

Format for ANSWERING REVIEWERS

June 20, 2015



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 19372-Review.doc).

Title: Vascular endothelial dysfunction and pharmacological treatment

Author: Jin Bo Su

Name of Journal: *World Journal of Cardiology*

ESPS Manuscript NO: 19372

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewed by 01198134

Comments To Authors

This review by Dr. Su aims at presenting state-of-the-art knowledge on the role vascular endothelial dysfunction in cardiovascular diseases and the pharmacological treatment for rescuing the vascular function. This manuscript was well-written. There were some typos needing to be fixed. 1. page 17, para 2, line 10, it may be better to use the word, homocysteine. 2. page 17, para 3, line 3, glutation should be " glutathione ". 3. page 18, para 2, line 10, hindlimb should be "hind limb". 4. page 19, para 1, line 17, atovastatin should be "atorvastatin". 5. page 19, para 1, line 22, arthriti should be "arthritis".

Response:

Thank you very much for your valuable comments.

As requested, the typos are corrected. All changes in response to your comments are highlighted by red color in the revised manuscript.

Comments To Authors

In this review manuscript, the author systematically and widely discussed the potential mechanisms responsible for vascular endothelial dysfunction and endothelial protective effects of pharmacological treatments in some clinical diseases. This review manuscript significantly enhances the information for the vascular endothelial dysfunction and potential therapeutics. However, the author should address some concerns this reviewer raised. 1. The author mentioned that “Among these mechanisms, a reduction in nitric oxide (NO) bioavailability plays a central role in the development of endothelial dysfunction”. Therefore, the author should give more detail about the relationship between NO and other endogenous substances related vascular endothelial dysfunction in each pathophysiological state (such as atherosclerosis, hypertension, diabetes, etc). 2. The author described that “there are specific mechanisms underlying endothelial dysfunction in different diseases”. The author should give a clear explanation about the discrepancy between “among these mechanisms, a reduction in nitric oxide (NO) bioavailability plays a central role in the development of endothelial dysfunction” and “there are specific mechanisms underlying endothelial dysfunction in different diseases”. Additionally, the author should clearly conclude how and what pharmacological treatments are selected in each pathophysiological state, and give the information about possible interaction among these pharmacological treatments. 3. Some cited references are outdated. For example: ref 233. Please give updated information and definition.

Response:

Thank you very much for your valuable comments.

1. As required, more details about the relationship between NO and other endogenous substances related vascular endothelial dysfunction in different pathophysiological states such as atherosclerosis, hypertension, diabetes and smoking are now added in the revised manuscript (page 11, last 2 lines and page 12, 1st paragraph; page 13, 1st paragraph, lines 6-13; page 13, 2nd paragraph, lines 10-15; page 14, 1st paragraph, last 3 lines and page 14, 2nd paragraph, lines 8-16). For your convenience, all changes in response to your questions are highlighted by cyan color in the revised manuscript.
2. As required, a clear explanation about the discrepancy between “among these mechanisms, a reduction in nitric oxide (NO) bioavailability plays a central role in the development of endothelial dysfunction” and

“there are specific mechanisms underlying endothelial dysfunction in different diseases” is now given in the new manuscript (page 26, lines 7-15).

Also as required, in addition to those already described in the previous version of manuscript, the statement of utilities of pharmacological drugs for the treatment of specific pathologies according to the mechanisms of action of drugs and involved mechanisms in the development of endothelial dysfunction in each pathological state are added in the revised manuscript (page 17, last paragraph, lines 1-4; page 20, 1st paragraph, lines 13-15; page 21, lines 1 and 2). The information about possible interactions among these pharmacological treatments are given in the revised manuscript (page 18, 1st paragraph, lines 8-15; page 19, 1st paragraph, last 2 lines; page 20, 1st paragraph, lines 10-12; page 20, last 5 lines and page 21, 1st line).

3. The reference 233 is replaced (reference 292) and updated information and definition are given now (page 24, last paragraph, lines 1-3).

Reviewed by 02737597

Comments To Authors

The work is interesting and well written, although it needs of more revisions, such as adding one of the most important peptides analyzed, as the adrenomedullin (ADM), the main vasodilator peptide, amplify the section on hypertension, and add more references as:

? Vizza CD, Letizia C, Badagliacca R, Poscia R, Pezzuto B, Gambardella C, Nona A, Papa S, Marcon S, Mancone M, Iacoboni C, Riccieri V, Volterrani M, Fedele F. Relationship between baseline ET-1 plasma levels and outcome in patients with idiopathic pulmonary hypertension treated with bosentan. *Int J Cardiol.* 2013 Jul 15;167(1):220-4. doi: 10.1016/j.ijcard.2011.12.104. Epub 2012 Jan 20. PubMed PMID: 22265324. ? Aversa A, Letizia C, Francomano D, Bruzziches R, Natali M, Lenzi A. A spontaneous, double-blind, double-dummy cross-over study on the effects of daily vardenafil on arterial stiffness in patients with vasculogenic erectile dysfunction. *Int J Cardiol.* 2012 Oct 18;160(3):187-91. doi: 10.1016/j.ijcard.2011.04.003. Epub 2011 May 5. PubMed PMID: 21546099. ? Iacobellis G, di Gioia CR, Di Vito M, Petramala L, Cotesta D, De Santis V, Vitale D, Tritapepe L, Letizia C. Epicardial adipose tissue and intracoronary adrenomedullin levels in coronary artery disease. *Horm Metab Res.* 2009 Dec;41(12):855-60. doi: 10.1055/s-0029-1231081. Epub 2009 Jul 21. PubMed PMID: 19623513. ? Rosato E, Letizia C, Proietti M, Aversa A, Menghi G, Rossi C, Torella E, Cotesta D, Petramala L,

Bruzziches R, Spera G, Pisarri S, Salsano F. Plasma adrenomedullin and endothelin-1 levels are reduced and Raynaud's phenomenon improved by daily tadalafil administration in male patients with systemic sclerosis. *J Biol Regul Homeost Agents*. 2009 Jan-Mar;23(1):23-9. PubMed PMID: 19321043. ? Vizza CD, Letizia C, Petramala L, Badagliacca R, Poscia R, Zeponi E, Crescenzi E, Nona A, Benedetti G, Ferrante F, Sciomer S, Fedele F. Venous endothelin-1 (ET-1) and brain natriuretic peptide (BNP) plasma levels during 6-month bosentan treatment for pulmonary arterial hypertension. *Regul Pept*. 2008 Nov 29;151(1-3):48-53. doi: 10.1016/j.regpep.2008.08.002. Epub 2008 Aug 16. PubMed PMID: 18796317. ? Florio P, Abella R, Marinoni E, Di Iorio R, Letizia C, Meli M, de la Torre T, Petraglia F, Cazzaniga A, Giamberti A, Frigiola A, Gazzolo D. Adrenomedullin blood concentrations in infants subjected to cardiopulmonary bypass: correlation with monitoring parameters and prediction of poor neurological outcome. *Clin Chem*. 2008 Jan;54(1):202-6. Epub 2007 Nov 16. PubMed PMID: 18024532. ? Proietti M, Aversa A, Letizia C, Rossi C, Menghi G, Bruzziches R, Merla A, Spera G, Salsano F. Erectile dysfunction in systemic sclerosis: effects of longterm inhibition of phosphodiesterase type-5 on erectile function and plasma endothelin-1 levels. *J Rheumatol*. 2007 Aug;34(8):1712-7. Epub 2007 Jul 1. PubMed PMID: 17611982.

? Vizza CD, Letizia C, Badagliacca R, Sciomer S, Poscia R, Della Rocca G, Iacoboni C, Leonardo de L, Quattrucci S, Dario C, Luigi P, Fedele F. Plasma adrenomedullin and endothelin-1 concentration during low-dose dobutamine infusion: Relationship between pulmonary uptake and pulmonary vascular pressure/flow characteristics. *Regul Pept*. 2006 Sep 11;136(1-3):85-91. Epub 2006 Jun 30. PubMed PMID: 16815566. ? Salsano F, Letizia C, Proietti M, Rossi C, Proietti AR, Rosato E, Pisarri S. Significant changes of peripheral perfusion and plasma adrenomedullin levels in N-acetylcysteine long term treatment of patients with sclerodermic Raynauds phenomenon. *Int J Immunopathol Pharmacol*. 2005 Oct-Dec;18(4):761-70. PubMed PMID: 16388726.

Response:

Thank you very much for your valuable comments.

As requested, a section of adrenomedullin has been added in the revised manuscript (page 8, 2nd paragraph and page 9, 1st paragraph) and the table 1 is accordingly modified.

The section about hypertension has been enhanced, especially about the role of endothelin-1 in pulmonary hypertension, AM in hypertension (page 10, 2nd paragraph, lines 6-10 and lines 14-15) and interactions between different endogenous endothelium-derived substances as required by another reviewer (page 10, 2nd paragraph, lines 10-15).

Moreover, your recommended references have been interpreted and integrated in the revised manuscript (page 10, lines 24 and 25; page 10, 2nd paragraph, lines 6-10, page 19, lines 14-17; page 21, 2nd paragraph, lines 11 and 12 as well as lines 18-24).

All changes in response to your comments are highlighted by green color in the revised manuscript.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Cardiology*

Sincerely yours,