0113

Short-coupled polymorphic ventricular tachycardia at rest linked to a novel ryanodine receptor (RyR2) mutation: leaky RyR2 channels under non-stress conditions

Albano Meli (1), Jim W. Cheung (2), Wenjun Xie (3), Sunee Mittal (4), Steve Reiken (3), Anetta Wronska (3), Linna Xu (2), Jonathan S. Steinberg (4), Steven M. Markowitz (2), Sei Iwai (5), Alain Lacampagne (1), Bruce B. Lerman (2), Andrew R. Marks (3)

(1) Université de Montpellier, INSERM U1046 – CNRS UMR2014, Montpellier, France – (2) Weill Cornell Medical College, Cardiology, New York, Etats-Unis – (3) Columbia University Medical Center, New York, Etats-Unis – (4) Valley Health System, Ridgewood, Etats-Unis – (5) Westchester Medical Center, Valhalla, Etats-Unis

The ryanodine receptor / Ca2+ release channel (RyR2) is one of the main actors of the excitation-contraction coupling in the heart. Single-point mutations on RyR2 have been associated with catecholaminergic polymorphic ventricular tachycardia (CPVT) and arrhythmogenic right ventricular dysplasia (ARVD) and sudden cardiac death. In this study, we characterized a novel heterozygous RyR2 mutation found in a 31-year-old female and her mother with syncope at rest and recurrent short-coupled premature ventricular contractions (PVCs) initiating polymorphic ventricular tachycardia (PMVT). Using site-directed mutagenesis, we expressed human RyR2-H29D mutant channels with its stabilizing protein calstabin2 (FKBP12.6). Single channel measurements of RyR2-H29D channels revealed significantly higher open probability (Po) and opening frequency (Fo) at diastolic levels of cytosolic Ca2+ when compared with RyR2-WT channels under non-stress conditions (i.e. in absence of PKA phosphorylation). This leaky phenotype at rest in RyR2-H29D channels was associated with a modest but significant depletion of calstabin2 binding from the RyR2 macromolecular complex when compared to RyR2-WT channels. Interestingly, under stress conditions, RyR2-H29D channels also exhibited a significant higher Po and Fo at diastolic concentrations of Ca2+ while no significant depletion of calstabin2 was observed.

In conclusion, the RyR2-H29D mutation is associated with a clinical phenotype of short-coupled PMVT at rest. In contrast to CPVT-associated RyR2 mutations, RyR2-H29D causes a leaky channel at diastolic levels of Ca2+ under non-stress conditions. Leaky RyR2 may be an under-recognized mechanism for idiopathic PMVT at rest.

0185

Genetic screening identifies a high proportion of mutations in patients with idiopathic ventricular fibrillation and sudden cardiac death

Vincent Probst (1), Solena Le Scouarnec (2), Florence Kyndt (3), Jean-Jacques Schott (2), Jean-Baptiste Gourraud (1), Frederic Sacher (4), Philippe Mabo (5), Matilde Karakachoff (2), Stephanie Bonnau (2), Jade Violleau (2), Eloi Marjion (6), Florence Dumas (6), Alain Cariou (6), Richard Redon (2), Pierre Lindenbaum (2), Xavier Jouven (6), Richard Redon (2)

(1) CHU Nantes HGRL, Institut du Thorax, Nantes, France – (2) CHU Nantes, Institut du Thorax, UMR 1087, IRT UN, Nantes, France – (3) CHU Rennes, Cardiologie, Rennes, France – (4) CHU Bordeaux, Hôpital Cardiologique, Bordeaux, France – (5) CHU Tours, Cardiologie, Tours, France – (6) CHU Toulouse, Cardiologique, Toulouse, France

Introduction: Several gene defects are associated with idiopathic ventricular fibrillation (IVF) and sudden cardiac death (SCD). The recent development of NGS-based mutation screening provides a unique opportunity to estimate extensively the spectrum and prevalence of rare variants in genes associated with cardiac diseases.

Methods: Cohort 1 was composed of 75 patients resuscitated from cardiac arrest due to IVF. All patients have undergone a complete clinical cardiac examination including 12 lead-ECG, cardiac echography, coronography and exercise test. Cohort 2 was composed of 99 victims of SCD related to ventricular fibrillation younger than 45 years old and without explanation for the SCD at the time of the reanimation.

Genetic screening was based on the use of the HaloPlex™ Target Enrichment System (Agilent Technologies) prior to HiSeq sequencing (Illumina).

The custom kit designed for this study covers 163 genes previously reported as involved in cardiac arrhythmias, conduction defect and cardiomyopathies.

Results: In cohort 1, the mean age was 36±10 years with a male predominance (52 males, 69%). In cohort 2, the mean age was 37±7 years with a male predominance (76 males, 79%).

In cohort 1, we identified 50 putative mutations in 35 patients (47%). In cohort 2, we identified 30 putative mutations in 24 patients (24%).

Abstract 0185-Table

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cohort 1 (n=75)</th>
<th>Cohort 2 (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN5A</td>
<td>7 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>HCM and DCM genes</td>
<td>22 (29%)</td>
<td>17 (17%)</td>
</tr>
<tr>
<td>ARVD/C genes</td>
<td>4 (5%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>LQTS genes (excluding SCN5A)</td>
<td>4 (5%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>CPVT genes (excluding SCN5A)</td>
<td>7 (9%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>BRS genes</td>
<td>3 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (4%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

Conclusion: Our study identified mutations in almost 50% of IVF patients after a complete cardiac evaluation. These results suggest that molecular analysis must be part of the work up in this kind of patients. In young patients affected by unexplained sudden death, the molecular analyses are less contributive probably because of a more important percentage of patients affected by ischemic cardiomyopathies.

0210

Effect of SCN5A mutations and SCN10A, SCN5A and HEY2 frequent variants on ECG of Brugada patients during ajmaline test


(1) Université de Montpellier, INSERM U1046 – CNRS UMR9214, Montpellier, France – (2) Weill Cornell Medical College, Cardiology, New York, Etats-Unis – (3) Columbia University Medical Center, New York, Etats-Unis – (4) Valley Health System, Ridgewood, Etats-Unis – (5) Westchester Medical Center, Valhalla, Etats-Unis – (6) Paris Sudden Death Expertise Center

Introduction: Inactivating mutations in the SCN5A gene are the most frequent cause of Brugada syndrome. The myocardial transmural electrical gradient that could explain the ‘Brugada’ ECG pattern, is considered as increased by inactivation of the sodium channel. Na channel blocker drug can likewise increase or unmask this pattern. To better assess phenotype correlation with those SCN5A mutation and frequent variants, we compare ECG parameters during Na channel blocker test according to the genetical status.

Methods: ECG parameters (P, PR, QRS, QT peak and QT end intervals; J wave amplitude in V1, V2, V3) were double measured in 73 unrelated Brugada patients with a positive Na blocker challenge. Data were measured at baseline and at the end of the test. Each patient was screened for SCN5A mutation and SCN10A, SCN5A and HEY2 frequent variants by direct sequencing and genotyped using Axiom Genome-Wide CEU 1 arrays (Affymetrix).

Results: The 10 patients carrying known SCN5A mutations (14%) didn’t show any clinical differences at baseline with those without SCN5A mutation. Baseline ECGs revealed a lengthening of PR (181 ±27 vs 156 ±30 ; p=0.017) and QRS interval (101 ±15 vs 89 ±14 ; p=0.020). No other parameter was significantly different. Once ECG parameters fulfilled diagnostic criteria for Brugada pattern, ECG parameters were not significantly different in the 2 groups. A similar effect on ECG was found in patients without SCN5A mutations but carrying more than 4 frequent variants. SCN10A polymorphism (rs10428132) was associated with a progressive effect on PR (p=0.044) and QRS (p=0.030) duration according to the risk allele number. According to the genetic status, no clinical difference was found after a mean follow up of 6 years.