APHRS Asia Pacific Heart Rhythm Society

News
Jan. 2015, No. 17

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New Year's Greetings

December 26, 2014

Dear colleagues,

As twelve months have passed and another twelve will come along, I'd like to extend my warmest greetings and best wishes for the New Year to all of you. Let me also take this opportunity to repeat my appreciation for your support and contributions towards a successful and fruitful APHRS 2014.

I wish you a healthy, happy and prosperous New Year and also hope the remaining days of the year 2014 will continue to go from strength to strength.

I greatly look forward to meeting you again at the 8th Asia-Pacific Heart Rhythm Society Scientific Session, which will be held in Melbourne, Australia, November 19-22, 2015 and again wish you all the best of luck for the New Year.

Warmest thoughts and best wishes for a wonderful holiday and a very happy New Year!

Sincerely yours,

President
Young-Hoon Kim

APHRS Asia Pacific Heart Rhythm Society

The 7th Annual Scientific Sessions of APHRS

Dr Mohan Nair

Chairman Cardiac Sciences, Heart Institute, Saket City Hospital, New Delhi, India
Chairman Organizing Committee, APHRS2014

The 7th Annual Scientific Sessions of APHRS, in Conjunction with the 10th Asia-Pacific Symposium on Atrial Fibrillation was held from Oct 29-Nov 1st, at New Delhi, India. The sessions, held in the convention facilities of Hotel Taj Palace and Hotel Maurya, which are considered amongst the best in the world, having played host to numerous visiting Heads of State and Royalty. The event, jointly organized by the Asia Pacific Heart Rhythm Society and Indian Heart Rhythm Society, attracted more than 2500 delegates and faculty from over 30 countries from across the world. Prof. Mohan Nair, Member of the Board of Trustees of APHRS was the Chairman, Organizing Committee, 7th APHRS.

For the first time, the Scientific Program Committee was delinked from the Organizing Committee, leading to a paradigm shift in the quality and scope of the deliberations. There were 3 pre-congress industry symposia, followed by 3 days of scientific sessions, different streams were held concurrently in 10 halls.

Another unique feature of the 7th APHRS was the pre-congress public awareness meet held on the 29th of November, where Prof. Kim and Prof. Nair interacted with the press and general public specifically on the subject of Prevention of Sudden Cardiac Arrest. Many of the attendees were students and young volunteers, who had received training in basic life support at the Saket City Hospital, in the 3 month run-up to the congress.

The congress was formally inaugurated on 30th October, by His Excellency Mr. Mohammad Hamid Ansari, the honorable Vice-President of India. Prof. M Khalilullah, the patron of the Organizing Committee gave the welcome speech and Prof. Young Hoon Kim, the president of HRS gave the presidential address.

President of the APHRS
Young-Hoon Kim, MD

The fields of discussion spanned from SVT to Atrial Fibrillation, Devices, New Anti-Arrhythmic and Oral Anticoagulants. Basic sciences and special sessions for fellows and allied professionals. The format of deliberations included symposia, debates, hands-on training, live telecast and joint sessions with EHRA and HRS.

Young investigators presented over 400 free papers and posters. All abstract presenters were registered free of cost. From these presentations, awards were given in the following categories: Young Investigator Award, Best oral presentation, best poster presentation and the best Indian presentation. For the first time, in addition to a certificate and cash award of USD 1000, each award winner has been offered a fully paid trip to the Gulf EP Summit in Dubai and the EHRA training sessions held during the Gulf EP Summit. In addition, one of the award winners has been nominated for the Biotronik EP training fellowship.

A view of Pre-Congress Public Awareness with a hall of audience

A view of meeting the Press on Sudden Cardiac Arrest with many discussants

The Scientific Content was richly complimented by the Industry, in the trade exposition, technology and VIP suits, and multiple lunch and evening symposia.

Following a packed day of scientific deliberations, the faculty and delegates had a chance to relax, interact and imbibe Indian traditions, culture and cuisine at the Faculty Dinner (30th October at India Habitat Center) and the Gala Dinner (31st October, at the Gymkhana Club). Delegates and faculty also had special pre and post conference conducted tours.

The congress closed on the 1st of November, with all attendees pledging to take the APHRS forward at the 8th Annual Scientific Sessions held in November 2015 at Melbourne, Autralia.

Chairman Organizing Committee of APHRS 2014
Mohan Nair, MD

The winner of Best Indian Young Investigator Award of APHRS2014
Dr Bijal (Ria) Vyas (in the middle)

Dancers performed at the Faculty Dinner

A group photo at Welcome Ceremony: (from left t right) Drs Vanita Arora, Wee Siong Teo, Chu-Pak Lau, Shu Zhang, Jonathan Kalman, Young-Hoon Kim, Mr. Mohammed Ansari(the honorable Vice-President), Richard I. Fogel, C. Narasimhan, M Khalilullah, Mohan Nair

APHRS Asia Pacific Heart Rhythm Society

The Role of Rare Genetic Variants in Atrial Fibrillation

Chia-Ti Tsai, MD, PhD

Associate Professor, Department of Internal Medicine, College of Medicine, National Taiwan University
Associate Professor, Graduate Institute of Clinical Medicine, National Taiwan University
Director, Department of Internal Medicine, National Taiwan University Hospital Yun-Lin
Secretary, Taiwan Heart Rhythm Society

Atrial fibrillation (AF) is the most common sustained arrhythmia and represents a major public health problem across the world, including the Asia-Pacific regions. Importantly, some patients develop AF in the absence of any known risk factor (lone AF), suggesting that there is a genetic predisposition for AF.

Over the past several years there has been great interest in identifying the genetic basis of common diseases.[1] Recently, researchers have used genome-wide association studies (GWASs) to identify common genetic variants (such as single nucleotide polymorphisms [SNPs]) that increase risk of common diseases. So far there have been many studies reporting the associations between common SNPs and common human diseases, e.g., AF.[2] Some of these results have yielded novel biological insights that will be useful for disease-mechanism research and therapeutic exploration.[3]

However, most of the identified genetic loci or SNPs by GWASs have very small effect sizes.[4] Moreover, GWASs usually do not include rare variants and thus cannot determine the effects of rare variants. These rare variants may have larger effect sizes and are traditionally thought to be disease-causing only in familial or Mendelian disorders. However, there are familial forms of common diseases and they may share the same disease mechanisms. For example, AF is a common disease; however there indeed are several families in which AF segregates in multiple familial members. Whether rare variants with large effect sizes also contribute to the genetic risks of common diseases remains largely unknown.[5]

Presently, researchers are searching for the "missing heritability" (heritability not explained by common variants) in a number of common diseases or complex traits.[6] Heritability explained by low-frequency or rare (frequency < 1%) genetic variants has recently become the focus of genetic study for common diseases.[7,8] Population genetic theory suggests that if the frequencies of disease-causing variants are decreased by purifying natural selection because they lead to a slight decrease in reproductive fitness in the individuals carrying them, a greater proportion of the heritability will be explained by low-frequency and rare variants than by common variants.[9,10] Although there have been several reported associations between low-frequency variants and complex traits, [11,12] the hypothesis that rare variants account for a proportion of the heritability of complex traits or common diseases remains to be tested. Using whole genome or exome sequencing, researchers could discover and test for associations between rare coding variants and common diseases and directly test the rare variant common-disease hypothesis. Such approaches have previously been successfully applied to the identification of new mutations responsible for Mendelian diseases[13-16], and are now ready to go with the complex traits or common diseases.

Accordingly, several recent studies have been conducted to evaluate the role of rare coding variants in determining the risk of AF.[17-19] Among them, two used a candidate gene approach, in which they searched the rare genetic variants in pre-selected interested genes.[17,18] The third was focusing on familial AF to identify disease-causing rare variants or mutations.[19]

In the first study[17], they performed a deep exon sequencing study of a large cohort of unrelated lone AF probands. The purpose of this study was to determine the spectrum and prevalence of rare amino acid coding variants in candidate AF genes. They sequenced 45 candidate genes in 303 European American lone AF probands in the Vanderbilt AF Registry (2002-2012). Variants detected were screened against 4300 European Americans from the Exome Sequencing Project (ESP) to identify very rare (minor allele frequency ≤0.04%) amino acid coding variants and these were further tested for AF co-segregation in affected family members where possible. At least one in five lone AF probands (20%) carried ≥1 very rare amino acid coding variant in a candidate AF gene, of which 53% had evidence of AF co-segregation. The fact that very rare amino acid coding variants in candidate genes were absent in nearly 80% of lone AF probands is suggestive of a complex AF inheritance pattern, unidentified candidate AF genes, or epigenetic or environmental factors.

Because of the high probability of unidentified

candidate AF genes in the first study, in the second study, another group performed exon sequencing of another 9 AF candidate genes with GWAS signals in 20 AF probands.[18] There are two distinct features of their targeted exon sequence strategy. First, they used an extreme-trait design to sequence carefully selected probands with extreme phenotypes, based on the hypothesis that rare variants are enriched in individuals with severe phenotypes of a common disease.[8] Second, based on the hypothesis that common and rare variants may co-locate in the same disease-causing gene, they sequenced 9 published AF genes identified by GWAS. They identified a novel mutation in the 5' untranslated region of the *PITX2* gene, which localizes in the transcriptionally active enhancer region.[20,21] They also identified one amino acid coding variant in *KCNN3*, two in *ZFHX3*, and one in *SYNE2*. Importantly, the authors also performed functional study and showed that the mutation in the 5' untranslated region of the *PITX2* gene significantly down-regulated *PITX2* expression in atrial myocytes. Interestingly, decreased *PITX2* function has been shown to increase the susceptibility to atrial arrhythmia in a mouse model of *PITX2* haploinsufficiency.[22] Their results have important implications for the design and interpretation of future genetic studies for AF. Sequencing the individuals with severe AF phenotypes may identify rare disease causing variant or mutation. Second, although genetic variants identified by GWAS are supposed to be common variants, genes harboring common variants with mild to modest effects on complex traits may also harbor rare variants or mutations with large effects.

In the third study, they employed whole exome sequencing (WES) in six familial AF kindreds with evidence of a Mendelian mode of inheritance pattern. By coupling family data with WES, they identified multiple very rare (minor allele frequency ≤0.04%) and putative pathogenic variants in five of six families. They failed to find single pathogenic variant or mutation for any kindred. Their results also have important implications. If rare coding variants are an important factor in familial AF risk, they are likely distributed across many genes. Second, there has been no well-documented method to determine which specific variant or mutation is the real disease-causing variant, or a large well-curated multi-generational pedigrees is needed to determine which specific rare variant is the real disease-causing variant.

Summary

So far there have been rare studies addressing the role of rare variants or mutations in determining the risk of AF. The results of these studies may suggest that mutations or rare variants are limited in explaining the heritability of AF because they only account for sporadic (severe phenotype) or familial cases of AF. Collectively, the findings from these studies represent important progress toward molecular genetics of lone AF and suggest a complex AF inheritance pattern. The implementation of high throughput sequencing technology and the new knowledge from the data of exome sequencing will hopefully help gain more insight into the mechanism of AF in the future.

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ECG Quiz

The model commentary will be provided in the next issue No.18

Dr. Mohan Nair[a], Dr. Vikas Kataria[b]

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20 year old girl with documented SVT (Figure 1) was subjected to EP study. After pacing from HRA, activation pattern in CS catheter shows two different responses in consecutive beats marked with arrows (Figure 2). What could be the possible explanation and what maneuver/s could be used to confirm?

Figure 1

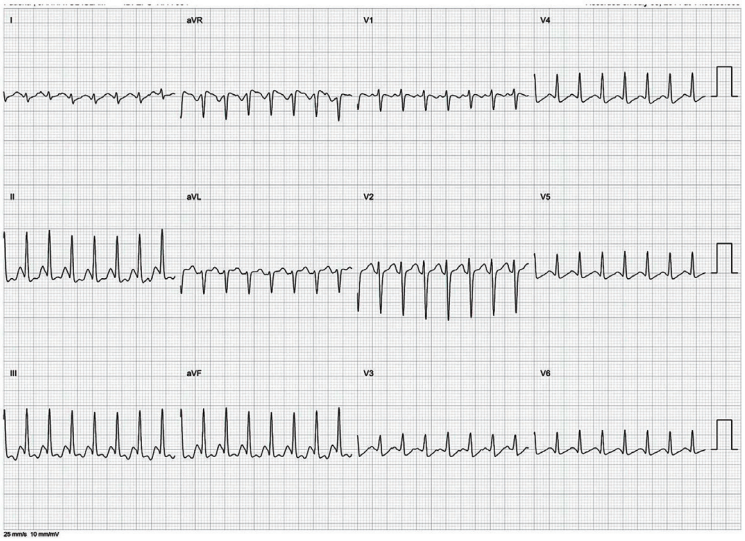
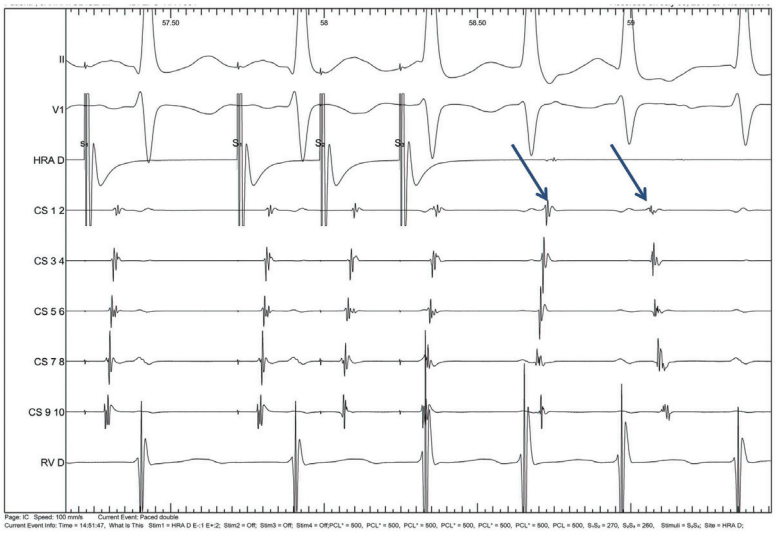


Figure 2



A) AV nodal echo followed by an atrial ectopic
B) AV nodal echo and Left accessory pathway
C) Both are typical AV nodal echo.
D) Both are AV nodal echo. Different CS activation pattern in the second marked beat is due to leftward extension of the retrograde pathway.

EP Image: Left Atrial Anomalous Band

Yasushi Miyauchi, MD, Shunsuke Uetake, MD

Nippon Medical School, Tokyo, Japan

A 72 year-old male with paroxysmal atrial fibrillation and flutter was referred to our hospital. Pre-operative transesophageal echocardiography demonstrated an anomalous band in the left atrium. A 64-slice multi-detector computed tomography showed that the anomalous band had a diameter of 3mm and a length of 39mm, and attached to the posterior edge of the oval fossa and posterior left atrial roof. The site of transseptal puncture was selected with an assistance of ICE to pay an attention not to injure the anomalous band. Circumferential antral PV isolation could be achieved successfully without any complication.

Left atrial anomalous band is thought to be a congenital abnormalities, which is associated with Chiari's network and patient foramen ovale in origin. Although the left atrial anomalous band is rarely identified in the clinical practice, a report on a series of 1,100 autopsy cases showed an incidence of 2%. The size of anomalous bands is shown to range from 1.5 to 4mm in width, from 0.5 to 2mm in thickness and from 4 to 55mm in lengths. If the LA anomalous band is identified in patients undergoing ablation, an attention should be paid to avoid any possible inadvertent manipulation of the transseptal puncture needle, ring catheters, or ablation catheter.

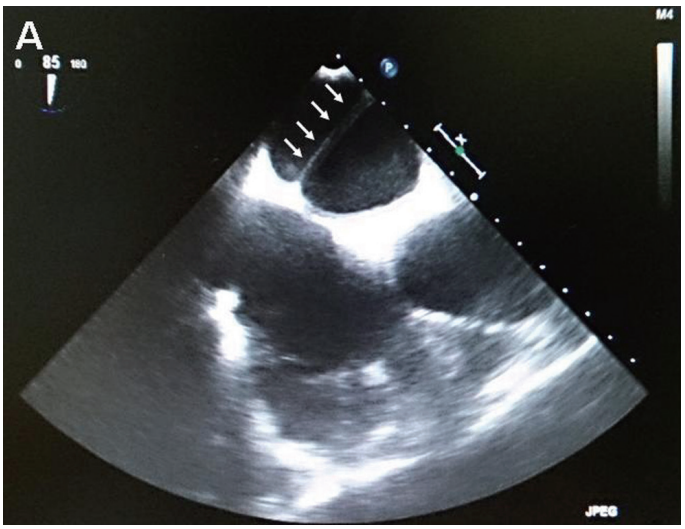


Figure A. Transesophageal echocardiography showed a LA anomalous band (arrows).

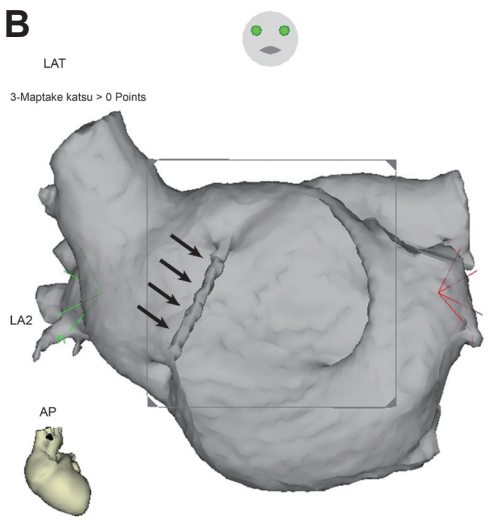


Figure B. Virtual endoscopic view of a 64-slice multi-detector computed tomography showed the anomalous band between the septum and the posterior roof of the LA.

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A Peek into the Philippine Heart Rhythm Society, Inc.

Maria Belen O. Carisma, M.D., FPCC, FACC, MBAH

While cardiac electrophysiology took roots in the Philippines way back in the mid 1980's with the return of **Dr. William T. Chua** from his cardiac electrophysiology training in Northwestern University in Chicago, USA, it has only been over two years ago that the 28 (now 30) cardiac electrophysiologists spread over the three main islands – Luzon, Visayas and Mindanao comprising the island- archipelago that is the Philippines, formally organized themselves as the Philippine Heart Rhythm Society, Inc.

Fueled by its Vision of being the leader in heart rhythm management in the Philippines recognized by the Asia-Pacific region by 2015, and its Mission of giving quality care to patients with cardiac rhythm disorders through advocacy, research and education, it held a one-day Inaugural Scientific Symposium last May 27, 2014 as a Preconvention to the Philippine Heart Association's 45th Annual Scientific Convention.

Held at Edsa Shangrila Plaza Hotel in Mandaluyong City, Metro Manila, it featured an arrhythmia case report competition open to all cardiology fellows from the 15 Philippine Heart

(Logo: Sculpture of Dr. William T. Chua depicting the P, QRS, T of the ECG)

Association – accredited - training institutions of the country, dubbed as the **"2014 Search for Best Arrhythmia Case Report"** and two plenary lectures on Atrial Fibrillation by **Dr. Rodrigo Chan** of Arizona, USA who talked about ""State of the Art Management of Atrial Fibrillation and **Dr. Giselle Gervacio** of the Philippines who dwelt on the "Initial Local Experience of Atrial Fibrillation Ablation in the Philippines".

The Search for Best Arrhythmia Case Report was enthusiastically supported by the training institutions with a total of 11 entries, each of which was given the opportunity to be orally presented to a panel of five judges headed by then Philippine Heart Association president, **Dr. Eugene Reyes**, with Dr. Ramon Abarquez, Dr. Ma. Teresa Abola, Dr. Loewe Go and Dr. Timothy Dy as members. Coveted prizes

aside from cash gifts were to be able to attend the Asia-Pacific Heart Rhythm Society Meeting in New Delhi, India plus a sculpture-trophy to the winning institution made by no less than Dr. William T. Chua, himself a duly-acclaimed artist dabbing in both sculpture and oil on canvas painting.

Adjudicated as top winner in the 2014 Search for Best Arrhythmia Case Report was Dr. Edgar Wilson Timbol, of the University of the Philippines – Philippine General Hospital, whose arrhythmia paper was entitled: " Inducible Focal Atrial Tachycardia of Coronary Sinus Origin Masquerading as Ventricular Tachycardia". Dr. Edgar Wilson Timbol happens to be the son of PHRS member – electrophysiologist and Director of the HB Calleja Cardiovascular Institute in Angeles, Pampanga, Dr. Edgardo Timbol.

The 2nd and 3rd place winners were: Dr. Jehan Karen Go Sumalpong of the Philippine Heart Center whose case report was on: " Suppression of Recurrent Electrical Storms in a Filipino Patient with Brugada Syndrome" and Dr. Reynaldo Cabalejo of Chong Hua Hospital, Cebu City whose paper was on: "Fetal Supraventricular Tachycardia with Hydrops Fetalis in a 20-Year Old Primigravida".

The day was capped by a fellowship night among all PHRS members including its 11 corporate members from 4 device and 7 pharmaceutical companies. Current PHRS officers and members of the Board for 2012 – 2015 include: Ma. Belen O. Carisma, MD as President, Anthony B. King, MD as Vice-president, Giselle G. Gervacio, MD as Secretary, Eden A. Gabriel, MD as Treasurer, Gladys Ruth S. David, MD, Erdie G. Fadreguilan, MD, Marilou P. Maglana, MD, Mavic Vestal, MD as Directors of the Board and William T. Chua, MD as Honorary President.

PHRS President, Dr. Ma. Belen O. Carisma, and Honorary President, Dr. William T. Chua handing plaque of appreciation to guest lecturer, Dr. Rodrigo Chan of Arizona, USA during the PHRS Inaugural Scientific Symposium held on May 27, 2014, Edsa Shangrila Plaza Hotel, Philippines.

PHRS Vice-President, Dr. Anthony B. King, President, Dr. Ma. Belen O. Carisma and Honorary President, Dr. William T. Chua handing plaque of appreciation to Dr. Giselle B. Domingo, Lecturer and PHRS Secretary during the PHRS Inaugural Scientific Symposium held at Edsa Shangrila Hotel, Philippines.

PHRS Officers and Board of Directors with Top Winner of 2014 Search for Best Arrhythmia Case Report, from L-R: Dr. Gladys Ruth S. David, Dr. Anthony B. King, Dr. Edgar Wilson Timbol (Top Winner), Dr. Edgardo Timbol, Dr. Giselle B. Gervacio, Dr. Eden A. Gabriel, Dr. Erdie G. Fadreguilan, Dr. William T. Chua.

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APHRS Asia Pacific Heart Rhythm Society

ECG Commentary Related to the Quiz in the No. 16 Issue

Masayasu Hiraoka, MD, PhD, FHRS

Answer

[A] Diagnosis of this arrhythmia is not so difficult. ECG tracings represent simultaneous recordings of the 6 limb and 6 precordial leads, respectively. The first beats in both tracings are sinus beats followed by 2 ectopic beats of wide QRS with ST-T changes and no preceding P wave, suggesting multifocal PVCs. But, after the 3rd beats more than 6 consecutive ectopic beats with different morphologies continue to confirm the diagnosis of VT. Further, QRS complexes during VT display alternating morphologies of amplitude and polarity, which indicates (3) bidirectional VT as a correct diagnosis. Tdp is excluded because of alternating QRS morphologies without twisting of QRS complexes along the baseline. VF is also excluded because of a clear distinction between QRS and ST-T waves.

Answer; (3) bidirectional VT.

[B] Bidirectional VT is a frequent manifestation of CPVT and occasionally seen in ATS patients. However, no previous history of syncope without family history of sudden cardiac death suggests hereditary CPVT or ATS unlikely. Digitalis intoxication is a frequent cause of polymorphic and bidirectional VT in the acquired conditions. While he has spent physically normal daily life without taking any medication until the day before the admission, digitalis intoxication can be excluded as a possible cause of this arrhythmia. The same reason is also applicable to exclude severe hypokalemia, which induces polymorphic VT/VF as fatal events. A sudden onset of clinical symptoms and arrhythmia indicates an intake of certain chemicals or toxins as a cause of his condition.

Answer; (4) Aconitine intoxication

In the emergency room, he continued to develop runs of bidirectional VTs, which were resistant to repeated DC shocks and several antiarrhythmic agents including sodium channel blockers and amiodarone. He was placed under PCPS to maintain his circulatory condition and finally recovered to sinus rhythm after 14 hours.

On admission, he explained that he took a wild grass (herbs) at breakfast and he had picked up the herbs several days before in the deep mountain area. Therefore, aconitine intoxication was suspected as a cause of his condition and his blood sample was sent to the toxicology laboratory revealing his serum aconitine concentration of 15.78 ng/ml, which was much higher than the level causing ventricular arrhythmias of > 0.12 ng/ml[1].

Aconitine is a toxin produced by the Aconitium plant and it belongs to aconitium alkaloids[2]. In China, aconitine is used as an herbal medicine against pain. In Japan, leaf of the Aconitium plant has a resemblance to a certain kind of wild grass which is good taste for eating. Therefore, occasional mistakes happen in persons not familiar with these plants for differentiation and eat the Aconitium plant in rare occasions.

Aconitine has been known as an arrhythmogenic agent and is used to an arrhythmia model caused by ectopic focus activity in laboratory experiments[3]. Aconitine produces early after-depolarization causing polymorphic tachycardia or fibrillation in atrial and ventricular tissues as well as whole heart preparations[4]. Aconitine has an affinity to bind to the sodium channel main subunit and induces the conformational change to stay the channel at the open state retarding the inactivation during continued depolarization[5]. Thus, sodium ions continue to flow into the cells during the plateau phase of cardiac action potentials inducing early after-depolarization and repetitive firings[4].

Clinical symptoms due to aconitine intoxication are paresthesia, confusion, sweating, nausea, vomiting, diarrhea, intense pain, paralysis of the skeletal muscle and life threatening arrhythmias of VT/VF. Death occurs as a result of cardiac arrest or respiratory paralysis.

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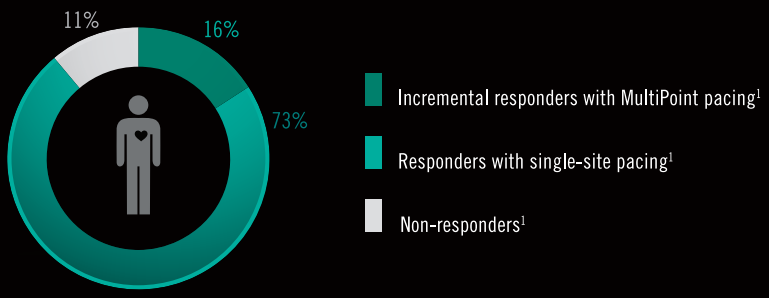
CLASSIFIED AS RESPONDERS

MultiPoint pacing may improve CRT responders rate: After 3 months, 22% more patients were classified as responders than with traditional Bi-V single-site pacing (73% vs. 89%).[1]



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A total of 43 patients implanted with a St. Jude Medical quadripolar CRT system were randomized to optimal vector conventional CRT (CONV) or optimal vector MultiPoint pacing (MPP); optimal vector was determined by pressure volume loop measurements at implant. Analysis of the first 20 patients at 3 months demonstrated a 22% increase in CRT responder rate determined by improvement in LV ESV >15% (73% vs. 89%).[1] Analysis of all 43 patients at 3 months demonstrated a 52% increase in CRT responder rate (50% vs. 76%).[2]
HFSA 2013 Late-Breaking Clinical Trials Poster Session. September 23, 2013.

1. Pappone C, et al. Improvement in 3-month Echocardiographic Response With Multisite Left Ventricular Pacing in Cardiac Resynchronization Therapy Patients. HRS 2013 Poster session P002. May 9, 2013.
2. Pappone C, et al. Multisite Left Ventricular Pacing in a Single Coronary Sinus Branch Improves 3-Month Echocardiographic and Clinical Response to Cardiac Resynchronization Therapy.

Brief Summary:
Prior to using these devices, please review the Instructions for Use for a complete listing of indications, contraindications, warnings, precautions, potential adverse events and directions for use.