Right Ventricular Function as a Predictor for Outcome in Heart Failure Patients

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Abstract

Background: Right ventricle (RV) function has been an important independent predictor of morbidity and mortality in patients with congenital heart disease, heart failure (HF), pulmonary hypertension, and coronary artery disease. The objective of this study was the early prediction of RV dysfunction as a predictor for outcome in HF patients according to ejection fraction (EF).

Methods: This prospective study involved 100 patients diagnosed with HF, both sexes. Patients were divided into two groups major adverse cardiovascular event (MACE) group (n=30) and No MACE group (n=70).

Results: There was a significant difference between patients who had MACE and patients who had not regarded SBP and NT-proBNP. There was a significant difference between patients who had MACE and patients who had not regarded LVEF, ePASP, RV FAC, right ventricular free wall longitudinal strain (RVFWLS), RVGLS, and NYHA classification. RV FAC yielded significant at cut off point of 32 with sensitivity of 83.6% and specificity of 82.8%. RV GLS yielded significantly at cut off point of -15.2 with sensitivity of 98.2% and specificity of 85.7%.

Conclusions: RV dysfunction is an independent determinant of outcomes in patients with HF, and it demonstrates that RV free wall strain is a stronger and more precise predictor of outcome than RV global strain in the presence of LV systolic dysfunction.

Keywords: Right Ventricle, Outcome, Heart Failure, Major Adverse Cardiovascular Event

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Introduction:

Heart failure (HF)is a clinical syndrome with symptoms and or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and or objective evidence of pulmonary or systemic congestion [1].

The American Heart Association and American College ofCardiology have defined four stages of HF to help people understand how the condition changes over time and the kinds of treatments that are used for each [2].

The right ventricle (RV)[3] has long been considered a dispensable cardiac chamber that does not contribute significantly to overall cardiac function. Yet studies published in the last several decades have revealed that RV function has been an important independent predictor of morbidity and mortality in patients with congenital heart disease, HF, pulmonary hypertension, and coronary artery disease, and the most recent investigations showed an undoubted correlation between RV hypertrophy and the risk of HF or death in a multiethnic population free of cardiovascular disease [4].

In clinical settings, 2-dimensional echocardiography (2DE) has been used for RV evaluation; however, cardiac magnetic resonance (CMR) has still been considered the gold standard for RV imaging. The introduction of new imaging techniques, especially echocardiographic tools such as tissue Doppler–derived strain, speckle tracking, and 3-dimensional echocardiography (3DE), could provide an accurate assessment of RV function, mechanics, and structure, comparable with CMR results [5].

Cardiac computed tomography (CT) provides precise and reproducible RV volume parameters compared with CMR, as well as comparing with 3DE, and can be considered a reliable alternative in the situation where 3DE is unavailable or the patient is not a suitable candidate for CMR [6].

The evaluation of RV diastolic function in clinical settings usually implies assessment of the RV inflow by pulsed wave Doppler and evaluation of inferior vena cava and hepatic veins. In the current guidelines, emphasized that the presence of RV diastolic dysfunction was associated with worse functional class and was an independent predictor of mortality in patients with chronic HF and pulmonary hypertension [7].

During acute RV pressure overload, RV diastolic function is not affected, whereas chronic RV pressure overload impacts RV diastolic dysfunction, resulting in prolonged diastolic relaxation time and increased RV diastolic stiffness. However, the latest study showed that during acute pressure overload, restoring forces initially decreased, but recovered at advanced stages. This biphasic response is associated with alterations of septal curvature provoked by variations in the diastolic LV-RV pressure balance [8].

The aim of this work wasthe early prediction of RV dysfunction as a predictor for outcome in HF patients.

Methods:

This prospective study involved 100 patients diagnosed with HFaccording to [Symptoms with or without signs of HF, elevated natriuretic peptides (NT-proBNP ≥125 pg/mL) and relevant structural heart disease: (LV hypertrophy (LV mass index ≥115 g/m2 in males and ≥95 g/m2 in females), left atrial enlargement (>34 mL/m2) or diastolic dysfunction (E/e′ ≥13 and a mean e′ septal and lateral wall <9 cm/s))], both sexes.

The research was conducted from June 2022 to June 2023, following approval by Zagazig University Institutional Review board (ZU-IRB#6776-24-2-2021) which confirmed that all methods were performed in accordance with the relevant guidelines and informed written consent was obtained from all patients.

Exclusion criteria were subjects who have any medical condition that affects RV as (Hypertension, diabetes mellitus, congenital heart disease, rheumatic heart disease, valvular heart disease, hypertrophic cardiomyopathy, congestive HF, kidney and liver disease).Subjects on drugs known to affect RV function as (Amphetamine derivatives, cathinone and phenylephrine).

A thorough medical historyincluding (age, sex, and risk factors for coronary artery disease (CAD) as hypertension, diabetes mellitus, and smoking, dyslipidemia, family history of premature coronary artery disease CAD), general, local examination and laboratory investigations (Complete blood count (CBC), hemoglobin (g/dl), TLC (x103/L), PLT (x103/L), kidney function test (serum creatinine and urea) and NT-proBNP).

Blood samples of the patients were obtained in the morning between 8:00am and 10:00am after a fasting period of at least 8 hours. The blood samples of all patients obtained for complete blood count, CBC, random blood glucose sugar, kidney function test (serum creatinine and urea), NT-proBNP were studied.

Hypertension is defined as values ≥140 mmHg SBP and/or ≥90 mmHg DBP according to ESH/ESC Guidelines for the management of arterial hypertension (2018) [9] .

Diabetes mellitus was diagnosed on basis listed by American Diabetes Association (2010) as: Fasting blood sugar ≥ 126 mg/dl or 2 hours postprandial blood sugar ≥ 200mg/dl or HBA1C ≥ 6.5 or Symptoms of diabetes plus casual plasma glucose concentration ≥ 200 mg/dl. Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss[10]. Smoking was defined as active smoking in the last 6 months [11].

Dyslipidemia was considered according to recommendations of Third Report of the National Cholesterol Education Program (NCEP), when any of the following was present: serum cholesterol ≥ 200 mg/dl, LDL ≥ 100 mg/dl, HDL < 40mg/dl for high-risk patients [12].

Family history of premature CAD, defined by the presence of at least a first degree relative with a cardiovascular event or premature SCD at a young age (< 65 years for women and < 55 years for men) [13].

General and local examination:

Blood pressure:

According to the JNC-8 recommendations, in the office, blood pressure was measured at least twice after 5 minutes of rest, with the patient seated in a chair, the back supported, and the arm bare at heart level. A large adult-size cuff was used to measure blood pressure in overweight adults, in whom use of a standard-size cuff can spuriously elevate readings. Tobacco and caffeine were avoided for at least 30 minutes.

Blood pressure was measured in both arms and after 5 minutes of standing, the latter to exclude a significant postural fall in blood pressure, particularly in older persons and in those with diabetes or other conditions that predispose to autonomic insufficiency.

Resting blood pressure was measured using a standard mercury sphygmomanometer on the right arm in a sitting position following a minimum of five minutes rest. Phases I and V Korotkoff sounds were used to determine systolic and diastolic BP measurements. The mean of the last two measurements was used in the analysis.

Body mass index (BMI):

BMI, defined as the body weight divided by the square of the body height in meters, and is universally expressed in units of kg/m^2, resulting from mass in kilograms and height in meters[14].

BMI classification:

Less than 18.5 was underweight, 18.5–24.9 was healthy weight range, 25–29.9 was overweight, 30 and over were obese.

Abdominal and chest examination:

Cardiac examination: including inspection, palpation, and auscultation.

Twelve-lead surface Electrocardiography:

All subjects had a resting simultaneous 12-lead electrocardiogram (ECG). At a paper speed of 25 mm/s with the machine control set at standard response, a standard lead II rhythm strip of 13–16 complexes and a minimum of three cardiac cycles per lead were recorded.

RVH criteria on ECG:

General ECG features include:

Right axis deviation (> 90 degrees), tall R-waves in RV leads; deep S-waves in LV leads, slight increase in QRS duration, ST-T changes directed opposite to QRS direction (i.e., wide QRS/T angle), may see incomplete RBBB pattern or qR pattern in V1 and evidence of right atrial enlargement.

Specific ECG features (assumes normal calibration of 1 mV = 10 mm):

Any one or more of the following (if QRS duration < 0.12 sec):

Right axis deviation (> 90 degrees) in presence of disease capable of causing RVH.R in aVR ≥ 5 mm.R in aVR > Q in aVR.

Any one of the following in lead V1:

R/S ratio > 1 and negative T wave.qR pattern.R gt; 6 mm, or S < 2mm, or rSR' with R' > 10 mm.

Other chest lead criteria:

R in V1 + S in V5 (or V6) 10 mm.R/S ratio in V5 or V6 < 1.R in V5 or V6 < 5 mm.S in V5 or V6 > 7 mm.

ST segment depression and T wave inversion in right precordial leads is usually seen in severe RVH such as in pulmonary stenosis and pulmonary hypertension [15] .

Conventional Trans-thoracic Echo-doppler study:

Trans-thoracic echocardiographic examination was done to all patients using HP SONOS (USA) and GE Vivid E9 (Norway) set with a 2.5 MHz transducerand SPECKLE TRACKING echocardiography was done by (Phillips, EPIC 7C; USA) with "S5-1" matrix array transducersequipped with STE technology and using a multi-frequency (1-5 MHz) for all cases. Images were taken while the patient in supine or in the left lateral position.

Right ventricular size:

Compare the RV and the left ventricle. This can also be done by visual assessment. The left ventricle is usually at least thirty percent larger than the right one.

In severe forms of RV dilatation, the apex of the heart is formed by the RV instead of the left one.

The size of the RV can be determined either with 2-D measurements, area or volume calculations. M-Mode measurements were used at the beginning of echocardiography (parasternal axis). However, as these measurements are very inexact and strongly depend on how the Mode "cuts" through the RV, they are no longer used. It is far better to measure distances in 2-D. This is best done on an optimized 4-chamber view or a subcostal view at end-diastole. Roughly, the ventricle appears triangular on these views. Thus, the diameter varies, depending on the level at which the measurements are performed.

Where to measure the dimensions of the RV in a four-chamber view Two sites are commonly used: the basal distance (at the tricuspid annulus) and the mid-right-ventricular measurement (in the middle segment of the RV).

Roughly, a mid-right-ventricular diameter of 35 to 40 mm or 42 to 45 mm at the base indicates right ventricular dilatation. Respiration influences the size of the RV. During inspiration it is slightly larger. It is important to take the patient's body surface area into account.

An apical transducer position that is too high lead to overestimation of RV size. It is also possible to measure the width of the RVOT on a parasternal short axis view at the base. Here the upper limit of normal is 33 mm for the proximal aspect and 27 mm for the distal aspect at the level of the pulmonary valve.

NYHA classification:

New York Heart Association (NYHA) functional class helps to classify congestive HF patients based on their symptoms.

Class I: No symptoms of HF.Class II: Symptoms of HF with moderate exertion, such asambulating two blocks or two flights of stairs.Class III: Symptoms of HF with minimal exertion, such asambulating one block or one flight of stairs, but no symptoms at rest.Class IV: Symptoms of HF at rest.

Statistical analysis:

All statistical analysis were performed using SPSS version 26 and Medcalc software as follow:Continuous data were represented as mean and standard deviation.Categorical data were represented as event and percentage. One way ANOVA was used for comparing the means of more than two groups.Chi-square test was used for comparing between categorical variables.Pearson correlation was used for assessing association between two continuous variables.Phi correlation was used for assessing association between two categorical variables.Point biserial correlation was used for assessing association between dichotomous and continuous variables.Binary logistic regression adjusted for baseline characters (glycemic status, age, sex) were used.Areas under ROC curves and their standard errors were determined using the method of Cantor, and compared using the normal distribution, with correction for correlation of observations derived from the same cases. Value of area under a ROC curve [16] indicates: 0.90 – 1 = excellent, 0.80-0.90 = good, 0.70-0.80 = fair; 0.60-0.70 = poor; and 0.50-0.6 = fail. The optimal cutoff point was established at the point of maximum accuracy.Significant when the probability of error is less than 5% ($p < 0.05$).Non-significant when the probability of error is more than 5% ($p > 0.05$).Highly significant when the probability of error is less than 0.1% ($p<0.001$).

Results:

30% of the patients among HF patients had Major adverse cardiovascular events(MACE). Moreover, the mortality rate was 10%. Table 1

Table 1: Outcome distribution among the studied patients

		Studied patients (n=100)
MACE	**Yes**	30 (30%)
	No	70 (70%)
Mortality	**Yes**	10 (10%)
	No	90 (90%)

Data are presented as number (%).MACE: Major adverse cardiovascular event.

There was a significant difference between patients who had MACE and patients who had not regarded SBP and NT-proBNP. Table 2

Table 2: Baseline data among the studied patients according to MACE occurrence

Variables		**MACE (n=30)**	**No MACE (n=70)**	**t / χ^2**	**P**
Age (years)		56.43 ± 12.77	54.81 ± 11.42	.627	.532
Sex	**Male**	14 (46.7%)	32 (45.7%)	.008	.930
	Female	16 (53.3%)	38 (54.3%)		
BMI (kg/m^2)		27.43 ± 3.83	27.83 ± 3.01	.557	.579
HR (beat/min)		93.1 ± 12.27	88.71 ± 11.67	1.68	.095
SBP (mmHg)		120.5 ± 6.87	116.57 ± 8.62	**2.21**	**.029**
DBP (mmHg)		75.5 ± 5.31	74.79 ± 4.62	.677	.500
Hemoglobin (g/dl)		12.47 ± 1.1	12.53 ± 1.23	.254	.800
TLC (x10^3/L)		8.45 ± 2.56	8.13 ± 2.39	.613	.541
PLT (x10^3/L)		211.03 ± 27.88	212.71 ± 22.68	.317	.752
RBS (mg/dl)		132.5 ± 16.88	130.33 ± 17.1	.584	.560
Creatinine (mg/dl)		0.918 ± 0.157	0.864 ± 0.159	1.56	.122
Urea (mg/dl)		26.64 ± 5.86	24.9 ± 5.44	1.43	.155
NT-proBNP (pg/ml)		955.1 ± 247.19	757.17 ± 322.68	**MW 698**	**.008**

Data are presented as Mean ± SD. BMI: body mass index. HR: heart rate. SBP: systolic blood pressure. DBP: dyastolic blood pressure. TLC: Total Leukocyte Count. PLT: platelet count. RBS: Random blood sugar. NT-proBNP: N-terminal prohormone of BNP.MACE: Major adverse cardiovascular event.

There was a significant difference between patients who had MACE and patients who had not regarding LVEF, ePASP, RV FAC, right ventricular free wall longitudinal strain (RVFWLS), RVGLS, and NYHA classification. Table 3

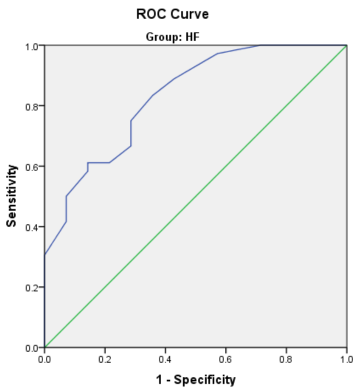
Table 3: Echo data among the studied patients according to MACE occurrence

Variables	**MACE** (n=30)	**No MACE** (n=70)	**t / χ^2**	**P**

LVEF (%)	43.4 ± 5.3	47.46 ± 6.28	**3.1**	**.003**
ePASP (mmHg)	30.8 ± 4.32	28.64 ± 3.19	**2.78**	**.007**
RVD mid cavity (cm)	2.78 ± 0.441	2.73 ± 0.471	.449	.654
RVD basal (cm)	3.3 ± 0.576	3.2 ± 0.632	.841	.403
Base-apex (cm)	6.35 ± 0.872	6.52 ± 0.818	.926	.357
RV FAC (%)	30.6 ± 2.65	33.1 ± 2.92	**4.03**	**<0.001**
TAPSE (cm)	16.12 ± 2.8	18.62 ± 3.09	**3.82**	**<0.001**
RVFWLS (%)	-14.16 ± 2.77	-16.53 ± 5.13	**3.27**	**<0.001**
RVGLS (%)	-14.99 ± 2.55	-17.56 ± 3.01	**4.1**	**<0.001**
NYHA classification				
II	12 (40%)	33 (47.1%)	**19**	**<0.001**
III	8 (26.7%)	50 (50%)		
IV	10 (33.3%)	2 (2.9%)		

Data are presented as Mean ± SD and number (%). MACE: Major adverse cardiovascular event. LVEF: Left ventricle ejection fraction. RVD: Right ventricle diameter. FAC: fractional area change. TAPSE: tricuspid annular plane systolic excursion. RVFWLS: Right ventricular free wall longitudinal strain. RVGLS: RV Global longitudinal strain.

RV FAC yielded significant at cut off point of 32 with sensitivity of 83.6% and specificity of 82.8%. RV GLS yielded significant at cut off point of -15.2 with sensitivity of 98.2% and specificity of 85.7%.Figure 1



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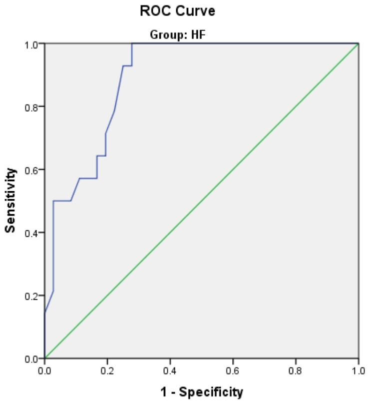

B

Figure 1: ROC curve of A) RV FAC B), RV GLS as a predictor of poor outcome among HF patients

Discussion:

Only a few studies have evaluated RV systolic function in the three categories of HF with regard for the importance of understanding changes in RV function and their effects on clinical presentation and outcomes; it is essential to define the prevalence and severity of RV dysfunction among the three groups and the degree of correlation between RV and LV systolic functions [17].

RV function has not been well studied in HFrEF; while it was recently studied in HFpEF, with the development of the new classification of HF (into preserved, mid-range, and reduced), the definition and orientation of the mid-range group is unclear.

In our study, we found that 30% of the patients among HF patients had MACE and the mortality rate was 10%. Also, we found a significant difference between patients who had MACE and patients who have not regarded LVEF, ePASP, RV FAC, RVFWLS, RVGLS, and NYHA classification.

Similarly, Carluccio et al. [18]reported that patients with events showed significantly higher brain natriuretic peptide levels, increasing New York Heart Association class, and increased pulmonary artery systolic pressure than event-free patients. Accordingly, Echo-HF score was greater than patients with events. Meanwhile, RV FAC was significantly impaired in patients with events.

In agreement with our findings, Carluccio et al. [19]compared with patients with events and event-free patients, they found that patients with events were older, prevalently male, and with more advanced NYHA class, higher BNP levels. With respect to echocardiographic data, compared with event-free patients, those who experienced events showed significantly lower LVEF and lower LVGLS, and increased sPAP. Both RVFWS and RVGLS were significantly impaired in patients with events, as was TAPSE.

According to ROC curve analysis were found that RV FAC yielded significant at cut off point of 32 with sensitivity of 83.6% and specificity of 82.8%. RV GLS yielded significant at cut off point of -15.2 with sensitivity of 98.2% and specificity of 85.7%.

Carluccio et al. [19]documented that the best cutoff values of RVGLS predicting outcome were ≥–14.6%.

Limitations of our study were single center study, small sample size and lack of a control group.

Our data may have important clinical implications because they suggest that in HFrEF, assessment of RV function by traditional measurements (ie, FAC) should be complemented by analysis of longitudinal strain, to improve the identification of patients who are at risk for adverse event

Conclusions:

RV dysfunction is an independent determinant of outcomes in patients with HF, and it demonstrates that RV free wall strain is a stronger and more precise predictor of outcome than RV global strain in the presence of LV systolic dysfunction.

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