The Johns Hopkins Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Precision Medicine Center of Excellence

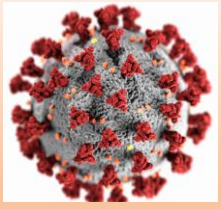
Volume 12, Issue 1 **Winter 2022**

Happy New Year from the ARVC team! We aim to publish a newsletter twice per year describing the highlights and important resources pertaining to ARVC or Arrhythmogenic Right Ventricular Cardiomyopathy, an inherited heart condition that you may have yourself, be at-risk of developing, or have family members impacted by ARVC and you just want to learn more.

Where do we even begin this year?? COVID-19 should be a thing of the past, at least that is what we were all hoping for. Unfortunately, it is still part of everyday life, reminding us in everything we do … masks … vaccines … boosters … quarantine … social distancing … rapid tests … PCR … omicron … avoid indoor gatherings … Zoom! Will we ever return to normal? I don't know if we will or what the new normal will look like, but I do know we need to work together. We need to remain vigilant and do what we can to reduce the spread of COVID-19 so we can protect ourselves, our loved ones, and our community. With that being said, our annual conference will be held virtually for the safety of our attendees and according to university guidelines. I know some are excited while others are disappointed with this decision. So, we won't make you sit on Zoom on a nice Spring day but instead wrapped in a blanket in the comfort of your home (or wherever!) on March 12th, 2022. We are excited to share with you updates on the research we've been conducting both locally at Hopkins and collaboratively with teams around the world. The field is moving forward, but not without YOU! Thank you for your continued partnership throughout the years and into the future.

~ The ARVC Program
Hugh Calkins, Hari Tandri, Cindy James, Brittney Murray, Crystal Tichnell

COVID-19 Update



We continue to follow guidelines set forth by the Center for Disease Control and Prevention (CDC) and Johns Hopkins Medicine. The ARVC program recommends vaccination against COVID-19, as well as a booster as soon as you are eligible for all patients and family members with ARVC, continue to physically distance, wear a mask, and practice hand hygiene.
https://www.cdc.gov/coronavirus/ https://coronavirus.jhu.edu/

23rd Annual ARVC Patient and Family Seminar

The Promise of Research in ARVC

Presented by

The Johns Hopkins ARVC Precision Medicine Center of Excellence

It's hard to believe we are saying this yet again, but due to the ongoing COVID-19 pandemic and University guidelines, this year's seminar will be held virtually on Saturday, March 12th, 2022. It is a bit earlier this year because if we can't gather together, who wants to spend another Saturday afternoon in a Zoom conference if it's beautiful outside?!?! We must carry on! This year we will highlight our recent research accomplishments and introduce some exciting steps forward in treatment. You won't want to miss these exciting updates! Our clinical and research teams work closely together to determine our next research plan of action and this year we are going to share some of our exciting research in the works.

Don't forget, many presentations from our past conferences are posted on our website, www.ARVD.com, under News and Events. This year's virtual conference will take place utilizing the WHOVA online platform again. Be sure to register and download the App so that you can take advantage of networking and viewing the agenda.

Registration will go live on January 15th using this link:

https://whova.com/portal/registration/jhmvs_202205/

ARVC Clinical Services

The Johns Hopkins ARVD/C Program provides a variety of clinical services. We see patients for second opinion consultations to discuss diagnosis and management, genetic counseling and testing, routine ICD management and family member screening. We also arrange concurrent cardiac testing.

Patients are seen in consultation with Dr. Hugh Calkins or Dr. Hari Tandri and our clinical genetic counselor, Brittney Murray, to discuss test results, family history, and to provide guidance regarding further management. We see all of our patients for genetic counseling to discuss the diagnosis, the psychosocial impact of living with ARVD/C and with an ICD, as well as to discuss the benefits and limitations of appropriate genetic testing. In selected cases we may recommend catheter ablation and/or sympathectomy as treatment options for difficult to manage ventricular tachycardia. Appointments with our heart failure specialist, Dr. Nisha Gilotra, can also be arranged. All appointments are billed to your health insurance.

With the COVID-19 pandemic becoming less of an impact in recent months (although possibly changing), state licensure waivers recognizing our out of state licenses are coming to an end. This means we are no longer able to legally offer telemedicine appointments to the extent we were over the past year. However, there may be some flexibility with our genetic counseling ONLY visits to be able to continue to offer this option. Please reach out to Crystal to see if you are eligible for a telemedicine appointment based on your appointment needs and physical location. Our clinics are fully open so please reach out to get scheduled.

Research Opportunities at Johns Hopkins

Why Participate in a Clinical Trial?

Clinical trials are so important in discovering new treatments and the safety of those treatments, particularly of rare conditions. The decision to participate in a clinical trial is a personal one and only you can decide if it's the right choice for you. As you think about whether to participate, please take a minute to consider the impact your participation or non-participation might have on overall clinical trials in ARVC. As we all know, ARVC is a rare condition and there isn't much funding for research. So, whatever funding we do get, we need to make the most of it. We need to prove to big funding agencies that individuals with ARVC are interested and willing to participate in new discovery research, otherwise, there will be huge delays in new discoveries, new treatment options, and ultimately finding a cure.

https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics

Clinical and Genetic Investigations of Right Ventricular Dysplasia (ARVD/C Registry)

Johns Hopkins IRB00041248

This registry is the heart of our program and from which all of our research projects originate. Both children and adults either diagnosed with ARVC or a family member of someone diagnosed with ARVC are eligible to participate. Participation involves submission of past medical records and continued followup for at least 5 years. A DNA sample may be collected for specific projects. Reach out to Crystal at 410.502.7161 or ctichnell@jhmi.edu to join.

Effects of Flecainide on Cardiac Arrhythmias in ARVC Patients

Johns Hopkins IRB00197430

Funded by The National Institute of Health (NIH)
Principal Investigator: Hugh Calkins, MD
Enrolling Site Coordinator: Crystal Tichnell, MGC, RN

The purpose of this study is to assess the effect of the antiarrhythmic drug, flecainide, on cardiac arrhythmias in individuals with ARVC. Participation in this study will last for about 10 weeks. This is a randomized, double-blinded, crossover study which means for part of the study you will be given the study drug, flecainide, and for the other part of the study you will be given a placebo. After 28 days you will switch, so everyone will be given the study drug at some point in the study. Neither you nor your enrolling physician will know if you are given the study drug or placebo first and that process is randomized.

We hope to finish up enrollment by March 2022.

Additional details about eligibility can be found on the next page.

Clinical Trials at Johns Hopkins

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During the study you will be asked to wear a monitor for 7 days on 2 occasions. We will also obtain ECGs and blood draws to assess flecainide levels through a home visit. Remote device interrogations will be obtained by your enrolling center. This study requires **0** in-person visits. All aspects of the study can be completed remotely.

To participate in this study you must:

- Be 18 years of age
- Meet the diagnostic criteria for ARVC
- Have a minimum of 500 PVCs on a recent 24-hour Holter monitor
- Have an implantable cardioverter defibrillator (ICD) with remote interrogation capability
- Be on a beta-blocker such as metoprolol, propranolol, atenolol, nadolol, carvedilol, unless contraindicated
- If prescribed, be willing to discontinue sotalol, quinidine, procainamide, propafenone, disopyramide, dronedarone, phenytoin, or mexilitene for 5 days with subsequent repeat 24-hour Holter
- Agree not to use any another antiarrhythmic medication during the 10 weeks of participation, unless for the management of life-threatening arrhythmias
- Agree to use medically acceptable contraceptive measures during participation unless documented as surgically sterile or post-menopausal

If you would like to learn more about this study or to discuss your eligibility, please contact Crystal Tichnell, MGC, RN at ctichnell@jhmi.edu or 410-502-7161. This is an important first clinical trial in ARVC and will pave the way for future clinical drug trials.

2021 Publications (Hopkins affiliated)

Scheel PJ 3rd, Murray B, Tichnell C, James CA, Tandri H, Calkins H, Chelko SP, Gilotra NA. **Arrhythmogenic Right Ventricular Cardiomyopathy Presenting as Clinical Myocarditis in Women.** Am J Cardiol. 2021 Apr 15;145:128-134. doi: 10.1016/j.amjcard.2020.12.090. Epub 2021 Jan 15. PMID: 33460606

Costa S, Medeiros-Domingo A, Gasperetti A, Akdis D, Berger W, James CA, Ruschitzka F, Brunckhorst CB, Duru F, Saguner AM**. Impact of Genetic Variant Reassessment on the Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy Based on the 2010 Task Force Criteria**. Circ Genom Precis Med. 2021 Feb;14(1):e003047. doi: 10.1161/CIRCGEN.120.003047. Epub 2020 Nov 24. PMID: 33232181

Wallace R, Calkins H**. Risk Stratification in Arrhythmogenic Right Ventricular Cardiomyopathy**. Arrhythm Electrophysiol Rev. 2021 Apr;10(1):26-32. doi: 10.15420/aer.2020.39. PMID: 33936740 Free PMC article. Review.

James CA, Jongbloed JDH, Hershberger RE, Morales A, Judge DP, Syrris P, Pilichou K, Domingo AM, Murray B, Cadrin-Tourigny J, Lekanne Deprez R, Celeghin R, Protonotarios A, Asatryan B, Brown E, Jordan E, McGlaughon J, Thaxton C, Kurtz CL, van Tintelen JP. **International Evidence Based Reappraisal of Genes Associated With Arrhythmogenic Right Ventricular Cardiomyopathy Using the Clinical Genome Resource Framework**. Circ Genom Precis Med. 2021 Jun;14(3):e003273. doi: 10.1161/CIRCGEN.120.003273. Epub 2021 Apr 8. PMID: 33831308 Free PMC article.

Hawthorne RN, Blazeski A, Lowenthal J, Kannan S, Teuben R, DiSilvestre D, Morrissette-McAlmon J, Saffitz JE, Boheler KR, James CA, Chelko SP, Tomaselli G, Tung L. **Altered Electrical, Biomolecular, and Immunologic Phenotypes in a Novel Patient-Derived Stem Cell Model of Desmoglein-2 Mutant ARVC**. J Clin Med. 2021 Jul 10;10(14):3061. doi: 10.3390/jcm10143061. PMID: 34300226 Free PMC article.

Bosman LP, Nielsen Gerlach CL, Cadrin-Tourigny J, Orgeron G, Tichnell C, Murray B, Bourfiss M, van der Heijden JF, Yap SC, Zeppenfeld K, van den Berg MP, Wilde AAM, Asselbergs FW, Tandri H, Calkins H, van Tintelen JP, James CA, Te Riele ASJM. **Comparing clinical performance of current implantable cardioverter-defibrillator implantation recommendations in arrhythmogenic right ventricular cardiomyopathy.** Europace. 2021 Sep 1:euab162. doi: 10.1093/europace/euab162. Online ahead of print. PMID: 34468736

Daimee UA, Assis FR, Murray B, Tichnell C, James CA, Calkins H, Tandri H. **Clinical outcomes of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular cardiomyopathy: Insights from the Johns Hopkins ARVC Program. Heart Rhythm.** 2021 Aug;18(8):1369-1376. doi: 10.1016/j.hrthm.2021.04.028. Epub 2021 Apr 30. PMID: 33933674

Dries AM, Kirillova A, Reuter CM, Garcia J, Zouk H, Hawley M, Murray B, Tichnell C, Pilichou K, Protonotarios A, Medeiros-Domingo A, Kelly MA, Baras A, Ingles J, Semsarian C, Bauce B, Celeghin R, Basso C, Jongbloed JDH, Nussbaum RL, Funke B, Cerrone M, Mestroni L, Taylor MRG, Sinagra G, Merlo M, Saguner AM, Elliott PM, Syrris P, van Tintelen JP; Regeneron Genetics Center, James CA, Haggerty CM, Parikh VN. **The genetic architecture of Plakophilin 2 cardiomyopathy.** Genet Med. 2021 Oct;23(10):1961-1968. doi: 10.1038/s41436-021-01233-7. Epub 2021 Jun 12. PMID: 34120153 Free PMC article.

Gasperetti A, James CA, Chen L, Schenker N, Casella M, Kany S, Mathew S, Compagnucci P, Müssigbrodt A, Jensen HK, Svensson A, Costa S, Forleo GB, Platonov PG, Tondo C, Song JP, Dello Russo A, Ruschitzka F, Brunckhorst C, Calkins H, Duru F, Saguner AM. **Efficacy of Catheter Ablation for Atrial Arrhythmias in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy-A Multicenter Study.** J Clin Med. 2021 Oct 26;10(21):4962. doi: 10.3390/jcm10214962. PMID: 34768482 Free PMC article.

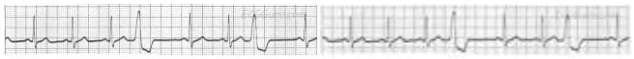
Assis FR, Sharma A, Daimee UA, Murray B, Tichnell C, Agafonova J, James CA, Calkins H, Tandri H. **Efficacy of catheter ablation for premature ventricular contractions in arrhythmogenic right ventricular cardiomyopathy**. J Cardiovasc Electrophysiol. 2021 Jun;32(6):1665-1674. doi: 10.1111/jce.15025. Epub 2021 Apr 14. PMID: 33783912

Featured Manuscripts

Efficacy of catheter ablation for premature ventricular contractions in arrhythmogenic right ventricular cardiomyopathy

Assis FR, Sharma A, Daimee UA, Murray B, Tichnell C, Agafonova J, James CA, Calkins H, Tandri H

Premature ventricular contractions or PVCs are common in ARVC and are present throughout the course of disease. A high number of PVCs has been associated with a risk of sustained ventricular tachycardia or VT. The goal of this study was to assess the efficacy of catheter ablation on PVC burden. This study examined eight patients who underwent catheter ablation of PVCs. Seven of these patients underwent an epicardial ablation. The mean daily burden of PVCs prior to ablation ranged from 5.4% to 24.8%. Complete acute elimination of PVCs was achieved in 50% of patients with no complications. Only 1 patient presented complete long-term success while 6 patients either maintained or increased the need for anti-arrhythmic medications after the ablation. PVC ablation may be reserved for highly symptomatic patients who failed anti-arrhythmic medications. Additional investigation is necessary to improve the efficacy of PVC ablation in ARVC patients.



International Evidence Based Reappraisal of Genes Associated With Arrhythmogenic Right Ventricular Cardiomyopathy Using the Clinical Genome Resource Framework

James CA, Jongbloed JDH, Hershberger RE, Morales A, Judge DP, Syrris P, Pilichou K, Domingo AM, Murray B, Cadrin-Tourigny J, Lekanne Deprez R, Celeghin R, Protonotarios A, Asatryan B, Brown E, Jordan E, McGlaughon J, Thaxton C, Kurtz CL, van Tintelen JP

Genetic testing is recommended for ARVC patients and their families and a pathogenic variant (mutation) in an ARVC-associated gene is a major criterion for ARVC diagnosis according to the 2010 Task Force Criteria. Incorrect attribution of a gene to ARVC can contribute to misdiagnosis and impair cascade screening in families. Therefore, we assembled an international panel of multidisciplinary ARVC experts and reviewed all the evidence in the scientific literature for the genetic basis of ARVC using the Clinical Genome Resource Gene Curation framework (https://clinicalgenome.org/curation-activities/gene-disease-validity/).

Of 26 genes reported to be potentially causative for ARVC in the scientific literature, only 6 (PKP2, DSP, DSG2, DSC2, JUP, and TMEM43) had strong evidence and were classified as definite ARVC genes. There was moderate evidence for 2 genes, DES and PLN. The remaining 18 genes had limited or no evidence. Importantly, in a publicly available genetics database (ClinVar), only 5 pathogenic/likely pathogenic variants (1.1%) in limited evidence genes had been reported in ARVC cases in contrast to 450 desmosome gene variants (97.4%). This is also similar to the genetic background of patients in our Johns Hopkins ARVC Registry.

Therefore, we concluded that only 8 genes (PKP2, DSP, DSG2, DSC2, JUP, TMEM43, PLN, and DES) had definitive or moderate evidence for ARVC, and these genes accounted for nearly all pathogenic/likely pathogenic variants in known ARVC patients. Therefore, only pathogenic/likely pathogenic variants in these 8 genes should yield a major criterion for ARVC diagnosis. Pathogenic/likely pathogenic variants identified in other genes should prompt further clinical evaluation as variants in many of these genes are associated with other cardiovascular conditions.

Sudden Arrhythmia Death Syndromes (SADS) Foundation Partnership

We continue to partner with the SADS Foundation to provide resources to our families impacted by ARVC. Please consider taking advantage of some of the support resources SADS has to offer, including some ICD support groups and upcoming webinars. Visit www.sads.org for more information.

SADS Connection: New breakout groups for adults with SADS conditions. Meet others with your condition (ARVC, Brugada, LQTS, CPVT). 3rd Wednesday of the month, 7:30 pm Eastern. Register at: https://www.sads.org/living-with-sads/Support-Groups/SADS-onnections#.YdhRxmDMLIU

Adult ICD Support Group: This virtual support group is a safe, open space to talk about your experience living with an ICD and meet your peers who know just what you're going through! This support group is facilitated by patients for patients. No medical questions will be answered. 1st Tuesday of the month, 7:30 pm Eastern. Sign up for our ICD Support Group: https://www.sads.org/living-with-sads/Support-Groups/ICD-Support-Group#.YdhSCGDMLIU

@younghearts Club: This is a virtual club kids/teens (ages 9-18) with a SADS condition or kids with an ICD. It will provide opportunities for social interaction and connection with others with a similar diagnosis. The @young hearts club will continue to be nurse-facilitated. Meets 2nd Tuesday of the month, 7:30 pm Eastern. To Register: https://www.sads.org/living-with-sads/Support-Groups/Youth-ICD-Support-Group#.YdhSvWDMLIU

Emotional support is crucial when living with a cardiac arrhythmia and /or the sudden loss of a loved one due to a cardiac arrhythmia. We encourage you to join and/or organize support groups that will facilitate emotional support, learning, healing, and increased knowledge. Because SADS diseases are not common and members are geographically spread out, online support groups are often the easiest way to connect with others who also have SADS diseases. Consider joining the SADS Foundation Facebook page as well.

SADS FOUNDATION
SUDDEN ARRHYTHMIA DEATH SYNDROMES

How You Can Help

Your Support of the Johns Hopkins ARVC Program Ensures Our Success

As a charitable, tax-exempt organization, Johns Hopkins Medicine relies on donations to make a difference in the lives of our patients. Supporters of Dr. Calkins, Dr. Tandri, and their team of experts in the ARVD/C Program, become part of our mission to provide exceptional personalized care and to find better ways to diagnose and treat our patients. Here are some of the many ways that you can help:

Make a Donation

Donations of all sizes, whether they're one-time or recurring, make a difference and can be made online at **www.arvd.com** or by mail (information below). There are a variety of ways to make a gift to support our efforts in the ARVD/C Program:

- Make an outright gift of cash or securities
- Become a monthly donor
- Give in honor or in memory of a loved one
- Give through IRA's, wills and trusts
- Leverage matching gifts through your workplace

Fundraising

There are many opportunities to become personally involved in raising awareness and much-needed funds on behalf of the Johns Hopkins ARVD/C Program:

- Create an online giving page and leverage social media
- Ask friends to make contributions in lieu of gifts
- Host your own event or auction
- Plan a fundraising event in your community or school
- Contribute a portion of your company's sales

The Johns Hopkins Heart and Vascular Institute Development Office is here to help!

We welcome your questions, concerns, ideas, and feedback. Please contact **Lisa Hammann,** Director of Development at hopkinsheart@jhmi.edu for more information.

Online contributions:

https://secure.jhu.edu/form/heart (*Select "ARVD Research" from the drop-down menu)*

Contributions by Mail:

Checks can be made out to "**Johns Hopkins Medicine**" and sent to the address below.
*Please indicate "**ARVD Program**" as the designation of your gift on the memo line.*
Johns Hopkins at Keswick
Office of Advancement Services
3910 Keswick Road, Suite N2100
Baltimore, MD 21211
Attn: RevMgmt-HVI

Support Resources

FACEBOOK Groups (private):
- ARVD/C Youth Society
- Hope for ARVD
- DSP Cardiomyopathy Support ***NEW***
  (https://www.facebook.com/groups/1125927951265992)
- SADS (Sudden Arrhythmia Death Syndromes) Foundation

DSP Support Group *NEW*
Organized by Christy Johnson. Email brixjohnson@hotmail.com for more information. This group holds monthly calls for those living with DSP (desmoplakin) cardiomyopathy or DSP associated ARVC.

PLN Heart Disease Foundation:
https://www.plnheartdiseasefoundation.org
Information for those of you affected by PLN or phospholamban type ARVC.

Precision Medicine Website:
Read "Feeling the Beat": Stories from the ARVC Community here:
http://www.hopkinsmedicine.org/inhealth/precision-medicine-centers/arvc

Sudden Arrhythmia Death Syndromes Foundation (SADS):
www.sads.org
An advocacy group for patients and families affected by a sudden arrhythmia death syndrome, including ARVC.

ARVC Program Information

ARVC Program Staff

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Emily Graham—Genetic Counselor Assistant
Christal Holmes-Igwebike—Clinic Coordinator
Catherine Pendelton—Research Program Coordinator
Alessio Gasperetti, MD—Research Fellow

Keep us informed of your most up-to-date contact info! For those enrolled in our Registry, we will periodically reach out for updates, but feel free to send us updated medical records at any time to Crystal via the contact info below.

Thank you!

CONTACT US!

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