Is Idiopathic Ventricular Fibrillation the same Disease as Brugada Syndrome? Unification Nomenclature Proposal

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Ventricular fibrillation is a very rapid, uncoordinated, ineffective series of contractions throughout the ventricles. Unless stopped, these chaotic impulses are fatal. The idiopathic form, known as idiopathic ventricular fibrillation (IVF) is defined as the one that occurs in absence of any structural heart disease (apparently normal hearts, with noninvasive methods) or functional underlying disease, i.e. in patients without recognizable heart disease. Figure 1.

It is known that the entity is caused by a mutation in the SCNSA gene. This is a missense mutation and exchanges serine by leucine (S1710L), and was identified in a Japanese family, the proband (an individual or member of a family being studied in a genetic investigation; also called index case, propositus) of which was a symptomatic patient with normal baseline ECG (without electrocardiographic Brugada-type pattern) and had IVF episodes in absence of structural heart disease and any typical electrocardiographic pattern [1].

A percentage of IVFs yet to be determined, correspond to Brugada Syndrome (BrS). Both entities have several points in common:

Figure 1: TRUE IDIOPATHIC VENTRICULAR FIBRILLATION ECG
12-lead ECG recording of recent onset VF. True Genetic Genuine IVF (GGIVF) It is a Na+ channel disorder that affects the cardiac alpha subunit: SCNSA. Akai et al have identified a heterozygous Ser1710-to-Leu missense mutation of the SCNSA gene in a 39-year-old man who was admitted to the hospital for recurrent syncope and suffered an episode of spontaneous VF while hospitalized. An ICD was successful in preventing further attacks of palpitations or syncope. Brugada syndrome was not present. The paternal grandfather and a paternal uncle had died suddenly in their sixth decade by unknown cause; the parents and siblings were asymptomatic.
1. Both are predominant in the male gender (much greater predominance of the male gender in BrS (8:1 or 10:1) in comparison to IVF, 2:1);
2. Both are observed more frequently in people in their middle age or in young adults;
3. Both occur in apparently normal hearts, without structural heart disease with noninvasive methods;
4. Both are not generally related to stress [2];
5. Both affect the same SCN5A gene;
6. Both have the same OMIM NO number (600163);
7. Both have the same locus 3p21-p24 (Note: variant 3 of long QT syndrome (LQT3) also has the same symbol of the SCN5A gene, the same OMIM NO number (600163) and the same locus (3p21-p24);
8. Both have a similar rate of spontaneous severe arrhythmic events;
9. Both have a similar rate of inducibility in electrophysiological study.

In spite of several coincidences, both entities differ regarding:

1. Percentage of predominance of the male gender: 8:1 or 10:1 for BrS versus 3:1 or 2:1 for IVF;
2. Positive family history mentioned frequently only in BrS. In IVF familial involvement is rare;
3. Incidence of events with a great predominance (80% of cases) during night sleep only in BrS [3];
4. Electrocardiogram: in IVF, QTc interval values show a tendency to be short (QTc ≤ 360 ms) in the male gender. Regrettably, short QTc interval values may be observed in normal people, especially with slow heart rates [4]. In BrS, in the dynamic, permanent, transitory or intermittent, or concealed form, there is the presence of the so-called electrocardiographic Brugada sign, electrocardiographic Brugada phenotype, or electrocardiographic Brugada pattern type 1, characterized by ST segment elevation \( ≥ 2 \) mm (0.2 mV) of superior convexity or downward straight, followed by negative T wave in right precordial leads (V1-V2) or in the antero-septal wall (V1-V3). Figure 2.

This electrocardiographic factor definitive for diagnosis indicates the need of performing a thorough analysis of baseline ECG and in all cases, ECG should be performed including high right accessory leads (V1H – over the 3rd or 2nd intercostal space, just to the right of the sternum and V2H – over the 3rd or 2nd intercostal space, just to the left of the sternum) because it is well known that they increase sensitivity to detect the characteristic electrocardiographic pattern [5; 6]. When present in baseline ECG, electrocardiographic patterns type 2 (saddleback appearance with a high take-off ST-segment elevation of ≥2 mm followed by a trough displaying ≥1 mm ST elevation followed by a positive T wave) or 3 (saddleback or coved appearance with ST segment elevation of <1 mm) in symptomatic patients with syncope by unknown cause or aborted sudden cardiac death, or before clinical suspicion by positive family history, pharmacological tests should be conducted using class IA (ajmaline and procainamide) and IC (flecainide and pilsicainide) antiarrhythmic agents, as they are the only resources capable of differentiating them. Due to its pharmacological kinetic profile, the drug of choice for this end is ajmaline. This drug is used endovenously in a 10 mg dose each two minutes, until a 1 mg/kg dose is reached. A QRS complex broadening >30% or appearance of typical Brugada pattern type 1, or premature contractions is considered events that indicate the test has ended [7].
The passage from normal electrocardiographic pattern or from Brugada type 2 or 3 into pattern type 1, is considered a positive test. In a patient with history of aborted sudden cardiac death or syncope, without structural heart disease, in whom EV ajmaline test causes electrocardiographic Brugada pattern type 1, implantation of automatic cardioverter defibrillator is indicated [8; 9; 10]. In some patients initially classified as IVF carriers, ajmaline or procainamide test unmasks typical Brugada pattern type 1 in ECG, suggesting that the percentage of IVF that are true BrS could be higher than what was previously suspected [11].

In patients with normal baseline ECG, approximately 2% of pharmacological tests results positive. The pharmacological test is indicated in all patients that suffered aborted sudden cardiac death or unexplained syncope, without structural heart disease, in whom baseline ECG is normal or showing electrocardiographic patterns types 2 or 3. It is also indicated in the relatives of affected patients. The pharmacological test in BrS is considered to be a very useful tool [12]. Probably, approximately a 40% to 60% of all cases of true IVF correspond to BrS [13].

Viskin et al [3], studied the prevalence of Brugada sign in 39 patients carriers of IVF and in 592 normal controls with matched ages. The electrocardiographic tracings were grouped in 3 categories according to pre-determined criteria:

1. Definitive presence of Brugada sign;
2. Questionable presence of Brugada sign;
3. Absence of Brugada sign.

The electrocardiographic tracings were analyzed in a blind way by 4 experts in electrocardiography (they ignored the clinical status of patients).

21% of patients (8 patients) carriers of IVF and none from the control group had criteria for the definitive presence of Brugada sign (p < 0.005). Thus, the presence of a sign of definitive Brugada in ECG constitutes a specific marker of arrhythmic risk.

The questionable presence of Brugada sign was observed in 2 patients carriers of IVF (5%) and in 1% of controls.

A normal baseline ECG was found in 31 from 39 patient’s carriers of IVF (79%). When both groups (IVF and Brugada) were compared, it was verified that both were similar in age and had a similar rate of spontaneous events, and had similar inducibility in electrophysiologic study; however, both groups were different regarding gender, positive family history, and incidence of events during night sleep.

Remme et al [14], studied retrospectively 37 patients who survived out-of-hospital cardiac arrest, referred to the UMC Utrecht Institute in The Netherlands, diagnosed as being carriers of IVF. From this set, 9 patients (24% group I) were diagnosed as potential carriers of BrS, based on the presence in baseline ECG of incomplete right bundle branch block (IRBBB) pattern and ST segment elevation ≥ 1 mm in the right precordial leads or from V1 through V3.

Three patients (8% group II) showed IRBBB and ST segment elevation ≥ 2 mm in right precordial leads or from V1 through V3.

When the intermittent presence of electrocardiographic manifestations or their appearance when using class I antiarrhythmic agents, the patients belonging to group I (a total of 9) were reduced to only 2 (5%) and from group II only 3%.

The authors concluded that depending on the criterion used, from all IVF, 3% to 24% belong to BrS. In a follow up of more than 6 years, the rate or recurrence of significant events such as syncope or sudden cardiac death was 43%.

It has been observed that some cases of IVF are due to sympathetic autonomic dysfunction, which can be shown by abnormal uptake of I 123 by using the scintilography technique with (123)I-meta-iodo-benzylguanidine ((123)I-MIBG SPECT) [15].

There are reports about a few patients in whom baseline ECG showed idiopathic J wave with J point and ST segment elevation with superior convexity, located in the inferior wall (DII, DIII, and aVF) and/or low left lateral wall (V5-V6) [16]. This electrocardiographic pattern is very similar by its profile, to the Greek letter Lambda, which is the name given to it by Gussak et al: "Lambda wave" [17], taking as basis the report of a case published by us [18]. Figure 3.
Regrettably, some authors call these cases as IVF [19]. We think and propose as a more appropriate name for these forms, BrS variant or atypical BrS, based on the fact that a G752R has been identified in the SCN5A gene [20].

The use of pilsicainide as pharmacological test may increase ST segment elevation in inferior leads and cause concomitant ST segment depression from V2 through V6, with appearance of premature ventricular contractions with two morphologies that may trigger polymorphic VT run [21].

Oseke et al [22], presented a case of a 21-year-old young man, who triggered a run of monomorphic VT in stress test, with complete left bundle branch block (CLBBB) pattern, and right inferior electric axis without proof of underlying structural heart disease, and whose ECG revealed ST segment elevation in the inferior wall after EV injection of propafenone.

It has been published that a patient carrier of classical electrocardiographic Brugada phenotype, with use of EV ajmaline developed additional paradoxical ST segment elevation in inferior wall leads [23].

A case of Brugada syndrome, genetically confirmed, and characterized by the presence of ST segment elevation concomitantly in the inferior wall and right precordial leads has been described [24].

Due to the reasons presented above, we propose that the entity currently called IVF should be called True Genetic Genuine Ventricular Fibrillation (GGVF), since it is due to a known mutation, and this form is no longer idiopathic, cryptogenetic, essential, or primary.

Additionally, the entity that presents spontaneous baseline ECG with ST segment elevation in the inferior or infero-apical wall without apparent structural heart disease should be called BrS variant or atypical BrS, but not IVF.

**Management**

The procedure of radiofrequency ablation in IVF could be indicated in cases of patients in whom cardioverter defibrillator was implanted, in order to decrease the number of shocks the device attempts to trigger. The catheter applies radiofrequency energy on the distal portion of the His-Purkinje system (focal ablation of triggering premature contraction). The procedure seems to be an efficient resource in IVF, and after the procedure the patient may remain noninducible [25].

Oversensing of T wave may complicate the clinical course after a successful ablation of malignant Purkinje ectopies [26].

On occasions, the source of origin is the right ventricle outflow tract (RVOT). The initial premature contraction in IVF shows the same morphology and a very short coupling (average of 245 +/- 28 ms). The application was efficient in 100% of the cases in a 16-patient population with a follow up of 54 +/- 39 months [27]. The treatment with radiofrequency energy may be efficient in the focal removal of premature contractions originating in the RVOT, and in the focal distal portion of the Purkinje system. This procedure is currently included in the guidelines of secondary prevention (recurrent syncope and patients who survived a prior episode of sudden cardiac death by cardiac arrest) of sudden death [28], and the patient usually remains noninducible [29].
Use of Implantable Cardioverter Defibrillator (ICD)

The treatment of choice is ICD in patients with spontaneous sustained VT/VF, poorly tolerated, without demonstrable heart disease, and in whom the pharmacological approach or ablative therapy cannot be performed or failed (level B of test) [30].

ICD in all cases is a palliative approach, since it does not prevent recurrence. Thus, when events recur or constitute electric storms, successive shocks could be painful and have disastrous consequences, causing a significant morbidity [31]. Additionally, ICD remains restricted in many countries, and is associated to prohibitive costs for the community. In such cases, ablation therapy with radiofrequency could be very useful [32].

In refractory cases with electric storm, a transitory biventricular circulatory support system Abiomed AB5000 could be implanted temporarily until a permanent solution is found [33].

Conclusion

IVF is defined as the ventricular fibrillation that occurs in absence of any structural or functional heart disease with normal baseline ECG and with a certain tendency to short QTc in males. It has a high rate of recurrence. It is caused by premature contraction originated in the peripheral region of the His-Purkinje system or in the RVOT. In some cases it has been shown that they are due to sympathetic autonomic dysfunction.

There are cases of arguable percentage, which could correspond to true BrS or its variant. We propose that IVFs should be called True Genetic Ventricular Fibrillation, since it is due to a known mutation, no longer being idiopathic, cryptogenetic, essential or primary.

The entities that show spontaneous baseline ECG with ST segment elevation in the inferior or infero-apical wall without apparent structural heart disease should be called BrS variant or atypical BrS, and not IVFs.

The management could include automatic implantable cardioverter defibrillator and/or application of radiofrequency energy in the distal portion of the His-Purkinje system and in the RVOT. A transitory biventricular circulation support system Abiomed AB5000 as a temporary solution until a permanent solution is found, may be applied in patients with spontaneous repetitive and sustained ventricular tachycardia.

Bibliography


CV of the author

- Professor of ABC Faculty Santo André São Paulo Brazil.
- Director of the Department of Electro-vectocardiography of the Cardiology, discipline of the ABC School of Medicine.
- Member of the Expert Committee of the Second Consensus Conference Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association about Brugada syndrome.
- Scientific President for the First Virtual Symposium about the Brugada Syndrome on the Internet (2002).
- Member of the Nomenclature Committee in Electrocardiogram in Rest by the Brazilian Society of Cardiology.
- Interpretation Guidelines of Electrocardiogram in Rest by the Brazilian Society of Cardiology (Arq Bras Cardiol 2003;80:1-18)
- Vice President of the Steering Committee of the ISHNE Heart failure World-Wide Internet Symposium April 1 April 30, 2006.
- Member of the Scientific Committee, as Coordinator of Lectures and Narrations, 5th Virtual Congress of Cardiology by the Internet, Argentine Federation of Cardiology, September 1st - November 30th, 2007.

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