Usefulness of right atrial volume index in predicting outcome in chronic systolic heart failure

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Background: Right ventricular (RV) dysfunction is associated with poor prognosis in patients with heart failure (HF). Echocardiographic assessment of RV systolic function is challenging. The ability to visualize the right atrium (RA) allows a quantitative, highly reproducible assessment of RA volume.

Objective: The aim is to study the relationship between the right atrial volume index (RAVI) and prognosis in patients with chronic systolic HF.

Methods: 120 patients with chronic systolic HF and left ventricular ejection fraction (LVEF) <40% were enrolled. The RA volume was calculated by Simpson's method using single-plane RA area and indexed to body surface area (RAVI). RV systolic assessment was done using the RV fractional area change (RVFAC), and peak systolic velocity (Sa_{tri}) using tissue Doppler imaging at the tricuspid annulus. The primary endpoint was death, urgent transplantation, or acute HF episode requiring hospital admission during a follow-up of 1 year.

Results: Follow up was complete for 117 of 120 patients. Fifty-two patients reached the primary endpoint. The mean RAVI was higher in patients with adverse events (45.5 ± 15 ml/m^2 versus 25.2 ± 11 ml/m^2, $p < 0.001$), and increased with worsening LVEF, RVFAC, Sa_{tri} (Spearman's $r = -0.46$, $r = -0.45$, $r = -0.59$, $p < 0.001$ for all). RAVI was not correlated with estimates of RV diastolic dysfunction. The cut-off threshold for RAVI to predict the primary endpoint using receiver-operating characteristic curve was 29 ml/m^2 (area under the curve was 0.89%, 95% confidence interval: 0.82–0.95) with a sensitivity of 92%, and a specificity of 75%. NYHA > 2 (OR = 2.1, $p < 0.01$), and RAVI (OR = 1.6, $p < 0.05$) were found to be independent predictors of adverse outcome.

Conclusion: In patients with chronic systolic HF, RAVI is an independent predictor of adverse outcome with a threshold value of 29 ml/m^2.

Keywords: Heart failure, Right atrium, Prognosis, Echocardiography

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Introduction

Patients with congestive heart failure (HF) still have a poor prognosis, even after recent advances in therapy [1,2]. It is, therefore, important to establish a reliable means of identifying those patients at higher risk. Right ventricular (RV) systolic dysfunction is associated with poor long-term prognosis [3,4]. However, precise echocardiographic assessment of RV systolic function is challenging, primarily because the morphology of RV is complicated.

The ability to visualize the right atrium (RA) allows a quantitative, highly reproducible assessment of the RA volume that can be indexed to the body surface area [5,6]. However, there have been no many studies correlating RA volume and prognosis in patients with chronic HF [6].

Objective

Is to determine the relationship between the right atrial volume index and prognosis in patients with chronic systolic heart failure.

Abbreviations

Aa	peak late diastolic TDI velocity
ACE	angiotensin converting enzyme
A-wave	peak late diastolic filling velocity
CABG	coronary artery bypass grafting
CI	95% confidence interval
DT	early diastolic deceleration time
Ea	peak early diastolic TDI velocity
E-wave	peak early diastolic filling velocity
HF	heart failure
IVC	inferior vena cava
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
RA	right atrium
RAVI	right atrial volume index
ROC	receiver operator characteristic
RV	right ventricular
RVFAC	right ventricular fractional area change
Sa	peak systolic TDI velocity
Sa_{tri}	peak tissue Doppler systolic velocity at the tricuspid annulus
sPAP	systolic pulmonary artery systolic pressure
TDI	tissue Doppler imaging
V_{max}	peak velocity

Methodology

Patient population

We enrolled consecutive patients with chronic heart failure evaluated at a tertiary cardiac center from 2009 to 2011. Inclusion criteria were age >18 years, symptomatic heart failure (New York Heart Association class II-IV), and left ventricular ejection fraction (LVEF) <40%. Exclusion criteria were mitral stenosis, mitral valve surgery, severe mitral regurgitation (>grade 3), severe aortic stenosis (peak velocity >4 m/s), malignancy, and severe renal failure requiring dialysis.

The study was approved by the medical ethics committee of our institution. The study protocol was designed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All patients gave informed consent before the procedure.

Echocardiographic examination

Comprehensive transthoracic echocardiography was performed using an Aloka alpha 5 echocardiography machine (Hitachi Aloka Medical, Ltd., manufactured in Tokyo, Japan) equipped with tissue Doppler imaging (TDI) technology. Two-dimensional, M-mode, Doppler echocardiography measurements and quantification were performed according to recommendations of the American Society of Echocardiography [7,8]. Right atrial volume was calculated using the Simpson's method from the apical four-chamber view at end systole [5,6]. The right atrial volume index (RAVI) was derived by dividing the volume by body surface area, which was calculated using the Du Bois and Du Bois formula [9]. Continuous Doppler echocardiography was used to measure pulmonary artery and aortic velocities, tricuspid regurgitation velocity, and mitral regurgitation velocity. Pulsed Doppler echocardiography for the assessment of the standard diastolic filling velocities of both ventricles was performed using the apical four-chamber view. Thus, the peak early diastolic filling velocity (E-wave), early diastolic deceleration time (DT), and peak late diastolic filling velocity (A-wave) were recorded. For the right ventricle 2D and TDI measurements, care was taken to obtain an ultrasound beam parallel to the tricuspid annulus motion. The RV endocardium was traced manually in systole and diastole. The RV fractional area change (RVFAC) was calculated using the formula: (end-diastolic area – end-systolic area)/end-diastolic area. Tricuspid annular TDI was acquired in the apical 4-chamber view. Peak systolic (Sa), early diastolic (Ea), and late diastolic (Aa) velocities of the tricuspid annulus were measured as recommended previously (sample TDI volume less than 5 mL and an angle between the TDI sample volume and the longitudinal myocardial wall vector less than 20°) [10]. The systolic pulmonary artery systolic pressure (sPAP) was

assessed by measuring the gradient between the right ventricle and the right atrium using the peak velocity (V_{max}) of the tricuspid regurgitation (sPAP = $4(V_{max})^2$ + right atrial pressure). The right atrial pressure was based on both the size of the inferior vena cava (IVC) and the change in diameter of this vessel during respiration [11]. Briefly, IVC diameter $\leqslant$2.1 cm that collapsed >50% with a sniff indicated normal RA pressure of 3 mmHg, whereas IVC diameter >2.1 cm that collapsed <50% with a sniff suggested high RA pressure of 15 mmHg. In scenarios in which IVC diameter and collapse did not fit this paradigm, an intermediate value of 8 mmHg was used. Pulsed-wave Doppler recording of the hepatic vein flow was done using a sample volume placed in the hepatic vein 1 cm proximal to junction of IVC and hepatic veins. Hepatic vein systolic/diastolic (S/D) ratio was calculated. Valvular regurgitation was graded according to guidelines of the American Society of Echocardiography [12]. All parameters were averaged over three heart cycles (five cycles for arrhythmia).

Clinical follow-up and endpoint definition

Clinical follow-up was for 1 year. The vital status of each patient was confirmed by a review of medical records or by telephone contact (family and/or patient). The primary endpoint was the combined risk of death or urgent heart transplantation or hospitalization for acute HF episode. Hospitalization for HF was defined as an admission for worsening HF in which intravenous therapy for HF was needed. The first event was considered for each patient.

Statistical analysis

The data were statistically analyzed using the Statistical Package for Social Sciences (SPSS) software version 17 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation and categorical variables as absolute numbers (percentages). Categorical variables were compared by Chi-square test. Continuous normally distributed variables were compared by two-tailed *t*-test. Correlations between RAVI and echocardiographic variables were tested with Spearman's *r*. The optimal cut-off for the prediction of primary event was determined by a receiver-operator characteristic (ROC) curve. ROC analysis was used to determine the sensitivity and specificity of RAVI in predicting the primary endpoint. Kaplan–Meier curves were constructed to show event-free survival according to time.

Table 1. Baseline demographic and clinical characteristics of the patients according to the incidence of primary outcome events.

Variables	Event		*P* value
	Yes (*n* = 52)	No (*n* = 65)	
Age (years)	54.5 ± 14.8	54 ± 14	NS
Body surface area (m^2)	1.81 ± 0.4	1.85 ± 0.2	NS
Systolic BP (mmHg)	120 ± 11	123 ± 12	NS
Diastolic BP (mmHg)	79 ± 4	80.3 ± 6	NS
Gender			
Male	42(80.8%)	45(69.2%)	NS
Female	10(19.2%)	20(30.8%)	
Etiology of HF			
Ischemic	24(46.2%)	26(40%)	NS
Non-ischemic	28(53.8%)	39(60%)	
NYHA class III–IV	50 (96.2%)	39(60%)	<0.001
Heart rate	87 ± 5	93 ± 20	NS
Hypertension	10(19.2%)	14(21.9%)	NS
Smoking	14(26.9%)	13(20%)	NS
Diabetes	25(48.1%)	18(27.7%)	<0.05
Previous myocardial infarction	19 (36.5%)	19(29.2%	NS
Previous of HF admission	36(69.2%)	21(32.3%)	<0.001
Previous PCI	3(5.8%)	2(3.1%)	NS
Previous CABG	3(5.8%)	5(7.7%)	NS
B-blockers	36(69.2%)	52(80%)	NS
ACE-inhibitors	48(92.3%)	65(100%)	NS
Diuretics	51(98.1%)	57(87.7%)	<0.05
Digitalis	31(59.6%)	27(41.5%)	<0.05
Spironolactone	36(69.2%)	32(49.2%)	<0.05

Data are expressed as a mean ± standard deviation or a number (percent). NS = non-significant, BP = blood pressure, HF = heart failure, NYHA = - New York heart association, PCI = percutaneous coronary intervention, CABG = coronary artery bypass surgery, ACE = angiotensin converting enzyme.

Table 2. Echocardiographic parameters of the patients according to the incidence of primary outcome events.

Variables	Event		*P* value
	Yes (n = 52)	No (n = 65)	
Left atrial diameter (mm)	48 ± 7	43.4 ± 3.9	0.0001
LV parameters			
LV end-diastolic dimension index (mm/m^2)	36.7 ± 5	35.8 ± 5	NS
LV end-systolic dimension index (mm/m^2)	32 ± 5	30.2 ± 5	NS
LV ejection fraction (%)	24.5 ± 5.4	31.4 ± 4.9	0.0001
Mitral early/late flow velocity	3.5 ± 1.4	2.5 ± 1.7	0.001
Mitral deceleration time (ms)	130 ± 27	143.5 ± 39	0.04
Mitral TD systolic velocity (cm/s)	4.5 ± 1.4	5.2 ± 1.4	0.007
Mitral TD early diastolic velocity (cm/s)	7.1 ± 2.5	7.6 ± 3.3	NS
Mitral TD late diastolic velocity (cm/s)	3.4 ± 1.2	4.8 ± 2.2	0.001
Right atrial volume index (ml/ m^2)	45.5 ± 15.7	25.2 ± 11.6	0.0001
RV parameters			
RV end-diastolic area (cm^2)	20.3 ± 6	15.9 ± 5	0.001
RV end-systolic area (cm^2)	14.5 ± 5	9.9 ± 4	0.001
RV fractional area change (%)	30.1 ± 11	43.7 ± 6	0.025
Tricuspid early/late flow velocity	1.2 ± 0.6	0.90 ± 0.4	0.03
Tricuspid TD systolic velocity (cm/s)	10.3 ± 1.7	12.9 ± 1.7	<0.001
Tricuspid TD early diastolic velocity (cm/s)	10.5 ± 5	10.7 ± 3	NS
Tricuspid TD late diastolic velocity (cm/s)	9.9 ± 4	12.6 ± 5	<0.05
Pulmonary artery systolic pressure (mmHg)	51 ± 13	39 ± 10.5	0.001
Hepatic vein systolic/diastolic ratio	1.1 ± 0.5	1.4 ± 0.7	0.086

NS = non-significant, LV = left ventricle. TD = tissue Doppler. Data are expressed as a mean ± standard deviation or a number (percent).

Table 3. Relation of all predictors to the event by logistic regression analysis.

Variables	Beta coefficient	Odd's (95% CI)	*P* value
NYHA class > 2	0.98	2.1(0.9–8.5)	<0.001
RAVI $\geqslant$ 29 ml/m^2	0.37	1.6(0.4–7)	<0.05
Sa_{tri} < 10 cm/s	0.30	1.5(0.2–6.95)	<0.05

CI: confidence interval, NYHA:New York heart association, RAVI: right atrial volume index, Sa_{tri} = Tricuspid TD systolic velocity.

Logistic regression backward likelihood ratio technique was used to find out the significant independent predictors of the primary endpoint. A p value $\leqslant$ 0.05 (2-tailed) was considered significant and a p value $\leqslant$ 0.01 was considered highly significant. Reproducibility of RAVI (intra-observer variability) was assessed by coefficient of variation for repeated measures in a random sample of 30 patients and was 6%.

Results

The study included 120 patients with chronic systolic HF and left ventricular ejection fraction (LVEF) <40%. Follow up was complete for 117 of 120 patients. Fifty-two (44.4%) of 117 patients reached the primary endpoint (7 deaths, and 45 hospital admission for HF). The baseline demographic and clinical characteristics of the studied patients are detailed in Table 1. Patients with the primary outcome events had higher incidence of advanced NYHA class, diabetes, and past heart failure admission. They also used more diuretics, spironolactone, and digitalis.

Echocardiographic variables in patients with and without an event are listed in Table 2. For left sided parameters, the group with outcome events showed lower LVEF, mitral DT, mitral Sa, and mitral Aa, together with higher LA diameter, and mitral E/A ratio. For right-sided parameters, the group with primary endpoint events showed higher RAVI, higher RV area, higher sPAP, lower RVFAC, lower tricuspid Sa, and lower tricuspid Aa.

In multivariate analysis, RAVI remained an independent predictor of adverse outcomes using logistic regression analysis (odd's ratio of 1.6, 95% confidence interval: 0.4–7, p value <0.05, Table 3).

The overall mean RAVI in the study population was 34.0 ± 16.7 ml/m^2. The mean RAVI was higher in men than in women (35.8 ± 17.5 vs. 28.9 ± 13.1,

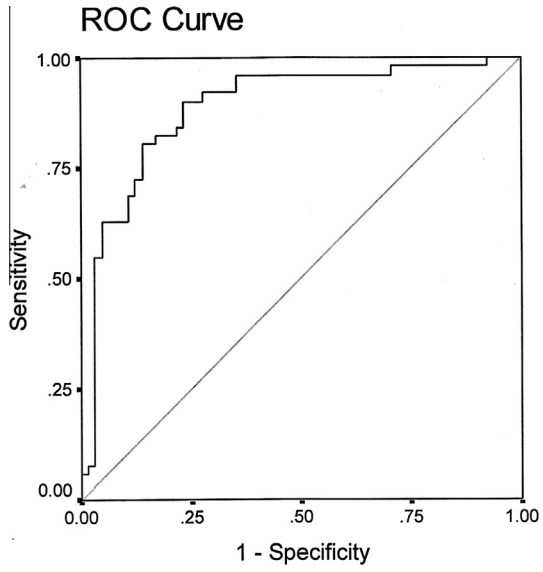

Figure 1. The cut-off value for RAVI using ROC curve was 29 ml/m^2, AUC (95% CI) = 0.89 (0.82–0.95).

$p = 0.048$). The mean RAVI was higher in patients with an event than in those without an event (45.5 ± 15.7 vs. 25.2 ± 11.6, p = 0.0001). The mean RAVI increased with worsening Sa_{tri}, NYHA class, LVEF, RVFAC (Spearman's $r = -0.59$, $r = -0.55$, $r = -0.46$, $r = -0.45$, $p < 0.001$ for all). RAVI was not correlated with estimates of RV diastolic dysfunction (tricuspid flow E/A ratio, or hepatic vein S/D ratio).

The cut-off threshold for RAVI to predict the primary endpoint using receiver-operating characteristic curve was 29 ml/m^2 (area under the curve was 0.89, 95% confidence interval: 0.82–0.95) with a sensitivity of 92%, and a specificity of 75% (Fig. 1). Kaplan–Meier event-free survival curves for RAVI $\geqslant$ 29 ml/m^2 (optimal cut-off value determined using receiver-operating characteristic analysis) are shown in Fig. 2. In the subgroup with RAVI $\geqslant$ 29 ml/m^2, 46 out of 64 patients had an event (71.9%). In the subgroup with RAVI < 29 ml/m^2, only 6 out of 53 patients had an event (11.3%).

Discussion

The present study shows that RAVI is an independent predictor of outcome (death, urgent heart transplantation, or hospitalization for acute HF episode) in patients with chronic systolic HF with reduced LVEF, when other important clinical and echocardiographic markers such as NYHA, LVEF, and Sa_{tri} are considered. This finding is important as it might help to identify the HF patient with poor prognosis.

Right atrial volume index and prognosis in heart failure

Right ventricular (RV) systolic dysfunction is associated with poor long-term prognosis in patients with HF [3,4]. Pulmonary artery pressure and thermodilution-derived RV ejection fraction were found to be independent predictors of adverse outcome on Cox multivariate survival analysis [3]. However, precise echocardiographic assessment of RV systolic function is challenging, primarily because the morphology of RV is complicated. The ability to visualize the RA allows a quantitative, highly reproducible assessment of the RAVI [5,6]. In the present study, RAVI remained an independent predictor of outcome even when RV echocardiographic markers such as RVFAC, Sa_{tri}, tricuspid E/A ratio, and hepatic vein S/D ratio are considered.

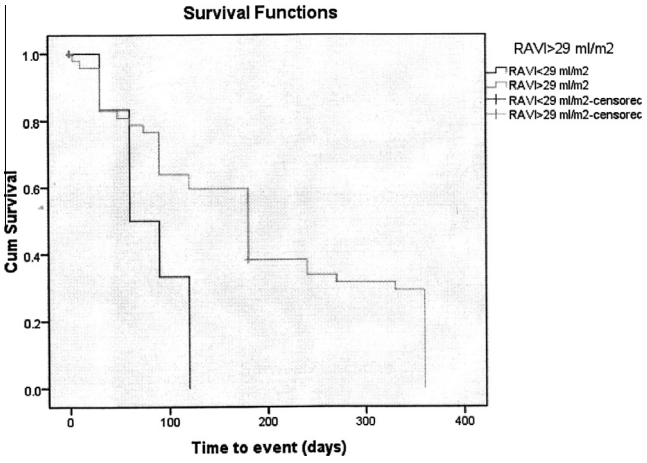

Figure 2. Kaplan–Meier curves for RAVI $\geqslant$ 29 ml/m^2 and event-free survival. Log Rrank (Mantel–Cox) between both lines is 0.009.

Sallach et al. showed that RAVI is an independent predictor of cardiovascular events in patients with chronic stable heart failure [6]. RAVI remained an independent predictor of poor outcomes after adjusting for age, brain naturetic peptide, LVEF, RV systolic dysfunction stage, and tricuspid E/Ea ratio ($p = 0.005$) [6]. In ROC analysis, RAVI $\geqslant 30.6$ ml/m^2 (optimal ROC cutoff) had a 78% sensitivity and a 77% specificity ($p < 0.0001$) for predicting RV systolic dysfunction stage $\geqslant 3$; and RAVI $\geqslant 41.6$ ml/m^2 (optimal ROC cutoff) had a 68% sensitivity and a 92% specificity ($p < 0.0004$) for predicting NYHA functional class $\geqslant 3$ [6]. D'Andrea et al. demonstrated that a right atrial area >16 cm^2 had 87.1% sensitivity and 95.4% specificity in predicting a negative response to cardiac resynchronization therapy in patients with dilated cardiomyopathy [13].

Right atrial volume index and right ventricular functions

The present study showed a good correlation between RAVI and worsening systolic right ventricular parameters (Sa_{tri}, and RVFAC). Similar findings were reported in previous studies [6,14]. RAVI showed good correlation with RV systolic dysfunction stage, and tricuspid annular Sa (Spearman's $r = 0.61$, and -0.34, respectively, $p = 0.0001$ for both) [6]. Another report demonstrated that RAVI showed good correlation with RV end-systolic diameter ($r = -0.484$, $p = 0.002$), and tricuspid annular plane systolic excursion ($r = -0.47$, $p = 0.001$) [14].

In the present study, RAVI was not correlated with estimates of RV diastolic dysfunction (tricuspid flow E/A ratio, or hepatic vein S/D ratio). This finding was consistent with findings of Sallach et al. [6]. They demonstrated that RAVI showed only a modest correlation with tricuspid flow E/A ratio, or hepatic vein S/D ratio, and no correlation with the tricuspid E/Ea ratio [6]. This suggests that RAVI may be reflective of the chronicity of RV diastolic function over time (similar to left atrial volume index) rather than a measure of instantaneous diastolic function [6]. This is also emphasizes the complexity of measuring right-sided diastolic function and the poor correlation of right atrial volume to RV filling pressure due to the additional effect of RA stiffness [15].

RV impairment secondary to LV failure usually initiates due to pressure overload, which is translated to tricuspid regurgitation, and evolves to right ventricular and right atrial dilatation [16]. Right atrial dilatation is usually observed at an advanced stage of pressure and volume overload. Thus, it may reflect a more severe clinical presentation in patients with heart failure and reduced LVEF.

Limitations of the study

The population studied was relatively small, but despite the sample size, there was a high event rate (44%). Therefore, we were able to reach several significant conclusions. The RA volumes were calculated using Simpson's method from only one view (the apical 4-chamber). This view places the right atrium in the far field; therefore, diminishing lateral resolution and adversely affecting visualization of right atrial endocardium. Finally the present study did not include biological markers for adverse outcome in heart failure such as brain naturetic peptide, but this would have increased the cost of the present study.

Conclusion and recommendations

In patients with chronic systolic heart failure and reduced LV ejection fraction, RAVI is an independent predictor of adverse outcome with a threshold value of 29 ml/m^2.

In view of the small sample size included in this report, larger clinical studies are needed to confirm these observations.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jsha.2013.09.002.

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