

THE JOHNS HOPKINS
ARRHYTHMOGENIC
RIGHT VENTRICULAR
DYSPLASIA PROGRAM

arvd

Johns Hopkins' Team Approach

This brochure was written to educate patients, their families, and their friends about the diagnosis, treatment, and genetics of ARVD/C. The team from Johns Hopkins Hospital is striving to understand the causes of ARVD/C, which can then, hopefully, lead to a cure. They are also part of national and international teams, working together to care for patients and conduct research. The most important people on these teams, however, are the patients themselves, whose questions spur the doctors to search for answers and whose participation in research makes those answers attainable. We are committed, on their behalf, to find a cure for this condition. Patients' friends, family, and community play an important role on their team, providing support. While some aspects of this disease are frightening, and many are still unknown, much has been learned about how to diagnose and treat ARVD/C over the past decade. This new knowledge is having a direct impact on improving ARVD/C patient's lives.

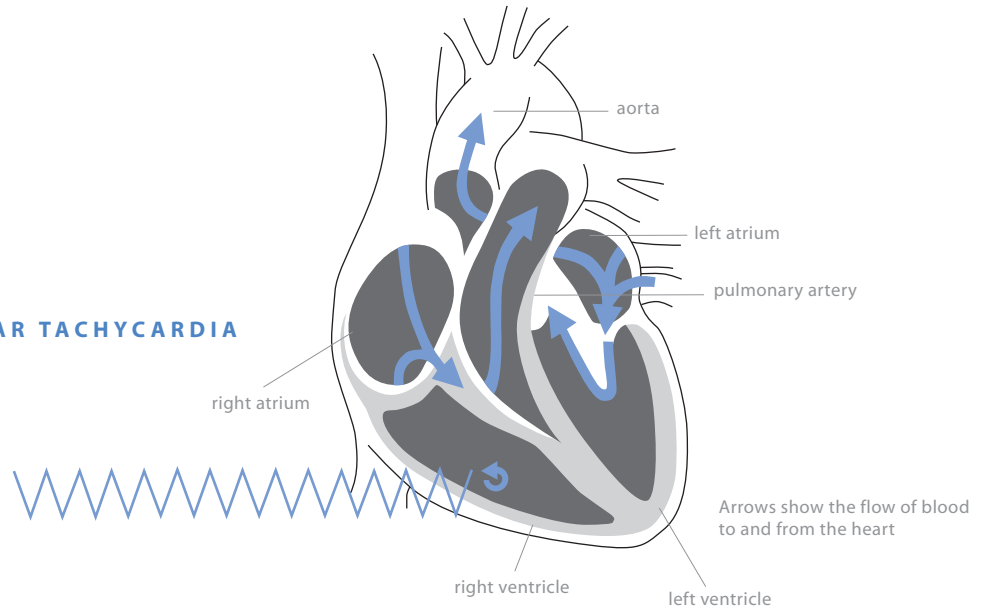
Drs. Frank Marcus and Guy Fontaine first described the clinical features of ARVD in 1982. This condition is now often referred to as Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC). ARVD/C is a leading cause of sudden death among young athletes, although people within a broad range of ages and activity levels have this condition. It affects men and women of all races, and approximately 1 out of every 5,000 is diagnosed with ARVD/C. It's possible to have this disease without knowing it. These silent carriers may not recognize its symptoms when—or if—they occur. Palpitations, fainting, chest pain, and rapid heartbeat are some warning signals of ARVD/C.

Common Symptoms of ARVD/C

An arrhythmia is an abnormality in the timing or pattern of the heartbeat. It can cause a variety of symptoms, including racing, skipping, or fluttering sensations (called palpitations) in your chest and throat. In some cases, if the heart cannot pump enough blood to its own muscle and to the lungs and body, syncope (fainting) or sudden death can result. Fortunately, sudden death is uncommon, particularly after ARVD/C is diagnosed and treated. Two typical arrhythmias in patients with ARVD/C are premature ventricular contractions (PVCs) and ventricular tachycardia (VT). PVCs are extra or irregular heartbeats that occur when the electrical signal starts in the lower chamber of the heart. Many people are unaware that they are experiencing occasional extra heartbeats. In other cases, the PVCs are bothersome, or may be associated with other types of sustained rapid heart rhythms, such as VT.

VT is a series of rapid heartbeats, originating in the ventricle. A VT episode can last only a few beats, or may continue and lead to life-threatening arrhythmias. VT may cause the heart to beat inefficiently, leading to lightheadedness, chest pain, or fainting if enough blood does not circulate throughout the body. VT can stop on its own, or it may require medications or electrical cardioversion to convert back to normal sinus rhythm. ARVD/C patients rarely experience arrhythmias that start in the heart's upper chambers (the atria). The most common types of supraventricular tachycardia (SVT) are atrial fibrillation and atrial flutter.

VENTRICULAR TACHYCARDIA



How ARVD/C Affects the Heart

Much has been learned about what causes ARVD/ C. It is now widely recognized that ARVD/C is often caused by mutations in desmosomal proteins. The desmosome is the mechanical bridge that links one heart cell to the next. The major components of the desmosome are plakophilin-2 (PKP2), desmoglein-2 (DSG2), desmocollin-2 (DSC2), desmoplakin (DSP), and plakoglobin (JUP). Patients with ARVD/C are commonly found to have genetic abnormalities in the genes that encode for these desmosomal proteins. Because of these desmosomal protein abnormalities, the mechanical bonds (or glue) between heart cells is defective. Over time the heart cells can pull apart, starting a process of scar and fat replacement.

The chance of heart cells pulling apart may be increased with high level exercise. This may explain why ARVD/C appears to be particularly common among athletes. The presence of scar and fat in the heart results in the heart being susceptible to the development of ventricular tachycardia and also may reduce heart function.

Although much has been learned we still do not have all the answers. It is possible that there are other causes of ARVD/C such as viral infections. There is a great deal of research on the mechanisms of ARVD/C underway and we should learn much more in the next five to 10 years.

How ARVD/C is Diagnosed

There is no single test that can either establish or exclude a diagnosis of ARVD/C. In 1994, researchers proposed a set of diagnostic criteria that took into account information from a physical exam, family history, and a number of cardiac tests to make the diagnosis. These criteria were revised in 2010 and now take into account genetic information.

There are several non-invasive and invasive cardiac tests, which are described in detail on the following pages.

NON-INVASIVE CARDIAC TESTS

1. Electrocardiogram (ECG)
2. Signal-Averaged Electrocardiogram (SAECG)
3. Holter Monitor
4. Exercise Stress Test
5. Echocardiogram
6. Cardiac Magnetic Resonance Imaging (MRI)

INVASIVE CARDIAC TESTS

1. Electrophysiology Study (EPS)
2. Angiography
3. Cardiac Biopsy

Non-Invasive Cardiac Tests

ELECTROCARDIOGRAM (ECG)

An electrocardiogram (ECG) is a print-out of the heart's electrical activity that doctors examine to diagnose various types of heart disease. During an ECG, you lie on a table, connected to an ECG machine, with wires taped to your chest and legs.

SIGNAL-AVERAGED ELECTROCARDIOGRAM (SAECG)

A signal-averaged electrocardiogram analyzes the electrical signals from the heart to determine the existence of scar tissue, which could cause an arrhythmia. Both ECG tests are painless and take only a few minutes.

HOLTER MONITOR

A Holter monitor is a continuous ECG recording taken for 24-48 hours while you perform your daily activities. It can detect abnormalities that may not occur during a resting ECG. Wires are connected to your chest and attached to

a small recording device that you carry with you. An event monitor is similar to a Holter monitor, but only records the heart rhythm when you activate it. This monitor typically is worn for 1 month, and if an event is recorded, the ECG tracing can be transmitted over the phone to a monitoring station and then sent to your doctor.

EXERCISE STRESS TEST

An exercise stress test, or treadmill test, is used to determine whether an arrhythmia occurs during exercise. Since some arrhythmias only occur with exercise, during this test you walk or run on a treadmill while connected to an ECG machine.

ECHOCARDIOGRAM

An echocardiogram, or echo, is a painless test that records images of your heart to determine whether it has normal function, size, and structure and how efficiently it is working. This test

cannot determine whether there is fatty or fibrofatty scar tissue in the heart muscle. To perform an echo test, a sound transducer is placed on your chest, and the echoes of the sound waves are monitored and used to produce an image of the heart.

CARDIAC MAGNETIC RESONANCE IMAGING (MRI)

Cardiac magnetic resonance imaging (MRI) uses magnetic waves to produce an image of the heart and can distinguish between fat and muscle. MRI also can look at the heart's movement and function. Until specific guidelines are developed for MRI diagnosis of ARVD/C, however, we recommend that your doctor consult a radiologist experienced in diagnosing ARVD/C. The diagnosis of ARVD/C should not be based solely on the MRI result.

Invasive Cardiac Tests

SEVERAL INVASIVE
CARDIAC TESTS
ARE OFTEN NEEDED
TO CONFIRM THE
DIAGNOSIS AND HELP
DIRECT TREATMENT
FOR ARRHYTHMIAS
CAUSED BY ARVD/C.

ELECTROPHYSIOLOGY STUDY (EPS)

An electrophysiology study (EPS) is used to determine whether you are at high risk of developing a serious arrhythmia so that preventive treatment can be provided. During an EPS, a number of IVs are inserted into a large vein in your leg. The doctor then passes several electrical catheters through the IVs and guides them into your heart. This allows the doctor to examine the electrical activity from inside the heart and determine whether it is abnormal. During this test you are sedated, and monitors track your blood pressure and heart rate. The EPS can be done on an outpatient basis. If you need an EPS, your doctor will discuss the risks and benefits and give you more instructions and information about this procedure.

ANGIOGRAPHY

Angiography uses contrast dye to determine the structure and function of the heart, including the right and left ventricles, plus the coronary arteries. Angiography can be performed at the same time as the EPS. For patients with ARVD/C, angiography can help determine how well different areas of the heart muscle are working.

CARDIAC BIOPSY

A cardiac biopsy allows a pathologist to examine a very small tissue sample from the right ventricle, which is removed through a catheter inserted into a large vein in the neck. A pathologist can examine the heart tissue to determine whether the muscle cells are abnormal.

How ARVD/C Is Treated

There are two primary goals of treatment: 1) To reduce the frequency and severity of ventricular arrhythmias (VT) and 2) To prevent or limit worsening of ventricular function and heart failure. Because studies have not determined which treatment is best for each patient, doctors base their decisions on a patient's cardiac test results, medical history, and the presence or absence of genetic mutations. The three most common treatments for arrhythmias are medications, implantable cardiac defibrillators, and catheter ablation.

MEDICATION

Medications can be used to decrease the number of episodes and the severity of VT. These medications alter the electrical properties of the heart either directly, by affecting the electrical currents in the heart, or indirectly, by blocking the effects of adrenaline or improving blood flow to the heart. Beta blockers lower the heart rate, blood pressure, and the effects of adrenaline, which seems to play a role in causing arrhythmias. Beta blockers are a safe and commonly used type of medica-

tion. If patients experience ventricular tachycardia despite treatment with beta blockers, antiarrhythmic medications such as sotalol or amiodarone may be recommended. ACE-inhibitors may also be helpful in reducing the workload on the heart and preventing the development of heart failure. Please keep in mind that all medications can cause side effects and that new medications are being developed every year.

IMPLANTABLE CARDIAC DEFIBRILLATOR (ICD)

Implantable Cardiac Defibrillators are commonly used to treat patients with ARVD/C. These devices continuously monitor the heartbeat and automatically deliver a small electrical shock to the heart if ventricular tachycardia or ventricular fibrillation (rapid sustained heart rhythms) occurs. The shock may cause momentary discomfort, which is described by some patients as being "kicked in the chest." ICDs also can function as pacemakers and can treat both slow and fast rhythms. They should be checked every 3 to 6 months, either in your doctor's office or remotely. The devices may need to be

replaced every 4 to 6 years, depending on the battery life. The ICD is usually implanted by making a 2-inch incision beneath the collarbone and creating a pocket for the device. Wires (called leads) are inserted into the heart and attached to the device. Your doctor will test the ICD by triggering an abnormal heart rhythm to determine how much energy is required to shock the heart back into normal rhythm.

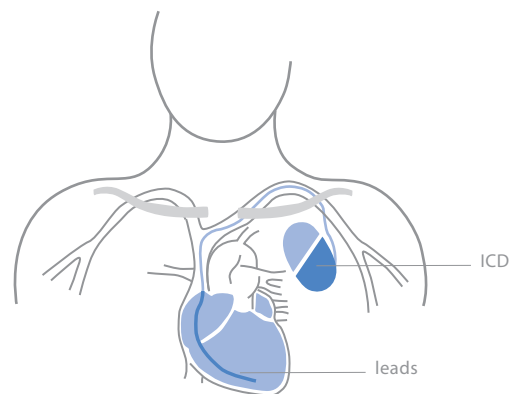
CATHETER ABLATION

During catheter ablation, areas of the heart that cause arrhythmias are located and eliminated by cauterization. This is an invasive procedure that is performed in an electrophysiology laboratory. Catheter ablation is performed to reduce the frequency of sustained VT episodes.

Because ARVD/C is a progressive condition, catheter ablation is not considered curative. Catheter ablation can help reduce the frequency of VT episodes and the

need for ICD therapies. It is important for patients with ARVD/C to have a careful discussion with their physicians about the risks and benefits of catheter ablation before undergoing this procedure.

IMPLANTABLE CARDIAC DEFIBRILLATOR



The Role of Genetics

We believe that ARVD/C in most cases is caused by a change (called a mutation) in a gene. A gene is a piece of DNA that encodes an instruction. Genes are packaged on chromosomes that are arranged in 23 pairs. One member of each pair is inherited from the mother and one, from the father. In the majority of families, ARVD/C is a dominant condition, meaning only one copy of the gene must carry the mutation for the condition to be present. The mutation may be inherited from a parent, or may occur by chance as a result of a new mutation. About 30 percent to 50 percent of people with ARVD/C have a family history of the disease. New mutations frequently occur in eggs and sperm of every adult, and it is just chance that the mutation occurs in a gene that causes ARVD/C.

Several genes have now been identified as being associated with ARVD/C. There are probably more that have not yet been discovered. Genetic testing is now available to determine who carries a mutation for ARVD/C. Usually, the individual who already has ARVD/C is the first person to be tested. A negative genetic test result in a person who has signs and symptoms of ARVD/C does not exclude the diagnosis of ARVD/C. They may have a mutation in a gene that current testing methods cannot identify. Once a

person has a mutation – whether due to inheritance or a new mutation – there is a 1 in 2 chance that the mutation will be passed on each time he or she has a child. It is also important to understand that not everyone who carries a mutation for ARVD/C will actually develop signs and symptoms of ARVD/C. We believe other factors are needed for someone to manifest ARVD/C, including environmental, and possibly other genetic factors. Some families may have more than one genetic mutation, so it is important to keep in touch with your physicians about current genetic testing options.

We recommend that all first-degree relatives of a person with ARVD/C be checked at regular intervals with non-invasive cardiac testing to look for signs of the disease. First-degree relatives are the parents, siblings, and children of the person with the diagnosis of ARVD/C. Second-degree relatives (grandparents, aunts, uncles, and cousins) usually do not need cardiac testing unless they have symptoms or have been found to carry a ARVD/C-associated genetic mutation. A genetic counselor can review your family history and make recommendations for testing.

Living With ARVD/C

While considerable progress has been made in understanding the genetic basis of ARVD/C, there are still many questions about how to best treat this disease and what to expect once the diagnosis is made. There have been no controlled studies to examine the specific effects of exercise, medications, or procedures on the long-term outcome of the disease. Nor have vitamin treatments and alternative therapies been studied. Thus, you and your doctor should discuss appropriate guidelines for diet and healthy living, as well as symptoms that could indicate a complication related to the disease, medications, or other treatments.

We have learned both from studying individuals who develop ARVD/C, as well as from mouse models with ARVD/C genetic mutations, that exercise appears to be a risk factor for developing ARVD/C. Exercise can not only provoke arrhythmias in some patients with ARVD/C; it may even accelerate progression of the disease. It is not known, however, what types or levels of intensity of exercise are considered safe. Generally, patients with ARVD/C are advised to focus on mild aerobic exercise such as walking, playing golf, or bowling – not competitive athletics. Patients also are advised to limit their intake of alcohol and caffeine, both of which may exacerbate arrhythmias.

After their diagnosis, many patients ask what will happen to their heart over the years. Some patients will have a stable functioning heart for decades, while others may have spells of arrhythmias that require changes in medication or ablations. Some patients develop such severe dysfunction or frequent episodes of ventricular tachycardia that a heart transplant may be necessary. Our research at Johns Hopkins has shown that the long-term outlook for most people who have been diagnosed with ARVD/C is relatively good. We believe that most people who die from ARVD/C today were not diagnosed before their death.

For many patients, the diagnosis of ARVD/C comes from out of the blue. For others, it explains a long history of symptoms that were never understood. In either case, patients and their families may feel a sudden loss of well-being and a perception of helplessness. With any diagnosis of a chronic illness, it usually takes time to adjust to the emotional and psychological impacts. Most people learn to cope by gathering information about the disease and find comfort knowing that with proper medical care, they can find ways to live healthy and productive lives.



“IT HAS BEEN A MONTH SINCE I WAS DIAGNOSED WITH ARVD. THINGS HAVE BEGUN TO SETTLE DOWN. IT SEEMS TO BE IN DIRECT PROPORTION TO OUR UNDERSTANDING OF THE DISEASE, ITS LONG TERM EFFECTS, AND MY LONG-TERM PROGNOSIS.”

(J. Campanella, 1997)

“AFTER LIVING WITH ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA FOR MORE THAN A DECADE, I KNOW I AM A BETTER PERSON. MY PERSPECTIVES AND PRIORITIES HAVE BEEN CHANGED IN A PROFOUND AND POSITIVE WAY.”

(J. Campanella, 2010)

Special thanks go to the patients and medical professionals at Johns Hopkins Hospital, the University of Arizona and elsewhere, who contributed their ideas and hard work essential to this brochure. The information in this brochure is accurate as of January 2010.

Thanks to Johns Campanella for sharing his personal experiences as a patient with ARVD.



**“FOR MY FAMILY, ARVD IS A DISEASE
THAT AFFECTS US DIRECTLY AND WE’RE
DETERMINED TO SEE IT CURED.**

JOHNS HOPKINS IS OUR PARTNER IN
WORKING TO MOVE THAT DAY CLOSER.
TOGETHER, WE HAVE CREATED ONE OF THE
MOST COMPREHENSIVE PROGRAMS FOR
STUDYING AND TREATING ARVD.”

