates whether the child's chest pain is or is not related to significant pathology in any of those fields," explains Dr. Flynn. "In addition to screening for medical pathologies, we are also able to advise the family, or the practitioner who referred the patient, whether or not the patient screens for a high likelihood of an anxiety disorder."

In more than 20 years as a pediatric cardiologist, Dr. Flynn has observed that the clinical workup of pediatric chest pain tends to move at a pace slower than a family anticipates. "Sometimes there's a certain threshold before a pediatrician decides to refer," he says. "Then there's a lag between the time that they are referred and seen, unless they come in to the emergency room. If they are sent to a cardiologist, they'll usually have an EKG and often an echocardiogram and an exercise stress test. But that rarely happens on the same day.

"In the end if all those tests were normal, but the pain continues," says Dr. Flynn, "the family would have to start another cycle of workups with a pediatric pulmonologist or pediatric gastroenterologist. That workup not only takes a long time on the calendar from start to finish, but it also takes multiple stops along the way. I don't look so much at this as trips to the hospital or to the doctor's office; I look at it as days away from school and time lost from the parents' work."

According to Dr. Flynn, the Pediatric Chest Pain Program provides a much-needed service for referring pediatricians who will have an efficient and easily accessible place to send their patients. "Again, we don't anticipate that we're going to find a lot of heart disease, but we do find it on occasion," says Dr. Flynn, who notes the leading significant cardiac diagnosis would be congenital abnormalities of the coronary arteries.

"Musculoskeletal chest pain is pervasive – and the leading cause of chest pain in adolescence is probably due to carrying a heavy load of books in a backpack," says Dr. Flynn. "I can't tell you how many times I have kids complaining of left-sided chest pain. When I ask how they carry their books, they throw their backpack on to show me. I'll say, 'How about throwing it over your other shoulder for the next three weeks?' They call back and tell me their chest pain is gone, or has magically moved to the right."

Dr. Flynn particularly wants to evaluate children and adolescents who experience chest pain upon exertion and those whose chest pain is disrupting daily living. "While the likelihood is high that any individual patient coming to the Chest Pain Program is going to have a normal cardiac workup, those with chest pain associated with syncope or palpitations are the ones with a higher likelihood of pathology and who need to be seen the most."

Cardiac Arrhythmias, continued from cover

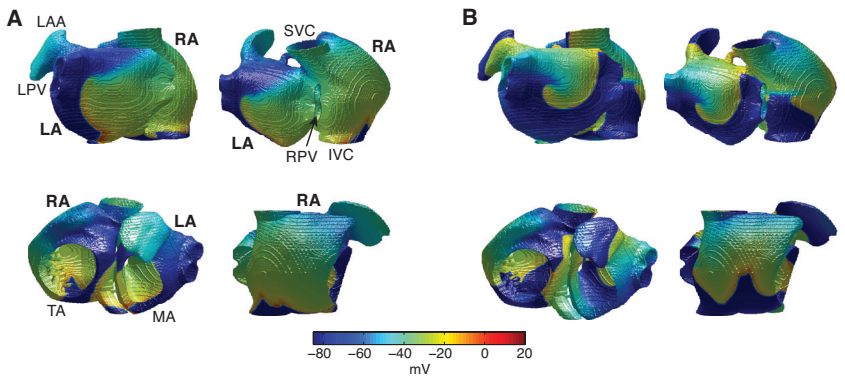
Supported by funding from the National Institutes of Health, including three R01 projects, Dr. Christini's research teams are studying the dynamics of arrhythmias from single cells to whole hearts; biophysical mechanisms of electrophysiological instabilities and arrhythmia onset; and arrhythmia prevention through termination of arrhythmia trigger events.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the developed world. According to Dr. Christini, because AF has several variants, is multifactorial, and evolves over time, it is very difficult to study comprehensively in large animal models. "This is, in part, due to the inherent technical difficulties of imaging whole-atria electrophysiology *in vivo*," says Dr. Christini. "Predictive multiscale computational modeling has the potential to fill this research void."

Dr. Christini and his colleagues are developing a multiscale modeling framework using data, including human MRI structural information and electrophysiological data, to clarify the impact of common ion channel gene polymorphisms on drug-channel interactions. This work is enabling the evaluation of potential pharmacological and device-based atrial fibrillation therapies.

"AF often progresses unfavorably," says Dr. Christini. "In patients with long-term atrial fibrillation, fibrillatory episodes are typically of increased duration and frequency of occurrence relative to healthy controls. This is due to electrical, structural, and contractile remodeling processes." Previous research by others in the field has shown that AF is more prominent in the context of alterations in atrial tissue properties – due to disease, arrhythmias, or age – known as remodeling. In fact, AF itself leads to remodeling, causing electrophysiological, contractile, and structural changes. Although AF can typically be reversed in its early stages, it becomes more difficult to eliminate over time due to this remodeling.

In a recent study, Dr. Christini's lab investigated mechanisms of how electrical and structural remodeling contribute to perpetuation of simulated atrial fibrillation using a mathematical model of the human atrial action potential incorporated into an anatomically realistic three-dimensional structural model of the human atria to represent its various disease states. It was the first such study of its type. The simulations demonstrated that disease-like modifications to cellular processes, as well as to the coupling between cells, perpetuate simulated atrial fibrillation by accelerating the rhythm and/or increasing the number of circulating activation waves.



(A) Reentrant activity in computer simulations of normal tissue and (B) tissue with full electrical plus structural remodeling. Fig. A shows an example of non-sustained reentrant activity in normal tissue. In contrast, when simulating full electrical plus structural remodeling, reentry was sustained for 60 s in 18 of 21 simulations. Fig. B shows that with such electrical plus structural remodeling the wavelength is much shorter than in normal tissue, and the reentrant wave in the left atrial free wall does not self-terminate.

"Given the model's ability to reproduce a number of clinically and experimentally important features, we believe that it presents a useful framework for future studies of atrial electrodynamics in response to ion channel mutations and various drugs," notes Dr. Christini.

Dr. Christini's lab is also investigating cardiac alternans, which is characterized by a beat-to-beat alternation in membrane potential that is known to trigger cardiac reentry in experiments and has been correlated with risk for clinical arrhythmias. "Although this phenomenon has been identified as a potential precursor to dangerous reentrant arrhythmias and sudden cardiac death, significant uncertainty remains regarding its mechanism and no clinically practical means of halting its occurrence or progression currently exists," says Dr. Christini. Studies have suggested that alternans may result from dynamical instabilities in either membrane voltage or calcium cycling. More recently, evidence for the calcium mechanism has accumulated, pushing that theory to the forefront. Dr. Christini's lab has demonstrated that the two mechanisms are intertwined and play varying, but quantifiable, roles for different cardiac cell types. These findings have important implications for their ongoing investigations into device and drug therapy of repolarization-triggered arrhythmias.

To facilitate new experimental paradigms, the Christini lab has developed a highly versatile real-time biological experimentation system known as Real-Time eXperiment Interface (RTXI; www.rtxi.org). "The ability to perturb biological systems has traditionally been limited to rigid pre-programmed protocols," says Dr. Christini. "In contrast, 'real-time control' allows the researcher to dynamically probe a biological system with parameter perturbations that are calculated functions of instantaneous system measurements, thereby providing the ability to address diverse unanswered questions that are not amenable to traditional approaches."

Reference Article

Krogh-Madsen T, Abbott GW, Christini DJ. Effects of electrical and structural remodeling on atrial fibrillation maintenance: a simulation study. *PLoS Computational Biology.* 2012;8(2):e1002390.

Long QT Syndrome, continued from cover

treatment of *SCN5A* mutations may be distinct from other forms of long QT syndrome. "Generally, Na+ channel blockers – such as mexiletine and flecainide – are effective in treating LQT-3 patients due to preferential inhibition of mutant Na+ channel activity," says Dr. Chung. "However, in this particular newborn, conventional drug therapy was ineffective."

Having diagnosed the baby's condition as genetic, Dr. Chung and her colleagues partnered with researchers, including Robert S. Kass, PhD, Chairman, Department of Pharmacology at Columbia University, in an effort to develop a therapy that would stop the refractory arrhythmias. From a skin sample they created beating heart cells in a dish in the laboratory that had the baby's entire genetic make-up, including the infant's mutant ion channel. They investigated the efficacy of three compounds – flecainide, mexiletine, and ranolazine – in correcting the biophysical dysfunction that provoked his arrhythmia in the past to see which drug might work best to stop his arrhythmias.

"Based on both his genetic diagnoses and the results of our tests, our goal was to be able to customize his medication," says Dr. Chung. "We essentially conducted clinical trials in a dish with skin cells converted to a type of all-purpose stem cell called induced pluripotent stem cells, which were made into cardiac myocytes. Using patch clamp analysis, which allowed us to study the ion channels in cells, we tried different ways of pacing his heart rate at the cellular level. This was not a trivial thing and took us over a year of experiments – going from bedside to bench and back again. But it provided us with proof of concept for a better model of personalized medicine – one in which a person's own cells can be used to determine which treatments should not be used and those that might work best for a particular condition."

Their research, reported in the December 2007 issue of *PLoS ONE*, revealed significant changes in channel biophysics, and detected subtle differences in drug action in correcting mutant channel activity, which, together with the known genetic background and age of the patient, contributed to the distinct therapeutic responses observed clinically. "The results of our study provide further evidence of the grave vulnerability of newborns with Na+ channel defects and suggest that both genetic background and age are particularly important in developing a mutation-specific therapeutic personalized approach to manage disorders in the young," says Dr. Chung.

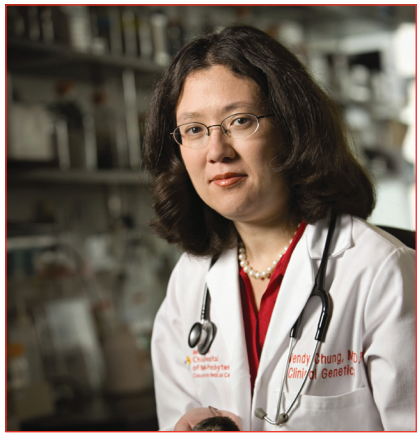
Medication Therapies: Let's Get Personal

The work of Drs. Chung, Kass, and their colleagues demonstrated that induced pluripotent stem cells (iPSCs) offer an unprecedented opportunity to investigate the pharmacology of disease processes in therapeutically and genetically relevant primary cell types *in vitro* and uncovered a novel method to evaluate treatment for heritable arrhythmias. The painstaking endeavor led to the first-time report of the application of iPSC technology to correlate basic pathophysiologic *in vitro* studies with medical treatment of an individual patient with a complex disease phenotype that was initially resistant to medical therapy.

"These arrhythmias are caused by inherited mutations in genes coding for ion channels and/or ion channel-related proteins expressed in the heart," says Dr. Kass. "Our work has contributed to an understanding of gene-specific risk factors caused by mutation-induced changes in heart ion channel activity, and to the development of a mutation-specific approach to manage these disorders. Implicit in this use of patient-specific iPSCs for disease modeling and drug screening is the promise of applying these cells to develop more individualized therapies to treat the patient from whom the cells are derived."

To translate information gleaned from their work back to the patient, the researchers developed three teams of basic scientists charged with establishing iPSC-derived beating cardiomyocytes from the child and his parents. These teams were not involved in the patient's care or clinical decisions, but interacted regularly with his clinical cardiologist to provide results from the *in vitro* model and to discuss correlation with response to treatment with standard FDA-approved drugs and electrical pacing therapy.

"Analysis of the molecular pharmacology of ion channels expressed in cardiomyocytes



Dr. Wendy K. Chung

differentiated from these iPSCs revealed the mechanistic basis for the resistance to therapy. They also correlated with clinical responses to a simplified therapeutic approach that has effectively controlled arrhythmic activity in the patient," says Dr. Chung.

Now nearly four years old, the child that Dr. Chung met in his first weeks of his life has all the protective devices and medications in place to help keep his arrhythmia at bay. He has remained free of any ventricular arrhythmias or shocks for eight months, in marked contrast to the average of 100 arrhythmias per month observed prior to the initiation of this study.

"We believe this to be the first clinical translation of iPSC technology to a patient's care," notes Dr. Chung. "The results of our study strongly support consideration of *in vitro* iPSC studies as a new method for optimization of personalized medicine. This first-in-man clinical application of iPSC technology to help understand response to therapy in an individual patient provides a proof-of-principle for personalized medicine employing iPSC model systems."

Reference Article

Terrenoire C, Wang K, Sampson KJ, Chan Tung KW, Lu J, Chung WK, Pass RH, Keller G, Jean J-C, Omari A, Kotton DN, Kass RS. Patient-specific induced pluripotent stem cells reveal mechanism of personalized therapy for an inherited cardiac arrhythmia. *Journal of General Physiology.* (Accepted for publication)

Columbia Investigators Lead Trial for New Robotic-Assisted Cardiac Stent System

Contributing faculty: **Giora Weisz, MD**

Thousands of cardiac stent procedures are successfully performed every year, but a key challenge is positioning the stent, guidewires, and catheter at the precise location of the blockage. In addition, even with the most sophisticated X-ray technology, the complex shape of the heart and the twists and turns of the coronary arteries make the exact size of the blockage difficult to visualize and measure. As a result of these challenges, 10 to 20 percent of patients require a second stent due to inaccurate placement or size of the first stent.

The CorPath® 200 System, a new robotic-assisted percutaneous coronary interventions (PCI) system, was recently approved for use by the FDA based on the findings of the CorPath PRECISE trial, led by investigators from NewYork-Presbyterian/Columbia and St. Elizabeth's Medical Center in Boston.

"This novel system, which enhances positioning by manipulating the catheter, stent, and guidewire at the same time, also provides improved visualization and blockage measurement," says Giora Weisz, MD, Director of Clinical Research at the Center for Interventional Vascular Therapy at NewYork-Presbyterian/Columbia and principal investigator of the trial. Equally important, he notes, the robotic system provides more control than the conventional approach by allowing physicians to move the guidewire and stent in increments as small as one millimeter.

Photo courtesy of Corindus Vascular Robotics

Dr. Giora Weisz

In addition, during traditional PCI procedures, interventional cardiologists are often exposed to significant levels of radiation, as well as physical stresses that place them at risk for orthopedic problems. With the CorPath 200 System, cardiac stent procedures can be performed remotely with the physician seated in a radiation-protected cockpit next to the patient's bed.

In the study, 164 patients at nine sites were treated with robotically enhanced PCI using the CorPath 200. PCI was successfully completed without having to convert to manual PCI in 98.8 percent of patients, without device-related complications. The overall procedure success rate was 97.6 percent. Physician exposure to radiation was reduced by 95.2 percent.

"The PRECISE trial demonstrates robotically assisted PCI is safe and feasible for most patients," says Dr. Weisz. "At the same time, robotic treatment can make the procedure safer for the interventional cardiologist by reducing the risk of radiation."

Dr. Antonio M. Gotto Jr. Receives Pasarow Foundation Award

Dr. Antonio M. Gotto Jr.

Antonio M. Gotto Jr., MD, DPhil, Dean Emeritus of Weill Cornell Medical College and Co-Chairman of its Board of Overseers, has been honored with the 24th Annual Robert J. and Claire Pasarow Foundation Award in Cardiovascular Research. Dr. Gotto was recognized by the Robert J. and Claire Pasarow Foundation for his long-time contributions and research excellence in the field of heart disease.

Dr. Gotto has made significant contributions during his career to the advancement of lipid therapy for the prevention and treatment of cardiovascular disease. His medical research has led to a better understanding of the structure, metabolism, and function of lipoproteins and apolipoproteins, including their relation to atherosclerosis. Dr. Gotto has investigated clinical disorders of lipid transport and has helped establish statin medication as a standard of care for heart disease.

"I am deeply honored to be recognized by the Pasarow Foundation for my research in the prevention and treatment of cardiovascular disease," says Dr. Gotto, who is also the Lewis Thomas University Professor at Weill Cornell and Vice President and Provost for Medical Affairs Emeritus for Cornell University. "The Foundation has greatly helped to stimulate medical research over the past 24 years."

As a renowned physician-scientist and former President of the American Heart Association and the International Atherosclerosis Society, Dr. Gotto has gained international recognition for his work. His research helped establish the link between cholesterol and the development of heart disease, and he has played a leading role in several landmark clinical trials demonstrating that statins can reduce the risk for heart disease. In addition, he and his team determined the complete cDNA and amino acid sequence of apo B-100, one of the largest proteins ever sequenced and a key protein in atherosclerosis.

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