conscious guinea pigs. Terbutaline also blocked sensory nerve activation. They concluded that β_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 β_2-agonist, procaterol (0.1 mg·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 mg·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 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.

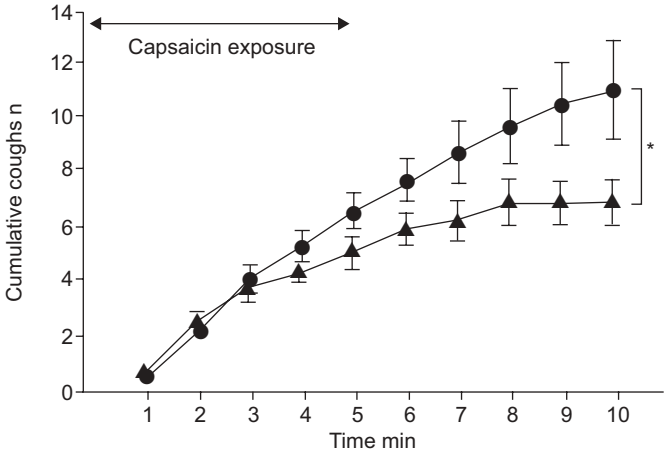

FIGURE 1. Cumulative number of coughs in conscious guinea pigs. Guinea pigs were exposed to aerosolised capsaicin (10^{-4} M) for 5 min and the number of coughs was measured for 10 min after the initiation of capsaicin exposure. Guinea pigs were assigned to one of two groups: the control group (●) and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

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From the authors:

We would like to thank N. Okhura 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 β_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 β_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, β_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 β_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 β_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 β_2-agonists in the clinic is routinely based around their

relaxant properties and not geared to their antitussive activities (which may require higher doses) and we propose that this may be why a dominant antitussive property of β_2-agonists has not hitherto been uncovered.

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