EDITORIAL COMMENT

Inheritance of Early Repolarization and Familial Malignant Forms*

Andrew D. Krahn, MD,†
Manoj N. Obeyesekere, MBBS‡
Vancouver, British Columbia, Canada; and Victoria, Australia

Recent studies have reported the association between early repolarization (ER) and an increased risk of death from cardiac causes and of idiopathic ventricular fibrillation (IVF) (1–3). ER should be viewed as largely benign. In some, ER is a modifier of the risk of underlying cardiac conditions, and very rarely ER represents a primary arrhythmogenic disorder (i.e., the ER syndrome when other etiologies have been systematically excluded and when ER is associated with IVF) (4).

ER is reported to be due to steep transmural action potential gradients that predispose to arrhythmogenesis (5). The risk of arrhythmia is reported to depend on the location, pattern, and magnitude of ER (1,2). The highest risk is associated with ER in the inferior limb leads with a high amplitude J-point/wave (>0.2 mV) and a horizontal or descending ST-segment after the J-point (compared with rapidly ascending/upsloping ST-segments) (1). These high-risk features are observed in <0.3% of the population (1). In the general population, ER is associated with an increased relative risk of death of between 1.3 and ~6 (1). Despite the high overall prevalence of ER in the general population (6% to 13%) and the even higher prevalence of ER in patients with IVF (~20% to 30% and as high as 50% to 60%), IVF itself is rare (ER is estimated to increase IVF risk from 3.4 per 100,000 to 11 per 100,000) (6). The critical issue of accurately identifying individuals with ER with an increased risk of death or IVF compared with the benign ER observed in a substantial proportion of the population remains elusive. Complicating the issue is the intermittent nature of the electrocardiographic pattern. Autonomic tone plays a role in ER variability with ER-associated IVF events more likely in vagal contexts (e.g., at night) (2,5).

Familial inheritance of ER has been suggested but not clearly demonstrated (7). Familial ER has been reported to have a probable autosomal dominant inheritance pattern with incomplete penetrance (8). A study involving Caucasian nuclear families found that individuals with at least 1 parent with the ER pattern had a 2.5-fold risk of demonstrating the same (7). Familial transmission appeared more frequent when the mother was affected. Reasons for unequal transmission include effects mediated via the sex chromosomes, transmission through mitochondrial DNA, and parental imprinting of autosomal genes. Heritability was also higher when ER was seen in the inferior leads or had a notched morphology. Whether familial ER portends a worse prognosis is not clearly known.

In this issue of the Journal, Gourraud et al. (9) report on 4 large French families with ER and characterize the heritability (302 relatives, electrocardiograms available for 171 and the Valsalva maneuver performed in 80). The study demonstrates that 1) the ER pattern can be heritable in a pattern consistent with an autosomal dominant mode, 2) familial ER can be associated with an increased incidence of sudden cardiac death (familial ER syndrome), and 3) the Valsalva maneuver can assist in unmasking/accentuating familial ER.

ER was noted in contiguous generations with male-to-male transmission (which excludes autosomal recessive, mitochondrial, and X-linked inheritance). These families had 22 sudden deaths (at least 4 were nocturnal). A high prevalence of ER (33% to 58%) was reported in these families. The sudden death rates in ER carriers ranged from 14% to 48%, suggesting modifying variables that contribute to variable expressivity between families (e.g., deaths were only noted in males in family C). The sudden death rate is clearly substantially higher than the rate associated with patients with the ER pattern in the general population, suggesting increased expressivity in these families.

The study also demonstrates that concealed ER can be manifest/accentuated by the Valsalva maneuver. The Valsalva maneuver reclassified 5 of 11 obligate carriers as affected (based on a presumed monogenic autosomal dominant inheritance pattern), initially deemed as unaffected by a standard resting electrocardiogram. The Valsalva maneuver also increased the degree of ER in 17 of 20 affected patients and identified 17 of 60 relatives previously deemed unaffected. In the 2 families in which the Valsalva maneuver was performed, penetrance of ER was increased from 33% to 60% in one and 90% to 100% in the other. A positive Valsalva maneuver was defined as an increase in J-wave amplitude of >0.5 mm, J-wave appearance in 1 new electrocardiographic lead, or the appearance of a significant
J-wave (>1 mm) in 2 consecutive leads in previously unaffected cases.

Although this valuable study demonstrates inheritance of ER and the utility of the Valsalva maneuver, a number of questions arise. First, a handful of reports implicate a gain-of-function missense mutation in the KCNJ8 gene in ER and IVF (10,11). Loss-of-function mutations in the L-type calcium channels (CACNA1C, CACNB2, and CACNA2D1) have also been implicated (12). Highly conserved residues in the SCN5A gene have also been associated with ER and IVF, although this remains disputed (13,14). Even though autosomal dominant inheritance with incomplete penetrance of ER is apparent, a simple Mendelian monogenic mode cannot be absolutely concluded without further evidence due to complex inheritance patterns/modifiers that may exist (i.e., multifactorial inheritance in which the ER and/or the IVF phenotype is influenced by many independent loci and in the way those loci interact). Gourraud et al. reported that there were no mutations in the KCNJ8 and SCN5A genes (direct capillary sequencing in 3 probands), and there was no evidence of linkage of CACNA1C, CACNB2, and CACNA2D1 with ER, suggesting further genetic and mechanistic heterogeneity of ER and IVF. Future (and undoubtedly ongoing) studies should seek to investigate gene variant(s) that clearly segregates with or contributes to the ER and/or IVF phenotype. Whole exome or genome studies will also be valuable.

The study does not provide data on the prevalence of the familial form of ER. It is likely that the vast majority of ER is predominantly isolated, given that this population was drawn from a registry of 148 symptomatic ER syndrome probands, which represents as little as 4 in 148 of cases (3%). Additionally, the vast majority of ER is relatively benign compared with these unique families. The families studied represent a rare cohort, and the findings can provide invaluable mechanistic clues, but should not be extrapolated to the general population. Population studies argue for the potential for autosomal dominant transmission of the ER syndrome. Gourraud et al. should be commended for advancing our understanding of ER as we journey toward a better understanding that translates into better care for patients. The key finding in this study is that ER associated with familial sudden death appears to be genetically mediated in an autosomal dominant inheritance pattern, with an ER phenotype that is indistinguishable from the much more common sporadic form associated with IVF and an electrocardiographic phenotype indistinguishable from the ER pattern reported in population studies that can modify arrhythmic risk or is benign. The promising role for the Valsalva maneuver needs further evaluation.

The relationship between ER manifested by the Valsalva maneuver and prognosis is not known. It is currently not possible to identify asymptomatic patients/families with ER at increased risk of sudden death with any meaningful degree of accuracy. There is currently no recommendation to screen the families of individuals with asymptomatic ER. The authors state that the Valsalva maneuver may assist in identifying concealed ER in symptomatic patients/relatives and their families. However, in the absence of accurate risk-stratification strategies, the clinical utility of family screening of asymptomatic relatives is questionable. In symptomatic patients, a systematic evaluation needs to be undertaken to establish the etiology of symptoms and whether an implantable cardioverter-defibrillator is indicated after cardiac arrest. There is no reliable risk-stratification strategy for asymptomatic patients with ER in the general population or within families with ER to warrant placement of an implantable cardioverter-defibrillator.

Innumerable questions still remain unanswered and warrant investigation, including the detailed mechanisms and relationship of ER to IVF, genetic determinants of ER/IVF, risk modulators, and the prognostic significance of the provocability of the various electrocardiographic patterns/distribution/degree of repolarization. Despite the limitations and future challenges, the current report is a substantial step forward in demonstrating the rare but important potential for autosomal dominant transmission of the ER syndrome. Gourraud et al. should be commended for advancing our understanding of ER as we journey toward a better understanding that translates into better care for patients. The key finding in this study is that ER associated with familial sudden death appears to be genetically mediated in an autosomal dominant inheritance pattern, with an ER phenotype that is indistinguishable from the much more common sporadic form associated with IVF and an electrocardiographic phenotype indistinguishable from the ER pattern reported in population studies that can modify arrhythmic risk or is benign. The promising role for the Valsalva maneuver needs further evaluation.

Reprint requests and correspondence: Dr. Andrew D. Krahn, Division of Cardiology, University of British Columbia, 2775 Laurel Street, Vancouver, British Columbia V5Z 1M9, Canada. E-mail: akrahn@mail.ubc.ca

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