

17 April 2014

Professor B.K. Puri

World Journal of Cardiology

Dear Editor,

Re: 8334 Respiratory modulation of cardiac vagal tone in Lyme disease by Puri *et al.*

I should like to thank the three reviewers for having kindly reviewed the above paper. Their comments have been very helpful and have been fully taken into account in the revised version.

Reviewer 00646232

Each of the valuable comments by this reviewer has been addressed in the revised version. In particular, the inclusion criteria and the exclusion criteria are now formally stated. Further clinical details are now given regarding the patients. The reviewer asks for a comment regarding the power of the study; as there has been no previous work published in this area, it was clearly not possible to calculate the value of β , and therefore the statistical power, of this study and this has now formally been explained in the revision. Relevant details regarding medication are now included. The model of the NeuroScope is now given. The discussion has been expanded. Finally, the reviewer makes the valuable point that the fact that *Borrelia* bacteria can undergo pleomorphic change and that this cystic form is often found in the brain stem cannot be an explanation of our findings. Accordingly, this point has been made in the revision.

Reviewer 02446043

This reviewer suggests that ‘the paper seeks to convince the reader that Lyme disease reduces vagal tone, a finding which contradicts the well established fact that Lyme disease is associated with various grades of atria-ventricular [sic] block, a high vagal state.’ I would respectfully point out to this reviewer that the paper does *not* seek to suggest that Lyme disease reduces vagal tone. In fact, the point is made that the resting cardiac vagal tone was not found to be statistically significantly different between the Lyme disease patients and the controls. The main finding being reported is in respect of *respiratory modulation* of cardiac vagal tone in Lyme disease. In order to prevent any readers from mis-understanding this point, a paragraph explaining this has been added to the discussion section. Points (i) and (iii) have been addressed fully in the revision. Regarding point (ii), in which the reviewer asks for ‘the actual IgM level of the patients’, I would respectfully point out that Western blot serological results do not provide quantitative data on actual IgM levels. Finally, in view of my comments

regarding the fact that the resting cardiac vagal tone did not differ significantly between the two groups, clearly the final reviewer comments regarding 'a reduced vagal tone in Lyme' are not germane.

Reviewer 00608305

The reviewer makes four valuable points. (1) Further details regarding the patients are now given in the revision. For those patients who underwent IgG testing, this was negative in all cases (by the CDC and NYS criteria). (2) There was no clinical evidence of these other diseases; none of the patients has subsequently developed evidence of syphilis or an autoimmune disease. (3) The reviewer makes a very valuable observation regarding the possibility that, in spite of matching on basal vagal tone, the controls had a slightly, non-significantly, higher basal vagal tone and lower heart rate, which might be consistent with the control subjects being more physically fit. I have now checked this and the reviewer turns out to be perfectly correct in his/her prediction. I thank the reviewer for this valuable observation, which is now detailed in the discussion section. (4) The reviewer asks for confirmation that arterial pressures in Table 1 are mean pressure values and suggests that additional information regarding heart rate during deep breathing be added. I am happy to confirm that the arterial pressures in Table 1 are mean pressure values and, in line with the reviewer's valuable suggestion, two further tables have been added to the revision, which detail the heart rate for each of the patients and each of the controls before, during, and following the deep breathing procedure.

In sum, I am very grateful to the three reviewers for their valuable comments.

I sincerely trust that the extensive revisions made will be found to be satisfactory. Please do let me know if any further revision is necessary.

With kind regards

Yours faithfully,

A handwritten signature in black ink, appearing to read 'B. K. Puri', with a horizontal line underneath.

Professor B. K. Puri