Heart failure, oxidative stress and allopurinol

Scompenso cardiaco e stress ossidativo: ruolo dell’allopurinolo

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ABSTRACT: Heart failure, oxidative stress and allopurinol. P. Biagi, L. Abate.

Oxidative stress is one of the new and most intriguing pathogenetic hypotheses of heart failure; it involves various mechanisms such as endothelial dysfunction, mechanoenergetic uncoupling and apoptosis.

Xanthine oxidase, a key enzyme in purine catabolism, is overexpressed in patients with heart failure, and it is also an important source of oxidizing activity molecules (free radicals, superoxide anion, oxygen peroxide, etc.). Allopurinol competitively inhibits the action of xanthine oxidase and effectively counteracts oxidative stress. It could thus prove useful in the treatment of heart failure: in fact it is the only drug that has been proven able to lower O$_2$ consumption of dysfunctioning myocardium.

The Authors briefly review the xanthine oxidoreductase enzyme system and in particular analyse the latest evidence reported in the literature on allopurinol in the treatment of heart failure.

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The burden of heart failure (HF) is increasing rapidly, on account of the aging population and the improving survival of patients with other heart diseases, most resulting in HF. It is further reflected in the associated mortality figures (first year mortality rates 25-35%) and substantial morbidity. The short-term intravenous acute HF treatment with inotropic agents such as dobutamine, amrinone effectively alleviate HF symptoms, but their use is limited by concerns about safety, particularly ventricular arrhythmias.1 Nesiritide (recombinant B-type natriuretic peptide, or BNP) is more effective than i.v. nitroglycerine in reducing pulmonary arterial pressure and pulmonary capillary wedge pressure, but clinically significant hypotension in some patients restricts its use and it is not yet licensed in Italy.2

To date, the current standard care for chronic oral HF therapy includes the administration of an angiotensin converting enzyme (ACE) inhibitor (or ATII antagonist), a diuretic (furosemide), a beta-blocker, a vasodilator, and possibly digoxin.

However, many patients remain symptomatic despite full therapy, and mortality continues to be significant, thus underlining the need for new therapeutic options.

Among the pathogenetic factors involved in HF recent theories include oxidative stress, which through the production of reactive oxygen species (ROS),3-5 induces apoptosis,6 endothelial dysfunction,7 and myocardial remodelling.8

Moreover in CHF, a phenomenon known as mechano-energetic uncoupling, that is an imbalance between left ventricular performance and myocardial oxygen consumption (MVO$_2$), leads to a decrease in cardiac contractile efficiency.9

Although there are many possible sources of ROS production, it has been shown that the enzyme xanthine oxidase (XO), undergoes overexpression at the endothelial level in such conditions as ischemia-reperfusion10 and heart failure11 and it is able to induce oxidative stress. Therefore we investigated the role of XO in the mechanisms of heart failure and analysed the potential of allopurinol, a XO inhibitor, in the treatment of heart failure.

The pathophysiological role of xanthino oxido-reductase

Xantino oxido-reductase (XOR), one of the molybdenum enzyme family,12 was discovered 100 years ago13 in human milk where it participate in antiseptic mechanisms, perhaps via a NO-dependent action, recently identified in vitro;14 in fact in newborn breastfed infants (whose mothers milk is rich in XOR), episodes of gastroenteritis are less frequent than in infants fed with artificial milk.15

In man, XOR is not particularly abundant.16 However, relatively high concentrations may be found in the endothelial cells of capillaries and sinuoids. The gene controlling its synthesis is located in the short arm of chromosome 2.17 Some cytokines, such as TNF-alpha, IFN-gamma, IL-1, IL-6, or treatment with desametasone, enhance its transcription in vitro.18

The gene expression of XOR in the endothelial cell is also dependent on partial tension of O$_2$; in fact in the ischemia-reperfusion phenomenon XOR overexpression in the ischemic limb is mediated through enhanced XOR transcription induced by hypoxia; on the contrary hyperoxia switches off transcription.
Actually the most important function is associated with the catabolism of purines.\textsuperscript{20} In the enzymatic steps to the end product (urate acid) XOR generates free radicals: in fact, XOR is converted by two reversible pathways which involve xanthine dehydrogenase (XDH) and XO respectively: the first produces uric acid and NADH, the second uric acid, free radicals and superoxide anion\textsuperscript{21} (figure 1).

In addition, as an alternative source of NO production, XOR seems to contribute to endothelial-dependent vasodilatation when the activity of NO-synthase is not functioning as, for example, in the case of hypoxia.\textsuperscript{22} This phenomenon has been reproduced experimentally in rats, in which production of NO has been demonstrated in conditions of heart hypoxia and of inhibition of NO-synthase, but not if XO is blocked by pre-treatment with allopurinol.\textsuperscript{23}

The activity of XO may increase the following vascular damage caused by ischemia-reperfusion, anoxia and inflammation\textsuperscript{24}, probably due to the lesion of the endothelial lining. Alternatively, interacting with non-ferritinic endocellular iron, through the conversion of the dehydrogenated form into the oxidized form, it may produce an excess of free radicals including hydrogen peroxide which is proven to be the most important for XO-induced endothelial damage.\textsuperscript{25}

In addition, superoxide radicals (O$_2^-$) produced by XO react with NO forming peroxynitrite (ONOO$^-$), a powerful oxidizing agent, which causes the deactivation of NO and contributes to endothelial damage.\textsuperscript{26}

In a small randomized trial the endoarterial administration of allopurinol, a competitive inhibitor of XO, improved endothelial dysfunction measured according to the model of venous forearm occlusion. This effect was also obtained by oral administration of allopurinol\textsuperscript{27} and confirmed by a randomized controlled double blind trial in CHF patients on optimized treatment (diuretics, ACE-inhibitors, beta-blockers):\textsuperscript{28} chronic oral treatment with allopurinol (300 mg/die) improved endothelial dysfunction.

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In heart failure the activity of XOR at cardiac and endothelial level is overexpressed, whilst the activity of superoxide dismutase (SOD) neutralizing the oxidizing effect of O$_2$ is significantly reduced.\textsuperscript{29} This imbalance enhances the production of ROS with the resulting reduction of NO bioavailability and increases the levels of peroxynitrite derived from the reaction between NO and superoxide\textsuperscript{30} (figure 2).

Heart dysfunction, initially characterized by impairment in heart contraction and then by hypertrophy and remodelling, is probably more the consequence of endothelial dysfunction\textsuperscript{31} than ROS-induced modulation of fibroblast proliferation and collagen synthesis.\textsuperscript{32} Alternatively the superoxide may interfere with intracellular key regulators of the energy metabolism such as ATP,\textsuperscript{33} high energy phosphate\textsuperscript{34} and calcium, inducing mechaneno-energetic uncoupling. This means that in HF in the presence of reduced ventricular...
function the energy cost (i.e. the consumption of \( O_2 \)) of contraction remains unchanged.

Allopurinol is an analog of hypoxanthine and acts via competitive inhibition of \( \text{XO} \), as well as by reducing the absorption of diet purines.

The inhibition of \( \text{XO} \) prevents the transformation of hypoxanthine into xanthine and thence into uric acid; to avoid the storage and hence increased excretion of xanthine and hypoxanthine, two metabolic processes are involved in the regulation of the biosynthesis of purines, namely:

- the first process, the “hypoxanthine saving pathway”, enables the hypoxanthine to be used again to produce nucleic acid; this process is supervised by the phosphoribosil-transferase hypoxanthine-guanine enzyme (HGPRTase);
- the second process inhibits the first stage of the synthesis of purines (guanilic acid -GMP- and adenilic acid -AMP- formation) blocking the phosphoribosil-pyrophosphate aminotransferase enzyme.

Allopurinol has been shown to increase cardiac efficiency in animal models of pacing-induced heart failure and to enhance the contractile response of the failing myocardium to dobutamine and to exercise. The increase in contractility without a disproportionate increase in \( MVO_2 \) is achieved by an increased sensitization of the cardiac myofilaments to calcium. This evidence in animals has been confirmed also in man where recently XOR activity has been found in the cardiac muscle.

The infusion of allopurinol in the coronary arteries of patients with dilated cardiomyopathy, led to improved ventricular contraction supported by reduced \( O_2 \) consumption. In addition, several randomized placebo-controlled clinical trials have shown allopurinol to improve cardiac performance and reduce the need for inotropic supportive therapy in patients undergoing cardiac surgery.

In a clinical study in nine HF patients allopurinol improved cardiac pressure efficiency by 22% and cardiac mechanical efficiency by 40%.

A recent cohort retrospective study of more than 1700 patients suffering from HF, divided into no treatment, low and high doses of allopurinol groups, showed that chronic treatment with high doses of allopurinol (\( \geq 300 \text{ mg/die} \)) was significantly related to lower total mortality, cardiovascular mortality, and hospitalization rate for cardiovascular disease (primary and combined end points).

Most probably effects of allopurinol are mediated by its conversion in the active metabolite oxipurinol, a powerful \( \text{XO} \) inhibitor and an orphan drug, available in USA since 1967 for patients intolerant to allopurinol.

Recent pilot studies concluded in 2004 show that oxipurinol may be useful as an acute intravenous and oral therapy in CHF: interim results of LaPlata Study and EXOTIC-EF (Evaluation of Xanthine Oxidase Inhibition on Cardiac Ejection Fraction) were presented at the Heart Failure Society of America’s annual meeting recently held in Toronto. Both studies showed a significant improvement of cardiac function as measured by the left ventricle ejection fraction (LVEF). The LaPlata Study, a blinded, placebo-controlled study showed an improvement of 3.3% (\( p < 0.010 \)) in LVEF vs. placebo 28 days after oral oxipurinol (600 mg/die). The EXOTIC-EF open-label study showed a 3.6% (\( p < 0.0032 \)) increase in LVEF after i.v. treatment with oxipurinol 400 mg/die.

The OPT-CHF study, an ongoing phase II-III prospective, randomized, double-blind, placebo-controlled trial, including 400 pts with stable NYHA class III and IV congestive HF, will test the benefit of oxipurinol 600 mg/die added to the standard optimized therapy on 6 months clinical outcomes. The end of the study is foreseen in the second half of 2005.

**Conclusion**

Although conclusive evidence is still lacking on the real burden of oxidative stress in heart failure and taking into account that no benefit of other anti-oxidative drugs (ascorbic acid, vitamin E etc...) has been proved, some data show that reducing the level of \( O_2 \) free radical may be useful in the management of HF.

In this setting AP could be an effective and inexpensive way of controlling oxidative stress and hence of improving endothelial dysfunction; moreover \( \text{XO} \) inhibitors are the first to be shown to reduce mechano-energetic uncoupling in the failing heart.

Obviously larger randomized and controlled trials are required to validate these preliminary results and to test the risk-benefit ratio for allopurinol side-effects not to be forgotten; a wider use of oxipurinol, a safer alternative to allopurinol intolerant patients, by i.v. or oral route may offer another therapeutic option: the results of the ongoing trials will be soon available.

At present, despite the fact that the treatment is not recommended in HF guidelines, it is common practice to prescribe allopurinol in addition to optimized therapy to control hyperuricemia induced by diuretics: in such a way we may join the “symptomatic” to an extended “pathogenetic” effect of allopurinol.

**Riassunto**

*Tra le più interessanti ipotesi patogenetiche recentemente poste riguardo allo scompimento cardiaco una concerne lo stress ossidativo che sembrerebbe condurre mediante l’attivazione di molteplici meccanismi (disfunzione endoteliale, disaccoppiamento meccano-energetico, apoptosi, etc...) alla disfunzione miocardica.*

*La xantina-ossidasi, enzima chiave nel catalismo delle purine, oltre che essere sovraespressa in condizioni di scompimento cardiaco, è anche una no- tevole fonte di produzione di molecole ad azione ossidante e è quindi potenzialmente implicata nella sua genesi. L’allopurinolo, un inibitore competitivo della xantina ossidasi, è pertanto in grado di contrastare lo stress ossidativo: in tal senso potrebbe costituire un farmaco utile nel trattamento della disfunzione ventricolare anche perché si è dimostrato essere l’unico in grado di ridurre, a parità di carico di lavoro, il consumo di \( O_2 \) da parte del miocardio.*

*Gli Autori, dopo aver preso in esame il complesso delle funzioni del sistema enzimatico della*
xantina ossido-reddutasi, analizzano le più recenti evidenze riportate in letteratura sull’impiego del l’allopurinolo nello scompenso cardioaco.

Parole chiave: scompenso cardiaco, acido urico, stress ossidativo, allopurinolo.

LIST OF ABBREVIATIONS OR ACRONYMS

ACE-inhibitor: Angiotensin Converting Enzyme inhibitor
AMP: Adenilic acid
AO: Aldehyde oxidase
ATP: Adenosine triphosphate
BNP: Brain natriuretic peptide
GMP: Guanilic acid
HF: Heart failure (according to Framingham criteria)
HGPRTasi: Phosphoribosyl pyrophosphate aminotransferase
IFN gamma: Interferon gamma
IL-1: Interleukin-1
IL-6: Interleukin-6
MVO2: Myocardial oxygen consumption
NO: Nitric oxide
O2: Molecular oxygen
O2-: Superoxide anion
ONO2: Peroxynitrite
SO: Sulphate oxidase
SOD: Superoxide dismutase
TNF-α: Tumor necrosis factor alpha
XDH: Xanthine dehydrogenase
XO: Xanthine oxidase
XOR: Xanthine oxi-do-reductase

References

24. Katz SD, Hryniewicz K, Hriljac I, et al. Vascular en-