Can we better understand sudden cardiac death by including data from unwitnessed victims?

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This editorial refers to 'Witnessed and unwitnessed sudden cardiac death: a nationwide study of persons aged 1–35 years', by J. Svane *et al.*, pp. 898–906.

Sudden cardiac death (SCD) remains a leading cause of death. Efforts to reduce its burden should focus on improving the early recognition of individuals at risk and the development of subsequent targeted (personalized) preventive and therapeutic strategies. These efforts are hampered by gaps in our knowledge of its underlying causes and risk factors, and their complex interactions. This stems from the fact that, despite the high incidence of SCD, collecting reliable data of SCD victims that can be used for scientific studies is very difficult. This difficulty is due to the nature of SCD, where death ensues within minutes after the onset of circulatory arrest if left untreated. There is only a brief time window for ascertainment (e.g. through electrocardiogram documentation of ventricular fibrillation) that the sudden death resulted from cardiac causes, and may be classified as SCD, rather than death from non-cardiac causes (e.g. stroke, pulmonary embolism, and ruptured aneurysm). Additionally, obtaining such ascertainment is problematic, since most SCD cases occur out-of-hospital.

Compounding these difficulties, in most cases, SCD occurs unwitnessed and victims are unexpectedly found dead. In these cases, the most reliable way to determine the cause of death is the use of an autopsy, but this is conducted only in a minority of potential SCD victims (<30%) in most countries.[1] Excluding unwitnessed SCD victims without autopsy from studies into the epidemiology and causes of SCD is problematic because it leads to a severe underestimation of the incidence of SCD. Additionally, it limits the number of patients to study that could help us close our knowledge gap in understanding the causes of SCD, while large numbers are needed to face the complexity of SCD and its multiple interacting causes.[2]

The most widely used definition of SCD is the one of the World Health Organization (WHO): a witnessed death occurring within 1 h of an observed acute change in cardiovascular status or, in case of unwitnessed death, being found dead within 24 h after seen alive and functioning normally. The validity of this definition has been investigated. For instance, a prospective community-wide autopsy-based study found that only 56% of victims of WHO-defined SCD were what the authors termed sudden arrhythmic deaths (deaths in which no identifiable non-arrhythmic cause was found at autopsy and in which underlying cardiac disease was, or may have been, associated).[3] Conversely, as many as 40% of deaths were non-cardiac. Importantly, there were significant differences between witnessed SCD cases and unwitnessed SCD cases. In the former group, the proportions of sudden arrhythmic death and non-cardiac death were 65% and 27%, respectively, while they were 53% and 44%, respectively, among unwitnessed SCD victims. The authors suggested that both categories might represent different subsets of patients, and that more stringent definitions of SCD should be used.[4]

The trade-off of more stringent definitions is, however, that even fewer victims of SCD could be included as study subjects. This is likely to affect unwitnessed SCD victims mostly because the proposed definition (being found dead within 1 h since last observed in usual health) is likely to limit their numbers greatly. In any case, it must be analysed whether unwitnessed SCD victims are sufficiently comparable to witnessed SCD victims to include them in (epidemiological) studies into SCD at all.

Svane *et al.*[5] present a study that was specifically designed to shed more light on this question. They compared the clinical characteristics between witnessed and unwitnessed SCD cases aged 1–35 years in Denmark through an in-depth analysis of SCD victims with the use of a comprehensive review of death certificates, autopsy reports and nationwide registries. Their key findings were: (i) 51% of SCD cases

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were unwitnessed, while 42% were witnessed (7% had unknown witness status); (ii) autopsy rates were 73% overall and similar in both groups; (iii) the majority of studied clinical characteristics were not different between both groups (only male sex, death during sleep, and a history of psychiatric disease were more prevalent among unwitnessed vs. witnessed SCD cases); and (iv) most autopsy findings were similar between both groups, but the proportion of sudden unexplained death cases (cases where an autopsy revealed no cause of death) was higher in the unwitnessed group. The authors have concluded that the great similarity in clinical and autopsy findings between both groups supports the inclusion of unwitnessed cases in epidemiological SCD studies.

Such an inclusion may be of potentially great relevance. For instance, it may provide data in support of re-appraising widely held assumptions regarding sex differences in SCD incidence. At present, it is widely assumed that SCD overwhelmingly strikes men rather than women, and that this sex difference is present across all ages.[6] Yet, a study of the SCD incidence in the general population of the Netherlands has found that women more often have unwitnessed SCD than men,[7] possibly due to having a higher life expectancy and therefore living alone more often. Exclusion of individuals who suffered unwitnessed SCD will underestimate the incidence of SCD more among women, in particular, elderly women. Inclusion of unwitnessed SCD victims will help rectify this underestimation.

Still, there are important caveats to following the recommendations of Svane et al. Firstly, whether the findings of their study may be generalized to different subgroups across society should be determined. For instance, the population studied was young (≤35 years) and may differ from older populations in several aspects. Younger SCD victims may be more frequently witnessed than older SCD victims,[7] and may have different causes of SCD, in particular, a higher likelihood of inherited disease causes. In the case of causative genetic variants in ion channels (primary electrical disease), structural abnormalities will usually be absent, resulting in a higher proportion of 'unexplained' SCD cases. Secondly, it should be ascertained that the findings of this study are applicable across different contexts and countries. When using death certificates to identify SCD cases (often a necessity in unwitnessed SCD cases in view of low autopsy rates[1]), it must be born in mind that the use of International Classification of Disease codes to define SCD may differ between studies.[8,9]

Svane et al. recognize these difficulties and the added uncertainties arising from their finding that the clinical characteristics in witnessed and unwitnessed cases, while mostly similar, are different in some respect. Consequently, they suggest that, when unwitnessed SCD victims are to be included in epidemiological SCD studies, the use of multiple categories with different level of certainty may be considered, e.g., 'definite SCD' and 'probable SCD', depending on witness status. A similar stratification is being used in the research area of

sudden unexpected death in epilepsy (SUDEP), where classification into six categories ranging from 'definite SUDEP' to 'not SUDEP' is made based on several aspects such as autopsy findings and witness status.[10]

Overall, this study provides an important boost to our efforts to understand the riddle of SCD better. By providing evidence that unwitnessed SCD victims are similar to witnessed SCD victims in most aspects, Svane et al. have given us much-needed reassurance that data from this large patient group may be used for SCD studies. Being able to use the large datasets from these SCD cases will aid in the development of personalized strategies for both preventions (e.g. personalized risk prediction scores) and treatment (e.g. systems for automatic alerting of medical care providers in the case of unwitnessed SCD). Ultimately, the new information to arise from such work may contribute to reducing the burden of SCD.

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References

1. Lunetta P, Lounamaa A, Sihvonen S. Surveillance of injury-related deaths: medicolegal autopsy rates and trends in Finland. Injury Prev 2007;**13**:282–4.
2. Empana JP, Blom MT, Böttiger BW, Dagres N, Dekker JM, Gislason G et al. Tan HL on behalf of the ESCAPE-NET Investigators. Determinants of occurrence and survival after sudden cardiac arrest - a European perspective: the ESCAPE-NET Project. Resuscitation 2018;**124**:7–13.
3. Tseng ZH, Olgin JE, Vittinghoff E, Ursell PC, Kim AS, Sporer K et al. Prospective countywide surveillance and autopsy characterization of sudden cardiac death: POST SCD study. Circulation 2018;**137**:2689–700.
4. Tseng ZH, Salazar JW, Olgin JE, Ursell PC, Kim AS, Bedigian A, Probert J et al. Refining the World Health Organization definition: predicting autopsy-defined sudden arrhythmic deaths among presumed sudden cardiac deaths in the POST SCD Study. Circulation 2019;**12**:e007171.
5. Svane J, Lynge TH, Hansen CJ, Risgaard B, Winkel BG, Tfelt-Hansen J. Witnessed and unwitnessed sudden cardiac death: a nationwide study of persons aged 1–35 years. Europace 2021; doi: 10.1093/europace/euab017.
6. Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. Circulation 2012;**125**:620–37.
7. Straus SMJM, Bleumink GS, Dieleman JP, Lei van der J, Stricker BHC, Sturkenboom MCJM. The incidence of sudden cardiac death in the general population. J Clin Epidemiol 2004;**57**:98–102.
8. Chugh SS, Jui J, Gunson K, Stecker EC, John BT, Thompson B et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large US community. J Am Coll Cardiol 2004;**44**:1268–75.
9. El-Assaad I, Al-Kindi SG, Aziz PF. Trends of out-of-hospital sudden cardiac death among children and young adults. Pediatrics 2017;**140**:e20171438.
10. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 2012;**53**:227–33.