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Relationship of reduced cerebral blood flow and heart failure severity in elderly males

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Abstract

Introduction. Brain detrimental effects are under-recognised complication of chronic heart failure (CHF). One of the major causes may be cerebral hypoperfusion. This study was designed to investigate the relationship between cerebral blood flow (CBF) and severity of CHF as well as to evaluate its determinants among different parameters of cardiac dysfunction.

Methods. Seventy-one CHF males with NYHA class II and III and 20 control subjects age ≥ 55 years were recruited. CBF was evaluated by colour duplex sonography of extracranial arteries. Echocardiography, 6-min walk test, quality of life and endothelial function were also assessed. Serum NT-pro-BNP and adipokines levels (adiponectin and leptin) were measured.

Results. CBF was significantly reduced in elderly patients with CHF compared to healthy controls (677 ± 170 *vs* 783 ± 128 ml/min, $p = 0.011$). Reduced CBF was associated with reduced left ventricular ejection fraction (LVEF) ($r = 0.271$, $p = 0.022$), lower 6-min walk distance ($r = 0.339$, $p = 0.004$), deteriorated quality of life ($r = -0.327$, $p = 0.005$), increased serum adiponectin ($r = -0.359$, $p = 0.002$), and NT-pro-BNP levels ($r = -0.375$, $p = 0.001$). In multivariate regression analysis, LVEF and adiponectin were independently associated with reduced CBF in CHF patients ($R^2 = 0.289$).

Conclusion. CBF was reduced in elderly males with mild-to-moderate CHF, and was associated with factors that represent the severity of CHF including high serum adiponectin and NT-pro-BNP levels, decreased LVEF, impaired physical performance, and deteriorated quality of life.

Keywords: *Cerebral blood flow, chronic heart failure, adiponectin, left ventricular ejection fraction*

Abbreviations: *CBF = cerebral blood flow, CHF = chronic heart failure, ICA = internal carotid artery, LVEF = left ventricular ejection fraction, VA = vertebral artery*

Introduction

Brain detrimental effects, such as impaired cognitive function, autonomic nervous system dysfunction associated with structural brain changes, are the important but under-recognised complication of chronic heart failure (CHF) [1–3]. In addition, CHF increases the risk of dementia and Alzheimer disease in later life [4]. One of the possible causes may be cerebral hypoperfusion secondary to low cardiac output in patients with CHF apart from biohumoral, clinical, socio-demographic and other potentially relevant factors [5,6]. Cerebral blood flow (CBF), as a measure of cerebral perfusion, can be non-invasively studied by flow volume measurements in extracranial cerebral arteries using Doppler and duplex methods [7].

Relationship of CBF to different markers of heart failure severity was only modestly presented in previous papers. Therefore, we aimed to investigate the relationship between CBF and CHF severity as well as to evaluate its determinants among different parameters of cardiac dysfunction.

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Methods

Study design

Having reviewed medical history archives of the Cardiology Department, Clinical Medical Center Zvezdara Belgrade, first contacts with eligible patients were made on the phone. For the baseline visit we screened 152 males aged 55 years and above with CHF due to ischemic or idiopathic dilated cardiomyopathy. Following the baseline visit 76 patients were selected all of whom met the study inclusion and exclusion criteria. Inclusion criteria were as follows: (1) duration of CHF for longer than 1 year; (2) echocardiographically assessed left ventricular ejection fraction (LVEF) $< 40\%$; (3) aetiology of CHF: ischemic or idiopathic dilated cardiomyopathy; (4) NYHA functional class II and III; (5) unchanged medication regimen within the previous 6 weeks; (6) clinically stable condition with no clinical evidence of decompensate heart failure, such as raised jugular venous pressure, ascites, hepatomegaly. Exclusion criteria were as follows: (1) diabetes mellitus determined by either self-reported histories or evidence within the hospital case notes; (2) primary lung disease including chronic obstructive pulmonary disease; (3) musculoskeletal diseases; (4) uncontrolled hypertension of more than 170/110 mmHg; (5) myocardial infarction or unstable angina within previous 3 months; (6) acute or chronic infection, inflammatory diseases such as sepsis, arthritis or systemic connective tissue disease; (7) symptomatic peripheral vascular disease; (8) alcohol abuse; (9) serum creatinine ≥ 200 μmol/l; (10) valvular cardiomyopathy or artificial heart valve; (11) malignant disease, significant liver, thyroid, suprarenal gland or pituitary disease; (12) cardiac cachexia defined as unintentional weight loss of $\geq 7.5\%$ body weight over 6 months [8]. Finally, we included 71 patients because 3 patients were characterised by occlusion of internal carotid artery, while vertebral artery was not visualised in 2 patients.

The control group consisted of 20 healthy male volunteers aged 55 years and above, who did not take medications. No previous medical illness was reported (including diabetes or any other cardiovascular disease). Written informed consent was obtained from all patients with CHF and healthy subjects prior to inclusion into the study. The study was conducted according to the principles outlined in the Declaration of Helsinki and was approved by Ethical Committee of Clinical Medical Centre Zvezdara.

Clinical, cardiovascular and carotid colour duplex sonography assessment

After the patient gave his written consent, the medical history was reviewed, including the cause of heart failure, comorbidities and medical history. Each patient with CHF was categorised according to the New York Heart Association (NYHA) criteria [9]. A physical exam was performed to assess CHF stability. The 6-min walk test was performed according to the standard protocol [10].

All patients underwent a two-dimensional Doppler echocardiography examination (GE Vivid 7). Systolic function was quantified by measurement of LVEF using the Simpson method. We also measured left ventricular end-diastolic diameter (LVEDD), right ventricular systolic pressure (RVSP) and left atrial volume (LAV) according to the ASE recommendation [11].

During an initial 20 min of rest with the subjects in a supine position, the extracranial arteries, i.e., the common carotid arteries, internal carotid arteries (ICA) and the vertebral arteries (VA) of both sides were explored with a 7.0 MHz linear transducer of a computed sonography system (Toshiba PowerVision 6000). The examination followed previously described protocol [7]. CBF volume was determined as the sum of the flow volumes of the ICA and the VA of both sides. Resistance index, as a measure of cerebrovascular resistance, was calculated as follows: (peak systolic velocity–end diastolic velocity)/peak systolic velocity [12]. The resistance index value averaged from both ICA and VA was used in all subsequent calculation [13]. Included subjects did not have hemodynamically significant stenosis of the common carotid artery, ICA and VA. The peak systolic velocity value averaged from both ICA and VA was used, as well. Intima-media thickness was measured on the far wall of the right and left common carotid artery, the carotid bulb, and the ICA [14]. The carotid intima-media thickness was defined as the mean of intima-media thickness measurements at these six sites.

Quality of life was estimated from The 'Minnesota-Living with Heart Failure Questionnaire' [15]. Endothelium-dependent, flow mediated dilation as a measure of endothelial function of the brachial artery was determined according to the standard protocol [16]. The Tei index is defined as the sum of isovolumic contraction and relaxation time divided by the ejection time. This index is a sensitive indicator of overall cardiac dysfunction in patients with mild-to-moderate CHF [17].

Laboratory analysis

Basal blood samples were taken at 8 am from an antecubital vein. Participants were asked to refrain from smoking more than 8 h before blood sampling, to be fasted from 9 pm the previous evening as well as to withhold vasoactive medication for 12 h prior to appointment. Serum samples were immediately deep frozen and kept at -70°C until assayed. Serum levels of natriuretic peptide N-terminal-pro-B-type (NT-pro-BNP), were measured with a fully automated 'sandwich' electrochemiluminescence method

using Elecsys analyser (Roche Diagnostics, GmbH, Mannheim; measuring range from 5 to 35,000 pg/ml). Total adiponectin and leptin levels in serum were measured by RIA (Linco Diagnostics, Inc., St/Charles, MO) lowest detectable concentrations, 1 μg/ml and 0.5 ng/ml, respectively. Estimated creatinine clearance was calculated from serum creatinine values using the Cockroft-Gault formula.

Statistical analysis

Descriptive statistics were presented as mean values with standard deviation or median with interquartile range for numeric variables, or as absolute numbers with percentages for categorical variables. Evaluation of normality was performed with Kolmogorov–Smirnov test. The log10-transformation was performed for NT-pro-BNP which follows exponential distribution. Student *t*-test was used to calculate differences between mean values. Mann–Whitney *U*-test was used to determine differences between median values. The Pearson coefficient was used for measuring linear correlation between variables. Partial correlation analysis was performed to adjust for age and body mass index. Finally, since variables are inter-related, multivariate regression analysis, backward method, was performed to asseses the independent variables that may explain CBF. A p value < 0.05 was considered to indicate statistical significance. Statistical analysis was performed using the SPSS software for Windows, version 15 (SPSS, Inc., Chicago, IL).

Results

Basic characteristics and biohumoral parameters of CHF patients and healthy subjects

The basic clinical and biohumoral parameters of studied subjects are shown in Table I. Atrial fibrillation was noted in 31%, left bundle branch block in 25%, while pacemaker was implanted in 9% of patients with CHF. History of myocardial infarction was presented in 63% of patients. Angiotensin-converting enzyme inhibitors were presented in 80% of patients, 75% were on β-blockers, 80% of patients were on loop diuretics, 55% were on spironolactone, 65% were on aspirin and 27% on statins. No differences in age, waist/hip ratio, body mass index and lipid profile were found between patients with CHF and healthy subjects. Patients with CHF had significantly higher serum NT-pro-BNP and adiponectin compared to healthy controls, while there was no difference in serum leptin levels. On the other hand, renal function was significantly decreased in patients with CHF.

Color duplex sonography of neck arteries and echocardiogaphic measurements

Color duplex sonography of neck arteries and echocardiogaphic measurements in studied subjects are presented in Table II. CBF was decreased in patients with CHF, while there was no difference in resistance index between studied groups. CBF decreased according to NYHA class ($p < 0.0001$), with those in NYHA class III having level of CBF

Table I. Demographic, clinical characteristics, and biohumoral parameters of CHF patients and healthy subjects.

Variable	CHF patients ($n = 71$)	Healthy subjects ($n = 20$)	p Value
Age (years)	68 ± 7	67 ± 7	0.909
Waist/hip ratio	1.03 ± 0.04	1.01 ± 0.06	0.086
BMI (kg/m^2)	28 ± 5	28 ± 3	0.496
Duration of disease (years)	5 ± 4	–	
Smoking former/active, n(%)	16(22)/10(14)	3(15)/5(25)	0.454
Ischemic/idiopathic dilatated CMP, n(%)	56(79)/15(21)	–	
NYHA class II/III, n(%)	54(76)/17(24)	–	
MLHFQ	30 ± 14	–	
Six-minute walking distance (m)	406 ± 84	578 ± 64	<0.0001
Mean blood pressure (mmHg)	101 ± 12	103 ± 7	0.387
Uric acid (μmol/l)	410 ± 106	373 ± 187	0.257
Fasting blood glucose (mmol/l)	5.3 ± 0.6	5.6 ± 0.4	0.044
Total cholesterol (mmol/l)	5.6 ± 1.1	6.0 ± 0.8	0.103
Tryglicerides (mmol/l)	1.5 ± 0.5	1.6 ± 1.2	0.599
HDL cholesterol (mmol/l)	1.3 ± 0.3	1.4 ± 0.4	0.155
LDL cholesterol (mmol/l)	3.5 ± 1.0	3.8 ± 0.8	0.295
Creatinine clearance (ml/min)	64 ± 21	78 ± 14	0.001
Adiponectin (μg/ml)	17.4 ± 9.5	9.6 ± 2.3	<0.0001
Leptin (ng/ml)	7.3 ± 6.0	5.9 ± 3.2	0.330
hs CRP (mg/l)	2.3 (2.7)	1.7 (2.5)	0.153
NT-pro-BNP (pg/ml)	1868 (2803)	68 (74)	<0.0001

Data are expressed as mean ± standard deviation (Mean ± SD) or median ± interquartile range (Me ± IQR) or as absolute number (percentage).

BMI = body mass index; CMP = cardiomyopathy; hs CRP = high sensitive C reactive protein; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NYHA = New York Heart Association; NT-pro-BNP = N-terminal pro-brain natriuretic peptide.

542 ± 104 ml/min that was 25% lower than CBF in NYHA class II patients (719 ± 166 ml/min). Carotid intima-media thickness was significantly greater, while flow mediated dilatation was lower in patients with CHF compared to healthy controls. Echocardiographic variables of systolic and diastolic function were impaired in patients with CHF.

Table II. Color duplex sonography of neck arteries, assessment of endothelial function and echocardiogaphic measurements.

Variable	CHF patients ($n = 71$)	Healthy subjects ($n = 20$)	p Value
ICA flow (ml/min)	505 ± 144	593 ± 118	0.014
VA flow (ml/min)	172 ± 68	190 ± 72	0.298
CBF (ml/min)	677 ± 170	783 ± 128	0.011
PSV (cm/s)	50 ± 10	55 ± 8	0.041
RI	0.65 ± 0.08	0.67 ± 0.06	0.244
CIMT (mm)	1.00 ± 0.12	0.92 ± 0.12	0.009
FMD (mm)	0.42 ± 0.17	0.76 ± 0.15	<0.0001
LAV (ml)	95 ± 42	46 ± 14	<0.0001
LVEDD (mm)	66 ± 9	49 ± 4	<0.0001
LVMi (g/m^2)	159 ± 44	81 ± 12	<0.0001
LVWT (mm)	20 ± 4	19 ± 1	0.018
LVEF (%)	29 ± 8	65 ± 5	<0.0001
RVSP (mmHg)	46 ± 16	29 ± 3	<0.0001
Tei index	0.61 ± 0.22	0.28 ± 0.12	<0.0001

CBF = cerebral blood flow; CIMT = carotid intima-media thickness; FMD = flow mediated dilatation; ICA = internal carotid artery; LAV = left atrial volume; LVEF = left ventricular ejection fraction; LVMi = left ventricular mass index; LVWT = left ventricular wall thickness; PSV = peak systolic velocity; RI = resistance index; RVSP = right ventricular systolic pressure ($n = 65/10$, CHF patients/healthy controls); VA = vertebral artery.
Data are expressed as mean ± SD.

Relations between CBF with demographic, cardiovascular and biohumoral parameters in patients with CHF

CBF in patients with CHF was positively correlated with 6-min walking distance, decreased LVEF (Figure 1a) and creatinine clearance, while negatively with impaired quality of life and RVSP (Table III). In addition, CBF inversely correlated with neurohormonal activation (NT-pro-BNP) and serum adiponectin (Figure 1b) levels among patients with CHF.

Table III. Correlation of cerebral blood flow with demographic, cardiovascular, and biohumoral parameters in CHF patients.

Variable	CBF
Age	
r (p)	−0.071 (0.557)
BMI	
r (p)	0.177 (0.154)
Mean blood pressure	
r (p)	0.039 (0.794)
MLHFQ	
r (p)	−0.333 (0.005)
Six-minute walking distance	
r (p)	0.342 (0.004)
FMD	
r (p)	0.171 (0.149)
LVEF	
r (p)	0.276 (0.022)
RVSP	
r (p)	−0.360 (0.004)
LVMi	
r (p)	−0.181 (0.133)
NT-pro-BNP	
r (p)	−0.375 (0.001)
Adiponectin	
r (p)	−0.369 (0.002)
Leptin	
r (p)	0.049 (0.747)
Creatinine clearance	
r (p)	0.262 (0.027)

BMI = body mass index; MLHFQ = Minnesota Living with Heart Failure Questionnaire; FMD = flow mediated dilatation; LVEF = left ventricular ejection fraction; RVSP = right ventricular systolic pressure ($n = 65/10$, CHF patients/healthy controls); LVMi = left ventricular mass index; NT-pro-BNP = N-terminal pro-brain natriuretic peptide.

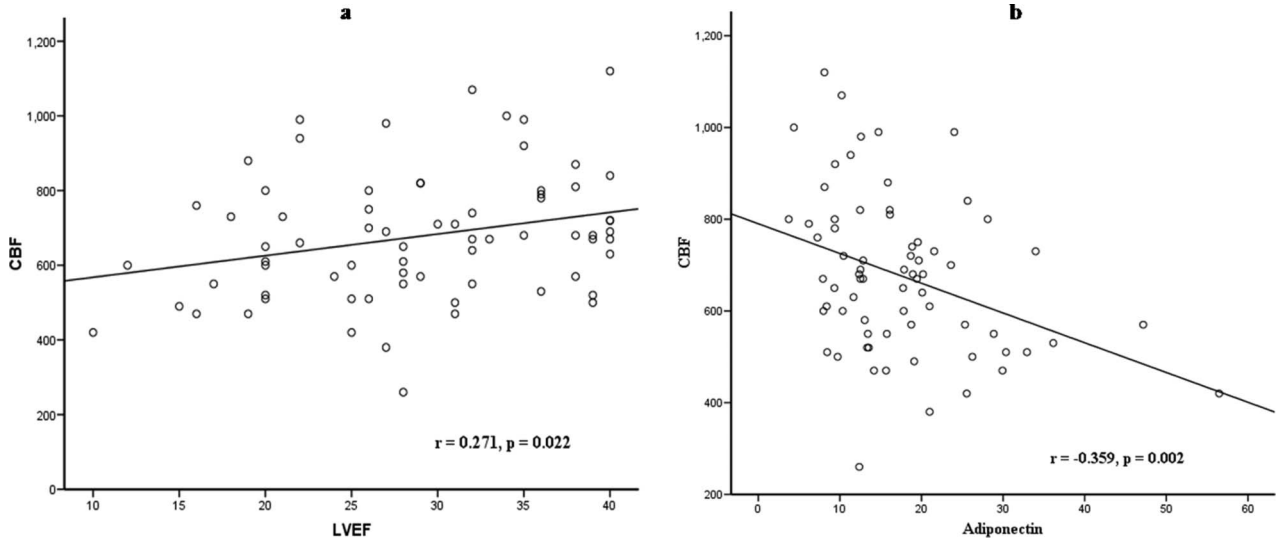

Figure 1. Scatter plots of the association between CBF and LVEF (a) and serum adiponectin levels (b) in elderly patients with CHF. CBF = cerebral blood flow; LVEF = left ventricular ejection fraction.

Table IV. Multivariate regression analysis (backward model) with cerebral blood flow as dependent variable in elderly CHF males.

Variable	*B*	*p* Value	*F*(*p*)
CBF			
(Constant)	0.454		5.121
MLHFQ	−0.003	0.049	(0.001)
LVEF	0.006	0.031	
Adiponectin	−0.004	0.044	
FMD	0.184	0.099	
Tei index	0.220	0.021	
$r^2 = 0.289$			

B = parameter estimate; *F* = Fisher test.
CBF = cerebral blood flow; FMD = flow mediated dilatation; LVEF = left ventricular ejection fraction; MLHFQ = Minnesota Living with Heart Failure Questionnaire.

The correlation between CBF and serum adiponectin was still significant even after adjustment for age and body mass index ($r = -0.326$, $p = 0.007$). Serum adiponectin was found to be positively correlated with serum NT-pro-BNP levels within patients with CHF ($r = 0.593$, $p < 0.0001$). When adiponectin was normalised for the BMI and age, the same relation existed with NT-pro-BNP levels ($r = 0.548$, $p < 0.0001$).

Multivariate regression analysis

Multivariate regression analysis with backward model was used to asses the independent variables that may affect CBF (Table IV). The independent variables entered in the model were: age, body mass index, mean blood pressure, quality of life score, 6-min walk distance, NT-pro-BNP (log-transformed), adiponectin, leptin, creatinine clearence, LVEF, Tei index and flow mediated dilatation. High serum adiponectin levels and low LVEF were independently associated with reduced CBF in patients with CHF.

Discussion

The objective of this study was to investigate the association of CBF with different parameters of heart failure severity in elderly males. The major observations in this study are that: (1) elderly men with CHF demonstrated reduced CBF and increased serum adiponectin levels compared to healthy controls; (2) reduced LVEF and serum adiponectin levels were independently associated with impaired CBF in patients with CHF; (3) reduced CBF was also associated with deteriorated physical performance capacity (6-min walk distance), neurohumoral activation (NT-pro-BNP), impaired quality of life, and pulmonary hypertension; (4) clinically more advanced CHF, expressed as NYHA class, was related to greater reduction of CBF.

In this study, CBF was significantly reduced by 14% in elderly patients with CHF compared to healthy controls. Similarly, Choi et al. [18] have shown that global CBF (measured by radionuclide angiography) was decreased by approximately 19% in patients with CHF compared with normal controls. Patients with heart failure showed damage to multiple brain regions that play significant roles in autonomic nervous system control and cognitive function including mood regulation, memory processing, pain and language [3]. One of the major factors that may lead to cognitive impairment is cerebral hypoperfusion demonstrated in our as well as in previous studies [5,19]. CBF is regulated by perfusion pressure and vascular resistance. The autoregulation of blood flow over a wide range of perfusion pressures is one of the characteristics of brain circulation. Compensatory mechanisms maintain perfusion to vital organs, such as brain in response to the progressive reduction of cardiac output. One of the chronic adaptations of the circulatory system is peripheral vasoconstriction which may be provoked by the heart failure-induced activation of neurohormonal systems [20]. In agreement with our results, cerebral vascular resistance, expressed by resistance index, was not elevated in patients with mild-to-moderate CHF compared to healthy controls [21]. Therefore, decreased perfusion pressure as a consequence of reduced systolic left ventricular function in patients with CHF may be marked as principal factor of reduced CBF. Low LVEF was the independent determinant of impaired CBF in our patients with CHF. Thus, it can be speculated that cerebral hypoperfusion due to left ventricular systolic dysfunction may contribute to brain injury secondary to low cardiac output. A correlation between cardiac index and intracranial hemodynamics has been reported [22]. However, Eicke et al. [23] showed no correlation between LVEF and CBF supporting the concept that CBF is independent of cardiac output. In addition, Choi et al [18] showed that CBF was not correlated to LVEF in patients with CHF, suggesting that the LVEF was not a factor determining the degree of breakdown of the autoregulation of CBF. This discrepancy may be explained that in the patients with more severe CHF such as those in the study of Choi et al, factors other than LVEF contributed more to CBF, such as NYHA functional class and neurohormonal activation.

As far as we know, our study is the first report of an association between reduced CBF and different parameters of CHF severity including serum adiponectin levels, impaired physical performance, and deteriorated quality of life. Similarly to others, we observed that serum adiponectin levels were significantly higher in patients with CHF than healthy controls and are predictors of mortality [24,25]. Adiponectin may exhibit a cardioprotective action through suppression of cardiac remodelling [26]. Similarly, adiponectin exhibits favourable effects on atherogenesis, endothelial function, glucose regulation, insulin resistance and vascular

remodelling. It is postulated that adiponectin is a metabolic, and NT-pro-BNP a hemodynamic biomarker of CHF. The favourable effects of adiponectin seem similar to the therapeutic and diagnostic strategies of natriuretic peptides [26]. The positive association has been shown between serum adiponectin and NT-pro-BNP in our patients with CHF, as previously demonstrated [24]. Increased neurohormonal activation, expressed by elevated serum NT-pro-BNP levels, was related to lower CBF in our patients with CHF, which is consistent to the recent report [18]. The same study reported an inverse association between CBF with RVSP which is in agreement with our finding. Finally, reduced CBF in our study was significantly associated with impaired physical performance; measured by 6-min walk test contrary to previous data [21]. The 6-min walk test is a safe and simple clinical tool that strongly and independently predicts morbidity and mortality in patients with CHF [27].

Colour duplex volumetric test of the brain-feeding arteries can only yield information about the relative contributions of the anterior and posterior cerebral circulation to global CBF volume. We found a contribution of the VA to global CBF volume of 25% which remained almost constant with increasing age. Previously, it was estimated that the VA contribute 24% of the global CBF volume in healthy subjects [7,28]. To date, there are no reports on the relative contributions of the anterior and posterior circulation to global CBF volume in patients with CHF.

In agreement with previous study, we demonstrated impaired endothelial function in patients with CHF compared to healthy controls [29]. In the previous reports, endothelial dysfunction was associated with an increased mortality risk within patients with CHF, as well [29,30]. Recent study is suggestive of the presence of pure endothelial dysfunction in patients with lacunar infarction of the brain [31]. To our knowledge, the association between endothelial function and CBF was not previously looked at even in a normal population. In our study, we did not find relation between endothelial function and CBF. However, in the multivariate regression model impaired endothelial function showed a tendency to be independently associated with CBF. Brachial flow mediated dilatation was not associated with carotid intima-media thickness in our patients with CHF. Carotid intima-media thickness was greater in our patients with CHF compared to healthy controls. High carotid intima-media thickness was marked as independent risk factor for incidence of heart failure requiring hospitalisation [32]. Increased carotid intima-media thickness was shown to be powerful predictor of coronary and cerebrovascular events, as well [33]. However, the literature data are rather ambigous regarding the relationship between intima-media thickness and endothelial function. Juonala et al. [34] reported relation between impaired brachial flow mediated dilatation and greater intima-media thickness in young adults explaining it by the idea that impaired systemic endothelial function is an early event in atherosclerosis. In contrast to this but in agreement with our results, brachial flow mediated dilatation and carotid intima-media thickness were not related in other studies [35,36]. Although both parameters were impaired in our patients, the lack of link between them suggests that they may represent independent surrogates that measure different pathophysiological aspect of heart failure progression.

Study limitation

The number of the studied patients was relatively small. Our cohort comprised a highly selected CHF sample and is thus less representative of the overall CHF population. The relations between CBF and different variables were examined in a cross-sectional study, which cannot prove a causal relation between these variables. Colour duplex volumetric examination of the brain feeding extracranial arteries is a highly reproducible and non-invasive technique [7]. The reliability of the method should be confirmed in comparative studies with established radionuclide procedures which is difficult for ethical reasons. However, reduction of CBF in our patients with CHF compared to healthy controls was similar to the value obtained by radionuclide technique [18]. In this study, we did not perform evaluation of mental status or brain imaging. Therefore, we cannot say that reduced CBF was associated with neuropsychiatric or brain morphologic disorders among patients with CHF. We also acknowledge that serum adiponectin and LVEF made only small contributions to the total variance in CBF. Finally, it would be of interest to evaluate the impact of diminished CBF on major clinical outcomes in future studies.

In conclusion, we have shown that CBF was reduced in elderly males with mild to moderate CHF, and was independently associated with factors that represent the severity of CHF including increased serum adiponectin and reduced LVEF. Reduced CBF was associated with neurohormonal activation (NT-pro-BNP), impaired physical performance, and deteriorated quality of life, as well. Future studies are now needed to tease out possible association of CBF with cerebral disorders known to be more potentiated in the population with heart failure as well as to investigate the possible underlying mechanisms.

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