Abstracts: EP & AA drugs & Ablation & Genetics

Part One

May 2012

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Background:

For ablation of atroventricular nodal reentrant tachycardia (AVNRT), cryoablation has been shown to be a safe alternative to radiofrequency ablation. However, previous studies have shown a higher recurrence rate with cryoablation compared to radiofrequency ablation.

Objective:

This study reviewed our experience using cryoablation for typical AVNRT using stringent endpoint criteria for slow pathway ablation, yet preserving the desirable safety profile of cryoablation.

Methods:

Seventy-five consecutive cases of typical AVNRT underwent cryoablation. Ablation of the AV nodal slow pathway was performed with the goal of eliminating tachycardia, AH jump, and retrograde atrial echo beats. The primary efficacy endpoint was freedom of recurrent supraventricular tachycardia at follow-up. Analysis of AVN characteristics, number of lesions, and complications was performed.

Results:

Seventy-two (96%) patients met the primary efficacy endpoint over an average follow-up of 34.6 (12.6–68.3) months. In patients who had complete elimination of the slow pathway, there were no recurrences. The presence of an AH jump with a single retrograde echo was highly associated with a recurrence (P = 0.0001). There were no complications, including AV conduction block.

Conclusion:

The efficacy of cryoablation for management of AVNRT can be comparable to radiofrequency energy if the suggested endpoint of elimination of tachycardia, AH jump with retrograde atrial beats, is met. Prior studies evaluating cryoablation in this setting did not require this endpoint, which could have contributed to the relatively higher rate of late recurrences.
Correlations among the frequencies of atrial activity on the surface electrocardiogram, intracardiac atrial electrograms, and the atrial effective refractory period in patients with atrial fibrillation

Merritt H. Raitt, Walter Kusumoto.

Correlations among the frequencies of atrial activity on the surface electrocardiogram, intracardiac atrial electrograms, and the atrial effective refractory period in patients with atrial fibrillation

Journal of Electrocardiology 2012 ; 45 / 3 ; 296-303, May 2012

Background

The frequency of surface atrial electrocardiogram (ECG) depolarization has been postulated to reflect the atrial effective refractory period (AERP).

Methods

Frequency analysis of surface ECGs after QRST subtraction and of electrograms from 4 right atrium and 4 coronary sinus electrode pairs was performed in 38 patients in atrial fibrillation. The AERP was measured in the right atrium and coronary sinus 10 minutes after cardioversion.

Results

The correlation between the dominant frequencies of intracardiac electrograms and atrial activity in leads I, II, and V1 were 0.89, 0.85, and 0.88, respectively (all \( P < .001 \)). The correlation between the average AERP and the frequency of atrial activity in the surface leads was 0.50, 0.45, and 0.47 (all \( P < .005 \)).

Conclusion

In atrial fibrillation, the frequency of atrial depolarization measured from the surface ECG is highly correlated with intracardiac atrial frequency. However, the correlation between the frequency of surface atrial activity and atrial refractoriness, although significant, is not strong.
The objective of this study was to determine whether patients with Parkinson's disease with and without rapid-eye-movement sleep behavior disorder and patients with idiopathic rapid-eye-movement sleep behavior disorder have an attenuated heart rate response to arousals or to leg movements during sleep compared with healthy controls. Fourteen and 16 Parkinson's patients with and without rapid-eye-movement sleep behavior disorder, respectively, 11 idiopathic rapid-eye-movement sleep behavior disorder patients, and 17 control subjects underwent 1 night of polysomnography. The heart rate response associated with arousal or leg movement from all sleep stages was analyzed from 10 heartbeats before the onset of the sleep event to 15 heartbeats following onset of the sleep event. The heart rate response to arousals was significantly lower in both parkinsonian groups compared with the control group and the idiopathic rapid-eye-movement sleep behavior disorder group. The heart rate response to leg movement was significantly lower in both Parkinson's groups and in the idiopathic rapid-eye-movement sleep behavior disorder group compared with the control group. The heart rate response for the idiopathic rapid-eye-movement sleep behavior disorder group was intermediate with respect to the control and the parkinsonian groups. The attenuated heart rate response may be a manifestation of the autonomic deficits experienced in Parkinson's disease. The idiopathic rapid-eye-movement sleep behavior disorder patients not only exhibited impaired motor symptoms but also incipient autonomic dysfunction, as revealed by the attenuated heart rate response.

Keywords: Parkinson's disease; REM sleep behavior disorder; arousal; sleep; heart rate response; autonomic dysfunction
Azithromycin and the Risk of Cardiovascular Death
Wayne A. Ray, KT Murray, K Hall, PG Arbogast, CM Stein.

BACKGROUND

Although several macrolide antibiotics are proarrhythmic and associated with an increased risk of sudden cardiac death, azithromycin is thought to have minimal cardiotoxicity. However, published reports of arrhythmias suggest that azithromycin may increase the risk of cardiovascular death.

METHODS

We studied a Tennessee Medicaid cohort designed to detect an increased risk of death related to short-term cardiac effects of medication, excluding patients with serious noncardiovascular illness and person-time during and shortly after hospitalization. The cohort included patients who took azithromycin (347,795 prescriptions), propensity-score-matched persons who took no antibiotics (1,391,180 control periods), and patients who took amoxicillin (1,348,672 prescriptions), ciprofloxacin (264,626 prescriptions), or levofloxacin (193,906 prescriptions).

RESULTS

During 5 days of therapy, patients taking azithromycin, as compared with those who took no antibiotics, had an increased risk of cardiovascular death (hazard ratio, 2.88; 95% confidence interval [CI], 1.79 to 4.63; P<0.001) and death from any cause (hazard ratio, 1.85; 95% CI, 1.25 to 2.75; P=0.002). Patients who took amoxicillin had no increase in the risk of death during this period. Relative to amoxicillin, azithromycin was associated with an increased risk of cardiovascular death (hazard ratio, 2.49; 95% CI, 1.38 to 4.50; P=0.002) and death from any cause (hazard ratio, 2.02; 95% CI, 1.24 to 3.30; P=0.005), with an estimated 47 additional cardiovascular deaths per 1 million courses; patients in the highest decile of risk for cardiovascular disease had an estimated 245 additional cardiovascular deaths per 1 million courses. The risk of cardiovascular death was significantly greater with azithromycin than with ciprofloxacin but did not differ significantly from that with levofloxacin.

CONCLUSIONS

During 5 days of azithromycin therapy, there was a small absolute increase in cardiovascular deaths, which was most pronounced among patients with a high baseline risk of cardiovascular disease.

(Funded by the National Heart, Lung, and Blood Institute and the Agency for Healthcare Quality and Research Centers for Education and Research on Therapeutics.)Supported by a grant from the National Heart, Lung, and Blood Institute (HL081707) and a cooperative agreement from the Agency for Healthcare Quality and Research Centers for Education and Research on Therapeutics (HS1-0384).Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.We thank the Tennessee Bureau of TennCare and Department of Health for providing the study data.
Apixaban cuts stroke risk in all types of AF, says ARISTOTLE

The primary conclusion of the ARISTOTLE trial, that the direct factor Xa inhibitor apixaban (Eliquis, Pfizer/Bristol-Myers Squibb) is better than warfarin at preventing stroke or systemic embolism in patients with atrial fibrillation (AF), applies regardless of whether AF is paroxysmal or either permanent or persistent [Al Khatib S].

That's from a prospectively planned secondary analysis of the trial that also shows that apixaban lowers the risk of bleeding complications better than the older anticoagulant in both types of AF. It was presented here last week at the Heart Rhythm Society 2012 Scientific Sessions by Dr Sana Al-Khatib (Duke Clinical Research Institute, Duke University, Durham, NC). Entry into ARISTOTLE called for AF plus at least one other stroke/embolism risk factor.

The analysis also showed a difference in embolic risk by type of AF regardless of treatment. Much of the data until now, she told heartwire, suggest that "the outcomes of patients with persistent or permanent atrial fibrillation and paroxysmal atrial fibr are similar with respect to stroke or systemic embolism. Our results actually challenge that view, because they clearly show that people with persistent or permanent AF have a higher risk of stroke or systemic embolism, and that was the case even when we adjusted for possible confounders."

ARISTOTLE randomized 18,201 patients with AF and at least one other stroke risk factor to receive apixaban at 5 mg twice daily or warfarin to a target INR of 2.0 to 3.0. As covered extensively by heartwire, apixaban led to a 21% reduction in the relative risk of stroke or systemic embolism (p=0.011), a 31% reduction in bleeding (p<0.001), and an 11% reduction in all-cause mortality (p=0.047) over a mean of 1.8 years, compared with warfarin.

In the current analysis, 2,786 patients (15.3%) had paroxysmal AF and 15,412 (84.7%) had persistent/permanent AF. The latter were older, more often male, and had a slightly but significantly higher CHADS2 score than the former.

The superiority of apixaban over warfarin for stroke or systemic embolism in the overall trial was replicated across the two types of AF, with the p value for interaction between apixaban and AF type at 0.71. The interaction p value for major bleeding was 0.50, for all-cause mortality was 0.75, and for the composite of stroke, systemic embolism, major bleeding, and all-cause mortality was 0.62.

Independently of treatment, those with paroxysmal AF, compared with those who had persistent/permanent AF, had a lower rate of stroke or systemic embolism (2.2% vs 3.5% per 100 patient-years of follow-up) with an adjusted hazard ratio (HR) of 0.70 (95% CI 0.51-0.93, p=0.015). No such significant differences were seen between the two AF types with respect to rate of major bleeding and all-cause mortality.

One implication of the findings: if apixaban is under consideration as an alternative to warfarin in a patient with AF, apixaban's appeal shouldn't necessarily vary from one type of AF to the other.

"Although in our study we show that patients with paroxysmal atrial fibr are at a lower risk of stroke or systemic embolism, given all the favorable effects of apixaban, especially on the safety end points," Al-Khatib said, "it may be a good idea to put people on apixaban..."
regardless of the type of atrial fib, if they have at least one other risk factor for stroke or system embolism."

Source Al-Khatib S, Thomas L, Wallentin L, et al. Outcomes with apixaban by type of atrial fibrillation: Results from the ARISTOTLE trial. Heart Rhythm Society 2012 Scientific Sessions; May 11, 2012; Boston, MA.

Abstract LB02-6.

Al-Khatib discloses receiving research grants from Bristol-Myers Squibb. Disclosures for the coauthors are listed in the abstract.
Bigger BP Drop Goal for Renal Denervation

More dramatic blood pressure reductions may be on the horizon for patients with resistant hypertension given the phalanx of renal denervation systems under development.

Results of pilot studies on a variety of novel renal sympathetic nerve ablation catheters are achieving in the range of 28/10 to 32/15 mm Hg blood pressure reductions at one month, researchers reported here at the EuroPCR meeting.

Clinical trials of the first such device -- the Symplicity single-electrode radiofrequency ablation device, on the market in Europe -- showed a 1-month drop in BP of 14/10 to 20/7 mm Hg in clinical trials.

"New second generation devices may be improving not only safety but also efficacy," Stephen Worthley, MBBS, PhD, of the University of Adelaide, Australia, told MedPage Today.

Although still in the early phases of clinical study, stenosis or other complications to the renal artery haven't been a problem across the systems, he and several other groups reported at sessions on the percutaneous renal denervation device pipeline.

"We do see local effects but they don't seem enduring," said one session chair Robert Whitbourn, MBBS, of St. Vincent's Hospital in Melbourne, Australia. "RF seems to be very clean energy. The artery does seem robust."

Nerves are more sensitive than arteries to damage from high temperatures, explained another moderator, Ron Waksman, MD, of Washington Hospital Center in Washington, D.C.

Arteries, too, vary in their tolerance, with the renal artery apparently able to handle damage better than the pulmonary artery, for example, he added.

Multi- or Large-Electrode Systems

First-in-man trial results with the four-electrode EnligHTN radiofrequency ablation device showed no serious complications related to the device or the procedure, such as renal artery dissection, aneurism, stenosis, or flow-limiting vasospasm.

The 46 resistant hypertension patients treated did have some minor procedural events, including four cases of hematoma, three vasovagal responses at sheath removal, and two cases of post-procedural transient bradycardia.

Renal function didn't appear affected at one month.

But office-measured blood pressure dropped by an average 28/10 mm Hg from a mean of 176/96 at baseline to 148/87 at 1 month (P<0.0001), Worthley reported.

Altogether, 78% of the patients were considered responders with at least a 10 mm Hg systolic reduction, and 41% got down to the goal of 140 mm Hg.

Another device with eight electrodes on a balloon catheter gave similar results in the first 10 patients reported by Raymond Cohen, CEO of device maker Vessix Vascular, in the REDUCE-HTN study.

No complications were seen, but 1-month blood pressure fell by 30/11 mm Hg, with all patients being responders.
Another design strategy is a spiral electrode around the catheter head to provide multiple ablations at once.

Preclinical results reported with the OneShot system showed effective ablation of renal nerves and an 84% reduction in renal norepinephrine content compared with controls, which would limit the sympathetic activation that raises blood pressure.

**RF Alternatives**

But not all the devices are sticking with radiofrequency ablation, generating elevated temperatures with other strategies instead.

The Paradise system, for example, uses an ultrasound catheter to heat circumferentially at a depth while cooling the endothelium of the vessel it is in direct contact with.

In the pilot REDUCE trial with that novel strategy, no serious device-related adverse events occurred among the 15 treated patients, although there was one artery dissection from the catheter sheath.

Office-measured blood pressure fell by an average 30/14 mm Hg at 1 month and was 32/16 below baseline at 3 months, Raoul Bonan, MD, of the Montreal Heart Institute in Canada, reported at the conference.

Two other groups reported on strategies without clinical experience yet:

- One using nanomagnetic particles attached to Botox B as a neurotoxin that are injected into the renal artery and then manipulated with an external magnet
- Another using a balloon catheter with holes to push the cancer drug vincristine (Oncovin, Vincasar) into the renal arterial wall where it has a neurotoxic effect

**Cautions for the Field**

Despite the promise of renal denervation for treating a difficult condition -- by definition persistent hypertension despite treatment with three or more antihypertensives, including a diuretic -- experts in the field urged a careful path for clinical practice and research alike.

The alteration in the renal artery is irreversible, Jean Renkin, MD, of St. Luc University Hospital in Brussels, Belgium, noted at the conference's "great debate" session.

"One of the main messages will be proper selection of patients for this procedure," he said.

That's key because patients are going to be driving demand for renal denervation, noted nephrologist William McKane, MB, of the Sheffield Kidney Institute in Sheffield, England.

"You're going to have patients knocking on your door asking for this treatment," he told attendees. "It's important to understand what we know but also what we don't know."

Some of those questions are how the treatments compare with sham control, which none of the studies yet have used, and what the long term outcomes will be with the denervation procedure.

Renal nerves can regrow, although data from the Symplicity trials suggest a durable effect over at least 3 years.

Also, the epidemiologic data projecting the effect of a particular blood pressure difference on mortality and other outcomes hasn't panned out quite as well in interventional trials, McKane cautioned.
Another concern is that renal artery stenosis may develop slowly, taking up to a decade to show up after radiation, he added.

The Symplicity trial excluded patients with even moderate or more advanced kidney disease and its quality of surveillance for complications wasn't compelling, McKane argued.

"It's too early to tell what the impact on GFR [glomerular filtration rate] is really going to be," he said.

For the time being, it's important to reserve renal denervation procedures to only good renal teams with representation by hypertension specialists, radiologists, and nephrologists that can carefully screen patients for truly medication-resistant hypertension, Renkin suggested.

"We need to be very careful that we do not kill a promising technology with incorrect patient selection," agreed Pierre-Francois Plouin, MD, of the Hospital Europeen Georges Pompidou in Paris, and a past president of the French Society of Hypertension.

reference:
Additional source: European Association of Percutaneous Cardiovascular Interventions
additional sourdes:
Grube E, et al "Cardiovascular innovation pipeline -- renal denervation" EuroPCR 2012

The EnligHTN trial was supported by St. Jude Medical. Worthley reported having no conflicts of interest to disclose. The REDUCE-HTN trial was supported by Vessix Vascular. Cohen reported being CEO of Vessix Vascular. The Paradise renal denervation device study was supported by ReCor Medical. Bonan reported consulting and being a stockholder in ReCor Medical. Whitbourn reported research support from Abbott Vascular, Boston Scientific, and Medtronic. Waksman and Plouin reported having no conflicts of interest to disclose. Renkin and McKane reported receiving honoraria from Medtronic.
Catheter ablation of idiopathic ventricular tachycardia originating from myocardial extensions into a noncoronary aortic cusp.

Hlivák P, Peichl P, Cihák R, Wichterle D, Kautzner J.
Catheter ablation of idiopathic ventricular tachycardia originating from myocardial extensions into a noncoronary aortic cusp.

We present a 34-year-old woman with idiopathic ventricular tachycardia that resisted 2 previous attempts for catheter ablation and was successfully ablated in the myocardial extension within the noncoronary aortic cusp.

Department of Cardiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic.
BACKGROUND:

Conventional catheter ablation of cardiac arrhythmias is associated with radiation risks for patients and laboratory personnel. However, nonfluoroscopic catheter guidance may increase the risk for inadvertent cardiac injury. A novel radiofrequency ablation catheter capable of real-time tissue-tip contact force measurements may compensate for nonfluoroscopic safety issues.

OBJECTIVE:

To investigate the feasibility of contact force-controlled zero-fluoroscopy catheter ablation.

METHODS:

In 30 patients (including 12 pediatric patients), zero-fluoroscopy catheter ablation of right-sided (right atrium, n = 20; right ventricle, n = 2) and left atrial (n = 8) arrhythmias was attempted. Inclusion criteria were symptomatic suspected atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia, focal right atrial and ventricular arrhythmias, and lone atrial fibrillation. A novel irrigated-tip catheter with an integrated contact force sensor was used for nonfluoroscopic 3-dimensional electroanatomical mapping and radiofrequency ablation. Transseptal access was gained under transesophageal guidance for ablation of left-sided arrhythmias.

RESULTS:

Procedural success without fluoroscopy was achieved in 29 of the 30 patients (97%). In 1 patient, endocardial nonfluoroscopic ablation failed because of an epicardial accessory pathway within a coronary sinus aneurysm. Mean total contact force and amplitude of force undulations were kept below 50 g during mapping and below 40 g during ablation to prevent contact force peaks (>100 g). Apart from a transient second-degree type I atrioventricular block, no complications occurred. The mean procedure time was 2.8 ± 0.9 hours. There were no arrhythmia recurrences during a mean follow-up of 6.2 ± 4.2 months.

CONCLUSION:

Contact force-controlled zero-fluoroscopy catheter ablation is generally feasible in right-sided and left atrial cardiac arrhythmias.
Compensatory properties of heart rate asymmetry.

Piskorski J, Guzik P.
Compensatory properties of heart rate asymmetry.

BACKGROUND:

Heart rate asymmetry (HRA) is a physiologic phenomenon that reflects a systematic and 1-directional difference between heart rate accelerations and decelerations. In terms of variance-based descriptors, HRA causes the contributions from heart rate decelerations to contribute more to short-term variability than accelerations, and for the long-term variability, the relation is reversed. The hypothesis tested in the present article is that this reversal is caused by a compensatory mechanism whose function is to keep the system in relative balance.

METHODS:

Thirty-minute electrocardiographic recordings from 420 young healthy volunteers were analyzed. The variance-based HRA descriptors were calculated. Cases with both short- and long-term HRAs were considered to show compensation. In the binomial test, we looked for statistically significant departures from independence in the distribution of cases possessing both types of asymmetry.

RESULTS:

Short-term asymmetry was observed in 77.6% of subjects (P < .0001), and long-term asymmetry, in 69.3% (P < .0001); both types of HRA coexisted in 66.9% (P < .0001) of the whole group. This result is significantly different (P < .0001) from the independent case (53.78%).

CONCLUSION:

The compensation effect between the short- and long-term asymmetries is present in supine resting electrocardiographic recordings in young healthy people.

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Comparison of Effectiveness of Ranolazine Plus Amiodarone Versus Amiodarone Alone for Conversion of Recent-Onset Atrial Fibrillation.


Ranolazine, an antianginal agent with antiarrhythmic properties, prevents atrial fibrillation (AF) in patients with acute coronary syndrome. In experimental models, the combination of ranolazine and amiodarone has marked synergistic effects that potently suppress AF. Currently, the clinical effect of the ranolazine-amiodarone combination for the conversion of AF is unknown. This prospective randomized pilot study compared the safety and efficacy of ranolazine plus amiodarone versus amiodarone alone for the conversion of recent-onset AF. We enrolled 51 consecutive patients with AF (<48-hour duration) eligible for pharmacologic cardioversion. Patients (33 men, 63 ± 8 years of age) were randomized to intravenous amiodarone for 24 hours (group A, n = 26) or to intravenous amiodarone plus oral ranolazine 1,500 mg at time of randomization (group A + R, n = 25). The 2 groups were well balanced with respect to clinical characteristics and left atrial diameter. Conversion within 24 hours (primary end point) was achieved in 22 patients (88%) in group A + R versus 17 patients (65%) in group A (p = 0.056). Time to conversion was shorter in group A + R than in group A (9.8 ± 4.1 vs 14.6 ± 5.3 hours, p = 0.002). According to Cox regression analysis, left atrial diameter and A + R treatment were the only independent predictors of time to conversion (hazard ratio 5.35, 95% confidence interval 2.37 to 12.11, p <0.001; hazard ratio 0.81, 95% confidence interval 0.74 to 0.88, p <0.001, respectively). There were no proarrhythmic events in either group. In conclusion, addition of ranolazine to standard amiodarone therapy is equally safe and appears to be more effective compared to amiodarone alone for conversion of recent-onset AF.

3rd Cardiology Department, Hippokrateion Hospital, Aristotle University Medical School, Thessaloniki, Greece.
Men and women with type 1 long QT syndrome (LQT1) exhibit time-dependent differences in the risk for cardiac events.

Objective

We hypothesized that sex-specific risk for LQT1 is related to the location and function of the disease-causing mutation in the KCNQ1 gene.

Methods

The risk for life-threatening cardiac events (comprising aborted cardiac arrest [ACA] or sudden cardiac death [SCD]) from birth through age 40 years was assessed among 1051 individuals with LQT1 (450 men and 601 women) by the location and function of the LQT1-causing mutation (prespecified as mutations in the intracellular domains linking the membrane-spanning segments [ie, S2–S3 and S4–S5 cytoplasmic loops] involved in adrenergic channel regulation vs other mutations).

Results

Multivariate analysis showed that during childhood (age group: 0–13 years) men had >2-fold (P < .003) increased risk for ACA/SCD than did women, whereas after the onset of adolescence the risk for ACA/SCD was similar between men and women (hazard ratio = 0.89 [P = .64]). The presence of cytoplasmic-loop mutations was associated with a 2.7-fold (P < .001) increased risk for ACA/SCD among women, but it did not affect the risk among men (hazard ratio 1.37; P = .26). Time-dependent syncope was associated with a more pronounced risk-increase among men than among women (hazard ratio 4.73 [P < .001] and 2.43 [P = .02], respectively), whereas a prolonged corrected QT interval (≥500 ms) was associated with a higher risk among women than among men.

Conclusion

Our findings suggest that the combined assessment of clinical and mutation location/functional data can be used to identify sex-specific risk factors for life-threatening events for patients with LQT1.

Keywords: Cytoplasmic-loop mutations, Sex, Long QT syndrome, Sudden cardiac death

Abbreviations: ACA, aborted cardiac arrest, C-loop mutations, cytoplasmic-loop mutations, HR, hazard ratio, ICD, implantable cardioverter defibrillator, LQT1, long QT syndrome type 1, MS, membrane spanning, QTc, corrected QT interval, SCD, sudden cardiac death

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Sauer AJ, Newton-Cheh C.
Clinical and genetic determinants of torsade de pointes risk.
Center for Human Genetic Research, Cardiovascular Research Center, Massachusetts General Hospital, 185 Cambridge Street, Boston, MA 02114, USA. PMID: 22474311
Coexisting early repolarization pattern and Brugada syndrome: recognition of potentially overlapping entities

William F. McIntyre, Andrés Ricardo Pérez-Riera, Francisco Femenía, Adrian Baranchuk.

Coexisting early repolarization pattern and Brugada syndrome: recognition of potentially overlapping entities


The Brugada type 1 electrocardiographic (ECG) pattern and the early repolarization pattern (ERP) are 2 ECG patterns characterized by the appearance of J waves. Although Brugada type 1 ECG pattern in the context of the Brugada syndrome (BrS) is well known for predisposing to life-threatening ventricular arrhythmias, it has only recently come to light that ERP, which was previously believed to be benign, may also be a marker for arrhythmogenic potential. ERP and BrS share many remarkable cellular, ionic, and ECG similarities and behave comparably in terms of their response to heart rate, pharmacologic agents, and neuromodulation. The extent to which ERP and BrS may overlap remains unclear.

Here, we present an illustrated case of a symptomatic patient whose ECG signature evolved spontaneously from ERP alone to ERP with a concomitant Brugada type 1 ECG pattern over a short number of days. This case lends further strength to the notion that these 2 ECG patterns may be more closely related than had been initially thought.

Keywords: Early repolarization pattern, Brugada syndrome, Ventricular repolarization, Sudden cardiac death Kingston General Hospital, Division of Cardiology, Queen's University, Kingston, Ontario, Canada // Corresponding author. Department of Medicine, Etherington Hall Queen's University, 94 Stuart St, Kingston, Ontario, K7L 3N6. // ABC Medical Faculty, ABC Foundation, Santo André, São Paulo, Brazil Unidad de Arritmias, Departamento de Cardiología, Hospital Español de Mendoza, Mendoza, Argentina Kingston General Hospital, Division of Cardiology, Queen's University, Kingston, Ontario, Canada / Received 8 September 2011 published online 19 December 2011.
Coexisting early repolarization pattern and Brugada syndrome: recognition of potentially overlapping entities

William F. McIntyre, Andrés Ricardo Pérez-Riera, Francisco Femenía, Adrian Baranchuk. Coexisting early repolarization pattern and Brugada syndrome: recognition of potentially overlapping entities

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Added Predictive Ability of the CHA₂DS₂VASc Risk Score for Stroke and Death in Patients With Atrial Fibrillation
The Prospective Danish Diet, Cancer, and Health Cohort Study


Added Predictive Ability of the CHA2DS2VASc Risk Score for Stroke and Death in Patients With Atrial Fibrillation

The Prospective Danish Diet, Cancer, and Health Cohort Study

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Background
The objective of this study was to evaluate the added predictive ability of the CHA₂DS₂VASc prediction rule for stroke and death in a nonanticoagulated population of patients with atrial fibrillation.

Methods and Results
We included 1603 nonanticoagulated patients with incident atrial fibrillation from a Danish prospective cohort study of 57,053 middle-aged men and women. The Net Reclassification Improvement was calculated as a measure to estimate any overall improvement in reclassification with the CHA₂DS₂VASc score as an alternative to the CHADS₂ score. After 1-year follow-up, crude incidence rates were 3.4 per 100 person-years for stroke and 13.6 for death. After a mean follow-up of 5.4 years (±3.7 years), the crude incidence rates for stroke and death were 1.9 and 5.6, respectively. During the entire observation period, the c-statistics and negative predictive values were similar for both risk scores. The Net Reclassification Improvement analysis showed that 1 of 10 reclassified atrial fibrillation patients would have been upgraded correctly using the CHA₂DS₂VASc score.

Conclusions—Both the CHADS₂ as well as the CHA₂DS₂VASc risk score can exclude a large proportion of patients from having high risk of stroke or death. However, using the CHA₂DS₂VASc risk score, fewer patients will fulfill the criterion for low risk (and are truly low risk for thromboembolism). For every 10 extra patients transferred to the treatment group at 5 years, using the CHA₂DS₂VASc risk score, 1 patient would have had a stroke that might have been avoided with effective treatment.

Key Words: atrial fibrillation stroke CHADS2 CHA2DS2VASc c-statistics AUC Net Reclassification Improvement oral anticoagulation risk score

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Clinical Mapping Approach To Diagnose Electrical Rotors and Focal Impulse Sources for Human Atrial Fibrillation

SANJIV M. NARAYAN, DE KRUMMEN, W-J RAPPEL.
Clinical Mapping Approach To Diagnose Electrical Rotors and Focal Impulse Sources for Human Atrial Fibrillation


Introduction:

The perpetuating mechanisms for human atrial fibrillation (AF) remain undefined. Localized rotors and focal beat sources may sustain AF in elegant animal models, but there has been no direct evidence for localized sources in human AF using traditional methods. We developed a clinical computational mapping approach, guided by human atrial tissue physiology, to reveal sources of human AF.

Methods and Results:

In 49 AF patients referred for ablation (62 ± 9 years; 30 persistent), we defined repolarization dynamics using monophasic action potentials (MAPs) and recorded AF activation from 64-pole basket catheters in left atrium and, in n = 20 patients, in both atria. Careful positioning of basket catheters was required for optimal mapping. AF electrograms at 64–128 electrodes were combined with repolarization and conduction dynamics to construct spatiotemporal AF maps. We observed sustained sources in 47/49 patients, in the form of electrical rotors (n = 57) and focal beats (n = 11) that controlled local atrial activation with peripheral wavebreak (fibrillatory conduction). Patients with persistent AF had more sources than those with paroxysmal AF (2.1 ± 1.0 vs 1.5 ± 0.8, P = 0.02), related to shorter cycle length (163 ± 19 milliseconds vs 187 ± 25 milliseconds, P < 0.001). Approximately one-quarter of sources lay in the right atrium.

Conclusions:

Physiologically guided computational mapping revealed sustained electrical rotors and repetitive focal beats during human AF for the first time. These localized sources were present in 96% of AF patients, and controlled AF activity. These results provide novel mechanistic insights into human AF and lay the foundation for mechanistically tailored approaches to AF ablation.

Computational Mapping of Rotors and Focal Impulses in Human AF.
Keywords: atrial fibrillation; catheter ablation; fibrillatory conduction; mapping; rotors
Background:

This study aimed to compare acute and late outcomes of VT ablation using the magnetic navigation system (MNS) to manual techniques (MAN) in patients with (SHD) and without (NSHD) structural heart disease.

Methods:

Ablation data of 113 consecutive patients (43 SHD, 70 NSHD) with ventricular tachycardia treated with catheter ablation at our center were analyzed. Success rate, complications, procedure, fluoroscopy, and ablation times, and recurrence rates were systematically recorded for all patients.

Results:

A total of 72 patients were included in the MNS group and 41 patients were included in the MAN group. Patient age, gender, and right ventricular and left ventricular VT were equally distributed. Acute success was achieved in 59 patients in the MNS group (82%) versus 27 (66%) patients in the MAN group (P = 0.046). Overall procedural time (177 ± 79 vs 232 ± 99 minutes, P < 0.01) and mean patient fluoroscopy time (27 ± 19 vs 56 ± 32 minutes, P < 0.001) were all significantly lower using MNS. In NSHD pts, higher acute success was achieved with MNS (83.7% vs 61.9%, P = 0.049), with shorter procedure times (151 ± 57 vs 210 ± 96, P = 0.011), whereas in SHD-VT these were not significantly different. No major complications occurred in the MNS group (0%) versus 1 cardiac tamponade and 1 significantly damaged ICD lead in the MAN group (4.9%, NS). After follow-up (20 ± 11 vs 20 ± 10 months, NS), VT recurred in 14 pts (23.7%) in the MNS group versus 12 pts (44.4%) in the MAN group (P = 0.047).

Conclusions:

The use of MNS offers advantages for ablation of NSHD-VT, while it offers similar efficacy for SHD-VT.

PMID: 22554147 // Clinical Electrophysiology, Department of Cardiology, Erasmus MC, Rotterdam, The Netherlands.
Free Fatty Acids May Point to Atrial Fibrillation Risk

In a study of community-dwelling elderly, high plasma levels of free fatty acids (FFAs) were a risk marker for atrial fibrillation (AF).

Dr. Owais Khawaja of Brigham and Women's Hospital in Boston, who led the study, told Reuters Health by email, "Free fatty acids can provide information above and beyond that of standard AF risk factors. Therefore, if our findings are confirmed by others, FFA may help identify older individuals at risk of future AF."

In an April 12th online paper in the American Journal of Cardiology, Dr. Khawaja and colleagues said high FFA levels have been associated with increased insulin resistance, hypertension and physical inactivity - but until now this putative relationship with AF risk factors has "not been investigated in the general population including older adults, a group extremely vulnerable to AF."

The new study involved 4,175 men and women at least 65 years old who were members of the prospective Cardiovascular Health Study cohort. Plasma FFA was measured in 1992 and 1993.

During a mean follow-up of 10 years, there were 1,041 new cases of AF. Crude incidence rates of AF per 1000 person-years across quartiles of plasma FFAs were 23.7, 23.3, 23.9 and 29.7.

Multivariable adjusted hazard ratios ranged from 1.0 at the lowest quartile to 1.29 at the highest. This relationship remained when follow-up was restricted to 5 years.

Confirmation is needed, but in the meantime the findings may have some value, the researchers believe. "Although prevention of AF may be difficult," they write, "novel therapies are increasingly available to convert and maintain normal sinus rhythm, and earlier identification of patients with AF might allow earlier use of anticoagulants to avert cerebrovascular events."


Am J Cardiol 2012.
WASHINGTON -- The FDA is proposing that makers of ionizing radiation devices add labels warning against use on children unless they have shown the devices are safe for pediatric use.

The requirement is part of proposed regulations announced Wednesday for pediatric use of x-ray imaging devices.

The FDA noted in a statement that ionizing radiation -- the type emitted by CT, fluoroscopy, and conventional x-ray imaging devices -- poses a greater cancer risk per unit dose in pediatric patients than in adults, and that patients receiving diagnostics from such devices at a young age have an additive exposure over the course of a lifetime.

They added that the amount of radiation required for an adult diagnostic scan may be larger than that required to diagnose a younger patient, resulting in a larger dose of radiation than is necessary.

"Properly used, x-ray imaging devices offer minimal exposure risks to pediatric patients. What the FDA is trying to do, however, has great merit in that the agency wants to make it much easier for x-ray technologists doing examinations on children to plan and perform those exams with the most efficiency at the least dose," Christopher Cassady, MD, chair of the section on radiology at the American Academy of Pediatrics, said in an email to MedPage Today.

In February 2010, the FDA launched a website outlining the risks and benefits to pediatric x-ray imaging. The agency also has allied with the Alliance for Radiation Safety in Pediatric Imaging and the Medical Imaging and Technology Alliance to develop safety materials for pediatric x-ray device use, the statement said.

The FDA will host a workshop on July 16 for industry, healthcare professionals working with x-ray imaging, and patient advocates to discuss the proposed guidelines.

The collaboration between groups is a positive step forward in reducing risks and increasing the safety profile of these radiation-emitting devices, Cassady added.

The agency is accepting public comment on the proposed regulations through early September.
Failed heart rate control with oral metoprolol prior to coronary CT angiography: effect of additional intravenous metoprolol on heart rate, image quality and radiation dose.

Jiménez-Juan L, Nguyen ET, Wintersperger BJ, Moshonov H, Crean AM, Deva DP, Paul NS, Torres FS.

The purpose of this study was to evaluate the effect of intravenous (IV) metoprolol after a suboptimal heart rate (HR) response to oral metoprolol (75-150 mg) on HR control, image quality (IQ) and radiation dose during coronary CTA using 320-MDCT. Fifty-three consecutive patients who failed to achieve a target HR of < 60 bpm after an oral dose of metoprolol and required supplementary IV metoprolol (5-20 mg) prior to coronary CTA were evaluated. Patients with HR < 60 bpm during image acquisition were defined as responders (R) and those with HR ≥ 60 bpm as non-responders (NR). Two observers assessed IQ using a 3-point scale (1-2, diagnostic and 3, non-diagnostic). Effective dose (ED) was estimated using dose-length product and a 0.014 mSV/mGy.cm conversion factor. Baseline characteristics and HR on arrival were similar in the two groups. 58% of patients didn't achieve the target HR after receiving IV metoprolol (NR). R had a significantly higher HR reduction after oral (mean HR 63.9 ± 4.5 bpm vs. 69.6 ± 5.6 bpm) (p < 0.005) and IV (mean HR 55.4 ± 3.9 bpm vs. 67.4 ± 5.3 bpm) (p < 0.005) doses of metoprolol. Studies from NR showed a significantly higher ED in comparison to R (8.0 ± 2.9 vs. 6.1 ± 2.2 mSv) (p = 0.016) and a significantly higher proportion of non-diagnostic coronary segments (9.2 vs. 2.5 %) (p < 0.001). 58% of patients who do not achieve a HR of <60 bpm prior to coronary CTA with oral fail to respond to additional IV metoprolol and have studies with higher radiation dose and worse image quality.

PMID:22527260 / Cardiothoracic Division, Department of Medical Imaging, Toronto General Hospital, University Health Network, Toronto, ON, Canada.
Electrophysiology Procedures in Adults with Congenital Heart Disease

Peter Ermis, W Franklin, J Kim, D Moodie, D Parekh. Electrophysiology Procedures in Adults with Congenital Heart Disease Congenital Heart Disease 2012; Article first published online: 27 APR 2012 // DOI: 10.1111/j.1747-0803.2012.00658.x

Background.

In adult congenital heart disease (CHD), arrhythmias contribute significantly to morbidity and mortality. Often, these adult patients are treated at a freestanding pediatric facility. Limited data exist looking at this cohort.

Methods.

A retrospective review was performed of all electrophysiology (EP) procedures performed in adults at our institution during a 5-year period from January 1, 2006 through December 31, 2010.

Results.

There were 99 cases performed in a total of 87 adults with CHD during this time period. The mean patient age was 27.1 years (18–51 years). The most common congenital cardiac diagnoses were: 27% with D-transposition of the great arteries (n = 27)—of which 85% (n = 23) have had a previous atrial switch procedure, 20% with tetralogy of Fallot (n = 20), and 16% with previous Rastelli repair (n = 16). Overall, 37 EP studies were performed, with the majority done in patients with complex CHD. There were 74 additional cases. These procedures consisted of: 38 pacemakers (51%), 26 implantable cardiac defibrillators (36%), six laser lead extractions (8%), two loop recorders (3%), and two pocket revisions (3%). During this 5-year period, there was one major complication (1%) and seven minor complications (7%).

Conclusions.

The complex care of adults with CHD requiring EP procedures can be safely and effectively accomplished in a freestanding pediatric hospital with low complications, provided institutional support of an adult CHD program.

Keywords: Adult Congenital Heart Disease; Electrophysiology; Pediatric Hospital
**Enhanced cardiac PI3Kα signalling mitigates arrhythmogenic electrical remodelling in pathological hypertrophy and heart failure.**

Yang KC, Jay PY, McMullen JR, Nerbonne JM.
Enhanced cardiac PI3Kα signalling mitigates arrhythmogenic electrical remodelling in pathological hypertrophy and heart failure.

**AIMS:**

Cardiac hypertrophy and heart failure are associated with QT prolongation and lethal ventricular arrhythmias resulting from decreased K(+) current densities and impaired repolarization. Recent studies in mouse models of physiological cardiac hypertrophy revealed that increased phosphoinositide-3-kinase-α (PI3Kα) signalling results in the up-regulation of K(+) channels and the normalization of ventricular repolarization. The experiments here were undertaken to test the hypothesis that increased PI3Kα signalling will counteract the adverse electrophysiological remodelling associated with pathological hypertrophy and heart failure.

**METHODS AND RESULTS:**

In contrast to wild-type mice, left ventricular (LV) hypertrophy, induced by transverse aortic constriction (TAC), did not result in prolongation of ventricular action potentials or QT intervals in mice with cardiac-specific expression of constitutively active PI3Kα (caPI3Kα). Indeed, repolarizing K(+) currents and K(+) channel subunit transcripts were increased in caPI3Kα + TAC LV myocytes in proportion to the TAC-induced cellular hypertrophy. Congestive heart failure in a transgenic model of dilated cardiomyopathy model is accompanied by prolonged QT intervals and ventricular action potentials, reduced K(+) currents and K(+) channel transcripts. Increased PI3Kα signalling, but not renin-angiotensin system blockade, in this model also results in increased K(+) currents and improved ventricular repolarization.

**CONCLUSION:**

In the setting of pathological hypertrophy or heart failure, enhanced PI3Kα signalling results in the up-regulation of K(+) channel subunits, normalization of K(+) current densities and preserved ventricular function. Augmentation of PI3Kα signalling, therefore, may be a useful and unique strategy to protect against the increased risk of ventricular arrhythmias and sudden death associated with cardiomyopathy.

Department of Developmental Biology, Washington University Medical School, 660 South Euclid Avenue Box 8103, St Louis, MO 63110-1093, USA.

**Comment**

Rozanski GJ
Physiological remodelling of potassium channels in the heart.
Duty-cycled unipolar/bipolar versus conventional RF ablation in paroxysmal and persistent atrial fibrillation

Christine Tivig, L Dang, H-P Brunner-La Rocca, S Özcan, F Duru, C Scharf.
Duty-cycled unipolar/bipolar versus conventional radiofrequency ablation in paroxysmal and persistent atrial fibrillation

Background

Duty-cycled (DC) radiofrequency ablation (RFA) for atrial fibrillation (AF) has been introduced, however, data on large patient series and comparison to conventional RFA are scarce.

Methods

Between 2006 and 2008 DC RFA was performed in 209 consecutive patients (143 (68%) paroxysmal and 66 (32%) persistent AF). As controls served 211 patients, 155 (73%) with paroxysmal and 56 (27%) with persistent AF (p=0.3). In DC RFA, the pulmonary veins (PV) were isolated followed by ablation at the septum and left atrium, if AF persisted. Conventional PV isolation was followed by anatomical lines at the roof and mitral isthmus.

Results

Freedom of paroxysmal AF was demonstrated after 1.08 DC RFA procedures per patient in 82% and after 1.19 conventional procedures in 87% after 8.5±6.5 months (ns). In persistent AF, success rates were 79% after 1.35 DC RFA procedures and 80% after 1.34 conventional procedures after 11.5±8.5 months (ns). The subgroup analysis of 119 patients with follow-up ≥12 months (17.5 [14.1–23.6] months) showed similar results. Left atrial flutter occurred in 3% and 8% after paroxysmal AF ablation (p<0.05) and in 12% and 23% after persistent AF ablation (p=0.1). Multivariate predictors for success in both groups were age, left atrial size, presence of persistent vs. paroxysmal AF and previous pacemaker implantation, but not the ablation technique used. Non-fatal complications were seen in 2.8% with no differences between the groups.

Conclusion

Outcome in DC RFA is similar to conventional RFA with a final success rate exceeding 80% in both paroxysmal and persistent AF in the absence of fatal complications.

Abbreviations: AF, Atrial fibrillation, AAD, Antiarrhythmic drugs, CTI, Cavotricuspid isthmus, CFAE, Complex fractionated atrial electrograms, DC RFA, Duty-cycled radiofrequency ablation, MAAC, Multi-Array Ablation Catheter, MASC, Multi-Array Septal Catheter, PV, Pulmonary vein, PVAC, Pulmonary Vein Ablation Catheter, RFA, Radiofrequency ablation /// Keywords: Atrial fibrillation, Radiofrequency ablation, Duty-cycled radiofrequency/// Cardiovascular Center, Clinic im Park, Seestrasse 220, 8027 Zurich, Switzerland Cardiology, University Hospital Maastricht, 6202 AZ Maastricht, the Netherlands Corresponding author. Tel.: +41 44 209 2124; fax: +41 44 209 2017. Received 25 April 2010; received in revised form 30 October 2010; accepted 4 December 2010. published online 03 January 2011.
Dynamicity of the j-wave in idiopathic ventricular fibrillation with a special reference to pause-dependent augmentation of the j-wave.


OBJECTIVES:

This study evaluated the pause-dependency of the J-wave to characterize this phenomenon in idiopathic ventricular fibrillation (VF).

BACKGROUND:

The J-wave can be found in apparently healthy subjects and in patients at risk for sudden cardiac death, and risk stratification is therefore needed.

METHODS:

Forty patients with J-wave-associated idiopathic VF were studied for J waves with special reference concerning pause-dependent augmentation. J waves were defined as those ≥0.1 mV above the isoelectric line and were compared with 76 non-VF patients of comparable age and sex.

RESULTS:

The J-wave was larger in patients with idiopathic VF than in the controls: 0.360 ± 0.181 mV versus 0.192 ± 0.064 mV (p = 0.0011). J waves were augmented during storms of VF (n = 9 [22.5%]), which was controlled by isoproterenol; they disappeared within weeks in 5 patients. In addition, sudden prolongation of the R-R interval was observed in 27 patients induced by benign arrhythmia, and 15 patients (55.6%) demonstrated pause-dependent augmentation (from 0.391 ± 0.126 mV to 0.549 ± 0.220 mV; p < 0.0001). In the other 12 experimental subjects and in the 76 control subjects, J waves remained unchanged. Pause-dependent augmentation of J waves was detected in 55.6% (sensitivity) but was specific (100%) in the patients with idiopathic VF with high positive (100%) and negative (86.4%) predictive values.

CONCLUSIONS:

Pause-dependent augmentation of J waves was confirmed in about one-half of the patients with idiopathic VF after sudden R-R prolongation. Such dynamicity of J waves was specific to idiopathic VF and may be used for risk stratification.

Niigata University Graduate School of Medical and Dental Science, Niigata, Japan.
Dilator method and needle method for atrial transseptal puncture: a retrospective study from a cohort of 4443 patients


Dilator method and needle method for atrial transseptal puncture: a retrospective study from a cohort of 4443 patients


Aims
To compare the safety and efficacy of a new dilator method vs the traditional needle method for transseptal puncture (TSP) in a large cohort study.

Methods and results
From February 1995 to December 2010, 4443 consecutive patients undergoing TSP done either by a needle method or by a new dilator method were reviewed retrospectively. Data as procedure-related time and complications were evaluated. For the standard needle method, TSP was performed by extending out the needle. In comparison, for the new dilator technique, TSP was performed without an outer sheath and with the needle kept within the dilator; the blunt tip of the dilator was used to help locating the position of the fossa ovalis on purpose. Transseptal puncture was performed by the new dilator method in 2151 patients (48.4%) and by the traditional needle method in 2292 patients (51.6%). The average TSP time needed by the dilator method was longer than that needed by the needle method (5.6 ± 3.9 vs. 3.8 ± 2.9 min, \(P<0.05\)). Additional left atrial angiography was required in seven (0.33%) patients for the dilator and in 39 patients (1.70%) for the needle method (\(P<0.05\)). The total rate of severe complications and obvious TSP-related complications was significantly lower in patients who underwent the dilator method than in those who underwent the needle method (0.33 vs. 1.18%, and 0.20 vs. 1.00%, respectively, \(P<0.05\)).

Conclusion
Our data suggest that the new dilator technique is much safer than that of the standard needle method. It needs relatively longer procedure time but results in significantly fewer episodes of severe complications. Particularly, the blunt tip of the dilator can be used to help locate the fossa ovalis. Therefore, the new dilator technique might be a better choice for relatively less-experienced operators.
Dual epicardial ventricular tachycardia: a tale of two VTs.


A young female with isolated ventricular noncompaction and acute myocarditis presented with incessant dual epicardial ventricular tachycardia consisting of a manifest reentrant circuit and a shorter cycle length concealed circuit. A single radiofrequency terminated both tachycardias.

Division of Cardiology, University Health Network, Toronto, Canada.
Dronedarone: review of trials and up-to-date recommendations

Bansilal S. Cannon C.
Dronedarone: review of trials and up-to-date recommendations
An article from the ESC Council for Cardiology Practice 2012 Vol10 N°28
(15 May 2012)

Dronedarone in high-risk permanent atrial fibrillation - PALLAS - was stopped for safety reasons leaving little post - trial discussion. It concluded that dronedarone should be avoided in patients with permanent atrial fibrillation and, as previously shown, in patients with heart failure. Find a short up-to-date review of trials and summary of recommendations concerning the drug here.

Background

When the antiarrhythmic dronedarone first made its appearance in 2009, it offered great promise: its lack of iodine, compared to amiodarone, would lead to reduced toxic effects on the thyroid and other organs while proving maintained efficacy.

In a broad range of patients with paroxysmal, persistent or permanent atrial fibrillation and heart failure, the DAFNE (2), EURIDIS (3), ADONIS (3) and ERATO (4) studies, dronedarone appeared safe and showed efficacy for rhythm control. Compared with amiodarone in DIONYSOS (5) it also had a good safety profile - albeit showing less efficacy in the latter study.

Dronedarone was then studied in a series of three large phase III studies-ATHENA (6), ANDROMEDA (7) and PALLAS (8); the latest of which found that dronedarone in permanent atrial fibrillation had a two fold increase in all-cause death, cardiovascular death, arrhythmic death, stroke, myocardial infarction, cardiovascular (CV) hospitalisation and hospitalisation for heart failure.

ATHENA & ANDROMEDA

ATHENA (6) randomised 4629 subjects with paroxysmal or persistent atrial fibrillation. Dronaderone showed a significant reduction in its primary composite endpoint of cardiovascular hospitalisations or death from any cause (24%, p<0.001). There was a consistent positive effect seen in reductions achieved, CV death (29%, p=0.03), arrhythmic death (45%, p=0.01) although all cause mortality was not significantly reduced (16%, p=0.18). In the permanent atrial fibrillation subgroup of patients there were trends for favourable CV outcomes (26% reduction in hospitalisation and death, 20% reduction in stroke, acute coronary syndromes and CV death).

ANDROMEDA (7) evaluated 627 subjects with heart failure (without atrial fibrillation) as a possible other indication for this agent however the study was terminated early due to a two-
fold increase in mortality (25 in the dronedarone group and 12 in the placebo group, HR=2.13; CI-1.07-4.25, p=0.03). The primary combined endpoint of all-cause mortality or hospitalisation for worsening heart failure was not significantly different between the two groups.

PALLAS

Following ATHENA, which studied subjects with paroxysmal or persistent atrial fibrillation and ANDROMEDA which studied subject with heart failure PALLAS was designed to study patients with permanent atrial fibrillation. Subjects with active decompensated heart failure were excluded. PALLAS was also halted abruptly for excess mortality. Full results were presented at the 2011 AHA scientific sessions which were also published in the New England Journal of Medicine (8). PALLAS recruited 3236 patients, and was halted at a median follow up of 3.5 months for two fold increases in the first composite primary outcome of stroke, systemic embolism, myocardial infarction or CV death (HR-2.29, C.I-134-3.94, p=0.002) and the second composite primary outcome of unplanned CV hospitalisation or death (HR-1.95, C.I= 1.45-2.64, p<0.001). All-cause death, CV death, arrhythmic death, stroke, MI, CV hospitalisation and hospitalisation for heart failure were all significantly higher in the dronedarone treated patients (Table), with a consistent hazard seen across all-defined subgroups. The fact that 21% subjects discontinued the study drug in the dronedarone arm versus 11% in the placebo arm highlights the poor tolerance of the drug in this subset of patients.

Such different results. What happened?

In trying to assess the reasons for the diametrically opposed results of ATHENA relative to PALLAS, some thoughts come to mind:

1. While no previous trials like PALLAS were carried out specifically in permanent AF patients, various previous experiences with antiarrhythmic drugs such as quinidine (10), d-sotalol (11), encainide (12), moricizine (13), flecainide (14) and amiodarone (15) have shown similar adverse results.
2. The hints of problems seen in ANDROMEDA in patients with heart failure, may have been true after all. There does appear to be an issue, albeit not fully defined, that increased cardiovascular event rates of all types are now seen with this agent.

Practice recommendations

While one is left to wonder about what is electrophysiologically so different in permanent atrial fibrillation, the results of PALLAS reflected in the recommendations from the US Federal Drug Administration (16) and the European Medicines Agency (17) are the following:

- Avoid dronedarone 1) in patients with permanent atrial fibrillation 2) previous amiodarone related liver toxicity 3) current symptoms or past symptoms of HF 4) left ventricular systolic dysfunction (EF <35%)*.
- Consider dronedarone as still an option 1) for paroxysmal or persistent atrial fibrillation patients who present in sinus rhythm and are clinically stable (EMA), 2) in patients who are proposed to be cardioverted (FDA).
- Monitor patients on dronedarone every 3 months for their heart rhythm.
Keep in mind that in permanent atrial fibrillation antiarrhythmic drugs carry significant risks with little benefit.

Focus on rate control and adequate antithrombotic therapy.

*only in FDA, in the context of Class IV NYHA heart failure.

Table 1. Cardiovascular outcomes - PALLAS

<table>
<thead>
<tr>
<th>End point</th>
<th>Dronedarone versus placebo Hazard ratio (95% Confidence Interval)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-primary end point: stroke, MI, systemic embolism, or CV death</td>
<td>2.29 (1.34-3.94)</td>
<td>0.002</td>
</tr>
<tr>
<td>Co-primary end point: death or unplanned CV hospitalisation</td>
<td>1.95 (1.45-2.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.94 (0.99-3.79)</td>
<td>0.049</td>
</tr>
<tr>
<td>CV death</td>
<td>2.11 (1.00-4.49)</td>
<td>0.046</td>
</tr>
<tr>
<td>Arrhythmic death</td>
<td>3.26 (1.06-10.00)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.32 (1.11-4.88)</td>
<td>0.02</td>
</tr>
<tr>
<td>HF hospitalisation</td>
<td>1.81 (1.10-2.99)</td>
<td>0.02</td>
</tr>
<tr>
<td>HF event or hospitalisation</td>
<td>2.16 (1.57-2.98)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Notes to editor Sameer Bansilal, MD, MS, Christopher P. Cannon MD TIMI Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 350 Longwood Avenue, 1st floor office suites, Boston, MA 02115, USA. Authors disclosures: None declared.

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17. European Medicines Agency, Multaq product information 2011
Dexmedetomidine: Therapeutic Use for the Termination of Reentrant Supraventricular Tachycardia

Constantinos Chrysostomou, Victor O. Morell, Peter Wearden, Joan Sanchez-de-Toledo, Edmund H. Jooste, Lee Beerman.

Objectives.

The current drug of choice for reentrant supraventricular tachycardia (SVT) is adenosine followed by verapamil or diltiazem. Although limitations and significant adverse events have been encountered over the years, an alternative effective and safe agent has not been available. Dexmedetomidine has recently been shown to have potential antiarrhythmic effects, and here we describe our experience in the acute termination of reentrant SVT.

Design.

Retrospective case series.

Setting:

Quaternary University Children's Hospital, Cardiac Intensive Care Unit.

Patients:

Patients who received dexmedetomidine for SVT in the past 5 years.

Interventions:

None.

Outcome Measures:

SVT episodes terminated with dexmedetomidine were compared with episodes terminated with adenosine.

Results.

Fifteen patients, median age of 10 days (6–16), were given 27 doses of dexmedetomidine, mean dose 0.7 ± 0.3 mcg/kg, for a total of 27 episodes of SVT. Successful termination occurred in 26 episodes (96%) at a median time of 30 seconds (20–35). Duration of sinus pause was 0.6 ± 0.2 seconds, there was one episode of hypotension and no bradycardia and sedation lasted for 34 ± 8 minutes. Five patients received 27 doses of adenosine, with an overall successful cardioversion in 17 patients (63%) (P=.0017). Transient bradycardia and hypotension was seen in three patients (11%), agitation in 16 patients (59%), and broncospasm in one patient. Median sinus pause was 2.5 seconds (2–9) (P < .001).

Conclusions.
Dexmedetomidine appears to have novel antiarrhythmic properties for the acute termination of reentrant SVT. Although adenosine is very effective, dexmedetomidine may prove to possess a more favorable therapeutic profile with increased effectiveness and fewer side effects.

Dexmedetomidine, a selective and potent α2-adrenoceptor agonist, was approved by the US Food and Drug Administration in 1999 for sedation of patients hospitalized in intensive care settings. Since then, a growing number of research articles have emerged reporting other possible indications, such as regional and general anesthesia (7, 8). Dexmedetomidine was reported to be effective in protecting against focal ischemia in rabbits, in cardiac I/R injury in rats in kidney I/R injury in rats, and in incomplete forebrain ischemia in rats (9–12). Despite its increased clinical use, frequently in critically ill patients, the effect of dexmedetomidine on liver I/R injury has not been yet investigated (13).
DIG revisited: Digoxin scrutinized anew for chronic heart failure.

Subgroup data from a 15-year-old trial, publicly released for the first time, suggests an old drug has potential for broader use in chronic heart failure even in the modern age of multidrug neurohormonal blockade, according to a presentation here at the Heart Failure Congress 2012 sessions of the European Society of Cardiology Heart Failure Association [sources].

More than half of the 6800 patients with systolic HF randomized in the placebo-controlled Digitalis Investigation Group (DIG) trial [2] fell into three high-risk subgroups, and in all three, HF-related mortality or hospitalization fell off significantly over two years for patients receiving digoxin. The composite of all-cause mortality or hospitalization also declined significantly but less sharply.

But mortality didn't figure much in either of the two benefits, which were driven primarily by fewer hospitalizations with digoxin, observed Dr Mihai Gheorghiade (Northwestern University Feinberg School of Medicine, Chicago, IL) when presenting the prespecified DIG high-risk subgroup analysis. That's consistent with the overall trial's negative outcome for its primary end point, all-cause mortality on its own.

Still, when HF-specific events are figured into the outcomes, he emphasized, the risk reductions were "robust" for all three high-risk subgroups: those in NYHA class 3 or 4, with an LVEF <25%, or with a cardiothoracic ratio (CTR) >55.

The FDA considered the high-risk-subgroup data when it approved digoxin for heart failure in 1998, according to Gheorghiade, yet the findings have never before been published or presented at a meeting. But he cautions against generalizing them to contemporary practice, as all patients in DIG were on ACE inhibitors and diuretics but few, if any, were on beta blockers or aldosterone antagonists.

Still, he said, "Based on this data, and this is consistent with the guidelines, I think digoxin therapy should be considered in patients who continue to have signs and symptoms in spite of available therapies. But this is not happening. There are many patients who continue to have signs and symptoms at my own institution, and digoxin is not even considered."

Maybe we should also have it in our minds for those intolerant of beta blockade.

As the featured discussant for Gheorghiade's presentation, Prof Theresa A McDonagh (King's College Hospital, London, UK) said the subanalysis "should have us revisit our thoughts about digoxin in heart failure." The drug has fallen out of favor in HF since DIG with the broadened use of neurohormonal blocking agents, but also "maybe because DIG was performed in the era of the all-cause-mortality trials and seen as a failed trial because it missed its primary end point. Since then, digoxin is no longer seen as a first-line therapy and has been relegated from the premier league of drugs for reduced-ejection-fraction heart failure."

The guidelines still say it should be considered for low-LVEF patients with heart failure "who have deteriorating symptoms despite conventional contemporary heart-failure treatment."

And, she added, "maybe we should also have it in our minds for those intolerant of beta blockade."
DIG prespecified high-risk-subgroup analysis: Hazard ratios (95% CI), p, for composite end points that include hospitalization

<table>
<thead>
<tr>
<th>End points</th>
<th>NYHA 3-4, n=2223</th>
<th>LVEF&lt;25%, n=2256</th>
<th>CTR &gt;55%, n=2345</th>
<th>Any of the 3 high-risk features, n=4367</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality or hospitalization</td>
<td>0.88 (0.80-0.97); p=0.012</td>
<td>0.84 (0.76-0.93); p=0.001</td>
<td>0.85 (0.77-0.94); p=0.002</td>
<td>0.87 (0.81-0.94); p&lt;0.001</td>
</tr>
<tr>
<td>Heart-failure-related mortality or hospitalization</td>
<td>0.65 (0.57-0.75); p&lt;0.001</td>
<td>0.61 (0.53-0.71); p&lt;0.001</td>
<td>0.65 (0.57-0.75); p&lt;0.001</td>
<td>0.66 (0.59-0.73); p&lt;0.001</td>
</tr>
</tbody>
</table>

CTR=cardiothoracic ratio

According to Gheorghiade, studies should explore whether digoxin should also have a role for patients hospitalized for heart failure, "where the event rate is unacceptably high in spite of available therapy."

Dr Piotr Ponikowski (Medical University, Clinical Military Hospital, Wroclaw, Poland) told the press that he agrees that DIG was performed in a previous era and "today we have a completely different population, because most of our patients are on neuroendocrine blockade." But the "reassuring" and "promising" DIG subgroup analysis should help revitalize interest in the drug for heart failure, he said. "I strongly believe we may need to revisit the data again in the contemporary population."

Often forgotten, according to Ponikowsky, is that digoxin lowers heart rate and so "is not just an inotrope." But it also has well recognized adverse side effects. "Obviously in ivabradine [Procoralan, Servier], which also lowers the heart rate, we have something powerful in our hands. The data are very clear that [it leads to] reductions in hospitalization and in heart-failure death, and the safety profile is also very encouraging—which gives us a little bit less enthusiasm for digoxin."


Gheorghiade discloses consulting for Bayer Healthcare, Abbott, Astellas, AstraZeneca, CorThera, Cytokinetics, DebioPharm, Errekappa Terapeutici, GlaxoSmithKline, Johnson & Johnson, Medtronic, Merck, Novartis, Otsuka, Pericor Therapeutics, Protein Design, Sanofi, Sigma Tau, Solvay, and Takada. McDonagh had no disclosures. Ponikowsky discloses consulting for Abbott Vascular
Older men's performance on a drawing exercise outperformed other neuropsychological tests for predicting an increased mortality risk among those who subsequently had strokes, Swedish investigators reported.

Poorer performance on Trail Making Test-A (TMT-A) almost doubled the risk of death during a median poststroke follow-up of 2.5 years (HR 1.88 per SD, 95% CI 1.31 to 2.71, \(P=0.001\)). Patients who performed the worst on the TMT-A had almost a three times greater mortality risk compared with patients who had the best scores on the test prior to stroke (HR 2.90 per SD, 95% CI 1.24 to 6.77, \(P=0.014\)).

**Action Points 1** Note that in this community-based study of Caucasian males, executive performance prestroke measured with Trail Making Test (TMT)-A and -B strongly predicts mortality after stroke.

**Action Points 2** However, cognitive testing with Mini-Mental State Examination was not related to the risk of poststroke mortality.

Similar differences were observed on the TMT-B but not a general screening test of cognitive function, according to an article published online in *BMJ Open*.

"Remarkable in this study ... is that the risk related to the tests seem to exist separately, beside the track of traditional stroke factors," Bernice Wiberg, MD, of Uppsala University in Sweden, and co-authors wrote of their findings.

"Thus, TMT-A and -B, easily accessible cognitive tests for clinical use, may not only be used as tools for identifying risk of stroke but may also be considered important predictors of poststroke mortality," they added.

The findings came from an ongoing investigation of risk factors for stroke. Previously, investigators reported that a poor performance on the TMT-B at age 70 predicted an increased stroke risk, particularly brain infarction (*Neurology* 2010;74:379-385). Lower test scores probably reflected subclinical cognitive deficits related to undiagnosed cerebrovascular disease, the authors wrote.

The study involved 155 participants in the Uppsala Longitudinal Study of Adult Men, followed for as long as 14 years after a first stroke or transient ischemic attack (TIA). The stroke patients were among 919 study participants who completed a battery of cognitive function tests at age 70, before any of the strokes occurred.

The TMT-A is a timed exercise that requires a participant to draw lines between numbers in ascending order. The TMT-B includes letters and numbers, and participants draw lines alternating between letters and numbers in ascending order.

The maximum time allowed to complete the TMT-B was 240 seconds, and 41 of men in the Uppsala study reached that level. Longer completion time reflects impaired psychomotor function, the authors noted in their background.

The primary outcome of the analysis was mortality after a first stroke or TIA. The median follow-up to first stroke or TIA was 11.2 years.

During poststroke follow-up, 84 of the 155 (55%) men died, including 22 who died within 1 month of the stroke/TIA and 42 who died within the first year after the event. The diagnosis was brain infarction in 97 cases, intracerebral hemorrhage in 24, and TIA or undetermined in the remaining cases.
Adjusted analyses identified three prestroke variables that predicted an increased mortality risk after stroke: diabetes (HR 1.67, \( P=0.035 \)), use of antihypertensives (HR 1.56, \( P=0.042 \)), and ECG evidence of left ventricular hypertrophy (HR 1.88, \( P=0.035 \)). The same three factors predicted poststroke mortality risk in the subgroup of patients with brain infarctions.

After controlling for age, education, social group, and traditional stroke risk factors, the investigators found that a poor performance on the TMT-A was associated with a mortality hazard of 1.88 \( (P=0.001) \). Comparison of patients in the highest and lowest tertiles for TMT-A scores yielded an even higher mortality risk (HR 2.90, \( P=0.014 \)).

Poor performance on the TMT-B was associated with an overall mortality hazard of 2.01 \( (P=0.002) \), and comparison of patients with the highest and lowest scores resulted in a hazard ratio of 3.53 \( (P=0.021) \). The MMSE was not associated with mortality risk in any of the analyses.


The study was supported by Uppsala University and by STROKE-Riksforbundet. Wiberg had no disclosures. Co-authors disclosed relationships with Itrim and AstraZeneca.
Long-Term Outcome of Catheter Ablation in Patients with Atrial Fibrillation Originating from the Superior Vena Cava.


Long-Term Outcome of Catheter Ablation in Patients with Atrial Fibrillation Originating from the Superior Vena Cava.

Long-Term Outcome of SVC AF Ablation
Introduction: Data of the long-term clinical outcome after superior vena cava (SVC) isolation are limited. We aimed to evaluate the long-term outcome in patients with atrial fibrillation (AF) who had triggers originating from the SVC and received catheter ablation of AF.

Methods and Results:
The study consisted of 68 patients (age 56 ± 12 years old, 32 males) who underwent the ablation procedure for drug-refractory, symptomatic paroxysmal AF originating from the SVC since 1999. Group 1 consisted of 37 patients with AF initiated from the SVC only, and group 2 consisted of 31 patients with both SVC and pulmonary vein (PV) triggers. During a follow-up period of 88 ± 50 months, the AF recurrence rate was 35.3% after a single procedure. The freedom-from-AF rates were 85.3% at 1 year and 73.3% at 5 years. In the baseline study, group 2 had larger left atrium (38 ± 4 mm vs 36 ± 5 mm, P = 0.04), left ventricle (50 ± 5 mm vs 46 ± 5 mm, P = 0.003), and PV diameters. Kaplan-Meier survival analysis showed a higher AF recurrence rate in group 2 compared to that in group 1 (P = 0.012). The independent predictor of an AF recurrence was a larger SVC diameter (P = 0.02, HR 1.4, 95% CI 1.1-1.8).

Conclusion:
Among the patients with paroxysmal AF originating from the SVC, 73% remained free of AF for 5 years after a single catheter ablation procedure. Superior vena cava isolation without PV isolation is an acceptable therapeutic strategy in those patients with AF originating from the SVC only. The SVC diameter was an independent predictor of AF recurrence.

PMID: 22554079 // Division of Cardiology, Taipei Veterans General Hospital, Taipei, Taiwan Division of Cardiology, Cheng Hsin General Hospital, Taipei, Taiwan Institute of Clinical Medicine and Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan Division of Cardiology, Chi-Mei Medical Center, Tainan, Taiwan Division of Cardiology, Department of Internal Medicine, National Defense Medical Center and Tri-Service General Hospital, Taipei, Taiwan National Yang-Ming University Hospital, Yi-Lan, Taiwan.
Late atrial tachycardia following pulmonary vein isolation: Analysis of successful discrete ablation sites

Franco Zoppo, G Brandolino, F Zerbo, E Bertaglia.
Late atrial tachycardia following pulmonary vein isolation: Analysis of successful discrete ablation sites

Background

The role of additional left atrial linear lesions performed during pulmonary vein isolation (PVI) to prevent atrial tachycardias (ATs) is not yet clear.

Objective

To analyse successful ablation sites of late-onset post-PVI AT, and to understand whether additional ablation lines at mitral isthmus and left atrium (LA) roof could have been useful in preventing these jatrogenic ATs.

Methods

From March, 2002 to August, 2008, 366 patients underwent PVI alone for drug-refractory atrial fibrillation (AF). Twenty-six (7.1%) of these patients developed late AT during follow-up, and were referred for ablation. Successful discrete ablation sites were analysed. In no patient the index AT was terminated by a linear lesion in mitral isthmus or LA roof.

Results

Twenty-seven ATs were mapped; mean CL was 261±71.6 ms. In 3/26 patients (11.5%), mapping was unsuccessful, while 23/26 (88.5%) patients underwent a successful procedure (24 AT morphologies in 23 patients — 3/24 were mapped as mitral isthmus, and 1/24, as LA roof-dependent AT).

Among the 24 successfully mapped ATs, 17/24 (70.8%) displayed a macroreentrant activation and the remaining 7/24 (29.1%), a focal pattern.

Finally, in 22/26 (84.6%) patients, ATs were no more inducible. At a mean f/u of 22.4±12.2 months, 23/26 (88.4%) patients remained AT-free (antiarrhythmic drugs prescribed in 5/26, 19.2% patients for AF prevention).

Conclusions

In our case series, less than one-fifth of late-onset post-PVI ATs were mapped as mitral isthmus- or LA roof-dependent circuits.
Failed heart rate control with oral metoprolol prior to coronary CT angiography: effect of additional intravenous metoprolol on heart rate, image quality and radiation dose.

Jiménez-Juan L, Nguyen ET, Wintersperger BJ, Moshonov H, Crean AM, Deva DP, Paul NS, Torres FS.

Failed heart rate control with oral metoprolol prior to coronary CT angiography: effect of additional intravenous metoprolol on heart rate, image quality and radiation dose.


The purpose of this study was to evaluate the effect of intravenous (IV) metoprolol after a suboptimal heart rate (HR) response to oral metoprolol (75-150 mg) on HR control, image quality (IQ) and radiation dose during coronary CTA using 320-MDCT. Fifty-three consecutive patients who failed to achieve a target HR of < 60 bpm after an oral dose of metoprolol and required supplementary IV metoprolol (5-20 mg) prior to coronary CTA were evaluated. Patients with HR < 60 bpm during image acquisition were defined as responders (R) and those with HR ≥ 60 bpm as non-responders (NR). Two observers assessed IQ using a 3-point scale (1-2, diagnostic and 3, non-diagnostic). Effective dose (ED) was estimated using dose-length product and a 0.014 mSV/mGy.cm conversion factor. Baseline characteristics and HR on arrival were similar in the two groups. 58 % of patients didn't achieve the target HR after receiving IV metoprolol (NR). R had a significantly higher HR reduction after oral (mean HR 63.9 ± 4.5 bpm vs. 69.6 ± 5.6 bpm) (p < 0.005) and IV (mean HR 55.4 ± 3.9 bpm vs. 67.4 ± 5.3 bpm) (p < 0.005) doses of metoprolol. Studies from NR showed a significantly higher ED in comparison to R (8.0 ± 2.9 vs. 6.1 ± 2.2 mSv) (p = 0.016) and a significantly higher proportion of non-diagnostic coronary segments (9.2 vs. 2.5 %) (p < 0.001). 58 % of patients who do not achieve a HR of <60 bpm prior to coronary CTA with oral fail to respond to additional IV metoprolol and have studies with higher radiation dose and worse image quality.

PMID:22527260 / Cardiothoracic Division, Department of Medical Imaging, Toronto General Hospital, University Health Network, Toronto, ON, Canada.
FDA Drafts Rules to Cut Radiation Exposure in Kids

WASHINGTON -- The FDA is proposing that makers of ionizing radiation devices add labels warning against use on children unless they have shown the devices are safe for pediatric use.

The requirement is part of proposed regulations announced Wednesday for pediatric use of x-ray imaging devices.

The FDA noted in a statement that ionizing radiation -- the type emitted by CT, fluoroscopy, and conventional x-ray imaging devices -- poses a greater cancer risk per unit dose in pediatric patients than in adults, and that patients receiving diagnostics from such devices at a young age have an additive exposure over the course of a lifetime.

They added that the amount of radiation required for an adult diagnostic scan may be larger than that required to diagnose a younger patient, resulting in a larger dose of radiation than is necessary.

"Properly used, x-ray imaging devices offer minimal exposure risks to pediatric patients. What the FDA is trying to do, however, has great merit in that the agency wants to make it much easier for x-ray technologists doing examinations on children to plan and perform those exams with the most efficiency at the least dose," Christopher Cassady, MD, chair of the section on radiology at the American Academy of Pediatrics, said in an email to MedPage Today.

In February 2010, the FDA launched a website outlining the risks and benefits to pediatric x-ray imaging. The agency also has allied with the Alliance for Radiation Safety in Pediatric Imaging and the Medical Imaging and Technology Alliance to develop safety materials for pediatric x-ray device use, the statement said.

The FDA will host a workshop on July 16 for industry, healthcare professionals working with x-ray imaging, and patient advocates to discuss the proposed guidelines.

The collaboration between groups is a positive step forward in reducing risks and increasing the safety profile of these radiation-emitting devices, Cassady added.

The agency is accepting public comment on the proposed regulations through early September.
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KCNJ8 mutation associated with early repolarization and atrial fibrillation

Jessica T. Delaney, R Muhammad, MA Blair, K Kor, FA Fish, DM Roden, D Darbar.

KCNJ8 mutation associated with early repolarization and atrial fibrillation

Aim
The Kir 6.1 K<sub>ATP</sub> channel is believed to play an important role in ventricular repolarization as determined from both functional and genetic studies of the potassium inwardly-rectifying channel, subfamily J, member 8 (KCNJ8)-S422L missense mutation in patients with J-wave syndromes. Although Kir6.1 is also present in atrial tissue, it is unknown whether this channel modulates atrial repolarization and hence whether the S422L mutation portends a greater risk of atrial arrhythmias. This study sought to examine whether there was an increased frequency of the KCNJ8-S422L mutation among patients with atrial fibrillation (AF) and early repolarization (ER) as a possible novel susceptibility gene for AF.

Methods and results
A total of 325 lone AF probands were identified from the Vanderbilt AF Registry, a collection of clinical data and DNA from consented, consecutively enrolled participants. The coding regions of KCNJ8 were sequenced, and the patient's presenting electrocardiogram (ECG) was reviewed by two independent physicians for ER abnormalities. The KCNJ8-S422L mutation was identified in two AF probands while no other candidate gene variants were identified in these cases. Twenty-two (7%) patients were found to have ER on the ECG, including the two probands carrying the S422L variant. In one small AF kindred, the S422L variant co-segregated with AF and ER.

Conclusions
The KCNJ8-S422L variant is associated with both increased AF susceptibility and ER, indicating a role for Kir 6.1 K<sub>ATP</sub> channel in both ventricular and atrial repolarization.

+ Author Affiliations Departments of Medicine and Pediatrics, Vanderbilt University Medical Center, Nashville, TN, USA *Corresponding author. Dawood Darbar, Division of Cardiovascular Medicine, Vanderbilt University School of Medicine, Room 1285A, MRB IV, Nashville, TN 37232-6602, USA. Tel: +1 615 936 3058; fax: +1 615 322 8818, Email: dawood.darbar@vanderbilt.edu Received February 14, 2012. Accepted April 7, 2012. Key words Atrial fibrillation Early repolarization KCNJ8 Kir6.1 Mutation/
Junctional bradycardia with verapamil in renal failure - care required even with mild hyperkalaemia.


Treatment for hypertension with verapamil has a favourable renoprotective effect and is generally considered safe in patients with mild to moderate renal failure. In this report, we highlight the vulnerability of patients with mild to moderate renal failure to verapamil side effects especially in the presence of hyperkalaemia. Case summary and what is new: verapamil therapy in the presence of mild hyperkalaemia in patients with mild to moderate chronic renal failure. Verapamil and hyperkalaemia may synergistically increase the vulnerability to atrioventricular conduction delay. Conclusion: Renal failure patients with baseline mild hyperkalaemia are particularly liable to bradyarrhythmias with SR verapamil. In such cases, we would recommend verapamil dose reduction and avoidance of SR formulation. In cases of verapamil toxicity, actively treating any level of hyperkalaemia is recommended.

Medical Department, Al Adan Hospital, Hadeya, Kuwait Cardiology Department, Al Adan Hospital, Hadeya, Kuwait.
Attention Points

- Angiotensin is well known to have remodeling effects on cardiac tissue that have been associated with the development of atrial fibrillation.
- Blockade of the renin-angiotensin system has been shown to counteract these pathogenic effects; however, clinical trials are inconclusive at this time.

While the precise cause of atrial fibrillation (AF) has not yet been definitively elucidated, structural remodeling (for example, left atrial dilation and fibrosis) and electrical remodeling are thought to play central roles. Other factors believed to contribute to the triggering of AF include: volume changes, increased afterload states, and hypertension. Against this background, blockade of the renin-angiotensin system (RAS) has received much interest as a potential strategy for preventing and treating AF.

Angiotensin is well known to increase left atrial pressure through increased left ventricular end-diastolic pressure. Conversely, a well-known effect of angiotensin converting enzyme (ACE) inhibitors is a reduction of left atrial pressure. Additionally, angiotensin receptor blockers (ARBs) have been shown to demonstrate similar reductions in left atrial pressure in animal models.

Fibrosis plays a key role in causing conduction abnormalities that contribute to the development of AF—and angiotensin is known to be proinflammatory, profibrotic, and causative of cardiac fibroblast proliferation. RAS blockade has been shown to inhibit fibrosis.

Electrical remodeling refers to changes to cardiac tissue that promulgate arrhythmia. One electrical abnormality that has been associated with an increased susceptibility to AF is a shortening of the refractory period of the cardiac action potential. Nakashima and colleagues, in dog models, have shown that RAS blockade inhibits such shortening.

These physiologic data support the ability of RAS blockade to effect change at the tissue and organ level. In both animals and humans, RAS blockade (via either an ACE inhibitor or an ARB) has been shown to provide both beneficial structural change and beneficial electrical remodeling. However, the clinical value of RAS blockade in preventing or treating AF has remained unclear, as trials have generated conflicting results.

In an attempt to clarify, Schneider and colleagues conducted a meta-analysis of 23 randomized controlled trials encompassing 87,048 patients. While individual trial results were not prospectively designed to demonstrate a reduction in AF, the results of the meta-analysis were notable. Overall, RAS blockade reduced by 33% the risk of developing AF (both primary and secondary prevention of recurrent AF). In the primary prevention of AF in patients with heart failure, risk was reduced by 48%. However, no significant benefit was found in the primary prevention of AF in patient subgroups with hypertension or post myocardial infarction. In the secondary prevention of recurrent AF, RAS blockade reduced risk by 45% to 63%.

In summary, there is compelling evidence suggesting that RAS blockade with either ACE inhibitors or ARBs may have a place in the prevention or treatment of AF. Future studies will be invaluable in definitely determining the answer to this meaningful clinical question.
are either underway or in design to evaluate ARBs in the secondary prevention of paroxysmal AF; to evaluate RAS blockade in patients undergoing cardiac surgery; and to evaluate RAS blockade in patients with hypertension and permanent pacemakers.6

References:

Increased temporal dispersion of myocardial repolarization in myotonic dystrophy Type 1: Beyond the cardiac conduction system

Damiano Magri, G Piccirillo, E Bucci, G Pignatelli, F Maria Cauti, S Morino, P Latino, D Santini, F Marrara, M Volpe, G Antonini, M Testa.

Increased temporal dispersion of myocardial repolarization in myotonic dystrophy Type 1: Beyond the cardiac conduction system

Background and objectives

The most frequently mechanism underlying sudden cardiac death in myotonic dystrophy type 1 (DM1) is bradyarrhythmias due to cardiac conduction abnormalities. However the risk of ventricular tachyarrhythmias remains a concern in clinical management as well as in its determinant. We therefore assessed autonomic nervous system activity aiming to disclose differences in the QT variability index (QTVI)—a marker of temporal myocardial repolarization lability—between DM1 patients and healthy controls. We also investigated the possible differences within DM1 patients by subdividing them according either to the presence of first degree atrioventricular block (1st AVB) or to the cytosine–thymine–guanine (CTG) repeat expansion size.

Methods

Sixty-two DM1 patients and 20 healthy subjects underwent neurological and cardiological examinations, the latter including ECG, echocardiography and 24-hour Holter monitoring. All underwent a 5-minute ECG recording to assess heart rate variability power spectral components, and the QTVI values.

Results

Power spectral data, namely total power, low frequency power and high frequency power, were lower, whereas QTVI values were higher in DM1 patients than in controls (p<.0001). Higher QTVI values were found in DM1 subgroups with 1st AVB (p=.009) and more than 500 CTG repeat (p=.014) with respect to DM1 patients without 1st AVB and CTG<500. Spectral data did not significantly differ. At multivariable analysis, QTVI and age were independently associated with PR interval and CTG repeat.

Conclusions

The increased values of QTVI argue in favour of an important heart involvement extending beyond the conduction system. Whether QTVI could be useful in predicting clinical course of DM1 clearly requires larger prospective studies.

Keywords: QT variability, Heart rate variability, Power spectral analysis, Autonomic nervous system, Myotonic dystrophy type 1, Ventricular arrhythmias // Cardiology Department, S. Andrea Hospital, "Sapienza" University of Rome, Rome, ItalyCorresponding author. Cardiology Department, S. Andrea Hospital, "Sapienza" University of Rome, Rome, Italy. Tel.: +39 0 6 33775561 63. Aging Department, Umberto I Hospital, "Sapienza" University of Rome, Rome, Italy Cardiology Department, S. Andrea Hospital, "Sapienza" University of Rome, Rome, Italy. Tel.: +39 0 6 33775561 63. Aging Department, Umberto I Hospital, "Sapienza" University of Rome, Rome, Italy Cardiology Department, S. Andrea Hospital, "Sapienza" University of Rome, Rome, Italy Cardiology Department, S. Andrea Hospital, "Sapienza" University of Rome, Rome, Italy Neurology Department, S. Andrea Hospital, "Sapienza" University of Rome, Rome, Italy. Tel.: +39 0 6 33775561 63. Aging Department, Umberto I Hospital, "Sapienza" University of Rome, Rome, Italy Cardiology Department, S. Andrea Hospital, "Sapienza" University of Rome, Rome, Italy Received 19 July 2010; received in revised form 4 October 2010; accepted 31 October 2010. published online 29 November 2010.
Fernández-Armenta J, Berruezo A, Ortiz-Pérez JT, Mont L, Andreu D, Herczku C, Boussy T, Brugada J.
Improving safety of epicardial ventricular tachycardia ablation using the scar dechanneling technique and the integration of anatomy, scar components, and coronary arteries into the navigation system.
Arrhythmia Section, Cardiology Department, Thorax Institute, Hospital Clinic, C/Villarroel 170, Barcelona, Spain. berruezo@clinic.ub.esPMID: 22431889
Idiopathic PVC and VTachys originating from the vicinity of tricuspid annulus: Results of RFCA in 35 pts

Li Yue-Chun, Zhang Wen-Wu, Zhou Na-Dan, Zhang Teng, Wang Pin-Xiao, Ge Bei, Li Jia, Ji Kang-Ting and Lin Jia-Feng

Background

In recent years, catheter ablation has increasingly been used for ablation of idiopathic premature ventricular complexes (PVCs) or ventricular tachycardias (IVTs). However, the mapping and catheter ablation of the arrhythmias originating from the vicinity of tricuspid annulus (TA) may not be fully understood. This study aimed to investigate electrophysiologic characteristics and effects of radiofrequency catheter ablation (RFCA) for patients with symptomatic PVCs and IVTs originating from the vicinity of TA.

Methods

Characteristics of body surface electrocardiogram (ECG) and electrophysiologic recordings were analyzed in 35 patients with symptomatic PVCs/IVTs originating from the vicinity of TA. RFCA was performed using pace mapping and activation mapping.

Results

Among the 35 patients with PVCs/IVTs arising from the vicinity of TA, complete elimination of PVCs/IVTs could be achieved by RFCA in 32 patients (success rate 91.43%) during a median follow-up period of 21 months. PVCs/IVTs originating from the vicinity of TA had distinctive ECG characteristics that were useful for identifying the precise origin. An rS pattern was recorded in lead V1 in 93.1% of patients with PVCs/IVTs from the free wall of TA, vs 16.7% of patients with PVCs/IVTs from the septal TA, whereas a QS pattern in lead V1 occurred in 83.3% of patients with PVCs/IVTs from the septal TA vs 6.9% of patients with PVCs from the free wall of the TA. The precordial R wave transition occurred by lead V3 or earlier in all patients with PVCs/IVTs originating from the septal portion of the TA, as compared to transition beyond V3 in all patients with PVCs/IVTs from the free wall of the TA.

Conclusions

RFCA is an effective curative therapy for symptomatic PVCs/IVTs originating from the vicinity of TA. There are specific characteristics in ECG and the ablation site could be located by ECG analysis.
Incomplete Endothelialization of Left Atrial Appendage Occlusion Device 10 Months After Implantation

LUCA MASSARENTI, ALAADDIN YILMAZ.
Incomplete Endothelialization of Left Atrial Appendage Occlusion Device 10 Months After Implantation

Incomplete Endothelialization of Left Atrial Appendage. We describe the case of a 74-year-old man with Rendu Osler Weber syndrome affected by permanent atrial fibrillation, who underwent percutaneous placement of a 24-mm Watchman left atrial appendage system. After anticoagulation therapy dismissal, he had a transient ischemic attack (TIA). Therefore he underwent surgical removal of the device, ablation of atrial fibrillation with Maze IV procedure and biatrial reduction. Very interestingly, no significant endothelialization of the device was observed 10 months after implantation. In conclusion, this case is important because, to our knowledge, it is the first finding of Watchman device with lack of endothelialization.

Keywords: anticoagulation; atrial fibrillation; left atrial appendage; stroke; Watchman device
Left atrial thickness under the catheter ablation lines in patients with paroxysmal atrial fibrillation: insights from 64-slice multidetector computed tomography

Kazuyoshi Suenari, Yukiko Nakano, Yukoh Hirai, Hiroshi Ogi, Noboru Oda, Yuko Makita, Shigeyuki Ueda, Kenta Kajihara, Takehito Tokuyama, Chikaaki Motoda, et al.

Left atrial thickness under the catheter ablation lines in patients with paroxysmal atrial fibrillation: insights from 64-slice multidetector computed tomography


A detailed understanding of the left atrial (LA) anatomy in patients with atrial fibrillation (AF) would improve the safety and efficacy of the radiofrequency catheter ablation. The objective of this study was to examine the myocardial thickness under the lines of the circumferential pulmonary vein isolation (CPVI) using 64-slice multidetector computed tomography (MDCT). Fifty-four consecutive symptomatic drug-refractory paroxysmal AF patients (45 men, age 61 ± 12 years) who underwent a primary CPVI guided by a three-dimensional electroanatomic mapping system (Carto XP; Biosense-Webster, Diamond Bar, CA, USA) with CT integration (Cartomerge; Biosense-Webster) were enrolled. Using MDCT, we examined the myocardial thickness of the LA and pulmonary vein (PV) regions in all patients. An analysis of the measurements by the MDCT revealed that the LA wall was thickest in the left lateral ridge (LLR; 4.42 ± 1.28 mm) and thinnest in the left inferior pulmonary vein wall (1.68 ± 0.27 mm). On the other hand, the thickness of the posterior wall in the cases with contact between the esophagus and left PV antrum was 1.79 ± 0.22 mm (n = 30). After the primary CPVI, the freedom from AF without any drugs during a 1-year follow-up period was 78 % (n = 42).

According to the multivariate analysis, the thickness of the LLR was an independent positive predictor of an AF recurrence (P = 0.041). The structure of the left atrium and PVs exhibited a variety of myocardial thicknesses in the different regions. Of those, only the measurement of the LLR thickness was associated with an AF recurrence.

Keywords Atrium – Atrial fibrillation – Catheter ablation – Computed tomography – Myocardial thickness
Long-term results of slow pathway ablation in patients with AVNRT: simple approach

Francisco Femenía, Mauricio Arce, Martín Arrieta, Jorge Palazzolo, Emilce Trucco.

Long-term results of slow pathway ablation in patients with atrioventricular nodal reentrant tachycardia: simple approach

Aims

The aim of this study was to report the short- and long-term results of slow pathway radiofrequency (RF) ablation in patients with atrioventricular (AV) nodal reentrant tachycardia (AVNRT) using a simplified approach (2 catheters and short applications of RF).

Materials and Methods

This was a retrospective study that included consecutive patients with AVNRT. We used an anatomical approach with only 2 catheters. Decremental AV nodal conduction and atrial-His conduction interval jump were measured. To detect the onset of the QRS, we used surface lead II. During the stimulation protocol, we performed S2-QRS and S3-QRS measurements. An increase in the S3-QRS3 interval of 50 milliseconds or greater in response to a decrease in the S2-QRS2 coupling interval of 10 milliseconds was defined as a discontinuous AV nodal function curve and taken as evidence of dual antegrade AV pathways. Atrioventricular nodal reentrant tachycardia was demonstrated by the presence of dual AV nodal physiology, atrial echoes, and tachycardia induction with a 1:1 AV relationship and a VA interval of less than 70 milliseconds. Short RF applications (10-15 seconds) were delivered at an intermediate point between the posteroseptal and medioseptal regions of the Koch triangle. The applications were considered effective when junctional rhythm appeared. The end point was the demonstration of slow pathway modification without AVNRT induction.

Results

Three hundred forty-four patients (age, 49.22 ± 17.47 years; 254 were female) were included. Discontinuous AV nodal function curves were found in 271 patients (78.77%), and short-term success was achieved in all patients. The anterograde jump in AV nodal conduction was abolished after RF in 222 patients (81.91%), and discontinuous AV nodal conduction and single AV nodal echo beats persisted in 49 cases (18%). The mean number of RF application was 7.79 ± 2.23, the mean number of effective applications was 4.63 ± 0.62, and the mean RF application time was 54.92 ± 8.03 seconds. The total procedure and fluoroscopy time was 29.45 ± 9.6 and 10.87 ± 2.36 minutes, respectively. After the procedure, all patients were followed up for a mean of 46.44 ± 18.89 months, and 7 patients (2%) presented AVNRT recurrences. Complications were observed in 4 patients (1.16%); no permanent AV block was observed.

Conclusion

In this study, slow pathway RF ablation using a simplified approach technique is an effective and safe approach for the treatment of AVNRT.

Keywords: Slow pathway ablation, Atrioventricular nodal reentrant tachycardia, Radiofrequency ablation, Simplified approach Corresponding author. Av. San Martín 965, Godoy Cruz, 5501 Mendoza, Argentina. Received 26 September 2011 published online 19 January 2012.
HRS 2012 poster highlights: ECGs, PVCs, OSA, Debates in AF ablation, and the dangers of cryoablation

ECG news: Place the darn leads correctly

A group from the University of North Carolina reports on the importance of placing leads correctly during routine ECG recordings in young athletes. The standard ECG calls for placing leads V1 and V2 in the fourth intercostal space. Sometimes, technicians place these leads higher. The researchers postulated that this might induce a Brugada-syndrome pattern. They were right. By doing two ECGs on each athlete, one with normal V1-V2 placement and the other with superiorly placed leads, they showed that a Brugada (incomplete RBB) pattern could be induced in one-third of the cases.

As many consider the merits of widespread ECG screening of young people, this study calls important attention to the correct placement of leads. We surely don't need any help creating more false-positive ECG interpretations.

PVC morphology and duration may matter

The patient with frequent premature ventricular contractions (PVCs) represents a common and tricky situation for both cardiologists and electrophysiologists. The question to treat the PVCs depends greatly on the presence or absence of cardiomyopathy. PVC-induced cardiomyopathy is neither rare nor well understood. Dr Frank Marchlinski's University of Pennsylvania group present data that shows the width of the PVC (>155 ms) and a terminal QRS delay in the PVC predicts the presence of cardiomyopathy. This finding also suggests "subclinical" cell-to-cell conduction abnormalities as a possible reason PVCs cause cardiomyopathy. This study adds nicely to similar findings published recently by the Michigan group.

Effects of metabolic syndrome and OSA on AF ablation results

If your patient has sleep apnea and metabolic syndrome, don't expect miracles from AF ablation. This is the message of a large study from Dr Natale's group. Only 35% of patients with both conditions (they often coexist) were free of AF at 34 months of follow-up.

Another abstract from a Spanish group showed that (in a rat model) obstructive sleep apnea (OSA) induces an increased deposit of collagen tissue in the atria. This physiology-intensive animal study suggests the association and AF and OSA may be mediated through fibrosis. Translation: Bad sleep induces heart scarring.

I mention these two abstracts because we specialists too often fail to emphasize the importance of primordial prevention of heart disease. What I mean is: to truly have an impact on the health of our patients, we must also pay attention to how well they sleep and how smartly they maintain their body weight. That's primordial—biology in the earliest stage.

On the best technique for ablating more advanced forms of AF

The great debate on left atrial appendage (LAA) isolation continues. Dr Natale's group persists in their attempt to convince the rest of the AF world that electrically isolating the left atrial appendage is a good idea. They say that encircling the LAA with extensive ablation improves the single procedure success rate in patients with advanced forms of AF. They presented data showing that patients who had standard ablation plus LAA isolation had a much higher three-year success rate.
Ah, but the problem here is that few other ablationists feel comfortable rendering the LAA noncontractile. For two reasons: One is that these patients must remain on anticoagulation. The other more important concern surrounds left atrial systole. Atria that are extensively ablated or markedly delayed (when LA activation follows the QRS) cannot contribute to cardiac output—and thus little is gained. Adding to these concerns are reports like this one, from the University of Pennsylvania, suggesting that the LAA is an infrequent source of non-pulmonary vein triggers. Their findings—made over a decade long experience—lead them to recommend against empirically isolating the appendage.

That's how complicated AF ablation is: One prominent group speaks of their maneuvers to avoid LAA isolation, while an equally prominent group recommends trying to ablate it. Put me in the camp that likes to burn less.

**Scary stuff on cryoablation of AF**

A group from Bonn Germany courageously reports a single case of atrial-esophageal (A-E) fistula following a standard cryoballoon ablation. Four weeks after the index procedure, a 78-year-old patient suffered cerebral air embolism and despite surgical intervention remains in a coma. Although A-E fistula is a rare but well-described complication of radiofrequency ablation, the authors claim this is the first report of this terrible complication with cryo techniques.

My take on this is that it's not that surprising. Ultimately, whether one burns or freezes the left atrium, the esophagus remains in proximity. RF ablaters have learned to modulate power delivery when burning on the posterior wall of the LA. We worry about the esophagus—a lot. Perhaps we will need to learn similar maneuvers for cryoablation. This case, along with the perforation risk of stiff sheaths needed for cryoballoon delivery and the risk of phrenic nerve injury, strengthen the argument that cryo techniques—in their present form—do not offer an easy answer to ablation. To be fair, the published data on cryoablation of paroxysmal AF compares favorably with RF energy. There are even data suggesting cryo—done well—may result in more durable PV isolation.
Free Fatty Acids May Point to Atrial Fibrillation Risk

In a study of community-dwelling elderly, high plasma levels of free fatty acids (FFAs) were a risk marker for atrial fibrillation (AF).

Dr. Owais Khawaja of Brigham and Women's Hospital in Boston, who led the study, told Reuters Health by email, "Free fatty acids can provide information above and beyond that of standard AF risk factors. Therefore, if our findings are confirmed by others, FFA may help identify older individuals at risk of future AF."

In an April 12th online paper in the American Journal of Cardiology, Dr. Khawaja and colleagues said high FFA levels have been associated with increased insulin resistance, hypertension and physical inactivity - but until now this putative relationship with AF risk factors has "not been investigated in the general population including older adults, a group extremely vulnerable to AF."

The new study involved 4,175 men and women at least 65 years old who were members of the prospective Cardiovascular Health Study cohort. Plasma FFA was measured in 1992 and 1993.

During a mean follow-up of 10 years, there were 1,041 new cases of AF. Crude incidence rates of AF per 1000 person-years across quartiles of plasma FFAs were 23.7, 23.3, 23.9 and 29.7.

Multivariable adjusted hazard ratios ranged from 1.0 at the lowest quartile to 1.29 at the highest. This relationship remained when follow-up was restricted to 5 years.

Confirmation is needed, but in the meantime the findings may have some value, the researchers believe. "Although prevention of AF may be difficult," they write, "novel therapies are increasingly available to convert and maintain normal sinus rhythm, and earlier identification of patients with AF might allow earlier use of anticoagulants to avert cerebrovascular events."


Am J Cardiol 2012.
Graphical representation of QT rate correction formulae: an aid facilitating the use of a given formula and providing a visual comparison of the impact of different formulae

Derek J. Rowlands.
Graphical representation of QT rate correction formulae: an aid facilitating the use of a given formula and providing a visual comparison of the impact of different formulae

The QT interval on the electrocardiogram is an increasingly important measurement, especially in relation to drug action and interaction. The QT interval varies inversely as the heart rate and numerous rate correction formulae have been proposed. It is difficult to compare the effect of applying different formulae at different heart rates and for different measured QT intervals. A simple graphical display of the results from different formulae is proposed. This display is dependent on the concept of the absolute correction factor. This graphical presentation is useful (a) in comparing the effect of the application of different formulae and (b) in directly reading the correction produced by any individual formula.

The Beeches Consulting Centre, Mill Lane, Cheadle, Cheshire SK8 2PY, United Kingdom. Received 12 November 2011 published online 23 February 2012.
Hands off my wife! Bahrain AED survey points to CPR barriers. Controversial findings from a small, survey-based study conducted here in the Middle East suggest that Arab men would "not accept" men of certain other nationalities performing CPR, chest compressions, or exposing the chest area for the purpose of applying an automated external defibrillator (AED) on a female companion.

Women surveyed, however, had no such concerns as to the race or sex of their rescuer.

"For the Middle East, my recommendation would be that female rescuers are acceptable to all sexes," lead author on the study, Orla Merrigan, an Irish nurse working at Royal College of Surgeons Ireland-Medical University of Bahrain, in Manama, told heartwire. "So maybe in shopping malls, for example, where they've trained male security guards [in AED usage], maybe they need to train female rescuers as well."

Merrigan presented the study here today at the World Congress of Cardiology (WCC) 2012. The idea for the study, she said, came from a similar survey conducted in Korea showing that many more men than women are surviving cardiac arrest. One explanation from the Korean group was that AEDs are used far less frequently in women than men, for cultural reasons.

"Would you expose your female relative's chest area?"

Merrigan's nursing students surveyed 229 males and 116 females over three days asking them general questions about AEDs as well as presenting them with different scenarios, including photographed vignettes, in which men or women of Arab, Indian, and European descent were shown readying a man or a woman for cardiopulmonary resuscitation (CPR) and application of an AED. Responders were asked if they would accept a man "exposing your female relative's chest area" to perform CPR, performing an electric shock, or applying chest compressions in public.

Survey scores were roughly the same in the scenarios where the man was the victim or when a woman was the victim with an Arab rescuer and when the woman was the rescuer. However, "If the victim was a Muslim female, a high percentage of [Arab] Muslim males would not allow an Indian male to expose the chest or provide CPR or an AED," Merrigan said. "When we questioned couples separately, the woman was quite happy to be rescued—she didn't care what nationality the rescuer
was, they could do everything. But for males, they would not allow certain nationalities to help a woman in cardiac arrest."

Women, she added to heartwire, were shocked to hear their husbands' responses: "When we were doing these interviews with couples, the women were simply horrified that the man would let them die."

Male respondents were less concerned when the would-be rescuer was of European descent.

**A big gap, worth filling**

Merrigan points out that the recent CPR recommendations urge communities to look for "gaps and weaknesses" in their systems to better improve survival rates. "This is a big gap," she said. "We can always look at closing that."

AEDs, she noted, are rare in Bahrain, but "we have anecdotal evidence in Bahrain that when women have collapsed that people have not allowed them to receive CPR when the rescuers are male."

Several Gulf states and cities are stepping up requirements for AEDs in public places, including a Dubai plan to have AEDs on school buses. But even here, said Merrigan, problems could arise if an Indian male driver tried to apply the AED on a female student and a brother intervened. One solution she proposed to Dubai policy makers is to have female teaching assistants on the buses.

"Ethnicity has implications for the delivery and training of AED usage and the possible selection of who should be trained," she argued. "Arab countries may need to adapt new guidelines on the selection of rescuers to overcome this cultural barrier and improve the survival rate of out-of-hospital cardiac arrests. And any Arab country purchasing AEDs must ensure that a majority of female [emergency personnel] are also trained in AED use."

**Explaining the findings**

A trio of Emirati women in hijab who spoke with heartwire after the session—but did not want to be named in the story—were dismissive of the results. One insisted that, faced with a real-life situation in which a female relative was in cardiac arrest, no man would refuse lifesaving assistance for his wife or sister, no matter who was providing it.

Another pointed out that Islam as it is practiced in the Gulf permits a woman to be uncovered when seeing her doctor, and in the scenario described, the bystander performing CPR would be a proxy for a physician.

Cardiologist Dr Said Mohamed Al-Hina (Diwan Medical Services, Muscat, Oman) also discounted the findings, pointing out that in life-and-death situations, practices that are haram—forbidden—in Islam are permitted. "I'm a Muslim; if I am in a desert and there is no water, only alcohol, for my survival, my
faith allows me to drink alcohol. If you tell me there is no food and to survive, I must eat pork; I don't eat pork, but in this situation I'm allowed. There are exceptions."

He believes Merrigan's findings are more revealing about the lack of knowledge of CPR and sudden cardiac death in the Gulf than they are about race, religion, or culture. "I don't think it is an issue of the ethnicity of the male, it is more the belief that no man should expose a woman's chest in public, even the husband."

He continued, "If they just see a man coming and trying to expose a woman's chest, they don't understand the benefit and what the dangers are if it is not done. I'm sure if you educate the people to a level similar to, say, the American level of the importance of AEDs, they would accept it."

Indeed, Merrigan's research also showed that two-thirds of people surveyed had never heard of an AED or how it was used and were unaware there was a device that could be used by a layperson to help someone in cardiac arrest.

**Everywhere has CPR barriers**

Following Merrigan's presentation, one of the moderators asked Dr Michael Sayre (Ohio State University, Columbus) if there were any comparable cultural barriers to CPR/AED use in the US. Sayre pointed to studies showing that CPR is much less common in poorer, often African American neighborhoods.

"I participated in a focus group with some of the neighborhoods in my city. In one neighborhood that has issues with violence, one comment was: 'I don't want to do CPR because I don't want to get shot.' That was really unlikely, but there was a perception that it was a problem."

Others said they don't feel safe among their neighbors and so wouldn't feel comfortable intervening and that is "a cultural issue that is probably similar to other countries."

A final factor, Sayre said, is that most Americans learn CPR at work. "So if you are living in a poor neighborhood, you are less likely to have a job and less likely to have been trained in CPR. So there could be several layers to the problem."
Positive vote from FDA advisors for subcutaneous ICD

The FDA's Circulatory System Devices Panel voted seven to one in favor of Cameron Health's premarket approval application for its subcutaneously implanted defibrillator.

Gaithersburg, MD - Cameron Health's subcutaneous implantable cardioverter defibrillator (S-ICD) seems to be on its way to becoming the first completely subcutaneous implantable defibrillator available in the US after an FDA advisory panel endorsed the company's premarket approval application at its April 26, 2012 meeting [1].

Panelist Dr Ralph Brindis (Oakland Kaiser Medical Center, CA) said, "The opportunity to be able to have a device to, in particular, manage patients who have infections of transvenous [ICD] systems is a very important adjunct to the armamentarium"
Statin therapy prior to CABG reduces the risk of postoperative AF,

Statins administered prior to cardiac surgery significantly reduced the risk of postoperative atrial fibrillation and resulted in a significantly shortened length of stay in the intensive care unit (ICU), according to the results of a new meta-analysis [1]. Preoperative statin therapy had no effect on short-term mortality and postoperative stroke rates, however.

Overall, investigators are cautious in their interpretation of the results, noting that patients primarily were treated with atorvastatin and underwent CABG surgery, making extrapolations to other statins and different types of cardiac surgery difficult.

"Nonetheless, it appears reasonable and in compliance with existing guidelines to advocate an intensified preoperative statin treatment, followed by a rigorous postoperative reinitiation regimen, in all hyperlipidemic patients with multiple cardiac risks and coronary heart disease scheduled for cardiac surgery," write Dr Oliver J Liakopoulos (University of Cologne, Germany) and colleagues in a new review published online April 18, 2012 in the Cochrane Database of Systematic Reviews.

Data from randomized, controlled trials

As reported previously by heartwire, the researchers have published results from a larger meta-analysis of patients undergoing cardiac surgery pretreated with statins, but many of these studies were observational. That analysis showed a significant reduction in the risk of early mortality, stroke, and atrial fibrillation among surgery patients pretreated with a statin. As they noted at the time, few studies have examined the use of statin therapy in patients undergoing cardiac surgery, and the existing published studies had reported conflicting results.

The latest meta-analysis included 11 randomized, controlled clinical trials with 984 patients undergoing on- or off-pump CABG surgery. Of these studies, six included patients treated with 20 mg or 40 mg of atorvastatin, two studies treated patients with 20 mg of simvastatin, while the remaining three studies treated patients with fluvastatin 80 mg, rosuvastatin 20 mg, and pravastatin 40 mg, respectively. The duration of preoperative statin intake ranged from the night before surgery to four weeks prior to the operation. Only three studies reinitiated statin therapy following CABG.

Among seven trials that reported short-term mortality, either in-hospital or 30-day mortality, there was no effect of preoperative statin treatment observed when compared with patients who did not receive statin therapy. Eight studies included data on the incidence of atrial fibrillation during a median follow-up of 22.8 days. Among these studies, 19% of the statin-treated patients developed atrial fibrillation compared with 35.6% of patients who did not receive the lipid-lowering drug. This translated into a 60% relative reduction in risk (odds ratio 0.40; p=0.01) and number needed to treat of seven.

In nine studies with 897 participants, there was a trend toward a short-term reduction in the risk of MI, but the between-group difference failed to achieve statistical significance. There was also a trend toward a lower risk of renal failure, but again this difference did not reach statistical significance. There was no significant effect on stroke risk. Hospital length of stay in the ICU and in the hospital was
significantly reduced in the statin-treated patients, although significant heterogeneity in the studies was observed.

The researchers conclude that the empirical use of statins for all patients should wait until more evidence is collected. To date, the data include mainly CABG-treated patients, and "there is sparse evidence for a benefit of a statin therapy for high-risk patient subgroups and those undergoing other cardiac procedures (for example, valvular operations or combined procedures)." Given that many high-risk patients with multiple comorbidities are slated for CABG these days, there is a need for data on the safety and effectiveness of statins in this high-risk cohort, they write. Also, the questions of the most beneficial statin and the optimal timing of pretreatment remain unanswered.

Source

Time to retire the Holter monitor? Long-term cardiac rhythm monitoring comes of age
Reviewed Rhythm Zio Patch

What took so long? More than 60 years after the invention of the Holter monitor, new technologies are—finally!—stepping in to offer simple and innovative devices to monitor cardiac arrhythmias. Is this one a "keeper"?

Have you used this device? Share your comments below and vote in the "What's your verdict?" section at right.

Follow Dr Topol on Twitter: @erictopol

Dr Topol has no relationship with the manufacturer of this device.

Website: http://www.irhythmtech.com/zio-solution/zio-patch/index.html
Electrical alternans is evident. What is its clinical significance?

- a) Cardiac tamponade should be considered
- b) The basic rhythm is supraventricular tachycardia (SVT), in which case electrical alternans is not associated with cardiac tamponade
FDA Staff Doubt New Type of Defibrillator Will Be Better Than Rivals.

WASHINGTON (Reuters) - U.S. medical device reviewers said the first defibrillator designed to be implanted completely under the skin may cause more infections, and work less quickly, than similar devices with leads that must be implanted in the heart, raising doubts that Cameron Health Inc's novel product would attract patients.

The initial review from the U.S. Food and Drug Administration comes after Boston Scientific Corp, a leading maker of heart devices, agreed in March to buy privately held Cameron Health.

But analysts said the FDA staff review, released online on Monday, may not dent Cameron's chances to win U.S. approval for its device to treat irregular heartbeat.

Cameron's defibrillator has been sold in major European countries since 2009, and the FDA staff said on Monday that the company met safety and effectiveness goals during clinical trials - though they worried about its battery depletion issues.

A panel of outside advisers to the FDA is due to vote on the device on Thursday, and the FDA will make a final decision later.

Cameron Health said about 850,000 people in the United States are at risk of sudden cardiac arrest and are eligible for an implantable defibrillator. Like similar devices, Cameron Health's defibrillator delivers electric shocks. But its electrodes are threaded under the skin along the breastbone, rather than in the heart.

Cameron Health has said its device is easier to implant than transvenous leads because it does not require an X-ray machine, and it may also be safer because it is easier to remove than devices inside the heart when there are problems.

Michael Weinstein, analyst at J.P. Morgan, said the issues raised by the FDA staff should not prevent the device from being approved, but he questioned how many patients would want to use it.

For example, it is bigger than some other in-heart defibrillators and delivers stronger shocks, which can be more painful, he said in a research note.

"Our view remains that the Cameron (device), if approved, is likely to be niche product," David Roman, analyst at Goldman Sachs, wrote in a separate note.

FDA staff said in clinical trials, 97.9% of people implanted with Cameron Health's device had no complications with their device after 180 days. The device also converted heart quivers to a normal rhythm in 98.9% of patients, meeting the company's goals.

But the device reviewers said they would not approve it until the company resolved issues with a battery that depletes earlier than it should.

Cameron Health's defibrillator should be able to give about 21 shocks over its five-year life, but the FDA staff said there have been three cases of premature battery depletion since June 2011, when the company announced the issue.

The FDA staff said they would not ask panelists to discuss the battery depletion issue on Thursday.
The FDA reviewers also focused on "inappropriate" shocks from the Cameron Health device, when 30.7% of patients received an electric shock to the heart without having an overly fast heart rhythm or quiver of the heart muscles. This could cause the device to run out of power even earlier.
Pacemakers and Implantable Cardioverter Defibrillators

Basic Concepts

Introduction

Pacemakers and implantable cardioverter defibrillators (ICDs) have been in use for more than 20 years. With expanding indications and an ever-growing elderly population, emergency physicians must be familiar with emergent indications for their application, discontinuation, and complications arising from a patient's existing device. This article introduces the common problems encountered with pacemakers and ICDs (see image below), and rescue techniques that may aid in treating such complications.

Intermittent periods of ventricular capture.

The goal of this article is to orient the reader to the basic function and use of pacemakers/ICDs and important complications of such devices, thus allowing the ED clinician to better understand and troubleshoot the causes of pacemaker/ICD failure and initiate appropriate therapy. The patient's electrophysiologist/cardiologist can also be an invaluable resource in these cases and should be contacted early during the emergency department evaluation.

Pacemaker and ICD basics

Permanent pacemakers are implanted devices that provide electrical stimuli, thereby causing cardiac contraction when intrinsic myocardial electrical activity is inappropriately slow or absent. These devices sense intrinsic cardiac electric potentials, and, if too infrequent or absent, they transmit impulses to the heart to stimulate myocardial contraction.

An ICD is a specialized device designed to directly treat a cardiac tachydysrhythmia. If a patient has a ventricular ICD and the device senses a ventricular rate that exceeds the programmed threshold, the device may elect to perform antitachycardia pacing or defibrillation. With antitachycardia pacing, the device fires a preset number of rapid pulses in succession in an attempt to terminate the ventricular tachycardia. If unsuccessful or if the rate falls in the preprogrammed cut of rate, the device will perform a cardioversion/defibrillation.
Newer-generation ICDs are also equipped with a demand pacing system and are a combination of an ICD and a pacemaker. It is important to be aware that some older models (>10 years old) may lack this function.

**Pacemaker/ICD anatomy and insertion**

Pacing systems consist of a pulse generator and pacing leads. With permanent systems, endocardial leads are inserted transvenously and advanced to the right ventricle and/or atrium where they are implanted into the myocardial tissue. The pulse generator is placed subcutaneously or submuscularly in the chest wall.

Pulse generators contain a battery as well as sensing, timing, and output circuits. The battery (most commonly lithium-iodide) typically has a life span of 5-10 years. Pulse generators can be set to fixed-rate (asynchronous) or demand (synchronous) modes. In the asynchronous mode, impulses are produced at a set rate independent of intrinsic cardiac activity. This mode carries a small but inherent danger of producing lethal dysrhythmias should the impulse coincide with the vulnerable period of the T wave. In the synchronous mode, the sensing circuit searches for an intrinsic depolarization potential. If this is absent, a pacing response is generated. This mode closely mimics intrinsic myocardial electric activity.

During pacemaker placement, signal amplitude and width are set high enough to reliably achieve myocardial capture, yet low enough to maximize battery life.

Temporary systems use an external pulse generator with leads placed either transcutaneously or transvenously. Transcutaneous leads are the easiest and most convenient to use for rapid application of temporary pacing and is the method of choice during ED resuscitation. Transcutaneous pacing may be uncomfortable, and patients may require mild sedation (eg, benzodiazepine). Transcutaneous pacing is discussed in detail in a separate article (see External Pacemakers). Once the patient is stabilized or central venous access is gained, transvenous leads provide the most reliable and comfortable pacing mechanism and are a good transition to permanent systems.

For transvenous temporary pacing, semirigid catheters are inserted through a central venous access. ECG monitoring (specifically V1) is used to track catheter positioning. For example, P-wave morphology is initially inverted and becomes upright as the catheter is in line with the SA node. QRS morphology is also initially inverted, transitioning to isoelectric and then upright as the tip is placed in the apex. An injury pattern resembling ST elevation ensures that the catheter tip is in proper positioning for pacing. Semifloating or flexible balloon-tipped catheters can be used in emergencies since they may be positioned without such monitoring.

**Pacing Codes**

The Heart Rhythm Society and the British Pacing and Electrophysiology Group (BPEG) have developed a code to describe various pacing modes.\[1\]

Table 1. Pacemaker Code Used to Describe Various Pacing Modes (Open Table in a new window)
<table>
<thead>
<tr>
<th>Chamber</th>
<th>Chamber</th>
<th>Response to</th>
<th>Rate Modulation</th>
<th>Multisite Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paced</td>
<td>Sensed</td>
<td>Sensing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A  A  T  O  O  
V  V  I  R  A  
D  D  D  V  D  
O  O  O  O  D

Abbreviations: A, atrium; V, ventricle; D, dual (both chambers); O, none; T, triggered; I, inhibited; R, rate adaptive.

**Pacing code explanation:**

A typical pacing code consists of 3-5 letters.

- The first letter indicates the chamber(s) paced.
  - A: Atrial pacing
  - V: Ventricular pacing
  - D: Dual-chamber (atrial and ventricular) pacing
- The second letter indicates the chamber in which electrical activity is sensed.
  - A, V, or D
  - O is used when pacemaker discharge is not dependent on sensing electrical activity.
- The third letter refers to the response to a sensed electric signal.
  - T: Triggering of pacing function
  - I: Inhibition of pacing function
  - D: Dual response (ie, any spontaneous atrial and ventricular activity will inhibit atrial and ventricular pacing and lone atrial activity will trigger a paced ventricular response)
  - O: No response to an underlying electric signal (usually related to the absence of associated sensing function)
- The fourth letter represents rate modulation.
  - R: Rate-response ("physiologic") pacing
  - O: No programmability or rate modulation
- The fifth letter represents multisite pacing
  - A: Atrial
  - V: Ventricular
  - D: Dual (pacing + shock)

Although the first 3 letters are used most commonly, a 5 position code is currently in use. The first position denotes the chamber(s) paced; the second position denotes the chamber(s) sensed; the third position denotes the action(s) performed; the fourth position denotes rate response; and finally, the fifth position denotes multisite pacing.

More modern pacemakers have multiple functions. The simplest settings are VVI and AAI. The VVI mode senses and paces the ventricle and is inhibited by a sensed
ventricular event. Alternatively, the AAI mode senses and paces in the atrium, and each sensed event triggers the generator to fire within the P wave.

The most common setting, DDD mode denotes that both chambers are capable of being sensed and paced. This requires two functioning leads, one in the atrium and the other in the ventricle. In the ECG, if both atrium and ventricle are being paced, there will be a pacing artifact before the P wave and preceding the QRS. The first pacing artifact indicates the atrial depolarization, and the second indicates the initiation of the QRS complex. Given that one of the leads is in the right ventricle, a left bundle-branch pattern may be evident on ECG.

Note that a 2-wired system does not necessarily need to be in DDD mode, since the atrial or ventricular leads can be programmed off. Additionally, single tripolar lead systems are available that can sense atrial impulses and either sense or pace the ventricle. Thus, this system provides for atrial tracking without the capability for atrial pacing and can be used in patients with AV block and normal sinus node function.

Pacemaker programming can be performed noninvasively by an electrophysiology technician or cardiologist. Because of the myriad of pacemaker types, patients should carry a card with them providing information about their particular model. Most pacemaker generators have an x-ray code that can be seen on a chest radiograph; however, the chest radiography may need to be zoomed onto the pacemaker generator for better resolution. The markings, along with the shape of the generator, may assist with deciphering the manufacturer of the generator and pacemaker battery.

For further information or locations of technicians for pacemaker devices, the device company can be contacted at the 24-hour help line telephone numbers below.[2]

- Guidant (Boston Scientific) - 800-CARDIAC (800-227-3422)
- Medtronic - 800-MEDTRONIC (800-633-8766)
- St. Jude Medical - 800-722-3774
- Biotronik – 800-547-0394

**Pacemaker and ICD Indications**

**Pacemaker indications**

Absolute indications for pacemaker placement include the following:

- Sick sinus syndrome
- Symptomatic sinus bradycardia
- Tachy-brady syndrome
- Atrial fibrillation with sinus node dysfunction
- Complete atrioventricular block (third-degree block)
- Chronotropic incompetence (inability to increase the heart rate to match a level of exercise)
- Prolonged QT syndrome
- Cardiac resynchronization therapy with biventricular pacing

Relative indications include the following:
- Cardiomyopathy (hypertrophic or dilated)
- Severe refractory neurocardiogenic syncope

Temporary emergency pacing is indicated for therapy of significant and hemodynamically unstable bradydysrhythmias and for prevention of bradycardia-dependent malignant dysrhythmias. Examples include refractory symptomatic sinus node dysfunction, complete heart block (see image below), alternating bundle-branch block, new bi-fascicular block, and bradycardia-dependent ventricular tachycardia.

Examples of indications for prophylactic temporary pacing include insertion of a pulmonary artery catheter in a patient with an underlying left bundle-branch block, use of medications that may cause or exacerbate hemodynamically significant bradycardia, prophylaxis during the perioperative period surrounding cardiac valvular surgery, Lyme disease or other infections (Chagas disease) that cause interval changes, and prolonged PR intervals.

ICD indications [3]

Initially, ICDs were used for secondary prevention in patients who had documented life-threatening ventricular arrhythmias and survivors of cardiac arrest. A meta-analysis of 3 large trials, principally, Antiarrhythmics vs Implantable Defibrillator (AVID) study,[4] the Cardiac Arrest Study Hamburg (CASH),[5] and the Canadian Implantable Defibrillator Study (CIDS),[6] showed patients in the ICD group had significant reduction in all-cause death and death from arrhythmia. Further analysis of the CIDS trial with an 11-year follow-up revealed that the benefit of ICD over amiodarone increased with time.[7]

Recent trials suggest ICDs are beneficial for primary prevention of sudden cardiac death. Multiple trials have demonstrated that primary prevention in post-MI patients with reduced ejection fraction, nonsustained VT, and inducible nonsuppressible VT in electrophysiological testing with ICD over conventional medical therapy saved lives.[8, 9] Further studies have shown that primary prevention using ICDs in other patient subset groups is also beneficial.[10, 11, 12, 13, 14]

In the case of post-MI patients, no mortality benefit was observed from placing ICDs in patients with reduced ejection fraction until after 40 days post-MI and patient reassessment. This is likely due to the fact that death in the first 40 days post MI may be attributed to causes other than arrhythmia.[15]

For further detailed discussion and evidence supporting ICDs, see Implantable Cardioverter-Defibrillators.

Indications for ICDs include the following:
• Survivors of cardiac arrest due to ventricular fibrillation (VF) or hemodynamically unstable sustained ventricular tachycardia (VT) after evaluation to define the cause of the event and to exclude any completely reversible causes
• Structural heart disease and spontaneous sustained VT (stable or unstable)
• Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study
• Patients with left ventricular ejection fraction (LVEF) < 35% due to prior myocardial infarction (MI) who are at least 40 days post-MI and are in New York Heart Association (NYHA) functional Class II or III
• Nonischemic dilated cardiomyopathy with LVEF ≤35% and NYHA functional Class II or III
• Left ventricular (LV) dysfunction due to prior MI, ≥40 days post-MI, with LVEF < 30%, and NYHA functional Class I
• Nonsustained VT due to prior MI, LVEF < 40%, and inducible VF or sustained VT at electrophysiological study
• Unexplained syncope, significant LV dysfunction, and nonischemic dilated cardiomyopathy
• Sustained VT and normal or near-normal ventricular function (see image below)
• Hypertrophic cardiomyopathy who have 1 or more major risk factors for sudden cardiac death (SCD)

(For further reading and a detailed list of indications, see ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities.\(^{[16]}\)

**Magnet Inhibition**

In most devices, placing a magnet over a permanent pacemaker temporarily "reprograms" the pacer into asynchronous mode. It does not turn the pacemaker off. Each pacemaker type has a unique asynchronous rate for beginning-of-life (BOL), elective replacement indicator (ERI), and end-of-life (EOL). Therefore, if the device company parameters are known, application of a magnet can determine if the pacer's battery needs to be replaced. Further interrogation or manipulating of the device should be performed by an individual skilled in the technique.

Although many different branded pacemaker/ICD magnets are available, emergency physicians should be aware that in general any pacemaker/ICD magnet can be used to inhibit the device.

It is worth mentioning that, when a magnet is applied to an ICD, it can temporarily turn off defibrillation therapy without altering its pacing ability, this is further described later in the article.

Also, note that the majority of devices have a magnet response; however, some devices can be programmed to not respond to magnet application and thus will need a device programmer to change the parameters.


**Pacemaker Malfunctions and Complications**

Major pacemaker malfunctions include the following:

- Failure to output
- Failure to capture
- Failure to sense
- Pacemaker-mediated tachycardia
- Runaway pacemaker
- Pacemaker syndrome
- Twiddler's syndrome
- Cardiac monitor pseudomalfunction
- Pacemaker pseudomalfunction

**Failure to output**

Failure to output occurs when no pacing artifact is present despite an indication to pace. This may be due to battery failure, lead fracture, fractured lead insulation, oversensing (inhibiting pacer output), poor lead connection at the takeoff from the pacer, and "cross-talk" (ie, a phenomenon occurring when atrial output is sensed by a ventricular lead in a dual-chamber pacer).

Management of pacer output complications includes medications to increase the intrinsic heart rate and placement of a temporary pacer. A chest radiograph is warranted to check pacer leads and to evaluate for possible lead fracture, which occurs most commonly at the clavicle or first rib. The patient's pacer identification card should be obtained and his or her electrophysiologist or cardiologist consulted. Lead impedance (resistance) may also be an indicator of lead malfunction. A very low impedance may signify a fracture of the insulation (ie, the energy is dissipating into the surrounding tissue), whereas infinite (or very high) impedance may signify either: (1) complete lead fracture, or (2) lead tip dislodged from endocardium.

**Failure to capture**

Failure to capture occurs when a pacing artifact is not followed by an atrial or a ventricular complex (see image below). This may be due to lead fracture, lead dislodgement, fractured lead insulation, an elevated pacing threshold, myocardial infarction at the lead tip, drugs (eg, flecainide), metabolic abnormalities (eg, hyperkalemia, acidosis, alkalosis), cardiac perforation, poor lead connection at the takeoff from the generator, and improper amplitude or pulse-width settings. Fibrosis at the endocardial surface where leads were implanted may also occur in the weeks following pacemaker implantation. The fibrosis may create an electrical resistance barrier preventing ventricular depolarization. This may detected as an abnormally high change in impedance (Δ impedance).
Intermittent periods of ventricular capture.

Managing pacer capture complications is similar to treating output complications, with extra consideration given to treating metabolic abnormalities and potential myocardial infarction. Temporary pacing is used to stabilize the patient until an electrophysiology technician or cardiologist can further evaluate the pacemaker.

**Oversensing**

Oversensing occurs when a pacer incorrectly senses noncardiac electrical activity and is inhibited from pacing. This may result in a heart rate lower than the preset rate. This form of output failure may be due to muscular activity (particularly the diaphragm or pectoralis muscles), electromagnetic interference (MRIs), or fractured lead insulation. Oversensing is one condition that is diagnosable and treatable with magnet application. As mentioned before, magnet application will convert the pacemaker to asynchronous mode, and it will then operate at the preset rate.

Of note, it has been reported that cellular phones held within 10 cm of the pulse generator may elicit this response.[17]

Individual ICD manufacturers also have recommendations for unsafe devices that may interact with the ICD (eg, Safe and Unsafe devices - Medtronic Brochure for Patients[18]).

**Undersensing**

Undersensing occurs when a pacer incorrectly misses intrinsic depolarization and paces despite intrinsic activity. The pacemaker is more or less operating in asynchronous mode. This may be due to poor lead positioning, lead dislodgment, magnet application, low battery, or myocardial infarction. Management is similar to that for other types of failures.

**Pacemaker-mediated tachycardia**

A premature ventricular contraction (PVC) in a dual-chamber pacemaker may precipitate a pacemaker-mediated tachycardia. If a premature ventricular contraction (PVC) is transmitted in a retrograde manner through the AV node, it may, in turn, depolarize the atria. This atrial depolarization is detected by the atrial sensor, which then stimulates the ventricular leads to fire, hence creating an endless loop. Although the maximum rate is limited by the pacemaker’s programmed upper limit, the possibility of developing ischemia exists in susceptible patients. This is another opportunity to use a magnet to diagnose and treat the arrhythmia. The magnet will place the pacemaker into asynchronous mode and sensing will be deactivated, thus preventing continuation of the reentrant dysrhythmia.
Runaway pacemaker

A malfunction of the pacemaker generator resulting in a life-threatening rapid tachycardia (up to 200 bpm) is known as runaway pacemaker. The generator may malfunction from various causes, although most commonly it is a battery failure or external damage. This rare medical emergency requires immediate action. An external magnet may induce slower pacing, but it is possible that the device will not respond to magnet application and more aggressive measures may be necessary. If a patient becomes unstable, treatment involves making an incision in the chest wall over the pacemaker and severing the pacemaker leads from the generator. Note that the patient may require temporary pacing as a result.

Pacemaker syndrome

Pacemaker syndrome is a phenomenon where a patient feels symptomatically worse after pacemaker placement and presents with progressively worsening symptoms of congestive heart failure (CHF). This is mainly due to the loss of atrioventricular synchrony whereby the pathway is reversed and now has a ventricular origin. The atrial contribution to the preload is lost and cardiac output as well as blood pressure fall. Immediate treatment is mainly supportive, whereas long-term treatment involves altering the pacemaker to restore atrial-ventricular synchrony and possible ventricular synchrony. For example, this may require changing the pacemaker from single-chamber to dual-chamber pacing or to dual-ventricular pacing.

For further reading, see Pacemaker Syndrome.

Twiddler's syndrome

Some patients will persistently disturb and manipulate the pacemaker generator resulting in malfunction. A chest radiograph may reveal twisting or coiling, or lead fracture, dislodgement, or migration. This situation will require surgical correction with further patient education and counseling.

Cardiac monitor pseudomalfunction

From time to time, cardiac monitors will report an incorrect heart rate, too low or too high, due to inappropriate interpretation of pacing artifacts. Clinicians faced with this issue should first palpate the pulse and correlate with a pulse oximeter plethysmogram to verify the findings on a cardiac monitor. New monitors have settings to adapt for patients with pacemakers and provide more accurate heart rates.

Pacemaker pseudomalfunction

In some clinical settings, an apparent pacing system malfunction is suggested; however, the apparent malfunction is a normal programmed pacer function. This is partly due to new algorithms to preserve intrinsic conduction and more physiologic pacing. These can sometimes be corrected by changing the programming, and, in other cases, the patient may need to have the device changed.
For further reading on pacemaker malfunctions, please see the eMedicine article Pacemaker Malfunction.

**Pacemaker complications**

Pacemaker complications include malfunction due to mechanical factors such as pneumothorax, pericarditis, infection, skin erosion, hematoma, lead dislodgment, and venous thrombosis. Treatment depends on the etiology. Pneumothoraces may require medical observation, needle aspiration, or even chest tube placement. Erosion of the pacer through the skin, while rare, requires device replacement and systemic antibiotics. Hematomas may be treated with direct pressure and observation, rarely requiring surgical drainage. Lead dislodgment generally occurs within 2 days of device implantation pacer and may be seen on chest radiography. Alternatively, fluctuating impedance may be a subtle clue as the patient may have normal impedance when the lead is in contact with the endocardium, but infinite (or very high) impedance when the lead is dislodged.

Free-floating ventricular leads may trigger malignant arrhythmias. Device-associated venous thrombosis is rare but generally presents as unilateral arm edema. Treatment includes extremity elevation and anticoagulation.

Advanced life support protocols, including defibrillation, may safely be performed for patients with pacemakers in place. Sternal paddles are placed at a safe distance (10 cm) from the pulse generator. Temporary pacing may become necessary in cases of myocardial infarction, as the current pacemaker discharge settings may be insufficient to stimulate ventricular contraction.

**ICD Complications**

Major implantable cardioverter defibrillator (ICD) complications are similar to those found in pacemakers and include operative failures, sensing and/or pacing failures, inappropriate cardioversion, ineffective cardioversion/defibrillation, and device deactivation.

Operative failures are identical to those found in regular pacemakers.

ICD sensing problems similar to those seen with pacers may also occur. An example of appropriate failure to treat is when a device has a cut-off rate of 180 bpm. If ventricular tachycardia occurs at 160 bpm, the device, appropriately, fails to cardiovert the patient since the rate of the dysrhythmia is below the programmed threshold.

Inappropriate cardioversion is the most frequent ICD-associated complication. This should be considered when a patient presents in atrial fibrillation or reports multiple shocks in rapid succession without preceding symptoms. Other causes include T-wave oversensing, lead fracture, lead insulation breakage, electrocautery, MRI, and electromagnetic interference.

Magnet use inhibits further ICD discharge. It does not, however, inhibit pacing. In some devices, application of a magnet produces a soft beep for each QRS complex.
If the magnet is left on for approximately 30 seconds, the ICD is disabled and a continuous tone is generated. To reactivate the device, the magnet must be lifted off the area of the generator and then replaced. After 30 seconds, the beep returns for every QRS complex. Indications for ICD deactivation are as follows:

- End-of-life care (after a discussion with the patient and family)
- Inappropriate shocks
- During resuscitation
- With transcutaneous pacing (external pacing can cause an ICD to fire)
- During procedures such as central lines or surgery with electrocautery

Failure to deliver a shock may be caused by failure to sense, lead fracture, electromagnetic interference, and inadvertent ICD deactivation. Management includes external defibrillation or cardioversion and antidysrhythmic medications.

Ineffective cardioversion may result from inadequate energy output, rise in defibrillation threshold (possibly due to antiarrhythmic medications such as amiodarone, flecainide, phenytoin), myocardial infarction at the lead site, lead fracture, insulation breakage, scarring at the lead implantation site, and lead dislodgment.

Many ICDs deliver a programmed set of therapies per dysrhythmic episode. The number of therapies per episode is programming specific. If a delivered therapy does not terminate the arrhythmia, the device proceeds to the next programmed therapy. For example, a total of 6 attempts at defibrillation are attempted per episode of ventricular fibrillation. The device attempts defibrillation and then reevaluates the cardiac rhythm. If the arrhythmia persists, it delivers therapy number two and so on, until all 6 attempts have been delivered. Once this occurs, the device does not deliver therapy until a new episode is declared. Note, as mentioned earlier in this article, initial therapy for ventricular tachycardia may be antitachycardia pacing (also known as overdrive pacing) rather than cardioversion.

ICDs do not prevent all sudden deaths, and acknowledging that cardiac arrest is not necessarily an ICD malfunction is important. The device may have properly delivered the required shocks for the triggering rhythm but was ineffective in resolving it.

**Resuscitation**

If a patient enters a life-threatening cardiac arrhythmia, advanced cardiac life support (ACLS) protocols should be initiated immediately. Although an implantable cardiac defibrillator (ICD) will attempt defibrillation, chest compressions should be continued. Note that some of the current may enter the rescuer, and, besides some mild discomfort, there has never been a reported case of rescuer injury from this.[2] Ventricular tachycardia and ventricular fibrillation refractory to ICD defibrillation will require external defibrillation and/or antiarrhythmic medications as dictated by ACLS protocols. If external defibrillation is required, attempt to keep the generator at least 10 cm away and out of the shock wave. Defibrillation that affects the generator may cause total device failure. However, do not withhold therapy for fear of damaging the ICD.
If rescuers are uncomfortable with ICD discharge during resuscitations, it is indicated to deactivate the ICD with a magnet, as described in Magnet Inhibition.

Central venous catheters

Pacemaker or ICD leads placed in the venous system often have surrounding thrombosis with 20% of patients having complete occlusion at 2 years.\(^\text{[19]}\) If the metal guidewire contacts the lead system during central line placement, there may be enough noisy artifact to trigger an inappropriate shock. Consideration should be given to either avoid a metal guidewire or deactivate the ICD during central line placement. Although the contralateral subclavian or internal jugular vein can be cannulated with care, the femoral vein access is a much safer option.

Admission and Difficulties Surrounding a Safe Discharge

One of the most difficult decisions after a patient presents to the ED complaining of an ICD discharge is to determine if the discharge was appropriate. Whenever possible, the device should be interrogated. Unless the shock and rhythm that preceded it was witnessed, it is not possible to determine shock appropriateness without investigation. Reasons for admission may include the following: device investigation to determine whether there is an eminent battery failure (multiple shocks will deplete battery life); addition of antiarrhythmic medications; treatment of myocardial infarction, which may be linked to the initial discharge; treatment of patient discomfort; and to give psychological support (up to 35% of people develop anxiety disorder following ICD placement).\(^\text{[20]}\)

References


Variation in Dual- vs Single-Chamber-ICD Use Highlights Missing Data

April 25, 2012 (Denver, Colorado) — A new study on the use of dual- and single-chamber implantable cardioverter defibrillators (ICDs) in patients without a pacemaker indication highlights the critical need for more research on the best device for these patients, according to the study’s lead investigator [1].

Dr Dan Matlock (University of Colorado Denver School of Medicine, Aurora) and colleagues conducted a cross-sectional study of hospital-level variation in the use of dual-chamber implantable defibrillators in patients without a documented pacing indication from 2005 through 2009 in the National Cardiovascular Data Registry (NCDR). Results of the study are published in the April 23, 2012 issue of the Archives of Internal Medicine. “The evidence on this has been conflicting. A lot of the trials studying ICDs use only single-lead ICDs, but there are some studies that suggest that a dual-lead ICD is better,” Matlock explained to heartwire.

For example, the DATAS study showed that dual-chamber ICDs reduced clinically significant adverse events compared with single-chamber ICDs in patients with a standard ICD indication. However, the dual-chamber devices’ ability to reduce inappropriate shocks remains controversial, according to Matlock et al, and recent research from the NCDR database showed that dual-chamber ICDs increase the risk of procedural complications, including in-hospital death, by over 40% compared with single-chamber ICDs.

“These were patients where the doctor had a choice of a single- or dual-lead ICD, and we found astounding variation,” Matlock said. The study shows that dual-chamber ICDs were implanted in about 58% of the 87,115 patients in the study, but the rates of dual-chamber implants for the 1293 hospitals ranged from 0% at 33 centers to 100% at 109 centers.

“What jumped out as surprising is what didn’t cause the variation: the patients had relatively little influence on whether or not the dual-lead was implanted,” he said. The study controlled for a variety of patient factors, including atrial fibrillation, diabetes, hypertension, and the use of dialysis, and found nothing in the patient characteristics that could explain the wide variation in dual- vs single-lead implants.

“And that was a bit of a surprise. In practice-variation research in general, the common criticism is that ‘it must be something about the patients.’ But here, because of the rich data in the NCDR registry, we were able to look at a lot of patient variables in ways that other recent variation studies haven’t been able to.”

Patient characteristics did not appear to influence the decision to use a dual- vs single-chamber ICD, but geographical region and type of hospital did, with the chances of a patient getting a dual-chamber device generally increasing the further west they lived. Only 36.4% of patients in New England received a dual-chamber device, compared with 66.4% of patients in the Pacific region.

Just under half of patients treated at university hospitals were implanted with a dual-chamber device, compared with over 69% of patients at private or community hospitals (odds ratio 0.65). Also, surgeons were about twice as likely to choose a dual-chamber device as an electrophysiologist.

Variation Does Not Mean Inappropriate

“We’re definitely not saying that physicians who are putting in dual leads are doing the wrong thing or that physicians putting in single leads are doing the wrong thing. That’s the wrong message to take,” Matlock said. “We’re trying to say that we clearly need more evidence on what is the right decision for patients who don’t have a clear indication for a dual-lead ICD.

“All of these physicians, when they’re putting in a single or dual lead, are doing what they think is right. There’s evidence pointing both ways, but the fact that it conflicts is why we’re seeing this variation,” he said. ”We need a
randomized trial of patients with single- and dual-lead ICDs, and we need better comparative-effectiveness data from large registries to generate some real-world knowledge."

In an accompanying editor's note, **Dr Rita Redberg** (University of San Francisco, California) is more pessimistic about the study's message. The paper by Matlock et al is included in the Archives ongoing "Less is More" series.

"Despite the absence of data to support benefit for patients receiving a dual-chamber implantable cardioverter-defibrillator compared with a single-chamber ICD for a nonpacing indication, most implants are of dual-chamber ICDs," Redberg said. "In contrast to the lack of data for benefit, there are data from multiple randomized and observational trials suggesting increased harm."

*Matlock was supported by the National Institute on Aging. Disclosures for the coauthors are listed in the paper.*

**References**

Eplerenone Reduces New-Onset Atrial Fibrillation/flutter in Mild Heart Failure

YORK (Reuters Health) Apr 24 - Patients with NYHA class II heart failure are less likely to develop atrial fibrillation or flutter when given eplerenone, according to findings appearing in the May 1st issue of the Journal of the American College of Cardiology.

Specifically, the authors report, "In patients with systolic HF and mild symptoms, addition of eplerenone to recommended therapy reduced the incidence of new atrial fibrillation by 42%.

Dr. Karl Swedberg, at Sahlgrenska University Hospital/Ostra in Gothenburg, Sweden, and colleagues point out that atrial fibrillation or flutter (AFF) often leads to further hemodynamic deterioration and is "clearly undesirable." Aldosterone antagonism to block activation of mineralocorticoid receptors may influence atrial remodeling, they continue, and thereby reduce the risk of AFF.

To see if treatment with the mineralocorticoid receptor eplerenone in this regard helped patients who were already receiving an ACE inhibitor or angiotensin receptor blocker, the team conducted a placebo-controlled trial involving 2,737 participants in the EMPHASIS-HF trial. All of the patients had NYHA class II heart failure and an ejection fraction no greater than 35%.

The risk of the primary endpoint - cardiovascular mortality or hospitalization for heart failure - was lower in the group that received eplerenone, with similar reductions in patients with or without AFF at baseline (hazard ratios 0.60 and 0.70, respectively).

At baseline, 1,794 of the participants were free of AFF. During follow-up, the incidence of new-onset AFF was 2.7% among patients given eplerenone and 4.5% among those in the placebo arm, the investigators found.

This translated to a hazard ratio of 0.58 (p=0.034), which was reduced after adjustment for covariables (hazard ratio 0.713; p=0.087).

The authors say the findings might not be applicable to all HF patients with mild symptoms, "because in this study patients were required to have additional factors known to increase cardiovascular risk, including age >55 years, in most cases an ejection fraction <30%, and a recent cardiovascular hospitalization."

Dr. Swedberg and colleagues also point out that class III antiarrhythmic drugs can prevent atrial fibrillation in HF, but they have unacceptable toxicity. "By comparison, eplerenone is a well-tolerated and safe alternative that has substantial additional clinical benefits, provided it is initiated under monitoring of serum potassium and creatinine as in our study," they conclude.


J Am Coll Cardiol 2012; 59:1598-1603.
Stent implantation for a totally occluded right coronary artery in a 6-year-old boy after Kawasaki disease: a case report
Ya-Chi Hsu, Kae-Woei Liang, Ming-Chih Lin, Yun-Ching Fu and Sheng-Ling Jan

Journal of Medical Case Reports 2012; Volume 6

Introduction
Coronary stenting is considered less feasible for children under 12 years old previously due to limitation of vascular access. We report a 6-year-old boy who successfully underwent stent implantation for his totally occluded right coronary artery.

Case presentation
A 6-year 9-month-old Taiwanese boy was found to be complicated with giant aneurysms after acute episode of Kawasaki disease. The angiography revealed totally occluded middle right coronary artery. A 0.014 inch guidewire was advanced to cross the totally occluded site. After pre-dilating the middle portion of right coronary artery with the 1.5mm balloon right coronary artery stenting was accomplished using a 2.5 mm X 28 mm and a 2.5 mm X 18 mm bare metal stent. Final angiography demonstrated no residual stenosis or dissection.

Conclusion
Coronary stenting could be a therapeutic option for children as young as 6-year-old. Close follow-up is mandatory because the long-term outcome is still unclear especially in such a small child.
Declining In-Hospital Mortality in Patients Undergoing Coronary Bypass Surgery in the United States Irrespective of Presence of Type 2 Diabetes or Congestive Heart Failure

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\textit{Clinical Cardiology 2012; Article first published online: 23 FEB 2012 // DOI: 10.1002/clc.21970}

Background:

Significant advances in surgical techniques and postsurgical care have been made in the last 10 years. The goal of this study was to evaluate any decline in the age-adjusted in-hospital mortality rate of patients undergoing coronary artery bypass grafting (CABG) using a national database from 1989 to 2004 in the United States.

Hypothesis:

Reduction in CABG related mortality in recent years.

Methods:

Using the Nationwide Inpatient Sample (NIS) database, we obtained specific ICD-9-CM codes for CABG to compile the data. To exclude nonatherosclerotic cause of coronary disease, we studied only patients older than 40 years. We calculated total and age-adjusted mortality rate per 100,000 for this period.

Results:

The NIS database contained 1 145 285 patients who had CABG performed from 1988 to 2004. The mean age for these patients was 71.05 ± 9.20 years. From 1989, the age-adjusted rate for all CABG-related mortality has been decreasing steadily
and reached the lowest level in 2004: 300.3 per 100,000 in 1989, (95% confidence interval [CI], 20.4-575.9) and 104.69 per 100,000 (95% CI, 22.6-186.7) in 2004. Total death also declined from 5.5% to 3.06%. This decline occurred irrespective of comorbidities such as congestive heart failure, diabetes, or acute myocardial infarction, albeit increasing the number of CABG procedures performed in high-risk patients.

**Conclusions:**

The age-adjusted in-hospital mortality rate from CABG has been declining steadily and reached its lowest level in 2004, irrespective of comorbidities. This decline most likely reflects advances in surgical techniques and the use of evidence-based medicine in patients undergoing CABG.
Intraaortic Balloon Pump: Incidence and Predictors of Complications in the Florence Registry

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Background:

The intraaortic balloon pump (IABP) is the most commonly used mechanical circulatory support for patients with acute coronary syndromes and cardiogenic shock. Nevertheless, IABP-related complications are still frequent and associated with a poor prognosis.

Hypothesis:

To prospectively assess the incidence and predictors of complications in patients treated with IABP.

Methods:

A total of 481 patients treated with IABP were prospectively enrolled in our registry (the Florence Registry). At multivariable logistic regression analysis the following variables were independent predictors for complications (when adjusted for age >75 years, eGFR and time length of IABP support): use of inotropes (OR 2.450, \( P < 0.017 \)), nadir platelet count (1000/µL step; OR 0.990, \( P < 0.001 \)), admission lactate (OR 1.175, \( P = 0.003 \)). Nadir platelet count showed a negative correlation with length
of time of IABP implantation ($r=0.31; P < 0.001$). A nadir platelet count cutoff value of less than 120,000 was identified using a receiver operating characteristic (ROC) curve for the development of complications (area under the curve [AUC] 0.70; $P < 0.001$).

**Results:**

Complications were observed in the 13.1%, among whom 33 of 63 showed major bleeding. The incidence of complications was higher in patients aged >75 years ($P = 0.015$) and in those who had an IABP implanted for more than 24 hours ($P = 0.001$). Patients with complications showed an in Intensive Cardiac Care Unit (ICCU) mortality higher than patients who did not (44.4% vs 17.2%, $P < 0.001$).

**Conclusions:**

In consecutive patients treated with IABP support, the degree of hemodynamic impairment and the decrease in platelet count were independent predictors of complications, whose development was associated with higher in-ICCU mortality
Impact of high-dose inotropic donor support on early myocardial necrosis and outcomes in cardiac transplantation

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Keywords:
- cardiac transplantation;
- donor selection;
- dopamine


Abstract: Background: Cardiac donors routinely require vasoactive agents for circulatory stability after brain death. Nevertheless, inotropes have been associated
with direct cardiac toxicity. Our study evaluated whether the use of high-dose inotropic support in potential donors was associated with increased early myocardial necrosis (MN) and worse clinical outcomes after cardiac transplantation.

Methods: The UTAH Cardiac Transplant Program (UCTP) and Intermountain Donor Services databases were queried for records between 1996 and 2009. The high-dose donor inotropic support (HDIS) group was defined as patients on dopamine >10 μg/kg/min. The incidence of early MN, intensive care unit (ICU) length of stay, length of ventilator support, and mortality was evaluated.

Results: Two hundred and forty-four recipients undergoing transplant met study criteria. The average donor age was 27 yr. The incidence of MN in the HDIS (n = 29) and non-HDIS (n = 204) groups was 14.8% and 6.7%, respectively, OR 2.67. Total ischemic time, ventilator support time, ICU stay, and actuarial survival were similar between both groups.

Conclusion: The use of high-dose inotropic support to maintain donor stability appears to have a higher trend for early post-transplant MN without an impact on clinical outcomes. With the current growing shortage of organ donors, it appears reasonable to use donors on high-dose inotropic support.
ApoA size independently associated with MI.

**Chicago, IL** - Apolipoprotein A (apoA) isoform size is associated with MI after adjustment for lipoprotein (a) (Lp[a]), according to a new analysis [1]. Results suggest that the role of apoA in MI deserves further scrutiny, according to Dr Lance A Bare (Celera, Alameda, CA), who presented the case-controlled study of nonfatal MI here at the *Arteriosclerosis, Thrombosis and Vascular Biology* (ATVB) 2012 Scientific Sessions.

Previous studies have shown that Lp(a) size and apoA size are associated with MI, but the mechanism behind the association is not clear. Nor is it clear if Lp(a) size and apoA size are independently associated with MI.

Lp(a) consists of an LDL-like particle with a covalently attached ApoA. ApoA contains a variable number of kringle IV type-2 (KIV-2) repeats (from two to more than 50). The number of repeats determines the number of different-sized apoA isoforms. When two different alleles are expressed, the smaller isoform is typically expressed at higher levels. ApoA isoform size is inversely correlated with Lp(a) levels, Bare explained.

The *Costa Rica Study* included Lp(a) and apoA isoforms of 433 subjects as determined by immunoturbidometric assay (Lp[a]) and Western blot (apoA). The subjects were randomly selected MI cases and population-based controls from 4186 study participants.

Association with MI was assessed using logistic regression models that included Lp(a) level and the size of the smaller isoform as explanatory variables.

The study found that Lp(a) levels were associated with apoA isoform size such that Lp(a) increased by 9.6 mg/dL for every decrease of five KIV-2 repeats (p<0.001). The Lp(a) level was associated with risk for MI. Small apoA isoforms were associated with risk of MI.

The association for apoA had an odds ratio (OR) of 1.48 (p=0.021) per decrease of five KIV-2 repeats. The association with Lp(a) level was an OR of 1.27 (p<0.001) per 10-mg/dL increase in Lp(a).

Further analysis revealed that small apoA isoform size was associated with MI after adjustment for Lp(a) level (OR 1.29; p=0.034). Moreover, the Lp(a) levels remained associated with MI after adjustment for the size of the smaller apoA isoform (OR 1.19; p=0.005). Large isoforms were not associated with nonfatal MI.

Bare acknowledged the study was small and did not include fatal MI cases. Moreover, plasma samples were collected after MI.

Of note, the study cohort—like the population of Costa Rica—was of mixed ancestry (European 58%, Native American 38%, and West African 4%)—but Bare noted that adjusting for ethnicity had little effect on the association of the smaller apoA isoform with MI (OR 1.38; p=0.056) or the association of Lp(a) levels with MI (OR 1.11, p=0.18).
Session moderator Dr Michael Davidson (University of Chicago, IL), called the results interesting, noting that apoA is "a test that's available now. Whether it has added value now is not known."


Bare works for Celera. Davidson reports no conflict of interest
Dabigatran cuts ICH mortality vs warfarin: RE-LY analysis.

Among patients stricken with intracranial hemorrhage (ICH) while on oral anticoagulation for nonvalvular atrial fibrillation (AF), the stroke is no more likely to be fatal for those on **dabigatran etexilate** (Pradaxa, Boehringer Ingelheim) than for those taking **warfarin**, suggests an analysis from the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial [1].

Given that RE-LY had already shown significantly reduced ICH rates with the new drug vs the very old one (p<0.001), the current findings suggest that when patients with AF receive dabigatran, “their overall risk of dying from ICH is 70% lower” than it is with warfarin, lead author **Dr Robert G Hart** (McMaster University, Hamilton, ON) observed for **heartwire**.

The analysis was published online in **Stroke** April 5, 2012. In the trial's primary finding, released in 2009 and reported by **heartwire** at the time, treatment with dabigatran at 150 mg twice daily cut the composite end point of stroke or peripheral embolic events by 34% per year compared with warfarin (p<0.001).

The trial had randomized >18 000 patients with AF (plus one other stroke risk factor) in 44 countries to receive dabigatran at either 110 mg or 150 mg two times daily or to warfarin adjusted to an INR of 2.0 to 3.0.

There were 154 instances of ICH in 153 patients, of which 46% were intracerebral bleeds and 45% were subdural hematomas. There was no significant difference in ICH-associated mortality between the three groups.

**Intracranial hemorrhage outcomes in the RE-LY trial (mean follow-up two years)**

<table>
<thead>
<tr>
<th>End point</th>
<th>Dabigatran 150 mg bid (n=37)</th>
<th>Dabigatran 110 mg bid (n=27)</th>
<th>Warfarin (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH (%/y)</td>
<td>0.31</td>
<td>0.23</td>
<td>0.76&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ICH mortality (% of ICH)</td>
<td>35</td>
<td>41</td>
<td>33</td>
</tr>
<tr>
<td>Subdural hematoma (%/y)</td>
<td>0.20</td>
<td>0.08&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.31</td>
</tr>
</tbody>
</table>

<sup>a</sup> p<0.001 for warfarin vs either dabigatran dosage  
<sup>b</sup> p=0.02 for dabigatran 110 mg bid vs 150 mg bid, p<0.001 for dabigatran 110 mg bid vs warfarin

In multivariate analysis, ICH predictors included warfarin as anticoagulant therapy (relative risk [RR] 2.9, p<0.001), using aspirin (which was at the physician's discretion) (RR 1.6, p=0.01), age (RR per added year 1.1, p<0.001), and history of stroke or transient ischemic attack (RR 1.8, p<0.001).

Hart cautions that the reduced ICH mortality with dabigatran may not extend to centers that are proficient in managing warfarin-related ICH: there is an antidote for the older drug, but none is currently available for dabigatran.
But most patients with warfarin-related ICH are not managed at such centers. "In real life, you'd have to go to a tertiary hospital," he said. "If you go to Massachusetts General Hospital or to the Mayo Clinic Rochester, where they're used to taking care of warfarin-associated ICH, well, there maybe you can get activated [prothrombin complex concentrates] PCCs. So maybe these results don't apply where vigorous aggressive treatment of warfarin hemorrhage is available." But at other centers and throughout most of the world, such "modern and expensive treatments for warfarin aren't available."

Hart also questioned the clinical importance of dabigatran's lack of an antidote. Although it's "logical" that reversal of warfarin with activated PCC would also reduce ICH mortality, there's no solid evidence that it does. "We still don't know if the outcome is changed."


*RE-LY was funded by Boehringer Ingelheim, for which Hart discloses serving as a consultant. Disclosures for the coauthors are listed in the paper; in particular, coauthor Dr Paul A Reilly is an employee of Boehringer Ingelheim.*
FDG PET/CT can identify infections around implanted device.

Combined fluorodeoxyglucose marked by fluorine-18 ($^{18}$F-FDG) positron-emission tomography (PET) and computed tomography (CT) distinguish between an active infection around a cardiovascular implantable electronic device and normal postoperative inflammation, a new study in the May 1, 2012 issue of the *Journal of the American College of Cardiology* shows [1].

It's always difficult to know for sure if there's infection when there's local inflammation, Dr Jean-Francois Sarrazin (Institut universitaire de cardiologie et pneumologie de Quebec, Quebec City) told *heartwire*. And if it is infected, it is not certain whether it's deeply infected, in which case the physician may need to remove everything, or if the infection is superficial and the site can be treated with antibiotics. Lead extraction is associated with significant morbidity (1.5% to 2% complication rate) and a mortality rate of about 0.8%, so accurately identifying patients whose only good option is lead extraction could prevent many complications and save the costs associated with extraction and device replacement, Sarrazin said. "Another difficult situation is when people get bacteremia and they have a device. Is the device infected? Is that the cause of infection?"

The value of $^{18}$F-FDG-PET/CT is already established in oncology for cancer diagnosis and staging and in cardiology to assess myocardial viability because it allows 3-D measurement of metabolic activity within an organ by measuring disintegration of the injected $^{18}$F-FDG, according to Sarrazin and colleagues. A few case reports and small studies suggest that $^{18}$F-FDG PET/CT can help diagnose device infections by highlighting cells with higher metabolic activity, so the authors expect this technique may show the extent of an infection to allow the physician to determine whether device extraction is worth the risks.

The study included three patient groups. Group A included 42 patients with suspected device infection based on normal symptoms of an infection. To compare the $^{18}$F-FDG PET/CT images of infection in that group with that of normal postimplant inflammation, Group B included 12 patients without signs of infection who had received a device within the past four to eight weeks, and Group C included 12 patients without signs of infection who received their devices at least six months prior to thoracic $^{18}$F-FDG PET/CT imaging for some other indication.

In Group A, all patients underwent $^{18}$F-FDG PET/CT for risk stratification, and 22 patients also had a transesophageal echocardiogram (TEE). The most common presenting symptom was local wound infection (n=16), followed by erosion of the pocket caused by the device (n=13), bacteremia (n=10), fever of unknown origin (n=1), local persistent swelling (n=1), and chronic wound discomfort (n=1). Eight patients without local signs of device infection showed signs of infective endocarditis. In Group A, 24 patients underwent extraction and 18 patients were treated with antibiotics only. After complete evaluation, 35 patients were confirmed to have device-related infections. Of the remaining seven patients, five patients were treated successfully for an infection unrelated to the cardiac device, one patient with a fever was finally diagnosed with reactive arthritis, and one patient previously treated for superficial infection followed by chronic local discomfort had no evidence of recurrent infection.

In Group B, patients showed mild uptake of the $^{18}$F-FDG seen at the level of the device connector, indicating inflammation. There was no such abnormal uptake in Group C.
The difference in the images between the infected and noninfected patients shows that this PET/CT method can distinguish between postoperative inflammation and active infection. Further, the patients with no $^{18}$F-FDG uptake despite some symptoms of infection had a good outcome with antibiotic therapy alone, suggesting that $^{18}$F-FDG PET/CT could help risk-stratify these patients and guide their treatment.

**Counting the cost**

Sarrazin told *heartwire* said that his institution is now routinely using $^{18}$F-FDG-PET/CT to identify device infection, but he expects future research to better clarify the patient population for which $^{18}$F-FDG-PET/CT imaging of possible device infection is cost-effective. "People don't like to do extraction because of the risk of rupture and perforation, and people can die as well. So if you can validate that it's really infected, it may save costs, because if you do the extraction and have to reimplant, it can be very expensive."

Sarrazin's group is currently studying $^{18}$F-FDG-PET/CT in patients with no definitive sign of local infection but with infection in their bloodstream and some signs of possible vegetation around the device leads. "Most people would say that you should take out the device from those patients," he said. But studies show that what appears to be infection vegetation on TEEs are often clots, fibrin, or other inflammatory tissue that isn't infected. If the false-negative rate of the $^{18}$F-FDG-PET test is not unacceptably high, this method may be able to pick out patients in this group that do not require immediate extraction and can instead be safely treated more conservatively, he said.

In an accompanying editorial [2], Dr Jeffrey Brinker (Johns Hopkins University, Baltimore, MD) writes that the evidence supporting routine $^{18}$F-FDG-PET/T imaging of suspected implanted device infection is "encouraging," but "wider experience is needed before such a recommendation can be made."

"The scan is relatively expensive (at least three times that of a TEE at my institution), and it exposes the patient to radiation, which admittedly is modest considering the importance of establishing a diagnosis. While its use at this time is justified in diagnostic dilemmas, a better appreciation of the incidence of false-negative and false-positive scans as well as the possible causes of such would be necessary before it is widely embraced."

**Subcutaneous ICD designed to prevent device infections**

On April 26, FDA's Circulatory System Devices Panel will review Cameron Health's premarket approval application for the S-ICD, a completely subcutaneous implantable defibrillator that does not require an electrode to be placed either on or in the heart and, unlike most ICD systems, does not require leads to be passed through the venous system. As reported by *heartwire*, an advantage of the S-ICD touted by Cameron is its lack of a transvenous pathway by which microorganisms can reach the endocardium.

In the 321-patient pivotal trial supporting Cameron's application, there were 18 total infections reported, four of which were system infections requiring explant. The rest were superficial. Overall,
over 97% of patients in the trial were complication-free at 180 days postimplant, which easily met the prespecified safety performance goal for the trial of a 79% complication-free rate.


All authors have reported that they have no relationships relevant to this paper to disclose.
ACE inhibitors better ARBs in new meta-analysis in hypertensives

new meta-analysis has shown that use of ACE inhibitors is associated with a 10% reduction in all-cause mortality over four years in hypertensive patients, compared with contemporary therapy that included blood-pressure lowering with drugs other than ACE inhibitors or angiotensin-receptor blockers (ARBs) [1]. In contrast, ARBs had a neutral effect on deaths, note Dr Laura C van Vark (Erasmus Medical Center, Rotterdam, the Netherlands) and colleagues in their report, published online April 17, 2012 in the European Heart Journal.

Even a small reduction in mortality in absolute terms would translate into lots of lives saved, at little cost, because most ACE inhibitors are now available generically.

This is the first study that scientifically evaluates the value of renin-angiotensin-aldosterone-system (RAAS) inhibitors on mortality in their main indication of hypertension, say van Vark and colleagues. All previous findings of reductions in both cardiovascular morbidity and mortality with ACE inhibitors and ARBs have been in trials that primarily enrolled patients with indications such as heart failure and coronary artery disease, she and her colleagues note.

Coauthor Dr K Martijn Akkerhuis (Erasmus Medical Center) told heartwire: "These new findings provide an additional argument to treat patients with hypertension with ACE inhibitors. This provides an extra mortality benefit, albeit small in absolute terms (3.8 per 1000 patient-years), but remember this was in addition to contemporary background therapy with aspirin, statins, and other agents.

"Also, because millions suffer from hypertension, even a small reduction in mortality in absolute terms would translate into lots of lives saved, at little cost, because most ACE inhibitors are now available generically. This finding will enhance the widespread use of these agents as a first-line treatment option," he stresses.

Controversial finding should be interpreted with caution

The researchers acknowledge that the differential effect between ACE inhibitors and ARBs "should be considered a post hoc observation and interpreted with caution." But Akkerhuis notes that a meta-analysis of 37 trials published last year also showed a neutral effect of ARBs on mortality in a broad population of patients. Dr Franz H Messerli (St Luke Roosevelt Hospital, New York, NY), who was senior author on this ARB meta-analysis but is not involved in the new research, told heartwire there are a couple of possible explanations.

Previous work has shown ACE inhibitors to be relatively more cardioprotective, whereas ARBs are more cerebroprotective, Messerli says. "Although stroke remains the most devastating complication of hypertension, many more people die of heart disease than of cerebrovascular disease. Thus, cardioprotection is prone to have a greater impact on mortality than cerebroprotection," he notes. And, on average, ARB trials were done more recently than ACE-inhibitor trials. "The event rate has been declining over the past few years due to concomitant statin treatment, etc, and obviously it is much harder to show benefits with low than with high event rates," he observes.
Dr Adrian Brady (University of Glasgow, Scotland), a European Society of Cardiology spokesperson on hypertension, says meta-analyses are "bouillabaisse. It depends what you put into them. van Vark [et al’s] findings are based on a selected set of trials, but they leave out some crucial ones, principally ONTARGET, which would negate their findings." Also, they "chose mortality as the only end point to analyze, which is unusual for a study of people who are basically healthy and middle-aged. And four-year mortality doesn't really tell you lifetime mortality."

Several other meta-analyses have shown equivalence between ACE inhibitors and ARBs in terms of outcomes such as MI and stroke, he asserts, adding that, in his opinion, "avoiding a nonfatal stroke is the most important end point, and on this all [antihypertensive] drugs are broadly similar."

"Lowering BP is the most important thing. Which drug you use is a long, long way secondary.

ACE inhibitors and ARBs "are both valuable classes of drugs," Brady stresses, and although there will always be individuals for whom one drug class is slightly better than another, "lowering BP is the most important thing. Which drug you use is a long, long way secondary."

Akkerhuis acknowledges: "What we found is kind of controversial. There are believers and there are nonbelievers. It would not surprise me if we get a lot of letters to the editor [on this]," he says, adding that there "should be more research on this topic."

**Treatment effect results entirely from ACE inhibitors**

van Vark et al analyzed 20 cardiovascular morbidity-mortality trials performed between 2000 and 2011; at least two-thirds of the patients in each trial had to have been diagnosed with hypertension—so that the expected benefits would come mainly from a decrease in BP—and randomized to treatment with a RAAS inhibitor or control (placebo, active control, or usual care).

They note that INVEST, ACCOMPLISH, and ONTARGET were excluded from the analysis because RAAS inhibitors were used simultaneously in both trial arms in these studies.

The evidence, apart from our study—the evidence in the whole spectrum of patients—is solid and substantial, and so much larger for ACE inhibitors than for ARBs.

Their cohort included 158,998 patients, 71,401 of whom took RAAS inhibitors and 87,597 control treatment. The incidence of all-cause death was 20.9 and 23.3 per 1000 patient-years in those randomized to RAAS inhibition and controls, respectively.

Overall, RAAS inhibition was associated with a 5% reduction in all-cause mortality (HR 0.95; p=0.032) and a 7% reduction in cardiovascular mortality (HR 0.93; p=0.018) over a mean follow-up of 4.3 years.

Although the primary aim was to evaluate RAAS inhibitors as a whole, ACE inhibitors and ARBs have partly different modes of action, so the researchers decided to also look at the two drug classes separately. Drilling down into the data in this way, they discovered that the observed treatment effect "resulted entirely from the class of ACE inhibitors," which were associated with a significant 10%
reduction in all-cause mortality (HR 0.90; p=0.004), whereas no mortality benefit could be demonstrated with ARB treatment (HR 0.99; p=0.683).

This mortality reduction was found when compared with placebo as well as in comparison with a broad range of other contemporary risk-reduction strategies, including statins, antiplatelet therapy, beta blockers, and diuretics, van Vark et al note. "The findings are firm," they state.

**Don’t change treatment recommendations at the moment**

This difference in treatment effect between ACE inhibitors and ARBs on all-cause mortality was statistically significant (p for heterogeneity=0.036). But the difference in effect on cardiovascular mortality between ACE inhibitors and ARBs was not, the researchers note, adding also that two previous studies designed to compare these two drug classes in a hypertensive population—ONTARGET and DETAIL—did not show a differential treatment effect.

"Thus, at present, the results of this analysis do not warrant changing clinical-practice treatment guidelines that recommend that an ARB may be used in ACE-inhibitor-intolerant patients," they state.

But Akkerhuis stresses that ACE inhibitors should be used as first-line treatment, unless there is a contraindication or the patient belongs to a group that is known not to respond well to ACE inhibitors (eg, African Americans).

"The evidence, apart from our study—the evidence in the whole spectrum of patients—is solid and substantial and so much larger for ACE inhibitors than for ARBs," he notes.

Brady observes, however, that while "it's always good to shake the tree of hypertension," ACE inhibitors themselves are not without drawbacks. There are a number of deaths per million users from angioedema with this drug class, and patient tolerability is an issue, with coughs on ACE inhibitors deterring many from taking their medication, he notes.

He adds that ARBs such as losartan and candesartan are now off patent in many markets, so cost comparisons between the two drug classes are also becoming less important.

Cutting, taxing salt would trim CVD deaths by 3% in half the world. A combined approach of reducing salt content by just 10% in processed foods and taxing foods with high salt content could reduce cardiovascular deaths in developing countries by as much as 3%, a new modeling study suggests. This two-pronged approach would also be cheap, Dr Thomas Gaziano (Harvard School of Medicine, Boston, MA) told journalists this past Saturday at the World Congress of Cardiology 2012.

"A 3% reduction is considerable," Gaziano told heartwire. "It would translate to 500 000 fewer deaths per year if there were global adoption or 250 000 in the 19 countries we [modeled]. Also several million nonfatal heart attacks and strokes would be prevented."

Hypertension is the number-one risk factor for death worldwide, accounting for 12.8% of deaths every year, Gaziano noted. It also accounts for 10% of all healthcare spending worldwide—$450 billion per year in the US alone.

Gaziano and colleagues modeled the impact of applying the approach to sodium reduction used in the UK to 19 developing countries, making up half the world's population. That approach includes voluntary collaboration on the part of food manufacturers to reduce sodium content by 10% and adding a 40% tax to salty foods—similar to the taxes applied to tobacco in many countries.

According to Gaziano, both strategies proved cost saving in all countries and would lead to a drop of roughly 3% in the rate of cardiovascular deaths. Stroke rates would drop even more sharply, he added, by as much as 5%.

Collaboration with industry to reduce sodium content in foods was the more effective strategy of the two and produced the most cost savings, he noted. Both, however, were cheap—in the range of $43 to $49 per capita over the lifetime of the individual.

**Screening would cut another 3%**

Gaziano and his coinvestigators also modeled a strategy of increased screening and treatment for high-risk hypertensives. Here, too, they found that population screening would also reduce cardiovascular deaths in low- and middle-income countries by roughly 3% and at a cost per disability-
adjusted life-year falling well below accepted cost-efficacy cut points used in the US and UK and by the World Health Organization.

In interviews, Gaziano stressed the model wasn’t ambitious in its salt targets—rather than set a specific level that industry would be asked to conform with, the model looked only at whether a 10% reduction would have any impact, even though, for many countries, a 10% reduction would still leave daily sodium-intake levels far higher than those recommended by groups such as the AHA and other professional organizations. Daily guidelines for maximum sodium consumption are 2300 mg among the general population and 1500 mg for specific, high-risk populations, such as African Americans and those with hypertension, diabetes, and chronic kidney disease—a broad group that likely covers more than half of the US population alone.

The countries modeled in Gaziano’s study were primarily in South and Central America, South and Central Africa, and the Middle East, as well as India, Russia, and China.

**Getting to global targets**

Also speaking with the press, World Heart Federation CEO Johanna Ralston pointed out that a 25% reduction in blood pressure, globally, is one of the targets set during last year’s UN Summit on Noncommunicable Disease in New York, which also set a 25% reduction in premature deaths due to cardiovascular causes overall. Global leaders are to sign on to the WHO’s cardiovascular mortality goals before May 2012.

"Timing of release of this study is extremely important," she said. "This study provides critical evidence to make the case to ministries of finance and other decision-makers of the importance of simple yet critical interventions in improving the health of their populations," she said.

Gaziano did the math for heartwire: "Each 3% is about 12.5% of that [WHO] target, meaning that you need about eight such interventions to achieve the goal [of 25%]. If, say, one salt intervention and the screening intervention were adopted, this would get the world 6%, or one-quarter, of the 25% goal. Smoking interventions, improvements in acute treatments, and other dietary interventions to reduce saturated or trans-fat, etc, will need to fill the gap."
Primary pericardial spindle cell sarcoma mimicking left main coronary artery disease

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Primary spindle cell sarcoma in the heart is a very uncommon disease. Although primary atrial or pulmonary vein spindle cell sarcomas have been sporadically reported, pericardial spindle cell sarcoma is rarely seen in currently available data. The commentary here is on a primary pericardial spindle cell sarcoma that was preliminarily misjudged to be left main coronary artery disease.

Key words Spindle cell sarcoma Pericardium - Coronary artery disease
A Pilot Study of Systolic Dyssynchrony Index by Real Time Three-Dimensional Echocardiography and Doppler Tissue Imaging Parameters Predicting the Hemodynamic Response to Biventricular Pacing in the Early Postoperative Period after Cardiac Surgery

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Keywords:
- cardiac resynchronization therapy;
- cardiac surgery;
- RT3DE echocardiography;
- systolic dyssynchrony index;
- heart failure;
- hemodynamics

Objective: To evaluate systolic dyssynchrony index (SDI) measured by real time three-dimensional echocardiography (RT3DE) and Doppler tissue imaging (DTI) dyssynchrony parameters in predicting the hemodynamic response to biventricular (BIV) pacing in the early postoperative period after cardiac surgery. To compare right ventricular (RV) and BIV pacing using invasively measured hemodynamic values.

Methods: A prospective randomized clinical study enrolling 11 patients with ischemic heart disease, concomitant valvular heart disease, and left ventricular ejection fraction (LVEF) ≤ 35% comparing preoperative SDI by RT3DE and DTI LV dyssynchrony parameters to hemodynamic values obtained during RV or BIV sequential (DDD) epicardial pacing in the first 72 hours after cardiac surgery. Results: BIV pacing produced a statistically significant higher cardiac output (CO) (6.27 ± 1.55 L/min) and cardiac index (CI) (3.44 ± 0.93 L/min per m²) than RV pacing (CO 5.44 ± 0.97 L/min, CI 3.03 ± 0.83 L/min per m², P < 0.05). We found a statistically moderate correlation between preoperative SDI by RT3DE and CO (r = 0.596, P < 0.05) and a
nonsignificant correlation to CI ($r = 0.535$, $P < 0.10$) during BIV pacing. No correlation was observed between DTI dyssynchrony parameters and measured hemodynamic values. BIV pacing reduced the ICU stay and inotropic support requirements of patients after heart surgery. Conclusions: SDI measured preoperatively using RT3DE can predict CO during BIV pacing in the early postoperative period after cardiac surgery. BIV pacing is more hemodynamically effective than RV pacing in patients with LV dysfunction after coronary artery bypass grafting with or without a valve procedure.
Scar Tissue Becomes Heart Muscle in Mice.

is possible to convert scar tissue in the heart to functioning cardiomyocytes following a myocardial infarction (MI), a proof-of-concept study in mice showed.

Both in cell culture and in mice, a combination of microRNAs reprogrammed cardiac fibroblasts to express genes and other characteristics of heart muscle cells, Maria Mirotsou, PhD, and Victor Dzau, MD, of Duke University, and colleagues reported online in Circulation Research.

"That's very encouraging," Dzau said in an interview. "Now let's prove that it really helps function and survival."

He said that until recently, no other approach to converting fibroblasts to functioning cardiomyocytes had been shown to work in a living animal. He noted that a research group from the University of California San Francisco led by Deepak Srivastava, MD, recently reported in Nature that using transcription factors could achieve direct reprogramming with low efficiency in mice.

What's different about the current study is the use of microRNAs, which are "master regulators" of numerous genes and -- with their smaller size -- are more easily used than transcription factors, according to Dzau.

It's too early to tell whether using transcription factors or microRNA is better, he said, but both groups have shown that transforming fibroblasts in a living animal is possible.

Several steps still need to be completed before the microRNA technique could be used to regenerate damaged heart muscle in humans, Dzau said.

First, the concentration and delivery of the microRNAs have to be optimized. Then, the findings in mice will have to be reproduced in larger animals -- such as mini pigs and nonhuman primates. Only then could human studies begin, starting with tests of toxicity.

Assuming the technique proves effective in humans, Dzau said "the sky's the limit" in terms of the potential clinical applications, not only in repairing a heart damaged by MI -- and possibly staving off heart failure -- but in regenerating all different types of tissues in the body.

"I think the excitement about this is you can bypass the use of stem cells," he said.

Mirotsou, Dzau, and colleagues selected six candidate microRNAs for their study based on the involvement of the molecules in cardiac muscle development and differentiation. The goal was to mimic the developmental process to reprogram the fibroblasts.

In cell cultures, the researchers found that a combination of four microRNAs -- 1, 133, 208, and 499 -- induced the fibroblasts to express genes specific to cardiomyocytes and display sarcomeric organization, spontaneous calcium oscillations, and mechanical contractions.

The efficiency of reprogramming was enhanced eight- to 10-fold by the addition of JAK inhibitor I treatment.
The same process proved effective when the microRNAs were administered to mice with induced heart attacks.

Currently, the microRNAs are delivered using viral vectors, and Dzau said he and his colleagues will be able to design a vector that contains all of the microRNAs because of their small size.

If used in humans, the vectors would be delivered down the coronary artery during angiography using catheters. If the vectors get washed out too quickly using that technique, different types of catheters can deliver them directly to the damaged site.

It is possible, Dzau said, that in the future the microRNAs will be able to be modified to allow for systemic administration.

reference: Jayawardena T, et al "MicroRNA-mediated in vitro and in vivo direct reprogramming of cardiac fibroblasts to cardiomyocytes" Cir Res 2012; DOI: 10.1161/CIRCRESAHA.112.269035. The study was supported by National Heart, Lung, and Blood Institute grants, the Edna and Fred L. Mandel Jr. Foundation, and the Foundation Leducq. Mirotou is also supported by an American Heart Association National Scientist Development Award. Two of the other study authors reported support from the NIH. The authors reported that they had no conflicts of interest.
HIV Linked to Risk of Sudden Cardiac Death

People with HIV have more than four times the risk of sudden cardiac death than the general population, researchers reported.

In a large cohort of HIV-positive people in San Francisco, the mean rate of sudden cardiac death over a 10-year period was 2.6 per 1,000 person-years, according to Zian Tseng, MD, of the University of California San Francisco, and colleagues.

That was 4.46 times higher than expected given the background rate of sudden cardiac death in the city (6.73 based on 2007 rate and population), Tseng and colleagues reported in the May 15 issue of the *Journal of the American College of Cardiology*.

The underlying mechanism that causes the increased risk remains unclear, the researchers noted, but the findings suggest that physicians treating HIV patients should be aware of the danger.

The study arose out of earlier research into sudden death in San Francisco, Tseng said in a statement.

"I noticed that many of these cases involved individuals with HIV infection who were dying suddenly," he said. "I wondered if there was some sort of connection there."

To find out, he and colleagues studied medical records of 2,860 consecutive HIV patients, all at least 18-years-old, enrolled between April 1, 2000, and Aug. 31, 2009 at a public HIV clinic in San Francisco.

Over a median follow-up of 3.7 years, there were 230 deaths in the cohort. Most of those, as expected, were from AIDS (131 or 57%), 30 (13%) met criteria for sudden cardiac death. There were also 25 deaths from other natural disease and 44 from overdose, suicide, or unknown cause.

All told, the 30 sudden cardiac deaths accounted for 86% of all 35 cardiac deaths, the researchers found.

Patients who died of sudden cardiac death were older than those who died of AIDS, had more robust immune systems, and had lower viral loads. Specifically, the average age of people who died of AIDS was 44.9, compared with 49 for those who had a sudden cardiac death. The difference was significant at \( P<0.02 \).

Also, the median count of CD4-positive T cells was 87 cells/mm³ of blood for those who died of AIDS, compared with 312 cells/mm³ of blood for those who had sudden cardiac death. The difference was highly significant at \( P=0.0001 \).

And for those who died of AIDS, the median plasma viral load was 4.8 log₁₀ copies of HIV RNA/mm versus 3.8 log₁₀ copies of HIV RNA/mm for those who had sudden cardiac death. The difference was significant at \( P=0.009 \).

Those findings suggest that patients are at risk for sudden cardiac death "even in the setting of mild HIV disease," the researchers argued.

On the other hand, some risk factors were evident, they reported.

Compared with those who died of AIDS or other natural causes combined, those who died of sudden cardiac death had elevated rates of the following:

- Prior myocardial infarction: 17% versus 1% (\( P<0.0005 \))
- Cardiomyopathy: 23% versus 3% (\( P<0.0005 \))
- Heart failure: 30% versus 9% (\( P<0.004 \))
- Arrhythmias: 20% versus 3% (\( P<0.003 \))

Tseng and colleagues cautioned that the study was retrospective and it is possible that the rate of sudden cardiac death was over-estimated. Nor did chart data allow extraction of the duration of antiretroviral treatment, which might be a risk factor.
Finally, they noted, patients with prevalent cardiovascular disease were over-represented in the cohort, which might have affected the outcome.

They called for further studies to look at the underlying mechanisms in this patient population, "which may include inflammation, antiretroviral therapy interruption, and concomitant medications," they said.


The study was supported by the National Heart, Lung, and Blood Institute, Veterans Affairs, and the NIH. Tseng reported financial links with Biotronik.
More on ECG screening to prevent sudden death in the young: On risk, the Italian experience, and notes from the real world

Posted May 06, 2012 at 09:44 AM, EDT by John Mandrola

Earlier this week, I wrote about one of my favorite topics in medicine: the ECG. This 12-pronged view of cardiac vectors catapulted my interest in the human heart. I love everything about ECGs. I see them as beautiful instruments for the diagnosis and treatment of heart disease. Niftier yet, ECG skills cannot be Googled; they must be gathered with mentoring and time. The story relayed in those squiggles has yet to be digitized. I like that too.

That's why it hurts to take the view that mandating the use of screening ECGs will not completely eliminate the chance that a young person dies suddenly. The buzz generated from my posts (here and here) earlier this week inspired me to again review the actual evidence. I have learned tons more and thought that I would share this incremental knowledge. I am interested in hearing your thoughts, too.

On the rareness of sudden death in the young

In our country alone, tens of millions of young people go out to play each day. The incidence of sudden death published in most studies range from one to two deaths per 100 000 patient-years. Another way of saying this: over a decade, the chances of a youngster dying from cardiac causes are one to two in a million. That's the problem; it's like lightning strikes. Imagine comparing strategies that could prevent one from dying from lightning. Other than never going outside (not ever playing), how would one show one avoidance strategy better than another? And what if the avoidance strategy caused problems in many more than the one in a million saved?

The Italian strategy

Much of the excitement about using ECGs for screening comes from the "evangelical zeal" with which Italy screens its young athletes. I spent a great deal of time learning the specifics of what happens in Italy. They do things very differently. As mandated by Italian law, all those who participate in sport must undergo a preparticipation evaluation, including an ECG. Unlike in the US, where any licensed medical person can certify a sports physical, in Italy, these evaluations are done in selected sports centers by specially trained experts. The Italian government funds the evaluations, and Italian doctors hold the final say as to whether a kid is disqualified.

The Italian data: Results

I was surprised to learn that data supporting the Italian experience comes from only one observational study from the Veneto region of Northern Italy, a small area that comprises only 8% of the population of Italy. The results of this 2006 JAMA study serve as an example of how relative risk reduction paints a different picture from that of absolute risk reduction. The Italian researchers reported that sudden death in athletes was reduced by 89% after an ECG screening program was instituted. That sounds impressive. But consider this: over a decade, the absolute number of deaths went from thirty in a million to four in a million. The question is not whether this is significant—any life saved is—it's whether these tiny absolute changes were the result of mandatory ECG screening.
The Italian data do not support the use of mandated and widespread screening ECGs? Here are three lines of reasoning.

First, the Italian findings cannot be corroborated in other countries. US researchers found that sudden death rates in non–ECG-screened Minnesotans did not differ from those in Veneto. When researchers from Israel compared the sudden death rates in the decade before mandatory ECG screening with the decade after, they found no difference. In Denmark, the presports evaluation is neither systematic nor mandated. Despite these lax requirements, this study found young Danes had the same (very low) sudden death rates as those in Italy and the US. What's more, this Danish trial revealed that sudden death occurred more often in nonathletes—a finding that supports Dr Barry Maron's recommendation that screening for sudden death must not be limited to young athletes.

The second counterargument centers on how Italian researchers compared death rates before and after the policy change. Mandatory ECG screening in Italy began in 1981. The researchers compared death rates in only the two years before (1979–81) with the 25 years after. That's not a good comparison. Among other potential confounders is the fact that rare events can vary greatly year to year. For example, in the Israeli study, if only the two years before ECG screening were used, there would have been a significant difference. When they used the 10-year window before and after, there was no difference.

Another confounding variable in the Italian study is the chance that improvements in resuscitation abilities over the past two decades caused the lower death rates. That's the problem with observational trials done over decades—it's hard to sort out what caused the difference, or if it was a real difference at all.

That's a lot of information. Let's summarize: The Italian experience, reported from a small homogenous region of a country with socialized medicine, shares no similarities to our risk-averse US healthcare system. The Italian thesis, that ECG screening saves lives, stems from one observational trial that cannot be confirmed by other researchers in other countries.

**My messages**

To parents who ask what are the best means to screen their young one, I'd have to answer that I don't know. It depends on your inherent feelings about risk. There's the risk of missing a rare heart disorder that may or may not increase the risk of sudden death. But then, there is—in the US for sure—a greater chance that "playing it safe" risks making your well child sick. There's also the chance that even an ECG would not find the abnormality—as in the third-leading cause of sudden death in the young, an anomalous coronary artery.

To US doctors clearing young athletes for sport, I'd recommend four focus points:

- Ask about heart symptoms, like fainting, rapid heartbeats, and chest pain. I know; this isn't as easy as it sounds—because the overwhelming majority of cross-country runners who faint or cry in pain after a race don't have heart disease. (Personal observation from years as a cross-country coach.)
- Ask about a family history of sudden death or fainting—an important clue for long-QT syndrome.
- Pay close attention to heart tones. Really listen for the murmur of hypertrophic cardiomyopathy.
- If you feel an ECG is needed, find a cardiologist that is both comfortable with ECG interpretation and gutsy enough to say normal is normal.
Big picture

The debate about how much sudden death risk we—as a society, as parents, as doctors—can tolerate speaks to where medicine is and where it is going. We can prod, and measure, and image, and worry, so much. But in the end, too much bubble wrap risks ruining the fun of life.

I'm sorry for not being more hopeful. I just can't see that mass ECG screening in the US would work. Do you? Yes, it's a paradox. While our medical advances have been breathtaking, we struggle mightily with the simple stuff. We need help with our risk aversion. For most doctors, even me, at this moment, it's so hard, so very hard, so risky, so scary, to say, "Yep, it's okay, you are good, no problems, you won't die."

So we don't say that. We say, "You need more tests; you need a signal-averaged ECG, an MRI, a genetic test." Or worse, we decree, "You can't play."

I'm open to hope on this matter. For the record, I have read reports of privately funded pilot projects in small enclaves of enlightened communities. Still, I am unconvinced about the effectiveness of mandates and widespread screening on a large scale.

Let's finish on an upbeat note.

At this time, the most actionable and effective means to prevent death from cardiac arrest is to advocate for AEDs and CPR education. Inexpensive AEDs improve survival—of the old and young as well as the athletic and nonathletic. We can all agree that widespread education on the importance of a rapid delivery of a shock (or effective CPR) to a person suffering cardiac arrest deserves more emphasis and funding. It's hard to see the downsides of having more lifesaving devices and more educated people around to use them.

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Viskin S. Antagonist: Routine screening of all athletes prior to participation in competitive sports should be mandatory to prevent sudden cardiac death. *Heart Rhythm* 2007; 4:525–528.
Predictors of long-term success after catheter ablation of atriofascicular accessory pathways.


BACKGROUND:

Electrophysiologic characteristics, mapping strategies, and acute success rates of radiofrequency catheter ablation of atriofascicular accessory pathways are well described. However, data on long-term prognosis and predictors for freedom from arrhythmias are lacking.

OBJECTIVE:

To report our 20-year single-center experience on ablation of atriofascicular fibers.

METHOD:

Between 1992 and 2010, 34 patients with atriofascicular accessory pathways underwent catheter ablation at our institution because of symptomatic antidromic atrioventricular reentrant tachycardias. Radiofrequency procedures were retrospectively analyzed, and patients were followed for recurrences of tachyarrhythmias. Electrocardiograms (before and after ablation and at follow-up) were analyzed for each patient.

RESULTS:

Successful catheter ablation of the atriofascicular fiber was achieved in 23 (68%) patients. Mechanical block during mapping occurred in 3 (9%) patients, and in 2 of them ablation was performed at the site of mechanical block. Mere modification of conduction properties of the pathway without complete block was achieved in 5 patients (15%). Fast pathway ablation was performed in 2 (6%) of the patients ablated in the early 1990s. During follow-up of 9.3 ± 5.5 years, 24 patients (71%) remained free of tachyarrhythmias, 7 reported significant improvement, and 3 (9%) had no change in symptoms after ablation. Long-term success was identical between patients from the first (1992-1999) and second (2000-2010) decade (12 of 17 [71%] vs 12 of 17 [71%]). It was 87% in those with complete block of the atriofascicular fiber while all patients with mechanical block during mapping reported recurrences. Fast pathway ablation was complicated by complete atrioventricular block in 1 patient, who required pacemaker implantation 18 years after ablation owing to loss of conduction properties of the atriofascicular fiber over the years. On analyzing patients with preexcitation before ablation (n = 16; 47%), we found that the PR interval after ablation was significantly longer only in those without recurrence (162 ± 21 ms vs 134 ± 21 ms; P = .042). None of the other analyzed electrocardiographic parameters, including PR, QRS duration, and preexcitation, had prognostic impact.
CONCLUSION:

Acute success of complete ablation of atriofascicular pathways is associated with excellent long-term success (87%). Mere modification of conduction properties of atriofascicular fibers or ablation at the sites of mechanical block are less promising end points of ablation with high recurrence rates. Technical innovations during decades may not further improve long-term outcome in these patients.

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Myofilament Ca Sensitization Increases Cytosolic Ca Binding Affinity, Alters Intracellular Ca Homeostasis, and Causes Pause-Dependent Ca Triggered Arrhythmia


Rationale:
Ca binding to the troponin complex represents a major portion of cytosolic Ca buffering. Troponin mutations that increase myofilament Ca sensitivity are associated with familial hypertrophic cardiomyopathy and confer a high risk for sudden death. In mice, Ca sensitization causes ventricular arrhythmias, but the underlying mechanisms remain unclear.

Objective:
To test the hypothesis that myofilament Ca sensitization increases cytosolic Ca buffering and to determine the resulting arrhythmogenic changes in Ca homeostasis in the intact mouse heart.

Methods and Results:
Using cardiomyocytes isolated from mice expressing troponin T (TnT) mutants (TnT-I79N, TnT-F110I, TnT-R278C), we found that increasing myofilament Ca sensitivity produced a proportional increase in cytosolic Ca binding. The underlying cause was an increase in the cytosolic Ca binding affinity, whereas maximal Ca binding capacity was unchanged. The effect was sufficiently large to alter Ca handling in intact mouse hearts at physiological heart rates, resulting in increased end-diastolic [Ca] at fast pacing rates, and enhanced sarcoplasmic reticulum Ca content and release after pauses. Accordingly, action potential (AP) regulation was altered, with postpause action potential prolongation, afterdepolarizations, and triggered activity. Acute Ca sensitization with EMD 57033 mimicked the effects of Ca-sensitizing TnT mutants and produced pause-dependent ventricular ectopy and sustained ventricular tachycardia after acute myocardial infarction.

Conclusions:
Myofilament Ca sensitization increases cytosolic Ca binding affinity. A major proarrhythmic consequence is a pause-dependent potentiation of Ca release, action potential prolongation, and triggered activity. Increased cytosolic Ca binding represents a novel mechanism of pause-dependent arrhythmia that may be relevant for inherited and acquired cardiomyopathies.

Key Words:  myofilament Ca sensitivity . familial hypertrophic cardiomyopathy / Ca buffering  . early afterdepolarizations / arrhythmia / Received March 22, 2012. Revision received May 17, 2012. Accepted May 21, 2012. + Author AffiliationsFrom the Division of Clinical Pharmacology (T.S., S.H., O.G., D.K., H.-S.H., B.C.K.), Department of Medicine, Vanderbilt University Medical School, Nashville, TN; and Biomedical Engineering and Physics (R.V., F.J.B.), Vanderbilt University, Nashville, TN. Correspondence to Björn C. Knollmann, MD, PhD, Professor of Medicine and Pharmacology, Division of Clinical Pharmacology, Oates Institute for Experimental Therapeutics, Vanderbilt University School of Medicine, Medical Research Building IV, Rm. 1265, 2215B Garland Ave, Nashville, TN 37232-0575. E-mail bjorn.knollmann@vanderbilt.edu
Meta-Analysis of Cardiovascular Outcomes With Dronedarone in Patients With Atrial Fibrillation or Heart Failure.

Chatterjee S, Ghosh J, Lichstein E, Aikat S, Mukherjee D.
Meta-Analysis of Cardiovascular Outcomes With Dronedarone in Patients With Atrial Fibrillation or Heart Failure.
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Dronedarone is a benzofuran derivative approved by the Food and Drug Administration to decrease the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) and associated cardiovascular risk factors who are in sinus rhythm or will undergo cardioversion. There has been recent evidence to suggest that dronedarone may not have a favorable safety profile. We decided to evaluate all available evidence on the cardiovascular safety of this drug. A systematic search was made of the PubMed, CENTRAL, and EMBASE databases for randomized controlled trials from 1966 through 2011 comparing dronedarone to comparators in AF/heart failure. Intervention was dronedarone for AF for some studies and heart failure for others. Comparators included standard medical therapy and/or placebo and amiodarone for 1 study. Outcomes assessed were all-cause mortality, cardiovascular mortality, ventricular arrhythmias, embolic events, acute coronary syndrome, heart failure exacerbations, and hospitalization rates in the intervention versus comparator group at the end of ≥3 months of follow up with abstraction of data by 1 author. Seven randomized controlled trials were included in our analysis. Dronedarone use was associated with a trend toward worse all-cause and cardiovascular mortalities and increased heart failure exacerbations. It also showed numerically higher event rates for all other outcome events except acute coronary syndrome.

Our pooled analysis showed increased all-cause and cardiovascular mortalities and increased heart failure exacerbations with use of dronedarone across a wide spectrum of populations.

In conclusion, we recommend exercising caution using dronedarone, especially in patients with cardiovascular risk factors.

Maimonides Medical Center, Brooklyn, New York.
Toward magnetic resonance-guided electroanatomical voltage mapping for catheter ablation of scar-related ventricular tachycardia: a comparison of registration methods.

Tao Q, Milles J, Van Huls van Taxis C, Lamb HJ, Reiber JH, Zeppenfeld K, Van Dder Geest RJ.

Toward magnetic resonance-guided electroanatomical voltage mapping for catheter ablation of scar-related ventricular tachycardias (VT). Accurate and fast image integration of DE-MRI with EAVM is desirable for MR-guided ablation.

INTRODUCTION:
Integration of preprocedural delayed enhanced magnetic resonance imaging (DE-MRI) with electroanatomical voltage mapping (EAVM) may provide additional high-resolution substrate information for catheter ablation of scar-related ventricular tachycardias (VT). Accurate and fast image integration of DE-MRI with EAVM is desirable for MR-guided ablation.

METHODS AND RESULTS:
Twenty-six VT patients with large transmural scar underwent catheter ablation and preprocedural DE-MRI. With different registration models and EAVM input, 3 image integration methods were evaluated and compared to the commercial registration module CartoMerge. The performance was evaluated both in terms of distance measure that describes surface matching, and correlation measure that describes actual scar correspondence. Compared to CartoMerge, the method that uses the translation-and-rotation model and high-density EAVM input resulted in a registration error of 4.32±0.69 mm as compared to 4.84 ± 1.07 (P <0.05); the method that uses the translation model and high-density EAVM input resulted in a registration error of 4.60 ± 0.65 mm (P = NS); and the method that uses the translation model and a single anatomical landmark input resulted in a registration error of 6.58 ± 1.63 mm (P < 0.05). No significant difference in scar correlation was observed between all 3 methods and CartoMerge (P = NS).

CONCLUSIONS:
During VT ablation procedures, accurate integration of EAVM and DE-MRI can be achieved using a translation registration model and a single anatomical landmark. This model allows for image integration in minimal mapping time and is likely to reduce fluoroscopy time and increase procedure efficacy.
Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic effects

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Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic effects
American Heart Journal 2012 . Article in Press

This White Paper, written collaboratively by members of the Cardiac Safety Research Consortium from academia, industry, and regulatory agencies, discusses different methods to characterize the QT effects for drugs that have a substantial direct or indirect effect on heart rate. Descriptions and applications are provided for individualized QT–R-R correction, Holter bin, dynamic QT beat-to-beat, pharmacokinetic-pharmacodynamic modeling, and QT assessment at constant heart rate. Most of these techniques are optimally performed using continuous electrocardiogram data obtained in clinical studies designed to characterize a drug's effect on the QT interval. An important study design element is the collection of drug-free data over a range of heart rates seen on treatment. The range of heart rates is increased at baseline by using ambulatory electrocardiogram recordings in addition to those collected under semisupine, resting conditions. Discussions in this study summarize areas of emerging consensus and other areas in which consensus remains elusive and provide suggestions for additional research to further increase our knowledge and understanding of this topic.

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Reprint requests: Christine E. Garnett, PharmD, 10903 New Hampshire Ave, Building 51, Room 1260, Silver Spring, MD 20993-0002. St Paul's Cardiac Electrophysiology and St George's, University of London, London, England iCardiac Technologies, Rochester, NY Office of Biostatistics, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD AMPS, Montichiari, Italy AstraZeneca Global Medicines Development, Wilmington, DE Department of Clinical Science and Education, Section of Cardiology, Karolinska Institute, South Hospital, Stockholm, Sweden Sager Consulting Partners, Los Angeles, CA Hoffmann–La Roche, Nutley, NJ Received 20 February 2012; accepted 20 February 2012, published online 07 May 2012. Corrected Proof
New guidance for young people with Wolff-Parkinson-White (WPW) syndrome

A "first-of-its-kind" consensus statement on the management of asymptomatic patients with Wolff-Parkinson-White (WPW) syndrome should help clarify which young people should undergo catheter ablation, authors of the document say [1].

"While it is a small chance that an asymptomatic young person could end up having a life-threatening heart event, the number is not zero," lead author on the statement, Dr Mitchell I Cohen (Phoenix Children's Hospital, AZ), said in a press statement [2]. "Yet, catheter ablation for every child who has ever had a WPW pattern is also not the answer."

Cohen and colleagues released the statement last Friday at the Heart Rhythm Society (HRS) 2012 Scientific Sessions.

The guidance is explicitly directed at physicians treating young patients with WPW and defines young people as between eight and 21. At the crux of the document is the question of just when physicians should intervene—and when they shouldn't—in young people found, on ECGs, to have the signature electrocardiographic WPW pattern. These are increasingly important questions, given increased emphasis on preparticipation screening for sports in young people.

The expert consensus statement, a joint effort of the Pediatric and Congenital Electrophysiology Society (PACES) and the HRS, estimates that from one to three young people per 1000 likely have WPW, although many—around 65%—are asymptomatic.

The guideline writers recommend the following:

- If a child is old enough to comply, an exercise stress test to look for persistent preexcitation is "reasonable." Clear loss of preexcitation at physiologic heart rates is associated with lower risk of sudden death due to accessory pathways.
- Where noninvasive testing shows persistent or uncertain loss of preexcitation, diagnostic transesophageal or intracardiac electrophysiology studies are warranted. Recommendations, based on test results, include ablation or continued awareness and observation for symptoms.
- Ablation is a "reasonable" consideration in young people with a shortest preexcited RR interval (SPERRI) <250 ms. Young people with SPERRI >250 ms are lower risk, and ablation may be deferred.
- Patients deemed low risk who subsequently develop symptoms like syncope or palpitations may be eligible for ablation.
- WPW in the setting of structural heart disease increases risk for both atrial tachycardia and atrioventricular (AV) reciprocating tachycardia. Patients can be considered for ablation.
- Ablation may also be considered in asymptomatic patients with WPW who have ventricular dysfunction secondary to dyssynchronous contractions.
- Attention-deficit disorder (ADD) drugs may be considered in young people with asymptomatic WPW (as per American Heart Association guidelines).


PURPOSE:

Magnetically guided irrigated ablation has been introduced for atrial fibrillation (AF) ablation. However, data on ablation of persistent AF is scarce, and first-generation platinum-iridium catheters were burdened by char formation at the catheter tip. Furthermore, energy transmission of these catheters may be suboptimal. Irrigated gold-tip catheters have been introduced to overcome these problems.

METHODS:

Antral pulmonary vein (PV) isolation (PVAI) was performed using a 5-mm irrigated gold-tip magnetic catheter (power setting, 48 °C maximum, 50 W, 15 s lesion duration; flow-rate, 30 mL/min). The catheter tip was guided by a uniform magnetic field and a motor drive. Left atrial maps were created using an impedance-based left atrial reconstruction and fused with a preprocedural CT or an intraprocedural rotational angiography-based scan.

RESULTS:

Fifty-seven patients (42 male, 61.9 ± 8.8 years) underwent PVAI for symptomatic, drug-refractory persistent AF. PVAI was performed successfully in all patients confirmed by entrance block. Procedure time (skin-to-skin) was 214 ± 47 min (104-354 min). Fluoroscopy time was 31 ± 21 min. Ablation time was 4,153 ± 1,350 s. No char or thrombus formation was found at the catheter tip. One pericardial tamponade was observed. Freedom from atrial tachyarrhythmias could be achieved in 57.9 % of the patients included in a follow-up of 11.6 ± 4.2 month. There was a trend to a better outcome in patients without previous attempts of AF ablation (n = 48; 60.4 % vs. 44.4 %, p = 0.47).

CONCLUSIONS:

Remote magnetic navigation for PVAI seems to be safe and feasible using an irrigated gold-tip catheter. Effectiveness of this novel technique can be confirmed by mid-term outcome.

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Nearly uniform failure of atrial flutter ablation and continuation of antiarrhythmic agents (hybrid therapy) for the long-term control of atrial fibrillation

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Nearly uniform failure of atrial flutter ablation and continuation of antiarrhythmic agents (hybrid therapy) for the long-term control of atrial fibrillation
Journal of Interventional Cardiac Electrophysiology 2012 ; 2012, DOI: 10.1007/s10840-012-9679-0.

Background
Ablation for atrial flutter and continued pharmacologic therapy (hybrid therapy) is a management strategy when treatment with class I antiarrhythmic drugs organize atrial fibrillation (AF) into flutter. Previous studies with 2–3-year follow-up have reported satisfactory control of AF burden.

Objective
We evaluated the effectiveness of hybrid therapy after a follow-up of 5 years. We hypothesized that longer term follow-up would demonstrate eventual failure of this strategy to control AF.

Methods
A consecutive, retrospective evaluation of all first time ablations of right atrial flutter at the University of Pennsylvania between August 2003 and August 2005 was performed (n = 179). The study population consisted of 33 patients who had atrial flutter only after treatment of AF with class I antiarrhythmic drugs and was continued on them post-ablation. Follow-up data were obtained by reviewing records from our institution, from referring cardiologists, and from direct patient questionnaires.

Results
Atrial fibrillation recurrence was noted in 28 of 31 patients (90.3 %) who completed 5 years of follow-up. AF recurrence typically resulted in significant symptoms, although 21 % developed persistent AF and were eventually minimally symptomatic on a rate control strategy. A wide range of time to recurrence was observed (0.2–64.5 months) with 39 % recurring greater than 2 years post-ablation.

Conclusion
Hybrid therapy is not effective for long-term control of AF. Patients should be counseled about the likelihood of eventual AF recurrence and anticoagulation should be maintained indefinitely when this strategy is used.

Keywords  Atrial fibrillation – Atrial flutter – Hybrid therapy – Catheter ablation
The termination of persistent atrial fibrillation (AF) during catheter ablation has been associated in some, but not all, studies with reduced arrhythmia during clinical follow-up. We sought to determine the rate of persistent AF termination achievable with a stepwise ablation strategy, the predictors of AF termination, and the clinical outcomes associated with termination and nontermination. A total of 143 consecutive patients (age 62 ± 9 years, AF duration 5.7 ± 5.2 years) with persistent and longstanding persistent AF resistant to antiarrhythmic medication who presented in AF for catheter ablation were studied. Ablation was done with a stepwise approach, including pulmonary vein isolation, followed by complex fractionated atrial electrogram ablation and ablation of resultant atrial tachycardias. Clinical follow-up was then performed after a 2-month blanking period to assess arrhythmia recurrence, defined as AF or atrial tachycardia lasting ≥30 seconds. AF termination by ablation was achieved in 95 (66%) of the 143 patients. Multivariate predictors of AF termination included longer baseline AF cycle length (p = 0.001) and smaller left atrial size (p = 0.002). AF termination by ablation was associated with both a lower incidence of arrhythmia recurrence after a single procedure without antiarrhythmic drugs (p = 0.01) and overall clinical success (single or multiple procedures, with or without antiarrhythmic drugs; p = 0.005). On multivariate analysis, the predictors of overall clinical success included AF termination by ablation (p = 0.001), a shorter ablation duration (p = 0.002), younger age (p = 0.02), male gender (p = 0.03), and the presence of hypertension (p = 0.03).

In conclusion, among patients with persistent AF, termination of AF by ablation can be achieved in most patients and is associated with reduced recurrence of arrhythmia.

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We report the initiation of pacemaker-mediated tachycardia by a St Jude implantable cardioverter-defibrillator with a programmed Ventricular Intrinsic Preference algorithm used for minimizing or inhibiting right ventricular pacing. This feature prolongs the atrioventricular (AV) delay periodically to determine if ventricular sensed events follow atrial events. Retrograde ventriculoatrial conduction and pacemaker-mediated tachycardia were initiated by long extended AV delays of 300 and 400 milliseconds. The 400-millisecond AV delay consisted of the programmed sensed AV delay (100 milliseconds) plus the Ventricular Intrinsic Preference increment (200 milliseconds) plus 100 milliseconds imposed by the AutoCapture algorithm when it detected loss of ventricular capture.

Keywords: Cardiac pacemaker, Implantable cardioverter-defibrillator, Pacemaker-mediated tachycardia, Retrograde ventriculoatrial conduction, AutoCapture
Nonfluoroscopic Catheter Ablation of Cardiac Arrhythmias in Adults - Feasibility, Safety, and Efficacy

MANSOUR RAZMINIA, MF MANANKIL, PLS ERYAZICI, C ARRIETA-GARCIA, et al.
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Feasibility, Safety, and Efficacy
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Background:

Catheter ablations are traditionally performed using fluoroscopic guidance, exposing both patients and medical staff to the risks of radiation. Nonfluoroscopic catheter ablation has been used successfully to treat limited types of arrhythmias in children, but whether this approach has broad application in adults is uncertain. The purpose of this study was to evaluate the feasibility, safety, and efficacy of fluoroless catheter ablation in adults being treated for a range of arrhythmias.

Methods and Results:

Retrospective analysis was performed in 2 patient groups (both n = 60): (1) the nonfluoroscopy (NF) group consisting of consecutive adult patients, in which catheter positioning was accomplished exclusively with intracardiac electrograms (IE), electroanatomic mapping (EAM), and intracardiac echocardiography (ICE); and (2) the fluoroscopy (F) group, in which catheter positioning was additionally guided by fluoroscopy. The patients in the F group were selected to match the types of arrhythmias in the NF group. All ablation procedures were performed by one operator. The total procedure time did not differ between groups for any specific type of arrhythmia ablated. Acute procedural success was similar in both groups (NF, 59/60 [98%] and F, 60/60 [100%]). The complications were limited to a groin pseudoaneurysm in the NF group, and pericardial effusion and groin hematoma in the F group.

Conclusion:

Catheter ablations were efficiently and effectively performed in adults with a variety of arrhythmias using only IE, EAM, and ICE for catheter guidance. This nonfluoroscopic technique was feasible, posed no additional safety concerns, and should be readily implementable in most electrophysiology laboratories.

Keywords: atrial flutter; atrial fibrillation; catheter ablation; electroanatomic mapping; nonfluoroscopic
Nonfluoroscopic Catheter Ablation of Cardiac Arrhythmias in Adults
People who report having palpitations appear to have an increased risk of being diagnosed with atrial fibrillation in the future, a Norwegian study showed.

Self-reported palpitations were associated with incident atrial fibrillation over an average of 11 years of follow-up in both women (HR 1.62, 95% CI 1.29 to 2.02) and men (HR 1.91, 95% CI 1.54 to 2.35), according to Audhild Nyrnes, MD, of the University of Tromsø in Norway, and colleagues.

Also, the study confirmed hypertension as a significant predictor of developing the arrhythmia in both women (HR 1.98, 95% CI 1.46 to 2.69) and men (HR 1.40, 95% CI 1.13 to 1.74), the researchers reported online in the *European Journal of Preventive Cardiology*.

"The clinical implication of this would primarily be to emphasize the importance of adequate treatment of high blood pressure," the authors wrote. "We should also bear in mind that subjects with palpitations could have paroxysms of atrial fibrillation, and should be investigated further, with prolonged ECG monitoring."

Numerous risk factors have been established for atrial fibrillation, including age, gender, hypertension, various heart disease, obesity, physical inactivity, smoking, diabetes, inflammation, nutritional factors, and genetics, and the researchers evaluated self-perceived palpitations as a candidate.

They examined data from the Tromsø study, a prospective population-based cohort study of individuals living in that Norwegian town. The current analysis included 22,815 individuals who participated in the 1994-1995 survey. All were free from diagnosed atrial fibrillation at baseline.

The participants' ages ranged from 25 to 96 (mean age 46) at baseline.

Through an average follow-up of 11.1 years, 3% of women and 4.2% of men developed atrial fibrillation.

Palpitations were more frequent among those who developed atrial fibrillation than among those who did not for both women (41.6% versus 26.6%) and men (31% versus 17.6%). Those differences remained significant after multivariate adjustment.

In addition to hypertension and palpitations, other factors that were associated with a greater risk of incident atrial fibrillation in both sexes included the following:

- Body mass index (HR for every 1 SD increase 1.16 for women and 1.47 for men)
- Coronary heart disease (HR 1.43 for women and 1.61 for men)
- Age (HR for every 1 SD increase 4.34 for women and 4.06 for men)
- HDL cholesterol (HR for every 1 SD increase 1.12 for women and 1.16 for men)

Height was significantly associated with developing the arrhythmia in men only (HR 1.33, 95% CI 1.16 to 1.53) and diabetes was a predictor in women only (HR 1.61, 95% CI 1.06 to 2.45).

Predictors of lone atrial fibrillation -- defined as the arrhythmia occurring in the absence of heart disease, hypertension, or diabetes -- included age, height, and BMI for men (HRs 1.90 to 2.13) and age, HDL cholesterol, and palpitations for women (HRs 1.60 to 2.74).

Systolic blood pressure was inversely associated with lone atrial fibrillation in both sexes, a finding that remains unexplained, according to the researchers.

They acknowledged some limitations of the study, including the possibility that the hospital discharge lists were incomplete, the possibility that some individuals had undiagnosed atrial fibrillation, and the small numbers of patients with lone atrial fibrillation.

The study was supported by the Norwegian EXTRAFoundation for Health and Rehabilitation through EXTRA FUNDS, the Norwegian Heart and Lung Patient Organization, the Simon Fougner Hartmann's Family Foundation, and the Norwegian Health Association.

The authors reported that they had no conflicts of interest.
Paradoxical Change in Atrial Fibrillation Dominant Frequencies with Baroreflex-Mediated Parasympathetic Stimulation with Phenylephrine Infusion.


Introduction:

Parasympathetic stimulation is known to promote atrial fibrillation (AF) through shortening of atrial refractory periods. We hypothesized that baroreflex-mediated parasympathetic stimulation via phenylephrine (PE) infusion would increase AF rate as measured by dominant frequency (DF).

Methods and Results:

The protocol was performed in 27 patients (24 M, 59 ± 1 years old) prior to AF ablation. For 10 patients in AF, PE was infused until systolic blood pressure increased ≥30 mmHg. Electrograms were recorded in the left atrium before and after PE. DFs of each recording were calculated offline. Atrial effective refractory periods (ERPs) were measured before and after PE in 11 patients who were in sinus rhythm during the procedure. DFs were also measured in 6 patients in AF before and after complete parasympathetic blockade with atropine (0.04 mg/kg). PE resulted in increased RR intervals during sinus rhythm (1,170 ± 77 to 1,282 ± 85 ms, 0.03), consistent with parasympathetic effect on the sinus and AV nodes, respectively. DFs were 0.004). PE decreased by PE in the left atrium (6.2 ± 0.2 to 6.0 ± 0.2 Hz, P 0.07). Atropine resulted in a decreasing trend in DF in the left atrium = ms (P 0.07).

Conclusions:

Despite baroreflex-mediated = (5.9 ± 0.1 to 5.8 ± 0.1 Hz, P parasympathetic effect, PE produced a slowing of AF along with lengthening of ERP, while parasympathetic blockade also slowed DF. It is therefore likely that the direct and indirect adrenergic effects of PE on atrial electrophysiology are more prominent than its parasympathetic effects.

From the Division of Cardiology and Bluhm Cardiovascular Institute, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA. Baroreflex Response and AF Dominant Frequency.
BACKGROUND:

The hereditary Long QT Syndrome is a common cardiac disorder where ventricular repolarization is delayed, abnormally prolonging the QTc interval on electrocardiograms. LQTS is linked to various genetic loci, including the KCNH2 (HERG) gene that encodes the α-subunit of the cardiac potassium channel that carries I(Kr). Here, we report and characterize a novel pathologic missense mutation, G816V HERG, in a patient with sudden cardiac death.

METHODS:

Autopsy-derived tissue sample was used for DNA extraction and sequencing from an unexpected sudden death victim. The G816V HERG mutation was studied using heterologous expression in mammalian cell culture, whole cell patch clamp, confocal immunofluorescence, and immunochemical analyses.

RESULTS:

The mutant G816V HERG channel has reduced protein expression and shows a trafficking defective phenotype that is incapable of carrying current when expressed at physiological temperatures. The mutant channel showed reduced cell surface localization compared to wild-type HERG (WT HERG) but the mutant and wild-type subunits are capable of interacting. Expression studies at reduced temperatures enabled partial rescue of the trafficking defect with appearance of potassium currents, albeit with reduced current density and altered voltage-dependent activation. Lastly, we examined a potential role for hypokalemia as a contributory factor to the patient's lethal arrhythmia by possible low-potassium-induced degradation of WT HERG and haplo-insufficiency of G816V HERG.

CONCLUSION:

The G816V mutation in HERG causes a trafficking defect that acts in a partially dominant negative manner. This intermediate severity defect agrees with the mild clinical presentation in other family members harboring the same mutation. Possible hypokalemia in the proband induced WT HERG degradation combined with haplo-insufficiency may have further compromised repolarization reserve and contributed to the lethal arrhythmia.
Mutations involving cardiac ion channels result in abnormal action potential formation or propagation, leading to cardiac arrhythmias. Despite the large impact on society of sudden cardiac death resulting from such arrhythmias, understanding of the underlying cellular mechanism is poor and clinical risk stratification and treatment consequently limited. Basic research using molecular techniques, as well as animal models, has proved extremely useful in improving our knowledge of inherited arrhythmogenic syndromes. This offers the practitioner tools to accurately diagnose rare disorders and provides novel markers for risk assessment and a basis for new strategies of treatment.

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Study of First-in-Class WATCHMAN® Device Shows 75 Percent Reduction in Stroke Risk in Patients with Atrial Fibrillation Not Eligible for Oral Anticoagulation Therapy

Results Presented at Heart Rhythm Society from ASA Plavix Study Evaluating Boston Scientific Left Atrial Appendage Closure Device

NATICK and BOSTON, Mass., May 11, 2012 /PRNewswire/ -- Boston Scientific Corporation (NYSE: BSX) announces results from the ASA Plavix (ASAP) Study, which studied the WATCHMAN® Left Atrial Appendage Closure (LAAC) device. The data showed a reduction in the risk of ischemic stroke by 75 percent in patients with atrial fibrillation who have a contraindication to oral anticoagulants such as warfarin. Vivek Reddy, M.D., Director of Cardiac Arrhythmia Service at Mount Sinai Medical Center in New York and Coordinating Investigator of the study presented results today during a late-breaking session at the Heart Rhythm Society's 33rd Annual Scientific Sessions in Boston.

The prospective multi-center ASAP Study evaluated 150 patients with contraindications to warfarin, who were implanted with the WATCHMAN Device and treated with dual antiplatelet therapy for six months post-procedure. Subjects were followed for a mean average of 14.4 months. The study employed the widely recognized CHADS2 risk stratification score, which provides a clinical prediction tool for estimating the risk of stroke in patients with atrial fibrillation. The CHADS2 score has been validated by numerous studies and is regularly used to determine whether treatment is required with anticoagulation or antiplatelet therapy.

"WATCHMAN is the most studied LAA closure device with more than 2,000 patients enrolled in prospective studies and nearly 4,000 patient-years of follow up," said Keith D. Dawkins, M.D., global chief medical officer for Boston Scientific. "This novel device has been well received in more than 30 countries where it offers a safe and effective alternative to long-term treatment with oral anticoagulants."

Atrial fibrillation affects approximately 15 million patients worldwide and is a disorder that disrupts the ability of the heart to beat regularly and pump blood efficiently. Patients in atrial fibrillation are at greater risk for stroke due to the migration of clots formed in the left atrial appendage (LAA). Anticoagulants such as warfarin have traditionally been the only therapy for reducing stroke risk in these patients. The Boston Scientific percutaneously delivered WATCHMAN Device is an alternative to long-term anticoagulation in patients eligible for anticoagulant therapy. It is designed to close the LAA, thereby preventing clots forming within the appendage and being dislodged into the bloodstream where they can potentially cause a stroke.

"Findings from the ASAP Study are promising in that closure of the LAA with the WATCHMAN Device produced a significant reduction in the expected ischemic stroke rate for this patient population," said Dr. Reddy. "These results are very impressive and show potential for an effective device-based solution for higher-risk patients with limited pharmacologic options to reduce their risk of stroke."

For patients in the ASAP Study, the average baseline CHADS2 score of 2.8 equated to a predicted ischemic stroke rate of approximately 7.1 percent per year. The observed rate of ischemic stroke for patients implanted with the WATCHMAN Device was 1.7 percent per year, a 75 percent reduction in stroke risk from the predicted stroke rate based on the CHADS2 score (p<0.01). The corresponding upper confidence bound yielded a stroke rate of 4.4 percent per year, lower than the predicted stroke rate of 7.1 percent.
Stroke rates in the ASAP study were similar to those observed in the PROTECT AF study, which assessed similar subjects not contraindicated to warfarin. In the multi-center, randomized PROTECT AF trial, the WATCHMAN Device proved to be non-inferior to warfarin and demonstrated a 38 percent relative risk reduction for stroke, cardiovascular death and systemic embolism compared to long-term warfarin therapy in 707 patients.

The WATCHMAN Device was approved for marketing in Europe and other CE Mark countries in 2009. Boston Scientific is currently enrolling U.S. patients in the PREVAIL study, a confirmatory study designed to gain U.S. Food and Drug Administration approval. Enrollment is expected to be completed in the second quarter of 2012. The WATCHMAN Device is contraindicated in patients who are not eligible for anticoagulation therapy. In the U.S., the WATCHMAN Device is an investigational device, limited by applicable law to investigational use and not available for sale. The device was developed by Atritech, which Boston Scientific acquired in March 2011. For more information, visit www.Atritech.net.
We searched for special features in patients with complete and incomplete right bundle branch block diagnosed as having arrhythmogenic right ventricular cardiomyopathy. Whether right bundle branch block is a frequent finding in arrhythmogenic right ventricular cardiomyopathy should be studied. The question is whether special features exist such as T-wave inversions, localized right precordial QRS prolongation and r'/s ratio<1.

Results

ARVC could be diagnosed according to ISFC/ESC criteria in 374 patients. CRBBB was found in 22 cases (6%) and iCRBBB was present in 47 cases (12.5%). In CRBBB T wave inversions≥V4 was found in 10 cases (n.s.) and r'/s ratio<1 was present in 12 cases (p<0.001). In iCRBBB T wave inversions≥V4 was found in 10 cases (n.s.) and ST segment elevation in right precordial leads was present in 19 cases (p<0.005). In all patients with ARVC localized right precordial QRS prolongation was found. Patients with CRBBB have a bad prognosis: 17 of 22 patients developed biventricular heart failure requiring heart transplantation and diuretic therapy.

Conclusions

CRBBB and iCRBBB are infrequent findings in arrhythmogenic right ventricular cardiomyopathy. Complete right bundle branch block is characterized by r'/s ratio<1. There are no significant T wave inversions≥V4. Incomplete right bundle branch block is characterized by ST segment elevation in right precordial leads but not by T wave inversions ≥V4.

Keywords: Complete right bundle branch block, r'/s ratio, T wave inversions, ST segment elevation, Localised right precordial QRS prolongation St. Antonius-Hospital Gronau GmbH, Cardiology, Germany // Corresponding author at: St. Antonius Hospital Gronau GmbH, Möllenweg 22, 48599 Gronau, Germany. Tel.: +49 2562 915 2052; fax: +49 2562 915 2055. St. Antonius-Hospital Gronau GmbH, Cardiology, Germany . Klinikum Quedlinburg, Cardiology, Germany / Klinikum Quedlinburg, Cardiology, Germany. Received 15 August 2011; accepted 17 September 2011. published online 31 October 2011.
RAAFT 2: Catheter ablation can be first line of defense against paroxysmal AF

Radiofrequency (RF) catheter ablation with pulmonary vein isolation is not only safe as a first-line treatment for paroxysmal or persistent atrial fibrillation (AF), it's more likely to suppress AF recurrences than is standard antiarrhythmic drug (AAD) therapy, suggests a randomized trial with a two-year follow-up—one of the longest for an AF-ablation trial. A single ablation procedure reduced the risk of AF recurrence by a significant 44% compared with AAD.

Importantly, in the second Radiofrequency Ablation vs Antiarrhythmic Drugs as First-Line Therapy of Atrial Fibrillation (RAAFT 2) trial, which followed all patients with transtelephonic monitoring (TTM), RF ablation's significant advantage over AAD was in reducing bouts of AF that were either symptomatic or asymptomatic.

"So to be able to claim victory with ablation, you really need to monitor these patients very judiciously," said RAAFT 2 co-principal investigator Dr Carlos Morillo (Hamilton Health Sciences-McMaster University, ON) when presenting the study here at the Heart Rhythm Society 2012 Scientific Sessions. Ablation also significantly cut the frequency of solely symptomatic AF, he said.

"These findings support the indication of radiofrequency pulmonary vein isolation as first-line therapy in patients with paroxysmal atrial fibrillation," he said, pointing out that the catheter therapy is currently relegated to second-tier status for paroxysmal AF not responsive to AAD in the most recent Canadian Cardiovascular Society guidelines.

US guidelines are even more restrictive. On the other hand, heartwire reported in 2010 that a European Society of Cardiology guidance supports catheter ablation for paroxysmal AF without an AAD attempt.

RAAFT 2 shows that catheter ablation as performed in the trial is a good therapy for paroxysmal AF, Morillo told heartwire, but also "that there's still 50% of patients who, after one single ablation, have a recurrence. Still, that's much better than the 72% at two years with antiarrhythmic drugs. So it's much better but still has limitations."

RAAFT 2 randomized 127 patients not previously treated with AAD—87.5% with a history of paroxysmal AF and the rest with persistent AF—either to undergo RF ablation within four to six weeks or to initiate AAD, with 90 days allowed for titrating doses. The patients, most from Canada or Germany but also some from Italy, the Czech Republic, and the US, had normal systolic function, and none had hypertension or heart failure. All were followed with TTM.

"These were highly symptomatic patients," Morillo said, noting that patients averaged about 47 AF episodes within the previous six months; yet they were low risk for stroke, with CHADS2 scores averaging 0.5 in the ablation group and 0.7 among those getting AAD.

In the ablation group, 15.2% required an additional ablation, including one during the initial treatment period and nine during follow-up. Seven patients (10.6%) went on AAD therapy.
In the AAD group, 59% had to discontinue at least one antiarrhythmic drug and 29 patients (47.5%) underwent catheter ablation during the follow-up; AAD consisted usually of either flecainide or propafenone (Rythmol, GlaxoSmithKline).

Morillo said patients in the trial were "highly committed," with 19% in both groups having been "fully compliant" with TTM (which meant transmissions biweekly and in the event of symptoms). In the ablation group, 86.4% were compliant at least 75% of the time, as were 78.7% of the AAD group.

**RAAFT-2 primary outcomes: Recurrence rates at two years for symptomatic or asymptomatic AF, atrial flutter, or atrial tachycardia lasting >30 seconds.**

<table>
<thead>
<tr>
<th>End point</th>
<th>Ablation, n=66 (%)</th>
<th>AAD, n=61 (%)</th>
<th>HR (95% CI) p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence of AF, atrial flutter, or atrial tachycardia</td>
<td>55</td>
<td>72</td>
<td>0.56 (0.35-0.90) 0.02</td>
</tr>
<tr>
<td>Symptomatic recurrence of AF, atrial flutter, or atrial tachycardia</td>
<td>47</td>
<td>59</td>
<td>0.56 (0.33-0.95) 0.03</td>
</tr>
<tr>
<td>Symptomatic AF only</td>
<td>41</td>
<td>58</td>
<td>0.52 (0.30-0.89) 0.01</td>
</tr>
<tr>
<td>Recurrence by clinical criteria only</td>
<td>24</td>
<td>31</td>
<td>0.86 (0.42-1.72) 0.66</td>
</tr>
</tbody>
</table>

"Of note," Morillo said in his presentation, "when we excluded the transtelephonic monitor, we couldn't show any difference in recurrence of the primary outcome, 31% in the antiarrhythmic drug [group] and 24% in the catheter ablation [group], highlighting the need for very strict monitoring in these patients to be able to define a successful outcome."

RF ablation also performed better than AAD for the trial's primary safety outcome, a cluster of adverse events specific to each therapy.

In the ablation group, 7.7% of patients had an event in the safety cluster, which included death, tamponade, severe pulmonary vein stenosis, thromboembolism, vascular complications, phrenic nerve injury, or complete AV block within 30 days; tamponade accounted for nearly all of it.

Of AAD patients, 19.7% experienced an event in the safety cluster, which contained death, torsades de pointes, bradycardia requiring a pacemaker, syncope, QRS-interval prolongation >50% of baseline, atrial flutter, or any other significant event leading to drug withdrawal—which accounted for most of the events.

The literature suggests that most patients with paroxysmal AF require more than one ablation to control symptoms, Morillo said, and based on RAAFT 2, it's far more likely to happen within a year of the first ablation. "Actually, we haven't seen many recurring in the second year."
Abstract LB02-1.
Sponsored by the Population Health Research Institute of McMaster University with support from Biosense Webster. Morillo discloses receiving consulting fees or honoraria from Boehringer Ingelheim, Sanofi, Medtronic, and Merck; being on a speaker's bureau for Boehringer Ingelheim and Merck; and receiving research grants from St Jude Medical, Boston Scientific, Biosense Webster, and Medtronic.
Recurrence of RVOT PVCs with a marked shift of its exit point. Gradual elimination of arrhythmogenic focus by multisite approach.


We present a case of recurrent outflow tract arrhythmia despite repeated ablations. Premature ventricular contractions (PVCs) morphology suggested a right-sided focus. However, electrograms preceding PVCs were recorded from the right and left outflow tracts, distal coronary sinus, and right sinus of Valsalva. Arrhythmia was eliminated after radiofrequency (RF) applications delivered from different sites. We conclude that, in patients with recurrent outflow tract PVCs, mapping all the sites mentioned above may be necessary to find the earliest activation site and carry out successful ablation. In some patients, RF applications from multiple sites may be necessary to completely eliminate arrhythmia.

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BACKGROUND:

Recombinant tissue plasminogen activator (rt-PA, alteplase) improved functional outcome in patients treated soon after acute ischaemic stroke in randomised trials, but licensing is restrictive and use varies widely. The IST-3 trial adds substantial new data. We therefore assessed all the evidence from randomised trials for rt-PA in acute ischaemic stroke in an updated systematic review and meta-analysis.

METHODS:

We searched for randomised trials of intravenous rt-PA versus control given within 6 h of onset of acute ischaemic stroke up to March 30, 2012. We estimated summary odds ratios (ORs) and 95% CI in the primary analysis for prespecified outcomes within 7 days and at the final follow-up of all patients treated up to 6 h after stroke.

FINDINGS:

In up to 12 trials (7012 patients), rt-PA given within 6 h of stroke significantly increased the odds of being alive and independent (modified Rankin Scale, mRS 0-2) at final follow-up (1611/3483 [46·3%] vs 1434/3404 [42·1%], OR 1·17, 95% CI 1·06-1·29; p=0·001), absolute increase of 42 (19-66) per 1000 people treated, and favourable outcome (mRS 0-1) absolute increase of 55 (95% CI 33-77) per 1000. The benefit of rt-PA was greatest in patients treated within 3 h (mRS 0-2, 365/896 [40·7%] vs 280/883 [31·7%], 1·53, 1·26-1·86, p<0·0001), absolute benefit of 90 (46-135) per 1000 people treated, and mRS 0-1 (283/896 [31·6%] vs 202/883 [22·9%, 1·61, 1·30-1·90; p<0·0001), absolute benefit 87 (46-128) per 1000 treated. Numbers of deaths within 7 days were increased (250/2807 [8·9%] vs 174/2728 [6·4%, 1·44, 1·18-1·76; p=0·0003), but by final follow-up the excess was no longer significant (679/3548 [19·1%] vs 640/3464 [18·5%, 1·06, 0·94-1·20; p=0·33). Symptomatic intracranial haemorrhage (272/3548 [7·7%] vs 63/3463 [1·8%, 3·72, 2·98-4·64; p<0·0001) accounted for most of the early excess deaths. Patients older than 80 years achieved similar benefit to those aged 80 years or younger, particularly when treated early.

INTERPRETATION:

The evidence indicates that intravenous rt-PA increased the proportion of patients who were alive with favourable outcome and alive and independent at final follow-up. The data strengthen previous evidence to treat patients as early as possible after acute ischaemic stroke, although some patients might benefit up to 6 h after stroke.
FUNDING:

UK Medical Research Council, Stroke Association, University of Edinburgh, National Health Service Health Technology Assessment Programme, Swedish Heart-Lung Fund, AFA Insurances Stockholm (arbetsmarknadens partners forsakringsbolag), Karolinska Institute, Marianne and Marcus Wallenberg Foundation, Research Council of Norway, Oslo University Hospital.

Division of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Edinburgh, UK.
Williams syndrome (WS) is a congenital, developmental disorder affecting 1 in 8,000 live births. The corrected QT (QTc) interval is prolonged in 13% of patients with WS. No data exist characterizing the ambulatory electrocardiographic findings in WS. A retrospective review of all patients with WS evaluated at our institution from January 1, 1980 to December 31, 2007 was performed. Patients with ≥1 ambulatory electrocardiogram (AECG) with sinus rhythm and measurable intervals were included. QTc measurements were made at the minimum and maximum heart rate. Logistic regression analysis was used to evaluate the correlation of ventricular ectopic complexes with QTc measurements. A statistical probability of p <0.05 was considered significant. Of 270 patients identified, 32 had AECGs available for review. Complete data were available for 56 AECGs from 26 patients (15 female; 58%). Their mean age was 15.6 ± 7.2 years at the initial AECG and 20.6 ± 8.6 years for all AECGs. The QTc interval increased with increasing heart rate. Ventricular premature complexes occurred in 40 (73%) of 56 AECGs and 21 (81%) of 26 patients. Ventricular tachycardia occurred in 5 (9%) of 56 AECGs and 4 (15%) of 26 patients. The mean length of ventricular tachycardia was 3.6 ± 0.5 beats at a rate of 171 ± 40 beats/min. The QTc interval at the minimum heart rate correlated directly with age (p <0.001), total ventricular premature complexes (p = 0.007), ventricular couplets (p = 0.002), and ventricular tachycardia (p = 0.011). The QTc interval at the maximum heart rate correlated directly with age (p <0.001), total ventricular premature complexes (p = 0.016), and ventricular couplets (p = 0.006).

In conclusion, the QTc interval correlated with ventricular ectopic complexes in patients with WS. The type of ventricular ectopic complexes suggested an alternate etiology of the QTc prolongation seen in WS from that seen in congenital long QT syndrome.
Sodium-channel blockers might contribute to the prevention of ventricular tachycardia in patients with long QT syndrome type 2: a description of 4 cases


Four patients with long QT type 2, aged 11 to 18 years from unrelated families, with recurrent syncope and polymorphic ventricular tachycardia were studied. Long QT syndrome was diagnosed in these children at ages 4 to 7 years. Syncope, QT prolongation on electrocardiogram (corrected QT interval ≥ 490 milliseconds), notched T-wave morphology, bradycardia, and polymorphic ventricular arrhythmia were found in all of the patients. The KCNH2-L586M; KCNH2-G604S, KCNH2-L1045F; and a combined mutation KCNH2 T613M + SCN5A R190G were genotyped. Syncope, implantable cardioverter-defibrillator shocks, and tachycardia persisted in these patients, although they were receiving a full dose of β-blocker therapy. Adding a sodium-channel blocker (IC class) led to a reduction in the polymorphic ventricular arrhythmia. No syncope episodes were registered during the patients' 8 to 60 months of follow-up on the combined antiarrhythmic therapy.

Further studies are needed to better define the possible role of sodium-channel blockers in patients with long QT type 2.

Keywords: Long QT syndrome, LQT2, Polymorphic ventricular arrhythmia, Sodium-channel blockers, Ventricular tachycardia, Clinical cases, Young Moscow Research Institute of Pediatrics and Pediatric Surgery, Federal Russian Centre for Children's Arrhythmia, Moscow, Russian Federation

Corresponding author. Moscow Research Institute of Pediatrics and Pediatric Surgery, Federal Russian Centre for Children's Arrhythmia, Moscow, Russian Federation // Received 7 State Research Center for Preventive Medicine, Moscow, Russian Federation // November 2011 published online 09 March 2012.
Stability of Complex Fractionated Atrial Electrograms:: A Systematic Review.

Lau DH, Maesen B, Zeemering S, Verheule S, Crijns HJ, Schotten U.


Introduction:
The efficacy of complex fractionated atrial electrograms (CFAE) ablation as additional substrate modification in atrial fibrillation (AF) patients has been shown to be highly variable. Recently, the validity of sequential CFAE mapping has been challenged by concerns regarding temporal stability of CFAE. Existing studies on CFAE stability are small with very different CFAE definitions. Here, we undertook a systematic literature review to address these controversial findings.

Methods and Results:
A systematic search of the scientific literature was performed through to September 1, 2011. From a total of 162 manuscripts, 7 were identified to contain assessment of the temporal stability of CFAE in human AF. These studies included a total of 96 (80 persistent/16 paroxysmal AF) patients (79% male, mean 58 years old). Varying CFAE mapping techniques or definitions were utilized. CFAE stability averaged 81% between 2 high-density sequential fractionation maps over an average time interval of 19 minutes. However, CFAE stability only averaged at 75% from shorter term continuous recordings (mean 15 comparisons within 75 seconds). Although the variability in CFAE cycle length was small (12-15 ms), coefficients of variation in continuous electrical activity were high (up to 300%). The overall spatial distribution of CFAE was found to be stable. Nevertheless, sequential mapping may not capture all CFAE sites given their dynamic characteristics.

Conclusion:
CFAE are temporally variable in keeping with the diverse mechanisms underlying their existence. The dynamic nature of CFAE will continue to pose a challenge for electrophysiologists in search of critical sites requiring ablation to combat AF.

PMID: 22554025 // Department of Physiology, Maastricht University, Maastricht, The Netherlands Department of Cardiology, Maastricht University Medical Centre, Maastricht, The Netherlands.
Sodium-channel blockers might contribute to the prevention of VTachy in pnts with long QT syndrome type 2: a description of 4 cases.

Ildarova R, Shkolnikova MA, Kharlap M, Bereznitskaya V, Kalinin L.

Sodium-channel blockers might contribute to the prevention of ventricular tachycardia in patients with long QT syndrome type 2: a description of 4 cases.

Four patients with long QT type 2, aged 11 to 18 years from unrelated families, with recurrent syncope and polymorphic ventricular tachycardia were studied. Long QT syndrome was diagnosed in these children at ages 4 to 7 years. Syncope, QT prolongation on electrocardiogram (corrected QT interval ≥ 490 milliseconds), notched T-wave morphology, bradycardia, and polymorphic ventricular arrhythmia were found in all of the patients. The KCNH2-L586M; KCNH2-G604S, KCNH2-L1045F; and a combined mutation KCNH2 T613M + SCN5A R190G were genotyped. Syncope, implantable cardioverter-defibrillator shocks, and tachycardia persisted in these patients, although they were receiving a full dose of β-blocker therapy. Adding a sodium-channel blocker (IC class) led to a reduction in the polymorphic ventricular arrhythmia. No syncope episodes were registered during the patients' 8 to 60 months of follow-up on the combined antiarrhythmic therapy. Further studies are needed to better define the possible role of sodium-channel blockers in patients with long QT type 2.

PMID: 22402334 // Moscow Research Institute of Pediatrics and Pediatric Surgery, Federal Russian Centre for Children's Arrhythmia, Moscow, Russian Federation.
Should rhythm control be preferred in younger atrial fibrillation patients?


PURPOSE:

Rate- and rhythm control are two fundamental strategies to treat atrial fibrillation (AF). However, there are inconsistent results between clinical trials about which treatment should be preferred. The aims of this study were to systematically summarize the clinical trials and compare rate- and rhythm control strategies regarding composite outcome of all cause mortality, worsening heart failure, and thromboembolic and bleeding events.

METHODS:

English and non-English studies that were published from 1966 onwards were included in this meta-analysis if they were prospective randomized controlled trials which compared rate- and rhythm control strategies in patients with AF. The individual and combined outcomes were analyzed quantitatively with odds ratio and 95 % confidence interval.

RESULTS:

Ten prospective randomized controlled trials with 7,876 patients were identified. There was no significant difference regarding primary composite outcome (11.47 vs. 11.03 % per year; odds ratio (OR), 1.03; 95 % confidence interval (CI), 0.90-1.20; P = 0.64) between rate- and rhythm control groups in overall age group. Meta-analysis for studies with mean age <65 years showed that rate control had significantly higher risk in primary composite outcome compared with rhythm control (8.74 vs. 4.80 % per year; OR, 1.89; 95 %CI, 1.26-2.86; P = 0.002).

CONCLUSIONS:

A significant trend towards that rhythm control may be a preferable strategy for younger AF patients was observed in this study.

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Systemic Magnesium to Reduce Postoperative Arrhythmias After CABG Surgery: A Meta-Analysis of Randomized Controlled Trials

Saadia Sherwani, RJ McCarthy, GS De Oliveira Jr, JS Knautz,
Systemic Magnesium to Reduce Postoperative Arrhythmias After Coronary Artery Bypass Graft Surgery: A Meta-Analysis of Randomized Controlled Trials
Journal of Cardiothoracic and Vascular Anesthesia 2012; Article in Press

Objective
To evaluate the effect of systemic magnesium on the prevention of postoperative cardiac arrhythmias after coronary artery bypass graft surgery.

Design
A meta-analysis.

Setting
Randomized controlled trials evaluating the effect of systemic magnesium on the incidence of postoperative arrhythmias.

Participants
Patients undergoing coronary artery bypass graft surgery.

Interventions
Systemic perioperative administration of magnesium sulfate.

Measurements and Main Results
Twenty studies evaluating 3,696 subjects were included. The combined effect suggested that systemic magnesium reduced the incidence of supraventricular arrhythmias compared with saline (odds ratio [OR] = 0.69; 95% confidence interval [CI], 0.53-0.90; number needed to treat [NNT] = 14). The effect was present for lower-quality studies (Jadad score ≤3; OR = 0.47; 95% CI, 0.28-0.81; NNT = 8), but it was not detected for higher-quality studies (Jadad >3; OR = 0.85; 95% CI, 0.66-1.11). There was no association between the total dose of magnesium administration and the incidence of supraventricular arrhythmias (p = 0.19). There was no effect of magnesium on the incidence of postoperative stroke, myocardial infarction, and death. In addition, magnesium did not reduce the hospital or intensive care unit lengths of stay (all p > 0.05).

Conclusions
The effect of magnesium sulfate in reducing postoperative supraventricular arrhythmias was significant when examined by lower-quality studies but not when examined by higher-quality studies. This fact probably is responsible for controversial findings reported in the literature. Also, magnesium sulfate did not reduce the incidence of complications associated with the development of postoperative cardiac arrhythmias. More effective strategies should be used to prevent complications caused by arrhythmias in this patient population.
Key words: magnesium, postoperative arrhythmia, coronary artery surgery, complications

Address reprint requests to Gildasio S. De Oliveira Jr, MD, MSCI, Department of Anesthesiology, Northwestern Memorial Hospital, 251 E. Huron Street, F5-704, Chicago, IL. Department of Anesthesiology, Northwestern University, Feinberg School of Medicine, Chicago, IL. Published online 07 May 2012. Corrected Proof.
The gradual loss of ventricular preexcitation during exercise stress testing (EST) has an unclear risk of an association with life-threatening arrhythmia and could be related to the accessory pathway (AP) location. We compared the loss of preexcitation during EST with the risk assessment during invasive electrophysiology testing and determined whether the loss of preexcitation correlates with the AP location. We retrospectively reviewed patients aged ≤21 years with ventricular preexcitation who had undergone both EST and an electrophysiology study. The patients were divided into 3 groups: sudden loss (SL), gradual loss (GL), or no loss (NL) of preexcitation during EST. A total of 76 patients were included, with 11 (14%) in the SL group, 18 (24%) in the GL group, and 47 (62%) in the NL group. The SL group demonstrated a longer cycle length with 1-to-1 conduction by way of the AP during incremental atrial pacing compared with the NL group (375 ± 135 ms vs 296 ± 52 ms, p = 0.002), with no difference between the GL and NL groups (325 ± 96 vs 296 ± 52 ms, p = NS). Of the patients with 1-to-1 AP conduction of <270 ms, none (0 of 11) were in the SL group compared to 18 of 47 in the NL group (p = 0.0017), with no significant difference in the GL group (5 of 18) compared to the NL group (p = NS). The patients in the GL group were more likely to have a left-sided AP (14 of 18) than the NL group (17 of 47, p = 0.002) and the SL group (3 of 11, p = 0.002). In conclusion, a sudden loss of preexcitation during an EST predicted a long cycle length with 1-to-1 conduction by way of the AP. Also, the AP conduction characteristics in patients with GL compared to those with NL did not differ, and the GL of preexcitation was more frequently seen in patients with a left-sided AP.
Resting QRS duration predicts sudden death in men.

Results of a new study published online May 21, 2012 in Circulation show that even a moderately prolonged QRS duration may suggest heightened risk for sudden cardiac death [source].

Previous research has shown that prolonged QRS interval on an electrocardiogram is associated with an increased risk of sudden cardiac death. However, large epidemiological surveys have not yet identified specific markers for sudden cardiac death in a general population, according to lead investigator Dr Sudhir Kurl (University of Eastern Finland, Kuopio).

Kurl and colleagues examined the relationship of QRS to sudden cardiac death in a cohort of 2049 men aged 42 to 60 years at baseline with a 19-year follow-up. "We wanted to find new useful clinical markers for sudden cardiac death, as sudden cardiac death typically occurs shortly after the onset of symptoms, leaving little time for effective clinical interventions, and the resting electrocardiogram is the most commonly used diagnostic tool in clinical practice."

During the 19-year follow-up, there were 156 sudden cardiac deaths in the study; as a continuous variable, each 10-ms increase in QRS duration was associated with a 27% higher risk for sudden cardiac death (relative risk, 1.27; p<0.001). Men in the study with a QRS duration longer than 110 ms—the highest quintile—were two and a half times more likely to suffer sudden cardiac death (p=0.002) than study subjects with a QRS shorter than 96 ms—the lowest quintile—after adjustment for demographic and clinical risk factors such as age, alcohol consumption, previous MI, smoking, serum low- and high-density lipoprotein cholesterol, C-reactive protein, type 2 diabetes mellitus, body-mass index, systolic blood pressure, and cardiorespiratory fitness.

In addition to QRS duration, smoking, previous MI, type 2 diabetes mellitus, cardiorespiratory fitness, body-mass index, systolic blood pressure, and C-reactive protein were also independently associated with a greater risk of sudden cardiac death.

"Our results show that even a moderate QRS duration—exceeding 110 ms, including incomplete bundle branch blocks—is a risk factor for sudden cardiac death. The risk remained even after accounting for left ventricular function of the heart," Kurl told us.

"This study shows that ECG should be regularly performed so as to enable the physician to prevent sudden cardiac death by using various interventions in case the QRS duration is prolonged," he said. "At the moment we do not have specific risk markers for sudden cardiac death in the general population. We still lack effective risk stratification and preventive interventions for the majority of the people who will ultimately experience sudden cardiac death."


No disclosures
Rationale:
In cardiac muscle, Ca\(^{2+}\)-induced Ca\(^{2+}\) release (CICR) from the sarcoplasmic reticulum (SR) is mediated by ryanodine receptor (RyR) Ca\(^{2+}\) release channels. The inherent positive feedback of CICR is normally well-controlled. Understanding this control mechanism is a priority because its malfunction has life-threatening consequences.

Objective:
We show that CICR local control is governed by SR Ca\(^{2+}\) load, largely because load determines the single RyR current amplitude that drives inter-RyR CICR.

Methods and Results:
We differentially manipulated single RyR Ca\(^{2+}\) flux amplitude and SR Ca\(^{2+}\) load in permeabilized ventricular myocytes as an endogenous cell biology model of the heart. Large RyR-permeable organic cations were used to interfere with Ca\(^{2+}\) conductance through the open RyR pore. Single-channel studies show this attenuates current amplitude without altering other aspects of RyR function. In cells, the same experimental maneuver increased resting SR Ca\(^{2+}\) load. Despite the increased load, Ca\(^{2+}\) spark (inter-RyR CICR events) frequency decreased and sparks terminated earlier.

Conclusion:
Spark local control after single RyR current amplitude, not SR Ca\(^{2+}\) load per se. Spark frequency increases with load because spontaneous RyR openings at high loads produce larger currents (ie, a larger CICR trigger signal). Sparks terminate when load falls to the point at which single RyR current amplitude is no longer sufficient to sustain inter-RyR CICR. Thus, RyRs that spontaneously close no longer reopen and local Ca\(^{2+}\) release ends.

Key Words: calcium-induced calcium release cardiac muscle ryanodine receptor sarcolemmal reticulum spark

Received January 25, 2012. Revision received May 14, 2012. Accepted May 16, 2012. //+ Author Affiliations From the Department Molecular Biophysics and Physiology, Section of Cellular Signaling, Rush University Medical Center, Chicago, IL. Correspondence to Dr. Michael Fill, Department of Molecular Biophysics and Physiology, Rush University Medical Center, 1750 West Harrison Street, Chicago, IL 60112. E-mail michael_fill@rush.edu
Introduction:

The Hansen Robotic system has been utilized in ablation procedures for atrial fibrillation (AF). However, because of the lack of tactile feedback and the rigidity of the robotic sheath, this approach could result in higher risk of complications. This worldwide survey reports a multicenter experience on the methodology, efficacy, and safety of the Hansen system in AF ablations.

Methods and Results:

A questionnaire addressing questions on patient's demographics, procedural parameters, ablation success rate and safety information was sent to all centers where more than 50 robotic AF ablation cases have been performed. From June 2007 to December 2009, 1,728 procedures were performed at 12 centers utilizing the Hansen robotic navigation technology. The overall complication rate was 4.7% and the success rate was 67.1% after 18 ± 4 months of follow-up. In 5 low volume centers there appeared to be a learning curve of about 50 cases (complication rate 11.2% for the first 50 cases vs 3.7% for the 51–100 cases; P = 0.044) and a trend showing a decrease of complication rate with increasing case volume. However, in the remaining 7 centers no learning curve was present and the complication rate was stable over time (3.7% for the first 50 cases vs 3.6% for the 51st case thereafter; P = 0.942).

Conclusion:

The Hansen robotic system can be used for AF ablation safely. In low volume centers, there appeared to be a learning curve of the first 50 cases after which the complication rate decreased. With a higher case volume, the success rate increased.
The phenomenon of “QT stunning”: The abnormal QT prolongation provoked by standing persists even as the heart rate returns to normal in patients with long QT syndrome

Arnon Adler, C van der Werf, PG Postema, R Rosso, J Benhorin, C Antzelevitch, AAM Wilde, S Viskin.

The phenomenon of “QT stunning”: The abnormal QT prolongation provoked by standing persists even as the heart rate returns to normal in patients with long QT syndrome
Heart Rhythm 2012 ; 9 / 6 : 901-908, June 2012

Background

Patients with long QT syndrome (LQTS) have inadequate shortening of the QT interval in response to the sudden heart rate accelerations provoked by standing—a phenomenon of diagnostic value. We now validate our original observations in a cohort twice as large. We also describe that this abnormal QT-interval response persists as the heart rate acceleration returns to baseline.

Objectives

To describe a novel observation, termed “QT stunning” and to validate previous observations regarding the “QT-stretching” phenomenon in patients with LQTS by using our recently described “standing test.”

Methods

The electrocardiograms of 108 patients with LQTS and 112 healthy subjects were recorded in the supine position. Subjects were then instructed to stand up quickly and remain standing for 5 minutes during continuous electrocardiographic recording. The corrected QT interval was measured at baseline (QTc_{base}), when heart rate acceleration without appropriate QT-interval shortening leads to maximal QT stretching (QTc_{stretch}) and upon return of heart rate to baseline (QTc_{return}).

Results

QTc_{stretch} lengthened significantly more in patients with LQTS (103 ± 80 ms vs 66 ± 40 ms in controls; \( P < .001 \)) and so did QTc_{return} (28 ± 48 ms for patients with LQTS vs −3 ± 32 ms for controls; \( P < .001 \)). Using a sensitivity cutoff of 90%, the specificity for diagnosing LQTS was 74% for QTc_{base}, 84% for QTc_{return}, and 87% for QTc_{stretch}.

Conclusions

The present study extends our previous findings on the abnormal response of the QT interval in response to standing in patients with LQTS. Our study also shows that this abnormal response persists even after the heart rate slows back to baseline.
Value of right ventricular mapping in patients with postinfarction ventricular tachycardia


Value of right ventricular mapping in patients with postinfarction ventricular tachycardia
Heart Rhythm 2012 ; 9 / 6 : 938-942, June 2012

Background

Postinfarction ventricular tachycardia (VT) typically involves the left ventricular endocardium. Right ventricular involvement in the arrhythmogenic substrate of postinfarction VT is considered unusual.

Objective

To assess the role of right ventricular mapping and ablation in patients with prior septal myocardial infarction.

Methods

From among 37 consecutive patients with recurrent postinfarction VT, 18 patients with evidence of left ventricular septal involvement of myocardial infarction were identified; these patients were the subjects of this report. In these 18 patients, 166 VTs (cycle length 372 ± 117 ms) were induced. Right ventricular voltage mapping was performed in all 18 patients with left ventricular septal myocardial infarction.

Results

Right ventricular voltage mapping showed areas of low voltage in 11 patients; pace mapping from these areas revealed matching pace maps for 17 VTs, and radiofrequency ablation from the right ventricular endocardium but not the left ventricular endocardium eliminated 14 of 17 VTs. VTs with critical components in the right ventricle had a left bundle branch block morphology that had similar characteristics as left bundle branch block VTs with critical areas involving the left ventricular septum. Patients with right ventricular VT breakthrough sites had a lower ejection fraction than did patients without VT breaking out on the right ventricular septum (18% ± 5% vs 33% ± 15%; \( P = .01 \)).

Conclusions

Right ventricular mapping and ablation may be necessary in order to eliminate all inducible VTs in patients with postinfarction VT. More than half the patients with septal myocardial infarction have right ventricular septal areas that are critical for postinfarction VT and that cannot be eliminated by left ventricular ablation alone.

Keywords: Ventricular tachycardia, Postinfarction, Mapping, Ablation

Abbreviations: ECG, electrocardiographic, ICD, implantable cardioverter-defibrillator, VT, ventricular tachycardia

Address for reprints and correspondence: Dr Frank Bogun, MD, Division of Cardiovascular Medicine, Cardiovascular Center, University of Michigan, SPC 5853, 1500 East Medical Center Dr, Ann Arbor, MI 48109-5853 Division of Cardiovascular Medicine, Cardiovascular Center, University of Michigan, Ann Arbor, Michigan published online 10 February 2012.
The Multiple Ion Channel Blocker CPUY11018 Prevents Aconitine-Induced Arrhythmias

Yi-Qun Tang, Peng Yu, Na Zhao, et al.
The Multiple Ion Channel Blocker CPUY11018 Prevents Aconitine-Induced Arrhythmias
Drug Development Research 2012; Article first published online: 18 MAY 2012 //
DOI: 10.1002/ddr.21009

In the present study, the potential antiarrhythmic activities of a new multiple ion channel blocker, CPUY11018 (Y18) were investigated. The effects of Y18 on \( I_{\text{Ca,L}} \) and \( I_{\text{Na}} \) were studied using whole-cell patch clamp techniques in ventricular muscle cells from normal rats and guinea pigs. The antiarrhythmic effects were tested using a rat model of aconitine-induced arrhythmias. The effects of Y18 on induction of QT prolongation and torsades de pointes (TdP) were investigated in anesthetized rabbits during stimulation with methoxamine. Y18 produced a concentration-dependent inhibition of \( I_{\text{Ca,L}} \) and \( I_{\text{Na}} \) in rat ventricular myocytes with \( IC_{50} \) values of 88 μmol/l and 6.5 μmol/l, respectively. In the Y18 treatment group, the development of arrhythmias was significantly delayed. Doses of aconitine that induced ventricular fibrillation were decreased following treatment with 6 mg/kg Y18 (3.8 ± 0.4 μg/100 g vs 6.2 ± 1.3 μg/kg). A significant decrease in the occurrence of atrial fibrillation (100% to 33%; \( P < 0.05 \)) occurred following Y18 administration. Y18 induction of TdP was significantly less than that seen with dofetilide and azimilide (Az). Thus, Y18 significantly inhibited the production of aconitine-induced arrhythmias with a low potency for TdP induction. These results suggest that Y18 is a multiple channel blocker with promising antiarrhythmic potential.

Keywords: CPUY11018; sodium channels; calcium channels; ventricular myocytes; arrhythmia Strategy, Management and Health Policy Enabling Technology, Genomics, Proteomics Preclinical Research Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics Clinical Development Phases I-III Regulatory, Quality, Manufacturing
Turning the AF ablation world upside down--FIRM ablation

On the atrial-fibrillation ablation front, the most striking news comes from Southern California. **Dr Sanjiv Narayan** has made himself famous with his paradigm-shifting work in the approach to AF ablation. To call his work "novel" understates it greatly. After his presentation yesterday, the father of catheter ablation, **Dr Sonny Jackman**, came to the microphone and said, "Amazing, this is about to turn the AF ablation world upside down." A senior electrophysiologist that I had dinner with last night was more skeptical, but when he heard Sonny was impressed, he took notice.

Current background on AF ablation

It's recently become understood that electrical rotors and nests of focal impulses play an important role in AF. For guys like me, these lofty notions of spinning waves of electricity, rooted deeply in complicated matters of optics and physics, have always been noteworthy but far too complicated and not clinically relevant enough to warrant much attention. Most "regular" ablationists have felt the same. We want to know about power, watts, where, how much, and in whom to burn. AF ablation has been about building electrical fences around pulmonary veins—which may or may not be critical. Since it ain't easy, we like to get moving on it fast. Smart people call this approach an anatomic one.

A component missing from this current strategy is the physiology of AF. Anatomic ablators ignore physiology. Dr Narayan's work changes that. By targeting rotors and focal impulses—which he and others believe important in AF initiation and maintenance—his work moves us closer to the root cause of AF. And anything that does that—especially if it shortens the case and improves outcomes—will be welcomed.

What is FIRM ablation?

Their technique involves placing commercially available multipole basket catheters into the atria. During AF, the thousands of signals are sent to an investigational computer system, which then displays optical images and movies of the activation. Distinct geographic "areas of interest" in either the right or left atrium can be seen in almost all cases of AF. Sometimes the rotors are located in areas typically targeted during pulmonary vein isolation (PVI), but in many cases they are not. Most remarkably, his prior work has shown that when these areas are ablated, AF terminates. That's striking. But it's not all. Patients who have undergone focal impulse and rotor modulation (FIRM) ablation in addition to standard PVI remain **AF free more often than those treated with standard PVI**.

Wednesday, Dr Narayan presented—to a crowded room—new data on the acute termination of AF with FIRM-guided ablation. In a cohort of patients with advanced AF, he showed that rotors or focal impulses could be seen in 98%. Ablation at these focal sites terminated, slowed, or converted AF to flutter in 88% of patients. Almost half converted to sinus rhythm. In one case, ablation for only one minute converted the patient to sinus rhythm.

And remember, he is ablating focally and terminating AF **before PVI**. Contrast this with the work of others that terminate AF after PVI and (hours of) extensive linear ablation. Dr Narayan has none of that. His magic entails finding the spot.

He gave us more good news. (That's the thing; he's always got more good news.) First, and most important in my mind, he now has a consortium of eight labs using his proprietary
system. One of the senior leaders emailed me to say that he was impressed and mused: "This was the real deal."

Second, he showed a couple cases of using FIRM only, without PVI. It's too early to say, but would not this be incredible—a complete change?

What to think of all this?

Students of AF ablation have heard similar stories before. Ablating at sites of complex fractionated electrical activity (so-called CFAE) held similar promise. This strategy has not proven successful. There have also been boastful labs from across the globe purporting 100% success in one-hour cases. They have never panned out. We AF docs, therefore, stay skeptical.

The next step with FIRM ablation must be to show that others can see the rotors that Dr Narayan does. That the proprietary software will work in other labs. And of course, the ultimate test will come when it is tested in randomized multicenter clinical trials.

Still. If it is true, magic it will

Narayan SM, Krummen DE, Rappel WJ. Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. J Cardiovasc Electrophysiol. 2012 May;23(5):447-54. doi: 10.1111/j.1540-8167.2012.02332.x. Epub 2012 Apr 26. Introduction: Computational Mapping of Rotors and Focal Impulses in Human AF. The perpetuating mechanisms for human atrial fibrillation (AF) remain undefined. Localized rotors and focal beat sources may sustain AF in elegant animal models, but there has been no direct evidence for localized sources in human AF using traditional methods. We developed a clinical computational mapping approach, guided by human atrial tissue physiology, to reveal sources of human AF. Methods and Results: In 49 AF patients referred for ablation (62 ± 9 years; 30 persistent), we defined repolarization dynamics using monophasic action potentials (MAPs) and recorded AF activation from 64-pole basket catheters in left atrium and, in n = 20 patients, in both atria. Careful positioning of basket catheters was required for optimal mapping. AF electrograms at 64-128 electrodes were combined with repolarization and conduction dynamics to construct spatiotemporal AF maps. We observed sustained sources in 47/49 patients, in the form of electrical rotors (n = 57) and focal beats (n = 11) that controlled local atrial activation with peripheral wavebreak (fibrillatory conduction). Patients with persistent AF had more sources than those with paroxysmal AF (2.1 ± 1.0 vs 1.5 ± 0.8, P = 0.02), related to shorter cycle length (163 ± 19 milliseconds vs 187 ± 25 milliseconds, P < 0.001). Approximately one-quarter of sources lay in the right atrium. Conclusions: Physiologically guided computational mapping revealed sustained electrical rotors and repetitive focal beats during human AF for the first time. These localized sources were present in 96% of AF patients, and controlled AF activity. These results provide novel mechanistic insights into human AF and lay the foundation for mechanistically tailored approaches to AF ablation. PMID: 22537106 Veterans' Affairs and University of California Medical Centers, San Diego, California, USA Institute for Theoretical Biological Physics, University of California, San Diego, California, USA.
Value of the aVR lead in differential diagnosis of atrioventricular nodal reentrant tachycardia

Majid Haghjoo, E Bahramali, M Sharifkazemi, S Shahrzad, M Peighambari.

Aims
Despite the several electrocardiographic (ECG) criteria, misclassification may still occur in differential diagnosis of the regular paroxysmal supraventricular tachycardia (PSVT). The aim of the present study was to evaluate the diagnostic accuracy of the aVR lead in ECG differentiation of atrioventricular nodal reentrant tachycardia (AVNRT) and atrioventricular reciprocating tachycardia (AVRT).

Methods and results
A 12-lead ECG was recorded in 150 consecutive patients (96 women, mean age, 45 ± 13.5 years) with drug-refractory regular PSVT during both sinus rhythm and tachycardia. All ECGs were reviewed by two experienced electrophysiologists who had no knowledge of the tachycardia mechanism. The ECG recordings were evaluated for standard criteria as well as our newly proposed criterion of pseudo- in the lead aVR. Mechanism of arrhythmia was confirmed by the electrophysiological study and the successful catheter ablation. Patients with AVNRT were older (50 ± 10 vs. 37 ± 15 years, P = 0.001), predominantly female (71 vs. 53%, P = 0.03), and presented with slower tachycardia (175 ± 25 vs. 186 ± 26 b.p.m., P = 0.01). Among the ECG criteria of the AVRT diagnosis, visible P-wave with RP interval ≥100 ms had highest diagnostic accuracy (sensitivity 79%, specificity 87%, and positive predictive value 79%). For AVNRT diagnosis, pseudo- in aVR had a higher sensitivity, specificity, and predictive values compared with the conventional criteria of the pseudo- in V1 and pseudo-s in inferior leads (all P < 0.05).

Conclusions
New criterion of pseudo- in lead aVR appears to be more accurate than the standard ECG criteria for ECG diagnosis of AVNRT.

Key words Atrioventricular nodal reentrant tachycardia Atrioventricular reciprocating tachycardia Electrocardiography Mechanism Non-invasive, + Author Affiliations Cardiac Electrophysiology Research Center, Rajaie Cardiovascular Medical Center, Tehran University of Medical Sciences, Mellat Park, Vali-E-Asr Avenue, PO Box: 15745-1341, Tehran 1996911151, Iran *Corresponding author. Tel: +98 21 2392 2163; fax: +98 21 2237 4288, Email: majid.haghjoo@gmail.com Received February 3, 2012. Accepted March 30, 2012.
Transseptal Puncture Through Amplatzer Septal Occluder Device for Catheter Ablation of Atrial Fibrillation: Use of Balloon Dilatation Technique

KE CHEN, CAIHUA SANG, JIANZENG DONG, CHANGSHENG MA.
Transseptal Puncture Through Amplatzer Septal Occluder Device for Catheter Ablation of Atrial Fibrillation:
Use of Balloon Dilatation Technique
Journal of Cardiovascular Electrophysiology 2012 ; Article first published online: 17 APR 2012 // DOI: 10.1111/j.1540-8167.2012.02306.x

Keywords: atrial fibrillation; atrial septal defect; catheter ablation; closure device; transseptal puncture

Transseptal Puncture Through Amplatzer Device
Transseptal puncture is required for catheter ablation of atrial fibrillation. We report on a 59-year-old woman presenting with atrial fibrillation after transcatheter closure of a large-sized secundum atrial septal defect with an Amplatzer septal occluder. Direct transseptal access through the device was achieved with the aid of an angioplasty balloon and atrial fibrillation was successfully ablated. Such an approach of transseptal puncture can facilitate obtaining left atrial access in complicated intervention procedures.
On the atrial-fibrillation ablation front, the most striking news comes from Southern California. **Dr Sanjiv Narayan** has made himself famous with his paradigm-shifting work in the approach to AF ablation. To call his work "novel" understates it greatly. After his presentation yesterday, the father of catheter ablation, **Dr Sonny Jackman**, came to the microphone and said, "Amazing, this is about to turn the AF ablation world upside down." A senior electrophysiologist that I had dinner with last night was more skeptical, but when he heard Sonny was impressed, he took notice.

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The next step with FIRM ablation must be to show that others can see the rotors that Dr Narayan does. That the proprietary software will work in other labs. And of course, the ultimate test will come when it is tested in randomized multicenter clinical trials.

Still. If it is true, magic it will
Individuals who experience paroxysmal atrial fibrillation (PAF) are at risk of serious sequelae, including stroke. PAF episodes usually occur in out-of-hospital settings, and patients seek emergency services for differential diagnosis and treatment.

Methods

Medical records of all subscribers to a telemedical system ('SHL'-Telemedicine) who had one or more episodes of recurrent PAF managed by the call center between 2/2002 and 8/2009 were retrieved. Treatment protocol consisted of initial electrocardiographic confirmation of PAF and repeat electrocardiograms within 24 h. Management was exclusively by telephonically transmitted recommendations (Group A) or also included intervention by the attending physician of a ‘SHL’-Telemedicine mobile intensive care unit (Group B).

Results

A total of 649 cardiac patients (1886 PAF episodes) were enrolled. The leading complaint was palpitation (57%). The 576 Group A patients had 1667 objectively documented PAF episodes, of which 1326 (79.5%) were converted into sinus rhythm by following telephonically delivered instructions. Their mean heart rate decreased from 85±15 to 66±10 beats per minute (bpm) ($P<0.001$). Heart rate remained unchanged (86±15 bpm) for those who remained in PAF. The 160 Group B patients (218 PAF episodes) had a conversion rate of 70% (153/218). The heart rate in converted cases decreased from 92±24 bpm to 68±21 bpm compared to a decrease from 90±21 bpm to 87±21 bpm in non-converted cases ($P<0.001$).

Conclusions

Telemedicine for rapid out-of-hospital diagnosis and provision of objective documentation and instructions for appropriate management of PAF is feasible and could avoid potential PAF-associated complications and unnecessary emergency room visits and hospitalizations.
The durability of pulmonary vein isolation using the visually guided laser balloon catheter: Multicenter results of pulmonary vein remapping studies

Srinivas R. Dukkipati, Petr Neuzil, Josef Kautzner, Jan Petru, et al.

The durability of pulmonary vein isolation using the visually guided laser balloon catheter: Multicenter results of pulmonary vein remapping studies
Heart Rhythm 2012 ; 9 / 6 : 919-925, June 2012

Background
The visually guided laser ablation (VGLA) catheter is a compliant, variable-diameter balloon that delivers laser energy around the pulmonary vein (PV) ostium under real-time endoscopic visualization. While acute PV isolation has been shown to be feasible, limited data exist regarding the durability of isolation.

Objective
We sought to determine the durability of PV isolation following ablation using the balloon-based VGLA catheter.

Methods
The VGLA catheter was evaluated in patients with paroxysmal atrial fibrillation (3 sites, 10 operators). Following transseptal puncture, the VGLA catheter was advanced through a 12-F deflectable sheath and inflated at the target PV ostium. Under endoscopic guidance, the 30° aiming arc was maneuvered around the PV and laser energy was delivered to ablate tissue in a contiguous/overlapping manner. At ~3 months, all patients returned for a PV remapping procedure.

Results
In 56 patients, 202 of 206 PVs (98%) were acutely isolated. At 105 ± 44 (mean ± SD) days, 52 patients returned for PV remapping at which time 162 of 189 PVs (86%) remained isolated and 32 of 52 patients (62%) had all PVs still isolated. On comparing the operators performing <10 vs ≥10 procedures, the durable PV isolation rate and the percentage of patients with all PVs isolated were found to be 73% vs 89% ($P = .011$) and 57% vs 66% ($P = .746$), respectively. After 2 procedures and 12.0 ± 1.9 months of follow-up, the drug-free rate of freedom from atrial fibrillation was 71.2%.

Conclusions
In this multicenter, multioperator experience, VGLA resulted in a very high rate of durable PV isolation with a clinical efficacy similar to that of radiofrequency ablation.

Keywords: Atrial fibrillation, Ablation, Laser, Paroxysmal, Pulmonary veins, Endoscopic visualization Abbreviations: AF, atrial fibrillation, PV, pulmonary vein, VGLA, visually guided laser ablation // Helmsley Electrophysiology Center, Mount Sinai School of Medicine, New York, New York Department of Cardiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic Department of Cardiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic Department of Cardiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic Cardiac Arrhythmia Research Centre, Centro Cardiologico Monzino, Milan, Italy Texas Cardiac Arrhythmia Institute, St. Davis Medical Center, Austin, Texas Texas Helmsley Electrophysiology Center, Mount Sinai School of Medicine, New York, New York Homolka Hospital, Prague, Czech Republic Address reprint requests and correspondence: Dr Vivek Y. Reddy, MD, Helmsley Electrophysiology Center, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1030, New York, NY 10029 published online 30 January 2012.
Early Repolarization in Noncompaction Cardiomyopathy

Background:
Early repolarization (ER) is associated with malignant ventricular arrhythmias, including ventricular fibrillation (VF) and sudden cardiac death (SCD). One possible mechanism is increased trabeculation with deep intramyocardial invagination, carrying the Purkinje system deeper into the myocardium resulting in delayed depolarization and inhomogenous repolarization. Noncompaction cardiomyopathy (NCCM) is a recently classified, primary cardiomyopathy with excessive trabeculations. In these patients ventricular arrhythmias, including sustained VT and VF, occur frequently. The aim of this study was to determine the prevalence of ER in NCCM patients, especially in those primarily presenting with malignant ventricular arrhythmias or SCD.

Methods:
We analyzed prospective data from our NCCM registry including 84 patients, median age: 40 (3-79) years.

Results:
Fourteen patients (17%) initially presented with sustained VT (n = 5) or VF (n = 9) and 70 (83%) with heart failure or else. After the exclusion of 20 patients with the left bundle branch block, 25 (39%) NCCM patients had ER; 3 (6%) located in inferior leads, 14 (27%) in lateral leads, and 8 (15%) in both. None had ER in leads V1 to V3. In those presenting with VT/VF, 9/12 (75%) had ER (2 in inferior leads, 3 in lateral leads and 4 in both), versus 16/52 (31%) in the other patients (P = 0.02). If the NCCM population was dichotomized according to the presence or absence of ER, the long-term outcome for VT/VF appeared worse in the ER positive patients (P = 0.05).

Conclusion:
There is a high prevalence of ER in NCCM patients, especially in those who present with malignant ventricular arrhythmias.

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The prevalence of mutations in KCNQ1, KCNH2, and SCN5A in an unselected national cohort of young sudden unexplained death cases

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The prevalence of mutations in KCNQ1, KCNH2, and SCN5A in an unselected national cohort of young sudden unexplained death cases

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Introduction

Sudden unexplained death account for one-third of all sudden natural deaths in the young (1-35 years). Hitherto, the prevalence of genopositive cases has primarily been based on deceased persons referred for post-mortem genetic testing. These deaths potentially may represent the worst of cases, thus possibly overestimating the prevalence of potentially disease causing mutations in the three major LQTS genes in the general population. We therefore wanted to investigate the prevalence of mutations in an unselected population of sudden unexplained deaths in a nationwide setting

Methods

DNA for genetic testing were available for 44 cases of sudden unexplained death in Denmark in the period 2000-2006 (equaling 33% of all cases of sudden unexplained death in the age group). KCNQ1, KCNH2 and SCN5A were sequenced and in vitro electrophysiological studies were performed on novel mutations.

Results

In total, 5 of 44 cases (11%) carried a mutation in one of the 3 genes corresponding to 11% of all investigated cases (R190W KCNQ1, F29L KCNH2 (two cases), P297S KCNH2 and P1177L SCN5A). P1177L SCN5A has not been reported before. In vitro electrophysiological studies of P1177L SCN5A revealed an increased sustained current suggesting a LQTS phenotype.

Conclusion

In a nationwide setting, the genetic investigation of an unselected population of sudden unexplained death cases aged 1-35 years finds a lower than expected number of mutations compared to referred populations previously reported. We therefore conclude that the prevalence of mutations in the three major LQTS associated genes may not be as abundant as previously estimated.

Keywords: Long-QT Syndrome; sudden cardiac death; genetics; molecular autopsy; sustained sodium current