Brugada syndrome versus ARVC/D

Dr. Andrés R. Pérez Riera

Increasing evidence suggests the presence of structural changes affecting the right ventricular outflow tract (RVOT) in patients with Brugada Syndrome (BrS). Patients with BrS frequently exhibit structural abnormalities localized to the RVOT and these changes may be age- and gene-dependent. The BrS may represent a heterogeneous group of disorders with a unifying ECG abnormality (**Gray B, Semsarian C, Sy RW.Brugada syndrome: a heterogeneous disease with a common ECG phenotype? J Cardiovasc Electrophysiol. 2014;25(4):450–6**.). Mutations or loss of expression of plakophilin-2; (PKP2) leads to reduced sodium current (INa), the PKP2-INa^{+}relation could be partly consequent to the fact that PKP2 facilitates proper trafficking of proteins to the intercalated disc, and additionally, PKP2 mutations can be present in patients diagnosed with BrS (BrS type 12) (**Ishikawa T, Sato A, Marcou CA, Tester DJ, Ackerman MJ, Crotti L, et al. A novel disease gene for Brugada syndrome: sarcolemmal membrane-associated protein gene mutations impair intracellular trafficking of hNav1.5. Circulation Arrhythmia and electrophysiology. 2012;5(6):1098-107**)., thus supporting the previously proposed notion that ARVC and BrS are not two completely separate entities, but "bookends" in a continuum of variable Na^{+}current deficiency and structural disease. An overlapping disease state of BrS12 and ARVC can change phenotypically during its clinical course. Therefore, careful examination and attentive follow-up are required for patients with BrS or ARVC.

Gray et al. demonstrated a high incidence of RVOT morphologic abnormalities in BrS as well as important relations between such abnormalities and clinical, genetic and electrical manifestations of disease. It confirmed that BrS is indeed a heterogeneous disorder covering the spectrum of channelopathy and “cardiomyopathy” with the abnormalities anatomically localized to the RVOT in many cases such as Alejandro case. Additionally, Increased RVOT volume and abnormal RVOT function related healthy cohort. Global RV dilatation or dysfunction however Absence of global RV dilatation or dysfunction. Spontaneous type 1 ECG pattern or late potentials is associated with lower RVEF (**Gray B, Gnanappa GK, Bagnall RD, et al. Relations between right ventricular morphology and clinical, electrical and genetic parameters in Brugada Syndrome. PLoS One. 2018;13(4):e0195594**.). (**Doesch C, Michaely H, Haghi D, Schoenberg SO, Borggrefe M, Papavassiliu T. How to measure the right ventricular outflow tract with cardiovascular magnetic resonance imaging: a head-to-head comparison of methods. Hellenic J Cardiol. 2014;55(2):107–18**.). BrS and ARVC/D clinical features can coexist in a single patient, and EPS might be useful for determining the phenotype of overlapping disease (e.g., BrS-like or ARVC/D-like) (**Kataoka S, Serizawa N, Kitamura K, et al. An overlap of Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy/dysplasia. J Arrhythm. 2016;32(1):70-3.**). An overlapping disease state of BrS and AC can change phenotypically during its clinical course. Therefore, careful examination and attentive follow-up are required for patients with BrS orAC. There are few studies that have systematically explored the association between structural abnormalities and the electrical and genetic profile of patients with BrS (**van Hoorn F, Campian ME, Spijkerboer A, Blom MT, Planken RN, van Rossum AC, et al. SCN5A mutations in Brugada syndrome are associated with increased cardiac dimensions and reduced contractility. Bastiaenen R, Cox AT, Castelletti S, Wijeyeratne YD, Colbeck N, Pakroo N, et al. Late gadolinium enhancement in Brugada syndrome: A marker for subtle underlying cardiomyopathy? Heart Rhythm. 2017;14(4):583–9.**)

BrS 12 has the following characteristics: **Cytogenetic Location:** 3p21.2-2-p14.3; **OMIM:** 602701; **Gene:** SLMAP Sarcolemma-Associated Protein. Immunohistochemical localization of SLAP in cardiac muscle revealed that SLAP associated with the sarcolemma and also displayed a reticular pattern of staining that resembled the transverse tubules and the sarcoplasmic reticulum. The SLAPs define a family of tail-anchored membrane proteins that exhibit tissue specific expression and are uniquely situated to serve a variety of roles through their coiled-coil motifs. (**Wigle JT, Demchyshyn L, Pratt MA, Staines WA, Salih M, Tuana BS. Molecular cloning, expression, and chromosomal assignment of sarcolemmal-associated proteins. A family of acidic amphipathic alpha-helical proteins associated with the membrane J Biol Chem. 1997;272(51):32384-94**).; **Ion channel and effect:** Ina^{+}loss-of-function; **Protein:** Sarcolemma membrane-associated protein, a component of T-tubes and the sarcoplasmic reticulum – influences trafficking of Nav1.5;**% Probands:** Rare.; **HGNC ID:**16643.

Cerrone et al mentioned that the patients with BrS diagnostic could represent a rather heterogenic group comprising of individuals with mutations of desmosomal genes in as much as 3% of cases (**Cerrone M, Lin X, Zhang M, Agullo-Pascual E, Pfenniger A, Chkourko Gusky H, Novelli V, Kim C, Tirasawadichai T, Judge DP, Rothenberg E, Chen HS, Napolitano C, Priori SG, Delmar M. Missense mutations in plakophilin-2 cause sodium current deficit and associate with a Brugada syndrome phenotype. Circulation. 2014; 129:1092–1103. doi: 10.1161/ CIRCULATION AHA.113.003077**)1 They suggests that mutations of PKP2 gene present in patients diagnosed with BrS and consecutive loss of desmosomal integrity could lead to reduced Na^{+}current and hereby arrhythmogenic state through delayed depolarization **Forkmann M, Tomala J, Huo Y, Mayer J, Christoph M, Wunderlich C, Salmas J, Gaspar T, Piorkowski C Epicardial Ventricular Tachycardia Ablation in a Patient With Brugada ECG Pattern and Mutation of PKP2 and DSP Genes. Circ Arrhythm Electrophysiol. 2015 Apr;8(2):505-7. doi: 10.1161/CIRCEP.114.002342.**

The relation between PKP2 and I_{na} described in the paragraphs above led Cerrone et al. to speculate that, if a PKP2 mutation primarily impacts I_{na} function (rather than desmosomal structure), its presence would manifest in a manner clinically similar to BrS. Interestingly, after the initial description of BrS, Corrado et al suggested that this condition could share several clinical features with ARVC, implying that these were not completely distinct clinical entities (**Corrado D, Basso C, Buja G, Nava A, Rossi L, Thiene G. Right bundle branch block, right precordial st segment elevation, and sudden death in young people. Circulation. 2001;103:710–717**.)(**Corrado D, Buja G, Basso C, Nava A, Thiene G. What is the Brugada syndrome? Cardiology in review.1999;7:191–195**). Cerrone et al screened by direct sequencing a cohort of 200 patients with clinical diagnosis of BrS and no mutations on the most prevalent genes. They discovered five single amino acid substitutions in five unrelated patients (**Cerrone M, Lin X, Zhang M, et al. Missense Mutations in Plakophilin-2 Cause Sodium Current Deficit and Associate with a Brugada Syndrome Phenotype. Circulation. 2014 Mar 11;129(10):1092-103. doi: 10.1161/CIRCULATION AHA.113.003077**). In order to assess if these missense variants in PKP2 could affect the cardiac I_{Na}, they used an HL-1 cell line, stably silenced for the endogenous PKP2. In the absence of PKP2, these cells showed a decrease in endogenous INa. Cells transiently transfected with each one of the PKP2 mutants associated with the BrS phenotype showed significantly decreased I_{Na}, when compared with cells transfected with wild type PKP2. Similar results were obtained when these authors used a line of human iPSC-derived cardiomyocytes from a patient lacking PKP2 at the cell membrane (**Awad MM, Dalal D, Tichnell C, et al. Recessive arrhythmogenic right ventricular dysplasia due to novel cryptic splice mutation in PKP2. Human mutation. 2006;27:1157**) (Kim C, Wong J, Wen J, et al. Studying arrhythmogenic right ventricular dysplasia with patient-specific iPSCs. Nature. 2013;494:105–110.). In these cells, I_{na} increased upon transfection with wild type PKP2. Transfection with one of the PKP2 mutants

associated with BrS was not able to restore normal I_{Na}. These data represent the first evidence that missense mutations in PKP2 can cause a decrease in cardiac I_{Na}. When combined with other factors (such as decreased electrical coupling and/or fibrosis), a reduction in I_{na} could facilitate the development of arrhythmias, even in the absence of a structural cardiomyopathy. Cerrone et al. propose that PKP2 mutations provide at least part of the molecular substrate of BrS. The inclusion of PKP2 as part of routine BrS genetic testing remains premature; yet, the possibility that some patients showing signs of disease may harbor PKP2 variants should be considered when the genotype is negative for other genes associated with BrS.

Campuzano et al have performed a genetic revision of all PKP2 genetic variants currently associated with BrS. In all variants the authors identified a lack of solid evidences in order to establish a definite genotype-phenotype association. Hence, despite they believe that PKP2 analysis should be considered as a part of molecular genetic testing in BrS patients, comprehensive clinical and molecular studies should be performed before establishing pathogenic association. Therefore,PK P2 variants in BrS cases should be interpreted carefully and additional studies including family segregation should be performed before translation into clinical practice. (**Campuzano O, Fernández-Falgueras A, Iglesias A, Brugada R. Brugada Syndrome and PKP2: Evidences and uncertainties. Int J Cardiol. 2016 Jul 1;214:403-5. doi: 10.1016/j.ijcard.2016.03.194).**

Summary of Differential Diagnosis Between ARVC/D and Brugada Syndrome

I) Age at presentation

➢**ARVC/D:** The mean age at diagnosis is 31 years (±13; range: 4-64 years).

➢**BrS:** presenting typically in the fourth or fifth decade of life.(35–40 years of age) over the last several years, there has been growing evidence in the literature of onset of the disease during childhood.

II) Sex, male/female ratio. Women with BrS typically show more benign clinical features with a lower percentage of type 1 BrP ECG and a lower prevalence of symptoms (**Benito B, Sarkozy A, Mont L, et al. Gender differences in clinical manifestations of Brugada syndrome. J Am Coll Cardiol 2008;52:1567–73**.). Males have a 5.5-fold increased risk of sudden cardiac death, and mean age for development of ventricular fibrillation is 41± 15 years (**Mizusawa Y, Wilde A. Brugada syndrome. Circ Arrhythm Electrophysiol 2012; 5: 606-616**.).

➢**ARVC/D:**

➢**BrS:**. The male/female ratio is 8/1 -10/1 (**Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 2013;10:1932–1963**.). Male predominance is significant in Asian countries (90%– 96%), but only 60%–70% of the patients were males in European studies (**Milman A, Gourraud JB, Andorin A, et al. Gender differences in patients with Brugada syndrome and arrhythmic events: data from a survey on arrhythmic events in 678 patients. Heart Rhythm 2018;XX:XX–XXX**). The clinical characteristics and risk markers of BrS depend on the characteristics of male patients. Females have lower incidences of symptoms and spontaneous type 1 ECG pattern than males (**Benito B, Sarkozy A, Mont L, Henkens S, Berruezo A, Tamborero D, Arzamendi D, Berne P, Brugada R, Brugada P, Brugada J. Gender differences in clinical manifestations of Brugada syndrome. J Am Coll Cardiol 2008; 52:1567–1573**). Ventricular fibrillation (VF) induced by programmed electrical stimulation (PES)

was less frequent in females than in males. Females had better prognosis (cardiac events ratio 0.56%/y) than did males (2.4%/y). They failed to identify a risk factor for VF in females because of the low event ratio, but found significant prolongation of PR and HV intervals in females in whom cardiac events occurred. Females had less frequent spontaneous type 1 ECG, less frequent PES-induced VF, and a lower incidence of arrhythmic events (0.7%) than males (**Sieira J, Conte G, Ciconte G, et al. Clinical characterisation and long-term prognosis of women with Brugada syndrome. Heart 2016;102:452–458**.). The multicenter international Survey on Arrhythmic Events in BrS included 59 females with BrS. The survey showed that the percentage of females was higher in Caucasians than in Asians. A history of VF, spontaneous type 1 ECG, and PES-induced VF were less frequent in females than in males. After excluding pediatric patients, the age at the onset of VF was older in females (49.5 years) than in males (43 years). An SCN5A mutation was found more frequently in females than in males. These gender differences became unclear in pediatric patients (age, 16 years) and elderly patients (age. 60 years) **Milman A, Gourraud JB, Andorin A, et al. Gender differences in patients with Brugada syndrome and arrhythmic events: data from a survey on arrhythmic events in 678 patients. Heart Rhythm 2018;XX:XX–XXX**.. Berthome et al included 494 female patients. The study showed that the frequencies of symptoms, spontaneous type 1 ECG, and PES-induced VF were lower in females than in males. Females had a long-corrected QT interval and narrow QRS interval. Age at the time of cardiac events was older in females (48.6 years) than in males (43 years). The incidence of events during follow-up was not high in females (0.4%/y), especially in asymptomatic females (0.2%/y), and gender was significantly associated with cardiac events. Multivariable analysis showed that index patients, previous SCD, syncope, fQRS, and broad QRS interval (l≥.120 ms) were independent predictors of cardiac events (**Berthome P, Tixier R, Briand I, et al. Clinical presentation and follow-up of women affected by Brugada syndrome. Heart Rhythm 2018;15:XX–XXX.**.. Common observations in those studies were that a history of VF, spontaneous type 1 ECG, and PES-induced VF were not frequent in females and that females had good prognosis. A history of aborted cardiac arrest is a powerful predictor of prognosis. ECG risk markers including prolongation of PR and QRS intervals, sinus node dysfunction, and fQRS were not coincident risk markers in those studies, but these markers were associated with conduction disturbance. The occurrence of any conduction abnormality might indicate that female patients are at a high risk of VF. According to the repolarization theory of BrS, the mechanism is epicardial action potential change caused by increased outward currents or decreased inward currents, which are the opposite directions males and females have different ion channel distributions, and moreover, sex hormones modulate ion currents (**Odening KE, Koren G. How do sex hormones modify arrhythmogenesis in long QT syndrome? Sex hormone effects on arrhythmogenic substrate and triggered activity. Heart Rhythm 2014;11:2107–2115**.). Females have larger calcium currents (ICa-L) and smaller potassium currents, including transient outward current (Ito), delayed rectifier potassium current (IK: IKr and IKs) and inward rectifier potassium current (IK1) than do males. Estrogen prolongs the QT interval in females with LQTS by decreasing Ito, IK, and IK1 and increasing ICa-L. Testosterone increases outward currents (Ito, IK1, and IKs), decreases ICa-L, and shortens the QT interval in male patients after puberty. Increase in Ito and decrease in ICa-L have a pivotal role in action potential changes, causing repolarization heterogeneity and phase 2 reentry in BrS (**Di Diego JM, Cordeiro JM, Goodrow RJ, Fish JM, Zygmunt AC, Perez GJ, Scornik FS, Antzelevitch C. Ionic and cellular basis for the predominance of the Brugada syndrome phenotype in males. Circulation 2002;106:2004–2011**). Estrogen relieves but testosterone enhances arrhythmogenic action potential change in BrS. Patients with BrS had a high level of

testosterone (**Shimizu W, Matsuo K, Kokubo Y, et al. Sex hormone and gender difference— role of testosterone on male predominance in Brugada syndrome. J Cardiovasc Electrophysiol 2007;18:415–421**) Additionally, reduction of testosterone by castration masked Brugada ECG (**Matsuo K, Akahoshi M, Seto S, Yano K. Disappearance of the Brugada-type electrocardiogram after surgical castration: a role for testosterone and an explanation for the male preponderance. Pacing Clin Electrophysiol 2003; 26:1551–1553**.) Low concentrations of sex hormones in children and elderly patients would be a reason why there are no gender differences in such periods. Protective effects of estrogen on arrhythmogenicity in BrS can explain the male predominance during adulthood. The mechanism of BrS has been debated, but the explanation of gender differences by hormonal changes indicates that repolarization changes are also important for arrhythmogenicity in BrS.

III) Race

➢**ARVC/D:** Caucasian predominance

➢**BrS:** Asian predominance

IV) Geographic distribution worldwide

➢**ARVC/D:** Endemic in Veneto area, and Greek Naxos island

➢**BrS:** Endemic in Thailand, Philippines, Japan Sudden unexplained nocturnal death syndrome (SUNDS) has been reported worldwide. SUNDS is endemic in Southeast Asia and is colloquially known as Bangungut in the Philippines, Lai Tai in Thailand, and Pokkuri in Japan. Although SUNDS in Thailand and Japan have been determined to be phenotypically, genetically and functionally identical to the Brugada syndrome, the relationship between Bangungut/SUNDS in the Philippines and the Brugada syndrome has not been clarified. Bangungut/SUNDS and the Brugada syndrome appear closely related. Pathophysiological mechanisms of the BrS may explain the enigma of Bangungut/SUND. Whether Bangungut/SUNDS is phenotypically, genetically and functionally an allele of the BrS remains inconclusive due to lack of research data..

V) Prevalence

➢**ARVC/D:** The estimated prevalence of ARVC/D in the general population is approximately 1:5000, affecting men more frequently than women with a ratio of 3:1, (**Corrado D, Thiene G. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: clinical impact of molecular genetic studies Circulation. 2006;113(13):1634–7**.) ARVC/D accounts for 11%–22% of cases of SCD in the young athlete patient population, accounting for approximately 22% of cases in athletes in northern Italy (**Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med.1988;318(3):129–33**) and about 17% of SCD in young people in the United States (**Dalal D, Nasir K, Bomma C, et al. Arrhythmogenic right ventricular dysplasia: a United States experience. Circulation. 2005;112(25):3823–32**.).

➢**BrS:** The BrS prevalence varies among regions and ethnicities, affecting mostly males. In the pediatric population is low (0.0098%) compared with the adult population (0.14–0.7%). Nevertheless, in recent years, there has been growing evidence in the literature of earlier onset of the disease (**Hermida JS, Lemoine JL, Aoun FB, Jarry G, Ray JL, Quiet JC. Prevalence of the Brugada syndrome in an apparently healthy population. Am J Cardiol 2000; 86: 91–94.**). The estimated worldwide prevalence of Brugada pattern ECG changes is 0.23%, and they are most commonly seen in people of Asian descent, followed by people in Europe and the United States.

VI) Incidence

➢**ARVC/D:** Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare (1:2000–1:5000) inherited cardiac condition (**Pilichou K, Thiene G, Bauce B, Rigato I, Lazzarini E, Migliore F, Perazzolo Marra M, Rizzo S, Zorzi A, Daliento L, Corrado D, Basso C (2016) Arrhythmogenic cardiomyopathy. Orphanet J Rare Dis 11:33**

➢**BrS:** The incidence of BrS is about 9 times more frequent in males than females (**Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013;10:1932–63**).

VII) Inheritance pattern

➢**ARVC/D:**

➢**BrS:** autosomal dominant inheritance with incomplete penetrance or sporadic (**Mizusawa Y, Wilde A. Brugada syndrome. Circ Arrhythm Electrophysiol 2012; 5: 606-616**.).

VIII) Genetic variants

➢**ARVC/D:**

Currently 60% of patients meeting Task Force Criteria (TFC) have an identifiable mutation in one of the desmosomal genes. Pathogenic mutations in genes encoding the cardiac desmosome can be found in approximately 60% of index patients, leading to our current perception of ARVC as a desmosomal disease. Bhonsale A, Groeneweg JA, James CA, et al. Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy−associated mutation carriers. Eur Heart J. 2015;36:847–855

In a cohort with o1 37 individuals Murray et a. describe that a small but significant percentage (4.3%) of individuals with ARVC may have putative likely pathogenic/pathogenic variants reported in the sarcomere genes. meeting 2010 TFC for a diagnosis of ARVC, negative for pathogenic desmosomal variants, TMEM43, SCN5A, and PLN were screened for variants in the sarcomere genes ACTC1, MYBPC3, MYH7, MYL2, MYL3, TNNC1, TNNI3, TNNT2, and TPM1) through either clinical or research genetic testing. A similar yield has recently also been reported by Medeiros et al. (**Medeiros−Domingo A, Saguner A, Magyar I, et al. Arrhythmogenic right ventricular cardiomyopathy: Implications of next−generation sequencing in appropriate diagnosis. Europace. 2016;9:1063–1069**.) **Murray B, Hoorntje ET, Te Riele ASJM, Tichnell C, van der Heijden JF, Tandri H, van den Berg MP, Jongbloed JDH, Wilde AAM, Hauer RNW, Calkins H, Judge DP, James CA, van Tintelen JP, Dooijes D. Identification of sarcomeric variants in probands with a clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC). J Cardiovasc Electrophysiol. 2018 Jul;29(7):1004-1009. doi: 10.1111/jce.13621. Epub 2018 May 21**. The ARVC/D Genetic Variants Database is a freely available collection of variants associated with ARVC and can be accessed via the link http://www.arvcdatabase.info/

Reduced $Na_V1.5$ at the ID in samples from patients with desmosomal mutations (**Noorman M, Hakim S, Kessler E, Groeneweg J, Gpj Cox M, Asimaki A, van Rijen HV, van Stuijvenberg L, Chkourko H, van der Heyden MA, Vos MA, de Jonge N, van der Smagt JJ, Dooijes D, Vink A, de Weger RA, Varro A, de Bakker JM, Saffitz JE, Hund TJ, Mohler PJ, Delmar M, Hauer RN, van Veen TA. Remodeling of the cardiac sodium channel, connexin 43 and plakoglobin at the intercalated disk in patients with arrhythmogenic cardiomyopathy. Heart rhythm. 2012;10:412–419**).Experimental models have shown correlation between loss of PKP2 expression,

and reduced I_{na} **Sato PY, Coombs W, Lin X, Nekrasova O, Green KJ, Isom LL, Taffet SM, Delmar M. Interactions between ankyrin-g, plakophilin-2, and connexin 43 at the cardiac intercalated disc. Circ res. 2011;109:193–201.)(Sato PY, Musa H, Coombs W, Guerrero-Serna G, Patino GA, Taffet SM, Isom LL, Delmar M. Loss of plakophilin-2 expression leads to decreased sodium current and slower conduction velocity in cultured cardiac myocytes. Circ res. 2009; 105:523–526**.) (Cerrone M, Noorman M, Lin X, Chkourko H, Liang FX, van der Nagel R, Hund T, Birchmeier W, Mohler P, van Veen TA, van Rijen HV, Delmar M. Sodium current deficit and arrhythmogenesis in a murine model of plakophilin-2 haplo insufficiency. Cardiovasc res.2012;95:460–468.) the co-existence of clinical sodium channelopathy (BrS) and genetic variation in PKP2. not only loss of PKP2, but also single amino acid mutations, can interfere with I_{Na}In some cases, mutations in PKP2 can be part of the BrS molecular substrate.