Introduction to a Compendium on Sudden Cardiac Death
Epidemiology, Mechanisms, and Management
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Overview of Sudden Cardiac Death and Scope of the Compendium
Sudden cardiac death (SCD) is a devastating complication of many forms of heart disease and on occasion presents in the absence of structural cardiac abnormalities. SCD caused by ventricular arrhythmias is a daunting public health problem with 200,000 to 450,000 events in the United States annually. There are many challenges in the definition, mechanisms, and management of SCD that will be addressed in the chapters of this compendium by leading experts in the field. The compendium will address gaps in our understanding of SCD and resuscitated SCD or sudden cardiac arrest (SCA) from genes to society and highlight opportunities for ongoing investigation.

The epidemiology of SCD/SCA is dynamic and heterogeneous as they are the proximate causes of sudden death. Secular trends in incidence, mechanisms, and survival will be addressed, as well as the epidemiology of rarer heritable causes of SCD. The evolution of the causes of SCD/SCA and the relatively poor survival from out of hospital cardiac arrest have motivated studies to better assess risk and to implement strategies for prevention of underlying cardiovascular diseases. Basic science studies aimed at understanding the mechanisms of ventricular arrhythmias and the basis of pulseless electric activity (PEA) may afford new insights into risk assessment and management of arrhythmic and nonarrhythmic causes of SCD/SCA and approaches to cardiac resuscitation.

Scope of the Problem—Epidemiology and Risk Stratification
A foundational problem is the absence of a clear understanding of the rates of SCD. Differences in the methods of counting events yield substantial differences in rates of SCD. Differences in data sources yield differences in rates that are complicated by problems in case definition, in part the result of the heterogeneity and changing causes of SCD.

Fundamental Biology and Omics
The promise of a more comprehensive understanding of the fundamental arrhythmic and myocardial mechanisms of SCD/SCA is improvement in risk stratification, prevention, and resuscitative treatment. An important foundational assumption about SCD/SCA is that there is a strong deterministic basis rather than occurrence by random chance. Recent evidence has provided fundamental insights into the genetic basis of cardiovascular diseases. Genetic factors play a significant role in SCD, and many studies have identified a family history...
of SCD as a powerful risk factor, independent of traditional risk factors for CAD and family history of myocardial infarction. Ion channel and excitability genes have been linked to rare, heritable arrhythmias and SCD. Other common channel variants have been linked to SCD\textsuperscript{7,8} or to electrocardiographic surrogate risk markers in apparently healthy populations.\textsuperscript{5–11}

The chapter by Bezzina et al\textsuperscript{3} reviews the literature on the genetics of Mendelian causes of SCD/SCA that have provided unique insights into the mechanisms of arrhythmias in these rare disorders but also more common acquired causes of SCD. They consider the genetics of the primary electric disorders and arrhythmogenic cardiomyopathies. They review contemporary evidence demonstrating that rare and common genetic variation can significantly modulate the phenotype of these Mendelian disorders. Bezzina et al\textsuperscript{3} present the challenges of more complex genetics and the implications of genome wide interrogation of variation on cardiac structure, function, and other surrogates of arrhythmic risk, such as electrocardiographic metrics, as well as SCD itself.

Disorders of ion channel function are centrally related to the development of cardiac arrhythmias, changes in the function of the diseased heart, and proarhythmic responses to therapeutics. The chapter by Yang et al\textsuperscript{12} tackles the topic that is at the intersection of metabolism, electric and structural remodeling, and arrhythmogenesis. Their focus is on a feature common to many forms of heart disease, oxidative stress. They summarize the current evidence on the mechanisms linking metabolic derangements and excessive oxidative stress to ion channel/transporter dysfunction that predisposes to ventricular arrhythmias and SCD. Metabolic regulation influences ion homeostasis in the heart, and the authors review the mechanistic connection between the redox state, ion channel and transporter activity, intercellular coupling, and ventricular arrhythmias. They highlight many chronic conditions that are associated with disordered metabolism and exaggerated oxidative stress. Such conditions comprise but are not limited to aging, sleep apnea, chronic renal disease, and diabetes mellitus and are associated with enhanced arrhythmic risk by many mechanisms that include maladaptive electric remodeling.

The role of disorders of ion homeostasis and in particular Na\textsuperscript{+} and Ca\textsuperscript{2+} handling is prominent in mechanical dysfunction of the heart and electric instability and arrhythmic risk. Wagner et al\textsuperscript{13} review Na\textsuperscript{+} and Ca\textsuperscript{2+} signaling in the heart and the major nodes of ion homeostasis, including channels and transporters in the cell membrane and sarcoplasmic reticulum, the ubiquitous Ca\textsuperscript{2+}-binding protein calmodulin, and key regulatory enzymes, such as protein kinase A and Ca\textsuperscript{2+}–calmodulin-independent protein kinase. This article reviews the fundamental features of excitation–contraction coupling and focuses on the contribution of altered Na\textsuperscript{+} and Ca\textsuperscript{2+} homeostasis on cellular and tissue mechanisms of cardiac arrhythmias. They consider genetically encoded changes in ion channels and regulatory proteins and acquired changes in structural heart disease that leads to Na\textsuperscript{+} and Ca\textsuperscript{2+} dysregulation and an increased risk of potentially lethal arrhythmias. The mechanistic links between aberrant ion regulation and dynamic instability in excitability, conduction, and repolarization are described. The role of Na\textsuperscript{+} and Ca\textsuperscript{2+} homeostasis in afterdepolarization-mediated action potential instability and electric alternans are considered in the context of the risk of VT/VF.

The development of structural heart disease produces changes in the electrophysiological phenotype that heightens SCD risk. Dysregulation of Na\textsuperscript{+} and Ca\textsuperscript{2+} is central to this adverse electric remodeling. The authors describe the changes in ion channel function and regulation that accompany heart failure (HF) and ischemia/reperfusion with a focus on the role of an increase in the late Na current and activation of Ca\textsuperscript{2+}-binding protein calmodulin kinase signaling and its effect on cell surface membrane and sarcoplasmic reticulum function. New mechanistic insights serve to identify novel therapeutic approaches to SCD.

### Macromolecular Complexes

The elemental units of the electric function of the heart are ion channels and transporters. Most often channels and transporters are part of structural and functional macromolecular assemblies required for normal function and regulation of cardiac electrophysiology. Heritable and acquired abnormalities in components of these complexes are responsible for or contribute to disease phenotypes. Abriel et al\textsuperscript{14} provide an overview of several of the most important macromolecular ion channel assemblies in the heart. They review the evidence for the role of such assemblies in channel biosynthesis, trafficking and targeting, regulation, and turnover. The promise of understanding the components of these macromolecular assemblies is that they are mechanistic links to disease and represent novel therapeutic targets. Spanning the knowledge gaps in understanding the large diversity of molecular interactions that underlie cardiac electrophysiology will be required to realize the promise of improved understanding of mechanisms of SCD and the development of newer and more effective treatments.

As the problem of SCD is one of the integrated systems, many models of disease and arrhythmia susceptibility may provide important insights. Sallam et al\textsuperscript{15} review the platforms and model systems available for studying arrhythmic disorders associated with SCD with a focus on induced human pluripotent stem cells (iPSCs). The use of cardiac myocytes (CMs) in primary culture to study ion channel and transporter behavior is well established as are the limitations of this methodology. The constellation of expressed ion channels in non-human cells often substantially diverges from that of human heart cells. Moreover, the process of cell culture promotes dedifferentiation and remodeling of cellular electrophysiology that limit the extrapolation of the information gleaned to adult myocardium. These limitations are highlighted in the methods that have been developed to assess the arrhythmic liability of drugs, which focuses disproportionately on the effect of compounds on the expressed gene product of KCNH2 (K\textsubscript{1.1.1} or hERG channel) that encodes the rapid component of the delayed rectifier. High-affinity block of this channel is a useful signal in risk assessment but is very insensitive in predicting the risk of drug-induced arrhythmias.\textsuperscript{16} There are many reasons for this insensitivity, prominently, the promiscuous nature of modulation of ion channel function by most compounds. The shared evolution of channel proteins coincides with the shared sensitivity to many channel-blocking
drugs. At a minimum, the effect of a drug on the integrated active membrane properties of a myocyte, reflected in the action potential, would be required to more reliably assess the risk of arrhythmias driven by altered repolarization reserve. CMs derived from iPSCs may circumvent some of the shortcomings of expressed currents and primary cells in culture. As described by Sallam et al., human iPSC-CMs express ion channels and transporters that recapitulate those found in adult heart exhibiting action potentials reminiscent of heart cells, both working and pacemaking myocytes. Although hiPSC-CMs are not a surrogate for mature adult ventricular cells, the similarity of the expressed human ionic currents in these cells commends them as a model for assessing electrophysiological liability that can be detected by effects on the action potential. Moreover, higher dimensional culture systems using CMs derived from iPSCs and other types of stem cells allow for the valuation of the effects of drugs on the network properties of a model cardiac tissue. Finally, the unlimited supply of patient-specific iPSC-CMs will permit more precise evaluation of drug effects, mechanistic studies of inherited rhythm disorders, and as a platform for tissue regeneration.

Neurohumoral Regulation of the Heart
The heart that is susceptible to the development of potential lethal arrhythmias is part of the system. This system is critically regulated by many feed forward and feedback loops that modulate electric and mechanical function on many times scales from minute-to-minute, to circadian to months to years. The chapter by Fukuda et al. describes the autonomic regulatory networks, the roles of the central and peripheral nervous system in structural and electric remodeling in the heart, and the intersection of neural and cardiac remodeling on arrhythmic risk. The sympathetic nervous system is a well-established participant in functional and structural remodeling and arrhythmogenesis, indeed neurohumoral blockade is a mainstay of therapy for the treatment of HF and cardiac arrhythmias. The chapter reviews the determinants of patterns of autonomic innervation during development and in the diseased heart focusing on the relationship to potentially lethal ventricular arrhythmias and SCD. A contemporary molecular understanding of cardiac and extracardiac neural remodeling including transdifferentiation of neurons in HF, anatomic, and functional denervation is reviewed through the lens of identifying new targets for prevention of arrhythmias.

The authors present many emerging features of the neural-cardiac axis in SCD risk and management. The parasympathetic arm of the autonomic nervous system is an important modulator of mechanical and electric function of the heart. Remodeling of innervation of the diseased heart is an important contributor to the changes in sympatho-vagal balance in health and the derangements that may produce arrhythmias. The mechanisms described rationalize recent therapeutic approaches to HF and arrhythmias that use autonomic stimulation (eg, vagal nerve stimulation).

Contemporary and Emerging Management of SCD/SCA
The limitations in understanding the mechanisms and susceptibility to SCD/SCA have necessitated widespread use of implantable cardioverter defibrillators (ICDs) in patients deemed to be at the highest risk. This strategy highlights persistent gaps in the contemporary management of SCD. First, existing risk stratification algorithms (based on left ventricular ejection fraction) are neither sensitive nor specific; they require implantation of >10 ICDs for every device that saves a life at 3 years. Second, the limitations of risk stratification, the expense, and procedural hazards limit the use of primary prevention ICDs to high-risk populations, whereas the overwhelming majority of SCDs occur in lower-risk patients. Finally, the strategy is reactive rather than preventive; ICDs are effective treatments for tachyarrhythmias and bradyarrhythmias but do not address the underlying causes of SCD/SCA.

The major criterion for selection of high-risk patients who undergo primary prevention ICD placement is left ventricular systolic function. More than 5.7 million Americans have HF, with an incidence of 850,000 annually (~1% in patients aged ≥65 years). Projections point to a future with a significantly increasing prevalence of HF. Improvements in the therapy of HF have delayed progression to terminal pump failure but paradoxically have increased SCD mortality. Yousuf et al. summarize the current clinical management of SCD/SCA with an emphasis on device and ablative strategies and antiarrhythmic strategies in future clinical trials. They review the landmark trials of primary and secondary prevention ICD treatment and studies of cardiac resynchronization therapy for HF; discuss the role of VT ablation as primary or adjunctive therapy; and discuss the role of cardiac sympathetic denervation particularly in the rare heritable causes of SCD, such as long QT syndrome and catecholaminergic polymorphic VT. They present preliminary information on the emerging studies of vagal nerve stimulation for HF and ventricular arrhythmias.

When efforts to prevent SCA fail, the only life-saving maneuver is prompt return of effective circulation. Temporary support of the circulation by chest compressions has been recognized in the medical literature since the 1860s, but widespread use was not adopted for over a century after the development of cardiac defibrillation. Modern, hands-only cardiopulmonary resuscitation is the mainstay of the treatment and the critical first link in the chain of survival for those who have SCA. Patil et al. provide an overview of the current treatment of cardiac arrest and newer mechanical devices used to provide cardiopulmonary resuscitation. They review the phases of ventricular arrhythmic SCA, which serves to rationalize contemporary treatment strategies. The phases of SCA due to VF are the electric (0–5 minutes), circulatory (5–10 minutes), and metabolic (>10 minutes) phases. These phases require prompt defibrillation, resumption of circulation with cardiopulmonary resuscitation then defibrillation, and salvage therapies (eg, cardiopulmonary bypass and extracorporeal membrane oxygenation) with protection from and prevention of reperfusion injury, respectively.

Resuscitative treatment is complicated by the changing patterns of SCA with declining numbers of out-of-hospital cardiac arrest because of VT/VF and a relative increase in the frequency of PEA. The authors review the epidemiology and mechanisms of PEA. They focus on the role of vascular tone and pressure, altered Ca²⁺ signaling and innate immunity in
PEA, and ischemia reperfusion injury in resuscitation. They review data concerning quaternary treatment protocols for SCA that include circulatory bypass or support and drug combinations to minimize reperfusion injury and restoration of normal mitochondrial function.23

SCD is a complex manifestation of many forms of cardiac disease. A more comprehensive understanding of the molecular structure, metabolism, and fundamental electrophysiology of the normal heart is a prerequisite for understanding the maladaptive remodeling of the substrate and the relationship to triggers that produce arrhythmias that result in SCA/SCD. Future advances in the prediction and treatment of this devastating complication of heart disease will require a vertically integrated, multidimensional approach to understanding ion channels and transporters, model systems, intact hearts, and patients. The spirit of this SCD compendium is to identify those areas where gaps in knowledge are large and where progress will be most impactful.

Sources of Funding
Dr Tomaselli was supported by the National Institutes of Health R01 HL091062, R01 HL050411, and 1P01 HL077180.

Disclosures
None.

References

Key Words: Editorials ■ defibrillators ■ genetics ■ ion channels ■ stem cells
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Circ Res. 2015;116:1883-1886
doi: 10.1161/CIRCRESAHA.115.306515

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