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Editorial

# Left Atrial Function and Sudden Cardiac Death

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***See article by Lydell et al., pages 1149–1157 of this issue.***

## The Prevention of Sudden Cardiac Death

Sudden cardiac death (SCD), presumed to be due to a cardiac arrhythmia or haemodynamic catastrophe, is defined as occurring within an hour of the onset of symptoms, or as an unwitnessed death occurring within 24 hours of being asymptomatic.[1] The incidence of SCD in the general population internationally ranges from 50 to 100 per 100,000 persons per year.[2] Approaches to the prevention of SCD may be divided into 2 categories: the prevention of the conditions leading to SCD, and the identification of those at increased risk of SCD followed by their treatment with interventions to reduce that risk. The placement of an implantable cardioverter-defibrillator (ICD) has been established to be effective in reducing the risk of SCD due to ventricular tachyarrhythmia (SCD-VA) in selected patients and is recommended in various society guidelines.[1,3] The risk of SCD-VA and the competing risks of nonsudden death and sudden death from noncardiac causes must be considered in each patient before ICD implantation to ensure that an ICD has a reasonable probability of increasing life expectancy.

Left ventricular ejection fraction (LVEF) is a useful marker of SCD-VA risk, but in isolation it has limited precision in predicting those most likely to benefit from an ICD.[4,5] Only a minority of those with SCD have impaired LVEF, and only a fraction of those with impaired LVEF experience SCD.[6] The development of a more refined assessment of SCD risk with the use of additional risk markers is an area of ongoing research. In the current issue of the *Canadian Journal of Cardiology*, Lydell et al. present one such study, in which they investigated whether indices of left atrial function may be of value in determining the risk of SCD-VA.[7]

## Study Design and Main Findings

Lydell et al. performed a retrospective study of 203 subjects with either ischemic cardiomyopathy (ICM) or nonischemic cardiomyopathy (NICM). All subjects underwent both the implantation of a primary-prevention ICD and preimplantation cardiac magnetic resonance imaging (CMRI) from which left atrial volumes and function were assessed. The study population was followed for a median of 4.5 years, with 80% followed for more than 2.7 years. The primary end point was either SCD or an appropriate ICD shock. Thirty-five subjects (17%) reached the primary end point, with the majority of these events (33/35) being ICD shocks. The authors performed univariate analysis and identified a statistically significant association between the primary end point and larger indexed left atrial (LA) volumes, lower LA emptying fractions (LAEFs), and lower indexed LA conduit volumes (LACV). Of these parameters, they selected LAEF for further analysis with the use of a survival probability approach. They identified an LAEF threshold of 30% below which the probability of the primary end point was significantly increased. They then dichotomised the study population with this threshold and performed a multivariate analysis, which found that subjects with an LAEF of $\leq$ 30% had a 4.7-fold higher risk ($P = 0.002$) of the primary end point.

They also performed a subgroup analysis by cardiomyopathy type. The rate of the primary end point was similar in both ischemic and nonischemic groups. In a multivariate analysis, LAEF $\leq$ 30% was significantly associated with the primary end point in the ICM group (hazard ratio [HR] 6.3; $P = 0.02$) but not in the NICM group. When analysed as a continuous variable, LAEF did have a significant association with the primary end point in the NICM group (HR 0.81 per 5% LAEF increment; $P = 0.04$).

## Strengths and Weaknesses

Lydell et al. demonstrated a clear association between LA function and appropriate ICD therapy in their cohort. An important strength of their methodology is that the measurements of left atrial volume and function that they used may be readily performed from standard CMRI cine sequences.

There are, however, important caveats to consider in their study. A more detailed description of device programming and the presence of cardiac resynchronization and mitral valve disease in their study population would help with the interpretation of their findings.[8] Consideration of

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See page 1092 for disclosure information.

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**Table 1.** Summary of studies of between left atrial (LA) imaging parameters and sudden cardiac death

| Reference | Study design | Study population | Primary end point | Variables with statistically significant association with primary end point in multivariable modelling |
|---|---|---|---|---|
| Rijnierse et al.[10] | Retrospective, patients referred for a primary-prevention ICD, ICM and NICM, assessed by CMRI | n = 229; 69% ICM | First appropriate device therapy | LAEF, total LV scar volume* |
| Negishi et al.[11] | Retrospective, patients with NICM referred for a primary prevention ICD, assessed by TTE | n = 124 | First appropriate device therapy | Mitral A-wave velocity |
| Pellicori et al.[12] | Retrospective, patients with a new diagnosis of heart failure, assessed by CMRI | n = 664 | Hospitalization for heart failure or all-cause mortality | LAEF |
| Gulati et al.[13] | Retrospective, patients with NICM, assessed by CMRI | n = 483 | All-cause mortality or cardiac transplantation | LA volume indexed to BSA |

BSA, body surface area; CMRI, cardiac magnetic resonance imaging; ICD, implantable cardioverter-defibrillator; ICM, ischemic cardiomyopathy; LAEF, left atrial ejection fraction; LV, left ventricular; NICM, nonischemic cardiomyopathy; TTE, transthoracic echocardiography.

*Assessed with the use of late gadolinium enhancement.

electrocardiographic characteristics known to be associated with SCD in their analysis would have been interesting to understand if LA function provides further information above these markers of SCD risk.[9]

## Previous Research in This Area

This study adds to previous work on LA parameters as predictors of SCD and all-cause mortality. Key elements of selected studies in this area are described in Table 1.

The studies examining SCD and arrhythmic end points reported that LA volume was not a significant predictor. Reports that atrial fibrillation, the end-stage manifestation of poor LA function, is a predictor for SCD also support the idea that LA function is more important than size in predicting ventricular arrhythmia.[14]

Lydell et al. point out that the mechanisms responsible for the association have yet to be fully elucidated. Increased LA volume and reduced LAEF have been strongly associated with increased LV end-diastolic pressure, which may be the result of diastolic dysfunction associated with fibrosis.[15,16] In this sense, LA function can be considered to be a further indirect measure of the burden of arrhythmic substrate in the LV. Yet LAEF has been found to be a predictor of SCD independently from LV scar volume assessed by means of CMRI, suggesting that it is a surrogate for proarrhythmic factors beyond scar burden.[10] Further research is needed in this area and should include the study of a more diverse population than that included in this study, namely, those that are not currently considered candidates for a primary-prevention ICD.

**Table 2.** Emerging risk markers for sudden cardiac death[17,18]

| Modality | Marker |
|---|---|
| Imaging | Left ventricular ejection fraction |
| | Mechanical dispersion by speckle-tracking echocardiography |
| | Left atrial emptying function |
| | Volume of denervated myocardium by 11C-HED positron-emission tomography (PET) |
| | Metabolism perfusion mismatch by $^{18}$F-FDG PET |
| | Left ventricular scar mass and extent of peri-infarct zone by cardiac magnetic resonance imaging with gadolinium enhancement |
| | Reversible perfusion defects by single photon–emission computed tomographic myocardial perfusion imaging |
| Electrical | Inducible ventricular arrhythmia by programmed ventricular stimulation |
| | Microvolt T-wave alternans |
| | Heart rate turbulence and variability |
| | QRS fragmentation and duration |
| | Signal averaged electrocardiography (late potentials) |
| Other | B-type natriuretic peptide |
| | Genetic markers |

## Future Directions in SCD Risk Stratification

LA function is one of a steadily expanding list of novel risk markers (Table 2). These markers have been found to be of some prognostic value but have not been widely used clinically and are not recommended as part of routine evaluation by current guidelines.[3] The REFINE-ICD study (NCT00673842) is testing the utility of a primary-prevention ICD in patients with the presence of these electrophysiologic risk markers in the setting of a previous myocardial infarction.[5]

## Conclusion

The use of markers such as LAEF and others may assist in risk-stratifying those individuals who would benefit most from ICD therapy beyond the accepted criteria using LVEF and heart failure severity. More research is needed to understand the pathophysiology of LA dysfunction and how it relates mechanistically to arrhythmic risk. The utility of these risk markers and to whom they should be applied also deserve further study. Ideally, future studies would have a prospective design and include a wide range of putative risk markers. This work may ultimately help us to move SCD risk stratification away from dichotomising patients on the basis of LVEF toward a multifactorial assessment that allows patients to be located in a continuous spectrum of SCD risk.

## Disclosures

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