Stratifying Risk for Sudden Cardiac Death

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A major challenge for the medical community is predicting who is at risk of sudden cardiac death (SCD), which occurs from tachyarrhythmic mechanisms in an estimated 50% to 70% of cases [Goldberger JJ et al. *Circulation* 2011]. Although the vast majority of SCD victims has underlying structural heart disease (in particular, advanced coronary artery disease [CAD]), a significant percentage of them have previously unrecognized cardiac disease [Adabag AS et al. *Am Heart J* 2010]. In the majority of patients, death is the first symptom of heart disease, making early risk stratification critical. Gordon F. Tomaselli, MD, Johns Hopkins University, Baltimore, Maryland, USA, discussed emerging strategies for risk stratification for SCD.

In the United States alone, the number of SCDs ranges from 184,000 to 462,000 a year [Golberger J et al. *Circulation* 2008]. The annual incidence is estimated at 1 per 1000 for adults aged >35 years and 1 per 100,000 for adolescents and young adults [Juntilla MJ et al. *Ann Med* 2011]. On autopsy, advanced CAD, with or without evidence of unstable plaques and acute or unhealed myocardial infarctions ([MIs]; often clinically silent), is commonly detected [Adabag AS et al. *Am Heart J* 2010].

Several studies have assessed the potential benefit of predicting the risk of SCD through the combined use of multiple noninvasive tools. Multidetector computed tomography coronary angiography (CTA) is a sensitive method for the diagnosis of CAD. However, in its current form, CTA is a purely anatomical modality and is limited in its assessment of myocardial ischemia. Dr. Tomaselli discussed a pilot study [George RT et al. *Circ Cardiovasc Imaging* 2009] that investigated whether the combination of CTA and adenosine stress CT myocardial infusion imaging could accurately detect atherosclerosis that causes perfusion abnormalities.

The study demonstrated that CT perfusion imaging, when performed with adenosine, can detect subendocardial perfusion deficits, and the combination of CTA and CT perfusion imaging can detect obstructive atherosclerosis that causes perfusion abnormalities—a finding that could have important implications on the future of the diagnostic evaluation of patients with suspected CAD.

Dr. Tomaselli also reported on a study using contrast-enhanced magnetic resonance imaging (ceMRI) to relate the extent of tissue heterogeneity in the infarct border to susceptibility for cardiac arrhythmias [Schmidt A et al. *Circulation* 2007]. Data indicate that tissue heterogeneity is quantifiable in human infarcts by ceMRI and is associated with inducibility for monomorphic ventricular tachycardia by programmed electrical stimulation [Esthner HL et al. *Heart Rhythm* 2011]. The researchers assessed contrast distribution within the scar, focusing on the "Gray Zone," a region of intermediate-intensity contrast enhancement that is prominent at the periphery of the scar. In a group of patients with significantly reduced ejection fractions that were associated with large, predominantly anterior, transmural infarctions, a larger extent of Gray Zone tissue correlated with an increased susceptibility to ventricular arrhythmias.

Although the most frequent cause of ventricular arrhythmias and SCD in patients aged >30 years is CAD, inherited cardiac disease is the most frequent cause in individuals aged <30 years [Zipes DP et al. *J Am Coll Cardiol* 2006]. Advances in genomewide testing technologies have had a profound effect on the study of the genetics of common diseases [Manolio TA et al. *J Clin Invest* 2008] and have provided new insights into the pathophysiology of many diseases. Such genomewide assessments have raised the possibility of using general population-based or more targeted screening of individuals with positive family histories to identify high-risk, presymptomatic patients; determine the earliest manifestations of conditions; and facilitate early trials of preventive therapies [Chamberlain M at al. *Surv Ophthalmol* 2006].

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Previous studies have identified family history of SCD as a powerful risk factor that is independent of traditional risk factors for coronary heart disease or a family history of MI [Friedlander Y et al. *Circulation* 1998; Jouven XP et al. *Circulation* 1999; Kaikkonen KS et al. *Circulation* 2006; Dekker et al. *Circulation* 2006]. Moreover, a number of genes have been linked to rare heritable arrhythmias that predispose one to SCD. However, the genetic factors that underlie SCD in the general population are largely unknown.

Nitric oxide synthase 1 adaptor protein (NOS1AP), which encodes a ligand of neuronal nitric oxide synthase, has been associated with the QT interval in white adults. A study by Arking et al. [*Nature Genetics* 2006] found that multiple single-nucleotide polymorphisms in NOS1AP were associated with prolonged QT intervals in whites ($p<0.0001$), a surrogate maker for SCD [Circulation 2009]. In another study, Kao et al. [*Circulation* 2009] found 2 single-nucleotide polymorphisms (SNP) that were independently associated with SCD. One SNP with a minor allele frequency of 22% was associated with a 31% greater risk of SCD for each copy of the variant allele, whereas a neighboring SNP (minor allele frequency 7%) was associated with a 43% lower risk for SCD. Two major cohort studies have also associated SNPs with the QT interval. Pfeufer et al. [*Nature Genetics* 2009] included 15,842 subjects, and Newton-Cheh et al. studied 13,685 subjects [*Nature Genetics* 2009].

Dr. Tomaselli discussed categories of serum and tissue biomarkers in SCD—including inflammatory factors (eg, CRP, myeloperoxidase); cytokines (eg, TNF, BMP); lipoproteins (eg, apoB, apoE); coagulation factors (eg, protein C); matrix proteins (eg, integrins); muscle proteins (eg, cTnT); neurohormones (eg, ANP); and lipids (eg, aldosterone). He also covered the limitations of protein biomarkers. Among others, are of sensitivity and specificity, as well as questions about what should be considered a risk marker (eg, persistently abnormal levels or changes over time).

Candidate protein biomarkers included hsCRP (the top quartile of subjects had an approximately 3-fold increased risk of SCD) [Albert CM et al. *Circulation* 2002]; TNF-α/TNFα2R, which was associated with development and progression of heart failure; abnormal Ca^{2+} handling; and altered Cx&K channel expression that increased with oxidant stress. Other markers included inflammatory (IL-6 and IL-10) and myocardial biomarkers (CKMB, cTnT, cTnI, myoglobin).

In summary, the prediction of SCD remains a challenging clinical problem. However, there are areas of promise. These include noninvasive tests that can identify anatomical disease, ischemia, and underlying structural and electrical remodeling that exaggerate the risk for ventricular tachycardia/ventricular fibrillation; genomic science that allows for comprehensive interrogation of genetic associations with complex traits and informs proteomic studies; and serum protein biomarkers that may be useful in evaluating risk of SCD and overall mortality. Because the majority of patients who have SCD is not known to have heart disease, identifying those who may benefit from these screening tests will remain a significant challenge.