PR Interval Shortening in Patients with Catecholaminergic Polymorphic Ventricular Tachycardia

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Every year in United States, between 5,000 and 7,000 children die, or 1.5 to 8.0 per 100,000. Sudden Cardiac Death (SCD) accounts for 5% of all cases of infantile deaths, excluding patients with Sudden Death Infant Syndrome (SIDS) (1). Usually, cardiological or non cardiological causes are found for SD (Sudden Death) in young people and children; nevertheless, in 18% of cases, these are not detected (1,2). One of the main causes for SCD in young people and children without underlying heart diseases, are primary electrical diseases or "channelopathies". Currently, "channelopathies" include: long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, and with some restrictions, arrhythmogenic right ventricular dysplasia/cardiomyopathy (2-9). Nearly all "channelopathies" are clinico-electrocardiographic syndromes, the initial diagnosis of which, in most cases, arises from typical ECG changes and "channelopathies" symptoms (syncopes, history of SCD in family members). In asymptomatic patients, diagnosis is based on typical ECG changes (QT prolongation or shortening, ST segment elevation, etc.)

For the differential diagnosis within the group of "channelopathies", the following electrocardiographic criteria may be used: ECG patterns of different variants of long QT syndrome (3), types of ST segment elevation in Brugada syndrome (4), variants of short QT (typical or pause-dependent) (5). "Minor" and "major" diagnostic criteria have been determined for arrhythmogenic right ventricular dysplasia (cardiomyopathy) (6). From all the mentioned pathologies, only catecholaminergic polymorphic ventricular tachycardia (CPVT) is diagnosed at the time of recording this typical ventricular arrhythmia, which may turn into a fatal disorder and

cause SCD (7-12). Therefore, to prevent SCD in these patients, it would be necessary to develop early and pre-clinical diagnostic criteria for CPVT. The main purpose of our research is to assess the specific features of sinus rhythm in CPVT patients, which may help in detecting early groups in high risk, both in the general population and in symptomatic patients.

Material and methods

There were 20 patients evaluated with CPVT, between 3 and 7 years old (average 10.6 ± 3.4 years old): 11 boys and 9 girls. The enrollment criteria, determined by ECG, treadmill test or Holter monitoring, were the following: tachycardia "runs" of 3 or more beats with broad QRS (> 120 ms); at least 2 complexes with different morphology within one "run"; rate greater than 120 bpm or superior to 25% of normal rate, corresponding to the age of the patient (13); AV dissociation within the "run". Patients with underlying heart diseases, long QT syndrome (QTc > 440 ms), or ST segment elevation in right precordial leads were excluded. None of the enrolled patients was receiving digoxin. To prove the idiopathic character of the arrhythmias in the selected patients and rule out structural heart diseases, coronary artery diseases, concomitant chronic diseases, electrolytic disorders, the following diagnostic methods were used: questions, physical examination, lab analyses (blood and urine), ECG, roentgenogram and echocardiography. Standard rest ECG and 24 h Holter monitoring (Oxford, Medilog, UK equipment) were conducted in all patients. The data obtained were compared with ECG (13) and Holter (14) guidelines corresponding to the age and gender of the patients. The QTc interval was estimated with the formula: $QTc = QT/\sqrt{RR}$ and the QTc interval value was considered as prolonged when it exceeded 440 ms. In the cases of sinus arrhythmias, to estimate QTc a mean value of RR intervals was used. With the results from Holter monitoring, average time-domain of heart rate variability (HRV) was evaluated and circadian index (CI) was estimated, as well as the relationship between daily and nightly HR (4,15).

Statistical estimations were made with the "Statistica" software package.

Results

The first events of polymorphic VT were diagnosed with the following methods: Holter monitoring – 12 (60%), rest ECG – 6 (30%), and treadmill test – 2 (10%). The recorded arrhythmias were bidirectional ventricular tachycardias, with transient anterior and posterior hemiblock morphology in standard leads and right bundle branch block morphology in precordial leads (Figure 1).

Fig. 1. Recording of bidirectional ventricular tachycardia with HR 140 bpm in a 1-year-old male patient. In standard leads there is evidence of electrical axis alternation in QRS complexes and right bundle branch block in precordial leads.

In 13 (65%) patients studied with rest ECG or Holter monitoring, transient PR interval shortening was detected (PR < 0.11 s), without electrocardiographic signs of Wolf-Parkinson-White syndrome (Fig. 2). Moreover, in 6 of these patients, Wolf-Parkinson-White syndrome had been ruled out with invasive or noninvasive electrophysiological studies. In 7 patients, PR shortening was transitory, with periodical normalization of AV conduction. During electrophysiological studies, VT was not triggered; however, one supraventricular tachycardia by nodal reentry occurred, which was ablated by radiofrequency. Nevertheless, in these patients with Holter monitoring, CPVT events were detected.

Fig. 2. In 12-lead ECG there is evidence of 50 bpm sinus bradycardia (A) with PR interval shortening (0.1 s); in Holter (B), bidirectional VT is detected with 160-180 bpm HR, triggered with physical stress in a 9-year-old girl.

In their clinical history, all patients with CPVT presented syncope events, caused by physical stress (dancing, strength training, athletics, etc.) or emotional stress. Six patients had received neurological treatment for alleged diagnosis of epilepsy. In the group without PR interval shortening, the rate of syncopal events before starting a treatment was 1 to 2 cases per year (an

average of 0.6 ± 0.89 cases per year); at the same time, between children with PR shortening, this rate was 9.1 ± 9.2 cases per year (3 to 36 cases per year). Four patients with PR shortening showed SCD and syncope background between first-degree relatives. Two patients died suddenly during follow up. Between the patients with PR shortening, rest HR was 56.3 ± 8.7 bpm, for a normal average value (for sex and gender) of 88 ± 11 bpm. In patients with preserved AV conduction, the corresponding values were 78.1 ± 2.8 and 83.1 ± 16.8 bpm ($p>0.05$). A patient with PR shortening presented complete right bundle branch block. During Holter monitoring, in 6 patients (46.2%) there were events of bidirectional VT and besides, "runs" of paroxysmal supraventricular tachycardia (PSVT) and paroxysmal AF, which occurred in isolation and also before, "within" or after VT events (Figure 3). Three patients (27.3%) presented AV dissociation. In Figure 4 we show circadian profile for 372 VT events recorded with Holter. In general, these VT events occurred during periods of activity of the patients, but sometimes, the events were recorded during sleep (with 110-120 bpm rate). There were no differences detected in the circadian profile of arrhythmias in patients with PR interval shortening and normal.

Fig. 3: Holter recording of an 11-year-old girl. PSVT is observed with 192 bpm and "runs" of bidirectional VT of 150-160 bpm "within" PSVT.

Fig. 4. Circadian profile of 372 events of bidirectional polymorphic VT, recorded in 20 patients from 3 to 17 (10.6 ± 3.4) years old, with Holter monitoring.

The values indicating HRV in all patients with PR shortening were increased, when compared with normal values (according to gender and age): mean 870.5 ± 125 ms vs. 706 ± 46 ms ($p<0.05$); SDNN 237 ± 71 ms vs. 153 ± 26 ms ($p>0.05$); SDNNi 130 ± 45 ms vs. 78 ± 14 ms ($p<0.05$); SDANNi 199 ± 68 ms vs. 134 ± 34 ms ($p>0.05$); rMSSD 117 ± 44 ms vs. 60 ± 12 ms ($p<0.05$); pNN50 47 ± 12% vs. 27 ± 12% ($p<0.02$); CI 1.49 ± 0.13 vs. 1.29 ± 0.03 ($p<0.05$). Under the management with beta-blockers (propranolol, atenolol, nadolol 1-2 mg/kg) and in a

case with propafenone (10 mg/kg) and combination of atenolol and verapamil (3 mg/kg), a mean increase was observed (decrease of HR) of 870.5 ± 114 ms up to 885.4 ± 113 ms, which usually occurs when using beta-blockers. However, the other indicators of HRV presented a statistically nonsignificant decrease with a tendency to normalization.

Discussion

In prior publications, the tendency to bradycardia has already been proved in patients with CPVT (7-12). Nevertheless, we did not find publications about the association between CPVT and PR interval shortening. Probably, this is due to the very small amount of this type of patients. Therefore, it is very difficult to assess the clinico-electrocardiographic features of this type of arrhythmias. To this date, the study by N. Sumimoto et al (8) has been the most important one. This study included 29 patients (mean age 10.3 ± 6.1 years old) with CPVT. The patients included did not present preexcitation syndrome and their average PR interval was 0.13 ± 0.02 s, which may be considered as a short PR interval, mostly within the context of HR of 59 ± 11 bpm. In patients who died suddenly, PR interval was shorter than between survivors (0.131 ± 0.07 vs. 0.135 ± 0.023, respectively). A. Leenhard et al (7) presented an analysis of 21 pediatric patients with CPVT. In this study, criteria similar to ours were taken into account: VT morphology, sinus bradycardia, PSVT, syncopes, and SCD family history, QT interval, etc. However, PR interval shortening was not triggered as a typical sign of these patients. In the work by H. Swan et al (12), 14 patients with CPVT were evaluated, and 9 among them presented syncopes induced by physical stress. In none of the patients AV conduction disorders were detected (neither in ECG nor in electrophysiological study (EPS)). It is noteworthy that invasive EPS did not trigger ventricular arrhythmias in none of the cases, which highlights the significant role of noninvasive electrocardiological studies to diagnose this type of arrhythmia.

Nevertheless, some reports of clinical cases were published, the authors of which mentioned PR shortening in patients with CPVT. Likewise, in the work by D. Reid et al (16), a 6-year-old English girl was reported as having a bidirectional VT event; her PR interval was short (0.11 s).

There were also other reports of PR interval shortening in patients with different ages and ethnicities, who presented CPVT events (17-19). All this supports our idea about PR interval shortening, as a typical electrocardiographic pattern of some variants of CPVT in children. The authors of the abovementioned works did not emphasize the association between PR shortening and CPVT, probably because the cases described were very isolated. However, we consider this association as a very important phenomenon, since it has been shown that this electrocardiographic pattern is frequently observed (more than what was believed previously) in patients with CPVT; moreover, it does not depend on the ethnicity of the patient (20). In our study, the ethnic group was not completely homogeneous, but most patients were Eastern European.

The relationship between AV conduction delay and the mechanisms for malignant ventricular arrhythmias development has not been very much studied yet. The appearance of supraventricular arrhythmias is quite typical in patients with PR interval shortening (21). This shortening is also typical for some congenital metabolic diseases (Pompe's disease, Fabri's disease) and dystrophies (22-24). Nevertheless, our study did not enroll patients with these pathologies. In the S. Hang et al study (25), PR shortening manifested with pathological increase of sympathetic stimulation in a patient with feochromocytoma, and such shortening disappeared after the removal of this catecholaminergic tumor. The mechanism for bidirectional VT development is related to exaggerated myocardial sensitivity to adrenergic stimulation. Between HRV markers, the one that most reflects increase of catecholamine susceptibility, is circadian index greater than 1.45 (15). The existence of accessory pathways in our patients was ruled out with EPS (performed in some of our patients) and with transient PR shortening. Different types of PSVT were reported in patients with CPVT (7-9); however, the prognostic value of PSVT in these patients is not defined yet.

Beta-blockers (1-2 mg/kg), calcium antagonists (verapamil) or combination with beta-blockers were used to treat our patients in cases of PSVT. In a single patient the management was started

with propafenone (10 mg/kg), which also has beta-blocking characteristics (26). Under the mentioned treatment, all the children showed improvement in their clinical symptoms: syncope events and ventricular tachycardia did not recur, or recurred less frequently. At the same time, 2 patients with transient PR shortening died suddenly during follow up.

All in all, children with the syncopal form of malignant CPVT have a typical electrocardiographic pattern that included: PR interval shortening, sinus bradycardia and increase of CI in Holter monitoring.

It is known that patients with CPVT usually have two types of genetic mutations: in genes encoding ryanodine 2 receptors (RyR2) and calsequestrin 2 (CASQ2), located in chromosome 1g42-g43. These mutations cause exaggerated release of Ca ions from the sarcoplasmic reticulum, thus producing intracellular calcium overload. This mechanism is the pathophysiological basis for type 1 CPVT; type 2 tachycardias (CPVT 2) are due to calsequestrin (CASQ2) disorders, a significant protein for calcium uptake in sarcoplasmic reticulum. This protein has a functional relationship with RyR2 receptors and also influences on intracellular calcium overload (7-9). The clinico-electrocardiographic criteria for differential diagnosis between the different types of CPVT are still not defined. Unlike other research groups, we have shown the association between PR interval shortening and CPVT malignant evolution. It would be necessary to carry out other electrophysiological and molecular genetic studies to correlate clinico-electrocardiographic changes and pathophysiological mechanisms of CPVT with genetic disorders at the level of cardiomyocites. The absence of these genetic studies was one of the significant limitations of our study.

Conclusions:

1. In children, CPVT is a heterogeneous disorder with different clinico-electrocardiographic manifestations;

2. One of the CPVT variants in children is characterized by sinus bradycardia and PR interval shortening;
3. In all patients with syncopes with unclear etiology, bradycardia and PR shortening, in order to rule out the possibility of CPVT, the following should be conducted: ECG, Holter monitoring and/or treadmill test.

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