0113

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


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 P3A 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 significantly 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


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

The custom kit designed for this study covers 163 genes previously reported with idiopathic ventricular fibrillation and sudden cardiac death. The recent developments 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 P3A 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 significantly 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.

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


Introduction: Inactivating mutations in the SCN5A and frequent variants in SCN10A, SCN5A and HEY2 genes have been both associated with 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 mutations and frequent variants by direct sequencing and frequent variants, we compare ECG parameters during Na channel blocker test according to the genetical status.

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.