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### Brugada syndrome : clinical and pathophysiological aspects

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**Publication date**  
2009

[Link to publication](#)

#### **Citation for published version (APA):**

Meregalli, P. G. (2009). *Brugada syndrome : clinical and pathophysiological aspects*. [Thesis, fully internal, Universiteit van Amsterdam].

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**Fever increases the Risk for  
Cardiac Arrest in the Brugada  
Syndrome**

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*Based on: Annals of Internal Medicine 2008; 149:216-8*

## Abstract

**Introduction:** Brugada syndrome manifests as ventricular tachycardia/fibrillation (VT/VF) and leads to syncope or sudden death in young individuals with structurally normal hearts. Episodes of arrhythmia are usually preceded by ST segment elevation in the right precordial leads. An estimated 20-30% of the patient carries a loss-of-function in the *SCN5A* gene. Case reports suggest that fever may be associated with cardiac arrest and preceding electrocardiographic (ECG) changes in affected individuals. Aim of the study is to establish the prevalence of fever-triggered cardiac arrest in a Brugada syndrome population. Moreover we aimed to investigate ECG changes provoked by fever in Brugada syndrome patients.

**Methods:** This is retrospective study. The prevalence of fever-triggered episodes of cardiac arrest or syncope with documented VT is assessed in consecutive Brugada syndrome probands (n=111) and compared to the prevalence of fever-triggered events in 41 controls who were admitted after an out-of-hospital cardiac arrest (OHCA) with documented VT/VF. ECG changes induced by fever were investigated in Brugada syndrome patients (n=24) and in control subjects (n=10).

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**Results:** We found that fever-induced cardiac arrests were present in 4/22 (18%) patients with Brugada syndrome, while none of the 41 control subjects had fever the day of the OHCA (0% [CI 0% to 9%]). The majority of the patients with fever-triggered events were carrier of a *SCN5A* mutation. The ECG changes provoked by fever consisted of the appearance of a type I ECG in all 24 Brugada syndrome patients in who a 12-lead ECG was taken before and during a febrile episode. This did not happen in any of the controls. Moreover, fever induced prolongation of PR/QRS and QTc durations only in patients affected by Brugada syndrome.

**Conclusions:** Fever represents a major risk factor for the occurrence of severe arrhythmic events in subjects affected by Brugada syndrome. ECG changes induced by fever are specific for the Brugada syndrome phenotype.

## **Introduction**

Brugada syndrome is a familial cardiac arrhythmic disorder with an autosomal dominant mode of inheritance and an incomplete pattern of penetrance. Its expressivity is also variable, from totally asymptomatic individuals to severe forms with sudden cardiac death (SCD) due to ventricular tachyarrhythmias <sup>1</sup>. Brugada syndrome is characterized by a peculiar electrocardiographic (ECG) pattern, consisting of ST segment elevations in the right precordial leads ( $V_1$  to  $V_3$ ) and an apparent right bundle branch block pattern <sup>2</sup>. The ECG characteristics are not related to detectable structural abnormalities, ischemia or electrolyte disturbances. In approximately 20-30% of the cases, Brugada syndrome has been linked to mutations in *SCN5A* gene <sup>3</sup>. This gene encodes for the  $\alpha$ -subunit of the human cardiac sodium ( $\text{Na}^+$ ) channel <sup>4</sup>.

The ECG characteristics in Brugada syndrome are often very dynamic and may be concealed. It is known that the diagnostic ECG pattern (type I) can be unmasked by several drugs, but especially by  $\text{Na}^+$  channel blocking drugs <sup>5</sup>. For this reason, provocation challenges with flecainide or ajmaline represents a cornerstone in the diagnostic work-up in patients suspected for Brugada syndrome <sup>6</sup>. The presence of a type I ECG represents also a risk factor for the development of arrhythmia and it has report that the degree of ST elevation augment just before an episode of ventricular tachycardia <sup>7</sup>. Interestingly, the concealed ECG pattern can also be unmasked by fever <sup>8-10</sup>, resulting in typical precordial ST segment elevations (Figure 1). Furthermore, an increasing number of case reports describe that patients affected by Brugada syndrome are at high risk for the development of life-threatening ventricular arrhythmias during febrile state <sup>11</sup>. Of note, the North-eastern part of Thailand, where the Brugada syndrome is endemic <sup>12</sup>, is known for its very hot climate, up to 41° C.

However, studies on a large scale on the incidence of fever-induced arrhythmias in Brugada syndrome are lacking. The aim of the present investigation was to examine the incidence of fever-induced arrhythmias in a population of Brugada syndrome patients. In addition, we aimed to study the electrocardiographic changes induced by fever in those Brugada syndrome patients in whom an ECG was taken before and during high body temperature.

## Methods

### Study Population

We retrospectively analyzed all Brugada syndrome patients that were diagnosed and followed in our institution from 1999 to the beginning of 2007 (average follow-up 35 months). The diagnosis of Brugada syndrome was made by ECG analysis, pharmacological challenge with  $I_{Na}$  blocking drugs, and, when possible, confirmed by *SCN5A* mutation analysis. Clinical data of interest were: 1) age at diagnosis, 2) gender 3) family history of SCD at young age, 4) results of pharmacological challenge performed with flecainide or ajmaline 5) results of genetic screening. We also obtained clinical data on the presence and circumstances of symptoms: whether a patient had experienced a cardiac event (unexplained syncope, documented VT/VF or aborted-SCD). In case patients had had one of those symptoms, we were able to detect whether this had occurred during an episode of fever. Febrile state was defined as elevated body temperature ( $\geq 38.5$  °C) with signs of febrile illness (malaise, specific infection-related symptoms). Unexplained syncope was defined as sudden and unexpected loss of consciousness, not caused by trauma, or triggered by drug or alcohol use, prolonged exercise, or other pathophysiological conditions that are known to affect orthostatic blood pressure regulation (i.e. anaemia, fatigue, pregnancy, menstruation). None of the included patient had overt structural heart disease (by chest roentgenogram, echocardiogram). Coronary angiogram was performed only in severely symptomatic individuals to exclude coronary artery disease and electrolyte disturbances were excluded by laboratory tests. The study protocol was approved by the institutional medical ethical review committee.

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To study whether fever-related onset of arrhythmias is specific for Brugada syndrome, we retrospectively included all consecutive resuscitated patients who suffered from out-of-hospital cardiac arrest (OHCA) with documented VT/VF and were admitted to the emergency room of our institution in the period between July 2006 and April 2007. This group of patients was used as control group. The medical records of these patients were searched for body temperature and some of the survivors were interviewed by telephone for symptoms of fever during

their event. In the majority of the cases (n=32) data on the body temperature was found in the medical records, in 18 cases (of the 39 survivors) we were also able to obtain the requested information at the telephone. Only the temperatures that were measured at the same day of the reanimation were included.

### **ECG Analysis**

All ECGs were analysed by expert cardiologists in the field of Brugada syndrome. ECG tracings were 800% enlarged in Adobe Portable Document Format (PDF) to facilitate manual analysis. ECG parameters of interest were: heart rate, PQ, QRS and QRS intervals (lead V<sub>3</sub>), and maximal ST segment elevation amplitude (among leads V<sub>1</sub> and V<sub>2</sub>). QT duration was corrected for heart rate using Bazett's formula ( $QTc = QT/\sqrt{RR}$ ).

Type I ECG was defined as precordial coved-type ST segment configuration with  $\geq 0.2$  mV elevation at its peak, followed, without isoelectric separation, by a negative T wave<sup>2</sup>.

In 24 patients affected by Brugada syndrome, 12-lead ECGs were available both with and without fever. ECGs made during fever were compared with ECGs at normothermia. The same analysis was performed in 10 control patients who were admitted at the department of Internal Medicine of our institution because of fever illnesses, but had no other cardiac co-morbidities. They were all admitted for the treatment of an uncomplicated febrile episode (two patients had pneumonia, two cholangitis, one had toxicodermia due to omeprazol use, one colitis, one central venous catheter infection, and in three patients no cause of fever was found). These patients had no cardiac history and used no medication with known effects on the cardiovascular system (including non-cardiac drugs which prolong QT interval, e.g., erythromycin)<sup>13</sup>. Structural cardiac disease and electrolyte disturbances were excluded by history, chest roentgenograms, and laboratory tests.

### **Genetic Analysis**

Genomic DNA was extracted from peripheral blood lymphocytes. The encoding exons of *SCN5A* were amplified by polymerase chain reactions using intronic primers<sup>14</sup>.

Single stranded conformation polymorphism (SSCP) was performed for comprehensive mutational analysis of all *SCN5A* exons. Direct DNA sequence analysis was subsequently performed. Absence of the DNA variant in 100 control individuals and its presence in highly conserved regions of *SCN5A* were used as criteria to verify that the DNA variants were disease-causing mutations<sup>15</sup>.

### Statistical Analysis

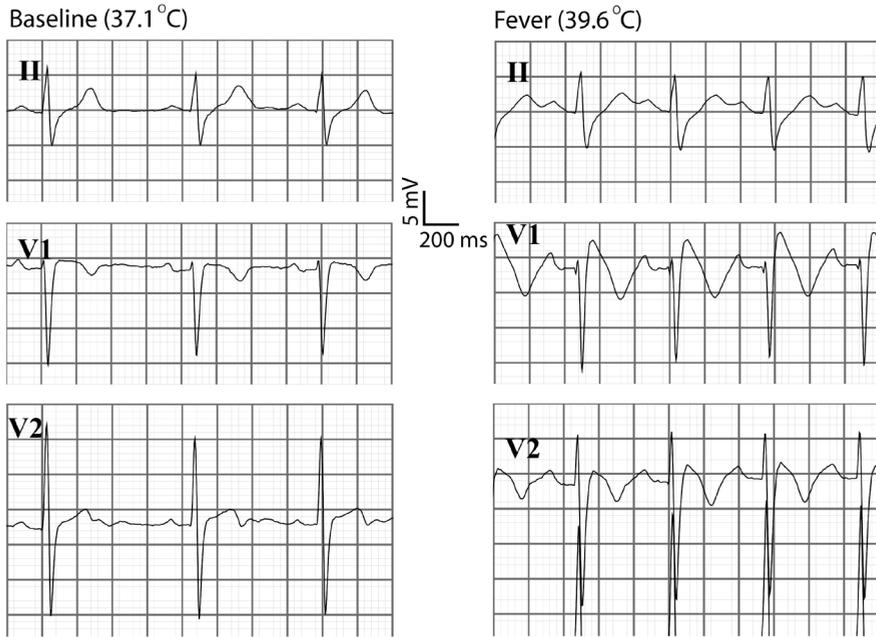
Values are expressed as mean  $\pm$  SD, when appropriate. To test for statistical differences between two mean values, the Student's t-test was performed. To analyze proportional differences between the groups, we used Chi-square test or Fisher's Exact test, where appropriate. To compare ECGs during and without fever, we used paired Student's t-test. Statistical significance was defined as  $p < 0.05$ .

## Results

### Clinical Characteristics

A total of 111 patients affected by Brugada syndrome constituted our database at the time of the analysis. Twenty-two of them had experienced a severe cardiac event, which was defined as cardiac arrest or syncope with loss of consciousness and documented VT (symptomatic group; 20%). The age at diagnosis in the severely symptomatic group ( $46 \pm 15$  years) did not significantly differ from the average age of the Brugada syndrome patients that did not experience a cardiac arrest ( $49 \pm 14$  years;  $p = 0.4$ ). The average follow-up period was longer in the symptomatic group, compared with the rest of our Brugada syndrome population, although this did not reach statistical significance ( $51 \pm 32$  vs.  $38 \pm 31$  months,  $p = 0.10$ ). There was a clear male predominance overall, but the male/female ratio was similar in both groups (% males: 86% vs. 71%,  $p = 0.16$ ). The presence of *SCN5A* mutation (10/21 vs. 23/78,  $p = 0.6$ ) and a positive family history for SCD (9/22 vs. 32/89,  $p = 0.5$ ) were not significantly different between these two groups. Next, we differentiated whether symptomatic patients had experienced cardiac arrest/syncope during fever. In total, 4 of the 22 symptomatic Brugada syndrome

patients (18%; all males) experienced cardiac arrest / syncope while having fever. Three of them carried a *SCN5A* mutation and two belonged to the same family (p.G1743E, c.3142-3143insTG). Nineteen of the other 89 subjects affected by Brugada syndrome had experienced at least a febrile episode over a time of  $38 \pm 31$  months (on average), but these episodes were not accompanied by documented arrhythmic events. The clinical data (in particular the presence of fever and quantification of body temperature) of the Brugada syndrome patients with a cardiac arrest were compared with the ones of control individuals (not previously known with Brugada syndrome) that were resuscitated with documented VT/VF (OHCA group). Between July 2006 and April 2007, the registry of the resuscitated subjects (only adults were selected) was constituted of 73 individuals. Totally, reliable information around the circumstances of their cardiac event and the presence of fever (in the medical records and/or by interviewing the survivors) was obtained for 41 subjects (average age  $62 \pm 15$  years, 80% males). None of these patients had fever the day of the cardiac arrest (0%, [95% CI, 0% to 9%]). Eighteen out of 39 survivors were successfully contacted by telephone. They all denied symptoms of fever before the event. Of 9 of these patients, the absence of fever was also confirmed in their medical records. Of the remaining 21 patients, body temperature was not measured on the day of the reanimation or was only measured after the cooling procedure had started to preserve cerebral function. Temperature during therapeutic hypothermia was considered to be a confounding factor, and those patients were, therefore, excluded from this analysis.



**Figure1:** ECG recording of the right precordial leads before (left panel) and during fever (right panel) in a patient affected by Brugada syndrome. Fever induced PR and QRS intervals prolongation. Note also the changes in the ST segments in leads V1 and V2, with the appearance of the typical coved-shape ST segment, followed by a negative T wave during fever (type I ECG).

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### **Clinical and ECG Characteristics of Brugada Syndrome Patients in whom an ECG both before and during a Febrile Episode was available**

Table 1 summarizes the clinical and electrocardiographic characteristics of the Brugada syndrome patients of whom a 12-lead ECG was available both during a febrile episode (body temperature > 38° C) and at normal body temperature (normothermia). This group is constituted by 3 children and 21 adults. Two of the 4 patients with fever-triggered cardiac arrest are included here. Also, the 3 children and 2 adults have been published previously<sup>16-18</sup>.

Most patients were males (71%), and the average age at fever was 42 ± 21 years. They belong to 21 families. Eight of the 19 probands, in whom genetic analysis was performed, were known to be carrier of a SCN5A mutation (42%). Two probands

did not undergo genetic testing. The three family members were also positive for the familial *SCN5A* mutation. The proportion of carriers was not significantly higher compared to the proportion of *SCN5A* mutation carriers in the whole Brugada syndrome registry of our institution (27%;  $p = 0.6$ ).

In 13 cases ECG analysis was performed during hospital admission, which was necessary to cure the fever-related illness (six of them also had unexplained syncope during fever). The remaining 11 Brugada syndrome patients had followed the advice to come to the first aid for ECG monitoring because of body temperature  $> 38^{\circ} \text{C}$ . They had all also used acetaminophen before coming to the hospital. Fever sources varied as follows: 1) unknown ( $n=8$ ); 2) pneumonia ( $n=5$ ); bronchitis ( $n=3$ ); tonsillitis ( $n=2$ ); phlebitis ( $n=2$ ); cholangitis ( $n=1$ ); gastroenteritis ( $n=1$ ), urinary tract infection ( $n=1$ ) and infected finger ulcer ( $n=1$ ).

ECG parameters before (normothermia) and during fever in the 24 Brugada syndrome subjects were compared. Fever-induced ECG changes in this group of patients were compared with the same changes in 10 control patients (all adults, average age at fever  $48 \pm 19$  years).

Mean febrile temperature was similar in the two groups ( $39.1^{\circ}$  vs.  $39.3^{\circ} \text{C}$ ;  $p = \text{ns}$ ).

At normothermia, 7 out of 24 (29%) Brugada syndrome patients had shown a type I ECG. None of the controls was known with a type I ECG. ECG data are summarized in table 2.

In all 24 Brugada syndrome patients, a type I ECG was documented during fever, while at normothermia only one patient had shown a type I ECG. In none of the controls, a type I ECG was seen. Heart rate was significantly higher during fever in both groups, compared with normothermia. Control reached a higher heart rate than Brugada syndrome patients at fever. In Brugada syndrome patients, mean PR and QRS durations were markedly increased during high body temperature, in comparison with normothermia ( $p < 0.05$ ). Conversely, during fever, both PQ and QRS durations, on average, decreased in the control group. The degree of ST segment elevation (maximal elevation between in lead V1 and V2) increased significantly during fever ( $p < 0.05$ ) only in the Brugada group. Also, QTc significantly increased during fever in the Brugada patients ( $p < 0.05$ ), while did not change significantly in controls.

**Table 1:** Clinical characteristics of the Brugada syndrome and the controls patients in whom a twelve-lead ECG was performed before and during fever. Data are given in average  $\pm$  SD, when appropriate.

	Brugada S. patients	Control group	p-value
Number	24	10	-
Age, years	42 $\pm$ 20	48 $\pm$ 19	ns
Males, %	71	80	ns
Type I ECG, n (%)	7 (29)	0	-
Febrile temperature, ° C	39.1 $\pm$ 0.9	39.3 $\pm$ 0.8	ns
Heart rate at fever, bpm	96 $\pm$ 16	101 $\pm$ 16	ns <sup>#</sup>

<sup>#</sup>: test performed with independent samples t-test.

**Table 2:** Electrocardiographic parameters showing the changes during normothermia and fever in patients with Brugada syndrome and in controls. ECG data are shown as average  $\pm$  SD.

	Brugada S. patients	p-value (fever vs. normothermia)	Control group	p-value (fever vs. normothermia)
Heart rate, bmp		< 0.001*		0.005*
No Fever	74 $\pm$ 14		81 $\pm$ 12	
Fever	96 $\pm$ 16		101 $\pm$ 16	
PQ interval, ms		0.012*		0.04*
No Fever	170 $\pm$ 29		151 $\pm$ 31	
Fever	181 $\pm$ 34		142 $\pm$ 28	
QRS duration, ms		< 0.001*		0.23
No fever	103 $\pm$ 21		87 $\pm$ 14	
Fever	113 $\pm$ 23		84 $\pm$ 17	
QTc, ms		0.012*		0.008*
No fever	404 $\pm$ 28		435 $\pm$ 18	
Fever	429 $\pm$ 41		434 $\pm$ 26	
ST elevation, mm		< 0.001*		0.5
No fever	1.9 $\pm$ 1.9		0.6 $\pm$ 0.1	
Fever	4.0 $\pm$ 2.3		0.7 $\pm$ 0.4	

A p value < .05 at paired samples t-test was considered significant.

## Discussion

In this single-centre retrospective cohort study, we aimed to investigate the prevalence of fever-triggered cardiac arrest / syncope due to malignant arrhythmias in Brugada syndrome patients. We found that fever was present in 4/22 (18%) of the cases of severely symptomatic Brugada syndrome patients. This is remarkable, considering that in none of the 41 control patients, high body temperature was discovered at the day of the cardiac event. Our data are in line with previous reports<sup>19</sup>, and underlie the crucial role of fever in triggering episodes of ventricular arrhythmias in Brugada syndrome. Interestingly, three of the 4 patients with fever-triggered cardiac arrest were also carriers of a *SCN5A* mutation. Overheating is a known risk factor for sudden infant death syndrome (SIDS) which is also linked to mutations in the *SCN5A* gene<sup>20</sup>. Of interest, mutations in genes encoding neuronal sodium channels have been linked to familial diseases with temperature-dependant symptoms, such as generalized epilepsy with febrile seizures (*SCN1A* mutations)<sup>21</sup> and inherited erythromelalgia with heat-triggered burning pain and skin redness (*SCN9A* mutations)<sup>22</sup>.

Up to now, all studied *SCN5A* mutations associated with Brugada syndrome, are known to cause a loss of function of the cardiac Na<sup>+</sup> channel<sup>23</sup>. Various experimental studies have shown that peak I<sub>Na</sub> reduction in Brugada syndrome-linked mutant Na<sup>+</sup> channels may be more pronounced at elevated temperature. Dumaine *et al.*<sup>24</sup> showed that accelerated inactivation of the mutant channels T1620M is present only at the physiological body temperatures (32%), but not at room temperature (22%). Keller *et al.*<sup>25</sup> showed that changes in temperature caused a shift of the voltage-dependent activation curve towards more positive voltages in mutant F1344S. These temperature-dependent properties of the mutant Na<sup>+</sup> channel result in a reduced I<sub>Na</sub> at higher temperatures and could explain fever-induced ECG exacerbations and arrhythmias in Brugada syndrome patients.

Another hypothesis is that the effects of high temperature may disturb the functioning of the other allele (the wild type, WT) since other experimental studies failed to show temperature-dependent differences in inactivation characteristics between mutant and WT channels. This suggestion came also from the observation

that a patient carrying the truncation mutation R535X in a heterozygous state (mutant channels generate no measurable  $I_{Na}$  at both room and body temperature) showed ST segment elevations only during fever<sup>26</sup>. Actually, if fever would affect the function of the WT channels, it is not clear why not all Brugada syndrome patients are fever-sensitive. Clearly, the effects of fever on the action potential are more complex and the role of fever in exacerbating Brugada syndrome can be determined by more than one factor. Such aggravating factors may include age, sex or additional changes in other cardiac ion currents than  $I_{Na}$  during fever. Moreover, fever acts also through secondary effects via the autonomic regulation. Young age represents anyhow a risk factor because of the facility of fever-related illnesses in childhood. We have already reported that in Brugada syndrome children younger than 16 years of age fever represented a major factor for the occurrence of syncope<sup>16</sup>.

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In order to better elucidate the mechanism by which fever induces ECG changes and life-threatening arrhythmias in some Brugada syndrome patients, we focussed the second part of the analysis on the group of patients in who ECG were available both before and during high temperature. Similarly to what happen with the administration of sodium channel blockers on ECG parameters, further  $I_{Na}$  reduction during fever led to worsening of conduction slowing in affected patients, in other words to PR and QRS durations prolongation. Fever also caused specific changes in the ST segment in all the Brugada patients in whom a twelve-lead ECG was taken before and during the febrile episode, and in two cases these changes preceded a cardiac arrest. These changes were not present in control patients during febrile state. Both group reached the same average heart rate while having fever. It is, therefore, plausible that the ECG changes are not merely caused by the presence of tachycardia, but by temperature-related factors. The amplitude of fever does also not seem to be related to the presence of ECG modifications of cardiac events.

Future studies are necessary to identify clinical of genetic characteristics that make some patients more prone to fever.

## **Conclusions**

This is the first time that the association between fever and cardiac arrhythmias in Brugada syndrome is systematically studied. We conclude that fever-triggered cardiac events are common in Brugada syndrome patients and that recommendation of prompt use of antipyretics is mandatory, especially in those patients that show ECG changes at high temperature. We also advise our patients to come to the hospital for ECG monitoring during fever. Patients displaying a type I ECG only at high temperatures are likely to develop arrhythmias and should be admitted for rhythm observation.

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