Viewpoint: Genetics and Arrhythmias

Carlo Napolitano, MD, PhD, senior scientist, Molecular Cardiology Laboratories, Fondazione Salvatore Maugeri, Pavia, Italy, discussed recent progress in genetic coding and cardiac arrhythmias with Ingrid Torjesen, BSc.

Many genes coding for cardiac arrhythmias have now been identified, and a great deal has been learnt about the pathophysiology and genotype-phenotype correlation in these diseases, yet genetic testing is not readily available for patients. Dr Napolitano, who has helped unravel the genetics of arrhythmias, is now attempting to improve testing techniques so that screening can be made more widely available. “The turnaround time of genetic testing, costs, and limited availability still hamper the possibility of large-scale genotyping,” he said, “so we are trying to develop new techniques for rapid screening.”

He explained that his laboratory offers genetic testing as a clinical service, but that part of the cost is covered by research funding rather than through reimbursement from the healthcare system. Access to genetic testing is even more difficult in countries with insurance-based health systems because either the test must be done fully on a research basis or the patient must pay everything.

Few centres at present have the expertise to offer patients counselling. “One way would be to try to put together the clinical expertise and the genetic expertise to try to optimise the approach to every single patient,” he explained. “What is needed in the future is at least 1 referral centre in every country that provides both genetic testing and advice to clinicians on the management of inherited arrhythmias.”

This integrated approach appears important in several situations. As an example, Dr Napolitano said, “With genetic testing, you are treating and testing individuals who do not yet have any symptoms, so of course this may have a negative psychological impact on their quality of life.” Dr Napolitano warned, “It is very important when we do genetic testing to counsel patients on whether they really want the results, and ensure that the proper information is delivered.”

When and how genetic testing should be used varies from disease to disease. “If the test is affordable, all patients with a diagnosis should be tested, because for some diseases the genetics are very important for management,” he said. “With long QT syndrome, knowing the genotype can have a significant impact on clinical management because you can stratify risk and know whether the patient is going to respond to therapy.”

Dr Napolitano continued, “There may be an indication for an implantable cardioverter-defibrillator because that specific patient is not going to respond well to the pharmacological treatment with β-blockers.”

Prenatal screening is still a debatable issue, but for some highly malignant conditions or in families with severe mutations, it would be advisable. For example, there is one variant of long QT syndrome (Timothy syndrome) that also includes developmental disorders and congenital heart defects. In such cases it is very rare for affected individuals to survive until adulthood. “Prenatal diagnosis in these families would be helpful because these patients really are in a bad situation and the therapies are still poorly effective.”

With some arrhythmias such as catecholaminergic ventricular tachycardia (VT) (see figure), sudden death may represent...
the first manifestation of the disease. As there is effective treatment to prevent symptoms once a genetic defect is identified, early genetic diagnosis is extremely useful. Catecholaminergic VT patients have a normal baseline resting ECG, so the diagnosis is often not straightforward.

Dr Napolitano became interested in the genetics of arrhythmias when the first long QT syndrome genes were discovered by Mark Keating, MD, and his group in Salt Lake City, Utah. At the time he was a student and fellow in cardiology following a number of long QT patients under Peter Schwarz, MD, professor of cardiology at the University of Pavia.

Since 1998, Dr Napolitano and Silvia G. Priori, MD, have undertaken a long-term project at the Molecular Cardiology Unit at the IRCCS Fondazione Salvatore Maugeri in Pavia in the field of inherited arrhythmogenic disorders. The project is aimed at providing patient care and at studying the pathophysiology of these lethal diseases.

“We thought it would be a good idea to start to develop genotype/phenotype correlations to enable us to take better care of our patients, and to try to use genetics to identify responders and nonresponders to therapy,” Dr Napolitano said. In 2001, Drs Priori and Napolitano discovered the first gene for catecholaminergic polymorphic ventricular tachycardia, a highly malignant form of cardiac arrhythmia and sudden death that occurs during exercise or acute emotional stress. In 2005, they identified a novel gene causing the short QT syndrome.

A major effort of the Molecular Cardiology Unit is now focussing on sudden cardiac death syndromes as a model to study the molecular basis of cardiac excitability and arrhythmias. “We are trying to develop transgenic models for inherited arrhythmogenic diseases, specifically those associated with genetic defects in intracellular calcium handling. The hope is that these models may have an impact in the arrhythmias occurring in other frequently occurring diseases such as heart failure.”

Dr Napolitano believes that several major genes for the known inherited arrhythmia syndromes have now been identified. “There are surely other genes to be identified, but in my opinion they are going to cover only very small percentages of patients,” he said. “For example, in the case of long QT syndrome, our findings cover approximately 75% of patients. There are 10 genes that have been identified, but 3 of them (the first 3 that were discovered by Dr. Keating’s group) cover more than 92% of successfully genotyped patients. Thus, it is likely that the remaining 25% to 30% of cases will involve genes covering small groups of patients rather than 1 gene.”

According to Dr Napolitano, a major goal will be to unravel the genetic factors that predispose to arrhythmias in acquired diseases. “There are single nucleotide polymorphisms that may affect the individual QT interval durations. These polymorphisms may contribute to determining whether a patient with acute myocardial ischaemia, or other acquired condition, is more vulnerable to life-threatening arrhythmias,” he said. However, large population studies will be needed to verify such an association, and they will be impossible until more laboratories are able to do the population-based screening required for epidemiological studies.

Ingrid Torjesen is a freelance health journalist.

Preventive Cardiology in Germany: HeartScore

HeartScore has recently been introduced in Germany as HeartScore Deutschland. Ulrich Keil, MD, MPH, PhD, the European Society of Cardiology’s national coordinator for CVD prevention in Germany, discussed with Mark Nicholls the potential of this initiative to improve cardiac health.

Cardiologists are hoping that a new prevention tool will help cut the incidence of cardiovascular disease (CVD) across Germany now that the country has embraced the HeartScore system, a prevention tool that aims to help physicians determine their patients’ absolute risk of CVD more accurately. Germany is the second country to adopt the system after Sweden, and more European countries are likely to follow suit.

HeartScore Deutschland is an interactive software programme designed to improve the assessment and management of CVD in the population, and was officially launched at the annual meeting of the German Cardiac Society (GCS) in Mannheim in April. Indications from Münster and North Rhine-Westphalia suggest that a number of physicians are already using the system, but those behind its introduction want to see far more.

Dr Ulrich Keil, professor of epidemiology and director of the Institute of Epidemiology and Social Medicine at the University of Münster, Germany, said, “The computer programme has only been around a short time, and from our survey we already think 15% to 20% of physicians are using it, but we would like to see that at 60% to 70%.”

HeartScore Deutschland has been developed after careful analysis of German national mortality data and health statistics, and this data is regarded as more accurate and relevant than that from the Framingham Study that is currently used by German physicians. The HeartScore Europe concept was first unveiled in April 2004 and divided Europe into high- or low-risk countries. Dr Keil said that Germany fell somewhere in the middle. At around the same time, members of Dr Keil’s study group from Münster also discovered that Framingham was less effective in assessing the risk in Germany. “It overestimates the risk in Germany and in Italy by 50% to 100%,” said Dr Keil. “Framingham may do a good job for Northern Europe and for the UK, but not for Central Europe or Europe and for the UK, but not for Central Europe.”
Southern Europe. Risk factors, but more so the absolute risk of CVD, vary from country to country, and we felt that risk in Germany was being overestimated.”

German cardiologists worked to calibrate HeartScore to meet the specific needs of their population. Dr Keil is a member of the SCORE (Systematic COronary Risk Evaluation) Europe steering committee, and believes that another advantage of HeartScore is that it comprises the whole spectrum of CVD, including stroke and peripheral vascular disease, whereas Framingham only looks at coronary heart disease. “HeartScore can also take in the most recent national mortality statistics, whereas Framingham and other scoring systems may include data that has been delayed by 10 to 15 years.”

Dr Keil explained, “We are looking at conventional risk factors — systolic blood pressure, total cholesterol, HDL cholesterol, smoking status, age, and sex. That has disappointed some people who think it is old-fashioned. But the thing is to look at these factors with a critical and constructive eye. We believe the conventional major risk factors do the job in terms of prediction.” He continued, “If you add additional risk factors such as fibrinogen, C-reactive protein, or homocysteine, it adds little to the predictive curve. But with HeartScore, we are saying we want to keep it simple so that physicians can use it for primary prevention.”

The computer program operates in a similar way to conventional risk charts, but the graphic shows the total risk partitioned by the major risk factors. The system also has the ability to show changing risk predictions with different target entries for blood pressure or cholesterol levels. It can also show the change in the risk prediction if, for example, a patient were to stop smoking. As Dr Keil said, “It helps doctors explain to their patients how a change of lifestyle factors such as blood pressure or cholesterol affects their risk of heart attack or stroke.”

HeartScore Deutschland has been driven by the GSC and financed by the ESC and the SCORE steering committee, and is funded by the European Union. It has the backing of cardiologists and general practitioners. But what has proved significant is that major German health insurers have embraced the system, even publishing the HeartScore Deutschland risk chart in brochures, said Dr Keil.

Dr Keil added that the aim of HeartScore Deutschland is to improve the primary prevention of CVD and to focus on multifactorial risk, total cardiovascular risk, and to help physicians improve preventative medicine for patients before they suffer myocardial infarction or stroke.

“We hope it will improve life expectancy, and we can improve that by lowering the risk for CVD,” he said. “We know from our analysis of life expectancy gains in Germany for the last 20 years that CVD is the field that is most advanced and where we can gain most. Much more can be done if we really apply these guidelines and inform physicians and the public about health prevention in this field.”

Dr Keil thinks that more countries will follow by adapting HeartScore Europe for their own populations. He revealed that Spain is about to adopt the system, and that Greece is looking at the initiative. Ireland has also been involved. German cardiologists liaised over its introduction with the Irish group, led by Ian Graham, RCSI, that devised the SCORE system.

At the time of its launch, Dr Graham, consultant cardiologist at Tallaght Hospital, Dublin, and associate professor of cardiology at Trinity College, Dublin, stated, “It is our hope that national cardiac societies across Europe will embrace the potential of HeartScore on a national level and work with us to develop national versions for their populations.”

Dr Keil added that, theoretically, there is the potential to regionalise HeartScore in Germany in areas of larger populations such as Bavaria or North Rhine-Westphalia. “As we know of a north-south gradient in CVD mortality in Germany, such data for different regions will be worthwhile to enable better planning for preventive action,” he said.

Mark Nicholls is a freelance medical writer.

Reference

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History of Medicine: Sir Dominic Corrigan, MD

Domnic John Corrigan was born in Dublin, Ireland, where his father was a wealthy retailer of agricultural machinery. His early education was at the Catholic College of St. Patrick at Maynooth near Dublin; he went on to study medicine at both Dublin and Edinburgh. On leaving school he was apprenticed to Edward Talbot O’Kelly, MD, who was the physician to his former college. Dr O’Kelly was so impressed by his young apprentice that he persuaded Corrigan’s father to send him to Edinburgh to complete his medical studies. He graduated with his doctorate in 1825. Interestingly, at Edinburgh, he was a contemporary of Dr William Stokes of “Adams-Stokes syndrome” fame.

After graduation, Dr Corrigan returned to settle in Dublin. In 1830, he became physician to the Jervis Street Hospital, and it was whilst working there in 1832 that he wrote the paper that was to make him famous and provide immortality, thanks to the continuing use of the eponymous term “Corrigan’s pulse.”

The paper, entitled On Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves,1 described the typical water-hammer pulse found in aortic incompetence, contrasting it with the plateau pulse of aortic stenosis.

Dr Corrigan first set out the rather “uncertain and unsatisfactory” nature of the general symptoms of aortic incompetence, including “frequent convulsive fits of coughing, more or less dyspnoea, sense of strangeness and oppression across the chest, palpitation after exercise, sounds of rushing in the ears and inability to lie down.” He then said that fortunately there are specific signs relative to the disease that are easily discernible both physically and with the use of the stethoscope. The first sign is the visible pulsation of arteries of the head and superior extremities; the second the bruit de soufflet in the ascending aorta, carotid, and subclavian arteries and, third, the bruit and frémissement, or strong rushing, that can be palpated with the finger in the carotid and subclavian vessels.

Dr Corrigan goes on to further stress the importance of the invariably full pulse. “When a patient affected by the disease is stripped [of clothing], the arteries of the head, neck and superior extremities immediately catch the eye by their singular pulsation. At each diastole the subclavian, carotid, temporal, brachial and in some cases even the palmar arteries are suddenly thrown from their bed, bounding up under the skin.”

Dr Corrigan’s fine clinical description of the syndrome was a first, and “Corrigan’s pulse” subsequently became recognised in England, France, and many other countries. He took a great interest in the then new science of pathology, and devoted himself to original work in the field. He was particularly interested in renal medicine, and his work was peer-reviewed by the renowned French physician Pierre-François Olive Rayer, MD, in Dr Rayer’s 1840 treatise on diseases of the kidney.2

Dr Corrigan achieved an excellent reputation as physician, pathologist, and teacher. He lectured on medicine and became one of Dublin’s most popular physicians. Legend has it that he had “a secret door built in his house in order to escape the endless stream of those who wished to consult him.”

In 1843, Dr Corrigan presented himself as candidate for membership of the Royal College of Surgeons of London. When at the viva voce the examining surgeon confirmed that he was indeed the same Dr Corrigan who was the author of the 1832 paper, he was awarded the diploma without further question! A rather similar event took place when he attended a ward round at Hôtel Dieu Hospital, Paris, France, where one of the patients had a board above his bed bearing the description Maladie de Corrigan. When the physician taking the round enquired whether he knew Dr Corrigan of Dublin, he was astonished by the prompt reply, “C’est mois, Monsieur.” At the end of the ward round, the students greeted their distinguished guest with deservedly loud acclaim.

In 1866, Dr Corrigan was created a baronet, and in 1870 he was appointed physician-in-ordinary in Ireland to Queen Victoria. The now Sir Dominic Corrigan was extremely successful in all projects that he undertook, except his excursion into politics. His time as Member of Parliament for Dublin was generally considered to be a failure.

Sir Dominic died at the age of 78 following a massive cerebral vascular accident. In his early professional career, when patients were few and fees infrequent, he was much heartened by reading The Lives of British Physicians from Linacre to Gooch, and referred to it as proving that “there is but one road to excellence and success in our profession, and that is by steady, sturdy and hard labour.”

Diana Berry is a medical historian and freelance writer.

References