

28th August, 2014

Dear Editor,

Please find enclosed the revised, invited manuscript in Word format (file name: 11704-review.doc, ID 02524528).

Title: The role of microparticles in endothelial dysfunction & arterial hypertension

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Name of Journal: *World Journal of Cardiology*

ESPS Manuscript NO: 11704

We hope that our manuscript now fulfills the criteria for getting published in the *World Journal of Cardiology*.

Sincerely yours,

Philipp Diehl

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Comments of reviewer 1:

This is a relatively short review article about role of microparticles in endothelial dysfunction and arterial hypertension. The topic is of interest and the paper like this is definitely suitable for the journal. However, this article is a little "superficial". Some important topics such as role of microparticles in hypertension associated with preeclampsia (e.g. Mol Biol Rep. 2013 Jul;40(7):4553-9), obstructive sleep apnoea, role of angiotensin II in microparticle formation have not been addressed. In addition, some recent seminal clinical studies (for example Amabile N Eur Heart J (in press), PLoS One. 2013 Jul 12;8(7):e68644) should cited and discussed.

We thank the reviewer for his valuable comments that helped us to significantly improve the quality of our manuscript. As recommended, we added and discussed the following publications

- Cinzia Cordazzo, Tommaso Neri, Silvia Petrini, Stefania Lombardi, Cristina Balia, Silvana Cianchetti, Yuri Carmazzi, Pierluigi Paggiaro, Roberto Pedrinelli, Alessandro Celi. Angiotensin II induces the generation of procoagulant microparticles by human mononuclear cells via an angiotensin type 2 receptor-mediated pathway. *Thrombosis Research* 131 (2013) e168–e174.
- Nicolas Amabile, Susan Cheng, Jean Marie Renard, Martin G. Larson, Anahita Ghorbani, Elizabeth McCabe, Gabriel Griffin, Coralie Guerin, Jennifer E. Ho, Stanley Y. Shaw, Kenneth S. Cohen, Ramachandran S. Vasan, Alain Tedgui, Chantal M. Boulanger, Thomas J. Wang. Association of circulating endothelial microparticles with cardiometabolic risk factors in the Framingham Heart Study. Epub ahead of print.
- Fabiana K. Marques, Fernanda M. F. Campos, Lirlandia P. Sousa, Andrea Teixeira-Carvalho, Luci M. S. Dusse, Karina B. Gomes. Association of microparticles and preeclampsia. *Mol Biol Rep* (2013) 40:4553–4559
- Simon Tual-Chalot, Frédéric Gagnadoux, Wojciech Trzepizur, Pascaline Priou, Ramarosan Andriantsitohaina, M. Carmen Martinez. Circulating microparticles from obstructive sleep apnea syndrome patients induce endothelin-mediated angiogenesis. *Biochimica et Biophysica Acta* 1842 (2014) 202–207.

- Chien-Yi Hsu, Po-Hsun Huang, Chia-Hung Chiang, Hsin-Bang Leu, Chin-Chou Huang, Jaw-Wen Chen, Shing-Jong Lin. Increased Circulating Endothelial Apoptotic Microparticle to Endothelial Progenitor Cell Ratio Is Associated with Subsequent Decline in Glomerular Filtration Rate in Hypertensive Patients. PLoS ONE 8(7): e68644.

Minor comment: 1) Page 4, line 7: "activate those" should be corrected to "activate them". 2) Some figure(s) summarizing the main facts mentioned in this review should be included.

The typo was corrected and a table summarizing microparticle studies was added.

Comments of reviewer 2:

The present review covers the potential role of microparticles as a surrogate markers for vascular inflammation and coagulation. The review is well written but some issues merit to be addressed.

1. The review is focused on endothelial dysfunction and arterial hypertension. The link between microparticles and endothelial dysfunction is well established. However, microparticles have been measured since a long time but never entered the clinical arena. There are several factors that may be accounted for one of the main is the lack of standardization. Please address.

We thank the reviewer for this very constructive comment. The issues why microparticles have not already been established as clinical disease surrogate markers are now discussed more profoundly.

2. Please give more practical implications to the present results.

We agree with reviewer 2 that the manuscript benefits from more practical implications to the presented results. Hence, these implications are now given in several parts of the manuscript.

3. In the section on future perspective it would be important to know what authors think of the possible role of microparticles in the clinical setting.

Please see also the answer to question 2. The role of microparticles as surrogate parameters in several different disease conditions is of great clinical impact. The authors of this manuscript are convinced that once microparticle measurements are standardized, microparticles can be used as valuable circulating markers indicating different aspects of for example altered coagulation and vascular inflammation. In the revised manuscript these issues are now clearly discussed.

4. Figures with scheme of pathophysiologic mechanisms both for endothelial dysfunction and hypertension would improve the quality of the manuscript.

We thank reviewer 2 for this comment. As several publications (such as Diehl et al., 2008) already contain figures illustrating the impact of microparticles on endothelial cells, we believe that a table summarizing studies that analyzed the effect of microparticles on endothelial cells, might be more helpful for the reader of the *World Journal of Cardiology*. Therefore, the authors of this article added a table summarizing current microparticle research with a focus on endothelial inflammation and arterial hypertension. We are convinced that this table gives readers of the *World Journal of Cardiology* an overview about up to date publications investigating the role of microparticles in endothelial dysfunction and arterial hypertension.