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### ESPS Peer-review Report

**Name of Journal:** World Journal of Respiriology

**ESPS Manuscript NO:** 2420

**Title:** High-frequency electrical stimulation of cervical vagi reduces airway response to methacholine

**Reviewer code:** 02416403

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2013-02-20 16:46

**Date reviewed:** 2013-03-11 10:25

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

### COMMENTS TO AUTHORS

This study by Zhuang et al. revealed that high-frequency electrical stimulation (HES) of bilateral vagal nerves could reduce the airway responses to methacholine. I believe that this trial has not been conducted before and the findings of the present study are novel. The experiments were well designed and the manuscript is also well written. I understand that a number of criticisms may be raised on the results of this study. However, the authors have already discussed these points in the manuscript and I appreciate the authors' effort.



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### ESPS Peer-review Report

**Name of Journal:** World Journal of Respiriology

**ESPS Manuscript NO:** 2420

**Title:** High-frequency electrical stimulation of cervical vagi reduces airway response to methacholine

**Reviewer code:** 01235072

**Science editor:** Wen, Ling-Ling

**Date sent for review:** 2013-02-20 16:46

**Date reviewed:** 2013-03-12 12:13

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input checked="" type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

### COMMENTS TO AUTHORS

This manuscript is well written. I suggest to accept at the current format.



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## ESPS Peer-review Report

Name of Journal: World Journal of Respiriology

ESPS Manuscript NO: 2420

Title: High-frequency electrical stimulation of cervical vagi reduces airway response to methacholine

Reviewer code: 00503929

Science editor: Wen, Ling-Ling

Date sent for review: 2013-02-20 16:46

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

REFeree'S COMMENTS Overview. The paper by Zhuang and colleagues describes the effects of different kinds of electric stimuli on RL and Cdyn in guinea pigs, both Ovalbumin-exposed and controls. Electric stimuli were either of low-frequency (LES) or high-frequency (HES), were delivered to the dissected cervical vagi in anesthetized and paralyzed animals which were undergoing mechanical ventilation with an oxygen-nitrogen mixture of fixed composition, and which were prepared for measurements of mean arterial blood pressure and heart rate through invasive procedures. LES and HES have quite different effects, while HES as a class present similar effects, despite major differences in frequency, duration and wave form of individual cycles of HES. Based on this, LES and HES are assumed to work through very distinct mechanisms, namely stimulation and blockade of vagal nerves, respectively. The authors made measurements of LES/HES effects before methacholine exposure as well as after methacholine responses, which are relatively short-lived, had reached their peak value. In the absence of methacholine, LES clearly has an effect on these parameters (Fig. 1), but different examples of HES lack any obvious effect. This could be interpreted as supporting the view that LES actively does something, as opposed to HES, which would merely prevent something from happening. Both assumptions would be consistent with the authors' view that AHR, namely the exacerbated responses to methacholine observed in asthmatic subjects as well as sensitized experimental animals, is due to an increased acetylcholine release from parasympathetic nerves innervating the airways. The prediction that ensues is that AHR could be undetectable in animals submitted to interventions that prevent release or action of acetylcholine. This model may be supported by a number of researchers, but there is also evidence from several groups that immunological processes, through inflammatory mechanisms, modify methacholine



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responses in the target organ, leading to what can be termed AHR, not necessarily depending on the integrity of parasympathetic innervation. Regardless of the relative importance of nerves versus target organ in the development of AHR, the authors did not address the status of cholinergic transmission in their paper, but the responses to nonspecific electrical stimulation in a nerve that contains a variety of afferent and efferent fibers. The effects of LES and HES are therefore discussed in the framework of changes in “vagal tone”, although exactly how vagal tone relates to cholinergic effects on the targets of parasympathetic targets remains open to question in their results. The nonspecificity of the electrical stimuli has an important consequence, namely that spread of current to neighboring structures might be a source of artifacts. The authors have themselves considered this possibility with respect to recruitment of adrenergic fibers by current spread, and concluded against it, in the case of HES. General comments on the manuscript. It is well-written, and adequate for a specialist journal. I think it might be improved by more detailed description of some methodological aspects, as specified below. It also discusses extensively the possibility of translating HES into clinical medicine. I think this discussion should be more concise, as it is far from the immediate concerns of the experimental work. Not enough attention has been given to the fact that asthma is a chronic condition, that the respiratory effect of HES is transient, and that repeated HES may have undesirable consequences, even though HES seems not to damage nervous fibers in a short round of treatment. Furthermore, no one would consider such a complex approach to relieving asthma symptoms, unless more conventional approaches have failed. It is therefore important to examine whether preexposure to the conventional treatments, including topical corticosteroids and bronchodilators, does not i