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Journal Name:	British Journal of Applied Science & Technology
Manuscript Number:	Ms_BJAST_22187
Title of the Manuscript:	The Spatial Response of Penh as a Secondary Readout for the Airway Hyper-reactivity in Three Different Rodent Models of Airway Inflammation
Type of the Article	Short Research Article

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This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	CRITIQUE In general, this paper is fairly well written. However, there are a number of major concerns that detract from the overall effort. Among them are: 1. Presentation of methodologies: It is still unclear why the concentration of Mch was used to assess the utility of the Penh as a secondary readout for the airway hyper-reactivity. If the Mch is the gold standard to assess the airway hyper-reactivity, it should be clearly described. If there are other indexes as the gold standard to assess it, it should be explained in detail why the Mch was used. Moreover, the description of Mch seems to be less and unclear considering the importance of the tables in this study. 2. Contents of methodologies: It is still unclear why the dose response of the three experiments were not assessed. Correlation between Penh (and/or Mch) and severity of the airway hyper-reactivity should be analyzed, if possible. It should be reconsidered.	Authors thanks reviewer's comments and points well taken Ans 1 : The use of Mch dose response to access Penh is well established. http://www.ncbi.nlm.nih.gov/pubmed/25462015 http://www.ncbi.nlm.nih.gov/pubmed/9309991 Part of the reason to use Mch is to amplify the Penh signal, and decrease the signal to noise ratio. We have measure the baseline Penh of the challenged animals, and they look only slightly higher than control. So Mch just magnifies the response, and lifts the data/response above the noise level. A sentence is added to the method section to make it clear. Ans 2: A revision has been made in the MS to Clearfield that the study is to use Penh is the measurement of airway hyperreactivity severity. The dose response can be found in Figures (we have make it clear by revised the MS) that dose response of Mch vs Penh (airway hypersensitivity) and Penh is the measurement of airway hyperreactivity severity. Ans3. The MS has been revised to make clear. The optimal Mch and Penh cut off is dependent on the severity of the disease of the specific



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	3. Prospect: To practicalize the Penh as a readout for the airway hyper-reactivity in the future, the optimal cut-off value should be analyzed and/or discussed in this study, if possible. For example, using ROC curve may be helpful.	animals/model/study, hence it is hard for us to recommend an optimal value. The rule of thumb is that the higher the Penh, the larger the window of separation between treatment groups and control. At too high of a Penh, the animals can die. The optimal value in one experiment can be lethal in another. If the maximum Penh value is desired, it should be evaluated for each model and experiment individually. The maximum value we used were derived from pilot studies and approved by the IACUC. We were not allowed to dose until lethality or adversely affect the animals' health.
<u>Minor</u> REVISION comments		
<u>Optional/General</u> comments		