Effect of Combination of L-Arginine and L-Carnitine on Serum AGEs Level, Kidney and Endothelial Function in Patients with Chronic Heart Failure

Olexandr Kuryata*, Oksana Sirenko and Abdunaser Zabida

State Establishment "Dnipropetrovsk Medical Academy of Health Ministry of Ukraine", 9, Vernadsky str. Dnipro, 49044, Ukraine

Abstract: The aim of the study to evaluate the effect of combination of L-Arginine with L-Carnitine on GFR, serum AGEs level and endothelial function in chronic heart failure (HF) patients with preserved ejection fraction (HFpEF).

Materials and Methods: 35 patients with mean age 60,1 [56,7; 77,3] years with an established diagnosis of HFpEF were enrolled. The patients were randomly and blindly divided into 2 groups: first (1st) group pts were treated with a combination of L-Carnitine and L-Arginine in addition to standard treatment; 2nd group pts – with L-Arginine in addition to conventional treatment. Standard laboratory blood tests, lipid profile, glucose, renal and liver function tests, serum advanced glycation end-product (AGEs) level, echocardiographic examination, flow-mediated dilatation (FMD%) were performed for all patients baseline and after 10 days of treatment. The glomerular filtration rate (GFR) was estimated using the CKD-EPI formula.

Results: Median level of AGEs was 1.72 [1.34; 1.93] mg/ml. The level of AGEs was correlated with age (R = 0.71, p<0.05), disease duration (R = 0.69, p<0.05). After 10 days of treatment with a combination of L-Carnitine with L-Arginine mean AGEs was decreased by 13.1% in comparison with L-Arginine treatment group (p=0.0003). After the treatment in 1st group mean AGEs was significantly lower in comparison with the 2nd group (p=0.004). Baseline median level of GFR was 81.2 [72,1; 86,2] ml/min and correlated with disease duration (R = 0.71, p<0.05), AGEs level (R = -0.73, p<0.05). The inclusion combination of L-arginine aspartate with L-Carnitine contributed to the significant increase of GFR level (p=0.003). The median FMD% level was 6.2 [4.4; 7.9] % and correlated with age (R=-0.61, p < 0.05), GFR (R=0.54, p < 0.05). After the 10 days it had been established significant increasing of FMD% level on 47.9 % in 1st group (p=0.0005), and on 29.3 % in 2nd group (p=0.003). Endothelial function normalizing was achieved in 10 (66 %) pts of 1st group and in 9 (45%) pts of 2nd group (p=0.002).

Conclusion: The combination of L-Carnitine, and L-Arginine improves kidney, endothelial function and contributes to decreasing of AGEs level in pts with HFpEF.

Keywords: L-arginine, L-carnitine, kidney function, endothelial function, chronic heart failure.

INTRODUCTION

HFpEF accounts for up to half of all HF in the developed world [1]. The reported population prevalence ranges from 1% to 3% and is predicted to rise further with lengthening life expectancy, greater diagnostic awareness, and increasing rates of obesity, diabetes, hypertension and atrial fibrillation [1].

Whether HFpEF constitutes a single syndrome or a collection of syndromes is debated, nevertheless the diagnostic label identifies patients with a poor quality of life, high rates of hospitalisation and premature mortality [1-3]. Clinical guidelines offer few evidence-based treatment recommendations [2-4]. Large randomised clinical trials of therapies improving outcomes in HF with reduced EF(HFrEF) have failed to demonstrate prognostic benefit in patients with HFpEF, obliging us to re-examine our understanding of the mechanisms driving morbidity and mortality in this syndrome, and the extent of their reversibility.

It is unclear whether patients with HF symptoms preserved EF and more than the mild epicardial coronary artery disease (CAD) can be considered to have HFpEF. CAD is widely noted in HFpEF cohorts and HF symptoms that are disproportionate to the severity of CAD or persist after revascularisation may represent one of several proposed HFpEF patient phenotypes [5]. Evidence of microvascular observational studies report abnormalities in cardiovascular structure and function in HFpEF which exceed those observed in age, sex and body size matched individuals without HF [6], even after adjusting for the cumulative burden of comorbidities [7].

Skeletal muscle mass is reduced in HFpEF, beyond that which is observed with normal ageing and directly contributes to exercise limitation [8]. Furthermore, mortality rates among patients with HFpEF exceed those for patients with similar age, sex and comorbidity distribution in trials of hypertension, diabetes, and

*Address correspondence to this author at the State Establishment "Dnipropetrovsk Medical Academy of Health Ministry of Ukraine", 9, Vernadsky str. Dnipro, 49044, Ukraine; Tel: +38(056) 766-48-09, +38(056) 766-48-41; Fax: +38(056) 766-48-10; E-mail: gt1@dsma.dp.ua

E-ISSN: 1929-5634/18

CAD, with a higher proportion of cardiovascular deaths observed in HFpEF [9].

In large observational cohorts, chronic kidney disease (CKD) [defined as an estimated GFR<60 mL/min/1.73m^2] is observed in 26–49% of patients with HFpEF [10,11]. This is similar to rates observed in HFrEF patients [12].

In a contemporary HFpEF population, impairment of renal function, defined as an GFR<60 mL/min/1.73m^2 or albuminuria, was present in 62% of patients; of these, 26% had albuminuria with normal GFR [13].

Several studies have investigated the association of impaired renal function and mortality in HFpEF patients. Hillege *et al*. found an association between impaired renal function and increased risk for death, cardiovascular death, and hospitalization for heart failure in HFpEF, similar to rates observed in HFrEF [14]. Multiple other studies have since confirmed these findings; some even suggest greater prognostic importance of CKD in patients with a preserved EF [15].

A meta-analysis, involving >1 million patients with heart failure, found that CKD was associated with an odds ratio (OR) of 3.22 [95% confidence interval (CI) 2.66–3.90] for all-cause mortality in patients with an ejection fraction (EF) >40%, compared with ORs of 2.00 (95%CI 1.81–2.21) and 2.56 (95% CI 2.24–2.93) for an EF <30% and between 30% and 40%, respectively [15].

The mechanisms underlying worsening renal function likely differ based on acute versus chronic HF. Chronic HF is likely to be characterized by a long-term situation of reduced renal perfusion, often predisposed by microvascular and macrovascular disease.

Although a greater proportion of patients with low estimated GFR have a worse New York Heart Association functional class, no evidence of an association between ejection fraction and estimated GFR can be consistently demonstrated. Thus, patients with chronic HF and preserved EF appear to have similar estimated GFR than patients with impaired LV (EF ≤ 45%) [16].

AGEs are a heterogeneous group of compounds derived from non-enzymatic glycation of proteins, lipids, and nuclear acids through complex and sequential reactions known as the Maillard reaction [17]. These versatile molecules play a major pathogenic role in many chronic diseases related to aging, diabetes, progression of diabetes complications and are of great interest to nephrologists (because of their nephrotoxic potential) and more recently to cardiologists [18,19]. Decreased clearance of serum AGEs may further increase tissue AGEs accumulation.

There are several reasons that point to a link between accumulation of AGEs and HF, including the high prevalence of heart failure and diastolic dysfunction in those conditions associated with increased AGEs accumulation, such as diabetes and CKD. Increased AGEs levels have been attributed to both impaired renal clearance and increased endogenous AGEs formation.

Patients with chronic HF have endothelial dysfunction of systemic arteries which may be partially reversed by administration of oral L-arginine substrate for endothelial nitric oxide (NO). There is also evidence of abnormal NO responses in pulmonary arteries in a canine model of heart failure. Therefore, we hypothesised that abnormalities in pulmonary endothelial function in chronic HF patients might contribute to exercise perfusion ventilation mismatch and breathlessness and that these abnormalities might be improved by administration of intravenous L-arginine (L-arginine is also a vasodilator) [20]. Recently several studies found an improvement in endothelial-dependent vasodilation, muscular blood flow during exercise, functional capacity on L-Arginine supplementation background in pts with HF [25].

On the other hand, there has been a growing appreciation of the more complex metabolic processes underlying HF pathophysiology and symptoms [21]. L-carnitine is a vitamin-like and modified amino acid that plays an important role in supporting the body's metabolic activities. There is growing evidence that high concentrations of L-Carnitine provide beneficial effects in various diseases such as coronary artery disease, congestive heart failure, peripheral vascular diseases, type 2 diabetes, dyslipidemia, and hypertension [22]. Particularly the recent meta-analysis demonstrates L-Carnitine treatment is effective for chronic HF patients in improving clinical symptoms and cardiac functions, decreasing serum levels of B-type natriuretic peptide (BNP) and N-terminal-pro-BNP [24].

The aim of this study to evaluate the effect of combination of L-Arginine with L-Carnitine on GFR, serum AGEs level and endothelial function in chronic heart failure patients with preserved ejection fraction.

MATERIALS AND METHODS

The study was conducted with approval from the Ethics committee at ‹State Establishment Dnipropetrovsk Medical Academy, Ministry of Health Ukraine› according to principles outlined in the Helsinki declaration.

Inclusion criteria

Patients with stable angina pectoris and HF with EF> 45% aged from 40 to 80 years. Patients with acute myocardial infarction (< 6 months), 2nd and 3rd degree heart block, diabetes mellitus, renal failure (GFR ≤ 60 ml/min/1.73m²), hepatic failure, and cancer were excluded. All patients got standard treatment for HF according to European Society Cardiology guidelines 2016 [23].

Standard laboratory blood tests for erythrocyte sedimentation rate, haematological parameters, lipid profile, glucose, renal and liver function tests were performed and calculated body mass index (BMI) for all patients. The GFR was estimated using the CKD-EPI formula.

Echocardiographic examination made by «VIVID 3», GE Medical Systems - USA in B, M, 2D, CFM, PW - mode pulse sensor 3S (3,5 MHz).Brachial artery measurements: measure the brachial artery diameter, determine flow-mediated dilatation (FMD%) and obtain baseline and hyperemic brachial artery flow velocities and derive the respective flow volumes.

The fluorescent AGEs in plasma were analysed by quantitative autofluorescence (fluorimeter Hoefer DQ 2000,USA) with fixed spectrum of excitation at 460 nm with 20% quinine solution as a standard with results expressed with conversion to glycated albumin.

Study Design

35 patients – 22 males and 13 females with mean age 60,1 [56,7; 77,3] years with an established diagnosis of HFpEF were enrolled. The patients were randomly and blindly divided into 2 groups. First (1st) group (n=15) pts with HFpEF treated with 100 ml Tivor-L (20mg Levocarnitine + 42mg L-Arginine hydrochloride per 1 ml, Yuriyapharm) intravenously daily for the 10 days in addition to standard treatment for Chronic HF. [23] Second (2nd) group (n=20) pts with HFpEF treated with 100 ml Tivortin (42mg L-Arginine hydrochloride per 1 ml, Yuriyapharm) intravenously daily for the 10 days in addition to conventional treatment. All the requirements of a double-blind study were observed.

Statistical Analysis

In order to accomplish the analysis of data, we used statistical program Statistics V.6.1 (StatSoftinc), and ‹Excel 2013› Microsoft. Data is shown as a number of subjects (%) or median [interquartile range] because data was not a normal distribution.

The Mann-Whitney U-test and Wilcoxon test were used to analyze differences between different independent and dependent groups respectively. Correlation coefficient Spearman (R) was calculated. A p value < 0.05 was considered statistically significant.

RESULTS

Observed patients were not significantly different in baseline characteristics (Table **1**).

Median level of AGEs was 1.72 [1.34; 1.93] mg/ml. The level of AGEs was correlated with age (R = 0.71, p<0.05), disease duration (R = 0.69, p<0.05). After 10 days of treatment with comparison of L-Carnitine with L-Arginine mean AGEs was decreased by 13.1% in comparison with L-Arginine treatment group (p=0.0003) (Figure **1**). After the treatment in 1st group mean AGEs was significantly lower in comparison with a 2nd group (p=0.004).

Baseline median level of GFR in HFpEF pts was 81.2 [72,1; 86,2] ml/min. The GFR level was correlated with disease duration (R = 0.71, p<0.05), AGEs level (R = -0.73, p<0.05). The inclusion combination of L-arginine aspartate with L-Carnitine contributed to the significant increase of GFR level (p=0.003). After 10 days the GFR level in the 1st group pts was significantly higher in comparison with the 2nd group (p=0.0004).

The majority of observed patients with HFpEF had established endothelial dysfunction – 26 (74.3 %). The median FMD% level was 6.2 [4.4; 7.9] % and was correlated with age (R=-0.61, p < 0.05), GFR (R=0.54, p < 0.05). After the 10 days it had been established significant increasing of FMD% level on 47.9 % in 1st group (p=0.0005), and on 29.3 % in 2nd group (p=0.003). The FMD% level was significantly higher to the end of observation in pts treated with L-Carnitine\L-Arginine combination in compare with L-Arginine group (p=0.0004). Endothelial function normalizing was achieved in 10 (66 %) pts of 1st group and in 9 (45%) pts of 2nd group (p=0.002).

Table 1: Baseline Characteristics of the Study Population

Characteristics		1st group CHFpEF Conventional treatment + Tivor-L (n=15)	2nd group CHFpEF With conventional treatment+L-Arginine (n=20)	P value
Gender	Male, no.(%)	10(67)	12(60)	0,234
	Female, no.(%)	6(40)	7(35)	0,123
Age (years)		59,6 [54,9; 76,4]	60,5 [57,7; 77,9]	0,209
NYHA functional class	2nd class,no.(%)	6(40)	13(65)	0,332
	3rd class,no.(%)	9(60)	7(35)	0,119
Arterial hypertension	Without AH	3(20)	3(15)	0,388
	2nd grade,no.(%)	7(47)	10(50)	0,321
	3rd grade,no.(%)	5(33)	7(35)	0,293
Heart rate		76,8 [74,6; 80,4]	78,4 [73,4; 82,1]	0,195
Body mass index		28,7 [23,9; 32,3]	29,6 [24,4; 34,4]	0,432
Blood plasma glucose level		5,6 [4,9; 5,9]	5,8 [5,1; 6,1]	0,365
Cholesterol		4,3 [4,0; 4,7]	4,5 [4,2; 4,8]	0,099
Triglyceride		2,2 [1,7; 2,4]	2,3 [1,9; 2,6]	0,145
GFR		81,3 [73,5; 85,4]	80,7 [71,9; 84,3]	0,142
Treatment history, no.(%)				
Renin angiotensin - aldosterone system inhibitors		9(60)	6(60)	0,164
Beta - blockers		12(85)	7(70)	0,129
Antagonist of aldosterone and other mineralocorticoids		13 (87)	15 (75)	0,205
statins		11(73)	8(80)	0,213
Aspirin		13(87)	9(90)	0,301

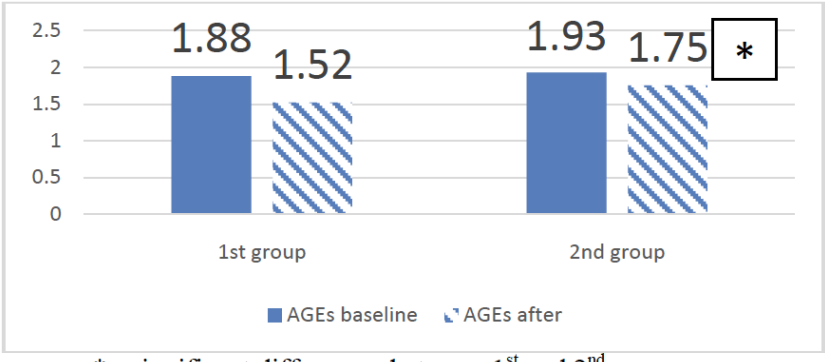
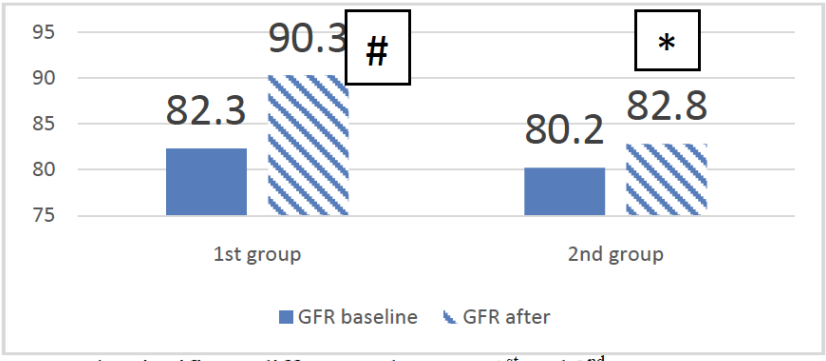


Figure 1: AGEs level in both groups before and after treatment.

During the observation period, there were no significant changes in the indicators characterizing liver and kidneys function. Thus, a combination of L-Arginine with L-Carnitine showed a good safety profile in HFpEF pts.

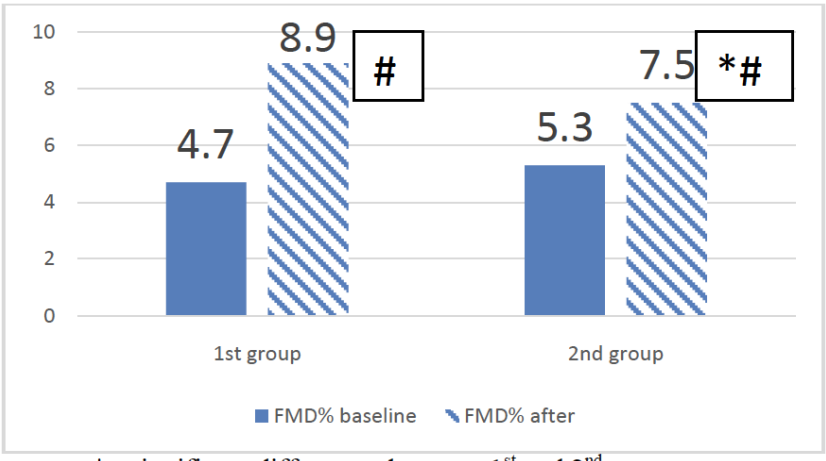
DISCUSSION

The pathophysiology of the cardiorenal syndrome is multifactorial and involves decreased renal perfusion, atherosclerosis and inflammation, endothelial dysfunction and neurohormonal activation [28,29].



* - significant differences between 1st and 2nd groups
\# - significant differences before and after treatment

Figure 2: AGEs level in both groups before and after treatment.



* - significant differences between 1st and 2nd groups
\# - significant differences before and after treatment

Figure 3: FMD% level in both groups before and after treatment.

Renal dysfunction is strongly associated with a poor clinical outcome in HF patients and AGEs are related to the severity of HF and renal dysfunction [30]. In this way, AGEs could be a promising prognostic marker in patients with the cardiorenal syndrome.

As known, CHF is a condition that requires multitargeted and phases dependent therapeutic methods. The European Society for Clinical Nutrition and Metabolism (ESPEN) (2009) guidelines recommended L-arginine for CHF treatment [32]. Thus in a previous study, we estimated that inclusion of L-arginine aspartate in a complex of treatment for post infarction HFpEF contributed to significant decrease AGEs level in > 60 years old patients and endothelial function improving [26, 27]. Searching for therapeutic options to improve prognosis in patient with CHF patients with preserved EF remains relevant.

ACCF/AHA recommendations noted that in addition to the classic toxins, a number of toxic agents may lead to LV dysfunction and HF. Particular, the deficiency in L-carnitine, a necessary cofactor for fatty acid oxidation, may be associated with a syndrome of progressive skeletal myopathy and cardiomyopathy [31]. In this way, L-Carnitine may be useful in patients with various toxic injuries, renal dysfunction, and oncology profile.

The recent meta-analysis demonstrated that the beneficial effects of L-Carnitine in CHF have been shown by the increase of overall efficacy, LVEF, stroke volume, cardiac output, decrease of left ventricular end-diastolic diameter, left ventricular end-systolic diameter, and left ventricular end-systolic volume and serum levels of BNP and NT-proBNP, and with satisfactory safety [24]. Some reports [21, 24, 25] indicated that clinical symptom, cardiac function, and renal function in CHF patients with renal insufficiency were more likely to be ameliorated with L-Carnitine treatment.

Our research showed that L-Carnitine represents a safe and effective adjuvant therapy in pts with HFpEF which, may have a synergistic effect with L-Arginine. According to the results of this study combination of L-Carnitine and L-Arginine improved kidney, endothelial function and contributed to a decrease of AGEs level in mentioned patients. In particular, established more significant endothelial function improving and AGEs level decreasing in 1st pts group can be explained by the effects of L-Carnitine on kidney function.

LIMITATIONS

However, the results of this study should be interpreted with caution because of several limitations. Therefore, only CHF pts with preserved ejection fraction were chosen for this study, and consequently, the results can only be applied to this population. It should be noted that there is no oral Tivor-L for continuation treatment after giving it intravenously. In this way, it could be perspectival to evaluate the hard endpoint with prolongation of this therapy. In our opinion, it is also promising to study the efficacy of therapy with L-Carnitine in patients with a cardio-oncology profile.

CONCLUSION

Combination of L-Arginine with L-Carnitine may improve kidney, endothelial function and contributes more significant serum AGEs level decreasing compare with L-Arginine monotherapy in chronic heart failure patients with preserved ejection fraction and has a good tolerance.

CONFLICT OF INTEREST DISCLOSURE

The authors declare that there is no conflict of interest regarding the publication of this paper.

REFERENCES

[1] Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 2017; 14: 591-602. https://doi.org/10.1038/nrcardio.2017.65

[2] Ponikowski P, Voors AA, Anker SD, *et al*. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-200. https://doi.org/10.1093/eurheartj/ehw128

[3] Yancy CW, Jessup M, Bozkurt B, *et al*. ACCF/AHA Guideline for the management of heart failure: a report of the American college of cardiology foundation. Circulation 2013; 128: 1810-52. https://doi.org/10.1161/CIR.0b013e31829e8807

[4] Yancy CW, Jessup M, Bozkurt B, *et al*. ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart failure society of America. Circulation 2017; 136: 137-161. https://doi.org/10.1161/CIR.0000000000000509

[5] Hwang SJ, Melenovsky V, Borlaug BA. Implications of coronary artery disease in heart failure with preserved ejection fraction. J Am Coll Cardiol 2014; 63: 2817-27. https://doi.org/10.1016/j.jacc.2014.03.034

[6] Lam CS, Roger VL, Rodeheffer RJ, *et al*. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation 2007; 115: 1982-90. https://doi.org/10.1161/CIRCULATIONAHA.106.659763

[7] Mohammed SF, Borlaug BA, Roger VL, *et al*. Comorbidity and ventricular and vascular structure and function in heart failure with preserved ejection fraction: a community based study. Circ Heart Fail 2012; 5: 710-9. https://doi.org/10.1161/CIRCHEARTFAILURE.112.968594

[8] Haykowsky MJ, Brubaker PH, Morgan TM, *et al*. Impaired aerobic capacity and physical functional performance in older heart failure patients with preserved ejection fraction: role of lean body mass. J Gerontol A Biol Sci Med Sci 2013; 68: 968-75. https://doi.org/10.1093/gerona/glt011

[9] Campbell RT, Jhund PS, Castagno D, *et al*. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-preserved, and I-PRESERVE? J Am Coll Cardiol 2012; 60: 2349-56. https://doi.org/10.1016/j.jacc.2012.04.064

[10] Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, Wehrens XH, Deswal A. Impact of noncardiac comorbidities on morbidity and mortalityin a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol 2012; 59: 998-1005. https://doi.org/10.1016/j.jacc.2011.11.040

[11] Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol 2006; 47: 76-84. https://doi.org/10.1016/j.jacc.2005.09.022

[12] McAlister FA, Ezekowitz J, Tarantini L, *et al*. Renal dysfunction in patients with heart failure with preserved versus reduced ejection fraction: impact of the new Chronic Kidney Disease-Epidemiology Collaboration Group formula. Circ Heart Fail 2012; 5: 309-314. https://doi.org/10.1161/CIRCHEARTFAILURE.111.966242

[13] Gori M, Senni M, Gupta DK, Charytan DM, Kraigher-Krainer E, *et al*. Association between renal function and cardiovascular structure and function in heart failure with preserved ejection fraction. Eur Heart J 2014; 35: 3442-3451. https://doi.org/10.1093/eurheartj/ehu254

[14] Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ. Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Investigators. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 2006; 113: 671-678. https://doi.org/10.1161/CIRCULATIONAHA.105.580506

[15] Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J 2014; 35: 455-469. https://doi.org/10.1093/eurheartj/eht386

[16] Bhatia RS, Tu JV, Lee DS, *et al*. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006; 355: 260 -9. https://doi.org/10.1056/NEJMoa051530

[17] Singh R, Barden A, Mori T, *et al*. Advanced glycation end-products: a review. Diabetologia 2001; 44: 129-146. https://doi.org/10.1007/s001250051591

[18] Raj DS, Choudhury D, Welbourne TC, *et al*. AGE: a nephrologist`s perspective. Am J Kidney Dis 2000; 35: 365-380. https://doi.org/10.1016/S0272-6386(00)70189-2

[19] Kioifman B, Wollam Y, Bogomolny N, *et al*. Improved cardiac performance by intravenous infusion of L-arginine in patients with moderate congestive cardiac failure. J Am Coll Cardiol 1995; 26: 1251-1256. https://doi.org/10.1016/0735-1097(95)00318-5

[20] Doehner W, Frenneaux M, Anker SD. Metabolic impairment in heart failure: the myocardial and systemic perspective. J Am Coll Cardiol 2014; 64: 1388-1400. https://doi.org/10.1016/j.jacc.2014.04.083

[21] Ferrari R, Merli E, Cicchitelli G, Mele D, Fucili A, Ceconi C. Therapeutic effects of L-carnitine and propionyl-Lcarnitine on cardiovascular diseases: a review. Ann N Y Acad Sci 2004; 1033: 79-91. https://doi.org/10.1196/annals.1320.007

[22] Ponikowski P, *et al*. ESC Guidelines for the diagnosis and treatment The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) Developed in collaboration with the Heart Failure Association (HFA) of the ESC. European Heart Journal 2016; 37(27): 2129-200. https://doi.org/10.1093/eurheartj/ehw128

[23] Song X, Qu H, Yang Z, Rong J, *et al*. Efficacy and Safety of L-Carnitine Treatment for Chronic Heart Failure: A Meta-Analysis of Randomized Controlled Trials. Biomed Res Int 2017; 2017: 6274854. https://doi.org/10.1155/2017/6274854

[24] Sciatti E, Lombardi C, Ravera A, *et al*. Nutritional Deficiency in Patients with Heart Failure. Nutrients 2016; 8(7): 442. https://doi.org/10.3390/nu8070442

[25] Kuryata OV, Abdunaser A. Zabida Effect of L-Arginine on the Serum Level of Advanced Glycation End Products in Patients with Post Infarction Chronic Heart Failure. J Nutr Therapeutics 2017; 6: 43-50. https://doi.org/10.6000/1929-5634.2017.06.02.1

[26] Tykhomyrov AA, Nedzvetsky VS, Zabida AA, Ağca CA, Kuryata OV. l-Arginine treatment improves angiogenic response and reduces matrix metalloproteinase activity in chronic heart failure patients with coronary artery disease. Pharma Nutrition 2018; 6: 137-146. https://doi.org/10.1016/j.phanu.2018.06.005

[27] Damman K, Navis G, Voors AA, Asselbergs FW, Smilde TD, *et al*. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. J Card Fail 2007; 13: 599-608. https://doi.org/10.1016/j.cardfail.2007.04.008

[28] Damman K, Deursen VM, Navis G, Voors AA, Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol 2009; 53: 582-588. https://doi.org/10.1016/j.jacc.2008.08.080

[29] Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, *et al*. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 2006; 113: 671-678. https://doi.org/10.1161/CIRCULATIONAHA.105.580506

[30] Yancy CW, Jessup M, Bozkurt B, *et al*. ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017; 136(6): 137-161. https://doi.org/10.1161/CIR.0000000000000509

[31] Anker SD, Laviano A, Filippatos G, John M, Paccagnella AP. *et al*. ESPEN Guidelines on parenteral nutrition: on cardiology and pneumology. Clin Nutr 2009; 28: 455-460. https://doi.org/10.1016/j.clnu.2009.04.023

Received on 23-10-2018 Accepted on 24-12-2018 Published on 18-01-2019

DOI: https://doi.org/10.6000/1929-5634.2018.07.03.2