Clinical update

Brugada syndrome 1992–2012: 20 years of scientific excitement, and more

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Received 28 November 2012; revised 5 February 2013; accepted 12 March 2013; online publish-ahead-of-print 1 November 2013

This is a review on the scientific progress achieved in our understanding of Brugada syndrome during the past 20 years.

Keywords
Brugada syndrome  •  Inherited arrhythmia disorders  •  Ventricular fibrillation  •  Sudden death  •  Syncope  •  Atrial fibrillation  •  Genetic arrhythmias

The start (1992)

In November 1992, an article co-authored by P.B. and J.B. was published in the Journal of the American College of Cardiology (JACC).1 Its title was: ‘Right Bundle Branch Block, Persistent ST Segment Elevation and Sudden Cardiac Death: A Distinct Clinical and Electrocardiographic Syndrome. A Multicenter Report’. The study described eight patients with a unique electrocardiographic pattern, a structurally normal heart and a family history of sudden death suggestive of a hereditary disorder. Three of the eight patients were children and two were siblings. The distinct electrocardiographic pattern (Figure 1) had not been described previously as such in the medical literature. Martini et al.2 had published a series of patients with idiopathic ventricular fibrillation, and, upon retrospective analysis, one had an electrocardiogram (ECG) with similar characteristics. However, in contrast to the report in JACC, their patients had structural heart disease with no evidence for a hereditary disorder.

The years preceding publication of the JACC article were stimulating and tumultuous. Clinical cardiac electrophysiology was emerging as a subspecialty within cardiology. Gone were the days when D.R. and P.B. spent endless hours together analysing analogue electrophysiology tracings printed with green ink on a 24-channel recorder. Since the seminal publications by Coumel et al.3 and Durrer et al.4 describing the first applications of programmed electrical stimulation to the human heart, clinical cardiac electrophysiology progressed in the late 1980’s and early 1990’s beyond esoteric thinking to reach full therapeutic applications in the cath lab and operating room. The technique of transcoronary chemical ablation was a noble attempt to find a targeted therapy for clinical cardiac arrhythmias.5 Although successful, this method could never compare to the simplicity of newer methods to come such as radiofrequency and cryo-ablation. Sophisticated cardiac pacemakers became the rule rather than the exception, with innovative features increasingly to the physician’s armentarium. The implantable cardioverter-defibrillator was becoming an accepted and respected therapy at the dawn of an era when pharmacological therapy for ventricular arrhythmias was disillusioned by the results of the CAST study.6 With all these ‘high-tech’ advances, the clinical cardiac electrophysiologist increasingly focused on the latest and progressively more sophisticated technical advances. It was, therefore, quite paradoxical that the major breakthrough in characterizing the Brugada syndrome resulted not from high-tech-driven research but, rather, an analysis of that old-fashioned paper recording called an ECG; not the 24-channel endocavitary recordings, just the standard 12-lead ECG, that had already existed for nearly a century.

The encounter

The weather was unusually pleasant nice the morning (1986) in Maastricht when, as Director of the Clinical Electrophysiology Laboratory, P.B. received a consultation for a 3-year-old boy, Lech, accompanied by his father Andreas. D.R. was working as a

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Fellow in Clinical Electrophysiology while J.B. laboured at the University of Limburg physiology lab deciphering complex double wave re-entrant circuits. Albert Waldo visited Allessie’s and discussed the novel concepts of transient and concealed entrainment. This academic environment in Maastricht served as a nursery for scientists to be, attracting a cluster of future stars, and producing a multitude of scientific miracles. All electrophysiology Fellows trained became respected cardiologists–electrophysiologists. And we had with us became later on respected cardiologists–electrophysiologists that occupied the most prominent positions within their Universities.

The excitement could not be greater for P.B. Intrigued by the unusual electrocardiographic pattern, he ensured that it was correctly recorded and questioned Lech’s father at length about pain or other symptoms. P.B. showed the ECG to numerous individuals. It elicited various degrees of interest and disinterest. P.B. kept a copy of the ECG on his desk and went back to see Lech who had been admitted to the coronary care unit. Andreas was very nervous. Lech had already survived several cardiac arrests, thanks to his father’s help who, as a mercenary, was fully trained in cardiopulmonary resuscitation. His anxiety boiled to near violence when he pleaded P.B. to help his son. Despite the language barrier, the family history underlying Andrea’s anger, resentment, and sense of helplessness was clarified. Eva, Lech’s sister, had died suddenly at 3 years of age after several cardiac arrests and in spite of pacemaker implantation and amiodarone therapy. It was only a few months later when Andreas returned from Poland (despite the Wall of Berlin) that Eva’s medical records from University Hospital of Warsaw became available. Amazingly, Eva’s ECG was identical to Lech’s.

Before leaving Maastricht, P.B. collected two additional cases of individuals with sudden cardiac death, structurally normal hearts, and the typical ECG pattern shown in Figure 1. An abstract with these four patients was presented at the annual meeting of the North American Society of Pacing and Electrophysiology (NASPE) in 1991. It was accepted as a poster presentation. P.B. and J.B. stood by the poster the entire allotted time greeting past Fellows from Europe, the USA, and South America. Melvin Scheinmann, who later played a major role in the publication of the 1992 article passed by. People were fascinated by these four patients and comments were directed towards the special dolphin-like shape of the right precordial leads. Interestingly, a few electrophysiologists (and past Fellows) recognized this pattern and volunteered to send cases. One such case was effectively shared by William G. Stevenson from UCLA (now at Harvard). Other cases followed from Richard Hauer in Utrecht, The Netherlands, The Cedars’ Sinai Medical Centre, Los Angeles, CA and others, though some did not fit the described pattern. The eight selected ECGs replicated the characteristics shown in Figure 1 and the same clinical features described in the poster.

The 1-year delay to publishing results seemed like a century. The paper was repeatedly rejected by prestigious journals. The three principle recurring comments were as follows:

1. ECGs shown are simply a normal variant.
2. ECGs shown are not novel as this appears to be long-QT syndrome.
3. ECGs are typical for coronary vasospasm.

It was a real challenge convincing reviewers that a novel and may be an important clinical syndrome was discovered and we increasingly lost confidence in the impartiality of the review process. Comments suggesting a ‘normal variant of the electrocardiogram’ were disputed on the grounds that if one dies from ventricular fibrillation at age 3 and has this characteristic electrocardiographic...
pattern, it is most likely abnormal. Reviewers that claimed it was simply long-QT syndrome were more difficult to convince. In fact, lead II did not show a prolonged QTc interval in our patients. However, one could question the duration of the QT and QTc interval if measured in the precordial leads, because of broad negative T-waves. Authors and reviewers finally agreed that the QTc measured in lead II was indeed not prolonged. To persuade reviewers concerned about coronary spasm, an ergonovine test was performed in several patients and was normal in all. Over time, it became increasingly clear that the electrocardiographic pattern was highly variable, with the ST segment elevation not present all times. Variation in ST segment elevation had been seen in only one of the original eight patients. The word ‘persistent’ was, however, added to the title to deal with concerns over vaso-spasm. The manuscript had, however, reached an impasse. A different strategy was required.

Melvin Scheinmann was Editor-in-Chief of JACC in 1991, when we held a meeting in Hamburg. We were invited by Karl Kuck who was enjoying growing success as Director of the Clinical Electrophysiology Laboratory years after training as a fellow in Maastricht when P.B. was Director of the EP lab. At dinner, after the scientific meeting, P.B. approached Melvin to discuss the manuscript: ‘Mel, I have this beautiful paper that has been rejected by every possible journal you can imagine. I believe these are important findings, but cannot get past the many reviewers who suggest that this is nothing new. May I send a copy to your personal attention?’ It was Melvin Scheinmann’s openness and foresight that finally rendered the publication possible. In poetry, they call this artistic consent. In science, this was a commitment to get further down the endeavour of scientific progress. The ST-segment elevation was variable, and not persistent, at least in one patient, but that would be explained in later publications. Finally, in November 1992, the paper appeared in JACC. Science had once more been helped by a chance encounter and by the inherent call to progress.

The early years (1992–96)

There was a lot of interest on the paper. Reprinted copies were requested from many centres and individuals. However, the general feeling was that we were dealing with a scientific curiosity, not a serious medical issue. The years to come would prove otherwise.

Karl Kuck visited Maastricht again in the late 1980s with the case of a female patient with repeated episodes of ventricular fibrillation and ST-segment elevation on the ECG. The ST elevation was presumed but not proved to be due to coronary artery spasm. In San Francisco, following a heavy discussion about the Fellowship program of the European Heart Rhythm Association, P.B. and Karl Kuck, discussed again this case. In retrospect recurrent episodes of ventricular fibrillation and ST-segment changes were typical for Brugada syndrome, although not recognized as such at that time. Unfortunately, that lady died suddenly at home, at age 32 years, at a time when the implantable cardioverter-defibrillator was not available in Europe. This was but one of the many examples that followed.

The 1992 paper in JACC began to be referenced only slowly after its publication. However, by 1996, Japanese researches had coined the term ‘Brugada syndrome’ when referring to the syndrome of ‘right bundle branch block, persistent ST-segment elevation and sudden death’. Conflicting publications suggested that Brugada syndrome was right-ventricular dysplasia, myocarditis, or imaginative diagnoses. Logically, this sparked numerous conferences, symposia, and lively discussions, until genetic analysis in 1998 proved without a doubt the reality of a new disease. P.B. and J.B. were initially uncomfortable with the term ‘Brugada syndrome’, as it felt strange, if not arrogant, to have name linked to a syndrome. Instead, they referred to the ‘syndrome of right bundle branch block, persistent ST segment elevation and sudden death’. Gil Jansen, a great scientist from Amsterdam, stood up P.B.’s presentation and said: ‘Pedro, why do you not change your name into right bundle branch block, persistent ST segment elevation and sudden death, and just talk about Brugada syndrome?’ From that day forward, P.B. and J.B. conceded and the term Brugada syndrome.

The controversial time (1996–98)

The years 1996–98 were marked by controversy regarding the existence of a real new syndrome. Ramon Brugada diligently worked in Houston with Jeff Towbin attempting to identify the gene and mutations involved in Brugada syndrome. By that time, the first gene and accompanying mutation linked to the long-QT syndrome was reported. Before 1998, scientific discussions were centred around the definition of the disease. When the first mutations in the sodium channel gene SCN5A were identified and published, discussions took on a different flavour. Little was known about mutations causing right-ventricular dysplasia with the exception of the Naxos disease variant. Recognition of sodium channel gene mutations in Brugada syndrome made it evident that mutations in Brugada syndrome were linked to the electrical activity of the heart, unlike Naxos disease, where mutations involved the physical and structural make-up of the heart. The discussion as to whether Brugada syndrome was a form of right-ventricular dysplasia persisted for a few years, until other mutations in the structural construction of the heart were identified in right-ventricular dysplasia, none of them akin to the ones known and subsequently described for Brugada syndrome.

The full development (1998–2010)

The year 1998 was a landmark year with the publication in Nature of the genetic defects involved in Brugada syndrome. It ended the discussions and speculations regarding the existence of a new syndrome. In fact, after identifying the cause of Brugada syndrome, the syndrome was technically no longer a syndrome but a disease. Papers related to Brugada syndrome increased in numbers. The citation index of P.B. saw an incredible increase from 1998 to almost 1000 citations per year, most of them related to the JACC and Nature papers. The decade that followed was one of scientific enthusiasm as more and more patients were identified with the disease. The pathophysiological mechanisms of Brugada syndrome were to become the focus of the scientific community.
The pathophysiological mechanisms of Brugada syndrome

Once again, intensive controversy surrounded the underlying mechanisms leading to the ECG abnormalities, arrhythmias, and sudden death. After the recognition of genetic abnormalities in the SCN5A gene, encoding for the cardiac sodium channel, other genetic abnormalities were to be discovered with at least 12 genetic variants now identified. For the SCN5A gene alone, already more than 300 mutations have been described. Mutations leading to a stop codon (where no sodium channel is created) seem to be associated with a poorer prognosis compared with mutations resulting in loss-of-function of the sodium channel. However, the SCN5A gene is only one of 12 different genes involved in Brugada syndrome. It is obvious that Brugada syndrome is a genetically heterogeneous disease which renders pathophysiological mechanisms heterogeneous. Because genetic abnormalities in germinal cells are found in no more than 30% of families with proven Brugada syndrome, the presence of other contributing abnormalities remain possible, such as somatic mutations that cannot be identified by blood samples or other samples linked to germinal cells (oocytes and spermatozoids). Figure 2 illustrates three different current theories related to Brugada syndrome. They can be summarized as follows: (i) The depolarization theory; (ii) The repolarization theory; and (iii) The neural crest theory. A detailed discussion can be found in a previous editorial. The depolarization theory is perfectly consistent with mutations in the sodium channel causing slow conduction and re-entry and is partly based on observations made on a patient undergoing heart transplant because of electrical storms. The repolarization theory is perfectly supported by mutations related to the calcium or potassium genes leading to a shortened action potential and phase 2 re-entry (as opposed to re-entry because of slow conduction). The neural crest theory provides a potential explanation for the 70% of patients with Brugada syndrome and the 50% isolated, non-familial cases where mutations in the germinal cells do not appear to play a role. Instead, Brugada syndrome may be caused by somatic mutations traceable only by local biopsy of the diseased cardiac muscle. Recent data from electrophysiological investigations with endo- and epicardial mapping and ablation of patients with Brugada syndrome and electrical storm favour the depolarization theory by showing extremely slow conduction of the electrical impulse at the right-ventricular outflow tract area. Ablation of the substrate abolished the arrhythmias and even normalized the ST elevation on the ECG. These findings are also in agreement with the possibility of somatic mutations (neural crest theory) that result in local slow conduction. The catheter ablation experience cannot be explained by shortening of the action potential in the epicardium (repolarization theory). So far no single clinical scenario has supported this theory in spite of its extremely high clinical relevance. It is obvious that different electrophysiological mechanisms require different diagnostic and therapeutic approaches. This discussion regarding pathophysiology is ongoing, and will remain a major challenge of the Brugada syndrome for many years to come, perhaps until a paradigm change in our approaches to genetic diseases occurs.

The present and future: changing paradigms. Reversed genetics?

Publications related to Brugada syndrome continue to flow at an incredible rate. Most do not address large patient series, prognostic factors, or genetic aspects. The scepticism has largely, though not entirely, abated as Brugada syndrome has become an everyday cardiological problem to be considered in patients and families...
with ventricular arrhythmias, syncope, and a structurally normal heart, but also in patients with isolated atrial fibrillation, that may be the first manifestation of Brugada syndrome.\textsuperscript{26}

Figure 3 illustrates the rapid progress that has been made in terms of understanding the genetic basis of inherited cardiac arrhythmias. From the initial description of the Wolff–Parkinson–White syndrome (WPW) it took decennia before the first genetic defect involved in a familial form of WPW was identified. Seventy years later, it took only 3 years to identify the first genetic defect of the short QT syndrome. Progress has been fast and will predictably grow faster still. The following paragraphs were slightly modified from the contribution from the next Brugada generation to the sixth edition of the Zipes and Jalife book entitled ‘Cardiac Electrophysiology: From Cell to Bedside’ (in press):

In recent years, cardiovascular studies have focused on personalized risk assessment and on how to determining optimal individual therapy. The Brugada syndrome has also benefited from this approach. There remains several key points to elucidate: Future genetic, epigenetic, transcriptomic, proteomic, metabolomic and animal model approaches can help us understand the complexity of Brugada syndrome-like diseases through the establishment and use of more reliable models at in silico, in vitro and in vivo levels. The genetic revolution in cardiac diseases was initiated with the knowledge of the human genome and has advanced exponentially paralleling the development of new genomic technologies (like Next Generation Sequencing). These new genetic technologies will allow comprehensive genetic analysis in Brugada syndrome patients, improving the identification of pathogenic variations. Research in stem cells is one of the last fields to be incorporated into the cardiac arrhythmia scenario. This research has improved the identification, derivation and characterization of human stem or progenitor cells, comprising embryonic stem cells, and the recently described induced pluripotent stem cells (iPS). The human iPS cells from patients diagnosed with the long QT syndrome can be differentiated into cardiomyocytes, allowing electrophysiological and molecular study of arrhythmic mechanisms. However, Brugada syndrome has not yet benefited from these advances.

Another interesting point is the use of animal models. They constitute useful tools for addressing the role of genetic and environmental modifiers on cardiac electrical activity. To date, the only genetic model of the Brugada syndrome is the SCNSA knockout mouse. The heterozygous SCNSA null allele results in impaired AV conduction, delayed intramyocardial conduction, abnormal ventricular refractoriness, and ventricular arrhythmias.

Computational power allows molecular modeling and molecular dynamics simulations of complex proteins. A full in silico model of potassium channel has been developed based on the available structures of channels which includes all transmembrane segments.

Altogether, there is still a long road ahead towards the future of cardiac diseases associated with sudden cardiac death, supporting the need to use all new emerging tools in the field of biomedicine. These words suggest a scientific scenario full of hope. Refining available tools can indeed result in a paradigm shift. The present scenario is one where physicians await for patients to present to medical attention with a medical problem. The issue is identified and studied. Mechanisms are explored and understood paving the way for potential solutions. Can we move into a world of ‘reversed genetics’ where we create the diseases in the lab, study the mechanisms, identify solutions, and then search for the disease in humans? At least from a theoretical perspective it is possible.

In conclusion, the past two decades have witnessed spectacular advances in our understanding of Brugada syndrome and other inherited arrhythmia disorders. The acceleration of knowledge and progress has helped physicians offer longer and better lives to many patients who would have otherwise succumbed condemned to untimely premature death. The future looks bright. In the interest of progress, our scientific community will be best served by collaborative multicentre and multidisciplinary efforts to improve the density and depth of experiences and knowledge regarding the many facets of Brugada syndrome.

Acknowledgements

The authors thank Dr Paul Khairy for his critical reading and corrections brought to the manuscript and Dr Ruben Casado for his practical help.

Conflict of interest: none declared.

References


Figure 3: Time interval in years between the initial description of five inherited arrhythmia disorders, and the discovery of the first causal gene. The numbers on the x-axis give the year of the clinical description of the disease. The y-axis gives the years passed between the description of the disease and the discovery of the first causal gene. The progress in cardiogenetic research is clearly evident. WPW, familial Wolff–Parkinson–White syndrome; LQT, long-QT syndrome; Cathecol VT, catecholamine-induced polymorphic ventricular tachycardia; Brugada, Brugada syndrome; Short QT, short-QT syndrome.
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