Sudden Cardiac Death in Women

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Women are at lower risk for development of sudden cardiac death (SCD) as compared with men. Women with SCD tend to have less structural heart disease and preserved left ventricular systolic function. Coronary artery disease (CAD) is the most common predictor of SCD in women, as it is in men. However, women with SCD are less likely to have underlying CAD than men, suggesting the need to identify risk factors other than CAD or systolic dysfunction for its prediction in women. SCD risk factors in women include heart failure with preserved left ventricular systolic function, abnormal sympathetic uptake as assessed by *meta*-iodobenzylguanidine uptake, depression, and/or use of antidepressants. This article reviews SCD in women and discusses areas for future research.

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KEY WORDS

Women • *m*IBG • Depression • Diastolic heart failure • Antidepressant use • Sudden cardiac death • Internal cardioverter defibrillator

Sudden cardiac death (SCD) accounts for > 50% of all cardiac deaths annually in the United States.[1] Although women are at lower risk compared with their male counterparts, they still account for 30% to 40% of the total, representing 120,000 to 400,000 SCDs annually. The etiology for SCD in women is poorly understood. In women with coronary artery disease (CAD), the risk for SCD is half as high as it is in men.[2-4] Unfortunately, a vast majority of women who suffer SCD do not fit the high-risk profile, making both prevention and prediction difficult.[5] A total of 63% of SCD in women occurs without a prior overt history of CAD.[2] Pathologic studies in women aged 35 to 44 years show that 50% of women had SCD of undetermined etiology compared with 24% of men.[6] These data

underscore the difficulty in prediction of SCD, differences in risk factors, and possibly an alternative pathophysiologic mechanism for SCD in women compared with men. CAD remains the most common predictor for cardiac arrest in women, compared with decreased left ventricular (LV) systolic function in men.[7] However, the majority of women with SCD are less likely to have underlying CAD compared with men (45% vs 80%).[7] Women also tend to have heart failure with preserved LV ejection fraction (LVEF), and it has been suggested that women with SCD may have significant diastolic dysfunction as the cause of their death.[8]

Mechanisms for SCD

The mechanisms for SCD in women are likely different than they are in men. Clinical heart failure is a major risk factor in women compared with CAD or structural heart disease. The theory that SCD pathogenesis in women differs from CAD or structural heart disease mechanisms is reinforced by studies that highlight the role of brain natriuretic peptide (BNP) as a risk factor, a decreased ability to induce ventricular tachycardia in women, and population-based estimates that 50% of SCDs occur in patients with normal LVEF.[9]

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The primary cause of SCD in women is different than that in men. Men are more likely to die from ventricular arrhythmias, whereas pulseless electrical activity and asystole are more common contributors of SCD in women.[8] In the Multicenter UnSustained Tachycardia (MUST) trial, which included patients with known CAD, LVEF 0.40, and asymptomatic nonsustained ventricular tachycardia documented 96 hours after myocardial infarction (MI), coronary angioplasty, or coronary artery bypass surgery, women were significantly less likely to have inducible ventricular tachycardia than men at electrophysiology study.[10] Women with decompensated congestive heart failure tend to have lower rates of ventricular premature beats, ventricular tachycardia, and ventricular bigeminy compared with their male cohorts.[11] On a similar note, women with CAD who have implantable cardioverter defibrillators (ICDs) are less likely to experience ventricular arrhythmias (34%) than men (52%).[12] Differences in ion channel activity and cardiac action potentials may be one explanation for the differences in arrhythmogenicity in women versus men. Women at baseline have a longer QRS duration compared with men. In the Oregon Sudden Unexpected Death Study, the mean QRS duration in both women and control subjects was prolonged compared with men (446 ± 47 ms in men compared with 457 ± 40 ms in women and 429 ms ± 38 in male control subjects compared with 442 ± 32 ms in female control subjects).[13]

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Female sex has also been shown to be a predictor of QT prolongation, reflecting differences in depolarization and repolarization of the ventricle. The greatest risk for SCD with a prolonged QT occurs in patients who use QT-prolonging drugs or have diabetes. Women are at increased risk for drug-induced QT prolongation arrhythmias and have longer QT intervals compared with men even prior to taking QT-prolonging medications.[14] Estrogen prolongs the QT interval whereas progesterone decreases it.[14] The risk of QT prolongation is development of torsades de points: two-thirds of the cases of drug-induced torsades de points occur in women.[14] QT prolongation is associated with an odds ratio of 5.53 for SCD.[13] The pathophysiologic mechanism as to why ventricular arrhythmias are triggered less frequently in women remains largely unknown; however, differences in the electrophysiologic properties of the myocardium or in autonomic responses to triggers may contribute to these observations.[12]

SCD in Women With Diastolic Dysfunction

Diastolic heart failure is a less recognized risk factor for SCD in women, but accounts for a majority of SCD in women.[13,15,16] In the Oregon Sudden Unexpected Death Study, 47% of SCD in women occurred in the setting of normal LVEF.[15] Although severe LV dysfunction continues to be a significant predictor of SCD in population-based studies, a higher percentage of women with normal LV systolic function continues to

be at risk for SCD, bringing the role of diastolic heart failure into question.

Heart failure admissions in those with normal LV function are most commonly seen in women.[17] Patients recently hospitalized with congestive heart failure with preserved LVEF have a 19% mortality rate in 1 year.[18] Some studies suggest that 50% of deaths in patients with chronic heart failure are sudden.[19] Patients with heart failure and LVEF > 50% have been found to have an overall mortality rate of 28%, with 7.3% of these deaths sudden, in a median 3.9-year follow-up period.[20] Restrictive filling grade on echocardiogram after MI was associated with a four times higher mortality when compared with patients without restrictive diastolic filling.[21] In this study, 20% of the patients had restrictive filling patterns after acute MI.[21] These observations from multiple studies clearly suggest a causative role of diastolic dysfunction in SCD in women. Incomplete myocardial relaxation can alter the myocardial repolarization and increase the risk of vulnerability for ventricular arrhythmias. Further bench and clinical studies are needed in understanding the role of diastolic function in SCD.

Risk Factors for SCD in Women

Traditional risk factors for CAD, including low high-density lipoprotein cholesterol, high low-density lipoprotein cholesterol, high triglycerides, and high-sensitivity C-reactive protein have not been shown to be associated with the risk of SCD in women.[5] The risk factors for SCD in women include elevated BNP levels, decreased LV systolic function, clinical heart failure (both with and without systolic dysfunction), decreased *meta*-iodobenzylguanidine (*m*IBG) cardiac uptake levels and washout rates.[5,22,23] Other findings, such as heart rate variability, micro T-wave alternans, and QT prolongation, have not been conclusively demonstrated to predict increased risk of SCD in women.[24] Heart rate variability has traditionally been thought of as a risk predictor for SCD because variability reflects cardiac sympathetic tone. However, recent studies have challenged this, showing no relationship between heart rate variability and cardiac norepinephrine spillover rate,[25] as well as no predictive value of heart rate variability for SCD in patients with heart failure.[22] Although CAD is a risk factor for SCD, in a recent study looking at an ambulatory population who met criteria for primary prevention ICD (LVEF < 35%) the rates of SCD were similar irrespective of the underlying cause of their LV dysfunction (ischemic or nonischemic).[24]

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BNP

BNP is synthesized and secreted from the ventricles and is released in response to pressure and volume overload. Elevated BNP levels have been associated with SCD in both men and women with reduced LV systolic function (LVEF < 35%) and after MI.[26] The reason for this relationship with SCD has long been thought to be due to increased LV strain and heart failure. However, in a subgroup analysis of the Nurses Health Study, elevated BNP levels (> 389 pg/dL) were associated with a fivefold increased risk of SCD in women even after correction for CAD and its risk factors.[5,23] Elevated BNP reflects the increased left atrial and ventricular pressure caused by diastolic LV dysfunction and microvascular angina. Microvascular changes lead to microinfarctions and fibrosis, which cause reentrant circuits to form and thus lead to SCD. Another theory into the pathogenesis of ventricular arrhythmias with elevated BNP levels is potentially a propensity for myocardial stretch-related arrhythmogenesis via ion channel depolarization.[23]

*m*IBG Uptake and Washout

Cardiac sympathetic imaging with the noninvasive marker I-123 *m*IBG in women in preliminary studies has been shown to be a very powerful predictor of survival and may be a new method for assessing SCD risk in women.[19] This noninvasive study assesses the reuptake of norepinephrine; however, unlike norepinephrine, *m*IBG is not metabolized. This makes it an excellent radioisotope for imaging sympathetic activity. *m*IBG imaging includes planar and single-photon emission computed tomography (SPECT) images obtained after 15 to 30 minutes with delayed images taken 3 to 4 hours after injection. Planar

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images provide information about global sympathetic innervation and SPECT images show regional sympathetic innervation of the heart.[27] The *m*IBG uptake is quantified using a heart to mediastinum ratio (HMR) after early and delayed images. A washout rate is calculated, which correlates well to norepinephrine retention in the synaptic cleft.[19] Decreased *m*IBG uptake is seen in patients with ischemia. A reduced late HMR has been a very powerful predictor of mortality in patients with both ischemic and nonischemic cardiomyopathy.[19,28-31] Merlet and colleagues[29] looked at 90 patients with nonischemic and ischemic cardiomyopathy and followed them for a maximum of 27 months. A delayed HMR was the best predictor of survival, even compared with a radionuclide derived LVEF ($P = .03$). Other studies have also shown that cardiac *m*IBG can help predict mortality in patients with dilated cardiomyopathy.[28] Recent studies have shown that abnormal *m*IBG uptake in patients with both nonischemic and ischemic cardiomyopathy may help determine who will benefit from implantation of ICDs based on the ability to predict sudden cardiac death.[30-32] Altered sympathetic activity in patients with chronic heart failure results in increased mortality related to heart failure and increased vulnerability to ventricular arrhythmias.[31] *m*IBG has been studied and found to be predictive of SCD in combination with both ischemia (elevated summed stress score) and heart failure (elevated BNP).[32,33] There are several studies looking at *m*IBG uptake and washout rates in response to medical therapy in patients with heart failure. A recent study showed that cardiac sympathetic nervous dysfunction and systemic inflammation (C-reactive protein) improved in patients with heart failure who responded to chronic resynchronization therapy.[34] Studies need to be performed to evaluate differences in *m*IBG uptake and washout in men versus women. The differences in cardiac adrenergic nerve function may explain some of the differences between SCD in men versus women.

Depression

Depression as it relates to risk of SCD in women is not clearly understood. Observational studies, such as the Nurses Health Study, suggested that antidepressant use is associated with an elevated risk of SCD. These are observational data only; no causal relationship can be implied.[35] Antidepressant use was not associated with recurrent MI. Depressive symptoms alone also did not predict increased SCD.[35] Many studies have suggested the etiology of increased SCD is related to increased arrhythmias with antidepressant medications.[36] In the Time to Ventricular Arrhythmias (TOVA) study, moderate to severe depression was associated with appropriate ICD shocks.[37] Depression is a risk factor for CAD, arrhythmia, and death in both men and women. Again, the reason for this is not well understood; however, antidepressant drug use has been implicated to increase the risk for SCD via the proarrhythmic potential of these agents.

In the Nurses Health Study (an observational study), antidepressant use was associated with SCD independent of the level of depression as rated on the Mental Health Index-5 Score.[38] Recent subgroup analysis of women in the Women's Ischemia Syndrome Evaluation (WISE) study separated depression into four groups: 1) no medication, 2) anxiolytics only, 3) antidepressants only, and 4) combined antidepressant and anxiolytics.[39] Women in the combined medication group (both anxiolytics and antidepressants) had higher risk for cardiovascular events with a hazard ratio (HR) of 3.98 and an HR for all-cause mortality of 4.70 when compared with women without antidepressant or antianxiety medication use.[40] In the Nurses Health Study, antidepressant use was related to SCD risk but the risk for SCD was not elevated in women with anxiety and depression without antidepressant medication use.[35,41] Antidepressants can prolong QT interval and thereby increase the probability of ventricular arrhythmias and SCD in large doses.[42] Notably, antipsychotic drug use also increases the QT interval in a dose-related manner and increases the risk of SCD.[43] Women are especially prone to QT prolongation given a baseline longer QT interval.

More research needs to be conducted to further delineate if depression is a risk factor for SCD or if antidepressant drug use is the trigger for SCD in these women.

Prevention of SCD: Utility of ICD Therapy in Women

Our current guidelines for ICD implantation rely on New York Heart Association functional class and LVEF. The current tools for SCD screening in women are inadequate. Newer imaging modalities could help predict who may benefit from ICD therapies. Over the past few years we have seen a decrease in mortality in patients with heart failure due to improved medical therapy; however, overall, mortality rates remain high: 80% of men and 70% of women younger than age 65 years will die within 8 years of diagnosis of heart failure.[44] Unfortunately, with the

low enrollment of women in ICD studies, we have been unable to prove a mortality benefit with ICDs in women.[44] This may be due to underpowered studies; however, we may also be screening women inaccurately. Indications for placement of ICDs in women will need to be modified in the future to demonstrate their benefit. Conversely, cardiac resynchronization therapy (CRT) seems to benefit women more than men.[45] This may be due to the remodeling process involved with this therapy and reduced mechanical stress.

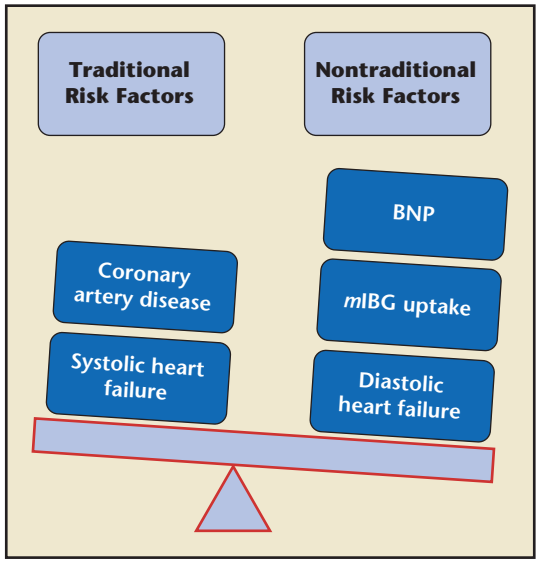

Figure 1. Reassessing the risk factors for sudden cardiac death in women. BNP, brain natriuretic peptide; *m*IBG, meta-iodobenzylguanidine.

Future Directions

Determining risk for SCD in women will need to involve nontraditional methods of assessment. We no longer will be able to only look at a depressed LVEF to determine ICD candidacy. We will need to focus more on heart failure classification, and may need to consider implantation of CRT devices earlier for improvement in overall function and improved cardiac remodeling. Noninvasive imaging remains a promising method for prediction of SCD in women. Traditionally, assessment of ischemic scar burden have been predictive of ventricular arrhythmias and SCD.[46] Methods such as late gadolinium enhancement have also been proven helpful in predicting SCD.[46] Future studies will need to consider parasympathetic and sympathetic innervations of the myocardium. Cardiac *m*IBG uptake will likely be used more frequently to assess for SCD risk. We need to focus on reducing the death rate in women with heart failure and preserved LVEF. Differences in arrhythmogenic substrate will also need to be evaluated. Recent studies have focused on looking at genetic markers, specifically the cardiac ion channel, to help predict and prevent SCD events in women. However, these studies are difficult to evaluate due to the low prevalence of these genetic mutations and the incomplete knowledge that we have available on genes associated with increased SCD risk.[47]

We will likely need to rely on a combination of available tests to determine risk. A potential area for research would be to calculate SCD risk score utilizing a combination of LVEF, BNP, previous ventricular arrhythmia, heart failure class, *m*IBG uptake, and genetic predisposition studies. We may need to re-evaluate the need and cost-effectiveness for ICDs in women with low LVEFs but normal *m*IBG uptake, BNP level, and functional class.

Conclusions

It is well known that arrhythmogenic risk in women is less. Risk factors such as elevated BNP and low *m*IBG uptake levels may be as good as LVEF in estimating the risk for SCD in women, especially in women with heart failure and preserved LVEF (ie, diastolic heart failure). It is time that we reassess the risk factors and algorithms used to determine benefit of ICD use in women (Figure 1). ICD use has not been shown to provide a mortality benefit in women; this may be due to inadequate assessment of risk and/or inadequate enrollment in trials. Future directions of study should include an increased assessment of noninvasive techniques for estimating cardiac risk, and potentially examining genetic variants for prediction of SCD in women. ■

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MAIN POINTS

- Sudden cardiac death (SCD) accounts for > 50% of all cardiac deaths annually in the United States; women comprise 30% to 40% of these deaths.
- A total of 63% of all SCDs in women occur in those without a history of coronary heart disease.
- Risk factors for SCD in women include elevated brain natriuretic peptide levels, a decreased left ventricular ejection fraction (LVEF), decreased *meta*-iodobenzylguanidine uptake levels and washout rates, and clinical heart failure.
- Future research should include a revision of current guidelines for implantable cardioverter defibrillator (ICD) insertion in women, as many of these risk factors are not included in current guidelines. Current guidelines for ICD implantation, which base ICD implantation primarily on LVEF, are inadequate for risk assessment in women.