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Review Article

A Comprehensive Review on Brugada Syndrome: Etiology, Hormonal role, Current Treatment Regimen, and Role of Polyunsaturated Fatty Acids

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ABSTRACT

Brugada syndrome is a disorder caused by alteration or mutation in the ion channels, abnormal ECG resulting in elevated ST segment and blockage of right bundle brank. It has a genetic history and can be passed down from the parents to their offspring and may be further complicated if someone already had a cardiac arrest or other cardiac-related issues. At present, there is no permanent cure strategy available to treat this disorder. However, some surgical and pharmacological intervention approaches, such as the use of defibrillators, catheters can provide some relief, but due to their excessive cost and complications, their use has been limited. Polyunsaturated fatty acids (PUFA) components: Eicosapentaenoic acid and docosahexaenoic acid were found to play a significant role in reducing the cardiovascular events and mortality rate. The primary sources of these fatty acids are fish and fish oils. This review attempts to summarize the cardioprotective role of PUFA in preventing ventricular arrhythmias and Brugada syndrome through alteration of cardiac ion channels.

Introduction

Brugada syndrome is a genetic disorder that occurs due to a mutation in the Cardiac Sodium channel gene. Echocardiogram observes the patient with brugada syndrome ST segment elevation in the right precordial loads and right bundle brank block. If the syndrome remains untreated cardiac death due to ventricular fibrillation can occur. It was first observed in the Western World in the year 1998.[1] At that time, the nocturnal death syndrome cause was not known, and later, it was called "Brugada Syndrome".[2] It has various names in various geographical regions like LaiTai (Thailand), Pokkuri (Japan). Nowadays, the occurrence of brugada syndrome is around 3–5 per 10,000 people, and it was observed that it is prevailing highest among young men of South-East Asia Origin. According to some recent reports, the cause of 12% of sudden death in patients with structurally normal hearts may be Brugada Syndrome.[3] Fish and fish oils contain an abundant amount of long-chain Omega 3 Polyunsaturated fatty acids. The two fatty acids that are important sources are eicosapentaenoic acid and docosahexaenoic acid. The fatty acid taken gets incorporated into the cell membrane phospholipid all over the body, especially in the heart and brain. These fatty acids play a crucial role in early brain development during the infant stage, and it plays a beneficial role in dementia, depression, and other neuropsychiatric disorder. From epidemiologic studies, it was found that the risk of coronary disease is lessened with the increase of fish consumption. From the studies, the cardioprotective role of the marine-derived fatty acids is identified. These also reduce the progression and occurrence of other types of cardiac

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disease like atherosclerosis, myocardial infarction, heart failure, arrhythmias, and stroke. Coronary microvascular dysfunction is an independent predictor of adverse events of the cardiovascular system.[4] Brugada syndrome is a rare disorder inherited through cardiac channels, and it happens due to alteration of ionic currents that leads to ventricular arrhythmia.[5] The etiology behind Brugada is defined via three theories, *i.e.,* repolarization, depolarization, and neural crest model.[5] The Brugada Syndrome can be diagnosed by observing the ST-segment elevation in the right precordial loads at baseline. It is a genetic disorder, so three different electrocardiographic patterns are often seen in families with this syndrome.

Type a: This type consists of a coved type ST-segment elevation of more than 2 mm, and descending negative T waves follow it in at least two right precordial leads.[6]

Type b: ST elevation saddleback-shaped patterns with a high initial increase, followed by an ST elevation greater than 2mm.

Type c: This particular type of ECG is relatively common and considered a normal variant where ST segment is saddleback and greater than 2 mm followed by elevated positive T waves. The diagnosis of brugada syndrome is nowadays possible only in patients with type 1 ECG.

Appropriate identification and proper treatment of a person at high risk for sudden cardiac death is one of the major challenges in the clinical manifestation of brugada syndrome patients.[7] When spontaneous coved (type 1) ECG pattern is present. It is a major indicator of the potential arrhythmic episode in patients with no symptoms. This review focuses on the several anomalies related to Brugada syndrome and possible intervention strategies to mitigate such irregularity. We outline the potential of Polyunsaturated Fatty Acids (PUFAs) as a promising agent to prevent the consequences of Brugada.

Mechanism of n-3 PUFA's: n-3 PUFA's are obtained from fish and fish oil when taken into the diet, absorbed from the gastrointestinal tract, and goes to the liver in the form of triglycerides via chylomicron particles. When transported to the liver, n-3 PUFA serves as a source of triglycerides in lipoprotein particles, including low-density lipoprotein. Triglycerides include oleic acids and saturated fatty acids, and phospholipids consist of PUFA's. n-3 PUFA's, which are released into the blood as plasma phospholipids from the liver, get incorporated into cell membrane phospholipids all over the body. From this, some are stored in the adipose tissue as triglycerides.[8]

n-3 PUFA's, a derivative of α linolenic acid, is metabolized by desaturase and elongase, two enzymes. Linolenic acid is metabolized into Arachidonic acid, the starting compound of eicosanoids like prostaglandin and thromboxanes.[9]

Genetic Aspects: Since it is a genetic disease, the hereditary nature is characterized by an autosomal dominant way of transmitting from one person to another. Chen *et al.* first found a connection between the syndrome and the α subunit of the sodium channel gene in cardiac muscle. At the physiological temperature, the premature inactivation of the channel was seen. From this, it was suggested that the syndrome is sometimes unmasked, and at the febrile state, the patient having the brugada syndrome is at increased risk.[10]

Cellular and ionic mechanism: the all or none repolarization concept of the ventricular action potential of phase 2 re-entry secondary to sodium channel block or ischemia were found in the 1990's. The elevation in the ST segment was thought to be due to the rebalancing of the current active sodium channel at the end of Phase-I, which leads to the activation of the action potential notch in RV epicardium.[10]

Clinical Features of Brugada Syndrome

Brugada syndrome is an inherited cardiac arrhythmic condition marked by particular aberrant electrocardiogram patterns and an increased risk of ventricular fibrillation and sudden cardiac arrest in healthy people who do not have any apparent structural heart abnormalities.[11,12] Brugada syndrome can be regarded as a hereditary illness, with a medical history of sudden cardiac arrest documented in around 26% of individuals.[13] Brugada syndrome patients exhibit a variety of prognoses. The major clinical symptom of the illness may be chest pain, nocturnal agonal breathing, syncope, and/or seizures caused by arrhythmias such as ventricular fibrillation or polymorphic ventricular tachycardia.[14] These individuals may develop sudden cardiac arrest and perhaps other arrhythmias such as Wolff-Parkinson-White syndrome, atrial fibrillation, atrial flutter, and other supraventricular arrhythmias if these rhythms continue.[14] Patients with a Brugada electrocardiogram pattern are frequently asymptomatic and stay so for the rest of their lives. Sudden unexplained nocturnal death syndrome is genetically, phenotypically, and functionally identical to Brugada syndrome. Sudden unexplained nocturnal death syndrome is a disease linked with the development of catastrophic arrhythmias contributing to an unexpected death in young, healthy individuals.[15] An elevation distinguishes Brugada syndrome in the ST-segment in the right precordial leads.[16] Even though there are three forms of ST-segment elevation, type-1 morphology is almost often utilized to diagnose Brugada syndrome. A coved ST-segment elevation, followed by a negative T wave, characterizes Type-1 morphology. This morphology can happen on its own or in the influence of stimulants such as sodium channel blockers (flecainide, procainamide, ajmaline, or pilsicainide). Patients with Brugada Type-1 ECG had a 1.9% syncope rate, a 7.7% sudden cardiac arrest rate, and a 0.5% asymptomatic rate of cardiac events each year.[12] Type-2 morphology, often known as the "saddle-back type," is characterized by a convex ST-segment elevation, followed by a positive T-wave. This morphology can be observed in various Brugada-like patterns such as left ventricular hypertrophy, arrhythmogenic cardiomyopathy, right

bundle branch block, and pectus excavatum, athletes.[12] A right precordial ST-segment elevation, coved type, saddleback type, or both are termed as type-3 morphology, which is no longer included in Brugada syndrome.[17]

Etiology of Brugada Syndrome

There are presently three theories suggested to explain the signaling pathways and etiology of Brugada syndrome: (1) the repolarization model, (2) the depolarization model, and (3) the neural crest model are described in Fig. 1.

According to the repolarization model, a transmural voltage gradient between the epicardium and endocardium of the right ventricle causes the development of fatal arrhythmias typical of Brugada syndrome.[3] The inward sodium current and transitory outward potassium current produce a dome and spike shape during phase 1 of the typical action potential.[18] However, with a lessened inward sodium current and an influential outward current, the action potential line in the right ventricular epicardium is exacerbated comparative to the endocardium, resulting in the generation of a transmural voltage gradient, which expresses as the distinctive feature coved ST-segment elevation seen in Brugada syndrome patient's electrocardiogram.[19] Consequently, epicardial dissemination of repolarization can occur due to this outward change in current balance and the disappearance of the action potential line after phase 1.[19] The formation of phase 2 re-entry occurs, which produces tightly linked premature beats, i.e., extrasystoles capable of triggering ventricular fibrillation or ventricular tachycardia, aided by this heterogeneous repolarization condition.[11] The parallels between Brugada syndrome and early repolarization syndrome in terms of clinical symptoms and treatment and the responsiveness to heart rate and pharmacologic interventions credence to this idea.[20]
According to the depolarization model, the arrhythmias of Brugada syndrome and electrocardiography alterations are caused by an intraventricular conduction deficit in the right ventricular outflow tract.[21] It implies that the distinctive coved ST-segment augmentation in Brugada syndrome is caused by a selective conduction delay in the outflow tract of the right ventricles. The aberrant current generated by the right ventricular outflow tract, premature depolarization also causes ventricular arrhythmias associated with Brugada syndrome.[20]

The neural crest model was postulated by Elizari *et al.,* as another mechanism behind Brugada syndrome pathology. Neural crest cells are situated in the extra-cardiac location and play a significant role in developing the right ventricular outflow tract myocardium and surrounding tissues.[22] Repolarization heterogeneities underpinning the Brugada syndrome phenotype can be produced by aberrant myocardialization driven by defective cardiac neural crest cell expression. Additionally, the upregulation of connexin-43, *i.e.,* a gap junction protein, has been linked to quicker or delayed migration of cardiac neural crest cells. According to the authors, aberrant cardiac neural crest cell migration causes non-uniform transmural and overexpression of connexin-43 in the right ventricle, resulting in right ventricular outflow tract conduction slowdown delayed activation in Brugada syndrome patients.[22]

Why it Occurs more Often in Men than in Women?

The clinical phenomenology of the Brugada syndrome is now thought to be 8 to 10 times more common in male patients than in female ones.[23] As a result, most clinical trials published have included 71% to 77% of the male population.[24,25] However, due to a lack of specific clinical evidence on the sex dichotomy, some studies recently attempted to examine sex differences in a large population of Brugada syndrome patients. Based on such findings, males with Brugada syndrome had a greater risk profile than females, appearing with symptoms at the time of spontaneous type-1 ECG and diagnosis. As a result, males in our study had a poor prognosis during follow-up.[26] The hormonal effect and the sex-related inherent variations in ionic currents have been presented as two primary explanations for the sex distinction, which may interact with one other.[27] In the arterially perfused canine heart preparations model, a study conducted by Di Diego and colleagues showed that transient outward potassium current density, as measured by whole-cell patch-clamp techniques, was substantially higher in males than females at right ventricle epicardia. It attempts to explain the deeper notch in phase 1 of the action potential in males compared to females.[27] In this model, terfenadine (a calcium and sodium channel blocker) caused ST-segment elevation and served as a foundation for phase-2 re-entry and ventricular fibrillation. Because of their stronger phase-1 magnitude at baseline, these occurrences were mostly found in male samples.[27] The significance of sex hormones in Brugada syndrome is still unknown; however, some evidence suggests that they may have a role in the phenotypic symptoms.[28] For example, in castrated men, the characteristic electrocardiogram abnormalities

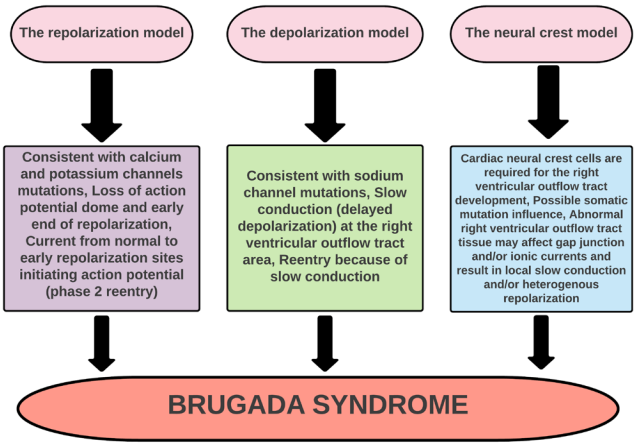

Fig. 1: Models in Brugada syndrome pathogenesis

have been observed to retrograde, and testosterone levels in Brugada male patients appear to be greater than in controls. In several experiments, hormones have been shown to alter ionic membrane currents, but their influence on humans is unknown.[29,30]

Genes Associated with Brugada Syndrome

Brugada syndrome is a genetic illness with a variable susceptibility and an autosomal dominant transmission pattern.[31] However, up to 60% of cases might be occasional and not present in other relatives.[32] The first catastrophic mutation in the SCN5A gene was recognized, which codes for the cardiac sodium channel-alpha subunit, discovered in 1998.[33] Since then, over 350 catastrophic mutations in various genes have been reported (SCN5A, SCN1B, SCN2B, SCN3B, GPD1L, SLMAP, RANGRF, KCND3, KCNE3, KCNJ8, KCNE5, TRPM4, CACNA1C, CACNB2B, CACNA2D1, and HCN4).[34] These genes code for cardiac calcium, potassium, and sodium channel subunits and genes that regulate the channels. In addition to SCN5A genes, numerous Brugada syndrome-related genes have a role in regulating sodium channel activity. A variation in the genes encode channels that conduct outward potassium currents (KCNE3, KCNE5, KCND3, and KCNJ8) has been hypothesized to predispose afflicted persons to acquire the Brugada syndrome phenotype.[35] Calcium channels were also shown to have Brugada syndrome pathogenic variants (CACNA1C, CACNB2b, and CACNA2D1). In probands with Brugada syndromes, mutations occur in the L-type calcium channel subunits, encoded by the gene CACNA2D1, CACNB2B, and CACNA1C, respectively. These genes cause only a small portion of Brugada syndrome.[36] Despite many genetic variations, only around 35% of patients with Brugada syndrome have been identified as having a genetic etiology. Approximately 30% of them have a catastrophic mutation in the SCN5A gene.[37] The other genes account for around 5% of all Brugada syndrome patients. As a result, genetics are not the cause of 65% of instances. Numerous variables might explain the large proportion of Brugada syndrome patients who did not have gene mutations following genetic testing. The Brugada syndrome genetic mutation may be identified in undiscovered genes, or the condition may be linked to epigenetic factors like as post-translational modification, DNA methylation, and RNA Mechanism.[38,39] Genes that are modulating or associated with Brugada syndrome were compiled in Table 1.

The Role of the Male Hormone (Testosterone) in Brugada Syndrome

Several clinical, experimental, and molecular genetic research have identified Brugada syndrome as a separate clinical entity within the last decade.[24,40,41] Many studies point towards the role of the male hormone testosterone in the disease. Di Diego *et al.,* reported the prevalence of higher densities of I_{to} currents in males in contrast to females as the reason behind the predominance of the disease in men.[42] Many studies show that the male hormone contributes to the overwhelming development of the outward transient potassium currents in contrast to delayed rectifier potassium current in the right ventricular epicardium. Such an outward shift of current repolarizes the voltage past the range at which the L-type Calcium channels activate, leading to loss of the Action Potential dome. Along with this, electrophysiological differences between the epicardium and endocardium generate a transmural voltage gradient, accentuating the right ventricular AP notch, which causes an ST elevation in an Electrocardiogram, an observable characteristic of Brugada.[43-45] Matsuo *et al.* reported the diminution of the outward repolarizing currents in two asymptomatic Brugada patients after orchiectomy, carried out as a part of their anti-cancer therapy. The Brugada ST pattern that existed for decades was wiped out after castration.[46] In a study, researchers' statistical analysis comparing age-matched groups indicated a strong association of testosterone and Brugada phenotype. Higher levels of testosterone were reported in males suffering from ventricular arrhythmia along with lower visceral fat.[47] Additionally, patients administered with anti-androgenic therapy showed a reduction in the ST elevation in an electrocardiogram which assures that the male hormone plays a role in the modulation of ventricular repolarization.[48]

Sexual reassignment requires hormonal administration, and in case a female wants to turn into a male, testosterone needs to be administered and maintained. This procedure is associated with cardiovascular risks when continued for the long term. Recently, two doctors reported a case of a genetic female who was under exogenous testosterone treatment. The patient had no previous family history of Brugada but suffered from ventricular arrhythmias, which were later treated using quinidine in low doses. Subsequently, the recurrent ventricular ectopy was treated using ablation. This is an example where the channelopathy got unmasked by the lifestyle of the patient.[49] The ECG pattern in a similar case normalized when the testosterone therapy was discontinued. However, the Brugada pattern in ECG reappeared again with its reintroduction.[50] These cases point that the male predominance of the disease is due to testosterone.

Current Treatment Regimen with People Suffering from Brugada Syndrome

Summarized information on the current treatment regimen and different medication for the therapy of Brugada syndrome were compiled in Table 2 and 3.

1. Surgical Intervention Using Defibrillators

Defibrillators are used for surgical intervention to rectify twitches of ventricles that interfere with blood supply. The fundamental system of the device that aids in the relay, monitor, and detection of signals, between the

Table 1: Gene modulating or associated with Brugada syndrome, encoding particular ion channel

Genes	*Locus*	*Protein*	*Potential effect on the ion channel*	*Probands percentage (%)*
Calcium channel [12,36]				
CACNA1C	12p13.3	$Ca_{v1.2}$	Decreased I_{Ca}	6.6
CACNB2b	10p12.33	$Ca_{v}\beta2$	Decreased I_{Ca}	4.8
CACNA2D1	7q21.11	$Ca_{v}\alpha2\delta$	Decreased I_{Ca}	1.8
Potassium channel [12,35,84,85]				
KCND3	1p13.2	$K_{v}4.3$, Ito	Increased I_{to}	Rare
KCNE3	11q13-14	MiRP2	Increased I_{to}	Rare
KCNJ8	12p11.23	Kir6.1	Increased $I_{K\text{-}ATP}$	2
ABCC9	12p12.1	SUR2A	Increased $I_{K\text{-}ATP}$	Rare
Sodium channel [12,86,87]				
SCN5A	3p21	$Na_{v}1.5$	Decreased I_{Na}	10-15 (Asian) 20-25 (Caucasian)
SCN1B	19q13.1	$Na_{v}\beta1/\beta1b$	Decreased I_{Na}	1.1
SCN2B	11q23	$Na_{v}\beta2$	Decreased I_{Na}	Rare
SCN3B	11q23.2	$Na_{v}\beta3$	Decreased I_{Na}	Rare
SCN10A	3p22.2	$Na_{v}\beta1.8$	Decreased I_{Na}	2.5 up to 16.7
Genes modulating Brugada syndrome [87-89]				
KCNH2	7q35	$K_{v}11.1$	Increased I_{Kr}	1-2
KCNE5	Xq22.3	MiRP4, $K_{v}4.3$	Increased I_{to}	Rare
HCN4	15q24.1	I_{f}	Decreased I_{f}	Rare
Potassium channel-associated [12]				
SEMA3A	7p12.1	Semaphorin	Increased I_{to}	Rare
Sodium channel-associated [12,90-94]				
RANGRF	17p13.1	MOG1	Decreased I_{Na}	Rare
GPD1-L	3p24	G3PD1L	Decreased I_{Na}	Rare
SLMAP	3p21.2-p14.3	SLMAP	Decreased I_{Na}	Rare
PKP2	12p11.21	Plakophillin-2	Decreased I_{Na}	2.5
TRPM4	19q13.33	$NSCC_{a}$	Decreased I_{Na}	6
HEY2	6q22	$Na_{v}1.5$	Decreased I_{Na}	Rare

Table 2: Summarized information on the current treatment regimen used in Brugada syndrome

Treatment regimen	*Site of administration*	*Mechanism of action*	*Route*	*Limitations*
Implantable cardioverter defibrillators (ICDs)	Myocardium, Subcutaneous tissue	Emits electrical shocks following pre-installed programs	Transvenous (conventional ICDs), Subcutaneous (SCIDs)	• Replacement of ICDs leads to infections. • Inappropriate shocks may lead to disorders. • Psychological problems.
Quinidine	Ventricular epicardium	Blocks transient outward K^{+} current	Oral	• Unavailability of the drug in many parts of the world
Catheter ablation	Ventricular epicardium	Blocks the passage of irregular electrical impulses due to scarring of the related tissues	Endovascular	• High chances of recurrence of the disease even after treatment.

Table 3: Summarized information on different medications for the therapy of Brugada syndrome

				Use based on studies			
Drugs	*Class*	*Route*	*Mechanism of action*	*Asymptomatic Brugada*	*Ventricular fibrillation prophylaxis*	*Storm*	*Reference*
Disopyramide	IA anti-arrhythmic drug	Oral	Blocks I_{Na} and I_{to} moderately		+		[95,96]
Isoproterenol	β-adrenergic agonist	Oral	Augments L-type calcium channels			+++	[97-99]
Denopamine	β-adrenergic agonist	Oral	Augments L-type calcium channels		+		[100,101]
Orciprenaline	β-adrenergic agonist	IV bolus and IV drip	Augments L-type calcium channels			+	[100,101]
Cilostazol	Phosphodiesterase inhibitors	Oral	Increases cellular L-type calcium currents and cellular cAMP	+			[102,103]
Bepridil	Non-selective, calcium channel blocker	Oral	Blocks of I_{to}, augmentation of I_{Na}	+			[103-105]

(+ - evidence from case reports; + + + - evidence from several intravenous)

heart and the device, constitutes wires known as leads and a pacemaker system. The device repairs the altered blood supply by emitting electric shocks to the heart per the pre-installed programs.[51] These are also termed Implantable Cardioverter-Defibrillator or ICD in short. The location of the leads determines their type. These may be regular (also called transvenous) ICD wherein the leads are implanted within the myocardium or subcutaneous ICD, placed beneath the skin surface. ICD was a better option for saving lives than beta-blocker drugs in a randomized trial on 86 patients with Sudden arrhythmic death syndrome.[52]

Past comparative trials favored the use of subcutaneous ICD against transvenous ICD due to its notable limitations.[53] Recently, a meta-analysis of 13 studies involving 9073 patients was carried. These patients required ICD, but there was no need for pacing. The results showed that patients using the two ICDs mentioned above were susceptible to complications to the same extent in such cases.[54] Risk stratification plays a major role in selecting the right ICD for individuals, and these have indeed been a boon.

2. Pharmacological Intervention Using Quinidine

The use of ICD has dramatically reduced fatalities in patients with ventricular fibrillation, but the high cost and associated disadvantages limit their use. In many cases, quinidine, the stereoisomer of Quinine, may prove advantageous. The drug belongs to the Class IA Antiarrhythmic category, which blocks the excessive transient outward potassium current (I_{to}) in Brugada. Therefore, the drug helps maintain the dome of epicardial action potential in the ventricles and averts ST elevation. The drug effectively prevents phase 2 re-entry, which initiates erratic heartbeats, thus proves to be a suitable pharmacological intervention.[12,17]

During the year, 1981 a male suffering from Ventricular fibrillation of idiopathic origin was administered quinidine orally. Even after a follow-up period of 39 years, the patient was free from heart palpitations without any surgical treatment.[55] Many studies suggest that the therapy guided electrophysiologically, can serve as a long-term therapy and alternative to ICDs.[56] The stereoisomer may serve as medication in patients experiencing electrical storms or who have ICDs implanted.[57] Asymptomatic patients seldom encounter arrhythmia, so we cannot draw an exclusive conclusion on this, but a study establishes the drug as a prospective therapy.[58]

3. Use of Catheter Ablation

When the surgical intervention and drugs fail to heal the patients, the physicians resort to using catheter ablation, which includes insertion of a thin catheter endovascularly to target and scar the affected cardiac tissues and thus, block the passage of irregular electrical impulses restoring the rhythm of the heart.[59]

The first study to assess the impact of catheter ablation was performed in the year 2002. Twenty-seven patients were part of the process. The process of mapping served as a tool for targeted delivery of Radiofrequency. It successfully treated the repetitive episodes of ventricular

fibrillation that originated from the Purkinje fibers.[59] The erratic electrical signals arising from the fibers and right ventricular outflow tract (RVOT) were eliminated by catheter ablation in 2003.[60] Subsequently, the specific sites that initiated ventricular ectopia were corroborated.[61]

In a separate study, the use of the catheter succeeded in controlling the Ventricular Fibrillation (VF) storm, reduced the recurrence of erratic heartbeat, standardized electrocardiogram. Patients were kept under surveillance for 12 to 30 months.[62] Catheter ablation on RVOT epicardium normalized ECG pattern and ventricular contractures in nine Brugada symptomatic patients. A long-term follow-up, more than 20 months, gave encouraging results.[63] The study was consolidated for up to 3years, which confirmed the role of ablation in normalizing the heart's electrical activity.[64] All the experiments effectively displayed the ability of catheter ablation; however, we need to consider that the related complications of its use are rare but of grave concern.[65]

Role of Polyunsaturated Fatty Acids in Cardiovascular Disease

Fatty acids are long-chain hydrocarbons having a carboxylic (-COOH) group (alpha terminal) and a methyl group (omega terminal) at the ends. PUFA can be categorized as omega-6 (ω-6 or n-6) and omega-3 (ω-3 or n-3) depending on carbon chain length and the location of the initial double bond from the methyl terminal. Linoleic acid is a n-6 polyunsaturated fatty acid, and α-linolenic acid is an n-3 polyunsaturated fatty acid. Linoleic acid and α-linolenic acid are called "essential fatty acids" as they cannot be synthesized by humans and must be ingested through diet. α-linolenic acid is metabolized to eicosapentaenoic acid docosahexaenoic acid.[4] n-3 polyunsaturated fatty acids are the precursors of anti-inflammatory molecules and are useful for chronic inflammatory conditions.[66] Long-chain omega-3 polyunsaturated fatty acids- eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are richly found in fish oils. Cardiovascular events and mortality can be minimized by the intake of fish or fish oil.[4] The cardioprotective action of n-3 polyunsaturated fatty acids has been linked to several pathways.

Enhanced Endothelial Function

Endothelial dysfunction caused by a loss of endothelium-derived nitric oxide results in atherosclerotic formation and severe vascular events.[4] Translocation and stimulation of endothelial nitric oxide synthase into the cytosol was caused by n-3 polyunsaturated fatty acids, which initiates vasodilation and enhances endothelial function.[67] EPA prevents saturated fatty acid-induced vascular endothelial dysfunction *via* modulating the expression of long-chain acyl-coA synthetase.[68] The endothelial function is enhanced by attenuating the expression of endothelial vascular adhesion molecules, which reduces the leukocyte adhesion to the endothelium.[69]

Influence on Lipid Metabolism

The activity of genes that control lipid homeostasis can be regulated by n-3 PUFA. Large fish oil doses can hinder the synthesis of very-low-density lipoprotein through the impediment of sterol receptor element-binding protein-1c, which lowers serum triglyceride levels.[70] n-3 PUFA alters the high-density lipoprotein by augmenting the large, cholesterol-rich HDL2 fraction and reducing the small, triglyceride-rich HDL3 fraction.[4]

Effect of Anti-inflammatory

Besides regulating lipids, n-3 PUFA exhibits pleiotropic effects.[4] Resolvins, protectins, and G protein-coupled receptor 120 are EPA and DHA metabolites and are engaged in the n-3 polyunsaturated fatty acid-induced anti-inflammatory effects.[71] They can decrease the amount of pro-inflammatory cytokines in the blood and control the intracellular signaling pathways for the inactivation of nuclear transcription factors.[4]

Stabilization of Plaque

The main step in the development of plaque is the multiplication and relocation of smooth muscle cells and EPA and DHA suppress this step. n-3 PUFA prevents the neovascularization of the vasa vasorum, thereby inhibiting plaque formation. Increased plaque stability can be attained by the elevated eicosapentaenoic acid and docosahexaenoic acid tissue levels, as they reduce the infiltration of macrophages and release of matrix metalloproteinases.[4]

Prevention of Cardiac Remodeling

Uptake of n-3 polyunsaturated fatty acid decreases the ventricular remodeling and myocardial fibrosis established by cardiac magnetic resonance.[72] Cardiac remodeling during high-pressure situations can be avoided by 18-hydroxy eicosapentanoic acid, an EPA metabolite.[73] The level of 18-hydroxy eicosapentanoic acid in the blood can be elevated by administering eicosapentanoic acid ethyl ester, thereby avoiding cardiac fibrosis.[71] Eicosapentaenoic acid and docosahexaenoic acid enhance adenosine triphosphate production that results in the better functioning of cardiac mitochondria.[74]

Attenuates Arrhythmia

n-3 polyunsaturated fatty acids avoid tachyarrhythmias and sudden cardiac death by controlling the multiple ion channels activity and stabilizing the cardiomyocyte membrane.[4] EPA & DHA regulate some calcium channels, reduced free cytosolic calcium, and decreased membrane excitability. In cardiac myocytes, they can obstruct the voltage-gated sodium channels, elevate the voltage

threshold for depolarization, and extend the refractory period.[71]

Anti-Thrombotic Effect

Eicosapentaenoic acid can inhibit platelet thromboxane A_2 production, which impacts platelet accumulation and vasoconstriction.[75] n-3 polyunsaturated fatty acids decrease fibrinogen levels and improve tissue plasminogen-activator concentrations.[76]

Enhanced Cognitive Function

One of the potential risks for cardiovascular events is poor cognitive function.[72] The low level of n-3 PUFA is a potential risk for cognitive dysfunction, and the increased n-3 PUFA intake can enhance the cognitive function, thereby decreasing the risk of cardiovascular events.[4]

Increased Exercise Capacity

The decreased exercise tolerance is also a known potential risk for cardiovascular disease. n-3 PUFA increases the exercise capacity in patients with cardiovascular disease. Their uptake leads to the modification of skeletal muscle function and erythrocyte rheology, improving exercise tolerance.[4]

Role of Polyunsaturated Fatty Acids in Brugada Syndrome

Various animal/clinical reports have been shown for secondary prevention of sudden cardiac death/ventricular arrhythmias after myocardial infarction or heart failure using n-3 polyunsaturated fatty acids.[77] It has been reported that dietary fish oil consumption is related with a reduced possibility of sudden cardiac death.[78] The causes of Brugada syndrome include genetic, environmental, and hormonal components.[79] The most feasible mechanism for n-3 polyunsaturated fatty acids' anti-arrhythmic action is altering the cardiac ion channels.[80] The rapid sodium channel current is inhibited by n-3 polyunsaturated fatty acids, while the transient outward potassium current and the delayed outward potassium current are promptly activated.[81] The impediment of transient outward potassium current by n-3 polyunsaturated fatty acids results in restoring electrical homogeneity. The trafficking of ion channels via the subcellular compartments and in lipid rafts may have an intense effect by an elevated concentration of n-3 polyunsaturated fatty acids components in the lipid membrane.[81] Low EPA and DHA are closely related to cardiac events and are the risk factors for ventricular fibrillation in Brugada syndrome patients, indicating that n-3 polyunsaturated fatty acids play significant roles in inhibiting ventricular fibrillation in patients with Brugada syndrome.[4]

Experimental Models of Brugada Syndrome

To understand the mechanism of pathophysiology of Brugada syndrome, it was investigated on various experimental animal models such as mice (murine models), canine models, and transgenic pork (porcine models) to study the mutation of SCN5A gene. This specific gene provides information about sodium channel proteins present in cardiac muscles.[82] In the murine model, the SCN5A gene is knocked out through targeted disruption and then transfected into blastocyst to give male chimera, which is again crossed with female wild type gene to form heterozygous offspring.[83] While, in canine models, the left and right ventricles are perfused arterially, and by far, it is the most widely used model to study cardiac electrophysiology. Although having electrophysiological similarity with the human heart, the porcine model has been limited due to expansiveness. Most of the results obtained from murine model study, using SCN5A gene supports the depolarization hypothesis but a clear interpretation is still yet to be known.[83] Thus, each method has its limitations and advantages where the canine models provide the key to understanding the arrythmia correlated electrocardiogram patterns in patients with brugada.[82]

Conclusion and Future Perspectives

After performing an extensive review of the available data associated with Brugada syndrome, diagnosis, etiology, hormonal role, and various prevention strategies available, it can be interpreted that Brugada syndrome is a disorder resulting from the defects in ion channels caused by genetic factors which can interrupt the normal heart's electrical signals. It can be passed down from the parents to the offspring, which means that if someone has any symptoms or has already had a cardiac arrest, they may stay on a vulnerable stage to develop brugada syndrome. Some triggers that can further complicate this phenomenon which should be avoided to prevent brugada are dehydration, drinking too much alcohol, having a high temperature, abnormal ECG etc.

Patients having abnormal cardiac behavior should undergo regular checkups to continue living a normal life with brugada syndrome keeping few things in mind such as early diagnosis of suffering from any symptoms, maintaining proper electrolyte balance in the body, drinking optimum level of water, getting proper treatment for previous abnormal heart rhythms etc. Few surgical treatments are available to restore the normal heart rhythm and ECG, but their use has been limited due to high cost and complications.

The cardioprotective role of PUFA has been identified. The n-3 polyunsaturated fatty acids were found to inhibit the rapid sodium channel current and the impediment of transient outward potassium current and activation of delayed outward potassium current that results in the restoration of electrical homogeneity. Thus, it can be suggested that high elevated concentrations of EPA and DHA levels from various fish and fish oils can serve

as a beneficial component to minimize cardiovascular events and mortality rate. This aspect can deliver a cost-effective and significant remedy for various cardiovascular arrhythmia-related disorders in the long run.

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Abbreviations

PUFA	Polyunsaturated fatty acids
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
ECG	Electrocardiogram
SCN5A	Sodium voltage gated channel alpha subunit 5
G3PD1-L	Glycerol-3 phosphate dehydrogenase1-like protein
SLMAP	Sarcolemmal membrane-associated protein
TRPM4	Transient receptor potential melastatin protein number 4
ICD	Implantable Cardioverter-Defibrillator
VF	Ventricular Fibrillation
HDL	High density lipoprotein
I_{to}	Outward potassium current
I_{Na}	Sodium current

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