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RESEARCH ARTICLE

Lipoprotein-associated phospholipase A2 activity in patients with preserved left ventricular ejection fraction

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Abstract

Background: A significant proportion of heart failure (HF) patients have preserved ejection fraction (EF). Considering that inflammation and oxidative stress are involved in HF evolution, we investigated lipoprotein-associated phospholipase A2 (LpPLA2), an enzyme involved in these pathophysiologic processes in relation to EF.

Methods and results: The study included 208 HF patients and 20 healthy controls. HF patients with preserved EF (HFpEF) represented 42.31% of all HF patients. LpPLA2 activity was significantly increased in HF patients when compared with controls and was higher in HFpEF than in HF with reduced EF patients (HFrEF). The incidence of left ventricular hypertrophy was higher in HFpEF than in HFrEF (EF < 50).

Conclusion: Confirming its role as a marker of vascular inflammation, LpPLA2 seems to be a biomarker constantly correlated with HF, regardless of etiology. Elevated plasma values of LpPLA2 in HFpEF are consistent with the exacerbated inflammatory status.

Keywords: Inflammation, lipoprotein-associated phospholipase A2, heart failure with preserved ejection fraction

Introduction

Despite important advances in our knowledge of its mechanisms and treatment, heart failure (HF) remains one of the most challenging conditions, in both basic research and treatment. A lot of processes are involved in the evolution of HF: inflammation, oxidative stress, neurohormonal activation, extracellular matrix remodeling, myocyte injury, and renal dysfunction. Approximately 50% of HF patients have a preserved ejection fraction (HFpEF) (Hogg, Ewedberg and Mc Murray 2004). Almost all aspects of this condition remain in dispute (Pieske 2011).

Biomarkers are increasingly used for diagnosis and disease monitoring, but none proved to be particularly useful in HFpEF. Brain Natriuretic Peptide and proBNP, the most important markers in EF evaluation are not sufficient to discriminate between HFpEF and other HF patients (De Keulenaer and Brutsaert 2008). Because inflammation and oxidative stress are involved in HF pathophysiology, we investigated lipoprotein-associated phospholipase A2 (LpPLA2), an enzyme involved in these pathophysiologic processes in relation to EF.

LpPLA2 (secreted by cells involved in atherogenesis), is now recognized as a marker of vascular inflammation which has a relative unique characteristic being independent from the body mass index and insulin resistance and also has low biologic variability, similar to lipids (Corson, Jones and Davidson 2008; Schmitz and Ruebsaamen 2010).

An independent association was reported between LpPLA2 and HF incidence in a population based cohort of healthy individuals (van Vark et al. 2006), and it was suggested that LpPLA2 may lead to a higher risk in HF (Gerber et al. 2009). An evaluation of LpPLA2 activity function of the EF value had not been investigated until now.

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Methods

The study included 208 patients with a discharge diagnosis of HF, categorized in two groups in relation to the EF: those with 50% ≤ EF ≤ 70 % (HFpEF) and those with EF < 50% (HF with reduced EF (HFrEF)) and 20 healthy controls, age and gender-matched. The study was approved by the local ethics committee and informed consent was obtained from all participants.

Patients with recent (<3 months) acute coronary syndrome or stroke were not included.

Plasma obtained from HF patients and healthy controls was frozen and stored at –80°C until analysis.

LpPLA2 activity was measured by the spectrophotometric method described by Kosaka et al., using Azwell Auto LpPLA2 kit and expressed as IU/L (Kosaka et al. 2000).

Baseline evaluation of HF patients included clinical examination, 12-lead electrocardiography (ECG) and ECG Holter monitoring, New York Heart Association class assessment, transthoracic echocardiography (evaluation of left ventricular ejection fraction and left ventricular wall thickness), left ventricular hypertrophy (LVH) estimation and routine laboratory tests.

Statistical analysis

All values were reported as mean ± standard deviation (SD). Comparisons between groups were carried out using analysis of variance. The significance of correlations was evaluated by determining Pearson's rank correlation coefficients. A two tailed p-value < 0.05 was considered to be significant for all analyses. The statistical analyses were performed with the SPSS software, version 11.0 (SPSS Inc., Chicago, Illinois, USA).

Results

The baseline characteristics of patients are presented in Table 1.

HFpEF patients represented 42.31% of all HF patients. 84.09% of HFpEF patients have non-ischemic etiology (arterial hypertension, hypertrophic cardiomyopathy, valvular aortic disease). Non-ischemic etiology was predominant in HFrEF too, but the distribution was more balanced (60.00% non-ischemic vs. 40.00% ischemic).

LVH was detected in 47.73% of HFpEF patients and only in 36.67% of HFrEF patients. LpPLA2 activity was higher in HF patients than in normal [(414.25 ± 105.81) U/L vs (225.65 ± 20.8) U/L ($p < 0.0001$)]. LpPLA2 activity was higher in HFpEF than in HFrEF [(442.44 ± 112.65) U/L vs (393.57 ± 96.29) U/L ($p < 0.001$)] (Figure 1).

The increase of LpPLA2 activity of HFpEF correlated to higher LDL-cholesterol values (Table 1). Pearson correlation coefficient (r) of LpPLA2 and LDL-cholesterol was 0.41 in HFpEF and 0.38 in HFrEF.

Discussion

HFpEF can be considered a heterogeneous disease that includes patients with predominant diastolic dysfunction and patients with systolic and diastolic dysfunction due to different pathophysiologic abnormalities (Tschöpe and Westermann 2009). As HFpEF represents a complex pathophysiologic entity, the results of a clinical trial could be confounded by the heterogeneous nature of the enrolled patients (Bench et al. 2009). The correlation between plasma LpPLA2 and increased LDL-cholesterol has been previously reported in several studies (Ballantyne et al. 2004; Brilakis et al. 2005). Elevated plasma values of PLA2 in HFpEF concord with exacerbated inflammation status existing in these patients, which is confirmed by higher percent of LVH incidence compared with HFrEF.

Atrial fibrillation, a parameter which has been associated with myocardial oxidative stress (Neumann et al. 2007) was more present in HFpEF patients.

Confirming its role as a marker of endothelial inflammation, LpPLA2 seems to be a biomarker constantly correlated with HF regardless of etiology.

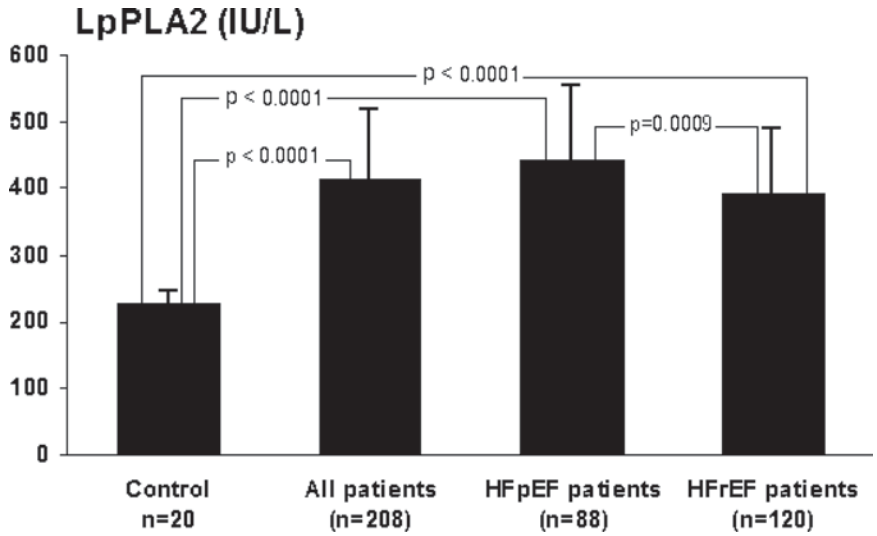

Figure 1. LpPLA2 values in HF patients. LpPLA2, lipoprotein-associated phospholipase A2; n, number of patients; HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction.

Table 1. Baseline characteristics of patients.

Variable	All patients ($n=208$)	Patients with HFpEF ($n=88$)	Patients with HFrEF ($n=120$)	p-value
Age, years (mean ± SD)	59.57 ± 11.67	57.59 ± 10.83	61.02 ± 12.08	0.0023
Male, *n* (%)	150 (72.12)	44 (50.00)	106 (88.33)	<0.0001
EF (%) (mean ± SD)	43.4 ± 13.81	55.9 ± 6.24	34.23 ± 10.16	<0.0001
NYHA class				
NYHA II, *n* (%)	80 (38.46)	44 (50.00)	36 (30.00)	<0.0001
NYHA III, *n* (%)	100 (48.08)	36 (40.91)	64 (53.33)	0.0057
NYHA IV, *n* (%)	28 (13.46)	8 (9.09)	20 (16.67)	0.0039
Medical history				
Hypertension, *n* (%)	112 (53.85)	54 (61.36)	58 (48.33)	0.0034
Diabetes, *n* (%)	42 (20.19)	18 (20.45)	24 (20.00)	0.9027
Dyslipidaemia, *n* (%)	122 (58.65)	54 (61.36)	68 (56.67)	0.2914
PHT, *n* (%)	52 (25.00)	20 (22.73)	32 (26.67)	0.3031
Laboratory measurements (mean ± SD)				
HDL-cholesterol (mg/dL)	42.72 ± 13.80	43.38 ± 15.92	42.38 ± 12.63	0.4596
LDL-cholesterol (mg/dL)	108.36 ± 50.65	123.93 ± 60.48	102.28 ± 45.23	<0.0001
Triglycerides (mg/dL)	124.30 ± 68.21	133.17 ± 72.65	119.15 ± 65.28	0.0263
Cardiac functional tests				
LVH incidence, *n* (%}	86 (41.35)	42 (47.73)	44 (36.67)	0.0153
VPB, *n* (%)	36 (17.31)	10 (11.36)	26 (21.67)	0.0004
AF, *n* (%)	85 (40.87)	41 (46.59)	44 (36.67)	0.0294
LBBB, *n* (%)	24 (11.54)	2 (2.27)	22 (18.33)	<0.0001
RBBB, *n* (%)	30 (14.42)	10 (11.36)	20 (16.67)	0.0668

AF, atrial fibrillation; EF, ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; *n*, number of patients; NYHA, New York Heart Association; PHT, pulmonary hypertension; RBBB, right bundle branch block; VPB, ventricular premature beats.

Conclusions

LpPLA2 seems to be a biomarker constantly correlated with HF regardless of etiology, confirming its role as a marker of oxidative stress and vascular inflammation. This study provides original data on the importance of LpPLA2 as a marker of inflammation in HFpEF.

Declaration of interest

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