

Right Precordial ST-Segment Elevation
in Patients with Arrhythmogenic
Cardiomyopathy and Primary or
Secondary Ventricular Fibrillation

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Abstract

Background: In arrhythmogenic cardiomyopathy ventricular fibrillation can be the first manifestation of the disease (primary VF). As an interaction between arrhythmogenic cardiomyopathy and Brugada syndrome with regard to the so-called connexome is possible the hypothesis is that primary ventricular fibrillation belongs to Brugada syndrome and later progresses to arrhythmogenic cardiomyopathy.

Method: A collective of 404 patients with arrhythmogenic cardiomyopathy were investigated to answer the question how many patients have right precordial ST-segment elevation in primary or in rare cases - secondary ventricular fibrillation.

Results: 9/14 patients had primary ventricular fibrillation and 2/9 patients (15 males, mean age 43.3 ± 9.6 years) had secondary ventricular fibrillation with had non-significant ($< 2\text{mm}$) coved-type ST elevation, Brugada type II ECG or atypical ST elevation in right precordial leads. Ajmaline challenge was not done in any case. In this cohort of patients coved-type or atypical right precordial ST-segment elevation was statistically significant ($p < 0.005$) for the development of ventricular fibrillation.

Conclusion: It seems that the so-called connexome is a relevant finding to predict ventricular fibrillation as the first manifestation of the disease with insignificant coved-type or atypical right precordial ST elevation.

Introduction

Right precordial ST-segment elevation belongs beyond highly specific features such as right precordial T-wave inversions and epsilon waves to typical ECG abnormalities of arrhythmogenic cardiomyopathy in about 25% of cases [1].

Since the description of the so-called connexome [2]. The interaction between desmosomal mutations, sodium channel complexes and reduced gap junctions-an association between arrhythmogenic cardiomyopathy and Brugada syndrome has been discussed.

Sudden cardiac death due to primary ventricular fibrillation as the first manifestation of arrhythmogenic cardiomyopathy is possibly caused by Brugada syndrome as a primary electrical disease before progressive arrhythmogenic cardiomyopathy develops (primary VF).

Later in the course of arrhythmogenic cardiomyopathy ventricular fibrillation can occur after recurrent events of ventricular tachycardia with the electrocardiographic picture of Brugada-like ECG (secondary VF).

Desmosomal gene mutations has been described for either arrhythmogenic cardiomyopathy or Brugada syndrome: plakophilin-2 in 2.5% [3], desmoglein-2 in 5.5% [4] and desmoplakin in 17% of cases [5].

Both, ARVC and Brugada syndrome are familial and genetic diseases, and fibrofatty change in the RV epicardium is a significant finding. In ARVC, progression of the disease frequently occurs and LV involvement causes heart failure. Occurrence of monomorphic VT is predominant and primary VF appears as the first manifestation in ARVC. In Brugada syndrome, occurrence of heart failure and monomorphic VT are very rare. Mechanism of the disease is similar but clinical phenotype is different between these diseases.

The objective of this study was to evaluate in how many patients with arrhythmogenic cardiomyopathy with primary or - in rare cases - secondary ventricular fibrillation some form of ST-segment elevation can be detected.

Method

To detect any form of ST-segment elevation in typical patients with arrhythmogenic

cardiomyopathy the initial ECG was analyzed in a cohort of 404 patients (267 males, mean age 46.3 ± 11.6 years). The diagnosis of arrhythmogenic cardiomyopathy was established by electrocardiography (right precordial T-wave inversion and epsilon waves as major criteria), imaging techniques (echocardiography, right ventricular angiography), the sort of ventricular arrhythmia (left bundle branch block - like with superior or inferior axis) and genetic mutation findings (plakophilin-2 in 17 patients, RYR-2 in 11 patients, TGF beta 3 in 5 patients and TMEM43 mutations in 3 patients, in most patients genetic screening was not done). Epsilon waves were found in 23% of cases, T wave inversions in right precordial leads were found in 55% of cases.

23 patients (15 males, mean age 43.3 ± 9.6 years) with typical arrhythmogenic cardiomyopathy with ventricular fibrillation as the first manifestation of the disease or secondary VF after VT recurrences had some form of ST elevation. Primary ventricular fibrillation as the first manifestation of the disease was present in 14 patients. Secondary ventricular fibrillation after recurrent ventricular tachycardia could be revealed in 9 cases.

Statistical analysis was done by x2 test with $p < 0.05$ as a significant finding.

Results

In the first group of 14 patients saddleback Brugada- type ST-segment elevation $> 2\text{mm}$ in right precordial leads could be found in 1 male patient who suffered sudden cardiac death. This patient was TMEM43 – gene positive. In the other 13 patients 8 cases had non-significant ($< 2\text{mm}$) covered-type (Figure 1, right side) and 5 patients atypical ST-segment elevation in right precordial leads including the brother of the TMEM43-positive patient who had the same gene defect. Ajmaline challenge was not performed in any patient mentioned above.

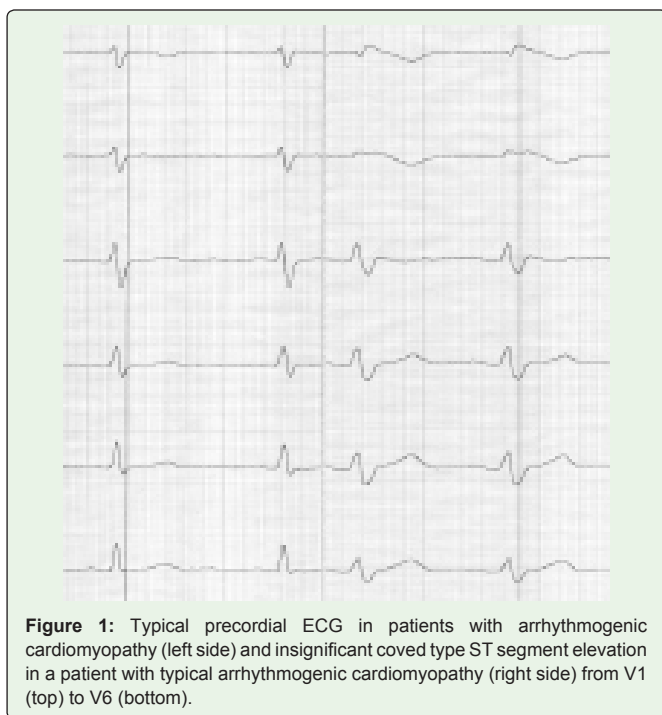


Figure 1: Typical precordial ECG in patients with arrhythmogenic cardiomyopathy (left side) and insignificant covered type ST segment elevation in a patient with typical arrhythmogenic cardiomyopathy (right side) from V1 (top) to V6 (bottom).

In only two patients with long-lasting recurrence of ventricular tachycardia and an episode of ventricular fibrillation non-significant ($< 2\text{mm}$) covered-type ST-segment elevation and in another case atypical ST elevation in right precordial leads was present. One of these patients had plakophilin-2 as the causative gene defect.

In a total of 59 of 381 patients ST-segment elevation was present without episodes of ventricular fibrillation in a long-term follow-up. In most cases ($n=38$) saddleback-type ST elevation was present, in the other cases non-significant covered-type ($n=3$) or atypical ST-segment elevation were present. Compared to 11 out of 23 cases with primary or secondary ventricular fibrillation these results were statistically significant (p value < 0.005). Typical precordial ECG without ST elevation is presented in figure 1 (left side).

Either in primary ventricular fibrillation as the first manifestation or after recurrent ventricular tachycardia the existence of right precordial ST-segment elevation are present in a total of 11 patients (48%), mostly in patients with initial sudden death (64%) and in rare cases with secondary ventricular fibrillation after recurrent ventricular tachycardia (22%).

Discussion

By the electrocardiographic profile of patients with arrhythmogenic cardiomyopathy and ventricular fibrillation a close association between arrhythmogenic cardiomyopathy and Brugada syndrome can be suspected in about half of patients. The concept of interacting of these two diseases is most relevant and is due to interaction of desmosomal mutations, sodium channel complexes and reduced gap junctions. This concept has been published by a minimum of three authors [2,6,7]. On the basis of right precordial ST-segment elevation ventricular fibrillation is a predictable event in the management of patients with arrhythmogenic cardiomyopathy. In 10-15% ST elevation is, indeed, a risk factor for sudden death in developing arrhythmogenic (right ventricular) cardiomyopathy in a phase of Brugada-like ECG.

In cases of incomplete right bundle branch block the angle of r' is most relevant. If the angle exceeds 58° positive ajmaline challenge can be expected [8,9]. If the angle is by far smaller than 58° "pure" incomplete right bundle branch block is present.

Without the association of desmosomal genes, sodium channel complex and gap junctions (= so-called connexome) secondary ventricular fibrillation typically affects patients with arrhythmogenic cardiomyopathy after recurrent ventricular tachycardia due to degeneration into ventricular fibrillation.

Only a single author queries the concept of interaction between arrhythmogenic cardiomyopathy and Brugada syndrome by the so-called connexome and plakophilin-2 as the first mentioned gene mutation for both diseases [10]. There are other desmosomal gene mutations (desmoglein-2 in 5.5% [4], and desmoplakin in up to 17% [5] of cases) who can cause arrhythmogenic cardiomyopathy and brugada syndrome by the concept of the connexome. As ajmaline testing was not done in any patient is possibly the reason why clear-cut brugada syndrome was not provoked.

Convex-type or covered-type ST-segment elevation in right precordial leads in patients with arrhythmogenic cardiomyopathy and ventricular fibrillation in TMEM43 gene mutations identified

in the male two brothers share the controversy, but still discussable final common pathway of TMEM43 gene mutation and desmosomal mutations [11].

An association between arrhythmogenic cardiomyopathy and Brugada syndrome is a clearly a matter of fact, and not only in Italy where Brugada syndrome has been described in combination with a localized form of arrhythmogenic cardiomyopathy years ago [12,13].

Very interesting is a recent study, where atypical ST-segment elevation in right precordial leads had an elevated risk of sudden cardiac death in comparison to Brugada type I or type II ECG over a period of 20 years in a middle-aged population [14].

As a conclusion, any form of ST-segment elevation (non-significant coved-type, saddleback type or atypical ST elevation) can be related to primary or in rare cases secondary ventricular fibrillation. In a majority of patients with arrhythmogenic cardiomyopathy brugada syndrome as a primary electrical disease can be suggested. In patients without ventricular fibrillation saddleback-type ST elevation dominants.

Limitations

By far the greatest limitation is that ajmaline testing was not done in any patient. The majority of patients with arrhythmogenic cardiomyopathy were diagnosed at the Medical School of Hannover, Germany, from 1985 until 1989 and at the Municipal Hospital of Oldenburg, Germany, from 1989 until 1993. Systematic ajmaline testing was first introduced in 1996. In patients with sudden death ajmaline challenge was not applied.

Inferolateral J wave abnormalities in type I Brugada ECG are demonstrated in patients with primary ventricular fibrillation [15]. These ECG findings were not present in patients with primary ventricular fibrillation due to arrhythmogenic cardiomyopathy.

Genetic mutation analysis was done only in desmosomal or known loci, but not in SCN5A mutations, although in a recent trial almost 2% of ARVD/C patients harbor rare SCN5A variants [16].

References

- Peters S, Trümmel M. Diagnosis of arrhythmogenic right ventricular dysplasia-cardiomyopathy: value of standard ECG revisited. *Ann Noninvasive Electrocardiol.* 2003; 8: 238-245.
- Cerrone M, Delmar M. Desmosomes and the sodium channel complex: implications for arrhythmogenic cardiomyopathy and Brugada syndrome. *Trends Cardiovasc Med.* 2014; 24: 184-190.
- Cerrone M, Lin X, Zhang M, Agullo-Pascual E, Pfenniger A, Chkourko-Gusky H, et al. Missense mutations in plakophilin-2 cause sodium current deficit and associate with a Brugada Syndrome phenotype. *Circulation.* 2014; 129: 1092-1103.
- DiResta C, Pietrelli A, Sala S, Della Bella P, DeBellis G, Ferrari M, et al. High-throughput characterization of a cohort of Brugada syndrome patients. *Hum Mol Genet.* 2015; 24: 5828-5835.
- Zhao Q, Chen Y, Peng L, Gao R, Liu N, Jiang R, et al. Identification of rare variants of DSP gene in sudden unexplained nocturnal death syndrome in the southern Chinese Han population. *Int J Legal Med.* 2016; 130: 317-322.
- Corrado D, Zorzi A, Cerrone M, Rigato I, Mongillo M, Bauce B, et al. The relationship between arrhythmogenic cardiomyopathy and Brugada syndrome. New insights from molecular biology and clinical implications. *Circ Arrhythm Electrophysiol.* 2016; 9.
- Peters S. The history of Brugada syndrome continuum with arrhythmogenic cardiomyopathy or lone disease ? *Int J Cardiol.* 2016; 211: 84-85.
- Ohkubo K, Watanabe I, Okumura Y, Ashino S, Kofune M, Nagashima K, et al. A new criteria differentiating Type 2 and 3 Brugada patterns from ordinary incomplete right bundle branch block. *Int Heart J.* 2011; 52: 159-163.
- Chevallier S, Forclaz A, Tenkorang J, Ahmad Y, Faouzi M, Graf D, et al. New electrocardiographic criteria for discriminating between Brugada type 2 and 3 patterns and incomplete right bundle branch block. *J Am Coll Cardiol.* 2011; 58: 2290-2298.
- Campuzano O, Fernandez-Falgueras A, Iglesias A, Brugada R. Brugada syndrome and PKP2: Evidences and uncertainties. *Int J Cardiol.* 2016; 214: 403-405.
- Franke WW, Dörfinger Y, Kuhn C, Zimbelmann R, Winter-Simanowski S, Frey N, et al. Protein LUMA is a cytoplasmic plaque constituent of various epithelial adherens junctions and composite junctions of myocardial intercalated discs: a unifying finding of cell biology and cardiology. *Cell Tissue Res.* 2014; 357: 159-172.
- Martini B, Nava A, Thiene G. Ventricular fibrillation without apparent heart disease: description of six cases. *Am Heart J.* 1989; 118: 1203-1209.
- Corrado D, Basso C, Buja G, Nava A, Rossi L, Thiene G. Right bundle branch block, right precordial ST-segment elevation, and sudden death in young people. *J Am Coll Cardiol.* 1996; 27: 443-448.
- Tsuneoka H, Takagi M, Murakoshi N, Yamagishi K, Yokoyama Y, Xu D, et al. Long-term prognosis of Brugada-type ECG and ECG with atypical ST-segment elevation in the right precordial leads over 20 years: results from the Circulatory Risk in Communities Study (CIRCS). *J Am Heart Assoc.* 2016; 5.
- Georgopoulos S, Letsas KP, Liu T, Kalafateli M, Korantzopoulos P, Bürkle G, et al. A meta-analysis on the prognostic significance of inferolateral early repolarization pattern in Brugada syndrome. *Europace.* 2017.
- Te Riele AS, Agullo-Pascual E, James CA, Leo-Macias A, Cerrone M, Zhang M, et al. Multilevel analyses of SCN5A mutations in arrhythmogenic right ventricular dysplasia-cardiomyopathy suggest non-canonical mechanisms for disease pathogenesis. *Cardiovasc Res.* 2017; 113: 102-111.