Reviews

What Causes Sudden Death in Heart Failure?

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Abstract—Patients with heart failure experience a number of changes in the electrical function of the heart that predispose to potentially lethal cardiac arrhythmias. Action potential prolongation, the result of functional downregulation of K currents, and aberrant Ca^{2+} handling is a recurrent theme. Significant alterations in conduction and activation of a number of initially adaptive but ultimately maladaptive signaling cascades contribute to the generation of a highly arrhythmogenic substrate. We review the changes in active and passive membrane properties, neurohumoral signaling, and genetic determinants that predispose to sudden arrhythmic death in patients with heart failure and highlight the critical unanswered questions that are ripe for future investigation. (***Circ Res**. 2004;95:754-763.*)

Key Words: arrhythmia ■ Ca^{2+} handling ■ cardiac electrophysiology ■ heart failure ■ ionic remodeling

Nearly 5 million Americans experience heart failure (HF) and >250 000 die annually. The incidence and prevalence has continued to increase with the aging of the US population.[1] Despite remarkable improvements in medical therapy, the prognosis of patients with myocardial failure remains poor, with almost 20% of patients dying within 1 year of initial diagnosis and >80% 8-year mortality. Of the deaths in patients with HF, up to 50% are sudden and unexpected; indeed, patients with HF have 6- to 9-times the rate of sudden cardiac death (SCD) of the general population.[1]

What causes SCD in patients with HF? It is safe to say that in any individual patient, the mechanism of SCD is uncertain. The uncertainty begins with the definition of sudden death, which describes a sequence of events, not a mechanism. The presumption is that SCD is produced by a lethal cardiac arrhythmia, most often ventricular tachycardia or fibrillation.

Bradyarrhythmias and pulseless electrical activity occur less frequently, and generally in hearts with more advanced structural disease. Some data suggest that bradyarrhythmias and pulseless electrical activity may account for an increasing percentage of SCDs, because the frequency of ventricular tachycardia and fibrillation (VT/VF) may be decreasing.[2] The World Health Organization definition of sudden death certainly leaves open the possibility that death may result from a precipitous decline in mechanical function of the heart, such as pulseless electrical activity. Even sudden witnessed death may be produced by a sudden mechanical or vascular catastrophe (pulmonary embolus, cardiac, or vascular rupture) rather than a malignant cardiac rhythm abnormality.

SCD most likely results from a cascade of "upstream" events that create an electrically unstable heart that most often is manifested by a ventricular tachyarrhythmia. Interestingly, it is the nonantiarrhythmic drugs, ie, those without

major direct electrophysiologic actions on cardiac muscle or specialized conducting tissue, that are probably acting on those upstream events, which have been shown effective for prevention of SCD. These drugs include β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor-blocking agents, lipid-lowering agents, spironolactone, magnesium, thrombolytic and antithrombotic agents, and perhaps omega-3 fatty acids.[3] A major, if not the major, unanswered question in SCD, is what is the immediate precipitating event that causes the SCD at a specific time in an otherwise stable patient, and does it involve those upstream events triggering electrical instability?[4] Understanding the trigger acting on the receptive substrate, which most likely may be different in different patients and may involve very small changes in conduction, refractoriness, and the like, is a major goal of SCD research.

What is certain about SCD in the setting of HF in particular is that there are a number of structural and functional changes in the heart and genetic predisposition that may contribute to an increased risk of dying suddenly. This review considers some of these factors, with a focus on changes that would be expected to enhance the risk of lethal ventricular arrhythmias. We head each section with the supposition that the abnormality reviewed is the cause of SCD in HF.

Action Potential Prolongation Is the Cause of SCD in HF

Abnormalities of atrial[5] and ventricular[6] electrophysiology in diseased human hearts have been recognized for more than four decades. Remodeling of ventricular myocyte electrophysiology in both human and animal models of HF is well-described.[7] Prolongation of the action potential (AP) is a hallmark of cells and tissues isolated from failing hearts independent of the cause, which has been observed in isolated myocytes[7] and intact ventricular preparations.[8] The AP prolongation is heterogeneous, resulting in exaggeration of physiological inhomogeneity of electrical properties in the failing heart.[8–11]

Alterations in the functional expression of ion channels and transporters underlie the changes in the AP profile observed in failing hearts. Ventricular myocytes contain several distinct classes of voltage-gated potassium (K) currents. The relative densities, precise molecular compositions, and responses to stress of these K currents vary considerably across species. Downregulation of I_{to} is the most consistent, albeit not invariant, ionic current change in HF that has been observed in cells isolated from terminally failing animal[12–14] and human hearts.[15–17] Changes in other K currents have also been reported in HF. I_{K1} (Kir2 family of genes) maintains the resting membrane potential and contributes to the terminal phase of repolarization in the ventricular myocyte. In ventricular-pacing tachycardia-induced HF, decreased[14,18] and unchanged[12] I_{K1} densities have been reported. In human HF, significantly reduced I_{K1} is observed at negative voltages.[15] The molecular basis of I_{K1} downregulation in human HF is uncertain, but two studies report no change in the steady-state level of Kir2.1 mRNA in failing compared with normal hearts.[19,20] Another study reported a differential reduction in I_{K1} in cells isolated from failing hearts with dilated versus

ischemic cardiomyopathy, with the former group exhibiting altered voltage dependence compared with the latter,[21] highlighting the importance of disease etiology in the details of electrical remodeling. Reduced delayed rectifier (I_K) density, slower activation, and faster deactivation kinetics have been reported in hypertrophied feline ventricles.[22] In addition, downregulation of both I_{Kr} and I_{Ks} have been reported in a rabbit model of ventricular-pacing tachycardia-induced HF,[23] and downregulation of I_{Ks} in all three layers of the canine left ventricular myocardium in ventricular-pacing tachycardia-induced HF without a change in I_{Kr} has been reported.[18] Purkinje myocytes are believed to be the sources of after-depolarizations associated with triggered arrhythmias in diseased hearts; these cells undergo substantial remodeling of both K and calcium (Ca) currents, which prolongs the AP, rendering repolarization labile in these cells.[24]

Normal impulse formation and conduction in cardiac myocytes depend on I_{Na}. This current is also an important contributor to the AP plateau. HF-induced changes in I_{Na} may play an important role in arrhythmias either by disrupting conduction or by prolonging repolarization.[25,26] The detailed changes in I_{Na} are likely to depend on the cause of HF. Prolongation of AP duration associated with downregulation of repolarizing and an increase in depolarizing currents lead to spatially and temporally labile repolarization that may predispose to afterdepolarization-mediated triggered activity and functional reentry. Remodeling of the AP may also predispose to dynamic wave instability by increasing the AP duration (APD) restitution slope.[27] The existence of afterdepolarizations and functional re-entry are not mutually exclusive, and early afterdepolarizations of sufficient amplitude may serve to initiate, whereas functional reentry may sustain, potentially lethal ventricular arrhythmias.

AP prolongation is a consistent and perhaps necessary, but insufficient, alteration in cardiac electrophysiology of the failing heart to produce VT/VF leading to SCD. AP prolongation in and of itself is likely to be an adaptive and perhaps an anti-arrhythmic response. The extent to which dispersion of repolarization accompanies AP prolongation is likely to be critical in determining whether this response of the failing heart promotes or prevents SCD. A major challenge is determination in individual patients of the extent to which the AP is prolonged, repolarization reserve is diminished,[28] and dispersion (temporal and spatial) of repolarization is enhanced. The extent to which AP prolongation correlates or is associated with altered dynamics of repolarization remains to be clarified.

The underlying basis of AP prolongation in the failing heart is likely to be multifactorial, with the extent to which reduction in functional expression of K currents versus other mechanisms (alterations in Ca^{2+} handling or changes in depolarizing currents) contribute to arrhythmia predilection being largely unknown. The temporal course of the development of changes in APD are understudied and molecular mechanisms are uncertain. It is likely that alterations in K channel expression and function are consequences of the activation of other upstream signaling cascades. Defining such systems, particularly those that are activated at the transition between reversible and irreversible structural

changes, is imperative in the development of novel and effective HF therapies.

Alterations in Calcium Homeostasis Are the Primary Reason for SCD in HF

HF is characterized by depression of developed force, prolongation of relaxation, and blunting of the force–frequency relationship. Fundamental changes in Ca^{2+} handling in HF are thought to account for abnormalities in excitation–contraction coupling. However, the cellular and molecular bases of these defects remain controversial. Importantly, defective calcium handling in HF not only affects ventricular mechanics but also affects its electrophysiology. Intracellular $[Ca^{2+}]$ and the AP are intricately linked by a variety of Ca^{2+}-mediated cell surface channels and transporters such as the L-type current (I_{Ca-L}), I_K, Ca^{2+}-activated Cl^- current, and NCX.

The density of I_{Ca-L} has been studied in a number of animal models of HF.[7] Most often I_{Ca-L} density is unchanged;[29,30] however, when a change in the L-type current has been reported, it is increased in mild-to-moderate hypertrophy and decreased in more severe hypertrophy and failure.[31] Ventricular myocytes from failing hearts also exhibit attenuated augmentation of I_{Ca-L} by β-adrenergic stimulation[14,31,32] and depression of rate-dependent potentiation compared with myocytes from normal hearts.[33,34] The basic electrophysiological features of I_{Ca-L} are altered in some studies of HF. The most common change is a significant slowing of the whole-cell current decay.[35] The mechanism underlying the prolonged whole-cell current decay is unknown, but a single-channel comparison of I_{Ca-L} in human ventricular myocytes suggests an increase in open channel probability likely attributable to a dephosphorylation defect.[36] The molecular bases of changes in the density of I_{Ca-L} are unknown. Variable changes in the density of DHP binding sites have been reported.[7] Similarly, studies of human Ca channel subunit mRNA in HF exhibit disparate findings.[37–39] The complexity of the molecular basis of channel remodeling is highlighted by reports of isoform switching of both $\alpha 1C$[39,40] and β subunits[41] in the failing heart.

The amplitude of the calcium transient (CaT) and its rate of decay are reduced in intact preparations[42] and cells[43,44] isolated from failing ventricles. Systematic comparisons of the CaT profile and dynamics in cells isolated from different regions of the failing heart are limited. In the normal canine heart, CaT decay is slower and alternans is enhanced in the endocardium compared with the epicardium.[45] CaTs in ventricular myocytes isolated from the endocardium of the rabbit left ventricle adjacent to a myocardial infarction exhibit depressed amplitudes and are shorter than cells from normal hearts. This is in striking contrast to cells isolated from the mid-myocardial and epicardial layers, which exhibit prolonged transients compared with cells isolated from the respective layers of normal hearts.[44] Sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a), its inhibitor phospholamban, and NCX are primary mediators of Ca^{2+} removal from the cytoplasm. Differential transmural expression of Ca^{2+} handling proteins has been reported in normal[45] and failing hearts.[43,46] In HF, ventricular myocytes exhibit a greater reliance on NCX for removal of Ca^{2+} from the cytosol and an increase in NCX function,[43,47] which leads to defective sarcoplasmic reticulum Ca^{2+} loading.[48] The altered NCX function in the failing heart significantly influences AP dynamics.[49] A number of studies have demonstrated reductions in SERCA2a and phospholamban mRNA, but fewer have shown a reduction in immunoreactive proteins. Increases in NCX mRNA and protein have been regularly observed in failing hearts.[7] Sarcoplasmic reticulum Ca^{2+} release is also defective in the failing heart and is associated with altered regulation of the ryanodine receptor (RyR), attributable to PKA hyperphosphorylation-induced FKBP12.6 dissociation from the channel that alters Ca^{2+} sensitivity and generates uncoupled gating of RyR.[50,51] Further complicating the mechanism of altered RyR function, levels of RyR mRNA, and protein in HF are variable.[52,53] Although alteration of the CaT is associated with and influences the static and dynamic changes in the ventricular AP, the precise relationship remains unclear and the role of spatial and temporal dispersion of CaT in arrhythmogenesis in the failing heart remains to be clarified. The failing heart exhibits a defect in Ca^{2+} cycling reserve, which may be particularly pronounced in the endocardium,[45] but the degree to which regional differences in the levels of cytosolic Ca^{2+} influence the progression of the failing phenotype and arrhythmic risk is an open question.

Abnormal Conduction Is the Proximate Cause of SCD in HF

A number of studies in animal models and humans have implicated altered conduction through the myocardium in sudden death. A hallmark of slowed conduction and poor coupling of myocardium in patients at high risk for sudden death is the presence of fractionated electrograms[54,55] and delayed-paced ventricular activation.[56–58] Abnormalities of conduction, and therefore ventricular activation, produce an exaggerated dispersion of recovery in infarcted and failing ventricles,[59,60] facilitating re-entrant excitation and ventricular tachyarrhythmias. The principal cellular and molecular determinants of conduction in ventricular myocardium are availability of sodium (Na) current, the size and shape of the ventricular myocytes, the quantity and distribution of fibrous tissue, and cellular coupling determined by the density and distribution of gap junction channels.

The role of changes in Na current density or biophysical properties in the failing heart is controversial. In some models, particularly in the myocardial infarct border zone, Na current density is decreased, availability at physiological voltages is reduced, and the recovery from inactivation is slowed consistent with reduced excitability.[25] Other chronic models of postinfarction HF have been associated with depressed excitability and reduced Na current densities.[61] Conversely, alterations of Na current kinetics are not a consistent feature of models of dilated, nonischemic cardiomyopathy.[14]

Fibrosis may alter a number of features of conduction through the myocardium, including a decreased safety factor for propagation,[62] alteration of the path of conduction, and the introduction of impedance mismatches. The consequences of the effects of fibrosis include an enhanced predisposition to

macroscopic discontinuities in conduction, unidirectional block, and re-entry. The pattern of fibrosis in the failing heart profoundly impacts on the electrophysiological consequences and presumably the risk of sudden death.[58]

Inexcitable barriers and other tissue discontinuities may be created by fibrosis in the failing heart; however, cellular coupling may be impacted by a significant reduction in the density and altered distribution of gap junction channels. For example, in hypertrophied and ischemic human ventricular myocardium, Cx43 is downregulated and redistributed from the intercalated disk to the entire cell border (lateralization),[63] a pattern observed in early cardiac development. This pattern of redistribution of Cx43 is prominent in the border zones of experimental myocardial infarction, which is characterized by slow conduction and is an important substrate for re-entrant ventricular arrhythmias.[64–66] Alterations in cell size and shape characterize the failing heart. Myocyte size is a critical determinant of the properties of anisotropic conduction in the ventricle.[67] Cellular hypertrophy with associated gap junction remodeling in the failing heart may contribute to alterations in electrical loading and macroscopic conduction.

The functional consequences of Cx43 downregulation and redistribution on cell-to-cell coupling, conduction, recovery, and arrhythmogenesis are incompletely understood but almost certainly contribute to risk for sudden death in HF.

The regulation of the control of cellular coupling in the heart is incompletely understood. A more complete understanding of the critical signaling cascades that influence connexon structure, function, and distribution in the normal and failing heart is necessary. The relative contributions of the interstitium, alterations in cell size, and intercellular ion channels to conduction in the failing heart will be required for a more fundamental understanding of SCD in patients with HF.

SCD Is a Manifestation of Myocardial Ischemia in HF

SCD is frequently associated with coronary artery disease (CAD),[68–72] even in young victims.[73] The majority of cases of HF in this country are the result of CAD,[74–81] most often chronic CAD in the setting of previous myocardial infarction. However, even in cases of nonischemic cardiomyopathy a mismatch between supply and demand is possible; thus, the potentially arrhythmogenic changes in ischemic and infarcted myocardium are germane to a discussion of SCD in a variety of settings.

The ischemic and infarcted myocardium exhibits regional cellular and tissue remodeling, as well as inhomogenities of sympathetic nervous system innervation, that creates a substrate that is exquisitely sensitive to arrhythmia triggers. The cellular substrate in regions remote from a scar and in chronically ischemic or hibernating myocardium consist of apoptosis with compensatory cellular hypertrophy.[82] Myocytes isolated from both noninfarcted regions[83] and hibernating myocardium[84] are characterized by prolongation of AP duration and abnormalities of Ca^{+2} handling. In chronically ischemic myocardium, redistribution of connexins,[85] elaboration of cytokines,[86] and increased interstitial connective tissue[82] have been described. Regional heterogeneity of the

electrophysiological properties of the infarcted heart is profound. The border zones of a myocardial infarction are extensively remodeled in both subacute and chronic phases, with alterations in the active membrane properties of myocytes,[83] reduced cellular coupling,[87] and connexin redistribution.[63] Thus, ischemic and uninvolved areas of infarcted myocardium exhibit arrhythmogenic abnormalities of both repolarization and conduction.

Chronic inflammation is an important mediator of atherosclerosis and in the conversion of quiescent vascular plaques to unstable thrombogenic lesions. Autopsy studies in patients with SCD reveal that a significant proportion exhibit acute plaque rupture and thrombosis.[88,89] Markers of inflammation, particularly C-reactive protein, predict future risk of myocardial infarction and, in at least one study, SCD.[90] Interestingly, in this case-control study, a history of diabetes and/or hypertension was the strongest predictor of SCD. Clearly, inflammation is likely to be a contributor to SCD in patients with ischemic cardiomyopathy, but even in patients with nonischemic HF irregularities of coronary arteries are commonly found and could be the site of acute thrombosis and SCD. However, the effect of inflammation to increase SCD risk is not limited to an enhanced thrombotic predilection. Cytokines and other mediators of inflammation have direct effects on ion channels[91,92] and Ca^{2+} homeostasis, perhaps exaggerating the arrhythmogenic risk in the failing electrically remodeled heart.

Altered Neurohumoral Signaling Causes SCD in HF

Neurohumoral activation may profoundly influence the substrate in the failing heart and triggers for lethal ventricular arrhythmias. The details of altered neurohumoral signaling are controversial, but universally accepted are the activation of adrenergic and renin-angiotensin-aldosterone (RAAS) signaling and its role in progression in the HF phenotype. Less certain is the effect of activation of these systems on risk of sudden death. A number of clinical studies suggest links between SCD and neurohumoral activation. For example, adrenergic and RAAS blockade in randomized clinical trials have been associated with reduction in overall and SCD mortality.[76–81,93] In ventricular biopsy and autopsy specimens, an increased density and exaggerated spatial heterogeneity of sympathetic nerves were associated with a previous history of ventricular arrhythmias. The association between altered sympathetic innervation and ventricular arrhythmias applies not only to the ischemic and infarcted heart but also to the myopathic heart.[94]

Arrhythmogenic regional heterogeneities of sympathetic innervation characterize the infarcted heart.[95,96] Myocardial infarction is associated with destruction of sympathetic nerves in both the infarct zone and distal myocardial segments. This denervation is associated with an exaggerated response to infused catecholamines or denervation supersensitivity in the form of exaggerated shortening of ventricular effective refractory periods and enhanced inducibility of ventricular fibrillation in the presence of catecholamines.[97] Alterations of sympathetic innervation are not limited to the acute and healing phases of myocardial infarction. A discor-

dance between iodine-123-metaiodobenzylguanidine (I-123-MIBG) and thallium-201 single-photon emission computed tomographic imaging in patients with ventricular tachycardia in the absence of CAD is consistent with sympathetic denervation in this cohort at high risk for sudden death.[98] Immunohistochemical correlates of heterogeneous sympathetic innervation of the heart have been demonstrated and include spatially variant expression of tyrosine hydroxylase, synaptophysin, and growth-associated protein 43.[99] Augmented sympathetic nerve regeneration (nerve sprouting) has been demonstrated in the explanted hearts of patients who had a history of potentially lethal ventricular arrhythmias compared with patients with similar structural heart disease but no arrhythmias.[94] Induction of sympathetic nerve sprouting, by infusion of nerve growth factor into the left stellate ganglion of an experimental model of cardiac hypertrophy and infarction, results in an inordinate risk of sudden death.[100]

The effect of sympathetic nervous system stimulation on the heart is complex and is governed by the state of the myocardium. In the normal ventricle, sympathetic stimulation shortens the APD and reduces the dispersion of repolarization, both associated with a decrease in the arrhythmogenic tendency.[101] However, in pathological states associated with reductions in repolarizing capacity of the ventricular myocardium such as HF, sympathetic stimulation is a potent stimulus for the generation of arrhythmias, perhaps by enhancing the dispersion of repolarization, which may be why β-blocker therapy reduces all-cause and sudden death mortality in patients with CAD.

Although innumerable studies emphasize the arrhythmogenicity of sympathetic stimulation and the protective effects of parasympathetic stimulation, the actual electrophysiologic (or other) mechanisms by which the autonomic limbs exert their effects are complex and incompletely known.

Transgenic mice with genetically clamped elevations in angiotensin II exhibit a high frequency of sudden death in the setting of profound ventricular hypertrophy.[102] Mice with transgenic overexpression of angiotensin-converting enzyme-related carboxypeptidase (ACE2) in the heart capable of cleaving angiotensin peptide have an increased rate of sudden premature death.[103]

RAAS signaling has numerous effects on the cardiovascular system that might enhance risk of SCD. These include, but are not limited to, induction of hypertrophy and expression of a fetal gene program,[104] proliferation of cardiac fibroblasts with increased synthesis and secretion of collagen,[105] transforming growth factor-β1[106] and fibronectin,[107] promotion of inflammation and thrombosis, generation of reactive oxygen species,[108] and modulation of active membrane properties.[105,109–116] Thus, neurohumoral activation may generate an arrhythmic substrate by the altering active membrane properties of the myocyte and modifying the cardiac network.

The two major effectors of the RAAS, angiotensin II and aldosterone, have prominent structural effects and direct effects on ion channel biophysics that influence integrated electrical activity of the heart. Angiotensin II delivered to the myocardium or produced locally by any one of a host of peptidases promotes the elaboration of cytokines, growth factors, and the elaboration of fibrosis by myofibroblasts.

Similarly, aldosterone and endothelin peptides are profibrotic. Myocardial norepinephrine (NE) release is promoted by angiotensin II, and in a feed-forward fashion NE further activates RAAS.[117] Natriuretic peptides (ANP, BNP) serve to antagonize the profibrotic action of the neurohumoral signaling cascades. It is likely the natriuretic peptides are insufficient to prevent phenotypic progression in the failing heart; indeed, elevations in BNP are potent predictors of SCD in HF.[118] Angiotensin II inhibits a number of K currents, including the Ca^{2+}-activated K current in vascular smooth muscle cells,[119] the transient outward K current (I_{to1}),[116] and delayed rectifier K currents in the heart and smooth muscle.[120–125] Other direct effects of angiotensin II on cardiac membrane transport include increasing chloride current[112] and decreasing electrogenic Na^+-K^+ ATPase.[126]

The function of a number of ion channels and electrogenic transporters are regulated by aldosterone. Chronic exposure of rat ventricular myocytes in culture to aldosterone inhibits I_{to} and increases I_{Ca-L} density.[127] The temporal relationship of the changes in current density and the effect of blockers of the L-type current are consistent with Ca^{2+}-dependent reduction of I_{to} density. In a postmyocardial infarction model of HF in rats, aldosterone antagonism had a number of effects, including inhibition of fibrosis, reducing myocardial norepinephrine content, and increasing the ventricular fibrillation threshold.[128]

There is increasing evidence that oxidative stress plays an important role in ventricular remodeling in the failing heart. The consequences of increased oxygen free radical production include impaired myocardial metabolism, myocyte hypertrophy, apoptosis, and fibrosis.[129,130] As described previously, the electrophysiological consequences of such changes include action potential prolongation and lability, as well as slowing and macroscopic discontinuity of conduction. These changes establish the conditions for re-entry, which may be the proximate cause of SCD in patients with HF. Overexpression of antioxidant enzymes prevents ventricular remodeling of the infarcted and failing heart.[131]

Free radical-induced oxidant stress has a number of time-dependent effects on cardiac excitability, in part through actions on membrane currents and Ca^{2+} homeostatic processes. Early decreases in resting membrane potential and prolongation of the action potential duration have been ascribed to inhibition of inward rectifier K currents.[132,133] More prolonged exposure activates IK-ATP, producing profound action potential shortening and inexcitability.[132–134] Free radicals mediate a host of other actions on membrane currents and electrogenic transporters in the heart; certainly, some of these effects are indirect but others appear to be the direct consequence of alteration of channel and transporter proteins. For example, a number of free radical generating systems reduce L-type Ca current in native ventricular myocytes[134–136] and heterologous expression systems[137] involving both indirect and direct effects on the channel protein. There is an increasing body of evidence that oxygen free radicals are increased,[130,138–140] and antioxidant reserve, in the form of a reduction in antioxidant enzymes,[141,142] is decreased in the failing heart. It is likely that this chronic alteration of the redox state of the failing heart adversely influences cardiac
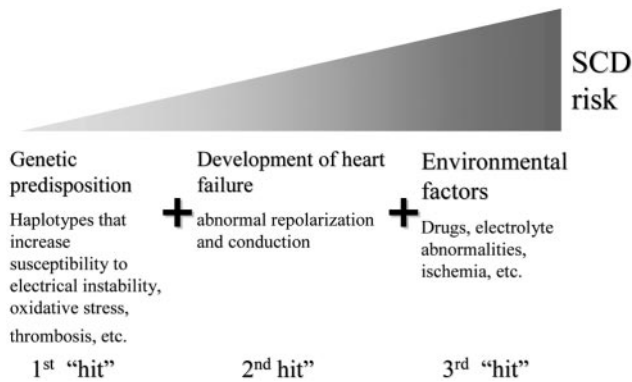
Multi-hit hypothesis of the development of SCD. Heart failure serves to enhance the risk by the associated alterations in the myocardial substrate and increasing the frequency/intensity of triggers of malignant arrhythmias.

electrophysiology, but the details of such interactions remain to be elucidated.

Genetic Predisposition Determines Who With HF Will Die Suddenly

All cardiac responses to *stressors* are, at least in part, genetically programmed. There are likely to be specific genetically determined factors that are associated with a phenotypic response to stressors that includes the development of malignant ventricular arrhythmias. A mechanistic analog for SCD is the "multi-hit" hypothesis of tumorigenesis (Figure). A number of modifiers of risk may conspire to produce SCD in patients with HF. Before the development of structural heart disease, the individual's genetic blueprint encodes an inherent susceptibility to the development of dangerous cardiac rhythms, maladaptive responses to stressors, and/or a predilection to the development of thrombosis or other potential pathological processes. HF is a systemic pathophysiological state associated with an increased risk of dying suddenly because of electrical remodeling previously described and, among other things, neurohumoral activation, which may serve as a trigger for arrhythmias in the diseased heart or may facilitate the progression of the failing phenotype. In the context of a genetic makeup with an increased susceptibility to lethal ventricular arrhythmias (first "hit"), the development of HF (second "hit") will greatly increase the risk of SCD in predisposed patients. Finally, a number of environmental influences (third "hit") may further enhance the risk of SCD.

Clinical evidence for a significant genetic influence in the risk of SCD comes from population-based studies that have demonstrated familial clustering of events. In the Paris Prospective study, a history of SCD in one parent increased risk by 80%; a history of SCD in both parents led to an extraordinary 880% increase in the risk of SCD for the offspring.[143] In a population-based case-control study, the rate of cardiac arrest in first-degree relatives of arrest victims was 50% statistically greater than the rate in control subjects and was independent of other risk factors for SCD.[144]

What are the genes whose polymorphisms or altered expression predispose to an arrhythmogenic substrate? Some clues come from consideration of rare diseases associated

with a high risk of SCD (rare disease paradigm). A number of genes have been linked to rare, heritable arrhythmias. In some cases the alteration in cardiac electrophysiology produced by the mutations linked to inherited arrhythmias resemble the electrical remodeling produced by HF. The congenital long QT syndrome is associated with gain-of-function mutations in SCN5A, the cardiac Na channel,[145] and loss of function in one of the genes that underlies the delayed rectifier K current (KCNH2, KCNQ1, KCNE1, KCNE2).[146] Both types of mutations presumably produce prolongation of the ventricular action potential[147] and exaggerated dispersion of repolarization, much like that in cells and tissues isolated from failing ventricles.[8] QT interval shortening has been associated with sudden death,[148–151] perhaps attributable to short but spatially heterogenous action potentials in the ventricle leading to ventricular fibrillation. The abnormal physiology of repolarization associated with the long QT syndrome may also predispose to lethal arrhythmias in the setting of ischemic heart disease.[28] Common polymorphisms in long QT genes have also been described that predispose drug-induced QT interval prolongation and ventricular arrhythmias.[152–154] It is possible that the same or other yet-to-be-discovered polymorphisms predispose to lethal arrhythmias in HF, a syndrome associated with diminished repolarizing reserve. Mutations in Ca^{2+} handling genes have been associated with lethal arrhythmias and SCD in patients with catecholaminergic polymorphic ventricular tachycardia[155] and arrhythmogenic right ventricular dysplasia.[156] These mutations highlight the importance in the links between cellular Ca^{2+} homeostasis and cardiac electrophysiology.

Allelic variation in candidate genes in a number of signaling systems that alter myocardial electrical substrate or triggers, cell survival pathways, and thrombotic cascades may enhance susceptibility to SCD in the failing heart.[157,158] Association studies have demonstrated an increased risk of sudden death in Finnish men with the A2 allele of the PIA1/A2 polymorphism of glycoprotein IIIa.[159] Another case-control study has demonstrated an association between 4G polymorphism of plasminogen activator type I.[160] Combinations of polymorphisms, such as that of the DD allele of the angiotensin-converting enzyme and the C allele of the angiotensin II type 1 receptor, have been associated with an increased risk of malignant ventricular arrhythmias in patients with CAD and left ventricular dysfunction.[161] Allelic variations in other genes (eg, β-adrenergic receptors, endothelial nitric oxide synthase, angiotensin-converting enzyme) may influence the rate of progression of HF and response to therapy,[162–164] thereby influencing the risk of sudden death from both mechanical and electrical causes.

There is likely to be a number of genetic factors that contribute to the complex phenotypic manifestation of SCD in the failing heart. Some of the contributors may be well-known candidate genes in signaling pathways associated with electrical instability, generation, or progression of the HF phenotype and/or triggers associated with neurohumoral signaling and ischemia. It is equally likely that unbiased genomic screening will reveal novel variations in known or unknown genes that are important contributors to sudden death. A major challenge will be in sorting out which of the

allelic variants, in what is likely to be many candidate genes, alter the risk for SCD independent of the context of the specific structural heart disease, as well as the mechanism by which they contribute to the initiation of VT/VF.

Conclusions

Sudden death in patients with HF is a complex phenotypic expression of a systemic disease that most often results from the unfortunate confluence of a number of factors.[165] These include, but are not limited to, a hospitable substrate, the result of remodeling of active and passive membrane properties of the heart, altered neurohumoral signaling, in many cases myocardial ischemia, and perhaps an underlying genetic predisposition to electrical instability. The risk of SCD is highly time-variant, reflecting temporal heterogeneity of both the myocardial substrate and triggers. This minute-to-minute variation in the risk makes SCD prediction in individual HF patients an enormous challenge.

Acknowledgments

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