Canadian Journal of Cardiology 35 (2019) 1149–1157

Clinical Research

Left Atrial Function Using Cardiovascular Magnetic Resonance Imaging Independently Predicts Life-Threatening Arrhythmias in Patients Referred to Receive a Primary Prevention Implantable Cardioverter Defibrillator

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See editorial by Lee and Parkash, pages 1091–1093 of this issue.

ABSTRACT

Background: In this study we aimed to investigate left atrial (LA) function, measured from routine cine cardiovascular magnetic resonance imaging, to determine its value for the prediction of sudden cardiac death (SCD) or appropriate implantable cardioverter defibrillator (ICD) shock in patients who received primary prevention ICD implantation.

Methods: We studied 203 patients with ischemic or idiopathic nonischemic dilated cardiomyopathy who underwent cardiovascular magnetic resonance imaging before primary prevention ICD implantation. LA volumes were measured at end-diastole and end-systole from 4- and 2-chamber cine images, and LA emptying function (LAEF) calculated. Patients were followed for the primary composite end point of SCD or appropriate ICD shock.

Results: Mean age was 61 ± 12 years with a mean left ventricular ejection fraction of 24 ± 7%. The mean LAEF was 27 ± 15% (range, 0.9%-73%). At a median follow-up of 1639 days, 35 patients (17%)

RÉSUMÉ

Introduction : Dans la présente étude, nous avions pour objectif d'examiner la fonction auriculaire gauche (AG), mesuré par ciné-imagerie cardiovasculaire par résonance magnétique (ciné-IRM cardiovasculaire) systématique, pour déterminer sa valeur prédictive de la mort subite d'origine cardiaque (MSOC) ou de la décharge électrique appropriée du défibrillateur cardioverteur implantable (DCI) chez les patients qui subissaient une implantation de DAI en prévention primaire.

Méthodes : Les 203 participants à l'étude étaient des patients ayant une cardiomyopathie dilatée ischémique ou non ischémique idiopathique qui avaient subi une IRM cardiovasculaire avant l'implantation du DCI en prévention primaire. Nous avons mesuré le volume de l'AG en fin de diastole et de systole à partir d'images de ciné-IRM, coupes 4 et 2 cavités, et calculé la fraction de vidange de l'AG (FVAG). Le suivi des patients a porté sur le critère de jugement principal composite de MSOC ou de décharge électrique appropriée du DCI.

Sudden cardiac death (SCD) is a leading cause of death in North America, affecting > 400,000 people each year.[1] Patients with reduced left ventricular (LV) systolic function secondary to ischemic or nonischemic injury are at greatest perceived risk.[2] However, LV ejection fraction (LVEF) as a solitary risk marker yields only modest precision for the selection of patients most likely to benefit from primary prevention implantable cardioverter defibrillators (ICDs),[3] an expanding concern recently highlighted by results of the Danish ICD Study in Patients With Dilated Cardiomyopathy (DANISH) study conducted in patients with nonischemic dilated cardiomyopathy (NIDCM).[4] Accordingly, markers that improve the prediction of SCD among patients with heart failure and reduced ejection fraction (HFrEF) are of immediate priority.

Several novel imaging markers have been explored from contrast-enhanced cardiovascular magnetic resonance (CMR)

Received for publication September 13, 2018. Accepted April 10, 2019.

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See page 1156 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.04.015

experienced the primary composite outcome. LAEF was strongly associated with the primary outcome ($P = 0.001$); patients with an LAEF $\leq$ 30% experienced a cumulative event rate of 26.1% vs 5.7% (hazard ratio, 5.5; $P < 0.001$) in patients above this cutoff. This finding was maintained in multivariable analysis (hazard ratio, 4.7; $P = 0.002$) and was consistently shown in the ischemic and nonischemic dilated cardiomyopathy subgroups.

Conclusions: LAEF is a simple, powerful, and independent predictor of SCD in patients being referred for primary prevention ICD implantation.

Résultats : L'âge moyen était de 61 ± 12 ans et la fraction d'éjection ventriculaire gauche moyenne était de 24 ± 7 %. La FVAG moyenne était de 27 ± 15 % (étendue, 0,9 %-73 %). Au suivi médian de 1639 jours, 35 patients (17 %) ont atteint le critère de jugement principal composite. La FVAG a fortement été associée au critère de jugement principal ($P = 0{,}001$); les patients ayant une FVAG $\leq$ 30 % ont expérimenté un taux cumulatif d'événements de 26,1 % *vs* 5,7 % (rapport de risque, 5,5; $P < 0{,}001$) chez les patients au-dessus de cette limite. Ce résultat a été maintenu dans l'analyse multivariable (rapport de risque, 4,7; $P = 0{,}002$) et a été démontré de manière constante dans les sous-groupes de cardiomyopathie dilatée ischémique et non ischémique.

Conclusions : La FVAG est un prédicteur simple, puissant et indépendant de la MSOC chez les patients dirigés pour une implantation de DCI en prévention primaire.

imaging that improve the prediction of arrhythmic events in patients with HFrEF, these being inclusive of: LV myocardial fibrosis burden, fibrosis pattern, and fibrosis signal characteristics.[5,6] However, noncontrast cine imaging might provide incremental value beyond the calculation of LVEF with left atrial (LA) size and function being investigated markers in heart failure populations.[7,8] The latter marker was first identified to predict nonarrhythmic heart failure outcomes[9] as well as atrial arrhythmias[10,11] in patients with HFrEF, but more recently has been identified to provide an independent association with appropriate ICD therapy.[12] Because of the importance of such a finding for risk prediction modelling in HFrEF populations, we sought to independently confirm this association and establish a practical threshold for use in clinical practice.

To explore this hypothesis, we quantified LA function using cine CMR imaging in a large cohort of patients referred for primary prevention ICD implantation. Our aim was to investigate the value of LA emptying function (LAEF) for the prediction of SCD or appropriate ICD shock in the context of contemporary risk markers; inclusive of CMR-based LVEF and late gadolinium enhancement (LGE) fibrosis volume.

Methods

Study population

We retrospectively studied 203 patients with ischemic cardiomyopathy (ICM) or NIDCM who underwent clinical CMR imaging and were clinically accepted for primary prevention ICD implantation (between October 2005 and November 2013 at the Foothills Medical Centre in Alberta, Canada). Acceptance for primary prevention ICD implantation was at the discretion of the primary electrophysiologist with access to all available imaging reports at the time of referral.

Objective criteria for ICM and NIDCM were applied. All patients were required to have confirmation of an LVEF $\leq$ 50% according to CMR imaging. A diagnosis of ICM mandated each patient to meet 1 of the following criteria: (1) presence of obstructive coronary artery disease with $\geq$ 70% stenosis in $\geq$ 1 epicardial coronary vessel on invasive angiography; (2) previous myocardial infarction; (3) previous percutaneous/surgical revascularization; or (4) presence of ischemic (subendocardial) injury on LGE imaging in absence of previous coronary angiography. Objective criteria for NIDCM were: (1) no criteria for ICM met; and (2) no known etiology for non-ICM (eg, hypertrophic cardiomyopathy, cardiac sarcoidosis, cardiac amyloidosis, or arrhythmogenic right ventricular cardiomyopathy).

Exclusion criteria included current or recent ($\leq$ 3 months) atrial fibrillation, previous mitral valve surgery, or recent acute coronary syndrome or revascularization ($\leq$ 3 months).

The study was approved the Conjoint Health Research Ethics Board at University of Calgary and all participants provided written informed consent.

CMR imaging and analysis protocol

CMR imaging was performed using a 1.5-Tesla or 3-Tesla clinical scanner (Avanto or Skyra, Siemens Healthineers, Erlangen, Germany). A standardized CMR imaging protocol was used, inclusive of cine steady-state free precession pulse sequences in standard 2, 3, and 4-chamber long axis views and sequential short-axis slices using typical imaging parameters. Long-axis views were manually prescribed from a set of single-shot steady-state free precession short axis scout images on the basis of typical anatomic landmarks. Cine imaging was followed by spatially matched LGE imaging, using a standard inversion recovery gradient echo pulse sequence 10 minutes after intravenous administration of gadolinium contrast (0.15-0.2 mmol/kg; Gadobutrol or Gadopentetate dimeglumine; Bayer, Inc, Whippany, NJ) as previously described.[13] All images were acquired at end-expiration.

Images underwent analysis by experienced core laboratory personnel blinded to all clinical data using commercially available software (cvi[42]; Circle Cardiovascular Inc, Calgary, Alberta, Canada). Cine images were analyzed using semi-automated contour tracing of endocardial and epicardial borders to obtain the LV end-diastolic volume and end-systolic volume, ejection fraction, and mass.[6] Mitral insufficiency, when present, was visually scored from long-axis cine images as being mild-moderate or severe (jet extending to posterior atrium).

LA volumes were measured using the bi-plane area-length method from temporally matched 4- and 2-chamber cine images, as shown in Figure 1. LA volumes were calculated at

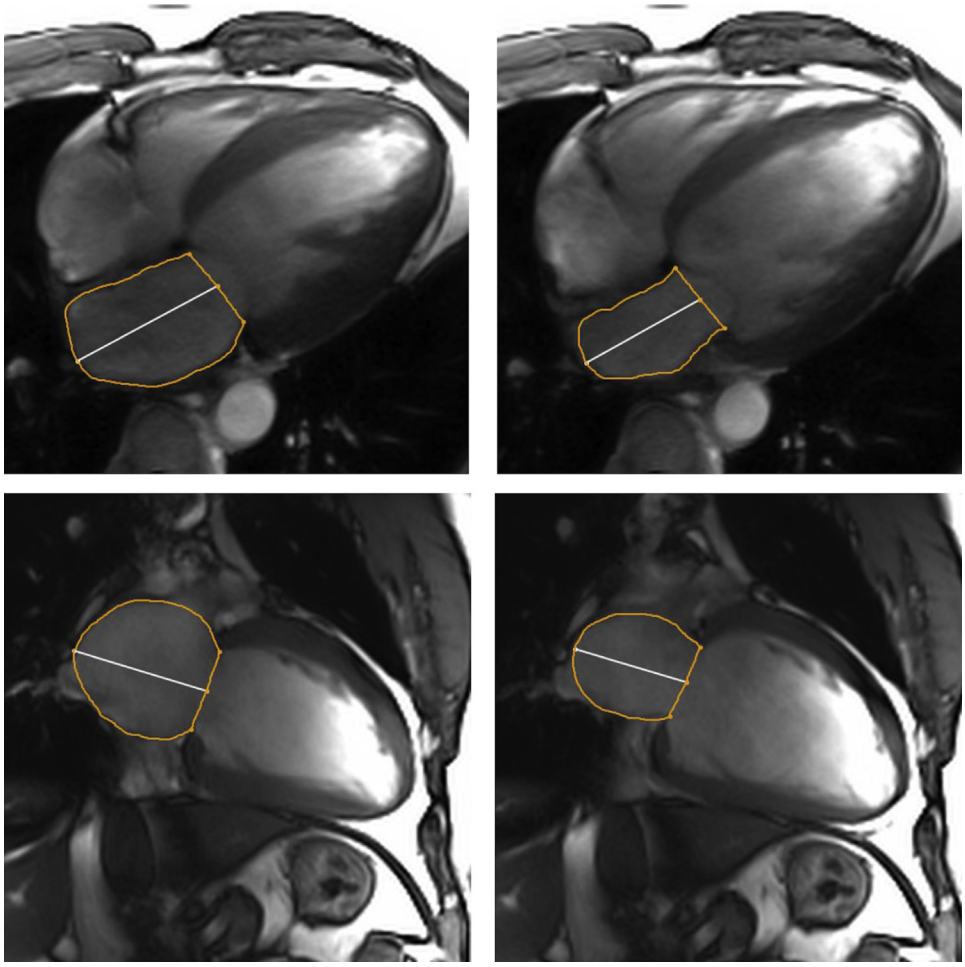

Figure 1. Left atrial volumetric measurement technique applied to 4-chamber (**top row**) and 2-chamber (**bottom row**) views to derive maximum and minimum left atrial volumes using the bi-plane area-length method. Length measurements were obtained perpendicular to the mitral annular plane with the shortest of each measurement applied for volume estimations. The pulmonary veins and left atrial appendage were excluded from analysis.

their maximal (LAmax) and minimal (LAmin) volume using the formula: LA volume = (8 × area 1 × area 2)/(3π × length), as previously described.[14] LAmax was measured 1 frame before mitral valve opening whereas LAmin was measured 1 frame after mitral valve closure. LA endocardial borders were traced from the insertion points of the mitral valve annulus with the exclusion of the pulmonary veins and the atrial appendage. LA length was measured perpendicular to the midpoint of the mitral annular plane with the shortest measurement of the 2 views used for volume calculations. As previously described, LA emptying function was calculated as ([LAmax − LAmin]/LAmax) × 100, where LAmax − LAmin is defined as the LA emptying volume.[14] LA conduit volume was determined according to the difference between LV stroke volume and LA emptying volume. All volumetric analyses were indexed to body surface area, where appropriate, using the DuBois and DuBois formula.

Total LV fibrosis was quantified from LGE images using a signal > 5 SD above the mean reference signal of normal (nonenhanced) myocardium and was expressed as a percentage of the LV mass. This threshold was chosen on the basis of our previous findings in NIDCM cohorts in whom we assessed optimal approaches to LGE segmentation for the prediction of arrhythmic events.[15] The visual presence and corresponding pattern of LGE was incrementally scored by 2 experienced readers who achieved consensus agreement.

Intra- and interobserver reproducibility testing of LA volumes and LAEF was studied in 20 randomly selected patients with repeat assessment by the same observer 1 month after the previous measurement, and by an independent observer.

Follow-up and clinical events

Clinical follow-up was conducted with review of medical records and of serial ICD device interrogations. All patients were followed from time of CMR imaging until they experienced a composite primary outcome (SCD or appropriate ICD shock), heart transplantation, death from another cause, or had their final study contact, whichever came first. SCD was defined as cardiac death occurring within 1 hour of symptom onset. ICDs were typically programmed with detection rates of ≥ 180 beats per minute for the ventricular tachycardia (VT) zone, and ≥ 250 beats per minute for the ventricular fibrillation (VF) zone, as previously described.[16] Appropriate ICD shock was defined as device shock for confirmed sustained fast VT or VF, as adjudicated by an

electrophysiologist. Our secondary composite end point was SCD, appropriate ICD shock, or appropriate antitachycardia pacing (ATP).

Statistical analysis

All descriptive statistics were expressed as mean ± SD. Comparison between 2 groups was performed with the independent Student *t* test or Mann-Whitney *U* test depending on the distribution. Fisher exact test was used to compare categorical data. Univariable associations between clinical or CMR characteristics and the study outcomes were performed using Cox proportional hazards regression. Multivariable Cox regression analysis was performed to assess associations between LAEF and the primary composite outcome. Similar analyses were performed for each of the ICM and NIDCM cohorts. Covariates reaching a significance value of $P < 0.05$ were considered eligible for adjustment within each multivariable model. All models were assessed for collinearity and proportional hazards assumption. We used the restricted cubic spline function to model the LAEF as a continuous variable and identified the optimal LAEF cutoffs of as 30% for dichotomization. The Kaplan-Meier method and the log rank test were used to compare the survival curves for those with LAEF > 30% and those with LAEF ≤ 30%. A competing risk analysis was also performed to ensure findings for the predictive utility of LAEF remained unchanged while treating the other cause of death as competing risk.

Inter- and intraobserver reproducibility were assessed using the Bland-Altman analysis. All statistical analyses were performed using SPSS for Macintosh, version 21.0 (IBM Corp, Armonk, NY) and R version 3.3 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org).

Results

Baseline characteristics

Of 203 patients who met study inclusion criteria 165 (81%) were male and the mean age was 61 ± 12 years. As shown in Table 1, 102 patients (50%) had ICM and 101 (50%) had NIDCM. The mean LVEF of the study population (according to CMR-based evaluation) was 24 ± 7% (range, 8%-47%) with a mean LV end-diastolic volume indexed to body surface area of 153 ± 40 mL/m^2.

LA volumetric quantification provided a mean LAmax, LAmin, and LAEF of 83 ± 27 mL/m^2, 63 ± 29 mL/m^2, and 27 ± 15%, respectively. Observed LAEF values ranged from 0.9% to 73%. No significant differences in baseline CMR characteristics were observed between the ICM and NIDCM subgroups with respect to either LV or LA volumetric measures.

The visual prevalence of myocardial fibrosis (any) according to LGE imaging was 100% in ICM patients and 53% in NIDCM patients. Among the latter subgroup, the following patterns were identified: septal striae (41%), right ventricular insertion site (43%), subendocardial (incidental small volume; 8%), and diffuse (2%). The mean fibrosis burden determined according to signal threshold analysis of LGE images was 11.8 ± 13.1% among the entire cohort with respective mean values of 20.5 ± 11.6% and 2.9 ± 7.4% in the ICM and NIDCM subgroups.

Primary and secondary clinical outcome

Over a median follow-up of 1639 days (interquartile range, 1318 days), a total of 35 patients (17%) experienced the primary composite outcome of SCD and appropriate ICD shock. This consisted of 32 patients with appropriate ICD shock and 3 patients who suffered SCD. In addition to the primary end point, 23 patients suffered a nonsudden (all-cause) death and 3 patients underwent cardiac transplantation. No patient was lost to follow-up.

Seventy-eight patients experienced the secondary composite outcome of SCD, appropriate ICD shock, or ATP. This included 51 patients with ATP as a first event, 15 with ICD shock as a first event, 9 with ATP and ICD shock on the same date, and 3 with SCD as a first event.

Predictors of the primary and secondary outcomes

Of all baseline clinical characteristics, only the use of diuretics was identified as a significant clinical predictor of the primary outcome for the entire population in univariable analysis, with a hazard ratio of 2.63 ($P = 0.01$). Of all CMR measurements, 3 variables were identified as significant predictors in univariable analysis; indexed LAmin (hazard ratio [HR], 1.15 per 10 mL/m^2; $P = 0.01$), LAEF (HR, 0.81 per 5%; $P = 0.001$), and indexed LA conduit volume (HR, 1.45 per 10 mL/m^2; $P = 0.01$). LAmax did not achieve significance for prediction of the primary outcome ($P = 0.08$). Neither LVEF, right ventricular ejection fraction, nor total LGE burden achieved statistical significance for an association with the primary outcome.

Restricted spline function analysis with a degree of 4 was used to detect nonlinear relationships between the primary outcome and LAEF. Using a Cox regression model a survival probability curve was estimated for the population over a 4-year period across the range of observed LAEF values (Fig. 2). This identified significant elevation of risk for the primary outcome when the LAEF was below a threshold value of 30%.

Applying this cutoff, patients with an LAEF ≤ 30% were found to have a 5.5-fold higher risk ($P < 0.001$) of the primary outcome vs those with an LAEF > 30% using univariable regression analysis. After multivariable adjustment for diuretic use, LAEF ≤ 30% remained a strong and independent predictor of the primary outcome with an HR of 4.7 ($P = 0.002$).

Figure 3 shows a Kaplan-Meier survival analysis curve for subjects with an LAEF above and below the threshold of 30%. Patients with LAEF ≤ 30% had significantly worse event-free survival compared with those with an LAEF > 30% ($P < 0.001$) with a cumulative event rate of 26.1% vs 5.7%, respectively. Corresponding annualized event rates were 6.0% vs 1.1% for the primary composite outcome.

Sensitivity analysis showed that LAEF ≤ 30% remained a significant independent predictor of the primary outcome with an HR of 5.1 ($P = 0.001$) after removal of patients with severe mitral insufficiency (n = 12).

Finally, we performed a competing risk analysis to assess the effect of those events unrelated to the primary outcome

Table 1. Baseline demographic characteristics of the cohort and the univariable associations with primary outcome

Characteristic	Total cohort (N = 203)	LAEF ≤ 30% (n = 115)	LAEF > 30% (n = 88)	HR (95% CI)	*P*
Age, years	61 ± 12	60 ± 13	61 ± 11	0.94 (0.82-1.08) per 5 years	0.38
Male sex, n (%)	165 (81)	101 (88)	64 (73)	2.54 (0.78-8.29)	0.12
Hypertension, n (%)	80 (39)	44 (39)	36 (41)	0.85 (0.42-1.71)	0.64
Diabetes, n (%)	64 (32)	30 (26)	34 (39)	1.61 (0.82-3.07)	0.17
Hyperlipidemia, n (%)	71 (35)	36 (32)	35 (40)	0.52 (0.24-1.15)	0.11
NYHA class 3-4, n (%)*	68 (36)	46 (44)	22 (27)	1.87 (0.96-3.63)	0.07
Ischemic cardiomyopathy, n (%)	102 (50)	58 (50)	44 (50)	0.92 (0.53-2.01)	0.92
Medications					
ACE inhibitor or ARB	169 (83)	91 (79)	78 (89)	0.79 (0.34-1.80)	0.57
Amiodarone	24 (12)	14 (12)	10 (11)	1.36 (0.53-3.52)	0.52
β-Blocker	180 (89)	100 (87)	80 (91)	0.93 (0.33-2.63)	0.89
Digoxin	36 (18)	24 (21)	12 (14)	1.17 (0.51-2.67)	0.72
Diuretic	99 (49)	64 (56)	35 (40)	2.63 (1.29-5.37)	0.01†
Spironolactone	90 (44)	58 (50)	32 (36)	0.90 (0.46-1.78)	0.77
CMR variables					
LVEDVI, mL/m^2	153 ± 40	160 ± 43	144 ± 35	1.00 (0.92-1.08) per 10 mL/m^2	0.93
LVESVI, mL/m^2	118 ± 39	127 ± 41	105 ± 33	1.00 (0.92-1.09) per 10 mL/m^2	0.94
LV mass indexed, g/m^2	84 ± 25	84 ± 24	85 ± 26	0.98 (0.86-1.12) per 10 g/m^2	0.76
LVEF, %	24 ± 7	22 ± 7	28 ± 7	0.92 (0.74-1.16) per 5%	0.50
RVEDVI, mL/m^2	81 ± 28	90 ± 30	69 ± 21	1.07 (0.95-1.20) per 10 mL/m^2	0.26
RVESVI, mL/m^2	45 ± 29	56 ± 29	31 ± 20	1.08 (0.96-1.20) per 10 mL/m^2	0.20
RVEF, %	49 ± 18	41 ± 15	59 ± 15	0.93 (0.84-1.02) per 5%	0.11
LA maximum volume indexed, mL/m^2	83 ± 27	95 ± 27	68 ± 17	1.11 (0.99-1.25) per 10 mL/m^2	0.08
LA minimum volume indexed, mL/m^2	63 ± 29	80 ± 26	40 ± 13	1.15 (1.04-1.27) per 10 mL/m^2	0.01†
LAEF, %	27 ± 15	16 ± 7	42 ± 9	0.81 (0.71-0.91) per 5 %	0.001†
LA conduit volume indexed, mL/m^2	15 ± 10	19 ± 10	10 ± 8	1.45 (1.10-1.92) per 10 mL/m^2	0.01†
Total LGE, % of LV mass	11.8 ± 13.1	12.1 ± 13.6	11.4 ± 12.6	1.06 (0.94-1.20) per 5%	0.35

Continuous data are expressed as mean ± SD, categorical data as n (%).

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; CMR, cardiovascular magnetic resonance; HR, hazard ratio; LA, left atrium; LAEF, left atrial emptying fraction; LGE, late gadolinium enhancement; LV, left ventricular; LVEDVI, left ventricular end diastolic volume indexed to body surface area; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end systolic volume indexed to body surface area; NYHA, New York Heart Association; RVEDVI, right ventricular end diastolic volume indexed to body surface area; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end systolic volume indexed to body surface area;

*Total number of the patients for the NYHA data is 187.

†$P < 0.05$.

that inherently prevent such outcomes from being experienced (ie, nonarrhythmic death). After this analysis, we observed cumulative incidence curves (Fig. 4) for LAEF ≤ 30% that maintained their predictive utility for the primary outcome.

For the secondary composite outcome of SCD or ICD shock or ATP, LAEF values were similarly significantly predictive of this outcome. This was observed for LAEF ≤ 30% as a dichotomous threshold (HR, 2.05; $P = 0.004$) and as a continuous variable (HR, 0.92 per 5%; $P = 0.03$, respectively).

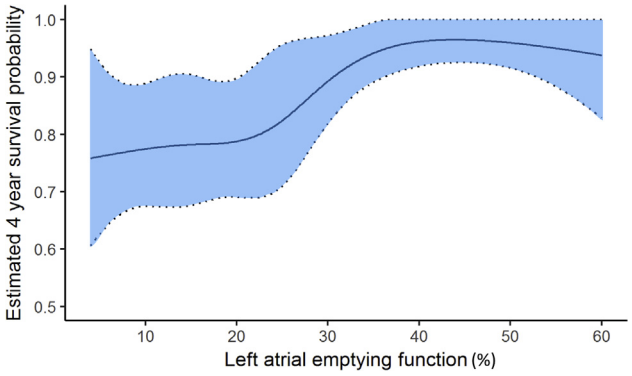

Figure 2. A Cox regression model survival probability curve estimated over a 4-year period across the range of observed left atrial emptying fraction values. This identifies significant elevation of risk for the primary outcome when the left atrial emptying fraction is below a value of 30%. The **dotted line** indicates the 95% confidence intervals for the prediction.

Subgroup analyses: ischemic vs non-ICM

Among patients with ICM (n = 102), 18 patients (18%) experienced the primary outcome. Baseline characteristics of the ICM cohort are shown in Table 2. Of all significant variables, strongest predictive value was provided by LAEF ≤ 30% with an HR of 8.1 ($P = 0.01$). After adjustment for the single eligible variable of New York Heart Association classification of III or IV, LAEF ≤ 30% was found to provide a significant independent association with the primary outcome with an HR of 6.3 ($P = 0.02$). Similar analysis for the secondary outcome identified lower but still significant predictive value with an HR of 2.94 ($P = 0.01$).

Among patients with NIDCM (n = 101), 17 patients (17%) experienced the primary outcome. Baseline characteristics of the NIDCM cohort are shown in Table 2. The strongest baseline variable for prediction of the primary outcome was LAEF ≤ 30% (HR, 3.96; $P = 0.03$). After adjustment for the single eligible variable of total LGE burden, LAEF ≤ 30% provided a nonsignificant trend with an HR of 3.4 (95% confidence interval, 0.96-12.06; $P = 0.06$). Repeating multivariable analysis using LAEF and

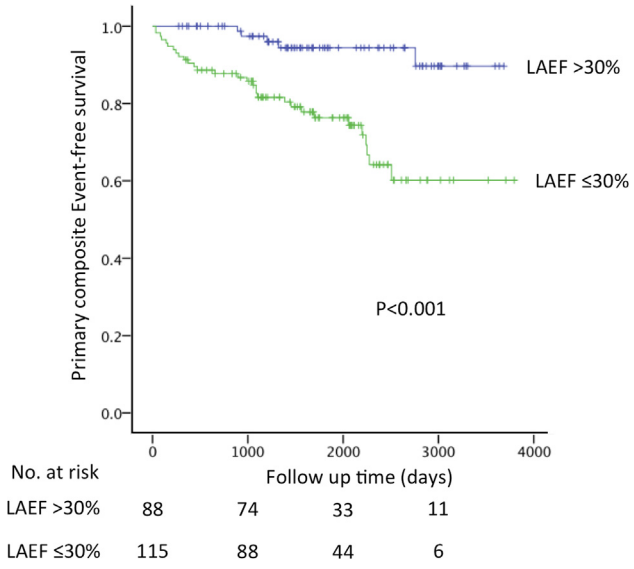

Figure 3. Kaplan-Meier analysis showing freedom from sudden cardiac death or appropriate implantable cardioverter defibrillator shock in patients with a left atrial emptying fraction (LAEF) above vs below 30%. Patients with LAEF $\leq$ 30% showed significantly worse event-free survival compared with those with LAEF $>$ 30% ($P < 0.001$).

total LGE as continuous variables provided a significant adjusted HR for LAEF of 0.81 per 5% ($P = 0.04$). Similar analyses for the secondary outcome did not reach statistical significance ($P = 0.08$).

Intra- and interobserver reproducibility

Intra- and interobserver variability for LAEF according to Bland-Altman analysis showed mean difference and 95% limits of agreement of $-0.77 \pm 4.89\%$ and $0.97 \pm 6.51\%$, respectively (Fig. 5).

Discussion

In this study we identified strong prognostic value for LAEF in the prediction of SCD or appropriate ICD shock in patients referred for primary prevention ICD. Patients with an LAEF $<$ 30% experienced a 5.5-fold higher risk of life-threatening ventricular arrhythmias with an annualized event rate of 6.0%.

Our findings provide objective validation of those recently published by Rijnierse et al.,[12] who similarly identified strong and independent associations between LAEF and incident ICD therapy in patients referred for primary prevention ICD. In this study we used similar imaging techniques and design to identify that each 10% decline in LAEF was associated with a 25% elevation in the occurrence of appropriate ICD therapy, defined according to either ATP or shock for VT or VF. The comparable risk observed in our study was 40% per 10% decline in LAEF but was achieved for the more discriminative outcome of sudden cardiac arrest or appropriate ICD shock. It is important to recognize, however, that our study provided a longer median period of follow-up (4.5 vs 3.9 years). Together, these 2 studies now provide independent and reproducible evidence for strong prognostic utility of LAEF as an independent predictor of ventricular arrhythmias in patients with HFrEF.

Although pathophysiologic insights linking LA functional impairment to the occurrence of ventricular arrhythmia must now be explored, the findings of our study are supported by previous reports by Negishi et al., who examined an echocardiographic surrogate of LA function (A-wave velocity) among 124 patients with NIDCM.[17] In that study an association between A-wave velocity and the composite clinical outcome of SCD or appropriated ICD therapy (shock or ATP) was similarly identified (adjusted HR of 0.97 per 1 cm/s increase; $P < 0.001$). Our current validation shows that LAEF, a rapidly obtained marker from routine long-axis cine images, is associated with higher rates of future arrhythmic events in patients referred for primary prevention ICD implantation. As an established reference standard for LVEF-based eligibility, the simple additional use of LAEF quantification can broaden its capacity to delineate patients at high vs low likelihood of clinical benefit.

In their previous study, by Pellicori et al. described similar measures of volumetric LA function according to CMR imaging for the prediction of heart failure-related hospitalization or all-cause mortality in patients with HFrEF.[9] Among 982 patients followed over a median duration of 833 days, each 10% decrease in LAEF was associated with a 19% increase in this primary composite outcome. Several additional echocardiography-based studies have incrementally shown associations between LAEF and other relevant end points[10,18] in this patient population. For example, in their study, Mazzone et al. identified that estimation of "LA work," a marker derived using the peak A velocity on transmitral Doppler, could predict cardiovascular death and heart failure hospitalization.[18]

Although the aforementioned studies, and our current study, consistently show LAEF to be a superior marker to LAmax for the prediction of future clinical events, it is important to highlight the results of previous studies that have examined LAmax as a risk marker in patients with HFrEF. For example, Gulati et al. performed CMR imaging in 483 patients with NIDCM and studied the predictive utility of LAmax for all-cause mortality or cardiac transplantation.[14] In patients with an LAmax volume $>$ 72 mL/m^2, a 3.0-fold (HR, 3.0; 95% confidence interval, 1.92-4.70; $P < 0.001$)

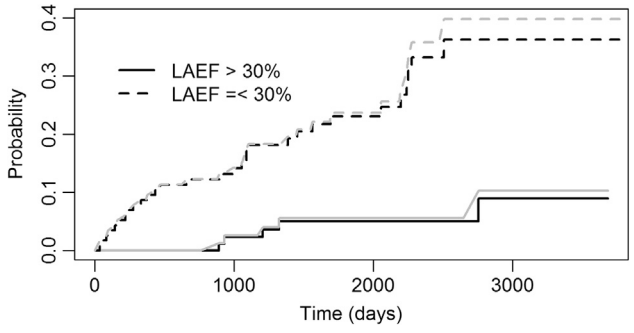

Figure 4. Cumulative incidence curves without accounting for other causes of death (**grey curves**) and after adjusting for the competing risk of other causes of death (**black curves**). Left atrial emptying fraction (LAEF) $\leq$ 30% maintained predictive utility with significant separation of risk.

Table 2. Univariable associations of clinical and CMR characteristics with primary outcome for patients with ICM and NIDCM

	ICM			NIDCM		
Characteristic	Value (n = 102)	HR (95% CI)	*P*	Value (n = 101)	HR (95% CI)	*P*
Age in years	62 ± 12	1.15 (0.92-1.43) per 5 years	0.22	59 ± 12	0.82 (0.69-0.97) per 5 years	0.02*
Male sex, n (%)	91 (89)	1.91 (0.25-14.41)	0.53	74 (73)	2.88 (0.66-12.60	0.16
Hypertension, n (%)	41 (40)	0.55 (0.20-1.56)	0.26	39 (39)	1.22 (0.46-3.22)	0.69
Diabetes, n (%)	37(36)	0.74 (0.26-2.07)	0.56	27 (27)	3.32 (1.28-8.61)	0.01*
Hyperlipidemia, n (%)	47(46)	0.62 (0.23-1.66)	0.34	24 (24)	0.39 (0.09-1.69)	0.21
NYHA class 3-4, n (%)†	34 (37)	2.97 (1.15-7.66)	0.03*	34 (36)	1.05 (0.39-2.86)	0.92
Medications						
ACE inhibitor or ARB	87 (85)	0.32 (0.11-0.90)	0.03*	82 (81)	1.85 (0.42-8.12)	0.41
Amiodarone	7 (7)	1.41 (0.32-6.18)	0.65	17 (17)	1.14 (033-4.00)	0.83
β-blocker	93 (91)	0.19 (0.05-0.73)	0.02*	87 (86)	3.04 (0.40-22.97)	0.28
Digoxin	17 (17)	1.03 (0.30-3.58)	0.96	19 (19)	1.26 (0.41-3.86)	0.69
Diuretic	58 (57)	4.63 (1.34-16.01)	0.02*	41 (41)	1.78 (0.68-4.61)	0.24
Spironolactone	43 (42)	1.88 (0.74-4.81)	0.19	47 (47)	1.34 (0.52-3.48)	0.55
CMR variables						
LVEDVI, mL/m^2	153 ± 40	0.96 (0.85-1.09) per 10 mL/m^2	0.54	154 ± 41	0.99 (0.88-1.12) per 10 mL/m^2	0.85
LVESVI, mL/m^2	116 ± 39	1.03 (0.91-1.15) per 10 mL/m^2	0.65	119 ± 39	0.97 (0.86-1.11) per 10 mL/m^2	0.69
LVEF, %	25 ± 8	0.77 (0.56-1.05) per 5%	0.10	24 ± 7	1.15 (0.84-1.59) per 10 mL/m^2	0.39
LV mass indexed, g/m^2	81 ± 22	0.94 (0.75-1.17) per 10 g/m^2	0.56	87 ± 27	0.99 (0.83-1.18) per 10 g/m^2	0.92
RVEDVI, mL/m^2	80 ± 29	1.00 (0.83-1.19) per 10 mL/m^2	0.96	81 ± 27	1.14 (0.97-1.35) per 10 mL/m^2	0.12
RVESVI, mL/m^2	44 ± 29	1.05 (0.89-1.24) per 10 mL/m^2	0.56	46 ± 29	1.10 (0.94-1.27) per 10 mL/m^2	0.24
RVEF, %	49 ± 17	0.93 (0.81-1.07) per 5%	0.32	48 ± 18	0.92 (0.81-1.05) per 5%	0.23
LA maximum volume indexed, mL/m^2	83 ± 27	1.10 (0.94-1.29) per 10 mL/m^2	0.25	83 ± 26	1.15 (0.96-1.38) per 10 mL/m^2	0.12
LA minimum volume indexed, mL/m^2	63 ± 30	1.14 (0.99-1.30) per 10 mL/m^2	0.06	62 ± 28	1.21 (1.02-1.42) per 10 mL/m^2	0.03*
LAEF, %	26 ± 15	0.79 (0.67-0.95) per 5%	0.01*	27 ± 16	0.81 (0.67-0.97) per 5%	0.02*
LA conduit volume indexed, mL/m^2	16 ± 10	1.20 (0.77-1.86) per 10 mL/m^2	0.43	14 ± 10	1.71 (1.22-2.40) per 10 mL/m^2	0.002*
LAEF ≤ 30%, n (%)	58 (57)	8.05 (1.84-35.31)	0.01*	57 (56)	3.96 (1.14-13.79)	0.03*
Total LGE, % of LV mass	20.5 ± 11.6	0.97 (0.78-1.20) per 5%	0.75	2.9 ± 7.4	1.33 (1.11-1.60) per 5%	0.002*

Continuous data are expressed as mean ± SD, categorical data as n (%).

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CI, confidence interval; CMR, cardiovascular magnetic resonance; HR, hazard ratio; ICM, ischemic cardiomyopathy; LA, left atrium; LAEF, left atrial emptying fraction; LGE, late gadolinium enhancement; LV, left ventricular; LVEDVI, left ventricular end diastolic volume indexed to body surface area; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end systolic volume indexed to body surface area; NIDCM, nonischemic dilated cardiomyopathy; NYHA, New York Heart Association; RVEDVI, right ventricular end diastolic volume indexed to body surface area; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end systolic volume indexed to body surface area.

*$P < 0.05$.

†Total number of the patients for the NYHA data is 187 (92 for ICM).

increased risk of the primary outcome was identified. These findings are supported by those published by Rossi et al. who, more than a decade before, showed echocardiography-derived measures of LAmax to be strongly associated with event-free survival in patients with NIDCM using a LAmax threshold of 68.5 mL/m^2.[19]

As similarly highlighted by Rijnierse et al.,[12] pathophysiologic mechanisms relating reduced LA function to incident ventricular arrhythmias in patients with HFrEF remains uncertain. As an "upstream" observer of LV filling, the LA is obliged to manage acute and chronic elevations in LV filling pressures throughout duration of a patient's disease.

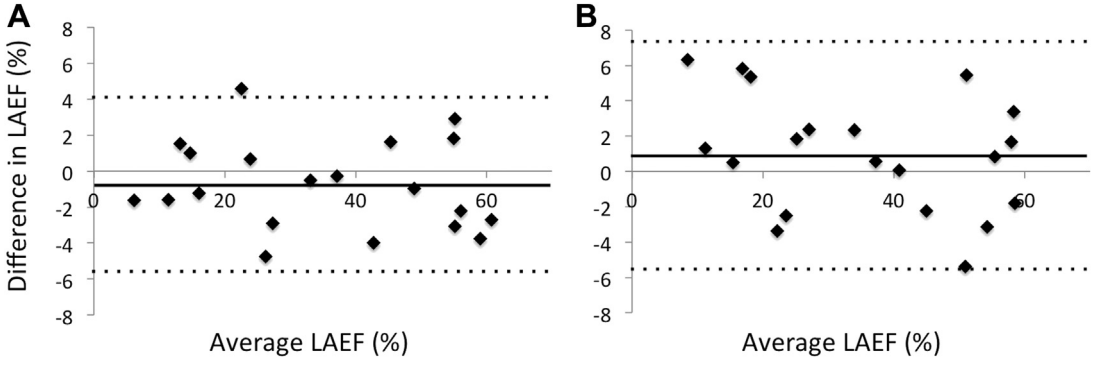

Figure 5. Intra- (**A**) and interobserver (**B**) variability for left atrial emptying fraction (LAEF) shown in Bland-Altman analysis. Mean difference and 95% limits of agreement were −0.77 ± 4.89% and 0.97 ± 6.51%, respectively.

Accordingly, adverse remodelling and contractile dysfunction of the LA might be a valuable marker of chronic ventricular disease and, within the present study, was shown to be a strong predictor of ventricular arrhythmia risk. This is well aligned with previous observations that elevations in B-type natriuretic peptide, this believed to closely parallel changes in LV filling pressures, has similarly been associated with an elevated risk of ventricular arrhythmias in patients with HFrEF.[20,21] It is also recognized that diastolic dysfunction is a significant and incremental contributor to LV filling pressure elevation beyond that implicated by systolic dysfunction, and has itself been associated with ventricular arrhythmias.[22]

Interindividual variability in profibrotic pathway upregulation could provide an explanation for the broad range of LAEF observed across this primary prevention ICD referral population.[23] Experimentally, the LA has been shown to be highly sensitive to gene upregulation in the setting of heart failure induction, inclusive of genes that modulate the extracellular matrix.[24] It is therefore plausible that interindividual differences in pathway activity might be identifiable via the assessment of LA contractile performance. Whether the latter identifies patients similarly predisposed to accelerated fibrosis within the LV myocardium, a nidus for ventricular arrhythmia, is unknown but of particular interest for future study.

Overall, these findings support contractile dysfunction of the LA to be a valuable marker of ventricular arrhythmic events. How such impairments in LA function are mediated, and how these might represent concurrent processes influencing ventricular electrical stability are an important area of future research.

Study limitations

This study was aimed at evaluating the role of volumetric LAEF as a rapid, clinically feasible, and routine measurement as a predictive marker of future ventricular arrhythmic events. As a composite measure of LA emptying, LAEF does not incrementally explore related subcomponents such as LA "booster" function. Accordingly, whether such subcomponents might provide greater predictive accuracy for ventricular arrhythmias remains a focus for future study. Evolving semiautomated approaches to dynamic LA functional analysis, such as those provided by feature-tracking strain analyses, might provide an alternate path to achieving more detailed functional analyses of the LA in the near future, and warrant exploration.

Inherent to the measurement of atrial function is need for organized atrial contraction, requiring our exclusion of patients in atrial fibrillation. Further, we excluded patients with recent cardioversion because of concern for related atrial stunning. Accordingly, our described results cannot be translated to such excluded patient cohorts.

The imaging protocol applied in this patient population does not routinely include phase-contrast flow analysis for the quantitative assessment of mitral insufficiency or transmitral flow. Accordingly, these variables were not available for consideration in multivariable analysis. Also, we applied a visual scoring of mitral insufficiency severity from long-axis cine imaging. Such an assessment might underestimate the severity of mitral insufficiency and therefore, might not fully address this as a potential confounder. It is recognized that dynamic alterations in loading conditions might influence LAEF in patients with HFrEF, and that the degree to which physiologic conditions or hydration status might confound such a measure are currently unknown. Finally, it is important to note that care must be taken for the appropriate prescription of long-axis imaging planes to achieve optimal atrial quantification. Without such attention, images optimized for ventricular visualization might provide a foreshortening of the atria that might lead to reduction in the accuracy of LAEF measurements. Finally, we recognize the size of our cohort limited our ability to assess associations in each of the ischemic and non-ICM subgroups. Expanded study in a larger population is therefore warranted.

Conclusions

LAEF is a highly reproducible imaging marker obtainable from routinely performed, noncontrast cine CMR imaging that might discriminate patients at high vs low risk of future life-threatening arrhythmic events.

Funding Sources

This work was funded, in part, by an unrestricted research grant from the Calgary Health Trust.

Disclosures

Dr J.A. White receives salary support from the Heart and Stroke Foundation of Alberta and is a shareholder of Cohesic Inc. Dr D. Exner has received consulting fees or honoraria from Boehringer Ingelheim, GE Healthcare, Medtronic, Sanofi-aventis, and St Jude Medical, and is a shareholder of Analytics4Life. The remaining authors have no conflicts of interest to disclose.

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