

RESPONSE TO REVIEWER LETTER

Subject: Revision of the Invited Manuscript no. 55527

World Journal of Cardiology

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REVIEWER #1

This review, focuses on the integrative and up-to-date overview of diagnostic modalities such as SNS imaging methods and novel laboratory biomarkers that could aid in the assessment of the degree of SNS activation and provide reliable prognostic information among patients with HF.

Dear Reviewer, thank you for your summary of our work. Also, allow us to thank you for your constructive comments that we feel have helped in significant improvement of the present manuscript. In this revision, we performed significant changes and additions to the manuscript, as per your suggestion. We created three new figures and two tables and generally refined our text, therefore, we believe that the manuscript in this current form offers a contemporary and up-to-date overview of heart failure in the context of sympathetic nervous system activity and novel biomarkers reflecting these pathophysiological interactions. We hope that in this current form our paper will be suitable for publication.

Major comments:

1. Pathophysiology and compensatory mechanisms of heart failure in the present version are relatively basic and overlapped. I would suggest combining the two subtopics, concising the text, and adding a basic diagram of causes, effects, and compensation.

Dear Reviewer, thank you for your suggestion. As per your instruction, these two subtopics were merged in the single section now named as „Pathophysiology and compensatory mechanisms in heart failure“ (Page 6, highlighted in yellow). This section has also been thoroughly checked for English language and shortened for a slightly less than 1 full page (from 1749 words to 1560 words) and is now more concise and easier to read. Accordingly, we constructed a diagram covering basic causes (etiologies), pathophysiological effects, and compensatory mechanisms that are activated in heart failure. This is shown in Figure 1 (Page 94), also indicated in the text, highlighted in yellow, page 10.

2. Physiology of sympathetic nervous system, cardiovascular reflexes, and adrenergic mechanism are also very basic and overlapped. I would suggest combining and consising them. Cardiovascular reflexes may be listed as a table.

Dear Reviewer, thank you for your observation. As you suggested, all subsections have been combined in a single section (starting on page 11), and text has been reduced and condensed while overlapping/too basic information has been removed. The text has been

reduced from 2100 words in the last version to 1722 words in this revision. According to your suggestion, we also created a **Table 1** that now lists all relevant cardiovascular reflexes and their implications in heart failure. Please see this table at the end of the manuscript (Page 101). We believe that the manuscript flow, overall presentation, and quality are significantly improved with this change.

3. The mechanism of how the SNS changes in heart failure should be more clarified.

Dear Reviewer, we agree with your comment. For this reason, this subsection of the manuscript that is designated as „**Sympathetic nervous system pathophysiology and adrenergic dysregulation in heart failure**“ has been partially rewritten (starting on page 16). Furthermore, some parts of this text were rearranged differently in order to have a more coherent structure and flow. Inspired by your comment, we created a new paragraph in this section (page 19, highlighted in yellow) that briefly discusses proposed temporal changes in SNS activity during the course of heart failure. We believe that this section is now clarified and covers all pertinent components of SNS activation in HF.

4. Figure 2 should be revised to indicate a step-by step from levels, effects, mechanisms, and heart failure, respectively.

Dear Reviewer, thank you for your suggestion. We agree that this figure could be better organized and, based on your input, we decided to present this information in the form of the table rather than figure diagram because we could fit more information in the table and present it in a more organized fashion. For this reason, we discarded Figure 2 completely and instead created **Table 2**, that now provides even more information than the previous figure. In this new table, each of the discussed biomarkers is put into perspective concerning four categories: pathophysiological effects in heart failure or cardiovascular diseases (I), the cellular mechanism (II), circulating levels in HF vs. controls (III), and association with mortality and morbidity in HF (IV). We think that this table provides a comprehensive and unique overview of the most pertinent pathophysiological implications of the discussed biomarkers with a special emphasis on HF-related endpoints and measurements. Please see **Table 2**, at the end of the revised Manuscript file to see these changes (Page 103-104).

5. Could endothelin and galanin be added to the Figure 3? Otherwise, a new figure is recommended.

Dear Reviewer, thank you for pointing this out. In order to dedicate a separate scheme for each of the respective biomarkers, we created two new figures to the manuscript depicting physiological effects/mechanisms of neuropeptide Y (NPY) and galanin, as presented in **Figure 3 (page 96)**, as well as endothelin pathway, as presented in **Figure 4 (page 97)**. Likewise, catestatin is presented in **Figure 5 (page 98)**. In total, there are now three figures depicting the main novel biomarkers that are discussed in the manuscript. We feel that the addition of these figures has greatly improved the manuscript quality and made it more attractive for potential WJC readership.

6. Heart rate variability has been widely used to indicate sympathetic and parasympathetic activity to the heart. Explanation of its basic, clinical application, limitation, and comparison to other techniques is recommended.

Dear Reviewer, thank you for pointing this out. HRV is indeed an established index used to assess sympathetic and parasympathetic activity to the heart and we agree that it deserves its place in the manuscript. A brief overview of HRV, its clinical applications, and limitations, as well as comparison to other techniques, is provided in a new paragraph (subsection) named „Heart rate variability“ as can be seen on pages 23 to 25 (highlighted in yellow). We believe that this is a fine addition to our manuscript.

Minor comments:

1. English should be carefully rechecked. UK or USA style must be consistent.

Dear Reviewer, thank you for this comment. We have thoroughly checked the whole manuscript text and made sure that the text is consistently in the USA style English language. For example, formerly used word „ageing“ (UK style) on page 8 has been replaced with the word „aging“ (USA style). Similar changes, where applicable, were introduced in the rest of the manuscript.

2. Abbreviations in the Figures must be fully explained in the figure legends.

Dear Reviewer, abbreviations in the Figures are now fully explained in the Figure legends section for each respective figure (highlighted in the yellow, manuscript pages 99-100).