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Sudden Arrhythmic Death: What is the Gold Standard?

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Sudden cardiac death (SCD) is often attributed to ventricular arrhythmias and remains a significant public health challenge associated with poor clinical outcomes, substantial long-term disability, and rising healthcare costs.[1] The prediction and prevention of sudden arrhythmic deaths (SAD) is of substantial clinical importance to the extent that implantable cardioverter-defibrillators treat ventricular arrhythmias and are well-established to improve survival in appropriately selected populations.[2, 3] Population-based estimates of SCD generally, and SAD specifically, have varied widely[4] as a consequence of several factors including the lack of consensus definition, limited availability of contextual data (clinical context, symptoms, medical history, emergency medical service presence, documentation of cardiac rhythm), the frequent temporal gap between death and contact with medical system, lack of a national surveillance system, and marked variability in rates of autopsy.[4]

The lack of a gold-standard definition of SAD is a well-recognized limitation in the cardiovascular and epidemiological communities. To that end, several multi-disciplinary working groups, including the National Institutes of Health (NIH)[5] and the World Health Organization (WHO),[6] have sought to standardize the approach to SAD adjudication. These definitions generally integrate features of context (unexpected), timing (rapid witness collapse or occurring within 1 hour of onset of symptoms), inferred arrhythmic mechanism (abrupt collapse of circulation), and exclusion of non-cardiovascular mechanism of death.[4, 5]

In this issue of *Circulation: Arrhythmia and Electrophysiology*, Tseng and colleagues[7] seek to improve the accuracy of identifying SAD by leveraging an observational, autopsy-based study of out-of-hospital deaths in San Francisco County between 2011 and 2016.[8] The analytic cohort included 615 WHO-defined SCDs,[6] characterized as sudden unexpected

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death either within 1 hour of symptom onset (witnessed) or within 24 hours of having been observed alive and symptom free (unwitnessed). The authors then examined whether there were characteristics that might help predict which of these WHO-defined SCDs would also fulfill their definition of SAD, defined as the absence of an identifiable non-arrhythmic cause of death on autopsy (e.g., acute cerebrovascular accident, vascular rupture, pulmonary embolism, hemorrhage, lethal toxicology/occult, infection, or acute pulmonary edema). Notable exclusion criteria for study entry included individuals who were less than 18 or greater than 90 years of age, under the care of a physician in the 3 weeks prior to their death, and by virtue of the study design, successfully resuscitated from sudden death. The authors derived and tested prediction models (parsimonious and comprehensive) for autopsy-defined SAD, stratified by witnessed and unwitnessed deaths.

Overall these data support the common practice of using short duration of symptoms (<1 hour) prior to death to enrich for SAD, but also suggest that there is room for improvement. In witnessed cases, the specificity of this one-hour definition was enhanced further by considering the presenting cardiac rhythm. Exclusion of deaths with PEA as the first documented rhythm resulted in a negative predictive value (NPV) for SAD on autopsy of 83% and increased the positive predictive value (PPV) to 71% without much impact on the sensitivity (97%). Alternatively, if SCDs were required to also have VT/VF as the presenting rhythm, the PPV for SAD on autopsy increased to 90%, at the expense of reducing both the NPV and sensitivity to such an extent that 54% of SADs would be missed. In unwitnessed cases, models integrating demographic (age, race, sex, age), contextual (hours since last seen well), and clinical (pharmacotherapy, illicit drug use) factors demonstrated reasonable discrimination of cases and non-cases, with an area under the receiver operating characteristic (ROC) curves of 0.68 to 0.75. Of the factors included in the unwitnessed prediction model, a short duration of time between being last seen well (1 hour) was a specific (95%) but insensitive (18%) marker of SAD on autopsy. The odds of finding SAD on autopsy decreased as the unwitnessed interval lengthened from 1 hour to 24 hours.

The authors should be congratulated for undertaking such a large and comprehensive autopsy study and commended for their thoughtful analytic approach to improve contemporary definitions of SAD. However, important aspects of the study design and cohort composition need to be considered when attempting to generalize these findings. First, in addition to the multi-ethnic nature of this metropolitan-based autopsy cohort, there were other features, such as the relatively high prevalence of background illicit drug use (15%) and alcohol abuse (23%), that might limit generalizability to other community-based populations. Indeed, these relatively high rates of illicit drug and alcohol use may account for the relatively high proportion of non-arrhythmic sudden deaths in this cohort (e.g. 13% attributed to occult overdose)[8] compared to prior autopsy studies of sudden death.[9, 10] Second, by virtue of the autopsy nature of the study, the analytic cohort did *not* include individuals who were successfully resuscitated from out of hospital cardiac arrest, and since VT/VF is the primary predictor of survival during cardiac arrest resuscitation,[11] the study's exclusion of successfully resuscitated cases may partly explain the relatively low prevalence of VT/VF (43 of 144) in the witnessed, out-of-hospital arrest subset of the study population compared to prior studies.[12, 13]

Third, the reporting of model sensitivity, specificity and predictive values assumes the presence of a 'gold-standard'. While an autopsy clearly enhances our ability to determine the underlying structural and pathologic causes of death, there are limitations to its use as a 'gold-standard' for mechanism of death. For example, there is no finding on autopsy that distinguishes between sudden unexpected death in epilepsy and SAD, and often this diagnosis is based on clinical suspicion. In addition, determining whether pathologic evidence of pulmonary edema or evidence of aspiration is a cause or consequence of an out of hospital arrest can be challenging. Fourth, the frequency of autopsy-identified causes of death was high in this study and the applicability of these risk prediction models to traditional autopsy-negative subgroups (e.g. younger individuals)[14] is less certain. Finally, while death adjudication in the study did integrate findings from pre-mortem medical records, autopsy, toxicology and forensic investigation (including next-of-kin interviews),[8] additional clinical and contextual factors included in operational SCD or SAD definitions may also be of value.[12, 15] For example, integrating antecedent history suggestive of a non-cardiac cause of death or documenting the presence of witnessed, abrupt collapse with loss of pulse are likely to improve the specificity of SAD detection.[16] Given that the medical examiner declined several potential SADs on the basis of recent physician contact,[8] the authors were not able to ascertain subacute changes in antecedent clinical history (e.g. new or unstable angina, worsening heart failure or dyspnea), which could be a sensitive marker of incipient SAD risk.

Taken together, this study from Tseng and colleagues[7] frames the potential advantages and disadvantages of using presenting rhythm (for witnessed cases) and time last seen well (for unwitnessed cases) to improve the specificity of SAD identification. Although clearly useful, rhythm monitoring is known to be present in less than 50% of individuals with SAD, even among patients with known coronary heart disease.[12] Thus, in a risk paradigm reliant on presenting rhythm, prediction of SAD in this substantial proportion of the population would remain uncertain. Excluding deaths without VT/VF would result in the exclusion of over half of all true SADs, and since the finding of VT/VF often correlates with other clinical characteristics, this might introduce systemic biases such that SAD cases are not adequately reflective of the population from which they were derived. In terms of case ascertainment, there is clear need for a national surveillance system – which includes resuscitated cardiac arrest – with standardized documentation of circumstances surrounding death, clinical factors, rhythm, and ideally autopsy. Looking ahead, these data further highlight the limitations of risk prediction incorporating cross-sectional risk factors. Given the proposed dynamic pathophysiology of sudden arrhythmic death[1], leveraging other data sets with continuous rhythm monitoring, either through wearable, implantable or intracardiac device monitoring, may provide important insights and incremental improvements in our ability to identify and predict SAD events. Whether other markers of risk including electrocardiography or biomarkers may add to the identification of SAD events is also unknown. For now, we should be grateful to the authors for refining our understanding of SAD and moving forward our efforts to tackle this major public health challenge.

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