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Letters

Familial Catecholamine-Induced QT Prolongation in Unexplained Sudden Cardiac Death

Despite major progress in molecular and phenotypic characterization of primary electrical disorders, many (aborted) sudden cardiac deaths (SCDs) occur in young victims without identifiable abnormalities (1). This study aimed to describe the use of mental stress test (MST) to identify catecholamine-induced QT prolongation (CIQTP) in SCD familial screening.

MST was performed in the screening of 65 consecutives families affected by unexplained SCD referred to the National Referral Centre for Inherited Cardiac Arrhythmias of Nantes. Conventional screening included echocardiography, exercise test, and epinephrine and ajmaline tests (1). MST was performed following a standardized protocol mostly based on mental arithmetic in stressful conditions (2). Two physicians blinded to patient clinical and genetic status reviewed all the electrocardiograms. Patients were considered affected for CIQTP when presenting prolonged QTc interval >480 ms or if >30 ms QT prolongation with the QTc interval >460 ms (1) during the different tests.

We fortuitously unmasked a significant prolongation of QTc duration in a young woman when mentioning the unexplained SCD of her sister at summer 2013. According to previous description of stress-induced repolarization abnormalities (2,3), we additionally performed MST during familial screening in 65 families with a familial history of SCD in young patients. Conventional screening identified 7 Brugada syndrome, 6 long QT syndrome (LQTS), and 3 familial cardiomyopathies. MST unmasked CIQTP in 4 families (mean age of SCD 18 years) (**Figure 1A**). In these families, 31 of the 57 tested family members were affected (QTc during MST 501 ± 36 ms vs. 430 ± 19 ms) with a flattening or double-hump T-wave aspect in 13 of 31 versus 1 of 26 in unaffected patients ($p < 0.001$) (**Figure 1B**).

In 9 patients (including 2 with previous reported syncope) MST was the only positive test. Eight of these patients did not receive an epinephrine test because of contraindication (<15 years old; n = 7) or refusal (n = 1). Epinephrine tests were positive in 20 of 21 affected patients (95%), whereas the exercise test failed to identify the QT prolongation in 18 of 30 affected patients (60%). After the diagnosis of CIQTP, 14 family members were treated by beta-blocker therapy and 2 were implanted by an implantable cardioverter-defibrillator. No symptom occurred during a median follow-up of 22 months, in contrast to 6 SCDs and 7 previous syncope. Genetic screening failed to identify any mutation in the 45 susceptibility genes tested (4).

We describe MST as a diagnostic tool, able to unmask CIQTP in a context of unexplained SCD even in patients previously negative after conventional exhaustive screening. Considering the family histories and the presence of CIQTP in symptomatic family members, it is highly probable that CIQTP was responsible of the familial SCD (2,3). CIQTP is distinguished from the classical form of LQTS by the normal baseline electrocardiogram without any QT prolongation, the saddleback T-wave occurring during MST, and the absence of mutations in the LQTS genes.

Even if CIQTP may be identified by both MST and epinephrine test, MST has the advantage of being safer, easier, and quicker to perform. On the other hand, the complex use of epinephrine test can lead to contraindication or misinterpretation. The use of MST in the context of unexplained SCD and LQTS deserves further investigations and comparative studies.

Our preliminary findings have identified CIQTP as a new specific familial phenotype characterized by normal QT duration at rest but major QT lengthening during mental stress. CIQTP seems to play an important role in unexplained ventricular fibrillation and MST appears to be a simple and efficient test to identify this pathology.

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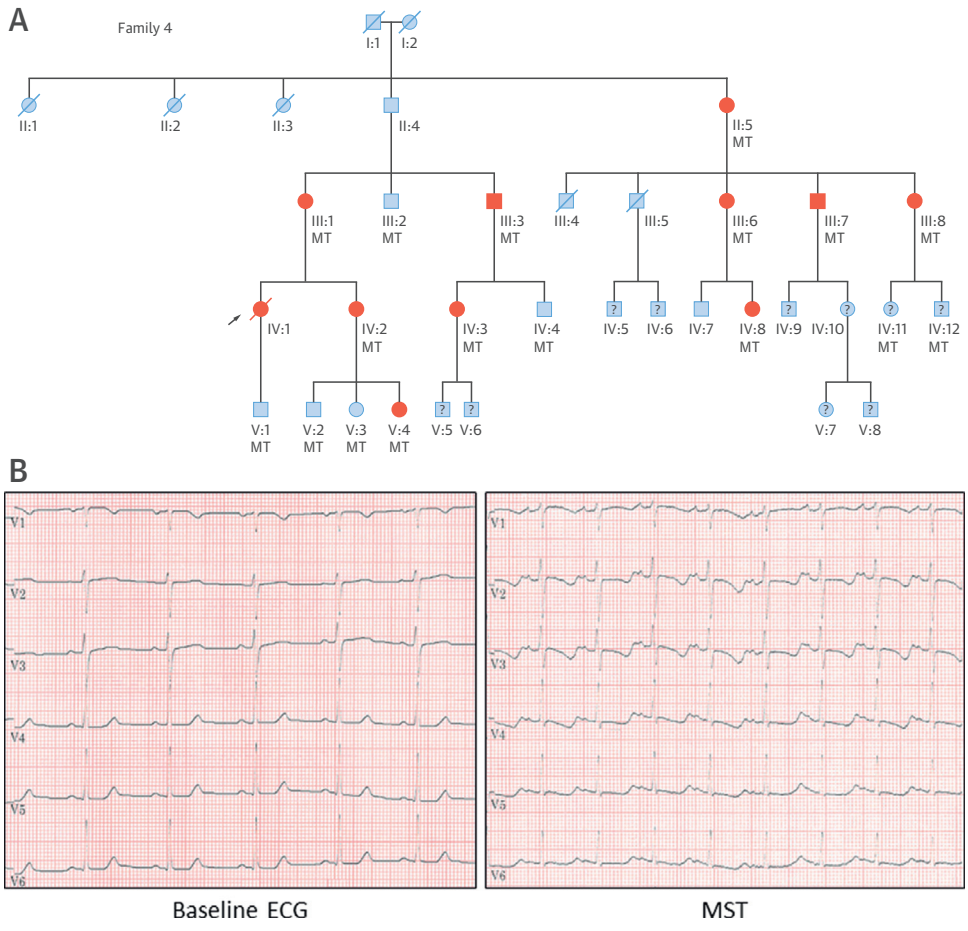
FIGURE 1 Familial Catecholamine-Induced QT Prolongation



(A) Example of familial inheritance of the pattern in a family: affected **(solid square and circle)**, nonaffected **(open square and circle)**, unknown **(open square and circle with question mark)**, mental stress test (MST) performed **(MT)**, and proband **(arrow)**. **(B)** Typical effect of mental stress test on QT interval.

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