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Sex and the Biology of Sudden Cardiac Death: Vive La Différence

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Despite advancements in prevention and resuscitation, sudden cardiac death (SCD) continues to take a major toll on society. Resulting in approximately 350,000 deaths in the US annually, this condition accounts for more years of potential life lost than any individual cancer affecting women or men.¹ Published observations regarding the manifestation of SCD suggest that the pathophysiology of SCD is likely to be sex-specific. For example, women are significantly less likely to have the classical precursors for SCD,² with half the likelihood of severe LV systolic dysfunction [OR 0.51 (0.31 – 0.84) vs. men] and a one-third likelihood of an established diagnosis of coronary artery disease (CAD) [OR 0.34 (0.20 – 0.60) vs. men].³ If we are going to make a real impact on the major public health burden of this condition, identification of any sex-specific pathways to SCD is of paramount importance.

In this issue of *Circulation*, Haukilahti, Junttila and co-workers examined sex differences in autopsy findings as well as archived ECGs available for a subset of patients, from the established Fingesture Study.⁴ Among >5800 subjects who presented with SCD during 1998 and 2017, approximately 80% were men and 20% were women. There were several sex differences identified on pathologic examination. Women were less likely to have coronary artery disease (72% vs. 76%, $P=0.005$), and more likely to have primary myocardial fibrosis (5% vs. 3%, $P=0.001$), valve disease (2% vs. 1%, $P=0.049$), myocarditis (2% vs. 1%, $P=0.020$) and structurally normal heart (0.6% vs. 0.2%, $P=0.015$). Body mass index and abdominal fat were slightly higher in women. Following a comprehensive analysis of the available antemortem ECGs, a few sex differences were observed. Women were more likely to have left ventricular hypertrophy by ECG criteria (18% vs. 11%, $P=0.001$), lower mean QRS complex duration (94 ms vs. 102 ms) and lower prevalence of Q-waves (8% vs. 16%, $P<0.001$). How does this large, carefully-conducted autopsy series advance our quest to identify sex-specific mechanisms of SCD?

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Disclosures
None.

While several statistically significant sex differences were observed on pathologic exam, the absolute magnitude of these differences was small. In fact, what is most striking about their findings is the relatively similar prevalence of abnormal cardiac structural findings in women and men. The >70% prevalence of coronary artery disease in women who suffered SCD is significantly higher than previously published autopsy series⁵ as well as antemortem findings recently reported from the Women's Ischemia Syndrome Evaluation (WISE) study.⁶ The latter study reported lower rates of SCD among women with obstructive CAD (27%) compared to those with none or minimal CAD (57%; information missing in 17%). Also, while a significantly higher prevalence of obstructive CAD among women was observed in Fingesture, it is possible that the diagnosis may not have been established prior to SCD in some proportion of these cases. Either way, since Finnish law mandates an autopsy in all sudden and unexpected deaths, this finding has potentially important public health implications at least at a regional level. As expected, Fingesture women were older than men, and other small sex differences in pathology could be age-related. The overall low proportion of women with SCD in Fingesture (20%) also appears to be unique to the Finnish population. In earlier analyses, men appeared to be three times more likely to experience SCA than women⁷. Framingham study data also showed that women with coronary artery disease (CAD) or risk factors had a lower incidence of SCA as compared with their male counterparts⁸. However, more contemporary data suggest that the sex gap in SCD burden may actually be narrowing, with a gradual increase from 20% to 35% in the proportion of women dying suddenly⁹.

Antemortem ECGs were available in a relatively small subset of Fingesture subjects with some potential for selection bias, and specific time points at which these were performed relative to the SCD were not made available. Nonetheless, their findings of higher rates of ECG left ventricular hypertrophy in women are of interest. In fact, ECG or "electrical" left ventricular hypertrophy may convey distinct information regarding risk prediction of SCD from echocardiographic or "anatomic" left ventricular hypertrophy.¹⁰ Sex differences in this electrical risk of SCD warrant further investigation.

While autopsy studies contribute significantly toward an improved understanding of lethal arrhythmia mechanisms, postmortem findings are "static" observations removed from the living state. Furthermore, all observations made in the postmortem setting represent associations that may or may not be causal for SCD. Learning from the evolving literature, there are other manifestations of SCD in women that appear to be unique, and an investigative focus in these areas may eventually lead to the discovery of sex-specific SCD mechanisms. It has been observed that 50% of either sex have warning symptoms well in advance of their SCD event, but as reported in a recent community-based study, symptoms can be sex-specific with a higher prevalence of dyspnea and lower rates of chest pain in women compared with men.¹¹ Most often patients and their families ignored these early warning signs, with only a minority (~20%) seeking emergent medical care by calling 911 in response to symptoms. Those who called 911 immediately following symptoms had >5-fold higher survival from SCA. Warning signs could represent an opportunity for near-term prediction of SCD, and sex differences may influence approaches that would triage patients to receive urgent pre-emptive interventions based on the level of SCD risk. With or without epicardial coronary artery disease, women may have a larger ischemic contribution from

microvascular coronary artery disease compared with men, a potential mechanism accounting for differences in patterns of warning symptoms.⁶

Mitral valve prolapse is significantly more common in women and there are data accumulating to suggest that it may often be an unrecognized cause of SCD.¹² Many high-risk patients have myocardial fibrosis in the region of the papillary muscles and infero-basal LV wall, potentially attributable to myocardial stretch by the prolapsing leaflet.¹³ This finding is now recognized as a structural hallmark potentially involved in the pathogenesis of re-entrant or focal ventricular arrhythmias. Myocardial imaging in patients with mitral valve prolapse needs further evaluation as a risk marker for lethal arrhythmias, with potential to lower SCD burden especially in women.

There is another sex difference in the manifestation of sudden cardiac arrest (SCA) that continues to defy mechanistic explanation. In the last 3 decades, the proportion of SCA presenting as pulseless electrical activity (PEA) has increased, and the relative rates of ventricular fibrillation (VF) have fallen. For unknown reasons, women are significantly more likely to present with PEA compared with men. Given that VF can be treated with therapeutic defibrillation, but there is no treatment for PEA, this is likely to have a major implications for SCD prevention, especially in women. In an earlier hospital-based study also from Finland, autonomic responses to abrupt coronary occlusion were evaluated among patients referred for single-vessel coronary angioplasty.¹⁴ Vagal activation manifesting as significant bradycardia or increased heart rate variability was significantly more common in women compared with men. More recently, in a large population-based study from Oregon, USA, individuals who presented with PEA were significantly more likely to have a diagnosis of vasovagal syncope during their lifetime.¹⁵ These findings suggest that especially in women, the pathophysiology of PEA may involve abnormally altered vagal tone in response to ischemic triggers. The investigation of sex-specific PEA mechanisms should be a priority.

Haukilahti, Junttila and co-workers are to be congratulated for publishing yet another important analysis from the established Fingesture study, with special strengths related to high autopsy rates of SCD and a comprehensive postmortem histopathological examination. While they have identified some sex differences that will certainly further our understanding of SCD, their findings are also notable for the relative similarities in rates of cardiac structural abnormalities between the sexes. Prevention of coronary artery disease could have a comparable impact on reducing SCD burden in women and men. There are several other sex differences in manifestation of SCD that should be explored including warning symptoms preceding cardiac arrest, mitral valve prolapse as a substrate for lethal arrhythmias, electrocardiographic risk profile, and higher rates of PEA in women. If we are going to provide equal opportunity to both sexes for prediction and prevention, the quest for sex-specific pathways leading to SCD must continue.

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