

latter paper, I noted that the authors never used a flanged mouthpiece nor did they make their  $P_{I,max}$  measurements from functional residual capacity but rather from residual volume. The type of mouthpiece and the way it is used result in large pressure differences obtained during the measurements of  $P_{I,max}$  and  $P_{E,max}$  [5]. Lung volumes also affect these measurements and appropriate reference values should be used [6].

**N.G. Koulouris**

**Correspondence:** N.G. Koulouris, Respiratory Function Laboratory, 1st Dept of Respiratory Medicine, University of Athens Medical School, "Sotiria" Hospital, 152, Mesogeion Ave, Athens GR-11527, Greece. E-mail: koulunik@med.uoa.gr

**Statement of Interest:** None declared.

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*From the authors:*

In response to the question raised by N.G. Koulouris, we confirm that vital capacity (VC) and the respiratory muscle strength were all performed in the seated posture. We agree with N.G. Koulouris that correlations between the supine Borg and the supine respiratory muscle strength values might be better and it would be relevant to verify this hypothesis. However, as a matter of routine, only the VC was performed in both the seated and supine positions.

Measurement of the maximal inspiratory pressure ( $P_{I,max}$ ) is conventionally easier to obtain from residual volume (RV) and greater inspiratory pressures are obtained at lower lung volumes. However, in the neuromuscular disorders, the recoil pressure of the respiratory system at RV may be a significant fraction of  $P_{I,max}$ . The recoil of the chest wall and lungs is equal at the functional residual capacity (FRC). The difference of values obtained from RV and FRC is not important in healthy subjects [1]. In patients with neuromuscular disorders, the advantage of measuring the voluntary inspiratory strength from FRC is that only the force of the inspiratory muscles is assessed and not the negative recoil pressure of the respiratory system. Changing the reference in the text, as demonstrated in a study by ULDRY *et al.* [2], is more suitable. Indeed, we used the predicted values of ULDRY *et al.* [2] which were measured at FRC.

N.G Koulouris demonstrates that better values of inspiratory strength were obtained with a tube mouthpiece rather than a flanged mouthpiece in healthy subjects [3]. Patients find the flanged mouthpiece easier than the tube explaining its widespread use [1]. In our experience with neuromuscular disorders, especially in amyotrophic lateral sclerosis with bulbar involvement, air leaks were less important with a flanged mouthpiece [4].

**N. Just, N. Bautin and T. Perez**

Service des Explorations Fonctionnelles Respiratoires, Clinique des Maladies Respiratoires, CHRU, Lille, France.

**Correspondence:** N. Just, Service de Pneumologie, Hôpital Victor Provo, 11-17 Bd Lacordaire, F-59100 Roubaix Cedex, France. E-mail: nicolas.just@ch-roubaix.fr

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# Do $\beta_2$ -agonists inhibit capsaicin-induced cough?

*To the Editors:*

We read with great interest the paper by FREUND-MICHEL *et al.* [1] in a recent issue of the *European Respiratory Journal*, because the results are inconsistent with the medical common

sense that  $\beta_2$ -agonists do not have common antitussive property.

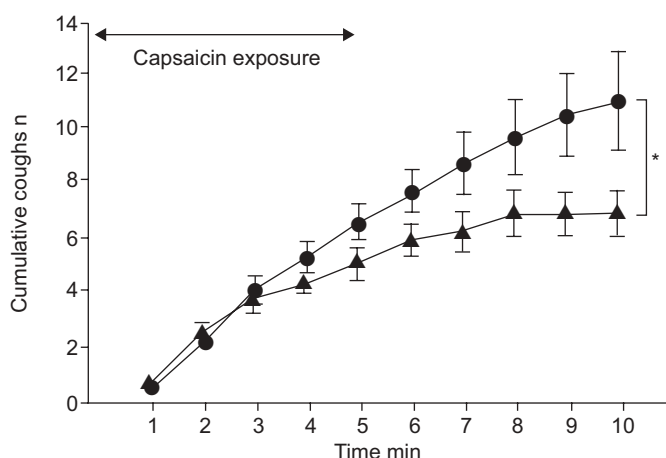
The authors showed that a  $\beta_2$ -agonist, terbutaline (0–3 mg·kg<sup>-1</sup>), dose-dependently inhibited 10<sup>-4</sup> M capsaicin-induced cough in

conscious guinea pigs. Terbutaline also blocked sensory nerve activation. They concluded that  $\beta_2$ -agonists are antitussive and directly inhibit sensory nerve activation.

We have shown that the number of  $10^{-4}$  M capsaicin-induced coughs was extremely increased 24 h after an antigen challenge in sensitised guinea pigs, and a  $\beta_2$ -agonist, procaterol ( $0.1 \text{ mg}\cdot\text{kg}^{-1}$ ), did not alter the increased cough response to capsaicin. In addition, procaterol did not influence the cough response to capsaicin in naïve guinea pigs. We concluded that airway allergy accompanied with airway eosinophilia induces transient increase in cough reflex sensitivity, which is not mediated by bronchoconstriction [2].

The discrepancy between these two studies may result from difference of methods to measure cough response in conscious guinea pigs. FREUND-MICHEL *et al.* [1] exposed capsaicin ( $10^{-4}$  M) for 5 min and measured the number of coughs for 10 min. However, we exposed capsaicin ( $10^{-4}$  M) for 2 min and measured the number of coughs for 3 min.

In order to elucidate the different results, we actually measured the number of coughs using the method described by FREUND-MICHEL *et al.* [1]. Guinea pigs were assigned to one of two groups: a control group and a procaterol group ( $n=6$  for each group). Procaterol ( $0.1 \text{ mg}\cdot\text{kg}^{-1}$ ) was administered 30 min prior to exposure to capsaicin. The results are shown in figure 1. There was no difference in the number of coughs during the initial 3-min period between the two groups: the mean number of coughs was 4 in the control group and 3.7 in the procaterol group. This result was the same as our previous results. On the other hand, the number of coughs during the 10-min period in the procaterol group was significantly decreased compared with that in the control group: the mean number of coughs was 6.8 in the procaterol group and 11 in the control group ( $p=0.028$ ). This finding was the same as those of FREUND-MICHEL *et al.* [1]. Thus, it is concluded that both our previous results and the results of FREUND-MICHEL *et al.* [1] are



**FIGURE 1.** Cumulative number of coughs in conscious guinea pigs. Guinea pigs were exposed to aerosolised capsaicin ( $10^{-4}$  M) for 5 min and the number of coughs was measured for 10 min after the initiation of capsaicin exposure. Guinea pigs were assigned to one of two groups: the control group (●) and procaterol group (▲),  $n=6$  for each group. Data are presented as mean  $\pm$  SEM. \*:  $p<0.05$  versus control group.

scientifically correct. It is very important to recognise that methods for evaluating cough response in guinea pigs strongly influence the results, and standardisation of the methods should be established in order to be translated to clinical practice.

**N. Ohkura, M. Fujimura, A. Tokuda and N. Katayama**

Respiratory Medicine, Kanazawa University Hospital, Kanazawa, Japan.

**Correspondence:** N. Ohkura, Respiratory Medicine, Kanazawa University Hospital, 13-1 Takara-machi, Kanazawa City, Ishikawa 920-8641, Japan. E-mail: nori@med3.m.kanazawa-u.ac.jp

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## From the authors:

We would like to thank N. Ohkura and co-workers for their interest in our manuscript and are pleased that they were able to reproduce our data in their laboratory. The length of time that the guinea pigs are monitored following a tussive challenge may well be important for obtaining a true and accurate picture of whether the cough reflex has been affected by interventional agents. We would question, however, whether the observation that  $\beta_2$ -agonists inhibit cough in a guinea pig model [1] actually argues against the conventional wisdom in the clinic. It may be simply that this question has not been objectively assessed in the optimal experimental paradigm. There are several papers which do observe antitussive effects of  $\beta_2$ -agonists [2–7] and a few that don't [8, 9] and, as such, we have proposed in our paper that we may have an answer as to why this confusion may exist. First, in most cases,  $\beta_2$ -agonists have not been assessed in double blind, placebo-controlled, randomised, crossover clinical trials where cough is the primary end point. Furthermore, there has only been symptom scoring and no objective measurement of cough. This is important given patients (especially those with chronic cough) find it very difficult to make an accurate assessment of their own cough. As such, there are issues with the subjective nature of the reporting of cough as a symptom; objective cough monitoring devices have only recently been developed and trials with  $\beta_2$ -agonists have not been performed. However, the discrepancies between the different clinical studies that report on cough may also be due to the fact that  $\beta_2$ -agonists activate a specific antitussive mechanism that is independent of its smooth muscle relaxant activity (as suggested by our paper). Currently, the dose regimen/protocol for  $\beta_2$ -agonists in the clinic is routinely based around their