Short-coupled variant of torsades de pointes and normal QT interval: differential diagnosis with Brugada syndrome

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Key words: Short-coupled variant of Torsades de Pointes and normal QT interval – Brugada syndrome – Torsade de Pointes – Polymorphic Ventricular Tachycardia.

Abstract

In this review, we show the main characteristics of the so-called short-coupled variant of torsades de pointes (TdP) and normal QT interval and the differential aspects with Brugada syndrome (BrS).

Both entities occur in patients without apparent structural heart disease, possibly with positive family background, predominantly affect people in their productive time of life, have a high tendency to appearance of syncope and/or sudden cardiac death as a consequence of bursts of polymorphic ventricular tachycardia (PVT) that degenerate into ventricular fibrillation (VF), not related to strain and in which an extremely short coupling of initial extra-systole, frequent episodes of electrical storm, normal(or near normal) QT/QTc interval on ECG and heterogeneity of ventricular refractoriness in some area of ventricular wall thickness are observed.

Additionally, both could be related to hypokalemia[1,2]. Even presenting so many coincidences, there are elements that enable a differentiation between both entities, such as the genetic aspects known only in BrS, race incidence and different predominant gender, ECG characteristics (although in both prominent J waves have been described)[3], morphological aspects of tachyarrhythmic events, and the presence of supraventricular arrhythmias, triggers, preferential moments of tachyarrhythmic events and different response to therapeutic measures. Analysis of the etiology and mechanism of the tachycardia is of paramount importance for initiation of specific therapies. Although mechanical cardiac function may seem normal, such patients might have certain discrete anatomic abnormalities, unidentifiable with current investigation tools[4].

The short-coupled variant of torsades de pointes and normal QT interval is a polymorphic, polymorphous or multiform[5] PVT with typical morphology of TdP: the QRS morphology shows alternating polarity in a modulating pattern, so that the complexes appear to be twisting around the baseline, observed in patients without organic heart disease, adverse drug effects, or electrolyte disturbances, which occurs spontaneously and initiated by short-

coupled premature ventricular complex (240 ms in average) in patients with normal QT interval[6].

The classical or typical TdP on the other hand is characterized not only by its particular ECG pattern, but also by its context of congenital or acquired long QT syndrome and with long coupling interval (telediastolic) of the initial premature beat. In short-coupled variant of TdP exists an unusual particularity: an extremely short coupling interval of the first beat or of the isolated premature beats. These patients have clinical and electrocardiographic abnormalities that are sufficiently coherent for them to constitute a new pathological entity, which Leenhardt et al., suggest calling "torsades de pointes with a short coupling interval"[7;8] (Leenhardt disease).

The entity is observed in young, healthy children and young adults (average: 34.6 years) and most probably covers several underlying electrophysiological abnormalities[9].

Some ECG recordings showed isolated ventricular extrasystoles with short coupling intervals. The PVT is characterized by changing QRS morphology, sometimes accompanied by slight changes in the rate. It is a particularly malignant form of PVT that is thought to be intermediate between ordinary PVT, and ventricular fibrillation (VF).

There are references in literature of electrical storm[10] (ES) and intractable VF lifesaving with cardiopulmonary bypass or deep sedation followed by a combination therapy using verapamil and mexiletine. In this case, the ECG pattern consisting of a prominent J wave in leads V3-V6 that disappears with the use of those drugs. The ES was evoked with autonomic receptor stimulation and a blockade test. The patient's frequent VF attacks were triggered by short-coupled premature ventricular contractions with RBBB morphology and left-axis deviation[3].

There are references of hypokalemia as etiology[3] (K=3.4 mmol/L). Monophasic action potential duration at 90% repolarization (MAPD90) in the right ventricular apex was very short (175 ms). The MAPD90 returned to normal after loading potassium (230 ms) and after oral amiodarone therapy (240 ms), and PVT no longer occurred. With continued oral amiodarone and spironolactone therapy, the patient has been free of syncope attack over a follow-up period of 5 years. A familial history of TdP and SCD was described[11].

Heterogeneity of ventricular refractoriness was observed together with shortness of the effective refractory period measured at the right ventricular inflow site where the paced QRS morphology was the same as that of the initial beat of TdP. Verapamil could suppress frequent ventricular premature complexes with a short coupling interval, which lead to TDP.

PVT can be induced by triple ventricular extrastimuli.

A pure potassium channel blocker was successful in inhibiting PVT inducibility by prolongation of refractoriness. These results suggested that triggered ventricular premature complexes might be representing the initiating mechanism, whereas the shortness of local refractory period and heterogeneity of ventricular refractoriness may play a role in the development and the maintenance of TdP[12].

This kind of VT had a high incidence of SCD, so it was very important for physicians to identify and treat it promptly with long-term verapamil[13]. Although verapamil is frequently recommended, mortality rates remain high[14].

The entity is a malignant disease that shares several characteristics with IVF.

In Table 1 below, we show the possible etiology of truly PVT and TdP.

ETIOLOGY OF POLYMORPHIC VENTRICULAR TACHYCARDIA
(TRULY PVT AND TdP)

A) WITH STRUCTURAL HEART DISEASE
    1) Chronic coronary heart disease;
    2) Prinzmetal variant;
    3) Acute myocardial infarction;
    4) Severe heart failure.
B) WITHOUT STRUCTURAL HEART DISEASE
    1) Congenital long QT syndrome: TdP associated with long QT interval related to bradyarrhythmia. The most prevalent inclusion bradyarrhythmia is > or = second-degree AV block, preceding pauses or electrolytes abnormalities.

Predictors for these are previous amiodarone or diuretic intake, presentation as syncope, low serum potassium level, and longer QTc at admission[15];

2) Congenital short QT syndrome;
3) Genuine idiopathic ventricular fibrillation with normal basal electrocardiogram;
4) Brugada syndrome;
5) Some Sudden Unexpected Nocturnal Death Syndrome (SUNDS) or SUDS;
6) Idiopathic ventricular tachycardia;
7) PVT of ventricular pre-excitation* (atrial fibrillation with a rapid ventricular response);
8) PVT verapamil sensitive or TdP with short coupling interval in a patient without organic heart disease and normal QT interval (Leenhardt disease);
9) Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT); catecholamine-sensitive polymorphic ventricular tachycardia or Familial Polymorphic Ventricular Tachycardia (FPVT).

* Presence of multiple accessory pathways, posteroseptal accessory pathways, and a pre-excited R-R interval of less than 220 ms during atrial fibrillation are associated with a higher risk for VF.

In Table 2 below we show the differential diagnosis between truly PVT and TdP.

Table 2

DIFFERENTIAL DIAGNOSIS BETWEEN TRULY PVT AND TdP

	SHORT-COUPLED VARIANT OF PVT	TdP
Couplet of initial premature ventricular complex:	very short: 240 ms in average.	long or telediastolic: 600 ms.
basal heart rate of ecg:	normal.	bradycardia tendency.
qt interval	normal	prolonged: in average 600 ms
u wave of basal ecg	absent	increases in voltage.
rate of event:	very fast. is frequent from	fast. rates typically greater

	260 to 352 bpm.	than 200 beats/m (200 to 250 bpm)
etiology	a) with structural heart disease: 1) Chronic coronary heart disease; 2) Prinzmetal variant; 3) Acute myocardial infarction; 4) Severe heart failure. b) without structural heart disease: 1) brs; 2) genuine ivf; 3) pvt of ventricular pre-excitation; 4) pvt verapamil sensitive; 5) catecholaminergic pvt.	LQTS: a) congenital; b) acquired: (including drug and metabolic causes[14])
Prevalence:	infrequent	more frequent
Magnesium IV therapy and other therapies:	ICD is not indicated in isolation, but associated in cases of verapamil-sensitive PVT, with high doses of verapamil. the drug increases the coupling interval of the extrasystoles and decreases or even suppresses some repetitive forms. this is the only drug apparently active on arrhythmias; however, it does not prevent sudden death (SD). in recurrent forms the indications for an icd should be considered. in BrS implantation of defibrillators is recommended associated with quinidine, cilostazol, isoproterenol. in CPVT beta-blockers are the treatment of choice[16]. in	Attenuation of early after depolarization in acquired forms. in congenitalLQTS therapeutic options include: beta-blockers, cardiac sympathetic denervation, and implantation of pacemakers or ICDand genotype-specific therapy[16].

	30% of patients an icd may be required. life-long beta-blocker therapy is required. in some patients SCD occurred, probably due to treatment interruption[8].	

Observation: There is a description in a 72-year-old woman with a history of recurrent syncope over 3 years of association with congenital long QT syndrome with late onset of bradycardia-dependent and short-coupled variant of TdP. The patient's stormy course was only controlled with pacing. She received a permanent dual-chamber pacemaker and prophylactically a beta-blocker was added. Over the subsequent 14 months she has remained asymptomatic[17].

In Table 3 below, we show the main differential characteristics between Brugada syndrome and short-coupled variant of torsades de pointes and normal QT interval.

Table 3

MAIN DIFFERENTIAL CHARACTERISTICS BETWEEN SHORT-COUPLED VARIANT OF TORSADES DE POINTES AND NORMAL QT INTERVAL AND BRUGADA SYNDROME

	SHORT-COUPLED VARIANT OF TORSADES DE POINTES AND NORMAL QT INTERVAL	BRUGADA SYNDROME
FAMILIAL BACKGROUND	There are references of familial forms.	Sporadic (approximately 65%) or autosomal dominant pattern of transmission (35%) characterized with incomplete penetrance
AGE:	Young, healthy children and young adults	Average 41±15 years. During adulthood may

	(average: 34.6 years).	be observed in infants, children and elderly people (less frequently).
RACE:	Caucasian predominance.	Yellow predominance.
RELATIVE SEX INCIDENCE:	Not referred. Women have a higher incidence of TdP[18].	8:1 to 10:1 men vs. women.
GENES/CHROMOSOME AFFECTED:	?	**SBr1:** SCN5A Nav1.5, the gene encoding for the alpha subunit of the cardiac Na^+ channel on chromosome 3 locus 3p21. Present in 18-30% of cases. **SBr2:** Locus3p24; I_{Na^+} channel; Gene GPD1L. **SBr3:** Locus 12p13.3; $I_{Ca^{+2}}$ channel; Gene: CACNA1C, $Ca_v1.2$ **SBr4:** Locus: 10p12.33; Channel: $I_{Ca^{+2}}$; Gene: CACNB2b, Cavβ2b.
ECG CHARACTERISTICS:	Normal. Some recordings show isolated premature ventricular contractions with short coupling intervals. There are references of prominent J wave in	Possibly, prolongation of P-wave duration, long PR interval (50%). This prolongation of the PR interval is observed predominantly in cases where the SCN5A gene mutation can be proven

	middle and left precordial leads V_3-V_6[10]. Normal QTc interval.	(carriers). ST-segment elevation in the right precordial leads (V_1-V_2) or from V_1 to V_3 (antero-septal wall): J wave (Brugada type 1, Brugada signal or Brugada phenotype). Exceptionally the ST segment elevation is observed in inferior leads[19] or left precordial leads[20]. The ECG changes are often dynamic or concealed. QTc interval: normal or slightly long[21].
SUPRAVENTRICULAR ARRHYTHMIAS:	Not mentioned in literature.	Present in 29% of cases. Paroxysmal atrial fibrillation; atrioventricular junctional rhythms episodes and Wolff-Parkinson-White syndrome[22].
TRIGGERS:	The ES was evoked with autonomic receptor	Fever, vagotonic agents or nocturnal vagotony, α

	stimulation and a blockade test. Shortness of local effective refractory period measured at the right ventricular inflow site where the paced QRS morphology was the same as that of the initial beat of TdP. Heterogeneity of ventricular refractoriness is the one of the main triggers. A pure potassium channel blocker was successful in inhibiting PVT inducibility by prolongation of refractoriness. They're a reference of hypokalemia as trigger.	adrenergic agonists, beta adrenergic blockers, tricyclic or tetracyclic antidepressants, first generation antihistamines (dimenhydrinate infusion), glucose associated with insulin, hypokalemia, antimalarials, anesthetics, alcohol and cocaine toxicity.
VT MORPHOLOGY:	Polymorphic and with alternating polarity in a modulating pattern, so that the complexes appear to be twisting around the baseline. Sometimes accompanied by slight changes in rate.	Polymorphic. Rarely monomorphic.
MOMENT OF PVT/VF EPISODES:	At rest.	At rest and at night

		during sleep (85% of cases). Nocturnal vagal predominance.
ELECTRICAL STORM/VF:	Frequent.	Frequent.
ES TREATMENT:	Cardiopulmonary bypass or deep sedation followed by a combination therapy using verapamil and mexiletine[10].	Cardiopulmonary bypass; general anesthesia; isoproterenol. Orthotopic transplantation was referred as heroic procedure[23].
IMPLANTABLE CARDIOVERTER/DEFIBRILLATOR ICD:	Although verapamil is frequently recommended, mortality rates remain high[16]. During a mean follow-up of 7 years of 14 patients, Leenhardt et al have 5 deaths (4 SD). Nine patients are alive, 3 with ICD and 6 treated with verapamil alone[8].	ICD is the only currently proven effective treatment. Inappropriate shocks also may be delivered for atrial fibrillation, and other types of supraventricular tachycardia, prompting ICD reprogramming and/or adjunctive therapy. Therapy with ICD remains restricted in many countries, and is associated with a prohibitive cost for the community, and may be a cause of significant morbidity in patients

		with frequent episodes of arrhythmia or ES.
RADIOFREQUENCY CATHETER ABLATION:	They cannot be treated by catheter ablation[24].	Haissaguerre et al[25], localized by mapping the earliest endocardial activity and by focal radiofrequency ablation of PVT/VF in three patients with Brugada Syndrome. The authors conclude that triggers from the Purkinje arborization or the RVOT have a crucial role in initiating VF associated with Brugada syndrome.
TREATMENT WITH DRUGS:	Verapamil had an excellent therapeutic effect for it. The drug could suppress frequent ventricular premature complexes with a short coupling interval, which lead to TdP[12] Deep sedation followed by a combination therapy using verapamil and mexiletine is mentioned as effective[10].	1) Quinidine: this drug in high doses (1200-1500 mg/day) is effective in restoring the epicardial AP dome, thus normalizing ST-segment and preventing phase 2 reentry and PVT, because it is a transient outward current blocker. In experimental models and clinically, quinidine may be an alternative strategy to ICD

		placement in asymptomatic patients with Brugada syndrome and inducible arrhythmia[26]. 2) Cilostazol: It is a quinolinone derivative that inhibits cellular phosphodiesterase type III. The drug acts by suppression of I(to) activity secondary to the increase in heart rate and/or to an increase in Ca^{2+} current due to an elevation of intracellular cyclic AMP concentration via inhibition of type III phosphodiesterase activity;[27]. 3) Isoproterenol: It is a drug that boosts the L-type Ca^{2+} current. It is indicated in ES in association with general anesthesia and cardiopulmonary bypass. Oral quinidine bisulphate at a dose of 1000mg/day can

		successfully suppress the ES[28]. 4) Sotalol: there is one reference in a 53-year-old man that carried a Brugada syndrome sodium channel SCN5A mutation (4189delT) with recurrent syncopal events and a malignant family history treated for 13 years with sotalol drug therapy with no further occurrence of symptoms[29].

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