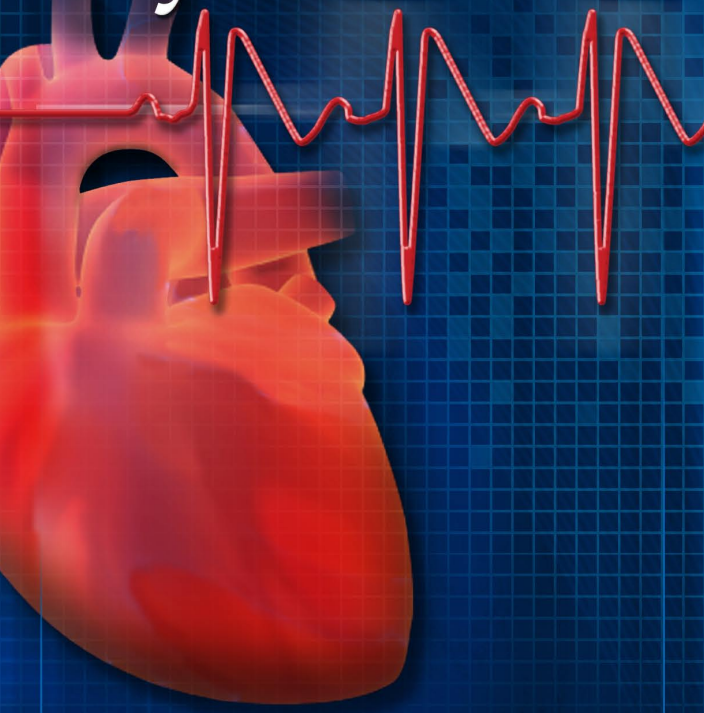
The Brugada Syndrome



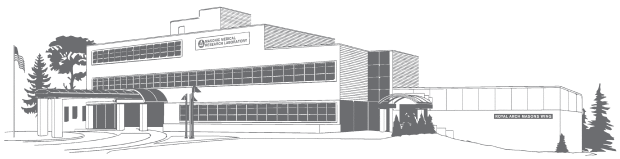
MASONIC MEDICAL RESEARCH LABORATORY®

Changing the face of medicine.

THE BRUGADA SYNDROME

The Brugada syndrome is an inherited cardiac arrhythmia syndrome that generally afflicts individuals as they reach their third and fourth decade of life. Some are indivduals who have not been sick a day in their lives until one day, they experience a cardiac arrest in their sleep, often without warning. This syndrome has confounded doctors for decades and has left many families devastated. A great deal of progress has been achieved in recent years in the identification of the pathophysiologic mechanisms and genetic basis for the syndrome. Using experimental models of the disease, investigators at the Masonic Medical Research Laboratory (MMRL) have identified a class of drugs, known as transient outward current blockers (e.g., quinidine), which can be used in conjunction with implantable cardiac defibrillators (ICDs) to protect patients from the arrhythmias that can lead to sudden cardiac death. Because of these advances, individuals with this disease can be identified genetically as well as clinically and appropriate therapy can be administered before a tragic outcome ensues.

MMRL investigators have co-authored a large number of reviews dealing with the Brugada syndrome published in prominent journals and textbooks. In 2003, the MMRL hosted an International Consensus Conference on the Brugada syndrome, co-chaired by Drs. Antzelevitch and Pedro Brugada. The consensus document, highlighting diagnostic criteria and approach to therapy, appeared in Circulation and Heart Rhythm in 2005. A book edited by Dr. Antzelevitch and the Brugada Brothers entitled "The Brugada Syndrome: From Bench to Bedside" was published soon after.



Questions and Answers

What is the Brugada syndrome?

The clinical entity now known as Brugada syndrome was first described by Drs. Pedro and Josep Brugada in 1992 and named "Brugada syndrome" by scientists at the MMRL in 1996 in honor of the two Brugada brothers. The cellular basis for the life-threatening abnormal heart rhythms associated with this syndrome was discovered by Dr. Antzelevitch and coworkers at the MMRL in the early 1990's. Brugada syndrome is an inherited cardiac arrhythmia syndrome that that can lead to life-threatening ventricular tachycardia and fibrillation. Ventricular fibrillation occurs when the electrical activity in the main pumping chambers of the heart (ventricles) goes into disarray, causing the muscle of the heart to beat in an uncoordinated fashion, thus preventing normal flow of blood to the rest of the body. If not corrected by the administration of an electrical shock to the victim's heart within several minutes, the patient could sustain brain damage (due to lack of oxygen) followed by or death.

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How common is the Brugada syndrome?

Because of its recent identification, the true incidence of the syndrome is not well established. We do know that in Southeast Asia and Japan it occurs in 5 out of 10,000 individuals, Available data indicates that there are numerous cases in the United States and Europe as well.

Can I inherit the syndrome from my parents?

Yes. Several arrhythmia syndromes can be inherited, including the Brugada syndrome, long

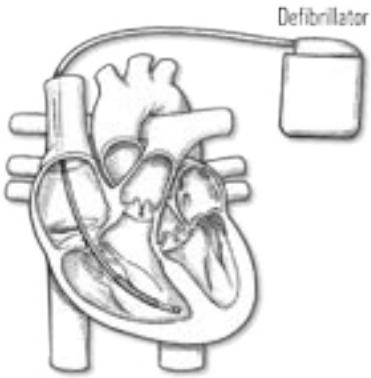
QT syndrome, short QT syndrome and atrial fibrillation. A parent with the Brugada syndrome usually has a 50% chance of transmitting the disease to his or her son or daughter.

How do I know if I have the disease?

An electrocardiogram (ECG) can often provide a definitive diagnosis. If the diagnosis is not clear, provocative tests can be performed using sodium channel blockers to unmask the typical ECG features of the disease. Genetic testing is useful in confirming the diagnosis and in identifying family members with the disease who should be closely followed-up by a qualified cardiac electrophysiologist or cardiologist.

Is there any treatment or cure for the Brugada syndrome?

There is no cure. The only proven effective treatment at present is the implantation of an implantable cardioverter defibrillator (ICD). This device automatically senses when the heart experiences a dangerous arrhythmia and automatically provides an electrical shock to restore normal sinus rhythm. Investigations conducted at the MMRL have delineated the ionic and cellular mechanism responsible for the arrhythmias that cause sudden death in patients with the Brugada syndrome. This work has identified a class of drugs known as transient outward current blockers (e.g., quinidine) that are useful as adjuncts to ICDs or as alternatives in those cases in which an ICD is not an option or in regions of the world where an ICD is unaffordable. Clinical studies indicate that quinidine may be effective in preventing arrhythmias in patients with Brugada syndrome, although placebo-controlled blinded studies are not available. An international registry for physicians to report their experience with quinidine in Brugada syndrome was recently launched http://clinicaltrials.gov/ct2/show/NCT00789165. Studies at the MMRL also identified other agents such as isoproterenol that have proven useful in quieting "electrical storms" sometimes encountered in patients with this disease. MMRL investigators are working with pharmaceutical companies to develop more cardioselective and specific transient outward current blockers to treat the Brugada syndrome.



What is an arrhythmia?

In very simple terms, an arrhythmia is an abnormal heart rhythm resulting from the electrical instability within the heart. Some arrhythmias such as extra beats are often benign, whereas others like atrial fibrillation are a nuisance, and still others like ventricular tachycardia and fibrillation are more ominous. Ventricular fibrillation is the arrhythmia usually responsible for sudden cardiac death.

Should certain drugs or conditions be avoided in patients with ?

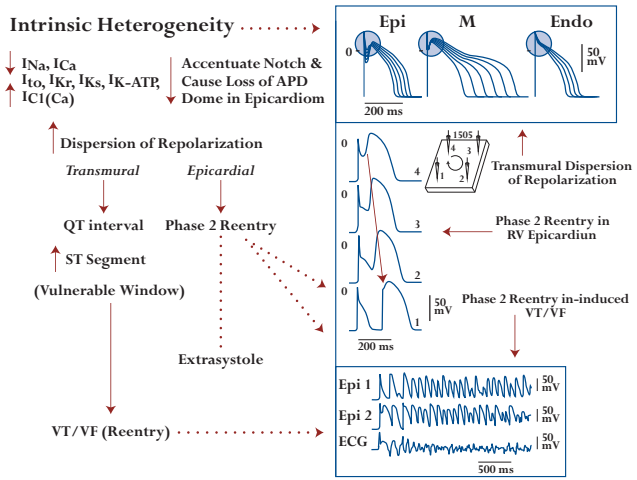
Drugs that are know to block the sodium channels in the heart should be avoided because they can aggravate the syndrome and precipitate life-threatening arrhythmias. Included are commonly used antiarrhythmic drugs, tricyclic antidepressants, fluoxetine, lithium, trifluoperazine, antihistamines, and cocaine. A more complete list can be found at www.burgadadrugs.org. Work at the MMRL conducted in 1998 identified fever as another important risk factor that should be avoided, particularly in children with the syndrome.

What is molecular genetics research?

Molecular genetics is the science that deals with the inheritance of traits including disease. We have approximately 20,000 - 25,000 genes in our bodies that encode for proteins responsible for the function of our organs. An error in the genetic code can cause the proteins to malfunction, thus causing disease. Understanding disease at the genetic level, means understanding the problem at its root cause. This provides us the capability to design more specific treatments and cures. Genetics holds the key to better diagnosis, prevention, and treatment of disease and a longer, healthier and more fruitful life.

In 1998, working together with colleagues worldwide, our scientists showed for the first time that a faulty gene that encodes the sodium channel (SCN5A) in the heart contributes to the development of this syndrome. Defects in seven different genes have been associated with the Brugada syndrome thus far. Five of the seven were discovered at the MMRL.

Brugada Syndrome



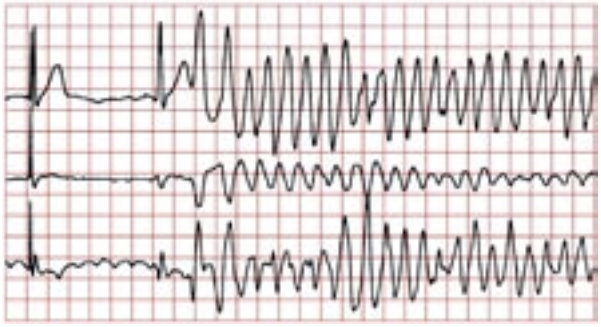
What happens once a defective gene has been identified as causing a life-threatening arrhythmia?

The first step is the identification of a defective gene. Once this has been detected, the mutated gene is isolated and studied in special cell types that allow us to assess how the function of the gene product (protein) is affected. This provides us an understanding of how the defective gene causes the disease. The next step is to try to correct this malfunction by designing specific drugs or other treatments.

How can I have my family genetically screened?

The world of science and medicine are ever-changing. Progress in recent years has been no less than remarkable regarding the Brugada syndrome and other diseases. The best that science and medicine have to offer is yet to come.

To stay abreast of the most current scientific investigations, clinical trials and publications, please visit our website at: www.mmrl.edu, where you will find updates and scientific articles dealing with this syndrome.



How can I support this life-saving research?

Our ability to ensure the health of those affected and of future generations is critically dependent on our base of support. Contributions may be made directly to the MMRL specifically earmarked for Brugada syndrome research. Only through a sustained investment in basic medical research will scientists at the bench have the means to design better and more rational medical treatments and cures. Gifts, Trusts and Bequests help make it possible for us to search for solutions to the Brugada syndrome and other aliments of the heart.

For more information please contact:

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