Sudden cardiac death (SCD) is generally defined as unexpected death as the result of cardiovascular causes in a person with or without preexisting heart disease, within 1 hour of onset of change in clinical status. Most instances of SCD are thought to involve ventricular tachycardia degenerating to ventricular fibrillation (VF) and subsequent asystole, although the percent of ventricular tachyarrhythmias found as the first rhythm at the time of collapse appears to be decreasing. In 60% to 80% of cases, SCD occurs in the setting of coronary artery disease. Nonischemic cardiomyopathy and infiltrative, inflammatory, and acquired valvular diseases account for most other SCD events. A small percentage of SCDs occur in the setting of ion channel mutations responsible for inherited abnormalities such as the long/short QT syndromes, Brugada syndrome, and catecholaminergic ventricular tachycardia. Although accounting for a small number of SCDs overall, these fascinating syndromes provide mechanistic insights never before available. In addition, other genetic abnormalities such as hypertrophic cardiomyopathy and congenital heart defects such as anomalous coronary arteries are responsible for SCD.

Despite widespread advances in the treatment of ischemic heart disease with early recognition and revascularization therapies and the growing use of automated external defibrillators and implantable cardioverter-defibrillators to detect and treat ventricular arrhythmias, SCD remains a major cause of death in industrialized countries, exceeding 300,000 events per year in the United States, or about 20% of all deaths annually. The only pharmacological advances have been achieved with drugs that affect “upstream” regulatory events, such as statins, angiotensin-converting enzyme inhibitors, fish oil, aspirin, β-blockers, and aldosterone inhibitors, rather than with “traditional” ion channel–blocking antiarrhythmic agents.

A frequently observed and notable aspect of SCD is its unpredictable and seemingly random nature of onset. Accordingly, one of the most vexing issues remains early identification of individuals at highest risk, especially the subset of patients with SCD without overt signs, symptoms, or evidence of heart disease. Although clinical studies have been largely unsuccessful at identifying global and specific markers of SCD risk in the general population, certain clinical and diagnostic findings are associated with increased risk of SCD, generally found in patients with established disease. These include markers such as abnormal left ventricular systolic function or ejection fraction, scalar electrical abnormalities such as microvolt T-wave alternans, increased QRS duration, and repolarization abnormalities, abnormal electrical activity during invasive electrophysiological testing, disordered autonomic nervous system function manifested by alteration and variability in resting and exercising heart rate and baroreflex sensitivity, and the presence of occult ventricular arrhythmias. Interestingly, some studies have reported circadian and seasonal variations on the rate of SCD. Despite these advances, the biomarkers presently used have insufficient predictive accuracy to identify the at-risk individual but instead identify groups of people at risk. Major advances in this area are needed to identify predisposing risks.

We also still lack fundamental understanding of the precipitating factors that underlie initiation of ventricular tachycardia/VF causing SCD at a specific time, hence the question we have raised, “Why did he die on Tuesday and not on Monday?” If we can identify the factors that probably represent interplay between a receptive substrate and a transient initiating event, we can begin to develop more effective strategies for prevention of SCD. The challenge is to determine the nature of the receptive substrate and how it interacts with the transient trigger. Moreover, we cannot forget that both the substrate and the trigger may change over time, so that an “ice pick” evaluation at 1 reference point may not provide useful information a few months later because short-term changes occur in a long-term disease. For example, recent studies have shown that the neural substrate, through nerve sprouting, can change over weeks as can the trigger, with T-wave alternans increasing before the development of ventricular tachyarrhythmias.

We can also rephrase the question of why some patients fibrillate to ask why some individuals at risk do not fibrillate. Do they have some sort of an “antifibrillatory reserve” that protects them? Do they require a double hit, that is, a confluence of events necessary to trigger the cascade leading to ventricular fibrillation, with the latter being the final common pathway in response to multiple and different inputs? We have learned that there are different mechanisms that can initiate and perpetuate atrial fibrillation. The same probably applies to ventricular fibrillation.

In this issue of Circulation, 2 articles attempt to identify risk factors for susceptibility to malignant ventricular arrhyth-
mias and SCD. Müller and coworkers\textsuperscript{12} investigated the conditions preceding cardiac arrest that occurred in the Berlin, Germany, emergency response network. Information on medical history, medications, first-registered arrhythmia, and signs or symptoms present for up to 24 hours before out-of-hospital cardiac arrest in 406 patients was collected by an emergency physician on the scene after successful resuscitation or declaration of death. The location of the events was at home in 72\% of cases. This is consistent with previous data from the United States.\textsuperscript{13} Notably, nearly two thirds of an emergency physician on the scene after successful resuscitation (CPR) was performed in only 20\% of these patients. Moreover, patients were more likely to receive bystander CPR in public than at home. Still, patients who received bystander CPR had significantly higher rates of successful resuscitation and eventual hospital discharge. Earlier studies have reported similar findings.\textsuperscript{14} Preexisting cardiac disease was present in 67\% of patients. Accordingly, the most frequently reported symptom was angina, followed by dyspnea, nausea/vomiting, and dizziness/syncope. No symptoms were reported in 25\% of patients. Interestingly, patients tolerated symptoms longer at home (75 minutes) than in public (20 minutes). The authors concluded that in the study population, signs and symptoms are present, often for a significant period of time, which could herald the onset of cardiac arrest. This observation suggests that symptoms are often present before cardiac arrest and draws attention to the important fact that patient and family education of the warning signs of cardiovascular disease and lay person interventions such as CPR might dramatically improve survival in cardiac arrest. Reports many years ago noted similar symptoms before cardiac arrest, but, in general, the symptoms were too nonspecific to trigger emergency action.\textsuperscript{15}

Also reported in this issue of \textit{Circulation}, Dekker and coworkers\textsuperscript{16} conducted a case-control study in survivors of primary VF that occurred in the setting of acute ST-segment elevation myocardial infarction (STEMI) with the goal of identifying risk factors for primary VF. Control patients were age- and sex-matched patients with STEMI with no primary VF. Both groups had no history of primary VF, myocardial infarction, or structural heart disease, and all participants underwent subsequent percutaneous coronary intervention. Baseline characteristics, including electrocardiographic parameters (heart rate, axis, PQ interval, QRS duration, and QT\textsubscript{c}), infarct size, culprit vessel, and presence of angina were similar between groups. Interestingly, atrial fibrillation was diagnosed in 21\% of cases and 0\% of control subjects who received prior cardiac care. For unknown reasons, atrial fibrillation has been shown to be a risk factor for sudden cardiac death in other studies as well.\textsuperscript{17} A major finding of the study was that cases had a significantly higher percentage of family history of SCD or aborted SCD (43\% versus 25\% in control subjects). Two prior studies have also noted an association between family history and SCD risk,\textsuperscript{18,19} but this is the first study to specifically study patients with STEMI. Additionally, cases had significantly increased ST-segment deviation, even on ECGs obtained before cardioversion, perhaps reflecting inherited repolarization “sensitivity” to ischemia and ventricular arrhythmias.\textsuperscript{20,21} The authors conclude that complex and multifactorial genetic and environmental factors may underlie the finding that family history predicted primary VF in this study and advocate using the family history as an integrating tool for risk stratification of patients with STEMI. Since a greater percentage of cases compared with control subjects sought cardiac care before having primary VF, perhaps a more thorough history taking might have changed the patients’ initial cardiac management, thus leading to further diagnostic testing and additional or different pharmacotherapy. Dekker and coworkers provide additional compelling evidence that a genetic mechanism may increase a patient’s propensity to have lethal arrhythmias and SCD. Recent studies support the notion that subtle genetic variations such as single nucleotide polymorphisms can influence the phenotypic expression of low penetrance ion channel mutations and increase propensity to ventricular arrhythmias and SCD.\textsuperscript{22} In the future, techniques such as genome-wide linkage analysis may allow the detection of polymorphisms and mutations that confer increased SCD risk in the general population without overt evidence of cardiovascular abnormalities.\textsuperscript{23}

It is clear from these and other studies that better understanding of the contribution of molecular and genetic/protein influences on the risk for developing, or for not developing, ventricular tachyarrhythmias, as well as understanding the mechanisms responsible for the onset and maintenance of arrhythmias in a variety of animal models, including human beings, is essential to both identify individuals at risk and to develop specific therapies to mitigate that risk. However, the future holds great promise, with advances in imaging capabilities and genetics, pharmacotherapy, and device technology, all playing increasing roles.

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**References**


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