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The impact of antiarrhythmics on human pulmonary arteries: Ex-vivo characterization

Rishab Makam, Nayla Tajmohamed, Syed Qadri, Mubarak Chaudhry, Michael Cowen, Mahmoud Loubani, Azar Hussain

Corresponding author
Rishab Makam
Allam Medical Building, Department of Medicine, The Hull York Medical School, University of Hull, Hull, United Kingdom, HU6 7RU

Handling editor:
Michal Heger
Department of Pharmaceutics, Utrecht University, the Netherlands
Department of Pharmaceutics, Jiaxing University Medical College, Zhejiang, China

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The Impact of Antiarrhythmics on Human Pulmonary Arteries: Ex-Vivo Characterisation
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Dear Mr Makam,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Jun 20, 2022.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: The manuscript is well-written with a few exceptions and structurally presented. The rationale for the study is clearly explained and builds on previous work. The importance of the research evident.

JCTR certainly has interest in the work and recommends the following revisions.

1. Please proofread the manuscript and eliminate any residual typos, including inserting a space between value and unit (e.g., 35 mL instead of 35mL), ensuring that experiment details are written in past tense, and consistency (e.g., amiodarone vs. Amiodarone).
2. For readers not familiar with the setup, please specify whether the system entails a circular test set-up or a wash-through experiment. In other words, is the exposure to serial concentrations of AF medications additive (previous concentration + new concentration) or normative (no dosage effect of previous concentration on new concentration)?
3. Please insert a panel in Figure 1 of an arterial segment in the control group (all reagents added except for AF medication). If the concentrations are additive, please ensure that the implications are accounted for in the results and discussion. Also make sure that the gradual build-up of AF medication in the vascular wall and the implications on the experimental results are discussed.
4. In Figure 1, it is not clear what the boxed numerical values represent along the x-axis. Also, what is the difference between a wash-out (amiodarone) and wash up (digoxin)?
5. Why is there a differential delta in gf after the addition of PGF2a between the vessel segment exposed to amiodarone (Fig. 1a) and digoxin (Fig. 1b)? It seems that the extent of initial constriction would affect the pharmacodynamics of the subsequently administered therapeutics. Moreover, this phenomenon conflicts with the statement "Once calibrated the PA rings are mounted onto the myograph with the resting tension (RT) set to 1.61 gram force (gf), (1 gf is equivalent to 0.009807 newtons) as this was determined to be the optimal resting tension from previous experiments (20)."
6. In Figure 2 and 3, what does the p=5 mean in the in-figure legend? Please specify in the text legend.
7. Please add information to the discussion section regarding the peak systemic concentration of amiodarone and digoxin after standard regimen administration in cardiovascular patients. This info is necessary for proper contextualization of your data. If the concentrations that you used differ significantly, please devote a part of the discussion to addressing the ramifications of these differences on the translational value of your results.

Authors' response

To Editor-in-chief,
Journal of Clinical and Translational Research,

Thank you for your comments and suggestions for revision. Please find below our responses to each of the comments in addition to the changes in the manuscript:

1. Please proofread the manuscript and eliminate any residual typos, including inserting a space between value and unit (e.g., 35 mL instead of 35mL), ensuring that experiment details are written in past tense, and consistency (e.g., amiodarone vs. Amiodarone).

All editions done.

2. For readers not familiar with the setup, please specify whether the system entails a circular test set-up or a wash-through experiment. In other words, is the exposure to serial concentrations of AF medications additive (previous concentration + new concentration) or normative (no dosage effect of previous concentration on new concentration)?

Explained in line 142 - 145

3. Please insert a panel in Figure 1 of an arterial segment in the control group (all reagents added except for AF medication). If the concentrations are additive, please ensure that the implications are accounted for in the results and discussion. Also make sure that the gradual build-up of AF medication in the vascular wall and the implications on the experimental results are discussed.

Control image added in part (c) and in green to differentiate from amiodarone and digoxin
Implications of gradual build-up of drugs discussed in line 266 - 270

4. In Figure 1, it is not clear what the boxed numerical values represent along the x-axis. Also, what is the difference between a wash-out (amiodarone) and wash up (digoxin)?

Explained in figure legend and label changed to washout as it is the same process

5. Why is there a differential delta in gf after the addition of PGF2a between the vessel segment exposed to amiodarone (Fig. 1a) and digoxin (Fig. 1b)? It seems that the extent of initial constriction would affect the pharmacodynamics of the subsequently administered therapeutics. Moreover, this phenomenon conflicts with the statement "Once calibrated the PA rings are mounted onto the myograph with the resting tension (RT) set to 1.61 gram force (gf), (1 gf is equivalent to 0.009807 newtons) as this was determined to be the optimal resting tension from previous experiments (20)."

The difference in delta is in variable due to the invariably different response from different patients' tissue. The implications of this are discussed in lines 260 – 265. The essence is that the vessel is pre-constricted in a way that aims to mimic conditions in pulmonary hypertension (as explained in the paper). The reason the PAs are set to resting tension is to ensure that any change in vessel tension is detected, they must be under minimal tension. Based on previous experiments using same sized artery samples, 1.61 gf was determined to be the optimal tension. Moreover, allowing the vessels to equilibrate means that they are more likely to respond reliably during the experiment as we know that any change in vessel tension is due to the reagents added and not because the vessel is still adjusting to the experimental setup.

6. In Figure 2 and 3, what does the p=5 mean in the in-figure legend? Please specify in the text legend.

Added to figure legend

7. Please add information to the discussion section regarding the peak systemic concentration of amiodarone and digoxin after standard regimen administration in cardiovascular patients. This info is necessary for proper contextualization of your data. If the concentrations that you used differ significantly, please devote a part of the discussion to addressing the ramifications of these differences on the translational value of your results.

We have used the therapeutic concentrations for context to our data as this would more accurately represent the long-term implications rather than short lived peak concentrations. This is detailed in the discussion in lines 245 to 255. These values fall within our experimental concentrations for both Amiodarone and digoxin.

Thank you for your consideration of this manuscript.
Sincerely,
Rishab Makam
5th Year Medical Student (MBBS)
Hull York Medical School
York, United Kingdom, YO10 5DD

2nd Editorial decision
13-Jun-2022

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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: