Cost-Effectiveness of Preparticipation Screening for Prevention of Sudden Cardiac Death in Young Athletes

Wheeler MT, Heidenreich PA, Froelicher VF, Hlatky MA, Ashley EA.
Cost-Effectiveness of Preparticipation Screening for Prevention of Sudden Cardiac Death in Young Athletes
Ann Int Med 2010 : 152 ; 276-286

Study Question:
What is the cost-effectiveness of electrocardiography (ECG) plus cardiovascular-focused history and physical examination compared with focused history and physical examination alone for preparticipation screening in young athletes?

Methods:
A decision model was used to project the costs and survival rates for US male and female athletes participating in high school or college interscholastic sports. Assuming a single screening evaluation in each athlete, models of no screening, only focused history and physical examination, and focused history and physical examination plus ECG were compared. Rates of sudden cardiac death were extrapolated from an Italian study (Corrado D, et al., JAMA 2006;296:1593-1601).

Results:
According to the authors’ model, addition of ECG to preparticipation screening saves 2.06 life-years per 1,000 athletes at an incremental total cost of $89 per athlete, and yields a cost-effectiveness ratio of $42,900 per life-year saved (95% confidence interval, $21,200 to $71,300 per life-year saved) compared with cardiovascular-focused history and physical examination alone. Compared with no screening, ECG plus cardiovascular-focused history and physical examination saves 2.6 life-years per 1,000 athletes screened and costs $199 per athlete, yielding a cost-effectiveness ratio of $76,100 per life-year saved ($62,400 to $130,000).

Conclusions:
The authors concluded that screening young athletes with 12-lead ECG plus cardiovascular-focused history and physical examination may be cost-effective.

Perspective:
No, no, no, no, no. This model—attempting to predict what might be, based on extrapolation of published data—used hotly contested data on sudden cardiac death rates in the Veneto region of Italy. Applied to the US population, the authors found, not surprisingly, that the conclusions drawn by the Italian authors would hold in the US, as well. However, there are very good reasons to believe that the Italian experience does not extrapolate to the US. The very high rate of sudden cardiac death in Italian athletes is due to arrhythmogenic right ventricular dysplasia, occurring at rates far higher than that seen in the US. Perhaps as a result, the rate of sudden cardiac death achieved with screening ECG in Italy now matches the low rates seen in the US without ECG screening. Rather than using the low rates of sudden cardiac death documented without ECG screening in the US, the authors appear to have essentially assured a ‘positive’ study by using data from different populations with different risks and different observed outcomes.
Atrial Fibrillation Originating From Superior Vena Cava Mimics Typical Atrial Flutter.


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Cryoablation versus radiofrequency ablation for AVNRT: patient pain perception and operator stress.


BACKGROUND:

Cryoablation (CRYO) is an alternative to radiofrequency (RF) ablation in the treatment of atrioventricular nodal reentrant tachycardia (AVNRT). This study aims to evaluate the differences in patient pain perception and operator stress between CRYO and RF ablation in the treatment of AVNRT.

METHODS:

Patients with supraventricular tachycardia underwent electrophysiology study. Twenty patients (eight males, age 46.5 ± 12.5 years) diagnosed with AVNRT were randomized to receive CRYO (11) with a 6-mm-tip catheter or RF (nine) with a 4-mm-tip catheter. Patients' pain perception and operator stress were assessed with a visual analogue scale (VAS) from 0 to 10 at the end of procedure.

RESULTS:

There was no significant difference in acute procedural success (CRYO 100% vs RF 89%, P = 0.257). There was no complication of permanent atrioventricular block in either group. The number of energy applications was significantly higher in the CRYO group (2.8 ± 1.2 vs 1.6 ± 0.9, P = 0.02). The fluoroscopic time was significantly reduced in the CRYO group (6.0 ± 4.9 vs 10.9 ± 5.4 minutes, P = 0.049) with no difference in procedure time (CRYO 49.3 ± 12.5 vs RF 54.5 ± 17.0 minutes, P = 0.462). Patients in the CRYO group experienced significantly less pain than patients in the RF group (VAS 2.3 ± 2.8 vs 5.4 ± 3.4, P = 0.024). The operator also experienced significantly less stress during CRYO than RF (VAS 1.9 ± 0.8 vs 6.2 ± 1.6, P < 0.001). There was no recurrence in both groups at 6-month follow-up.
CONCLUSIONS:

CRYO, as compared with RF, produces less pain in patients and less stress in operator in the treatment of AVNRT.

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Comment


Ablation of Ventricular Fibrillation in an Orthotopic Heart Lung Transplant.


Arrhythmia is well described following cardiac transplantation. We report a case of recurrent ventricular fibrillation (VF) originating from an orthotopic cardiac allograft. VF was consistently initiated on each occasion by a relatively early-coupled monomorphic ventricular ectopic. Antiarrhythmic agents failed to suppress the arrhythmia. Electrophysiological testing with noncontact mapping showed a high-frequency potential at the earliest activation site. Radiofrequency ablation resulted in abolition of ventricular ectopy with no further VF recurrence. Although there is substantial experience with ablation of atrial tachycardias in this setting, experience with ablation for ventricular arrhythmias is limited and ablation of VF not described.

PMID: 21438890 Cardiology Department, Royal Brompton and Harefield NHS Foundation Trust, London, UK.
Atrial fibrillation in emergency department: prevalence of sinus rhythm 1 week after discharge.

Camilla Fundarò, Andrea Galli, Stefano Paglia, Silvia Colombo, Angelo Rovellini, Livio Colombo, Valter Monzani, Daniele Coen, Stefano Guzzetti

Atrial fibrillation in emergency department: prevalence of sinus rhythm 1 week after discharge.

Background
Current guidelines do not provide definitive indications about the treatment in emergency departments (ED) of patients with recent-onset atrial fibrillation (AF).

Methods
A multicentre observational study involving four general hospitals of the same metropolitan area was conducted. All consecutive adult patients admitted to the ED with recent symptoms of AF (<48 h duration) and discharged home were considered. Patients who underwent ED early cardioversion were enrolled in group A. Patients managed with ventricular rate control were enrolled in group B.

Results
On the 24 h Holter recordings at 1-week follow-up, stable sinus rhythm was detected in 46/58 (79.3%; 95% CI 68.9 to 89.7) patients in group A and 8/33 (24.2%; 95% CI 9.6 to 38.9) patients in group B (p<0.01).

Conclusion
According to the study results, rhythm at the time of ED discharge is a poor indicator of the short-term evolution of AF.

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Calcium channel blockers are independently associated with short sleep duration in hypertensive patients with obstructive sleep apnea

Flávia Ba Nerbass, Pedrosa RP, Genta PR, Drager LF, Lorenzi-Filho G.
Calcium channel blockers are independently associated with short sleep duration in hypertensive patients with obstructive sleep apnea

Objective:

Obstructive sleep apnea (OSA) and hypertension (HYP) frequently coexist and have additive harmful effects on the cardiovascular system. There is also growing evidence that short sleep duration may contribute independently to poor cardiovascular outcome. The aim of this study was to evaluate the potential influence of antihypertensive medication on sleep parameters objectively measured by standard polysomnography in hypertensive patients with OSA.

Methods:

We evaluated consecutive patients with a recent diagnosis of OSA by full polysomnography (apnea hypopnea index ≥5 events/h) and HYP. Smokers, patients with diabetes mellitus, heart failure, or using hypnotics and benzodiazepines were excluded.

Results:

We evaluated 186 hypertensive patients with OSA, 64% men. All patients were on at least one antihypertensive medication, including angiotensin-converting enzyme inhibitors (37%), beta-blockers (35%), angiotensin receptor blockers (32%), diuretics (29%) and calcium channel blockers (21%). Backward multiple regression analysis showed that age (P ≤ 0.001) and the use of calcium channel blockers (P = 0.037) were the only factors inversely associated with lower total sleep time. Sleep efficiency was inversely associated only with age (P ≤ 0.001), whereas the use of calcium channel blockers had a nonsignificant trend (P = 0.092). Use of calcium channel blockers was associated with significant reduction in total sleep time (−41 min, P = 0.005) and 8% lower sleep efficiency (P = 0.004). No other antihypertensive medication, including diuretics and beta-blockers, was associated with sleep impairment.

Conclusion:

Calcium channel blockers may impact negatively on sleep duration in hypertensive patients with OSA. The mechanisms and significance of this novel finding warrants further investigation.
**Study Question:**
For purposes of screening college athletes before athletic participation, how do history and physical examination alone compare with a strategy including routine electrocardiography (ECG)?

**Methods:**
Over a 3-year interval, 510 collegiate athletes at Harvard University (Cambridge, MA) who underwent preparticipation screening at the University Health Services were studied. Each participant underwent routine history, physical examination, ECG, and transthoracic echocardiography (TTE) to detect or exclude cardiac findings relevant to sports participation. TTE results were taken as the “gold standard” for disease presence. The performance of screening with history and physical examination only was compared with that of screening integrating history, examination, and ECG.

**Results:**
Cardiac abnormalities relevant to sports participation risk were observed on TTE in 11 of 510 participants (prevalence, 2.2%; including mitral valve prolapse [n = 3], bicuspid aortic valve [n = 2], pulmonic stenosis [n = 1], left ventricular [LV] hypertrophy [n = 2], LV dilation [n = 2], and right ventricular dilation [n = 1]). Screening history and physical examination alone detected abnormalities in 5 of these 11 athletes (sensitivity 45.5%; 95% confidence interval [CI], 16.8-76.2% and specificity 94.4%; CI, 92.0-96.2%). ECG detected five additional participants with cardiac abnormalities (total 10 of 11 participants), with overall sensitivity of 90.9% (CI, 58.7-99.8%). However, including ECG reduced the specificity of screening to 82.7% (CI, 79.1-86.0%) and was associated with a false-positive rate of 16.9% (vs. 5.5% for screening with history and examination only). After further evaluation, athletic participation was restricted in three athletes (one each with TTE findings of pulmonic stenosis, LV hypertrophy, LV dilation).

**Conclusions:**
Adding ECG to medical history and physical examination improves the overall sensitivity of preparticipation cardiovascular screening in athletes. However, this strategy is associated with an increased rate of false-positive results when current ECG interpretation criteria are used.

**Perspective:**
The debate continues as to whether US amateur athletes should undergo a mandatory screening ECG (as is the policy in Italy, and subsequently adopted by the European Union) in addition to only screening history and physical examination (as is the long-standing US policy). On the surface, this study appears to add weight to the argument for routine preparticipation ECG. However, caveats abound, many of which were discussed in an accompanying editorial (Maron BJ, *Ann Intern Med* 2010;152:324-6). In addition:

The population of student athletes at Harvard might be anticipated to be poorly reflective of all amateur athletes in the US. (In this study, only 10% of screened athletes were black.) Because nonpathologic ECG abnormalities are far more prevalent in black than in white athletes, it could be anticipated that such benign but abnormal ECGs likely were under-represented in this study, and would have served to further reduce the specificity of the ECG.
Low test specificity and the associated high rate of false-positives is a major issue with the routine use of preparticipation ECG. The best-case scenario is that more money is spent to do more tests to prove that everything was OK to begin with. The worse (and probably more realistic) outcome is that amateur athletes are denied the ability to participate—including many with no underlying cardiac disease, and others with disease, but no prohibitive risk. In a country plagued by obesity, diabetes, and their various sequelae, physical activity should be encouraged not just in principle but in practice. Setting a low threshold for exclusion from athletics only will serve to worsen our obesity epidemic.

The authors used as a ‘gold standard’ for disease any abnormality of an echocardiogram. But of the 11 athletes with an ‘abnormal’ TTE, athletic participation was limited in only three (one of whom had an abnormal physical examination). If our societal goal is to detect any cardiac disease in any child or young adult, then intended athletic participation is impertinent, and screening should be instituted universally. If our goal is to detect disease that might pose a risk to the athlete, then the denominator in this study should have been at most three, not 11 students.
Contribution of late sodium current (INa-L) to rate adaptation of ventricular repolarization and reverse use-dependence of QT-prolonging agents

Donglin Guo, J Lian, T Liu, R Cox, KB Margulies, PR Kowey, G-X Yan, Contribution of late sodium current (INa-L) to rate adaptation of ventricular repolarization and reverse use-dependence of QT-prolonging agents

Heart Rhythm 2011 ; 8 / 5 : 762-769, May 2011

Background

Abnormal rate adaptation of ventricular repolarization is arrhythmogenic. There is controversy on the underlying ionic mechanisms for rate-dependent change in repolarization.

Objective

The purpose of this study was to examine the role of the late sodium current (INa-L) in normal rate-dependence of ventricular repolarization and reverse use-dependence of QT-prolonging agents.

Methods

The effects of INa-L blockade, INa-L enhancement, IKr blockade, and changes in extracellular potassium concentration ([K+]o) on rate adaptation of the QT interval and action potential duration (APD) were examined in isolated rabbit ventricular wedges and single myocytes. Rate dependence of INa-L, delayed rectifier potassium current (IKr), and L-type calcium current (ICa) was determined using a whole-cell, voltage clamp technique.

Results

At control, APD exhibited rate-dependent changes in the multicellular preparations as well as in the isolated single ventricular myocytes when [K+]o remained constant. The rate dependence of APD was significantly enhanced by reduction of [K+]o from 4 to 1 mM or by INa-L enhancement but was markedly blunted by the selective sodium channel blocker tetrodotoxin. The IKr blocker dofetilide (3 nM) amplified the QT to basic cycle length slope (71.2 ± 13.1 ms/s vs 35.1 ± 8.8 ms/s in control, n = 4, P <.05). This reverse use-dependence was abolished by tetrodotoxin at 5 μM (11.4 ± 4.3 ms/s, n = 4, P <.01). There were no significant differences in ICa or IK over the range of basic cycle lengths from 2,000 to 500 ms. However, INa-L exhibited a significant rate-dependent reduction.

Conclusion

INa-L is sensitive to rate change due to its slow inactivation and recovery kinetics and plays a central role in the rate dependence of APD/QT and in the reverse use-dependence of select APD/QT-prolonging agents.

Keywords: Action potential duration, Delayed rectifier potassium current, IKr block, Late sodium current, Rate adaptation, Reverse use-dependence V

Abbreviations: APD, action potential duration, ATX-II, Anemonia sulcata toxin, BCL, basic cycle length, LV, left ventricle, TTX, tetrodotoxin / Received 28 September 2010; accepted 15 December 2010. published online 23 December 2010.
A 75-year-old woman with chronic atrial fibrillation presented to the hospital with a 2-day history of colicky abdominal pain. The physical examination revealed hypoactive bowel sounds and diffuse abdominal tenderness. Laboratory tests showed a white-cell count of 19,400 per cubic millimeter with 92% neutrophils, a blood urea nitrogen level of 42 mg per deciliter (15 mmol per liter), and a serum creatinine level of 3.0 mg per deciliter (267 μmol per liter). Abdominal computed tomography with contrast material showed occlusion of the main trunk of the superior mesenteric artery with mesenteric venous gas (Panel A, reconstructed coronal image, arrow) and pneumatosis intestinalis (arrowhead). Laparotomy revealed ischemic changes with congestion and transmural necrosis of the small bowel (Panel B) and ascending colon. The superior mesenteric artery is susceptible to embolic occlusion because of its large caliber and narrow take-off angle from the aorta. Although surgical resection of the necrotic bowel is the treatment of choice, the patient and her family opted for conservative treatment. The patient died 3 days later.

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A Complex Double Deletion in LMNA Underlies Progressive Cardiac Conduction Disease, Atrial Arrhythmias and Sudden Death.


A Complex Double Deletion in LMNA Underlies Progressive Cardiac Conduction Disease, Atrial Arrhythmias and Sudden Death.
Circ Cardiovasc Genet. 2011 Mar 15. [Epub ahead of print]

BACKGROUND: - Cardiac conduction disease is a clinically and genetically heterogeneous disorder characterized by defects in electrical impulse generation and conduction, and associated with sudden cardiac death.

METHODS AND RESULTS: - We here studied a four-generation family with autosomal dominant progressive cardiac conduction disease, including atrioventricular conduction block, sinus bradycardia, atrial arrhythmias and sudden death. Genome-wide linkage analysis mapped the disease locus to chromosome 1p22-q21. Multiplex ligation-dependent probe amplification (MLPA) analysis of the LMNA gene, which encodes the nuclear-envelop protein lamin A/C, revealed a novel gene rearrangement involving a 24-bp inversion flanked by a 3.8-kb deletion upstream and a 7.8-kb deletion downstream. The presence of short inverted sequence homologies at the breakpoint junctions suggested a mutational event involving serial replication slippage in trans during DNA replication.

CONCLUSIONS: - We identified for the first time a complex LMNA gene rearrangement involving a double deletion in a four-generation Dutch family with progressive conduction system disease. Our findings underscore the fact that if conventional PCR-based direct sequencing approaches for LMNA analysis are negative in suggestive pedigrees, mutation detection techniques capable of detecting gross genomic lesions involving deletions and insertions should be considered.

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Mauriello DA, Johnson JN, Ackerman MJ.

Background:

Long QT syndrome (LQTS) is a potentially lethal cardiac channelopathy that affects one in 2,000 persons; causes syncope, seizures, and sudden death; and is both under- and overdiagnosed. LQTS diagnostic miscues have stemmed from assessment of ambulatory electrocardiographic monitoring (Holter) results. Objective:

We sought to determine the prevalence of positive Holter monitor tests and its diagnostic significance in evaluating LQTS.

Methods:

We performed an institutional review board-approved review of patients evaluated in our LQTS clinic from 2000 to 2009 who had Holter testing during their evaluation. Included patients (N = 473) were diagnosed with LQTS or dismissed as otherwise normal. Holters classified as positive had an episode of nonsustained ventricular tachycardia, supraventricular tachycardia, ≥4 couplets/day, ≥10 premature ventricular contractions/hour, or >5-second sinus pause.

Results:

Among 209 patients dismissed as normal (128 females, average age 21 ± 15 years, average QTc 424 ± 39 ms), 27 (12.9%) had a positive Holter, while among 264 patients with LQTS (149 females, average age 22 ± 16 years, average QTc 472 ± 41 ms), 30 (11.3%) had a positive Holter (P = NS). Patients with LQT3 (5/23, 21%) and genotype-negative LQTS (5/19, 26%) had a higher rate of positive Holter testing compared to LQT1 patients (7/124, 6%, P < 0.03). Among the 473 Holters, only one (0.2%) impacted clinical decision making.

Conclusion:

Routine Holter monitoring appears to be of minimal clinical utility from a diagnostic and prognostic perspective in evaluating LQTS, and may not be cost effective. Whether Holter monitoring aids in therapeutic decisions such as dosing or whether ambulatory QTc measurements, provided by some newer devices, might help in the diagnostic evaluation warrants further scrutiny.

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**Esophageal injury after atrial fibrillation ablation with an epicardial high-intensity focused ultrasound device.**

Prasertwitayakij N, Vodnala D, Pridjian AK, Thakur RK.  
Esophageal injury after atrial fibrillation ablation with an epicardial high-intensity focused ultrasound device.  
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**Founder mutations in the Netherlands: familial idiopathic ventricular fibrillation and DPP6.**

Founder mutations in the Netherlands: familial idiopathic ventricular fibrillation and DPP6.  
*Neth Heart J.* 2011 Apr 22. [Epub ahead of print]  
In this part of a series on founder mutations in the Netherlands, we review familial idiopathic ventricular fibrillation linked to the DPP6 gene. Familial idiopathic ventricular fibrillation determines an intriguing subset of the inheritable arrhythmia syndromes as there is no recognisable phenotype during cardiological investigation other than ventricular arrhythmias highly associated with sudden cardiac death. Until recently, it was impossible to identify presymptomatic family members at risk for fatal events. We uncovered several genealogically linked families affected by numerous sudden cardiac deaths over the past centuries, attributed to familial idiopathic ventricular fibrillation. Notably, ventricular fibrillation in these families was provoked by very short coupled monomorphic extrasystoles. We were able to associate their phenotype of lethal arrhythmic events with a haplotype harbouring the DPP6 gene. While this gene has not earlier been related to cardiac arrhythmias, we are now able, for the first time, to identify and to offer timely treatment to presymptomatic family members at risk for future fatal events solely by genetic analysis. Therefore, when there is a familial history of unexplained sudden cardiac deaths, a link to the DPP6 gene may be explored as it may enable risk evaluation of the remaining family members. In addition, when closely coupled extrasystoles initiate ventricular fibrillation in the absence of other identifiable causes, a link to the DPP6 gene should be suspected.  
PMID: 21512816  
Department of Cardiology and Heart Failure Research Center, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands.

**Exercise testing and asymptomatic pre-excitation.**

Silverman DE  
Exercise testing and asymptomatic pre-excitation.  
drdavidsilverman@hotmail.co.uk PMID: 21036799
Sudden cardiac death from ventricular fibrillation during myocardial infarction is a leading cause of total and cardiovascular mortality. This multifactorial, complex condition clusters in families, suggesting a substantial genetic cause. We carried out a genomewide association study (GWAS) for sudden cardiac death, in the AGNES (Arrhythmia Genetics in the Netherlands) population, consisting of patients with (cases) and without (controls) ventricular fibrillation during a first ST-elevation myocardial infarction. The most significant association was found at chromosome 21q21 (rs2824292; odds ratio = 1.78, 95% CI 1.47-2.13, \( P = 3.3 \times 10^{-10} \)), 98 kb proximal of the CXADR gene, encoding the Coxsackie and adenovirus receptor. This locus has not previously been implicated in arrhythmia susceptibility. Further research on the mechanism of this locus will ultimately provide novel insight into arrhythmia mechanisms in this condition.
Genetics of sudden cardiac death syndromes.

Chopra N, Knollmann BC.
Genetics of sudden cardiac death syndromes.
Curr Opin Cardiol. 2011 Mar 22. [Epub ahead of print]

PURPOSE OF REVIEW: To survey recent developments in the field of genetics encompassing discovery of new candidate genes, new diagnostic strategies, and new therapies for sudden cardiac death (SCD) syndromes.

RECENT FINDINGS: In addition to new mutations in known SCD genes, several novel genes not previously implicated in SCD causation have been found, particularly in long QT syndrome (e.g., KCNJ5, AKAP9, SNTA1), idiopathic ventricular fibrillation (e.g., DPP6, KCNJ8), dilated cardiomyopathy (e.g., NEBL), and hypertrophic cardiomyopathy (HCM; e.g., NEXN). Genetic SCD animal models have provided novel insights into the cellular mechanism and pathogenesis of nearly all the major SCD syndromes, which has led to several new drug therapies for patients with genetic arrhythmia syndromes (e.g., flecainide in catecholaminergic polymorphic ventricular tachycardia). Furthermore, genetic contributions to acquired heart diseases are increasingly being recognized. For example, a 21q21 locus is strongly associated with ventricular fibrillation after myocardial infarction. Near this locus is CXADR, a gene encoding a viral receptor implicated in myocarditis and dilated cardiomyopathy. Finally, common variants in cardiac ion channels and proteins likely contribute to common cardiac phenotypes.

SUMMARY: Major strides have been made in uncovering new genes, mechanisms, and syndromes that have significantly advanced the diagnosis and treatment of genetic SCD disorders.

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Half of all cases of atrial fibrillation (AF) are due to cardiovascular risk factors such as hypertension, diabetes, obesity, and smoking, new research shows [1]. And it's not just those with obviously high levels who are at risk, but even those with borderline BP, blood glucose, and body-mass indexes (BMIs), say the researchers, whose findings, from the Atherosclerosis Risk in Communities (ARIC) study, are published online March 28, 2011 in Circulation.

Hypertension was the strongest predictor of AF, accounting for almost a quarter of all cases if borderline BPs were included.

"Our study shows that AF is preventable through encouraging individuals to adopt and maintain healthy diet and lifestyles, the same as for other forms of cardiovascular disease," lead author Dr Rachel R Huxley (University of Minnesota, MN) told the press.

Second study to quantify the burden of AF from risk factors

Huxley and colleagues followed 14 598 middle-aged Americans participating in the ARIC study. On the basis of previously established AF risk factors—including hypertension, elevated BMI, diabetes mellitus, cigarette smoking, and prior cardiac disease—individuals were categorized into groups: optimal, borderline, or elevated. The population-attributable fraction (PAF) of AF resulting from having a nonoptimal risk profile was estimated separately by race and gender.

During a mean follow-up of 17.1 years, 1520 cases of incident AF were identified. The age-adjusted incidence rates were highest in white men and lowest in black women (7.45 and 3.67 per 1000 person-years, respectively).

The overall prevalence of an optimal risk profile was 5.4% but varied according to race and sex: 10% in white women vs 1.6% in black men.

"This is only the second study to attempt to quantify the burden of AF resulting from major and modifiable risk factors," say Huxley and colleagues. The previous study, based on the Framingham cohort, found that smoking, diabetes, hypertension, and prevalent CHD combined explained 44% of the burden in men and 58% in women, figures that are "broadly comparable to those in the present study," they observe.

And the fact that the new study seeks to quantify the burden of AF resulting from having borderline, rather than just elevated, levels of risk factors is an "important consideration, given that a significant proportion of the population has suboptimal BP, levels of blood glucose, and BMIs," the researchers point out.

"From a public-health perspective, our data highlight the substantial potential for AF risk reduction through primary-prevention strategies that target modification and improvement in behavioral and dietary risk factors," they note.

Paradoxical racial findings for AF: Does genetics play a greater role?

While elevated levels of risk factors explained 50% of the overall incidence of AF in this ARIC cohort, this is lower than previously reported ARIC estimates of the PAF for heart
failure, coronary heart disease, and stroke, Huxley et al note, "suggesting that other factors, possibly genetic, may have a greater role in the etiology of AF."

The lower risk of AF in blacks compared with whites is actually very interesting, because prevalence of most risk factors for AF are higher in African Americans than whites.

Senior author Dr Alvaro Alonso (University of Minnesota, MN) told the press that the lower risk of AF in African Americans observed in this study is something that has been observed previously. "We are not sure yet about the reasons, but a hypothesis is that genetic factors are responsible for this difference: some genetic variants present in whites but not in blacks could be associated with a higher risk of AF, or genetic variants in blacks could protect against AF.

"The lower risk of AF in blacks compared with whites is actually very interesting, because prevalence of most risk factors for AF, such as high blood pressure and obesity, are higher in African Americans than whites, so we would expect higher incidence of AF among blacks, not lower," he notes. And the risk of other cardiovascular diseases, such as stroke, MI, or heart failure, is higher in African Americans than whites, "so what we see for AF is an exception to this 'rule.' "


The authors declare they have no conflicts of interest
Desmosomal Mutations Across the Fence A Comment.

Bhuiyan ZA, Wilde AA. Desmosomal Mutations Across the Fence. Heart Rhythm. 2011 Mar 31. [Epub ahead of print]
Laboratoire de Génétique Moléculaire, Service de Génétique Médicale, Centre Hospitalier Universitaire Vaudois (CHUV), 1011 Lausanne, Switzerland. PMID:21459163

Population-prevalent desmosomal mutations predisposing to ARVD


BACKGROUND:

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a progressive myocardial disorder caused by mutations of desmosomal cell adhesion proteins. The prevalence of these variants in the general population is yet unknown.

OBJECTIVE:

This study examined the spectrum and population prevalence of desmosomal mutations predisposing to ARVC in Finland.

METHODS:

We screened 29 Finnish ARVC probands for mutations in the DSP, DSG2, and DSC2 genes. All Finnish-type ARVC-associated mutations, including those three previously identified in PKP2 in the same patient group, were analyzed in the population-based Health 2000 cohort of 6,334 individuals and tested for association with electrocardiographic variables.

RESULTS:

We detected two novel mutations: DSG23059_3062delAGAG and DSP T1373A. DSG23059_3062delAGAG was present in a family with five mutation carriers. The endomyocardial samples of the DSG2deletion carrier showed reduced immunoreactive signal for desmoglein-2, plakophilin-2, plakoglobin, and desmoplakin. DSP T1373A was found in one proband with typical right ventricular disease and exercise-related ventricular tachycardia. In the population sample, the collective prevalence of all five mutations identified in the 29 ARVC patients (PKP2Q62K, Q59L, N613K, DSG23059_3062delAGAG, and DSP T1373A) was 31 out of 6,334 individuals, or 0.5%. The apparent founder mutation PKP2Q59L is present in 0.3% of Finns and was previously shown to have an approximately 20% disease penetrance.

CONCLUSION:

One out of 200 Finns carries a desmosomal mutation that may predispose to ARVC and its clinical sequelae. ARVC-associated mutations may thus be more prevalent in the population than expected based on the published ARVC prevalence data.
Mutations in the cardiac L-type calcium channel associated with inherited J-wave syndromes and sudden cardiac death.


BACKGROUND:

L-type calcium channel (LTCC) mutations have been associated with Brugada syndrome (BrS), short QT (SQT) syndrome, and Timothy syndrome (LQT8). Little is known about the extent to which LTCC mutations contribute to the J-wave syndromes associated with sudden cardiac death.

OBJECTIVE:

The purpose of this study was to identify mutations in the α1, β2, and α2δ subunits of LTCC (Ca(v)1.2) among 205 probands diagnosed with BrS, idiopathic ventricular fibrillation (IVF), and early repolarization syndrome (ERS). CACNA1C, CACNB2b, and CACNA2D1 genes of 162 probands with BrS and BrS+SQT, 19 with IVF, and 24 with ERS were screened by direct sequencing.

METHODS/RESULTS:

Overall, 23 distinct mutations were identified. A total of 12.3%, 5.2%, and 16% of BrS/BrS+SQT, IVF, and ERS probands displayed mutations in α1, β2, and α2δ subunits of LTCC, respectively. When rare polymorphisms were included, the yield increased to 17.9%, 21%, and 29.1% for BrS/BrS+SQT, IVF, and ERS probands, respectively. Functional expression of two CACNA1C mutations associated with BrS and BrS+SQT led to loss of function in calcium channel current. BrS probands displaying a normal QTc had additional variations known to prolong the QT interval.

CONCLUSION:

The study results indicate that mutations in the LTCCs are detected in a high percentage of probands with J-wave syndromes associated with inherited cardiac arrhythmias, suggesting that genetic screening of Ca(v) genes may be a valuable diagnostic tool in identifying individuals at risk. These results are the first to identify CACNA2D1 as a novel BrS susceptibility gene and CACNA1C, CACNB2, and CACNA2D1 as possible novel ERS susceptibility genes.

Comment

The atrioventricular conduction axis, located in the septal component of the atrioventricular junctions, is arguably the most complex structure in the heart. It fulfils a multitude of functions, including the introduction of a delay between atrial and ventricular systole and backup pacemaking. Like any other multifunctional tissue, complexity is a key feature of this specialised tissue in the heart, and this complexity is both anatomical and electrophysiological, with the two being inextricably linked. We used quantitative PCR, histology and immunohistochemistry to analyse the axis from six human subjects. mRNAs for ~50 ion and gap junction channels, Ca²⁺-handling proteins and markers were measured in the atrial muscle (AM), a transitional area (TA), inferior nodal extension (INE), compact node (CN), penetrating bundle (PB) and ventricular muscle (VM). When compared to the AM, we found a lower expression of Nav1.5, Kir2.1, Cx43 and ANP mRNAs in the CN for example, but a higher expression of HCN1, HCN4, Cav1.3, Cav3.1, Kir3.4, Cx40 and Tbx3 mRNAs. Expression of some related proteins was in agreement with the expression of the corresponding mRNAs. There is a complex and heterogeneous pattern of expression of ion and gap junction channels and Ca²⁺-handling proteins in the human atrioventricular conduction axis that explains the function of this crucial pathway.

Research Highlights
► Complex expression of ion channels in the atrioventricular (AV) conduction axis. ► Heterogeneous pattern of expression of ion channels explains the function of this pathway. ► Lower expression of Nav1.5, Kir2.1 in the AV node when compared to the atrial muscle. ► Higher expression of HCN1, HCN4, Cav1.3, Cav3.1 in the AV node when compared to the atrial muscle.

Keywords: Atrioventricular node, Ion channels, Gap junctions, Arrhythmias

Molecular architecture of the human specialised atrioventricular conduction axis
J Mol & Cell Cardiol 2011 ; 50 / 4 : 642-651. (April 2011)
KATP channel-dependent metaboproteome decoded: systems approaches to heart failure prediction, diagnosis, and therapy

D. Kent Arrell, J Zlatkovic Lindor, S Yamada, A Terzic
KATP channel-dependent metaboproteome decoded: systems approaches to heart failure prediction, diagnosis, and therapy

Systems biology provides an integrative platform by which to account for the biological complexity related to cardiac health and disease. In this way, consequences of ATP-sensitive K+ (KATP) channel deficiency for heart failure prediction, diagnosis, and therapy were resolved recently at a proteomic level. Under stress-free conditions, knockout of the Kir6.2 KATP channel pore induced metabolic proteome remodelling, revealing overrepresentation of markers of cardiovascular disease. Imposed stress precipitated structural and functional defects in Kir6.2-knockout hearts, decreasing survival and validating prediction of disease susceptibility. In the setting of hypertension, a leading risk for heart failure development, proteomic analysis diagnosed the metabolism-centric impact of KATP channel deficiency in disease. Bioinformatic interrogation of KATP channel-dependent proteome prioritized heart-specific adverse effects, exposing cardiomyopathic traits of aggravated contractility, fibrosis, and ventricular hypertrophy. In dilated cardiomyopathy induced by Kir6.2-knockout pressure overload, proteomic remodelling was exacerbated, underlying a multifaceted molecular pathology that indicates the necessity for a broad-based strategy to achieve repair. Embryonic stem cell intervention in cardiomyopathic KATP channel knockout hearts elicited a distinct proteome signature that forecast amelioration of adverse cardiac outcomes. Functional/structural measurements validated improved contractile performance, reduced ventricular size, and decreased cardiac damage in the treated cohort, while systems assessment unmasked cardiovascular development as a prioritized biological function in stem cell-reconstructed hearts.

Thus, proteomic deconvolution of KATP channel-deficient hearts provides definitive evidence for the channel's homeostatic contribution to the cardiac metaboproteome and establishes the utility of systems-oriented approaches to predict disease susceptibility, diagnose consequences of heart failure progression, and monitor therapy outcome.

Key words: ATP-sensitive K+ channel, Bioinformatics, Cardiac, KATP channel, Kir6.2, Genetics, Heart disease, Metabolism, Networks, Protein expression, Proteomics, Regenerative medicine, SUR2A, Stem cells, Systems biology. doi: 10.1093/cvr/cvr046 First published online: February 14, 2011. + Author Affiliations 1 Marriott Heart Disease Research Program, Mayo Clinic, Stabile 5, 200 First Street SW, Rochester, MN, USA 2 Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, Stabile 5, 200 First Street SW, Rochester, MN, USA 3 Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Stabile 5, 200 First Street SW, Rochester, MN, USA 4 Department of Medical Genetics, Mayo Clinic, Stabile 5, 200 First Street SW, Rochester, MN, USA Corresponding author. Tel: +1 507 284 2747, fax: +1 507 266 9936, Email: terzic.andre@mayo.edu // Received November 11, 2010. //Revision received January 16, 2011. // accepted February 8, 2011.
OBJECTIVES:

This study sought to determine comprehensively the incidence of pediatric out-of-hospital cardiac arrest (OHCA) and its contribution to total pediatric mortality, the causes of pediatric OHCA, and the outcome of resuscitation of pediatric OHCA patients.

BACKGROUND:

There is a paucity of complete studies on incidence, causes, and outcomes of pediatric OHCA.

METHODS:

In this prospective, population-based study, OHCA victims younger than age 21 years in 1 province of the Netherlands were registered through both emergency medical services and coroners over a period of 4.3 years. Death certificate data on total pediatric mortality, survival status, and neurological outcome at hospital discharge also were obtained.

RESULTS:

With a total mortality of 923 during the study period and 233 victims of OHCA (including 221 who died and 12 who survived), OHCA caused 24% (221 of 923) of total pediatric mortality. Natural causes of OHCA amounted to 115 (49%) cases, with cardiac causes being most prevalent (n = 90, 39%). The incidence of pediatric OHCA was 9.0 per 100,000 pediatric person-years (95% confidence interval: 7.8 to 10.3), whereas the incidence of pediatric OHCA from cardiac causes was 3.2 (95% confidence interval: 2.5 to 3.9). Of 51 resuscitated patients, 12 (24%) survived; among survivors, 10 (83%) had a neurologically intact outcome.

CONCLUSIONS:

Out-of-hospital cardiac arrest accounts for a significant proportion of pediatric mortality, and cardiac causes are the most prevalent causes of OHCA. The vast majority of OHCA survivors have a neurologically intact outcome.

PMID:21527156 .. Heart Failure Research Center, Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands.
**Left atrial wall thickness in paroxysmal atrial fibrillation by multislice-CT is initial marker of structural remodeling and predictor of transition from paroxysmal to chronic form**

Koki Nakamura, Nobusada Funabashi, Masae Uehara, Marehiko Ueda, Taichi Murayama, Hiroyuki Takaoka, Issei Komuro.

Left atrial wall thickness in paroxysmal atrial fibrillation by multislice-CT is initial marker of structural remodeling and predictor of transition from paroxysmal to chronic form

International Journal of Cardiology 2011; 148/2: 139-147, 14 April 2011

**Purpose**

We used ECG-gated MSCT to evaluate alterations in the LA wall in patients with paroxysmal atrial fibrillation (AF) (PAF) and compared with chronic AF (CAF) and normal sinus rhythm (NSR).

**Materials and methods**

We enrolled 3 groups, each consisting of 62 patients with either recurrent PAF (48 males, 65±11 years), CAF (43 males, 69±9 years), or NSR without any history of AF (40 males, 64±11 years) for a total of 186 study patients. In CT, the *absolute LA wall thickness (LAT)* and LA volumes were calculated.

**Results**

In CT, patients with PAF had significantly thicker LAT than those with either CAF or NSR (2.4±0.2 mm in PAF > 2.1±0.2 mm in CAF or 1.9±0.2 mm in NSR, *p*<0.01). Patients with CAF had significantly larger LA volume than those with either PAF or NSR (*p*<0.01). Subsequently, 9 of the 62 patients with PAF developed CAF over a mean follow-up period of 19±22 months. The mean LAT was significantly thinner in patients who had transitioned from PAF to CAF than in those who had not (2.2±0.2 mm and 2.4±0.2 mm, respectively) (*p*<0.01). Receiver operating characteristic analysis demonstrated that the area under the curve for LAT was greater than that for LA volume in CT and LAD in transthoracic echocardiogram. In the Kaplan–Meier analysis, the transition from PAF to CAF was observed more frequently in patients with LAT<2.4 mm than LAT ≥2.4 mm (*p*=0.018).

**Conclusions**

Alteration of the LA wall may suggest a part of structural remodeling in AF before the occurrence of LA dilatation. **The absolute LA wall thickness (LAT)** in CT seems to be a useful predictor of the transition from PAF to CAF in patients with PAF.

Keywords: Left atrial wall thickness, Paroxysmal atrial fibrillation, Multislice-CT, Initial marker, Structural remodeling, Transition from paroxysmal to chronic form Received 26 August 2009; accepted 18 October 2009. published online 11 November 2009.
Improving safety in the electrophysiology laboratory using a simple radiation dose reduction strategy: a study of 1007 radiofrequency ablation procedures

Dominic P S Rogers, F England, K Lozhkin, MD Lowe, PD Lambiase, AWC Chow.

Improving safety in the electrophysiology laboratory using a simple radiation dose reduction strategy: a study of 1007 radiofrequency ablation procedures
Heart 2011;97:366e370. doi:10.1136/hrt.2010.204222

Background
The use of fluoroscopic screening involves exposure to ionising radiation for both patients and operators. Objective To assess the effects of radiation dose reduction manoeuvres (DRM) during radiofrequency ablation (RFA) procedures.

Design
Prospective study of DRM.

Setting
Tertiary cardiac centre.

Interventions
Two DRM were combined: removal of the secondary radiation grid and programming an ultra-low pulsed fluoroscopy rate. These methods were assessed using an anthropomorphic phantom model to measure skin entrance dose rates. Procedures were classified as complex (ablation of atrial fibrillation, ventricular tachycardia or complex congenital heart disease arrhythmias) or simple (all other RFA).

Main outcome measures
Dose area product and screening times were compared for ablations performed before and after DRM. Equivalent doses to organs and malignancy risk were determined by computer modelling.

Results
Over a 39-month period, 1007 ablation procedures were performed (631 simple, 376 complex). Radiation dose was significantly reduced after DRM for both simple (20.46±26.9 Gycm² vs 8.06±10.3 Gycm², p<0.00001) and complex ablations (63.36±50.1 Gycm² vs 32.86±31.7 Gycm², p<0.00001) with no difference in screening times. The mean lifetime risk of fatal cancer attributable to radiation exposure per million procedures was reduced from 182 to 68 for simple ablations and from 440 to 155 for complex ablations.

Conclusions
Significant reductions in radiation exposure during RFA were achieved using simple DRM, corresponding to a two-thirds reduction of the risk of excess fatal malignancy.

< Additional appendices are published online only. To view these files, please visit the journal online (http://heart.bmj.com).

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Correspondence to Dr Anthony Chow, Department of Cardiac Electrophysiology, The Heart Hospital, UCLH Trust, 16e18 Westmoreland Street, London W1G 8PH, UK; anthony.chow@uclh.nhs.uk Accepted 9 September 2010 Published Online First 29 October 2010 366
Manifest disease, risk factors for SCD, and cardiac events in a large nationwide cohort of predictively tested HCM mutation carriers: determining the best cardiological screening strategy.


Manifest disease, risk factors for sudden cardiac death, and cardiac events in a large nationwide cohort of predictively tested hypertrophic cardiomyopathy mutation carriers: determining the best cardiological screening strategy.


Aims
We investigated the presence of a clinical diagnosis of hypertrophic cardiomyopathy (HCM), risk factors for sudden cardiac death (SCD), and cardiac events during follow-up in predictively tested—not known to have a clinical diagnosis of HCM before the DNA test—carriers of a sarcomeric gene mutation and associations with age and gender to determine the best cardiological screening strategy.

Methods and results
One hundred and thirty-six (30%) of 446 mutation carriers were diagnosed with HCM at one or more cardiological evaluation(s). Male gender and higher age were associated with manifest disease. Incidence of newly diagnosed manifest HCM was <10% per person-year under the age of 40 years and >10% in older carriers, although numbers were small in carriers <15 years. Twenty-three percent of carriers, with and without manifest disease, had established risk factor(s) for SCD (no significant difference). During an average follow-up of 3.5 ± 1.7 years two carriers, both with manifest disease, died suddenly (0.13% per person-year). A high-risk status for SCD (≥2 risk factors and manifest HCM) was present in 17 carriers during follow-up (2.4% per person-year). Age but not gender was associated with a high-risk status for SCD.

Conclusion
Thirty percent of carriers had or developed manifest HCM after predictive DNA testing and risk factors for SCD were frequently present. Our data suggest that the SCD risk is low and risk stratification for SCD can be omitted in carriers without manifest disease and that frequency of cardiological evaluations can possibly be decreased in carriers between 15 and 40 years as long as hypertrophy is absent.

PMID:21459882 // Department of Clinical Genetics, Academic Medical Centre, Amsterdam, the Netherlands.
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PMID:21459882 // Department of Clinical Genetics, Academic Medical Centre, Amsterdam, the Netherlands.
Meta-analysis of catheter ablation as an adjunct to medical therapy for treatment of ventricular tachycardia in patients with structural heart disease.


BACKGROUND:
Most studies of catheter ablation for the treatment of ventricular tachycardia (VT) are relatively small observational trials.

OBJECTIVE:
The purpose of this study was to define the relative risk of VT recurrence in patients undergoing catheter ablation as an adjunct to medical therapy versus medical therapy alone in a pooled analysis of controlled studies.

METHODS:
Randomized and nonrandomized controlled trials of patients who underwent adjunctive catheter ablation of VT versus medical therapy alone were sought. MEDLINE, EMBASE, the Cochrane central register of controlled trials (CENTRAL), and Web of Science were searched from 1965 to July 2010. Supplemental searches included Internet resources, reference lists, and reports of arrhythmia experts. Three authors independently reviewed and extracted the data regarding baseline characteristics, ablation methodology, medical therapy, complications, VT recurrences, mortality, and study quality.

RESULTS:
Five studies were included totaling 457 participants with structural heart disease. Adjunctive catheter ablation was performed in 58% of participants, whereas 42% received medical therapy alone for VT. Complications of catheter ablation included death (1%), stroke (1%), cardiac perforation (1%), and complete heart block (1.6%). Using a random-effects model, a statistically significant 35% reduction in the number of patients with VT recurrence was noted with adjunctive catheter ablation (P<.001). There was no statistically significant difference in mortality.

CONCLUSIONS:
Catheter ablation as an adjunct to medical therapy reduces VT recurrences in patients with structural heart disease and has no impact on mortality.

PMID: 21147263 // Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.
Inherited cardiomyopathies are a major cause of heart disease in all age groups, often with an onset in adolescence or early adult life. Not only the patients but also their families can be severely burdened by these illnesses. More than 20 years ago, the first “disease gene” for hypertrophic cardiomyopathy was identified.1,2 This finding led to the concept that hypertrophic cardiomyopathy is a disease of the sarcomere.3 Similar advances in the elucidation of the genetic basis of other forms of cardiomyopathy, as well as in other inherited cardiovascular diseases, soon followed.

The identification of disease genes in numerous inherited
Statin use in patients with nephrotic syndrome is associated with a lower risk of venous thromboembolism

Mohammad Resh, BK Mahmoodi, GJ Navis, NJGM Veeger, WM Lijfering

Statin use in patients with nephrotic syndrome is associated with a lower risk of venous thromboembolism
Thrombosis Research 2011 : 127 / 5 : 395-399 (May 2011)

Background

Nephrotic syndrome (NS) is a well-known risk factor for venous thromboembolism (VTE), however preventive measures are not routinely taken. In non-renal populations, statins are associated with lower risk of VTE. Hence, we set up this single-center retrospective cohort study to assess whether statin use influenced VTE risk in NS subjects.

Methods

We analyzed 289 consecutive patients with NS (defined by proteinuria ≥ 3.5 g/day) who were aged >18 years at the study entry and followed for at least 6 months. Use of statins and concomitant medication were determined.

Results

Of patients with NS (59% men; mean age, 42 years), 48% used statins for at least 1 month during NS. Using univariate and time-dependent Cox regression analyses, hazard ratio for VTE in statin users versus non-users was 0.2 (95%CI, 0.1-0.7) and 0.6 (95% CI, 0.2 -2.0), respectively. Adjustments for potential confounders did not change outcomes. Three VTE events occurred in a total of 812 statin-years, corresponding to an annual incidence of 0.37% (95%CI, 0.12-1.15). In contrast, 17 VTE occurred in a total of 2106 patient-years without statin exposure, annual incidence 0.81% (95%CI, 0.50-1.30).

Conclusions

Although statistically significant, the hazard ratio of 0.2 for VTE risk in statin users versus non-users could have been biased, but the time-dependent hazard ratio of 0.6 was probably not. As the association was in the same direction for both analyses, we conclude that statin use is associated with a lower risk of VTE in patients with NS.

Keywords: Statins, Nephrotic syndrome, Venous thrombosis/ a Division of Hemostasis and Thrombosis, Department of Hematology, University Medical Center Groningen, The Netherlands // b Department of Nephrology, University Medical Center Groningen, The Netherlands // c Trial Coordination Center, Department of Epidemiology, University Medical Center Groningen, The Netherlands // Corresponding author. Division of Hemostasis and Thrombosis, Department of Hematology, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands. Tel.: +31 50 3612791; fax: +31 50 3611790. //

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

Ayman A. Hussein, WI Saliba, DO Martin, M Shadman, M Kanj, M Bhargava, T Dresing, M Chung, T Callahan, B Baranowski, P Tchou, BD Lindsay, A Natale, OM Wazni.

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

Circulation. 2011 ; Published online before print May 2, 2011.

Background

Plasma B-type natriuretic peptide (BNP) is abnormally elevated in patients with lone atrial fibrillation (AF). The exact significance and prognostic implications of this elevation have yet to be determined. Little is known about BNP in lone AF patients undergoing arrhythmia ablation. We sought to determine the relationship between BNP levels and the risk of recurrent arrhythmia after ablation of lone AF.

Methods and Results

We followed up 726 patients with lone AF undergoing first-time arrhythmia ablation. All had BNP levels measured on the day of ablation with of the point-of-care Triage Meter assay (Biosite Diagnostics, San Diego, CA). At baseline, factors associated with elevated BNP levels in multivariable linear regression analysis (with log BNP being the dependent variable) were older age (β regression coefficient for +1-year change, 0.025; P<0.0001), longer duration of AF (β for +1-year change, 0.031; P=0.01), nonparoxysmal AF (versus paroxysmal; β, 0.52; P<0.0001), and larger left atrial size (β for +1-cm² change, 0.040; P<0.0001). The BNP levels were strongly associated with arrhythmia recurrence in univariate- (hazard ratio for +1-log-BNP change, 2.32; 95% confidence interval, 2.11 to 2.74; P<0.001) and covariate- (hazard ratio for +1-log-BNP change, 2.13; 95% confidence interval, 2.06 to 2.38; P<0.001) adjusted Cox proportional hazards analysis. The covariate-adjusted hazard ratios for recurrent arrhythmia were 1.6, 2.7, 4.3, and 5.7 for the second, third, fourth, and fifth quintiles, respectively, compared with patients in the lowest quintile (P for trend across quintiles <0.001).

Conclusions

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

Key Words: atrial fibrillation • catheter ablation • natriuretic peptides  Received August 12, 2010; accepted March 14, 2011. doi: 10.1161/CIRCULATIONAHA.110.007252 // From the Center for Atrial Fibrillation, Cleveland Clinic Foundation, Cleveland, OH (A.A.H., W.I.S., D.O.M., M.S., M.K., M.B., T.D., M.C., T.C., B.B., P.T., B.D.L., O.M.W.); and St. David’s Hospital, Austin, TX (A.N.). Correspondence to Oussama M. Wazni, MD, Cardiac Pacing and Electrophysiology, Department of Cardiovascular Medicine/J2–2, 9500 Euclid Ave, Cleveland, OH 44195. E-mail waznio@ccf.org
A major challenge in current cardiology is to predict who will die suddenly from ventricular arrhythmias. Ventricular arrhythmias are the most common cause of sudden cardiac death, occurring in about 1–2:1,000 inhabitants yearly, and is most frequently due to coronary artery disease. Patients with increased risk of ventricular arrhythmias can be offered medical treatment and ultimately an implantable cardioverter defibrillator (ICD). Left ventricular ejection fraction (EF) is currently the main risk stratification tool used to select patients for ICD therapy. However, EF is insufficient in predicting arrhythmic risk. A number of techniques have been presented to improve arrhythmic risk stratification without having reached clinical utility. Conduction abnormalities and dispersion of action potential duration forms the substrate for malignant ventricular arrhythmias in infarcted tissue as in several cardiomyopathies. The ability to assess electrical dispersion in patients noninvasively has been limited. Myocardial strain by echocardiography has been presented as an accurate tool for assessing myocardial function and timing. Inhomogeneous and dispersed myocardial contraction has been related to the occurrence of ventricular arrhythmias and seems to be a promising tool in risk stratification. This review focuses on arrhythmia mechanisms and novel echocardiographic tools for assessing risk of ventricular arrhythmias.

Author Contacts; Jan P. Amlie Department of Cardiology, Oslo University Hospital, Rikshospitalet Sognsvannsveien 27 NO–0027 Oslo (Norway) Tel. +47 2307 0000, E-Mail jamlie@ous-hf.no Article Information Received: January 18, 2011 Accepted after revision: March 1, 2011 Published online: May 10, 2011 / Key Words ‘ Ventricular arrhythmias Risk stratification Strain echocardiography Ventricular function aDepartment of Cardiology and bInstitute for Surgical Research, Oslo University Hospital, Rikshospitalet, and cUniversity of Oslo, Oslo, Norway Address of Corresponding Author
P-wave dispersion and atrial fibrillation risk: methodological considerations.

Dilaveris P, Stefanadis C.
P-wave dispersion and atrial fibrillation risk: methodological considerations.
Am J Cardiol. 2011 May 1;107(9):1405.

PMID:21497213

RADAR: First significant clinical use of novel reversible anticoagulation system

A phase 2 trial of a novel anticoagulation system that involves first giving a factor IX inhibitor and then administering a reversal agent has shown preliminary encouraging results, albeit with a question about potential allergic reactions.

REG1 (Regado Biosciences) consists of an RNA aptamer of factor IX—pegnivacogin—which binds to and inhibits the factor IX molecule for a 24-hour duration, and the reversal agent—anivamersen, which binds to and inactivates pegnivacogin.

Presenting results of the trial at the American College of Cardiology 2011 Scientific Sessions, Dr Thomas J Povsic (Duke University, Durham, NC) explained: "The system allows very high levels of anticoagulation for a short period, and then, on administration of the reversal agent, coagulation levels go back to normal quickly, so it is ideal for use in procedures such as PCI, where you just need high levels of anticoagulation during the procedure itself. We found that because we can normalize anticoagulation levels more quickly with the REG1 system, this allows faster removal of the sheath."

He added that the REG1 system would also be suited to other percutaneous procedures such as the new valvular procedures where large sheath sizes are used. And there is also a program looking into its use in open-heart surgery.

Povsic reported results of the first significant clinical use of REG1 system in the phase 2 RADAR trial. A very small phase 2a study has been reported previously. In the trial, 640 ACS patients scheduled for catheterization were randomized to pegnivacogin 1 mg/kg (n=479) or heparin (n=161) in an open-label fashion. Then, after the PCI procedure, anivamersen was given at four different doses (corresponding to 25%, 50%, 75% and 100% reversal) in a blinded fashion to the patients who had been given pegnivacogin.

The data safety and monitoring board stopped the lowest-dose anivamersen arm (25% reversal) early on in the trial because of a high bleeding rate. "So we showed that enough anivamersen to give at least 50% reversal of pegnivacogin is needed," Povsic said.

The three other arms showed good results, with a rate of total ACUITY bleeding similar to heparin, with the suggestion of a stepwise reduction in major bleeding with higher doses of the reversal agent.

RADAR: Major results

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Povsic noted that overall bleeding rates were hard to compare between the REG1 and heparin groups because of the open nature of pegnivacogin administration. "Less severe bleeding is quite a subjective measure, and operators may be more sensitive to minor bleeding with a new investigational agent," he commented to heartwire.

He reported that in the overall REG1 population there was a suggestion of a reduced rate of ischemic events (3.0% vs 5.7% on heparin), but this was based on a very small number of events (23 in total, mostly MIs), and no definite conclusion on efficacy could be drawn from a trial of this size.

Sheaths were removed an average of 24 minutes after the procedure in the REG1 patients vs three hours in the heparin group.

**Allergy question mark**

However, there were three allergic reactions in the trial. Povsic reported that these all occurred near the end of the trial in Europe shortly after administration of pegnivacogin. They ranged from a mild dermal reaction to one patient who needed hemodynamic support. "These reactions do not appear to be related to drug stability or contamination, and we need to get a better handle on what happened. Investigations are still under way," Povsic told the press.

The investigators are now working on the design of a phase 3 trial, which is likely to be a PCI study in both ACS and elective patients.
Radiofrequency ablation of the cavotricuspid isthmus is the first-line treatment for typical atrial flutter. Despite the close proximity of the right coronary artery (RCA) to the cavotricuspid isthmus, only four cases of arterial injury have been reported during radiofrequency ablation, all detected postablation by inferior ST elevation. Here, we report atrioventricular (AV) conduction delay during coronary sinus pacing as a possible early sign of RCA involvement and review the previous literature on RCA damage and variations of AV nodal circulation.

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Reciprocal control of hERG stability by Hsp70 and Hsc70 with implication for restoration of LQT2 mutant stability.


RATIONALE:

The human ether-a-go-go-related gene (hERG) encodes the α subunit of the potassium current I(Kr). It is highly expressed in cardiomyocytes and its mutations cause long QT syndrome type 2. Heat shock protein (Hsp)70 is known to promote maturation of hERG. Hsp70 and heat shock cognate (Hsc70) 70 has been suggested to play a similar function. However, Hsc70 has recently been reported to counteract Hsp70.

OBJECTIVE:

We investigated whether Hsc70 counteracts Hsp70 in the control of wild-type and mutant hERG stability.

METHODS AND RESULTS:

Coexpression of Hsp70 with hERG in HEK293 cells suppressed hERG ubiquitination and increased the levels of both immature and mature forms of hERG. Immunocytochemistry revealed increased levels of hERG in the endoplasmic reticulum and on the cell surface. Electrophysiological studies showed increased I(Kr). All these effects of Hsp70 were abolished by Hsc70 coexpression. Heat shock treatment of HL-1 mouse cardiomyocytes induced endogenous Hsp70, switched mouse ERG associated with Hsc70 to Hsp70, increased I(Kr), and shortened action potential duration. Channels with disease-causing missense mutations in intracellular domains had a higher binding capacity to Hsc70 than wild-type channels and channels with mutations in the pore region. Knockdown of Hsc70 by small interfering RNA or heat shock prevented degradation of mutant hERG proteins with mutations in intracellular domains.
CONCLUSIONS:

These results indicate reciprocal control of hERG stability by Hsp70 and Hsc70. Hsc70 is a potential target in the treatment of LQT2 resulting from missense hERG mutations.

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Regular exercise can help preserve/build heart mass

Another benefit of regular exercise has been discovered—preventing the reduction in heart mass normally seen with aging. Speaking at a press conference on the opening day of the ACC 2011 Sessions, Dr Paul Bhella (John Peter Smith Hospital, Fort Worth, TX) explained that heart muscle size—typically measured by left ventricular (LV) mass—peaks early in life and diminishes with sedentary aging.

Bhella conducted a study to look at the effect of regular exercise on this process and found that being physically active over the course of a lifetime can "preserve the heart's youthful elasticity." He noted that as the heart muscle atrophies with age, the heart becomes weaker, less capable of responding to increasing demands such as those associated with physical activity, and, in many circumstances, this leads to a stiffening of the heart by increasing the relative proportion of connective tissue compared with cardiac muscle.

In the study, Bhella and his colleagues compared two groups of people: 81 healthy but sedentary individuals aged 21 to 82 years; and 67 people aged 65 or older who had exercised regularly throughout their lives. The second group was subdivided into those who had exercised two to three times per week, four to five times week, and six to seven times per week. Exercise was defined as a period of at least 20 to 25 minutes of aerobic activity. Study participants underwent cardiac MRI to estimate cardiac mass and LV mass.

Results showed that in the sedentary group, LV mass reduced with age from an average of 55 g/m² in those in their 30s to 24 g/m² to those in their 60s. In contrast, in those older individuals who had done regular exercise, LV mass either stayed stable or actually increased, and there was a clear dose-dependent effect with the amount of exercise taken. Those who had did exercise two to three times were per week, had an average LV mass of around 53 g/m², and this increased to about 62 g/m² in those exercising four to times a week and to about 68 g/m² in the six-to-seven-times/week group. Similar results were seen with peak oxygen uptake. This decreased steadily with age in the sedentary group but increased with increasing exercise levels in the active group. Those individuals aged over 65 who exercised four to five times a week had a higher level of peak oxygen uptake than those aged under 34 who were sedentary.

"Use it or lose it"

To the press, Bhella commented: "You have to use it or lose it. It is never too late to start exercising. Exercising twice a week can prevent age-related loss of cardiac mass, while exercising four to five times a week can rebuild cardiac mass. This is the first time anybody has shown this."

He explained that while higher cardiac mass has not directly been shown to cause better outcomes, it is associated with increased levels of fitness, which has been shown to be associated with better outcomes. He stressed that all the increases were in the healthy range and that cardiac mass did not start to become pathologic until levels of around 130 g/m², which happens in left ventricular dysfunction. "The increase we are seeing is a healthy remodeling of the heart, associated with delivering more blood effectively to the body. So oxygen uptake increases, and in turn fitness increases," he explained.
Lead investigator of the study, **Dr Benjamin Levine**, said in an ACC press release: "The data suggest that if we can identify people in middle age and get them to exercise four to five times a week, this may go a very long way in preventing some of the major heart conditions of old age, including heart failure. Defining how to intervene at the right time and with the right dose [of physical activity] are critical questions we need to answer from a public-health standpoint, but also as cardiologists we want our patients to remain healthy and forestall heart problems."

**ST-segment changes after direct current external cardioversion for atrial fibrillation. Incidence, characteristics and predictive factors.**


**ST-segment changes after direct current external cardioversion for atrial fibrillation. Incidence, characteristics and predictive factors.**

*Int J Cardiol.* 2009 Dec 24. [Epub ahead of print]

**BACKGROUND:**
Incidence, characteristics and predictive factors of transient ST-segment changes after DC shock are poorly known.

**METHODS:**
91 consecutive pts referred for external cardioversion of atrial fibrillation (AF) (61 men, 69+/-10yo) were prospectively included. The presence of ST elevation or depression was assessed on 12 lead-ECG immediately after the first DC shock. Correlations with DC shock characteristics (monophasic/biphasic and energy), clinical variables, echocardiographic parameters, biological parameters, medications, anesthetic drugs as well with morphological features were made.

**RESULTS:**
18 and 20 pts underwent 200J or 300J monophasic and 53 pts 200J biphasic DC shocks. We found an incidence of 48% for ST-segment changes: 35% for ST elevation and 13% for ST depression. ST changes did not induce significant cardiac events or alter AF recurrences. ST changes were not related to energy but ST elevation was significantly more often induced by monophasic (76% vs 6%, p<0.0001) and ST depression by biphasic DC shocks (26% vs 3%, p=0.01). Using multivariate analysis, independent predictors for ST elevation were the use of monophasic DC shocks, of propofol and increased CRP, while a low ejection fraction and use of biphasic DC shocks were independent predictors of ST depression.

**CONCLUSION:**
ST-segment changes after external cardioversion with DC shock are common, short living and do not carry clinical significance. They are related to the monophasic or biphasic configuration of DC shock, to the use of propofol, to the ejection fraction and to an increased CRP.

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INTRODUCTION:

We sought to compare the results of pulmonary vein (PV) ablation using the high-density Mesh Ablator catheter (MESH) versus the cryoballoon (CRYO).

METHODS AND RESULTS:

From August 2007 to November 2009, all patients with paroxysmal atrial fibrillation scheduled for a first procedure of PV isolation were screened by cardiac computed tomography for anatomical suitability to undergo ablation with a circumferential ostial ablation catheter. The procedure was finally performed in 79 out of 120 patients matching the criteria of four clearly separated PVs with an ostial diameter of 15-25 mm. The first consecutive 43 patients were treated with the MESH; the following 36 consecutive patients were treated with the CRYO. The procedures were performed with up to 900 s of either pulsed radiofrequency energy delivered by the MESH or cryoenergy applied with the CRYO. The clinical success rate was evaluated 6 months after a single procedure. Isolation of all PVs could be achieved in 40 patients (93%) in the MESH group compared to 31 patients (89%) in the CRYO group (p = ns). Major complications consisted of one tamponade in the MESH group and one reversible phrenic nerve palsy in the CRYO group. After 6 months, the clinical success rate was 44% (19/43 P) in the MESH versus 69% (25/36 P) in the CRYO group (p < 0.05).

CONCLUSION:

Both methods of simplified circumferential PV ablation reveal a high acute success rate. The clinical 6-month results of the MESH are statistically significant inferior compared to the CRYO.

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RR-interval irregularity precedes ventricular fibrillation in ST elevation acute myocardial infarction.


BACKGROUND:
Sudden cardiac arrest is a leading cause of death in industrialized countries, and ischemic ventricular fibrillation (VF) is a frequent cause.

OBJECTIVE:
The purpose of this study was to determine whether patients with ST elevation myocardial infarction (STEMI) who develop ischemic VF show more overall RR-interval irregularity (RRI) than do STEMI patients without ischemic VF.

METHODS:
Ischemic VF was identified in 41 patients from 1,473 digital 12-lead Holter recordings from three separate STEMI studies. Continuous 3-lead and 12-lead electrocardiogram (ECG) snapshots recorded every minute were compared between all ischemic VF patients and 123 random patients without ischemic VF. Time intervals from start of Holter to ischemic VF and equivalent intervals in the controls were used for calculations. ECG variables related to conduction intervals and severity of ischemia were measured using the most ischemic 12-lead ECG. RRI was calculated as the square root of the mean squared differences of successive RR intervals. For RRI, all QRS complexes, including ventricular ectopic beats, were used.

RESULTS:
No baseline differences were observed between the study and control groups, except for male preponderance among ischemic VF patients (90% vs 72%, P = .019). QRS interval, ECG ischemia severity, RRI, and number of ventricular ectopic beats were significantly associated with ischemic VF. Multivariate analysis revealed RRI (odds ratio 1.006, 95% confidence interval 1.001-1.010, P = .016) and ST deviation score (odds ratio 1.073, 95% confidence interval 1.041-1.106, P <.001) as the only statistically significant predictors of ischemic VF.

CONCLUSION:
In the period before ischemic VF, RRI and ST deviation score are associated with ischemic VF in STEMI patients. These findings could have important pathophysiologic and clinical implications.

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Yoga found to reduce AF episodes

Taking a 45-minute yoga class three times a week was associated with a halving of episodes of atrial fibrillation (AF) in a new small study.

The study, presented today at the opening press conference of the American College of Cardiology 2011 Scientific Sessions, was conducted by a team led by Dr Dhanunjaya Lakkireddy (University of Kansas Hospital, Kansas City).

He said he started the study after a patient had reported a great improvement in her AF after having started practicing yoga. For the study, 49 patients with paroxysmal AF underwent a three-month control phase in which they could engage in any type of physical activity they were previously accustomed to doing. They then underwent a three-month study phase where they participated in a supervised yoga program consisting of breathing exercises, yoga postures, meditation, and relaxation. They were also encouraged to practice the exercises at home on a daily basis. All participants were new to the practice of yoga, and the program was designed to allow beginners to progress safely from basic movements to more advanced practice over the course of the study.

Results showed that during the yoga-intervention phase, the number of episodes of AF was significantly reduced—from a mean of 3.8 to 2.1. The number of phantom episodes was also reduced, from a mean of 2.6 to 1.4. In addition, 22% of patients did not have any AF episodes during the yoga phase.

Lakkireddy reported that there was also a "drastic" improvement in quality of life, with significant reductions in anxiety and depression scores.

He said: "It appears yoga has a significant impact on helping to regulate patients' heartbeat and improves their overall quality of life. Any intervention that helps in reducing or controlling the arrhythmia burden in atrial fibrillation can have a huge impact on public health."

He recommended that yoga be used as a supplemental therapy in AF. "I am not suggesting that patients should stop taking their medication, but if used as a supplement to medication, yoga could really make a dramatic difference," he added. He also stressed that yoga cannot prevent stroke, and patients definitely need to continue on their anticoagulant treatment.

He said he did not know how the yoga was working but suggested that it might prevent the peaks in sympathetic and parasympathetic tone that precede AF episodes. "It looks as if yoga is reducing the triggers of AF, but we would like to do more studies to look into the mechanisms further," Lakkireddy added. He suggested that yoga may also bring about this effect by reducing systemic inflammation and endothelial dysfunction.

He commented to the press: "Yoga also helps reduce blood pressure, cholesterol, and stress, so it is a comprehensive lifestyle change that can have a broad effect."
Asked if clinical recommendations could be made on the basis of a 49-patient study, Lakkireddy said: "We're not claiming yoga fixes everything in AF, and we are advising patients to continue taking their medication, but we have shown some impressive effects. Everything has to start somewhere."

**The funny current channel HCN4 delineates the developing cardiac conduction system in the chicken heart.**

The funny current channel HCN4 delineates the developing cardiac conduction system in the chicken heart.
Heart Rhythm. 2011 Mar 18. [Epub ahead of print]

**BACKGROUND:**
Hyperpolarization-activated cyclic nucleotide-gated channel 4 (HCN4) in the mouse is expressed in the developing cardiac conduction system (CCS). In the sinoatrial node (SAN), HCN4 is the predominant isoform responsible for the funny current. To date, no data are available on HCN4 expression during chicken CCS development.

**OBJECTIVE:**
To provide the full-length sequence of Hcn4 and describe its expression pattern during development in relation to the CCS in the chicken embryo.

**METHODS:**
Hcn4RNA expression was studied by in situ hybridization in sequential chick developmental stages (HH11-HH35) and immunohistochemical stainings were conducted for the myocardial protein cTnI and the cardiac transcription factor Nkx2.5.

**RESULTS:**
We obtained the full-length sequence of Hcn4 in chick. Hcn4 expression was observed early in development in the primary heart tube. At later stages, expression became restricted to transitional zones flanked by working myocardium, comprising the sinus venosus myocardium where the SAN develops, the atrioventricular canal myocardium, the primary fold (a myocardial zone between the developing ventricles), and the developing outflow tract. Further in development, Hcn4 expression was restricted to the SAN, the atrioventricular node, the common bundle, the bundle branches and the internodal and atrioventricular ring myocardium.

**CONCLUSION:**
We have identified Hcn4 as a marker of the developing CCS in the chick. The primary heart tube expresses Hcn4, which is later restricted to the transitional zones and eventually the elements of the mature CCS. Furthermore, we hypothesize that expression patterns during development may delineate potential arrhythmogenic sites in the adult heart

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The short QT syndrome.

The short QT syndrome.

The New England Medical Cardiac Arrhythmia Center, Tufts Medical Center, Tufts University School of Medicine, 750 Washington Street, Boston, MA, 02111, USA. PMID: 21491125/


Krul SP, Driessen AH, van Boven WJ, Linnenbank AC, Geuzebroek GS, Jackman WM, Wilde AA, de Bakker JM, de Groot JR.
Circ Arrhythm Electrophysiol. 2011 Apr 14. [Epub ahead of print]

BACKGROUND:
Thoracoscopic pulmonary vein isolation (PVI) and ganglionated plexus (GP) ablation is a novel approach in the treatment of atrial fibrillation (AF). We hypothesize that meticulous electrophysiological confirmation of PVI results in fewer recurrences of AF during follow-up.

METHODS AND RESULTS:
-Surgery was performed through three ports bilaterally. GPs were localized and subsequently ablated. PVI was performed and entry and exit block was confirmed. Additional left atrial ablation lines (ALAL) were created, and conduction block verified, in patients with non-paroxysmal AF. The left atrial appendage was removed. Freedom of AF was assessed by ECGs and Holter monitoring every 3 months or during symptoms of arrhythmia. Anti-arrhythmic drugs (AAD) were discontinued after 3 months and oral anticoagulants were discontinued according to the guidelines. Thirty-one patients were treated (16 paroxysmal AF, 13 persistent AF, 2 long standing persistent (LSP) AF). Thirteen patients with non-paroxysmal received ALAL. After one year, 19/22 patients (86%) had no recurrences of AF, atrial flutter or atrial tachycardia and were not using AAD (11/12 paroxysmal, 7/9 persistent, 1/1 LSP). Three patients had a sternotomy because of uncontrolled bleeding during thoracoscopic surgery. Four adverse events were; 1 hemothorax, 1 pneumothorax and 2 pneumonia. No thromboembolic complications or mortality occurred.

CONCLUSIONS:
-Thoracoscopic surgery with PVI and GP ablation for AF is a safe and successful procedure with a single procedure success rate of 86% at one year. Electrophysiological guided thorough PVI and ALAL creation presumably contributes in achieving a high success rate in the surgical treatment of AF.

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