Acute ischaemia as a trigger of sudden cardiac death

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Sudden cardiac death remains a major mode of exitus in the general population but its mechanisms are incompletely clarified. Several triggers of sudden death have been described. Acute myocardial ischaemia from sudden worsening of coronary artery disease may be one of the most important. This review discusses current concepts regarding ischaemia as the trigger of sudden cardiac death.

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The problem of SCD definition

Efforts to understand sudden cardiac death (SCD) and its underlying mechanism, treatment, and, ultimately, prevention have been hampered by the multiplicity of definitions used to characterise it. Unfortunately, the definition of the World Health Organisation does not contribute to clarifying the matter as it states, that SCD can be caused by many mechanisms and no all-purpose definition can be applied to every situation.\textsuperscript{1}

Recently, the ESC Task Force on SCD has suggested the use of the Myerburg and Castellanos\textsuperscript{2,3} definition as follows: natural death due to cardiac causes, heralded by abrupt loss of consciousness within 1 h of the onset of acute symptoms; pre-existing heart disease may have been known to be present, but the time and mode of death are unexpected. On the other hand, it is important to point out that the operational definition of SCD differs among clinicians, epidemiologists, pathologists and scientists attempting to clarify the pathophysiological mechanism.\textsuperscript{3}

The disparity of SCD classification

Disparities in defining SCD are reflected on the death certificate diagnosis of the cause of death. The Minnesota Communities mortality data demonstrated that only 27% of the cases labelled out-of-hospital SCD on the death certificates agreed with the physician-based validated diagnosis. It was concluded that death certificate diagnosis of out-of-hospital SCD included many erroneous cases and may not have been suitable for study of etiologic factors such as cardiac arrhythmias.\textsuperscript{4}

The imprecision of classifying SCD is illustrated in a study by Pratt et al.\textsuperscript{5} In a large ICD database, a wide range of SCD rates, greater than fourfold, could be created using the identical clinical database with different objective prespecified criteria. The authors concluded that the potential for misclassification and the competing cardiac and non-cardiac mechanism involved in many deaths support the wisdom of considering total mortality as the only interpretable endpoint of cardiovascular clinical trials.\textsuperscript{5}

Differentiating the mode (sudden unexpected vs. non-sudden expected) and cause of death is also reflected in various categories of clinical trials in which the term sudden death is often used to mean arrhythmic death, although the evidence may be lacking that the sudden death is due primarily to arrhythmia rather than recurrent coronary event.\textsuperscript{6}

Stratifying high-risk candidates for SCD

The population subset with high-risk arrhythmia markers constitute <10% of the total patient population for SCD attributable to coronary artery disease. Patients with acute coronary syndromes contribute another 20% to the
SCD incidence. More than 50% of the total SCD burden is accounted for by those whose first clinical presentation is SCD or those who have known coronary disease but low risk of SCD. A number of tests have been developed to stratify cardiac patients as to the risk of dying suddenly. These tests address different cardiac and non-cardiac factors that have been shown to affect mortality. However, some of those factors have shown to be predictors of both pump failure death and SCD. Moreover, common arrhythmia risk markers, particularly the autonomic and standard ECG markers, seem to lose some of their predictive power among patients who are receiving β-blocking therapy after myocardial infarction.

It is therefore noteworthy, that although insight into mechanisms and circumstances of SCD is increasing, our methods for identifying the high-risk candidate and predicting efficacy of measures to prevent SCD are still inadequate.

Autopsy data for SCD in myocardial infarction

The frequency of unstable plaques and coronary thrombosis in SCD secondary to atherosclerosis is extremely variable, and the reported percentages of active coronary lesions observed at autopsy in SCD victims range from less than 20% to more than 80%. However, even when there is evidence of healed myocardial infarction, sudden death has often been attributed to active coronary lesions (plaque rupture or coronary thrombosis).

These data suggest that myocardial ischaemia is a major cause of SCD in patients with CAD. It may be the sole cause in the absence of a previous myocardial infarction or it may trigger ventricular fibrillation in its presence.

Mechanisms for SCD in heart failure

The identification of the mechanisms and presentation of SCD in patients with heart failure is complicated by the fact that such patients comprise a mixed population. From large randomised heart failure trials it is demonstrated that SCD constitutes 25–50% of all deaths. The possible mechanism of SCD in heart failure has been scrutinised by Uretsky and Sheahan, who put forward the theory that in the patient with heart failure from ischaemic cardiomyopathy a small infarction may tip the balance into profound and terminal myocardial failure if the acute ischaemic event does not produce a fatal arrhythmia (Fig. 1).

Autopsy findings for SCD in heart failure

This viewpoint is supported by observations from the ATLAS trial with almost 1400 deaths, of which 171 were autopsied. A greater number of myocardial infarction than expected was found in the autopsied group with SCD. Twenty-eight percent in the autopsy group versus 4% in the non-autopsy group showed evidence of a recent myocardial infarction or fresh coronary thrombosis. The autopsies demonstrated that the prevalence of acute coronary findings was highest in patients with CAD and SCD (54%), intermediate in coronary artery disease patients who died of heart failure (32%), and infrequent in patients without coronary artery disease dying of any course (Fig. 2).

These findings lead to the conclusion that an acute ischaemic event appears to be a major trigger of SCD in the heart failure population.

Healed plaque ruptures and SCD

The autopsy findings of the ATLAS heart study are supported by pathological data in a series of male SCD patients. This study showed that repeated plaque ruptures that heal are frequent in men who die suddenly. The data further suggest that silent ruptures result in significant increase in plaque burden and negative remodeling. Thus, in many cases, fatal ruptures may represent the final stage of an ongoing process of arterial instability and healing.

The magnitude of SCD risk is strongly age-related, inasmuch as there is a marked increase in risk in the
The high prevalence of histological correlates of acute SCD most often occurs from hypertrophic cardiomyopathy, and in older athletes from CAD. In contrast, acquired and inherited disorders are considered to be the probable etiologies in younger age groups. In young athletes ≤ 35 years SCD most often occurs from hypertrophic cardiomyopathy, and in older athletes from CAD. On the other hand, histopathological studies of culprit lesions in hearts of 11 young adults (≤ 35 years), who had died within 1 h after onset of symptoms and presented with a coronary thrombotic occlusion showed that plaque erosion had occurred in nine and deep rupture in two cases. These observations suggest the presence of plaque instability for some time, since thrombus formation had occurred at least days to weeks prior to the acute event.

Inherited and genetic basis of SCD

Sudden cardiac death may occur because of inherited genetic abnormality affecting individual cardiac proteins or changes in ion channels. Conditions as long QT syndrome, Brugada syndrome as well as hypertrophic, dilated or arrhythmogenic right ventricular cardiomyopathies are well-known examples of monogenic diseases predisposing to SCD.

Thrombosis and infarction resulting from coronary artery disease probably represent the largest predecessor of lethal arrhythmias in the general cardiac disease population. How genetic variation plays a role in acute plaque rupture is beginning to be known, and new clues are beginning to emerge, such as the observation of heritable alterations in matrix metalloproteinases, which promote degradation of the fibrin cap. Also, molecular variants within pathways of platelet adhesion, arterial thrombosis, and the clotting cascade appear to be likely candidates for enhancing SCD susceptibility. The possibility of differences in SCD susceptibility from polymorphisms in cell receptors such as the sarcosomal \( \beta \)- and \( \alpha \)-receptors requires further study.

Strategies to prevent SCD

The high prevalence of histological correlates of acute ischaemia in autopsy studies of heart failure and myocardial infarction underscores the importance of developing strategies to manage coronary heart disease beyond the treatment of coronary artery stenosis and to prevent acute ischaemia in order to decrease the incidence of sudden cardiac death.

References