Unravelling the Genetics of Arrhythmias and Working to Prevent and Treat Heart Failure

Professor Pedro Brugada talks to Ingrid Torjesen, BSc, about the pioneering work he has carried out with his brothers on the syndrome bearing the family name, and current and future provisions for managing heart failure and arrhythmias in Belgium.

Pedro Brugada, MD, PhD, professor of cardiology and physiology, Universitair Ziekenhuis Brussel–Vrije Universiteit Brussel, Brussels, Belgium, entered cardiology by chance. When he graduated from the University of Barcelona Medical School at the age of 22, he wanted to be a haematologist, but he found that he would have to wait a year for a job. “My wife was already pregnant, and I needed a job. There was a place free in cardiology, so that is how I started,” he explains.

Professor Brugada reads and writes widely about all types of medicine; his interest in cardiac electrophysiology began after he tried to read a book on it. “I did not understand a single word, so I thought I should go away somewhere from Spain to try to find out what was going on.”

When Professor Brugada left Barcelona, initially for the Netherlands, a former colleague said to him, “Are you going to do something in clinical electrophysiology? There is nothing new; everything has already been done.” This occurred before the defibrillator and before the Duchamp double pacemaker, when cardiologists had little appreciation of cardiac arrhythmias or their genetics. “Just imagine what a bad prediction that was,” Professor Brugada laughs.

Professor Brugada has achieved a great deal, and, not surprisingly, the achievement in which he takes the most pride is the discovery with one of his brothers, Josep Brugada, MD, PhD, of the syndrome bearing their name. It all began in 1987 when Professor Brugada was running the electrophysiology laboratory at the University of Maastricht in the Netherlands and a Polish man brought his son to see him. The boy was 3 years old and had a history of repeated episodes of fainting and cardiac arrest; his father had resuscitated him several times. His sister had suffered similar symptoms and had died at the age of 3 in spite of treatment with a pacemaker and amiodarone.

“The electrocardiogram of that boy was a very special one. It was something I had never seen before and something you could not find in any publication,” Professor Brugada remembers. “I was very fortunate that the father was able to return to Poland and bring the electrocardiograms of the sister, which turned out to be exactly the same as those of the brother. Remember, it was 1987; the Berlin Wall was still there, so everything that this guy was doing was illegal.”

It took 4 years for the Brugadas to find 2 more patients with similar ECGs (Figure 1)—one from the Netherlands and the other from Belgium. They presented the 4 cases as an abstract to an American Heart Association conference, and several doctors who had come across similar cases contacted them. A year later, they published details of 8 patients.1

On other pages...

The Italian Association for the Fight Against Thrombosis

The president and founder of The Italian Association for the Fight Against Thrombosis, Lidia Rota Vender, MD, and the vice president, Alessandro Orlandi, MBA, speak to Robert Short, BSc, about the work of the organisation and the consultation it has started among interested Italian groups on policies to combat childhood obesity and to develop national guidelines.
“Since then, it has become an explosion,” Professor Brugada says. “We thought it was a curiosity, but it has become very important in epidemiology because the major contribution of that boy is to put the whole genetics of cardiac arrhythmias in another context.”

Brugada syndrome was not the first arrhythmia to be shown to be genetically determined—long-QT syndrome came first. But, teaming up with a third brother, Ramon Brugada, MD, it took the Brugadas only 6 years to progress from the description of Brugada syndrome to the publication of its genetic basis, whereas with long-QT syndrome it took much longer.

In 2000, the Brugadas discovered another genetically determined arrhythmia—short-QT syndrome—and, 3 years later, the brothers succeeded in describing the genetic defect responsible. Professor Brugada says, “The progress that has been made by the entrance of the genetics of cardiac arrhythmias has been enormous. The time between the description of the disease and the recognition of the genetic defect and the pathophysiological mechanisms is shortening more and more. Our youngest brother Ramon was crucial in this very difficult endeavour.”

The Brugadas recently reported another genetically determined cardiac disease, Wolff–Parkinson with cardiac hypertrophy, which involves structural abnormalities of the heart as well as an arrhythmia.

Now, rather than simply identifying the genetics of diseases, they are attempting “reverse genetics.” Professor Brugada explains: “Instead of waiting for the disease to come to us, we are trying to predict the disease on the basis of the genetic defects that could cause it. The problem is that we need as many people as in the human genome project to be able to do that in the short term. But it could be a very interesting thing—create the mutations, look at the pathophysiological changes in the laboratory, and see which type of disease fits with what we produce.”

Better treatment of heart failure means that a shortage of hearts for transplantation has had a less significant effect than expected. Professor Brugada explains, “It is not just the drugs that have been developed in the past few years, but major developments have also come from electrophysiology—in particular, cardiac resynchronisation therapy. Pacing the left ventricle has made it possible to reorder the contraction of a heart that has lost the good order of contraction and become a rocking heart.” The most difficult challenge during the next few years in electrophysiology will involve ensuring the availability of appropriate treatment to everyone who requires it. At present, 600000 people in Europe qualify as candidates for implantation of a defibrillator, but only 8% receive them. Atrial fibrillation ablation faces a similar situation, which will only worsen in Europe as the baby boom generation reaches 65 years, he says.

“There is going to be a real doubling in the next 10 to 20 years of the number of people with heart failure, atrial fibrillation, hypertension, and diabetes. We have a real shortage of facilities to treat them—the physicians, nursing staff, and hospitals. It is going to be a major problem. There is not only the practicality of implanting these 600000 defibrillators—there is also the financial cost.”

Professor Brugada believes that hospitals will not have the capacity to take care of all patients with chronic diseases and that they will need to rely increasingly on e-medicine—monitoring patients outside the hospital in cooperation with general practitioners and nursing homes.
Professor Brugada has recently started working with the Belgium Heart League to raise public awareness of how people can prevent sudden cardiac death. “Sudden cardiac death is one of the most important causes of death in the whole cardiovascular field, and the risk factors for sudden death are the same as for coronary heart disease.”

Professor Brugada also feels concerned about the significant shortage of donor organs for transplantation. “The number of transplants has decreased because there are fewer fatal car accidents, because of the restrictions that have been imposed to traffic,” he says. “We are now doing 20 or 30 transplants a year, in Belgium no more than that.” In theory, Belgium should have around 600 donor organs available, because that is the number of people who die in car accidents in the Flemish area and the Belgian government considers people donors unless they deny permission before their death. However, in practice, the family of the deceased can prevent organs from being used.

Professor Brugada says that the medical profession needs to do more to raise the issue with the necessary organisations and, in particular, to work with patient organisations to raise awareness of the plight of people with heart failure in the same way as with AIDS or multiple sclerosis. In this way, he adds, “You might reduce the threshold for the family to give the organs when someone is deceased if they understand that it is of benefit for someone else. Usually, these people are not involved with heart failure or kidney failure; they are a little bit too far from the reality.”

Professor Brugada adds that along with reducing the number of organs available for transplantation, the slowing of road traffic has also had a negative impact on the number of people surviving myocardial infarctions, which medical professionals must address. “Many people who have their first myocardial infarction do not reach the hospital in time, and progress in resuscitation outside the hospital and survival have been very poor. We are now putting automatic defibrillators at locations where there are lots of people, like airports, to try to improve this,” he explains. “Emergency units have major difficulty in arriving at houses in time because of the traffic, and because there are bumpers on the street, making them smaller.”

Prevention of cardiovascular disease also needs more emphasis and has to begin in the teenage years, he says. “You have to start fighting sitting in front of the TV, not exercising or doing any sport, and eating hamburgers and chips at a very early age, because the process of atherosclerosis starts from birth. It is a very slow process, but 30 or 40 is not the age to start prevention. It is already too late” In Belgium, only 50 per cent of people have had readings taken for cholesterol, blood pressure, and blood sugar at the age of 50.

References

Ingrid Torjesen is a freelance medical writer.

The Italian Association for the Fight Against Thrombosis

A Mission to Improve Heart Health and Reduce the Impact of Thrombosis-Related Diseases

In Italy in the 1980s Lidia Rota Vender, MD, a consultant haematologist in Milan, felt that thrombosis research, prevention, and treatment did not have the central role that it deserved in research funding, in the training of doctors, or in the public mind. Dr Rota Vender now serves as director of the Thrombosis Centre at the Istituto Clinico Humanitas IRCCS in Milan, Italy. Dr Rota Vender took 2 significant actions to increase the focus on thrombosis. The first occurred in 1986, with the creation of the Italian Association for the Fight Against Thrombosis (Associazione per la Lotta alla Trombosi, or ALT). She founded ALT together with Pier Mannuccio Mannucci, MD. Professor Mannucci now serves as professor and director of the Department of Medicine and Medical Specialities in Maggiore Hospital in Milan, Italy, and as director of the Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre in the city.

The president and founder of the The Italian Association for the Fight Against Thrombosis, Lidia Rota Vender, MD, and its vice president, Alessandro Orlandi, MBA, speak to Robert Short, BSc, about its goals and activities.

In 1978, 2008
The mission of ALT is to prevent and reduce the impact of thrombosis-related diseases through education and information campaigns and by financing scientific research. The association encourages a multidisciplinary approach to the prevention and treatment of thrombosis by the training of doctors, education of the public, and development of research programmes.

A scientific committee, which includes representatives of each specialty where thrombosis plays a major role, determines the clinical and scientific projects of ALT. The relevant specialties include cardiology, angiology, lipid metabolism, internal medicine, ophthalmology, and oncology.

The committee does not limit itself to doctors from Italy. Some years ago, Valentin Fuster, MD, PhD, applauded the focused approach of the foundation and agreed to chair its scientific committee. Professor Fuster also serves as president of the Scientific Advisory and External Evaluation Committee at the Fundacion Centro Nacional de Investigaciones Cardiovasculares Carlos III in Madrid, Spain. Other international members of the committee include John Martin, MD, British Heart Foundation Professor of Cardiovascular Science at University College, London, and Zaverio Ruggeri, MD, chief of the Department of Research on Atherothrombosis, Roon Research Institute, La Jolla, Calif.

Dr Rota Vender’s second action took place in 1997, when she created a Thrombosis Centre that truly reflected her philosophy. The centre, at the Istituto Clinico Humanitas IRCCS in Milan, exists independently of ALT but acts as a model that ALT encourages. Dr Rota Vender says, “What is unique about this centre is that it provides a daily interface with every medical and surgical speciality. Every specialist can refer to us for help to diagnose, treat, understand, or prevent thrombosis—or manage bleeding—in their patients.”

**Organisation of ALT**

The ALT head office is in Milan, but 3 other offices now exist in the north and south of Italy—in Bergamo, Cremona, and Bari. Alessandro Orlandi, MBA, vice president of ALT, says, “We will probably have about 10 of these local offices by the end of 2009.” He says that the new offices will enable ALT to access and influence institutions at the regional level and also reinforce ALT’s national influence. He explains, “For example, this will help with ALT’s ‘Three Axis Project,’ which is focused on having an impact on the health, physical activity, and diet of the Italian population.” Mr Orlandi says that ALT is creating partnerships with government institutions at the regional level. The Italian regions have their own health budgets, so ALT tries to encourage the financing of regional programmes that improve health in the population and prevent cardiovascular diseases.

In addition, the branch offices of ALT foster and support the creation of thrombosis centres in the main regional hospitals in Italy. With this objective in mind, ALT has formed an alliance with the Società Italiana per lo Studio dell’Emostasi e della Trombosi, the leading Italian scientific society of experts in the field of thrombosis and haemostasis.

**ALT Activities**

ALT doubtlessly has great influence, despite its status as a small organisation in terms of revenue, raising only €250 000 a year. ALT belongs to the Italian Summit of Solidarity, an alliance of nongovernmental organisations focused on health, and it also belongs to the European Heart Network. Jointly with the European Heart Network, ALT lobbied Italian members of the European Parliament on the European Heart Health Initiative, a pan-European programme focused on prevention of cardiovascular diseases through the modification of well-known risk factors, particularly those linked to lifestyle.

ALT served as the Italian coordinator of the pan-European project “Children, Obesity and Associated Avoidable Diseases,” completed in 2006. It facilitated the agreement of Italian stakeholders on the policy options to combat childhood obesity. These policy options informed the development of national guidelines for addressing childhood obesity. ALT also participates in several national forums and initiatives on cardiovascular disease. In November 2007, ALT launched the “European Heart Health Charter” in Italy on cardiovascular disease prevention, in partnership with the Italian Society of Cardiology and the Italian Heart Foundation, and with the support of the Milan municipality.

Another activity of ALT involves the lobbying of the Italian Senate to introduce legislative changes that facilitate lifestyle changes to reduce the risk of cardiovascular diseases in Italians. Indeed, ALT has enrolled the members of the senate in a personal risk-reduction programme. Each senator has twice received a questionnaire, and ALT members have computed answers to provide the respondents with individual reports of the impact of lifestyle, nutritional habits, physical activity, and genetic factors on their risk of cardiovascular disease. The ALT scientific committee prepared the questionnaire, and they will repeat the programme on the members of the chamber of deputies.

The same questionnaire provides the basis for the programme “Health Month,” developed for the employees of large companies to identify their individual risk of cardiovascular disease. In general, a large proportion of both management and employees from several organisations have taken part in the programme, to date totalling more than 80 000 people.

**Education and Research**

About half of the €250 000 ALT raises each year goes to education and research. The association funds the training of a number of specialists in internal medicine at medical schools and universities, encouraging these doctors to focus on thrombosis. Dr Rota Vender says, “We put a good portion of our energy into training young doctors to
have a multidisciplinary insight into thrombosis.” ALT also devotes a dedicated fund for training nurses who specialise in dealing with patients affected by cardiovascular diseases. The association is building up other dedicated funds for the training of specialists in lung disease, particularly for pulmonary embolism, and also a fund for stroke.

The Scripps Research Institute, La Jolla, Calif, in cooperation with the University of Milan, has completed a major research project studying the mechanisms of thrombosis. This project received its funding from ALT and the Cariplo Foundation, Milan. The Vicenza Thrombosis and Atherosclerosis study, an important ongoing study funded by ALT, collected DNA from 15,000 people in the Italian town of Vicenza, to explore the genetic basis of predisposition to thrombosis.

Three years ago, ALT started an epidemiological survey of the Italian population. This study, called Cardiolab, has moved forward in partnership with a major pharmaceutical company. The investigators have installed a mobile unit (Figure 1) for 1 week in more than 100 cities in Italy. The unit, with the help of the local general practitioners, has provided basic cardiovascular risk stratification, free of charge, to more than 10,000 citizens. Every single person who comes to the unit receives individual advice from ALT on the corrections to his or her lifestyle that can improve their health and quality of life.

ALT is financing the setting up of what is probably the only paediatric thrombosis registry in Europe. Funded by ALT, a scientific committee of representatives of the major scientific societies involved in paediatric thrombosis manages the registry. The scientific committee includes paediatricians, paediatric radiologists, experts in thrombosis, and neuropaediatricians. The diagnosis and treatment of thrombosis in the newborn and in children differs greatly between hospitals and according to the speciality of the doctor who assesses the patient. Every doctor in Italy can access the registry, and doctors can submit their data to the registry. Dr Rota Vender says, “At the end of a period, the scientific committee of the registry will analyse the data and establish which modes of diagnosis and treatments are most effective. The registry will allow specialists to extrapolate information on the best practices in diagnosis and treatment of thromboembolic diseases, arterial or venous, in children and even the newborn.”

ALT is currently piloting another project focussed on prevention of thrombosis in pregnancy, in Cremona, near Milan. The current stage of this programme entails making healthcare professionals sensitive to the diagnosis and treatment of thrombosis in pregnancy and at delivery. In its next stage, the programme will encourage women not to underestimate the importance of certain symptoms, and it will encourage them to report such symptoms to their doctor or prenatal clinic. Assuming the success of the pilot study, a larger study will be launched in more towns in Italy.

**Fundraising**

Even before the start of ALT, Dr Rota Vender recognised the difficulty of explaining to the public the importance of thrombosis and attracting its financial support. The association has to compete against organisations with AIDS or cancer in their names, which appeal to the public much more readily.

Dr Rota Vender says that in a survey done in 1986, most people saw thrombosis as a disease that affected only very old people. She adds, “Some people knew about stroke, but most people at that time had the perception that thrombosis was much less important than cancer and HIV.” The donors to ALT tend to have had personal experience with thrombosis. She explains, “From our research, we also know that people who make donations for children and certain other diseases donate in order to help other people. In contrast, people who donate to ALT donate for themselves. So, it is a different and harder task for us to attract donors.”

That said, ALT does not lack imaginative schemes to attract donations from the public (Figure 2). Most funds come from ordinary people. “We do about 3 or 4 fundraising campaigns every year. We do it with a professional in direct marketing, and we get from €20 to €100 from people who are interested in supporting us,” says Dr Rota Vender.
ALT reaches single donors through several approaches. Programmes include direct mail to associates, telemarketing, face-to-face sales, and dedicated events. They also have included innovative initiatives such as the launch of an ALT credit card and a partnership with a financial corporation.

ALT has sponsored a golf tournament for 18 years, with more than 30 national golf clubs involved, encouraging healthy physical activity. Most recently, ALT has agreed to a sponsorship programme with a European nutritional company marketing a special type of tuna with a low salt content.

**Publications**

As its most important tool for the education of healthy people on thrombosis, ALT publishes a quarterly magazine, SALTO. This publication covers a different topic in each issue. In partnership with the national newspaper *Corriere della Sera*, ALT also distributed its own “Health Diary” for 2007. Dr Rota Vender says, “The 2007 edition was devoted to women and contained day-by-day information and recommendations on prevention of vascular diseases. The 2008 edition of the diary includes some interesting cooking recipes, and some tables to stimulate readers to check their risk factors and modify them.”

Dr Rota Vender has published a collection of short stories with happy endings, each describing a thrombotic event in a woman. ALT also is working on a publication for patients called *Thrombosis: 100 Questions and Answers*, and is considering a translation of Professor Fuster’s Spanish book, *Take Care of Your Heart: It Is Never Too Late, Never Too Early*. More than 200,000 copies of this book have already circulated in Spain.

Dr Rota Vender concludes, “People have the right to information about thrombosis. They need it expressed in simple clear language, so that they can take charge of their lives and prevent thrombotic events and cardiovascular disease in themselves and in their families. ALT exists to meet this need.”

Robert Short is a freelance medical journalist.

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**Chat Corner**

Would you like to be a correspondent for Chat Corner? For our regular new Chat Corner feature, we’re looking for correspondents from every European country to let us know about what’s going on in cardiology in their country, such as any new appointments, healthcare policies, and initiatives, or special prizes and awards. If you are interested, please e-mail Lindy van den Berghe, at lindy@FLMC.co.uk.

The American Heart Association is to launch its first new journals in nearly 3 decades

As extensions of *Circulation*, the new *Circulation* portfolio of journals will deliver tightly focussed information on areas at the cutting edge of cardiology, as well as clinical information designed to help practitioners in their daily practice. For information about the journals, please go to http://www.ahajournals.org/misc/circ_subspecialty_journals.dtl.