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Evaluation of oxidant status in both systolic and diastolic heart failure

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Abstract

Objective: Oxidative stress status in subgroup of heart failure (HF) syndrome still remains unknown. We aimed to study Total Antioxidant Status (TAS), Total Oxidant Status (TOS) and Oxidative Stress Index (OSI) in both systolic and diastolic HF, and also in both ischemic and non-ischemic HF.

Materials and Methods: Consecutive 123 chronic HF patients were included in this cross-sectional study. Group 1 consisted of 73 systolic HF patients (50 ischemic patients and 23 non-ischemic patients) and group 2 consisted of 50 diastolic HF patients. As a control group (group 3), 37 healthy subjects were included. Echocardiographic evaluation was performed and TAS, TOS and OSI were studied in all patients.

Results: The highest TAS value (1.10±0.24) was found in Group 1, but the lowest in Group 2 (0.90±0.14). Diastolic HF group had the highest TOS value (37.2±10.41) while systolic HF group (32.9±7.26) and control group (26.19±8.00) followed it. OSI was found the highest in diastolic HF group (4.37±1.24) and the lowest in systolic HF group (2.24±0.80). TOS and OSI were similar between ischemic and non-ischemic subgroups of systolic HF but TAS was statistically higher in non-ischemic (p:0.0005).

Conclusions: We found higher oxidative stress in HF patients, predominantly in diastolic HF patients. The difference between diastolic and systolic HF with regard to oxidative and antioxidative status seems to come from distinct drugs usage between the groups, which have potential effects on oxidative and antioxidative parameters. To reduce, at least, oxidative stress in diastolic HF patients, medical therapy is needed.

Key words: Total Antioxidant Status, Heart Failure, Systolic, Diastolic, Oxidative Stress Index

Introduction

Congestive heart failure (HF) is a progressive clinical syndrome that affects the pumping power of the heart muscles leading to buildup of fluid around the heart and increased left ventricular filling pressures (1). HF can lead to myocardial, valvular, pericardial or non-cardiac pathologies and can affect various organ functions such as renal, pulmonary, endocrine and skeletal muscle (1,2).

While reactive oxygen species (ROS) are continuously produced by many tissues, they are eliminated by antioxidant defense systems. Increase in radical productions or decrease in antioxidant defenses give rise to oxidative stress. Increased ROS ultimately damage biological structures (3). Damaged lipids, proteins and nucleic acids may aggravate current disease or lead to occurrence of new diseases (4).

The role of oxidative stress in the pathogenesis of many heart diseases has been well established (5–8). Many studies have shown an imbalance between oxidant production and antioxidant response in HF (9–11). It is known that chronic systolic HF is associated with increased ROS and decreased antioxidant level. Furthermore, the imbalance between oxidants and antioxidants is clearly associated with poor prognosis in patient with chronic systolic heart failure (10).

Although oxidative stress status in subgroup of HF syndrome still remains unknown. We aimed to study Total Antioxidant Status (TAS), Total Oxidant Status (TOS) and Oxidative Stress Index (OSI) in both systolic and diastolic HF, and also in ischemic and non-ischemic HF.

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Materials and Methods

Study Design and Patients

Consecutive 123 chronic HF patients that were admitted between 2012 January and 2013 January to cardiology outpatient clinic of our hospital and agreed to participate the study, were included in this cross-sectional study. Exclusion criteria were as follow: acute coronary syndrome and decompensate HF currently or within the last month, congenital cardiovascular abnormalities, chronic obstructive pulmonary disease or cor pulmonale, chronic liver disease, chronic kidney disease, anemia, surgery within the last month, neoplastic diseases, rheumatic diseases, thyroid dysfunction, acute infection and using medicines that have antioxidant properties such as vitamin pills, except for HF medicines. Patients were divided into two groups, i.e group 1, consisted of 73 systolic HF patients (50 ischemic patients and 23 non-ischemic patients) and group 2, consisted of 50 diastolic HF patients. Also 37 healthy subjects, group 3, without systolic or diastolic HF were included in the study Local ethics committee approval and written informed consent of patients was received for the study

Blood Sample Collection and Storage

Venous blood (10 cc) was collected from each patient in a serum separator tube. All tubes were first placed at room temperature for one hour followed by a 10 min centrifuged at 5000 rpm. All serum samples were stored in -20 cc Eppendorf tubes until assayed.

Total Antioxidant Level Measurement

TAS was measured using a fully automatic method developed by Erel (12). Briefly, radicals Fe2+ o-dianisidine complex and hydrogen peroxide generates OH radical with a Fenton type reaction. These powerful reactive oxygen species react with Odianisid, a colorless molecule, and produce yellow-brown dianisidyl radicals at low pHs. The formed dianisidyl radicals increase color formation by taking part in advanced oxidative reactions. However, antioxidants suppress oxidation reaction and prevent the color formation.

The reaction is measured by spectrophotometrically in automatic analyzer, and results are expressed as "mmol Trolox equivalent / L.

Total Oxidant Level Measurement

TOS was measured using an automated method developed by Erel (13). Briefly, oxidants present in the samples oxidized ferrous ion-o-dianisidine complex to ferric ion. Ferric ions form a colored complex with Xylenol Orange in acidic medium. The intensity of color, which is associated with the amount of oxidants in samples, is measured spectrophotometrically and the unit is µmol H2O2 equivalent / L.

Oxidative Stress Index

OSI was determined by the formula TOS/TAS.

The Measurement of Other Biochemical Parameters

Serum sodium (Na), potassium (K), urea, creatinine, fasting blood glucose, triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) levels were measured commercially-available assay kits (Abbott®) in an auto analyzer (Aeroset®, Germany).

Echocardiographic Study

Echocardiographic examination was performed at the left lateral decubitus position as recommended by American Society of Echocardiography's (14). The parasternal long axis, short axis and apical 2-4-5-chamber images were obtained with Vivid S6 (General Electric, Horton, Norway) with 2.5 MHz transducer. M-mode, two-dimensional, pulse wave Doppler, continuous wave Doppler, color Doppler and tissue Doppler assessments were done respectively to the patients. Using the parasternal long axis and apical four-chamber view, EF was measured using modified Simpson's method (15). Maximal early (E) and ate (A) trans mitral velocities in diastole as well as E-wave deceleration time were obtained by Pulsed Doppler method. These measurements were done in the apical view with a cursor at the mitral inflow. For Tissue Doppler measurements, the sample volume was located on the lateral side of the mitral annulus. Early diastolic mitral annulus (Em), and peak late diastolic (Am) and peak systolic flow (Sm) velocities were recorded. The E/Em ratio was also calculated. 'Normal' diastolic function was defined as $0.75 < E/A < 1.5$, E-wave deceleration time >140ms and $E/Em < 10$. If $E/A < 0.75$ and $E/Em < 10$, these patients were accepted to have 'mild' diastolic dysfunction. 'Moderate' and 'severe' diastolic dysfunction were respectively defined as [$0.75 < E/A < 1.5$, E-wave deceleration time >140ms and $E/Em > 10$] and [$E/A > 1.5$, E-wave deceleration time < 140ms and $E/Em > 10$] (16).

Basic Measurements and Definitions

On the basis of 2012 European HF diagnosis and treatment guide, we divided the HF patient in groups based on systolic, diastolic, ischemic, and non-ischemic. Hypertension was defined as ≥140 mm Hg systolic blood pressure, and/or ≥90 mm Hg diastolic blood pressure and/on the use of antihypertensive medications (17). Diabetes Mellitus was defined as fasting blood sugar ≥126 mg /dL at least in two measurements or using insulin and/or oral hypoglycemic medicines (18). Dyslipidemia was determined according to the European Dyslipidemia Guide (19). Systolic HF was defined as HF symptom with ventricular ejection fraction (EF) ≤ 40%. Diastolic HF was defined as clinical sign and symptoms of HF with left ventricular EF ≥ 50% which accompanies left ventricular diastolic dysfunction determined by Doppler echocardiography (20).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 11.5 was used for all statistical analyses. Kolmogorow Smirnow test was used to determine normal distribution. The parametric data was expressed as mean ± SD and

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nonparametric data as percentage (%). Comparisons among the groups for continuous variables, were performed by one-way ANOVA. Chi-square test was used to compare categorical variables. Correlation analyses were performed with the Pearson correlation method. Systolic HF was assigned to ischemic and non-ischemic groups. One-sample t-test compared these two sub-groups. Linear regression analysis was performed to determine independent associations between TAS, TOS, OSI and potential associated factors. A p-value <0.05 was accepted as significant.

Results

Demographic, clinical and biochemical data, cardiovasculary risk factors and medicines are demonstrated in Table 1. Heart rate, diabetes mellitus, family history for coronary heart disease and cigarette smoking were similar between the groups (p>0,05). The control group (Group 3) consisted of younger participants than the systolic (Group 1) and diastolic (Group 2) HF patients (p=0.001). There was no statistically significant difference between Group 1 and Group 2 with regard to age. While nearly half of the patients were male in Group 2 (42.3%) and Group 3 (45.9%), there was clear male predominance in Group 1 (69.3%) (p=0.004). Hypertension was more in Group 1 (54.1%) and Group 2 (61.5%) than Group 3 (27%).

Medication use (calcium canal blockers and klopidogrel) was similar between the groups (p>0.05).

However Group 1 used more asetilsalisilik asit, ACE inhibitors, diuretics, nitrats, statins and trimetazin than group 2 (p<0.05) whereas the use of ARB was higher in group 2.

Urea, creatinine and fasting blood glucose levels were significantly higher in Group 1 when compared to Group 2 and 3 (p<0.005).

Oxidative stress parameters are shown in Table 1. The highest levels of TAS were found in group 1 (1,10±0,24) and the lowest were found in Group 2 (0.90±0.14) (Figure 1). The levels of TOS were the highest in group 2 (37,2±10,41) followed by group 1 (32.9±7.26) and group 3 (26.19±8.00). Oxidative stress index was the highest in group 2 (4.37±1.24) and the lowest in group 1 (2.24±0.80).

Linear regression analysis of TAS, TOS, OSI are shown in Table 2. Pearson correlation analysis revealed a weak negative association between TAS and TOS/EF and a weak positive association between TAS and urea/creatinine. There was a weak positive correlation between TOS and EF/systolic-diastolic blood pressure. As far as OSI is concerned, a weak positive correlation was found between OSI and diastolic blood pressure/EF as well as weak negative correlation between OSI and urea/creatinine. In linear regression analysis only EF was independent associated parameter for TAS,TOS and OSI.

We also compared ischemic and non-ischemic subgroups of systolic HF with regard to TAS, TOS and OSI. TOS and OSI were similar but TAS was statistically higher in non-ischemic group (p=0.0005) (Table 3).

Table 1: Comparison of demographic, clinical characteristics and laboratory findings including Total Antioxidant Status (TAS), Total Oxidant Status (TOS) and Oxidative Stress Index (OSI) levels among systolic heart failure patients (group 1), diastolic heart failure patients (group 2) and control group (group 3).

Parameters	Group I n=73	Group II n=50	Group III n=37	P Value
Age (year)	57.9±14.2$^{\infty}$	56.96±9.20	41.73±10.76	0.0001
Gender (female %)	30.7	57.7	54.1	0.004
Systolic Blood Pressure (mmHg)	128±18$^{\Sigma}$	136±21	125±17	0.029
Diastolic Blood Pressure (mmHg)	76±11§	80±14	76±11	0.006
Pulse (rate/minute)	83±17	77±14	79±13	0.093
Diabetes mellitus (%)	18.9	25	8.1	0.127
Hypertension (%)	54.1	61.5	27.0	0.004
Dyslipidemia (%)	21.3	38.5	16.2	0.033
Smoking (%)	36.5	32.7	37.1	0.908
Family History (%)	6.7	11.5	18.9	0.155
Acetyl Salicylic acid (%)	90.7	42.9	13.5	0.0002
Beta-blocker (%)	92	43.9	24.3	0.0001
ACE inhibitors (%)	57.3	13.7	8.1	0.0003
Calcium Channel blocker (%)	5.4	9.8	0	0.175
Dıuretic (%)	63.9	23.1	0	0.0001
ARB (%)	13.3	29.4	8.1	0.016

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Parameters	Group I n=73	Group II n=50	Group III n=37	P Value
ARB (%)	13.3	29.4	8.1	0.016
Nitrate (%)	22.7	4	0	0.003
Statin (%)	25.3	13.7	0	0.002
Trimetazidine (%)	10.7	3.9	0	0.063
Clopidogrel (%)	6.7	5.9	0	0.287
Ejection Fraction (%)	34±9*	62±5	61±3	0.0001
Sodium (mEq/L)	137.9±3.4	139.1±1.9	139.6±2.1	0.068
Potassium (mEq/L)	4.5±0.4	4.4±0.4	4.4±0.4	0.500
Urea (mg/dL)	41.2±14.6**	33.4±11.1	34.2±16.7	0.008
Creatinine (mg/dL)	0.83±0.19$^{\lambda}$	0.71±0.14	0.71±0.13	0.001
Fasting Blood Sugar (mg/dL)	138.8±62.3$^{\Omega}$	113.4±37.3	106.0±26.9	0.002
HDL-Cholesterol (mg/dL)	40±10	45±12	44±14	0.068
LDL-Cholesterol (mg/dL)	108±42	122±42	119. ±37	0.200
Total Cholesterol (mg/dL)	201±166	209±51	195±41	0.879
Triglyceride (mg/dL)	169±106	212±118	174±64	0.121
TAS (m mol Trolox® equivalents/l)	1.10±0.24$^{\alpha}$	0.90±0.14	0.94±0.14	0.0009
TOS (mic mol H_2O_2 equivalents/l)	32.9±7.26$^{\beta}$	37.2±10.41	26.19±8.00	0.0002
OSI (arbitrary units)	2.24±0.80$^{\mu}$	4.37±1.24	2.94±1.12	0.0005

ACE (Angiotensin converting enzyme), ARB (Angiotensin receptor blocker), HDL (High Density Lipoprotein), LDL (Low Density Lipoprotein), TAS (Total Antioxidant Status) and TOS (Total oxidant status), OSI (Oxidative Stress Index),
$^{\infty}$: p <0.05 (For group I–III and group II–III); p >0.05 (For group I–II)
$^{\Sigma}$: p <0.05 (For group II–III) ; p >0.05 (For group I–III and group I–II)
§ : p <0.05 (For group I–II) ; p >0.05 (For group I–III group II–III)
* : p <0.05 (For group I–II and group I–III) ; p >0.05 (For group II–III)
**: p <0.05 (For group I–II) ; p >0.05 (For group I–III and group II–III)
$^{\lambda}$: p <0.05 (For group I–II and group I–III) ; p >0.05 (For group II–III)
$^{\Omega}$: p <0.05 (For group I–II and group I–III) ; p >0.05 (For group II–III)
$^{\alpha}$: p <0.05 (For group I–II and group I–III) ; p >0.05 (For group II–III)
$^{\beta}$: p <0.05 (For group I–II and group II–III) ; p >0.05 (For group I–III)
$^{\mu}$: p <0.05 (For group I–II. group II–III and group I–III)

Tablo 2. Pearson correlation and Linear regression analysis showing associations between oxidative parameters and related parameters

		Correlation Coefficient	P Value	Regression Coefficient	P Value
TAS	**TOS**	-0.205	0.022	-0.006	0.952
	EF	-0.474	0.0001	-0.424	0.0001
	Urea	0.248	0.003	0.118	0.199
	Creatinine	0.292	0.0001	0.112	0.237
TOS	**TAS**	-0.205	0.022	-0.032	0.744
	Systolic BP	0.236	0.007	0.133	0.305
	Diastolic BP	0.299	0.001	0.090	0.476
	EF	0.382	0.0001	0.329	0.001
OSI	**Diastolic BP**	0.261	0.004	0.107	0.221
	EF	0.533	0.0001	0.482	0.0002
	Urea	-0.230	0.016	-0.076	0.405
	Creatinine	-0.199	0.038	0.033	0.725

TAS (Total Antioxidant Status) and TOS (Total oxidant status), OSI (Oxidative Stress Index), EF (Ejection fraction), BP (Blood pressure)

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Table 3: Comparison of oxidative parameters between ischemic and non-ischemic heart failure patients

	Ischemic HF n=50	Non ischemic HF n=23	P value
Total Antioxidant Status (mmol Trolox® equivalents/l)	**1.03±0.22**	**1.2425±0.23**	**0.0005**
Total Oxidant Status (micmol H_2O_2 equivalents/l)	23.82±7.26	24.1624±7.47	0.878
Oxidative stress index (arbitrary units)	2.35±0.85	2.0339±0.67	0.188

HF: Heart failure

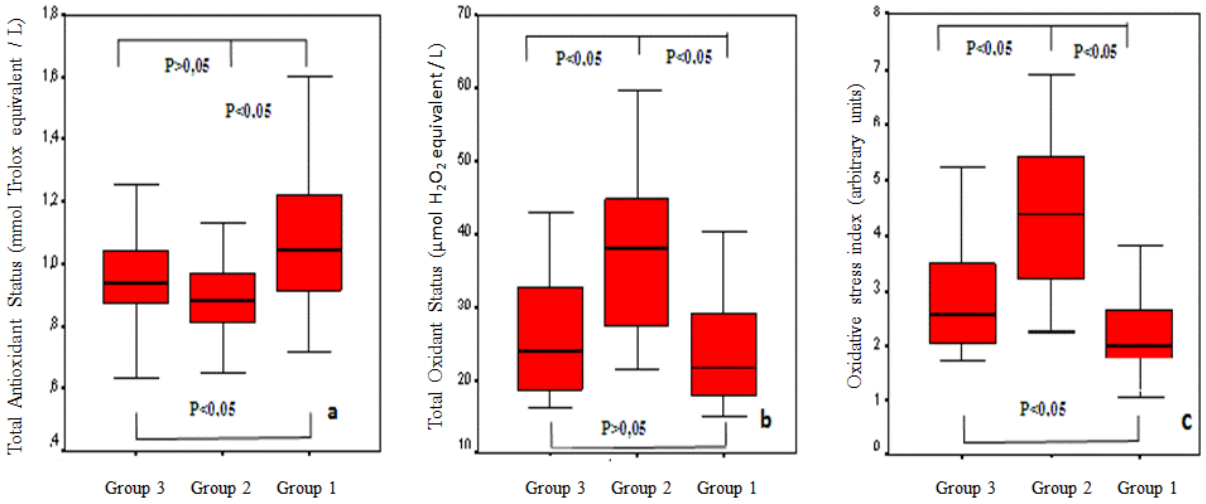

Figure 1: Comparison of Total Antioxidant Status, Total Oxidant Status and Oxidative Stress Index between the groups

Discussion

This study showed an increase of TOS and OSI in diastolic compensated HF patients. Studies have shown increased oxidative stress and ROS in HF patients (9,21–23). However, most studies only evaluated one oxidative stress parameter. Belch and et al. showed that HF patient had high levels of malonaldehide and low levels of thiol with a weak association between thiol and EF (Ejection Fraction) (9). Also, Hill and et al. found increased oxidative stress resulting from reduction of antioxidants in an experimental rat model with systolic HF subsequent to myocardial infarction (24). Another studies have showed increased 8-iso-PGF2α (an oxidant molecule) in pericardial effusion in HF patients with an association between 8-iso-PGF2α level and functional deterioration (22). Increased total peroxide levels in dilated cardiomyopathy and negative relation between this parameter and EF have been confirmed by the study conducted by Demirbag and et al (23).

It is more reasonable to investigate the total oxidative reflection of all antioxidants instead of just one oxidative parameter in a certain clinical situation (12,13). We found increased TOS level in HF which is confirmed by prior studies showing increase in a variety of oxidative parameters. Increase in TOS was more apparent in diastolic HF patients, however no difference was found between ischemic and non-ischemic systolic HF patients in terms of oxidative stress.

Endothelial cells, neutrophils and cardiac myocytes are the main sources of ROS within the cardiovasculare system (24). NAD(P)H oxidase, nitric oxide synthases (NOS), xanthine oxidase and mitochondrial electron transport chain activity are possible sources of oxidative species in HF (24–28). Also, decrease in protective enzyme concentrations against oxidative stress and reduced levels of endogenous antioxidants may result in increased oxidative stress in failing heart since an imbalance between ROS levels and members of antioxidant defense system leads to oxidative stress (29).

Human studies as well as animal studies have shown that superoxide plays a role in the progression of myocardial dysfunction (30,31). Preliminary evidence suggests that failing hearts express increased inducible isoform of nitric oxide (NO) synthase (24). Peroxynitrite, an ion formed by the reaction of superoxide with NO is increased in HF and detrimental effect of this anion on cardiac function have been demonstrated by previous studies (32–34). Peroxynitrite induces activation of matrix metalloproteinase precursors which give rise to myocardial tissue injury and progression of HF (35). Also, the relation between cardiac remodeling –one of main underlying mechanisms of progression of HF- and oxidative stress was confirmed by variety of studies (24).

We found higher TOS levels in diastolic HF patients compared to those in both systolic HF patients and in controls without HF. Although TOS levels were higher in systolic HF patients than those in controls, this difference did not reach statistically significances. We speculate that these finding are related to the antioxidants properties of the drugs used (statins, β-adrenergic antagonists, angiotensin converting enzyme inhibitors, nitrates, trimetazidine and angiotensin receptor blockers) which are effectively used in coronary artery disease and systolic HF.

Antioxidant levels and their activities decrease in HF. Although TAS is a marker of antioxidant status this parameter has not been studied widely in HF. Here, we show higher levels of TAS in systolic HF compared to both diastolic HF and controls. We speculate that the finding regarding TAS ad TOS are related to drug use, but more comprehensive researches is needed.

This study has limitations. First, this study was dissimilarity between groups with regard to demographic, clinic, biochemical properties and drug usage. However, these results are worth to be interpreted since it is a unique study evaluating oxidative and antioxidative status in diastolic HF. Secondly, sample sizes in each group is small. Larger studies are needed to confirm our findings.

Conclusions

In consistent with the literature, we found higher oxidative stress in HF patients, predominantly in diastolic HF patients. The difference between diastolic and systolic HF with regard to oxidative and antioxidative status seems to come from distinct drugs usage between the groups which have potential effects on oxidative and antioxidative parameters. According to our results, we can speculate that medical therapy consisted of β-adrenergic antagonists, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, nitrates, trimetazidine or statins is needed, at least, to reduce oxidative stress in diastolic HF patients.

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Ethical issues: All Authors declare, Originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the Authors responsibilities. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

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