Sudden Cardiac Death

Editorial

M. R. Rosen

171

Lead Article

Sudden cardiac death: risk factors, treatment, and prevention - A. J. Camm, T. Pakrashi, I. Savelieva

175

Expert Answers to Three Key Questions


205

How will genomic approaches translate into clinical applications in sudden cardiac death? - P. M. Spooner

213

How can we reduce sudden death in the community? - G. Nichol, M. L. Weisfeldt

221

Fascinoma Cardiologica

Icons of Cardiology: André Frédéric Courand: integration of pulmonary and cardiovascular pathophysiology - A. M. Katz

231

Matters @ Heart: The Nobel Prize and its history - R. J. Bing

236

Summaries of Ten Seminal Papers - M. J. Janse

239

Termination of ventricular fibrillation in man by externally applied electric countershock – P. M. Zoll and others

Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia - A. J. Moss and others; MADIT I Investigators

A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias – AVID Investigators

Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction – A. J. Moss and others; MADIT II Investigators

Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report – P. Brugada and J. Brugada

A molecular basis for cardiac arrhythmia: HERG mutations cause Long QT Syndrome – M. E. Curran and others

Bibliography of One Hundred Key Papers

251
Editorial

Michael R. Rosen, MD
Guest Editor

“...Her hands made futile gestures, she turned her head
Fighting for breath; her cheeks were flushed to scarlet,—
And, suddenly, she lay dead.
And all the dreams that hurried along her veins
Came to the darkness of a sudden wall.
Confusion ran among them, they whirled and clamored,
They fell, they rose, they struck, they shouted,
Till at last a pallor of silence hushed them all.”

Conrad Aiken
House of Dust—A Symphony, 1920

As is clear from the poem and from the experience of many patients and physicians, any death is personal, the final voyage taken by the self. Whether accompanied by an accepting and loving family or by interventionist and neutral resuscitators, it remains the slipping of the soul into a vortex experienced by most individuals only once, and rarely told to another. It is the sound of one hand clapping. There is much to commend a death that is sudden. To the individual dying it is a moment of... shock? terror? regret?... and then nothing—or eternity. But to those left behind it represents the cruelest loss: that for which there has been no preparation. Central to the mystique of sudden death is its untimely occurrence. After all, a sudden end to a debilitating, painful illness is likely kind, and sometimes sought. But untimely, unforeseen death can hurt loved ones forever. Sudden death and its aftershocks can occur from the earliest months of life as with sudden infant death syndrome. The pain associated with the unfortunately named SIDS is far better imparted by the earlier descriptor “crib death,” the juxtaposition of a symbol of the hopeful beginnings of life with its immediate termination. But sudden death persists in its occurrence throughout young and adult life: congenital long QT syndrome,2 athletes dying young,3,4 and myocardial ischemia–induced lethal arrhythmias5 are three familiar examples. Those doing basic and clinical research in the field of sudden death recognize that they seek to minimize the occurrence of an event that many in our society might view as a positive way to die. Yet, they recognize as well that the pain and suffering of family, and the economic loss to society make sudden untimely death not only a valid, but a pressing target for investigation.

Michael R. Rosen, MD, Gustavus A. Pfeiffer Professor of Pharmacology, Professor of Pediatrics, College of Physicians and Surgeons of Columbia University, Department of Pharmacology, 630 West 168 Street, Ph 7 West-321, New York, NY 10032, USA (e-mail: mrr1@columbia.edu)
This volume focuses our attention on the subject of sudden death in four papers. The Lead Article by Drs A. John Camm, Tapesh Pakrashi, and Irina Savelieva provides an overview of the causes and the variety of approaches now being taken toward prevention of sudden death. They make the point that while sudden cardiac death “can now be effectively prevented, predicted, and treated, the burden of cardiovascular disease is rising again, making the availability of cost-effective therapy for life-threatening ventricular arrhythmias an increasingly significant challenge.” Drs Silvia G. Priori and Marina Cerrone discuss the congenital long QT syndromes, whose study for the past quarter century has paved the way to our comprehension of the molecular/genetic determinants of not only this family of diseases, but the far larger population of individuals having genetic/environmental predispositions to lethal cardiac arrhythmias. Dr Peter M. Spooner focuses our attention on genomic approaches to sudden cardiac death, which emphasize the identification of minor variations in a variety of different DNA sequences, “each of which may convey subtle dimensions of arrhythmia risk in both rare and common forms of heart disease.” These approaches are being applied clinically to risk stratification and selection of therapy, both impacting on the prevention of sudden cardiac death. Finally it should be remembered that the early work on sudden death by Leonard Cobb, Frank Pantridge, and others starting in the late 1960s6-14 first brought us hope that patients dying suddenly outside the hospital need not be given up on, but might be resuscitated and given a meaningful life thereafter. The paper by Drs Graham Nichol and Myron L. Weisfeldt takes us through modern times and calls our attention to the advances in community effort and technology that continue to focus on improving “quality survival from cardiac arrest.” And it is at the level of community responders that sudden death victims have their last, best chance at salvage.

In closing, this issue of Dialogues summarizes way stations in the continued study and attempts at rescue of a population at risk that has already benefited considerably from biomedical research and its clinical application, but that still has “miles to go.” Importantly, enough has been done so that a positive end is in sight, an end that is far more optimistic than the proverbial “light at the end of the tunnel” that characterizes so many medical settings. However, much remains to be done, as will become apparent to those who read the contributions in this volume.
REFERENCES

1. Aiken C.
The House of Dust: A Symphony.

2. Priori SG, Cerrone M.
Congenital long QT syndrome: how big a problem, how best to manage?

3. Housman AE.
To an athlete dying young. In: Williams O, ed.

4. Firoozi S, Sharma S, McKenna WJ.
How does the cardiologist evaluate and advise young individuals with potentially dangerous cardiac conditions who want to engage in competitive sports?

5. Camm AJ, Pakrashi T, Savelieva I.
Sudden cardiac death: risk factors, treatment, and prevention.

6. Cobb LA, Conn RD, Samson WE, Philbin JE.
Pre-hospital coronary care: the role of rapid response mobile intensive coronary care system.
Circulation. 1971;44(suppl II):II45.

7. Lewis RP, Frazier JT, Warren JV.
An approach to the early mortality of myocardial infarction.

Telemetry-medical command in coronary and other mobile emergency care systems.

9. Cobb LA, Baum RS, Alvarez HA, Schaffer WA.
Resuscitation from out-of-hospital ventricular fibrillation: 4 years follow-up.
Circulation. 1974;51-52(suppl III):III223-III228.

10. Baum RS, Alvarez HA, Cobb LA.
Survival after resuscitation from out of hospital ventricular fibrillation.

11. Schaffer WA, Cobb LA.
Reccurrent ventricular fibrillation and modes of death in survivors of out-of-hospital ventricular fibrillation.

12. Pantridge JF, Geddes JS.
A mobile intensive-care unit in the management of myocardial infarction.

13. Pantridge JF.
Mobile coronary care.

14. Pantridge JF, Adgey AA.
Pre-hospital coronary care. The mobile coronary care unit.
Am J Cardiol. 1969;24:666-673.
Sudden cardiac death (SCD) is "natural death due to cardiac causes, heralded by abrupt loss of consciousness within 1 hour of the onset of acute symptoms." Annual incidence is 0.36 to 1.28 per 1000 inhabitants. Epidemiology differs greatly (100-fold) between young and old, and between developing and developed worlds. Coronary artery disease (CAD) is the commonest cause in the developed world, while in younger patients, the major causes are inherited arrhythmogenic right ventricular cardiomyopathy (ARVC), hypertrophic cardiomyopathy (HCM), anomalous coronary arteries, and hereditary channelopathies, eg, long QT syndrome (LQTS). Prevalence is 3- to 4-fold higher in men, reflecting that of CAD.

In adults, the incidence of CAD-related SCD varies with geography and age, mirroring the increase in CAD with age. However, the proportion of CAD-related SCD decreases with age. The increasing incidence of congestive heart failure (CHF), stroke, cancer, and metabolic syndrome will increase the incidence of SCD, particularly in the developed world. Although SCD is often synonymous with death from ventricular tachyarrhythmia (ventricular fibrillation [VF] and ventricular tachycardia [VT]), 25% of cases are due to bradyarrhythmia, asystole, or electromechanical dissociation, particularly in advanced heart disease.

**PATHOPHYSIOLOGY AND RISK FACTORS**

Table 1 (page 178) lists the risk factors for sudden cardiac death, a description of which is given below.

**Coronary heart disease**

Coronary thrombi and plaque rupture or erosion are found in two thirds of SCD. A 2006 review of over 400 autopsies reported figures of 60%, 55% to 60%, and 30% to 35%, respectively, plus a calcified nodule in 2%
to 7% to 25% of acute myocardial infarction (MI). Erosion occurred mainly under age 50 and accounted for most acute premenopausal coronary thrombi, particularly in conjunction with hyperlipidemia. In women over 50, rupture accounted for 80% of coronary thrombi. Coronary thrombi were absent in 40% of autopsies, but healed MI and total occlusion were observed in the vast majority, suggesting that SCD is precipitated by scar-related reentrant ventricular tachyarrhythmia or electrically unstable hypertrophied myocardium. Superimposed myocardial ischemia can destabilize altered substrate and trigger VT/VF.

Coronary involvement differs between studies. Single-vessel critical flow-limiting CAD (≥75% occlusion) was observed in 16% to 44% of hearts, 2-vessel disease in 27% to 32%, 3-vessel disease in 22% to 47%, and 4-vessel disease in 1% to 10%, suggesting that plaque characteristics (eg, vulnerability) are crucial in pathogenesis. Severe coronary stenosis in the absence of acute thrombi or total occlusion caused only 15% of SCD. No specific pattern of coronary lesion distribution was associated with an increased incidence of SCD.

**Left ventricular dysfunction**

Post-MI left ventricular (LV) dysfunction ± symptomatic CHF triples SCD risk. Absolute risk increases with worsening heart failure, but the proportion of SCD relative to other modes of death decreases. Yet, SCD accounts for one third of fatalities even in New York Heart Association (NYHA) class IV (Figure 1, page 178). Conversely, a 10% improvement in ejection fraction (EF) reduces SCD risk by 40%.

The commonest mechanism of SCD, reentry around scar tissue, is supplanted in advanced heart failure by activation of stretch-modulated ionic currents, calcium overload-induced early afterdepolarizations, cell-to-cell uncoupling, and interstitial fibrosis. Hyperpolarization-activated cyclic nucleotide-gated (HCN) channel density increases. HCN channels normally carry the If current in pacemaker cells within the sinus node and are functionally inactive in the His-Purkinje system and ventricular myocardium. When overexpressed, they may increase automaticity.

**Hypertension and left ventricular hypertrophy**

Hypertension is not only a major CAD risk factor, but it also disproportionally increases SCD risk. Even well-controlled hypertensives are at greater SCD risk than nonhypertensives. Left ventricular hypertrophy (LVH) is an independent risk factor for SCD; electrocardiographic (ECG) LVH increases 5-year mortality by 33% in men and 21% in women. In 1638 patients from the Multicenter Unsustained Tachycardia Trial (MUSTT) receiving neither drug nor device antianhythmic therapy, LVH increased the risk of arrhythmic death by 35% irrespective of electrophysiological findings and was the

---

**SELECTED ABBREVIATIONS**

- AED: automatic external defibrillator
- ARB: angiotensin receptor blocker
- ARVC: arrhythmogenic right ventricular cardiomyopathy
- CAD: coronary artery disease
- CHF: congestive heart failure
- CRT: cardiac resynchronization therapy
- CPR: cardiopulmonary resuscitation
- CPVT: catecholaminergic polymorphic ventricular tachycardia
- DCM: dilated cardiomyopathy
- EF: ejection fraction
- HCM: hypertrophic cardiomyopathy
- HCN: hyperpolarization-activated cyclic nucleotide-gated
- HERG: human ether-a-go-go-related gene
- ICD: implantable cardioverter-defibrillator
- ICER: incremental cost-effectiveness ratio
- LQT1, 2, 3: long QT syndrome type 1, 2, and 3
- LVH: left ventricular hypertrophy
- LYS: life-year saved
- MI: myocardial infarction
- PAD: public access defibrillator
- PEA: pulseless electrical activity
- PUFA: polyunsaturated fatty acids
- QALYS: quality-adjusted-life-year saved
- RyR: ryanodine receptor
- SCD: sudden cardiac death
- TCRT: total cosine R-to-T
- TWA: T-wave alternans
- VF: ventricular fibrillation
- VT: ventricular tachycardia
- WPW: Wolff-Parkinson-White
### TRIAL ACRONYMS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPHA</td>
<td>T-wave ALternans in Patients with Heart Failure</td>
</tr>
<tr>
<td>AMIOVIRT</td>
<td>AMIOdarone Versus Implantable cardioverter-defibrillator Trial</td>
</tr>
<tr>
<td>ASCOT</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial</td>
</tr>
<tr>
<td>AVID</td>
<td>Antiarrhythmics Versus Implantable Defibrillators</td>
</tr>
<tr>
<td>ARREST</td>
<td>Amiodarone for Resuscitation in REfractory Sustained Tachycardia</td>
</tr>
<tr>
<td>BHAT</td>
<td>Beta-blocker Heart Attack Trial</td>
</tr>
<tr>
<td>CABG-Patch</td>
<td>Coronary Artery Bypass Graft Patch study</td>
</tr>
<tr>
<td>CAMIAT</td>
<td>Canadian Amiodarone Myocardial Infarction Arrhythmia Trial</td>
</tr>
<tr>
<td>CAPRICORN</td>
<td>CArvedilol Post infarction survival COntrol in left ventricular dysfunctioN</td>
</tr>
<tr>
<td>CARE-HF</td>
<td>Cardiac RESynchronization in Heart Failure</td>
</tr>
<tr>
<td>CASH</td>
<td>Cardiac Arrest Study Hamburg</td>
</tr>
<tr>
<td>CASS</td>
<td>Coronary Artery Surgery Study</td>
</tr>
<tr>
<td>CHARM</td>
<td>Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity</td>
</tr>
<tr>
<td>CHF-STAT</td>
<td>Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy</td>
</tr>
<tr>
<td>CIDS</td>
<td>Canadian Implantable Defibrillator Study</td>
</tr>
<tr>
<td>CLARIDI</td>
<td>Cholesterol Lowering and Arrhythmia Recurrences after Internal Defibrillator Implantation</td>
</tr>
<tr>
<td>COMPANION</td>
<td>COmparison of Medical therapy, PAcing, aNd defibrillatION in heart failure</td>
</tr>
<tr>
<td>DEFINITE</td>
<td>DEFibrillators In Non-Ischemic cardiomyopathy Treatment Evaluation</td>
</tr>
<tr>
<td>DINAMIT</td>
<td>Defibrillator IN Acute Myocardial Infarction Trial</td>
</tr>
<tr>
<td>EMIAT</td>
<td>European Myocardial Infarct Amiodarone Trial</td>
</tr>
<tr>
<td>EPHEUS</td>
<td>Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SUrvival Study</td>
</tr>
<tr>
<td>EUROPA</td>
<td>EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease</td>
</tr>
<tr>
<td>FAAT</td>
<td>Fatty Acid Antiarrhythmia Trial</td>
</tr>
<tr>
<td>GESICA</td>
<td>Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina</td>
</tr>
<tr>
<td>GISSI-Prevenzione</td>
<td>Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico Prevenzione</td>
</tr>
<tr>
<td>HOPE</td>
<td>Heart Outcomes Prevention Evaluation</td>
</tr>
<tr>
<td>ISAR</td>
<td>Innovative Stratification of Arrhythmic Risk</td>
</tr>
<tr>
<td>LIFE</td>
<td>Losartan Intervention For Endpoint reduction in hypertension</td>
</tr>
<tr>
<td>MADIT I, II</td>
<td>Multicenter Automatic Defibrillator Implantation Trial (First, Second)</td>
</tr>
<tr>
<td>MAGIC</td>
<td>MAGnesium In Coronaries</td>
</tr>
<tr>
<td>MUSTT</td>
<td>Multicenter UnSustained Tachycardia Trial</td>
</tr>
<tr>
<td>OPALS</td>
<td>Ontario Prehospital Advanced Life Support</td>
</tr>
<tr>
<td>OPTIC</td>
<td>Optimal Pharmacological Therapy In Cardioverter defibrillator patients</td>
</tr>
<tr>
<td>PainFREE Rx</td>
<td>PACNfng Fast ventricular tachycardia REDuces shock thErapiies</td>
</tr>
<tr>
<td>PEACE</td>
<td>Prevention of Events with Angiotensin-Converting Enzyme inhibition</td>
</tr>
<tr>
<td>RALES</td>
<td>Randomized ALdactone Evaluation Study</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>Sudden Cardiac Death in Heart Failure Trial</td>
</tr>
<tr>
<td>SCORE</td>
<td>Systematic COronary Risk Evaluation</td>
</tr>
<tr>
<td>SHIELD</td>
<td>SHock Inhibition Evaluation with azimiLiDe</td>
</tr>
<tr>
<td>SOFA</td>
<td>Study on Omega-3 Fatty Acids</td>
</tr>
<tr>
<td>VAL-HeFT</td>
<td>VALsartan Heart Failure Trial</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>West Of Scotland COronary Prevention Study</td>
</tr>
</tbody>
</table>
sole predictor of arrhythmic events independently of total mortality. Risk multiplies with the development of a typical strain pattern (i.e., ST-segment depression and T-wave inversion) in response to LVH. When present on both ECG and echocardiogram, LVH confers greater risk than if present on either investigation alone.

Other conditions producing LVH (aortic stenosis and regurgitation, coarctation, pulmonary hypertension) increase SCD risk, as does idiopathic HCM, particularly in the young. LVH is invariably associated with abnormal repolarization and predisposes to triggered activity. An ECG pattern of LV strain may reflect true subendocardial ischemia in the absence of CAD, as when increasing coronary artery size fails to match increasing LV mass or wall thickness. Interstitial fibrosis, gap junction dysfunction, and excessive adrenergic stimulation are all arrhythmogenic. The precise effect of blood pressure reduction on SCD risk is difficult to quantify, but trials in hypertensive subgroups show significant decreases in SCD, LVH reversal, and a resolved strain pattern.
**Lifestyle risk factors**

Alcoholism, particularly binge drinking, increases SCD risk, probably by prolonging the QT interval. Moderate alcohol consumption is protective. Smoking is an independent long-term risk factor irrespective of preexisting heart disease. Current and ex-smokers in the Multicenter Automatic Defibrillator Implantation Trial (MADIT II) experienced more implantable cardioverter-defibrillator (ICD) shocks than never-smokers: 1.9-fold and 1.43-fold for fast ventricular tachyarrhythmias, and 2- to 3-fold for rapid supraventricular arrhythmias.

Dyslipidemia, diabetes, metabolic syndrome, and a variety of biological markers (microalbuminuria, C-reactive protein, fibrinogen, etc) are established cardiovascular risk factors, thus predisposing to SCD. Their effect on SCD prevalence in the general population may differ from that in subgroups with MI, CAD, or hypertension. Some population studies cite a doubled risk.

Diet, eg, regular fish consumption, may halve the risk. Regular moderate exercise is protective, strenuous exercise in unfit men predisposes to SCD. Enhanced platelet aggregation and adhesiveness during sporadic vigorous exercise triggers MI, particularly in CAD, with acute plaque rupture a common autopsy finding.

Obesity is an independent risk factor, with an incidence of unexplained sudden death up to 40-fold higher in the severely obese than in the age-matched general population. In addition to its association with hypertension, sleep apnea, and metabolic syndrome, obesity may reflect an independent predisposition to life-threatening VT/VF, conduction abnormalities, and QT interval prolongation.

**Noncoronary causes of SCD**

The 5% to 10% of SCD cases in which the heart is structurally normal often reveal molecular pathophysiology, particularly involving membrane ion channels, thus offering clues to risk stratification. Subclinical genetic abnormalities may interact with concomitant pharmacotherapy and changes in autonomic tone to induce ventricular arrhythmias.

In 427 cases of SCD in 5- to 35-year-olds, causes were cardiac in 56%, noncardiac in 39%, and undetermined in 4%. Over two thirds of victims were male. The commonest cardiac cause in those with little or no structural disease was presumed arrhythmia (29%). SCD had occurred in a first-degree relative in 4.5% of cases. Other cardiac causes were acute MI (24.5%), myocarditis (11.6%), HCM (5.8%), aortic dissection (5.4%), and dilated cardiomyopathy (DCM [5.4%]).

**Wolff-Parkinson-White (WPW) syndrome**

Accessory pathways capable of fast anterograde conduction (those with an effective refractory period <250 ms) may trigger SCD by causing atrial fibrillation with ultrarapid ventricular response, possibly degenerating into VF (Figure 2).

Estimated overall mortality is 1.5 per 1000 patient-years. Syncope with a preexcitation ECG pattern is an indication for electrophysiological studies. Catheter ablation is an effective first-line therapy.

**Congenital atrioventricular block**

Complete atrioventricular block is usually recognized in utero or post partum, but may be fatal if unrecognized or untreated. Other congenital bradyarrhythmias can be fatal, with bradyarrhythmic arrest being the terminal event in 88% of neonates, 67% of infants, and 64% of children in 100 cases of pediatric arrest.

**Dilated cardiomyopathy**

SCD accounts for about 30% of dilated cardiomyopathy (DCM) deaths and increases in frequency, as does all-cause mortality, with increasing cardiac dysfunc-
tion. Enhanced automaticity, bundle-branch reentry, and bradyarrhythmias are responsible, rather than ischemic heart failure. Risk factors are those for worsening heart failure, but these are not specific for arrhythmic death, nor is a low EF highly predictive of SCD. Specific mutations, notably in the cardiac troponin T and lamin A/C genes, account for aggressive DCM with frequent SCD. Arrhythmias were found in 92% of 299 lamin A/C mutation carriers over age 30, and heart failure in 64% after age 50; SCD is the commonest mode of death (46%), and carriers often require pacing for sick sinus syndrome or atrioventricular block (28%).

Hypertrophic cardiomyopathy

Unrecognized HCM is the commonest cause of death in young athletes, with SCD usually following ventricular tachycardia precipitated by outflow tract obstruction, ischemia, or atrial fibrillation. The most significant risk factors are phenotypic and genotypic. A family history of SCD, previous cardiac arrest, recurrent syncope, nonsustained ventricular tachycardia on Holter, abnormal blood pressure response to exercise (a fall or sustained failure to rise ≥20 mm Hg during, in patients <50 years of age), extreme LV hypertrophy (maximum LV thickness ≥30 mm on echocardiogram) are major risk factors and an indication for ICD therapy (Figure 3).

Arhythmgogenic right ventricular cardiomyopathy

ARVC is a familial autosomal dominant disorder characterized by patchy myocarditis and apoptosis, and myocyte depletion in the right ventricular myocardium with fatty or fibro-fatty deposition resulting in segmental or diffuse wall thinning. Clinical features include right ventricular dilatation, abnormal segmental wall motion, and aneurysm formation, together with T-wave inversion and epsilon waves in the right precordial leads (reflecting depolarization of the dilated right ventricle), and exercise-induced right ventricular VT. The evidence base for risk stratification and management is incomplete. SCD is often the first manifestation of ARVC and often occurs spontaneously, notably in certain subsets.

Other causes of cardiomyopathy

Idiopathic restrictive cardiomyopathy is rare, with 50% 2-year survival. Most deaths are from SCD. Sarcoidosis confers increased risk. Heart block, bradyarrhythmia, and drug-resistant VT are common. Diagnosis is via a combination of ECG, Holter monitoring, echocardiography, myocardial perfusion imaging, magnetic resonance imaging, and endomyocardial biopsy. Treatment includes steroids and immunosuppressive therapy, and monoclonal antibodies against tumor necrosis factor in refractory cases. Cardiac amyloidosis is an important cause of heart block and asystole in the elderly. Infection-induced cardiomyopathy is a major cause of CHF in endemic regions. One third of the 18 million South Americans with Chagas disease will develop cardiomyopathy. Heart failure and SCD are the leading mechanisms of death. VT degenerating into VF is the main cause, followed by bradyarrhythmia and cerebral emboli. SCD also affects Chagasic patients without cardiomyopathy.
Isolated noncompaction of LV myocardium is increasingly recognized as causing heart failure and SCD. Myocardium remains spongiform, as in mid-late embryonic life, with trabeculae resembling multiple papillary muscles.

**Mitral valve prolapse**

Mitral myxomatous degeneration occurs in 2% to 3% of the general population, usually with good prognosis and few events, SCD included. Indeed, SCD may not greatly exceed that in the general population, occurring mainly in over-50s with severe regurgitation and systolic dysfunction.

**Primary electrical heart disease**

Rare inherited conditions such as LQTS, Brugada syndrome, and catecholaminergic polymorphic VT share a genetic predisposition to VT and SCD in the absence of demonstrable structural heart disease (Table II).

**Long QT syndrome**

Congenital or acquired long QT syndrome (LQTS) is characterized by prolonged ventricular repolarization and tachyarrhythmia. Congenital LQTS occurs in 1 in 3000 to 5000 individuals. Variants include the Romano-Ward, Jervell and Lange-Nielsen, Anderson-Tawil, and Timothy syndromes. Mean age at presentation is 12 years, but ranges from 1 to 60 years. Presentations extend from marked QT prolongation and recurrent syncope to subclinical borderline QT prolongation. Although rarely documented, SCD results from torsades de pointes, a distinctive polymorphic VT, which may be the first presentation of the disease. Eight gene mutations have thus far been identified, seven of which encode cardiac ion channel subunits and one the anchoring protein, ankyrin B. Ankyrins are a protein family involved in the localizing of diverse membrane ion channels and transporters.

QT interval duration remains the strongest risk factor. A corrected QT >500 ms confers a high risk of symptoms by age 40. Risk is highest in Jervell and Lange-Nielsen syndrome and other homozygous disorders. Prior cardiac arrest increases risk 12.9-fold. However, a family history of SCD is not a risk factor. Risk stratification algorithms incorporate gender, genotype, and QT interval, with highest risk in LQT1 and LQT2 with QTc intervals >500 ms, and in men with LQT3, regardless of QT duration (Figure 4, next page). Stress, emotion, and exercise may all trigger syncope and ventricular arrhythmia in LQTS. β-Blockade greatly reduces risk in LQT1, but less in LQT2 and LQT3. The class Iα antiarrhythmic flecainide and potassium channel opener nicorandil may be effective in LQT2.

**Brugada syndrome**

This channelopathy, described in 1992, is characterized by distinct coved-type ST-segment elevation ≥2 mm followed by a negative T wave in leads V1 to V3, complete or incomplete right bundle-branch block in some patients, and increased SCD risk. SCD follows rapid polymorphic VT or VF at rest or during sleep. ECG abnormalities may be transient and only one locus, the
cardiac sodium channel gene SCN5A, has been unequivocally implicated, although specific mutations do not predict SCD risk. Syncope and SCD predominate in young men, but occur in women and at all ages.

A history of syncope and spontaneous ECG changes doubles SCD risk. The ECG pattern may be unmasked or modulated by sodium channel blockers, fever, vagotonics, α-adrenergic agonists, β-blockers, tricyclic or tetracyclic antidepressants, a combination of glucose and insulin, hypokalemia and hyperkalemia, hypercalcemia, alcohol, and cocaine. Diagnosis is facilitated by challenge with sodium channel blockers such as procainamide (North America), flecainide and ajmaline (Europe), and pilsicainide (Japan), although patients responding to challenge with the typical ECG changes are at lower risk. The utility of invasive electrophysiological testing is disputed. Quinidine, a transient outward current (Ito) blocker, and agents enhancing the L-type calcium current (isoproterenol) may reverse abnormal repolarization.

Catecholaminergic polymorphic ventricular tachycardia

Patients with this rare autosomal dominant or recessive disorder develop polymorphic or bidirectional VT during acute emotion or physical activity. Catecholaminergic polymorphic ventricular tachycardia (CPVT) confers a high risk of SCD (30% to 50%) by age 20 to 30.25

Mutations occur in the genes encoding the cardiac ryanodine receptor 2 (RyR2), the main calcium release channel on cardiomyocyte sarcoplasmic reticulum, or calsequestrin 2 (CASQ2). Patients showing an RyR2 mutation are more likely to present in childhood than those with nongenotyped CPVT. Mutations in the calsequestrin gene are described in autosomal recessive CPVT. The probable mechanism of VT is delayed afterdepolarization-induced triggered activity. The only therapy is β-blockade.

Short QT syndrome

Described in 1999, this syndrome is associated with syncope, paroxysmal atrial fibrillation, and predisposition to SCD.26 The QTc interval is very short (<300 ms) and reacts abnormally to heart rate, shortening paradoxically in bradycardia. Multigenic in origin, it usually affects young healthy subjects with structurally normal hearts. Risk stratification combines clinical presentation with genetic studies.

Screening of short QT families with a strong SCD history has identified gain-of-function mutation in the KCNH2 gene encoding the HERG protein. This significantly increases I_K, during the action potential plateau, shortening the action potential, as opposed to loss-of-function mutation in the KCNH2 gene causing type 2 LQTS. There is no specific drug therapy, but quinidine may normalize QT response to heart rate.26
Although an ICD is the therapy of choice, inappropriate shocks may be triggered by atrial fibrillation or T-wave oversensing due to short, coupled, high-amplitude intracardiac T waves (Table II).

**RISK STRATIFICATION**

Risk factor identification may increase the proportion of SCD within a risk group, but as the group becomes better focused and progressively smaller, so does the absolute number of deaths per group (Figure 5). Clinical implementation of risk stratification with provision of beneficial, but costly, therapy to risk groups is thus problematic. In 20% to 25% of cases, SCD is the first presentation of underlying disease, while in 30% to 40% it occurs in low-risk patients. High-risk patients with arrhythmia (eg, nonsustained VT) and/or hemodynamic impairment (eg, low EF) account for surprisingly little SCD (5%-15%).

ICDs have provided effective primary prevention in several randomized trials, including MADIT II and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). They decreased relative mortality risk by 31% and 23%, but achieved low absolute mortality benefit (5.6% and 7.2%). Many never delivered appropriate therapy. 100 ICDs had to be implanted to prevent 11 and 17 SCDs, respectively, making prophylactic ICD therapy relatively expensive. Health care providers recognize the efficacy of ICDs, but require better risk stratification to improve cost-effectiveness.

**Noninvasive markers of SCD risk**

No marker (Table III, next page) has proved sufficiently sensitive in predicting high risk. Some are difficult to implement. Few composite markers have been adequately tested in patients treated according to current guidelines. All common variables have limited efficacy in post-MI patients in the contemporary setting. Noninvasive autonomic tests are nonpredictive in MI survivors with EF >35%. It is unclear whether restricting risk stratification to low EF improves the cost-effectiveness of preventive therapy (eg, ICD). However, two variables, heart rate and T-wave alternans (TWA), seem promising.

**Heart rate**

Increased heart rate irrespective of heart disease is an independent risk factor for SCD (Figure 6, next page). All-cause mortality, nonsudden cardiac death, and SCD each increased with increasing resting heart rate over 23 years follow-up in 5713 men aged 42 to 53 without cardiovascular disease. The relationship was steepest for SCD. European Systematic COronary Risk Evaluation (SCORE) investigators found heart rate an independent predictor of death in 21 766 men after adjustment for cardiorespiratory fitness. In the Coronary Artery Surgery Study (CASS) registry, all-cause and cardiovascular mortality in 24 913 patients with suspected or proven CAD was directly related to resting heart rate at entry, independently of age, gender, body mass index, physical activity, smoking, hypertension,
Table III. Noninvasive electrophysiologic markers of increased risk for sudden cardiac death.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Prognostic value</th>
<th>Guide to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holter monitoring</td>
<td>Disputed</td>
<td>Nonsustained VT used as entry criterion in several ICD studies and as risk marker in ICD primary prevention guidelines (eg, NICE)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Useful</td>
<td>Used routinely: sinus tachycardia indicates decompensating HF, and need for β-blocker or other bradycardic agent; inappropriate sinus bradycardia is a pacemaker indication</td>
</tr>
<tr>
<td>Exercise stress test</td>
<td>Limited</td>
<td>Poor chronotropic response to exercise is incorporated in HCM risk stratification and combined with other variables to guide ICD primary prevention; also used to assess the response to medical or ablation therapy in catecholaminergic VT</td>
</tr>
<tr>
<td>Heart rate variability</td>
<td>Useful</td>
<td>Not used</td>
</tr>
<tr>
<td>Heart rate turbulence</td>
<td>Useful</td>
<td>Not used</td>
</tr>
<tr>
<td>Baroreflex sensitivity</td>
<td>Useful</td>
<td>Not used</td>
</tr>
<tr>
<td>QRS duration on 12-lead ECG</td>
<td>Useful, but more for all-cause death than for SCD</td>
<td>A criterion for resynchronization therapy in HF and risk marker in ICD primary prevention guidelines</td>
</tr>
<tr>
<td>Signal-averaged ECG</td>
<td>Limited, useful in differential diagnosis of syncope</td>
<td>Not used</td>
</tr>
<tr>
<td>QT interval</td>
<td>Limited in the general population, but included in risk stratification in LQTS</td>
<td>Combined with other variables to guide ICD therapy</td>
</tr>
<tr>
<td>QT variability</td>
<td>Probably useful, but limited experience in SCD</td>
<td>Not used</td>
</tr>
<tr>
<td>T-wave alternans</td>
<td>Useful</td>
<td>Currently not used; prospective ICD data awaited</td>
</tr>
<tr>
<td>T-wave morphology</td>
<td>Probably useful, but limited experience in SCD</td>
<td>Not used</td>
</tr>
</tbody>
</table>

Abbreviations: HCM, hypertrophic cardiomyopathy; HF, heart failure; ICD, implantable cardioverter defibrillator; LQTS, long QT syndrome; NICE, UK National Institute for health and Clinical Excellence; SCD, sudden cardiac death; VT, ventricular tachycardia.

Figure 6. A: Resting heart rate as a risk factor for arrhythmic death 5 years post myocardial infarction, in patients (n=579) stratified by relative risk (RR) interval <716 ms and <716 ms (≥84 bpm). B: Resting heart rate as a risk factor for all-cause mortality (light green bars) and cardiovascular mortality (dark green bars) in 24,913 participants in the Coronary Artery Surgery Study (CASS) registry, 14.7 years follow-up.

diabetes, or LV dysfunction. Low heart rate may reduce coronary atherosclerosis and plaque rupture via various mechanisms including reduced shear stress.

**Repolarization abnormalities**

**QT interval**

Other ECG risk factors include abnormal ORS duration and repolarization. Ventricular repolarization was traditionally quantified by measuring the QT interval on the 12-lead ECG and correcting for heart rate using the Bazett or Fridericia formulas. A QTc interval >440 ms doubles or triples SCD risk in general population studies, but not in high-risk individuals with advanced underlying heart disease, particularly CHF.

**QT variability**

Repolarization duration depends on the preceding RR cycle. Patterns of QT interval adaptation to changes in heart rate (QT/RR variability) may be important. Altered circadian variation in the QT and RR intervals may indicate autonomic imbalance with loss of parasympathetic tone and/or sympathetic hyperactivity. The partial mismatch between ventricular recovery time and cycle length first noted in LQTS has since been reported after MI and in CHF. Spatial QT dispersion has been abandoned as a risk factor on conceptual and technical grounds, but QT temporal variability appears more promising. Assessment usually requires high-resolution digital Holter recording and may be investigated on a beat-to-beat basis independently of heart rate or by applying more complex frequency analyses.

**T-wave morphology**

M cells deep in ventricular myocardium directly determine T wave inscription and the genesis of QT prolongation and related T-U wave abnormalities. Alternation of M cell action potential duration results in exaggeration of transmural dispersion during alternate beats, predisposing to torsades de pointes. However, experience with this risk predictor is limited. Quantitative analyses of temporospatial dispersion of repolarization based on signal decomposition have been screened for prognostic information independent of that provided by conventional markers. They include principal component analysis of the T-wave loop, assessing the complexity of repolarization, total cosine R-to-T (TCRT), characterizing a 3-D relationship between repolarization and depolarization wave fronts, akin to Wilson’s ventricular gradient, and T-wave residuum extracted using signal decomposition to the 4th to 8th eigenvalues, reflecting nondipolar components of the repolarization signal. These analyses have mostly been applied to ECG databases from community studies or randomized trials. The results show more adverse events (all-cause death, sustained VT, and cardiac arrest) with abnormal repolarization, but require careful interpretation because of relatively low sensitivity and specificity, wide confidence intervals, and borderline significance. These markers appear nonrobust predictors of cardiac events.

**T-wave alternans**

TWA involves detecting every-other-beat morphological alternations thought to represent abnormalities in intracellular calcium handling that predispose to VT/VF. TWA has been linked to alternation in M cell action potential duration and increased transmural dispersion of repolarization. It is rarely detectable in the surface ECG, usually requiring sophisticated data processing based on spectral analysis. The TWA predictor has been extensively assessed in MI, CHF, and survivors of SCD. In 768 patients with CAD, EF ≤35% and no prior history of VT/VF, positive or indeterminate TWA conferred a 2.3-fold higher risk of arrhythmic mortality versus negative TWA. This con-

---

**Figure 7.** Mortality rates and appropriate shock rates in a prospective cohort of 768 patients with ischemic cardiomyopathy and ejection fraction ≤35% during 35 months of follow-up. Nonnegative T-wave alternans (TWA) include positive and indeterminate results. ICD, implantable cardioverter defibrillator.

firmed a meta-analysis in 2608 subjects from 19 studies showing that a positive TWA was associated with univariate risk ratios of 2.45 for secondary arrhythmic events and 4 for primary events. TWA demonstrated good negative predictive accuracy by identifying low-risk patients with a normal TWA test, whose 2-year survival rate was 97.5%, regardless of EF, etiology of cardiomyopathy, age, gender, diabetes, or severity of heart failure. In ICD patients, a nonnegative TWA showed a trend toward more frequent appropriate shocks. The hazard ratio was 3.8 in favor of negative TWA, but nonsignificant (95% confidence interval [CI], 0.88-15.91; P=0.07).

In a hypothetical 65-year-old cohort with CAD and EF ≤30%, TWA-guided ICD therapy was more cost-effective than ICD therapy without risk stratification (ICD-for-all strategy) or medical treatment. 83% of total potential ICD benefit could be achieved by implanting ICDs in the 67% of patients testing TWA nonnegative. The prospective Alternans Before Cardioveter Defibrillator (ABCD) and T-wave Alternans in Patients with Heart Failure (ALPHA) studies have yet to report the validity of TWA risk stratification before ICD implantation. ABCD aims to determine whether a TWA test is equivalent to programmed ventricular stimulation in predicting arrhythmic events and all-cause mortality in CAD with EF <40% and nonsustained VT. Patients positive for either or both receive an ICD.

However, TWA is invalidated by:

- Absent sinus rhythm or abnormal conduction (sinus tachycardia, atrial fibrillation, left bundle-branch block, ventricular pacing, etc)
- Failure of heart rate to respond to exercise (unless using atrial pacing or positive chronotropes)
- β-Blockade
- Poor recording quality.

Results are often “indeterminate.” Like most noninvasive electrophysiological markers, TWA has a high negative predictive value (97%), but in identifying patients requiring primary ICD prophylaxis, a positive predictive value for arrhythmic events is more clinically relevant.

**Other ECG markers of SCD risk**

**Nonsustained ventricular arrhythmias**

Although premature ventricular complexes and nonsustained VT indicate electrical instability, routine screening for nonsustained ventricular arrhythmias to guide ICD therapy has proven of limited value.

**Heart rate turbulence**

Heart rate analysis has yielded potential risk stratification parameters. Independently of heart rate variability and baroreflex sensitivity, heart rate turbulence predicts SCD risk and total mortality after MI. It describes the physiological biphasic response of the sinus node to a premature ventricular beat. In healthy subjects and low-risk patients, ventricular ectopics are followed by brief heart rate acceleration then deceleration. Response in high-risk patients is blunted. Turbulence also occurs after atrial premature beats, but is attenuated. The practical drawback is that the method depends on ventricular or atrial ectopics (typically 200) occurring during Holter monitoring.

In the 22-month Innovative Stratification of Arrhythmic Risk (ISAR) study in 2611 post-MI patients receiving conventional therapy (primary angioplasty: 89%), heart rate turbulence and EF were the only independent predictors of all-cause mortality and appropriate ICD shock. Turbulence increased risk 7-fold in the EF 30% to 50% subgroup. When applied to European Myocardial Infarction Amiodarone Trial (EMIAT) patients with MI and EF ≤40%, turbulence induced by atrial premature beats doubled mortality risk after adjustment for other ECG markers.

**Wide QRS**

Left bundle-branch block and nonspecific intraventricular conduction delay are associated with increased total mortality and SCD, whereas right bundle-branch block is nonpredictive. A wide QRS, usually ≥120 ms, occurs in one third of cardiomyopathy patients. In the general population, left bundle-branch block was associated with a 4.2-fold increase in out-of-hospital SCD among middle-aged men. Bundle-branch block increased progression to high-degree heart block 13-fold and nearly doubled the risk of all-cause death. The relationship between QRS widening and adverse outcome is unexplained. In intracardiac mapping studies, QRS width correlated with the degree of LV myocardial abnormalities and disruption of His-Purkinje conduction. QRS widening occurs in LV dilatation, stretch, and hypertrophy, myocardial fibrosis, conduction system involvement in the ischemic or scar area, and with drugs associated with adverse outcome. It could signify a more damaged heart with an increased risk for adverse events. It may directly contribute to LV dysfunction by causing mechanical dyssynchrony and functional mitral regurgitation due to papillary muscle dysfunction. Long-term right ventricular pacing has a similar effect on LV function but only in patients with significant underlying heart disease.
was absent in a large cohort with congenital heart block. In cardiomyopathy, especially if nonischemic, a wide QRS predisposes to bundle-branch reentrant VT.

QRS duration ≥120 ms indicates significant ventricular dyssynchrony and is an indication for resynchronization therapy in symptomatic heart failure. All the major randomized trials have shown reduced all-cause mortality with resynchronization therapy, but few have found matching benefit in SCD. QRS duration has no consensus risk stratification value in SCD. It did not predict post-MI SCD or serious arrhythmia in the ISAR study, or VT/VF in ICD recipients for primary and secondary prevention in the PACING Fast ventricular tachycardia REDuces shock ThErapies (PainFREE Rx II) study, even when the QRS was dichotomized at 120 ms or other cutoffs. A MADIT II subgroup analysis showed similar mortality reductions across six groups stratified by QRS duration (<0.09 s to >0.16 s). Increase in total mortality associated with wide QRS probably outweighs the increase in arrhythmic death risk.

**Signal-averaged ECG**

Late potentials on the signal-averaged ECG may indicate delayed conduction, providing the electrical substrate for reentrant ventricular tachyarrhythmias. The explosion of reperfusion techniques (percutaneous angioplasty, fibrinolysis, or revascularization) has laterly reduced the predictive power of the signal-averaged ECG, but its high negative predictive accuracy (89%-99%) may be useful in the differential diagnosis of unexplained syncope.

**Electrophysiological study**

Because inducible sustained VT/VF during programmed electrical stimulation was considered a risk marker for subsequent SCD, antiarrhythmic strategy was based on suppressing VT inducibility. Programmed ventricular stimulation was used to select candidates for ICD therapy (MADIT I) or antiarrhythmic drug therapy and/or ICD therapy (MUSTT). MUSTT reported significantly higher prevalence of cardiac arrest or arrhythmic death in untreated patients with inducible sustained VT versus registry patients with noninducible VT (18% vs 12% at 2 years, and 32% vs 24% at 5 years). However, electrophysiological testing failed to identify the 12% of subsequent SCDs (negative predictive value 88%). Progression of CAD and LV dysfunction, compounded by the day-to-day and long-term variability of electrophysiological testing (ranging from 10% to 50%), may account for poor predictive accuracy.

Once ICD therapy was found to improve survival in cardiac arrest survivors, as in the Antiarrhythmics Versus Implantable Defibrillators (AVID) study, routine electrophysiological testing became unnecessary in such patients. MADIT II and SCD-HeFT confirmed the survival benefit in LV dysfunction without using arrhythmia markers. Electrophysiological testing should thus be confined to elucidating syncope, and is a redundant preliminary to ICD implantation in post-MI patients with a low EF.

**ACUTE MANAGEMENT**

Treatment depends on the presenting arrhythmia. Much work on the mechanisms and management of VF is based on the physiology of VT. The two have much in common, but are not identical. This may explain problems in treatment efficacy and the difficulty of achieving specificity in risk stratification.

**Mechanism and survival of cardiac arrest**

Ventricular tachyarrhythmia (pulseless VT/VF) is the commonest cause of SCD. VF, found in 40%, features multiple wave fronts of electrical activation. The relationship between heart rate and action potential duration — the restitution hypothesis — describes the stability of these reentrant circuits. Action potential duration decreases as heart rate increases. At rapid heart rates, action potential durations can oscillate. These oscillations then magnify with the variations in myocardial conduction velocity and refractory period duration, disrupting the activation sequence and producing VF. Milder oscillations produce more stable, single-wave, reentry circuits.

With increasing treatment delay, asystole and pulseless electrical activity (PEA) or electromechanical dissociation become the predominant presenting rhythms. The true incidence of bradyarrhythmia may be less than suspected in that primary tachyarrhythmia may degenerate into asystole by the time the ECG is recorded. In two thirds of cases, the Ontario Prehospital Advanced Life Support (OPALS) study of 9072 out-of-hospital SCDs, including 610 (6.7%) witnessed by emergency services, found asystole or PEA at initial contact. Both are associated with low rates of prehospital resuscitation and survival to discharge, survival is significantly higher with VF as the primary arrhythmia, and highest of all with sustained VT: in 5505 cardiac arrests in Göteborg, survival to discharge was 3 5 times higher with VF or VT at presentation than with other arrhythmias. 65
Acute treatment

“Chain of survival” strategy
Survival after out-of-hospital SCD is 6%. Of initial survivors, 40% leave hospital without major neurological disability. The American Heart Association (AHA) therefore emphasizes the importance of the “chain of survival” for cardiac arrest in the community,66 backed by avoidance of arrhythmogenic medication, antiarrhythmic drug therapy, device and ablation therapy, and surgery. Improved access to prehospital defibrillation provided by automated external defibrillators (AEDs) has significantly increased survival. Successful resuscitation requires the four links in the chain to work effectively:

- Early recognition
- Early bystander cardiopulmonary resuscitation
- Early defibrillation
- Early advanced care.

Irrespective of the arrhythmia, time to treatment is critical. Survival probability decreases 7% to 10% per minute of delay to defibrillation, reaching <25% at 4 to 5 minutes, and <10% at 10 minutes. Survival from VF arrest is 90% for times to defibrillation <1 minute (coronary care units).

Public access defibrillators
Bystanders can now perform three of the links in the chain. Bystander cardiopulmonary resuscitation (CPR) increases survival 2- to 4-fold.65 The AHA backs lay rescuer (“public access”) AED programs enrolling firefighters, police, security staff, airline crew, and community first-aiders; in airports, casinos and police calls, these programs achieve defibrillation within 3 to 5 minutes, resulting in 49% to 74% survival in out-of-hospital VF.67 In the Public Access Defibrillation (PAD) trial with 20,000 volunteer first responders from 993 North American communities, half were trained in standard CPR and half in CPR + AEDs, made accessible in 1260 public and residential facilities. AEDs doubled survival to discharge from out-of-hospital arrest versus CPR alone, with no inappropriate shocks during 24,000 person-months’ exposure.68 Generalized AED access and training would save 2000 to 4000 lives annually.

Asystolic arrest
Survival from bradyarrhythmic or asystolic arrest, managed by continuous CPR, infusion of atropine, epinephrine or isoproterenol, and external pacing, is <1%,1 with just one survivor from 288 asystolic arrests in Melbourne (mean time to resuscitation by ambulance crew: 9.8 minutes). The prognosis of asystole or PEA caused by defibrillation for prolonged VF may be even worse than that for primary bradyarrhythmia. However, outcome after witnessed asystole or PEA receiving bystander CPR may be better than thought.69

Advanced life support guideline
The International Liaison Committee on Resuscitation (ILCOR) produced advanced life support protocols in 2004 designed to maximize ventilation and hemodynamics by establishing an effective cardiac rhythm.70 They incorporate fundamental changes, eg, the recommendation that five cycles of CPR be given between rhythm checks during pulseless arrest and only one defibrillation shock before initiating CPR for VF and pulseless VT. In arrhythmia unamenable to defibrillation, treatment is CPR until the precipitating metabolic or other clinical factors are corrected. Optimized oxygenation and restored electrolyte imbalance, particularly K+, Ca++, and pH, are critical for maintaining electrophysiological stability.

Acute antiarrhythmic therapy
Amiodarone is routinely used as an intravenous bolus (300-400 mg) in shock-refractory VF. In randomized double-blind trials it improved survival to hospital admission versus placebo or lidocaine. In the Amiodarone for Resuscitation in Refractory Sustained Tachycardia (ARREST) trial, 44% of patients survived to admission with a spontaneously perfusing rhythm versus 34% on placebo.71 Amiodarone doubled survival to admission versus lidocaine (23% vs 12%).72 Neither study showed improved survival to hospital discharge. Given that VF recurs within seconds to minutes in over half of initial resuscitations, it makes sense to consider amiodarone. However, routine amiodarone is not routinely recommended for defibrillation responders in stable rhythm.

Lidocaine is reserved for amiodarone-refractory VT/VF after MI, and procainamide for persistent hemodynamically stable arrhythmia. Most antiarrhythmic drugs increase the defibrillation threshold and make defibrillation more difficult. Intravenous amiodarone is perhaps the only antiarrhythmic conferring definitive benefit.

Magnesium
Magnesium has several effects useful in the acute situation: it suppresses automaticity in partially depolarized cells, inhibits calcium flux, eliminates early and late afterdepolarization, and interacts with potassium to stabilize cell membranes. In a meta-analysis of randomized trials in acute MI, magnesium halved ventricular arrhythmias.73
Survival (ISIS-4) confirmed the reduction in VF after acute MI. However, later randomized studies in out-of-hospital arrest and the Magnesium in Coronaries (MAGIC) trial in acute MI showed no significant benefit versus placebo in VF suppression or survival to discharge. Intravenous magnesium is particularly effective in arrhythmias due to early or delayed afterdepolarization, notably in torsades de pointes VT accompanying both congenital and acquired LQTS, but is ineffective in polymorphic VT unassociated with LQTS.

**PREVENTION**

**Long-term survival after cardiac arrest**

Out-of-hospital SCD is usually fatal. Overall US survival is 5%, ranging from 0.8% in African-Americans in Chicago to 43% with bystander-initiated CPR in Seattle. Overall survival from 2329 consecutive arrests in New York with attempted resuscitation was 1.4%, and survival from witnessed VF was 5%. European experience is similar.

Long-term survival in survivors remains lower than in the general population or matched individuals without arrest. Analysis of 1571 cardiac arrests in the UK showed 51 deaths exceeding life-table prediction in the first 200 days. Risk is maximal in the immediate aftermath, then declines until 2 years. Nonfatal VT/VF may recur in 30% to 40% of victims in the first 2 years. Primary and secondary prevention is thus paramount.

Options include pharmacotherapy, ablation, surgery, and ICDs. Despite the advent of ICDs, the greatest impact on SCD mortality, except for β-blockers, comes from indirectly acting cardiovascular drugs, perhaps by modulating “upstream” ischemic, biochemical, and fibrotic processes (ventricular remodeling) predisposing to VT/VF.

**Pharmacological therapy**

No large randomized controlled trial in CAD has shown benefit with routine class I or III antiarrhythmic prophylaxis.

**Amiodarone**

Amiodarone is the only potentially useful antiarrhythmic for high-risk post-MI or nonischemic cardiomyopathy compounded by severe LV dysfunction and/or frequent ventricular ectopics. Although meta-analysis suggests that amiodarone reduces arrhythmic death by 29% and all-cause mortality by 13% to 15% versus placebo or untreated controls, the Canadian Amiodarone Myocardial Infarction Trial (CAMIAT) and EM lat indicated that benefit over placebo is dependent on the presence of β-blockade.

Amiodarone may be more effective in non-CAD subgroups. In the Grupo de Estudio de la Sobreviva en la Insuficiencia Cardiaca en Argentina (GESICA) study in Chagas cardiomyopathy and Congestive Heart Failure–Survival Trial of Antiarrhythmic Therapy (CHFSTAT), amiodarone was superior to placebo in nonischemic cardiomyopathy. The AMiodarone Versus Implantable cardioverter-defibrillator Trial (AMIOVIRT) found it as effective as ICD therapy. However, the larger SCD-HeFT contradicted these findings, showing no survival benefit from amiodarone versus placebo in CHF and EF ≤35% irrespective of etiology, whereas ICD therapy reduced all-cause mortality by 23% in all patients and by 27% in those with nonischemic cardiomyopathy. This prompted expanded ICD indications to all-cause cardiomyopathy with EF ≤35%.

**Antiarrhythmic drugs as ICD adjuncts**

Up to half of ICD patients eventually receive antiarrhythmics to prevent symptomatic tachyarrhythmia and reduce shock rates. The Optimal Pharmacological Therapy In Cardioverter defibrillator patients (OPTIC) study in 412 patients with an ICD for spontaneous or induced sustained VT/VF found that amiodarone + β-blocker prevented one third of all shocks versus β-blocker alone and 14% versus sotalol. In the SHock Inhibition Evaluation with azimiLiDe (SHIELD) study, azimilide halved appropriate ICD shocks and the frequency of pacing-terminated VT, and suppressed electrical storms. However, SHIELD also confirmed reports of increased torsades de pointes VT with azimilide.

All studies enrolled only patients with secondary prevention ICDs, ie, for spontaneous or induced sustained VT/VF. Whether patients with primary prevention ICDs would derive similar benefit from antiarrhythmic drug therapy is unclear. They may have a lower risk of shocks triggered by ventricular arrhythmias, but a similar risk of inappropriate shocks.

**β-Blockers**

Large controlled trials have confirmed reduced mortality and arrhythmia with β-blockade, notably after MI and in CHF. In a meta-analysis of 22 trials in 10 135 patients with CHF, β-blockade reduced mortality by 35%, primarily by preventing heart failure progression, but also by significantly reducing SCD. In the pioneering Beta Blocker Heart Attack Trial (BHAT), propranolol virtually halved SCD risk. Even in the modern era of...
thrombolysis and primary angioplasty, the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial showed reductions of one third in SCD and >70% in VT/VF.  

**Angiotensin-converting enzyme inhibitors**

Reduced mortality and arrhythmia with angiotensin-converting enzyme (ACE) inhibitors has also been confirmed by multiple large controlled trials. Meta-analysis of 15 randomized trials in MI with LV dysfunction or heart failure showed that ACE inhibition reduced SCD risk by 20%. 88 In the Heart Outcomes Prevention Endpoint (HOPE) trial, ramipril reduced SCD by 21% (hazard ratio 0.79, 95% CI [confidence interval], 0.64-0.98) versus placebo. 89 The European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) recently reported a trend toward reduced cardiac arrest with perindopril (hazard ratio 0.54, 95% CI, 0.20-1.47) in more than 12 000 patients with stable CAD ± previous MI in a population at lower risk than that of the HOPE study. 90 The European Society of Cardiology (ESC) Task Force on Sudden Cardiac Death has classified the evidence level for the survival benefits of ACE inhibition as high and ranked ACE inhibitors, along with β-blockers and aldosterone receptor antagonists, as class I nonelectrophysiological agents for primary prevention of sudden death in MI and CHF. 3 Various mechanisms may account for this effect. By increasing prostacyclin production, ACE inhibition reduces circulating levels of angiotensin II, which facilitates adrenergic transmission and is directly proarrhythmic. Indirect antiarrhythmic effects include antagonism of sympathetically mediated vasoconstriction, protection against hypokalemia, increased baroreflex sensitivity, and decreased ventricular dilatation. ACE inhibitors protect against recurrent MI and SCD by slowing smooth muscle proliferation and plaque development. They also have direct electrophysiological effects, prolonging action potential duration and reducing the \( I_K \) current while increasing the L-type calcium current.

**Angiotensin II type 1 receptor blockers**

Angiotensin II type 1 receptor blockers (ARBs) have a similar effect on SCD risk. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study indicated that losartan offered better protection than atenolol against SCD in diabetic hypertensives with LVH. 91 Similarly, the Candesartan in Heart failure Assesment of Reduction in Mortality and morbidity (CHARM) study found a 15% reduction in SCD. 92 Some ARBs specifically antagonize the abundant AT1 receptors in the atrioventricular node and Purkinje fibers, possibly accounting for the antiarrhythmic effect. ARBs also block the arrhythmogenic effects of angiotensin II,

**Aldosterone antagonists**

Aldosterone is central to CHF pathophysiology, mediating not only endothelial dysfunction and microangiopathy, but also cardiovascular fibrosis. Some cardiac effects may be mediated by the β-adrenergic pathway. Long-term aldosterone blockade by spironolactone reduces macrovascular fibrosis and enhances compliance. In the Randomized Aldactone Evaluation Study (RALES) in 1663 patients with severe CHF and EF ≤35%, spironolactone reduced all-cause death by 30% and SCD by 29% versus placebo. 93 Similarly, the Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SUrvival Study (EPHESUS) showed reductions of 31% in 30-day all-cause mortality and 37% in SCD after acute MI with EF ≤40%. 94 Statistical analysis in addition to lowering lipid levels, statins influence endothelial function, inflammation, plaque stability, platelet aggregation, and thrombosis. They may also alter the lipid portions of the membrane penetrated by ion channels, thus modulating ion-channel conductance, and perhaps stabilizing the membrane. The mechanism of their putative antiarrhythmic effect is unknown. Statins reduce all-cause mortality, including SCD, in high-risk patients. In a meta-analysis of 12 randomized double-blind trials in 41 167 patients, statins decreased all-cause mortality by 22% and SCD by 14% over 2.9 years, independently of changes in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol. Secondary prevention benefit exceeded that in primary prevention (relative risk reduction 18% vs 5%). 95 In the AVOID, MADIT II and DEFibrillators In Non-ischemic cardiomyopathy Treatment Evaluation (DEFINITE) trials, statins decreased the VT/VF requirement for ICD therapy by 33% 96-98 In the Cholesterol Lowering and Arrhythmia Recurrences after Internal Defibrillator Implantation (CLARIDI) trial, atorvastatin 80 mg reduced appropriate ICD shocks by 53% versus placebo over 1 year in 106 CAD patients with cholesterol levels <250 mg/dL. 97 In the MADIT-II substudy, statins reduced VT/VF or cardiac death by 35%. Efficacy extends to nonischemic cardiomyopathy: the DEFINITE study reported only 1 arrhythmic death in 110 statin patients versus 18 in 348 nonstatin patients. 98
**Omega-3 fatty acids**

Dietary fish oil containing long-chain n-3 polyunsaturated fatty acids (PUFAs) equivalent to 1 to 2 fatty fish meals per week virtually halved SCD risk in large prospective cohorts,

14,100 while intravenous n-3 PUFA infusion suppressed inducibility of sustained VT.

101 In vitro, n-3 PUFAs decrease myocyte excitability and cytosolic calcium fluctuation by inhibiting Na+ and L-type Ca2+ channels, this may account for their antiarrhythmic potential. 14 However, three randomized trials in secondary prevention ICD recipients, including the Fatty Acid Antiarrhythmia Trial (FAAT) and Study on Omega-3 Fatty Acids (SOFA), found no protective effect against shock frequency, although subgroup analyses suggested benefit in certain severe subgroups (MI, EF ≤30%, and VF). 102-104 Size, follow-up duration, and/or the enrollment of high-risk secondary prevention ICD patients versus healthy or low-risk subjects could account for the discrepancy with population studies or the Gruppo Italiano per lo Studio della Sopravivenza nell’Infarto Miocardico (GISSI)-Prevenzione trial. 100

**Device therapy**

ICD therapy has dispelled the skepticism of the 1980s to prove highly effective at decreasing SCD and all-cause mortality in heart disease. Indications have expanded incrementally from documented VF-induced

---

**Table IV.** Comparison of ACC/AHA/ESC guidelines for the management of patients with ventricular arrhythmias and prevention of sudden cardiac death, NICE guidelines, and other guidelines related to primary prevention of sudden cardiac death.

**Abbreviations:** ACC, American College of Cardiology; AHA, American Heart Association; EF, ejection fraction; EP, electrophysiological study; ESC, European Society of Cardiology; HF, heart failure; ICD, implantable cardioverter defibrillator; LOE, level of evidence; MI, myocardial infarction; NASPE, North American Society of Pacing and Electrophysiology; NICM, nonischemic cardiomyopathy; N/A, not applicable; NICE, UK National Institute for health and Clinical Excellence; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PM, pacemaker; SCD, sudden cardiac death; STEMI, ST-segment elevation myocardial infarction; VAs, ventricular arrhythmias.

**Sources:** 1ACC/AHA Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult; 2ESC Guidelines for the Diagnosis and Treatment of Chronic Heart Failure; 3ACC/AHA Guidelines for the Management of Patients with ST Elevation Myocardial Infarction; 4ACC/AHA/NASPE Guideline Update for Implantation of Cardiac Pacemakers and Arrhythmia Devices; 5NICE Guideline Update for Implantable Cardioverter Defibrillator Implantation; 6ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death.
cardiac arrest in 1986, through spontaneous or induced sustained VT in 1999 and, spurred by the MADIT II data, through prophylaxis in high-risk ischemic cardiomyopathy in 2003, to all-cause cardiomyopathy with EF ≤35% in 2004-2005, prompted by the SCD-HeFT results. However, guidelines retain inconsistencies (Table IV, page 191). New guidelines have combined all trials enrolling patients with MI and LV dysfunction into class I recommendations with evidence level A and expanded the indication to NYHA class I and EF ≤30%-35% (class IIa, evidence level B) (Figure 8).105 Nonischemic NYHA class II and III cardiomyopathy is a class I recommendation with evidence B. ICD therapy is not indicated in NYHA class I MI or nonischemic cardiomyopathy (class IIb recommendation, evidence level B).

Secondary prevention

In AVID, the Canadian Implantable Defibrillator Study (CIDS), and the Cardiac Arrest Study Hamburg (CASH), ICDs increased overall survival in life-threatening ventricular tachyarrhythmias versus empiric amiodarone, guided sotalol, and empiric metoprolol.63 AVID was the first large trial to compare ICDs with antiarrhythmic drug therapy for secondary prevention.106 ICDs more than halved absolute risk of arrhythmic death at 2 years. In a meta-analysis of three secondary prevention trials dominated by the AVID study, ICDs reduced total mortality by 28% versus amiodarone. Guidelines stipulate that except for arrest occurring within 24 to 48 hours of MI, survivors should receive an ICD unless threatened by other active disease.107

Primary prevention

MADIT was the first randomized trial to show survival benefit from primary prevention ICDs, increasingly implanted via the transvenous approach.61 Patients were at high risk of SCD (EF <35%, nonsustained VT on Holter monitoring) after remote MI. The trial was terminated after significant improvement in the first 196 patients. ICDs reduced the relative risk of total mortality by 54% and absolute 2-year mortality by 19%.

Recently published primary prevention trials in MI and CHF are listed in Table V. By showing that ICDs reduced arrhythmia and all-cause mortality in patients with remote MI and EF <30%, without other risk stratification being required, MADIT II redefined the target population,28 prompting significant worldwide uptake and debate over resource allocation and risk stratification. Benefit becomes evident after the first 6 months post-MI. The Defibrillator IN Acute Myocardial Infarction Trial (DINAMIT) in LV systolic dysfunction and imbalance in cardiac autonomic tone after MI found no difference at 30 months in all-cause mortality between the two groups, but this was because increased mortality from nonarrhythmic cardiovascular causes offset the significant decrease in arhythmic mortality.108

SCD-HeFT enrolled 1310 patients with a 2-year history of heart failure after MI.29 ICD therapy reduced all-cause mortality by 23% versus placebo, primarily in NYHA class II. Patients in class III derived no mortality benefit. SCD-HeFT revealed that long-term benefit is determined by heart failure severity, irrespective of cause, and emphasized that ICD therapy is not a homogeneous treatment, given the programming and pacing spectra currently available. Nevertheless, ICDs undoubtedly offer the best protection against SCD in CAD with LV dysfunction (Figure 9). On the other hand, they are not cheap and more accurate risk stratification markers remain urgently required.

ICD prophylaxis in cardiomyopathy

Dilated cardiomyopathy

The utility of primary prevention ICD in tachyarrhythmic DCM remains unproven, despite three specific studies. The Cardiomyopathy Trial (CAT) was terminated due to low all-cause mortality in the control group; it found no case for prophylactic ICD implantation for recent-onset cardiomyopathy.109 AMIOVIRT, also terminated prematurely for futility, observed no significant difference in mortality or quality of life versus amiodarone.80 The DEFINITE trial recorded 35% relative risk reduction with ICD implantation and standard med-

<table>
<thead>
<tr>
<th>NYHA</th>
<th>EF (%)</th>
<th>I</th>
<th>II (+QRS)</th>
<th>III (+QRS)</th>
<th>IV (+QRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ICD</td>
<td>ICD (+CRT)</td>
<td>ICD (+CRT)</td>
<td>(CRT/CRT-D)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>ICD</td>
<td>ICD (+CRT)</td>
<td>ICD (+CRT-D)</td>
<td>(CRT/CRT-D)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 8. Evidence-based indications for device therapy (implantable cardioverter defibrillators and/or cardiac resynchronization) in patients with left ventricular dysfunction.

Abbreviations: CRT, cardiac resynchronization therapy; CRT-D, CRT plus ICD therapy; EF, ejection fraction; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association.

SCD-HeFT enrolled 1310 patients with a 2-year history of heart failure after MI.29 ICD therapy reduced all-cause mortality by 23% versus placebo, primarily in NYHA class II. Patients in class III derived no mortality benefit. SCD-HeFT revealed that long-term benefit is determined by heart failure severity, irrespective of cause, and emphasized that ICD therapy is not a homogeneous treatment, given the programming and pacing spectra currently available. Nevertheless, ICDs undoubtedly offer the best protection against SCD in CAD with LV dysfunction (Figure 9). On the other hand, they are not cheap and more accurate risk stratification markers remain urgently required.
ical therapy versus standard medical therapy alone after 2 years, but failed to reach statistical significance (hazard ratio, 0.65; 95% CI, 0.40–1.06; \( P = 0.06 \)). Subgroup analysis confirmed benefit to NYHA class III heart failure.110 SCD-HeFT (n=792) confirmed smaller studies by identifying a trend toward improved survival in nonischemic cardiomyopathy (hazard ratio 0.73; 95% CI 0.50–1.07; \( P = 0.06 \)).29 Relative risk reduction was sim-

Table V. Overview of selected primary prevention ICD trials in myocardial infarction and congestive heart failure (published in 2002-2005).

<table>
<thead>
<tr>
<th>Study</th>
<th>MADIT II</th>
<th>DINAMIT</th>
<th>BEST-ICD</th>
<th>DEFINITE</th>
<th>AMIOVIRT</th>
<th>CAT</th>
<th>SCD HeFT</th>
<th>COMPANION*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>1232</td>
<td>674</td>
<td>143</td>
<td>458</td>
<td>103</td>
<td>104</td>
<td>2521</td>
<td>1520</td>
</tr>
<tr>
<td>Disease</td>
<td>MI &gt;30 days</td>
<td>MI &lt;40 days</td>
<td>MI &lt;30 days</td>
<td>NICM</td>
<td>NICM</td>
<td>NICM</td>
<td>CHF, 48% NICM</td>
<td>CHF, 45% NICM</td>
</tr>
<tr>
<td>NYHA I/II/III/IV</td>
<td>37/34.5/24/4.5</td>
<td>13/60/27/…</td>
<td>Not stated; CHF in CCU in 51.1%</td>
<td>21.6/57.4/21.0/…</td>
<td>13/64/24/…</td>
<td>65/33.7/…</td>
<td>70/30/…</td>
<td>85/15/…</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>≤30 (23)</td>
<td>≤30 (28)</td>
<td>≤35 (31)</td>
<td>≤35 (21)</td>
<td>≤35 (23)</td>
<td>≤30 (24)</td>
<td>≤35 (25)</td>
<td>≤35 (21)</td>
</tr>
<tr>
<td>Risk factor</td>
<td>None required</td>
<td>None required</td>
<td>VPBs ≥310/h, SDNN &lt; 70 ms, SAECG, inducible VT</td>
<td>No ICD (OPT)</td>
<td>NSVT</td>
<td>NSVT</td>
<td>None required</td>
<td>None required</td>
</tr>
<tr>
<td>Comparator</td>
<td>No ICD</td>
<td>No ICD</td>
<td>No ICD (OPT)</td>
<td>No ICD (OPT)</td>
<td>Amiodarone</td>
<td>No ICD</td>
<td>Amiodarone, placebo</td>
<td>Amiodarone, CRT, OPT</td>
</tr>
<tr>
<td>1o end-point</td>
<td>ACM</td>
<td>ACM</td>
<td>ACM</td>
<td>ACM</td>
<td>ACM</td>
<td>ACM</td>
<td>ACM</td>
<td>ACM+ACH</td>
</tr>
<tr>
<td>Follow-up, months</td>
<td>20</td>
<td>30</td>
<td>45</td>
<td>29</td>
<td>24</td>
<td>66</td>
<td>45.5</td>
<td>11.9 - 16.2</td>
</tr>
</tbody>
</table>

Table V. Overview of selected primary prevention ICD trials in myocardial infarction and congestive heart failure (published in 2002-2005).

**Abbreviations:** ACH, all-cause hospitalization; ACM, all-cause mortality; ACC, American College of Cardiology; CCU, coronary care unit; CHF, congestive heart failure; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; NICM, nonischemic cardiomyopathy; PVC, premature ventricular complex; SAECG, signal-averaged electrocardiogram; SDNN, standard deviation of normal RR intervals (measure of heart rate variability); VT, ventricular tachycardia.

**Trials:** AMIOVIRT, AMIOdarone Versus Implantable cardioverter-defibrillator Trial; BEST-ICD, Beta-blocker Strategy plus Implantable Cardioverter Defibrillator; CAT, Cardiomyopathy Trial; DEFINITE, Defibrillators In Non-Ischemic cardiomyopathy Treatment Evaluation; DINAMIT, Defibrillator IN Acute Myocardial Infarction Trial; MADIT II, Second Multicenter Automatic Defibrillator Implantation Trial; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; COMPANION, Comparison of Medical therapy, Pacing aNd defibrillatION in heart failure. 

* COMPANION compared ICD + resynchronization therapy vs resynchronization therapy only or optimal medical therapy,

![Figure 9. The effects of implantable cardioverter defibrillator (ICD) therapy on all-cause death in ICD primary prevention trials.](image-url)

**Abbreviation:** CAD, coronary artery disease; MI, myocardial infarction; NICM, nonischemic cardiomyopathy.

**Trials:** AMIOVIRT, AMIOdarone Versus Implantable cardioverter-defibrillator Trial, CABG-Patch, Coronary Artery Bypass Graft Surgery-Patch; DEFINITE, Defibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT, Defibrillator IN Acute Myocardial Infarction Trial; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MUSTT, Multicenter UnSustained Tachycardia Trial; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.
ilar in ischemic and nonischemic heart failure, but absolute mortality was lower in the nonischemic group, implying that ICD benefit was relatively slight. In CAT, AMIOVIRT, DEFINITE, and SCD-HeFT, annual mortality in nonischemic cardiomyopathy was 7%, with ICDs reducing relative risk by 30% and all-cause mortality by 2%. 25 patients with nonischemic cardiomyopathy would need to be treated to prevent one death at 2 years,111 versus 15 with ischemic cardiomyopathy. Only in the COMparison of Medical therapy, PAcing, aNd defibrillatION in heart failure (COMPANION) trial, which used a dual cardiac resynchronization and defibrillation device, was ICD therapy significantly superior to optimal medical therapy in reducing all-cause mortality in cardiomyopathy.112

**Hypertrophic cardiomyopathy**

There have been no randomized trials in HCM. Multiple risk factors and/or a strong family history of SCD are indications for implantation. In patients at risk of SCD, but with no SCD history, the annual appropriate ICD shock rate was 4%.113 Risk factors for shock were syncope, nonsustained VT, and massive hypertrophy. In one quarter of patients, implantation preceded the first appropriate shock by 4 to 9 years.

**ICD in primary electrical disorders**

An ICD is the only effective therapy in high-risk LQTS, Brugada syndrome, and other inherited channelopathies. Two consensus indications in LQTS are previous cardiac arrest (class I) and recurrent syncope despite β-blockade (class IIa). SCD risk is highest in Jervell and Lange-Nielsen syndrome: 27% of patients arrested despite β-blockade, and symptoms persisted or emerged on therapy in 51%, while event rates exceeded those in type 3 LQTS during β-blockade (14%-17%). ICD therapy significantly lowered 3-year all-cause mortality versus drug therapy in 234 patients with LQTS and SCD or syncope (1.3% vs 16%). One third of a multicenter Brugada registry (n=690) received an ICD for high-risk SCD: 27% had at least one appropriate shock in 2.5 years. ICD therapy is a class I indication for primary prevention in syncope with a spontaneous type 1 Brugada ECG and a class IIa indication in asymptomatic patients with spontaneous type 1 Brugada ECG changes and inducible VT.24

**Cardiac resynchronization therapy (CRT)**

The advent of CRT as an effective option has advanced the debate on device therapy. In the COMPANION trial in NYHA III-IV heart failure with interventricular conduction delay, CRT reduced the primary end point of death or hospitalization by 19% versus 20% with CRT + ICD (CRT-D).112 Relative risk reduction in the secondary end point, mortality, was 36% with CRT-D (P<0.003), suggesting a role for prophylactic biventricular pacing and ICD therapy in selected patients. However, the CArdiac REsynchronization-Heart Failure (CARE-HF) study showed that CRT reduced the incidence of SCD and death from worsening heart failure versus optimal medical therapy.114 The precise indications for CRT and/or CRT-D thus remain unclear (Figure 8), but ICD therapy is generally advised in ventricular dysfunction.

**Cost-effectiveness of device therapy**

Propylactic ICD implantation is expensive in terms of device cost and its potential beneficiaries, estimated at 500 000 in the US by the Center for Medicare and Medicaid Services (CMS). The cost-effectiveness ratio in six randomized primary prevention trials showing reduced mortality with ICDs (Table VI) was $50 700 per life-year saved (LYS).115 A ratio of $40 001 to $60 000 (€31 850 to €47 770) represents borderline cost-effectiveness. However, as benefit accrues for years after implantation, cost-effectiveness improves with follow-up. SCD-HeFT reported a ratio of $38 897 per LYS at 3 years with a single-chamber conservatively programmed ICD in moderate heart failure and EF ≤35%.30 However, at 3.5 years in MADIT-II, the incremental cost-

---

<table>
<thead>
<tr>
<th>Study</th>
<th>Absolute risk reduction per year</th>
<th>Number needed to treat</th>
<th>Costs per life-year saved</th>
<th>Costs per life-year saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVID</td>
<td>8.2%</td>
<td>9</td>
<td>$66 677</td>
<td>€53 086</td>
</tr>
<tr>
<td>MADIT I</td>
<td>10.2%</td>
<td>4</td>
<td>$30 337</td>
<td>€24 154</td>
</tr>
<tr>
<td>MADIT II</td>
<td>5.6%</td>
<td>11</td>
<td>$235 000*</td>
<td>€187 101</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>7.5%</td>
<td>17</td>
<td>$38 389</td>
<td>€30 564</td>
</tr>
<tr>
<td>COMPANION CRT-D</td>
<td>7.0%</td>
<td>14</td>
<td>$36 870</td>
<td>€29 355</td>
</tr>
</tbody>
</table>

**Table VI.** Cost-effectiveness of implantable cardioverter defibrillator therapy. 

Abbreviations: AVID, Antiarrhythmics Versus Implantable Defibrillators; COMPANION, COmparison of Medical therapy, PAcing, aNd defibrillatION in heart failure; CRT-D, Cardiac Resynchronization Therapy-Defibrillator; MADIT I & II, Multicenter Automatic Defibrillator Implantation Trial; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

*Incremental cost-effectiveness ratio (ICER).
effectiveness ratio (ICER) was $235 000 per LYS. In 2004, total health care expenditure on inpatient intervention in Western Europe was €286.7 bn, including 0.493 bn euros (0.2%) for ICD therapy (implantation and follow-up costs). Thus, in the wider context, even if implantation rates tripled, the overall cost would barely exceed 0.5%. By comparison, atrial fibrillation accounts for over 1% of UK and French health care budgets.

In LOTS, ICD primary prevention had an ICER of $3328 per quality-adjusted-life-year saved (QALYS) in men and $7102 in women versus medical therapy. It was also cost-effective in HCM, for both primary and secondary prevention ($17 500-$23 000 per QALYS), but not in low-risk patients with LOTS or HCM ($400 000-$600 000 per QALYS).

Catheter ablation

Catheter ablation of the right bundle branch cures almost all bundle-branch reentry VT that uses the right bundle branch anterogradely and left bundle branch retrogradely (accounting for 20% of cardiac arrests in DCM). Focal automaticity is the VT mechanism in 25% of DCM and may cause tachycardia-induced cardiomyopathy reversing after ablation. Endocardial reentry around the tricuspid or pulmonary valve, or both, often causes VT in ARVC of 19 patients ablated for ARVC-related VT, 17 had no VT and two had infrequent recurrence with no arrhythmic death over 27±22 months; linear lesions with signal amplitude <0.5 mV extended 2.0 to 8.6 cm from the most abnormal myocardium, through abnormal endocardium to annular structures. Automaticity and reentry in the Purkinje system can initiate VF in LQTS and torsades de pointes VT. In LQTS and Brugada syndrome associated with frequent isolated or repetitive premature beats and multiple episodes of VF, no VF, SCD or syncope was reported after ablation over 24±20 months (n=4) and 9±8 months (n=4). However, this selected cohort may be irrelevant to patients with few premature beats. In ICD patients, ablation can also control recurrent hemodynamically unstable VT, causing frequent multiple shocks despite antiarrhythmic drug therapy and reprogramming of device settings.

CONCLUSION

SCD remains a major public health problem and is most commonly caused by CAD. Risk stratification is effective for groups, but difficult in individuals. Advances in molecular biology are elucidating arrhythmic risk in hereditary disease and may prove relevant to the much larger population at risk. The key to treatment is prompt resuscitation. Device therapy has greatly enhanced primary and secondary prevention. Primary prevention trials have targeted severe structural heart disease, with EF ≤35% and high SCD risk. However, SCD often occurs in subjects with EF >35%. Few data guide primary preventive strategy in this group with low SCD event rates, but high cumulative numbers. Various disparate and disease-specific characteristics can identify those at greatest risk, but more accurate clinical and genetic risk profiling is urgently needed. As the number of potential beneficiaries has increased, so ICD guidelines have simplified, becoming largely EF-driven. However, a more comprehensive scoring system integrating EF with noninvasive and genetic information should improve risk prediction and broaden the eligible population. SCD has become a manageable medical condition, but still needs major improvements in prevention, risk prediction, secure resuscitation, and therapy.

REFERENCES


6. Virmani R, Burke AP, Farb A.
Sudden cardiac death.

7. Virmani R, Burke AP, Farb A, Kolodgie FD.
Pathology of the vulnerable plaque.

Temporal trends on the risk of arrhythmic vs non-arrhythmic deaths in high-risk patients after myocardial infarction: a combined analysis from multicentre trials.
Eur Heart J. 2006;26:1385-1393.

Electrocardiographic predictors of arrhythmic death and total mortality in the Multicenter Unsustained Tachycardia Trial.

Echocardiographic and electrocardiographic diagnoses of left ventricular hypertrophy predict mortality independently of each other in a population of elderly men.
Circulation. 2001;103:2346-2351.

Change in systolic left ventricular performance after 3 years of antihypertensive treatment: the Losartan Intervention for Endpoint (LIFE) study.

Cigarette smoking and the risk of supraventricular and ventricular tachyarrhythmias in patients with ischemic left ventricular dysfunction.

Predicting sudden cardiac death in the population: the Paris Prospective Study I.

14. Leaf A, Kang JX, Xiao YF, Billman GE.
Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils.

Sudden death in the young.

16. Walsh CK, Krongrad E.
Terminal cardiac electrical activity in pediatric patients.

17. Il S, Cesario D, Valderrabano M, Shivkumar K.
The molecular basis of cardiac arrhythmias in patients with cardiomyopathy.

Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: do lamin A/C mutations portend a high risk of sudden death?

Sudden death in hypertrophic cardiomyopathy: identification of high risk patients.
J Am Coll Cardiol. 2000;36:2212-2218.


Risk stratification in the long-QT syndrome.

Circulation. 2001;103:89-95.

Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome.

Brugada syndrome: report of the second consensus conference.

Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia.

Short QT syndrome: pharmacological treatment.


85. Brophy JM, Joseph L, Rouleau JL. 
Beta-blockers in congestive heart failure: a Bayesian meta-analysis. 

86. Chadda K, Goldstein S, Byington R, Curb D. 
Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. 

Antiarrhythmic effect of carvedilol after acute myocardial infarction: results of the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial. 

88. Domanski MJ, Exner DV, Borkowf CB, Geller NL, Rosenberg Y, Pfeffer MA. 

Effect of ramipril in reducing sudden deaths and nonfatal cardiac arrests in high-risk individuals without heart failure or left ventricular dysfunction. 

90. The European trial on Reduction Of Cardiac events with Perindopril in stable coronary Artery disease Investigators. 
Efficacy of perindopril in reduction of cardiovasculaer events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicentre trial (the EUROPA Study). 

Effect of losartan on sudden cardiac death in people with diabetes: data from the LIFE study. 

Effect of candesartan on cause-specific mortality in heart failure patients: the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) program. 

93. RALES Investigators. 
Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). 

Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. 

95. Hersl AS, Shukla DD, McAreavey D, Mitchell RT, Exner DV. 
Reducing sudden death: the impact of statin therapy. 
*Heart Rhythm.* 2006;3(suppl):S120. Abstract.

Reduction in ventricular tachyarrhythmias with statins in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). 


Effects of statin therapy on arrhythmic events and survival in patients with nonischemic cardiomyopathy: a DEFINITE substudy. 

Does statin therapy decrease mortality in patients with cardiomyopathy? Unanticipated observations from SCD-HeFT. 

Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction; time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI)-Prevenzione. 

Immediate effects of n-3 fatty acid infusion on the induction of sustained ventricular tachycardia. 

Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. 

Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. 


Sudden Cardiac Death

Expert Answers to Three Key Questions

1. Congenital long QT syndrome: how big a problem, how best managed?
   
   **S. G. Priori, M. Cerrone**

2. How will genomic approaches translate into clinical applications in sudden cardiac death?
   
   **P. M. Spooner**

3. How can we reduce sudden death in the community?
   
   **G. Nichol, M. L. Weisfeldt**
Molecular genetics has recently entered the field of sudden cardiac death (SCD). The pioneering work of Mark Keating and his group has opened the way to the understanding of the role of inherited ion channel abnormalities and their links to cardiac arrest. In less than one decade, different syndromes caused by genetically determined ion channel dysfunctions have been described: long QT syndrome (LQTS); Brugada syndrome; Lev-Lenegre syndrome; catecholaminergic polymorphic ventricular tachycardia; short QT syndrome. At present, many genes have been associated with such syndromes and it is now possible to evaluate the impact that genetics has had, not only on our understanding of the pathophysiology of SCD, but also in shaping “locus-specific” clinical management of patients.

LQTS is characterized by a prolongation of the QT interval on the surface ECG and by the occurrence of syncope and cardiac arrest precipitated by emotion or exercise. The typical arrhythmia in LQTS is a polymorphic ventricular tachycardia (VT) called “torsades de pointes,” which is triggered by early afterdepolarizations. In addition to this dramatic presentation, many patients experience a benign course and remain asymptomatic.

Subsequent to the initial description of the syndrome, it was noted that QT interval prolongation is not always present, as approximately 30% of gene carriers present a normal QT interval on baseline ECG.
This feature reflects “incomplete penetrance” and is related to factors that attenuate the phenotype in some individuals, despite the presence of a genetic mutation. These factors are referred to as “modifiers”—but to date none of them has been discovered. As such, they represent one of the challenges of ongoing research in the field of inherited arrhythmogenic diseases.

However, recent data from large series of patients indicate that silent gene-carriers have a 15% to 20% risk of becoming symptomatic and that they are at increased risk of ventricular arrhythmias if exposed to such environmental factors as hypokalemia or drugs that block the potassium current $I_{Kr}$ and prolong the QT interval. In these subjects, genetic analysis offers the sole opportunity to establish a correct diagnosis and to protect them from arrhythmias. Moreover, by knowing their status as carriers, they can avoid risk factors, take prophylactic therapies, and make informed decisions based on awareness of the probability of having affected offspring.

**GENETIC HETEROGENEITY: THE LONG QT SYNDROMES**

Two patterns of transmission are known for LQTS: the Romano-Ward syndrome presents only the cardiac phenotype and is autosomal dominant; the Jervell and Lange-Nielsen syndrome is characterized by prolonged QT interval and neurological deafness, and is autosomal recessive. In the early 1990s, Keating and colleagues described the initial set of genes thought responsible for LQTS: $KCNQ1$, responsible for the Romano-Ward variant defined as LQT1; $KCNH2$, responsible for the Romano-Ward variant LQT2; $KCNQ1$ and $KCNH2$, responsible for the Romano-Ward variant LQT3; $ANKB$, responsible for the Romano-Ward variant LQT4; $KCNQ1$ and $KCNH2$, responsible for the Romano-Ward variant LQT5 and LQT6; and $KCNQ1$, responsible for the Jervell and Lange-Nielsen syndrome JLN1. In the last decade, several additional genes have been associated with LQTS and at present we can identify genetic mutations in almost 60% of clinically affected individuals. All the genes involved in the pathophysiology of LQTS encode subunits of cardiac ion channels with the exception of $KCNQ1$, which encodes the ion channel responsible for the slowly activating component of the delayed rectifier current $I_{Kr}$, which is a major determinant of phase 3 repolarization of the cardiac action potential. Mutations in $KCNQ1$ are responsible for the Romano-Ward variant defined as LQT1. Another form of Romano-Ward, LQT2, results from mutations in the $KCNH2$ gene that encodes the rapidly activating component of $I_{Kr}$. In LQT4, which encodes ankyrin, a chaperone molecule controlling the proper intracellular localization of several ion channels and transporters.

**Table 1. Genetic bases of the long QT syndrome.**

<table>
<thead>
<tr>
<th>Genetic variant</th>
<th>MIM-ID</th>
<th>Clinical phenotype</th>
<th>Inheritance</th>
<th>Locus</th>
<th>Gene</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>192500</td>
<td>Romano-Ward</td>
<td>AD</td>
<td>11p15.5</td>
<td>$KCNQ1$</td>
<td>KvLQT1</td>
</tr>
<tr>
<td>LQT2</td>
<td>152427</td>
<td>Romano-Ward</td>
<td>AD</td>
<td>7q35-q36</td>
<td>$KCNH2$</td>
<td>HERG</td>
</tr>
<tr>
<td>LQT3</td>
<td>603830</td>
<td>Romano-Ward</td>
<td>AD</td>
<td>3p21-p23</td>
<td>$SCN5A$</td>
<td>Nav 1.5</td>
</tr>
<tr>
<td>LQT4</td>
<td>600919</td>
<td>Romano-Ward</td>
<td>AD</td>
<td>4q25-q27</td>
<td>$ANKB$</td>
<td>Ankyrin</td>
</tr>
<tr>
<td>LQT5</td>
<td>176261</td>
<td>Romano-Ward</td>
<td>AD</td>
<td>21q22 1-p22.2</td>
<td>$KCNE1$</td>
<td>MinK</td>
</tr>
<tr>
<td>LQT6</td>
<td>603796</td>
<td>Romano-Ward</td>
<td>AD</td>
<td>21q22 1-p22.2</td>
<td>$KCNE2$</td>
<td>MiRP1</td>
</tr>
<tr>
<td>LQT7</td>
<td>170390</td>
<td>Andersen syndrome</td>
<td>AD</td>
<td>17q23-24</td>
<td>$KCNJ1$</td>
<td>Kir 2.1</td>
</tr>
<tr>
<td>LQT8</td>
<td>601005</td>
<td>Timothy syndrome</td>
<td>AD</td>
<td>12p13 3</td>
<td>$CACNA1C$</td>
<td>Cav 1.2</td>
</tr>
<tr>
<td>JLN1</td>
<td>220400</td>
<td>Jervell and Lange-Nielsen</td>
<td>AR</td>
<td>11p15.5</td>
<td>$KCNQ1$</td>
<td>KvLQT1</td>
</tr>
<tr>
<td>JLN2</td>
<td>220400</td>
<td>Jervell and Lange-Nielsen</td>
<td>AR</td>
<td>21q22 1-q22.2</td>
<td>$KCNE1$</td>
<td>MinK</td>
</tr>
</tbody>
</table>

*Only sporadic cases have been reported with the exception of one case of parental mosaicism. AD: autosomal dominant; AR: autosomal recessive.

Considering that at least 8 different genes (Table 1) have been linked to the disease, LOTS is no longer considered as a single entity, but as a group of diseases that share the feature of prolonged repolarization, while presenting different severity and prognosis, based on the underlying genetic defect.
and \( I_{K1} \), respectively. Jervell and Lange-Nielsen syndrome is caused by mutations either in the \textit{KCNQ1} gene or the \textit{KCNE1} gene, as in the LQT1 and the LQT5 Romano-Ward syndromes, but is inherited in a homozygous or compound heterozygous fashion.\(^7\) All the mutations in genes encoding potassium channels that have been identified in patients with LQTS produce a loss of function and therefore cause a decrease in repolarizing currents that leads to a prolongation of the QT interval.

**Sodium channel mutations: LQT3**

The cardiac sodium channel that conducts the depolarizing current \( I_{Na} \), responsible for the phase 0 upstroke of the cardiac action potential is encoded by the \textit{SCN5A} gene. Mutations in this gene have been linked to the Brugada syndrome,\(^14\) the Lev-Lenegre syndrome,\(^15\) and one variant of LOTS, called LQT3.\(^1\) Mutations in the \textit{SCN5A} gene, responsible for LQT3, induce a variety of electrophysiological abnormalities of the alpha subunit of the cardiac sodium channel, including the development of a late sustained current, a slower rate of current inactivation, a faster recovery from inactivation, and gating shifts;\(^16\) all these defects concur to enhance the sodium current and lead to QT interval prolongation.

**Ankyrin mutations: LQT4**

In the early 1990s, linkage analysis performed in a large French family described another variant of Romano-Ward syndrome, not associated with mutations in the already known genes. The genetic bases of this variant, identified as LQT4, are mutations in the ankyrin B gene, a protein that regulates the proper localization of ion channels in the membranes of cardiac myocytes.\(^11\) Therefore, although ankyrin B is not a cardiac ion channel, its function confirms a unifying pathogenetic mechanism implicating genes that encode ion channels or modifiers of ion channel function as central in causality of LQTS.

**Long QT interval and extracardiac phenotypes**

Recently, the genetic substrates of two other forms of autosomal dominant LOTS associated with extracardiac phenotypes have been discovered. Andersen syndrome, known as LQT7, presents three main characteristics: QT prolongation with giant U wave and ventricular arrhythmias, potassium-sensitive periodic paralysis, and dysmorphisms (hypertelorism, micrognathia, short stature, broad forehead).\(^17\) It is remarkable that even when QT prolongation is present and ventricular arrhythmias are common, very few cases of SCD have been reported in patients affected by Andersen syndrome. Approximately 60% of subjects with Andersen syndrome carry mutations in the \textit{KCNJ2} gene,\(^12\) which encodes the cardiac ion channel for the inwardly rectifying current \( I_{K1} \). \( I_{K1} \) participates in the late phase of repolarization and in the maintenance of a negative resting membrane potential. Mutations in this channel associated with Andersen syndrome are loss-of-function mutations through a dominant negative effect. Computer simulations demonstrated that impairment in \( I_{K1} \) prolongs the terminal phase of action potential repolarization and induces spontaneous arrhythmias.\(^12\)

At the end of 2004, collaborative work between our group and that of Keating led to elucidation of the genetic substrate of a new form of LOTS with an extracardiac phenotype, called Timothy syndrome.\(^13\) Here, QT prolongation is associated with syndactyly of hands or feet, intermittent hypoglycemia, immune deficiency, paroxysmal hypothermia, and cognitive abnormalities similar to autism. In afflicted individuals, QT interval is markedly prolonged, often exceeding 550 ms, such that functional 2:1 atrioventricular block may evolve. T-wave alternans is also frequent. Timothy syndrome has been linked to a single missense mutation in the \textit{CACNA1C} gene, encoding for the L-type voltage-gated channel, \( I_{Ca,L} \). This mutation leads to gain of function in the current, by delaying its inactivation. The resultant net increase in \( I_{Ca,L} \) is consistent with prolongation of the QT interval duration.\(^13\)

**GENOTYPE-PHENOTYPE CORRELATIONS AND RISK STRATIFICATION**

The collection of large databases of patients in the United States and in Europe, beginning with the first descriptions of the syndrome, has resulted in access to a large number of genotyped individuals. It has become evident that three forms of LOTS syndrome are the most frequently represented among genotyped individuals. LQT1 accounts for almost 50% of affected patients, LQT2 is present in 35% to 40%; and LQT3 is recognized in approximately 15%. Thanks to the availability of such registries, gene-specific ECG patterns (Figure 1, next page) and risk stratification algorithms based on the different genetic substrates have recently entered clinical practice.

LQT1 patients experience most of their symptoms during physical exercise, mainly while swimming. Loud noise or emotions represent the most common triggers in LQT2. In contrast, individuals afflicted with the LQT3 variant are at major risk...
of arrhythmic events while resting or sleeping. This information has had an important clinical impact, as it has led to preventive strategies, for example, avoidance of strenuous exercise in children with LQT1, and eliminating sources of abrupt noise, such as alarm clocks or telephones in bedrooms of children with LQT2.

Genotype also exerts a strong influence on the clinical outcome of patients. We have published data on 647 genotyped patients, demonstrating that LQT1 subjects have a lower probability of developing symptoms, even if left untreated, as compared with individuals with LQT2 and LQT3. Moreover, female gender is a strong risk indicator in the LQT2 genotype, while in LQT3, male gender is associated with an increased risk. (Figure 2). The presence of a QT interval >500 ms is a further strong risk indicator in both LQT1 and LQT2 genotypes.

These results have significant clinical impact, as follows: a clinical cardiologist who knows that a LQTS patient belongs to a specific genotype can avail himself of information predicting the natural history of the disease in that subject. This facilitates provision of better protection based on knowledge of outcomes associated with the different genetic defects. In the near future, we predict that clinicians will incorporate genetic results in their armamentarium of prognostic parameters to define the clinical profiles of individual patients. One example of how genotyping can facilitate understanding of prognosis is seen in the Jervell and Lange-Nielsen syndrome, which is a highly malignant form of LQTS. Families of infants born with this genotype can expect early occurrence of symptoms, by age 8, approximately 90% of subjects have had their first cardiac event.

ANTIADRENERGIC THERAPY AND DEVICE INDICATIONS

Since most of symptoms in LQTS are triggered by an increase in adrenergic tone, antiadrenergic therapy, principally β-blockers, has been considered the main treatment for the disease. Data from the International Registry of LQTS showed that β-blockers significantly reduce the incidence of symptoms.

Figure 1. Genotype-specific ECG patterns in the three major LQTS variants: LQT1, broad-based and smooth T wave; LQT2, low amplitude, notched T wave; LQT3, straight ST segment with small, peaked T waves.

Figure 2. Risk stratification in the long QT syndrome (LQTS). The figure is based on the quantification of risk of a first cardiac event (syncope or cardiac arrest) before any LQTS-related therapy and at age <40 years. Three major risk groups are identified, which include subgroups of patients with similar risk level according to genotype, QT interval, and gender.

ever, these drugs do not confer full protection in all patients. To illustrate this, the same study revealed that among patients symptomatic before starting β-blockers, 32% experienced a recurrence within 5 years of onset of therapy. Moreover, among patients who experienced an aborted cardiac arrest before starting therapy, 14% experienced another arrest within 5 years, despite therapy.¹⁹

Our group has investigated the relationship of the response to medical therapy to the different LQTS genotypes.⁶ Our analysis of 335 genotyped patients demonstrated that LQT2 and LQT3 forms have an increased risk of recurrences on therapy as compared with LQT1 (Figure 3). Other risk indicators of failure of medical treatment were the presence of a QT interval >500 ms and the history of a first cardiac event before age 7. This is another example of how information derived by genetic analysis is helpful in clinical practice: when treating a symptomatic LQT2 or LQT3 patient who presents a very prolonged QT interval, physicians should consider adding an implantable cardioverter-defibrillator (ICD) to β-blocker therapy.

Less reassuring are the data on the Jervell and Lange-Nielsen syndrome. Preliminary data¹⁸ on the largest series of patients reported showed that the rate of recurrences during β-blocker treatment was about 50%. Taking into account that Jervell and Lange-Nielsen subjects have a high incidence of symptoms, especially in early childhood, these patients comprise a group in which implantation of an ICD should be carefully considered.

Thus far, only retrospective studies have been published on the protective role of ICDs in LQTS. The largest series, reported by Zareba et al.,²⁰ compared mortality in two groups of patients: one receiving β-blocker therapy, the other, β-blockers + ICD. In the ICD group the 3-year mortality rate was 2%, while in the β-blocker group it was 9%, thus confirming the utility of ICD therapy in high-risk patients.

Before the present availability of ICD therapy, another antiadrenergic treatment was proposed for LQTS patients unresponsive to β-blockers: left cardiac sympathetic denervation (LCSD), in which the lower part of the stellate ganglion and the first 3 to 5 thoracic ganglia are surgically removed. The rationale for this intervention was based on the arrhythmogenic potential of left-stellate ganglion stimulation and the antifibrillatory effect of stellectomy in animal models.²¹ A recent large report of the long-term effect of this intervention has shown a 10-year survival rate of 90% in patients treated by LCSD.²² At present, there are no data on whether the efficacy of left cardiac denervation is influenced by the genotype of patients.

HOW TO DEAL WITH ASYMPTOMATIC PATIENTS

One open issue in the management of LQTS relates to whether asymptomatic subjects should be treated with antiadrenergic therapy for the primary prevention of sudden cardiac death. No data exist to prove the long-term benefit of administration of β-blockers to asymptomatic individuals. However, most of the physicians with large experience in the treatment of LQTS patients agree on the opportunity of giving prophylactic antiadrenergic therapy to all patients with LQTS diagnosis irrespective of their symptoms. It is unknown whether any of the different genetic forms of LQTS may benefit more than others from the prophylactic administration of β-blockers.
FUTURE DIRECTIONS: GENE-SPECIFIC THERAPY

A novel direction in the management of LQTS is based on the effort to use drugs to specifically counteract the electrophysiological consequences of the genetic defects. This approach is often called "gene-specific therapy" to express the concept that it is a treatment tailored to correct the consequences of the genetic abnormalities identified in the patients. In the next few paragraphs we will discuss the most recent views on gene-specific therapy for different variants of the long QT syndrome.

Gene-specific targeting of LQT3-related SCN5A mutations

Mutations linked to the LQT3 genotype result in increased inward sodium current that depolarizes the cardiac cell during early repolarization. For this reason, the therapeutic potential of sodium channel blockers has been investigated. Preliminary experiments demonstrated that mexiletine shortened the action potential in cardiac myocytes. Later, mexiletine-induced shortening of QT interval duration was shown in small series of LQT3 patients and short-term efficacy was reported. However, long-term data demonstrating improved survival in this group are still lacking. Another sodium channel blocker that has been proposed for use in LQT3 is flecainide. Unfortunately, this drug can elicit ST-segment elevation, resembling a Brugada syndrome ECG pattern in many patients. There-fore, test dosages of flecainide should be administered to all LQT3 patients in whom its use is considered, and therapy should be limited to those who do not manifest ST-segment elevation. Experimental data from our laboratory have suggested that the efficacy of sodium channel blockers may be predicted by the biophysical properties of a mutation. For example, in vitro testing of mexiletine on two SCN5A mutants (P1332L, Y1795C) led to reliable "prediction" of the response to the drug of the mutation carriers. The same study also showed that a specific mutation can respond differently to different sodium channel blockers: for example, the missense mutation D1790G is blocked by flecainide, but not by lidocaine.

In conclusion, clinical data suggest that sodium channel blockers, mainly mexiletine, may be used as a therapy, together with β-blockers and ICD in the attempt to prevent ventricular arrhythmias in high-risk LQT3 patients.

Gene-specific therapy for loss-of-function mutations in potassium channels

No attempts to find a gene-specific treatment in LQT1 have been reported. This is consistent with the demonstration that β-blockers are highly effective in this group and can prevent SCD occurrence in the great majority of cases. However, the characteristics of IKr channels and the incomplete protection that β-blockers confer to LQT2 patients have led to bench investigations of the possibility of correcting the physiological consequences of KCNH2 mutations. For example, extracellular K+ increases the conductance of IKr channels. On this basis, a pilot study has begun to investigate whether an increase in extracellular plasma levels of K+ via oral supplements can shorten the QT intervals of LQT2 patients. However, it will be important to demonstrate if this treatment prevents ventricular arrhythmias before proposing it as adjunctive therapy. An important functional consequence of some KCNH2 mutations is a defective intracellular trafficking of the mutant protein. Zhou et al showed that the IKr blockers E4031, astemizole, and cisapride can restore trafficking of the protein into the membrane. Unfortunately, because these drugs block IKr, they induce an acquired LQTS that reproduces the clinical outcomes of LQT2-related mutations. Moreover, the rescue in protein trafficking occurs at drug concentrations at which channel blocking occurs; hence, these drugs cannot be proposed as therapy for LQT2. Other drugs, like fexofenadine and thapsigargin, have shown a promising effect at the experimental level, as they restored the trafficking without blocking IKr. While these studies remain at the level of cellular investigation, they represent a promising field for identifying novel pharmacological approaches for LQT2 therapy.

Gene-specific therapy for calcium channel mutation

Timothy syndrome has been diagnosed in only 13 families. Therapy is mainly based on empiricism and no indication of effectiveness of β-blockers is available. Since the mutation linked to this phenotype provokes an increase in ICa,L similar to that proposed in LQT3 patients, the possible role of calcium channel blockers has been investigated. In one child with Timothy syndrome, we observed that the acute administration of diltiazem was able to interrupt an arrhythmic storm even without shortening the QT interval duration. Therefore, until larger series of patients are identified, calcium channel blockers cannot be proposed as an effective gene-specific therapy for Timothy syndrome.
CONCLUSIONS

In the past decade, molecular biology has led to clarification of the genetic background of several forms of idiopathic ventricular fibrillation. In the case of LQTS, genetics has already entered clinical cardiology, demonstrating a powerful role for diagnosis and a strong potential for novel risk-stratification strategies. The discovery of functional consequences of mutations related to LQTS has already identified a new, exciting challenge for this field: that is, the attempt to find a molecular cure for these patients, based on their specific gene defects.

REFERENCES


Differential response to Na+ channel blockade, beta-adrenergic stimulation, and rapid pacing in a cellular model mimicking the SCN5A and HERG defects present in the long-QT syndrome. 

Long QT syndrome patients with mutations of the SCN5A and HERG genes have differential responses to Na+ channel blockade and to increases in heart rate. Implications for gene-specific therapy. 

Effects of flecainide in patients with new SCN5A mutation: mutation-specific therapy for long-QT syndrome? 

The elusive link between LQT3 and Brugada syndrome: the role of flecainide challenge. 

27. Rivolta I, Giarda E, Nastoli J, Ronchetti E, Napolitano C, Priori SG. 
In vitro characterization of the electrophysiological effects of mexiletine on SCN5A mutants predicts clinical response in LQT3 patients. 

28. Sanguinetti MC, Jurkiewicz NK. 
Delayed rectifier outward K+ current is composed of two currents in guinea pig atrial cells. 

Genetically defined therapy of inherited long-QT syndrome. Correction of abnormal repolarization by potassium. 

30. Zhou Z, Gong O, January CT. 
Correction of defective protein trafficking of a mutant HERG potassium channel in human long QT syndrome. Pharmacological and temperature effects. 

31. Rajamani S, Anderson CL, Anson BD, January CT. 
Pharmacological rescue of human K+ channel long-QT2 mutations: human ether-a-go-go-related gene rescue without block. 
How will genomic approaches translate into clinical applications in sudden cardiac death?

Peter M. Spooner, PhD

Associate Professor of Cardiology - Department of Medicine - Donald W. Reynolds Cardiovascular Clinical Center
Johns Hopkins University - Baltimore, Md - USA

The Human Genome and Haplotyping mapping projects provide powerful new technologies for identifying gene variations that contribute to complex conditions like the susceptibility to sudden cardiac death (SCD). “Genomic” approaches to SCD, in contrast to “genetic” views focused on “high-impact” mutations in a small number of genes, seek to identify minor variations in many different DNA sequences, each of which may convey subtle dimensions of arrhythmia risk in heart disease. Just as family-based linkage studies on the monogenic Mendelian syndromes, like the various long QT conditions, facilitated diagnosis of rare arrhythmias in families, genomics promises insight into the “low-impact” variations distributed widely throughout the population. Clinical applications, eg, in risk stratification, therapy selection, and SCD prevention, are anticipated in the very foreseeable future.

**Genomics, while still an emerging discipline, appears poised to offer a new generation of strategies and technologies to advance our fundamental understanding of electrical pathologies that lead to sudden cardiac death (SCD). New concepts of how minor differences in hundreds of genes, shared by thousands of individuals, affect disease susceptibility or resistance, and how they function collectively to alter disease expression in a range of environments, are providing truly revolutionary insights on many conditions that result in fatal arrhythmias. Investigators in academia as well as in the biotechnology and drug industries are rapidly exploiting these approaches in developing technologies that promise: (i) improved clinical tools to screen for common gene variants that affect SCD incidence and susceptibility; (ii) improved algorithms for assessment of SCD risk in patients with diverse cardiac comorbidities; (iii) better individually targeted therapies and guidelines for avoidance of proarrhythmic agents and environmental exposures; (iv) more accurate outcome prognoses; and (v) improved clinical guidelines for allocation of limited or expensive medical resources, such as implantable defibrillators. While the principal benefits of “genomic studies” are anticipated to involve better understanding of SCD susceptibility in complex, that is, polygenic “acquired” cardiac conditions—such as heart failure and ischemic infarction, which collectively result in more than 300,000 SCDs in the US each year—these methods should also help resolve perplexing issues in rare-disease arrhythmia research, such as “variable penetrance” and differences in phenotype “expressivity” observed in patients with “monogenic” or Mendelian arrhythmia syndromes.1**

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>dbSNP</td>
<td>Single Nucleotide Polymorphism Database</td>
</tr>
<tr>
<td>GWA</td>
<td>Genome-wide association</td>
</tr>
<tr>
<td>HGP</td>
<td>Human Genome Project</td>
</tr>
<tr>
<td>LD</td>
<td>Linkage disequilibrium</td>
</tr>
<tr>
<td>LQTS</td>
<td>Long QT syndrome</td>
</tr>
<tr>
<td>MAF</td>
<td>Minor allele frequency</td>
</tr>
<tr>
<td>SCD</td>
<td>Sudden cardiac death</td>
</tr>
<tr>
<td>siRNA</td>
<td>Small interfering RNA</td>
</tr>
<tr>
<td>SNP</td>
<td>Single nucleotide polymorphism</td>
</tr>
</tbody>
</table>

**GENETIC VERSUS GENOMIC**

The basis by which such impressive accomplishments may be achieved rests in the hypothesis that what has been ascribed to the inheritable component of “family history” on SCD incidence, represents only the tip of larger, more obscure dimensions of influence exerted by combinations and permutations of “low-
How will genomic approaches translate into clinical applications? - Spooner

Changes in function in one gene affect function and expression of other genes and regulatory sequences within the genome itself. This greatly complicates distinguishing primary and secondary causation and identification of influences, such as how gene variation may affect expression patterns throughout development, aging, or disease. Understanding complex genetic changes, like those encountered in structural and electrical remodeling using single-gene approaches, without consideration of intragenic or gene environment interactions, would be an impossible task. Combined with advances in expression analysis, however, it is one that can be addressed with a fundamental knowledge of the genomic diversity in the population affected. The likelihood that multigene interactions may play a role in cardiac arrhythmogenesis seems far from speculative, as recently illustrated, for example, by a report indicating that a single-base mutation in the cardiac SCN5A Na channel gene resulted not just in anticipated disturbances in electrogenesis, but delayed secondary enhancements in myocardial structure and fibrosis, normally considered characteristic of the aging heart. If confirmed, this extraordinary finding could be instructive in providing clues on how a primary genetic lesion elicits complex cascading influences on unrelated downstream pathways involving multiple genes. Such approaches may thus offer exciting new views on intragenic events important in arrhythmia pathology and the regulatory continuum between genetics and genomics that may be involved in their generation.

GENOMIC STRUCTURE AND VARIATION

Two extraordinary accomplishments are responsible for our increasing ability to pursue questions within this complicated new world of intragenic regulation and functional genomics. The first is the completion of a “consensus” human genome sequence, a near complete nucleotide-by-nucleotide delineation of each of the human 23 chromosomes in the “Human Genome Project” (HGP). The second is completion of the first phase of an effort to catalog millions of genetic variants, those which have little individual impact on phenotypes, but which collectively define the differences between individuals, in a single database, the Single Nucleotide Polymorphism Database (dbSNP), developed by the International Hap (haplotype) Map project. HapMap was undertaken to provide chromosomal positional information on more than 5 million polymorphic single nucleotide polymorphism (SNP) markers identified within the genomes of 269 reference individuals from four populations (White European–derived Americans, Chinese Han, black Nigerian Yoruba, and native Japanese), and was designed specifically to facilitate dissection of “polygenic” disease inheritance.

Largely completed at the end of 2004, the HGP established a consensus genomic database consisting of ≈3.08 giga nucleotide bases (www.ncbi.nlm.nih.gov/Genbank/index). Surprisingly, this massive amount of genetic information was found to code for no more than approximately 20 000 to 24 000 different genes. These were assembled from sequences in ≈231 667 coding “exons,” whose multiplying permutations, once translated into specific amino acid sequences, result in an approximately 8- to 10-fold greater number of different individual proteins. Coding exonic sequences are not linearly contiguous, but instead are interrupted by many thousands of noncoding “introns,” and related regions with functional and
nonfunctional roles. These include regulatory elements, such as promoters and enhancers, as well as others that specify functional, nontranslated RNAs, e.g., inhibitory small interfering RNAs (siRNAs), and transfer and ribosomal RNAs. HGP also revealed vestigial DNA regions, for example, “pseudogenes,” which are dead, nonfunctional genes, and vast regions of untranscribed, often repetitive sequences whose function and architecture remain unknown.

Interestingly, only about 5% of the genome was found to directly code for functional proteins. This diversity and size of the genome as we know it now underscores one of the major challenges of genetic studies. The number of potential sites where mutations could occur is inordinately huge, while the percentage of those that might be detected via a change in primary amino acid sequence in a specific protein is minuscule. If mutagenesis is indeed random, which appears at least partly to be the case, then one might expect the majority of functional variants to occur outside regions of exonic coding, and outside the universe of variation described in Mendelian views of how genetic variation influences disease incidence and expression.

Another important observation from these two major gene projects was that differences in DNA sequence between any two individuals are probably defined by no more than 500 to 1000 bases. The common of those discovered are the SNPs, or single-base transversions, like replacing a T allele with A, and it is these variants, millions of them, that have been and continue to be catalogued in the dbSNP. This plethora of markers is a great advantage in providing a very dense map for determining chromosomal positions. From a mechanistic perspective, it is thought the majority are functionally benign and of little individual significance, although this remains largely an assumption. On average approximately 100 to 300 SNPs were observed in a gene of “average size” and of these only 40% were found to be “common,” that is, distributed with a minor allele frequency (MAF) of >5% across a population, making it easier to identify those that may be functionally important. Recognizing that identification of susceptibility alleles using conventional linkage and positional cloning methods would be high impossible in the face of this extensive amount of variation, HapMap investigators focused on developing a simplified means to facilitate identification of disease-related variants within this universe without having to rely on base-by base resequencing methods. Their approach, termed “haplotype” mapping, takes advantage of the fact that recombination within chromosomes is less likely to separate sequences closer together, than those more widely separated. Physically congruent sequences that travel together from one generation to another can be represented in block-like structures, or “haplotypes” amenable to statistical analysis once their nature and frequency have been established. Variants in high “linkage disequilibrium,” or association, with one of the mapped markers or “tag-SNPs” listed in the dbSNP may thus be identified by looking for signal changes in tag-SNP distributions representative of the entire region. The concept of using tag-SNPs to simplify interrogation of much larger regions of genomic sequence of a specific individual is illustrated in Figure 1 (next page), while Figure 2 (page 217) illustrates how many such analyses within a particular population can be used to map the full range of variation and linkage disequilibrium (LD) across specific regions of individual chromosomes. The potential and limitations of using SNP maps in identifying disease-associated gene mutations has been discussed extensively in the recent literature and is clearly a most powerful approach and one that continues to evolve.

**VARIATION AND SUSCEPTIBILITY TO ARRHYTHMIAS**

Together, the consensus genome and haplotype projects provide, for the first time, an ability to evaluate whether what has been termed the “common-disease / common gene variant” hypothesis applies to precipitating the conditions that lead to arrhythmia and SCD. Dissection of the arrhythmogenic Mendelian channelopathies was possible because the “high-impact” channel mutations causing these syndromes result in easily recognized phenotypes (ie, syncope, QTc prolongation, and SCD) allowing linkage to specific chromosomal regions of interest using widely dispersed conventional chromosomal markers. Positional cloning, fine mapping, and exploration of nearby candidate genes then provided the pathway to identification of affected genes, a process that often took years. While cumbersome, this process resulted in much progress; yet what those methods could not provide was an unbiased means to screen for mutations or polymorphisms outside the distribution of known previously identified genes. Since the identity of less than half of the human complement of coding genes remains to be discovered, and because little was known regarding regulatory regions of the genome, this resulted in major dilemma in the search for unknown variants, especially those with but minor influences on phenotype. Nevertheless, as the cat-
How will genomic approaches translate into clinical applications? - Spooner


alog of rare channel mutations expanded, (eg, see http://pc4.fsm.it:81/cardmoc/htm for a catalog of hundreds of LQTS-inducing mutations) this approach became such a predominant paradigm, that it led to the hypothesis that population-wide distributions of equally rare, but less functionally disruptive, “low-impact” or “subclinical” mutations in these same molecular entities might also underlie SCD susceptibility in more common “acquired” cardiac diseases. This “rare variant/common disease” channel-delimited view of genomic causation contrasted with the predominant “common variant/common disease” view developed in the study of other complex conditions, such as hypertension or atherosclerosis. While addressing a logical target in an implicated biological process — membrane electrogenesis — the “rare channel variant” view was limited in that it failed to acknowledge potential contributions of genomic variation in nonchannel pathways, eg, those affecting sympathetic-parasympathetic balance or lead to conduction abnormalities that support reentry. Determining the extent to which either the “rare” or “common” variant views contributes to SCD susceptibility in the population at large is a central issue in finding new approaches to therapy. To wit: if rare variants in multiple genes predominate, therapies applicable to larger numbers of patients will be difficult to identify, while if common variants can be identified, then new therapies targeted to those specific pathways might be more readily achievable. As is often the case in biology, and as appears with other complex disease susceptibilities, for example those that lead to familial forms of atherosclerosis, it may be that rare and common variants both contribute in different ways with differing comorbidities.

Meanwhile, convincing evidence on the problem is scarce. To date, there has been but one substantiated finding suggesting common ion channel polymorphisms play a significant role in common, as opposed to rare, SCD susceptibilities. The S1103Y polymorphism in the cardiac SCN5A gene reported present in 5% to 15% of African-Americans was linked by one study to enhanced arrhythmia susceptibility in the context of concurrent exposure to a proarrhythmic drug. This same variant was subsequently identified at higher than expected frequencies in a series of unexplained SCDs in US blacks. With this exception, screening for common variants in ion channel–related pathways has notably failed to provide substantive evidence that mechanisms of this nature play a significant role. Even the most comprehensive screens done to date show that while both polymorphisms and mutations occur with high frequency in myocardial ion channel coding sequences, reliable associations with risk-conferring phenotypes are not significant. Lack of causative relevance is also supported by studies showing that prevalence and distribution of rare and common channel gene variants is not different in patients referred for LQTS gene diagnosis and those in unaffected control subjects. The results
of these and similar studies suggest that the search for heritable influences that affect SCD susceptibility observed in prior epidemiological studies needs to be extended well beyond the present channel centric focus if we are to make progress on the common disease problem.

**GENOME-WIDE ASSOCIATIONS**

Availability of the new genomic databases and continuing developments in genome-wide association (GWA) studies thus provide a timely opportunity to explore additional influences. GWA studies are based on the recent development of high-density microchip array technologies, which test for variation in specific DNA sequences, such as tag SNPs, in very small samples. Their availability has enabled an ability to look at tag SNP distributions systematically in thousands of individuals and at moderate, though not inconsiderable, cost. Current estimates are that a chip marker set of 500,000 to 1,000,000 tag SNPs is probably sufficient to detect variants present at MAFs of ≈5%, assuming unambiguous phenotypes. Chip sets with the ability to assay between 100,000 and 500,000 tag SNPs have become available commercially and represent a critical advance in this field. Figure 3 illustrates a general approach to applying this technology toward the identification of new mutations as well as common variants. Many such studies today use arrays, as suggested in the figure, simply to detect alterations in tag SNPs, comparing samples from case-control population studies, to look for associations with a given disease phenotype.

While still evolving, it is apparent that GWA approaches will be useful in identifying causal elements for many complex diseases with robust statistical power and discrimination. The first issue in using this approach is obviously to secure DNA from a suitable number of individ-
How will genomic approaches translate into clinical applications?

Figure 3. Whole genome association for common diseases. Individual steps and considerations in using genome-wide association (GWA) studies to identify common gene variants (e.g., single nucleotide polymorphisms [SNP] distributions) in searching for causal variants in candidate genes. Characteristics encountered in the dissection of “common” complex diseases are suggested in the center of the upper panel, with the bottom panel showing possible sites of chromosomal mutation within a small sequence of coding and regulatory elements.

Figure modified from a schematic provided courtesy of Dr D. Arking. All rights reserved.

Dialogue in Cardiovascular Medicine - Vol 11 No. 3 2006

How will genomic approaches translate into clinical applications?

How will genomic approaches translate into clinical applications?

Whole genome

Multiple genes
Low-impact
Common variants
Coding mutations
Regulatory mutations
Genes & environment

Candidate genes

Marker SNP
Disease mutation
Marker SNP
Marker SNP
Identify candidate genes
haplotype associations

SNP arrays concordance with consensus sequence genomic position

Intron
Marker SNP
Exon
Regulatory elements: promoters, enhancers, etc

Figure 3. Whole genome association for common diseases. Individual steps and considerations in using genome-wide association (GWA) studies to identify common gene variants (e.g., single nucleotide polymorphisms [SNP] distributions) in searching for causal variants in candidate genes. Characteristics encountered in the dissection of “common” complex diseases are suggested in the center of the upper panel, with the bottom panel showing possible sites of chromosomal mutation within a small sequence of coding and regulatory elements.

Figure modified from a schematic provided courtesy of Dr D. Arking. All rights reserved.

One approach used effectively in dealing with this problem in investigations of other multifactorial diseases (e.g., hypertension) is that of focusing instead on heritable intermediate phenotypes, chosen to include different dimensions of risk believed important in determining outcomes. Figure 4 illustrates one view of how this concept can be applied to the SCD problem. With such a design it is then possible to assess how strongly patterns of gene variation contribute to a risk-conferring intermediate phenotype. In the case of SCD susceptibility, one might use, for example, electrocardiographic QTc prolongation as a measure of repolarization risk, heart rate or QTc variability as a measure of autonomic risk, and QRS width or other parameters as a measure of conduction. This is the strategy our cardiovascular genomics group has begun to pursue using GWA to identify tag SNPs associated with extremes in the distribution of QTc in normal subjects. Variant alleles and haplotypes identified on Affymetrix gene chips were subsequently genotyped in SCD cases and compared with unaffected controls. Our initial experiments assayed ≈120,000 tag SNP markers in a multistage analysis of more than 4000 normal subjects. QTc was chosen first as it is moderately heritable (30%-40%) and its prolongation is associated with elevated SCD risk in community-wide and drug-induced SCD mortality studies. Our results suggested that ion channel variants may have moderating effects, the major QT effect was conveyed by variation in the gene CAPON, while the variant allele is commonly distributed in the population examined (MAF >30%), and located in a regulatory 5′ region of the gene. This was a fascinating result as this gene has not previously been associated with cardiac electrical function. We do not yet know if this variant acts by altering the translation of CAPON, or whether the effect is entirely mediated via QTc changes. We do know CAPON encodes a regulatory ligand of neuronal nitric oxide synthase (nNOS) present in nerve and heart, and is involved in Ca regulation, but the biology of the effect uncovered remains largely unknown. While it is too soon to speculate on our functional relevance, initial findings, if confirmed, would represent a significant new step in understanding the biological and medical underpinnings of SCD risk in patients.
FUTURE APPLICATIONS

Back to the question: How will genomic approaches translate into clinical applications? Obviously, answers and identification of relevant arrhythmogenic pathways are not yet available, but it is clear that new diagnostic applications are well within our grasp. Whether constellations of risk-conferring alleles can be identified in common arrhythmia-prone syndromes is a problem only beginning to be studied and it is likely, as with other such searches, that many false positive and negative findings will be encountered on the way.

Developments to date suggest improvements in SCD risk analysis can be achieved in the not too distant future and one might even envision development of clinically applicable dedicated gene chip technologies, like those recently commercialized to assess cytochrome P-450 gene variants affecting drug metabolism (Figure 5). It is also worth noting that high throughput approaches have been developed to screen for previously identified channel mutations in patients suspected of harboring susceptibility to one of the rare SCD syndromes such as LQTS or Brugada syndrome, as well as so-called “acquired LQTS,” which may occur in response to drugs that interact with myocardial K channels.23 Such analyses are now commercially available and can be critical in assessing risk in individuals suspected of inheriting channel mutations. Application of genomic technologies in such families may thus be helpful in understanding causative factors, which determine expressivity and penetrance in specific patients.

![Figure 4. Potential intermediate phenotypes for sudden cardiac death susceptibility. Primary risks and intermediate phenotypes useful in identifying genomic susceptibilities for ventricular tachycardias (VT), ventricular fibrillation (VF), and sudden cardiac death (SCD). As reliable risk stratifiers for SCD have not been discovered, combinations of influences, including gene variation, environmental factors, and comorbidities may be useful collectively in helping predict enhancements in susceptibility in different subjects. The three intermediate electrophysiological phenotypes illustrated each have a significant component of heritability and provide insight into different dimensions of cardiac electrical instability, assessable using electrocardiography and clinical data readily assembled from the large populations required for such studies. In the case of the variables illustrated, the electrocardiographic QT duration and measures such as T-wave alternans can be construed as indices of delayed repolarization; heart rate, heart rate variability, and QT variability might be considered parameters that reflect alterations in autonomic tone, while QRS duration, or signal-averaged ECG data provide information regarding heterogeneity in pathways of conduction. Looking for patterns of common genomic variation in each of these dimensions is suggested as one way to provide useful information regarding which risks may be relevant to a specific patient. One advantage of using intermediate phenotypes, as opposed to a binary clinical outcome event, like death, is that the number of influences affecting each primary risk is reduced in complexity and can be analyzed in greater isolation.](image)

![Figure 5. Diagnostic Affymetrix Microarray Gene Chip. Example of diagnostic gene chip technology presently commercially available and CE approved. Sample shown is a Roche Diagnostics Affymetrix Amplichip CYP450 test set, which detects variations in two genes coding for cytochromes P450-2D6 and P450-3C19. Specific variations in these two genes are predictive of “poor,” “intermediate,” or “rapid” drug metabolizing phenotypes useful in predicting drug responses and potential adverse interactions in individual patients. Reproduced courtesy of Roche-Affymetrix Diagnostics Inc. All rights reserved.](image)
Thus, while speculative, the "genomic" tea leaves are promising, and it is encouraging that prospects of success are sufficiently exciting that literally dozens of pharmaceutical and biotechnology concerns are investing tens of millions of dollars, pounds, yen, yuan, and euros in exploring this very possibility.

Dr Peter M. Spooner gratefully acknowledges support provided by a Clinical Cardiovascular Center grant from the D. W. Reynolds Foundation and the Leducq Foundation’s Alliance Against Sudden Cardiac Death Transatlantic Network of Excellence.

REFERENCES

1. Priori SG.
   Inherited arrhythmogenic diseases: the complexity beyond monogenic disorders.

2. Wilde AA, Bezzina CR.
   Genetics of cardiac arrhythmias.
   Heart. 2005;91:1352-1358.

3. Spooner P.
   Genetic factors underlying susceptibility to common arrhythmias.

4. Morita H, Seidman J, Seidman CE.
   Genetic causes of human heart failure.

5. van Veen TA, Stein M, Royer A, et al.
   Impaired impulse propagation in Scn5a-knockout mice: combined contribution of excitability, connexin expression, and tissue architecture in relation to aging.

   Finishing the euchromatic sequence of the human genome.

   A haplotype map of the human genome.

8. Crawford DC, Akey DT, Nickerson DA.
   The patterns of natural variation in human genes.

   The international HapMap Project.

10. Crawford DC, Nickerson DA.
    Definition and clinical importance of haplotypes.

11. Farrall M, Morris AP.
    Gearing up for genome-wide gene-association studies.

12. Botstein D, Risch N.
    Discovering genotypes underlying human phenotypes: past successes for mendelian disease, future approaches for complex disease.

13. Keating MT, Sanguinetti MC.
    Molecular and cellular mechanisms of cardiac arrhythmias.

    Multiple rare alleles contribute to low plasma levels of HDL cholesterol.

    Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9.

    Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia.

    Role of SCN5A Y1102 polymorphism in sudden cardiac death in blacks.

    Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing.

    Predicting sudden death in the population: the Paris Prospective Study I.

20. de Bakker PI, Yelensky R, Pe’er I, Gabriel SB, Daly MJ, Altshuler D.
    Efficiency and power in genetic association studies.

    Genomics in sudden cardiac death.

    A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization.

23. Roden DM, Viswanathan PC.
    Genetics of acquired long QT syndrome.
How can we reduce sudden death in the community?

Graham Nichol*, MD, MPH; Myron L. Weisfeldt†, MD

*Medic One Chair - University of Washington - Harborview Center for Prehospital Emergency Care - Seattle, Wash - USA
†Sir William Osler Professor of Medicine - Johns Hopkins University School of Medicine - Baltimore, Md - USA

Cardiac arrest outcomes have not improved for 30 years. Survival from defibrillation within 3 minutes of ventricular tachycardia/fibrillation (VT/VF) onset is 70% to 80%. However, VT/VF accounts for only 30% to 40% of arrests. In non-VT/VF arrest and VT/VF arrest without an automated external defibrillator (AED) on site, survival from manual cardiopulmonary resuscitation (CPR) is 2% to 8%, vs 20% to 30% from witnessed arrests in communities offering bystander CPR and rapid arrival of trained personnel with an AED. Hence the drive to simplify CPR instruction, emphasizing proper chest compression, full release between compressions, and avoidance of overventilation. Drugs and devices other than defibrillators have demonstrated no long-term survival benefit. Currently, concentration of effort is on simplifying CPR instruction with emphasis on proper chest compression. Overventilation and lack of full release between chest compressions are of importance in performance of manual CPR. Hypothermia may benefit those who survive to reach the hospital, but remain unconscious. Community efforts and technology advances do hold considerable hope for improving quality survival from cardiac arrest.

DEFINITION

Cardiac arrest is the “cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation.”1 This syndrome leads to death within 15 to 30 minutes from onset of first symptoms. First symptoms are most commonly loss of consciousness or cessation of spontaneous breathing. No pulse is detectable. If an emergency medical service (EMS) provider or physician did not witness the event, then it may be difficult to ascertain whether a cardiac arrest has occurred. “Presumed cardiac etiology” is frequently used to subcategorize cardiac arrest, but can only accurately be determined by conducting a postmortem examination. Since it is impractical to conduct an autopsy on every out-

SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
</tr>
<tr>
<td>AED</td>
<td>automated external defibrillator</td>
</tr>
<tr>
<td>CPR</td>
<td>cardiopulmonary resuscitation</td>
</tr>
<tr>
<td>EMS</td>
<td>emergency medical service</td>
</tr>
<tr>
<td>ICD</td>
<td>implantable cardioverter-defibrillator</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>PAD</td>
<td>public-access defibrillation</td>
</tr>
<tr>
<td>VF</td>
<td>ventricular fibrillation</td>
</tr>
<tr>
<td>VT</td>
<td>ventricular tachycardia</td>
</tr>
</tbody>
</table>

Keywords: CPR (cardiopulmonary resuscitation) mechanics; CPR devices; AED (automated external defibrillator); sudden death; cardiac arrest

Address for correspondence:
Myron L. Weisfeldt, MD, Sir William Osler Professor of Medicine, Johns Hopkins University School of Medicine, 1830 East Monument Street, Rm 9026, Baltimore, MD 21224, USA
(e-mail: mls56@jhmi.edu)

Dialogues Cardiacease Med. 2006;11:221-230

Copyright © 2006 LLS SAS. All rights reserved
www.dialouges-cvm.org
of-hospital death, the likelihood of underlying disease remains uncertain, and many studies presume that an arrest is of cardiac origin unless there is another obvious cause. \(^1\) Traumatic sudden death is usually considered separately from unexpected cardiac death because the treatment and prognosis of traumatic and nontraumatic arrest differ from each other. For the purpose of this article, we will use unexpected cardiac death, EMS-treated cardiac arrest, or nontraumatic out-of-hospital cardiac arrest as synonyms for cardiac arrest of presumed cardiac etiology.

### INCIDENCE

The incidence of cardiac arrest is the attack rate of cardiac arrest in the community. Risk factors for increased incidence of cardiac arrest include cellular (eg, gene mutations that predispose to arrhythmias), environmental, social, educational, behavioral (eg, activity level, smoking), clinical (eg, atherosclerosis, reduced ventricular function, diabetes), or health system risk factors. \(^2\) Unexpected cardiac death generally occurs in persons with known or previously unrecognized ischemic heart disease. Early identification of modifiable risk factors and use of certain pharmaceutical agents (aspirin and β-blockers) can reduce an individual’s risk of cardiac arrest.

The true incidence of out-of-hospital cardiac arrest is unknown. Overall, cardiovascular disease contributes 30.9% of global mortality. About half of coronary heart deaths are sudden. \(^3\) Since there were 7.2 million coronary heart deaths worldwide in 2002 (http://www3.who.int/whosis/), this implies there were 3.6 million unexpected cardiac deaths. About two thirds of these occur without prior recognition of cardiac disease. About 60% are treated by EMS. \(^4\)

Although the proportion of those treated by EMS is likely less in those countries that have limited access to emergency services, this implies that as many as 2.2 million cardiac arrests are treated by EMS worldwide annually.

The reported incidence of unexpected cardiac death in the US is 1.9/1000 person years among those aged 50 to 79 years. \(^5\) Since the US population aged 50 to 79 is 68 million (http://www.census.gov/), this implies 130,000 out-of-hospital cardiac arrests. The reported incidence of EMS-treated cardiac arrest is 36/100,000 to 81/100,000 total population. \(^4\) Since the total US population is 300 million (http://www.census.gov/), this implies 107,000 to 240,000 treated arrests occur in the United States annually. Of these, 20% to 38% have VF/VT as the first recorded rhythm. \(^5\) This implies 21,000 to 91,000 treated ventricular fibrillation arrests annually.

### SURVIVAL

There is a wide geographic variation in outcomes after the onset of cardiac arrest. \(^10\) This is attributable in part to regional differences in the availability of emergency cardiac care. Also, there is regional variation in EMS processes such as EMS service level provided, number of EMS providers responding, use of procedures or drugs in field, training, quality assurance/feedback, and response time intervals. \(^11\) No published analysis has had adequate power to detect the independent effects of all of these factors.

The median reported rate of survival to discharge after out-of-hospital unexpected cardiac death with any first recorded rhythm is only 6.4%. \(^11\) It is likely that this overestimates the actual rate of survival in many communities because of publication bias. In many large urban areas the rate is less than 2%, \(^16\) and it is even lower in some rural areas. The reported average survival to dis-
charge after out-of-hospital pediatric cardiac arrest is 6.7%. Most communities are not aware of their own survival rates, as cardiac arrest data are not routinely tracked. Yet, a city with an organized EMS system and dedicated quality assurance can achieve survival of 15% to 20% (see reference 5, and unpublished data, L. Cobb). If the average survival could be improved from 5% to 20% by optimizing the chain of survival, the premature deaths of 16,000 to 36,000 subjects in the United States could be prevented each year.

**EVILOVATION OF PRESENTATION OF SUDDEN DEATH**

From the dawn of defibrillation and modern CPR, the ECG of the vast majority of adult patients recorded in the first 10 to 15 min after cardiac arrest showed VT/VF. Beginning 10 years ago, an increasing incidence of asystole, or an organized electrical rhythm without perfusion, has been recognized. The evolution of presentation has been rapid and profound numerically: from 80% to 90% VT/VF to as low as 20% to 30% VT/VF today. At the same time, there has been some evolution of demographics, which may in part be causal. The average age of the victims of cardiac arrest is strikingly older with the overall incidence in the US not much changed.

Another likely possibility is that primary prevention of acute myocardial infarction, revascularization of patients with severe coronary stenosis, and effective medical (drug) management of patients with coronary disease and particularly chronic coronary disease with congestive heart failure have reduced VT/VF as the cause of cardiac arrest. A final and rapidly growing participant in this prevention strategy is the implantation of defibrillators in large groups of patients with a history of nonfatal arrhythmic events or a left ventricular ejection fraction of less than 35%. In such populations, randomized clinical trials suggest that about 5% of these patients with an implantable cardioverter-defibrillator (ICD) implant will be saved from VT/VF cardiac arrest per year. If the number of appropriate implants performed in the US is 100,000 per year, 75,000 VT/VF arrests will be prevented over 5 years.

The etiology of VT/VF arrest is acute coronary occlusion or reentry around scar in chronic coronary disease with heart failure, but the underlying cause and the proximate cause for non-VT/VF arrests are unclear. Also, effective therapeutic strategies for such arrests are poorly studied and remain elusive. Rapid electrical intervention such as defibrillation and pacing have little if any role in survival of this growing and important group of out-of-hospital cardiac arrest victims.

**CARDIOPULMONARY RESUSCITATION**

**Bystander CPR**

CPR is important both before and after shock delivery in patients with pulseless ventricular tachycardia or ventricular fibrillation, as well as throughout resuscitative efforts in those with asystole or pulseless electrical activity. When performed immediately after collapse from VT/VF, CPR can double or quadruple the victim’s chance of survival.19-22 After 5 minutes of untreated VF, outcome may or may not be better if attempted defibrillation is preceded by a period of CPR.23-25 Therefore, it remains unclear whether rhythm analysis to confirm the presence or absence of VF should precede CPR for undifferentiated cardiac arrest.

**Compressions-only CPR**

Multiple animal studies of arrhythmic arrest suggest that compressions-only CPR may be as effective as standard CPR.26-32 However, there are no directly relevant prospective human studies. Observational or secondary analyses of a trial dataset provide limited insight into the effectiveness of compressions-only CPR. In a Belgian cohort, 14-day survival after treatment by bystanders was 5% with ventilation alone (n=97 eligible), 9% with compression alone (n=258) and 12% with ventilation and compressions (n=561, P=0.09 calculated from data).33,34 In a Swedish cohort, survival to discharge was 4.3% with ventilation alone (n=620 eligible), 6.8% with compression alone (n=278), and 9.7% with ventilation and compressions (n=897, P<0.01 calculated from data).21 In a secondary analysis of a Dutch randomized trial, survival to discharge was 7% with ventilation alone (n=15 eligible), 15% with compression alone (n=41) and 14% with ventilation and compressions (n=437, P=0.7).35 In all of these studies, lay responders who had been trained to perform compression and ventilations chose at the time of an emergency response to provide either or both. Therefore, these studies were subject to selection bias because the decision to provide some, but not all, components of CPR likely reflected the presence of responder discomfort with CPR skills or adverse patient characteristics. It is difficult to distinguish asphyxial versus arrhythmic arrest at the time of resuscitative efforts. Compressions-only CPR may be detrimental to patients in asphyxial arrests.

Thus, in adults with cardiac arrest treated by lay responders trained in standard CPR, survival with compressions-only CPR is almost certainly better than with no CPR, but...
may not as good as with both compressions and ventilation. Until there is evidence to the contrary, compressions and ventilations should be given during CPR unless a responder is unwilling to provide mouth-to-mouth ventilation.

**Dispatcher instruction in CPR**

A randomized trial in Seattle, Washington, evaluated the effectiveness of CPR telephone instructions provided when no one on the scene was performing CPR and the caller was willing to be instructed. Survival was better among patients assigned to lay responder instruction in chest compressions alone than among those assigned to instruction in compression and ventilations (14.6% vs 10.4%, \(P=0.18\)). However, instructions were delivered completely in only 62% of compressions and ventilation episodes versus 81% of episodes assigned to compressions alone (\(P=0.005\)). It is unclear whether the differential survival reflects the benefit of compressions-alone, or the harm of prolonged dispatcher instructions for compressions and ventilations.

**NEED FOR IMPROVED CPR PERFORMANCE**

Recent studies of cardiac arrest in the out-of-hospital setting in Milwaukee, Wisconsin, Tucson, Arizona, and Europe have suggested that CPR is not performed as recommended. These results were confirmed by a recent study in the hospital setting in Chicago, Ill. Relevant factors include interruption of CPR, and adequate provision of key components of CPR and ventilation.

**Interruption**

Several observational studies show that chest compressions are interrupted for 24% to 49% of the duration of resuscitation efforts in patients with cardiac arrest. The small size and lack of controls in these studies make it difficult to correlate interruption of CPR with clinical outcomes. However, a surrogate measure of the effectiveness of CPR is coronary perfusion pressure. This is the pressure gradient generated between aorta and right atrium during the decompression phase of CPR. Blood flows through coronary arteries predominantly during this chest decompression phase. Coronary perfusion pressures increase with ongoing chest compressions, but rapidly diminish with cessation of compressions to administer ventilation or other maneuvers. Greater survival in animals and greater restoration of circulation in humans are associated with greater coronary perfusion pressure. Therefore, interruptions of compressions should be minimized.

**Components of CPR**

There are several key components of CPR. At least 80 chest compressions should be given per minute (ie, rate of 100 per minute to allow for no compressions during pauses) with sternal compression of 1.5 to 2 inches in adults to achieve optimal forward flow during CPR. Complete chest wall recoil improves hemodynamics during CPR by generating a relatively negative intrathoracic pressure during decompression, which increases venous return and hence cardiac preload for the next compression. In a single EMS system (n=13 arrests), persistently positive airway pressures were recorded in 46% of episodes. Such pressures are likely due to incomplete chest wall recoil, and are potentially deleterious. Therefore, rescuers should allow complete chest recoil after each compression, while maintaining hand position in the lower half of the sternum between the nipples.

**Components of ventilation**

Hyperventilation during resuscitation of patients in cardiac arrest has been observed in some, but not all, settings. Excess ventilation increases intrathoracic pressure during the diastolic phase of chest compression, decreases venous return, and may decrease survival.

The rate of ventilation should not be reduced by prolonged inspira- tion, which is associated with persistent positive intrathoracic pressure and decreased venous return. Retraining, quality assurance, and use of devices such as metronomes or timing lights may reduce hyperventilation and integrate ventilation with performance of chest compressions.
How can we reduce sudden death in the community? - Nichol and Weisfeldt

Importance of feedback to improve cardiopulmonary resuscitation

Real-time monitoring and feedback of the components of the CPR process is associated with significant improvement in compliance with resuscitation guidelines and may be associated with improved short-term outcomes (see references 32 to 47 and personal communication, P. Steen, January 25, 2006). Ongoing study is needed to determine whether feedback improves survival to discharge.

Timing of Defibrillation

Based on reasonably solid experimental animal and correlative human data, Weisfeldt and Becker proposed that effective therapy of VT/VF arrest could be conceptualized in three sequential phases. The most effective therapy for VT/VF is defibrillation during the first 4 to 5 minutes of cardiac arrest. This was called the "electrical phase of resuscitation." After 4 to 5 minutes, and for at least 10 minutes after cardiac arrest, is the second or circulatory phase. During this phase, immediate defibrillation provides worse outcomes in pigs and dogs than delaying defibrillation for 90 seconds to 3 minutes of effective CPR. Finally, there is a somewhat ill-defined metabolic phase where hypothermia and/or yet to be discovered metabolic interventions may aid circulation and defibrillation in leading to survival with reasonably good neurologic status.

Studies of rapid defibrillation for VT/VF arrest in the first 3 minutes of out of hospital cardiac arrest suggest that 70% to 80% long-term survival can be expected. Findings from ICD studies show that defibrillations within 20 seconds result in almost uniform survival. These studies suggest that epidemiologic studies underestimate the survival results of early defibrillation likely due to imprecise timing of the onset of cardiac arrest. Also, such epidemiologic studies underestimate the fall-off in survival once 4 to 5 minutes of cardiac arrest without bystander CPR has taken place. Clinical studies suggest that after 5 minutes of cardiac arrest, prompt defibrillation is associated with a less than 5% survival, but that a period of CPR followed by defibrillation could result in 20% to 30% survival (Figure 3, next page).

The evidence of the high survival from defibrillation during the electrical phase led to the concept of public-access defibrillation (PAD): simple self-instructional AEDs are made available to any willing and trained provider for use. A randomized trial of community implementation of AEDs showed that survival is doubled in community sites with this approach. Today, this approach is of unproven value in the home, where the majority of arrests occur. Also, AEDs are not cost-effective if less than one cardiac arrest
is likely to occur in 5 years. The higher the frequency of cardiac arrest in a given site, the greater value of a PAD-AED program. Increasingly, transportation facilities, airplanes, gaming and high stress and exercise environments, and large public buildings are being equipped with AEDs in clear public view. Technology advances may bring lay or part/neighbor defibrillation into the home. Soon a small implantable ECG monitor may, through an electronic page system, signal a partner or neighbor that VT/VF is present. Even more remarkable, a global position sensor may tell the partner and/or the EMS system the victim’s location. Such an approach in high- or moderate-risk patients may be more acceptable and have greater cost effectiveness than defibrillator implantation.

**CPR ASSIST DEVICES**

Since conventional CPR, even when performed optimally, leads to brain blood flow of 30% to 50% of normal and myocardial blood flow of 10% to 20% of normal, there is considerable interest in devices that may enhance survival by improving blood flow. One of the closest correlates of survival in man is the coronary perfusion pressure gradient. Studies primarily in animal models with correlates in man establish that in general blood moves forward during CPR as a result of the increase in intrathoracic pressure accompanying chest compression. In some patients, direct cardiac compression between bony structures may also occur during chest compression and is additive to the thoracic pressure rise.

Mechanical sternal compression devices have long been employed in some EMS systems and hospitals and provide a solution to rescuer fatigue and CPR during transportation. Of greater interest are devices that increase the rise in intrathoracic pressure during the compression phase such as inflatable vests or mechanical chest squeezing devices. Also, devices have been developed to obstruct airflow back into the chest between compressions. The latter type of device increases blood flow during manual CPR by providing increased venous return between compressions as a result of the induced negative intrathoracic pressure.

To date, none of these devices has been proven in randomized trials to improve long-term survival over conventional manual CPR. There is some evidence that the more complicated vest and chest-squeezing devices are inferior in terms of survival compared with best manual CPR, perhaps because these devices are bulky and burdensome compared with rapid performance of best manual CPR. The negative airway devices are small and simple and have resulted in improved short-term survival (ie, admission to the hospital). They require an occlusive airway device (intubation) or tight sealing mask and require optimal chest compression technique with full “hands or pressure off” the chest between chest compression. Such proper chest compression requires careful instruction and likely leads to earlier fatigue of the rescusitator. The AHA and the International Liaison Committee have given this airway device a favorable IIa rating in the most recent guidelines document.

Other mechanical or invasive approaches to CPR are performed from time to time in settings with spe-
cialized interests or skills. These approaches include internal cardiac massage and use of various degrees of cardiopulmonary bypass. One group reports remarkably favorable results of full cardiopulmonary bypass with cardiac decompression and correction of reversible cardiac problems in patients who have failed “in-hospital” prolonged periods of CPR.37

**DRUGS DURING CPR**

No drug has been shown to improve long-term survival from cardiac arrest in clinical trials in man. Short-term survival was shown in two studies to be associated with administration of amiodarone intravenously in refractory VT/VF: either persistent or recurrent VT/VF despite CPR and defibrillation. In neither of the two reported studies was there even a trend toward improved survival to hospital discharge. Over the years, opinions, some based on animal data, have dominated the guidelines with regard to advice regarding the use of drugs. For example, repeat administration of sodium bicarbonate has come and gone from the guidelines, as has high-dose epinephrine. Epinephrine continues to be advised on the basis of animal studies. The l-mg dose IV continues to be a mainstay of pharmacological management of cardiac arrest once initial CPR and defibrillation fail or with non-VT/VF arrest. Magnesium and calcium are used in special cases: the former when torsades de pointes is present and the latter with hyperkalemia. Other antiarrhythmics are now rarely employed. Vasopressin showed impressive results in animal models, but unimpressive results in man, and is considered in general an alternative to epinephrine. Vasopressin may have added value to epinephrine in the very challenging non-VT/VF arrest patient.37 Studies of fibrinolytic agents are ongoing in special subsets of cardiac arrest patients and there is interest in alternative vasconstrictors, inotropic agents, β-blockers, and agents to reduce ischemic damage such as erythropoietin, antioxidants, and neuroprotective or antiapoptotic or anti-inflammatory agents. A safe aqueous preparation of amiodarone would also warrant testing in man during CPR since there is suspicion that the hypotensive effects of the diluent of currently available amiodarone accounts for its lack of long-term survival benefit.

**TAILORED APPROACH TO RESUSCITATION**

A tailored approach to prevention and treatment of unexpected cardiac death is desirable since there is wide geographic variation in the incidence of cardiac arrest, resources available to treat it, existing rate of survival, and how much society is willing to pay to avert an arrhythmic death. Although some segments of the population are at higher risk of cardiac arrest than others, more episodes occur in those at lower risk because there are many more low-risk individuals. Consequently, primary prevention of cardiac arrest by reducing modifiable risk factors in individuals without apparent cardiac arrest could have a large public health impact.

The risk of cardiac arrest varies by location as well as by individual (Table I). Each site participating in the PAD trial identified distinct units within their service area (eg, office buildings, public areas). Due to the large variety of settings studied in this trial, there was limited precision in the estimate of the incidence of cardiac arrest by location. However, a cohort study of out-of-hospital cardiac arrest in Seattle and King County, Washington, described the incidence of cardiac arrest by public location.48

**HYPOTHERMIA**

Therapeutic hypothermia consists of initiation and maintenance of reduced whole body temperature. Hypothermia reduces intracranial pressure as well as production of glutamate and oxygen-free radicals.
that are associated with reperfusion injury after restoration of spontaneous circulation. Two moderately sized randomized trials demonstrated that initiating and maintaining mild hypothermia (32°C to 34°C for at least 12 hours) via external cooling methods is safe and improves neurologic outcomes in comatose survivors of out-of-hospital VT/VF arrest. Endovascular methods of therapeutic hypothermia may achieve more rapid, controlled, or sustained cooling that would be associated with additional benefits, but have not been evaluated in adequately powered randomized trials in patients with cardiac arrest. Concurrent medication including buspine and meperidine may be necessary to facilitate cooling and patient comfort. The duration of rewarming may be as important as the duration or depth of cooling, since rapid rewarming of patients who underwent therapeutic hypothermia has been associated with adverse effects.

FUTILITY

In recent years, the assessment and determination of futility with regard to meaningful patient survival after cardiac arrest has progressively become a mandate. In the presence of futility, CPR is avoided or stopped. In some states in the US, with no “do not resuscitate” (DNR) order, there is no legal basis for such withholding or stopping of CPR efforts when a judgment of futility is made. Such legal statutes are, in the judgment of these authors, unfortunate. By oath, physicians are committed to not provide care that has no possible benefit to the patient. The unfortunate conflicts between legal statutes and futility has resulted in the ethically corrupt performance of slow or improper CPR. Instead, CPR should be liberally and fully provided if meaningful survival is possible and withheld by patient preference (DNR documentation) or futility.

HORIZONS

The current state of resuscitation resembles a Dickensian novel. It is the best of times; it is the worst of times: there are multiple promising interventions, but outcomes have not improved for 30 years. Future interventions may yet improve outcomes associated with cardiac arrest in the future. These include effective devices and/or drugs (as discussed), methods of early identification (eg, a wearable or implantable ECG alarm), defibrillation by family members of those at moderate or high-risk of cardiac arrest (http://www.clinicaltrials.gov/show/NCT00047411); tailored therapy (eg, defibrillation guided by waveform analysis) and faster or simpler methods of implementing and maintaining therapeutic hypothermia. Broad training of the lay public in simpler methods of CPR is particularly promising because it requires less time and is at least as efficacious as traditional methods of training. Training of advanced EMS or hospital providers in advanced cardiac life support may be facilitated by adoption of simulation methods.

REFERENCES


How can we reduce sudden death in the community? - Nichol and Weisfeldt


One of the major advances in cardiology began in the 1930s when André Cournand (Figure 1), a pulmonary physiologist, and Dickinson W. Richards (Figure 2), an expert on cardiovascular medicine, collaborated in a long-term effort to integrate the roles of the heart, the lungs, and the peripheral circulation in gas exchange. Among the initial clinical goals of this research was a clearer understanding of the pathophysiology of pulmonary disease that could answer such questions as the consequences of thoracoplasty and other means then used to collapse the lungs in patients with tuberculosis; it was only later that diagnosis of heart disease emerged as a major practical benefit of this work. Central to the success of this research was a means to quantify pulmonary blood flow using the three variables that make up the Fick equation: total body oxygen consumption and the oxygen contents of the blood entering and leaving the lungs. The first is readily determined by collecting and measuring the volume and oxygen content of expired air, while the third is easily measured using samples of arterial blood; the problem faced by Cournand and Richards was how to obtain mixed venous blood to determine the second variable. Because blood returning to the right heart from some organs, such as the kidneys, is rich in oxygen, whereas other organs, notably the heart, extract virtually all of the oxygen delivered in the arterial blood, the first and third variables were easily determined, and the remaining variable (oxygen content of mixed venous blood) was the focus of efforts to provide a practical solution to this problem. A solution to this problem had been foreshadowed more than a decade earlier by Werner Forssmann (Figure 3, next page), who in 1929 described passing a catheter into his own right atrium without ill effects.

A solution to this problem had been foreshadowed more than a decade earlier by Werner Forssmann (Figure 3, next page), who in 1929 described passing a catheter into his own right atrium without ill effects. During the 1930s, several angiographers had introduced catheters into the right atrium of humans to perform pulmonary angiography, and Forssmann’s technique had been used by a few clinical physiologists to obtain mixed venous blood. However, the potential physiological applications of these observations were not appreciated; as noted by Cournand, although “many possibilities were envisaged… no systemic plan, nor the proper scientific background and facilities for its wide-scale implementation, were then available.”

Address for correspondence:
Prof Arnold M. Katz, 1592 New Boston Road, PO Box 1048, Norwich VT, 05055-1048, USA
(e-mail: arnold.m.katz@dartmouth.edu)

Copyright © 2006 LLS SAS. All rights reserved
www.dialogues-cvm.org
tory at Bellevue hospital, led by Cour- 

nand and Richards (see below), where 
the effort to obtain mixed venous blood 
for determination of cardiac output 
was part of an ongoing long-term re- 
search effort. Cournand describes a 
planning session in the early 1930s at 
which Richards “produced an issue of 
the 1929 Klinische Wochenschrift de- 
scribing Forssmann’s self-experiment.”2 
This conversation led Cournand, in 
1936, to visit a former teacher in Paris 
who had performed pulmonary angiog-

raphy in about 100 patients. Upon his 
return, Cournand, along with Richards 
and their colleagues in the Cardio-
pulmonary Laboratory, familiarized 
themselves with this method and 
placed catheters first in the right atri-
um of dogs and chimpanzees, then in 
cadavers, and in 1941 in living humans.3 
The observation that the tips of right 
atrial catheters could suddenly appear 
in the pulmonary artery led to cather-
ization of the right ventricle in 1941, 
and in 1944 of the pulmonary artery 
(Figure 4).4

ANDRÉ FRÉDÉRIC 
COURNAND

Cournand5-7 was born on September 
24, 1895, in Paris, where his father was 
a prominent dentist who held several 
patents in dental technology. He stud-
ied both science and the humanities 
at the Sorbonne and after he received 
his BA in 1913 began medical school. 
These studies were interrupted by 
World War I, in which he served from 
1915 to 1919 as an “auxiliary battle 
surgeon” (a rank established for med-
ical students) and was both wounded 
and gassed. Among his tasks was to 
retrieve wounded soldiers from no-
mans-land, which exposed him to the 
terrible prognosis of hemorrhagic and 
traumatic shock. After serving in the 
trenches for 3 years, for which he re-
ceived the Croix de Guerre with 3 
bronze stars, he returned to medical 
school and from 1924 to 1939 was a 
house officer at the Hôpitaux de Paris.

It was at this time that his interest in 
the physiological basis of medicine matured; he published papers on sev-
eral subjects, including the excitability 
of the facial nerve, the effects of drugs 
on blood sugar, and the use of epi-
nephrine in infants with pulmonary 
edema. His interest in pulmonary dis-
ease emerged in 1928 when he pub-
lished papers on bronchiectasis, dis-
seminated nodular tuberculosis, and 
surgical therapy for pulmonary tubercu-
losis. In 1930, he was awarded the MD 
degree for which he wrote a thesis on 
multiple sclerosis, after which he came 
to the United States for further train-
ing as a first year resident on the 
well-known Columbia Chest Service 
at Bellevue Hospital in New York. He

Figure 3. Werner Forssmann in his laboratory in 1956. © Bettmann/CORBIS.

Figure 4. Recordings of right ventricular pressure in humans. 
A: Normal young female. 
B: Young male with extensive pulmonary fibrosis with normal sized heart showing elevated pressure and increased respiro-
tory variations in pressure. 
C: Patient with mitral stenosis and insufficiency, aortic insuf-
ficiency, and atrial fibrillation showing elevation of both sys-
tolic and diastolic pressures. 
D: Same patient as C after treatment with digitalis and bed rest. 
Reproduced from reference 4: 
Cournand A, Lauson HD, 
Bloomfield RA, Breed ES, 
Baldwin E de F. Recording of 
right heart pressures in man. 
1944;55:34-36. Copyright 
© 1944, Blackwell Science.
subsequently learned that he had been recommended as “a nice young Frenchman who did not speak a word of English.”

Although Cournand was qualified to begin a private practice in France at the end of this training, he chose instead to pursue a full-time career that combined clinical practice, research, and teaching. In 1932, he became Chief Resident on the chest service and, in 1933, was asked to develop a laboratory for the study of pulmonary function in collaboration with Dickinson Richards who, after completing his residency in Medicine at Columbia 5 years before, had been a fellow in London with Sir Henry Dale, a Nobel Laureate. Although Richards was then uptown at Columbia Presbyterian Hospital, his interest in gas exchange by the peripheral circulation fit closely with that of Cournand, which was in gas exchange by the lungs.

THE CARDIOPULMONARY LABORATORY AT BELLEVUE HOSPITAL

Cournand and Richards together established the Cardiopulmonary Laboratory at Bellevue where, during the 1930s, they worked to characterize the movements of oxygen from the lungs to peripheral tissues by way of the circulation (Figure 5). Their first projects included a study of the role of the respiratory muscles in causing dyspnea, the effects of the various forms of collapse therapy then used to treat pulmonary tuberculosis, and an effort to characterize the inhomogeneous distribution of inspired gases in the lungs that contributed to the arterial hypoxia seen in patients with chronic obstructive lung disease. A major discovery during these early years was the demonstration that the hemodynamics in patients with chronic obstructive pulmonary disease differed from those in heart failure. The imminence of World War II, which recalled the terrible prognosis in soldiers with hemorrhagic and traumatic shock that Cournand had seen during World War I, led to efforts to define the effects of severe injury on hemodynamics, oxygen transport, and tissue metabolism; one practical benefit was the development of dextran to expand blood volume. These studies, along with the challenges posed by high altitude aviation, also stimulated work to develop mechanical respirators. Of course the most important scientific advance to come from this laboratory was the introduction of cardiac catheterization described above. Although this technique was initially developed to calculate cardiac output, within a year a detailed description of the abnormal hemodynamics in patients with heart failure was published.

Because of the need to learn more about shock, a major focus of medical research during World War II, cardiac catheterization was used in the Cardiopulmonary Laboratory to measure cardiac output, blood volume, intracardiac and intra-arterial pressures, blood gases, pH, respiratory gas exchanges, and even renal blood flow in patients with various forms of this syndrome. At the same time, this technique continued to be used to define the hemodynamics of rheumatic heart disease, cor pulmonale, and hypertension.

Following the end of World War II, in 1945, Cournand’s collaboration with Richards was facilitated when the latter moved to Bellevue to become director of the First (Columbia) Medical Service, which, by combining a high-quality academic program and a city hospital, established one of the top training programs in the US. Cournand continued to direct the Cardiopulmonary Laboratory, which became the international focal point for research into the pathophysiology of pulmonary diseases and so provided the foundation for modern pulmonary medicine.
addition to characterizing the hemodynamic and ventilatory abnormalities in patients with pulmonary fibrosis and emphysema, Cournand and his group discovered that hypoxia constricts the pulmonary arterioles, rather than elucidating the vasodilatory response seen in virtually every other tissue. At the same time, they continued to characterize the hemodynamic abnormalities in rheumatic and congenital heart disease, the circulatory effects of cardiac glycosides and antiarrhythmic drugs, and the hemodynamic consequences of chronic atrial arrhythmias. Many of those trained at the Cardiopulmonary Laboratory went on to leadership positions in academic medicine; the list includes 8 chiefs of pulmonary medicine, 7 chiefs of cardiology, 5 chiefs of medicine or experimental medicine, 3 chiefs of cardiac surgery, 2 professors of physiology, and 1 chief of pediatric cardiology.

Cournand at that time is described as physically vigorous, endowed with gravitas and unbounded scientific curiosity and kindness, but “enthusiastically volatile under appropriate stimulation.” Enson and Chamberlin tell of a junior fellow who told Cournand that his critique of a recently published paper seemed paranoid, which caused the latter to spring to his feet, confront the fellow nose-to-nose, and state: “Correct! And by the end of your fellowship, doctor, you will also have a yellow streak of paranoia down your back eighteen inches wide.” A similar portrait is provided by Riley, who describes Cournand as “arguing violently with Israel Rappaport… trading insults with his beloved associate, Aaron Himmelstein… running to Dick Richards to settle particularly intractable controversies… He was outrageous at times and always exciting to be with. His moods changed from moment to moment, sometimes bringing about a graceful end to an argument with a sudden tension-releasing: ‘You are right,’ and sometimes, if you were not right—and occasionally even if you were—a withering exclamation: ‘That man is impossible!’”

Although the work for which Cournand shared the Nobel Prize centered on a physiological technique, he was a sensitive clinician who understood that the patient, not the test, is central in medicine; as noted by Lequime, Cournand recognized that the application of new methods requires not only a profound knowledge of the techniques used, but also that of the patient under examination: the value of precise physiological measurement is all the greater when the clinical study is more elaborated; before presenting his conclusions, the investigator must always ensure that he has explored in all its clinical aspects the problem which he proposes to resolve.

“RETIRED”

Cournand officially retired in 1964, but remained active until his death in 1988. During these later years his interests expanded to a consideration of the philosophy of scientific research, and in 1970 led to a remarkable article describing the importance of “the growing involvement of science in social life.” Writing with Harriet A. Zuckerman, then an Assistant Professor of Sociology at Columbia, Cournand emphasized 7 principles, which I have abridged slightly from ref. 12:

- **Intellectual Integrity and Objectivity:** Scientists are obliged to approach the natural world and their own investigations of it with as much objectivity and care as they can summon.
- **Tolerance:** …it is wise to be tolerant of [new ideas] and to see if their factual bases appear to fall within the boundaries of sound science. Tolerance is also expressed through dissent as long as mutual respect is maintained between dissenters.
- **Doubt of Certitude:** …[because] truth emerges from the confrontation of contraries, scientists must approach what is generally considered certain with an ever-questioning mind. The tension so created is one of the main-
springs in the pursuit of knowledge.

- **Recognition of Error:** The systematic application of doubt is apt to reveal errors that must be recognized and acknowledged publicly.
- **Unselfish Engagement:** Scientists should be motivated by the desire to extend knowledge and not by the wish for personal gain or by the desire to foster the primacy of one intellectual perspective.
- **Sense of Belonging:** Scientists should conceive of their work as being part of a larger enterprise, and of themselves as joined to their scientific colleagues through collective contributions to this enterprise.
- **Recognition of Priorities:** Scientists are required to recognize as scrupulously as possible other investigators’ priorities in discovery.

This description of the qualities of the ideal scientist, which is as important today than when it was written 35 years ago, ranks with contributions to cardiopulmonary science and medicine that together represent André Cournand’s magnificent legacy.

**REFERENCES**


Page blanche pour conserver, en pdf, la présentation, en vraies doubles, de la maquette finale
above my desk hangs the photograph of a man with sideburns and a bow tie. The sideburns suggest that the picture was taken at the latter part of the 19th century. What puzzled me in this photo is the inscription "To my friend Berthold Bing, from Emmanuel Nobel." Berthold Bing was my grand-father.

Who was Emmanuel Nobel? Was he related to Alfred Nobel, the inventor of dynamite who left his fortune for the benefit of scientists, poets, and peacemakers? In researching the story of Emmanuel Nobel, I became familiar with the life of Alfred Nobel, the torturous history of the Nobel Foundation, and the origin of the Nobel Prize.

Emmanuel Nobel, the bearded man in my photograph, was the nephew of Alfred Nobel. He deserves great credit together with Ragnar Sohlman, an executive of the will of Alfred Nobel, for bringing Nobel’s legacy to fruition. It seems strange today when the Nobel Prize is hailed as the ultimate sign of recognition and honor, that Nobel’s legacy was bitterly contested not only by his family but also by Swedish scientific institutions and by the King of Sweden. Nobel’s family attempted to get their hands on the considerable amount of money. Family members fought bitterly amongst themselves and it needed the diplomacy and patience of Emmanuel Nobel and Ragnar Sohlman to settle the estate. But the opposition of the scientific institutions which had been entrusted to administer Alfred Nobel’s bequest is difficult to understand. Different academic institutions were involved in Nobel’s will: The Swedish Academy of Sciences, Stockholm University, and the Karolinska Institute. None of these institutions showed any eagerness to take

Adapted from:

Address for correspondence:
Richard J. Bing, MD, Director, Experimental Cardiology, Em, HMRI – Huntington Medical Research Institute, 99 N Cl Molino Avenue, Pasadena, CA 91011, USA
(e-mail: cardio@hmri.org)
Dialogues Cardiovasc Med. 2006;11:236-238

Swedish chemist Alfred Nobel (1833-1896), famously known as the inventor of dynamite, in 1893. An explosives specialist and prolific inventor and manufacturer, he also invented gelignite, gutta-percha, and a special variety of steel for armour-plating, and amassed a huge fortune, which he left to endow five yearly Nobel prizes, in physics, chemistry, physiology/medicine, literature, and peace, to which a sixth, economics, was added in 1968. © Bettmann/CORBIS.
over the authority to administer and distribute the awards. Fears were even voiced that the participation in such a task would be detrimental to Swedish science and to the prize-giving institutions. Dispute between these scientific organizations became very bitter. Members of the Karolinska Institute even opted for complete reorganization of Nobel’s donation, suggesting that each institute use a share of the money for its own purpose. Some of the scientific administrators doubted that the members of these organizations were capable of choosing a winner. It needed the patience and arbitration of Ragnar Sohlman and Emmanuel Nobel to come to an agreement. Alfred Nobel’s family finally accepted the will. Yet, there was still the King of Sweden who had to approve these arrangements. Emmanuel Nobel was summoned by the king who pronounced that the bequest of his uncle could only cause trouble, telling him: “Your uncle was talked into this by fanatic womenfolk mostly”; he also called it a “nonsensical idea.” Today the King of Sweden proudly hands the Nobel diploma to winners to the glory of Sweden.

Matters were also difficult because of the dispersion of various enterprises of Alfred Nobel in Italy, Russia, and France. To get these valuable stocks out of France into Sweden, Sohlman had to remove them secretly from a bank in Paris and bring them to the Swedish embassy in a horse drawn carriage, with Sohlman carrying a pistol to ward off any attempted robbery.

What was Alfred Nobel like? He was an ingenious inventor. Aside from nitroglycerine, he worked on the use of guided rocket missiles and of the production of artificial gems, ideas which were truly visionary. But a man’s character cannot be summarized in a paragraph. Life is a mosaic, defying simple definition. It is known that Nobel was a lonely man. From his earliest years he searched in vain for tenderness and love, and he was thwarted by skepti-
cism and self-doubt. As he wrote, “I personally find the conversation of Parisian women the dreariest thing I know, whereas it is delightful to meet cultured and not excessively emancipated Russian ladies. Unfortunately they have an aversion to soap—but one must not expect too much.” While on a vacation to Austria, the 50-year-old Nobel met a 20-year-old Viennese girl who worked in a flower shop. There could not have been a more incompatible couple, but Nobel loved her and cared for her. In the course of time he wrote her over 200 letters. Then the relationship cooled, and they drifted apart. Nobel died a lonely man, surrounded only by his servants. Nobel died from coronary heart disease, which handicapped him through his adult life. As he wrote, “Isn’t it the irony of fate that I have been prescribed nitroglycerine to be taken internally! They call it Trinitrin, so as not to scare the chemist and the public.”

It is a sign of human frailty that Nobel’s vision to create the great legacy which bears his name was opposed by many, including the scientific community. Emmanuel Nobel, his nephew, whose photograph made me write this column, fought to bring Alfred Nobel’s great dream to fruition. The award named after him is recognition of a great, noble but tragic man.

**REFERENCE**


---

<table>
<thead>
<tr>
<th>Year</th>
<th>Category</th>
<th>Laureates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1901</td>
<td>Chemistry</td>
<td>Jacobus H. van ‘t Hoff</td>
</tr>
<tr>
<td></td>
<td>Literature</td>
<td>Sully Prudhomme</td>
</tr>
<tr>
<td></td>
<td>Medicine</td>
<td>Emil von Behring</td>
</tr>
<tr>
<td></td>
<td>Peace</td>
<td>Henry Dunant</td>
</tr>
<tr>
<td></td>
<td>Physics</td>
<td>Wilhelm Conrad Röntgen</td>
</tr>
<tr>
<td>1902</td>
<td>Chemistry</td>
<td>Emil Fischer</td>
</tr>
<tr>
<td></td>
<td>Literature</td>
<td>Theodor Mommsen</td>
</tr>
<tr>
<td></td>
<td>Medicine</td>
<td>RonaldRoss</td>
</tr>
<tr>
<td></td>
<td>Peace</td>
<td>Élie Ducommun</td>
</tr>
<tr>
<td></td>
<td>Physics</td>
<td>AlbertGobat</td>
</tr>
<tr>
<td></td>
<td>Physics</td>
<td>Hendrik A. Lorentz</td>
</tr>
<tr>
<td></td>
<td>Physics</td>
<td>PieterZeeman</td>
</tr>
<tr>
<td>1903</td>
<td>Chemistry</td>
<td>Svante Arrhenius</td>
</tr>
<tr>
<td></td>
<td>Literature</td>
<td>Björnstjerne Bjørnson</td>
</tr>
<tr>
<td></td>
<td>Medicine</td>
<td>Niels Ryberg Finsen</td>
</tr>
<tr>
<td></td>
<td>Peace</td>
<td>RandalCremer</td>
</tr>
<tr>
<td></td>
<td>Physics</td>
<td>Henri Becquerel</td>
</tr>
<tr>
<td></td>
<td>Physics</td>
<td>Pierre Curie</td>
</tr>
<tr>
<td></td>
<td>Physics</td>
<td>Marie Curie</td>
</tr>
<tr>
<td>1904</td>
<td>Chemistry</td>
<td>Sir William Ramsay</td>
</tr>
<tr>
<td></td>
<td>Literature</td>
<td>José Echegaray</td>
</tr>
<tr>
<td></td>
<td>Literature</td>
<td>Frédéric Mistral</td>
</tr>
<tr>
<td></td>
<td>Medicine</td>
<td>Ivan Pavlov</td>
</tr>
<tr>
<td></td>
<td>Peace</td>
<td>Institute of International Law</td>
</tr>
<tr>
<td></td>
<td>Physics</td>
<td>Lord Rayleigh</td>
</tr>
<tr>
<td>1905</td>
<td>Chemistry</td>
<td>Adolf von Baeyer</td>
</tr>
<tr>
<td></td>
<td>Literature</td>
<td>Henryk Sienkiewicz</td>
</tr>
<tr>
<td></td>
<td>Medicine</td>
<td>Robert Koch</td>
</tr>
<tr>
<td></td>
<td>Peace</td>
<td>Bertha von Suttner</td>
</tr>
<tr>
<td></td>
<td>Physics</td>
<td>PhilippLenard</td>
</tr>
<tr>
<td>1906</td>
<td>Chemistry</td>
<td>Henri Moissan</td>
</tr>
<tr>
<td></td>
<td>Literature</td>
<td>Giosuè Carducci</td>
</tr>
<tr>
<td></td>
<td>Medicine</td>
<td>Camillo Golgi</td>
</tr>
</tbody>
</table>

Sudden Cardiac Death

Summaries of Ten Seminal Papers

Michiel J. Janse, MD

The Experimental and Molecular Cardiology Group - Academic Medical Center - University of Amsterdam
Meibergdreef 9 - 1105 AZ Amsterdam - THE NETHERLANDS (m.j.janse@amc.uva.nl)

Dialogues Cardiovasc Med. 2006;11:239-249

1. Termination of ventricular fibrillation in man by externally applied electric countershock
   P. M. Zoll and others. N Engl J Med. 1956

2. Electrical stimulation of the heart in patients with ventricular tachycardia
   H. J. J. Wellens and others. Circulation. 1972

3. Survival after resuscitation from out-of-hospital ventricular fibrillation
   R. S. Baum and others. Circulation. 1974

4. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings

5. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction

6. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia

7. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias

8. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction

9. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report

10. A molecular basis for cardiac arrhythmia: HERG mutations cause Long QT Syndrome
    M. E. Curran and others. Cell. 1995

Copyright © 2006 LLS SAS. All rights reserved

www.dialogues-cvm.org
The history of defibrillation is quite long. Hoffa and Ludwig in 1850 were the first to show that electrical currents applied to the heart could cause ventricular fibrillation. This was confirmed by Prevost and Batelli in 1899, who also showed that similar shocks could restore sinus rhythm. It is perhaps surprising that it took more than half a century before defibrillation by electrical countershock became common clinical practice. In the beginning of the 20th century there was not much interest in ventricular fibrillation, probably because its documentation in man was difficult and because nothing much could be done about it. When in the 1920s and 1930s more and more electrical devices were installed in households, a considerable number of people were accidentally electrocuted. This eventually prompted electricity companies such as Con Edison to provide grants to University departments to investigate the effects of electrical currents on the heart. This led, among others, to the rediscovery by Wiggers and Wégria of the vulnerable period during which the heart is most susceptible for ventricular fibrillation and, according to Gordon K Moe, it was on Wiggers’ advice that a defibrillator was installed in the operating room of Claude Beck, the cardiac surgeon: “One day, Claude, you will save a life.” In 1947, Beck defibrillated a patient who developed ventricular fibrillation during chloroform anesthesia by applying countershock directly to the heart.

Zoll reasoned that since in the laboratory animal ventricular fibrillation had been successfully terminated by the external application of countershock current across the closed chest, this would be a procedure with much wider clinical applicability. In this paper, he terminated ventricular fibrillation 11 times in 4 patients by externally applied countershock. Ventricular fibrillation occurred in the course of acute myocardial infarction, after intravenous administration of procaine amide for a rapid ventricular tachycardia, in digitoxin intoxication, and in Stokes-Adams disease. Quite a mixed bag. Although defibrillation was always immediately successful, 3 patients died, 1 from asystole, 1 from recurrent ventricular fibrillation, and 1 from electromechanical dissociation. The fourth patient was defibrillated three times in the course of 1 week, and was well 3 months later. It was recognized that successful defibrillation depended on immediate recognition of the arrhythmia and the prompt application of the external defibrillator. In the 3 patients that died, “circulation had been ineffective for 7 minutes or more before defibrillation.”

The key feature of this classic paper is of course the application of countershock (at voltages ranging from 240 to 720 volts!) without opening the chest. This approach did not always gain support. During the third Einthoven meeting, held at Leiden in 1983, Dr Zoll told the audience that one day he “unfortunately preceded Dr Claude Beck in a symposium on cardiac arrest” at which he proposed an initial trial of external stimulation for a few seconds before the undertaking of a thoracotomy, direct cardiac massage, and direct electric defibrillation, which was then the officially accepted program. Dr Beck then rose very forcefully to condemn my proposal as wasteful of precious time and most likely to jeopardize recovery.

Dr Zoll also mentioned a surprising objection to electrical resuscitation on religious grounds that his activities contravened the will of God.

Clearly, the path of pioneers is not always strewn with roses.

Termination of ventricular fibrillation in man by externally applied electric countershock

P. M. Zoll, A. J. Linenthal, W. Gibson, M. H. Paul, L. R. Norman


1956

US actress Grace Kelly marries Monaco’s Prince Rainier III; heavyweight boxing champion Rocky Marciano retires undefeated from boxing; and Ampex first demonstrates videotape at the National Association of Radio and Television Broadcasters convention in Chicago, Illinois
Electrical stimulation of the heart in patients with ventricular tachycardia

H. J. J. Wellens, R. M. Schuilenburg, D. Durrer

*Circulation.* 1972;46:216-226

Intracardiac electrical stimulation of the heart, combined with intracardiac recording of electrograms, now known as programmed electrical stimulation, began in 1967 with the simultaneous publication of papers from the Amsterdam group of the above-mentioned authors and from the Paris group of Coumel, Slama, and coworkers. They could initiate and terminate supraventricular tachycardias by well-timed premature stimuli in patients with accessory atrioventricular pathways. These arrhythmias are not hemodynamically compromising, and not life-threatening. Ventricular tachycardias, on the other hand, can be potentially lethal, and it took considerable courage to initiate this arrhythmia by premature stimulation.

This paper reports on 5 patients with recurrent attacks of ventricular tachycardia. Four patients had a previous myocardial infarction, the 5th had a myocarditis. Four catheters were introduced, two for stimulation of the right atrium and right ventricle, one for recording the His bundle electrogram, and one for registering the unipolar intracavitary right atrial complex. In all patients, the tachycardia could be initiated by a single right ventricular premature beat. The synchronizing circuit of the stimulator permitted sensing of the QRS complex during the tachycardia and delivering premature stimuli at progressively shorter intervals. In 3 patients, a single premature beat terminated the tachycardia, in 2 patients two right ventricular premature beats were needed. The authors concluded that reentry was the most likely mechanism for the tachycardia, and discussed several possible reentrant circuits, even though they could not be delineated.

Programmed electrical stimulation of the heart has been used to determine arrhythmogenic mechanisms, to identify patients at high risk for sudden death, and to select antiarrhythmic drugs most likely to suppress the arrhythmia in question. Initiation and termination of a tachycardia most often indicates that the arrhythmia is caused by reentry or by triggered activity based on delayed afterdepolarizations. A distinction between the two can be made on the basis of the relationship of the coupling interval of the initiating premature beat and the first tachycardia interval.

Long periods of nonsustained ventricular tachycardia and sustained monomorphic or polymorphic ventricular tachycardia cannot be initiated in the normal heart, but ventricular fibrillation can be induced in normal hearts when using an “aggressive” stimulation protocol with three to four successive strong premature stimuli. Inducibility of tachycardias is a very strong indicator that these arrhythmias may also occur spontaneously and it has been used as an entry criterion for many clinical trials.

For many decades it was thought that an antiarrhythmic drug that made an arrhythmia noninducible during programmed electrical stimulation would be effective in abolishing the arrhythmia during long-term follow-up. One must now conclude that this approach has been disappointing. The greatest benefit of programmed electrical stimulation seems to be that so much has become known about arrhythmogenic mechanisms in the human heart. No other technique can equal this success.
As early as 1889 McWilliam wrote that sudden death in patients with obstruction of some portion of the coronary system is "very probably determined or ensured by the occurrence of fibrillar contractions in the ventricles. The cardiac pump is thrown out of gear, and the last of its vital energy is dissipated in a violent and prolonged turmoil of fruitless activity in the ventricular walls." Thirty-four years later, he complained that little attention had been given to his new view. Indeed, ventricular fibrillation did not receive much attention in the first half of the 20th century. Only in the 1960s did the medical profession begin to appreciate that ventricular fibrillation in acute ischemia and in the early phase of myocardial infarction was a frequent event. In the late 1960s, the delay between onset of symptoms of acute ischemia and admission to a coronary care unit was about 4 hours (patient delay about 90 minutes, doctor delay about 1 hour, some 30 minutes before the ambulance arrived, and 1 more hour to the admission in the coronary care unit).

As stated in the opening sentences of the present paper, it became apparent that approximately two thirds of patients who die from coronary artery disease do so before reaching medical care. Mobile coronary care units were used by the group of Pantridge in 1967 in Belfast in an attempt to resuscitate victims of cardiac arrest outside the hospital.

The unique features of the approach of the Seattle group described in this paper are: (i) a single emergency telephone number, with an initial response by firefighters trained as emergency medical technicians. The initial response was, astonishingly, on average less than 3 minutes; (ii) a secondary response unit consisted of paramedical personnel with a 1000-hour training program; and (iii) finally, when indicated, the patient was transferred to one of fourteen hospitals. This initial paper reported on 821 patients who were in ventricular fibrillation when medical assistance first arrived, as well as 65 additional patients who developed this arrhythmia in the ambulance. There were 146 long-term survivors. The mortality rate of these patients was 26% after 1 year, and 38% after 2 years. A surprising finding was that only 17% of patients surviving hospitalization following out-of-hospital defibrillation had a transmural myocardial infarction. The mortality rate of these patients was relatively low. About one half of the patients had evidence of myocardial necrosis, based on new Q waves and abnormal LDH isoenzyme patterns. The rest apparently had transient ischemia. The patients who showed no evidence of myocardial necrosis had a markedly greater mortality rate in the postresuscitation period.

In later publications of the Seattle group, it was found that cardiopulmonary resuscitation (CPR) by bystanders greatly improved prognosis. By 1979, over 223 000 people had been trained in CPR. In 1999, the group reported on the neurological status of 288 survivors. Four levels were distinguished: level 1 patients (n=184) had apparent intact brain function with minor short-term memory deficits or generalized weakness, level 2 patients (n=31) had major memory loss, and coordination deficits, level 3 patients (n=64) were awake with obviously impaired neurological status—they might be without language, and were, as were the level 2 patients, entirely dependent on others, level 4 patients (n=9) were unresponsive, and comatose or vegetative. Improved neurological recovery was only evident in cases with initial response intervals of less than 4 minutes.

It is clear that such results can only be achieved by a large commitment of the community, and a level of traffic that allows the very rapid initial response of the firefighters. Possibly because of these features, similar programs in other cities have not been as successful.

Ricky Ponting, Australian cricket captain and prodigious batsman, is born; Greek voters reject a proposal to restore the Greek monarchy; and Darwin, Australia, is almost completely destroyed by cyclone Tracy.
One of my most vivid memories is of Dr Mirowski showing a movie during a meeting in Copenhagen in 1977. A dog had been implanted with both a fibrillator and a defibrillator, and the film showed the dog trotting along with, on the lower part of the screen, his ECG. The fibrillator delivered a shock, the ECG showed ventricular fibrillation, and the dog fell on the floor. Within a few moments the device had recognized the arrhythmia and delivered a countershock; sinus rhythm ensued, the dog jumped up and tip-toed away. It was impossible not to associate this sequence with super 8 home movies depicting the holidays of friends; when the host had shown his wife elegantly diving in the pool of the Parador, he reversed the projector and there she emerged from the water, feet first, to land safely at the pool’s edge. Dr Mirowski did not take kindly to levity where it concerned his defibrillator, and understandably so. He should be admired for his perseverance in developing the implantable automatic defibrillator in the face of skepticism and antagonism. Although the movie clearly showed proof of concept, very few in the audience envisaged the possibility that within 3 years the defibrillator would be implanted in a patient. In 1972, when he was working together with Dr Mower in developing the device and testing it on dogs, an editorial by Lown and Axelrod questioned the desirability of the implantable defibrillator. Although subsequent events proved them wrong, one caveat is still valid: “for whom is such a device intended?”

The 1980 paper described 3 patients in whom the defibrillator was implanted. “The criteria for entry into the pilot study were stringent. The initial subject had to have survived at least two episodes of cardiac arrest not associated with acute myocardial infarction, with ventricular fibrillation documented at least once. One such episode had to have occurred despite presumably effective antiarrhythmic treatment (…) The extremely poor prognosis of patients with these features is exemplified by the fact that 4 patients identified as candidates for implantation of the device died before transfer to this hospital.” The first implant of an automatic implantable cardioverter defibrillator (AICD) took place on February 4, 1980. The patient was a 57-year-old woman with a previous myocardial infarction and subsequent multiple episodes of cardiac arrest. As Dr Mower recalled in 1995, “Following implantation of the device the patient was induced into ventricular fibrillation using alternating current, and the device was allowed to automatically detect and defibrillate. The detection time for this first episode was over 30 seconds and very nearly led to aborting of the test using external defibrillation. One can only speculate how much time this would have set us back in the project had that occurred.” The authors of the 1980 paper emphasized that the device “is not a definitive treatment for recurrent malignant arrhythmias” and could be seen as providing “a critical backup safety mechanism”.

It is gratifying to note that Dr Mirowski, despite his untimely death in 1991, lived to see how the use of his device skyrocketed: in 1985, the US Food and Drug Administration approved market release of the device, in August 1990, well over 10,000 units had been implanted; in 1995, this number had increased to 65,000. For many cardiologists today, the AICD is the cornerstone of the treatment of sudden cardiac death.

Two-month-old Australian baby Azaria Chamberlain disappears from a campsite near Ayers Rock, reportedly taken by a dingo; the UN Security Council condemns the Israeli declaration that all of Jerusalem is its capital; and Jack Nicklaus wins the PGA Golf Championship for the 5th time.
Several studies in the late 1970s and early 1980s had shown that the presence of frequent and repetitive forms of ventricular premature beats in patients that had survived a myocardial infarction were independent risk factors for sudden death. Prior studies with antiarrhythmic drugs in postinfarction patients (14 short-term and 6 long-term studies, totaling over 4500 patients) were seriously flawed in the sense that the number of patients was too small, entry criteria were not strict enough, dosage of the drugs was too low, so that “the effect of antiarrhythmic drugs has not been fairly tested.” These criticisms do not apply to the Cardiac Arrhythmia Suppression Trial (CAST) study, which at a cost of $18 million, tested encainide, flecainide, and moricizine, prospectively, randomized, double-blind, and vs placebo, in 2309 postinfarction patients with asymptomatic, or mildly symptomatic, ventricular premature beats. In a preceding Cardiac Arrhythmia Pilot Study these drugs were tested for their ability to suppress the arrhythmias adequately in the target population. The 1727 responders were then randomized to drug or placebo. The trial produced surprising results: despite effective suppression of ventricular premature beats, the arms with encainide and flecainide were prematurely stopped because these drugs significantly worsened total mortality compared to the placebo group.

A remarkable aspect of CAST was the very low mortality in the placebo group: during the 10-month follow-up period, total mortality was 3.0%, and sudden death mortality was 1.2%. (The investigators had anticipated a sudden death mortality in the placebo group of 4.5%). In the encainide- and flecainide-treated patients, these numbers were 7.7% and 4.5%, respectively. With such a low mortality in the control group, one would have needed a miracle drug to further lower it. CAST demonstrated convincingly the value of a placebo-controlled trial. Had “historical” control groups been used from earlier antiarrhythmic drug trials, with 1-year mortalities varying from 4.1% to 20%, encainide and flecainide could have come out as successful drugs. There are several reasons for the low mortality in the placebo group. First, during the pilot study, 19% of the patients were excluded because of drug inefficacy or intolerance, proarrhythmia, or death. Secondly, there is a historical trend towards lower mortality in coronary artery disease because of new therapy such as thrombolysis, angioplasty, and coronary bypass surgery. Thirdly, patients entering a trial generally receive intensive control and therapy. Finally, patients with salvos or nonsustained ventricular tachycardia were underrepresented. It is more difficult to explain the unexpected high mortality in the two treatment arms. Classic proarrhythmia occurs early, but this was not the case in CAST. Animal studies have shown that in the 4-day-old infarct, flecainide slows conduction and enables sustained reentry to occur more easily.

The impact of CAST was enormous. For decades, asymptomatic ventricular premature beats were treated with antiarrhythmic drugs by more than 50% of cardiologists, and repetitive forms by more than 90%. Have these doctors been “bumping their patients off,” as a famous epidemiologist once implied? The use of sodium channel–blocking agents dramatically decreased after CAST. Hopes were focused on “pure” class III drugs, blocking potassium channels, but trials like SWORD (Survival With ORal D-sotalol) abolished these hopes because this drug also proved to be harmful. The only antiarrhythmic drug that doesn’t kill is amiodarone, but although the drug reduced arrhythmic mortality, total mortality was not affected. By and large, CAST put an end to efforts to reduce mortality due to ventricular arrhythmias by antiarrhythmic drugs.

The comic strip Bloom County by Berke Breathed ends; two million Estonians, Latvians, and Lithuanians join hands to form a 600-km long human chain to demand independence from the Soviet Union; and Voyager II passes the planet Neptune and its moon Triton
Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia


After the Cardiac Arrhythmia Suppression Trial (CAST) and Survival With Oral D-Sotalol (SWORD) trial had shown that sodium and potassium channel blockers may be harmful in postinfarction patients, the only promising antiarrhythmic drug was amiodarone. The European Amiodarone Infarct Amiodarone Trial (EMIAT) showed that the drug reduced arrhythmic death from 7% in the placebo group to 4% in the amiodarone group. Total mortality, however, remained unchanged. In the Canadian Amiodarone Myocardial Infarction Trial (CAMIAT) again, arrhythmic mortality was reduced, from 6% to 3.3%, but total mortality was unaffected. The benefit of amiodarone was in both trials associated with cotreatment with β-blocking agents.

A meta-analysis of 13 randomized amiodarone trials, involving 6553 patients, revealed a significant reduction of not only sudden death mortality, but also of total mortality. Still, for the prevention of sudden death in high-risk patients, the implantable defibrillator seemed a far better choice than amiodarone therapy. Many studies had confirmed that the device was able to terminate ventricular fibrillation automatically, but no randomized trial had been conducted to test the device against antiarrhythmic drug therapy.

The pioneering Multicenter Automatic Defibrillator Implantation Trial I (MADIT I) of Moss and coworkers described here began recruiting patients in 1990. Since nonsustained ventricular tachycardia in patients with a previous infarction had a high mortality rate, this arrhythmia was the main entry criterion of the study. In addition, patients had to have inducible sustained ventricular tachycardia that could not be suppressed by IV injection of procainamide, and an ejection fraction of less than 35%. It took 5 years to recruit 196 patients that were randomized to an implantable defibrillator and “conventional” medical therapy. After 1 month, 74% of the conventionally treated patients used amiodarone, but sotalol and class I antiarrhythmics were also prescribed by the attending physician. During an average follow-up of 27 months, 19 patients died in the defibrillator group (11 from cardiac causes), versus 39 in the conventionally treated patients (27 from cardiac causes).

The hazard ratio for total mortality was 0.46, with a 95% confidence interval of 0.26 to 0.82, *P*=0.009.

This was the first study that proved the superiority of the implantable defibrillator over antiarrhythmic drugs. It was criticized because at 1 month 26% of patients in the defibrillator group received β-blockers, versus only 8% in those on conventional therapy. β-Adrenergic agonists had been shown to provide benefit after myocardial infarction, and the use of these agents in the defibrillator group was seen as a confounding factor. The authors could show that after accounting for the use of β-blockers, the benefit in the defibrillator group remained statistically significant.

A more important question is whether this study definitively proved that the implantable defibrillator is the therapy of choice to prevent sudden death. From the analysis of Myerburg in 1992, it appeared that the overall incidence of sudden death in the general adult population is in the order of 0.1%, but the total number of events per year in the USA is very high, ie, 300,000. The incidence in the patients with the characteristics of the MADIT I study described here is very high, in the order of 35%, but the total number of events is approximately 20,000. Even if all patients with the MADIT I entry criteria could be identified, which is an impossibility given the fact that nonsustained ventricular tachycardia must be documented, and programmed electrical stimulation must be carried out, the implantable defibrillator would only have a limited impact on the total number of people dying suddenly.

Mother Teresa receives honorary US citizenship; Uday Hussein, eldest son of Saddam Hussein, is seriously injured in an assassination attempt in Iraq; and fire destroys La Fenice, Venice’s opera house
A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias

Antiarrhythmics Versus Implantable Defibrillator (AVID) Investigators


own and Axelrod, in their Editorial of 1972, questioned “whether an indication can be spelled out for the use of an implanted standby defibrillator” and they stated that at that time “there is no precise method for identifying the susceptible subject.” Twenty-five years later, the Multicenter Automatic Defibrillator Implantation Trial (MADIT I) study had identified a small subset of patients that did indeed benefit from the implantable defibrillator and, in the Antiarrhythmics Versus Implantable Defibrillators (AVID) study, another category of patients was investigated. These were patients that had been resuscitated from near-fatal ventricular fibrillation and patients with ventricular tachycardia with syncope, or with an ejection fraction of 40% or less with symptoms suggesting severe hemodynamic compromise, such as near-syncope, congestive heart failure, and angina.

Of 1016 patients that entered the study, 45% had ventricular fibrillation and 55% ventricular tachycardia. They were randomly assigned to treatment with an implantable cardioverter-defibrillator or to treatment with antiarrhythmic drugs. Incidentally, 6035 patients were screened, and 1885 patients were found to be eligible for randomization. This points to a characteristic aspect of a clinical trial, namely that only a portion of patients with the entry criteria participate in the study.

Most of the 509 patients assigned to drug therapy received amiodarone, and only a few were maintained on sotalol. Of the patients with a cardioverter-defibrillator, 80 died, versus 122 deaths in the antiarrhythmic drug group. Over a mean follow-up of over 18 months, the mortality rate was 15.8% in the defibrillator group, and 24.0% in the antiarrhythmic drug group. This was a significant difference, with a P value of 0.02. However, the average unadjusted length of additional life associated with the cardioverter-defibrillator therapy was only 2.7 months at 3 years. As in the MADIT I study, there was significantly greater use of β-blockers in the patients receiving a cardioverter-defibrillator, and it is uncertain whether the benefit of defibrillator therapy might have partially been due to β-blocker therapy.

It is evident that the mere presence of a cardioverter-defibrillator is not life-saving, and it is of interest to see how often the device was activated. For the patients with ventricular fibrillation an appropriate shock was given in 15% at 3 months, 39% at 1 year, 53% at 2 years and 69% at 3 years. Thus, after 3 years, roughly one third of the patients had not received a shock. This indicates that the identification of patients who will develop ventricular fibrillation is still not very precise. Although the AVID trial expanded the criteria for implanting a cardioverter-defibrillator, Myerburg and Castellanos, in an accompanying Editorial, wrote: “It is unlikely that more than 5% to 10% of the total number of sudden deaths from cardiac causes in the United States occur among patients who would be candidates for implantable-defibrillator therapy according to the entry criteria of the AVID trial and MADIT.”

In the same issue of the Journal, the Coronary Artery Bypass Graft (CABG) Patch Trial was published. Patients undergoing coronary bypass surgery who had an abnormal signal-averaged electrocardiogram (considered to be a marker of high risk of arrhythmic death) and an ejection fraction below 36% were randomized to defibrillator therapy and a control group. No benefit was conferred by the defibrillator. The first discharge of the device occurred in 50% of patients after 1 year, in 57% at 2 years.

Thus, in 1997, we were still unable to define precisely the patients that needed a defibrillator, and even in high-risk patients, a substantial portion of patients in whom the defibrillator was implanted received no appropriate shock within 2 to 3 years.

1997

Ramzi Yousef is found guilty of masterminding the 1993 World Trade Center bombing; sixty-two people are killed by Islamic militants outside the Temple of Hatshepsut in Luxor, Egypt; and Michael Hutchence, the lead singer of INXS, dies.
Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction


Seeking to expand the indications for implantable cardioverter-defibrillator (ICD) therapy, the Second Multicenter Automatic Defibrillation Implantation (MADIT II) investigators used simple entry criteria: patients with a previous myocardial infarction and an ejection fraction of 30% or less were randomized to the defibrillator or conventional therapy. During an average follow-up of 20 months, the mortality rates were 14.2% in the defibrillator group and 19.8% in the conventional therapy group. Again, an impressive result.

The authors were quick to point out the potentially far-reaching consequences of this study, and wrote: “An estimated 3 million to 4 million patients have coronary heart disease and advanced left ventricular dysfunction in the United States (…) If a meaningful number of these patients receive an ICD prophylactically, the cost to the health care system would be substantial. We hope that marketing forces will drive down the cost of this therapy.” In a letter to the Editor, the cost was estimated at 12 billion dollars annually, three times the budget for the Centers for Disease Control and Prevention.

Later analyses came up with some surprising results. During a 17.2-month average follow-up, appropriate shocks were observed in 169 (24%) of 719 patients. The index arrhythmia was ventricular fibrillation in only 30 patients, ventricular tachycardia (VT) in 139 patients. The authors wrote that “it would be inappropriate to conclude that each of the discharges for ventricular tachycardia represents the prevention of a lethal event. Many of the VT episodes would probably have terminated spontaneously.” Thus, only in the 30 patients out of 719 in whom ventricular fibrillation developed was the device definitively life-saving. Another worrying aspect was that “patients receiving ICD therapy are at higher risk for developing heart failure and late non-sudden cardiac death.” Could it be that in exchange for the prevention of sudden, arrhythmic death, the patient will die later from intractable heart failure?

The MADIT II study offered food for a debate on the question of whether all patients with a previous infarction and an ejection fraction lower than 30% should receive an automatic ICD. Dr A. E. Buxton thought that a low ejection fraction is far from an ideal risk-stratification test. He argued that the major mechanism responsible for sudden death is ventricular fibrillation induced by acute ischemia, and most of these patients do not have markedly abnormal ventricular function. The mechanism for ventricular tachycardia/fibrillation in patients with a healed infarct is different from that during acute ischemia, and requires reentrant pathways formed by surviving myocardial bundles within the infarct. Again, a low ejection fraction need not be present. In hypertrophy and heart failure, arrhythmogenic mechanisms are different from those during ischemia and those in the chronic phase of myocardial infarction. In a study from Maastricht, more than half of the cases of sudden death occurred in patients with an ejection fraction above 30%. In short, it appears that we need a more refined risk stratification profile to answer the question already posed in 1972: “For whom is such a device intended?” If patients who would profit from a defibrillator can be more precisely identified, the number of implanted patients who never receive an appropriate shock will diminish, and the cost will go down as well.

The European Space Agency’s Envisat environmental satellite is successfully launched into orbit by Ariane 5 in Kourou, French Guyana; Abdul Mohsen Musalam is jailed in Saudi Arabia following the publication of his poem *The Corrupt on Earth* criticizing the state’s Islamic judiciary; and novelist Arundhati Roy is convicted of contempt of court by the Supreme Court in New Delhi over his role in the Narmada Dam Project protests.
Brugada syndrome quickly caught on as a name for the syndrome described in this paper, even though the Brugada brothers initially carefully avoided using the term; however, since everybody else did so, they finally yielded. In their landmark report they describe 8 patients, seen over a 5-year period, who all presented with a syncopal episode without any prodrome. The ECG showed a right bundle-branch block and persistent ST-segment elevation in V1 to V2-V3. The cause of the aborted sudden death was a polymorphic ventricular tachycardia with a very short cycle length (between 170 and 230 ms). During programmed electrical stimulation, a nonsustained ventricular tachycardia could be induced in some patients, a sustained polymorphic tachycardia degenerating into ventricular fibrillation in other patients. No structural cardiac abnormalities could be detected “by our present methods of investigation.” A hereditary factor was suspected (occurrence of the syndrome in two siblings and a family history of unexplained sudden death in two others). Four patients were treated with an implantable defibrillator.

In 1998, it was found that the syndrome was associated with mutations in the cardiac sodium channel–encoding gene SCN5A, leading to loss of function of the channel. However, the syndrome is associated with sodium channel mutations in only 20% of patients. Possible explanations for this discrepancy are failure of standard screening techniques to detect mutations, and the coexistence of other genetic factors. Since mutation is found in 80% of patients, it is questionable whether the syndrome should be characterized as a “channelopathy.” As a potential arrhythmogenic mechanism, transmural dispersion of repolarization in the right ventricular wall leading to phase 2 reentry has been hypothesized. Also, ST-segment elevation has ascribed to localized conduction delay. Nowadays, a provocation test with sodium channel blockers, which can induce ST-segment elevation, is added to the diagnostic arsenal.

Recently, the heart of a patient diagnosed as having Brugada syndrome by Pedro Brugada 13 years earlier became available. The patient had an implantable defibrillator, but received so many shocks for recurrent episodes of ventricular fibrillation that he required cardiac transplantation. Study of the explanted heart showed slowing of conduction and localized interstitial fibrosis in the endocardium of the right ventricular outflow tract. Endocardial reentry was responsible for ventricular fibrillation. There was no transmural gradient in repolarization. A mutation was found in the sodium channel gene, and HEK293 cells expressing the mutated sodium channel showed enhanced slow inactivation compared with wild-type channels. The patients had no structural heart disease recognizable by our present methods of investigation. It is therefore possible that localized structural abnormalities, such as interstitial fibrosis, may be present in other Brugada syndrome patients, that are undetected by routine clinical methods.

It is the great merit of the Brugas to have recognized the syndrome on the basis of simple clinical and ECG characteristics. Brugada syndrome accounts for 4% to 12% of all sudden deaths. The incidence is in the order of 5 per 10,000 inhabitants. Apart from accidents, it is the major cause of death in young Asian males. This study beautifully shows that 97 years after Einthoven published his paper entitled “On the form of the human electrocardiogram,” careful observation of the form of the ECG could lead to the discovery of a new syndrome.

1992

The Church of England votes to allow the ordination of women; the Czechoslovakia Federal Assembly votes to split the country into the Czech Republic and Slovakia; and Bill Clinton defeats incumbent President George Bush and candidate Ross Perot in the US presidential election.
Long QT syndrome (LQTS) is an uncommon familial disorder that frequently leads to sudden death caused by a specific polymorphic ventricular tachycardia, torsades de pointes, usually before the age of 20 years. It is estimated to affect 1 in 5000 individuals. For many decades it was thought to be caused by an imbalance in the sympathetic nervous system, and, apart from β-blockade, one of the treatments used was left-sided cardiac sympathetic denervation. A single case history proved the sympathetic imbalance hypothesis untenable: after complete denervation of the heart of a child with LQTS, the child continued to have a long QT interval, arrhythmias, and eventually suffered sudden death. In a review of 1991, Zipes concluded that “the weight of the evidence suggests that an intrinsic myocardial abnormality in repolarization is responsible for LQTS.”

In 1991, Keating and coworkers reported a “linkage of cardiac arrhythmia, the long QT syndrome, and the Harvey ras-1 gene,” but no mutation was described. In the early 1990s, it had become clear that LQTS is a heterogeneous disease, with different loci: on chromosome 11 (LQTS1), on chromosome 7 (LQTS2), and on chromosome 3 (LQTS3). The study of Curran et al was the first to describe a mutation in the human-ether-a-go-go-related gene (HERG), a gene encoding a potassium channel. The study opened up a new specialty, that of molecular genetics of arrhythmias, a field that developed explosively. Genetic aberrancies have been identified in a large number of patients. Molecular genetic research, combined with basic electrophysiological studies in heterologous expression systems, and computer models have shown that both “gain of function” mutations and “loss of function” mutations can cause a number of different diseases. LQTS1 and LQTS2 are due to “loss of function” mutations in genes encoding potassium channels (the slowly activating delayed rectifier $I_{Kr}$, and the rapidly activating delayed rectifier $I_{Kr}$, respectively). The resultant loss of outward current carried by potassium ions prolongs the cardiac action potential and the QT interval. A “gain of function” mutation in the gene encoding the sodium channel causes LQTS3. Here, the action potential and the QT interval are prolonged by a residual inward current carried by sodium ions during the plateau phase of the action potential. A “loss of function” mutation is responsible for the Brugada syndrome.

Interestingly, genetic aberrancies in the cardiac sodium channel have been shown to cause a variety of clinical phenotypes: QT prolongation in LQTS3, precordial ST-segment elevation in the Brugada syndrome, conduction slowing, and sinus node dysfunction. Various families have been described with such “overlap syndromes,” in which different combinations of these characteristics occur. Although the link between a mutation in a gene encoding an ion current involved with repolarization and the clinical phenotype seems logical and straightforward, many carriers of a particular mutation never show signs or symptoms. In particular, in LQTS and Brugada syndrome, some individuals carrying the mutation may show abnormalities in the electrocardiogram, arrhythmias, and suffer from sudden death, while other family members carrying the same mutation never show electrocardiographic abnormalities, and never develop arrhythmias. This has far-reaching consequences for diagnosis, treatment, and genetic counseling, because the silent mutation carriers may transmit the genetic defect to their offspring. It implies that genetic modifiers may determine the ultimate phenotype in the presence of a specific mutation. In some cases of LQTS, such modifiers, undetected by routine genetic testing, have already been identified.

Georges Kohler, the German Nobel prizewinning biochemist for his work on monoclonal antibodies, dies; Color of Night, starring Bruce Willis, wins worst film at the 15th Golden Raspberry Awards; and Polish Prime Minister Waldemar Pawlak resigns and is replaced by ex-communist Jozef Oleksy
<table>
<thead>
<tr>
<th>Citation</th>
<th>Bibliography Entry</th>
</tr>
</thead>
</table>
## Bibliography of One Hundred Key Papers

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title of Paper</th>
<th>Journal</th>
<th>Year</th>
</tr>
</thead>
</table>
Davies MJ, Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. 

Delacretaz E, Stevenson WG, Ellison KE, Maisel WH, Friedman PL. Mapping and radiofrequency catheter ablation of the three types of sustained monomorphic ventricular tachycardia in nonischemic heart disease. 

*JAMA.* 2004;292:2874-2879.

Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. 


Hartikainen JEK, Malik M, Staunton A, Poloniecki J, Camm AJ. Distinction between arrhythmic and nonarrhythmic death after acute myocardial infarction based on heart rate variability, signal-averaged electrocardiogram, ventricular arrhythmias and left ventricular ejection fraction. 

Bibliography of One Hundred Key Papers

Hazinski MF, Idris AH, Kerber RE, et al; American Heart Association Emergency Cardiovascular Committee; Council on Cardiopulmonary, Perioperative, and Critical Care; Council on Clinical Cardiology. Lay rescuer automated external defibrillator (“public access defibrillation”) programs: lessons learned from an international multicenter trial; advisory statement from the American Heart Association Emergency Cardiovascular Committee; the Council on Cardiopulmonary, Perioperative, and Critical Care; and the Council on Clinical Cardiology. Circulation. 2005;111:3336-3340.


<table>
<thead>
<tr>
<th>Reference</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Title</td>
</tr>
<tr>
<td>-----------</td>
<td>--------</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Title</td>
</tr>
<tr>
<td>----------</td>
<td>-------</td>
</tr>
</tbody>
</table>