Uric acid, xanthine oxidase and heart failure: Unresolved issues

Keywords: Uric acid; Xanthine oxidase; Endothelial function; Chronic heart failure; Oxidative stress

In response to the letter from Wolfram Doehner et al. the authors respond as follows:

To the Editor

As stated in our article [1], the role of uric acid in heart disease remains poorly understood. Although epidemiological studies have shown independent associations between elevated uric acid serum levels and mortality [2], this association may depend largely on other related risk factors [3,4], generating an obvious limitation for the interpretation of a causative role of endogenously-generated uric acid in cardiovascular disease.

Animal models have established that xanthine oxidase participates in the development of heart failure [5–7]. However, the relative contribution of xanthine oxidase-derived superoxide (as opposed to other sources of superoxide) is unclear. In a previous work by Landmesser et al. [8], xanthine oxidase activity explained barely 12% of the observed changes in endothelial function ($r^2 = 0.12$). In our heart failure cohort no correlation was observed (Fig. 1, unpublished data); this difference may depend on demographic or aetiologic factors, disease stage [9], etc.

A commonly disregarded fact is that, within physiologic levels, uric acid levels and xanthine oxidase activity are tightly regulated. Tan *et al.* showed that uric acid 150 and 300 mM decreased the oxidation of xanthine to uric acid and formation of superoxide by 23 and 32%, respectively [10]. These results indicate that uric acid is an effective inhibitor of the formation of superoxide and hydrogen peroxide by xanthine oxidase at the levels found in human plasma, reflecting the complex interaction between oxidative and antioxidant systems. In humans, uric acid is maintained at a concentration close to maximum solubility and is the most important aqueous antioxidant, contributing near two thirds of total plasma antioxidant capacity [11]. Besides its ability to directly scavenge oxygen radicals, uric acid stabilizes ascorbate through iron-chelation in a reaction that does not imply uric acid degradation. These observations had led to propose that uric acid may be an evolutionary adaptation to our inability to synthesize ascorbic acid [12].

In our study we demonstrated a positive correlation between endogenously-generated uric acid, endothelium-bound superoxide dismutase and flow-dependent, endothelium-mediated vasodilation, suggesting that the effect of xanthine oxidase on superoxide production and endogenously-derived uric acid antioxidant capacity on flow-dependent, endothelium-mediated vasodilation is modulated by interaction with other antioxidant/oxidative systems. These interactions may include concurrent medication: diuretics elevate uric acid in heart failure patients as well as healthy subjects by elevating net uric acid reabsorption in the nephronal proximal tubule. Beta-blockers tend to elevate uric acid; on the contrary, angiotensin-converting enzyme inhibitors increase uricosuria blunting the rise provoked by diuretics if used at sufficiently high doses.

We agree that there is a considerable body of evidence that demonstrates that xanthine oxidase inhibition is safe and potentially useful in several pathologic states, including heart failure [13]. However, we hypothesize that the efficacy of such interventions are likely to depend on the aetiology and stage of the disease. In the recently published OPT-CHF trial, oxypurinol, a potent xanthine oxidase inhibitor, failed to demonstrate clinical improvements in unselected patients with moderate-to-severe heart failure [14]. Our data supports further investigation on the subject, aiming at a stratified and personalized approach to heart failure treatment.

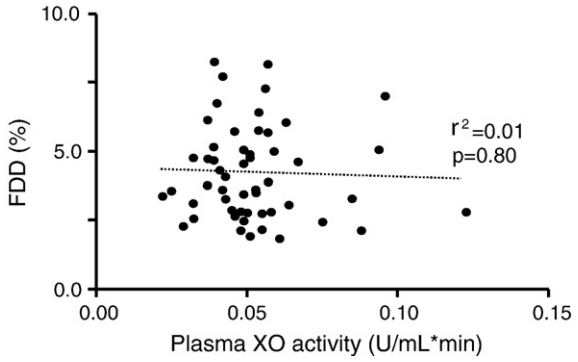

Fig. 1. Plasma xanthine oxidase activity does not correlate with flow-dependent, endothelium-mediated vasodilation in a cohort of 75 heart failure patients (New York Heart Association, functional class II-IV). FDD: Flow-dependent, endothelium-mediated vasodilation. XO: xanthine oxidase.

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Hugo Verdejo
Douglas Greig
Pablo Castro
Departamento Enfermedades Cardiovasculares,
Facultad de Medicina,
Pontificia Universidad Católica de Chile
E-mail address: pcastro@med.puc.cl
Corresponding authors.
Castro is to be contacted at Facultad de Medicina,
Pontificia Universidad Católica de Chile,
Marcoleta 367, Santiago, Chile.
Tel.: +56 02 978 2919; fax: +56 02 978 2912.
Lavandero, Centro FONDAP CEMC,
Facultad de Ciencias Químicas y Farmacéuticas,
Universidad de Chile, Olivos 1007,
Santiago 8380492, Chile.

Hernan Alcaino
Lorena Garcia
Mario Chiong
Sergio Lavandero
Centro FONDAP Estudios Moleculares de la Célula,
ICBM, Facultad de Medicina,
Universidad de Chile, Santiago, Chile
E-mail address: slavander@uchile.cl
Corresponding authors.
Castro is to be contacted at Facultad de Medicina,
Pontificia Universidad Católica de Chile,
Marcoleta 367, Santiago, Chile.
Tel.: +56 02 978 2919; fax: +56 02 978 2912.
Lavandero, Centro FONDAP CEMC,
Facultad de Ciencias Químicas y Farmacéuticas,
Universidad de Chile, Olivos 1007,
Santiago 8380492, Chile.

Marcela Pizarro
Hernan Alcaino
Lorena Garcia
Mario Chiong
Sergio Lavandero
Facultad de Ciencias Químicas y Farmacéuticas,
Universidad de Chile, Santiago, Chile