Figure. Percentage of US Heart Disease (HD) Deaths by Age Group and HD Subtype, 2000-2010

The HD subtypes were classified using International Classification of Diseases, Tenth Revision, codes: total (I00-I09, I11, I13, I20-I51); CHD (I20-I25); heart failure (I50); hypertensive HD (I11, I13); valvular HD (I33-I38); arrhythmia (I47-I49); pulmonary HD (I26-I28); and other (I00-I09, I30-I33, I40-I46, I51). Y-axis scale shown in blue indicates range of deaths from 0% to 20%.

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.


Follow-up From Childhood to Adulthood of Individuals With Family History of Brugada Syndrome and Normal Electrocardiograms

Brugada syndrome is an inherited primary arrhythmia syndrome characterized by coved-type ST-segment elevation in the right precordial leads without structural heart disease and is associated with increased risk of sudden death. The syndrome is genetically and clinically heterogeneous and can present within the first months of life, although more typically in the fourth or fifth decade. The diagnostic type 1 electrocardiogram (ECG) may manifest spontaneously, increasing with age. Sex hormones have been suggested as potential responsible factors.

Ajmaline challenge is recommended to unmask the diagnostic ECG pattern in patients with suspected disease. Although screening of first-degree relatives is common, no evidence-based guidelines exist, particularly for children with normal ECGs. We investigated the clinical significance of repeat testing after puberty in asymptomatic children with a family history of Brugada syndrome who had an initial negative ajmaline test.

Methods | All asymptomatic individuals with a first-degree relative with Brugada syndrome and negative ajmaline test performed before 16 years of age between 1992 and 2010 seen at the university hospital of Brussels, Belgium (UZ Brussel-VUB) had an ECG repeated annually and were scheduled to repeat the test after puberty (≥16 years of age with onset of secondary sexual characteristics). Ajmaline challenges were repeated between 2008 and 2013, at least 3 years after the first test, and were performed and evaluated as previously described. Follow-up of patients with positive repeat tests continued until February 2014. Written informed consent was obtained from parents or patients.
older than 18 years. The ethics committee of the UZ Brussel-VUB approved the study protocol.

Statistical analyses were conducted using SPSS software version 22 (SPSS Inc). The $\chi^2$ and Fisher exact tests were used to analyze categorical variables and the unpaired or paired $t$ test was used for continuous variables. A 2-tailed probability value of $<.05$ was deemed significant.

Results | There were 53 asymptomatic children scheduled to repeat the ajmaline test after puberty. Nine are younger than 16 years and 1 presented with spontaneous Brugada type 1 ECG at age 16 years. The remaining 43 individuals from 23 different families repeated the test (Table 1). Ajmaline challenge unmasked type 1 ECG in 10 patients (23%) (Table 2). Age at the time of the repeat test was similar between individuals with positive (mean [SD], 21.2 [1.3] years) and negative (mean [SD], 19.3 [2.2] years) results ($P = .15$).

Before the repeat test, 4 patients developed symptoms (3 had syncope and 1 had nocturnal agonal respiration). The mean (SD) age at symptom appearance was 22.5 (3.2) years. A significantly higher proportion of symptomatic than asymptomatic patients had a positive repeat test (3 [75%] vs 7 [18%], respectively, $P = .03$). During the repeat test, 1 patient experienced refractory ventricular fibrillation. Genetic testing was obtained in all patients with a positive repeat test and 5 had a SCN5A mutation. Two patients received an implantable cardioverter-defibrillator.

After a mean (SD) follow-up of 42 (14) months (range, 11.0-67.0 months), no patient with a positive repeat test died suddenly. One patient who experienced syncope 7 years after the first ajmaline challenge had an episode of spontaneous ventricular fibrillation successfully treated with an implantable cardioverter-defibrillator. Spontaneous type 1 ECG occurred in another patient during a febrile episode. The follow-up of the remaining patients was uneventful.

Discussion | Repeat ajmaline challenge after puberty unmasked Brugada syndrome in 23% of relatives with a previously negative drug test performed during childhood.

The ECG phenotype does not appear during childhood in most cases, but may develop later in response to hormonal, autonomic, or genetic factors. To our knowledge, this is the first report of changes in the response to ajmaline over time.

Limitations of the study include the small number of patients, which limits the ability to analyze subgroups.

Screening of asymptomatic first-degree relatives of patients with Brugada syndrome is advisable, although the ideal

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**Table 1. Clinical Characteristics and Electrocardiogram Parameters of Study Population**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Ajmaline Challenge, y</th>
<th>Sex</th>
<th>Family History of Sudden Death, No. (%)</th>
<th>Baseline ECG</th>
<th>Symptoms a</th>
<th>EPS</th>
<th>SCN5A Mutation</th>
<th>Appropriate ICD Intervention or Sustained VA During Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>Male</td>
<td>Yes</td>
<td>Normal</td>
<td>Syncope</td>
<td>Positive</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>Male</td>
<td>Yes</td>
<td>Type 2</td>
<td>Asymptomatic</td>
<td>Negative</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3b</td>
<td>11</td>
<td>Female</td>
<td>Yes</td>
<td>Normal</td>
<td>Asymptomatic</td>
<td>NP</td>
<td>(p.[2632C &gt; T] + [ = ]) (p.[R878C] + [ = ])</td>
<td>No</td>
</tr>
<tr>
<td>4b</td>
<td>14</td>
<td>Female</td>
<td>Yes</td>
<td>Normal</td>
<td>Asymptomatic</td>
<td>NP</td>
<td>(p.[2632C &gt; T] + [ = ]) (p.[R878C] + [ = ])</td>
<td>No</td>
</tr>
<tr>
<td>5b</td>
<td>14</td>
<td>Female</td>
<td>Yes</td>
<td>Normal</td>
<td>Nocturnal agonal respiration</td>
<td>Negative</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6b</td>
<td>18</td>
<td>Female</td>
<td>Yes</td>
<td>Type 2</td>
<td>Asymptomatic</td>
<td>NP</td>
<td>(p.[2632C &gt; T] + [ = ]) (p.[R878C] + [ = ])</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>17</td>
<td>Female</td>
<td>No</td>
<td>Normal</td>
<td>Asymptomatic</td>
<td>NP</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>Female</td>
<td>Yes</td>
<td>Normal</td>
<td>Asymptomatic</td>
<td>Negative</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>16</td>
<td>Male</td>
<td>No</td>
<td>Type 2</td>
<td>Asymptomatic</td>
<td>NP</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>24</td>
<td>Female</td>
<td>No</td>
<td>Normal</td>
<td>Syncope</td>
<td>NP</td>
<td>(p.[4719C &gt; T] + [ = ]) (p.[665C673Gly]); c.[274-24C &gt; T] + [ = ] variant</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: ECG, electrocardiogram; EPS, electrophysiological study; ICD, implantable cardioverter-defibrillator; NP, not performed; VA, ventricular arrhythmias.

* Refers to the period between first and repeat drug test.

* These 4 are members of the same family.
timing is unknown. Relatives developing symptoms should always be investigated with ajmaline challenge even if they had a negative drug test performed before puberty. These findings support the need for repeat monitoring of family members of patients with Brugada syndrome, including those initially considered at low risk because of young age.

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Study supervision: All authors.

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COMMENT & RESPONSE

Red Blood Cell Transfusion Strategies and Health Care–Associated Infection

To the Editor In a meta-analysis, Dr Rohde and colleagues1,2 which demonstrated an association between a restrictive red blood cell transfusion strategy compared with a liberal transfusion strategy and the risk of serious nosocomial infections (risk ratio [RR], 0.82 [95% CI, 0.72-0.95]) and infections after orthopedic surgery (RR, 0.70 [95% CI, 0.54-0.91]). The study by Karam et al3, which was included in the meta-analysis for assessment of the association of transfusion strategy and the risk of serious infections, is a subgroup analysis of stable, critically ill children enrolled in a randomized trial, Transferfusion Requirements in the Pediatric Intensive Care Unit (TRIPICU) study,3 which compared a hemoglobin threshold of 7 g/dL with a threshold of 9.5 g/dL. As seen in Figure 2 in the article, the TRIPICU study was also included in the meta-analysis, so these data were included twice.

In the meta-analysis for comparison of postoperative infection rates in orthopedic surgery between the restrictive strat-