Circulation Topic Review

Circulation Editors’ Picks
Most Read Articles in Arrhythmia and Electrophysiology

The Editors

The following articles are being highlighted as part of Circulation’s Topic Review series. This series will summarize the most important manuscripts, as selected by the editors, published in Circulation and the Circulation subspecialty journals. The studies included in this article represent the most read manuscripts published on the topic of arrhythmia and electrophysiology within the last year. (Circulation. 2012;126:e69-e80.)

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

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). In order 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.1

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

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 dromedaron, 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 comparator 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 Comparator 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.2

Renal Function After Catheter Ablation of Atrial Fibrillation

Summary: Kidney function is crucial for the management of patients with heart disease because even mild to moderate kidney dysfunction affects cardiovascular morbidity and mortality. Atrial fibrillation (AF) is more likely to develop in patients with advanced age, hypertension, or structural heart disease, which also precipitates kidney dysfunction. AF and kidney dysfunction often coexist in an individual patient; however, less is known about the association between AF and kidney function. We assessed changes in estimated glomerular filtration rate (eGFR) over 1 year after catheter ablation of AF. At baseline, 26% and 66% of patients had eGFR of 30 to 59 and 60 to 89 mL·min⁻¹·1.73 m⁻², respectively. During follow-up, 72% of patients were free from tachyarrhythmias after the ablation, 13% of whom were taking antiarrhythmics. Over a 1-year follow-up, patients who were free from tachyarrhythmias after ablation showed a significant increase in eGFR, whereas patients with recurrent arrhythmias showed a significant decrease in eGFR. After adjustment for age, type of AF, baseline eGFR, and baseline left ventric-
ular ejection fraction, multivariate analysis demonstrated that freedom from tachyarrhythmia after ablation was associated with an increase in eGFR over 1 year after ablation. This study demonstrated a link between AF and kidney dysfunction. Further investigation is required to clarify the causal relationship between these 2 diseases. **Conclusion:** Elimination of AF by catheter ablation was associated with improvement of kidney function over a 1-year follow-up in patients with mild to moderate kidney dysfunction.\(^3\)

### Colchicine Reduces Postoperative Atrial Fibrillation: Results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) Atrial Fibrillation Substudy

**Summary:** Postoperative atrial fibrillation (POAF) is the most common complication after cardiac surgery; it is reported in 10% to 65% of cases. POAF increases patient morbidity, length of hospital stay, and management costs. Its prevention is an important management goal. Systemic and local inflammatory responses are believed to contribute to the pathogenesis of POAF. Inflammation, inhomogeneity of atrial conduction, and the incidence of POAF are decreased by corticosteroids. Because of its anti-inflammatory effects for the treatment and prevention of pericarditis, colchicine has the potentiality to prevent POAF. The Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) POAF substudy is the first trial designed to assess the efficacy and safety of colchicine for POAF prevention. It is a substudy of the COPPS trial, in which colchicine halved the occurrence of the postpericardiotomy syndrome. On the third postoperative day, consecutive adult patients undergoing cardiac surgery and without contraindications to colchicine were randomized to receive placebo or colchicine on top of standard therapy. The substudy primary efficacy end point was the incidence of POAF on placebo/collchicine treatment at 1 month. Patients on colchicine had a reduced incidence of POAF (12.0% versus 22.0%, respectively; \(P=0.021\); relative risk reduction, 45%; number needed to treat, 11) with a shorter in-hospital stay (9.4+3.7 versus 10.3+4.3 days; \(P=0.040\)) and rehabilitation stay (12.1+6.1 versus 13.9+6.5 days; \(P=0.009\)). Side effects were similar in the study groups. Such findings may be particularly important for clinical practice because colchicine might represent a cheap and relatively safe option for the prevention of both the postpericardiotomy syndrome and POAF, 2 common and troublesome complications of cardiac surgery. **Conclusion:** Colchicine seems safe and efficacious in the reduction of POAF with the potentiality of halving the complication and reducing the hospital stay.\(^4\)

### Derivation and Validation of a Simple Exercise-Based Algorithm for Prediction of Genetic Testing in Relatives of LQTS Probands

**Summary:** Diagnosis of long-QT syndrome (LQTS) is relatively straightforward in patients with overt QT prolongation or symptoms based on existing clinical criteria; however, diagnosis may be challenging in asymptomatic relatives of patients with established LQTS, especially in the context of normal or borderline QT prolongation. Accurate identification of LQTS carriers in this subgroup is important because they remain at significant risk of life-threatening cardiac events. Although genetic testing can identify LQTS carriers, and a moderate degree of accuracy for predicting LQTS subtype compared with genetic testing as a gold standard. The screening algorithm appears useful as an interim test while formal genetic results are awaited, or as a diagnostic test in centers where genetic testing is unavailable. **Conclusions:** A simple algorithm that incorporates resting and exercise-recovery QTc is useful in identifying LQTS in asymptomatic relatives.\(^5\)

### Defects in Ankyrin-Based Membrane Protein Targeting Pathways Underlie Atrial Fibrillation

**Summary:** Atrial fibrillation (AF) is the most prevalent sustained arrhythmia in clinical practice. In fact, in the United States alone, AF is present in >2 million individuals. Despite the high incidence of AF in the population, surprisingly little is known regarding the molecular mechanisms underlying this complex disease. Ankyrin proteins target and stabilize proteins at specialized membrane domains. Notably, dysfunction in ankyrin- and ankyrin-associated pathways has been linked with disorders including spherocytosis, spinocerebellar ataxia, diabetes mellitus, neurogenic deficits, and cardiac arrhythmias. Nearly a decade ago, ankyrin-B (ANK2) was discovered as a critical component of heart, and work in humans and mice has implicated ankyrin-B as critical for cardiac function. In fact, human ANK2 loss-of-function variants are associated with potentially fatal ventricular arrhythmias. In the present study, we demonstrate the importance of ankyrin-B for atrial function and identify an association between ankyrin-B dysfunction and AF. Individuals harboring ANK2 variants display AF, and these phenotypes are reproduced in mice deficient in ankyrin-B. Ankyrin-B is expressed in the atria, and ankyrin-B^-/- myocytes display shortened action potentials, a hallmark of AF, and decreased L-type calcium channel current. We show that Ca\(_{\text{a1,3}}\), responsible for 1 component of L-type calcium channel current in atria, is a novel ankyrin-binding partner and that Ca\(_{\text{a1,3}}\) expression/activity is reduced in ankyrin-deficient atrial myocytes. Finally, ankyrin-B is reduced in atrial samples from human AF patients, further supporting the role of ankyrin-B in normal atrial function. Together, our work implicates ankyrin-B as a surprising yet critical component of atrial excitability and supports the role of atypical myocyte proteins in disease pathogenesis. **Conclusions:** These findings support that reduced ankyrin-B expression or mutations in ANK2 are associated with AF. Additionally, our data demonstrate a novel pathway for ankyrin-B-dependent regulation of Ca\(_{\text{a1,3}}\) channel membrane targeting and regulation in atrial myocytes.\(^6\)

### n-3 Polysaturated Fatty Acids in the Prevention of Atrial Fibrillation Recurrences After Electric Cardioversion: A Prospective, Randomized Study

**Summary:** Atrial fibrillation (AF) is the most common sustained arrhythmia and represents a growing burden on the healthcare system. The prevalence of AF increases with age and has been estimated at 3.8% in persons \(>60\) years of age and at 9.0% in those \(\geq 80\) years of age. Atrial fibrillation is associated with considerable morbidity and mortality, related mainly to increased risk of thromboembolic events and of new-onset or worsening heart failure. Treatment of AF remains controversial. Although rhythm control and rate control strategies seem to provide comparable results, restoration and maintenance of sinus rhythm would be the preferable pathophysiological approach. However, current pharmacological antiarrhythmic therapies have limited efficacy and poor safety profiles, and invasive or surgical treatments are indicated only in a minority of patients and are not free of failure and procedural risks.
In this study, we tested the efficacy of n-3 polyunsaturated fatty acids in the prevention of AF recurrences in 199 patients with persistent AF on amiodarone and a renin-angiotensin inhibitor. Participants were randomized to n-3 polyunsaturated fatty acids 2 g/d or placebo followed, after at least 4 weeks, by direct current cardioversion. At 1 year, the probability of maintenance of sinus rhythm was significantly higher in the n-3 polyunsaturated fatty acids group than in the placebo group. Our results indicate that the addition of n-3 polyunsaturated fatty acids 2 g/d in patients with persistent AF and structural heart disease and on amiodarone and a renin-angiotensin inhibitor may exert beneficial effects in the prevention of AF recurrence.

Conclusions: In patients with persistent atrial fibrillation on amiodarone and a renin-angiotensin-aldosterone system inhibitor, the addition of n-3 PUFAs 2 g/d improves the probability of the maintenance of sinus rhythm after direct current cardioversion. Our data suggest that n-3 PUFAs may exert beneficial effects in the prevention of atrial fibrillation recurrence. Further studies are needed to confirm and expand our findings.

Atrial Sources of Reactive Oxygen Species Vary With the Duration and Substrate of Atrial Fibrillation: Implications for the Antiarrhythmic Effect of Statins

Summary: Atrial fibrillation (AF) is a very common arrhythmia, and its therapy remains a challenge. There is considerable interest in developing treatment strategies that target mechanisms upstream of ion channel modifications; however, whereas ion channel modifications are the common denominator of virtually all types of AF, the myocardial signaling upstream of atrial electric and structural remodeling differs with the stage and substrate of AF, demanding a more refined ad hoc approach to the prevention and management of this arrhythmia. Here, we show that the mechanisms responsible for the nitric oxide-redox imbalance in the fibrillating atrial myocardi um change with the duration of AF and the development of atrial structural remodeling. Upregulation of atrial NOX2 activity and expression is an early but transient event in the natural history of AF and may be causally linked to both new-onset AF and early AF-induced atrial remodeling. Once AF becomes established and atrial structural remodeling ensues, the oxidase systems underlying the increase in reactive oxygen species shift from NOX2 to mitochondrial oxidases and uncoupled nitric oxide synthases. Ex vivo atorvastatin induces a mevalonate-reversible inhibition of atrial Rac1 and NOX2 activity in patients who developed AF after cardiac surgery, but it does not affect atrial reactive oxygen species production and nitric oxide synthase activity in patients with permanent AF. These findings imply that NOX2 inhibition by drugs such as statins may be effective only in preventing new-onset AF or early AF-induced electric remodeling of the atrial myocardium.

Conclusions: Upregulation of atrial NADPH oxidases is an early but transient event in the natural history of AF. Changes in the sources of reactive oxygen species with atrial remodeling may explain why statins are effective in the primary prevention of AF but not in its management.

Striking In Vivo Phenotype of a Disease-Associated Human SCN5A Mutation Producing Minimal Changes in Vitro

Summary: A conventional approach to characterize the function of ion channel mutations is to compare wild-type and variant channel function by heterologous expression in mammalian, noncardiac cells like Chinese hamster ovary or human embryonic kidney cells. The cardiac sodium channel mutation D1275N has been reported in multiple individuals and families with a range of phenotypes, including arrhythmias and dilated cardiomyopathy; however, conventional heterologous expression studies have not identified major differences between wild-type and D1275N function. Thus, it has even been uncertain whether this mutation causes the clinical phenotypes with which it has been associated. In this study, we addressed this issue by studying mice in which the cardiac sodium channel locus had been disrupted and replaced with full-length human wild-type or D1275N mutant sodium channels. We observed slowed and disordered cardiac conduction and decreased contractile function in mice bearing the mutation; mice with 2 D1275N alleles displayed worse phenotypes than those with 1 variant allele. In vitro electrophysiological studies identified reduced peak cardiac sodium current as a key defect, and this is consistent with the observed reduced conduction velocity. The major clinical implication of these findings is that heterologous expression may be insufficient to assess mutant channel function. In addition, the data lend support to the concept that sodium channel mutations are associated not only with arrhythmias but also with dilated cardiomyopathy phenotypes. The mutant mice will be an invaluable tool to dissect mechanisms underlying these findings.

Conclusions: Although D1275N produces near-normal currents in multiple heterologous expression experiments, our data establish this variant as a pathological mutation that generates conduction slowing, arrhythmias, and a dilated cardiomyopathy phenotype by reducing cardiac sodium current.

Genetic Variation in Titin in Arrhythmogenic Right Ventricular Cardiomyopathy–Overlap Syndromes

Summary: Arrhythmogenic 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 arrhythmogenic 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 arrhythmogenic 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.

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

Mobile Thrombus on Device Leads in Patients Undergoing Ablation: Identification, Incidence, Location, and Association With Increased Pulmonary Artery Systolic Pressure

Summary: This article describes the frequent (30% of patients) presence of sizable mobile thrombus on pacemaker and defibrillator leads identified with careful intracardiac echocardiographic assessment during ablation procedures for atrial fibrillation and ventricular tachycardia. These thrombi were more frequently seen on the atrial portion of the leads. Prior use of oral anticoagulants or antiplatelet agents, the number and age of leads, and presence of a superior vena cava coil were not specifically associated with lead thrombi during...
the procedure. The group with thrombus had a higher pulmonary artery pressure, suggesting the possibility that patients with lead thrombi may have subclinical pulmonary emboli elevating the pressure and/or that higher pulmonary artery pressure predisposes to thrombus formation in right-sided cardiac chambers. Further study is warranted to identify hematologic or other clinical factors that may increase patients' risk of forming device lead thrombi and to assess the potential clinical impact of these thrombi.

Conclusions: Mobile thrombi on cardiovascular implantable electronic device leads are present in 30% of patients undergoing ablation and are readily identified with intracardiac echocardiography despite being underrecognized with transesophageal echocardiography. Further study is warranted to determine whether lead thrombi are a clinically relevant source of pulmonary emboli in some patients with cardiovascular implantable electronic devices.11

Mutation-Linked Defective Interdomain Interactions Within Ryanodine Receptor Cause Aberrant Ca\(^{2+}\) Release Leading to Catecholaminergic Polymorphic Ventricular Tachycardia

Summary: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited disease characterized by stress- or exercise-induced polymorphic ventricular tachycardia, frequently leading to sudden cardiac death. A considerable body of evidence accumulated over recent years suggests that mutation-linked cardiac ryanodine receptor defects cause Ca\(^{2+}\) leak from sarcoplasmic reticulum, which triggers delayed afterdepolarization and ultimately leads to CPVT. However, the underlying mechanism, by which a single mutation in such a large molecule causes drastic effects on the channel function, remains unresolved. Here we report that introduction of a human CPVT mutation S2246L (serine to leucine mutation at residue 2246) into the mouse ryanodine receptor induces aberrant activation of channel gating by forming an abnormally tight domain-domain interaction between the S2246L mutable domain (residue 2232–2266) and the K201-binding domain (residue 2114–2149). This produces more global conformational change in the ryanodine receptor: an aberrant domain unzipping in the ryanodine receptor defects cause Ca\(^{2+}\) leak from sarcoplasmic reticulum, which triggers delayed afterdepolarization and ultimately leads to CPVT. The coupled conformational changes in these local and global domains cause Ca\(^{2+}\) release and lethal arrhythmia. Pharmacological correction of the defective interdomain interactions can stop the aberrant Ca\(^{2+}\) release and lethal arrhythmia. These results provide a new pathogenic mechanism of CPVT and a novel therapeutic strategy against CPVT.

Conclusions: The catecholaminergic polymorphic ventricular tachycardia–linked mutation of RyR2, S2246L, causes an abnormally tight local subdomain-subdomain interaction within the central domain involving the mutation site, which induces defective interaction between the N-terminal and central domains. This results in an erroneous activation of Ca\(^{2+}\) channel in a diastolic state reflecting on the increased Ca\(^{2+}\) spark frequency, which then leads to lethal arrhythmia.12

Sports-Related Sudden Death in the General Population

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 fewer than one third of cases. Given the often predictable setting of sports-related SD and that prompt interventions including bystander CPR 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.13

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

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. But, the incidence and prognosis of ERP in an Asian population have not yet been elucidated. We investigated 9776 atomic-bomb survivors followed up for \(\sim5\) 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: Early repolarization pattern is associated with an elevated risk of unexpected death and a decreased risk of cardiac and all-cause death. Specific early repolarization pattern morphologies and location are associated with an adverse prognosis.14

Repolarization Alternans Reveals Vulnerability to Human Atrial Fibrillation

Summary: Human atrial fibrillation (AF) is a highly prevalent disease whose mechanisms are poorly understood. Ectopic beats from the pulmonary veins may trigger AF, but this likely also requires substrate, because ectopy rarely triggers AF in control subjects. We hypothesized that beat-to-beat oscillations in atrial repolarization (action potential duration (APD)) may provide an AF substrate and explain the spectrum of AF vulnerability from subjects without AF to those with paroxysmal and persistent AF. We found that APD alternans invariably preceded AF initiation. Notably, APD alternans arose at near-resting heart rates (100–120 bpm) in persistent AF patients, a finding that is difficult to explain by current theories and animal experiments. Action potential duration alternans onset required progressively faster rates for patients with paroxysmal AF and control subjects, in whom alternans developed only at very rapid rates (>230 bpm) just preceding induced AF. Furthermore, in patients in whom rapid pacing failed to initiate AF, APD alternans did not develop. In conclusion, APD alternans indicates dynamic substrates for AF and arises most readily in patients with persistent AF and least readily in control subjects without AF. Action potential duration alternans preceded every AF episode, yet was absent when AF was not induced. Accordingly, APD alternans provides a clinical tool to identify AF vulnerability and may be useful in refining diagnosis or monitoring the effectiveness of AF therapy.

Conclusions: Atrial APD alternans reveals dynamic substrates for AF, arising most readily (at lower rates and higher magnitudes) in
persistent AF then paroxysmal AF, and least readily in controls. APD alternans preceded all AF episodes and was absent when AF did not initiate. The cellular mechanisms for APD alternans near resting heart rates require definition.\textsuperscript{15}

**Risk of Recurrent Cardiac Events After Onset of Menopause in Women With Congenital Long-QT Syndrome Types 1 and 2**

Summary: Prior studies have shown that women with congenital long-QT syndrome experience increased risk for cardiac events after the onset of adolescence and during the postpartum period. This risk increase was shown to be more pronounced among women with the LQT2 genotype, suggesting that sex hormones may modify the clinical course of patients with this inherited arrhythmic disorder. The present study is the first to assess the clinical course of long-QT syndrome women after the onset of menopause. We show a genotype-specific association with the risk for cardiac events during the perimenopausal period, including a pronounced increase in the risk for cardiac events (dominated by recurrent episodes of syncope) among LQT2 women and an opposite reduction in the rate of cardiac events in LQT1 women. Notably, the pronounced effect of menopause on the clinical course of long-QT syndrome women was independent of the administration of estrogen therapy. The study also shows that β-blocker therapy is associated with a significant reduction in the risk of recurrent episodes of syncope in long-QT syndrome women during this time period, supporting the continued use of this mode of medical therapy in all women with the LQT2 genotype (without contraindications) even after the onset of menopause. Thus, the present findings suggest that a genotype-specific approach should be used for risk assessment and management of long-QT syndrome women even after the onset of menopause.

Conclusions: The onset of menopause is associated with a significant increase in the risk of cardiac events (dominated by recurrent episodes of syncope) in LQT2 women, suggesting that careful follow-up and continued long-term therapy are warranted in this population.\textsuperscript{16}

**Early Repolarization: Electrocardiographic Phenotypes Associated With Favorable Long-Term Outcome**

Summary: Previous reports have characterized inferior early repolarization (ER) as a harbinger of increased risk for sudden death. In the present study, the investigators analyzed ER from 12-lead ECGs of 10,864 randomly selected middle-aged subjects and tested the hypothesis that variations in the ST-segment characteristics after the ERP waveforms may have prognostic importance. The novel observations from the present community-based study suggest that ERP with rapidly ascending ST segment in inferior or lateral leads of a 12-lead ECG, which is frequently observed in young healthy athletes, is a benign variant, similar to that observed in leads V1–V3, at least in middle-aged subjects. Subjects with this ECG pattern should not be profiled as high risk, and would not require specific cardiovascular evaluations or treatment if they are asymptomatic without a family history of sudden cardiac death or serious arrhythmias. In contrast, a specific ERP pattern in inferior leads of a standard 12-lead ECG with a horizontal/descending ST segment appears to be associated with an increased risk of arrhythmic death and a high amplitude of J-point elevation increases the risk even further. The pathogenesis, background, and treatment of such subjects with high-amplitude ERP and horizontal/downsloping ST segment warrant further research.

Conclusions: ST-segment morphology variants associated with ER separates subjects with and without an increased risk of arrhythmic death in middle-aged subjects. Rapidly ascending ST segments after the J-point, the dominant ST pattern in healthy athletes, seems to be a benign variant of ER.\textsuperscript{17}

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

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 (\(\approx 50\%\)) 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 (SD) 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 SD in patients who are not candidates for implantable cardioverter-defibrillator will need to take into account the circumstances of SD events.\textsuperscript{18}

**Long-Term Complications Related to Biventricular Defibrillator Implantation: Rate of Surgical Revisions and Impact on Survival: Insights From the Italian Clinical Service Database**

Summary: Cardiac resynchronization therapy (CRT) alone or associated with an implantable cardioverter-defibrillator (CRT-D) is now a common therapy for patients with symptomatic heart failure and evidence of ventricular dyssynchrony. Although several reports have described periprocedural adverse events and early complications of CRT implantation, long-term data on the burden of device-related untoward events are lacking. This study enrolled 3253 CRT-D patients to quantify the frequency of repeat invasive procedures and the nature of long-term complications in clinical practice and to examine possible predictors of device-related events as well as their association with long-term outcome. Four years after implantation, 50% of CRT-D patients underwent surgical revision for battery depletion and 14% for unanticipated events, such as device-related infections or lead dislodgments. For comparison, at 4 years, surgical revision for battery depletion occurred in 10% and 13% of patients who received single- and dual-chamber defibrillators at the study centers, and unanticipated events were reported in 4% and 9%, respectively. Infections occurred at a rate of 1.0%/yr, and the risk of infections increased after device replacement procedures (hazard ratio, 2.04; 95% confidence interval, 1.01–4.09; \(P=0.045\)). Left ventricular lead dislodgements occurred at a rate of 2.3%/yr and were predicted by longer fluoroscopy time and higher pacing threshold on implantation, both signs of a challenging implantation procedure. Nonetheless, device-related events were not associated with an increased risk of death. In conclusion, this study demonstrated that in current clinical practice, device-related events are more frequent in CRT-D than in single- or dual-chamber defibrillators, and frequently require surgical intervention for system revision. This information is particularly important because, although device-
related events do not seem to be associated with a worse clinical outcome, they represent a source of incremental costs to the healthcare system. Therefore, efforts to reduce them could have significant financial as well as clinical benefits.

Conclusions: In current clinical practice device-related events are more frequent in CRT-D than in single- or dual-chamber defibrillators, and are frequently managed by surgical intervention for system revision. However, a worse clinical outcome is not associated with these events.19

Continuous Low-Level Vagus Nerve Stimulation Reduces Stellate Ganglion Nerve Activity and Paroxysmal Atrial Tachyarrhythmias in Ambulatory Canines

Summary: The present study was conducted in ambulatory dogs with continuous recording of left stellate ganglion nerve activity and left vagus nerve activity before, during, and after low-level vagus nerve stimulation (LL-VNS) of the left cervical vagal nerve. We showed that LL-VNS can effectively suppress stellate ganglion nerve activity while not increasing or decreasing thoracic vagus nerve activity. The most significant stellate ganglion nerve activity reduction occurred in the morning when the sympathetic outflow was the highest. Immunohistochemical studies of the left stellate ganglion showed significant neural remodeling, including reduced sympathetic nerve structures, 1 week after cessation of LL-VNS. We further demonstrated that LL-VNS can suppress paroxysmal atrial tachycardia and paroxysmal atrial fibrillation induced by intermittent rapid atrial pacing. A possible clinical implication is that LL-VNS can be used as a nonpharmacological approach to controlling paroxysmal atrial tachycardia and paroxysmal atrial fibrillation through the suppression of cardiac sympathetic outflow. This method may also apply to other clinical conditions in which hyperactivity of the stellate ganglion and increased sympathetic outflow are responsible for the pathogenesis of the diseases. For example, previous studies have shown that the risk of sudden death is the highest in the morning. Low-level vagus nerve stimulation, which selectively suppresses sympathetic outflow in the morning, may be used to reduce the risk of sudden death. Other possible clinical applications include the suppression of ventricular tachyarrhythmias, including those associated with long-QT syndrome, catecholaminergic polymorphic ventricular tachycardia, or structural heart diseases. It may also be effective in noncardiac diseases caused by increased sympathetic outflow.

Conclusions: Left-sided low-level vagus nerve stimulation suppresses stellate ganglion nerve activities and reduces the incidences of paroxysmal atrial tachyarrhythmias in ambulatory dogs. Significant neural remodeling of the left stellate ganglion is evident 1 week after cessation of continuous LL-VNS.40

Plasma B-Type Natriuretic Peptide Levels and Recurrent Arrhythmia After Successful Ablation of Lone Atrial Fibrillation

Summary: The exact pathophysiology of atrial fibrillation (AF) is obscured by the effects of the arrhythmia itself because it leads to both mechanical and electric remodeling. This is particularly true for patients with lone AF, which is AF in the absence of heart disease or comorbidities predisposing to the arrhythmia. Plasma B-type natriuretic peptide is abnormally elevated in patients with lone AF, but the exact significance and prognostic implications of this elevation have yet to be determined. In the present study, we followed up 726 patients with lone AF undergoing first-time arrhythmia ablation over a median of 26 months after the ablation procedure. B-type natriuretic peptide levels were found to correlate with lone AF burden (chronicity, altered hemodynamics, and anatomic remodeling with left atrial dilation) and to be a stronger predictor of arrhythmia recurrence after AF ablation than previously described risk factors. This robust and graded association persisted in multivariable analyses. Elevated B-type natriuretic peptide levels may reflect increased cardiac chamber wall stress and/or intrinsic atrial disease in these patients, thus increasing the risk of arrhythmia recurrence.

Conclusions: B-type natriuretic peptide levels correlate with AF burden (chronicity, altered hemodynamics, and anatomic remodeling) in patients with lone AF and are strong predictors of recurrent arrhythmia after ablation. Elevated BNP levels may reflect increased cardiac chamber wall stress and/or intrinsic atrial disease, thus increasing the risk of arrhythmia recurrence.21

Mechanical Coupling Between Myofibroblasts and Cardiomyocytes Slows Electric Conduction in Fibrotic Cell Monolayers

Summary: Myocardial infarction engages a fibrotic process in which myofibroblasts secrete extracellular matrix proteins to replace the injured tissue. The contractile properties of myofibroblasts help to ensure a smaller and stronger scar area and to preserve mechanical function. However, in the infarct border zone, arrhythmias are prone to initiate owing to slowed and heterogeneous conduction. Although fibrosis has classically been considered arrhythmogenic because of the creation of an inexorable region, together with zigzag conduction in the border zone, we tested the hypothesis that myofibroblasts can actively influence electrophysiological function through mechanoelectric coupling to the cardiomyocytes. In this study, impaired electric conduction in cocultured monolayers of myofibroblasts and cardiomyocytes can be dramatically improved by applying an excitation-contraction inhibitor or mechanosensitive channel blockers. Our findings advocate a novel mechanism whereby cardiac myofibroblasts exert tension on the myocyte membrane, which leads to slowed and heterogeneous electric conduction through the action of mechanosensitive ion channels. Provided that these in vitro results are corroborated in the intact heart, inhibition of this form of mechanoelectric interaction in the heart may be a way to decrease susceptibility to arrhythmias.

Conclusions: These observations suggest that myofibroblast-myocyte mechanical interactions develop during cardiac injury, and that cardiac conduction may be impaired as a result of increased mechanosensitive channel activation owing to tension applied to the myocyte by the myofibroblast.22

Implantable Cardioverter-Defibrillator Registry Risk Score Models for Acute Procedural Complications or Death After Implantable Cardioverter-Defibrillator Implantation

Summary: Implantable cardioverter-defibrillators represent a potentially lifesaving therapy for patients at high risk of sudden cardiac death. In general, the procedure is safe, but complications can and do occur, even among the most experienced implanters. The present study examined data from the National Cardiovascular Data Registry (NCDR) ICD Registry, which has prospectively gathered data on patients undergoing ICD implantation since 2006. The rates of in-hospital complication and mortality were studied in patients from 268,701 hospitalizations at 1,300 hospitals. Clinical variables available to the clinician before the procedure were then used to derive a model identifying factors associated with adverse events. This information was used to create a simple risk score to identify patients at high and low risk of adverse events. Patients with low risk scores may not require the level of care usually provided to patients undergoing ICD implantation. Conversely, among patients with high risk scores, the timing of ICD implantation may warrant reevaluation. Practically, the model will be a valuable tool in prospectively assessing whether patients should be admitted to the hospital or remain as outpatients.
Conclusions: A simple risk score consisting of readily available clinical variables can identify high- and low-risk subsets of patients undergoing ICD implantation. This information can guide the physician in patient selection and determining the intensity of care required post procedure.23

Late Sodium Current Contributes to the Reverse Rate-Dependent Effect of $I_{Kr}$ Inhibition on Ventricular Repolarization

Summary: The reverse rate-dependent effect of drugs, especially those that inhibit $I_{Kr}$ to prolong ventricular repolarization, has long been recognized as an important proarrhythmic risk factor. We hypothesize that inhibition of the small physiological late Na⁺ current (late $I_{Na}$) will reduce reverse rate dependence associated with $I_{Kr}$-blocking drugs. Late $I_{Na}$ is greater, and reverse rate dependence of APDQT interval is prominent in patients with structural heart diseases (heart failure, myocardial ischemia, etc.), especially after treatment with an $I_{Kr}$-inhibiting drug. In this study, the amplitude of endogenous or physiological late $I_{Na}$ in myocytes was increased as the frequency of stimulation slowed. Inhibition of late $I_{Na}$ by tetrodotoxin or ranolazine diminished the reverse rate dependence of action potential duration and beat-to-beat variability of repolarization caused by $I_{Kr}$ inhibitors in isolated hearts. Results of computer simulations of the effect of $I_{Kr}$ block in the absence and presence of late $I_{Na}$ block were consistent with the results of the experimental studies. The findings can explain, at least in part, why drugs that inhibit both $I_{Kr}$ and late $I_{Na}$ (ie, amiodarone and ranolazine) have no reverse rate-dependent effect and little or no proarrhythmic activity, whereas proarrhythmic activity associated with more selective $I_{Kr}$ blockers is exacerbated when late $I_{Na}$ is increased. This concept may be used to explain the occurrence of slow rate– or pause-triggered cardiac arrhythmias, and may be relevant in the choice of treatment drug(s) in patients with compromised repolarization reserve resulting from increased late $I_{Na}$ or decreased $I_{Kr}$ such as patients with heart failure.

Conclusion: Endogenous late $I_{Na}$ contributes to the reverse rate dependence of $I_{Kr}$ inhibitor–induced increases in action potential duration and beat-to-beat variability of repolarization and to bradycardia-related ventricular arrhythmias.24

Mortality Associated With Atrial Fibrillation in Patients With Myocardial Infarction: A Systematic Review and Meta-Analysis

Summary: This is the first systematic review and meta-analysis of studies addressing the prognostic impact of atrial fibrillation in the setting of myocardial infarction. In this meta-analysis of 43 studies involving 278,854 patients, atrial fibrillation was associated with at least a 40% increase in the risk of mortality among patients with myocardial infarction, regardless of the timing of the atrial fibrillation. This worse prognosis persisted even after the studies adjusted for age, diabetes mellitus, hypertension, prior myocardial infarction, heart failure, and coronary revascularization. These findings indicate that atrial fibrillation can no longer be considered a trivial event during the acute phase of myocardial infarction. Research is needed to evaluate potential strategies and interventions to reduce this risk.

Conclusions: Atrial fibrillation is associated with increased risk of mortality in myocardial infarction (MI) patients. New AF with no history of AF before MI remained associated with an increased risk of mortality even after adjustment for several important AF risk factors. These subsequent increases in mortality suggest that AF can no longer be considered a nonsevere event during MI.25

Prevention of Ventricular Fibrillation Episodes in Brugada Syndrome by Catheter Ablation Over the Anterior Right Ventricular Outflow Tract Epicardium

Summary: Several studies have indicated that the right ventricular outflow tract (RVOT) is likely to be the electrophysiological substrate site in patients with Brugada syndrome (BrS). However, controversy exists as to whether the underlying electrophysiological mechanism that causes an abnormal ECG pattern and ventricular tachycardia/ventricular fibrillation (VT/VF) in BrS patients is due to a repolarization or depolarization abnormality. We performed electroanatomical mapping of the right ventricular (RV) endocardium and both ventricular epicardium in 9 patients with symptomatic BrS who had frequent implantable cardioverter defibrillator discharges due to VT/VF. All 9 patients were found to have abnormal low voltage (<1 mV) and fractionated late potentials present almost exclusively over the anterior aspect of the RVOT epicardium and not elsewhere. These abnormal electrograms are also characterized by markedly prolonged duration of the signals that represent delayed depolarization coinciding with timing of the J-point ST elevation of the typical type 1 Brugada ECG pattern. Furthermore, ablation at the anterior RVOT epicardium resulted in normalizing Brugada ECG pattern in 8 of the 9 patients (89%) and prevented VT/VF induction in 7 of the 9 patients (78%). All patients except 1 were free of VT/VF episodes after at least 1 year of follow-up. These findings suggest that the anterior RVOT epicardium is the arrhythmogenic substrate site in BrS patients, and abnormal delayed depolarization is likely the main electrophysiological mechanism underlying the BrS. This study is also the first to show that epicardial ablation over the anterior RVOT is effective in preventing recurrent VT/VF.

Conclusions: The underlying electrophysiological mechanism in patients with BrS is delayed depolarization over the anterior aspect of the RVOT epicardium. Catheter ablation over this abnormal area results in normalization of the Brugada ECG pattern and prevents VT/VF, both during electrophysiological studies as well as spontaneous recurrent VT/VF episodes in patients with BrS.26

Left Ventricular Lead Position and Clinical Outcome in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) Trial

Summary: Although cardiac resynchronization therapy is an accepted therapeutic modality for patients with heart failure and conduction disturbances, a significant proportion of patients remain nonresponsive to this treatment. An important determinant of successful cardiac resynchronization therapy for heart failure is the position of the left ventricular (LV) pacing lead. The aim of this study was to analyze the impact of the LV lead position on outcome in patients randomized to cardiac resynchronization therapy–defibrillation in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) study. The LV lead position was assessed in 799 patients by means of coronary venograms and chest x-rays recorded at the time of device implantation. The LV lead location was classified along the short axis into an anterior, lateral, or posterior position and along the long axis into a basal, midventricular, or apical region. The results demonstrate that LV lead location along the short axis (ie, anterior, lateral, or posterior walls) does not influence the primary end points of heart failure hospitalization and all-cause mortality. A midventricular (lateral, anterior, or posterior) position was found in 506 (63%), a basal position in 183 (23%), and an apical position in 110 (14%) patients. The apical lead location compared with leads located in the nonapical position (basal or midventricular region) was associated with a significantly increased risk for heart failure and death (hazard ratio=1.71; 95% confidence interval, 1.09–2.71; $P=0.019$) after adjustment for the clinical covariates. LV leads positioned in the apical region were associated with an unfavorable outcome, suggesting that this lead location should be avoided in cardiac resynchronization therapy.

Conclusion: LV leads positioned in the apical region were associated with an unfavorable outcome, suggesting that this lead location should be avoided in cardiac resynchronization therapy.27
Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT)

Summary: There is an increasing interest and need to identify heart failure patients who benefit from cardiac resynchronization therapy (CRT), as well as those who do not. In patients with a wide QRS complex who qualify for CRT, QRS morphology indicates different conduction delays as represented on the ECG as left bundle-branch block (LBBB), right bundle-branch block (RBBB), or nonspecific intraventricular conduction disturbances. The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) demonstrated that in patients with mild to moderate heart failure, CRT with defibrillator implantation (CRT-D) significantly reduced the risk of heart failure events or death compared with treatment with only an implantable cardioverter-defibrillator. This analysis of the MADIT-CRT trial data demonstrated that compared with non-LBBB patients (those with RBBB or nonspecific intraventricular conduction disturbances), patients with LBBB QRS morphology showed significant clinical benefit from CRT-D therapy, as measured by reduced risk of heart failure event or death and risk of ventricular tachycardia/fibrillation or death. Non-LBBB patients did not benefit clinically despite a significant reduction in left ventricular volumes. These findings formed the basis for recent Food and Drug Administration approval of new broadened indications for CRT in mild or asymptomatic heart failure patients with LBBB. There is still a question as to whether CRT therapy should be used in non-LBBB patients even when advanced heart failure is present and which CRT indications might still benefit clinically from CRT. Further research investigating the rationale, mechanisms, and clinical benefit is needed to determine whether CRT therapy should be pursued in non-LBBB patients.

Conclusions: Heart failure patients with New York Heart Association class I or II and ejection fraction ≤30% and LBBB derive substantial clinical benefit from CRT-D: a reduction in heart failure progression and a reduction in the risk of ventricular tachyarrhythmias. No clinical benefit was observed in patients with a non-LBBB QRS pattern (right bundle-branch block or intraventricular conduction disturbances).

Intracardiac Electrogram T-Wave Alternans/Variability Increases Before Spontaneous Ventricular Tachyarrhythmias in Implantable Cardioverter-Defibrillator Patients: A Prospective, Multi-Center Study

Summary: Clinically, T-wave alternans (TWA), the surface ECG manifestation of action-potential repolarization alternans, is measured to estimate long-term risk of VT/VF. TWA and nonalternans variability (TWA/V) also increases immediately before ventricular tachycardia (VT) or fibrillation (VF) under some conditions. This suggests that TWA/V may warn of VT/VF in implantable cardioverter-defibrillator patients. Recently, we described a method for measuring TWA/V from intracardiac electrograms stored in implantable cardioverter-defibrillators (ICDs) before VT/VF. In the present prospective, multicenter study, we found that electrogram TWA/V was greater (by a factor of 2–4) before VT/VF than during 4 independent types of control recordings. However, improved specificity is required before electrogram TWA/V can be applied as a clinical tool in ICDs. Software that measures electrogram TWA/V on a continuous, real-time basis in ICDs is necessary to optimize specificity of electrogram TWA/V. If VT/VF can be predicted with sufficient accuracy, even with a warning as short as ~15 seconds, adaptive pacing algorithms could be initiated to prevent VT/VF. Warning times of several minutes would permit patients to cease activities such as driving and to avoid fall-related injuries or other accidents. Longer warnings might permit titration of antiarrhythmic drugs during periods of greater vulnerability to VT/VF.

Conclusions: In implantable cardioverter-defibrillator patients, electrogram (EGM) TWA/V is greater before spontaneous VT/VF than in control recordings. Future implantable cardioverter-defibrillators that measure EGM TWA/V continuously may warn patients and initiate pacing therapies to prevent VT/VF.

Permanent Pacemaker Insertion After CoreValve Transcatheter Aortic Valve Implantation: Incidence and Contributing Factors (the UK CoreValve Collaborative)

Summary: Transcatheter aortic valve implantation has entered mainstream interventional cardiology as a treatment for aortic stenosis in patients with prohibitively high operative risk. This is a growing cohort of patients globally, given the increased longevity and prevalence of significant comorbidities. The CoreValve Revalving system (CoreValve Medtronic, Luxembourg) is one of the 2 prostheses currently in use, and it has been noted to be associated with an increased need for permanent pacemaker implantation. This study represents the largest analysis of the rates of permanent pacemaker implantation in patients receiving a CoreValve implant and uses clinical ECG data to create an electroanatomic model to explain the phenomenon. Consideration of these factors as addressed in this study has not only implications for the future designs of transcatheter aortic valve implantation devices but also immediate clinical impact on the standard of care of this increasingly numerous patient group.

Conclusion: One third of patients undergoing a CoreValve transcatheter aortic valve implantation procedure require a permanent pacemaker (PPM) within 30 days. Periprocedural atrioventricular block, balloon predilatation, use of the larger CoreValve prosthesis, increased interventricular septum diameter and prolonged QRS duration were associated with the need for PPM.

Endogenous Circadian Rhythm in Vasovagal Response to Head-Up Tilt

Summary: Vasovagal syncope, the most common type of syncope, displays a daily pattern with more occurrences during the morning (6 AM to noon). This pattern could be caused by the daily distribution of behavioral/emotional stimuli and/or modulation of physiological responses by the endogenous circadian system ("body clock"). The present study provides strong evidence that the circadian system could contribute to the daily pattern of vasovagal syncope via its influences on hemodynamic and autonomic responses to tilt stressor. We found that the vulnerability to presyncope caused by head-up tilt has a strong endogenous circadian rhythm, with susceptibility 9 times greater at the circadian times between 10:30 PM and 10:30 AM compared with between 10:30 AM and 10:30 PM. This finding highlights the importance of performing tilt-table tests at similar circadian times when comparing responses of different individuals or the same person before and after treatments for syncope. Additionally, a higher sensitivity may be achieved by performing tilt-table testing during early morning hours or the nighttime. The identified vulnerable period may have relevance to individuals who remain awake or wake up frequently during the nighttime such as night-shift workers, parents feeding their infants, and elderly people with increased nocturia and insomnia. These people may be at higher risk for syncope as a result of their exposure to postural stress during the nighttime. Moreover, the morning broad peak of vasovagal syncope observed in the epidemiological studies might be a combined effect of the endogenous circadian system and daily patterns of external behavioral stimuli.

Conclusions: The circadian system affects cardiovascular responses to postural stress, resulting in greater susceptibility to presyncope during the night. This finding suggests that night-shift workers and people with disrupted sleep at night may have greater risk of syncope.
as a result of their exposure to postural stress during the biological night.31

Longevity of Sprint Fidelis Implantable Cardioverter-Defibrillator Leads and Risk Factors for Failure: Implications for Patient Management

Summary: The main findings in this study are that Sprint Fidelis implantable cardioverter-defibrillator leads continue to fail and that younger patients, women, and patients with certain cardiovascular diseases are more likely to suffer Fidelis fractures than patients who are older and have ischemic or nonischemic cardiomyopathy. Except for inappropriate shocks, there were no deaths or serious injuries associated with Fidelis failure in this large multicenter study. Thus, these data suggest that most Fidelis patients can be managed with careful monitoring using algorithms that mitigate inappropriate shocks. Quattro Secure implantable cardioverter-defibrillator leads performed well (failure rate <0.5%/yr) in all patient subgroups during 7 years of follow-up.

Conclusions: Compared with Quattro leads, the survival of Fidelis leads continues to decline, and Fidelis failure is notably higher in younger patients, women, individuals with hypertrophic cardiomyopathy, and patients with arrhythmogenic right ventricular dysplasia or channelopathies. These findings have significant implications for the management of patients who have Fidelis leads, and they demonstrate the importance of weighing clinical variables in assessments of implantable cardioverter-defibrillator lead performance.32

Dabigatran versus Warfarin in Patients With Atrial Fibrillation: An Analysis of Patients Undergoing Cardioversion

Summary: Cardioversion in atrial fibrillation is associated with an increased thromboembolic risk. The current recommendation is therapeutic anticoagulation with warfarin for at least 3 weeks before and after cardioversion; this recommendation is based on small nonrandomized observational and retrospective studies. Dabigatran is a novel oral direct thrombin inhibitor with rapid onset of action (peak levels in 2 hours) and a half-life of 12 to 17 hours. It was recently approved for stroke prevention in atrial fibrillation. With 18 113 patients, RE-LY is the largest atrial fibrillation trial and provided a unique opportunity to evaluate the postcardioversion thromboembolic risk in patients who underwent cardioversion. A total of 1983 cardioversions were performed during the RE-LY study: 647, 672, and 664 in the dabigatran 110 mg, dabigatran 150 mg, and warfarin groups, respectively. The frequencies of stroke and major bleeding within 30 days of cardioversion on the 2 doses of dabigatran were low and comparable to those on warfarin with or without transesophageal echocardiography guidance. Dabigatran is a reasonable alternative to warfarin in patients requiring cardioversion.

Conclusions: This study is the largest cardioversion experience to date and the first to evaluate a novel anticoagulant in this setting. The frequencies of stroke and major bleeding within 30 days of cardioversion on the 2 doses of dabigatran were low and comparable to those on warfarin with or without transesophageal echocardiography guidance. Dabigatran is a reasonable alternative to warfarin in patients requiring cardioversion.33

Mechanisms of Atrial Tachyarrhythmias Associated With Coronary Artery Occlusion in a Chronic Canine Model

Summary: Coronary artery disease is an important risk factor for atrial fibrillation (AF), but the underlying mechanisms have not been explored extensively. In this study, we considered the hypothesis that chronic obstructive coronary artery disease can create a substrate for AF initiation and maintenance by altering atrial properties. In a chronic dog model, we ligated a small coronary artery that provides blood flow only to a portion of the right atrial free wall. After coronary artery ligation, dogs showed increased occurrence of spontaneous atrial ectopy and atrial tachyarrhythmias, along with a substrate for AF maintenance. Cellular studies showed that spontaneous ectopy was related to triggered activity caused by Ca2+ handling abnormalities, including enhanced Na+-Ca2+ exchange current and spontaneous quantal Ca2+ releases (sparks) occurring during adrenergically driven Ca2+ loading. AF maintenance was related to stable rotors located in the border zone of the atrial infarction resulting from coronary artery occlusion. Local conduction abnormalities in the heterogeneous border zone of the infarction provided the substrate for reentry. These results show that chronic occlusive disease of coronary arteries supplying atrial tissue produces atrial abnormalities that provide both triggers for AF initiation and a substrate for AF maintenance. They indicate a potential mechanism for the observed association between coronary artery disease and AF. These mechanistic concepts may be useful for understanding AF pathophysiology and developing new mechanism-based approaches to patient-specific therapeutics.

Conclusions: Chronic atrial ischemia/infarction creates substrates for both spontaneous ectopy (Ca2+-release events, increased Na+-Ca2+ exchange current) and sustained reentry (conduction abnormalities that anchor reentry). Thus, chronic atrial infarction in dogs promotes both AF triggers and the substrate for AF maintenance. These results provide novel insights into potential AF mechanisms in patients with coronary artery disease.34

Novel Chemical Suppressors of Long QT Syndrome Identified by an In Vivo Functional Screen

Summary: Long QT syndrome (LQTS), caused by either genetic defects or pharmaceutical agents, carries a risk of sudden death. Despite significant medical advances in our understanding of the molecular and cellular mechanisms of these syndromes, there are still no therapies that directly address the underlying physiological problem of prolonged repolarization time. In this study, we used a zebrafish model of LQTS type 2 that harbors a mutation in the KCNH2 gene. The diminutive physical size of zebrafish enabled a small-molecule screen for compounds that rescued the LQTS phenotype. We identified 2 compounds, 2-methoxy-N-(4-methylphenyl) benzamide and the steroid flurandrenolide, that reproducibly rescued the zebrafish LQT mutant in a dose-dependent fashion by shortening both spontaneous ectopy (Ca2+-release events, increased Na+-Ca2+ exchange current) and sustained reentry (conduction abnormalities that anchor reentry). These 2 molecules and future discoveries from this screen provide the substrate for reentry. These results show that chronic occlusive disease of coronary arteries supplying atrial tissue produces atrial abnormalities that provide both triggers for AF initiation and a substrate for AF maintenance. They indicate a potential mechanism for the observed association between coronary artery disease and AF. These mechanistic concepts may be useful for understanding AF pathophysiology and developing new mechanism-based approaches to patient-specific therapeutics.

Conclusions: Chronic atrial ischemia/infarction creates substrates for both spontaneous ectopy (Ca2+-release events, increased Na+-Ca2+ exchange current) and sustained reentry (conduction abnormalities that anchor reentry). Thus, chronic atrial infarction in dogs promotes both AF triggers and the substrate for AF maintenance. These results provide novel insights into potential AF mechanisms in patients with coronary artery disease.34
Cardiac Arrhythmogenic Remodeling in a Rat Model of Long-Term Intensive Exercise Training

Summary: Despite the well-recognized benefits of exercise training in healthy individuals and in patients with cardiovascular disease, increasing evidence has suggested that long-term high-level exercise practice (as in athletic contexts) can increase the risk of developing cardiac arrhythmias. Both atrial tachyarrhythmias (particularly atrial fibrillation) and (much more rarely) potentially malignant ventricular arrhythmias have been associated with sustained high-level endurance training. There have been debates about whether these arrhythmias are due to undiagnosed underlying cardiac arrhythmogenic diseases, with long-term exercise being a triggering factor, or whether high-intensity long-term exercise can actually be a primary cause of arrhythmia susceptibility. To provide insights into the ability of sustained high-level exercise to cause arrhythmogenic cardiac remodeling, we applied an experimental model in which male rats were trained to run vigorously 1 hour daily for 16 weeks and compared them with a parallel group of sedentary control rats. We found that intense long-term exercise induced morphological and functional changes characteristic of the “athlete’s heart” as described in humans, along with extracellular matrix changes and fibrosis affecting all chambers except the left ventricle. Ventricular arrhythmia susceptibility to programmed electric stimulation was enhanced in exercise-trained rats. The fibrotic changes caused by 16 weeks of vigorous exercise training were reversible within several weeks of exercise cessation. These results, if confirmed in humans, suggest that long-term vigorous endurance exercise training may cause cardiac remodeling that serves as a substrate for arrhythmia vulnerability. Our findings may have important potential implications for arrhythmia risk assessment and management in individuals performing high-level exercise training.

Conclusions: In this animal model, we documented cardiac fibrosis after long-term intensive exercise training, together with changes in ventricular function and increased arrhythmia inducibility. If our findings are confirmed in humans, the results would support the notion that long-term vigorous endurance exercise training may in some cases promote adverse remodeling and produce a substrate for cardiac arrhythmias.

Randomized Ablation Strategies for the Treatment of Persistent Atrial Fibrillation: RASTA Study

Summary: The single-procedure efficacy of pulmonary vein isolation (PVI) for ablation of persistent atrial fibrillation (AF) is less than ideal, and the approach to additional ablation is controversial. The inability to achieve durable PV isolation and consistently target AF triggers and substrate outside the PVs contribute to failures. This trial assessed the benefit of additional ablation at complex fractionated electrogram (CFE) regions or common sites of non-PV triggers in patients with persistent AF undergoing PVI plus ablation of provokable AF triggers. We randomized patients to receive no additional ablation, additional ablation of left atrial CFE sites, or ablation at predefined common sites of non-PV triggers. Single-procedure efficacy was <50% in all groups, and CFE ablation beyond PVI did not significantly enhance the single-procedure efficacy. Moreover, in those patients with arrhythmia recurrence who underwent repeat ablation, all had reconnection of at least 1 PV; targeting these alone improved long-term AF control. These findings imply that PVs remain critical in the genesis of persistent AF for many patients.

Conclusions: These data suggest that additional substrate modification beyond PVI does not improve single-procedure efficacy in patients with persistent AF.

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

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 1,429 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 a 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.

Inhibition of Cardiac Ca\(^{2+}\) Release Channels (RyR2) Determines Efficacy of Class I Antiarrhythmic Drugs in Catecholaminergic Polymorphic Ventricular Tachycardia

Summary: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare familial arrhythmia syndrome characterized by emotional or physical stress-induced polymorphic or bidirectional ventricular tachycardia. CPVT has been linked to mutations in genes that regulate Ca\(^{2+}\) release from the sarcoplasmic reticulum (eg, RyR2, CASQ2). Although ß-blockers are first-line therapy, they are not always effective, and better drug therapy is needed. We recently discovered that the class I antiarrhythmic drug flecainide directly targets the molecular defect in CPVT by blocking RyR2 Ca\(^{2+}\) release channels and prevented CPVT in mice and humans. In the present study, we extended this work and tested the efficacy of all Food and Drug Administration-approved class I antiarrhythmic drugs on RyR2 channels, in isolated myocytes, and in vivo using a mouse CPVT model. We found that only propafenone and flecainide inhibit RyR2 channels and prevent exercise-induced CPVT in mice, whereas all other class I drugs lack RyR2 inhibitory properties and were ineffective. This result suggests that RyR2 channel inhibition importantly contributes to antiarrhythmic efficacy in CPVT and should be considered when selecting drug therapy for CPVT patients. As illustrated by the CPVT case report, propafenone may be a promising alternative to flecainide for CPVT patients whenever flecainide is not clinically available or not tolerated. However, RyR2 channel inhibition by propafenone is stereoselective, with R-propafenone being significantly more potent than S-propafenone. Because propafenone is available clinically only as racemate and its metabolism is also stereoselective, large interindividual differences in clinical response may be expected when treating CPVT patients with propafenone.

Conclusions: RyR2 cardiac Ca\(^{2+}\) release channel inhibition appears to determine efficacy of class I drugs for the prevention of CPVT in Casq2\(^{-/-}\) mice. Propafenone may be an alternative to flecainide for CPVT patients symptomatic on ß-blockers.
Early Repolarization Pattern in Competitive Athletes: Clinical Correlates and the Effects of Exercise Training

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 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 HR. 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 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.40

Thoracoscopic Video-Assisted Pulmonary Vein Antrum Isolation, Ganglionated Plexus Ablation, and Periprocedural Confirmation of Ablation Lesions: First Results of a Hybrid Surgical-Electrophysiological Approach for Atrial Fibrillation

Summary: Medically refractory atrial fibrillation (AF) has been subject to treatment with pulmonary vein isolation (PVI) by catheter ablation or surgically, particularly by the Cox-Maze III procedure. Multiple studies have been published recently using minimal invasive surgery, which aims to combine the success rate of surgical treatment with a less invasive approach. We report our first results using a hybrid approach with extensive epicardial periprocedural electrophysiological testing during thoracoscopic PVI and ganglionated plexus ablation. PVI was performed using a bipolar clamp with radiofrequency energy, and the left atrial appendage was removed in all patients. Additional left atrial ablation lines (ALAL) were created in patients with nonparoxysmal AF. The single procedure success rate without the use antiarrhythmic drugs was 86% at 1 year (11/12 in patients with nonparoxysmal AF. The single procedure success rate of 86% at 1 year presumably contributes to a high single procedure success rate. Electrophysiological testing during thoracoscopic PVI and ganglionated plexus ablation for AF is a safe and successful procedure with minimal changes in vitro. The majority of athletes 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 HR. 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 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.40

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