THE POSSIBLE BENEFICIAL EFFECT OF ALLOPURINOL, XANTHINE OXIDASE INHIBITOR, IN PATIENTS WITH SYSTOLIC HEART FAILURE

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ABSTRACT

Objective: Evaluated the beneficial effects of Allopurinol on left ventricular remodeling and function in patients with chronic heart failure and documented LV systolic dysfunction (LVEF ≤ 50%) on optimal drug therapy for HF. Background: Reactive oxygen species are important mediators of myocardial remodeling, myocyte hypertrophy, and myocardial fibrosis; xanthine oxidase produces ROS such as superoxide and increase oxidative stress and cardiac remodeling; so, xanthine oxidase inhibitor; Allopurinol reduces ventricular remodeling and improve left ventricular function. Also by blocking xanthine oxidase allopurinol might prevent oxygen losing and thereby increase the supply of molecular oxygen in the ischemic tissue. These due to xanthine oxidase is known to use molecular oxygen to produce oxidative stress. Methods: Only 60 patients included. All patients diagnosed as having chronic heart failure and documented LV systolic dysfunction (LVEF ≤ 50%). Patients divided as follows: Group one includes 20 patients with normal serum uric acid receiving the study drug Allopurinol (300mg twice daily) along with standard medication as assessed by their treating physicians. Group two: includes 20 patients with high serum uric acid receiving the study drug Allopurinol (300mg twice daily) along with standard medication as assessed by their treating physicians. Group three (control): includes 20 patients with normal serum uric acid receiving the standard medication as assessed by their treating physicians. The duration of treatment was two months. The Patients assessed for the following parameters at the baseline, one month and two months after treatment: Oxidized low density lipoprotein (oxLDL), total oxidant status(TAS), N-Terminal proBrain natriuretic Peptid.
Natriuretic peptide (NTproBNP), high-sensitivity C-reactive protein (hs-CRP), left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and left ventricular endsystolic volume (LVESV). **Results:** Group one and group two showed a significant lowering of uric acid, oxLDL, hs-CRP, and NTproBNP. Only group two showed a significant increasing of TAS. Group one and group two showed a significant increasing in left ventricular ejection fraction (LVEF). Group one and group two showed a significant lowering of left ventricular end systolic volume (LVESV) and left ventricular end diastolic volume (LVEDV). **Conclusions:** allopurinol in high doses produce many positive effects on remodeling and function of the left ventricle in patients with chronic heart failure and normal or high uric acid level.

**KEYWORDS:** Allopurinol; chronic heart failure; oxidative stress; uric acid level.

**INTRODUCTION**
In animal models of HF and HF patients reduced myocardial antioxidant activity, increased oxidant damage and markers of oxidative stress increased.[1] The Thesis that reactive oxygen species (ROS) may contribute to the progression of myocardial failure support by these data. The potential stimuli for production of ROS in HF is Xanthine oxidase (XO) and may be an important target for therapy.[2] Production of superoxide and uric acid (UA) increased during purine metabolism in HF is associated with an increase in the activity of XO. 25% of patients with HF and reduced ejection fraction have significant hyperuricemia (i.e., serum UA ≥ 9.5 mg/dl).[3][4]

Activation of pro-inflammatory cytokines, impaired vascular and renal function, as well as loop diuretic therapy all, contribute to hyperuricemia in HF in addition to nitroso-redox imbalance.[5] There is a strong relationship between high UA levels and worsening symptoms,[6] impaired exercise tolerance,[7] and increased mortality[3] in patients with HF. So serum UA levels have been included in HF risk scores.[8][9] Allopurinol, an XO inhibitor, therapy associated with improved survival in both chronic and acute HF patients with gout.[10-12] Nitric Oxide Signaling and also myofilament sensitivity to calcium and contractility decreased by Superoxide.[13]

Hypoperfusion of the heart and another organ, increases anaerobic metabolism, leads to depletion of ATP and accumulation of hypoxanthine (the substrate of XO) this occurred by Decreased cardiac contractility.
METHODS: The present study was achieved at Al-Basra general hospital from December 2013 until December 2014. Only 60 patients included. All patients diagnosed as having chronic heart failure and documented LV systolic dysfunction (LVEF ≤ 50%). The treating physician made the diagnosis.

Patients divided as follows: Group one includes 20 patients with normal serum uric acid receiving the study drug Allopurinol (300mg twice daily) along with standard medication as assessed by their treating physicians.

Group two: includes 20 patients with high serum uric acid receiving the study drug Allopurinol (300mg twice daily) along with standard medication as assessed by their treating physicians.

Group three (control): includes 20 patients with normal serum uric acid receiving the standard medication as assessed by their treating physicians. The duration of treatment was two months. The patients assessed for the following parameters at the baseline, one month and two months after treatment: Oxidized low density lipoprotein (oxLDL), total oxidant status (TAS), N-Terminal proBrain Natriuretic peptide (NTproBNP), high-sensitivity C-reactive protein (hs-CRP), left ventricular ejection fraction (LVEF), (LVESV) and (LVEDV).

Table (2.1) Groups of subjects who participated in the present study. Age and body mass index (BMI) introduced as mean ± standard error of the mean.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>NUMBER OF SUBJECTS</th>
<th>AGE</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group one</td>
<td>20</td>
<td>61±3.1</td>
<td>31.58±1.55</td>
</tr>
<tr>
<td>Group two</td>
<td>20</td>
<td>65.8±2.11</td>
<td>31.97±1.01</td>
</tr>
<tr>
<td>Group three (control)</td>
<td>20</td>
<td>58.15±3.82</td>
<td>34.56±3.66</td>
</tr>
</tbody>
</table>

Statistical analysis: Data prepared as mean ± standard error of the mean. Paired and independent t-test as well as one way annova used for stat istic al analysis by using SPSS 18. P<0.05 used as the level of significance.

RESULTS AND DISCUSSION
In HF patients reduced myocardial antioxidant activity and increased oxidant damage and markers of oxidative stress. [14] also in chronic heart failure (CHF) patients with Myocardial XO expression has been shown to increased. [15] These data support the thesis that the
progression of myocardial failure may contribute to reactive oxygen species (ROS). Xanthine oxidase (XO) may be an important target for therapy because it is among the potential stimuli of formation of ROS in HF. \[^{15}\] XO inhibitors exert certain helpful effects both in animals and humans with heart failure. Allopurinol and its active metabolite oxypurinol are relatively safe drugs and well-known that have been used for decades to treat gout. Allopurinol would be expected to potentiate the beneficial effects of conventional therapeutic agents (e.g., betablockers and angiotensin-converting enzyme inhibitors) because its mechanism of action is unique. \[^{16}\] The question shows up whether allopurinol might be a novel addition to the treatment of patients with CHF. Low-dose allopurinol treatment increased mortality, whereas high-dose treatment with allopurinol was found to affect survival beneficially. \[^{17}\] In this study, we use 600mg daily allopurinol safely to produce maximum effect. Hypoxanthine and xanthine are two oxidants plays a pathologic role in heart failure their production catalyzed by xanthine oxidase. \[^{18}\] In the current study figure,(3.1) showed that group one and group two showed a significant lowering of uric acid compared to group three(control). These results indicate the xanthine oxidase inhibition by allopurinol in both groups that reduce the uric acid is a risk score for heart failure .

![Figure (3.1): Diagram showing the serum level of uric acid in group one, group two and group three at the pretreatment, one month and two months after treatment.](image)

Figure 3.2 showed that group one and group two showed a significant lowering of oxLDL compared to group three(control) only after two months of treatment. This indicate that allopurinol is effective in lowering the oxygen free radical production and significantly lowering oxidative stress, therefore, its provide beneficial effect on endothelial function as well as on the heart failure pathogenesis and progression; as on initiation and progression of atherosclerotic disease.
Figure (3.2) diagram shows the serum level of oxLDL in group one, group two and group three at the pretreatment, one month and two months after treatment.

Figure 3.3 showed that there was significant increasing in serum TAS in group one only after one month not after two months of treatment compared to pretreatment values and group two showed a significant increasing of TAS compared to group three (control) after one and months of treatment.

Figure (3.3): Diagram showing the serum level of TAS in group one, group two and group three at the pretreatment, one month and two months after treatment.

Figure 3.4 showed that there was significant lowering in serum hs-CRP in group one and group two patients only after two months not after one month of treatment compared to pretreatment values. Therefore, allopurinol reduced the inflammatory progression in patients with heart failure independent of uric acid serum level after two months of treatment.
Figure (3.4): Diagram showing the serum level of hs-CRP in group one, group two and group three at the pretreatment, one month and two months after treatment.

In this current study Figure, 3.5 showed that there was significant increasing in serum NTproBNP in group one patient only after one month, not after two months of treatment compared to pretreatment values. While group two patients, there was a significant lowering of serum level of NTproBNP after one month and after two month's treatment compared to pretreatment values. Also, group one showed a significant lowering of NTproBNP compared to group three (control) only after two months of treatments. While group two showed a significant lowering of NTproBNP compared to group three (control) only after one month of treatment.

Figure (3.5): Diagram showing the serum level of NTproBNP in group one, group two and group three at the pretreatment, one month and two months after treatment.

Age, sex, hypertension and history of heart failure are affecting NTproBNP; these entire variables are distributed evenly between treatment groups. Creatinine clearance is the other factor that could affect NTproBNP.\cite{[19]} figure(3.6) showed that there was group one and group two showed a no significant increasing in serum creatinine compared to group
three(control). The significant increasing in serum NTproBNP in group one patient only after one month not after two months of treatment compared to pretreatment values may be due to significant increasing in serum creatinine in group one patients only after one month not after two months of treatment. While in group two patients there was a significant increasing in serum creatinine after two months of treatment but there was a significant lowering of serum level of NTproBNP after one month and after two months of treatment compared to pretreatment values not affected by serum creatinine level.

![Figure (3.6): Diagram showing the serum creatinine in group one, group two and group three at the pretreatment, one month and two months after treatment.](image)

So B type natriuretic peptide, a surrogate marker for prognosis in chronic heart failure reduces in both groups.

Figure (3.7) showed that group one and group two showed a significant increasing in left ventricular ejection fraction compared to group three(control).

![Figure (3.7): Diagram showing the left ventricular ejection fraction in group one, group two and group three at the pretreatment, one month and two months after treatment.](image)
Figure 3.8 showed that group one and group two showed a significant lowering of left ventricular end-systolic volume compared to group three (control).

![Diagram showing the left ventricular end-systolic volume in group one, group two and group three at the pretreatment, one month and two months after treatment.](image1)

Figure (3.8): Diagram showing the left ventricular end-systolic volume in group one, group two and group three at the pretreatment, one month and two months after treatment.

Figure 3.9 showed that group one showed a significant lowering of LVEDV compared to group three (control) after one month and two months of treatment. While group two showed a significant lowering of LVEDV compared to group three (control) only after two months of treatment.

![Diagram showing the left ventricular end-diastolic volume in group one, group two and group three at the pretreatment, one month and two months after treatment.](image2)

Figure (3.9): Diagram showing the left ventricular end-diastolic volume in group one, group two and group three at the pretreatment, one month and two months after treatment.

This determine the positive results of allopurinol treatment on left ventricular remodeling and function in both group one and group two patients independent of serum uric acid level and this positive results may be due to many beneficial effects of allopurinol on myocardium function such as: i. Allopurinol reduced consumption of myocardial oxygen and improved
myocardial efficiency.\textsuperscript{[15],[20] \textsuperscript{[21]}} ii. reduce cardiac hypertrophy \textsuperscript{[22]} and improve contractile dysfunction\textsuperscript{[23]}. iii. Cardiac myofilaments calcium- sensitization \textsuperscript{[24]} iv. Improve myocardial efficiency by preserving NO- bioactivity \textsuperscript{[21]} v. hydroxyl radical scavenging capacity.\textsuperscript{[25]} vi. Improves peripheral vasodilator competence and blood flow both locally and systemically in hyperuricemic CHF patients.\textsuperscript{[26]}

**CONCLUSION**

Allopurinol in high dose: 1- reduces uric acid, the risk score for heart failure, in patients with chronic heart failure and normal or high uric acid level. 2- Reduces oxLDL and increase TAS in CHF patients with normal or high uric acid level. 3-effective in attenuating the inflammatory process which correlated with bad prognosis in chronic heart failure.4- Reduces B-type natriuretic peptide.5- Increase left ventricular ejection fraction and lower left ventricular end-systolic volume and left ventricular end diastolic volumes. These results determine the the positive effects of allopurinol therapy on remodeling and function of the left ventricular in patients with chronic heart failure and normal or high uric acid level.

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