Impact of Increased Right Atrial Size on Long-Term Mortality in Patients With Heart Failure Receiving Cardiac Resynchronization Therapy

Alexandre Altes, MD[a], Ludovic Appert, MD[a], François Delelis, MD[a], Yves Guyomar, MD[a], Aymeric Menet, MD, PhD[a], Pierre-Vladimir Ennezat, MD, PhD[b], Raphaëlle A Guerbaai, MsC, RN[c], Pierre Graux, MD[a], Christophe Tribouilloy, MD, PhD[d,e], and Sylvestre Maréchaux, MD, PhD[a,e,*]

The ability to visualize the right atrium (RA) by echocardiography allows a quantitative, highly reproducible assessment of the RA volume (RAV). The aim of this study is to evaluate the relation between RAV and long-term mortality in a prospective cohort of heart failure and reduced ejection fraction patients in sinus rhythm receiving cardiac resynchronization therapy. 172 patients were included. The right atrium volume index (RAVI) was calculated using Simpson's method from the apical four-chamber view and indexed to body surface area. The relation between RAVI and mortality during follow up was studied. Median follow up was 68 months (interquartile range 62 to 73 months). Mean RAVI was 27 ± 14 mL/m^2 (IQR 22 to 33 mL/m^2). Cumulative 5-year all-cause mortality was 22 ± 6% in patients with RAVI ≤ 19 mL/m^2, 24 ± 6% for RAVI 19 to 29 mL/m^2 and 58 ± 7% for RAVI >29 mL/m^2 (p for trend <0.001). After adjustment on clinical and echocardiographic predictors of outcome including indices of right ventricular function, there was a significant increase in overall mortality risk with increasing RAVI (adjusted hazard ratio 1.02 [95% confidence interval, 1.00 to 1.03], per 1 mL/m^2 increment; p = 0.042). Patients in the highest tertile (RAVI >29 mL/m^2) had significantly greater risk of death compared with those with RAVI ≤29 mL/m^2 (adjusted hazard ratio 2.01 [95% confidence interval, 1.15 to 3.50]; p = 0.014). In conclusion, RA enlargement is a powerful and highly reproducible independent predictor of long-term mortality in patients with heart failure and reduced ejection fraction in sinus rhythm receiving cardiac resynchronization therapy. **(Am J Cardiol 2019;123:936−941)**

Introduction

Right ventricular (RV) dysfunction is a powerful independent factor of poor prognosis in patients with heart failure (HF) and reduced ejection fraction (HFrEF).[1,2] RV dysfunction has also been associated with an increased risk of long-term mortality in HFrEF patients receiving cardiac resynchronization therapy (CRT),[3] but does not seem to be the right predictor to determine response to CRT.[4] Accurate echocardiographic assessment of RV systolic function is challenging and relies mainly on the assessment of RV longitudinal function.[5] In contrast, the ability to visualize the right atrium (RA) allows a quantitative, highly reproducible assessment of the RA volume. Right atrium volume indexed to body surface area (RAVI) has been associated with adverse outcome in patients with pulmonary hypertension[6] and with RV systolic dysfunction in HFrEF patients.[7] However, the impact of RA dilatation on mortality in patients with HFrEF has not been investigated. To address this issue, we studied here the relation between RAVI and outcome in a prospective cohort of HFrEF patients receiving CRT.

Methods

The present cohort consisted of ambulatory patients with HFrEF in sinus rhythm referred to Hôpital Saint Philibert (Lille Catholic University), Lomme, France, for CRT device implantation between December 2010 and January 2015, in whom echocardiographic evaluation allowed reliable measurement of RA volume. CRT was indicated according to current heart failure guidelines. Exclusion criteria included: (1) myocardial infarction, acute coronary syndrome, or coronary revascularization in the past 3 months; (2) primary mitral or aortic valve disease; (3) atrial fibrillation. Patients received a maximum tolerated dose of heart failure treatments. Blood was sampled for serum creatinine and plasma BNP levels before CRT device implantation. The study was approved by the Lille Catholic University ethics committee for noninterventional research. Informed consent was obtained at the time of enrollment from all patients.

[a]Université Lille Nord de France, GCS-Groupement des Hôpitaux de l'Institut Catholique de Lille, Laboratoire d'échocardiographie, service de cardiologie Nord, Centre des Valvulopathies, Faculté de Médecine et de Maïeutique, Université Catholique de Lille, Lille, France; [b]Centre Hospitalier Universitaire de Grenoble, Service de cardiologie, Grenoble, France; [c]Department Public Health (DPH), Faculty of Medicine, University of Basel, Basel, Switzerland; [d]Centre Hospitalier Universitaire d'Amiens, Amiens, France; and [e]INSERM U 1088 Université de Picardie, Amiens, France. Manuscript received October 18, 2018; revised manuscript received and accepted December 13, 2018.

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*Corresponding author: Tel: +33 3 20 22 59 24.

E-mail address: sylvestre.marechaux@yahoo.fr (S. Maréchaux).

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Comprehensive transthoracic echocardiography was performed in all patients the day before CRT implantation using a GE Vivid E9 ultrasound system (General Electric healthcare, Velizy, France) according to current guidelines.[8] All images and loops were stored and measured later by an independent investigator blinded to the clinical data. Right atrium volume (RAV) was calculated using Simpson's method from the apical four-chamber view, by tracing the inner border of the right atrium at end systole.[8] Volumes are computed using the disks summation technique. RAVI was derived by dividing the RAV by body surface area. Significant mitral regurgitation was considered if effective regurgitant orifice area was $\geq$ 10 mm^2.[9] Significant tricuspid regurgitation was considered if $\geq$moderate to severe.[10] To assess the intra- and interobserver variability of RAVI, stored echocardiograms from 20 randomly selected patients were separately studied by two readers (SM and AA), during two reading sessions at 1-month interval. Three cardiac cycles were measured and averaged from the same echocardiographic study, in a random order, blinded to previous measurements.

During follow up, patients were monitored by their general physicians. Events were ascertained by clinical interviews and/or by means of phone calls to physicians, patients, and (if necessary) next of kin. Death status was available for all participants. The primary end point of the study was overall mortality and secondary end point was cardiovascular mortality. Cardiovascular mortality was considered if death was related to HF, myocardial infarction, arrhythmia, or sudden death.

Quantitative data are presented as mean $\pm$ standard deviation or median [25th to 75th percentile]. Qualitative data are presented as absolute numbers and percentages. Continuous variables for the three groups of RAVI tertiles were compared using one-way analysis of variance (for normally distributed variables) or Kruskall−Wallis test (for skewed variables). Comparison of categorical variables was carried out using a chi-square test or a Fisher exact test as appropriate. Intra and interobserver variability was expressed by means of the intraclass correlation coefficient with its 95% confidence interval [CI]. Median follow up time was obtained using the reverse Kaplan−Meier

Table 1
Baseline demographic, clinical, laboratory and echocardiographic data in the study population and according to right atrial volume index (RAVI) tertiles.

		RAVI (mL/m^2)			
	All	≤19	19 to 29	>29	p value
Variable					
Age (years)	70 ± 11	69 ± 11	69 ± 11	74 ± 11	**0.026**
Men	119(69%)	37(64%)	36(63%)	46(81%)	0.070
Body mass index (kg/m^2)	27 ± 5	28 ± 6	27 ± 5	26 ± 4	0.167
Body surface area (m^2)	1.89 ± 0.24	1.91 ± 0.23	1.90 ± 0.27	1.87 ± 0.22	0.590
Hypertension	75(43%)	26(45%)	26(46%)	23(40%)	0.829
Diabetes mellitus	52(30%)	21(36%)	17(30%)	14(25%)	0.396
Dyslipidemia	68(39%)	23(40%)	25(44%)	20(35%)	0.632
Coronary artery disease	67(39%)	20(34%)	25(44%)	22(39%)	0.586
NYHA functional class III−IV	83(48%)	19(33%)	26(46%)	38(67%)	**0.001**
Heart rate (bpm)	71 ± 11	70 ± 10	69 ± 9	75 ± 14	**0.023**
Systolic Blood Pressure (mm Hg)	120 [110−135]	120 [110−130]	120 [110−140]	115 [100−130]	**0.003**
Diastolic Blood Pressure (mm Hg)	70 [60−80]	70 [60−80]	70 [60−80]	70 [60−77]	0.236
QRS width (ms)	160 [150−180]	160 [150−180]	160 [150−175]	160 [152−190]	0.462
Left bundle branch block	136(79%)	51(88%)	44(77%)	41(72%)	0.099
Implantable cardioverter defibrillator	142(83%)	53(91%)	57(82%)	42(74%)	**0.044**
Mineralocorticoid receptors antagonists	49(28%)	17(29%)	14(25%)	18(32%)	0.698
Use of diuretics	135(78%)	44(76%)	38(67%)	53(93%)	**0.002**
Beta blockers	152(88%)	55(95%)	50(87%)	47(82%)	0.115
Angiotensin-converting enzyme inhibitors/Angiotensin receptor blocker	153(89%)	53(91%)	50(88%)	50(88%)	0.769
Creatinine (mg/dL)	11 [9−14]	10 [9−14]	10 [8−13]	13 [11−19]	**<0.001**
BNP (pg/mL)	384 [144−879]	207 [91−410]	316 [128−778]	760 [416−1556]	**<0.001**
Left ventricular ejection fraction (%)	26 ± 5	29 ± 5	28 ± 4	24 ± 5	**< 0.001**
Left ventricular end-diastolic diameter (mm)	67 ± 8	66 ± 9	66 ± 8	68 ± 8	0.296
Left ventricular end-systolic diameter (mm)	57 ± 10	56 ± 11	56 ± 9	59 ± 8	0.153
Left ventricular end-diastolic volume (mL)	243 [201−296]	231 [189−289]	222 [197−284]	269 [212−301]	**0.037**
Left ventricular end-systolic volume (mm)	175 [143−222]	171 [136−210]	164 [142−201]	193 [163−245]	**0.011**
Left atrial volume index (mL/m^2)	37 ± 13	32 ± 11	36 ± 12	44 ± 11	**< 0.001**
E/e' ratio	12 [10−17]	11 [9−17]	12 [9−15]	15 [10−19]	**0.040**
E/A ratio	1.0 [0.6−1.8]	0.7 [0.6−1.1]	0.9 [0.6−1.3]	1.7 [0.8−2.3]	**< 0.001**
Myocardial scar	25(14%)	8(14%)	8(14%)	9(16%)	0.947
Mitral regurgitation Effective regurgitant orifice area > 10 mm^2	36(21%)	7(12%)	6(10%)	23(40%)	**< 0.001**
RAVI (mL/m^2)	27 ± 14	15 ± 3	23 ± 3	42 ± 13	**By design**
Tricuspid annular plane systolic excursion (mm)	20 ± 5	21 ± 4	22 ± 5	18 ± 5	**0.001**
Doppler-derived tricuspid annular systolic velocity (cm/s)	10 ± 3	10 ± 3	10 ± 3	9 ± 3	**0.015**
Systolic pulmonary arterial pressure (mm Hg)	34 [24−45]	28 [23−36]	28 [23−38]	43 [34−51]	**< 0.001**
Tricuspid regurgitation $\geq$ moderate to severe	14(8%)	2(3%)	2(3%)	10(17%)	**0.013**

method. Event rates +/− SEs of the overall population and of the three groups were estimated according to the Kaplan−Meier method and compared using log-rank tests. Univariate and multivariate analyses of time to events were performed using Cox proportional-hazards models. We did not use model building techniques; covariates were entered in the models which were considered of potential prognostic impact on an epidemiologic basis. These covariates were age, coronary artery disease, left ventricular ejection fraction (LVEF), QRS width, left bundle branch block, functional class NYHA III/IV, creatinine serum and TAPSE or S'. Because of skewness, BNP data were log-transformed when added to multivariable models. In case of missing values (<10% of the data used in this study), the multivariate imputation by chained equations algorithm in R was used. All p values are the results of two-tailed tests. For all analyses, a p value of <0.05 was considered statically significant. Data were analyzed with SPSS version 20.0 (IBM, Amonk, New York) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

One hundred and seventy-two patients were enrolled in the present study. Patient's characteristics, overall and according to RAVI tertiles are detailed in **Table 1**. Mean RAVI was 27 ± 14 mL/m^2 (median, 23 mL/m^2; IQR, 17 to 33 mL/m^2). Intra- and interobserver variability were good for RAVI (intraclass correlation coefficient: 0.98 [95% CI, 0.95 to 0.99], and 0.95 [95% CI, 0.87 to 0.98], respectively). Patients in the highest tertile of RAVI were older, more symptomatic according to functional class NYHA, had a higher heart rate and lower systolic blood pressure, were more treated by diuretics, had lower implantable cardioverter-defibrillator rates, and had higher creatinine and BNP serum levels. Patients in the highest tertile had a lower EF and a more depressed RV systolic function, higher LV and LA volumes, LV filling pressures and pulmonary pressure (**Table 1**). RAVI modestly correlated with BNP at inclusion (r = 0.43; p < 0.001).

Median follow up was 68-months (interquartile range 62 to 73 months). As depicted in **Figure 1**, cumulative all-cause mortality at 1 year, 3 years, and 5 years was respectively 5 ± 3%, 17 ± 5%, 22 ± 6% for the first tertile (RAVI ≤19 mL/m^2), 0%, 14 ± 5%, and 24 ± 6% for the second tertile (RAVI 19 to 29 mL/m^2) and 19 ± 5%, 40 ± 6%, and 58 ± 7% for the third tertile (RAVI >29 mL/m^2) (p for trend <0.001). All-cause mortality was higher in patients with RAVI >29 mL/m^2, compared with patients with either RAVI ≤19 mL/m^2 (p < 0.001) or RAVI 19 to 29 mL/m^2 (p < 0.001). Survival free from all-cause mortality was similar between patients with RAVI ≤19 mL/m^2 compared with those with RAVI 19 to 29 mL/m^2 (p = 0.815). Consequently, survival from overall mortality was still significantly reduced in patients with RAVI > 29 mL/m^2 compared with those with RAVI ≤29 mL/m^2 (p < 0.001) (**Figure 2**)

On multivariable analysis, there was a significant increase in mortality risk with increasing RAVI (adjusted hazard ratio [HR] 1.02 [95% confidence interval (CI), 1.00 to 1.03], per 1 mL/m^2 increment; p = 0.042) (**Table 2**). Patients with RAVI >29 mL/m^2 had significantly greater

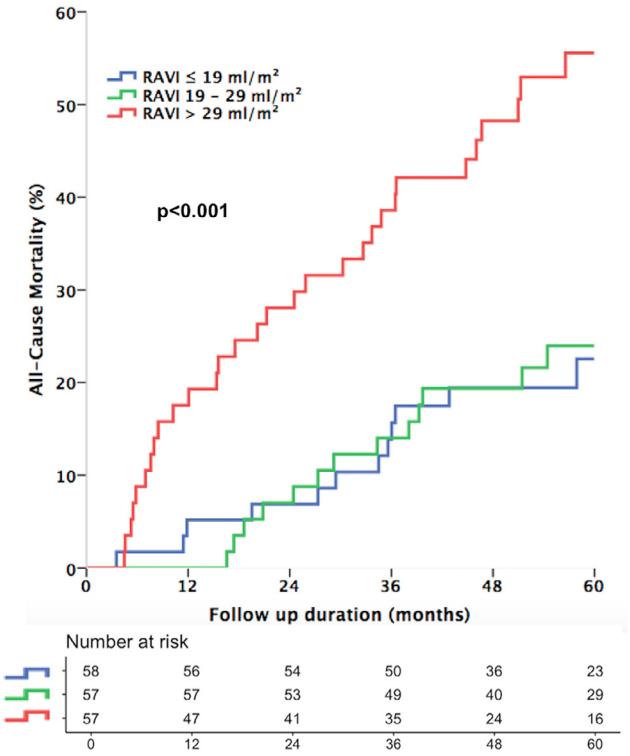

Figure 1. Kaplan−Meier event-free survival for overall mortality according to right atrial volume index (RAVI) tertiles.

risk of death compared with those with RAVI ≤29 mL/m^2 (adjusted HR 2.01 [95% CI, 1.15 to 3.50]; p = 0.014). (**Figure 2**). After further adjustment on systolic pulmonary pressure, significant tricuspid and mitral regurgitation, left atrial volume index and logBNP, the association between RAVI >29 mL/m^2 and mortality remained unchanged (adjusted HR 2.64 [95% CI, 1.25 to 5.56]; p = 0.010). Adding RAVI >29 mL/m^2 to this fully adjusted multivariate model without RAVI >29 mL/m^2 improved the performance of the Cox multivariate model with an increase in the Harrell C statistic from 0.776 to 0.782. Replacing TAPSE by S' in this multivariate model did not alter the strength of the relation between RAVI >29 mL/m^2 and mortality (adjusted HR 2.92 [95% CI, 1.41 to 6.05]; p = 0.004).

As shown in **Figure 2**, RAVI (>29 mL/m^2 or ≤29 mL/m^2) was also associated with CV mortality. After adjustment, RAVI >29 mL/m^2 remained significantly associated with a significant increase in cardiovascular mortality risk (adjusted HR 3.98 [95% CI, 1.72 to 9.21]) (**Table 2**; **Figure 2**).

Discussion

To the best of our knowledge, we demonstrate here for the first time that in HFrEF patients without atrial fibrillation receiving CRT, RAVI is a strong independent predictor of death. The effect of RA dilatation on outcome was powerful and remained valid after adjustment for factors known as major determinants of prognosis.

Right ventricular systolic dysfunction is associated with poor long-term prognosis in patients with HF.[11,12] Baseline

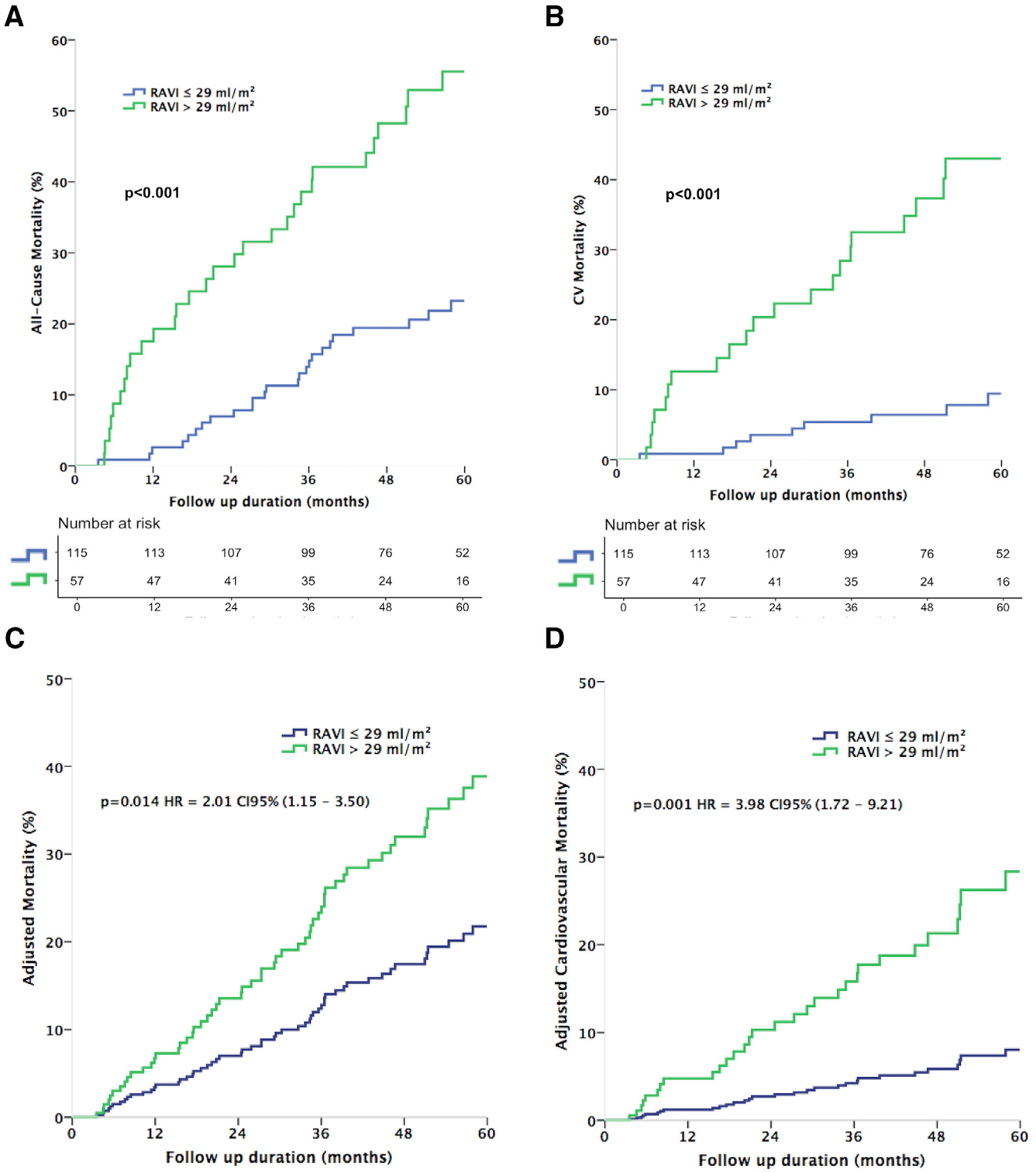

Figure 2. Kaplan–Meier event-free survival for overall and cardiovascular mortality according to right atrial volume index RAVI ≤ 29 mL/m^2 and RAVI > 29 mL/m^2 *(A and B)*. Cumulative hazard of overall *(C)* and cardiovascular *(D)* mortality according to right atrial volume index RAVI ≤ 29 mL/m^2 and RAVI > 29 mL/m^2

RV dysfunction has also been demonstrated to be associated with a poor prognosis among HFrEF patients who underwent CRT.[3,13] Indeed, multiple mechanisms may negatively impact on RV contractility, including increasing afterload, ventricular interdependence, or neurohormonal activation.[14] These features are usually found in advanced stages on the underlying disease. Therefore, assessment of RV function should be part of every echocardiographic examination at the time of first diagnosis of HF and during serial follow up. However, although there have been

Table 2
Relationship between right atrial volume index RAVI > 29 mL/m^2 and all-cause mortality, cardiovascular mortality by Cox analysis.

		All-cause mortality		Cardiovascular mortality	
Univariate analysis		HR (CI 95%)	p	HR (CI 95%)	p
	RAVI (per 1 mL/m^2 increment)	1.04 (1.02−1.05)	<0.001	1.05 (1.03−1.07)	<0.001
	RAVI > 29 mL/m^2	3.61 (2.20−5.94)	<0.001	7.68 (3.57−16.53)	< 0.001
Multivariate analysis		Adjusted HR (CI 95%)	p	Adjusted HR (CI 95%)	p
	RAVI > 29 mL/m^2	2.01 (1.15−3.50)	0.014	3.98 (1.72−9.21)	0.001
	Age	1.05 (1.02−1.08)	0.001	1.04 (1.00−1.08)	0.035
	QRS width	0.99 (0.98−1.00)	0.151	0.99 (0.98−1.01)	0.241
	NYHA functional class III/IV	1.91 (1.09−3.36)	0.023	141 (0.80−3.68)	0.158
	Coronary artery disease	1.38 (0.84−2.28)	0.203	1.35 (0.68−2.68)	0.848
	Creatinine serum	1.05 (1.02−1.08)	0.003	1.05 (1.01−1.10)	0.017
	LV ejection fraction	0.96 (0.91−1.02)	0.181	0.94 (0.87−1.02)	0.144
	Left bundle branch block	0.92 (0.50−1.69)	0.798	1.60 (0.64−3.94)	0.311
	Tricuspid annular plane systolic excursion	0.92 (0.50−1.69)	0.120	0.93 (0.86−1.00)	0.063

significant improvements in RV imaging, at the era of multimodality imaging, precise assessment of RV systolic function is still challenging.[15,16,17] Therefore, it is important to acknowledge that our study used RAVI as an "easy-to-measure" highly reproducible surrogate of RV function, since reproducible quantifiable RV assessment can be limited. In our population study, RA mean values were slightly lesser than in previous studies that utilized a monoplane Simpson's rule, probably because of exclusion of patients with atrial fibrillation, as atrial enlargement can occur as a consequence of atrial fibrillation.

A strong relation between RA volume and RV systolic dysfunction has been previously demonstrated.[7] Increased RAVI may predict low functional capacity, especially in the subgroup of patients with RV systolic dysfunction.[18] RV impairment secondary to LV failure is usually a consequence of pressure overload, which is translated to RV pressure and tricuspid regurgitation, and evolves to RV and atrial dilatation. Then, impaired RV contractility may cause compensatory elevated RA volume for increasing blood volume reservoir.[19] However, the pathophysiology of elevated RA volume in HFrEF is not fully understood, and it is unclear if RA volume has a direct effect on impaired hemodynamics, more than just being a surrogate of severity in chronic HF. Few studies have investigated the prognostic impact of RA enlargement in HFrEF.[7] In our population study, patients with elevated RA volume shared as expected clinical, biologic and echocardiographic features of a more advanced stage of HF. Interestingly, in our population study, increased RA volume was not exclusively associated with RV systolic dysfunction but also with LA dilation, significant mitral regurgitation and tricuspid regurgitation. This could suggest that RA dilatation may reflect a more severe global clinical presentation and/or advanced stage in patients with HFrEF, independently from RV function. Therefore, the results of the present study suggest that patients with increased RA size before CRT should be carefully monitored, to ensure timely referral for advanced therapy (heart transplantation, left ventricular assist device. . ..) before worsening of their clinical condition.

Whereas echocardiograms were prospectively collected, follow-up data were obtained retrospectively. Moreover, all patients with HFrEF from the present report received CRT; hence, the present data cannot be fully extrapolated to the broad population of patients with HF. We purposefully used mortality which is an unbiased end point in contrast to hospitalization for heart failure during follow up, which is highly influenced by salt intake and adherence to medications. The measurement of RAV on the apical 4-chamber view places the RA in the far field, diminishing lateral resolution and adversely affecting visualization of its endocardium. However, a strong correlation has been shown between estimation of RAV by this method and cardiac MRI.[20]

In conclusion, our study shows that RA enlargement is independently predictive of long-term mortality in patients with HF with reduced ejection fraction in sinus rhythm receiving cardiac resynchronization therapy. Detection of RAVI >29 mL/m^2 is associated with major increase in the risk of death during follow up.

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