Independent predictors of developing pulmonary hypertension in heart failure with reduced versus preserved ejection fraction

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Objectives: **To investigate the different clinical and echocardiographic predictors of evolving PH in patients with heart failure with and without reduced ejection fraction.**

Methods and Results: **The study included 153 heart failure patients with reduced ejection fraction (HFrEF) (n = 89) and preserved ejection fraction (HFpEF) (n = 64) both of which were subdivided into 2 subgroups according to the presence of PH. All patients were subjected to detailed clinical assessment and full transthoracic echocardiogram. There were significant differences between the 2 HFrEF subgroups regarding systolic BP, presence of diabetes, dyslipidemia, diuretics usage, all LV parameters, LAD, LAV and LAV indexed to BSA, E/A ratio, DT and severity of TR. Using multivariate analysis, the presence of diabetes (P = 0.04), diuretics usage (P = 0.04), LAV (P = 0.007) and TR grade (P < 0.001) were significant independent predictors for the development of PH among HFrEF patients. There were significant differences between the 2 HFpEF subgroups regarding presence of hypertension, diuretics usage, LAD, LAA, TR severity. Using multivariate analysis, only diuretics usage (P = 0.02) and TR grade (P < 0.0001) were significant independent predictors for the development of PH among HFpEF patients.**

Conclusion: **Neither the decrease in EF among HFrEF patients nor the DD grade in HFpEF patients act as independent predictor for evolving PH. Common independent predictors for evolving PH in both HFrEF and HFpEF patients are TR grade and use of diuretics. Other independent predictors in HFrEF and not HFpEF patients are the presence of diabetes and increased LAV.**

Keywords: Pulmonary hypertension, Heart failure, Ejection fraction, HFrEF, HFpEF

1. Introduction

Pulmonary hypertension (PH) due to left heart disease, classified as Group 2 according to the Dana Point 2008 classification, is believed to be the most common cause of PH and is associated with high morbidity and mortality [1]. Although initial studies suggested that reduced left ventricular (LV) ejection fraction (EF) is the main cause of PH, more recent studies could establish an association between PH and diastolic

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dysfunction, and consider PH as a marker of poor prognosis in these patients [2]. It was also shown that PH depends on the severity of mitral regurgitation as well as left atrial (LA) function [3].

Improved understanding of the different predictors of development of PH in heart failure (HF) patients with and without reduced function is essential to determine an effective follow-up and treatment strategies to reduce morbidity and mortality in these patients. We sought to study different clinical and noninvasive echocardiographic parameters in patients with HF with and without reduced LV functions to determine the independent predictors of early PH in these patients and whether they differ between HF patients with reduced EF (HFrEF) and HF patients with preserved EF (HFpEF) or not.

2. Methods

This study complies with the Declaration of Helsinki and was approved by the institutional review board of the Faculty of Medicine Ain Shams University (Cairo, Egypt), and informed consent was obtained from all enrolled patients.

2.1. Study population

This was a prospective observational study that included all HF patients with and without reduced EF referred for an elective transthoracic echocardiogram in the Cardiology Department Ain Shams University Hospital in the period from June 2015 to December 2015. The study included a total of 153 patients who were subdivided into two groups; Group 1 included HFrEF patients ($n = 89$) and Group 2 included HFpEF patients ($n = 64$). A cut-off point for EF of $\geqslant 50\%$ was used to differentiate between the two groups [4,5].

We excluded patients with: atrial fibrillation; significant valvular heart disease; chronic obstructive pulmonary disease; primary PH or secondary PH due to causes other than left-sided heart disease; and acute decompensated or Stage D HF [6].

2.2. Clinical assessment

All patients were clinically assessed for risk factors, typical signs and symptoms of HF and antifailure medications [4]. Also the stage of HF was determined. Drugs recorded included digoxin, β-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and diuretics. Other medications used were listed as others and were considered irrelevant in the final statistical analysis as they were not prescribed to sufficient number of patients to allow for relevant comparisons. The use of any of these medications in the full therapeutic dose for the last 6 months prior to the study was considered positive to consider a patient receiving such a medication.

Abbreviations

DT	deceleration time
EF	ejection fraction
HF	heart failure
HFrEF	heart failure reduced ejection fraction
HFpEF	heart failure preserved ejection fraction
LAA	left atrial area
LAAP	left atrial anteroposterior dimension
LAV	left atrial volume
LAVEF	left atrial volume emptying fraction
LV	left ventricle
PASP	pulmonary artery systolic pressure
PH	pulmonary hypertension
RAP	right atrial pressure
TR	tricuspid regurgitation

2.3. Transthoracic echocardiogram

All patients were studied in the left lateral decubitus position using an ultrasound system (Vivid 9; GE Healthcare, Chalfont-St Giles, Buckinghamshire, UK). Standard two-dimensional and M-mode echocardiograms were obtained according to the American Society of Echocardiography guidelines. LV measurements included LV wall thickness, internal dimensions, end-diastolic and end-systolic volumes, EF by M mode, and modified Simpson's rule.

LA size and function were assessed as follows [7]:

- LA anteroposterior dimension (LAD): was recorded from the standard parasternal short axis view at the level of the aorta from the edge of the posterior aortic wall to the LA edge at end systole.
- LA area (LAA): was traced at end systole just before opening of mitral valve by tracing the LA inner border, excluding the area under the mitral valve annulus and the inlet of the pulmonary veins.
- LA volume (LAV): was obtained using the biplane area–length formula of [0.85 × (LAA in apical four chamber view) × (LAA in the apical two chamber view)]/shortest length from the mitral annulus mid-plane to the superior border of the LA in the four- and two-chamber views.
- LAV emptying fraction: The maximum and minimum LA volumes were calculated from the four-chamber view using Simpson's

Table 1. Clinical and demographic characteristics of the study groups.

Characteristics	Group 1 (HFrEF patients)			Group 2 (HFpEF patients)		
	1A Normal PASP $n = 30$	1B PH $n = 59$	p	2A Normal PASP $n = 31$	2B PH $n = 33$	p
Sex (M/F)	21/9	42/17	0.757	26/5	27/6	0.826
Age (y)	59.5 ± 6.9	59.3 ± 7.2	0.226	57.35 ± 9.4	56.0 ± 3.25	0.491
Weight (kg)	79.8 ± 7.1	82.0 ± 6.9	0.137	80.8 ± 7.5	80.0 ± 5.13	0.745
BSA (m^2)	1.9 ± 0.1	1.9 ± 0.09	0.035*	1.91 ± 0.08	1.94 ± 0.07	0.354
SBP (mmHg)	123.15 ± 16.3	114.6 ± 14.7	0.238	121.9 ± 13.8	126.3 ± 14.3	0.370
DBP (mmHg)	72.6 ± 13.3	68.4 ± 13.2	0.951	71.3 ± 10.56	77.3 ± 13.5	0.141
Risk factors for heart failure						
Diabetes	16 (53.3%)	48 (81.3%)	0.04*	12 (38.8%)	21 (63.6%)	0.282
Dyslipidemia	15 (16.6%)	26 (44.1%)	0.005*	11 (35.5%)	6 (18.2%)	0.492
Hypertension	22 (73.3%)	41 (69.5%)	0.128	20 (64.5%)	30 (90.9%)	0.020
Obesity	11 (36.6%)	26 (44.0%)	0.521	9 (29.03%)	6 (18.2%)	0.761
Drug history						
Digoxin	0 (0%)	11 (18.6%)	0.080	0 (0%)	0 (0%)	–
ARBs/ACEi	30 (100%)	59 (100%)	–	20 (64.5%)	27 (81.8%)	0.222
Diuretics	17 (56.6%)	56 (94.9%)	0.003*	7 (22.5%)	24 (72.7%)	0.009*
Beta blocker	28 (93.3%)	57 (96.6%)	0.541	20 (64.5%)	26 (78.8%)	0.252

Data are presented mean ± standard deviation or n (%).
ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blockers; BSA = body surface area; DBP = diastolic blood pressure; HFpEF = heart failure patients with preserved ejection; HFrEF = heart failure patients with reduced ejection fraction; PASP = pulmonary artery systolic pressure; RB = angiotensin receptor blocker; SBP = systolic blood pressure.
* $p < 0.05$.

method (maximum volume at end systole just before opening of mitral valve while minimum volume just before mitral valve closure). The LAV emptying fraction was calculated as follows

$$\text{LAV emptying fraction} = \{[(\text{max.LAV} - \text{min.LAV})] / \text{max.LAV}\} \times 100$$

Diastolic dysfunction assessment

A composite of mitral inflow peak E velocity to peak A velocity ratio (E/A), mitral inflow deceleration time (DT), and an average of the lateral and medial mitral annular tissue Doppler velocities (E′) and (E/e′) ratio were used to grade diastolic dysfunction as: (1) normal; (2) mild; (3) moderate (impaired relaxation or pseudonormal with moderate elevation of filling pressures); (4) severe (advanced reduction in compliance); or (5) indeterminate diastolic function.

Normal diastolic function included subjects with septal E′ ⩾ 8, lateral E′ ⩾ 10, and LA volume indexed <34 mL/m^2. Those with one or more elevated values for these variables were considered abnormal, and additional measurements were used to determine the grade of diastolic dysfunction. Mild diastolic dysfunction (Grade I) was classified as a mitral E/A ratio <0.8, DT >200 ms, and an E/e′ ratio <8. Moderate diastolic dysfunction (Grade II) was classified as a mitral E/A ratio of 0.8–1.5, average E/e′ ratio of 9–12, and DT of 160–200 ms. Severe diastolic dysfunction (Grade III) was characterized by restrictive filling with an E/A ratio ⩾2, DT <160 ms, and average E/e′ ratio >13 or septal E/e′ ratio ⩾15 and lateral E/e′ ratio >12. Participants were required to meet two Doppler criteria for moderate or severe diastolic dysfunction to be so classified. Patients meeting one criterion for moderate or severe diastolic dysfunction or those with borderline parameters were classified as indeterminate rather than normal [8].

Mitral and tricuspid valve regurgitation assessment [9]

Any degree of mitral regurgitation was documented and rheumatic etiology of mitral regurgitation was excluded for all patients enrolled in the study. Severity of mitral regurgitation was determined according to the color flow jet area and vena contracta according to the American Society of Echocardiography recommendations [9] where mild regurgitation has vena contracta <0.3 cm and a regurgitant jet area <4 cm^2, whereas severe mitral regurgitation, had vena contracta >0.7 cm and a regurgitant jet area >10 cm^2. The same recommendations were applied to grade

the severity of tricuspid regurgitation (TR). TR jet area <5 cm^2 was considered mild TR, those between 5 cm^2 and 10 cm^2 are moderate while severe TR has an area >10 cm^2.

Pulmonary artery systolic pressure assessment

Color flow guided continuous wave Doppler was applied to determine the peak tricuspid regurgitant velocity. The highest velocity obtained from multiple views measured in meter per second was used. Pulmonary artery systolic pressure (PASP) was calculated using the equation:

$$PASP = 4V^2 + RAP$$

where V = the maximal tricuspid regurgitation jet velocity, and RAP = right atrial pressure. RAP was determined according to the inferior vena cava diameter and its collapsibility with inspiration.

Patients were considered to have PH based on the intermediate or high echocardiographic probability of PH stated in the European Society of Cardiology and the European Respiratory Society guidelines for the diagnosis and treatment of PH [10]. Intermediate echocardiographic probability of PH was considered with peak velocity of TR ranging from 2.9 m/s to 3.4 m/s, whereas high probability of PH was considered with peak velocity of TR > 3.4 m/s [10].

2.4. Statistical analysis

All data were gathered, tabulated, and statistically analyzed on a PC using a commercially available statistical software package MedCalc version 11.6.1.0 (MedCalc Software, Mariakerke, Belgium). Qualitative variables are expressed as frequency and percentage and compared using chi-squared test. Quantitative variables are expressed as mean ± standard deviation and assessed using independent sample t test. Multivariate analysis was done using multiple regression with stepwise approach. Only significant variables in the univariate analysis were entered in the multivariate analysis model. A p value was considered significant if <0.05 and $p < 0.01$ was considered highly significant.

3. Results

The study included a total of 153 patients who were divided into two groups; Group 1 included 89 patients with HFrEF and Group 2 included 64 patients with HFpEF.

3.1. Evaluation of HFrEF patients

Eighty-nine patients with HFrEF were subdivided into two subgroups according to the presence of PH; Group 1A with normal PASP (mean PASP of 21.05 ± 7.69 mmHg; $n = 30$) and Group 1B with PH (mean PASP of 43.9 ± 4.95 mmHg; $n = 59$). There was no significant difference between the two subgroups regarding demographic and clinical characteristics with the exception of systolic BP ($p = 0.035$), presence of diabetes

Table 2. Independent sample t test between heart failure patients with reduced ejection fraction (HFrEF) with normal pulmonary artery systolic pressure (PASP; Group1A) and those with pulmonary hypertension (Group 1B) with regard to different echocardiographic parameters measured.

Variables	HFrEF patients		Independent sample t test	
	Group 1A (normal PASP)	Group 1B (PH)	t	p
LV ESD	4.29 ± 0.69	4.90 ± 0.79	2.986	0.004
LV EDD	5.94 ± 0.63	6.31 ± 0.68	2.098	0.04
LV FS	27.91 ± 5.87	22.32 ± 5.67	−3.703	0.0004
LV EF (M-mode)	52.84 ± 8.94	43.36 ± 8.99	−3.999	0.0001
LV EDV	108.12 ± 40.46	140.65 ± 52.37	2.476	0.015
LV ESV	63.93 ± 26.07	90.56 ± 40.39	3.344	0.002
LV EF (SIM)	42.43 ± 6.95	36.66 ± 7.92	−2.839	0.006
LAD	3.99 ± 0.45	4.53 ± 0.34	5.555	<0.0001
LAA	21.03 ± 14.99	22.59 ± 3.75	0.449	0.66
LAV	51.47 ± 18.98	79.11 ± 23.00	4.739	<0.0001
LAV/BSA	27.02 ± 10.13	40.64 ± 11.67	4.560	<0.0001
LAVEF	37.94 ± 12.32	35.15 ± 12.61	−0.843	0.40
E/A	0.87 ± 0.46	1.37 ± 1.06	2.889	0.005
DT	250.00 ± 50.90	205.17 ± 57.05	−3.114	0.003
E′	0.078 ± 0.02	0.10 ± 0.10	1.616	0.11
E/e′	8.26 ± 2.57	8.92 ± 3.82	0.718	0.47

Data are presented as mean ± standard deviation.
BSA = body surface area; DT = deceleration time; EDD = end diastolic diameter; EDV = end diastolic volume; EF = ejection fraction; ESD = end systolic diameter; ESV = end systolic volume; FS = fractional shortening; LAA = left atrial area; LAD = left atrial diameter; LAV = left atrial volume; LAVEF = left atrial volume emptying fraction; SIM = Simpson's model.

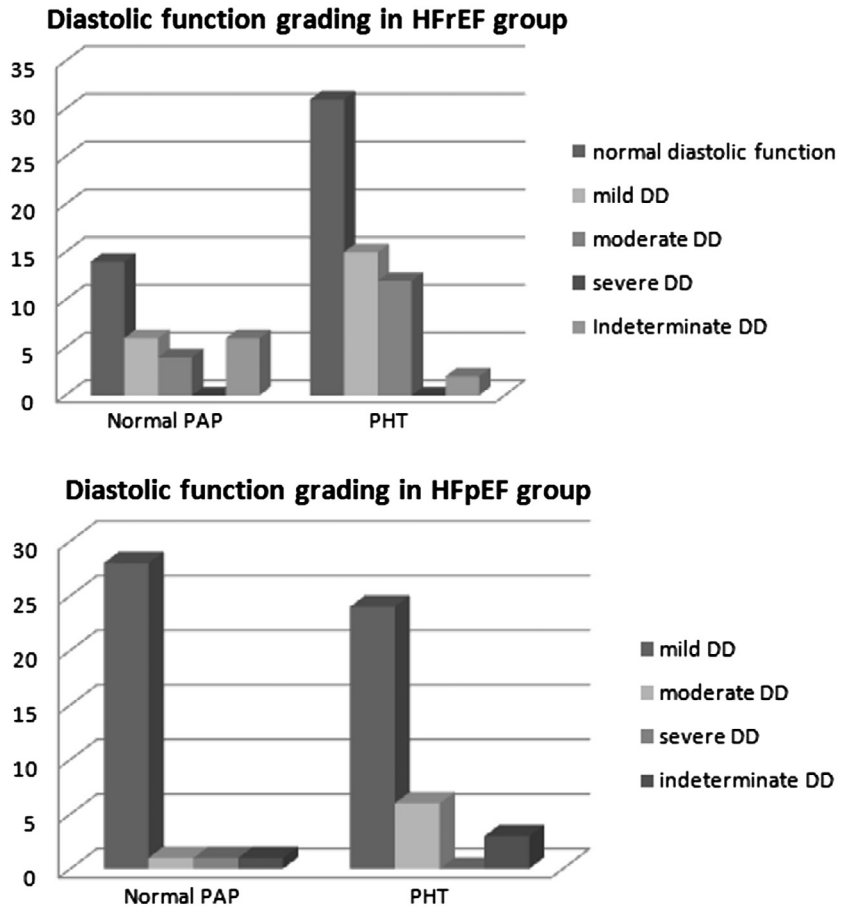

Fig. 1. Comparison between the normal pulmonary pressure subgroup and the pulmonary hypertensive subgroup in (A) heart failure patients with reduced ejection fraction and (B) heart failure patients with preserved ejection fraction patients with regard to diastolic function. DD = diastolic dysfunction; HFpEF = heart failure preserved ejection fraction; HFrEF = heart failure reduced ejection fraction; PAP = pulmonary artery pressure; PHT = pulmonary hypertension.

($p = 0.04$), presence of dyslipidemia ($p = 0.005$), and diuretics usage ($p = 0.003$; Table 1).

Univariate analysis of the echocardiographic parameters showed significant differences between the two subgroups with regard to all LV parameters, LAD, LAV, LAV indexed to body surface area, E/A ratio, and DT, whereas the differences regarding LAA, LAV emptying fraction, e′, or the E/e′ ratio were not significant (Table 2).

There was no significant difference with regard to diastolic function grading, 14 patients (46.6%) in Group 1A and 31 patients (52.5%) in Group 1B had normal diastolic function while 16 patients in Group 1A and 28 patients in Group 1B had different grades of diastolic dysfunction (Fig. 1).

There was significant difference between the two subgroups with regard to mitral regurgitation grading, whereas 94.9% of the PH patients (Group 1B) had mild ($n = 40$) or moderate ($n = 16$) mitral regurgitation compared to 83.3% of patients with normal PASP (Group 1A) who had mild or moderate mitral regurgitation ($p = 0.04$; Fig. 2). There was also significant difference between the two subgroups with regard to TR severity, whereas most of the patients with normal PASP had mild TR and most of the patients with PH had moderate TR; seven patients in this group had severe TR ($p < 0.001$; Fig. 3).

On the basis of the data obtained from the univariate analysis, multiple regression was used to establish a multivariate model for the development of PH. In this multivariate model, the presence of diabetes ($p = 0.04$), diuretics usage ($p = 0.04$), LAV ($p = 0.007$), and TR grade ($p < 0.001$) were significant independent predictors for the development of PH among patients with HFrEF. The overall significance of the model was highly significant with $p < 0.001$, the coefficient of determination (R^2) was 0.69 and the multiple correlation coefficient was 0.83.

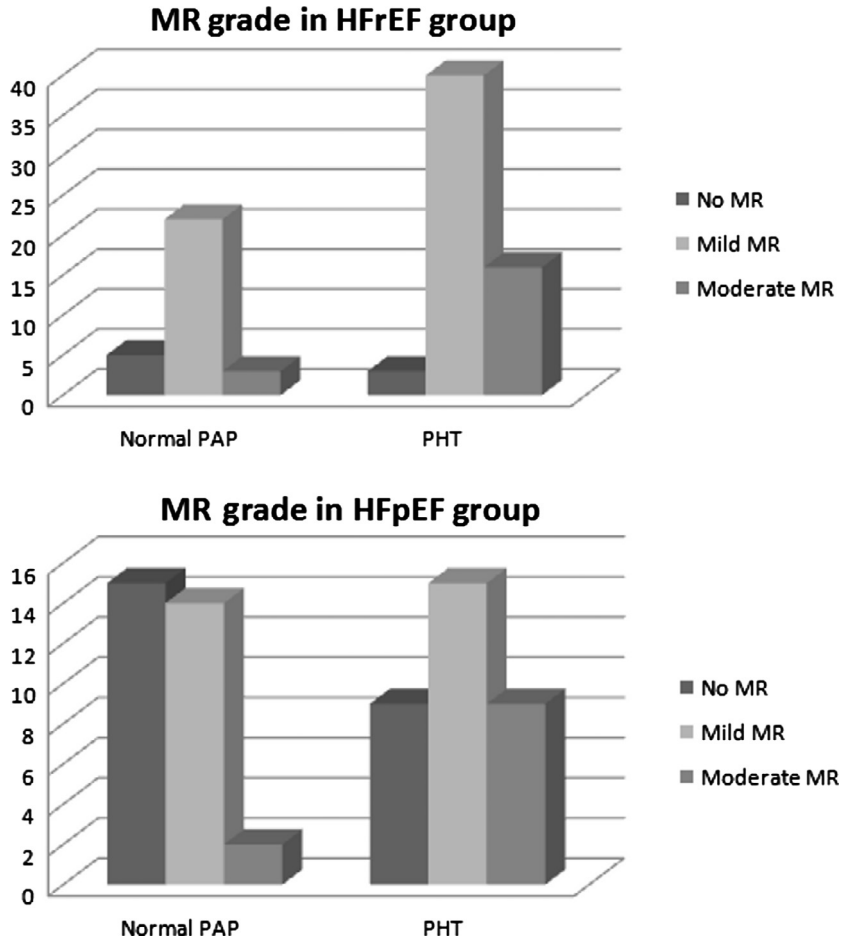

Fig. 2. Comparison between the normal pulmonary pressure subgroup and the pulmonary hypertensive subgroup in (A) heart failure patients with reduced ejection fraction and (B) heart failure patients with preserved ejection fraction with regard to mitral regurgitation grade. HFpEF = heart failure preserved ejection fraction; HFrEF = heart failure reduced ejection fraction; PAP = pulmonary artery pressure; PHT = pulmonary hypertension; MR = mitral regurgitation.

3.2. Evaluation of HFpEF patients

Sixty-four patients with HFpEF were subdivided into Group 2A with normal PASP (22.62 ± 6.16 mmHg; $n = 31$) and Group 2B with PH (40.7 ± 2.95 mmHg; $n = 33$). There was no significant difference between the two subgroups regarding demographic and clinical characteristics with the exception of presence of hypertension, which was present in 90.9% of patients in Group 2B compared to 64.5% of patients in Group 2A ($p = 0.02$), and diuretics usage where 72.7% of Group 2B patients used diuretics compared to 22.5% of Group 2A patients ($p = 0.009$; Table 1).

Univariate analysis of the different echocardiographic parameters showed no significant difference between the two subgroups with regard to LV systolic or diastolic function parameters. Concerning the LA measurements there was significant difference regarding LAD and LAA ($p = 0.02$ and 0.015 respectively) (Table 3).

There was no significant difference in diastolic function grading, 28 patients (90.3%) in Group 2A and 24 patients (72.7%) in Group 2B had mild Grade I diastolic dysfunction (Fig. 1).

Mitral regurgitation grade differed significantly between the two subgroups whereas 72.2% of patients in Group 2B had mild ($n = 15$) and moderate ($n = 9$) mitral regurgitation compared to 51.6% of patients in Group 2A who had mild or moderate mitral regurgitation ($p = 0.05$; Fig. 2). There was also significant difference between the two subgroups with regard to TR severity, whereas most of the patients with normal PASP had mild TR and most of the patients with PH had moderate TR ($p < 0.0001$; Fig. 3).

Using multiple regression analysis, only diuretics usage ($p = 0.02$) and TR grade ($p < 0.0001$) were found to be significant independent predictors for development of PH. The overall significance of the model was highly significant with $p < 0.001$, the

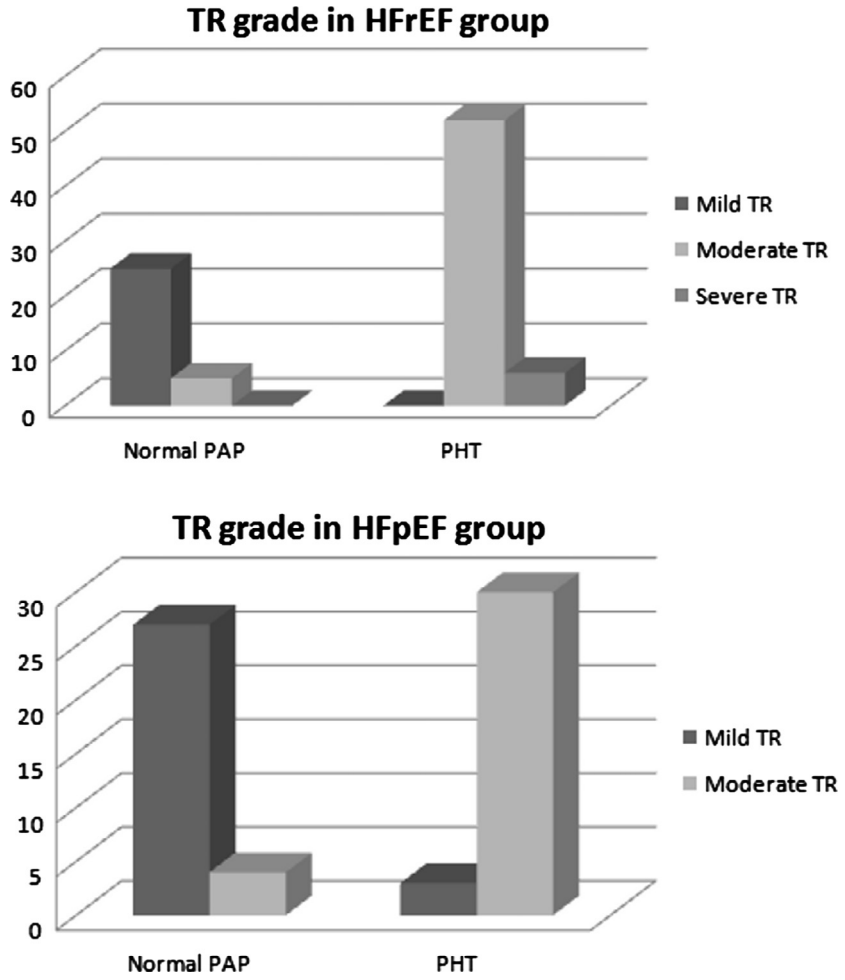

Fig. 3. Comparison between the normal pulmonary pressure subgroup and the pulmonary hypertensive subgroup in (A) heart failure patients with reduced ejection fraction and (B) heart failure patients with preserved ejection fraction with regard to tricuspid regurgitation grade. HFpEF = heart failure preserved ejection fraction; HFrEF = heart failure reduced ejection fraction; PAP = pulmonary artery pressure; PHT = pulmonary hypertension; TR = tricuspid regurgitation.

coefficient of determination (R^2) was 0.59 and the multiple correlation coefficient was 0.76.

4. Discussion

PH secondary to left heart disease is a common complication especially to HF with preserved or reduced EF; when present it results in more severe symptoms and more exercise intolerance [11]. We sought to compare the different predictors of PH in patients with HFrEF versus patients with HFpEF. To the best of our knowledge this is the first study to compare PH in HFrEF versus HFpEF. This study is also characteristic in utilizing the intermediate or high echocardiographic probability of PH stated in the European Society of Cardiology and the European Respiratory Society guidelines for the diagnosis and treatment of PH as a differentiating point between patients with normal PASP and those with PH [10]. Thus, the study is not concerned with the presence or absence of any degree of PH but is mainly concerned with the development of PH. We sought this using a low threshold for PH, which will help to establish early diagnoses for patients at high risk of developing progressive PH in the future. Also, the independent predictors for PH in this study were not only limited to the causal determinants but also included other variables that could act as warning signs to alert the treating physician to follow-up HF patients accurately for the development of PH.

PH was present in 66.3% of patients with HFrEF and 51.5% of patients with HFpEF. This was in agreement with earlier studies that stated that PH ranged from 33% to 83% in HF patients [12,13].

In the current study, there was significant difference between HFrEF patients with normal PASP and those with mild PH with regard to LV dimensions, volumes, and EF. This difference was still

Table 3. Independent sample t test between heart failure patients with preserved ejection fraction (HFpEF) with normal pulmonary artery systolic pressure (PASP; Group 2A) and those with pulmonary hypertension (Group 2B) with regard to different echocardiographic parameters measured.

Variables	HFpEF patients		Independent sample *t* test	
	Group 2A (normal PASP)	Group 2B (PH)	*t*	*p*
ESD	3.56 ± 0.46	3.50 ± 0.44	−0.382	0.70
EDD	5.44 ± 0.44	5.30 ± 0.42	−0.909	0.37
FS	35.09 ± 4.21	33.99 ± 4.85	−0.715	0.48
EF (M-mode)	63.76 ± 5.55	61.56 ± 5.57	−1.127	0.27
EDV	30.19 ± 11.12	33.38 ± 9.42	0.849	0.40
ESV	72.85 ± 21.03	76.79 ± 17.21	0.554	0.58
EF (SIM)	58.35 ± 5.30	57.90 ± 4.80	−0.250	0.80
LAD	3.92 ± 0.38	4.29 ± 0.58	2.408	0.02
LAA	16.03 ± 3.84	19.90 ± 5.60	2.542	0.015
LAV	47.50 ± 16.26	64.94 ± 27.12	2.009	0.066
LAV/BSA	24.77 ± 8.25	33.54 ± 13.77	1.989	0.07
LAVEF	47.44 ± 11.81	39.46 ± 13.42	−1.858	0.07
E/A	0.81 ± 0.31	1.09 ± 0.52	1.679	0.12
DT	254.19 ± 50.99	238.00 ± 34.73	−0.972	0.34
E′	0.088 ± 0.02	0.10 ± 0.03	0.989	0.33
E/e′	7.43 ± 3.52	7.60 ± 2.63	0.147	0.88

Data are presented as mean ± standard deviation.
BSA = body surface area; DT = deceleration time; EDD = end diastolic diameter; EDV = end diastolic volume; EF = ejection fraction; ESD = end systolic diameter; ESV = end systolic volume; FS = fractional shortening; LAA = left atrial area; LAD = left atrial diameter; LAV = left atrial volume; LAVEF = left atrial volume emptying fraction; SIM = Simpson's model.

significant with regard to E/A ratio, DT, and degree of mitral regurgitation. Miller et al. [14] found that elevated PASP complicating chronic systolic HF had lower EF and DT and higher degree of functional mitral regurgitation. Nevertheless, these parameters were not independent predictors of PH in HFrEF patients in our study; this was partly in agreement with Enriquez-Sarano et al. [15], who found that DT and the effective regurgitant orifice area of mitral regurgitation but not EF or end systolic volume were independent predictors of PH in LV dysfunction. An association between the severity of LV diastolic dysfunction and increasing PASP has been shown previously [16]. However, there was no significant difference between the two subgroups in the current study with regard to diastolic function grading. We assume that this finding could be related to the low threshold of PH used in the current study and to the fact that most of the patients in both subgroups had mild degree of diastolic dysfunction.

There was significant difference between the two subgroups with regard to LAD, LAV, and LAV indexed to body surface area. LA size and function has been actively studied as a predictor of many adverse cardiovascular outcomes [17,18] These LA parameters are believed not only to measure the left atrium but also to act as a surrogate for either diastolic dysfunction or degree of mitral regurgitation or both and thus have their role in the pathogenesis of PH in left heart disease.

Also, there was significant difference with regard to TR with Group 1B showing increase in the severity of TR compared to Group 1A. Although TR severity varies among patients with comparable degrees of PH and right ventricular remodeling, tricuspid leaflet area is usually increased in PH and the adequacy of this increase determines TR severity [19].

The presence of diabetes ($p = 0.04$), diuretics usage ($p = 0.04$), LAV ($p = 0.007$), and TR grade ($p < 0.001$) were significant independent predictors for the development of PH among patients with HFrEF. In agreement with our results, Hansmann et al. [20] showed that PH is linked to insulin resistance and other authors suggested that insulin resistance can act as a novel disease modifier in PH [21,22]. In an editorial focus published nearly a decade ago, the author stated that ''Whether the increase in diabetes will be associated with an (delayed) increase in PH over the next few years and decades is not clear, but remains a possibility'' [23].

Tumminello et al. [24] also stated that LAV act as independent predictor of PASP in HF patients at rest. PASP is known also to be a strong determinant of TR severity among other factors as stated by Mutlak et al. [25]. The increased use of diuretics in patients with increasing PASP perhaps represent a marker of disease presence where the

increased pulmonary venous congestion and PH is relieved by decongesting the lungs through diuretics and thus an increased compliance of these patients to diuretics is seen.

Concerning the HFpEF group, there was no significant difference concerning diastolic dysfunction grading between the two subgroups, which may indicate precipitating factors for PH other than diastolic dysfunction itself, especially in the early phase of PH. There was significant difference between the two subgroups with regard to presence of hypertension ($p = 0.02$), and diuretics usage ($p = 0.009$). The increased usage of diuretics in the PH subgroup may be due to the role of diuretics in reducing PH through a reduction in left-sided filling pressures [10]. Concerning LA measurements, there was significant difference between the two subgroups with regard to LAD and LAA. According to Thenappan et al. [26] the presence of hypertension as well as left atrial enlargement among other factors best differentiated PH in HFpEF from PH alone or normal controls.

There was significant difference between patients in the HFpEF subgroups with regard to severity of both mitral regurgitation and TR with more patients having higher grade of mitral regurgitation and TR in the PH subgroup. This is believed to be related to the fact that mitral regurgitation plays a role in the development of PH [27], whereas TR is a reflection of severity of this PH. This was in agreement with recent studies that concluded that TR progression was associated with worsening PH [28,29].

In the current study, only diuretics usage ($p = 0.02$) and TR grade ($p < 0.0001$) were significant independent predictors for evolving PH among patients with HFpEF. This was in agreement with earlier studies that showed that TR velocity was an independent predictor of exercise-induced PH in patients with normal left ventricular systolic function [30]. Lam et al. [12] hypothesized that PH would be related to the development and severity of clinically significant pulmonary congestion, thus distinguishing HFpEF from preclinical hypertensive heart disease without overt HF. In this context, the significant increase in diuretic usage among HFpEF patients in the PH subgroup could be explained.

4.1. Study limitations and recommendations

Many studies have tried to determine independent predictors of PH among HF patients. The diversity of the results of these studies is mainly due to the different definitions of PH used as well as the different predictors studied. As the current study is unique in applying low threshold for the development of PH in heart failure patients, it showed disagreement with number of earlier studies who studied predictors for the development of higher degrees of PH and thus our hypothesis is that different predictors affect different degrees of PH. Also the predictive value of the parameters studied for subsequent progression of PH would require a long-term follow-up study, which is being prepared.

The role of diabetes in the development of PH in HFrEF patients should be further evaluated by using different biochemical markers to determine if the mere presence of diabetes, its duration, the levels of control of blood sugar, or all these factors contribute to PH among HF patients. Establishing different cut-off points for biochemical markers for diabetes and relating these cut-off points to the development of PH is currently an area of active research in our institute.

5. Conclusion

PH is an important cause of increased morbidity and mortality among HF patients. The early detection of PH among these patients would allow for proper patient care and careful follow-up, thus reducing both morbidity and mortality by applying targeted therapies suitable for these patients.

In the mild degree of PH neither the decrease in EF among HFrEF patients nor the diastolic dysfunction grade in HFpEF patients act as independent predictors for evolving PH. Common independent predictors for evolving PH in both HFrEF and HFpEF patients are the increased severity of TR and increased use of diuretics. Other independent predictors present in HFrEF and not in HFpEF patients are the presence of diabetes and increased LAV.

Conflict of interest

All authors have no conflicts of interest to declare.

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