ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Recent Status in Brugada Syndrome

Brugada Sendromunda Son Durum

REVIEW
DERLEME

ABSTRACT

Brugada syndrome was first described in 1992 as right precordial ST-segment elevation in patients with structurally normal hearts and sudden cardiac death. Brugada Syndrome is one of the most common reasons for sudden cardiac death (4-12%) and is a hereditary disease with an autosomal dominant pattern of transmission with nearly 300 pathogenic variants in 19 responsible genes published. The present review focuses on the diagnosis, genetics, risk stratification, and management of patients with Brugada Syndrome.

Keywords: Arrhythmia, Brugada syndrome, sudden cardiac death

ÖZET

Brugada sendromu (BrS), ilk olarak 1992 yılında, yapısal kalp hastalığı olmayan ve ani kardiyak ölüm gelişen hastalarda sağ prekordiyal derivasyonlarda ST segment elevasyonu olarak tanımlanmıştır. BrS, ani kardiyak ölümün en sık nedenlerinden olan (%4-12), otosomal dominant geçiş paterni gösteren herediter bir hastalıktır (bilinen 19 gende 300 civarı patojenik varyant). Bu derleme, BrS tanısı, genetik değerlendirmesi, risk strafikasyonu ve tedavileri konularını ayrıntılamaktadır.

Anahtar Kelimeler: Aritmi, Brugada sendromu, ani kardiyak ölüm

Brugada syndrome (BrS) was first described in 1992 in 8 patients with right precordial ST-segment elevation, structurally normal hearts, and sudden cardiac death (SCD).[1] BrS has integrations with syndromes like idiopathic ventricular fibrillation (VF) and sudden unexplained death syndrome. BrS is one of the most common causes of SCD (4-12%).[2,3]

The overlapping syndromes with BrS and long or short QT interval have a common pathophysiological background: alteration of ionic currents resulting in depolarization and repolarization abnormalities and ventricular arrhythmias.

Electrocardiographic features and diagnosis

The echocardiographic (ECG) hallmark of BrS is the transient or persistent appearance of typical ST-segment elevation in the right precordial leads. The second Brugada Syndrome Consensus Report[4] stated the following diagnostic criteria. Three different ECG patterns (Figure 1) have been recognized: type I is the only pattern that is diagnostic for BrS. It consists of a coved-type ST-segment elevation greater than 2 mm, followed by a descending negative T wave in at least 1 right precordial lead (V_1-V_3). Types II and III are saddleback-shaped patterns, with a high initial augmentation followed by an ST-segment elevation greater than 2 mm for type II and less than 2 mm for type III. Both patterns are not diagnostic for BrS.

An important problem in the diagnosis of BrS is the great variability of the ECG pattern. Repetitive ECG recordings are mandatory in patients with or suspected of having the syndrome. Brugada ECG pattern can be intermittent and can be provoked with physical activity, fever, cocaine, excessive alcohol use, electrolyte imbalances.[5] Several medications like calcium antagonists, phenothiazines, selective serotonin reuptake inhibitors can also provoke BrS ECG pattern.[5-7] Regression of typical ECG features has been reported in castrated men,[8] and levels of testosterone seem to be higher in male Brugada patients compared with those in control males.[9] Consequently, in agreement with the hormonal hypothesis, the phenotypic presentation in children do not seem to differ between boys and girls.[10]

Fatih Bayrak M.D.[1]
Pedro Brugada M.D.[2]

[1]*Department of Cardiology, Acıbadem Mehmet Ali Aydınlar University School of Medicine, İstanbul, Turkey*
[2]*Heart Rhythm Management Centre, UZ Brussel-VUB, Brussels, Belgium*

Corresponding author:
Fatih Bayrak
✉ dfatihbayrak@yahoo.com

Received: March 3, 2021
Accepted: April 21, 2021

Cite this article as: Bayrak F, Brugada P. Recent status in brugada syndrome. Turk Kardiyol Dern Ars 2022;50(2):137-144.

DOI:10.5543/tkda.2022.21020

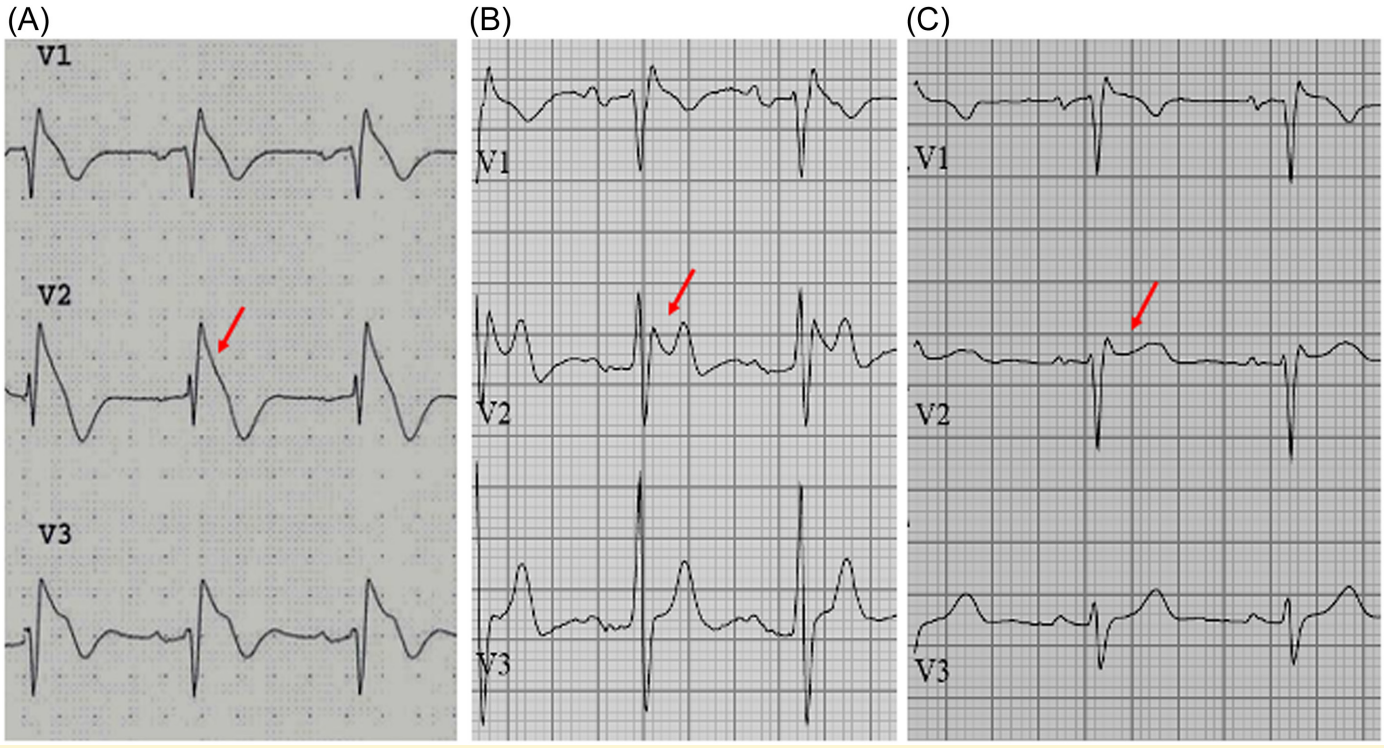

Figure 1. Brugada electrocardiogram (ECG) patterns. (A) A diagnostic coved-type (type I) Brugada ECG pattern documented in a 9-year-old girl who presented with syncope and positive family history of Brugada syndrome (BrS). (B) Baseline ECG of a 58-year-old asymptomatic man with a positive family history of BrS. Example of a type II saddleback Brugada ECG pattern. Genetic analysis revealed a mutation in the *SCN5A* gene. (C) Example of a baseline type III saddleback Brugada ECG pattern documented in a 61-year-old asymptomatic man who was diagnosed based on a positive result on class IC antiarrhythmic drug testing.

Previously, BrS diagnosis was based on the presence of type 1 ECG pattern (spontaneous or drug induced) and clinical findings suggestive of ventricular arrhythmias (syncope, inducible or documented VF, agonal breathing, and family history of SCD). But, it is also well known that many patients with a type 1 ECG are asymptomatic. In 2013, an expert consensus statement proposed a definition only based on ECG appearance of typical type 1 pattern which does not require any further evidence of malignant arrhythmias for BrS diagnosis.[11,12]

Intravenous administration of ajmaline, flecainide, pilsicainide, or procainamide can unmask the coved-type BrS ECG pattern and is used commonly for provocation of typical ECG pattern and for the diagnosis of BrS. Ajmaline, in a dose of 1 mg/kg, appears to be the best drug. The full stomach test was proposed as an alternative tool in diagnosing BrS.[13] ST segment changes appear to be provoked by enhanced vagal tone after a large meal. It is important to exclude other causes of ST-segment elevation before making the diagnosis of BrS (Table 1).

ABBREVIATIONS

AC	Arrhythmogenic cardiomyopathy
AF	Atrial fibrillation
BrS	Brugada Syndrome
CI	Confidence interval
ECG	Echocardiographic
EPS	Electrophysiological study
ERS	Early Repolarization Syndrome
HR	Hazard ratio
ICD	Implantable cardioverter defibrillators
LQTS	Long QT syndrome
PCCD	Progressive cardiac conduction disease
RVOT	Right ventricular outflow tract
SCD	Sudden cardiac death
SSS	Sick sinus syndrome
VF	Ventricular fibrillation

Pathophysiologic mechanisms for ventricular arrhythmias in Brugada syndrome

Three possible mechanisms have been proposed for ventricular arrhythmias in BrS:[14] depolarization abnormality leading to slow conduction and reentry in the right ventricular outflow tract (RVOT); repolarization abnormality leading to shortened action potential in the epicardium of the right ventricle; and development abnormality originating from abnormal neural crest cells that participate in the development of the RVOT.

Genetics

BrS is a hereditary disease with an autosomal dominant pattern of transmission with more than 300 pathogenic variants in 19 responsible genes (Table 2). The first gene documented to be associated with BrS was *SCN5A*, encoding the α-subunit of the cardiac sodium channel.[15] The *SCN5A* gene is related to the sodium current responsible for phase 0 of the cardiac action potential. Mutations in *SCN5A* result in loss of function of the sodium channel. A mutation in the *SCN5A* gene is found in 25-30% of individuals with BrS.[16] Potassium and calcium channel mutations are also related to BrS.[17-22] Despite all the advances in genetics, only 30-35% of clinically diagnosed BrS patients have genetically diagnosed mutation.[16]

Table 1. Acquired Brugada Syndrome: Differential Diagnosis of ST-Segment Elevation in Electrocardiogram Leads V_1 and V_2

Drugs	
Antiarrhythmic drugs	• Class 1C sodium channel blockers (e.g., flecainide, pilsicainide, propafenone) • Class 1A sodium channel blockers (e.g., procainamide, disopyramide, cibenzoline) • Verapamil (L-type calcium channel blocker) • β-Blockers (inhibit $I_{Ca,L}$)
Antianginal drugs	• Nitrates • Calcium channel blockers (e.g., nifedipine, diltiazem)
Psychotropic agents	• Tricyclic antidepressants (e.g., amitriptyline, desipramine, clomipramine, nortriptyline) • Tetracyclic antidepressants (e.g., maprotiline) • Phenothiazines (e.g., perphenazine, cyamemazine) • Selective serotonin uptake inhibitors (e.g., fluoxetine) • Cocaine intoxication
Antiallergic agents	• Histamine H1 antihistaminics. First generation (dimenhydrinate)
Acute ischemia in RVOT	
Electrolyte disturbances	• Hyperkalemia • Hypercalcemia
Hyperthermia and hypothermia	
Elevated insulin level	
Mechanical compression of RVOT	

RVOT, right ventricular outflow tract.

Table 2. Brugada Syndrome Mutation Types

Inheritance	**Locus**	**Gene**	**Protein**
(Sodium) Autosomal dominant	3p21-p24	*SCN5A*	$Na_V1.5$
	3p22.3	*GPD1-L*	Glycerol-3-P-DH-1
	19q13.1	*SCN1B*	$Na_V\beta1$
	11q24.1	*SCN3B*	$Na_V\beta3$
	11q23.3	*SCN2B*	$Na_V\beta2$
	3p22.2	*SCN10A*	$Na_V1.8$
	17p13.1	*RANGRF*	RAN-G-release factor (MOG1)
	3p14.3	*SLMAP*	Sarcolemma-associated protein
	12p11.21	*PKP2*	Plakofilin-2
(Potassium) Autosomal dominant chromosome X	12p12.1	*ABCC9*	Adenosine triphosphate-sensitive
	11q13-q14	*KCNE3*	MiRP2
	12p12.1	*KCNJ8*	Kv6.1 Kir6.1
	15q24.1	*HCN4*	Hyperpolarization cyclic nucleotide-gated 4
	1p13.2	*KCND3*	Kv4.3 Kir4.3
	Xq22.3	*KCNE5*	Potassium voltage-gated channel subfamily E member 1
(Calcium) Autosomal dominant	2p13.3	*CACNA1C*	Cav1.2
	10p12.33	*CACNB2B*	Voltage-dependent β-2
	7q21-q22	*CACNA2D1*	Voltage-dependent α2/δ1
	19q13.33	*TRPM4*	Transient receptor potential M4

In addition, the incomplete penetrance of the disease, as well as the variable expressivity, has brought into question the role of additional genetic factors in the final phenotype. Several single nucleotide polymorphisms were identified to define this variability.[23-27]

Familial screening

First-degree affected relatives should be screened by clinical examination, interrogation, and performance of a 12-lead ECG (basal and upper intercostal space recording). Genetic tests should be performed in index cases, and when there is a positive

result, mutations should be identified in children to follow the recommendations on fever control and avoidance of dangerous drugs. Mutation carriers should be annually screened with an ECG when asymptomatic.

Overlapping and discordant intrafamily syndromes

Some families with BrS show diverse and discordant phenotypes among their members. These overlapping syndromes represent a challenge to physicians for diagnosis and risk stratification.

Early repolarization syndrome (ERS) is a common ECG variant characterized by J-point elevation, upper concave ST-segment elevation, and prominent T waves in at least 2 contiguous leads.[28] ERS and BrS have common genetic and ECG pathologies (appearance of J waves), but the degree to which ERS and BrS may overlap is still undetermined.[29,30] Reports have been published on patients with BrS and ERS (J-wave syndromes).[31]

Progressive cardiac conduction disease (PCCD, Lev-Lenègre syndrome) is characterized by disruption of the cardiac conduction system with syncope and even SCD. The presence of PCCD in BrS families is not uncommon; asystole and advanced atrioventricular (AV) block are the causes of SCD in this patient population. First mutations associated with PCCD were described in the gene *SCN5A*[32,33] and in its B1 subunit.

Sick sinus syndrome (SSS) is characterized by sinus bradycardia, sinus arrest, and atrial arrhythmias. Patients may exhibit varied symptoms, including syncope, and may be diagnosed after an aborted SCD episode. The course of SSS can be unpredictable and is related to the severity of the underlying heart disease.[34] An association between *SCN5A* mutations and congenital SSS was reported.[35] A novel *SCN5A* mutation was identified in patients presenting with both SSS and BrS.[36] Presence of SSS is a very negative prognostic factor for patients with BrS, particularly in children.

Atrial fibrillation (AF) is the most common atrial arrhythmia found in BrS. About 9-53% of patients with BrS develop AF.[1,37-45] AF can be the first manifestation of BrS with high incidence of embolic events. BrS patients with AF demonstrated 13.9% cardioembolic stroke after a mean follow-up period of 11 years, despite low CHA_2DS_2VASc scores.[46]

BrS should be excluded by drug challenge in young individuals with atrial flutter or AF and a normal heart and normal ECG because administration of antiarrhythmic drugs such as class I group can lead to VF and sudden death in this patient population. The presence of AF in BrS is associated with a malignant course, with a higher incidence of ventricular arrhythmias and inappropriate shocks in patients with implantable cardioverter defibrillators (ICD).[40]

Antiarrhythmic drugs effective in preventing malignant arrhythmias in BrS such as quinidine might also be used for AF in BrS.[44] Medical management of AF is challenging in BrS. Invasive treatment with pulmonary vein isolation is an attractive treatment option. Recent studies demonstrate favorable outcomes with reduced recurrence of atrial arrhythmias and elimination of inappropriate ICD interventions.[48,49]

Long QT syndrome (LQTS) is a genetic disease characterized by prolonged QT interval, ventricular tachyarrhythmias, and SCD. Type 3 (LQT3) accounts for 7-10% of all LQTS subjects.[50] Interestingly, some family members may display the ECG pattern of LQT3, while others display the pattern of BrS.[51,52] This discordant intrafamily phenotype with LQT3 and BrS phenotypes in the same family was also reported in other *SCN5A* mutations.[53]

BrS and epilepsy may overlap. *SCN5A* mutations may confer susceptibility for recurrent seizure activity, supporting the concept of a genetically determined cardiocerebral channelopathy.[54,55]

Risk Stratification

Identification and treatment of individuals at high risk for SCD is the main objective in patients with BrS. Several clinical variables have been demonstrated to predict a worse outcome in BrS. Previous cardiac arrest, syncope, spontaneous type 1 ECG at baseline, and male gender have consistently shown to be related to cardiac events in follow-up.[56-58] A previous cardiac arrest is a risk marker for future events with 17-62% recurrence of arrhythmic event within 48 and 84 months. Syncope identifies patients with a high risk for events (6-19% in 24-39 months). Spontaneous type 1 ECG is a predictor of ventricular arrhythmias in the largest BrS patient population published to date[58] (hazard ratio, 1.8; 95% CI, 1.03-3.33; $P = .04$). Male sex has consistently shown a trend to more arrhythmic events in several studies and has even been defined as an independent predictor for a worse outcome in a meta-analysis.[59]

Spontaneous AF, which can appear in 10-53% of cases, has been shown to have prognostic significance, and spontaneous AF was associated with higher incidence of syncopal episodes (60.0% vs. 22.2%, $P < .03$) and documented VF (40.0% vs. 14.3%, $P < .05$).[60]

The issue of risk stratification of asymptomatic or only drug-induced (absence of spontaneous type I ECG) BrS patients remains controversial.[61] Recently, Sieira et al[62] showed that arrhythmic events in asymptomatic BrS patients are not insignificant (0.5% annual incidence rate), and inducibility of ventricular arrhythmias, spontaneous type I ECG, and presence of sinoatrial node dysfunction are major risk factors. A recently published meta-analysis also showed that asymptomatic subjects with either a spontaneous diagnostic ECG pattern or inducible ventricular arrhythmias on programmed ventricular stimulation are at increased risk.[63]

The risk of lethal or near-lethal arrhythmic episodes among previously asymptomatic patients with BrS varies among different series: 8% at 33 ± 39 months of follow-up reported by Brugada et al[64]; 6% at 34 ± 44 months by Priori et al.[65] 1% after 40 ± 50 months and 30 ± 21 months of follow-up by Eckardt et al[66] and Giustetto et al,[67] respectively; and finally, Probst et al[58] reported a 1.5% rate at 31 months of follow-up.

Although large registries agree that inducible ventricular arrhythmias at electrophysiological study (EPS) are most frequent among BrS patients with previous sudden death or syncope,[64] there is no consensus on the value of the EPS in predicting outcome. Brugada et al[64] found that inducibility during

EPS is an independent predictor for cardiac events, and Giustetto et al[67] stressed the negative predictive value (none of the patients with a negative EPS developed arrhythmic events vs. 15% of patients with a positive EPS result during 30 ± 21 months of follow-up); however, the other registries failed to demonstrate this association.[59] The largest series of BrS patients published so far found that inducibility of sustained ventricular arrhythmias was significantly associated with a shorter time to first arrhythmic event in univariate analysis, however, not in multivariable analysis.[58] A single-center study shows the results of a cohort of 96 BrS patients with various clinical presentations and who had inducible VF using an aggressive programmed ventricular stimulation protocol. The authors reported an excellent protective effect of class 1 anti arrhythmic drugs (AAD) (mainly quinidine) during EP testing and an excellent clinical outcome in drug-treated patients.[68] In addition, Sieira and colleagues published a series of 403 BrS cases. The authors concluded that programmed ventricular stimulation was a good predictor of outcome in individuals with BrS. Programmed stimulation might be of special value to guide management in asymptomatic individuals in whom non-inducibility has a very high negative predictive value for future arrhythmic events.[69] European SCD guidelines does not recommend routine use of EP testing but state that if inducible ventricular arrhythmia is present, ICD may be considered.[12]

A family history of sudden death or the presence of an *SCN5A* mutation has not been proven to be risk marker in any of the large studies.[59] However, the presence of mutations leading to a truncated protein, or the presence of some polymorphisms in *SCN5A*, might have some prognostic implications.[70] Meregalli et al[70] showed a significantly higher rate of syncope among patients carrying *SCN5A* truncation mutations (caused by a premature stop codon), but they could not demonstrate a higher rate of serious arrhythmic events (SCD or VF) in those patients with mutations encoding nonfunctional Na^+ channels. In a recent study conducted for the validation of Shanghai scoring system in the diagnosis of BrS, patients with a positive genetic test had slightly higher risk for ventricular arrhtymias.[71]

In summary, symptomatic patients, sudden death survivors, patients with syncope, and males are at higher ventricular arrhythmia risk. Unfortunately, asymptomatic patients may also die suddenly. Thus, at present, the biggest challenge is the detection of these few asymptomatic patients who will develop symptoms. In asymptomatic patients with BrS, EP testing and some other noninvasive markers may be of value for risk stratification.

Presence of QRS fragmentation, ST-segment elevation during the recovery phase of exercise test, early repolarization pattern in inferolateral leads, late potentials with signal-averaged ECG, S wave width >80 milliseconds in lead V1, a corrected QT interval > 460 in lead V2, aVR sign (R wave > 0.3 mV or R/q > 0.75 in lead aVR), and prolonged QRS in precordial leads have been shown to be markers of ventricular arrhythmia risk.[72-75]

Shanghai Score System is validated for the diagnosis and risk stratification of BrS patients, but we should keep in mind that it was developed only as a diagnostic tool. Parameters for the proposed system are demonstrated in Table 3. Patients are divided into 3 groups as >3.5 points: probable and/or definite BrS; 2-3 points: possible BrS; <2 points: nondiagnostic. Definite BrS patients with 3.5 points had a moderate risk for VT/VF, patients with 4-5 points were at high risk, and patients with 5.5 points were in the highest risk. In nondiagnostic group, no arrhythmic events were observed. Patients with positive genetic test results were at a slightly higher risk.[71]

Table 3. Shangai Scoring System

Parameter	Point
1. ECG	
a. Spontaneous type	13.5
b. Fever-induced type	13
c. Drug-induced Type	12
2. Clinical history	
a. Unexplained cardiac arrest, documented VT, VF	3
b. Nocturnal agonal respiration	2
c. Suspected arrhythmic syncope	2
d. Syncope of unclear etiology	1
e. Atrial flutter/fibrillation under 30 years age	0.5
3. Family history	
a. First of second degree relative with definite BrS diagnosis	2
b. Suspicious SCD (fever, nocturnal, drug) in first of second degree relative	1
c. Unexplained SCD < 45 years in in first of second-degree relative	0.5
4. Genetic testing	
a. Probable pathogenic mutation	0.5

BrS, Brugada syndrome; ECG, electrocardiogram; SCD, sudden cardiac death; VF, ventricular fibrillation.

Therapeutic options for Brugada syndrome

Lifestyle changes with education, ICD implantation, quinidine, and catheter ablation are proven effective therapies for the prevention of SCD in BrS patients.

All BrS patients should be informed of the conditions, medications, and substances that might induce ventricular arrhythmias. Fever should be managed aggressively, and competitive endurance sports should be restricted. Following implantation of an ICD, resumption of leisure or competitive sports should be considered after shared decision making in individuals who have not experienced recurrent arrhythmias over 3 months after ICD implantation.[76] Contraindicated medications and substances (cocaine, excessive alcohol, etc.) should be avoided.

The risk of cardiac events in asymptomatic BrS patients is low,[58,59,77-79] but in a long follow-up (5 years) of asymptomatic BrS with ICDs, nearly 6% had appropriate shocks, and in contrast, almost half (48%) of the BrS patients with prior-aborted SCD had appropriate shocks.[46] On the other side, inappropriate shocks (23%), lead failure (15.9%), and device infection (2.4%) were quiet frequent complications.[46] Incidence of inappropriate shocks is significantly lower using an integrated bipolar lead system than when using a dedicated bipolar lead system, and hence, the latter should be routinely used in BrS cases.[80]

In patients with BrS with spontaneous type 1 Brugada ECG pattern and cardiac arrest, sustained VA or a recent history of syncope presumed due to VA, an ICD is recommended if meaningful survival of greater than 1 year is expected.[81]

In patients with asymptomatic BrS and a spontaneous type 1 Brugada ECG pattern, an EPS with programmed ventricular stimulation using single and double extra stimuli may be considered for further risk stratification.[81]

Drugs that inhibit the Ito current or increase the Na^+ and Ca^{2+} currents have been tested in BrS. Isoproterenol (which increases the Ica L current) has proved to be useful for the treatment of electrical storm in BrS.[82]

Quinidine, a class Ia AAD with Ito and I-Kr blocker effects, has been shown to prevent induction of VF and suppress spontaneous ventricular arrhythmias in observational studies,[68] being currently used in patients with ICD and multiple shocks, cases in which ICD implantation is contraindicated, or for the treatment of supraventricular arrhythmias, but side effects of quinidine occur in up to 37% of patients which makes routine clinical use impossible.

Unfortunately, in SABRUS registry, quinidine was ineffective to prevent recurrent arrhythmic events and cannot be considered as an alternative to the ICD.[83]

Nademanee et al[84] presented the first series showing that the RVOT ablation can prevent VF inducibility in a high-risk population. A study focused on epicardial ablation has been published showing an apparent elimination of the BrS phenotype.[85]

Ablation of epicardial late activation areas in the right ventricle outflow tract can suppress recurrent VA as shown in small studies.[84-87] In these studies, type 1 Brugada pattern on ECG may be eliminated in >75% of patients, and recurrences of VT/VF are markedly reduced.[84,86] Nowadays, catheter ablation of right ventricle outflow tract epicardium is recommended only in patients with BrS experiencing recurrent ICD shocks for polymorphic VT and who either are not candidates for or decline an ICD.[81]

Structural changes in Brugada syndrome

BrS patients with ventricular arrhythmias show subtle epicardial and interstitial fibrosis and conduction delay in the RVOT epicardium.[88,89]

Autopsy studies of SCD patients with a family history of BrS demonstrated increased collagen in all ventricular walls, when compared with controls,[89] and also epicardial and interstitial fibrosis and reduced gap junction expressions in the RVOT. Corrado et al[90] demonstrated that 12 of 13 (92%) SCD victims with Brugada ECG pattern had arrhythmogenic cardiomyopathy (AC) features like fibrofatty infiltration of the right ventricle, suggesting a BrS-AC overlapping syndrome. As previously thought, BrS may not be an isolated electrical ionic dysfunction because of the presence of subtle structural changes in the right ventricular epicardium.

Conclusions and the Future

BrS is a rare genetic disease with typical ECG findings and SCD. BrS is one of the most common reasons for SCD (4-12%). Despite all the advances, risk stratification of BrS patients still remains as a challenge for clinicians. ICD implantation is the most common therapy for high-risk patients. Quinidine and RVOT epicardial ablation are possible alternative treatments in patients with recurrent VA.

Research in stem cells has been incorporated into the cardiac arrhythmia field. The human iPS cells from patients diagnosed with LQTS can differentiate to cardiomyocytes, allowing electrophysiological and molecular improvement of arrhythmic mechanisms.[91,92] However, BrS has not yet benefited from these advances.

The only genetic model of the BrS to date is the *SCN5A* knockout mouse. The heterozygous *SCN5A* null allele results in impaired AV conduction, delayed intramyocardial conduction, increased ventricular refractoriness, and ventricular tachycardia.[93] Use of animal models in the future will address the role of genetic and environmental modifiers on cardiac electrical activity. Altogether, there is still a long way to go toward the future of cardiac diseases associated with SCD, supporting the need to use the new emerging tools in the field of biomedicine.

Peer-review: Externally peer-reviewed.

Declaration of Interests: None.

Funding: This study received no funding.

References

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol*. 1992;20(6):1391-1396. [CrossRef]
2. Nademanee K, Veerakul G, Nimmannit S, et al. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. *Circulation*. 1997;96(8):2595-2600. [CrossRef]
3. Guazon M. Algunas notas sobre bangungut. *Rev Filipina Med Farm*. 1917;8:437-442.
4. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference. *Heart Rhythm*. 2005;2(4):429-440. [CrossRef]
5. Coppola G, Dendramis G, Corrado E, et al. Measles and Brugada pattern: a case report. *Int J Cardiol*. 2013;165(3):e41-e42. [CrossRef]
6. Junttila MJ, Gonzalez M, Lizotte E, et al. Induced brugada-type electrocardiogram, a sign for imminent malignant arrhythmias. *Circulation*. 2008;117(14):1890-1893. [CrossRef]
7. Barajas-Martínez HM, Hu D, Cordeiro JM, et al. Lidocaine-induced Brugada syndrome phenotype linked to a novel double mutation in the cardiac sodium channel. *Circ Res*. 2008;103(4):396-404. [CrossRef]
8. 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(7 Pt 1):1551-1553. [CrossRef]
9. 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(4):415-421. [CrossRef]
10. Probst V, Denjoy I, Meregalli PG, et al. Clinical aspects and prognosis of Brugada syndrome in children. *Circulation*. 2007;115(15):2042-2048. [CrossRef]
11. Priori SG, Wilde AA, Horie M, et al. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace*. 2013;15(10):1389-1406. [CrossRef]

12. Priori SG, Blomström-Lundqvist C. European Society of Cardiology guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2015;36(41):2757-2759. [CrossRef]
13. Ikeda T, Abe A, Yusu S, et al. The full stomach test as a novel diagnostic technique for identifying patients at risk of Brugada syndrome. *J Cardiovasc Electrophysiol*. 2006;17(6):602-607. [CrossRef]
14. Brugada P, Brugada J, Roy D. Brugada syndrome 1992-2012: 20 years of scientific excitement, and more. *Eur Heart J*. 2013;34(47):3610-3615. [CrossRef]
15. Chen Q, Kirsch GE, Zhang D, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature*. 1998;392(6673):293-296. [CrossRef]
16. Kapplinger JD, Tester DJ, Alders M, et al. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. *Heart Rhythm*. 2010;7(1):33-46. [CrossRef]
17. Delpón E, Cordeiro JM, Núñez L, et al. Functional effects of kcne3 mutation and its role in the development of Brugada syndrome. *Circ Arrhythm Electrophysiol*. 2008;1(3):209-218. [CrossRef]
18. Haïssaguerre M, Chatel S, Sacher F, et al. Ventricular fibrillation with prominent early repolarization associated with a rare variant of kcnj8/katp channel. *J Cardiovasc Electrophysiol*. 2009;20(1):93-98. [CrossRef]
19. Medeiros-Domingo A, Tan BH, Crotti L, et al. Gain-of-function mutation s422l in the kcnj8-encoded cardiac k(atp) channel kir6.1 as a pathogenic substrate for j-wave syndromes. *Heart Rhythm*. 2010;7(10):1466-1471. [CrossRef]
20. Giudicessi JR, Ye D, Tester DJ, et al. Transient outward current (i(to)) gain-of-function mutations in the kcnd3-encoded Kv4.3 potassium channel and Brugada syndrome. *Heart Rhythm*. 2011;8(7):1024-1032. [CrossRef]
21. Antzelevitch C, Pollevick GD, Cordeiro JM, et al. Loss-of function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST segment elevation, short qt intervals, and sudden cardiac death. *Circulation*. 2007;115(4):442-449. [CrossRef]
22. Burashnikov E, Pfeiffer R, Barajas-Martinez H, et al. Mutations in the cardiac l-type calcium channel associated with inherited j-wave syndromes and sudden cardiac death. *Heart Rhythm*. 2010;7(12):1872-1882. [CrossRef]
23. Poelzing S, Forleo C, Samodell M, et al. SCN5A polymorphism restores trafficking of a Brugada syndrome mutation on a separate gene. *Circulation*. 2006;114(5):368-376. [CrossRef]
24. Lizotte E, Junttila MJ, Dube MP, et al. Genetic modulation of Brugada syndrome by a common polymorphism. *J Cardiovasc Electrophysiol*. 2009;20(10):1137-1141. [CrossRef]
25. Bezzina CR, Shimizu W, Yang P, et al. Common sodium channel promoter haplotype in Asian subjects underlies variability in cardiac conduction. *Circulation*. 2006;113(3):338-344. [CrossRef]
26. Makita N, Mochizuki N, Tsutsui H. Absence of a trafficking defect in R1232W/T1620M, a double SCN5A mutant responsible for Brugada syndrome. *Circ J*. 2008;72(6):1018-1019. [CrossRef]
27. Cordeiro JM, Barajas-Martinez H, Hong K, et al. Compound heterozygous mutations P336L and I1660V in the human cardiac sodium channel associated with the Brugada syndrome. *Circulation*. 2006;114(19):2026-2033. [CrossRef]
28. Miyazaki S, Shah AJ, Haïssaguerre M. Early repolarization syndrome—a new electrical disorder associated with sudden cardiac death. *Circ J*. 2010;74(10):2039-2044. [CrossRef]
29. Antzelevitch C, Yan GX. J wave syndromes. *Heart Rhythm*. 2010;7(4):549-558. [CrossRef]
30. Antzelevitch C, Yan GX. J-wave syndromes: Brugada and early repolarization syndromes. *Heart Rhythm*. 2015;12(8):1852-1866. [CrossRef]
31. McIntyre WF, Pérez-Riera AR, Femenía F, Baranchuk A. Coexisting early repolarization pattern and Brugada syndrome: recognition of potentially overlapping entities. *J Electrocardiol*. 2012;45(3):195-198. [CrossRef]
32. Schott JJ, Alshinawi C, Kyndt F, et al. Cardiac conduction defects associate with mutations in SCN5A. *Nat Genet*. 1999;23(1):20-21. [CrossRef]
33. Wang DW, Viswanathan PC, Balser JR, George AL, Benson DW. Clinical, genetic, and biophysical characterization of SCN5A mutations associated with atrioventricular conduction block. *Circulation*. 2002;105(3):341-346. [CrossRef]
34. Brignole M. Sick sinus syndrome. *Clin Geriatr Med*. 2002;18(2):211-227. [CrossRef]
35. Benson DW, Wang DW, Dyment M, et al. Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (SCN5A). *J Clin Invest*. 2003;112(7):1019-1028. [CrossRef]
36. Smits JP, Koopmann TT, Wilders R, et al. A mutation in the human cardiac sodium channel (E161K) contributes to sick sinus syndrome, conduction disease and Brugada syndrome in two families. *J Mol Cell Cardiol*. 2005;38(6):969-981. [CrossRef]
37. Eckardt L, Kirchhof P, Loh P, et al. Brugada syndrome and supraventricular tachyarrhythmias: a novel association? *J Cardiovasc Electrophysiol*. 2001;12(6):680-685. [CrossRef]
38. Itoh H, Shimizu M, Ino H, et al. Arrhythmias in patients with Brugada-type electrocardiographic findings. *Jpn Circ J*. 2001;65(6):483-486. [CrossRef]
39. Morita H, Kusano-Fukushima K, Nagase S, et al. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. *J Am Coll Cardiol*. 2002;40(8):1437-1444. [CrossRef]
40. Bordachar P, Reuter S, Garrigue S, et al. Incidence, clinical implications and prognosis of atrial arrhythmias in Brugada syndrome. *Eur Heart J*. 2004;25(10):879-884. [CrossRef]
41. Letsas KP, Sideris A, Efremidis M, et al. Prevalence of paroxysmal atrial fibrillation in Brugada syndrome: a case series and a review of the literature. *J Cardiovasc Med (Hagerstown)*. 2007;8(10):803-806. [CrossRef]
42. Bigi MA, Aslani A, Shahrzad S. Clinical predictors of atrial fibrillation in Brugada syndrome. *Europace*. 2007;9(10):947-950. [CrossRef]
43. Schimpf R, Giustetto C, Eckardt L, et al. Prevalence of supraventricular tachyarrhythmias in a cohort of 115 patients with Brugada syndrome. *Ann Noninvasive Electrocardiol*. 2008;13(3):266-269. [CrossRef]
44. Giustetto C, Cerrato N, Gribaudo E, et al. Atrial fibrillation in a large population with Brugada electrocardiographic pattern: prevalence, management, and correlation with prognosis. *Heart Rhythm*. 2014;11(2):259-265. [CrossRef]
45. Francis J, Antzelevitch C. Atrial fibrillation and Brugada syndrome. *J J Am Coll Cardiol*. 2008;51(12):1149-1153. [CrossRef]
46. Sacher F, Probst V, Maury P, et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study-part 2. *Circulation*. 2013;128(16):1739-1747. [CrossRef]
47. de Asmundis C, Mugnai G, Chierchia GB, et al. Abnormally high risk of stroke in Brugada syndrome. *J Cardiovasc Med (Hagerstown)*. 2019;20(2):59-65. [CrossRef]
48. Conte G, Chierchia GB, Wauters K, et al. Pulmonary vein isolation in patients with Brugada syndrome and atrial fibrillation: a 2-year follow-up. *Europace*. 2014;16(4):528-532. [CrossRef]
49. Yamada T, Yoshida Y, Tsuboi N, et al. Efficacy of pulmonary vein isolation in paroxysmal atrial fibrillation patients with a Brugada electrocardiogram. *Circ J*. 2008;72(2):281-286. [CrossRef]
50. Kramer DB, Zimetbaum PJ. Long-QT syndrome. *Cardiol Rev*. 2011;19(5):217-225. [CrossRef]
51. Bezzina C, Veldkamp MW, van Den Berg MP, et al. A single Na^+ channel mutation causing both long-QT and Brugada syndromes. *Circ Res*. 1999;85(12):1206-1213. [CrossRef]
52. Wilde AAM, Amin AS. Clinical spectrum of SCN5A mutations: long QT Sydrome, Brugada syndrome, and cardiomyopathy. *JACC Clin Electrophysiol*. 2018;4(5):569-579. [CrossRef]
53. Grant AO, Carboni MP, Neplioueva V, et al. Long QT syndrome, Brugada syndrome, and conduction system disease are linked to a single sodium channel mutation. *J Clin Invest*. 2002;110(8):1201-1209. [CrossRef]

54. Parisi P, Oliva A, Coll Vidal M, et al. Coexistence of epilepsy and Brugada syndrome in a family with SCN5A mutation. *Epilepsy Res*. 2013;105(3):415-418. [CrossRef]
55. Camacho Velásquez JL, Rivero Sanz E, Velazquez Benito A, et al. Epilepsy and Brugada syndrome. *Neurologia*. 2017;32(1):58-60. [CrossRef]
56. Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST-segment elevation in leads V1 through V3: a marker for sudden death in patients without demonstrable structural heart disease. *Circulation*. 1998;97(5):457-460. [CrossRef]
57. Benito B, Sarkozy A, Mont L, et al. Gender differences in clinical manifestations of Brugada syndrome. *J Am Coll Cardiol*. 2008;52(19):1567-1573. [CrossRef]
58. Probst V, Veltmann C, Eckardt L, et al. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the finger Brugada syndrome registry. *Circulation*. 2010;121(5):635-643. [CrossRef]
59. Gehi AK, Duong TD, Metz LD, Gomes JA, Mehta D. Risk stratification of individuals with the Brugada electrocardiogram: a meta-analysis. *J Cardiovasc Electrophysiol*. 2006;17(6):577-583. [CrossRef]
60. Kusano KF, Taniyama M, Nakamura K, et al. Atrial fibrillation in patients with Brugada syndrome: relationships of gene mutation, electrophysiology, and clinical backgrounds. *J Am Coll Cardiol*. 2008;51(12):1169-1175. [CrossRef]
61. Adler A, Rosso R, Chorin E, Havakuk O, Antzelevitch C, Viskin S. Risk stratification in Brugada syndrome: clinical characteristics, electrocardiographic parameters, and auxiliary testing. *Heart Rhythm*. 2016;13(1):299-310. [CrossRef]
62. Sieira J, Ciconte G, Conte G, et al. Asymptomatic Brugada syndrome: clinical characterization and long-term prognosis. *Circ Arrhythm Electrophysiol*. 2015;8(5):1144-1150. [CrossRef]
63. Letsas KP, Liu T, Shao Q, et al. Meta-analysis on risk stratification of asymptomatic individuals with the Brugada phenotype. *Am J Cardiol*. 2015;116(1):98-103. [CrossRef]
64. Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. *Circulation*. 2003;108(25):3092-3096. [CrossRef]
65. Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. *Circulation*. 2002;105(11):1342-1347. [CrossRef]
66. Eckardt L, Probst V, Smits JP, et al. Long-term prognosis of individuals with right precordial ST-segment-elevation Brugada syndrome. *Circulation*. 2005;111(3):257-263. [CrossRef]
67. Giustetto C, Drago S, Demarchi PG, et al. Risk stratification of the patients with Brugada type electrocardiogram: a community-based prospective study. *Europace*. 2009;11(4):507-513. [CrossRef]
68. Belhassen B, Rahkovich M, Michowitz Y, Glick A, Viskin S. Management of Brugada syndrome: a 33-year experience using electrophysiologically-guided therapy with class 1a antiarrhythmic drugs. *Circ Arrhythm Electrophysiol*. 2015;8(6):1393-1402. [CrossRef]
69. Sieira J, Conte G, Ciconte G, et al. Prognostic value of programmed electrical stimulation in Brugada syndrome: 20 years experience. *Circ Arrhythm Electrophysiol*. 2015;8(4):777-784. [CrossRef]
70. Meregalli PG, Tan HL, Probst V, et al. Type of SCN5A mutation determines clinical severity and degree of conduction slowing in loss-of-function sodium channelopathies. *Heart Rhythm*. 2009;6(3):341-348. [CrossRef]
71. Kawada S, Morita H, Antzelevitch C, et al. Shanghai Score System for diagnosis of Brugada syndrome: validation of the score system and reclassification of the patients. *JACC Clin Electrophysiol*. 2018;4(6):724-730. [CrossRef]
72. Morita H, Kusano KF, Miura D, et al. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. *Circulation*. 2008;118(17):1697-1704. [CrossRef]
73. Subramanian M, Prabhu MA, Harikrishnan MS, Shekhar SS, Pai PG, Natarajan K. The utility of exercise testing in risk stratification of asymptomatic patients with type 1 Brugada pattern. *J Cardiovasc Electrophysiol*. 2017;28(6):677-683. [CrossRef]
74. Kawata H, Morita H, Yamada Y, et al. Prognostic significance of early repolarization in inferolateral leads in Brugada patients with documented ventricular fibrillation: a novel risk factor for Brugada syndrome with ventricular fibrillation. *Heart Rhythm*. 2013;10(8):1161-1168. [CrossRef]
75. Huang Z, Patel C, Li W, et al. Role of signal averaged electrocardiograms in arrhythmic risk stratification of patients with Brugada syndrome: a prospective study. *Heart Rhythm*. 2009;6(8):1156-1162. [CrossRef]
76. Pelliccia A, Sharma S, Gati S, et al. ESC Guideline on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J*. 2021;42(1):17-96.
77. Casado-Arroyo R, Berne P, Rao JY, et al. Long-term trends in newly diagnosed Brugada syndrome: implications for risk stratification. *J Am Coll Cardiol*. 2016;68(6):614-623. [CrossRef]
78. Hiraoka M, Takagi M, Yokoyama Y, et al. Prognosis and risk stratification of young adults with Brugada syndrome. *J Electrocardiol*. 2013;46(4):279-283. [CrossRef]
79. Priori SG, Gasparini M, Napolitano C, et al. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. *J Am Coll Cardiol*. 2012;59(1):37-45. [CrossRef]
80. Rodríguez-Mañero M, de Asmundis C, Sacher F, et al. T-wave oversensing in patients with Brugada syndrome: true bipolar versus integrated bipolar implantable cardioverter defibrillator leads: multicenter retrospective study. *Circ Arrhythm Electrophysiol*. 2015;8(4):792-798. [CrossRef]
81. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2017;72(14):e91-e220.
82. Maury P, Hocini M, Haïssaguerre M. Electrical storms in Brugada syndrome: review of pharmacologic and ablative therapeutic options. *Indian Pacing Electrophysiol J*. 2005;5(1):25-34.
83. Michowitz Y, Andorin A, Gourraud JB, et al. Profile of young patients with Brugada syndrome and Arrhythmic events; Characterization, management and risk factors for Arrhythmia Recurrence. *Circulation*. 2018;15(5):716-724.
84. Nademanee K, Veerakul G, Chandanamattha P, et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. *Circulation*. 2011;123(12):1270-1279. [CrossRef]
85. Brugada J, Pappone C, Berruezo A, et al. Brugada syndrome phenotype elimination by epicardial substrate ablation. *Circ Arrhythm Electrophysiol*. 2015;8(6):1373-1381. [CrossRef]
86. Zhang P, Tung R, Zhang Z, et al. Characterization of the epicardial substrate for catheter ablation of Brugada syndrome. *Heart Rhythm*. 2016;13(11):2151-2158. [CrossRef]
87. Rodríguez-Mañero M, Sacher F, de Asmundis C, et al. Monomorphic ventricular tachycardia in patients with Brugada syndrome: a multicenter retrospective study. *Heart Rhythm*. 2016;13(3):669-682. [CrossRef]
88. Martini B, Nava A, Thiene G, et al. Ventricular fibrillation without apparent heart disease: description of six cases. *Am Heart J*. 1989;118(6):1203-1209. [CrossRef]
89. Nademanee K, Raju H, De Noronha SV, et al. Fibrosis, connexin 43, and conduction abnormalities in the Brugada syndrome. *J Am Coll Cardiol*. 2015;66(18):1976-1986. [CrossRef]
90. 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(5):710-717. [CrossRef]
91. Itzhaki I, Maizels L, Huber I, et al. Modelling the long QT syndrome with induced pluripotent stem cells. *Nature*. 2011;471(7337):225-229. [CrossRef]
92. Moretti A, Bellin M, Welling A, et al. Patient-specific induced pluripotent stem-cell models for long-QT syndrome. *N Engl J Med*. 2010;363(15):1397-1409. [CrossRef]
93. Derangeon M, Montnach J, Baró I, Charpentier F. Mouse models of SCN5A-related cardiac arrhythmias. *Front Physiol*. 2012;3:210. [CrossRef]