Prevalence of Supraventricular Tachyarrhythmias in a Cohort of 115 Patients with Brugada Syndrome

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Background: The Brugada syndrome is characterized by ST segment elevation in leads V₁ to V₃ and a right bundle branch block like pattern. It is associated with an increased risk of syncope and sudden cardiac death. Initial reports in small numbers of patients suggest an association between supraventricular tachycardias and Brugada syndrome with a prevalence varying between 13% and 40%.

Objective: Aim of this study was to evaluate the prevalence of AV nodal reentrant tachycardia, AV reentry tachycardia, and/or atrial fibrillation in a large cohort of patients diagnosed as Brugada syndrome.

Methods and Results: From three different European centers 115 consecutive patients with a Brugada syndrome were evaluated noninvasively and invasively (mean age 45 ± 12 years, n = 82 men, n = 33 women). Nineteen of 115 patients (17%) had a history of previous cardiac arrest. Syncope was reported by 58 patients (50%), 33 patients had a positive family history of sudden cardiac death (29%). Supraventricular tachycardias were documented in 26 of the patients (23%); Eight patients (7%) had AV-nodal reentrant tachycardias and two patients had AV-reentry tachycardias; atrial tachycardias were documented in three patients, and another 13 patients (11%) suffered from atrial fibrillation/atrial flutter. Additionally, atrial fibrillation was inducible by programmed atrial stimulation in nine patients (8%).

Conclusions: Supraventricular tachycardias occur in 23% of patients with Brugada syndrome. Documentation of atrial fibrillation especially in the young or supraventricular tachycardias associated with syncope should give reason to screen for Brugada syndrome.

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Brugada syndrome; atrial fibrillation; supraventricular tachycardias; sudden cardiac death; primary electrical disease; syncope

INTRODUCTION

Atrial fibrillation and other supraventricular tachycardias represent a common disorder, which constitutes a relevant cause of mortality, morbidity, and economic consequences due to repetitive hospitalizations. Main risk factor for the development of atrial fibrillation are arterial hypertension and structural heart disease but nevertheless, still 5–30% of patients with atrial fibrillation suffer from lone atrial fibrillation, which may be in rare cases of familial origin.¹ In recent years, new genetic causes

for familial atrial fibrillation, the Brugada syndrome and the short QT syndrome could be identified.^{2–6} Notably, the initial report on the Brugada syndrome described that two out of eight affected individuals had paroxysmal atrial fibrillation; one patient was suffering from episodes of atrial fibrillation soon after birth, preceding syncopal episodes in childhood.⁵ Initial casuistic reports and studies in small cohorts of patients with Brugada syndrome suggest an association between supraventricular tachyarrhythmias and Brugada syndrome. The prevalence of supraventricular arrhythmias in

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Brugada syndrome is still unknown. The aim of this study was to evaluate of the prevalence supraventricular arrhythmias in a large multicenter analysis of patients with a Brugada syndrome.

METHODS

The patient group consisted of 115 consecutive patients with Brugada syndrome of three different centers, which were diagnosed between 1995 and 2004 (Table 1). Diagnosis of the syndrome was based on the recommendations of the Brugada consensus reports.^{6,7} Patients that did not fulfill the criteria of the Brugada consensus conference were not included. Structural heart disease was excluded in all patients by noninvasive and invasive diagnostic work-up including echocardiography, cardiac magnetic resonance imaging, right- and left-heart catheterization. After obtaining written informed consent an electrophysiologic study was performed in 106 of 115 patients. The electrophysiological study included basal measurements of AH-, HV-intervals, AV-node Wenckebach cycle length during incremental atrial pacing, sinus node recovery time, and programmed atrial stimulation. Furthermore, programmed ventricular stimulation was performed at two right ventricular sites using three different driving cycle lengths with up to three extrastimuli.

RESULTS

The patients had a mean age of 45 ± 12 years, 82 patients were male (71%). Fifty-eight patients presented with a syncope (50%) and 19 patients survived ventricular fibrillation (17%, Table 1). A

positive family history of syncope and/or sudden cardiac death was present in 33 patients (33%). A positive baseline ECG with a Brugada type I ECG was documented in 83 patients (72%), whereas a suspicious baseline ECG in the remaining patients changed to diagnostic type I ECG after intravenous drug challenge by either flecainide or ajmaline.

Eleven patients revealed spontaneous episodes of either paroxysmal or persistent atrial fibrillation and another two patients presented with sustained atrial flutter (13%). During the invasive electrophysiological study atrial fibrillation was inducible in another nine patients without a history of atrial fibrillation. In three patients atrial fibrillation could be induced during programmed atrial stimulation and has been clinically documented. The mean HV interval was 48 ± 10 ms. A HV interval >55 ms was identified in 20 of 106 (19%) and >60 ms in 13 of 106 (12%) of the patients, whereas, no association of a prolonged HV interval to the occurrence of supraventricular tachycardias could be found (HV >55 ms, $n = 5$ patients, HV <55 ms, $n = 21$ patients). Ventricular fibrillation was inducible in 55 patients, in three patients polymorphic ventricular tachycardia ($n = 58/55\%$). Furthermore, eight patients presented with AV nodal reentrant tachycardia, two patients with accessory pathways with antegrade conduction, and another three patients with ectopic atrial tachycardia. Thus 26 of 115 patients (23%) with a Brugada syndrome had supraventricular tachycardias. From 115 patients 75 were genotyped, whereas, 11 patients were positive for a SCN5 A mutation (10%) and 64 patients were negative. From 11 patients with a SCN5 A mutation, nine patients had no history of supraventricular tachycardias and two patients had episodes of paroxysmal atrial fibrillation.

Table 1. Clinical and Diagnostic Characteristics of Patients with Brugada Syndrome

Number of patients	115
Males	82
Females	33
Aborted SCD	19
Syncope	58
Family history (SCD/syncope)	33
Mean HV-interval	48 ± 10 ms
AF inducible	12
Spontaneous AF/AFL	13
SVT (AVRT/AVNRT)	10
VF inducible	55

SCD = sudden cardiac death; AF = atrial fibrillation; AFL = atrial flutter; VF = ventricular fibrillation; SVT = supraventricular tachycardia; AVRT = atrioventricular reentry tachycardia; AVNRT = atrioventricular nodal reentry tachycardia.

DISCUSSION

The Brugada syndrome constitutes a primary electrical disease with a substantial risk of sudden cardiac death. Recently, case reports and subsequently two further studies raised the question of an association of Brugada syndrome and benign but clinically relevant supraventricular tachycardias.^{5,8-11}

In this study of a large cohort of patients with Brugada syndrome, the mean age of the patients (45 ± 12 years) was consistent with actual available data on patients with Brugada syndrome

(41 ± 15 years in n = 547 patients in¹²), as well as, the gender distribution (n = 82/115 male/71.3% vs 408/547 male/74.6% in¹²). Furthermore, a basal abnormal ECG could be found in a comparable percentage of 70% of patients with Brugada syndrome (72.2% vs 71.4% in¹²).

The first report on the Brugada syndrome revealed two out of eight affected individuals with a history of atrial fibrillation (25%).⁵ Eckardt et al.⁸ reported a low prevalence of atrial fibrillation in a group of 35 patients with Brugada syndrome (n = 1, 3%) but a relevant number (n = 10) of supraventricular tachycardias.

Another 30 Japanese patients with Brugada syndrome revealed a relevant number of individuals (n = 9) with additional episodes of atrial fibrillation (30%).⁹ Morita et al.¹⁰ studied 18 consecutive patients with Brugada syndrome and compared the electrophysiological findings to an age- and gender-matched population without evidence of heart disease. Spontaneous atrial fibrillation occurred in 7 of 18 (39%) patients with Brugada syndrome but none of the control subjects. However, intraatrial conduction times were significantly increased in patients with Brugada syndrome as compared to the control group and atrial fibrillation was inducible in eight patients with Brugada syndrome but in none of the control subjects. The authors concluded, that atrial vulnerability is increased in patients with Brugada syndrome. Recently, Bordachar et al.¹¹ compared 59 patients with Brugada syndrome to an age-matched control group. Patients with an HV interval >55 ms had significantly more atrial arrhythmic events as compared to patients with a normal HV interval. However, in this study the clinical occurrence or inducibility of atrial fibrillation was not associated with a prolonged HV interval and a SCN5 A mutation.

The prevalence of atrial fibrillation in the normal population is about 2.3% in persons above 40 years of age and increases with an abrupt rise after the age of 65.¹³ Taking the current published observations into account the overall prevalence of atrial fibrillation/atrial flutter in patients with Brugada syndrome is approximately 17% and thus substantially higher (Table 2).

The first detailed report on the association of supraventricular tachycardias and Brugada syndrome was provided by Eckardt et al.⁸ From 35 consecutive patients with Brugada syndrome 10 were found to have supraventricular tacharrhythmias

Table 2. Brugada Syndrome and Atrial Fibrillation/Atrial Flutter

Brugada 1992 ⁵	2/8 pts	25%
Itoh 2001 ⁹	9/30	30%
Morita 2002 ¹⁰	7/18	39%
Bordachar 2004 ¹¹	11/59	19%
Probst 2007 ²⁰	3/30	10%
Multicenter study (see text)	13/115	11%
Total	45/260	17.3%

Frequency of spontaneous atrial fibrillation/atrial flutter in patients with Brugada syndrome. About 17.3% of patients with Brugada syndrome may present with episodes of atrial fibrillation/atrial flutter.

(29%, ANVRT/AVRT, n = 8, atrial tachycardia, n = 2 with one patient in addition to an AVNRT, atrial fibrillation, n = 1).

The overall incidence of AVNRT and AVRT in an unselected population is not well documented. Paroxysmal supraventricular tachycardias in the general population are rare. A systematic epidemiologic survey by Orejarena et al.¹⁴ estimated a low frequency of AVNRT and/or AVRT, which account for approximately 0.25% in the population. Thus, in the present group of 115 patients with Brugada syndrome less than one patient would be expected to have an AVNRT or AVRT. However, in the actual group of patients with a Brugada syndrome 10 of 115 patients (9%) could be identified. Potentially an involvement of perinodal atrial tissue with increase of conduction time may lead to two pathways with the propensity to AV-nodal reentrant tachycardias.¹⁵ However, the electrophysiological basis for a potential association of Brugada syndrome with AVNRT or AVRT or atrial fibrillation still remains unclear.

In rare but clinically relevant cases patients with antegrade conducting accessory pathways Brugada syndrome may be concealed.¹⁶ Therefore, additional history of syncopes or ventricular tachyarrhythmias which can not be explained by the refractory period of the accessory pathway should encourage complete diagnostic work-up including programmed ventricular stimulation in order to unmask other underlying conditions such as the Brugada syndrome.^{8,16,17}

The therapy of choice in symptomatic patients with Brugada syndrome and supraventricular tachyarrhythmias such as AVNRT or AVRT is radiofrequency catheter ablation. As supraventricular tachyarrhythmias may interfere with ICD detection algorithms leading to inappropriate ICD

interventions, the curative approach is the treatment of choice in this condition. Antiarrhythmic drug treatment of supraventricular tachyarrhythmias is not without risk, which has been shown during application of class Ic drugs in patients with atrial fibrillation unmasking underlying Brugada syndrome.^{18,19} Thus, especially in young patients with a history of supraventricular tachyarrhythmias exclusion of Brugada syndrome is essential.²⁰

CONCLUSIONS

Approximately 20% of patients with Brugada syndrome suffer from supraventricular tachyarrhythmias. The potential association of Brugada syndrome and supraventricular tachycardias underlines the importance of a complete electrophysiologic study, including programmed atrial and ventricular stimulation during the diagnostic work-up. Furthermore, in 11% of patients with Brugada syndrome atrial fibrillation/atrial flutter can be clinically documented.

Therefore, in young patients with supraventricular tachycardias and/or a history of syncope or sudden cardiac death Brugada syndrome should be considered as a potentially underlying disorder.

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