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Evaluation of Short Term Effect of Atorvastatin on Myocardial Performance and Its Pleiotropic Effects on Ischemic Heart Failure

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Authors' contributions

This work was carried out in collaboration between all authors. Author AES designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author SKH managed the literature searches, analyses of the study performed the spectroscopy analysis and author MKA managed the experimental process and author MAH identified the species of plant. All authors read and approved the final manuscript.

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ABSTRACT

Background: statins are used routinely in patients with coronary artery disease for their lipid lowering effects. Some clinical studies have found that statins do not affect clinical outcomes in patients with chronic heart failure (CHF), while others have found that statins have many beneficial effects. The aim of this study was to evaluate the pleiotropic effects of atorvastatin on patients with chronic heart failure of ischemic etiology (IHF) using conventional echocardiography and tissue *doppler* imaging.
Patient & Methods: Forty-eight patients with (CHF) were divided randomly into two equal groups; Atorvastatin group (received conventional therapy of HF plus atorvastatin 20 mg/d orally) and

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Control group (received conventional therapy only) for 3 months. Patients were examined both before and after treatment for biochemical tests; serum tumor necrosis factor α (TNF-α), serum high sensetive c reactive protein (hs-CRP), oxidized low density lipoprotein (ox- LDL), noradrenaline, adrenaline, renin, brain naturetic peptide (BNP-32), Troponin-I, total lipid profile and malondialdehyde. Conventional Echocardiography including left ventricle (LV) dimensions & wall thickness, ejection fraction (EF), E/A ratio, and tissue Doppler imaging (TDI) including Isovolumic contraction (IC), mitral annulus systolic velocity(S-peak), early (E) and late (A) diastolic peak velocities and Tei index were performed.

Results: Atorvastatin group showed statistically significant decreased in TNF- α, hs-CRP, ox-LDL, BNP-32 and noradrenaline compared to their baseline values before the study. Conventional echo failed to detect significant changes in each group except for significant increase in E/A ratio in atorvastatin group. DTI demonstrated that atorvastatin group showed significant improvement in systolic function [significant increase in S wave & isovolumic contraction (IC) peak velocities and better diastolic function [E peak velocity increased & E/E' ratio decreased significantly]. Tei index and heart rate improved significantly in atorvastatin group.

Conclusion: Atorvastatin improved cardiac function, decreased inflammatory and oxidative stress parameters as well as modulated the neurohormonal imbalance in CHF patients.

Keywords: Chronic heart failure; atorvastatin; pleitropic effects; echocardiography; tissue doppler imaging.

1. INTRODUCTION

Heart failure is no longer regarded as an isolated cardiac intity, but a systemic disorder involving several, initially adaptive and later detrimental, neurohormonal and inflammatory compansatory mechanisms.

Several complementary mechanisms pathways contribute to the physiological adjustment necessary for optimum cardiac function in health and disease. After an insult to cardiac function occurs, however, these mechanisms may cause a paradoxical worsening of cardiac function causing structural and functional abnormalities of the heart through, vascular injury, endothelial dysfunction, neurohormonal factors, oxidative stress accompanied by effort intolerance, fluid retention and reduced longtevity [1] Fig. 1.

Chronic heart failure (CHF) is associated with intensified oxidative stress; activated inflammation and unbalanced neurohormones [2] which are thought to be important in mediating the progression of heart failure [3].

Atorvastatin:

Competitively inhibit 3-hydroxy-3 -methylglutaryl-CoA (HMG- Co A) reductase, thereby reducing the available L-mevalonate and cholesterol biosynthesis. The resulting decrease in hepatic cholesterol concentration leads to a compensatory increase in expression of hepatic low-density lipoprotein (LDL) receptors, which clear cholesterol-rich LDL and LDL precursors from the circulation. The rapidity and effectiveness with which statins decrease coronary events has led already a few years ago to the hypothesis that statins might influence vascular biology through mechanisms beyond cholesterol reduction. Beyond cholesterol-lowering, improvement of endothelial function, decrease of vascular inflammation and reduced activation of the immune response may lead to attenuated atherosclerotic plaque formation. Recent studies suggest that most of the pleiotropic effects be mediated by the inhibitory action of statins on isoprenoid synthesis [4].

By inhibiting the production of L-mevalonate, statins also prevent the synthesis of other important isoprenoid molecules such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). These molecules are important for the posttranslational modification (isoprenylation) of a large variety of proteins among which the small GTP-binding proteins Ras, Rac and Rho [5] Fig. 2.

Why Atorvastatin:

The CURVES study, which compared the effecacy of different doses of Atorvastatin, Simvastatin, Pravastatin, Lovastatin and Fluvastatin for reducing LDL and total cholesterol in patients with hypercholesterolemia found that Atorvastatin was more effective without increasing adverse effects [6]. After initiation of the dose, lipid levels should be analyzed within 1–3 months [7].

Current therapy for patients with HF focuses on improving cardiac and exercise performance and correcting neurohormonal imbalances. However, despite aggressive medical therapy, CHF remains to be a major cause of morbidity and mortality worldwide [8].

The (HMG-CoA) reductase inhibitors (statins) are used routinely in therapy for patients with coronary artery disease for their lipid lowering effects and other multiple benefits called pleiotropic effects including anti –inflammatory, plaque stabilizing and other different effects. Some clinical studies have found that statins do not affect clinical outcomes in patients with chronic heart failure of ischemic or non- ischemic etiology [9,10]. Other clinical trials have found that statins lower serum markers of inflammation [11], improve endothelial and cardiac functions [12], inhibit reactive oxygen species production, inhibit ventricular remodeling [13], improve neurohormonal imbalance [3] and reduce hospitalization rates in patients with CHF [14]. Based on these findings, we hypothesized that, treatment patients with ischemic cardiomyopathy with New York Heart Assosiation (NYHA) classification II-IV, with atorvastatin would improve cardiac function due to the pleiotropic effects of atorvastatin.

The aim of this study is to investigate the short term effect of atorvastatin on cardiac function, oxidative and neurohormonal changes in patient with chronic heart failure of ischemic etiology.

1.1 Significance of the Study

The guidelines for the primary and secondary prevention of coronary artery disease (CAD) by the lowering of LDL cholesterol are well established [15].

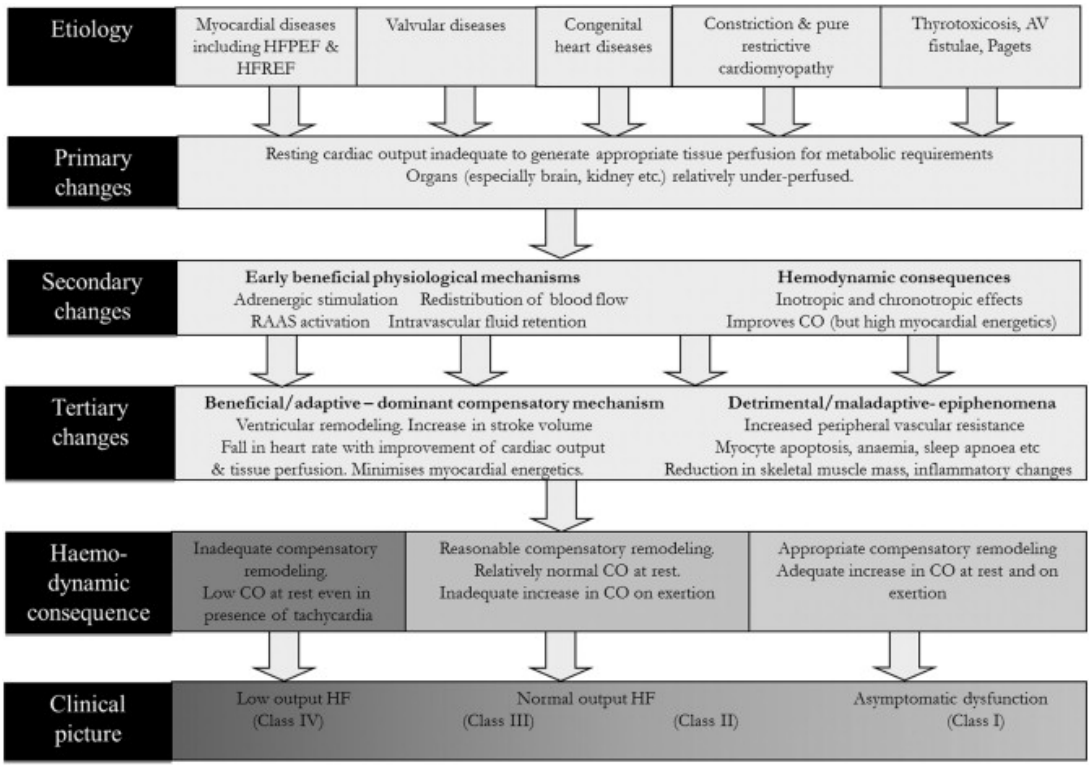

Fig. 1. A schema to understand heart failure. This figure shows the single early pathological process (primary changes) of reduced stroke volume/cardiac output less than the requirements of the metabolizing tissues. Initial compensatory response (secondary) is shown. It is proposed that the dominant compensatory mechanism (tertiary) in chronic stable heart failure is normalization of stroke volume through regulation of end-diastolic volume. This is associated with adverse and maladaptive processes. The hemodynamic consequences and likely clinical picture are presented

Statins: Mechanism of action

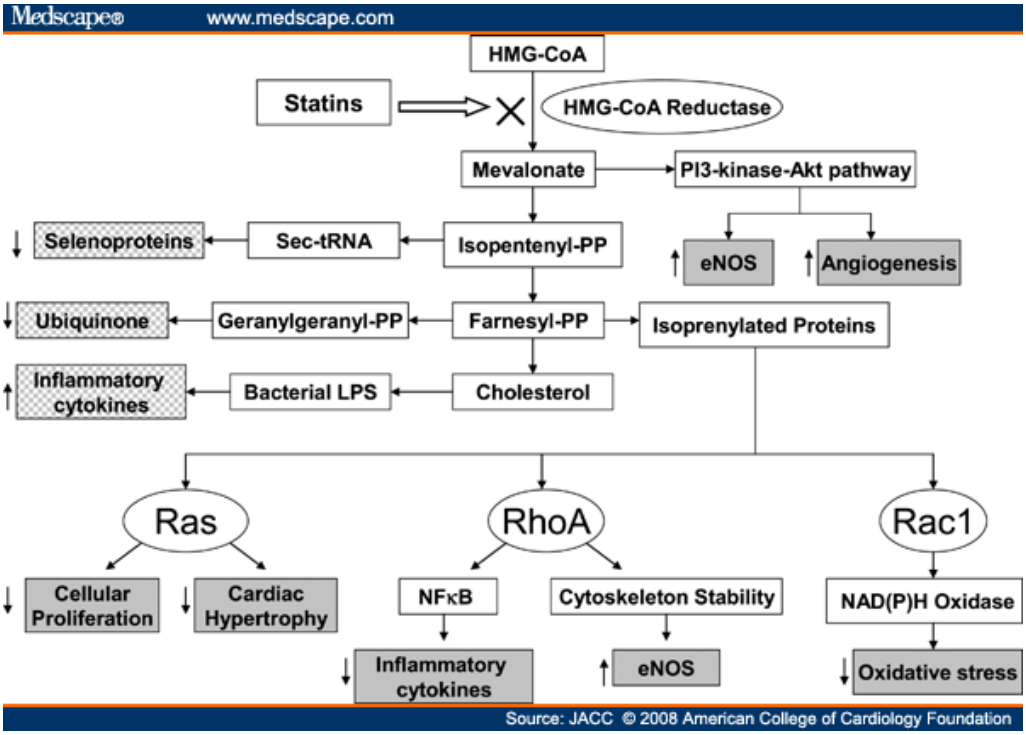

Fig. 2. The HMG-CoA reductase pathway, which is blocked by statins via inhibiting the rate limiting enzyme HMG-CoA reductase

The efficacy of statins in the prevention of CAD events has been demonstrated in five randomised placebo controlled trials involving a total of 30,817 patients [16,17] Treatment for 5 years reduces the risk of major coronary events by 34 and 30% in primary and secondary prevention, respectively. These benefits occur regardless of plaque regression [18] in patients with normal cholesterol and after a relatively short period of time, implicating the non-sterol effects of statins as being responsible for their early clinical benefits [19].

2. PATIENTS AND METHODS

2.1 Study Design

The study is a single center, blind randomized investigational study conducted in the cardiology department, Menofya university hospital started from July 2010 to March 2011.

All participants provided an informed consent and the study protocol was approved by the Institutional Ethics Committee.

Forty eight patients with systolic heart failure (EF <40%) of ischemic etiology proved by one of the following: evidence of previous infarction or ischemia on Electrocardiogram (ECG) or isotopic scanning or angiographic evidence of <50% lesion in 1 or more of the three major coronary vessels. Patients were excluded if they had acute coronary syndrome, coronary artery bypass graft surgery or coronary angioplasty in the last 6 months; hypertrophic or congenital cardio-myopathy, used anti-oxidants or statins in the previous 2 months, or other conditions that affect determination of oxidative stress status, such as renal failure, autoimmune diseases, neoplasia, advanced liver or pulmonary disease, and acute or chronic inflammation.

Patients were interviewed for complete history taking and clinical examinations, and randomly divided into two groups: group I consisted of 24 patients received 20 mg capsules of atorvastatin daily for 3 months (Ator20 mg; EIPECO Pharmaceutical Company, 10th of Ramaden City, Cairo, Egypt) plus the conventional therapy ;and Group II consisted of 24 patients received the conventional therapy only. Participants were

followed up every 2 weeks to ensure compliance, and to report any dropout or adverse effects.

2.3 Samples Collection

About 10 ml of blood was taken from each patient after fasting overnight, supine position for 30 min before withdrawal of samples both before and after the treatment course, and the blood sample was prepaired and stored at-80°C.

3. BIOCHEMICAL TESTS

3.1 Anti-Inflammatory Activities

Serum hs-CRP was assayed using commercially available enzyme-linked immunosorbent assay ELISA kit [LDN (Labor Diagnostika Nord)-Nordhorn-Germany] [20,21] and serum tummer necrosis factor (TNF- α) was assayed using the Enzyme-linked immunosorbent assay technique (ASSAYPRO LLC-USA) kit. [22,23]

3.1.1 Antioxidant activities

Plasma oxidized low density lipoprotein (ox-LDL) activity was assayed using ELISA assay (USCNK-Life science Inc. Wuhan –China) kit. [24,25] and plasma malondialdehyde (MDA) was estimated fluorometricaly by determination of thiobarbituric acid reactive substances (TBARS) using the method of Mak and Weglicki [26]. The method depends on the reaction between MDA and thiobarbituric acid in an acidic medium at high temperature to produce a pink color product, which is extracted in n-butanol and measured at 535 nm.

3.1.2 Imunohormonal modulator activities

Measurement of plasma levels of NorEpinephrine and Epinephrine using commercially available ELISA assay kit (LDN (Labor Diagnostika Nord)-Nordhorn-Germany) [27,28] and plasma level of Renin was determined using commercially available ELISA assay kit (USCNK-Life science Inc. Wuhan – China) kits [29,30].

3.2 Cardiac Markers

Estimation of Brain naturetic peptide-32 (BNP-32) extracted from plasma using commercially available ELISA assay kit (Phoenix Pharmaceuticals (USA) kits. [31,32] and serum Troponin-I was assessed using commercially available ELISA assay kit (Biocheck, Inc-Foster City- California) [33,34].

Measurement of serum Total cholesterol, Triglycerides and High density lipoprotein using NDC (Human, Germany) kits while Low density lipoprotein calculated manually [35-37].

3.2.1 Evaluation of cardiac function

Conventional and DTI echocardiography was performed using commercially available GE Vivid 5 Vingmed Horten , Norway machine equipped 1.7- 4 M. Hertz sector transducer probe, All measurements were carried out by the same echocardiographer, who was blinded to the treatment arm to which subjects belonged, LV dimensions, wall thickness, peak velocities of trans-mitral early (E) and late diastolic(A) LV filling and the ratio of trans-mitral early to late (E/A ratio) LV filling velocity were calculated. All measurements were calculated according to the recommendations in the combined American Society of Echocardiography/European Society of Cardiology guidelines; LVEF was calculated according to Simpson's rule [38]. TDI measurements was done by placing the sample volume at the four sides of the mitral annulus and taking the average result from the four sides of mitral annulus, measurements included peak velocity of isovolumic contraction (IC), systolic velocity (S -peak) , early (E') diastolic velocity, The trans-mitral early diastolic flow wave(E) to mitral annular early diastolic velocity ratio (E/E') were calculated. Tei index (Myocardial Performance Index) was calculated by adding ICT plus IRT divided on the S wave duration (ICT +IVR/ S wave duration) where, isovolumic contraction time [ICT: begnning to QRS to start of S wave] and isovolumic relaxation time (IRT: end of S wave to start of E' wave) Fig. 5.

3.3 Statistical Analysis

The collected data were organized, tabulated and statistically analyzed using SPSS software (Statistical Package for the Social Sciences, version 16, SPSS Inc. Chicago, IL, USA). For quantitative data, the range, mean, median and standard deviation were calculated. For qualitative data, comparison between two groups and more was done using Chi-square test (X^2). For comparison between means of two groups, parametric analysis unpaired (t-test) was used. For comparison between means of the same group before and after treatment, parametric analysis paired t-test was used. Correlation

between variables was evaluated using Pearson's correlation coefficient. Significance was adopted at ($p<0.05$) for interpretation of results of tests of significance.

4. RESULTS

Demographic data of two groups showed there were no significant difference between two groups at the beginning of the study as regarding age (p- value 0.91), sex (p- value 0.55), NYHA classification (p- value 0.927), history of hypertension (p- value 0.773), history of diabetis mellitus(p-value 0.712) and smoking (p- value 0.85). Biochemical, conventional echo and DTI parameters showed there were no significant differences between two groups at the beginning of the study except IC& S- peak velocities which were higher in control group, (Table 1.).

Table 1. Changes in biochemical parameters and Echocardiographic findings both before and after three months of treatment course in ischemic heart failure patients

Parameters	Atorvastatin group(n=24)		Control group(n=24)	
	Before treatment	After treatment	Before treatment	After treatment
Hs-CRP(ng/ml)	1002.92±285.66	784.38±269.58**	987.58±266.97	1049.38±231.60[a]
OXLDL (pg/ml)	443.92±133.14	328.33±112.18**	427.71±121.21	428.33±131.05[a]
TNF-α(ng/l)	39.83±9.86	30.92±8.23**	38.71±8.95	41.33±9.09[a]
MDA(mg/l)	4.51±0.81	3.18±0.68**	4.11±1.17	4.27±1.19[a]
NE(pg/ml)	722.79±242.53	593.33±213.27**	716.58±263.03	731.54±263.99[a]
Renin (pg/ml)	305.00±56.39	255.42±36.02**	314.38±79.96	324.79±75.25[a]
Adrenaline (pg/ml)	68.00±12.73	57.17±11.08**	63.33±11.98	70.63±11.71[a]
BNB(pg/ml)	418.75±76.60	348.54±68.04**	431.04±63.04	451.46±63.3[a]
Troponin.I (ng/ml)	1.29±0.22	1.07±0.18*	1.32±0.19	1.40±0.20[a]
LDL(mg/dl)	169.58±31.46	132.00±26.68**	156.92±29.83	192.83±26.28**[a]
Total Cholesterol (mg/dl)	235.29±39.94	193.54±32.35**	225.54±30.96	261.71±26.33**[a]
Triglyceride (mg/dl)	188.13±36.68**	146.58±36.14**	181.29±36.33**	218.88±35.29**[a]
HDL(mg/dl)	28.13±4.61	31.46±4.33*	30.58±5.62	27.46±5.09*[a]
LVEDD (cm)	6.58±0.95	6.32±0.88	6.41±0.76	6.54±0.95
LVESD(cm)	5.60±1.07	5.28±1.05	5.45±0.79	5.70±0.90
LVEF (%)	33.75±7.80	35.62±8.06	32.75±5.82	31.12±6.12
E/A ratio	0.60±0.11	0.75±0.11**	0.69±0.17	0.66±0.12
LVMI	152.75±19.33	150.46±18.33	154.75±19.85	158.58±21.15
HR (b/m)	79.21±9.87	74.37±10.31**	74.50±5.93	78.42±6.58**
●E-wave flow Velocity (cm/s)	60± 12.2	77±10.5**	62/±10.2	65±11.5
●A-wave Velocity (cm/s)	90±10.32	92±8.7	88±8.35	87±7.65
IVC (ms)	3.48±0.73	4.83±0.91**	4.28±1.26	4.48±1.22
●S-peak Velocity (cm/s)	4.19±1.12	5.64±0.90**	4.75±0.62	4.52±0.73
●E-wave Velocity (cm/s)	4.54±1.10	6.79±1.27**	4.85±1.38	4.83±1.34
Tei index	0.84±0.15	0.74±0.14**	0.78±0.12	0.83±0.11**
●E/ E' -wave Velocity (cm/s)	19.2±6.5	15.1±5.23*	18.3±7	18.6±6.5

*Atorvastatin group: patients with systolic heart failure of ischemic etiology received normal treatment plus Atorvastatin 20 mg /day) for 3 months; Control group: patients with systolic heart failure of ischemic etiology received normal treatment only for 3 months; Hs-CRP, high sensitive C reactive protein ; Ox-LDL, Oxidized low density lipoprotein; TNF-α, Tumer necrosis factor–α; MDA, Malondialdehyde ; NE, Noradrenaline ; BNP-32, Brain naturetic peptide-32 ;LDL, Low density lipoprotein; HDL, High density lipoprotein; LVEDD, Left ventricular end diastolic diameter ; LVESD, Left ventricular end systolic diameter ;LVEF, Left ventricular ejection fraction; LVMI, Left ventricular mass index ; HR, Heart rate;E-wave, trans-mitral early diastolic LV filling; A wave , trans-mitral late diastolic LV filling; E/A ratio, the ratio of trans-mitral early to late LV filling; IVC, Isovolumic contraction velocity; S-peak, systolic peak velocity; (E') wave, early diastolic velocity; (E/E') ratio, The trans-mitral to mitral annular early diastolic velocities ; Tei index, (Myocardial Performance Index); Data are presented as mean± standard deviation; *: Significant difference after treatment compared with their respective values before treatment ($p < 0.05$). ;**: highly significant difference after treatment compared with their respective values before treatment ($p< 0.001$). a: Significant difference between the mean values of the two groups after treatment ($p < 0.05$).*

During follow up, four participants were dropped out from the study and were replaced by new participants to maintain the study sample size. The higher dropout was observed in the control group owing to death (two cases) and the other was due to severe worsening.

4.1 As Regarding Biochemical Parameters

After three month of atorvastatin administration the treated group showed a highly statistically significant decrease in serum level of hs-CPR level and TNF- α, (Inflammatory markers), also there were significant reduction in oxidative stress markers manifested by significant decrease in plasma ox-LDL and plasma malondialdehyde levels. On the other hand the control group showed non-significant changes in both inflammatory and oxidative stress markers, (Table 1).

BNP-32&serumTroponin- I levels (markers of myocyte stress & myocyte injury respectively) were significantly decreased in atorvastatin treated group only (Table1).

Epinephrine, Nor Epinephrine and Renin levels (as neurohormonal markers) significantly decreased compared to its baseline values before the study in atorvastatin treated group while in control group their values increase but not reach the significant level.

Treatment with atorvastatin also responsible for significant decrease in serum total cholesterol, Triglycerides, and Low density lipoprotein .While there was significant increase in high density lipoprotein level compared to their baseline values before the study, while in control group the opposite occurs (Table 1).

4.2 Echocardiographic Assessment

Conventional and DTI examination presented in (Table 1.) did not show any significant difference between both groups at the start of examination except for IC & S- waves peak velocities which were higher in control group. In spite of inability of conventional echo to detect significant changes in each group before and at the end of study except for the improvement of diastolic function [significant increase in E/A ratio in atorvastatin group ($p< 0.05$)]. The DTI showed significant improvement in systolic function as evidence by significant increase in peak velocities of S & IC waves. Also there was better diastolic function after atorvastatin administration as there were increased E peak velocity and deceased E/E´ ratio. Tei index reflecting global LV function improved significantly in atorvastatin group while it worse in control group by significant degree (Fig. 3). The heart rate decreased in atorvastatin group ($p< 0.05$) and increased in control group by significant values (Table 1).

Tables (2 and 3) showed comparison between the mean percent of changes of post than pretreatment values of different biochemical, conventional and TDI parameters of the two groups, as there were highly significant difference between the mean percent of change of post than pretreatment values of different parameters between Atorvastatin group and control group except for TDI E wave, there was no significant change (Figs. 3 and 4).

As regarding correlation between echocardiographic parameters and biochemical marker the post treatment Tie index was positively correlated to MDA($r=0.461, p=0.023$) and DTI E -wave peak velocity were negatively correlated significantly with Epinephrine ($r=0.70, p=0.001$), NorEpinephrine ($r=0.462, p=0.044$), and Troponin I ($r=0.614, p=0.001$), also the E/A was correlated egatively with renin ($r= 0.798$,$p= 0.001$) (Fig. 6).

5. DISCUSSION

Chronic heart failure is a major healthcare problem associated with high morbidity and mortality. Despite significant progress in treatment strategies, the prognosis of heart failure patients remains poor [39].

The present study evaluated the short term administration of Atorvastatin in patients with ischemic systolic heart failure; the results emphasized the potential benefits of addition of Atorvastatin to standard CHF therapy owing to its ability to decrease inflammatory, oxidative stress markers, restore the neurohormonal imbalance and investigate whether atorvastatin treatment may influence myocardial performance evaluated by TDI in subjects with CHF. The underlying mechanisms associated with the observed improvements pointed to the pleiotropic effects that deserve careful consideration.

Table 2. Mean percent of change of post than pretreatment values of different biochemical markers including brain naturetic peptide-32 (BNP-32) , Troponin I, high sensitivity C-reactive protein (Hs CRP) , tumor necrosis factor alpha (TNF-α), oxidizrd low density lipoprotein (oxi-LDL), malondialdetyide (MDA),Adrenaline , Noradrenaline, Renin, Total cholesterol (TC), high-ensity lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides (TG) among the studied patients with systolic heart failure of ischemic etiology (n=48)

Mean % of change of post than pre treatment parameters among the studied the patients with systolic heart failure of ischemic etiology (n=48)				
Parameters	**Atorvastatin group (n=24)**	**Control group (n=24)**	**Z-test**	**P**
	Mean±SD	**Mean±SD**		
● BNP-32 (pg/ml)	↓16.83±3.69	1.20±3.11	5.939	0.0001*
● Troponin I (ng/ml)	↓16.63±4.01	0.25±0.77	20.251	0.0001*
● hs -CRP (ng/ml)	↓22.66±7.38	4.10±12.63	5.444	0.0001*
● TNF-α (ng/L)	↓22.74±3.50	1.64±4.13	5.941	0.0001*
● oxi–LDL (pg/ml)	↓26.80±5.43	0.09±2.52	5.945	0.0001*
● MDA (mg/l)	↓29.50±8.92	4.65±16.90	5.465	0.0001*
● Adrenaline (pg/ml)	↓15.97±3.28	2.95±9.85	5.444	0.0001*
● Noradrenaline (pg/ml)	↓18.38±4.56	3.96±9.41	5.093	0.0001*
● Renin (pg/ml)	↓25.51±6.48	2.82±7.57	5.941	0.0001*
● TC (mg/dl)	↓17.46±6.35	16.92±10.05	14.163	0.0001*
● HDL (mg/dl)	12.63±9.46	↓10.11±4.96	10.429	0.0001*
● LDL (mg/dl)	↓21.94±9.67	24.56±13.52	13.700	0.0001*
● TG (mg/dl)	↓22.19±12.17	21.85±9.25	14.117	0.0001*

**Significant (P<0.05)*

The present study revealed that Atorvastatin therapy decrease the inflammatory process associated with heart failure as it significantly decrease the serum level of both hs-CPR level and TNF- α, (inflammatory markers). This effect could be related with the ability of statins to inhibit isoprenylation and the activation of members of the Rho family, blocking pro-inflammatory transduction pathways [40].

Our results were in accordance with Castro PF et al. (40) who evaluate the effect of 20 mg of atorvastatin in 38 patients with systolic chronic heart failure for 8 weeks measuring plasma malondialdehyde (MDA) levels, matrix metalloproteinase-2 activity (MMP-2), hs-CRP, TNF-α, interleukin-6(IL-6). They found significant decrease in plasma MDA, (MMP-9), hs-CRP high- IL-6, and plasma MDA. Also Dimitris Tousoulis et al. [41] found that the serum levels of TNF-α was significantly decreased in atorvastatin-treated group.

However these results were opposite to Takahisa Yamada et al. [3] who study the effect of 10 mg Atorvastatin on 38 patients with CHF for 3 years. They measured hs-CRP, NE, and BNP every 6 months. They found that hs- CRP tended to decrease in statin treatment group but the differences did not reach statistical significance.

The present study results were augmented by the results of meta-analysis of 10 studies to evaluate the effect of statin on inflammatory markers in chronic heart failure patients (6052 patients) and done by Lei Zhang et al. [2], they found that statin therapy was associated with significant decreased in hs-CPR level but against our result they found that TNF- α level was not changes significantly with statin therapy, however this may be due to heterogeneous

patient group, different statin medication and duration. As different lipophilicity and hydrophilicity among statins can lead to different effect, the lipophilic simvastatin and atorvastatin had a higher uptake in cardiac tissue than the hydrophilic rosuvastatin. The greater uptake of lipophilic statins by the heart might contribute to the improvement in cardiac function and subsequently improve the clinical outcomes of chronic HF patients in treatment with atorvastatin or simvastatin.

In the present study we found that patients with CHF had increased oxidative stress markers determined by higher plasma MDA and high ox-LDL levels than normal Atorvastatin therapy decrease significantly both ox-LDL and plasma MDA levels. These results were in agreement with Gjin Ndrepepa et al. [42] who demonstrated that patients received statins have lower levels of OxLDL compared with patients who do not receive statins. Also the results were compatible with Luca Puccetti et al. [43] proved that atorvastatin caused a significant reduction in lipid peroxidation estimated by level of (OX-LDL). While Castro PF et al. (39) and J. R. Morrow [44] showed significant reduction in plasma MDA level.

The data from the present study confirmed the results of Hisato Takagi et al. [45] who reported after metanalysis of many randomized trials that Atorvastatin, not rosuvastatin, improves cardiac function in heart failure patients concomitantly with significant reduction in NorEpinephrine level. Also M. Szramka et al. [46] who reported that treatment with atorvastatin significantly reduced plasma levels of NorEpinephrine in patients with coronary artery disease. On the other hand these results were against to Takahisa Yamada et al. [3] who found that there was no significant change in plasma NE concentration after Atorvastatin administration.

Table 3. Mean percent of change of post than pretreatment values of conventional echocardiography findings (heart rate (HR), E/A ratio, left ventricular mass index (LVMI), ejection fraction (LVEF), end-diastolic (LVEDD) and end-systolic diameters (LVESD),and Tissue Doppler imaging (TDI) parameters including Isovolumic contraction duration (IVC), S- peak velocity ,E-wave velocity and Tei index among the studied patients with systolic heart failure of ischemic etiology (n=48)

Mean percent of change (%) of post than pre treatment parameters among the studied the patients with systolic heart failure of ischemic etiology (n=48)				
Parameters Mean±SD	**Atorvastatin group (n=24) Mean±SD**	**Control group (n=24) Mean±SD**	**Z-test**	**P**
Conventional Echocardiographic parameters				
● HR (b/m)	↓5.82±9.29	5.39±6.15	4.931	0.0001*
● E/A ratio	13.11±12.38	↓8.73±12.44	6.095	0.0001*
● LVMI	↓1.43±1.84	2.42±2.28	6.438	0.0001*
● LVEF (%)	5.91±7.59	↓5.07±5.90	5.594	0.0001*
● LVEDD (cm)	↓3.90±4.07	1.93±7.69	3.285	0.002*
● LVESD (cm)	↓5.68±7.01	4.54±5.84	5.487	0.0001*
Tissue Doppler imaging parameters				
IVC (ms)	20.17±19.33	6.41±17.12	2.609	0.012*
● S-peak Velocity (cm/s)	13.65±13.95	↓5.01±6.96	5.867	0.0001*
● E-wave Velocity (cm/s)	5.34±13.72	1.84±20.44	0.697	0.489
Tei index	↓12.02±10.38	7.31±9.26	6.808	0.0001*

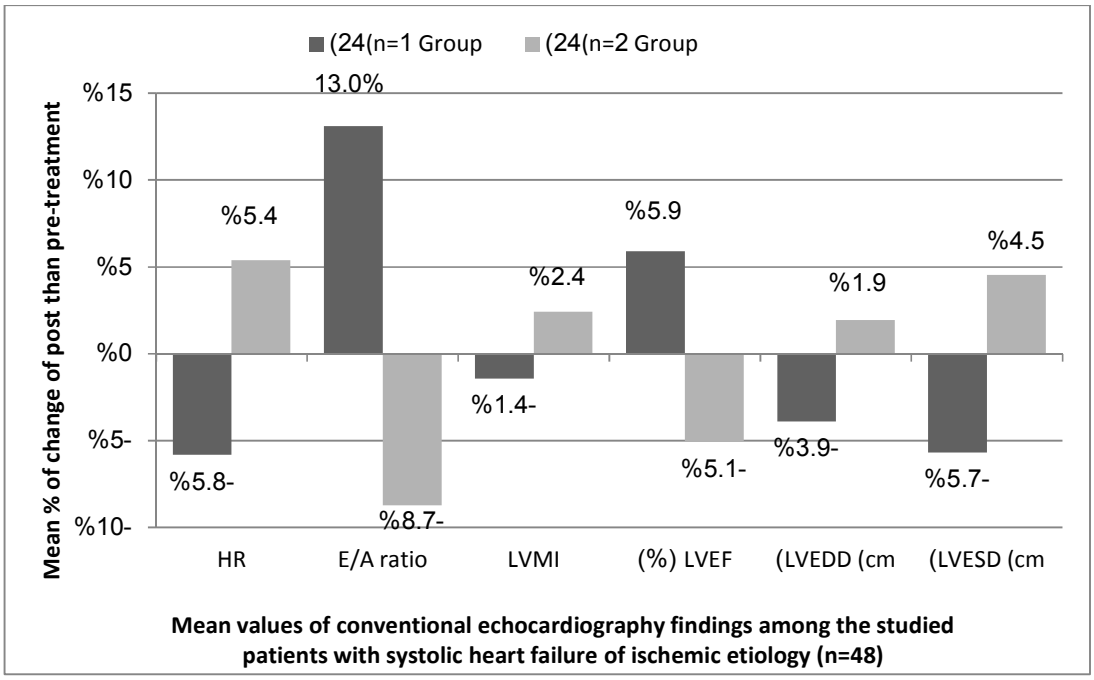

Fig. 3. Mean percent of change of post than pretreatment values of conventional echocardiography findings among the studied patients with systolic heart failure of ischemic etiology (n=48)

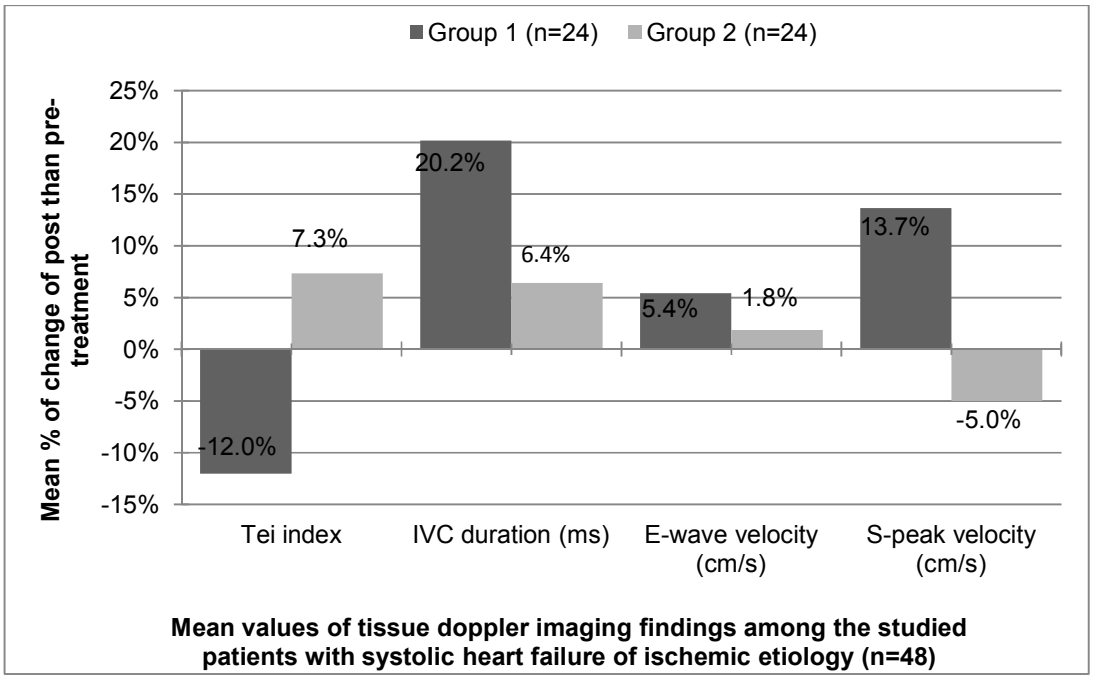

Fig. 4. Mean percent of change of post than pretreatment values of Tissue Doppler imaging (TDI) among the studied patients with systolic heart failure of ischemic etiology (n=48)

IVC=Isovolumic contraction duration

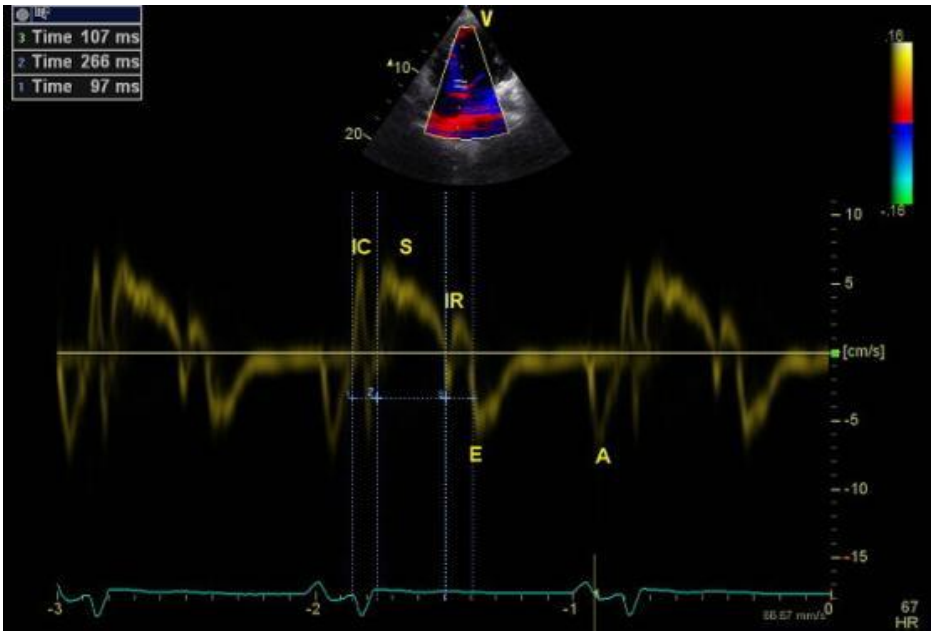

Fig. 5. TDI Measurements recorded at the septal mitral annulus in the apical four- chamber view: ICT [ICT: end of A´wave to start of S wave] and isovolumic relaxation time (IRT: end of S wave to start of E' wave), Tei index (Myocardial Performance Index) was calculated by adding ICT plus IRT divided on the S wave duration (ICT +IVR/ S wave duration) from TDI

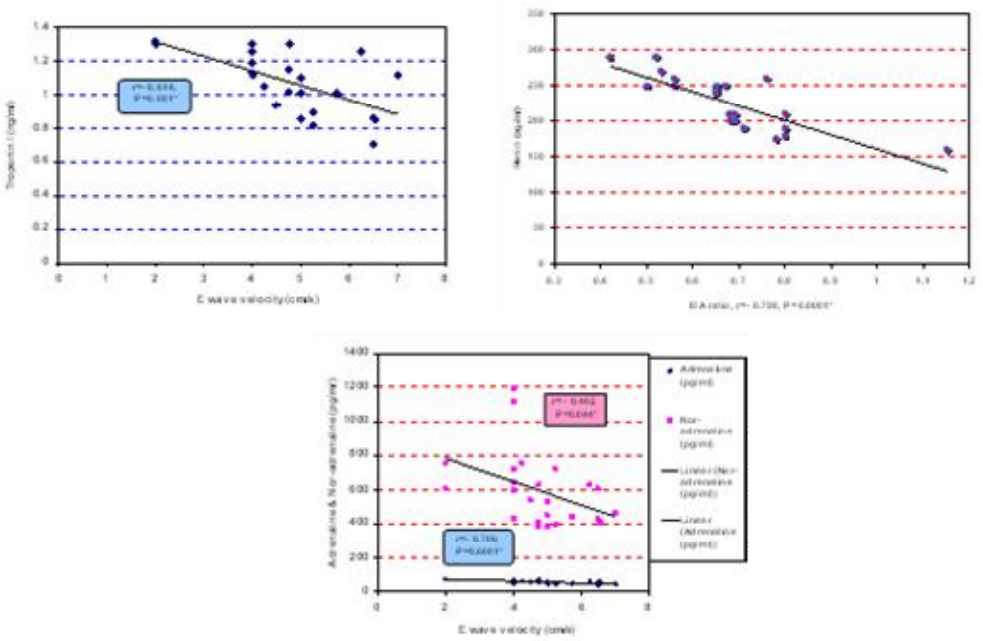

Fig. 6. 1) Correlation between post-treatment Renin and E/A ratio among the studied patients with systolic heart failure of ischemic etiology treated with Atorvastatin (n=24)
2) Correlation between E wave velocity post-treatment and Troponin I among the studied patients with systolic heart failure of ischemic etiology treated with Atorvastatin (n=24)
3) Correlation between post-treatment E wave velocity and both adrenaline and nor-adrenaline among the studied patients with systolic heart failure of ischemic etiology treated with Atorvastatin (n=24)

In this study Atorvastatin significantly decrease plasma BNP level (as markers of myocyte stress). This result was forced by Takahisa Yamada et al. [3] who found that the plasma BNP level significantly decrease in statin group but not in control group during the initial 6 months of treatment and thereafter. The present study showed that serum Troponin- I levels (as markers of myocyte injury) were significantly decreased in atorvastatin treated group, (Table 1).

CHF patients show higher levels of inflammatory and oxidative stress markers .Both increased oxidative stress and inflammatory markers are associated with CHF progression manifested by adverse ventricular remodelling as oxidative stress is involved in necrotic cardiomyocyte death since it leads to mitochondrial calcium overloading, opening of the mitochondrial permeability transition pore, mitochondrial swelling, and ATP depletion, which triggers necrotic cell death. In addition, lipid peroxidation may also contribute to cardiomyocyte necrosis [47]. This increased cardiomyocyte necrosis may explain the elevated levels of troponin-I in ischemic cardiomyopathic patients included in our study. In human CHF studies, both inflammatory and oxidative stress markers have been associated with increased rates of mortality and morbidity due to major cardiovascular events [13].

Regarding to Echocardiographic findings; conventional echo was unable to detect significant changes at the end of study except for the improvement of diastolic function [significant increase E/A ratio in atorvastatin group ($p< 0.05$)], while DTI showed significant improvement in systolic function as evidence by significant increase in peak velocity of S & IC, and diastolic function (increased E peak velocity and deceased E/E´ ratio) also better global LV function (decreased Tei index)

Inability of conventional echocardiography to detect changes in left ventricular systolic function and dimension can be attributed to the short duration of the study which did not allow time for changes in myocardial structure and architecture. The result of the current study was in agreement with the Daunia Heart Failure Registry [39], as there was improvement in E/E' ratio and DTI parameters (S wave E and E/E' ratio improve significantly in atorvastatin group) however the study was opposite to our result regarding LVEDD which was improved in Daunia study and it could be explained by the longer duration of follow up in Daunia study (318±262 days) which allow time for better LV remodeling.

Also our result and Daunia study were contradictory to Takahisa Yamada et al. [3] and srikanth sola et al. [48] who found that The LVSD significantly decreased, and LVEF significantly increased in the statin group. In the present study Atorvastatin increased the mitral E/A ratio, decreased Tei index, E/E´ ratio and troponin- I, which means that Atorvastatin improves left ventricular dysfunction and may decrease ischemic-induced myocardial damage in CHF.

6. CONCLUSION

Atorvastatin improved cardiac performance assessed by TDI, decreased inflammatory and oxidative stress parameters as well as modulated the neurohormonal disturbance in patients with CHF, So further studies may be required to evaluate long term effects of Atorvastatin on myocardial performance.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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