Growth/differentiation factor-15 (GDF-15) as a predictor of serious arrhythmic events in patients with nonischemic dilated cardiomyopathy

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April 05, 2024

Abstract

Introduction: Cardiac biomarkers have been proposed as a new tool to improve risk stratification of serious arrhythmic events in patients with heart failure (HF) beyond estimates of left ventricular ejection fraction. Growth differentiation factor (GDF)-15, a stress-induced cytokine, has been found to correlate with markers of myocardial fibrosis and adverse clinical outcomes, but its role as a predictor of arrhythmic events in patients with nonischemic HF is uncertain. Methods and Results: A prospective observational study was conducted in 148 nonischemic patients with HF who underwent comprehensive clinical and laboratory evaluation, including measurement of serum GDF-15. The study endpoints were serious arrhythmic events (which included appropriate implantable cardioverter-defibrillator therapy and sudden cardiac death) and all-cause mortality. Mean age of the cohort was 54.8±12.7 years, and mean left ventricular ejection fraction (LVEF) was 27.4±7.5. During a mean follow-up time of 42 months, arrhythmic events occurred in 28 patients (19%), and 40 patients (27%) died. An increase in serum GDF-15 (log-transformed) correlated linearly with a higher risk of serious arrhythmic events (HR 1.14, 95% CI 1.01-1.28, p=0.03) even after adjustment for other potential clinical predictors (HR 1.16, 95% CI 1.02-1.32, p=0.02). GDF-15 was also strongly and independently associated with all-cause mortality (HR 1.17, 1.05-1.31, p=0.004). Conclusion: In this cohort of nonischemic HF patients on optimized medical treatment, serum GDF-15 levels were independently associated with major arrhythmic events and overall mortality. This biomarker may add prognostic information beyond LVEF to better stratify the risk of sudden death in this particular population.

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Funding: Fundo de Incentivo à Pesquisa e Eventos (FIPE) do Hospital de Clínicas de Porto Alegre

Disclosures: None

Conflict of interest: The authors report no relationships

that could be construed as a conflict of interest

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ABSTRACT

Introduction: Cardiac biomarkers have been proposed as a new tool to improve risk stratification of serious arrhythmic events in patients with heart failure (HF) beyond estimates of left ventricular ejection fraction. Growth differentiation factor (GDF)-15, a stress-induced cytokine, has been found to correlate with markers of myocardial fibrosis and adverse clinical outcomes, but its role as a predictor of arrhythmic events in patients with nonischemic HF is uncertain.

Methods and Results: A prospective observational study was conducted in 148 nonischemic patients with HF who underwent comprehensive clinical and laboratory evaluation, including measurement of serum GDF-15. The study endpoints were serious arrhythmic events (which included appropriate implantable cardioverter-defibrillator therapy and sudden cardiac death) and all-cause mortality. Mean age of the cohort was 54.8±12.7 years, and mean left ventricular ejection fraction (LVEF) was 27.4±7.5. During a mean follow-up time of 42 months, arrhythmic events occurred in 28 patients (19%), and 40 patients (27%) died. An increase in serum GDF-15 (log-transformed) correlated linearly with a higher risk of serious arrhythmic events (HR 1.14, 95% CI 1.01-1.28, p=0.03) even after adjustment for other potential clinical predictors (HR 1.16, 95% CI 1.02-1.32, p=0.02). GDF-15 was also strongly and independently associated with all-cause mortality (HR 1.17, 1.05-1.31, p=0.004).

Conclusion: In this cohort of nonischemic HF patients on optimized medical treatment, serum GDF-15 levels were independently associated with major arrhythmic events and overall mortality. This biomarker may add prognostic information beyond LVEF to better stratify the risk of sudden death in this particular population.

Keywords: Heart Failure; Growth Differentiation Factor 15; Sudden Death; Mortality; Cardiomyopathies

INTRODUCTION

Heart failure is a major public health issue associated to a high prevalence worldwide and a decay in health-related quality of life and overall mortality. In approximately 35% to 50% of patients, the etiology of ventricular dysfunction is nonischemic. Estimates of the prevalence of coronary disease among HF patients vary considerably around the globe. However, myocardial infarction is playing a less prominent role in heart failure etiology in recent years. Despite recent therapeutic advances, patients with heart failure with reduced ejection fraction still experience elevated mortality due to progressive heart failure (HF) and sudden cardiac death (SCD).[1]

The central strategies for primary prevention of SCD in nonischemic HF patients include implementation of guideline-directed medical therapy (GDMT) for heart failure and implantable cardioverter-defibrillator (ICD) placement. Current guideline recommendations for ICD implantation are based only on New York Heart Association (NYHA) functional class and left ventricular ejection fraction (LVEF).[2,3] However, trials assessing ICD effectiveness in nonischemic patients, including the DANISH trial, have failed to show a consistent benefit regarding total mortality.[4-7] Furthermore, a recent analysis of SCD-HeFT trial demonstrated that patients with nonischemic cardiomyopathy (NICM) did not experience long-term survival benefit from ICD implantation.[8] Recent uncertainties about long-term benefit and cost constraints make it clear that ICDs cannot be implanted in all patients fulfilling recommended guideline criteria. Identification of subgroups at higher or lower risk of SCD might help improve the cost-effectiveness of such therapy.[9-12]

Myocardial fibrosis identified by late gadolinium enhancement (LGE) on cardiovascular magnetic resonance imaging (MRI) has emerged as a strong predictor of SCD in nonischemic patients.[13,14] Growth differentiation factor (GDF)-15 is a protein belonging to the transforming growth factor-beta family. It is usually expressed in low concentrations in most organs and up-regulated in response to oxidative stress, tissue injury, and inflammation.[15] GDF-15 has been

correlated with the presence of focal and diffuse fibrosis detected by MRI in HF patients, regardless of etiology and LVEF.[16] Also, a positive correlation of this biomarker with the amount of myocardial fibrosis was demonstrated on cardiac biopsies in a population with advanced disease.[17] A recent small cohort study showed an association of increased risk of SCD and elevated levels of GDF-15 in patients with NICM.[18]

The present cohort study aims to determine the prognostic value of plasmatic GDF-15 as a predictor of serious arrhythmic events and all-cause mortality in nonischemic HF patients in contemporary cohort of patients on optimal guideline-directed medical therapy.

METHODS

Study design and population

This is an observational prospective study of participants included in a previous cohort published in 2017, which was designed to assess SCD predictors of risk in patients with NICM and LVEF $\leq$ 40%.[19] NICM was defined as the absence of atherosclerotic coronary lesions with greater than 75% stenosis at coronary arteriography, or absence of necrotic or ischemic areas by cardiac single photon emission computed tomography (SPECT) or cardiac magnetic resonance. Participants were followed-up at the Heart Failure and Cardiac Transplant clinic of Hospital de Clínicas de Porto Alegre (Porto Alegre, RS, Brazil), and enrolled from March 2011 to June 2016. All patients received standard drug and non-pharmacological management as recommended by contemporary guidelines.

The study protocol was approved by the Hospital de Clínicas de Porto Alegre Ethics Committee and written informed consent was obtained from all participants. After consent, patients underwent a detailed clinical evaluation, routine laboratory tests, non-invasive cardiac examination (EKG, Holter monitoring, two-dimensional echocardiography and cardiopulmonary exercise testing (CPET)), and invasive electrophysiological (EP) study. During the EP study, blood was drawn for

further biochemical analysis, including measurement of GDF-15. The clinical decision regarding ICD placement was taken by the clinical staff involved in routine care, with no direct interference of the research protocol or investigators.

Serum GDF-15 measurement

A 20-mL blood sample was collected from the patient by aspiration through the venous sheath by the time of the EP study. The blood sample was centrifuged in a dedicated research laboratory and stored at -70°C. Circulating GDF-15 was measured by enzyme-linked immunosorbent assay (ELISA), in duplicate, as instructed by the manufacturer (catalog no. EHGDF15, Thermo Fisher Scientific Inc., Frederick, MD, USA).

Follow-up and outcomes

Patients were followed in outpatient visits at 3, 6, 12 months and annually thereafter. Patients who failed to return were contacted by telephone, home visits, or indirectly through relatives. The clinic staff had access to all data collected during the research protocol.

The primary endpoint was the occurrence of serious arrhythmic events, defined as appropriate ICD therapy or SCD. Therapies were considered to be appropriate if the triggering rhythm was ventricular fibrillation or ventricular tachycardia. The secondary endpoint was death from any cause. Classification of outcomes was performed by an independent committee (composed of two researchers separately), blinded to the initial evaluation, based on clinical history, statements from family members, review of ICD or pacemaker electrograms, hospital charts, and death certificates. Definitions of discordant cases were evaluated by consensus.

Statistical analysis

Data are expressed as mean ± standard deviation, median and interquartile range (IQR), or absolute and relative frequencies, as appropriate. Comparisons between groups (with and without

events) were performed using Student's *t*-test or chi-square test for normally distributed variables, and nonparametric tests for variables with non-normal distribution. GDF-15 values were log-transformed because of skewed distribution. Cox regression was used for univariable and multivariable analysis of potential predictors for the primary and secondary outcomes. All statistical analyses were carried out in the SPSS (version 19.0) and R (version 3.1.3) statistical packages. A two-tailed p-value of 0.05 was considered statistically significant.

RESULTS

Study population and clinical outcomes

The study included 148 patients, mostly male (60%), with severe ventricular dysfunction, predominantly caused by idiopathic dilated cardiomyopathy. The mean age of the study cohort was 54.8±12.7 years. The mean LVEF was 27.4±7.5, and most were in New York Heart Association (NYHA) functional class I and II (82%) at enrollment. Regarding HF treatment, 144 (97%) were on ACE inhibitors or angiotensin receptor blockers (ARB) and on beta-blockers. Mean follow-up was 42±25 months. During the study, 40 (27%) patients received an ICD implant (19 single-lead and 4 dual-lead systems; 17 an ICD-R device). Eight patients (5.4%) underwent heart transplantation. No patients were lost during follow-up.

The primary endpoint occurred in 28 patients (19%), comprising sudden cardiac death in 17 patients (60%) and appropriate ICD therapy in 11 (40%). Forty patients died (27%). Table 1 shows baseline clinical characteristics of the study population stratified by the outcomes. Patients with serious arrhythmic events had larger left ventricular diameter and higher prevalence of exercise periodic breathing on CPET and non-sustained VT on 24-hour Holter. Patients who died from any cause were older, had larger left ventricular diameter, lower LVEF, lower peak oxygen uptake (VO_2), and higher GDF-15 levels.

GDF-15 and serious arrhythmic events

The median GDF-15 value in the entire cohort was 1302 ng/L (IQR: 855-1979). GDF-15 levels were higher in the group with arrhythmic events (1563 *versus* 1270 ng/L, p=0.14), although the difference was not statistically significant.

In univariable Cox regression analysis, each 30% increment in baseline GDF-15 concentration (log-transformed) was associated with an increased risk of ventricular arrhythmias or SCD (HR 1.14, 95% CI 1.01-1.28, p=0.03). In addition, left ventricular end-diastolic diameter (LVEDD), exercise periodic breathing (EPB) identified in CPET, and non-sustained ventricular tachycardia (NSVT) were associated with a higher risk of the primary outcome **(Table 2, left).** GDF-15 remained an independent predictor after adjustment for these clinical variables (HR 1.16, 95% CI 1.02-1.32, p=0.02), as well as LVEDD and NSVT **(Table 2, right).** The risk of serious arrhythmic events increased linearly with increasing baseline GDF-15 values **(Figure 1).**

GDF-15 and all-cause mortality

Median GDF-15 levels were significantly higher in patients who died from any cause (1723 *versus* 1183 ng/L, p<0.001). Each 30% increase in serum GDF-15 (log-transformed) was strongly associated with higher risk of all-cause mortality (HR 1.17, 1.05-1.31, p=0.004). Other clinical variables predictive of total mortality were LVEDD, EPB and peak VO_2. In multivariable analysis, only GDF-15 and LVEDD remained independently associated with total mortality **(Table 3).**

DISCUSSION

Improved prediction of arrhythmic events is an unmet need in clinical practice, as there is uncertainty of the clinical benefits of ICD implantation as a routine strategy in NICM patients. In this prospective study, we demonstrated that GDF-15 was an independent predictor of serious arrhythmic events and total mortality in a cohort of nonischemic HF patients on contemporary

treatment. Although its biological function remains unclear, previous studies suggested that GDF-15 represents a broad marker of disease severity.[20,21] The current analysis, restricted to nonischemic patients, indicates that GDF-15 may help in the prognostication of both arrhythmic and non-arrhythmic death in patients with NICM.

Few studies have specifically addressed the value of GDF-15 in predicting arrhythmic events in this particular population. In a smaller study including 52 nonischemic HF patients with LVEF < 50%, Stojkovic et al. also demonstrated that GDF-15 was associated with increased risk of arrhythmic death and resuscitated SCD.[18] Scott et al. followed-up 156 patients with an ICD and did not observe an association between GDF-15 levels and appropriate ICD therapy. However, only 18% of patients were non-ischemic, and 63% had an ICD implanted as secondary prevention.[22] Differences in long-term benefits of ICD placement in ischemic and nonischemic patients have been recently enlightened by the results of the DANISH trial and the long-term outcomes of the SCD-HeFT trial.[8,23] Our findings suggest that GDF-15 might be an independent marker of arrhythmic risk beyond LVEF in patients with NICM. As previously suggested, the increased risk of serious arrhythmic events predicted by GDF-15 may be related to increased amounts of myocardial fibrosis. Presence of myocardial fibrosis has been consistently established as a strong risk factor for SCD and ICD shocks in patients with NICM[14]. Kanagala et al demonstrated that GDF-15 is a reliable biomarker of both focal and diffuse fibrosis in HF patients[16].

In approximately 4 years of follow-up, almost 20% of the participants from our cohort had sudden death or received appropriate ICD therapy, which represents a concerning incidence in a non-ischemic population. Current risk stratification based only on LVEF and HF functional class performs poorly. As such, prediction of adverse outcomes remains challenging in clinical practice. We have previously identified 3 simple clinical predictors of arrhythmic events (LVEDD > 73 mm, EPB, and NSVT on 24-hour Holter monitoring) in NICM patients.[19] Based on current findings, GDF-15 may be included as part of predictive rule to identify patients at high risk for SCD.

Refining risk stratification might help to increase likelihood of benefit of ICDs if prospective validated, thus increasing the cost-effectiveness of this therapy.

Our data showing that GDF-15 can predict overall mortality are consistent with previous studies. In an analysis of 1734 patients randomized in the Val-HeFT trial (44% of non-ischemic etiology), GDF-15 was independently associated with mortality.[24] In the HF-ACTION study, which included 2331 patients (49% of non-ischemic etiology), GDF-15 predicted overall mortality independently of other biomarkers.[25] Recently, a sub-study of the pivotal PARADIGM-HF trial, including 1935 patients (37% of non-ischemic etiology), also demonstrated that GDF-15 was associated with increased overall mortality.[26] Interestingly, GDF-15 values were not significantly modified by sacubitril/valsartan use, suggesting that GDF-15 might be related to a mechanism of tissue injury involving pathophysiologic processes not affected by these class of drugs. One can speculated that a better understanding of the cellular mechanisms involved in GDF-15 production can help in the development of new therapies for HF.

Some methodological aspects of our study deserve consideration. We acknowledge that our sample size and number of events is relatively small, although larger than previous studies assessing the role of GDF-15 measurement as a marker of arrhythmic events in NICM patients. As such, our study is hypothesis-generating and our findings need validation in larger samples. GDF-15 was measured only once at the time of the EP study, so we are unaware if the kinetics of GDF-15 or the time between the sample extraction and the outcomes could modify the observed results. We also did not measure other biomarkers related to HF prognosis. Observational studies demonstrated a correlation of GDF-15 with other biomarkers, especially BNP, but the prognostic value of GDF-15 was not affected by most of them in prior multivariate models.[24-27]

In conclusion, in this cohort study of nonischemic HF patients on optimized contemporary pharmacological treatment, GDF-15 was independently and strongly associated with serious arrhythmic events and total mortality. Leveraging simple clinical data and new biomarkers, our results reinforce that risk prediction of arrhythmic events in NICM can be substantially improved in

clinical practice. Additional studies, however, are needed to confirm the role of GDF-15 in the management and risk stratification of chronic outpatients with nonischemic HF.

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Figure 1. Relationship between growth differentiation factor-15 (GDF-15) levels and the risk of serious arrhythmic events

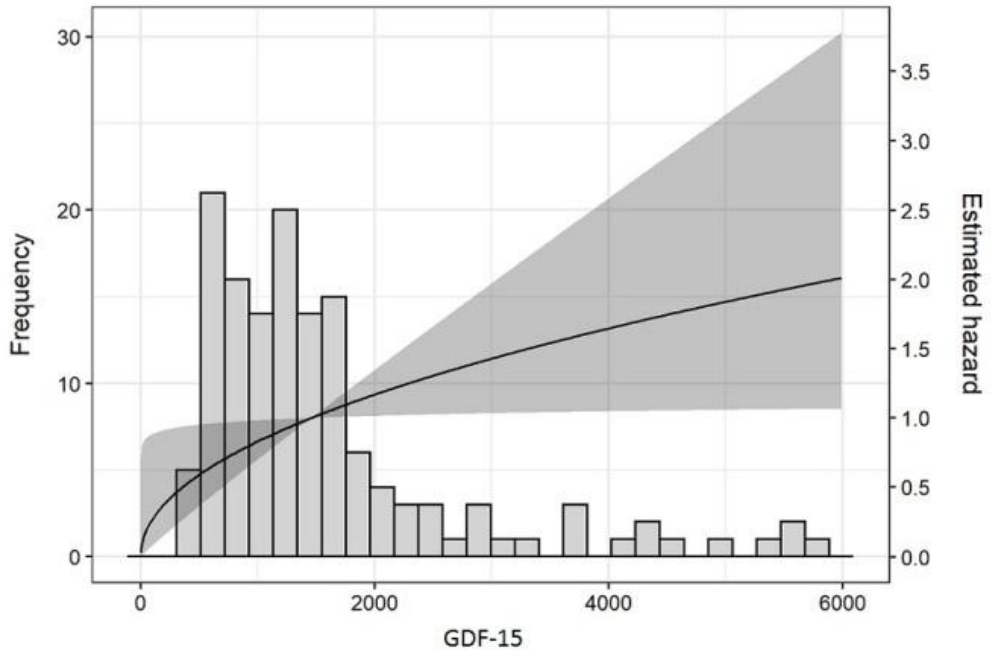

Table 1. Clinical characteristics of the study population stratified by clinical outcomes

	All patients	**With serious arrhythmic events**	**Without serious arrhythmic events**	**P value**	**Dead (all causes)**	**Alive**	**P value**
	n = 148	**n = 28**	**n = 120**		**n = 40**	**n = 108**	
Age (years)	54.8±12.7	54.5±14	54.9±12.4	0.94	59±12	53±12	0.002
Male gender (%)	88 (59.5)	18 (62)	70 (59)	0.54	30 (75)	58 (53.7)	0.02
NYHA Class (%)							
I	63 (42.6)	15 (52)	44 (37)	0.12	18 (45)	45 (41.7)	0.74
II	59 (40)	12 (41)	51 (43)		14 (35)	45 (41.7)	
III	26 (17.6)	2 (7)	24 (20)		8 (20)	18 (16.7)	
IV	0	0 (0)	0 (0)		0 (0)	0 (0)	
Laboratory values							
Hemoglobin (g/dL)	13.4±1.6	13.6±1.6	13.4±1.6	0.78	13.3±1.8	13.4±1.5	0.80
Creatinine (mg/dL)	1.1±0.73	1.17±0.5	1.14±0.8	0.20	1.28±0.5	1.10±0.7	0.002
Sodium (mEq/L)	140±2.8	140±2.1	139±2.9	0.86	139±2.6	140±2.8	0.76
GDF-15 (ng/L)	1302 (855-1979)	1563 (939-2555)	1270 (827-1841)	0.14	1723 (1169-3373)	1183 (791-1650)	<0.001
Echocardiography							
LV EF (%)	27.4±7.5	26.4±6.8	27.8±8.1	0.97	25±7.5	28.5±7.5	0.015
LV diastolic diameter (mm)	67.5±10.2	71.9±10	66.1±10	0.005	71±9.6	66.2±10.2	0.004
LV systolic diameter (mm)	58.7±10.1	60.3±13.7	58.2±8.8	0.15	62±10	57.2±9.6	0.004
EKG							
Atrial fibrillation	22 (14.9)	5 (17)	17 (14)	0.56	6 (15)	16 (15)	1.00

	All patients	With serious arrhythmic events	Without serious arrhythmic events	P value	Dead (all causes)	Alive	P value
	n = 148	n = 28	n = 120		n = 40	n = 108	
LBBB	60 (40.8)	14 (50)	47 (39)	0.39	21 (52)	40 (37)	0.09
24-hour Holter Monitoring							
Non-sustained VT (%)	54 (36.5)	17 (60)	37 (31)	0.005	16 (40)	38 (35)	0.70
CPET							
Peak VO_2 (mL/kg.min)	18±5.1	17±5.8	18.2±4.9	0.25	16±4.8	18.6±5	0.02
VE/VCO_2 slope	41.5±11.7	46±14.5	40.3±10.3	0.07	47.4±14.7	39.5±9.9	0.008
Periodic ventilation (%)	26 (17.5)	9 (32)	17 (14)	0.04	12 (30)	14 (13)	0.02
Medication							
Beta-blocker (%)	144 (97.3)	29 (100)	115 (96.5)	0.57	39 (97.5)	105 (97.2)	0.70
ACEi or ARB (%)	144 (97.3)	27 (94.1)	116 (98.2)	0.45	39 (97.5)	105 (97.2)	0.70
Spironolactone (%)	103 (69.6)	18 (64.7)	84 (71)	0.07	24 (60)	79 (73)	0.15
Digoxin (%)	121 (81.8)	24 (85)	95 (80)	0.49	35 (87.5)	86 (79.6)	0.34
Antiarrhythmic (%)	8 (5.4)	1 (3.4)	7 (5.8)	0.41	1 (2.5)	7 (6.5)	0.68

Data expressed as mean ± standard deviation, median (interquartile range),or n (%).

CPET: cardiopulmonary exercise test; NYHA: New York Heart Association; GDF-15: growth differentiation factor 15; LV: left ventricular; EF: ejection fraction; LBBB: left ventricular bundle branch block; VT: ventricular tachycardia; VO_2: oxygen consumption; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

Table 2. Univariate analysis and Cox proportional hazard model for serious arrhythmic events

	Univariable analysis			**Multivariable analysis***		
	HR	95% CI	*p*	HR	95% CI	*p*
GDF-15 (HR per 30% increase, log-transformed)	1.14	1.01-1.28	0.03	1.16	1.02-1.32	0.02
LVEDD (mm)	1.09	1.04-1.13	<0.001	1.09	1.04-1.13	<0.001
LBBB	1.54	0.73-3.25	0.25			
Atrial fibrillation	1.24	0.47-3.27	0.66			
EPB	2.77	1.25-6.14	0.01	1.85	0.82-4.20	0.13
NSVT	3.03	1.41-6.48	0.004	2.21	1.00-4.87	0.049
Positive EPS	2.05	0.76-5.51	0.15			

GDF-15: growth differentiation factor-15; LVEDD: left ventricular end-diastolic diameter; EPB: exercise periodic breathing; LBBB: left bundle branch block; NSVT: non-sustained ventricular tachycardia.
*adjusted by LVEDD, EPB and TVNS

Table 3. Univariate analysis and Cox proportional hazard model for all-cause mortality

	Univariable analysis			**Multivariable analysis***		
	HR	95% CI	*p*	HR	95% CI	*p*
GDF-15 (HR per 30% increase, log-transformed)	1.18	1.07-1.30	0.001	1.17	1.05-1.31	0.004
LVEDD (mm)	1.05	1.01-1.09	0.003	1.06	1.02-1.10	0.002
LBBB	1.81	0.96-3.39	0.06			
Atrial fibrillation	1.06	0.44-2.54	0.89			
Peak VO2 (mL/kg/min)	1.07	1.01-1.19	0.03	1.06	0.99-1.13	0.24
EPB	2.62	1.32-5.18	0.006	2.16	1.08-4.30	0.03
NSVT	1.36	0.72-2.57	0.33			

GDF-15: growth differentiation factor-15; LVEDD: left ventricular end-diastolic diameter; LBBB: left bundle branch block; Peak $VO_{2:}$ peak oxygen consumption; EPB: exercise periodic breathing; NSVT: non-sustained ventricular tachycardia.
*adjusted by LVEDD, peak VO2 and EPB