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Research Article

Prognostic Impact of Right Ventricle Dysfunction and Associated Echocardiographic Data in Heart Failure Patients with Reduced Ejection Fraction

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Abstract

Introduction: There is growing attention for the study of the right ventricle (RV) in heart failure (HF). Right ventricular dysfunction (RVD) is an important predictor of impaired prognosis. Echocardiography is the most performed imaging modality to evaluate HF patients.

Methods: It's a transversal retrospective study conducted between May 2006 and June 2020 including all patients with HF with reduced ejection fraction (HFrEF), followed-up in the therapeutic unit of HF of our department. We studied 2 groups of patients: group 1 with impaired and group 2 with preserved RV systolic longitudinal function.

Results: Among 3412 patients, 1312 (38.5%) patients had impaired longitudinal systolic RV function (group 1) and 2100 had preserved systolic longitudinal RV function (group 2). Regarding etiologies of HFrEF: ischemic heart disease was represented in 54.9% versus 61%, dilated cardiomyopathy in 9.9% versus 10.5%, valvar hear disease in 4.7% versus 3%, chemotherapy induced cardiomyopathy in 2.4% versus 1.5%, peripartum cardiomyopathy (PPCM) in 0.4% versus 0.3%, tach cardiomyopathy in 0.3% versus 0.3% ($p = 0.001$). Cardiovascular risk factors accounted for 41.7% versus 37.1% ($p = 0.007$) for hypertension, 32.6% vs 29% ($p = 0.023$) for diabetes mellitus, 14.4% vs 7.1% ($p < 0.001$) for dyslipidemia, and 35.6% vs 29.9% ($p < 0.001$) for tobacco use. For comorbidities: Chronic obstructive pulmonary disease (COPD) was represented in 3.3% versus 1.7% ($p = 0.004$). Group 1 patients were more symptomatic according to NYHA classification and had more right-sided HF symptoms. 12.1% vs 8.8% were in atrial fibrillation ($p < 0.001$). For echocardiographic data: mean LVEF was 30.36 ± 7.41% vs 42.75 ± 6.80% ($p < 0.001$), significant functional tricuspid regurgitation was present in 11.3% vs 4.2% ($p < 0.001$), significant functional mitral regurgitation was detected in 30.3% vs 23.1% ($p < 0.001$), LV filling pressure was high in 27.2% vs 13.8% ($p < 0.001$), SPAP was 42.03 ± 15.30 vs 37.27 ± 15.43 mmHg ($p = 0.034$). Betablockers were prescribed in 88% vs 86.3% ($p = 0.092$), Ivabradine in 2.4% vs 7.3% ($p < 0.001$), loop diuretics in 47.7% vs 43.4% ($p < 0.001$), Spirinolactone in 58.5% vs 55.5% ($p < 0.001$), ACE-I were prescribed in 83.3% vs 78% ($p < 0.001$) and ARB in 11% vs 22.5% ($p < 0.001$). HF hospitalization represented 23.8% vs 16% ($p < 0.001$) and global mortality accounted for 3.4% vs 1.7% ($p < 0.001$).

Conclusion: Our study shows the importance of RV systolic function evaluation for the risk stratification of patients. RV systolic dysfunction identifies patients at increased risk of hospitalization for heart failure and mortality.

Keywords: *Right Ventricular Dysfunction; Heart Failure with Reduced Ejection Fraction; NYHA Functional Class; Hospitalization for Heart Failure; Mortality*

Abbreviations

ACE-I: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin II Receptor Blockers; CHF: Chronic Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; CRT: Cardiac Resynchronization Therapy; DCM: Dilated Cardiomyopathy; DBP: Diastolic Blood Pressure; HF: Heart Failure; HFrEF: Heart Failure with Reduced Ejection Fraction; HR: Heart Rate; IHD: Ischemic Heart Disease; LV: Left Ventricle; LVEF: Left Ventricular Ejection Fraction; LVFP: Left Ventricular Filling Pressure; MPI: Myocardial Performance Index; MR: Mitral Regurgitation; NYHA: New York Heart Association Classification for Dyspnea; PPCM: Peri-Partum Cardiomyopathy; RV: Right Ventricle; RVD: Right Ventricular Dysfunction; RVEF: Right Ventricular Ejection Fraction; RVFAC: Right Ventricle Fractional Area Change; RVs': Systolic Excursion Velocity of Tricuspid Annulus Free Wall; SBP: Systolic Blood Pressure; sPAP: Systolic Pulmonary Artery Pressure; TAPSE: Tricuspid Annular Plane Systolic or Diastolic Excursion; TDI: Tissue Doppler Imaging; TR: Tricuspid Regurgitation; VHD: Valvar Heart Disease

Introduction

The prevalence of heart failure (HF) is increasing in developed and developing countries because of the rising burden of cardiovascular risk factors [1,2].

Even though heart failure syndrome includes symptoms of left and/or right heart failure, little interest is attributed to the function of the right ventricle (RV), including methods of detecting RV dysfunction (RVD) and its prognostic impacts in heart failure patients [3]. The RV is affected by most cardiovascular diseases and contributes to a number of disease processes [4-6]. Because of the specific anatomy and the lower pressure system in right heart, the evaluation of RV function is more difficult than the left heart [7]. Markers such as tricuspid annular plane systolic or diastolic excursion (TAPSE), Tissue Doppler imaging (TDI) measuring the systolic excursion velocity of tricuspid annulus free wall: S-wave velocity (RV s'), RV ejection fraction (RVEF), RV index of myocardial performance (Tei index), RV strain, right atrial size, and RV dilatation among others are useful in assessing for RVD [8-10]. Even if many markers of RV function exist, most reports do not comment on the impact of RVD in patients with HF.

Among HF phenotypes, heart failure with reduced ejection fraction (HFrEF) patients have the worst outcomes and are challenging to manage. In addition, it is now increasingly recognized that right heart dysfunction is common and contributes importantly to poor prognosis in HFrEF. More insights into the development of right heart dysfunction in HFrEF may aid to our knowledge about this complex disease and may eventually lead to better treatments to improve outcomes in these patients.

This study is aiming to evaluate clinical and prognostic impact of RVD and echocardiographic data in heart failure patients with reduced ejection fraction in a specialized cardiac facility in Casablanca, Morocco

Materials and Methods

Study population

We have conducted a transversal retrospective study between May 2006 and June 2020 including all patients with HFrEF, followed-up in the therapeutic unit of HF of the cardiology department of IBN Rochd University hospital in Casablanca, Morocco.

HFrEF is defined as a left ventricular ejection fraction (LVEF) ≤ 40% according to 2021 Europen Society of Cardiology guidelines.

We excluded patients with insufficient echocardiography or examination data.

When the initial cause of hospitalization was acute HF, the echocardiography assessment at discharge was retained.

This database was crossed with hospitalization records, clinical, echocardiographic and mortality data in order to study the prognostic impact of RV dysfunction in patients with HFrEF.

Follow up

Follow-up was censored on 1st June 2020, and consisted of a retrieval of last consultation data and verification of hospitalization and mortality registers. For all patients, we recorded data on the occurrence of death and hospitalization for HF.

Echocardiographic assessment

Transthoracic echocardiograms were recorded on various generations of Vivid systems. Measurements were made according to guidelines [11,12]. LV ejection fraction (LVEF) was measured according to Simpson's method.

Diastolic function analysis was based on mitral-pulsed Doppler inflow and tissue-Doppler imaging at the lateral mitral annulus. Left atrial area was measured from the apical four-chamber view. Color-Doppler studied the existence and the severity of mitral and tricuspid regurgitation.

TAPSE was measured by M-mode, after two-dimensional echocardiography guidance at the lateral tricuspid annulus, as the maximal systolic excursion. Tissue Doppler imaging at the tricuspid annular free wall allowed the assessment of S-wave velocity (S'RV). Systolic pulmonary artery pressure was calculated from tricuspid regurgitation (TR) flow added to right atrial pressure estimated from the inferior vena cava. Right and left atrial areas were measured at end-ventricular systole in an apical four-chamber view.

Right ventricle systolic longitudinal dysfunction is defined as TAPSE ≤ 15 mm and/or S'RV ≤ 9.5 cm/s.

Statistical analysis

Data were collected on Excel and analyzed using SPSS 2.0 software. All continuous variables are described as means ± standard deviations; all categorical variables are described with frequencies.

Patients were divided into two groups according to the presence (group 1) or absence (group 2) of RVD. Comparisons of the occurrence of HF hospitalization or death according to the presence or absence of RVD were realized with Student's t test for continuous variables and the Chi2 test for discrete variables. Differences were considered statistically significant when $p < 0.05$.

Results

Among 3412 patients, 1312 (38.5%) patients had impaired longitudinal systolic RV functionn (group 1) and 2100 had preserved systolic longitudinal RV function (group 2). Mean age was 65.70 ± 13.03 years in patients of group 1 vs 64.43 ± 12.69 years in patients of group 2 ($p = 0.005$). 64.3% of patients in group 1 were male versus 63.4% of patients in group 2 ($p=0.575$).

Regarding cardiovascular risk factors: hypertension was represented in 41.7% versus 37.1% ($p = 0.007$), diabetes mellitus in 32.6% vs 29% ($p = 0.023$), dyslipidemia in 14.4% vs 7.1% ($p < 0.001$), tobacco use 35.6% vs 29.9% ($p < 0.001$).

Regarding etiologies of HFrEF: ischemic heart disease (IHD) was represented in 54.9% versus 61%, dilated cardiomyopathy (DCM) in 9.9% versus 10.5%, valvar hear disease (VHD) in 4.7% versus 3%, chemotherapy induced cardiomyopathy in 2.4% versus 1.5%, peripar-

tum cardiomyopathy in 0.4% versus 0.3%, tach cardiomyopathy in 0.3% versus 0.3% (p = 0.001). Demographics, cardiovascular disease risk factors, comorbidities and etiologies of HF are represented in table 1.

	Group 1 (n = 1312)	Group 2 (n = 2100)	P value
Age	65.70 ± 13.03	64.43 ± 12.69	0.005
Male Gender	64.3 %	63.4%	0.575
History of hypertension	41.7%	37.1%	0.007
History of diabetes mellitus	32.6%	29%	0.023
Dyslipidemia	14.4%	7.1%	< 0.001
Smoking	35.6%	29.9%	< 0.001
History of COPD	3.3%	1.7%	0.004
Etiologies of HF:			
IHD	54.9%	61%	< 0.001
DCM	9.9%	10.5%	
VHD	4.7%	3%	
Chemotherapy induced cardiomyopathy	2.4%	1.5%	
PPCM	0.4%	0.3%	
Tachycardiomyopathy	0.3%	0.3%	

Table 1: *Demographics, cardiovascular disease risk factors, comorbidities and etiologies of heart failure.*

(HF: Heart Failure, IHD: Ischemic Heart Disease, DCM: Dilated Cardiomyopathy, VHD: Valvar Heart Disease, PPCM: Peripartum cardiomyopathy).

Regarding comorbidities: Chronic obstructive pulmonary disease (COPD) was represented in 3.3% versus 1.7% (p = 0.004). Patients were classified according to NYHA class I in 13.2% in group 1 vs 24.9% in group 2, class II in 61.3% vs 52.3%, class III in 23.4% vs 16.9%, class IV in 2.1% vs 1.8% (p < 0.001). we have observed left HF signs in 9.8% vs 8.7% (p = 0.546) and right HF signs in 7.8% vs 5.7% (p = 0.024). Therefore, patients with RVD were more symptomatic. There was no statistical difference between the two groups concerning blood pressure and heart rate (HR). Results showed more atrial fibrillation in patients with RVD compared to Group 2 (12.1% vs 8.8%, p < 0.001). Clinical and electrical data are reported in table 2.

	Group 1 (n=1312)	Group 2 (n=2100)	P value
NYHA			
Class I	13.2%	24.9%	< 0.001
Class II	61.3%	52.3%	
Class III	23.4%	16.9%	
Class IV	2.1%	1.8%	
Signs of left HF	7.8%	5.7%	0.024
Signs of right HF	8.8%	4.2%	< 0.001
Mean HR	77.17 ± 16.76 bpm	77.11 ± 16.35 bpm	0.911
Mean SBP	128.98 ± 24.86 mmHg	128.12 ± 22.87 mmHg	0.316
Mean DBP	73.95 ± 13.70 mmHg	74.92 ± 13.23 mmHg	0.042
Persistent atrial fibrillation	12.1%	8.8%	< 0.001

Table 2: *Clinical and electrical data.*

(NYHA: New York Heart association classification of Dyspnea; HR: Heart Rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure).

Echocardiographic data have shown that LV function was more impaired in Group 1 patients, mean LVEF was 30.36 ± 7.41% vs 42.75 ± 6.80% (p < 0.001). Patients with RVD were more likely to have significant functional mitral regurgitation 30.3% vs 23.1% (p < 0.001), high LV filling pressure was high in 27.2% vs 13.8% (p < 0.001), as well as significant functional tricuspid regurgitation in 11.3% vs 4.2% (p < 0.001). SPAP was also higher in patients with RVD, mean systolic pulmonary artery pressure (sPAP) was 42.03 ± 15.30 vs 37.27 ± 15.43 mmHg (p = 0.034). Mean TAPSE/sPAP ratio was 0.29 ± 0.02 in group 1 patient's vs 0.70±0.03 in group 2. Transthoracic echocardiography data are reported in table 3.

	Group 1 (n=1312)	Group 2 (n=2100)	P value
Mean LVEF	30.36 ± 7.41%	42.75 ± 6.80%	< 0.001
Elevated LVFP	27.2%	13.8%	< 0.001
Mean SPAP	42.03 ± 15.30 mmHg	27 ± 15.43 mmHg	0.034
Mean TAPSE/SPAP ratio	0.29 ± 0.02	0.70 ± 0.03	< 0.001
Significant functional TR	11.3%	4.2%	< 0.001
Significant functional MR	30.3%	23.1%	< 0.001

Table 3: *Transthoracic echocardiography data.*

(LVEF: Left Ventricle Ejection Fraction, LVFP: Left Ventricle Filling Pressures, SPAP: Systolic Pulmonary Artery Pressure, TR: Tricuspid Regurgitation, MR: Mitral Regurgitation).

Regarding pharmacotherapy prescription: Betablockers were prescribed in 88% vs 86.3% (p = 0.092), Ivabradine was prescribed in 2.4% vs 7.3% (p < 0.001), loop diuretics were prescribed in 47.7% vs 43.4% (p < 0.001), Spirinolactone was prescribed in 58.5% vs 55.5% (p < 0.001), ACE-I were prescribed in 83.3% vs 78% (p < 0.001), ARB were prescribed in 11% vs 22.5% (p < 0.001). Pharmacotherapy prescription data are represented in table 4.

	Group 1 (n = 1312)	Group 2 (n = 2100)	P value
Beta-blockers	88%	86.3%	0.092
Ivabradine	2.4%	7.3%	< 0.001
Loop diuretics	47.7%	43.4%	< 0.001
Spironolactone	58.5%	55.5%	< 0.001
ACE-I	83.3%	78%	< 0.001
ARB	11%	22.5%	< 0.001

Table 4: *Heart failure medical therapy.*

(ACE-I: Angiotensin Converting Enzyme Inhibitors, ARB: angiotensin II receptor blockers).

Regarding HF hospitalization: The hospitalization rate for HF was 23.8% for Group 1 vs 16% for group 2 (p < 0.001). Regarding global mortality: death occurred in 3.4% of patients in group 1 vs 1.7% in group 2 (p < 0.001). Hospitalization and mortality rates are reported in table 5.

	Group 1 (n = 1312)	Group 2 (n = 2100)	P value
HF Hospitalization	23.8%	16%	< 0.001
Mortality rate	3.4%	1.7%	< 0.001

Table 5: *HF hospitalization and mortality rates.*

(HF: heart failure).

Discussion

By defining RV function based on a threshold of TAPSE of 15 mm or a RV s' threshold of 9.5cm/s in HFrEF, our study showed that RVD was present in 38.5% of HFrEF patients. HF patients with impaired RV had more cardiovascular risk factors, were more symptomatic and had more atrial fibrillation along with worse echocardiographic variables including worse LVEF, diastolic dysfunction, mitral and tricuspid regurgitation. RVD was also associated with a higher risk for HF hospitalization and death in patients with HFrEF.

Considering the prognostic impact of RVD in cardiovascular disease and HF, the evaluation of RV performance and structure is crucial for the clinical management of patients [13]. Transthoracic echocardiography is an essential tool for the assessment of RV structure and function. The parasternal and the apical views allow the analysis of RV morphology, diameters and function. In HFrEF patient, the LV dysfunction causes RV overload and dilatation, resulting in a paradoxical interventricular septum motion as well as RV function impairment [12].

The intrinsic evaluation of RV function remains a challenge with echocardiography, since most of the variables are load dependent [14]. TAPSE is the most described variable, and it is also the most routinely and easily performed measurement available in practice to assess RV systolic function, A value of TAPSE < 16 mm indicates RVD [12]. In patients affected by chronic HF (CHF), TAPSE was independently associated with a worse prognosis [10,15]. In a study conducted on HFrEF patients, an initial and a 6-month echocardiography were performed in order to evaluate the prognostic role of RV function and reversibility of RV impairment, reduced RV function at baseline was independently associated with poor outcome and the reversibility of abnormal RV function was associated with a better prognosis, regardless of LVEF improvement [16].

In TDI a peak systolic velocity value RVs' less than 9.5 cm/s suggests RV systolic dysfunction and is indicative of poor prognosis [17,18].

RV systolic function can also be evaluated with Right ventricle fractional area change (RVFAC), it represents the di*ff*erence between RV end-diastolic and end-systolic areas fractioned RV end-diastolic area. In several studies lower values of RVFAC are associated with an increased risk of all-cause mortality, cardiovascular death, sudden death, HF, and stroke [19].

RV myocardial performance index (MPI) or Tei index, using a pulsed-Doppler is a relatively less load dependent parameter [9]. When combined with the other systolic and diastolic RV functional parameters, Tei index allows to further stratify patients with symptomatic HF [20].

RV strain is a new echocardiographic parameter of RV function that can be obtained by TDI or speckle-tracking imaging allowing to analyze both the free wall and the interventricular septum. Usefulness of RV strain in clinical practice is supported by literature data suggesting that RV strain provide a more accurate and less preload dependent estimation of RV function [21]. Several studies have dem-

onstrated the independent prognostic value of strain measures [22,23], even in patients who have undergone cardiac resynchronization therapy (CRT) [24], and in those with normal TAPSE [25].

sPASP can be estimated by combining transvalvular maximal gradient with an estimate of the right atrial pressure, obtained from the inferior vena cava diameter and its respiratory changes. The combined assessment of RV function and sPAP estimation seems to be a more accurate index of RV performance status [26]. Using echocardiography and combining TAPSE and Doppler estimated sPAP, it is possible to further stratify patients through a non-invasive index of RV arterial coupling. A TAPSE/*s*PAP ratio that studies ventriculo-arterial coupling. A TAPSE/PASP ratio < 0.36 mm/mmHg identifies patients with worse outcomes, regardless of LVEF. In our study mean TAPSE/sPAP ratio was 0.29 ± 0.02 in group 1 patients vs 0.70 ± 0.03 in group2, suggesting a worse prognosis in group 1 patients. In very advanced stages of RV dysfunction, the increase in right atrial pressures and severe impairment of RV contractility can be responsible for a very low peak velocity of tricuspid regurgitation. In these patients and causes further dilation of cava vein and a worse prognosis [27].

In HFrEF patients, the backward transmission of elevated left ventricular end-diastolic pressure causes hydrostatic and vasoreactive changes including vasospasm, vasoconstriction and remodeling of pulmonary vasculature that leads to pulmonary hypertension. Pulmonary hypertension due to left heart disease is the most common cause of RV dysfunction [28]. The degree of pulmonary hypertension is correlated with the severity of the LV dysfunction and the impact on the RV. This explains our study finding that HF patients with RVD had a lower LVEF and a HIGHER sPAP.

Cardiac magnetic resonance can provide advanced tissue characterization imaging of the RV myocardium and allows to detect signs of inflammatory activity, i.e., in myocarditis involving the RV. It represents the gold standard for determining right heart size and function, the practical use is limited by its availability and the compatibility with several cardiac devices [18].

According to latest guidelines, there are no treatments that target RVD in patients with HFrEF. Standard therapies of HF including (ACE-inhibitors, Angiotensin II Receptor Blockers, Sacubitril-Valsartan, Mineralocorticoid antagonists, Beta-blockers and SGLT2 inhibitors) are indicated because of their beneficial effect on mortality in HFrEF patients [29]. However, data from literature are controversial regarding the direct effect of HF therapies on RV remodeling and function. Some findings suggest that ACE inhibitors reduce RV remodeling and improve cardiac function and survival [30,31]. Whereas in other studies, ACE inhibitors and ARB (Ramipril, Losartan and Valsartan) failed to improve RV function, exercise capacity and quality of life [32,33].

Data are scarce concerning effects of beta-blockers on RVD in patients with CHF. Few studies have showed improvement of RV function along with LV systolic function improvement after treatment with carvedilol [34,35].

In HFrEF with or without RVD, an optimized HF therapy in indicated, however further studies are needed to evaluate the direct effect of HF therapy on the RV.

In decompensated HF with RVD, volume overload is associated with worse prognosis. In order to achieve depletion, loop diuretics should be used in addition to salt and fluid restriction. RV unloading increases RV contractility, cardiac output, and renal perfusion in acute setting. In stable CHF patient with RV dysfunction, doses of diuretics should be adjusted to avoid hypotension [18].

In HFrEF patients with intraventricular conduction delay that are still symptomatic three months after an optimal HF therapy, cardiac resynchronization therapy (CRT) is recommended [29]. The benefit of CRT for patients with right sided HF is not well established, CRT seems to induce both LV and RV reverse remodeling and improve RV function [36].

In the present study, we found that RVD was a frequent finding in Moroccan HFrEF patients. In addition, and most importantly, RVD was associated with a worse clinical status, worse echocardiographic findings and more hospitalization for acute decompensated HF and mortality.

Conclusion

Our study shows the importance of RV function evaluation for the risk stratification of patients. RVD identifies patients at increased risk of hospitalization for heart failure and mortality. TAPSE and RV s' are the most used and the easiest echocardiographic parameters for RV function assessment. Recent studies are focusing on the importance of RV free wall Strain and Strain rate to further stratification.

Conflict of Interest

We Declare no conflict of interest.

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