Pathogenesis of Sudden Unexpected Death in a Clinical Trial of Patients With Myocardial Infarction and Left Ventricular Dysfunction, Heart Failure, or Both

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Summary: Sudden unexpected death is highest in the early post–myocardial infarction period. Yet, the Defibrillator in Acute Myocardial Infarction Trial and the Immediate Risk Stratification Implantable Cardioverter-Defibrillator in Acute Myocardial Infarction With Angiotensin II Antagonist Losartan review of autopsy records in a series of cases classified as sudden cardiac death was found in 55% (37 of 67) of the deaths classified as sudden death. This lack of precision in classification might have serious implications. To better understand the pathophysiological events that lead to sudden unexpected death after myocardial infarction, we assessed autopsy records in a series of cases classified as sudden cardiac death in patients from the Valsartan in Acute Myocardial Infarction Trial. The present study demonstrates that recurrent myocardial infarction or myocardial rupture account for a high proportion of sudden unexpected deaths in the early period after acute myocardial infarction, whereas arrhythmic death may be more likely subsequently. These findings may help explain the lack of benefit of early implantable cardioverter-defibrillator therapy.

Conclusions: Recurrent myocardial infarction or cardiac rupture accounts for a high proportion of sudden death in the early period after acute myocardial infarction, whereas arrhythmic death may be more likely subsequently. These findings may help explain the lack of benefit of early implantable cardioverter-defibrillator therapy.

Incidence of Sudden Cardiac Death in National Collegiate Athletic Association Athletes

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Summary: This report more accurately estimates the incidence of sudden cardiac death (SCD) in athletes using improved methodology compared with previous studies. It demonstrates an overall rate of SCD of 1:43 000, with some subpopulations showing a risk of SCD as high as 1:3000. The rate of SCD has been commonly cited as 1:200 000. From a clinical perspective, this is critically important information. The preparticipation examination, or sports physical, is a core part of the practice of sports medicine and primary care physicians alike. The purpose of the preparticipation examination, according to the latest American Heart Association Scientific Statement, is to identify conditions that may lead to SCD. The current recommendation of the American Heart Association is that this is best done, in the United States, by the use of a directed history and physical examination. There is increasing evidence that this strategy is neither effective nor cost-effective. In other countries, an ECG is a routine part of a sports physical, or in some cases a well-child visit. The information presented in this report will inform the ongoing discussion about SCD in young people and how best to prevent it. There may be subpopulations of athletes or young people in which screening with an ECG by use of modern interpretation criteria would be highly cost-effective, and others in which it would not. This report will have significant ramifications for clinical practice as we strive to understand how to best use our resources, fulfill the primary objective of the sports physical, prepare for sudden cardiac arrest, and ultimately prevent SCD.

Conclusions: SCD is the leading medical cause of death and death during exercise in National Collegiate Athletic Association student athletes. Current methods of data collection underestimate the risk of SCD. Accurate assessment of SCD incidence is necessary to shape appropriate health policy decisions and develop effective strategies for prevention.

Common Variants in Cardiac Ion Channel Genes Are Associated With Sudden Cardiac Death

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Summary: Sudden cardiac death (SCD) results in 250 000 to 400 000 deaths in the United States annually, and the majority are unheralded, occurring as the initial manifestation of heart disease. Because there is a heritable component to SCD risk, genetic markers may aid in the identification of individuals who are at an elevated risk for arrhythmic death within the population. Because rare variants in cardiac ion channel genes have been associated with SCD
in rare primary arrhythmic syndromes, it is plausible that common variants in these same genes may be associated with more common forms of SCD. To address this hypothesis, we assembled SCD cases from 6 National Institutes of Health–funded prospective cohorts and used a prospective nested case-control design to test for associations between common genetic variation in coding and noncoding regions in 5 cardiac ion channel genes implicated in congenital long-QT syndrome and SCD among individuals of European ancestry. A noncoding variant in KCNQ1 (P = 0.0002) and a noncoding variant in SCN5A (P = 0.0005) were significantly associated with SCD after adjustment for multiple testing. The at-risk alleles are common, with population frequencies of 67% for the T-allele at rs2283222 in KCNQ1 and 60% for the C-allele at rs11720524 in SCN5A. These findings suggest that common variants with modest effects as well as rare variants with strong effects in these genes contribute to SCD risk. Further investigation into the functional abnormalities associated with noncoding variation in these genes may lead to important insights into predisposition to lethal arrhythmias in the population.

Conclusions: In this combined analysis of 6 prospective cohort studies, 2 common intronic variants in KCNQ1 and SCN5A were associated with SCD in individuals of European ancestry. Further study in other populations and investigation into the functional abnormalities associated with noncoding variation in these genes may lead to important insights into predisposition to lethal arrhythmias.

Prolonged Tpeak-to-Tend Interval on the Resting ECG Is Associated With Increased Risk of Sudden Cardiac Death

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Summary: The interval from the peak to the end of the T wave (TpTe) on the 12-lead ECG is a measure of transmural dispersion of repolarization in the left ventricle and a possible marker of ventricular arrhythmogenesis. We evaluated the association between TpTe and risk of sudden cardiac death (SCD) in the general population. TpTe interval was significantly prolonged in cases compared with controls. Cases of SCD also had a longer QRS duration and corrected QT interval than controls. TpTe remained a significant predictor of SCD after adjustment for age, sex, other ECG intervals, and left ventricular systolic dysfunction. The predictive value of TpTe was higher among subjects with unmeasurable QT because of prolongation of QRS duration compared with subjects with normal QRS duration. Furthermore, TpTe was associated with the risk of SCD in subjects with a normal QT interval. TpTe is likely to be a novel marker of SCD in the community, with particular utility when the corrected QT interval cannot be measured. These findings are likely to contribute to the enhancement of SCD risk stratification and merit evaluation in additional populations.

Conclusions: Prolongation of the TpTe interval measured in lead V5 was independently associated with SCD, with particular utility when the QTe was normal or not measurable because of prolonged QRS.

Circumstances and Outcomes of Sudden Unexpected Death in Patients With High-Risk Myocardial Infarction: Implications for Prevention

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Summary: Sudden unexpected death is a frequent catastrophic complication in patients after myocardial infarction. For patients such as those with reduced ejection fraction immediately after myocardial infarction who are not eligible for implantable cardioverter-defibrillator therapy, strategies for prevention have remained elusive. In this study, we explored the circumstances of sudden death events in patients with high-risk myocardial infarction. We showed that only half of sudden death events occurring at home were witnessed, in part because of a high proportion (≈50%) of events occurring during sleep. We also demonstrated that early after myocardial infarction there was an increased likelihood of sudden death events occurring in hospital (44% within the first 40 days versus 21% for the entire follow-up period). Taken together, these findings help to explain the lack of efficacy of home automatic external defibrillators and suggest that strategies for prevention in this patient population should take into account the circumstances of sudden death events. Finally, we assessed the outcomes of patients who were successfully resuscitated after cardiac arrest, illustrating the benefit of secondary-prevention implantable cardioverter-defibrillator therapy (hazard ratio for death, 0.36; P = 0.04).

Conclusions: A high proportion of sudden death events after high-risk myocardial infarction occurred at home, but in-hospital events were more common early on. Patients who were asleep were more likely to have unwitnessed arrests. Alternative strategies for the prevention of sudden death in patients who are not candidates for implantable cardioverter-defibrillator will need to take into account the circumstances of sudden death events.

Primary Prevention of Sudden Cardiac Death in Silent Cardiac Sarcoidosis: Role of Programmed Ventricular Stimulation

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Summary: Cardiac involvement in sarcoidosis is uncommon but can cause ventricular tachycardia (VT) and sudden cardiac death. PET scanning and cardiac MRI can detect myocardial involvement before cardiac symptoms, but the means to predict arrhythmia risk are not well defined. This study examined the use of programmed electric stimulation in patients with evidence of cardiac sarcoidosis on imaging, but without prior cardiac symptoms. Of 76 patients who underwent programmed electrical stimulation, 8 had inducible VT and received an implantable defibrillator. Left ventricular ejection fraction was lower in the inducible group. Over a median follow-up of 5 years, 6 of the 8 with inducible VT died or had spontaneous VT requiring defibrillator therapy. One of the 68 patients without inducible VT died. Our study suggests that programmed ventricular stimulation may assist in assessing arrhythmia risk in this population.

Conclusions: In patients with biopsy-proven sarcoidosis and evidence of cardiac involvement on PET or cardiac MR alone, positive programmed electric stimulation may help to identify patients at risk for ventricular arrhythmia. More importantly, patients in this cohort with a negative programmed electric stimulation appear to have a benign course within the first several years following diagnosis. Programmed electric stimulation may help to guide the use of implantable cardioverter defibrillators in this population.

Modeled Economic Evaluation of Alternative Strategies to Reduce Sudden Cardiac Death Among Children Treated for Attention Deficit/Hyperactivity Disorder

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Summary: Stimulants are commonly used to treat children with attention deficit/hyperactivity disorder. These drugs have adrenergic properties and may increase the risk for sudden cardiac death in individuals with cardiac abnormalities such as cardiomyopathies or conduction defects. Although the possible value of routine ECG screening before stimulant treatment is an object of debate, current clinical guidelines recommend medical history–taking and physical examination, with ECG and cardiology evaluation only for the
Benefits of ECG screening arise primarily by restricting children for whom cardiology referral on ECG is indicated, with the intent of preventing sudden cardiac death. The effectiveness may be improved by basing cardiology referral on ECG screening with ECG has a borderline cost-effectiveness according to generally accepted willingness-to-pay criteria. These analyses provide useful estimates that contribute to the current debate on the possible role of ECG for preventing sudden cardiac death in childhood.

Conclusions: Relative to current practice, adding ECG screening to history-taking and physical examination pretreatment screening for children with attention deficit/hyperactivity disorder has borderline cost-effectiveness for preventing sudden cardiac death. Relative cost-effectiveness may be improved by basing cardiology referral on ECG alone. Benefits of ECG screening arise primarily by restricting children identified with sudden cardiac death risk from competitive sports.

Relationship Between Nonsustained Ventricular Tachycardia After Non-ST-Elevation Acute Coronary Syndrome and Sudden Cardiac Death: Observations From the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) Randomized Controlled Trial

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Summary: Nonsustained ventricular tachycardia (VT) occurs frequently in patients hospitalized with acute coronary syndromes, although the clinical implications of VT remain uncertain. In particular relative to the absolute risk of sudden cardiac death in patients with shorter episodes of ventricular ectopy and the relationship between the timing of VT after hospital admission and prognosis. In this study of 2630 patients admitted with non-ST-elevation acute coronary syndrome and enrolled in the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial who had 7-day continuous ECG monitoring, we found a 2-fold increase in the risk of sudden cardiac death in patients with both short (4–7 beats in length) and longer (≥8 beats in length) episodes of VT compared with patients with no VT. This relationship was unchanged after adjustment for clinical characteristics, including left ventricular ejection fraction and natriuretic peptides. In contrast, there was no increased risk of sudden cardiac death in patients with ventricular triplets. In regard to timing of VT, we found that only episodes occurring ≥48 hours after admission were associated with an increased risk of sudden cardiac death, whereas earlier episodes within 48 hours did not carry the same risk. In several subgroups (history of heart failure, depressed left ventricular ejection fraction, and defibrillation were significantly associated with improved survival in the present study, these data have implications for health services planning.

Conclusions: Nonsustained VT is common after admission for non–ST-elevation acute coronary syndrome, and even short episodes of VT lasting 4 to 7 beats are independently associated with the risk of sudden cardiac death over the subsequent year.8

Factors Associated With Pulseless Electric Activity Versus Ventricular Fibrillation: The Oregon Sudden Unexpected Death Study

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Summary: In this population-based study, details of preclinical conditions were combined with emergency medical services data to identify correlates of pulseless electric activity versus ventricular fibrillation and asystole. As expected, cases of cardiac arrest that presented with pulseless electric activity were significantly less likely to survive, and age, black race, female sex, and pulmonary disease were significant correlates of pulseless electric activity. As anticipated, ventricular fibrillation was more likely to be associated with a diagnosis of hyperlipidemia or coronary artery disease. However, there were no differences in the overall disease burden or resuscitation response time that explained occurrence of pulseless electric activity. In addition to reporting specific clinical correlates of pulseless electric activity, this study has identified a novel and significant association between lifetime syncope and previous pulseless electric activity that was not explained by a higher prevalence of cardiac conduction system disease on the resting 12-lead ECG. Given the well-established rising prevalence of pulseless electric activity and significantly worse survival outcome compared with ventricular fibrillation, enhancing the mechanistic understanding of pulseless electric activity is a high priority. These findings, particularly the potential link between syncope and pulseless electric activity, are likely to provide a basis for new investigative approaches to evaluate mechanisms of this condition.

Conclusions: Pulseless electric activity cases had a significantly higher prevalence of syncope in their lifetime, with other correlates, including black race, that were distinct from ventricular fibrillation cases. Potential mechanistic links between syncope and future manifestation with pulseless electric activity warrant further exploration.9

Sports-Related Sudden Death in the General Population

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Summary: To date, the majority of data regarding sports-related sudden death (SD) have focused on young competitive athletes, and few data concerning sports-related SD in the general population have been available. In this 5-year observational study of SD occurring during sports in competitive and recreational participants 10 to 75 years of age, we have found that although the risk for sports-related SD remains higher in young competitive athletes than in young noncompetitive sports participants, the absolute risk is otherwise higher in the general population. The present study revealed approximately 800 cases in France each year compared with the 15 annual cases among young competitive athletes. Case subjects were relatively young (46±15 years), predominantly males (95%), and without any prior history of heart disease. Half of the observed cases occurred in sports facilities, and almost 90% of events were witnessed; however, the rate of bystander cardiopulmonary resuscitation was low, initiated in less than one-third of cases. Given the often predictable setting of sports-related SD, prompt interventions including bystander cardiopulmonary resuscitation and defibrillation were significantly associated with improved survival in the present study, these data have implications for health services planning.

Conclusions: Sports-related sudden death in the general population is considerably more common than previously suspected. Most cases are witnessed, yet bystander cardiopulmonary resuscitation was only initiated in one-third of cases. Given the often predictable setting of sports-related sudden death and that prompt interventions were significantly associated with improved survival, these data have implications for health services planning.10
Efficacy and Safety of Celivarone, With Amiodarone as Calibrator, in Patients With an Implantable Cardioverter-Defibrillator for Prevention of Implantable Cardioverter-Defibrillator Interventions or Death: The ALPHEE Study

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Summary: Sudden cardiac death is preventable with implantable cardioverter-defibrillators. These devices can now be placed not only in patients who have had a sustained arrhythmia, but also in those deemed high risk for whom a mortality benefit can also be derived. Unfortunately, a sizable percentage of patients who receive these devices may have frequent or inappropriate shock therapy. We have learned that these events are psychologically devastating, cause frequent hospitalizations, and predispose to morbidity and mortality events. Although antiarrhythmic drugs are frequently used to prevent frequent device discharges, no drug has gained US regulatory approval for this indication. On the basis of favorable data obtained in a small phase IIa trial, we studied the efficacy and safety of celivarone, a novel benzofuran derivative and congener of amiodarone and droperidone, for the prevention of device activation and sudden death. In a multinational, multicenter, prospective, double-blind, randomized, parallel-group trial, we compared 3 doses of celivarone with placebo and included an amiodarone calibrator arm to confirm the adequacy of the design and the study population. Although it proved to be well tolerated and safe, we found no significant benefit for celivarone for this indication at any dose. Amiodarone, as expected, reduced device activations, including shocks, but was associated with a higher mortality than placebo, whereas celivarone was mortality neutral. The search for drugs to prevent device activation and death in implantable cardioverter-defibrillator patients will continue. The Dose Ranging Study of Celivarone With Amiodarone as Calibrator for the Prevention of Implantable Cardioverter Defibrillator Interventions or Death (ALPHEE), although a negative trial, provides a precedent for the study of new drugs for ventricular indications.

Conclusions: Celivarone was not effective for the prevention of implantable cardioverter-defibrillator interventions or sudden death.11

Mode of Death in Patients With Heart Failure and a Preserved Ejection Fraction: Results From the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) Trial

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Summary: Defining the mode of death in patients with heart failure and a preserved ejection fraction (HFPEF) may help to improve our understanding of the underlying pathophysiology in these patients with heart failure and provide insights into appropriate targets for the development of new therapies. Despite advanced age and the presence of comorbid states in patients with HFPEF, the mode of death was cardiovascular in 60% of the patients. In addition, the most common modes of cardiovascular death in patients with HFPEF were heart failure death and sudden death. These facts have implications both for the development of novel management strategies and for the design of future studies to test these strategies in patients with HFPEF. Management strategies that reduce causes of sudden death (such as reduction of arrhythmias) and prevent progression of heart failure (such as improvement in diastolic function and reduction of diastolic pressures) may be able to decrease cardiovascular death rates in patients with HFPEF. Therefore, new management strategies for patients with HFPEF should focus on treatments that can reduce arrhythmias and improve diastolic function. However, management strategies that target cardiovascular causes of mortality are not likely to affect the 30% of mortalities caused by noncardiovascular modes of death. Therefore, treatment of patients with HFPEF should also target the noncardiovascular comorbid states that are commonly present in these patients.

Conclusions: Sixty percent of the deaths in patients with HFPEF were cardiovascular, with sudden death and heart failure death being the most common. Treatment with irbesartan did not affect overall mortality or the distribution of mode-specific mortality rates.12

Genetic Variation in Titin in Arrhythmic Cardiomyopathy—Overlap Syndromes

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Summary: Arrhythmic right ventricular cardiomyopathy is a serious inherited myocardial disease characterized by fibrofatty replacement of the myocardium and a predisposition to cardiac arrhythmias and sudden death. Although genetic mutations affecting a number of protein components of intercalated disks, providing structural and electric connections between contracting myocytes, have been implicated in arrhythmic right ventricular cardiomyopathy in the majority of cases, the underlying genetic defect is unknown. In this study, we evaluated the giant muscle protein titin as a candidate arrhythmogenic right ventricular cardiomyopathy gene because of the known functional link between titin and elements of the intercalated disk and the prior finding of an arrhythmic right ventricular cardiomyopathy genetic locus mapping to the titin region on chromosome 2. Screening of all 312 cardiac titin gene exons detected several variants, including 1 variant (Thr2896Ile) that showed strong genetic segregation evidence for being pathogenic. In vitro studies of the Thr2896Ile mutation support that structural impairment of the titin spring is a likely cause of arrhythmogenic right ventricular cardiomyopathy and that this constitutes a novel mechanism underlying myocardial remodeling and sudden cardiac death.13

Conclusions: Our data provide evidence that titin mutations can cause arrhythmic right ventricular cardiomyopathy, a finding that further expands the origin of the disease beyond desmosomal proteins. Structural impairment of the titin spring is a likely cause of arrhythmic right ventricular cardiomyopathy and constitutes a novel mechanism underlying myocardial remodeling and sudden cardiac death.13

J Wave, QRS Slurring, and ST Elevation in Athletes With Cardiac Arrest in the Absence of Heart Disease: Marker of Risk or Innocent Bystander?

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Summary: The ECG pattern of early repolarization (ie, J wave, QRS slurring, and/or ST-segment elevation) in the inferior and lateral ECG leads is a common finding in the general population and is even more frequently observed in athletes. Recent studies have suggested a potential proarhythmic significance of these findings in the general population, but data are lacking in athletes. We investigated whether QRS-ST changes are markers of risk for cardiac arrest or sudden death in athletes without underlying heart disease. In a selected group of 21 young, competitive athletes who had cardiac arrest in the absence of heart disease, the prevalence of J wave and/or QRS slurring in the inferior (II, III, and aVF) and lateral leads (V1 to V6) was not significantly different from that in a control group of 56 athletes without evidence of cardiac disease. However, in athletes with cardiac arrest, the J wave and ST-segment elevation were significantly more frequent than in controls [P = .01 and P = .02, respectively]. These findings suggest that J waves and ST elevations may be markers of risk in athletes with cardiac arrest in the absence of heart disease.
Conclusions: J wave and/or QRS slurring was found more frequently among athletes with cardiac arrest/sudden death than in control athletes. Nevertheless, the presence of this ECG pattern appears not to confer a higher risk for recurrent malignant ventricular arrhythmias.14

Prophylactic Implantable Defibrillator in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia and No Prior Ventricular Fibrillation or Sustained Ventricular Tachycardia

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Summary: Arrhythmogenic right ventricular cardiomyopathy/dysplasia is an inheritable heart muscle disease with a natural history that is related predominantly to sudden death, mostly in young people. There is general agreement that an implantable cardioverter-defibrillator (ICD) is indicated in arrhythmogenic right ventricular cardiomyopathy/dysplasia patients who survived an episode of ventricular fibrillation or sustained ventricular tachycardia, whereas prophylactic ICD therapy in patients with no history of sustained tachyarrhythmias or cardiac arrest is still an unsolved issue. There is a tendency to implant an ICD once the disease has been diagnosed, regardless of symptoms or life-threatening ventricular arrhythmias. Hence, a growing cohort of young arrhythmogenic right ventricular cardiomyopathy/dysplasia patients such as asymptomatic relatives and healthy gene carriers who are identified by cascade family screening may undergo unnecessary ICD implantations with significant economic costs and quality-of-life concerns. The present multicenter study assessed the long-term outcome and determinants of ICD therapy in a large arrhythmogenic right ventricular cardiomyopathy/dysplasia population with no prior ventricular fibrillation or sustained ventricular tachycardia. The study results suggest that ICD implantation is as necessary in patients with a history of syncope as it is in those who suffer arrhythmic cardiac arrest. However, prophylactic ICD implantation may not be justified in asymptomatic patients regardless of family history of sudden death or results of programmed ventricular stimulation because of their favorable long-term outcome. Programmed ventricular stimulation, traditionally used to stratify the risk of arrhythmogenic right ventricular cardiomyopathy/dysplasia patients without spontaneous ventricular tachyarrhythmias, is of limited value in predicting appropriate ICD interventions and should not be used as a routine prognostic strategy.

Conclusions: One-fourth of patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior sustained ventricular tachycardia or ventricular fibrillation had appropriate ICD interventions. Syncope was an important predictor of life-saving ICD therapy in a large arrhythmogenic right ventricular cardiomyopathy/dysplasia population with no prior ventricular fibrillation or sustained ventricular tachycardia. Consideration of adrenergic effects is important in the pediatric risk assessment. In addition, isoproterenol was often required for induction of atrioventricular reentrant tachycardia and had a dramatic effect in some asymptomatic patients. We believe that our report suggests a reasonable strategy for the electrophysiological evaluation of pediatric patients with ventricular preexcitation under general anesthesia. Consideration of adrenergic effects is important in the pediatric population with accessory pathways.

Conclusions: In anesthetized children with ventricular preexcitation, accessory pathways display shorter conduction properties at younger ages and important adrenergic sensitivity at all ages. Use of low-dose isoproterenol resulted in a substantial increase in the number of patients who would otherwise meet typical criteria for ablation.17

The Extent of Left Ventricular Scar Quantified by Late Gadolinium Enhancement MRI Is Associated With Spontaneous Ventricular Arrhythmias in Patients With Coronary Artery Disease and Implantable Cardioverter-Defibrillators

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Summary: The identification of patients at high risk for sudden cardiac death remains a challenge in the application of implantable cardioverter-
defibrillator (ICD) therapy. Late gadolinium enhancement cardiac MRI (LGE-CMR) can accurately and reproducibly identify areas of myocardial scar, and the amount of left ventricular scar quantified by LGE-CMR has been shown to predict overall mortality in patients with coronary artery disease independent of LV ejection fraction. In the present study, 64 consecutive patients (average age, 66±11 years; male sex, 51) with coronary artery disease who had undergone LGE-CMR before receiving an ICD were studied. The extent of left ventricular scar on LGE-CMR was characterized in terms of percent scar, scar surface area, and number of transmural scar segments. The primary end point was appropriate ICD therapy (as a surrogate for sudden cardiac death). During a mean follow-up period of 19 months, 19 (30%) patients received appropriate ICD therapy. In an analysis including clinical, biochemical, and CMR variables, the number of transmural scar segments had the strongest association with the occurrence of appropriate ICD therapy. Furthermore, the burden of ventricular arrhythmias was significantly associated with scar burden. These data suggest that scar quantification by LGE-CMR may be a valuable risk stratification tool for the occurrence of ventricular arrhythmias, which may have implications for patient selection for ICD therapy.

**Conclusions:** In this pilot study, the extent of myocardial scar characterized by LGE-CMR was significantly associated with the occurrence of spontaneous ventricular arrhythmias. We hypothesize that scar quantification by LGE-CMR may prove a valuable risk stratification tool for the occurrence of ventricular arrhythmias, which may have implications for patient selection for ICD therapy.

**Long-Term Prognosis of Patients Diagnosed With Brugada Syndrome: Results From the FINGER Brugada Syndrome Registry**

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**Summary:** Brugada syndrome is characterized by ST-segment elevation in the right precordial leads and an increased risk of sudden cardiac death. Fundamental questions remain on the best strategy for assessing the real disease-associated arrhythmic risk, especially in asymptomatic patients. The aim of the present study was to evaluate the prognosis and risk factors of sudden cardiac death in Brugada syndrome patients in the FINGER (France, Italy, Netherlands, Germany) Brugada syndrome registry. The registry included 1029 consecutive individuals (72% men). In the registry, 36% of the patients were symptomatic, and 64% were asymptomatic. The cardiac event rate per year was 7.7% in patients with aborted sudden cardiac death, 1.9% in patients with syncope, and 0.5% in asymptomatic patients. Symptomatic and spontaneous type 1 ECG were predictors of arrhythmic events, whereas sex, familial history of sudden cardiac death, inducibility of ventricular tachyarrhythmias during electrophysiological study, and the presence of an SCN5A mutation were not predictive of arrhythmic events. In the FINGER registry, the rate of cardiac events in the asymptomatic Brugada syndrome patients was low, and the inducibility of ventricular tachyarrhythmias during electrophysiological study did not properly stratify the arrhythmic risk.

**Conclusions:** In the largest series of Brugada syndrome patients thus far, event rates in asymptomatic patients were low. Inducibility of ventricular tachyarrhythmia and family history of sudden cardiac death were not predictors of cardiac events.

**Trends in Out-of-Hospital Deaths Due to Coronary Heart Disease in Sweden (1991–2006)**

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**Summary:** One of the most frightening aspects of coronary heart disease is that many people die suddenly, out of the hospital, and with little or no warning. With modern treatment and with decreasing case severity in hospitalized cases, hospital mortality, at least among younger patients, is now low, and the in-hospital course is very different from the large untreated infarctions of the early 1980s and before. Accordingly, the true seriousness of coronary disease may be underestimated by younger members of the medical profession. The Swedish registries, with national, almost complete coverage and the possibility of linking hospital and death registries through personal identifiers, provide unique opportunities to investigate this issue. In a study of trends in out-of-hospital deaths due to coronary heart disease in Sweden from 1991 to 2006, among 384 597 first events, it was confirmed that the great majority of all fatal coronary events occur outside the hospital and that this proportion is increasing, particularly among younger individuals: Almost 9 of 10 fatal first events now occur in persons not admitted to a hospital. The autopsy rate for these young individuals was 81%, which implies that misclassification is probably minor. To achieve further reduction in coronary heart disease–related case fatality, primary prevention is increasingly more important, as are efforts to persuade individuals to seek hospital treatment as soon as symptoms of a major coronary event occur. There is an important public health message in these data, as well as a message for the medical profession.

**Conclusions:** The great majority of all fatal coronary events occur outside the hospital, and this proportion is increasing, particularly among younger individuals.

**Clinical Characteristics and Genetic Background of Congenital Long-QT Syndrome Diagnosed in Fetal, Neonatal, and Infantile Life: A Nationwide Questionnaire Survey in Japan**

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**Summary:** The congenital long-QT syndrome (LQTS) diagnosed at prenatal life and through infancy is associated with high morbidity and mortality rates. However, data on the clinical presentation and genotype-phenotype correlation of this youngest age group of LQTS are limited. A nationwide survey was conducted in Japan, and 58 cases (18 fetuses, 31 neonates, and 9 infants) were registered. Among them, the peak age at diagnosis was 0 to 2 days, and the 3 most frequent clinical presentations included sinus bradycardia, ventricular tachycardia/torsades de pointes, and atrioventricular block. The genotype was confirmed in 29 (71%) of 41 patients who underwent genotyping; the incidence resembled that of child LQTS. Patients who presented with early-onset ventricular tachycardia/torsades de pointes and atrioventricular block were almost exclusively those with LQT2 and LQT3 among the 3 major genes, but a considerable number of genetically unidentified ones were included. Sudden cardiac death/aborted cardiac arrest were prevalent in the latter. LQT1 patients tended to show only sinus bradycardia or positive family history of LQTS. These results mean that many early-onset episodes observed in early-onset LQTS should be treated immediately and aggressively even without knowledge of the genotype. On the other hand, the present study was encouraging in that the outcome of patients was favorable with multiple pharmaceutical agents, typically with β-blockers, mexiletine, and magnesium and with pacemaker implantation/implantable cardioverter-defibrillator, independent of the genotype. Further application of gene testing is needed to establish the most appropriate genotype-specific strategy for these patients.
Conclusions: Patients with LQTS who showed life-threatening arrhythmias at perinatal periods were mostly those with LQT2, LQT3, or no known mutations. Independent of the genotype, aggressive intervention resulted in effective suppression of arrhythmias, with only 7 deaths recorded.  

Mechanisms Underlying the Lack of Effect of Implantable Cardioverter-Defibrillator Therapy on Mortality in High-Risk Patients With Recent Myocardial Infarction: Insights From the Defibrillation in Acute Myocardial Infarction Trial (DINAMIT)

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Summary: In the Defibrillation in Acute Myocardial Infarction (DINAMIT) study, implanted defibrillators did not reduce mortality in high-risk patients if implanted early after myocardial infarction. In patients randomized to an implantable cardioverter-defibrillator (ICD), sudden deaths were reduced but nonarrhythmic mortality was increased. In an analysis of the potential causes of this finding, patients who are destined to receive therapy from their ICD (compared with those destined not to receive therapy) have clinical features that also increase their risk of non-sudden death, including risks related to heart failure and recurrent ischemic events. During follow-up, patients who receive therapy from their ICD are more likely to have intercurrent cardiac clinical adverse events both before and after ICD therapy compared with patients who receive no therapy or do not have an ICD. In an early post-myocardial infarction setting, the same clinical circumstances that increase the risk of ventricular arrhythmias also increase the risk of non-sudden death; in addition, ICD therapies themselves may increase the risk of subsequent death. These findings underscore the limitations of a strategy of ICD implantation in certain high-risk groups, especially early after acute myocardial infarction.

Conclusions: In patients receiving ICDs early after myocardial infarction, those factors that are associated with arrhythmia requiring ICD therapy are also associated with a high risk of non-sudden death, negating the benefit of ICDs in this setting.

Incidence and Prognostic Value of Early Repolarization Pattern in the 12-Lead ECG

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Summary: Recent studies have suggested a potential arrhythmogenicity and a higher risk of cardiac or all-cause death of early repolarization pattern (ERP) in Western populations. However, the incidence and prognostic of ERP in an Asian population have not yet been elucidated. We investigated 5976 atomic bomb survivors followed up for ~5 decades. Early repolarization pattern was a very common finding throughout the survivors’ entire lives, yielding a lifetime positive rate of 23.9%, an incidence rate of 715 per 100,000, and male predominance. In this study, ERP patients had an increased risk of unexpected death and a decreased risk of cardiac and all-cause death. The ERP manifestation of both slurring and notching and the manifestation of the J wave in broad leads were associated with unexpected death. The hazard ratio for unexpected death in ERP was lower than that in Brugada-type ECG. However, because ERP is a very common finding, ERP has a greater public health implication.

Conclusions: ERP is associated with an elevated risk of unexpected death and a decreased risk of cardiac and all-cause death. Specific ERP morphologies and location are associated with an adverse prognosis.

Long-Term Benefit of Primary Prevention With an Implantable Cardioverter-Defibrillator: An Extended 8-Year Follow-Up Study of the Multicenter Automatic Defibrillator Implantation Trial II

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Summary: Current guidelines for device-based therapy provide a recommendation for primary prevention with implantable cardioverter-defibrillator (ICD) therapy in patients with an ejection fraction of \( \leq 35\% \). Presently, however, there are no data from clinical trials on the long-term benefit of ICD therapy. The present study is the first to assess the long-term survival benefit associated with primary prevention with an ICD in the low-ejection fraction population. We provide 8-year follow-up data for all participants in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II). The study shows that the life-saving benefit of the ICD was sustained during the extended follow-up period, providing a significant 34% reduction in the risk of death during 8 years of follow-up. The survival benefit of the ICD was evident during both the early (0–4 years) and late (5–8 years) phases of the extended follow-up period. Furthermore, we show enhanced long-term survival benefit from primary ICD therapy among patients who received backup pacing devices and among those who did not develop symptomatic heart failure after ICD implantation. Our findings on the continued life-prolonging benefit of the ICD during long-term follow-up provide support for a more widespread use of the ICD in a primary prevention setting. However, our data also suggest that more measures should be taken to improve long-term device efficacy in the low-ejection fraction population, including appropriate device programming as well as measures for prevention of heart failure progression after ICD implantation.

Conclusions: Our findings demonstrate a sustained 8-year survival benefit with primary ICD therapy in the MADIT-II population.

Ethnic Differences in Out-of-Hospital Fatal Pulmonary Embolism

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Summary: This report presents the first epidemiological study involving a large number of autopsy-based, out-of-hospital fatal pulmonary embolism investigations in New York City, with its diverse ethnic population. New data presented should alert and aid clinicians in evaluating patients at risk for acute and fatal pulmonary embolism on the basis of different ethnic backgrounds. Because blacks and Hispanics suffer fatal pulmonary embolism at a significantly younger age than whites, physicians should closely monitor these populations for known risk factors (such as body mass index) and counsel healthy lifestyles, especially at younger ages. Because of the large number of prothrombin G20210A carriers observed in white and Hispanic out-of-hospital pulmonary embolism decedents, testing for prothrombin G20210A in high-risk patients is indicated. Finally, our results clearly point to the need for additional research to identify other genetic causes of fatal pulmonary embolism, especially in blacks, who have low frequencies of known genetic risk factors.

Conclusions: There are unique epidemiological differences in out-of-hospital fatal pulmonary embolism between ethnic groups in New York City.
Role of RBM25/LUC7L3 in Abnormal Cardiac Sodium Channel Splicing Regulation in Human Heart Failure

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Summary: We have previously shown that human heart failure is associated with abnormal mRNA splicing of the cardiac sodium channel. This abnormal mRNA splicing results in truncated sodium channels that are nonfunctional and a reduction in sodium channel current to levels known to cause sudden death. We explored the mechanisms by which this abnormal splicing occurs. Using microarray comparisons of diseased and normal human hearts, we identified 2 splicing factors, RBM25 and LUC7L3, that were necessary and sufficient to cause the abnormal sodium channel splicing. These factors were upregulated by hypoxia and elevated angiotensin II, conditions known to be present in heart failure. Moreover, we showed that the responses of white cells and heart to these 2 inciting stimuli were equivalent. The potential clinical implications of these findings include a possible mechanism whereby hypoxia is arrhythmogenic and blockade of the renin-angiotensin system is antiarrhythmic. Moreover, while white cell sodium channel splicing in vivo correlates with that in the myocardium, it may be possible to develop a blood test to assess sodium channel availability and arrhythmic proclivity. Finally, this work defines potential therapeutic targets to address arrhythmic risk in human heart failure.

Conclusions: Of the 17 mRNA splicing factors upregulated in heart failure, RBM25 and LUC7L3 were sufficient to explain the increase in truncated forms and the reduction in full-length Na⁺ channel transcript. Because the reduction in channels was in the range known to be associated with sudden death, interruption of this abnormal mRNA processing may reduce arrhythmic risk in heart failure.

Mice With Cardiac Overexpression of Peroxisome Proliferator–Activated Receptor γ Have Impaired Repolarization and Spontaneous Fatal Ventricular Arrhythmias

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Summary: Diabetes mellitus and obesity confer an increased risk of sudden cardiac death and are associated with cardiomyocyte lipid accumulation and altered cardiac electric properties (demonstrated by prolongation of the QRS and QT intervals). To study the effects of metabolic abnormalities on arrhythmias without the complex systemic effects of diabetes mellitus and obesity, we studied a mouse model with cardiac-specific overexpression of peroxisome proliferator–activated receptor γ (PPARγ), a transcription factor that is a key regulator of glucose and lipid metabolism. These PPARγ transgenic mice develop abnormal accumulation of intracellular lipids and die as young adults, before any significant reduction in systolic function. We found that these mice have prolongation of the QT interval and spontaneous ventricular arrhythmias, including polymorphic ventricular tachycardia and ventricular fibrillation. Isolated cardiomyocytes demonstrated prolonged action potential duration caused by reduced potassium currents, which are responsible for repolarization. Short-term exposure to pioglitazone, a PPARγ agonist, had no effect on mortality or rhythm in wild-type mice.
but further exacerbated the arrhythmic phenotype and increased mortality in the PPARγ mice. Our findings support an important link between PPARγ activation, cardiomyocyte lipid accumulation, ion channel remodeling, and increased cardiac mortality. This mouse model may help identify the molecular mechanisms leading to sudden death in diabetic and/or obese patients.

**Conclusions:** Our findings support an important link between PPARγ activation, cardiomyocyte lipid accumulation, ion channel remodeling, and increased cardiac mortality.29

### Early Repolarization Pattern in Competitive Athletes: Clinical Correlates and the Effects of Exercise Training

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**Summary:** Emerging evidence suggests that early repolarization pattern (ERP) on the 12-lead ECG, particularly when observed in the inferior leads, may be associated with increased risk of sudden cardiac death. Although it is well known that ERP is particularly common among young athletes, its prevalence, morphology, clinical and echocardiographic correlates, and association with intense physical training remain unknown. The present study examined a large group of collegiate athletes to address these areas of uncertainty. In this cohort of nearly 900 competitive athletes, roughly one-fourth were found to have ERP on the preparticipation screening ECG. The majority of athletes who had ERP confined to the lateral leads, with inferior ERP present in only 4%. In a multivariable model, ERP was associated with black race, increased QRS voltage, and slower heart rate. There were no associations between ERP and echocardiographic measures of left ventricular remodeling. After a discrete period of intense physical training, the prevalence of ERP increased, suggesting that ERP in young athletes is a dynamic phenomenon related to the magnitude of physical activity.

**Conclusions:** Nonanterior ERP, including the inferior subtype, is common and has strong clinical associations among competitive athletes. The finding of increased ERP prevalence after intense physical training establishes a strong association between exercise and ERP.30

### A Novel Lead Configuration for Optimal Spatio-Temporal Detection of Intracardiac Repolarization Alternans

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**Summary:** Repolarization alternans (RA) reflects oscillations in cardiac repolarization that occur on an every-other-beat basis. The presence of RA has been associated with an increased risk of sudden cardiac death, and numerous studies have mechanistically linked RA to reentrant arrhythmias. Although implantable cardioverter-defibrillators (ICDs) have demonstrated efficacy in prevention of sudden cardiac death, a major drawback of current ICD therapy is the ability to terminate an arrhythmia only after the arrhythmia has started, thereby exposing patients to hemodynamic consequences such as loss of consciousness during arrhythmia and uncomfortable ICD shocks. Therefore, although unproven, the ability to detect a potentially unstable arrhythmic substrate could result in delivery of therapy before the clinical onset of arrhythmia, which could potentially be an attractive way to improve current ICD technology. The present study investigated the hypothesis that a minimum-order intracardiac lead configuration may be developed to accurately estimate the presence of intracardiac RA. We probed this hypothesis in a swine acute myocardial ischemia model, in which intracardiac RA and body surface RA were estimated from electrograms obtained from catheters placed in the right ventricle, coronary sinus, left ventricle, and left ventricular epicardium (transperi-

Long-Term Outcome and Impact of Surgery on Adults With Coronary Arteries Originating From the Opposite Coronary Cusp

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**Summary:** The presence of an anomalous coronary artery arising from the opposite sinus of Valsalva may increase the risk of sudden death risk in children and young adults, but its impact and management in the adult are poorly defined. The recently published American College of Cardiology/American Heart Association Guidelines for the Management of Adults With Congenital Heart Disease suggest an important role for surgical revascularization when such a lesion is discovered, but the recommendation is based on few clinical data. We examined a large single institution’s experience over a 40-year period to further assess the importance of these lesions and the impact of surgery. We identified 301 patients with anomalous coronary artery arising from the opposite sinus of Valsalva, with anomalous right coronary arteries being found more commonly than anomalous left coronary arteries (~4:1). In 54 patients, the lesion passed between the aorta and the pulmonary artery (interarterial course), anatomy that has been believed to place the patient at substantially higher risk. Surgery was more commonly performed in patients with anomalous left coronary arteries, interarterial course, positive stress testing, and in the presence of concurrent coronary disease and appeared to become the highly favored strategy over the past decade. Among the patients with interarterial course, 28 underwent surgical repair with no perioperative deaths but with long-term survival similar to that of the unrepaired cohort. Quality of life was not formally assessed in this study. Our results suggest that anomalous coronary artery arising from the opposite sinus of Valsalva with interarterial course, particularly if incidentally discovered, may not carry the same associated mortality risk in older adults. Prospective studies are needed to formally examine management strategies.

**Conclusions:** In this single-center cohort study of patients with an anomalous coronary artery from the opposite sinus of Valsalva, surgical management appears to have been favored recently. Despite no perioperative mortality, a positive impact on long-term survival was not observed. The impact of surgery in older adults with anomalous coronary arteries arising from the opposite coronary sinus with interarterial course deserves further study.31

### Clinical Characteristics and Long-Term Prognosis of Vasospastic Angina Patients Who Survived Out-of-Hospital Cardiac Arrest: Multicenter Registry Study of the Japanese Coronary Spasm Association

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**Summary:** Myocardial ischemia is an important cause of out-of-hospital cardiac arrest (OHCA). Coronary artery spasm is a known cause, but there is limited information about the clinical characteristics and long-term
prognosis of patients with vasospastic angina (VSA) who survive OHCA. The present multicenter study by the Japanese Coronary Spasm Association describes a large cohort of 1429 patients with VSA and compares 35 who survived OHCA with those without OHCA. Survival rate free from major adverse cardiac events was significantly lower in the OHCA survivors as compared with the non-OHCA patients, including appropriate implantable cardioverter-defibrillator shocks for ventricular fibrillation in 2 patients. Subgroup analysis of all OHCA cases presenting to 7 hospitals suggests a 6% incidence of VSA in survivors of OHCA from cardiac cause. These results indicate that VSA patients who survived OHCA are high-risk population. Further studies are needed to determine whether implantable cardioverter-defibrillator therapy improves their prognosis.

Conclusions: These results from the largest vasospastic angina cohort indicate that vasospasm patients who survived OHCA are high-risk population. Further studies are needed to determine whether implantable cardioverter-defibrillator therapy improves patient prognosis.53

**Ryanoide Receptor Phosphorylation by Calcium/Calmodulin-Dependent Protein Kinase II Promotes Life-Threatening Ventricular Arrhythmias in Mice With Heart Failure**

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Summary: Despite recent therapeutic advances including β-adrenergic blockers and implantable cardioverter-defibrillators, ventricular arrhythmias remain a prominent cause of death in patients with heart failure. Diastolic Ca2+ leak from the sarcoplasmic reticulum is believed to contribute to arrhythmia initiation in failing hearts, although the underlying mechanisms remain poorly understood. The expression and activity of the enzyme Ca2+/calmodulin-dependent protein kinase II (CaMKII) are upregulated in heart failure. Although increased CaMKII activity has been implicated in arrhythmogenesis, the specific CaMKII targets contributing to arrhythmia heart failure. Although increased CaMKII activity has been implicated in arrhythmogenesis, the specific CaMKII targets contributing to arrhythmia susceptibility have remained elusive. Our data revealed that mice in which the CaMKII phosphorylation site on the cardiac ryanodine receptor is constitutively activated exhibit an increased likelihood of intracellular Ca2+ release. These diastolic Ca2+ leak leads to an increased susceptibility to ventricular tachycardia in mice. Moreover, constitutive CaMKII phosphorylation of ryanodine receptors caused an increase in arrhythmogenic sudden cardiac deaths after induction of experimental heart failure. Conversely, mice with genetic ablation of the CaMKII site on ryanodine receptors exhibited protection from induced ventricular arrhythmias due to heart failure. Taken together, our studies suggest that CaMKII phosphorylation of ryanodine receptors is an important downstream target of CaMKII that could be exploited therapeutically to minimize arrhythmia susceptibility in heart failure. Future studies utilizing pharmacological inhibition of this signaling event, once tested, may be a new avenue for reducing risk of sudden death in patients with heart failure.

Conclusions: Our results suggest that Ca2+/CaMKII phosphorylation of RyR2 Ca2+ release channels at S2814 plays an important role in arrhythmogenesis and sudden cardiac death in mice with heart failure.34

**Electrocardiographic Characteristics and SCN5A Mutations in Idiopathic Ventricular Fibrillation Associated With Early Repolarization**

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Summary: Idiopathic ventricular fibrillation associated with early repolarization is a new arrhythmia syndrome entity, although early repolarization has been considered benign for decades. Early repolarization is a heritable electrocardiographic phenotype, and there is a positive family history in 10% to 20% of patients with idiopathic ventricular fibrillation associated with early repolarization. Recent studies have identified the causative genes of the arrhythmia, all of which are associated also with Brugada syndrome. In this study, SCN5A, which encodes the predominant cardiac sodium channel α subunit and is critical for cardiac conduction, was screened in patients with idiopathic ventricular fibrillation associated with early repolarization. The screening identified 3 patients carrying an SCN5A mutation, and His-ventricular interval was prolonged in all patients. All of the mutations are predicted to substitute amino acids highly conserved across species and failed to produce any detectable sodium current. To identify electrophysiological characteristics in idiopathic ventricular fibrillation associated with early repolarization, we compared electrocardiograms between patients with the arrhythmia and healthy controls. We found that patients with the arrhythmia exhibited slower heart rate and slower cardiac conduction properties than controls. Our findings suggest that there are underlying electrophysiological abnormalities resulting in slow heart rate, slow cardiac conduction, and early repolarization, and ventricular fibrillation, partially explained by sodium channel dysfunction. Idiopathic ventricular fibrillation associated with early repolarization and Brugada syndrome share genetic, clinical, and pharmacological characteristics, but other factors that modify the clinical phenotypes are unknown. Further studies to identify the modifiers are warranted.

Conclusions: We found reductions in heart rate and cardiac conduction and loss-of-function mutations in SCN5A in patients with idiopathic ventricular fibrillation associated with early repolarization. These findings support the hypothesis that decreased sodium current enhances ventricular fibrillation susceptibility.35

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Circ Arrhythm Electrophysiol. 2012;5:e48-e58
doi: 10.1161/CIRCEP.112.971838

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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