Journal of Research and Development
ISSN: 2311-3278

Berezin et al., J Res Development 2015, 3:1
DOI: 10.4172/2311-3278.1000121

Research Article Open Access

Circulating Osteoprotegerin as Predictor of Global Systolic Dysfunction in Type Two Diabetes Patients with Chronic Heart Failure

Berezin AE[1]*, Kremzer AA[2] and Samura TA[2]

[1]Internal Medicine Department, State Medical University, Zaporozhye, Ukraine
[2]Clinical Pharmacology Department, State Medical University, Zaporozhye, Ukraine

Abstract

Background: Biomechanical stress and inflammatory biomarkers relate to global contractility dysfunction, however, adding these biomarkers into a risk model constructed on clinical data does not improve its prediction value in chronic heart failure (CHF).

Objectives: The aim of this study was to evaluate the interrelationship between left ventricular global contractility function and circulating biomarkers in diabetic patients with ischemia-induced CHF.

Patients and methods: The study retrospectively selected 54 T2DM subjects from 388 patients who had systolic or diastolic ischemia-induced CHF, that was defined as left-ventricular ejection fraction ≤ 45% or 46-55% respectively assessed by quantitative echocardiography and other conventional criteria according to current clinical guidelines. Two-dimensional transthoracic echocardiography and Tissue Doppler Imaging were performed according to a conventional method. Serum adiponectin, NT-proBNP, osteoprotegerin, and hs-CRP were determined at baseline by ELISA.

Results: We found lower global longitudinal strain and strain rate in T2DM patients with LVEF <45% when compared with those who did not have (P=0.001 for all cases). Multivariate logistic regression reported that NT-proBNP (r=0.432; P=0.001 and r=0.402; P=0.001 respectively), osteoprotegerin (r=0.422; P=0.001 and r=0.401; P=0.001 respectively), hs-CRP (r=0.408; P=0.001 and r=0.404; P=0.001 respectively) were independently inversely associated with global longitudinal strain and global longitudinal strain rate in CHF patients.

Conclusion: We suggest that osteoprotegerin may be useful for improvement of NT-proBNP based model as predictor of decreased global contractility function in T2DM patients with CHF.

Keywords: Chronic heart failure; Global longitudinal strain and strain rate; Osteoprotegerin; Brain natriuretic peptide

Background

Chronic heart failure (CHF) remains a leading cause of cardiovascular morbidity and mortality worldwide [1,2]. There are evidences that metabolic comorbidities i.e. diabetes mellitus, obesity, insulin resistance, are reported as predictors of CHF in generally population as well as they are discussed aggravating factors for worsening CHF [3, 4]. The importance of coexistence of dysmetabolic conditions with CHF is not universally recognized. Indeed, dysmetabolic conditions including diabetes may contribute decreasing of global cardiac deformations frequently affected both right and left ventricles and associated with worsening of longitudinal, radial, and circumstance strain and strain rate [5,6]. Although global longitudinal strain is well validated as reproducible technique for the measurement of ventricular longitudinal deformation with predictive value regarding a composite of cardiac death, malignant arrhythmia, hospitalization due to CHF, urgent valve surgery or heart transplantation, as well as acute coronary ischemic events [7], the exact innate mechanisms that directly mediate cardiac mechanical disturbance are still uncertain [8]. Moreover, whether predictive value of left ventricular global longitudinal strain is similar for patients with declined and preserved left ventricular ejection fraction (LVEF) is under recognized [9]. In this context, discover and validate novel biomarkers for improving prediction value of global longitudinal strain is considered [10].

Currently emerging inflammatory (high-sensitive C-reactive protein [hs-CRP], osteoprotegerin) and biomechanical stress (N-terminal brain natriuretic peptide [NT-proBNP]) biomarkers are independently associated with all-cause mortality in patients with acute, acutely decompensated and chronic heart failure [11-14]. However, adding this biomarker into a risk model constructed on clinical data does not improve its prediction value, especially in diabetic population, while they relate to global contractility dysfunction [15].

Objectives

The aim of this study was to evaluate the interrelationship between left ventricular global contractility function and circulating biomarkers in diabetic patient with ischemia-induced CHF.

Patients and Methods

Patients

The study retrospectively selected 54 T2DM subjects from 388 patients who had systolic or diastolic ischemia-induced CHF, that was defined as left-ventricular ejection fraction ≤ 45% or 46-55%

***Corresponding author:** Alexander E Berezin, MD, PhD, Internal Medicine Department, State Medical University, Zaporozhye, Ukraine, Tel: 380612894585; E-mail: dr_berezin@mail.ru

Received January 29, 2015; **Accepted** February 20, 2015; **Published** March 02, 2015

Citation: Berezin AE, Kremzer AA, Samura TA (2015) Circulating Osteoprotegerin as Predictor of Global Systolic Dysfunction in Type Two Diabetes Patients with Chronic Heart Failure. J Res Development 3: 121. doi:10.4172/2311-3278.1000121

respectively assessed by quantitative echocardiography and other conventional criteria according to current clinical guidelines [16]. Criteria of ischemic-induced CHF were discharge from the hospital after Q-wave myocardial infarction (MI) more than 3 months prior study entry or undergone coronary angiography/revascularization procedures performed between February 2010 and July 2014. All the patients have given their written informed consent for participation in the study. The following are exclusion criteria: severe kidney and liver diseases; malignancy; brain injury within 3 months before the enrollment; ischemic stroke; intracranial hemorrhage; pulmonary edema; valvular heart disease; thyrotoxicosis; acute infections; trauma; inflammations within a previous month; pregnancy; implanted pacemaker.

T2DM was diagnosed with revised criteria provided by American Diabetes Association [17]. When one or more of the following components were found (glycated hemoglobin [HbA1c] ≥ 6.5%; fasting plasma glucose ≥ 7 mmol/L; 2-h plasma glucose ≥ 11.1 mmol/L during an oral glucose tolerance test; a random plasma glucose ≥ 11.1 mmol/L; exposure of insulin or oral antidiabetic drugs; a previous diagnosis of T2DM) T2DM was determined. Current smoking was defined as consumption of one cigarette daily for three months. Anthropometric measurements were made using standard procedures included weigh, body mass, waist circumstance measurement at study entry. Patients with T2DM were treated with life-style modification, diet and orally taken antidiabetic drugs except sulfonylurea derivates and glitazones. Metformin was given in individually optimized daily doses to be achieving full or partly full control for T2DM. Therefore, insulin was not used in enrolled patients.

Transthoracic echcardiography

Two-dimensional transthoracic echocardiography and Tissue Doppler Imaging were performed according to a conventional method on ACUSON scanner (SIEMENS, Germany) equipped with an phased probe of 2.5-5.0 MHz. Left ventricular (LV) end-diastolic (LVEDV) and LV end-systolic volumes (LVESV), and LV ejection fraction (LVEF) were measured by modified Simpson's method [18]. Inter- and intra-observer variability coefficients for LVEF were 3.2% and 1.1% respectively. The strain rate curves were recorded in the apical four-chamber, two-chamber view, and three-chamber views, as well as in short parasternal view with Speckle Tracking Two-Dimensional Echo-Cardiography [19]. Radial, longitudinal, and circumferential strain and strain rate values are obtained by Speckle-Tracking Imaging analysis of both basal and apical LV long-axis views. The analysis was performed off-line using the original program with Two-Dimensional Strain Rate Imaging Software (SIEMENS, Germany) according conventional method [20]. All ECG recording were collected and reviewed by single operator. The average peak systolic (Sm), early diastolic (Em), and late diastolic (Am) myocardial velocities were measured in the mitral annulus area, followed by calculating velocity of early diastolic left ventricular filling (E) to the Am (E/Am) ratio and to the Em (E/Em) ratio [21].

Calculation of glomerular filtration rate

Glomerular filtration rate (GFR) was calculated with CKD-EPI formula [22].

Measurement of circulating biomarkers

To determine circulating biomarkers, venous blood samples were collected at baseline in the morning (at 7-8 a.m.) into cooled silicone test tubes wherein 2 mL of 5% Trilon B solution were added. Then they were centrifuged upon permanent cooling at 6, 000 rpm for 3 minutes. Plasma was collected and refrigerated immediately to be stored at a temperature -70°C. Serum adiponectin, NT-proBNP, osteoprotegerin were measured by high-sensitive enzyme-linked immunosorbent assays using commercial kits (R&D Systems GmbH, Wiesbaden-Nordenstadt, Germany) according to the manufacturers' recommendations. The inter-assay coefficients of variation were as follows: adiponectin=5%, NT-proBNP=6.8%, OPG=8.2%. High-sensitive C-reactive protein (hs-CRP) was measured by commercially available standard kit (R&D Systems GmbH, Wiesbaden-Nordenstadt, Germany). The intra-assay and inter-assay coefficients of variation were <5%. Fasting insulin level was measured by a double-antibody sandwich immunoassay (Elecsys 1010 analyzer, F. Hoffmann-La Roche Diagnostics, Mannheim, Germany). The intra-assay and inter-assay coefficients of variation were <5%. The lower detection limit of insulin level was 1.39 pmol/L. Insulin resistance was assessed by the homeostasis model assessment for insulin resistance (HOMA-IR) [23] using the following formula:

HOMA-IR (mmol/L × μU/mL)=fasting glucose (mmol/L) × fasting insulin (μU/mL)/22.5

Insulin resistance was defined when estimated HOMA-IR value was over 2.77 mmol/L×μU/mL. Concentrations of total cholesterol (TC) and cholesterol of high-density lipoproteins (HDL-C) were measured by enzymatic method. Concentration of cholesterol of low-density lipoproteins (LDL-C) was calculated according to the Friedewald formula (1972) [24].

Statistical analysis

Statistical analysis of the results obtained was performed in SPSS system for Windows, Version 22 (SPSS Inc, Chicago, IL, USA). The data were presented as mean (M) and standard deviation (± SD) or 95% confidence interval (CI); as well as median (Me) and 25%-75% interquartile range (IQR). To compare the main parameters of patient cohorts, two-tailed Student t-test or Shapiro–Wilk U-test were used. To compare categorical variables between groups, Chi^2 test ($\chi 2$) and Fisher F exact test were used. Predictors of decreased global strain rate in patients were examined in univariable and multivariable linear regression analysis. C-statistics, integrated discrimination indices (IDI) and net-reclassification improvement (NRI) were utilized for prediction performance analyses. A two-tailed probability value of <0.05 was considered as significant.

Results

General characteristic of patients participating in the study is reported in Table 1. The mean age for patients with T2DM was 48.50 years. Sixty three percent of the subjects were male. The median of body mass index (BMI) and waist circumference were referred 28.5 kg/m^2 and 89 sm. Hypertension, dyslipidemia, and smoking were found 66.7%, 61.1%, and 27.7% patients. The most subjects were experienced III (61.1%) and IV (29.6%) class NYHA of CHF. Circulating biomarkers of inflammatory activity (hs-CRP), biomechanical stress (NT-proBNP, osteoprotegerin), dysmetabolic changes (adiponectin) were elevated slightly-to-moderately. There were no significant difference between T2DM subjects with LVEF <45% and >46% regarding demographic, BMI, waist circumference, lipid abnormalities, blood pressure, heart rate, fasting blood glucose, and creatinine. However, hypertension, adherence to smoking, NYHA class II and III were found frequently in T2DM patients with LVEF ≥ 46% when compared with those who had LVEF <45%. Subjects with LVEF <45% demonstrated higher HOMA-IR, insulin, hs-CRP, NT-proBNP, osteoprotegerin, and adiponectin

	Entire cohort of enrolled T2DM patients (n=54)	Subjects with LVEF <45% (n=29)	Subjects with LVEF ≥ 46% (n=25)	P value
Age, years	48.50 ± 6.60	49.10 ± 5.30	46.88 ± 4.87	NS
MALES, N (%)	34 (63.0%)	18 (62.1%)	16 (64.0%)	NS
BMI, kg/m^2	28.5 (25-75% IQR=16.8–32.1)	28.2 (25-75% IQR=16.9–31.2)	29.1 (25-75% IQR=17.1–32.0)	NS
Waist circumference, sm	89 (25-75% IQR=72–100)	86 (25-75% IQR=70–98)	92 (25-75% IQR=71–102)	NS
Hypertension, n (%)	36 (66.7%)	15 (51.7%)	21 (84%)	<0.001
Dyslipidemia, n (%)	33 (61.1%)	17 (58.6%)	16 (64%)	NS
Adherence to smoking, n (%)	15 (27.7%)	6 (20.7%)	9 (36%)	<0.001
NYHA class II	5 (9.3%)	2 (6.9%)	3 (12.0%)	<0.001
NYHA class III	33 (61.1%)	16 (55.1%)	17 (68.0%)	<0.001
NYHA class IV	16 (29.6%)	11 (37.9%)	5 (20.0%)	<0.001
Systolic BP, mm Hg	136 ± 5	133 ± 4	138 ± 3	NS
Diastolic BP, mm Hg	86 ± 4	85 ± 5	88 ± 3	NS
Heart rate, beats per 1 min.	72 ± 5	72 ± 4	71 ± 5	NS
fasting blood glucose, mmol/L	5.54 (95% CI=4.49-9.0)	5.60 (95% CI=4.47-9.3)	5.52 (95% CI=4.46-9.1)	NS
HbA1c, %	8.14 (95% CI=7.29-9.3)	8.10 (95% CI=7.15-9.1)	8.19 (95% CI=7.20-9.2)	NS
Insulin, μU/mL	15.6 (25-75% IQR=12.9-16.8)	16.0 (25-75% IQR=13.3-17.5)	15.3 (25-75% IQR=12.4-16.3)	<0.001
HOMA-IR, mmol/L × μU/mL	3.86 (25-75% IQR=3.41-4.10)	4.82 (25-75% IQR=4.15-5.20)	3.75 (25-75% IQR=3.32-4.00)	<0.001
CREATININE, MMOL/L	71.2 (95% CI=59.9–87.2)	73.4 (95% CI=61.4–86.5)	70.2 (95% CI=59.2–84.6)	NS
Total cholesterol, mmol/L	5.4 (95% CI=4.8-5.8)	5.39 (95% CI=4.35-5.61)	5.49 (95% CI=4.55-6.1)	NS
LDL-C, mmol/L	3.80 (95% CI=3.20–4.20)	3.72 (95% CI=3.28–4.50)	3.85 (95% CI=3.15–4.66)	NS
HDL-C, mmol/L	0.94 (95% CI=0.88–1.04)	0.92 (95% CI=0.85–1.00)	0.95 (95% CI=0.87–1.08)	NS
TG, mmol/L	1.45 (95% CI=1.42–1.51)	1.49 (95% CI=1.44–1.60)	1.41 (95% CI=1.37–1.53)	NS
hs-CRP, mg/L	8.10 (25-75% IQR=4.80 – 9.54)	8.35 (25-75% IQR=5.10 –10.70)	7.83 (25-75% IQR=4.55 – 9.12)	<0.001
NT-proBNP, pg/mL	2126.20 (25-75% IQR=1035.1-3540.1)	2977.50 (25-75% IQR=1286.1-3339.5)	1673.50 (25-75% IQR=1044.2-3110.5)	<0.001
Osteoprotegerin, pg/mL	732.1 (25-75% IQR=587.5-866.3)	794.5 (25-75% IQR=622.1-890.5)	715.8 (25-75% IQR=565.9-855.7)	<0.001
Adiponectin, mg/L	14.12 (25-75% IQR=10.12-23.10)	16.30 (25-75% IQR=11.55-25.90)	13.47 (25-75% IQR=9.50-18.20)	<0.001

Table 1: General characteristic of patients participating in the study.*Note:* Data are presented as mean and ±SE or 95% CI; median and 25-75% IQR. Categorical variables are expressed as numerous (n) and percentages (%). P-value is a comparison of mean or median variables between both subject cohorts (ANOVA test).

	Entire cohort of enrolled T2DM patients (n=54)	Subjects with LVEF <45% (n=29)	Subjects with LVEF > 46% (n=25)	P value
LVEF, %	46.07 ± 5.73	48.62 ± 4.04	40.15 ± 3.98	<0.001
Global longitudinal strain, %	-8.12 (95% CI=-10.80 – -6.10)	-9.85 (95% CI=-11.2 – -8.61)	-7.40 (95% CI=-10.24 – -6.67)	0.001
Global radial strain, %	13.82 (95% CI=9.25 – 20.7)	14.1 (95% CI=11.2 – 19.2)	11.84 (95% CI=9.55 – 16.37)	NS
Global circumferential strain, %	-10.24 (95% CI=-14.72 – -6.85)	-11.20 (95% CI=-14.10 – -6.82)	-9.33 (95% CI=-13.15 – -6.74)	NS
Global longitudinal strain rate, c^{-1}	-0.52 (95% CI=-0.68 – -0.37)	-0.50 (95% CI=-0.66 – -0.41)	-0.42 (95% CI=-0.56 – -0.38)	0.001
Global radial strain rate, c^{-1}	0.88 (95% CI=0.61 – 1.30)	0.91 (95% CI=0.62 – 1.25)	0.79 (95% CI=0.63 – 1.21)	NS
Global circumferential strain rate, c^{-1}	-0.76 (95% CI=-1.10 – -0.49)	-0.78 (95% CI=-1.08 – -0.52)	-0.74 (95% CI=-0.92 – -0.54)	NS
E/A`, Units	26.6 ± 2.94	26.1 ± 2.61	27.2 ± 2.55	NS
E/E`, Units	21.6 ± 3.00	19.1 ± 1.68	22.5 ± 1.66	NS

Table 2: Echocardiographic performances in T2DM patients with CHF.*Notes*: LVEF – left ventricular ejection fraction, E` – early diastolic myocardial velocity, A` – late diastolic myocardial velocity, E – peak early left ventricular diastolic filling, NS - not significant.

levels when compared with patients with LVEF ≥ 46%. The basic echocardiographic performances in CHF patients are presented in Table 2. We found lower longitudinal global strain and strain rate in T2DM patients with LVEF <45% when compared with those who did not have (P=0.001 for all cases). Global longitudinal strain and strain rate abnormalities that are suitable for both patient cohorts are reported in Figure 1. The concomitant treatment of CHF patients is presented in Table 3. All patients were treated with ACE inhibitors and angiotensin-II receptor blockers. There were no significant difference between both cohort patients in mineralocorticoid antagonist, beta-blocker, ivabradine, loop diuretic, and statin use. Aspirin was given frequently in subjects with LVEF ≥ 46% (P=0.042), in opposite, other antiplatelets were added frequently to the concomitant drugs in subjects with LVEF <45% (P=0.046). Using univariate logistic regression we found that global longitudinal strain and global longitudinal strain rate closely associated with NT-proBNP (r=0.502; P=0.001 and r=0.414; P=0.003 respectively), NYHA class (r=0.405; P=0.001 and r=0.402; P=0.001 respectively), osteoprotegerin (r=0.426; P=0.001 and r=0.402; P=0.006 respectively), hs-CRP (r=0.412; P=0.002 and r=0.406; P=0.001 respectively), HOMA-IR (r=-0.353; P=0.009 and r=-0.348; P=0.001 respectively), LVEF (r=0.24; P=0.001 and r=0.26; P=0.001 respectively), LDL cholesterol (r=0.204; P=0.001 and r=0.206; P=0.001 respectively), and age of the patients (r=0.202; P=0.001 and r=0.204; P=0.001 respectively). Multivariate logistic regression reported that NT-proBNP (r=0.432; P=0.001 and r=0.402; P=0.001 respectively), Osteoprotegerin (r=0.422; P=0.001 and r=0.401; P=0.001 respectively), hs-CRP (r=0.408; P=0.001 and r=0.404; P=0.001 respectively) independently inversely associated with global longitudinal strain and global longitudinal strain rate in CHF patients. Therefore, we found closely association between osteoprotegerin and NT-proBNP

	Entire cohort of enrolled T2DM patients (n=54)	Subjects with LVEF <45% (n=29)	Subjects with LVEF > 46% (n=25)	P value
ACE inhibitors or ARBs, n (%)	54 (100%)	29 (100%)	25 (100%)	NS
Beta-blockers, n (%)	42 (77.7%)	23 (79.3%)	19 (76.0)	NS
Ivabradine, n (%)	39 (72.2%)	21 (72.4%)	18 (72.0%)	NS
Mineralocorticoid receptor antagonists, n (%)	23 (42.6%)	12 (41.3%)	11 (44.0%)	NS
Loop diuretics, n (%)	54 (100%)	29 (100%)	25 (100%)	NS
Aspirin, n (%)	48 (88.9%)	25 (86.2%)	23 (92.0%)	0.042
Other antiplatelets, n (%)	6 (11.1%)	4 (13.8%)	2 (8.0%)	0.046
Statins, n (%)	54 (100%)	29 (100%)	25 (100%)	NS

Table 3: Concomitant treatment of CHF patients.*Notes*: ACE – angiotensin-converting enzyme, ARBs – angiotensin-2 receptor blockers. Categorical variables are presented as numerous (n) and frequency (%), NS - not significant.

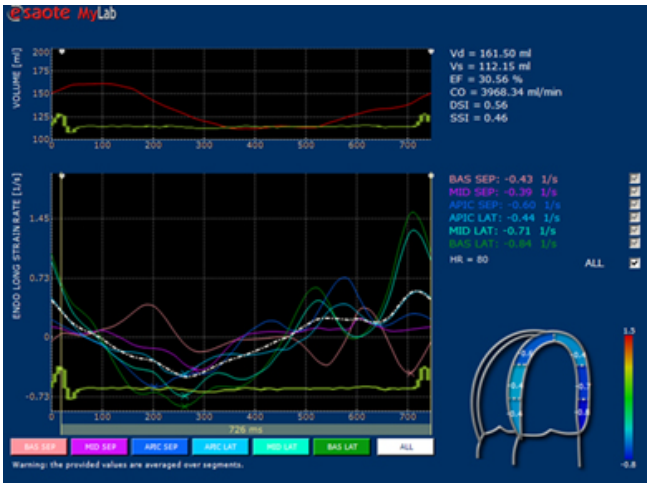

Figure 1a: Shows declined global strain rate for T2DM patients with reduced LVEF.

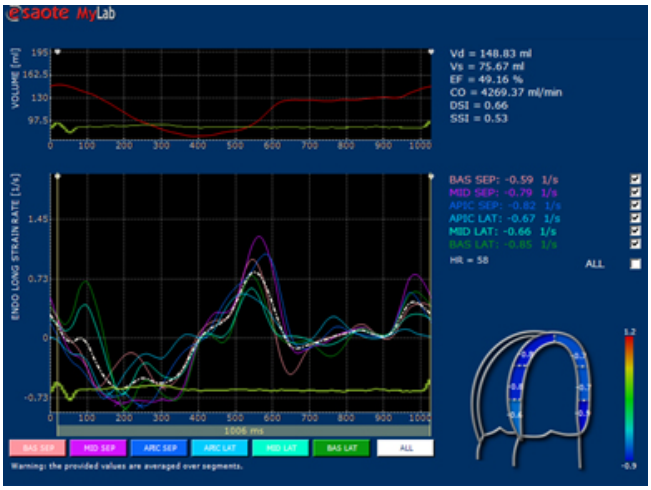

Figure 1b: Shows declined global strain rate for T2DM patients with preserved LVEF
Abbreviations: LVEF – left ventricular ejection fraction.

(r=0.436; P=0.001), adiponectin (r=-0.443; P=0.001), BMI (r=0.422; P=0.003), and NYHA class (r=0.402; P=0.001). Using C-statistics for Models with NT-proBNP, hs-CRP, osteoprotegerin and adiponectin as continuous variables we found that adding osteoprotegerin to the based ABC model (NT-proBNP) improved the relative IDI by 9.8% for decreased global left ventricular function defined as worsening both global longitudinal strain and global longitudinal strain rate (Table 4). Therefore, combination of osteoprotegerin and hs-CRP added to ABC model improved the relative IDI by 10.1%. When we compared both models constructed on combination osteoprotegerin + hs-CRP + based model and osteoprotegerin alone + based model we did not obtain a significant difference between relative IDI (P=0.058). When we used other model constructed on entering of variables, IDI appears to be improved up to 5% for decreased global left ventricular function (available for osteoprotegerin as continuous variables) (Table 5). In patient study population for category-free NRI, 5% of events (p=0.001) and 11% of non-events (p=0.001) were correctly reclassified by the addition of OPG to the base model (NT-proBNP) for decreased global left ventricular function.

Discussion

The results of our study shown that osteoprotegerin added to NT-proBNP predicts declining of global contractility function in T2DM patients with CHF. Surprisingly, hs-CRP, adiponectin, and clinical criteria (NYHA class) were not defined as powerful independent tools for determination of worsening global contractility function. Although global longitudinal strain is an excellent predictor of adverse LV remodeling and cardiac events in acute and decompensated heart failure with preserved LVEF, T2DM patients with CHF are not considered optimal candidates for global longitudinal strain and strain rate measurements [25]. In fact, diabetic subjects without overall obesity and lower LVEF may have significantly declining global longitudinal strain and strain rate. Therefore, a reasonable correlation between LVEF and global longitudinal strain was found in CHF subjects with declined LVEF ≤ 40% [26]. CHF with preserved LVEF is frequently reported among T2DM patients, while reproducibility of speckle tracking echocardiography remains a matter of controversy [27]. Taken together these facts appear to be argument for discover a novel biological markers for risk stratification of the patients with CHF that may increase an utility of speckle tracking echocardiography. Osteoprotegerin, hs-CRP, and NT-proBNP are defined as emerge biomarkers related to inflammatory activity and biomechanical stress that are associated with all-cause and cardiovascular mortality in heart failure [11,12]. It has reported that osteoprotegerin was found to be an independent predictor of impaired global longitudinal strain in hypertensive T2DM patients with subclinical left ventricular dysfunction i.e. euvolemic subjects [12]. We shown that osteoprotegerin added to NT-proBNP predicts well worsening of global longitudinal strain and strain rate in both cohorts of T2DM patients with moderate-to-severe CHF including reduced LVEF and preserved LVEF. Recently osteoprotegerin was defined potentially biomarker for cardiovascular

Models	Dependent variable: decreased global left ventricular function			
	AUC (95% CI)	ΔAUC	IDI (± SE)	Relative IDI (%)
Model 1 (based model: NT-proBNP)	0.655	-	-	-
Model 1 + OPG	0.687	-	-	-
Model 1 + OPG vs Model 1	-	0.032; P<0.05	0.05 ± 0.008	9.80%
Model 1 (based model: NT-proBNP)	0.655	-	-	-
Model 1 + hs-CRP	0.678	-	-	-
Model 1 + hs-CRP vs Model 1	-	0.023; P=0.048	0.03 ± 0.010	5.00%
Model 1 (based model: NT-proBNP)	0.655	-	-	-
Model 1 + OPG + hs-CRP	0.689	-	-	-
Model 1 + OPG + hs-CRP vs Model 1	-	0.034; P<0.05	0.06 ± 0.009	10.10%
Model 1 (based model: NT-proBNP)	0.655	-	-	-
Model 1 + adiponectin	0.675	-	-	-
Model 1 + adiponectin vs Model 1	-	0.020; P=0.055	0.02 ± 0.010	4.30%
Model 1 (based model: NT-proBNP)	0.655	-	-	-
Model 1 + adiponectin + OPG	0.684	-	-	-
Model 1 + adiponectin + OPG vs Model 1	-	0.029; P<0.05	0.05 ± 0.009	8.30%
Model 1 (based model: NT-proBNP)	0.655	-	-	-
Model 1 + hs-CRP + OPG + adiponectin	0.687	-	-	-
Model 1 + hs-CRP + OPG + adiponectin vs Model 1	-	0.032; P<0.05	0.05 ± 0.011	10.20%

Table 4: C-statistics for Models with NT-proBNP, hs-CRP, OPG, and adiponectin as Continuous Variables *Note*: Relative IDI – calculated as the ratio of IDI over the discrimination slope of the model without NT-proBNP.

Parameters	Model 2 versus Model 1
Categorical NRI	0.12 (95% CI 0.10-0.18)
Percentage of events correctly reclassified	5 (p=0.12)
Percentage of non-events correctly reclassified	8 (p=0.016)
Categorical free NRI	0.24 (95% CI 0.20-0.28)
Percentage of events correctly reclassified	5% (p=0.001)
Percentage of non-events correctly reclassified	11% (p=0.001)

Table 5: Prediction Performance Analyses for Models constructed on NT-proBNPand circulating osteoprotegerin as Continuous Variables for decreased global left ventricular function. *Note*: Model 1- NT-proBNP; Model 2 – NT-proBNP + OPG.

risk in the metabolic syndrome and adipose tissue was identified as a potential source of osteoprotegerin synthesis [28]. We confirm coexisting association between adiponectin and osteoprotegerin in CHF patients with T2DM, while adding adiponectin in based model constructed on NT-proBNP is not able to improve predictive value for entire model regarding declining of global contractility function. Overall, combination of both biomarkers included NT-proBNP and osteoprotegerin appears to be superior when compared with other models regarding lower global contractility function of left ventricle. Probably, biochemical stress that limits capacity of myocardial wall to deformation may be discussed as causal factor contributed in strain and strain rate. Indeed, osteoprotegerin is a member of tumor necrosis factor superfamily [29] and it is expressed *in vivo* osteoblasts, endothelial cells, smooth muscle cells and cardiomyocytes [30]. Osteoprotegerin is a specific receptor for the ligand receptor activation of nuclear transcription factor kappa beta and TNF-alpha-dependent ligand inducing apoptosis [31]. Osteoprotegerin is often seen as an indicator of inflammatory activation in opposite of NT-proBNP, which is reported as marker of biomechanical stress [32]. Although causality factors that mediate secretion of both biomarkers are different, osteoprotegerin and NT-proBNP are able to emerge as result in stretch and tenderness of myocardial wall. Recent clinical studies are discussed such reaction in context of volume overload, worsening of CHF and acute heart failure presentation [33,34]. We report that both biomarkers may useful for prediction of decreased left ventricular global contractility in T2DM patients with moderate-to-severe CHF, but adiponectin did not. It is unexpected result because of a closely association of plasma osteoprotegerin and adiponectin was found in diabetic patient population [35]. Therefore, it is well known that hs-CRP and adipocytokines are not able to improve integrative prediction for survival and admission rate in CHF patients, while natriuretic peptides, such as NT-proBNP, are able to increase of precision of prediction model based on clinical findings. Thus, we suggest that osteoprotegerin may be useful for improvement of NT-proBNP based model as predictor of decreased global contractility function in T2DM patients with CHF.

Study limitation

This study has some limitations. The first limitation is small sample size. However, this was not a randomized and controlled study. The authors believe that a greater cohort of patients with more incidences detected is desirable to improve the credibility of the study. Therefore we used the HOMA-IR equation for IR determination, while the euglycemic-hyperinsulinemic clamp technique is recommended optionally. Therefore, all CHF patients enrolled in the study were treated adequately and presented stable clinical status. Antidiabetic drugs were given in several dose ranges that were adjusted individually and fixed by physician as optimal for patient. Probably, hypervolemic patients might be reported other results and we emphasize that euvolemic state beyond fluid retention at rest is study limitation. Moreover, this fact should be taken into consideration before extrapolation of our results on another population. We did not divide T2DM patients with CHF regarding normal weight, overweight, and obesity, because of small size was presented. Overall, this is study limitation that was not able to check interplay between body mass and circulating level of biological markers in patients with strain and strain rate declining. However,

the authors suppose that these restrictions might have no significant impact on the study data interpretation. To be better understanding the role of biomarkers in prediction of declining of left ventricular global contractility function more investigations with increased sample size are required.

Conclusion

We found that adding of osteoprotegerin to NT-proBNP improves prediction of the standard model regarding declined global contractility function in T2DM patients with CHF.

Acknowledgment

We thank all patients for their participation in the investigation, staff of the Regional Zaporozhye Hospital (Ukraine), and the doctors, nurses, and administrative staff in Regional Center of Cardiovascular Diseases (Zaporozhye, Ukraine) and City Hospital # 6 (Zaporozhye, Ukraine), general practices, and site-managed organizations that assisted with the study.

References

1. Dunlay SM, Roger VL (2014) Understanding the epidemic of heart failure: past, present, and future. Curr Heart Fail Rep 11: 404-415.
2. Chamberlain AM, St Sauver JL, Gerber Y, Manemann SM, Boyd CM, et al. (2015) Multimorbidity in heart failure: a community perspective. Am J Med 128: 38-45.
3. Zafrir B, Goren Y, Salman N, Amir O (2014) Comparison of body mass index and body surface area as outcome predictors in patients with systolic heart failure. Cardiol J.
4. Khalid U, Ather S, Bavishi C, Chan W, Loehr LR, et al. (2014) Pre-Morbid Body Mass Index and Mortality After Incident Heart Failure: The ARIC Study. J Am Coll Cardiol 64: 2743-2749.
5. Li ZJ, Du LF, Luo XH (2014) Evaluation of ventricular-vascular coupling in patients with type 2 diabetes mellitus using 2-dimensional speckle tracking imaging. J Huazhong Univ Sci Technolog Med Sci 34: 929-934.
6. Cheng S, McCabe EL, Larson MG, Chen MH, Osypiuk, et al. (2015) Left ventricular mechanical function: clinical correlates, heritability, and association with parental heart failure. Eur J Heart Fail 17: 44-50.
7. Kalam K, Otahal P, Marwick T (2014) Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. Heart 100: 1673-80.
8. Morris DA, Boldt LH, Eichstädt H, Ozcelik C, Haverkamp W (2012) Myocardial systolic and diastolic performance derived by 2-dimensional speckle tracking echocardiography in heart failure with normal left ventricular ejection fraction. Circ Heart Fail 5: 610-620.
9. Ersbøll M, Valeur N, Mogensen UM, Andersen MJ, Møller JE, et al. (2013) Prediction of all-cause mortality and heart failure admissions from global left ventricular longitudinal strain in patients with acute myocardial infarction and preserved left ventricular ejection fraction. J Am Coll Cardiol 61: 2365-2373.
10. den Ruijter H, Pasterkamp G, Rutten FH, Lam CS, Chi C, et al. (2015) Heart failure with preserved ejection fraction in women: the Dutch Queen of Hearts program. Neth Heart J 23: 89-93
11. Aramburu BO, García-CB, Salamanca BP, GuisadoEME, AriasJJL, et al.(2014) Relationship between osteoprotegerin and mortality in decompensated heart failure with preserved ejection fraction. J Cardiovasc Med.
12. Kalaycıoğlu E, Gökdeniz T, Aykan A, Hatem E, Gürsoy MO, et al. (2014) Osteoprotegerin is associated with subclinical left ventricular systolic dysfunction in diabetic hypertensive patients: a speckle tracking study. Can J Cardiol 30: 1529-1534.
13. Don-Wauchope AC, McKelvie RS (2014) Evidence based application of BNP/NT-proBNP testing in heart failure. Clin Biochem.
14. Huynh K, Van Tassell B, Chow SL (2015) Predicting therapeutic response in patients with heart failure: the story of C-reactive protein. Expert Rev Cardiovasc Ther 13: 153-161.
15. Kodziszewska K, Leszek P, Korewicki J, Piotrowski WO (2014)New approach to assessment of risk in heart failure Kardiol Pol.
16. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, et al. (2012) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC Eur Heart J 14: 1787-1847.
17. Executive summary: Standards of medical care in diabetes-2013. (2013) Diabetes Care 36 Suppl 1: S4-10.
18. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, et al. (1989) Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 2: 358-367.
19. Geyer H, Caracciolo G, Abe H, Wilansky S, Carerj S, et al. (2010) Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. J Am Soc Echocardiogr 23: 351-369.
20. Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, et al. (2014) Global longitudinal strain: a novel index of left ventricular systolic function. J Am Soc Echocardiogr 17: 630-633.
21. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, et al. (2009) Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 22: 165-193.
22. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, et al. (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150: 604-612.
23. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, et al. (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28: 412-419.
24. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18: 499-502.
25. Wang Q, Gao Y, Tan K, Li P (2014) Subclinical impairment of left ventricular function in diabetic patients with or without obesity : A study based on three-dimensional speckle tracking echocardiography.
26. Benyounes N, Lang S, Soulat-Dufour L, Obadia M, Gout O, et al. (2015) Can global longitudinal strain predict reduced left ventricular ejection fraction in daily echocardiographic practice? Arch Cardiovasc Dis 108: 50-56.
27. Fontana A, Zambon A, Cesana F, Giannattasio C, Trocino G (2012) Tissue Doppler, triplane echocardiography, and speckle tracking echocardiography: different ways of measuring longitudinal myocardial velocity and deformation parameters. A comparative clinical study. Echocardiography 29: 428-437.
28. PérezdCC, Moreno M, Restituto P, Bastarrika G, Simón I, et al. (2014) Circulating osteoprotegerin is increased in the metabolic syndrome and associates with subclinical atherosclerosis and coronary arterial calcification. Clin Biochem 47: 272-278.
29. Montagnana M, Lippi G, Danese E, Guidi GC (2013) The role of osteoprotegerin in cardiovascular disease. Ann Med 45: 254-264.
30. Emery JG, McDonnell P, Burke MB, Deen KC, Lyn S, et al. (1998) Osteoprotegerin is a receptor for the cytotoxic ligand TRAIL. J Biol Chem 273: 14363-14367.
31. Olesen P, Ledet T, Rasmussen LM (2005) Arterial osteoprotegerin: increased amounts in diabetes and modifiable synthesis from vascular smooth muscle cells by insulin and TNF-alpha. Diabetologia48: 561-568.
32. Andersen G, Knudsen EC, Aukrust P, Yndestad A, Oie E, et al. (2011) Elevated serum osteoprotegerin levels measured early after acute ST-elevation myocardial infarction predict final infarct size. Heart 97:460-465.
33. Hofbauer LC, Schoppet M. (2004) Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. JAMA 292:490-495.
34. Røysland R, Masson S, Omland T, Milani V, Bjerre M, et al. (2010) Prognostic value of osteoprotegerin in chronic heart failure: The GISSI-HF trial. Am Heart J 160: 286-293.
35. Chen WJ, Rijzewijk LJ, Van der Meer RW, Heymans MW, Van Duinkerken E, et al. (2011) Association of plasma osteoprotegerin and adiponectin with arterial function, cardiac function and metabolism in asymptomatic type 2 diabetic men. Cardiovasc Diabetol 10: 67.