

We thank all of the reviewers for taking time to read the submitted manuscript and for their helpful suggestions; their commentary has helped to improve this paper which we hope is now acceptable for publication in the *World Journal of Cardiology*.

Reviewer 1:

This reviewer suggested that several published works be cited and discussed in the manuscript; all of the papers have been included in the bibliography along with additional discussion of the role of G-protein-coupled receptors in cardiac function (lines 179-186). We also added a schematic as suggested by this reviewer.

Reviewer 2:

This reviewer suggested the addition of a schematic (as per Reviewer 1); a new figure has been added. We have also shortened the Introduction as requested. Clinical findings regarding vagal stimulation has been added to the text (lines 368-379). Additional information regarding HEXA and DCN are now included in the revised text (lines 395-410). We hope it is now clear that conditioning stratagems used in the clinic have not been successful.

Reviewer 3:

This reviewer had concerns regarding length of this manuscript. We have shortened the Introduction and have revised the remainder of the text; however, we added a section on Heart Failure. Since this reviewer had difficulties with the term 'white paper', we now refer to a position paper published by Ardell and colleagues.

Reviewer 4:

This reviewer had no major concerns regarding this paper.