Sudden cardiac death (SCD), which is defined as an unexpected, usually arrhythmic death occurring in asymptomatic individuals shortly after the onset of symptoms, is responsible for more than half of the total cardiac mortality in developed countries throughout the world.² It frequently appears as the first and only manifestation of previously undetected coronary heart disease.² At least half these deaths occur outside a hospital setting, and, according to recent Centers for Disease Control data, this proportion, as well as the overall prevalence in the United States, continues to increase.³

**Sudden Death Predictors**

An Inflammatory Association

Peter M. Spooner, PhD; Douglas P. Zipes, MD

Pharmaceutical strategies to prevent SCD have been largely ineffective, and because device therapy is designed to rescue patients once an event has already occurred, primary SCD prevention has become one of today’s most critical public health challenges. Progress has been difficult, in part because although overall incidence in healthy adults is very low, it is precisely this group that continues to contribute the most to overall prevalence in the total population.⁴ Compared with identifying risk markers for secondary prevention, where the importance of clinical phenotypes such as low ejection fraction clearly has been established, work on reliable markers for primary SCD prevention has advanced much more slowly. Traditionally, approaches most often have been based on algorithms involving risk factors predictive of atherosclerotic and hypertensive coronary heart disease (CHD), yet these markers are often absent in a significantly large proportion of SCD victims. Although several population stratification approaches (like those based on the landmark Framingham Heart Study, which is now entering its third generation of analysis) have been quite successful in predicting SCD events in large community groups,⁵ their ability to detect susceptibility in specific asymptomatic subjects with high sensitivity and specificity has been found to be much more limited. Thus, efforts to reduce SCD risk via targeted alterations in conventional CHD risk factors, such as elevated cholesterol, LDL and HDL lipoproteins, tobacco use, blood pressure, and diabetic factors, have been most successful in a secondary setting with patients who have already survived one or more life-challenging events.⁶ Although advances continue to be made in the discovery of new markers, especially with some of the newer noninvasive diagnostic technologies, like T-wave alternans detection of calcium deposition by radiographic tomography and increasingly effective magnetic resonance protocols, cost-effective indications for the commitment of the medical resources required by these technologies are likely to remain problematic.

Despite difficulties in establishing new prognostic approaches and reliable phenotypic markers for SCD, detailed autopsy and morphological studies continue to affirm that underlying but undetected CHD is likely to be a factor in a majority (∼65%) of SCD cases. Structural and congenital abnormalities, fibrosis, and conditions such as myocarditis, in which other diagnostic criteria may apply, constitute most of the remainder.⁷ It is this pathological information that has continued to focus attention on the question of whether early indicators of vascular events might be useful in screening for primary SCD risks in routine evaluation of asymptomatic individuals, in the same way, for example, that routine ECG screening is used today. One new set of clues suggesting that there may be useful, but as yet undetected, SCD markers has emerged recently. Population studies have reported that “familial clustering of SCD events” is an important independent factor in multifactorial analyses of SCD risk. These data imply that shared environmental or genetically transmittable abnormalities may be quite useful in this effort. Evidence favoring a focus on genetic factors was presented in two major recent epidemiological studies that suggested not only that familial risks for SCD appear substantial, but that they are statistically distinct and separable from familial risks for myocardial infarction.⁸,⁹ What has remained lacking in this line of inquiry has been a reliable distinction between the potential contributions of genetic and environmental factors, information on which pathological mechanisms might be involved, and clues about which types of biological or genetic markers might be useful in detecting such risks in subjects in sufficient time to intervene or provide protection—for example, in the form of an implanted defibrillator.

A National Heart, Lung and Blood Institute–sponsored workshop, convened almost two years ago, considered the nature and evidence for the involvement of specific genetic risks predisposing individuals to SCD. The summary published from this meeting suggested that genetically based contributions were indeed likely to be involved in the...
increasing prevalence of asymptomatic SCDS and that useful new markers were likely to cluster under three general categories: (1) detection of factors that most directly facilitate development of ischemia and infarction, including activators of plaque rupture and thrombogenesis; (2) assessment of alterations in neuro-endocrine signaling, including alterations and polymorphic variation in transmitter pathways leading to changes in sympathetic-parasympathetic balance; and (3) analysis of potential triggers and modulators of cardiocyte membrane excitability and transcellular conduction, and the heterogeneous distribution of these elements in different regions of the heart.10,10a

Patient-derived evidence about potentially mediating events, especially in cases where there is evidence for genetic variation between individuals, however, has remained sparse. Last year Jouven et al11 published evidence for genetic variation between individuals, however, with the highest levels of CRP (mean \( \sqrt{1.7}, \) \( P=0.05 \)) in their cohort of \( >5000 \) middle-aged Parisian civil servants. Although increases in NEFA levels were relatively small (\( \approx 23\% \) increase in basal levels), there was a clear statistical difference linking increased CRP events with quintile increments in NEFA levels. Although information on mechanisms was not assessed, it was suggested that such effects could well have been due to increases in adrenergic tone, reflected secondarily in NEFA levels, or perhaps through more direct effects on membrane elements like ion channels and transporters. Genetically influenced variations in related enzyme systems, such as lipoprotein lipase, have been known for some time.12

In this issue of Circulation, Albert and coworkers13 advance the goal of improving individual SCD prediction by providing the first evidence that a marker of chronic inflammation, high-sensitivity C-reactive protein (CRP), also may be a long-term marker for unexpected SCD. They report that CRP levels from SCD victims in blood samples taken at the beginning of the prospective 17-year Physicians’ Health Study (PHS) of 15,000 participants across the United States, conducted retroactively with the use of a case-control design, were highly predictive in identifying SCD victims. The relative increase in SCD risk was not reflected in parallel measurements of homocysteine, triglycerides, or total, HDL, or LDL cholesterol, and concentrations of these markers appeared relatively uninformative. Multivariate evaluation suggested increased relative SCD risk signaled by CRP occurred independently of these and other traditional markers of CHD risk per se. Of the 97 cases of SCD studied, subjects with the highest levels of CRP (mean \( \approx 0.44 \text{ mg/dL} \)) showed an almost 3-fold enhancement in relative risk of SCD, and the CRP level for all 97 SCDS (mean \( \approx 0.17 \text{ mg/dL} \)) was significantly higher than the CRP level in matched case controls (mean \( \approx 0.10 \text{ mg/dL} \)). Quite remarkably, the increase in CRP was found to be elevated, on average, \( \approx 9 \) years before SCD occurred. Given the observation that these findings are confirmed, this work suggests that enhanced levels of a relatively nonspecific biomarker, produced in the liver in response to multiple inflammatory, infectious, and immunological challenges, represents the earliest predictor for SCD yet discovered!

Elevations in circulating CRP levels frequently have been observed in patients with accelerated atherosclerosis, enhanced short- and long-term risk of MI, and increases in stroke and vascular disease in female as well as male adults, and there is some suggestion that it also may be a direct participant or mediator of cytokine-linked plaque instability.14 Whether prolonged elevations in CRP or cytokines like interleukin-6, which enhance its production, are directly proarrhythmic is unclear. As noted by Albert et al, it is of interest that Van Waggoner’s group15 recently reported on an elevation in circulating CRP associated with “lone” atrial fibrillation, as well as atrial fibrillation in patients with other forms of cardiac insult. Cytokines and factors such as platelet activating factor also have received attention in studies on postischemic and reperfusion-induced ventricular arrhythmias, but the significance of these data remains inconclusive.16 Additional inferences about how directly CRP participates in the arrhythmogenesis of SCD obviously must await studies with the ability and power to discriminate among the multitude of causative and correlative events that occur in this clearly very complex pathology.

Important and clearly acknowledged limitations of the Albert study suggest caution in overinterpreting these initial results: Conclusions were based on single (not sequential) measurements of samples stored over a considerable time period and taken from individuals known to be taking aspirin during the run-in period. Furthermore, except for the fact that a lower occurrence of SCD was reported in subjects randomized to aspirin therapy as part of the PHS study protocols, it is not indicated whether other treatments in this study (eg, vitamin E, \( \beta \)-carotene) might have influenced event distribution, and information on other possible confounders over the 9-year average event period might be difficult to retrieve. Finally, although it seems that a determined effort was made to adhere rigorously to a standardized definition of SCD in the interpretation and review of recorded events, pathological autopsy information, which is helpful in confirmation of cause of death and in guiding subsequent mechanistic approaches, might have been useful.

Given the potential importance of these findings, one can ask whether there are new implications for SCD prevention. Several recent studies, including those involving this same group of investigators, provide evidence that “statin” inhibitors of hydroxyglutaryl CoA reductase may significantly reduce CRP expression levels17 after brief or multi-year periods of statin therapy. The broad, systemic, antiinflammatory effects of these increasingly popular cardiovascular drugs are a topic of intense investigation in many ongoing clinical and observational studies, and it would thus seem worthwhile to begin examining CRP levels in patient protocols that could provide information on the questions raised by this study by Albert et al.13 It would seem helpful, for example, to obtain information on whether and how CRP levels change sequentially over time in female as well as male cohorts and to determine what nutritional, physiological, environmental, and medical factors influence its levels. It also would seem important to ask if there is a basis here for considering whether genetic variation in these pathways might be important in influencing individual and familial...
SCD susceptibility. The potential of the present findings to contribute to the new strategies and new insights in SCD prevention thus would seem considerable.

References

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