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(Article begins on next page)

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Editorial.

Drug- induced type 1 Brugada ECG: lights and shadows.

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Brugada syndrome (BrS) is an inherited arrhythmogenic disorder characterized by ST-segment elevation in the right precordial leads and an increased risk of sudden death due to ventricular fibrillation, mostly in young and otherwise healthy adults. There are 2 electrocardiographic patterns: the diagnostic type 1, characterized by coved ST-segment elevation ≥2 mm, followed by a negative T wave in at least 1 right precordial lead and the suspect, non-diagnostic, type 2, characterized by saddle-back ST elevation, in which the diagnosis must be confirmed through a drug test with sodium channel blockers. The Literature considers spontaneous type 1 ECG pattern as a risk factor for sudden death [1-4]. In the study by Brugada et al. [1] a spontaneously abnormal type 1 ECG increased the risk of arrhythmic events with a hazard ratio (HR) of 7.69 at the univariate analysis. In the metanalysis by Gehi et al. [2] patients with a spontaneous type 1 ECG had a 4.6 fold increased risk of events as compared to subjects with drug-induced type 1. In the FINGER study [3], patients with spontaneous type 1 ECG had a shorter time to first arrhythmic event, with a HR of 2.1 and similar results were also shown in the PRELUDE study [4] (p=0.004).

In their retrospective study, Delise, Schwartz et al. [5] reported 26 patients with BrS and aborted sudden death collected between 2010 and 2016 from their own Institutions and 207 patients from 3 large studies published between 2002 and 2013, all with spontaneous or drug-induced type 1 ECG unrecognized before the event. The stated goal was to disprove the concept that patients with drug-induced Brugada pattern carry always a benign prognosis, focusing on BrS patients presenting with the most severe phenotype. Among their 26 patients, a drug-induced type 1 ECG was detected in 11 (42%) and only 1 out of 11 showed a spontaneous type 1 pattern during the follow-up. The Authors thus underline the unexpectedly higher frequency of drug-

induced Brugada type 1 ECG pattern in aborted cardiac arrest (ACA) survivors as compared to that reported in earlier studies.

A limit of the study by Delise et al. [5] is that most of the patients included belong to previous studies not designed to answer that specific question, therefore it is not known whether these patients had the arrhythmic event during fever or taking medications that might cause drug-induced BrS, how many patients with drug-induced ECG developed spontaneous type 1 ECG during the follow-up and we do not know whether these patients were systematically re-evaluated with ECG during the follow-up. It is well known that the Brugada pattern may be underestimated, due to the characteristic electrocardiographic fluctuations. The probability to identify a spontaneous type 1 ECG increases with the number of ECG performed and even more with the 12-lead 24-hour Holter monitoring, at least by 20% [6].

This study is however in line with the recently published paper by Sieira et al.[7], which reports that ACA was the clinical presentation in 3.8% of the 343 patients with drug-induced Brugada ECG pattern, with a high rate of recurrences during the follow-up; those with syncope and drug-induced type 1 had an event rate of 1.9% per year vs 2.3% per year in the patients with spontaneous type 1 ECG (p= NS), while the arrhythmic event rate in the 244 asymptomatic patients with drug-induced type 1 was very low (0.4% per year vs 1.2% in those with spontaneous type 1, p=0.049). The Authors conclude that a lower risk of arrhythmic events is present in asymptomatic individuals with drug-induced Brugada pattern, while patients with initial presentation as syncope or ACA might have a similar bad prognosis, irrespective of the ECG pattern. In 2011 Raju et al. [8] reported a retrospective analysis of a cohort of individuals who experienced unexplained sudden death, with a diagnosis of BrS established following familial evaluation. Antemortem ECGs were available only for 5 out of 50 probands and only 1 demonstrated a spontaneous type 1 pattern, thus questioning that its absence could be a marker

of low risk.

Delise et al. [5] suggest different possible interpretations for ACA in subjects with only drug-induced type 1 Brugada pattern: 1) these patients had idiopathic ACA and incidental minor Brugada pattern; 2) the presence of a spontaneous type 1 has been missed; 3) not all patients with a drug-induced BrS ECG are at low risk of future events. None of these possibilities may be excluded.

The variable we do not know is how many subjects in the general population have a suspect, non-diagnostic Brugada ECG pattern. In a study by Konigstein, Viskin et al. [9], dealing with ventricular arrhythmias in subjects with Brugada ECG pattern induced by non-cardiac drugs, subtle abnormalities in the right precordial leads were found in the vast majority of "off-drug ECGs" of patients with drug-induced Brugada type 1 (80%), but also in most of control subjects (62%), when ECGs were analyzed by an expert in BrS. The Authors concluded that pre-treatment screening is impractical because of a prohibitive false-positive rate. In another study by Hermida et al. [10], on 1,000 ECGs of healthy adults, a type 2-3 Brugada pattern was observed in 6% of ECG tracings, but it was not associated with an increased cardiovascular mortality.

What we certainly know is that asymptomatic individuals with type 2-3 Brugada pattern have an excellent long-term prognosis, however they have to keep in mind some recommendations, such as avoiding sodium channel blocker drugs, treating fever properly, promptly reporting the onset of symptoms and they should be followed over time to detect the possible change to a spontaneous type 1 Brugada pattern.

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