ORIGINAL ARTICLE

The serum concentration of brain-derived neurotrophic factor is lower in ambulatory and clinically stable patients with more advanced systolic heart failure

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KEY WORDS

brain-derived neurotrophic factor, echocardiography, heart failure, implantable cardioverter defibrillator, natriuretic peptides

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ABSTRACT

INTRODUCTION Brain-derived neurotrophic factor (BDNF) is decreased in heart failure (HF), but whether serum BDNF concentration is related to the severity of HF with reduced left ventricular (LV) ejection fraction (LVEF) below 50% is uncertain.

OBJECTIVES We aimed to compare cardiac structure and function in ambulatory and clinically stable patients with HF and LVEF below 50% for lower and higher BDNF serum concentrations.

PATIENTS AND METHODS A total of 361 ambulatory patients with a compensated HF and LVEF below 50% underwent cardiac evaluation and measurement of serum BDNF and N-terminal pro–B-type natriuretic peptide (NT-proBNP). Patients from the lower (below median) and higher (equal to or above median) BDNF serum concentration groups were compared by analysis of covariance (ANCOVA) adjusted for age, sex, body mass index, resting heart rate, and systolic blood pressure.

RESULTS The patients were at a median age of 63.8 (interquartile range [IQR], 57.7–71.5) years and had a median LVEF of 31.0% (IQR, 23.0–37.4). Individuals with lower BDNF (<23.5 ng/ml) had significantly ($P \leq 0.05$) more dilated right and left atria both before and after emptying, larger right ventricular end-diastolic diameter, LV end-systolic diameter, lower tricuspid annulus plane systolic excursion, shorter pulmonary acceleration time, higher mitral E to A waves ratio and mitral E wave to tissue Doppler e' wave ratio, and higher concentration of NT-proBNP.

CONCLUSIONS HF patients with LVEF below 50% and lower serum BDNF concentration present more advanced cardiac remodeling and dysfunction than individuals with higher BDNF. Potential mechanisms and clinical consequences of these findings require further investigation.

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INTRODUCTION Reduced left ventricular ejection fraction (LVEF) below 50% is a feature of systolic dysfunction of the left ventricle (LV) and systolic heart failure (HF). Most commonly, systolic HF is of ischemic (eg, postinfarction) or nonischemic (eg, postmyocarditis, dilated cardiomyopathy) origin but, regardless of the cause, patients with systolic HF usually have a poorer quality of life and an increased risk of premature death.[1-3] A reduced LV systolic function is associated with inadequate cardiac output at rest and/or during exercise leading to poor tissue and organ perfusion in the kidneys, liver, muscles, or brain. A search for new indicators of different aspects of HF continues. For example, Szczurek-Wasilewicz et al[4] reported that lower fetuin-A levels are associated with an increased risk of death from end-stage HF.

WHAT'S NEW?

Brain-derived neurotrophic factor (BDNF) is vital for the function of neurons in the central and peripheral nervous system. The serum BDNF concentration varies widely in patients with systolic heart failure (HF). Individuals with lower BDNF (<23.5 ng/ml) have more severe HF. Their cardiac chambers are more dilated, and the right ventricular systolic and left ventricular diastolic functions are more impaired.

Brain-derived neurotrophic factor (BDNF) is a neurotrophin (responsible for neuron development) and myokine (exercise-induced cytokine).[5,6] The neurogenic (brain) and muscle tissues are the primary expression sites of BDNF,[7] and its release into circulation depends on blood perfusion, which is usually compromised in individuals with systolic HF.

Serum BDNF concentration is decreased in HF patients,[8-11] but whether this reduction is related to the HF severity has not been established. It is hypothesized that patients with a lower serum BDNF concentration may have a more advanced systolic HF than those with higher BDNF, so we compared different characteristics of the cardiac function in patients with lower (below median) and higher serum BDNF concentrations in a group of hemodynamically stable ambulatory patients with HF and LVEF below 50%.

PATIENTS AND METHODS

Study design We performed a post hoc, prospective, observational analysis of ambulatory patients with stable systolic HF, diagnosed and treated according to the clinical guidelines of the European Society of Cardiology binding at the enrollment time, that is, in the years 2010–2014.[2] The patients were recruited under the project "Predicting adverse clinical outcomes in patients with implanted defibrillating devices" (grant TEAM/2009–4/4) from the Foundation for Polish Science within the TEAM program.

A total of 457 HF patients with implanted cardiac defibrillating devices were recruited from our outpatient clinic. All the patients had a previously implanted cardiac device, either an implantable cardioverter-defibrillator (ICD) or a cardiac resynchronization therapy defibrillator (CRT-D). Participation in the study was voluntary. All patients were informed about the study aim and gave their written informed consent. The Bioethical Committee approved the study design at the Poznan University of Medical Sciences (363/10 in 2009), Poznań, Poland.[12] All personal details were kept confidential and the data used in the analyses were anonimized.

For this study, from all the recruited patients, we selected those with (1) the presence of a significant LV systolic dysfunction defined as LVEF below 50%; and (2) available results of BDNF measurement. Finally, 361 patients were selected for further analysis.

Clinical assessment All participants underwent a detailed clinical evaluation that included current symptoms and past medical history for information about days from implantation of ICD or CRT-D, current pharmacological treatment, New York Heart Association (NYHA) class, and other comorbidities.

Standard cardiac physical examination was performed in all patients. It included measurement of resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) by a brachial blood pressure monitor Omron M3 (Omron, Kyoto, Japan) on both right and left arms after the participants were seated for 3 minutes. The higher reading was taken for further analysis. Additionally, we measured body mass and height, waist and hip circumference, and derived body mass index (BMI) and waist-to-hip ratio (WHR). Resting 12-lead electrocardiography to identify the type of rhythm, that is, sinus, paced, or atrial fibrillation / flutter, or other and determining the mean heart rate, was carried out.

Biochemical analysis Venous blood samples were collected after overnight fasting for the following biochemical and hematological tests on the same day (fasting blood glucose, creatinine, sodium, potassium, C-reactive protein, N-terminal pro–B-type natriuretic peptide [NT-proBNP], and red blood cell count). All analyses were performed in the Central Laboratory of the Heliodor Święcicki University Hospital in Poznań, Poland, according to routine methods. Analysis of fasting glucose concentration (hexokinase method), creatinine concentration (kinetic colorimetric assay based on the Jaffa method), sodium and potassium concentrations (indirect ion-selective electrode method), C-reactive protein (immunoturbidimetric assay), NT-proBNP (electrochemiluminescence assay) were performed on the Cobas 6000 platform (Roche Diagnostics GmbH, Mannheim, Germany), and red blood cell count (RBC) was analyzed on the Sysmex XT2000 analyzer (Sysmex, Kobe, Japan). For BDNF, the serum samples were frozen (–80 °C) until analysis. BDNF concentration was determined by the sandwich-enzyme-linked immunosorbent assay (ELISA) using BDNF-specific monoclonal antibodies (Quantikine ELISA, Human BDNF, R&D Systems, Minneapolis, Minnesota, United States).[13] Most BDNF in the circulating blood is bound to platelets with a small free plasma fraction,[14] with serum BDNF concentration proportional to the total amount of peptide circulating in the blood.

Echocardiography Patients underwent resting transthoracic echocardiography (either Acuson CV70, Siemens, Erlangen, Germany or MyLab 30 CV, Esaote, Florence, Italy) with ultrasound transducers ranging from 1 to 4 MHz. According to the guidelines of the American Society of Echocardiography and the European Association of Echocardiography current to the enrollment time, different parameters were measured for different views.[15] For the parasternal long axis view they included aortic valve ring diameter, right

ventricular end-diastolic diameter (RVEDD), intraventricular septum thickness and left ventricular posterior (basal segment of the inferolateral) wall thickness. For the apical 4-chamber view we measured diastolic and systolic left atrial area (right before the mitral valve closure and opening, respectively), left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters, mitral E and A wave amplitude and the E wave deceleration time by pulse-wave Doppler, left ventricular end-diastolic area, and end-systolic area. The parameters assessed for the modified apical 4-chamber view for the right heart were diastolic and systolic right atrial area (measured right before the tricuspid valve closure and opening, respectively), tricuspid annulus plane systolic excursion (TAPSE), and right ventricular end-diastolic area, and end-systolic area (RVESA). Pulse-wave Doppler measured the pulmonary maximum flow velocity and acceleration time in the parasternal short axis view. The continuous wave Doppler estimated the maximum aortic velocity in the apical 5-chamber view. The e' by the tissue Doppler from the e' waves was measured at the basal segments of the inferoseptal and anterolateral walls in the apical 4-chamber view and then averaged to get the mean e'. Additionally, E/A and E/e' were derived, and the LVEF was estimated using the biplane Simpson method from both the apical 2- and 4-chamber views.

Mini-Mental State Examination The patients were assessed with the Mini-Mental State Examination (MMSE), a 30-point questionnaire estimating the their mental status to detect possible dementia.[16]

Statistical analysis Most of the continuous and discrete data were not normally distributed according to the Shapiro–Wilk test, therefore they were reported as median and interquartile range (IQR). All data were divided into 2 groups according to the BDNF value, below the median (lower BDNF) and equal to the median or higher (higher BDNF). The Mann–Whitney test was applied to compare all continuous and discrete parameters between the lower and higher BDNF groups. The parameters describing the cardiovascular system, which differed statistically in the Mann–Whitney test, were then compared between the BDNF groups by analysis of covariance (ANCOVA) a priori adjusted for the following clinically relevant covariates: age, sex, BMI, resting heart rate (HR), and SBP. Estimated marginal means (EMM) with SE show the mean response in the lower and higher BDNF groups when effects of covariates (ie, adjusting factors) are balanced in the ANCOVA model. As most of the adjusting factor data distribution was not normal, EMM and SE were only of exploratory value. Qualitative data were presented as numbers and corresponding percentages. The Fisher exact test or Pearson χ^2 test was used to compare the frequency of specific qualitative parameters between the patients in the lower or higher BDNF group. Only the results of statistical analyses with a P value below 0.05 were considered significant. For the statistical analysis we used MedCalc Statistical Software version 20.110 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022).

RESULTS **General characteristics of the study population** In TABLE 1 we present the baseline clinical characteristics of all patients for continuous and discrete data, while TABLE 2 provides the qualitative data. The median age of all patients was 64 years, and most were male (84.5%). As many as 44% of the patients had implanted cardiac devices, with either ICD or CRT-D for primary prevention in 82% of the patients, and the median time after the device implantation was 530 days. HF developed after previous myocardial infarction (MI) in 45% of cases, two-thirds of the patients were in the I or II NYHA functional class, and the median LVEF was 31%. Most individuals had hypertension (81.4%), 41% had paroxysmal or chronic atrial fibrillation, one-third suffered from diabetes, and 10% survived a transient ischemic attack or stroke. A total of 14% of the patients were actively smoking, and on average the investigated individuals were overweight. As many as 84% of the patients were on an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), diuretic, and β-blocker, 75% on at least a single antiplatelet drug, 79% were taking a statin, and two-thirds an aldosterone antagonist.

The patients generally had mild thickening of the LV walls and systolic and diastolic LV dilatation. The median concentration of NT-proBNP was 960 pg/ml (cutoff, 125 pg/ml) and of BDNF 23.5 ng/ml (reference range, 6.19–42.58 ng/ml, mean 27.79 ng/ml).

Comparison of patients with lower and higher brain-derived neurotrophic factor serum concentration Patients from the lower BDNF group had statistically more dilated left and right atria before and after emptying, and had larger LVESD. They also presented a higher E wave velocity and E/e' values, shorter acceleration time over the pulmonary valve, and reduced TAPSE, and those with either sinus rhythm or effective atrial pacing presented lower velocity of A wave and higher E/A ratio, and higher concentration of NT-proBNP. The patients from the lower BDNF group were less frequently on ACEI or ARB (79% vs 87.2%) but more commonly on oral anticoagulation (28.7% vs 18.9%). No significant differences were observed in the remaining parameters.

Adjusted comparison of cardiovascular structure and function of patients with lower versus higher brain-derived neurotrophic factor serum concentration In TABLE 3 we summarize the ANCOVA results adjusted for age, sex, BMI, resting HR, and SBP for cardiac structure and function descriptors. After the adjustment, the ANCOVA confirmed significant

TABLE 1 Summary of continuous and discrete data of the clinical characteristics of ambulatory patients with stable systolic heart failure and comparison of patients with low versus high BDNF concentration

Parameter	All patients				Lower BDNF (<23.5 ng/ml)				Higher BDNF (≥23.5 ng/ml)				*P* value
	Median	IQR	Mean	SEM	Median	IQR	Mean	SEM	Median	IQR	Mean	SEM	
Age, y	63.8	57.74–71.61	63.8	0.52	64.88	57.95–71.97	64.72	0.73	62.48	57.59–70.25	62.92	0.73	0.08
BMI, kg/m^2	28.1	25.25–31.45	28.7	0.27	28.06	24.95–31.13	28.49	0.36	28.21	25.67–31.85	28.91	0.39	0.43
WHR	1.0	0.96–1.07	1.01	0.00	1.02	0.97–1.06	1.01	0.01	1.01	0.95–1.06	1.01	0.01	0.47
HR, bpm	69	61–76	69	0.60	67	61–76	68	0.82	69	62–76	70	0.87	0.10
SBP, mm Hg	111.3	100.65–123.78	112.9	0.90	109.18	98.83–120.93	111.68	1.33	112.99	102.33–126.16	114.25	1.21	0.15
DBP, mm Hg	69.3	61.66–76.43	69.2	0.67	67.08	60.75–76.44	68.81	1.02	69.80	63.29–76.43	69.56	0.87	0.58
NT-proBNP, pg/ml	960.0	393.90–2555.00	1847.1	132.67	1231.00	555.35–2734.00	2199.58	219.52	723.20	331.35–1935.00	1490.66	143.87	0.007
BDNF, ng/ml	23.5	19.40–27.85	23.9	0.37	19.41	16.14–21.35	18.48	0.27	27.87	25.69–31.10	29.27	0.40	<0.001
Aortic valve ring, mm	22.3	20.53–24.30	22.4	0.15	22.40	20.88–24.43	22.53	0.23	22.10	20.20–24.00	22.20	0.20	0.28
RVEDD, mm	28.3	25.45–31.95	28.9	0.31	29.30	24.90–32.73	29.46	0.50	27.90	25.83–31.20	28.46	0.38	0.15
RVEDA, cm^2	18.6	14.51–23.31	19.5	0.35	18.56	14.62–24.24	20.09	0.76	18.53	14.48–22.39	18.93	0.44	0.28
RVESA, cm^2	13.6	10.91–16.84	14.5	0.29	13.82	11.40–18.19	15.31	0.48	13.20	10.84–16.13	13.76	0.34	0.04
IVS, mm	11.1	9.60–12.40	11.2	0.14	10.90	9.40–12.55	11.21	0.23	11.20	9.90–12.30	11.20	0.17	0.96
LVPWT, mm	11.6	9.95–13.30	11.7	0.12	11.40	9.58–12.93	11.51	0.19	11.70	10.53–13.40	11.94	0.16	0.08
LVEDD, mm	61.6	55.70–69.05	62.2	0.55	62.70	56.60–69.25	62.95	0.82	60.70	55.63–66.88	61.54	0.73	0.20
LVESD, mm	52.7	45.10–60.00	52.6	0.64	53.80	45.70–62.15	53.92	0.94	51.20	44.83–57.40	51.34	0.87	0.04
LVEDA, cm^2	45.2	37.80–51.75	45.2	0.57	44.21	38.06–50.37	44.66	0.76	45.18	37.48–53.16	45.74	0.86	0.40
LVESA, cm^2	36.4	28.36–43.33	36.4	0.57	34.44	28.46–43.02	35.86	0.75	35.81	28.05–44.36	35.81	0.84	0.56
LAA diastole, cm^2	18.8	14.62–24.96	20.1	0.39	20.90	15.52–26.49	21.43	0.60	18.38	14.35–22.70	18.96	0.51	0.002
LAA systole, cm^2	23.0	18.21–28.50	23.9	0.43	24.58	19.00–29.95	25.16	0.63	21.67	17.73–26.81	22.78	0.58	0.006
RAA diastole, cm^2	14.6	11.46–18.35	16.1	0.40	15.83	12.61–21.00	17.94	0.68	13.36	11.14–16.43	14.47	0.41	<0.001
RAA systole, cm^2	17.8	14.61–22.51	19.8	0.45	19.59	15.302–25.163	21.43	0.78	16.60	14.28–20.66	18.35	0.46	<0.001
Simpsons LVEF, %	31.0	23.00–37.44	30.6	0.52	30.80	22.23–37.56	30.12	0.74	31.00	24.74–36.98	30.95	0.72	0.42
Ao V_{max}, cm/s	124.0	104.00–144.00	127.6	1.98	118.50	104.00–141.00	124.66	2.72	126.50	103.00–148.00	130.32	2.86	0.15
E wave, cm/s	64.0	48.00–92.00	71.7	1.76	71.00	51.00–103.00	78.53	2.84	60.00	48.00–78.75	65.35	2.05	<0.001
Mitral decceleration time, ms	204.0	160.00–272.00	215.7	4.75	204.00	145.00–272.00	212.42	6.64	204.00	160.00–272.00	218.75	6.78	0.51
A wave, cm/s	69.0	42.75–87.25	67.8	1.61	65.00	39.50–85.00	64.81	2.56	72.00	50.00–88.25	70.36	2.02	0.09
E/A	0.8	0.60–1.78	1.3	0.06	1.03	0.62–2.14	1.51	0.10	0.74	0.578–1.24	1.17	0.08	0.008
e' mean, cm/s	7.6	6.50–9.50	8.1	0.14	7.88	6.50–9.50	8.18	0.19	7.50	6.33–9.00	8.00	0.21	0.54
E/e'	8.1	5.82–11.37	9.6	0.31	8.80	6.23–13.02	10.46	0.51	7.77	5.58–10.67	8.83	0.34	0.008
PV V_{max}, cm/s	73.0	63.25–88.00	76.4	1.12	72.00	62.25–84.75	74.19	1.39	75.00	64.00–89.50	78.35	1.72	0.06
PV AccT, ms	96.0	80.00–112.00	98.0	1.57	92.00	76.00–110.00	93.71	2.19	100.00	80.00–120.00	101.90	2.21	0.009
TAPSE, mm	19.4	15.45–23.10	19.3	0.37	17.10	13.95–22.80	18.29	0.57	19.90	16.83–23.45	20.26	0.48	0.008
Time from implantation, d	530.0	183.00–968.25	631.8	26.59	581.50	192.00–1036.00	657.44	37.73	462.00	171.25–917.00	605.93	37.47	0.33
MMSE, points	26.0	24.00–28.00	25.67	0.20	26.00	23.00–28.00	25.41	0.28	27.00	25.00–28.25	25.92	0.30	0.21

Abbreviations: A, A wave—peak velocity flow in late diastole (atrial contraction); Ao V_{max}, aortic maximal velocity; BDNF, brain-derived neurotrophic factor; BMI, body mass index; DBP, diastolic blood pressure; E, E wave—peak velocity blood flow from left ventricle in early diastole; e', peak early diastolic velocity measured by tissue Doppler imaging; LVEF, left ventricular ejection fraction; HR, heart rate; IVS, intraventricular septum thickness; LAA, left atrial area; LVEDA, left ventricular end-diastolic area; LVEDD, left ventricular end-diastolic diameter; LVESA, left ventricular end-systolic area; LVESD, left ventricular end-systolic diameter; LVPWT, left ventricular posterior wall thickness; MMSE, Mini-Mental State Examination score; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PV AccT, pulmonary valve acceleration time; PV V_{max}, pulmonary valve maximal velocity; RAA, right atrial area; RVEDA, right ventricular end-diastolic area; RVEDD, right ventricular end-diastolic diameter; RVESA, right ventricular end-systolic area; SBP, systolic blood pressure; TAPSE, tricuspid annulus plane systolic excursion; WHR, waist-to-hip ratio

TABLE 2 Summary of qualitative data on the clinical characteristics of ambulatory patients with stable systolic heart failure and comparison of patients with low vs high brain-derived neurotrophic factor concentration

Parameter	All patients	Lower BDNF (<23.5 ng/ml)	Higher BDNF (≥23.5 ng/ml)	*P* value
Male sex	305 (84.5)	155 (85.6)	150 (83.3)	0.55
CRT-D	161 (44.6)	80 (44.2)	81 (45)	0.88
Implantation – secondary indications	64 (17.7)	35 (19.3)	29 (16.1)	0.42
History of mycardial infarction	163 (45.2)	90 (49.7)	73 (40.6)	0.08
History of arterial hypertension	294 (81.4)	141 (77.9)	153 (85)	0.08
History of diabetes mellitus	129 (35.7)	62 (34.3)	67 (37.2)	0.56
NYHA class III and IV	122 (33.2)	69 (38.1)	53 (29.4)	0.10
Ex-smoker	220 (60.9)	108 (59.7)	112 (62.2)	0.11
Active smoker	51 (14.1)	22 (12.2)	29 (16.1)	
Previous stroke or TIA	36 (10)	15 (8.3)	21 (11.7)	0.28
Paroxysmal atrial fibrillation	67 (18.6)	35 (19.3)	32 (17.8)	0.09
Chronic atrial fibrillation	80 (22.2)	46 (25.4)	34 (18.9)	
ACEI/ARB	300 (83.1)	143 (79)	157 (87.2)	0.04
Aldosterone antagonist	238 (65.9)	125 (69.1)	113 (62.8)	0.21
Diuretic	303 (83.9)	151 (83.4)	152 (84.4)	0.79
Digoxin	28 (7.8)	12 (6.6)	16 (8.9)	0.42
β-Blocker	305 (84.5)	151 (83.4)	154 (85.6)	0.58
Nitrate	36 (10)	15 (8.3)	21 (11.7)	0.28
Single antiplatelet therapy[a]	271 (75.1)	135 (74.6)	136 (75.6)	0.83
Dual antiplatelet therapy	56 (15.5)	28 (15.5)	28 (15.6)	0.98
Insulin	33 (9.1)	14 (7.7)	19 (10.6)	0.35
Oral antidiabetic drug	16 (4.4)	9 (5)	7 (3.9)	0.62
Statin	285 (78.9)	142 (78.5)	143 (79.4)	0.82
Amidarone	77 (21.3)	39 (21.5)	38 (21.1)	0.92
Oral anticoagulation	86 (23.8)	52 (28.7)	34 (18.9)	0.03

Data are presented as number (percentage) of patients.

a Acetylsalicylic acid or clopidogrel

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CRT-D, cardiac resynchronization therapy-defibrillator; NYHA, New York Heart Association scale score for assessment of symptoms of heart failure; TIA, transient ischemic attack; others, see **TABLE 1**

differences yielded by the Mann–Whitney test for the same parameters and additionally revealed that patients from the higher BDNF group had smaller RVESA. HF patients in the lower BDNF group had a significantly higher concentration of NT-proBNP, more dilated right and left atria both before and after their emptying, larger RVEDD and LVESD, higher values of mitral E wave velocity, E/A, E/e', and a reduced TAPSE.

DISCUSSION We found that ambulatory, clinically stable, and optimally (according to the guidelines current to the time of enrollment) treated patients with systolic HF (LVEF <50%) and lower serum concentrations of BDNF had an increased plasma NT-proBNP levels, more dilated atria, end-diastolic RV, and end-systolic LV, poorer RV systolic function and further deterioration of LV diastolic function than those with higher BDNF concentrations. The more advanced cardiac remodeling and functional impairment in individuals with HF, LVEF below 50%, and lower BDNF were independent of patient age, sex, BMI, resting HR, and SBP.

Brain-derived neurotrophic factor in heart failure

Several studies have demonstrated that serum BDNF concentration is lower in patients with HF.[8-11,17-20] Barman et al[8] studied 160 HF patients with an average LVEF of 27% (13% had an ICD) and found that patients with LVEF below 35% had a higher NT-proBNP concentration and lower BDNF than individuals without a cardiac disease. Kadowaki et al[10] observed that in patients with chronic HF, serum BDNF was lower than in control subjects, and that BDNF concentration decreased with advancing NYHA functional class. Takashio et al[19] reported that plasma BDNF concentration correlated negatively with plasma B-type natriuretic peptide in patients with HF and a low BDNF was accompanied by higher all-cause mortality and more severe HF defined as higher NYHA functional class, more frequent

TABLE 3 Analysis of covariance results comparing selected clinical parameters of patients with systolic heart failure with lower and higher brain-derived neurotrophic factor concentrations with estimated marginal means and SE adjusted for age, sex, body mass index, resting heart rate, and systolic blood pressure[a]

Parameter	Lower BDNF (<23.5 ng/ml)		Higher BDNF (≥23.5 ng/ml)		*P* value
	EMM[b]	SE	EMM[b]	SE	
NT-proBNP, pg/ml	2159.49	175.59	1453.31	179.23	0.005
LVESD, mm	53.84	0.90	51.04	0.88	0.03
RVESA, cm^2	15.28	0.42	13.72	0.40	0.008
LAA diastole, cm^2	21.14	0.56	19.89	0.54	0.005
LAA systole, cm^2	24.80	0.61	22.93	0.59	0.02
RAA diastole, cm^2	17.82	0.56	14.60	0.53	<0.001
RAA systole, cm^2	21.32	0.64	18.53	0.61	0.002
E, cm/s	78.37	2.53	65.78	2.46	<0.001
E/A	1.50	0.09	1.18	0.09	0.02
E/e'	10.40	0.44	8.72	0.43	0.008
PV AccT, ms	94.11	2.18	100.50	2.11	0.04
TAPSE, mm	18.37	0.54	20.32	0.51	0.01

a The presented data do not have a normal distribution and are shown without any transformation (eg, natural logarithm [ln]) for a more straightforward clinical interpretation. It is noteworthy that after the transformation by ln, the comparisons between the lower and higher BDNF groups remain statistically different for all parameters. Therefore, for statistical correctness, the ANCOVA results should be considered exploratory.

b EMMs are means extracted from the ANCOVA model representing an average response of a variable (eg, NT-proBNP) for lower and higher BDNF values.

Abbreviations: ANCOVA, analysis of covariance; EMM, estimated marginal means; others, see **TABLES 1** and **2**

previous hospitalization for HF, and the usage of a loop diuretic and aldosterone antagonists. Barman et al[8] and Fukishima et al[9] reported that higher NT-proBNP and lower BDNF are interdependent indicators of survival time and time until rehospitalization due to HF. However, these authors did not study the relationship between BDNF concentration and the severity of HF using echocardiography. There are several differences between previous studies and our investigation. For instance, our patients had a defibrillating device implanted and were optimally pharmacologically treated in outpatient conditions, but they presented very advanced systolic HF with LVEF of around 31%, and thicker LV walls with larger end-systolic and end-diastolic LV cavities. The patients in the study of Barman et al[8] were aged 67.6 years on average and 69% had hypertension, 48% diabetes, 64% coronary artery disease (CAD), 41% chronic atrial fibrillation, and 20% chronic renal failure. Our patients were younger (63.8 years), had a similar occurrence of atrial fibrillation, less commonly diabetes (36%), more commonly hypertension (81%), and 45% of our patients had a history of MI. Also, 100% of our patients had an implanted cardiac defibrillating device (55% ICD and 45% CRT-D), whereas only 13% of the patients from the study by Barman et al[8] had an ICD. Barman et al[8] analyzed patients who were on β-blockers (80%), ACEIs (70%), spironolactone (38%), and digoxin (23%), whereas our patients were more commonly on an aldosterone antagonist (66%) and ACEIs (83%), and less commonly received digoxin (8%). Additionally, Barman et al[8] compared the HF patients with a control group of age- and sex-matched healthy individuals. Takashio et al[19] also showed a control group of non-HF patients and compared them with patients at an average age of 71 years and with acute decompensated HF. The patients in the study by Takashio et al[19] were on diuretics (66%), β-blockers (76%), ACEIs (87%), aldosterone antagonists (60%), and digoxin (13%), similarly to our study (differences in the proportions up to 10%). Takashio et al[19] showed that BDNF concentrations were significantly lower in the loop diuretics and aldosterone antagonists users than nonusers. Takashio's patients had hypertension (65%), diabetes (38%), and an ischemic etiology of HF (35%). Our patients had a similar occurrence of diabetes, were more often hypertensive, and 45% of them had MI in the past. Takashio et al[19] reported only 2 echocardiographic parameters: LVEDD (average 54.9 mm in the HF group) and LVEF. In comparison, our patients had more dilated LV with a median LVEDD of 61.6 mm. For LVEF, Takashio et al[19] reported that 27% of their patients had HF with preserved ejection fraction, whereas the remaining group had reduced LVEF. No other details on LVEF were provided and no information was given regarding implanted intracardiac devices. Noteworthy, Takashio et al[19] found that the plasma BDNF concentration was significantly higher at discharge after the patients were stabilized.

Although Barman et al[8] and Takashio et al[19] reported an association between BDNF and natriuretic peptides, and they did not find any other associations. Even though our patients appeared to have highly advanced systolic HF, low BDNF was accompanied by further cardiac structural and functional deterioration.

Brain-derived neurotrophic factor and cardiovascular disease The relation between BDNF concentration and cardiovascular disease remains unclear. Barman et al[8] found no differences in serum BDNF concentration in patients with or without CAD, but patients with HF and lower BDNF have a higher risk of future cardiac events.[8-10,20,21] Kadowaki et al[10] found that serum BDNF below 12.4 ng/ml in patients with HF was an independent risk factor for cardiac events. Barman et al[8] set the cutoff for adverse cardiac outcomes at below 9.10 ng/ml and Fukushima et al[9] at below 17.4 ng/ml. Jiang et al[21] reported that patients with lower plasma BDNF were older, more commonly diabetic, and male.

In a recent review by Halloway et al[18] BDNF concentrations were higher in acute forms of cardiac disease such as MI and unstable angina but lower in chronic conditions, such as stable coronary disease or congestive HF. Ejiri et al[22] found

that BDNF is expressed in atherosclerotic coronary arteries, with enhanced expression in patients with unstable angina, as compared with those with stable angina pectoris. Wu et al[23] suggested that higher BDNF concentration in acute diseases might be caused by increased inflammatory processes. The exact mechanisms for such an increase in acute settings are uncertain. Whether enhanced inflammation and platelet activation might contribute is unresolved.

In general, our patients were clinically and hemodynamically stable (no cardiogenic shock nor hypertensive crisis, average SBP and HR were within normal ranges). Nevertheless, BDNF concentration falls within a wide range of values even in a group with chronic HF. Lower BDNF in patients with advanced systolic HF might reflect the disease that lasts longer or has induced more serious chronic adaptation in the heart. However, we cannot exclude the influence of other comorbidities, such as diabetes, hypertension, CAD, or atrial fibrillation.

Heart failure and cognitive impairment Some studies[24,25] demonstrated that general cognitive functioning, memory, and attention deficits occur in 30%–80% of patients with congestive HF. Zuccala et al[26] found that cognitive impairment shortens survival in older patients hospitalized for HF and their 1-year survival after discharge. Approximately 40% of patients with HF show cognitive deficits, resulting in a higher rehospitalization rate and increased mortality.[27] Recently, Festa et al[28] reported that reduced LVEF was associated with an impaired memory function only in older patients over 63 years. Although the median MMSE of our patients was 26, close to the mild cognitive impairment, it did not differ between those with lower and higher BDNF and did not correlate with any indices of cardiac structure or function (data not shown), except for NYHA functional class—those with more limited functional capacity had lower MMSE ($\rho = -0.14$; $P = 0.009$).

Brain-derived neurotrophic factor serum concentration in heart failure: perspectives BDNF measurement might help identify patients with more advanced systolic HF. Several interventions (eg, increased physical activity, use of imipramine[29] or S-citalopram[30]) have been demonstrated to increase the BDNF concentration. With the exception of increased physical activity and cardiac rehabilitation programs, the clinical value of other interventions on the clinical course of advanced HF is unknown. Nevertheless, the association between the BDNF concentration and the clinical features in patients with advanced systolic HF deserves further studies.

Study limitations Our study was observational and did not aim at identifying potential mechanisms of the relationship between BDNF and the severity of systolic HF. The enrolled patients were studied once at different stages of their disease, although all were ambulatory and clinically compensated. A potential limitation is the lack of a control group of healthy people to compare BDNF between them and the patients with HF. However, this information is already available and thus was not the goal of our study, as we aimed to analyze the potential relationship between the BDNF concentration and the severity of systolic HF. The next limitation is related to the measurement of BDNF concentration. Comparison of absolute values of BDNF concentration with other studies is limited by potential differences in methodology, for example, time of sample collection, time of clot formation, technical details of the sample centrifugation and storage, or the preparation of blood samples for analysis. All of these factors can influence the results of BDNF measurement. Platelets are the main reservoir of BDNF in the circulating blood,[31-34] but it is unclear whether BDNF is produced by megakariocytes or acquired by platelets from other sources.[33] The majority of patients were on at least a single antiplatelet drug. These factors further confounded any conclusions on the BDNF source in HF patients. However, in our whole study group, the same method for BDNF analysis was used (material type, preparation, detection). Furthermore, numerous comorbidities in the HF patients alter BDNF synthesis, release, and metabolism, and it is impossible to control all of them. Our final comparisons of various cardiac parameters between the patients with lower and higher BDNF were only adjusted for age, sex, BMI, resting HR, and SBP. Nevertheless, even after the adjustment, the patients with lower BDNF had more advanced cardiac remodeling and porer systolic RV and diastolic LV function.

Conclusions The serum concentration of BDNF is linked with the clinical condition, including cardiac function and remodeling, of patients with systolic HF. Those with lower BDNF concentrations have higher plasma NT-proBNP, more dilated cardiac chambers, and poorer systolic RV and diastolic LV function than the individuals with higher BDNF. These effects are independent of the patient age, sex, BMI, SBP, and HR.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT PG provided the study concept and design. PG was the Primary Investigator of the project "Predicting adverse clinical outcomes in patients with implanted defibrillating devices" supported by the Foundation for Polish Science, TEAM program. MP and PG prepared the draft and final version of the manuscript. AP-B, JT, DP-S, AN, AS, MB, and TK recruited all patients and collected the data for the study. DP--S and AS performed all echocardiography studies. MB controlled the implanted devices and interpreted the readings. TK was responsible for database management. JK was responsible for the biochemical methodology and analyses. PG and JP were responsible for statistical analysis and interpretation. AP-B, JT, DP-S, AN, AS, TK, MP, JP, AW, and PG interpreted clinical data. All authors have read, corrected, and agreed to the submitted version of the manuscript.

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