Author’s response to reviews

Title: Associations of AMP and adenosine induced dyspnea sensation to large and small airways dysfunction in asthma

Authors:

Claire Cox (c.a.cox@umcg.nl)
Ilse Boudewijn (i.m.boudewijn@umcg.nl)
Sebastiaan VRoegop (j.s.vroegop@gmail.com)
Siebrig Schokker (s.schokker@umcg.nl)
Anne Lexmond (a.j.lexmond@rug.nl)
Henderik Frijlink (h.w.frijlink@rug.nl)
Paul Hagedoorn (p.hagedoorn@rug.nl)
Judith Vonk (j.m.vonk@umcg.nl)
Martijn Farenhorst (m.p.farenhorst@umcg.nl)
Nick ten Hacken (n.h.t.ten.hacken@umcg.nl)
Huib Kerstjens (h.a.m.kerstjens@umcg.nl)
Maarten van den Berge (m.van.den.berge@umcg.nl)

Version: 1 Date: 19 Oct 2018

Author’s response to reviews:

Reviewer 1 (Tobias Müller)

In this manuscript Cox and coworkers compared dyspnea in 2 different bronchoprovocation tests using either adenosine or AMP. In general, the manuscript is well written and contains some new data which are of interest. However, several points should be addressed:

1. In general: The authors hypothesize that due to particle size AMP targets large airways whereas adenosine targets small airways. However, this is neither supported by the data presented in the manuscript nor by data derived from the literature. Therefore, this point remains speculative.
Answer: We are well aware our assumption about the deposition is speculative as deposition studies remain to be executed. We added emphasis to the speculative nature of our assumption in the manuscript.

2. What was the asthma diagnosis of patients included into the study based on?

Answer: Subjects invited for the screening/baseline phase of the OLiVIA study had a doctor’s diagnosis of asthma. For the initial OLiVIA study subjects without hyperresponsiveness to adenosine (PD20 adenosine >20 mg) were rejected for randomization. In the current study, however, we were interested in the origin of dyspnea. Therefore we included all subjects that performed both provocations and experienced dyspnea, irrespective of having a positive or negative provocation tests. In the manuscript we have elaborated the study design and patients section to clarify which asthmatics were studied.

3. The authors suggest that adenosine induces dyspnea via a different mechanism compared to AMP. Hence, studies to reveal the underlying mechanisms should be performed. However, this point is also speculative as the effects on pulmonary function induced by adenosine and AMP were very similar.

Answer: This is a correct point from the reviewer. We show that the overall degree of dyspnea is similar between the two agents, but dyspnea sensation evoked with dry powder adenosine more closely reflects small airways involvement. This suggests that dry powder adenosine and AMP evoke dyspnea via different processes, possibly by differential deposition of inhaled particles. However, we agree that this point remains speculative and deserves further study. We now make this more clear in discussion.

4. Both AMP and adenosine are indirect acting agents for bronchoprovocation. Comparing either adenosine of AMP to a direct acting agent (e.g. methacholine) would be of greater interest.

Answer: We agree that comparing dyspnea induced by a direct agent to an indirect agent would have been a nice addition to our study. The interaction pathways of direct and indirect agents are clearer distinguished and therefore an observed difference in dyspnea sensation or airways parameters would have been easier linked to a mechanism. Unfortunately, this study could only accommodate two agents. As the OLiVIA study was partially designed to validate small particle dry powder adenosine provocation[i], AMP seemed the logical counter agent.

5. Did the authors also perform body plethysmography? It would be of interest whether the degree of dyspnea is correlated to airway resistance or hyperinflation.

Answer: Body plethysmography was performed once, prior to any provocation tests. Both RV and RV/TLC were within the normal ranges (104 %pred (IQR 87-129) and 95 %pred (IQR 85-
109), respectively), arguing against (major) hyperinflation in these relatively mild asthma subjects. Unfortunately, we did not study hyperinflation induced by the provocation tests, which would have been a good addition.

Reviewer 2

REVIEWER COMMENTS FROM REPORT: It is an interesting and well conducted study. It joins classical routinely used indexes of flow resistance to more sophisticated evaluation of segmental respiratory resistance using IOS. The main drawback is that authors make the assumption that adenosine is mainly delivered to the small airways, yet they have no proof of this.

Answer: This is correctly pointed out by the reviewer. We indeed lack data on AMP and adenosine deposition as deposition studies are very difficult to carry out. We now explicitly state that these conclusions are based on assumptions based on the article of Usmani[ii] and taking into account MMAD- and flow-related deposition laws.

Further, as the authors hypothesize a different pathway for dyspnea by stimulation with ATP other than bronchoconstriction of large airways, I suggest to hypothesize afferents from interstitial J receptors activated by subthreshold interstitial edema.

Answer: See next remarks answer.

REQUESTED REVISIONS:

I suggest the authors include a short discussion concerning sensitive afferents from the lung interstitial space in case of dyspnea elicited by ADP stimulation.

Answer: Thank you for this interesting view. We have added the suggestion to the manuscript (line 197, 203-205). To avoid misunderstanding of the readers we only used the term AMP, and focused on interstitial edema in the bronchial wall.

References used in the response


** All revisions made to the manuscript are made in blue. Text that is deleted is crossed out.**