Sudden Cardiac Death, Genes, and Arrhythmogenesis
Consideration of New Population and Mechanistic Approaches From a National Heart, Lung, and Blood Institute Workshop, Part I*

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Abstract—Malignant ventricular arrhythmias are the leading mechanism of death in patients with acute and chronic cardiac pathologies. The extent to which inherited mutations and polymorphic variation in genes determining arrhythmogenic mechanisms affect these patients remains unknown, but based on recent population studies, this risk appears significant, deserving much greater investigation. This report summarizes a National Heart, Lung, and Blood Institute workshop that considered sources of genetic variation that may contribute to sudden cardiac death in common cardiac diseases. Evidence on arrhythmogenic mechanisms in recent population studies suggests a significant portion of the risk of sudden cardiac death in such broad populations may be unrelated to traditional risk factors for predisposing conditions such as atherosclerosis, hypertension, and diabetes and instead may involve unrecognized genetic and environmental interactions that influence arrhythmic susceptibility more directly. Additional population and genetic studies directed at discovering the sources of inherited molecular risk that are most directly linked to arrhythmia initiation and propagation, in addition to studies on previously well-described risk factors, would appear to have considerable potential for reducing premature cardiovascular mortality. (Circulation. 2001;103:2361-2364.)

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

Major disturbances in cardiac rhythm—ventricular fibrillation, tachyarrhythmias, bradyarrhythmias, and asystole—represent one of the most pervasive mechanisms of premature cardiovascular death. More than half of deaths due to ischemia and myocardial infarction, and at least half of those due to congestive, hypertrophic, and dilated cardiomyopathies, are directly related to these causes.¹² Large population studies indicate that coronary artery disease (CAD), its antecedents (eg, atherosclerosis and hypertension), and associated “acquired,” progressive cardiac conditions in which there is extensive structural, electrical, and neural remodeling are the principal risk factors for arrhythmia development in adults. However, sudden, predominantly arrhythmic cardiac deaths (SCDs) also occur in apparently healthy individuals of all ages, usually unexpectedly, and their number represents a significant percentage of those who die of cardiovascular causes.³ Lethal arrhythmias in such individuals may arise as the initial indicator of silent acquired pathology or, less frequently, as a manifestation of electrical or structural abnormalities related to such diverse causes as congenital malformations (eg, defects in myocardial or conducting tissue development), environmental interactions (eg, with proarrhythmic therapeutic or illicit drugs), or more rare “idiopathic” and inherited syndromes. The latter would include changes due to mutations involved in accelerated atherosclerosis and hypertension, as well as in proteins that more directly affect the heart’s electrical, structural, and contractile performance.⁴ This heterogeneity in factors contributing to

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arrhythmic pathophysiology has made the identification of primary predisposing risks for SCDs within broad populations a major medical challenge. Progress in reducing cardiac mortality in these groups is urgently required, because it is within these cohorts that little progress has been made in prevention.

To explore these issues, the National Heart, Lung, and Blood Institute (NHLBI) convened an Expert Workshop to consider the evidence that new elements of familial association may be involved, to explore etiologies of these relationships, and to provide ideas on how they might best be addressed. This report represents the results of those deliberations. The ideas expressed here represent the views of the participants, not opinions or positions endorsed in any way by the NHLBI. The workshop considered four major questions: (1) What factors contribute to arrhythmia susceptibility? (2) Do new data on familial SCD risks justify a search for additional susceptibility elements? (3) What molecular processes might be involved? and (4) How can new genetic and population investigations help resolve these issues? The major focus of the discussions involved the identification of “susceptibility candidates” most likely to elevate risk of SCD in common cardiac conditions. The approach taken in the discussion that follows is to consider factors that contribute to lethal arrhythmias in rare inherited cardiac conditions and then to explore new evidence on risk factors for SCD in common patient populations.

Inherited Causes of SCD and Ventricular Arrhythmias

In the last decade, ground-breaking genetic studies began to reveal how mutations in ion channel genes cause tachyarrhythmias in patients with rare inherited arrhythmias and increase the likelihood of ventricular fibrillation and SCD (reviewed in Priori et al.4 and Keating and Sanguinetti5). These studies focused initially on the long QT syndrome (LQTS) and more recently expanded to related diseases (ie, Brugada syndrome6 and Lev’s syndrome or progressive cardiac conduction disease7). Cardiac channel gene mutations implicated to date are those in the depolarizing SCN5A Na channel (LQT-3); 2 genes for the repolarizing K channel α-subunits KvLQT1 (LQT-1) and Herg (LQT-2); 2 genes coding the K channel regulatory β-subunits, minK (LQT-5) and MIRP1 (LQT-6); and a gene associated with one form of LQTS, designated LQT-4, of unknown origin (reviewed in Roden and Spooner8). Most recently, mutations in the cardiac ryanodine receptor Ca channel gene were identified in a related form of inherited tachycardia.9

In addition to the rare, ion channel–based arrhythmias, occurrence of inherited susceptibility to SCD is associated with other, less well understood pathologies. Prominent among these are mutations in contractile, structural, and cytoskeletal proteins. Familial hypertrophic cardiomyopathies with a high incidence of SCD have been linked to mutations in at least 9 cardiac sarcomeric proteins (the β-myosin heavy chain, myosin binding protein C, α-actin, troponins I and T, α-tropomyosin, the cardiac essential and regulatory light chains, and titin [reviewed in Bonne et al.10 and Seidman and Seidman11]). Enhanced SCD has also been reported in inherited dilated cardiomyopathy to be associated with mutations in cytoskeletal proteins such as dystrophin, desmin, and α-actin and the nuclear envelope proteins lamin A and C, with the latter involving primarily conduction system disease.12,13 With some of these conditions, there appear to be plausible functional associations (eg, alterations in Ca handling) between molecular aberration and electrical performance, whereas with others (eg, mutations in lamin or NKKX2.514) in which there are overt electrical disturbances, connection with processes that could affect electrical stability would appear far downstream of the lesions detected to date. As with LQTS, most of these aberrations have been thought to reflect effects in the working myocardium, but defects in sinoatrial or AV node cells and His-Purkinje conduction may also occur and manifest clinically with symptoms of heart block and bradyarrhythmias. For other conditions, of which arrhythmogenic right ventricular cardiomyopathy is a prime example, genes are just beginning to be identified, but chromosomal sites, now at least 7 in number, have been mapped and the incidence of electrical disturbances, as well as extensive myocardial remodeling, has been well documented. In the first case to be successfully resolved, a mutation in the structural protein plakoglobin, a component of adherent intercellular junctions, was identified in an autosomal recessive form of arrhythmogenic right ventricular cardiomyopathy, Naxos disease, but whether this results in altered patterns of cell-cell conduction has not been established.15

SCD: The “Phenotype Problem”

The number of cardiac syndromes being linked with familial forms of SCD is thus increasing rapidly, and clinical phenotypes involving many different electrical and structural changes in virtually all cardiac cell and tissue types are being identified. In addition to the ion “channel-opathies” expected to directly affect electrogenesis and the increasingly apparent alterations in intracellular Ca handling,16,17 potential effects on microscopic and macroscopic pathways of conduction provide one of the few other potential links in mechanisms of causation. This diverse etiology highlights a central problem in discovering the role of genetic variation in arrhythmogenesis and in deciphering the relevance of specific molecular disturbances in “purer” inherited forms of arrhythmic disease such as LQTS to more common clinical conditions. The problem lies in determining which elements of an inherited SCD phenotype also occur in individuals with an acquired, multifactorial, genetic etiology. Furthermore, whereas it has been common to regard many of the inherited syndromes as single-gene or “monogenic” disorders, clinical presentations are most often diffuse, and threatening SCD events seem to occur transiently in response to specific behavioral or environmental influences.18 Additional confusion comes from finding wide variations in ECG patterns and lethality associated with different mutations or polymorphisms in the proteins affected. For example, nucleotide transitions affecting an amino acid at the 403 position of the β-myosin heavy chain in hypertrophic cardiomyopathy are associated with high mortality, whereas mutations in nearby sites on the same or other contractile proteins may not be.19 Expression of
mutations present from birth also may not be apparent until early adolescence, whereas others may not be expressed until late in life. Changes in the same gene are also often confusing; for example, the KPQ deletion mutation in the SCN5A Na channel that causes one form of LQT-3 may or may not express defining symptoms (ie, an abnormal QT interval), whereas deletions or missense replacements at a different position in the same exon can give rise to a phenotype with the signature ECG characteristics of both LQTS and the related Brugada disease. This wide variance in phenotypic presentation associated with “biological translation” of a particular mutational event in many of these proteins has thus resulted in the suspicion that other factors modifying expression of these mutations are likely to exist. These may involve incomplete penetrance or secondary modifying influences and susceptibility factors, such as mutations or polymorphic variation in structural or noncoding regulatory sequences for other proteins that affect gene expression or directly affect cardiac excitability in different ways, but little is really known of the mechanisms involved. One clue supporting the involvement of external factors comes from studies indicating that certain mutations in the minK channel subunit gene, and a polymorphism in the MiRP1 subunit, are expressed only on exposure to exogenous pharmaceuticals.

Phenotypic dissonance with inherited forms of SCD may thus be similar to that encountered with other complex, multigene diseases, such as highly familial forms of hypertension, diabetes, or atherosclerosis, but with little in the way of identification of the specific traits involved. Genetic influences on SCD events are suggested, however, by observations such as the finding that women have a lower overall incidence of SCD than men yet also appear more sensitive to drug-induced or LQTS arrhythmias. Such findings may be attributable in part to differences in repolarization parameters that are under hormonal control, and it seems likely that other factors are also involved.

Much of the genotype-phenotype problem with arrhythmic diseases also reflects the fact that SCD simply represents a clinical outcome, ie, cardiac arrest, a common mechanism of death, rather than a change in identifiable metabolic, biochemical, or pathological events. As such, it can be the result of various clinical events, and the standard accepted definition of SCD (any near instantaneous, electrically based, cessation of cardiac output in individuals with otherwise uncompromised circulatory function) is, from a mechanistic perspective, as ambiguous a phenotype imaginable. At issue is the differentiation of comorbid conditions from proximal arrhythmogenic events. Until we learn more about the combinations of terminal processes in arrhythmogenesis in different acquired diseases, it seems unlikely a more precise characterization of common high-risk SCD phenotypes, which apply in progressive chronic diseases, will emerge. What may be possible instead is identification of “signature” combinations of particularly destabilizing molecular events that could then help guide prevention efforts. In conjunction with conventional stratification approaches including standard and T-wave alternans, ECG analyses, or ejection fraction, improved SCD phenotyping with new approaches and recognition of new information, for example, on ventricular ectopy, could add considerably to our abilities to recognize differing degrees of arrhythmia risk.

Multiple Elements of SCD Risk
Clinical approaches in assessing risks for common causes of SCD have traditionally been organized into 3 dimensions of susceptibility. Principal risks are envisioned to arise from (1) local or regional electrical instabilities in the myocardial “substrate”; (2) acute, transient triggering influences that result in aberrant impulses; and (3) degenerative processes that result in their continued propagation. In terms of deciphering genetic influences on SCD, this perspective is also useful in considering how dysfunction in different cellular and molecular processes might contribute to one or more dimensions of instability. Thus, for example, in trying to identify and counter arrhythmic risks in a progressive multifactorial disease, one would want to consider information on genetic variation identified in each of these dimensions before considering individual approaches to thwart suspected specific risks at a molecular level. As increasing amounts of information about changes in processes such as channel and transporter regulation, membrane remodeling, and alterations in signaling pathways emerge, our ability to localize destabilizing influences to each of these dimensions should markedly improve, and this information may be especially useful in considering different options for therapy with different pathologies.

New studies on conventional risk factors in population-based studies on coronary heart disease, hypertension, atherosclerosis, and other predisposing conditions will also be important in therapy selection. There are now abundant data from large-scale epidemiological studies undertaken over the past 20 years, such as the Framingham Heart Study, the Physicians’ Health Study, and the Nurses’ Health Study, as well as others, that are proving quite useful in deciphering heritable arrhythmia susceptibilities. In the past, such approaches have proven most useful in identifying traditional metabolic, behavioral, and dietary risk factors for CAD, such as blood pressure, smoking, gender, diabetes, physical inactivity, and triglyceride, cholesterol, LDL, and HDL levels and ratios, as well as their influence on overall cardiac mortality. In many of these studies, however, it has not been possible to determine whether the resulting morbidity and mortality data can be directly associated with an arrhythmic pathology. The work has nevertheless been valuable in identifying relative and absolute risks associated with these elements, and the results have had important public health implications. Algorithms that attempt to extend conventional risk factor prediction studies to assessment of specific individuals and classes of cardiac patients have also been promulgated but appear to be of much more limited value. This reflects many factors, including reliance on population-based “normal values” and the problem that extension of norms to individuals does not generally consider differences in genetic diversity between the groups sampled and those being assessed. Evidence of the unreliability of focusing on only those previously identified risk factors for CAD as a means of reducing premature cardiovascular mortality is, for example,
well reflected in the observation that a high percentage of SCDs still occur in individuals with no elevation in currently recognized traditional risk factors. New approaches applicable to understanding individual and disease-specific elements of molecular SCD susceptibility are thus likely to play an increasingly significant role in reducing cardiovascular mortality in the future.

Appendix

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