Sudden Cardiac Death, Genes, and Arrhythmogenesis

Consideration of New Population and Mechanistic Approaches From a National Heart, Lung, and Blood Institute Workshop, Part II*

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Abstract—This is Part II of a 2-part article dealing with malignant ventricular arrhythmias, which are the leading mechanism of death in common cardiac diseases. Genetic population studies directed at discovering common proximal sources of inherited molecular risk most directly linked to arrhythmia initiation and propagation would appear to have considerable potential in helping reduce cardiovascular mortality. **(*Circulation*. 2001;103:2447-2452.)**

Key Words: genetics ■ death, sudden ■ arrhythmia ■ tachyarrhythmias ■ epidemiology ■ mortality ■ ion channels

New Sudden Cardiac Death Population Studies

Recently, 2 new genetically oriented population studies with important implications for risk stratification of sudden cardiac death (SCD) were published, and their results have already begun to help address the possibility that new molecular approaches to SCD risk stratification may be a useful addition to present strategies. The first publication[1] reported findings of a population-based, case-control study of >500 subjects who experienced primary cardiac arrest in Seattle, Wash. Its results, summarized in part in Table 1, suggest on the basis of a multivariable analysis of conventional biological, dietary, and environmental coronary artery disease (CAD) risk factors that family history appears to be a significant, independent element of risk for SCD in this heterogenous population. Odds ratio calculations for elevated risk due to familial association indicate the risk of SCD events increases 1.57-fold, independent of other risk factors, if a first-degree relative has a history of myocardial infarction or primary cardiac arrest, and this was the fourth strongest association in the analysis.

The second study, the Paris Prospective Study I,[2] was an even larger prospective analysis of >7000 men followed up for an average of 23 years. This work analyzed traditional risk factors in 118 SCDs and 192 myocardial infarction deaths that occurred in previously healthy participants who had no history of cardiac disease on enrollment. In addition to increased mortality associated with conventional CAD risk factors, the analysis, summarized in Table 2, also independently supports the postulate that family history is a strong, independent predictor of SCD susceptibility. Parental history of SCD increased the relative risk of SCD to 1.8 after adjustment for conventional CAD risk factors indicated in Table 2 but did not elevate risk for deaths coded as nonsudden cases of myocardial infarction. In a small subset in which there was a history of both maternal and paternal SCD events, the relative risk for SCD in offspring was a remarkable 9.4. Risk of fatal myocardial infarction due to parental history of infarction (relative risk=2.30, Table 2) was surprisingly unaffected in families in which parental sudden arrhythmic events had been observed. Remarkably, the converse was also true, and increased risk of SCD in offspring was not associ-

Received November 7, 2000; revision received February 1, 2001; accepted February 16, 2001.

*The first part of this two-part article appeared in the May 15, 2001, issue of *Circulation*.

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TABLE 1. Risk of Primary Cardiac Arrest Associated With Selected Risk Factors in First-Degree Relatives in the Seattle-King County Case-Controlled Study

	OR	95% CI
Age (for 10 y)	1.11	0.91–1.34
Male sex	1.33	0.81–2.17
Diabetes	4.25	1.98–9.12
Hypertension	1.62	1.02–2.58
Hypercholesterolemia	1.21	0.78–1.86
Education (<high school)	1.49	0.97–2.30
Current smoking	4.90	3.00–8.00
High coffee intake (≥5 cups/d)	1.33	0.80–2.19
Physical activity (>20th percentile)	0.54	0.37–0.81
High fat intake (>80th percentile)	1.03	0.67–1.58
High BMI (BMI>29.0)	1.10	0.71–1.69
Family history in first-degree relatives	1.57	1.27–1.95

BMI indicates body mass index.

Logistic modeling of the risk of primary cardiac arrest (cardiac arrest not secondary to noncardiac causes) (eg, trauma, drugs). Table lists ORs and 95% confidence limits. Population studies included all cases of out-of-hospital primary cardiac arrest found by metropolitan paramedics to have expressed a sudden pulseless condition between October 1988 and July 1994. Subjects were excluded if they had a clinical history of heart disease (angina, prior infarction, bypass surgery, angioplasty, congestive failure, arrhythmias, or cardiomyopathy) or congenital or valvular disease or other comorbidities. Only individuals aged 25 to 74 years were included. Control subjects for each of the 418 eligible cases were randomly matched for age (±7 years) and sex, and only subjects who had no prior history of heart disease or other comorbidity were included. Risk factor presence was determined by detailed family interviews, medical records, and autopsy records. Modified from Reference 1.

ated with parental risk of infarction. Although questions remain about the distinction between deaths classified as sudden and nonsudden in the 2 studies, there seems little doubt this work provides strong evidence for familial SCD aggregation independent of the distribution of the classic risk factors that have been the primary focus of most previous attention regarding strategies for cardiovascular mortality reduction.

With respect to genetic implications, it should, however, be noted that "familial" associations in both these studies would include both chromosomally transmitted and shared nongenetic risks, including factors such as common in utero or postnatal environmental exposures. It will therefore be important to determine whether these associations are attributable to heritable genetic effects that continue to be expressed in additional generations of the same families. Studies on twins would also be helpful. In addition to confirming direct genetic susceptibility, another important goal for both types of studies would be to determine whether such findings might also be influenced by unexpected statistical interactions or confounding effects in the analyses used in the 2 previous works.

Risk Factors and Genetic Influences on SCD Susceptibility

The Figure suggests 3 broad pathways by which genetic variation in physiological and pathological mechanisms may contribute to risk for SCD. These include (1) processes and factors that contribute to the formation and stability of atherosclerotic plaque, thrombosis, and ischemia within the coronary circulation; (2) cellular elements and pathways that directly affect alterations in electrogenesis and conduction; and (3) those elements of central and local control that influence myocardial excitability and vascular contractility.

Atherosclerosis, thrombosis, and infarction resulting from CAD probably represent the largest predecessor of lethal arrhythmias in the general cardiac disease population, and there is much evidence that genetic variability plays a significant role in their development. Increased cardiac mortality has been reported in association with inherited changes in HDL and LDL levels; changes in modifying influences such as apolipoprotein (Apo) E polymorphisms; changes in levels of ApoA-I, ApoB, lipoprotein(a), and lipoprotein receptors (eg, the hepatic LDL receptor); lipase variants (eg, lipoprotein lipase); homocysteine levels; and various metabolic and endocrine influences that contribute to plaque formation. At least a dozen such associations for CAD have been mapped to different chromosomal sites.[3] Inflammatory vascular processes, especially those signaled by chronic elevations in markers such as hepatic C-reactive protein,[4] as well as cytokines like tumor necrosis factor-α and interleukin-1[5] and adhesion molecules like intercellular adhesion molecule-1,[6] are recent additions to this list. Along with changes in macrophage and lymphocyte invasion, such markers are probably best characterized as important contributing factors reflecting distal upstream mechanisms.

Despite genetic association between facilitators of CAD and SCD, most of these types of markers remain indicators of predisposing conditions (ie, occlusive vascular disease and ischemia) rather than markers of ventricular arrhythmogenesis per se. There is overlap in causation, but there is dissociation between the two, a distinction readily apparent in the clinical observation that at least half of all SCD events likely occur in subjects with normal lipid and lipoprotein levels and a virtual absence of elevations in other conventional risk factors.[7] Although they are obviously contributory, the predisposing influences on risks for CAD are clearly not necessarily indicators of arrhythmias or SCD in all individuals.

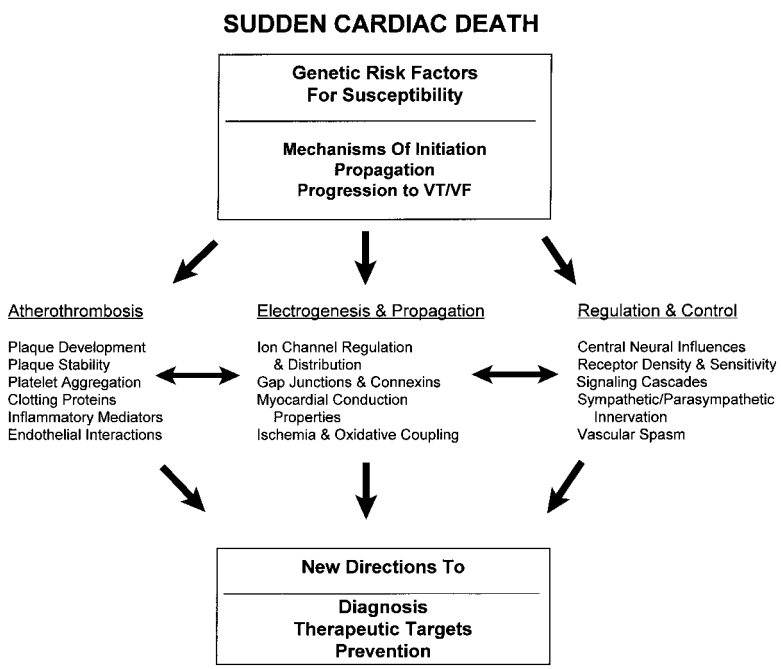
In terms of factors whose genetic variation might relate more directly to SCD susceptibility, alterations in mechanisms of plaque rupture and vulnerability appear positioned more proximally to enhanced susceptibility to acute arrhythmogenesis. There is good evidence, for example, of genetic differences in plaque lability between men and women, and differential sensitivities to environmental factors such as stress, physical exertion, and tobacco smoke, as well as age and hormonal state, have been studied with positive results. Autopsy studies suggest that thrombosis and plaque rupture may be more common in men, especially smokers or those who experience cardiac events during physical exertion, whereas plaque erosion appears to be the predominant causal factor in premenopausal but not postmenopausal women.[8]

TABLE 2. Multivariate Relative Risk for SCD and Myocardial Infarction: The Paris Prospective Study I

	Sudden Death		Fatal Myocardial Infarction	
Variables	RR (95% CI)	*P*	RR (95% CI)	*P*
Age at entry	1.02 (0.84–1.24)	...	1.11 (0.96–1.33)	...
Body mass index	1.21 (1.03–1.87)	0.03	0.97 (0.84–1.14)	0.03
Tobacco	1.34 (1.11–1.51)	0.0001	1.25 (1.13–1.36)	0.0001
Diabetic status	2.21 (1.10–4.44)	0.02	1.18 (0.55–2.52)	...
Heart rate	1.22 (1.12–1.49)	0.007	1.25 (1.11–1.35)	0.006
Systolic blood pressure	1.23 (1.02–1.46)	0.02	1.37 (1.19–1.56)	0.0001
Cholesterol	1.23 (1.13–1.72)	0.0001	1.18 (1.09–1.53)	0.009
Triglycerides	0.93 (0.62–1.38)	...	1.11 (0.80–1.56)	...
Parental myocardial infarction	1.16 (0.60–2.25)	...	2.30 (1.47–3.60)	0.0003
Parental SCD	1.80 (1.11–2.88)	0.01	0.85 (0.52–1.39)	...

Multivariate modeling of risk for either SCD or fatal myocardial infarction in a longitudinal cohort of 7079 French male civil servants enrolled (1967–1972) and followed up for an average of 23 years through 1993. Sudden death was defined as natural death occurring within 1 hour of acute cardiac symptoms; fatal myocardial infarction cases were recorded only if there was evidence of infarction. A total of 118 sudden deaths and 192 myocardial infarctions were studied. Table lists adjusted relative risk (RR), 95% confidence limits, and *P* values using a proportional hazard analysis. Risk factors and family occurrence of SCD or myocardial infarction were determined by interview, family histories, and autopsy records at entry and throughout the follow-up period. Data on cause of death were reviewed by an independent committee. Average age of death was 59.2±6 years for sudden deaths and 64.3±64 years for myocardial infarction. Increased risk of an event for a 1-SD increase in the variables indicated: age, 1 SD=1.9 years; body mass index, SD=3.3 kg/m^2; tobacco consumption, SD=10.5 g/d; heart rate, SD=10.2 bpm; systolic blood pressure, SD=20 mm Hg; cholesterol, SD=42 mg/dL; and triglycerides, SD=112 mg/dL. Modified from Reference 2.

How genetic variation plays a role in acute plaque rupture is beginning to be known, and new clues are beginning to emerge, such as the observation of heritable alterations in matrix metalloproteinases (for instance, stromelysin), which promote degradation of the fibrin cap.[9] Also, molecular variants within pathways of platelet adhesion, arterial thrombosis, and the clotting cascade appear to be likely candidates for enhancing SCD susceptibility. Formation of a platelet-rich thrombus is mediated via binding of fibrin to the activated platelet glycoprotein IIb/IIIa receptor, and heightened platelet aggregation, for example, is associated with increased mortality in patients with CAD who have the PI^{A2} polymorphism in the IIIa gene.[10] The PI^{A2} variant also was associated with myocardial infarction and mortality in coronary patients.[11]



Mechanistic pathways through which variant alleles in susceptible individuals could affect mechanisms of initiation of arrhythmogenesis, propagation, and conduction of aberrant electrical impulses and transitions between potentially lethal ventricular tachycardias (VT) and ventricular fibrillation (VF) leading to SCD. Potential and documented elements of potential risk are depicted for 3 broad pathways: atherothrombosis, electrogenesis, and neural regulation and control. Dissection of molecular events involved in each pathway will provide new directions to improve diagnostics, identification of new targets for pharmacological or electrical therapies, and prevention.

Variation at this locus does not appear to be associated with development of CAD itself, indicative of more proximal effects in an already atherosclerotic phenotype. Mutations and polymorphisms in additional thrombotic factors, including relatively well-studied ones like the G20210A transition in the prothrombin gene,[12] clotting factor VII,[13] integrins,[14] clotting factor V Leiden,[15] and plasminogen activator inhibitor type 1,[16] have been suggested to increase cardiac mortality, but results have been inconsistent, reflecting perhaps different levels of risk in differing ethnic and age groups and differences in arterial versus venous processes. For instance, genetic variance affecting platelet function appears to be important in younger subjects, in whom a thrombogenic origin might appear likely, but not in older individuals, in whom discrete thrombi might be lacking. Nevertheless, genetic variation at this level could be quite important, as evidenced by elevated levels of D-dimer, a fibrinolytic plaque degradation product, which appears to be a strong risk predictor in patients vulnerable to SCD by virtue of prior, sublethal coronary events.[17]

Genetic variations that predispose to vasospasm and other vascular changes that lead to ischemic arrhythmias have been variously reported in the full physiological range of mediators that influence the vascular endothelium and smooth muscle. This would include those that affect responses to adrenergic, cholinergic, hormonal, and metabolic factors, as well as local mechanisms of control. A recent example of the latter was noted in studies on the vascular endothelial nitric oxide (NO) synthase (eNOS) system. Changes in tissue NO levels occur in patients with chronic hypertension, atherosclerosis, and thrombotic disorders, and polymorphic forms of eNOS have been described,[18] as have mutations in the promoter sequence for this gene.[19] One variant (ie, the eNOS 4/4 allele), appears particularly sensitive to an environmental influence (cigarette smoke), and inducible changes in eNOS gene expression may be a useful model for the study of external influences on triggering SCD in high-risk genotypes.

A final example of how genetic variation is likely to be especially important for SCD susceptibility involves autonomic neural influences, especially increased adrenergic and decreased cholinergic activity.[20] Genetic studies on normal and patient populations suggest there are a number of independent loci that influence cardiac excitability, directly affecting indicators of autonomic state such as resting heart rate and its variability.[20,21] Genetic variation at this level is suspect because (1) there is a close clinical relationship between increased SCD events and alterations in indicators of neural cardiac electrical control[22]; (2) adrenergic agonists trigger ventricular arrhythmias, and their circulating levels show similar diurnal patterns as SCD events[23]; and (3) adrenergic activation is known to directly initiate destabilizing changes in cardiac ion currents.[24] Polymorphic variation in β_1- and β_2-adrenergic receptors has been noted in patients with dilated cardiomyopathies[25] and has been reported to influence mortality in heart failure patients.[26] A direct role for alterations in sympathetic influence in SCD triggering has also been supported by observations on the effects of adrenergic agonists and antagonists in patients with the inherited long-QT syndrome, and preliminary data indicate that polymorphisms in the β_2-receptor gene may influence arrhythmia susceptibility in this syndrome (personal communication, R. Kass, PhD, 2001). Variation in pathways modulating systemic and local responses to autonomic transmitters thus appears highly likely to be involved in the onset of SCD events and constitutes one of the highest priority areas for future research.

Targeting Variation in Therapy

Although there exist multiple sources of molecular variation with potential to alter cardiac electrical performance, it is also apparent that we are only just beginning to identify those that may have functional significance in the occurrence of SCD events. Nevertheless, recent findings such as those discussed above suggest that there are new biochemical and molecular dimensions of risk that need to be explored. It is also apparent that the association of arrhythmia risk with various genotypes is likely to offer therapeutic advantages only if quantitatively significant levels of susceptibility are discovered to play a causative role in specific disease conditions, and if so, if such discoveries have meaningful implications in terms of therapeutic options for arrhythmia prevention. Today's reliance on the postevent "rescue" of patients with an implantable defibrillator reflects in large part the finding that pharmacological antiarrhythmic therapies to date have been largely unsuccessful in preventing sudden death in high-risk individuals.

Another application of these new data thus lies in the possibility that improved diagnostic approaches might also be useful in focusing pharmacogenetic strategies with current drugs as a first step in offering improvements in patient care. Such strategies could include, for example, different combinations of pharmaceuticals directed at constellations of inherited molecular risks and polymorphisms in different individuals or more predominant in one versus another form of disease. Information on physiological implications of specific variations would also be useful in both primary and secondary prevention and in deciding whether alternative therapies such as implantable cardioverter-defibrillators would be effective in specific patients. Advances in microarray diagnostic technologies for rapidly screening large numbers of suspect variations in DNA and proteins should soon reach the stage at which analyses of large numbers of patients for specific molecular risks would become feasible. New technologies appear to be essential, because although SCD is fairly common (≈250 000 deaths per year in the United States alone), incidence in the overall population is quite infrequent, occurring in roughly 1 of 1000 persons. Accurate risk detection, therefore, is critical, and development of useful screens is thus most likely to occur in the context of individuals identified by means of clinical presentation or familial association to carriers. Progress in establishing criteria for molecular screening would thus seem most feasible if limited numbers of high-risk alleles could be linked with particular disease phenotypes. If common lethal arrhythmias turn out to be most frequently associated with a relatively small number of incrementally cumulative, low-risk variants, genotypic screening might be efficacious. The extension of approaches now most useful for patients with rare conditions to routine diagnosis would thus appear to be dependent on new discoveries regarding risk alleles present in common

TABLE 3. Sources of Molecular Diversity in Acute SCD Susceptibility

Mediators of infarction and ischemia
Facilitators of plaque development and rupture
Activators of thrombogenesis, coagulation, and platelets
Modulators of vascular tone
Mediators of neural excitation
Activation of central pathways
Neural transmitters and peptides
Autonomic balance and adrenergic pathways
Mediators of membrane excitability and tissue conduction
Ionic, metabolic, and peptide modifiers
Subunit permutations: channel and transporter interactions
Redox and energetic metabolites
Factors affecting coupling and cell-cell conduction

Individual factors considered in the text are stratified, from distal to proximal, by their relative proximity to initiation of acute destabilizing electrical events. Distal factors are those considered to be related to processes with more remote or less direct probability of causing an acute arrhythmogenic event, whereas proximal factors are those more directly involved in final common pathways in SCD initiation.

disease populations, the factors that modify their expression, and new technologies for their assessment.

Progress toward these goals is occurring rapidly, and future needs are being defined. Alternative means of gene or protein screening other than complete linear sequencing are under development in several centers, and new technologies to assess protein functionality[27] and specific patterns of multigene expression may provide useful options. How such analyses can be accomplished reliably for potentially so many proteins seems problematic but surmountable. Large-scale scanning for endogenous genetic modifiers, sensitivity to environmental interactions, or normally silent DNA changes in various ethnic and subgroup populations is another area for exploration. Continued investigation of variation in penetrance in families with monogenic SCD conditions is a third area that can be expected to contribute to each of these aims.

A major goal in each of these future approaches should be to define molecular risks most directly associated with arrhythmia initiation and the transition from stable tachyarrhythmia to fibrillation, as opposed to establishing additional genetic elements in the occurrence of already well-established risk factors. Table 3 suggests one approach to stratifying sources and candidate pathways in a way that emphasizes understanding of final common elements of arrhythmogenesis as a new focus in reducing arrhythmia mortality. Emphasis is placed on identifying proximal effects most closely associated with electrical or ischemic processes rather than a more distal pathology already being addressed by other modes of therapy.

Population Approaches and Directions for the Future

Given this recommended change in focus, a key question becomes how proximal molecular risks can best be identified and strategies for their remediation devised. Studies at all levels of basic, clinical, and population science, especially those comparing low- and high-risk patient groups, those with families having defined mutations, and those with asymptomatic populations, are likely to be required. The exploitation of data and samples available from previous population and family studies and the design of new genetic-epidemiological approaches will be helpful. Also critical will be better integration of clinical information and exploration of behavioral, neural, and pharmacological stressors, as well as the role of genetic modifying influences as predisposing factors. Because increased susceptibility in individuals with progressive cardiac diseases will most likely involve both acquired and inherited factors in different dimensions of arrhythmic risk, different studies in various populations should be especially useful. Table 4 summarizes a number of strategies by which new data might be approached. A broad range of studies using different approaches with different subject groups should be helpful in delineating different disease conditions. For example, the search for genetic variation in ion channels or adrenergic receptors in both narrowly defined long-QT syndrome family linkage studies, as well as in populations of survivors of previous SCD events, or broad association studies such as the Paris Prospective Study I, the Seattle Familial Heart Study, the Framingham Heart Study, and the Physicians' and Nurses' Health Studies populations, should provide complementary sets of information. Dissection of contributing susceptibilities in patients with little or no preexisting pathology but who experience life-threatening arrhythmias in response to various physiological, ambient, chemical, or behavioral triggers may be especially helpful in

TABLE 4. Genes and SCD: Population Approaches

Identify resources and subjects in completed and ongoing epidemiological and clinical patient studies.
Characterize specific clinical SCD phenotypes within "normal" and high frequency event populations. Correlate by age, disease, sex, conventional risk factors, etc. Assessments should include:
Survivors of documented SCD events.
Elderly and adult patients with definable electrical, structural, neural, and functional risks.
Adults aged 25 to 55 years without apparent clinical disease, irrespective of known risk factors.
Young (age <25 years) victims and familial cohorts with both known or unknown congenital risk histories.
For informative groups, archive DNA and document clinical histories and familial pedigrees.
Evaluate associations between SCD events over time with known and candidate genetic risks.
Analyze existing (LQTS, HCM, ARVD, AF, etc) and newly identified familial SCD populations for associations with potential modifying loci.
Evaluate familial segregation of cardiac events within defined SCD phenotypes to identify:
Subgroup specific risks
Shared environmental risks
"Final common pathway" risks
New direct or modifying genetic risk

LQTS indicates long-QT syndrome; HCM, hypertrophic cardiomyopathy; ARVD, arrhythmogenic right ventricular dysplasia; and AF, atrial fibrillation.

providing information on final common pathways. Because very large samples will be required for many of these studies, the sharing of resources will be absolutely central to progress. In addition to clinical data and physiological samples, the sharing of expertise from different disciplines ranging from epidemiology to genetic and basic electrophysiology will also be necessary if these efforts are to be effective. The evidence, reviewed above, that such approaches are likely to be fruitful is now in hand; the challenge lies in determining how the power of this new information and the new technologies can best be used to improve patient care.

Acknowledgments

Dr Spooner wishes to thank Michelle Cummings and Margaret King for secretarial assistance and Dr Michael Rosen for constructive comments during the preparation of the manuscript.

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