Author's response to reviews

Title: Early endothelial dysfunction in cholesterol-fed rabbits: a non-invasive in vivo ultrasound study.

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Author's response to reviews: see over
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Dr Eugenio Picano, MD PhD
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Dr Picano,

We submit the following revised manuscript to your Journal: “Early endothelial dysfunction in cholesterol-fed rabbits: a non-invasive in vivo ultrasound study.”

This manuscript was recently submitted to your journal and was accepted for publication with minor revision. We sincerely think we have answered all their interrogations and hope that our manuscript will be considered for publication in its revised version.

Here is a list of the changes made to the manuscript in response to the comments received.

**General comments:**

1. Acetylcholine short half-life in rabbits…
   Acetylcholine half-life is in fact very short. It has to be noticed that rabbits were given a continuous infusion for two minutes. We have included in the new version of the manuscript a figure showing representative blood pressure changes (New Figure 2) during the drug infusions as well as the time frame of echo analysis.

2. Graph showing correlation between ex vivo and in vivo analysis…
   This could have been possible with rabbits at 8 weeks. In fact, the same rabbits were followed longitudinally at week 0, 2 and 8. Additional rabbits were used for the ex vivo analysis at week 0 and week 2 for a total of 24 rabbits. Since correlation is in fact, an improper term here, we used another terminology to compare ex vivo and in vivo studies. As for 8-week rabbits, as illustrated in Figure 6A (previously 4A), the abdominal aorta sections from these rabbits displayed the largest heterogeneity in their response to acetylcholine.

3. A new figure specifying the protocol…
In addition to new figure 2, we add a new Figure (figure 1) illustrating the conditions used during the in vivo experiments. This figure in addition of Figure 2 and the corresponding figure legends should complement the Material and Methods section’s description of the set-up used.

**Other comments**

1. Abstract sub-divisions
   Sub-divisions have been added as asked.

2. Page 3 final paragraph
   Objective of the study has been shortened.

3. Statistical analysis
   This section has been remodeled.

4. page 10
   This sentence has been re-written.

5. Legend of figure 1 (now figure 3)
   The ¶ symbol was used for the statistical comparison between week 2 and week 0 results as described in the Figure legend.

In summary, we have provided answers to all the comments that were given to us by the reviewers to the best of our knowledge. We hope that the changes we have made to our manuscript are satisfactory.

Best regards,

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