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.

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. 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.

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

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