Author's response to reviews

Title: Relationship between serum uric acid and internal carotid resistive index in hypertensive women: a cross-sectional study

Authors:

José A Cipolli (jale34@gmail.com)
Maria C Ferreira-Sae (mcarolsf@gmail.com)
Rafael P Martins (rafael.prado@terra.com.br)
José A Pio-Magalhães (piomagalhaes@terra.com.br)
Vera R Bellinazzi (verarbellinazzi@gmail.com)
José R Matos-Souza (betojrms@gmail.com)
Wilson Nadruz Junior (wilnj@fcm.unicamp.br)

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Author's response to reviews: see over
To:
Prof. Jigisha Patel  
*BMC Cardiovascular Disorders* Editor-in-Chief

Dear Prof. Patel:

We are submitting the revised version of the manuscript entitled “**Relationship between serum uric acid and internal carotid resistive index in hypertensive women: a cross-sectional study**” (MS: 8983075087164060) by Cipolli JA *et al* as a Research Article for publication in *BMC Cardiovascular Disorders*. Your reviewers’ comments have been very helpful, and the manuscript has been revised and altered to deal with their concerns and specific questions. Specific responses to the editor’s and reviewers’ comments are appended.

All authors have read and approved the submission of the manuscript; the manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language, except as an abstract. In addition, the authors declare no conflict of interest.

We thank you in advance and hope this manuscript is now suitable for publication in *BMC Cardiovascular Disorders*.

Sincerely yours,

Wilson Nadruz Junior

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Wilson Nadruz Junior, MD, Ph.D.  
Departamento de Clínica Médica  
Faculdade de Ciências Médicas,  
Universidade Estadual de Campinas  
Cidade Universitária “Zeferino Vaz”  
13081-970 Campinas, SP, Brasil.  
Phone/FAX: (55) (19) 3521 7836  
E-Mail: wilnj@fcm.unicamp.br
Answers to Reviewers

We thank the reviewers for their challenging and insightful comments. We believe that our revision based on their comments and suggestions has clarified and strengthened the manuscript. In addition, in the new version of the manuscript, we preferred to merge the “Results” and “Discussion” sections into one section: “Results and Discussion”.

Reviewer: Leonardo Zornoff

Uric acid is known to induce proliferation, inflammation and oxidative stress in cultured vascular smooth-muscle cells, promote endothelial dysfunction and activate the renin–angiotensin system. Therefore, would be interesting to study the relationship between SUA and carotid structural and hemodynamic parameters in subjects without hypertension. However, only hypertensive patients were studied. Please justify.

We agree with the reviewer that it would be interesting to study the relationship between SUA and carotid structural and hemodynamic parameters not only in hypertensive but also in normotensive individuals. Nevertheless, the present study was originally designed to evaluate the relationship between SUA and carotid parameters only in hypertensive subjects, since current knowledge indicates that SUA is particularly associated with increased cardiovascular risk in this population (Chobanian et al, JAMA 2003; 289:2560-2572). On the other hand, we were unable to enroll a sample of normotensive subjects with clinical features (e.g. gender, age and body mass index) that matched to those of the hypertensive subjects included in the present study. Therefore, only hypertensive patients were evaluated in our protocol.

In the regression analyses (stepwise and logistic regression analyses), the authors should justify the different variables utilized as confounders.

We thank the reviewer’s suggestion. This topic is addressed in new Methods section (Lines 157-160) and in new Table 5 legend (Lines 507-508).
Reviewer: Tomasz Zapolski

1) Data concerning methodology:

• The Authors should specify precisely in Methods the method of uric acid measurement as this is main marker in presented study. This issue is addressed in new Methods section (Lines 99-100)

• The method of BMI calculation should be changed. Particularly calculation of body surface – calculation as $S=\text{height}^2[m^2]$ is too simply and used in normal practice. For such kind of professional research more reliable is for example Mosteller, Gehan and George formula: $S=0.0235 \times L^{0.42246} \times M^{0.51456}$

In the present report we aimed to evaluate the role of an index of general adiposity rather than a measure of body surface area in our analysis. For this reason, we calculated the body mass index [weight (kg) / height (m)$^2$].

2). In results:

• It is known that the concentration of uric acid is influenced by renal function. Moreover uric acid is a novel independent predisposing factor for renal dysfunction. Thereby the Authors should include into analysis renal function and analyze the possible correlations between uric acid and creatinine, and GFR. A useful paper summarizing some of these factors is Zapolski et al. Kardiol. Pol. 2011; 69: 319-326.

In the new version of the manuscript, we evaluated the impact of renal function on the relationship between serum uric acid (SUA) and internal carotid resistive index (ICRI) in women. Briefly, markers of renal function (creatinine or creatinine clearance) did not influence the relationship between SUA and ICRI in this population. This topic is addressed in new Methods (lines 97-99), Results and Discussion (lines 174, 184, 190, 195-196) sections and in new Tables 1, 4 and 5.

• In stepwise regression analysis has been shown that ICRI was associated not only with uric acid but also with CRP level. CRP is a biomarker of both atherosclerosis and inflammation. It may also influence on arteries. What about correlation between uric acid and CRP (and/or other markers of inflammation state) – did Authors analyze it. It is very important issue in study concerning arterial impedance which is manifestation of atherosclerosis.

We thank the reviewer’s suggestion. This topic is addressed in new Results and Discussion section (lines 224-232).

3). In discussion:

• It is well known that some drugs, particularly ARB’s may influence (decrease) the uric acid serum concentration. The issue of drug treatment in studied patients should be more precisely discussed, not only mentioned as a limitation, otherwise this could be in fact important limitation of this study.

This issue is addressed in new Results and Discussion section (lines 262-270) and in new references 31 and 32.
This study has been shown that uric acid level correlated with carotid artery stiffness. The role of uric acid in pathogenesis of arterial stiffness should be more widely discussed.

Actually, in our sample, serum uric acid (SUA) did not show any significant relationship with measurements of carotid stiffness (stiffness index and Young’s Elastic Modulus) or elasticity (arterial compliance) in both genders. Conversely, SUA showed a significant association with internal carotid resistive index in women. Given that the resistive index of an artery reflects the vascular impedance of the territory irrigated by the vessel (Staub et al. Stroke. 2006; 37:800-805), and higher resistive index values are considered a manifestation of local arteriolopathy (Staub et al, Stroke. 2006; 37:800-805; Berni et al, Am J Hypertens. 2010; 23:675-680), we preferred not to widely discuss the role of uric acid in the pathogenesis of arterial stiffness.

Essential Revisions
1). In last, the aim of study should be detailed and presented as a separate part of manuscript (entitled shortly: Aim) just after Introduction.

The manuscript was changed in accordance with the reviewer’s suggestion. Please see new line 78.
Reviewer: Giuseppe Mule'

Statistical analysis (Page 6. Line 143): The terms “parametric and nonparametric” used to describe the statistical distribution of the variables are employed inappropriately. The terms parametric and non-parametric refer to the statistical methods used to process variables with and without gaussian distribution, respectively. Therefore, the sentence may be reformulated as follows: “Continuous variables with and without gaussian (or normal) distribution are presented ……”. We thank the reviewer’s suggestion. The manuscript text was modified. Please see Methods section (Line 148).

(Pages 6-7. Lines 146-147 and Line 149): see the previous comment. The manuscript text was modified. Please see new Methods section (Lines 152 and 155).

Results
May you clarify how you assessed the correlation between carotid variables and antihypertensive medication or statins?
This topic is addressed in new Methods section (Lines 177-179)

Discussion
It is possible that carotid resistive index, like renal resistive index, is more a marker of systemic vascular damage, rather than an organ-specific marker. Therefore, the hypothesis according to which the findings of the authors suggest that SUA may be related to intracranial microangiopathy in female gender (Abstract; lines 46-47 and Discussion page 9; lines 200-201) may be accepted with some caution.
Based on the reviewer’s comments, we preferred to change the manuscript text. Please see new Abstract (Lines 45-47) and Results and Discussion (Line 216) sections.

Another potential reason of the discrepancies concerning the influence of SUA on structure and function of large arteries may be the fact that in many studies aortic stiffness, instead of carotid elastic properties, was studied. Even if similar, the two arterial districts may be somewhat different from a structural and functional point of view (see also Paini A et al. Carotid and aortic stiffness: determinants of discrepancies. Hypertension. 2006; 47: 371).
We thank the reviewer’s suggestion. This issue is addressed in new Results and Discussion section (Lines 255-258) and in new reference 28.

Quality of written English: Needs some language corrections before being published
We apologize for any flaws in the revision of the old version of the manuscript. We performed an extensive language revision in the new version of the article.
Reviewer: Qin Li

1. Were study participants randomly selected? However, the selection of the participants is not clearly indicated. Authors should clearly describe this point. This topic is clarified in new Methods section (Lines 85-88)

2. As mentioned in the ms that SUA is associated with intracranial microvascular damage, then how the prevalence of subjects with brain infarction in this research?
The prevalence of previous symptomatic stroke in our sample was of 7% in women and of 11% in men. These data are presented in new Table 1.

3. How the prevalence of subjects with anti-uremic medication (for example, Allopurinol, Benzbromarone) were evaluated?
Only 5% of women and 6% of men were using allopurinol, while none of them used Benzbromarone. However, use of allopurinol showed no significant correlation with internal carotid resistive index or SUA in our sample. This issue is addressed in new Results and Discussion section (Lines 179, 191, 197), in new Table 1 and in new Table 5 Legend (Line 509).

4. In my opinion, the therapeutic potential in this research area should be discussed. For example a discussion concerning the current knowledge from trials about the effect on CVD/risk factors when reducing SUA by treatment with allopurinol.
We thank the reviewer’s suggestion. This topic is addressed in new Results and Discussion section (Lines 199-205) and in new references 21, 22 and 23.