

## The Prevalence and Incidence of the Brugada-Type

### Electrocardiogram:

*Is the Brugada-Type Electrocardiogram*

*at Risk of Sudden Death?*

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## Abstract

**Background** Brugada syndrome is characterized by right bundle branch block and ST-segment elevation in right precordial leads, plus sudden death caused by ventricular fibrillation. However, epidemiological information about the Brugada-type ECG is scarce.

**Methods** The prevalence, incidence, and prognosis of the Brugada-type ECG were investigated in 4,788 subjects (1,956 men and 2,832 women), who were under age 50 in 1958 and had undergone biennial health examinations through 1999.

**Results** The total number of Brugada-type ECG cases was 32, and the prevalence and incidence were 146.2 persons/100,000 persons and 14.2 persons/100,000 person-years, respectively. The incidence was 9 times higher among men than women, and the average age at presentation was  $45.0 \pm 10.5$  years. The Brugada-type ECG appeared intermittently in most cases. Mortality from unexpected death was significantly higher in Brugada-type ECG cases than in controls ( $p < 0.01$ ). Unexpected deaths were more frequent among Brugada-type cases with a history of syncope ( $p < 0.05$ ).

**Conclusions** The Brugada-type ECG is not a very rare condition in the adult Japanese population. Subjects with the Brugada-type ECG have an increased risk of unexpected death.

## Introduction

In 1992, Brugada and Brugada<sup>1</sup> reported 8 patients with idiopathic ventricular fibrillation (VF) , which is characterized by evidence of right bundle branch block and ST-segment elevation in right precordial leads. This ECG pattern, i.e., the Brugada-type ECG, was once considered a probable normal variant.<sup>2</sup> Since the Brugas' report,<sup>1</sup> however, attention has been direct to the relationship between the Brugada-type ECG and sudden death. Nevertheless, epidemiological information about the Brugada-type ECG is scarce.

The present study based on a 40-year follow-up of 4,788 subjects in Nagasaki was carried out to investigate the prevalence and incidence, and the long-term prognosis of the Brugada-type ECG in the general population.<sup>3</sup>

## Methods

A total of 7,564 subjects have received biennial examinations in Nagasaki since 1958 as the follow-up program of the Radiation Effects Research Foundation. Of those subjects, we investigated 4,788 (1,956 men and 2,832 women) who were under age 50 in 1958. Data from 1958 to 1959 (the first examination) through 1998 to 1999 (the 21st examination) were analyzed in the present study.

### Definition of the Brugada-type ECG

We defined an ECG as the Brugada type if it showed the following,<sup>4-6</sup>

1. a terminal r' wave in lead V1 characterizing a right bundle branch block,
2. convex curve or "coved"-type ST-segment elevation of  $\geq 0.1$  mV in lead V1, or in leads V1 and V2, and
3. "saddle shaped"-type ST-segment elevation of  $\geq 0.1$  mV in leads V2 and/or V3.

The time course of ST-segment abnormalities was classified into one of two groups,

1. a persistent course showing permanent abnormalities or

2. an intermittent course showing transient normalization of ST-segment pattern during follow-up.

#### **Definition of Sudden death and Unexplained Accidental Death**

We ascertained the cause of death in all deceased subjects from the death certificates. Death was defined as sudden if

1. it occurred within one hour of the onset of acute symptoms,
2. it occurred outside of a hospital, and
3. it was due to unknown causes.

In addition, we investigated deceased cases associated with accidents and extracted cases that were liable for those accidents. We defined these cases as unexplained accidental death cases because VF might have been the cause of the accidents.

Finally, we defined unexpected death as sudden death or the unexplained accidental death.

#### **Data and Statistical Analysis**

1. Of the 4,788 subjects, we extracted cases that showed a Brugada-type ECG and we calculated prevalence at the time of the first examination and 40-year incidence stratified according to age. Total incidence was adjusted by the 1985 World population model.<sup>7</sup>
2. We showed age at death, interval between onset of symptoms and death, place of death, cause of death, and circumstances of accidents in all deceased cases of the Brugada-type ECG.
3. In Brugada-type ECG cases, we compared clinical characteristics, time courses of ST-segment abnormalities, and parameters of 12-lead ECGs between the unexpected death group and the "other" group, which included people who died of other causes and those who were still alive. Continuous variables were tested using the Wilcoxon rank sum test. Categorical data were analyzed by logistic analysis.

4. The long-term prognosis of cases showing the Brugada-type ECG was studied. The cases were compared to all control subjects with respect to mortality from unexpected death, and mortality except for unexpected death. We used the Cox-proportional hazard model to assess difference between each pair.

Statistical Analysis System (SAS) procedures were used for analysis.<sup>8</sup> The level of significance was set at  $P < 0.05$ .

## Results

### 1. Prevalence and incidence of the Brugada-type ECG

The total number of Brugada-type ECG cases was 32 (27 men and 5 women). At the first examination, 7 cases (all male) had already presented with the Brugada-type ECG, and they were referred to as the prevalence cases. The prevalence of the Brugada-type ECG was 146.2 persons/100,000 persons (Table 1). Incidence analysis was based on the remaining 25 cases (20 males and 5 females), who manifested the Brugada-type ECG during subsequent examinations. In the 25 incidence cases, the average age at presentation was  $45.0 \pm 10.5$  years. The incidence of the Brugada-type ECG was 14.2 persons/100,000 person-years, and it was 9 times higher among men than women (Table 2). Of the 28 cases for whom we could assess time course of ST-segment elevation, 25 (89 %) showed an intermittent course of ST-segment elevation.

### 2. Cause of death of the Brugada-type ECG cases

Of 32 cases of the Brugada-type ECG, 16 were still alive, 8 died of illness, 5 died suddenly. Of 3 accidental death cases, two (Cases 6 and 7) died associated with unexplained accident that may be due to VF. Before their deaths, none of the 16 cases had indicated any history of chest pains, neither on effort nor at rest. The average age at death in sudden and unexplained accidental death cases combined was  $57.1 \pm 14.2$  years (Table 3).

### 3. Factors associated with unexpected death in Brugada-type ECG cases

The frequency of Brugada-type ECG cases who had a history of syncope was significantly higher in the unexpected death group than in the "other" group (Table 4). The course of ST-segment elevation and ECG parameters were not significantly different between the groups (Table 5).

### 4. Prognosis of the Brugada-type ECG cases

Of the 4,788 subjects (32 cases of the Brugada-type ECG and 4,756 controls), 1,263 (16 cases and 1247 controls) were dead by the last follow-up. Twenty-seven of those deaths were classified as unexpected, 15 (5 cases and 10 controls) as sudden, and 12 (2 cases and 10 controls) as unexplained accidents. When age and sex were incorporated into the Cox-proportional hazard model, mortality from unexpected death was significantly higher in the cases than in the controls. Mortality for other than unexpected death, however, was similar for both groups (Table 6).

## Discussion

### Prevalence and incidence

In the present study, the prevalence of the Brugada-type ECG was 146.2 persons/100,000 persons and it frequently manifested in middle-aged adult male, which is consistent with data of several studies.<sup>9-12</sup>

To the best of our knowledge, however, this is the first report of the incidence of the Brugada-type ECG, which was 14.2 persons/100,000 person-years. Also, the incidence of the Brugada-type ECG was 9 times higher among men than women and the average age at presentation was  $45.0 \pm 10.5$  years. Furthermore, our long-term observation clarified the intermittent manifestation of the coved-type ST-segment elevation in most cases. These results suggest that the Brugada-type ECG is not a very rare condition in the adult Japanese population, and subjects with the Brugada-type ECG even in asymptomatic cases similar to symptomatic patients with Brugada syndrome regarding the sex ratio, age

distribution, and course of ECG findings.<sup>4-6</sup>

### **Prognosis**

Mortality from unexpected death was significantly higher in Brugada-type ECG cases than in controls, and unexpected death was associated with a history of syncope among Brugada-type ECG cases. However, a history of syncope may not be useful for predicting sudden death because more than half of the unexpected deaths might occur at the first attack. The magnitude of ST segment-elevation did not distinguish the Brugada-type ECG cases having unexpected death from the "other" cases and so it might also not be useful.

It is impossible to exclude the possibility of coronary artery disease or ruptured aortic aneurysm without autopsy information as causes of unexpected death in this epidemiological study. If the Brugada-type ECG was not implicated in unexpected death, the prognosis would have been the same for Brugada-type ECG cases and controls. Mortality from unexpected death, however, was significantly higher in the cases than in the controls, whereas mortality except for unexpected death was similar for both groups. Thus, the death certificate bias was the same for Brugada-type ECG cases and controls.

### **Limitations**

1. Since the Brugada syndrome is believed to be a type of idiopathic VF,<sup>13</sup> it is important to exclude structural heart disease. However, we could not perform echocardiography or cardiac catheterization in our epidemiological study.
2. Because of the intermittent nature of the manifestation of Brugada-type ECG, the incidence may depend on the frequency of ECG recording. Thus, it is stressed that the present study shows results based on biennial ECG recording.
3. Uncertainty of the cause of sudden or unexplained accidental death may cast a shadow on the present results in the absence of autopsies. To solve this crucial problem, we compared a risk of unexpected death between the cases and controls under the same conditions.

## **Conclusions**

Long-term follow-up is useful for identifying the Brugada-type ECG, which was not a very rare condition in adult Japanese population. The results of the male preponderance, age distribution of a peak around the fourth decade and intermittent manifestation of ECG abnormalities in our Brugada-type ECG cases were consistent with the results in Brugada syndrome patients. Because Brugada-type ECG cases are associated with an elevated risk of unexpected death, more definitive ECG criteria will be needed to screen the Brugada syndrome.

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**Table 1. Prevalence of the Brugada-Type ECG**

Age (yrs)	No. at the First Examination*		No. with Brugada -Type ECG at the First Examination		Prevalence per 100,000 Persons	
	Male	Female	Male	Female	Male	Female
=19	164	159	0	0	0	0
20-29	434	563	1	0	230.4	0
30-39	593	1,244	2	0	337.3	0
40-49	491	611	3	0	611.0	0
50-59	203	195	1	0	429.6	0
60-69	68	55	0	0	0	0
70-79	3	4	0	0	0	0
=80	0	1	0	0	0	0
Total	1,956	2,832	7	0	357.9	0
	4788		7		146.2	

\*Although all 4788 subjects were under age 50 in 1958, 529 were 50 years old or over at the first examination because not all the subjects underwent the first examination at 1958.

**Table 2. Incidence of the Brugada-Type ECG**

Age (yrs)	Person-Years in Incidence Study *		No. with Brugada-Type ECG After the First Examination		Incidence per 100,000 Person-Years	
	Male	Female	Male	Female	Male	Female
=19	429	452	0	0	0	0
20-29	2,407	3,173	1	0	41.5	0
30-39	7,099	11,822	7	1	98.6	8.5
40-49	9,425	16,764	6	2	63.7	11.9
50-59	10,535	17,228	5	1	47.5	5.8
60-69	7,570	12,594	1	1	13.2	7.9
70-79	2,799	4,507	0	0	0	0
=80	519	731	0	0	0	0
Total	40,783	67,271	20	5	31.4†	3.5†
	108,054		25		14.2†	

\*Value of years in incidence study is the aggregate number of years contributed to each age category from 1958 to 1999 by all subjects remaining at risk for the Brugada-type electrocardiogram (ECG). †Values are adjusted with the 1985 World population model.

**Table 3. Causes of Death of Brugada-type ECG Cases**

Case	Sex	Age at death (yrs)	Interval between onset of symptoms and death	Place of death	Classification of death	Cause of death
1	Male	41	Several minutes	Other	Sudden	Unknown
2	Male	61	20 minutes	Home	Sudden	Unknown
3	Male	63	Several minutes	Other	Sudden	Unknown
4*	Female	71	Several minutes	Home	Sudden	Unknown
5	Male	76	Several minutes	Home	Sudden	Unknown
6†	Male	42	18 hours	Hospital	Accidental	Rupture of the liver
7‡	Male	46	17 hours	Hospital	Accidental	Cerebral contusion
8¶	Female	66	40 minutes	Hospital	Accidental	Cerebral contusion
9	Female	46	6 days	Hospital	Illness	Brain edema
10	Male	50	10 days	Hospital	Illness	Uremia
11	Male	62	6 month	Hospital	Illness	Hepatocellular carcinoma
12	Male	70	5 days	Hospital	Illness	Cerebral hemorrhage
13	Male	76	3 month	Hospital	Illness	Pneumonia
14	Male	76	10 years	Hospital	Illness	Prostatic cancer
15	Female	79	2 months	Hospital	Illness	Lung cancer
16	Female	85	5 years	Hospital	Illness	Old brain infarction

\*Case 4 had an episode of syncope 15 years before she died. †Case 6 drove his automobile into a parked truck. ‡Case 7 was injured when he fell into a river just after palpitations preceding syncope. ¶Case 8 was hit by an automobile.

**Table 4. Clinical Characteristics of Brugada-Type ECG Cases**

	Unexpected Death Group (n = 7)	“Other” Group (n = 25)	p Value
Sex			
Male	6	21	0.91
Female	1	4	
Age at entry	30.2 ± 7.0	32.9 ± 7.5	0.31
Age at diagnosis*	37.5 ± 9.3	47.3 ± 10.0	0.06
Syncope			
Presence	3	1	0.02
Absence	4	24	

\*Data is based on the 25 incidence cases, 6 in the unexpected death group and 19 in the “other” group.

**Table 5. ECG Parameters of Brugada-Type ECG Cases**

	Unexpected Death Group (n = 7)	“Other” Group (n = 25)	p Value
Type of Courses of ST-segment elevation*			
Persistent	1	2	0.61
Intermittent	5	20	
Heart rate (beats per minute)	58.3 ± 4.8	62.7 ± 7.4	0.14
Magnitude of ST-segment elevation (mV)			
Lead V1	0.14 ± 0.05	0.15 ± 0.05	0.94
Lead V2	0.21 ± 0.07	0.23 ± 0.11	0.74
QRS width (s)	0.10 ± 0.01	0.09 ± 0.01	0.09
Corrected QT interval (s <sup>1/2</sup> )	0.42 ± 0.02	0.41 ± 0.03	0.66

\*Data is based on the 28 cases for which time course of ST-segment elevation could be assessed.

**Table 6. Age and Sex-Standardized Mortality of 32 Cases of the Brugada-Type ECG and 4,756 Control Subjects**

	Cases (n)	Controls (n)	Odds Ratio	95% Confidence Interval
Mortality From Unexpected Death	7	20	52.63	22.78-127.75
Mortality Except for Unexpected Death	9	1227	1.40	0.37-3.11