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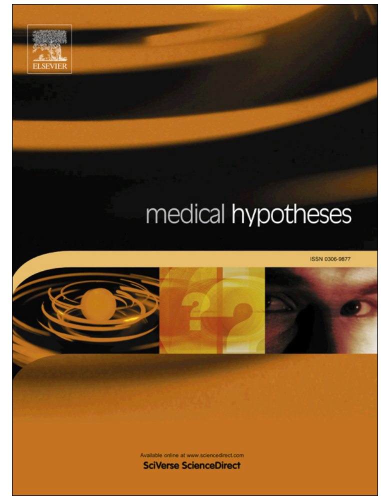

Could reflex cough induced through nebulized capsaicin achieve airway clearance in patients with acute retention of lung secretions?

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ABSTRACT

Nasotracheal suctioning (NTS) is a procedure commonly performed by respiratory physiotherapists and nurses to remove excess respiratory secretions from the tracheobronchial tree in a self-ventilating, non-intubated and non-tracheotomized patient. NTS is an important treatment modality for patients with acute secretion retention who are at high risk of progressive respiratory deterioration and arrest. However, NTS is a blind invasive procedure with risk of serious adverse events, and the patient experience of NTS is often extremely negative.

Capsaicin, a substance extracted from cayenne pepper, elicits reflex coughs when inhaled. It is hypothesized that capsaicin-induced reflex cough may offer an alternative treatment option to NTS. It is suggested that repeated reflex cough bouts, elicited through inhalation of nebulized capsaicin via a facemask, could achieve clearance of retained secretions from the tracheobronchial tree to the oropharynx, thereby avoiding the need for NTS.

This hypothesis is supported by preliminary cough flow data from a stroke trial. Stroke patients underwent assessments of peak cough flow (PCF, a measure of cough effectiveness) of both maximal volitional cough and capsaicin-induced reflex cough. In a sub-group of 20 stroke patients with weak volitional cough (mean PCF 220 L/min, SD 80), PCF of capsaicin-induced reflex cough was on average 184 L/min (SD 130) higher than PCF of subjects' maximal volitional cough effort. Cough flow traces indicate a pattern of cough augmentation during consecutive reflex cough bouts.

It is suggested that the hypothesis may best be tested in a pragmatic applied clinical study, *i.e.* through the application of nebulized capsaicin in relevant clinical situations, as opposed to observational or experimental physiological studies.

Key words: airway clearance, capsaicin, respiratory physiotherapy, nasotracheal suctioning, peak cough flow, reflex cough

BACKGROUND

Nasotracheal suctioning (NTS) is a procedure for removing excess respiratory secretions (phlegm, mucus) from the tracheobronchial tree (1-3). NTS is indicated in patients who are unable to cough and clear excess respiratory secretions, and who are therefore at high risk of serious breathing difficulty due to impaired ventilation and gas exchange (1-5). Patients receiving NTS typically develop excess respiratory secretions acutely, for example due to pneumonia, and often against the background of acquired neuro-disability, a degenerative neurological condition, dementia, old age, chronic respiratory disease, decreased immune response, or general frailty. Inability to actively cough and clear in such a patient may be due to difficulty in initiating volitional coughs, for example in patients with cognitive impairments or reduced level of consciousness; insufficient effort of volitional cough; respiratory muscle weakness; or poor neuro-muscular co-ordination of cough. The latter refers to co-ordination between respiratory muscle action and rapid glottis closure and opening, which is achieved by intrinsic laryngeal muscle action and is a defining feature of cough (6). Any of these problems may be compounded by high viscosity of secretions, bronchospasm, pain when breathing or coughing, and patient immobility.

NTS is most commonly performed by physiotherapists and nurses, as a last-resort treatment when alternative, non-invasive and non-pharmacological modalities for secretion clearance have been unsuccessful (4,5). Examples for commonly applied non-invasive non-pharmacological treatments for secretion clearance are positioning, mobilisation, manually assisted cough, intermittent positive pressure breathing, and mechanical insufflation-exsufflation (2-5,7,8). For the purpose of this paper, NTS refers to the insertion of a flexible suction catheter (typically around 50 cm in length and with a diameter of 2-6 mm, *e.g.* Pennine Healthcare, Derby, England) to the patient's trachea. The suction catheter is inserted through either the nostril or the mouth, usually with the use of a nasopharyngeal or oropharyngeal (Guedel) airway, in a self-ventilating, non-intubated and non-tracheotomized patient (figure 1). NTS does not refer to suctioning of an intubated or tracheotomized patient, where the suction catheter is inserted through the endotracheal tube, tracheostomy tube, or a patent tracheostomy.

INSERT FIGURE 1 ABOUT HERE

In the United Kingdom, patients requiring NTS may receive hospital care under an agreed 'ceiling of treatment', which stipulates that the patient will receive active 'ward-based' treatment (intravenous antibiotics and fluids, supplemental high flow oxygen, humidification and nebulisation, intensive respiratory physiotherapy); but will not receive intubation and ventilation (*i.e.* intensive care level of treatment). Under these circumstances, NTS is often an important treatment modality for preventing progressive respiratory deterioration and arrest during an acute episode of care. Another clinical scenario, in which NTS may be applied, is assisted airway clearance following removal of an endotracheal tube (extubation) or tracheostomy tube (decannulation). Secretion clearance in patients with impaired but recovering cough may for a period of time be assisted through NTS, potentially preventing the need for re-intubation or re-insertion of a tracheostomy tube, and thus supporting a successful respiratory wean. In some healthcare systems, NTS may also be delivered preventatively as part of a 'bronchopulmonary hygiene' protocol for patients who are at high risk of developing acute hypersecretion and secretion retention.

NTS is regarded a core clinical skill within the scope of respiratory physiotherapy practice in the United Kingdom. But while NTS is a regularly performed and valuable procedure, it is also:

(a) a highly unpleasant procedure for patients, because it is performed without sedation or local anaesthetic (2,3,9);

(b) a blind invasive procedure, with risk of serious adverse events, such as hypoxaemia, bradycardia due to vagal stimulation, cardiac arrhythmia, bronchospasm, laryngospasm, introduction of pathogens to the lungs via the suction catheter, and trauma and bleeding from the mucosa or tracheal wall (1-3);

(c) an advanced technical skill, requiring staff training and practice for competent execution and skill maintenance (1-3).

These three aspects of NTS – negative patient experience, risk of adverse events, and technical skill required – provide the rationale for exploring a potential alternative that is non-invasive and carries much fewer risks; is convenient to adopt widely in clinical practice; and could achieve the same objective as NTS, but providing better patient experience.

THE HYPOTHESIS

It is hypothesized that instead of having to undergo NTS, a patient could clear retained lung secretions by inhaling nebulized capsaicin, which stimulates short-lived but vigorous bouts of reflex coughing. These bouts of reflex coughing could achieve movement of secretions from the lungs into the oropharynx, allowing the patient to spit out or have secretions cleared by suctioning from the oropharynx.

The application of capsaicin-induced reflex cough for this purpose presents a novel and original hypothesis, developed by the author and based on his clinical experience in respiratory physiotherapy and research experience in clinical neuroscience.

EVALUATION OF THE HYPOTHESIS

The hypothesis presented here is based on the following stepwise rationale:

(1) In health, respiratory secretions (phlegm, mucus) are cleared continuously from the lower airways into the oropharynx, mainly through the mucociliary escalator mechanism, supplemented by occasional clearing of the throat and infrequent coughs (8,10).

(2) If there is hypersecretion, cough becomes an increasingly important additional mechanism for clearing secretions from the lower airways (8,10).

(3) The mechanism by which cough achieves movement of respiratory secretions from the lungs into the oropharynx is high expiratory airflow during the expulsive

phase of cough. The resulting sheer forces achieve movement of secretions along the bronchi and trachea (8,10-12).

(4) Patients who require NTS are unable to effect sufficiently high expiratory cough flow in either volitional or spontaneous cough. But it is a common clinical observation that during NTS, patients will often exhibit reflex coughs in response to mechanical stimulation of the tracheal wall or carina by the suction catheter tip. These reflex coughs triggered during NTS often shift secretions from the bronchial tree towards the trachea, where they are suctioned; or achieve clearance of secretions from the lower airways into the oropharynx.

(5) It is hypothesized that instead of having to undergo NTS, a patient could inhale nebulized capsaicin. Vigorous capsaicin-induced reflex coughs could achieve movement of secretions from the lungs into the oropharynx, allowing the patient to spit out or have secretions cleared by suctioning from the oropharynx, thus avoiding the need for suction catheter penetration to the trachea.

Application of capsaicin in medical research and practice

Capsaicin is a component extracted from cayenne pepper, with the molecular formula $C_{18}H_{27}NO_3$ (13,14). Above a certain threshold, inhaled nebulized capsaicin will trigger reflex coughs in humans by acting on chemoreceptors in the lower airways (15-18). Since the 1980s, this property of capsaicin has been utilized for cough sensitivity testing in respiratory research (17). In cough sensitivity testing, nebulized irritants (most commonly citric acid, tartaric acid and capsaicin) are administered in increasing concentration and inhaled by the subject, until a reflex cough response is elicited (17). In this context, capsaicin has been administered to multitudes of healthy individuals and patients of different age groups over the years, including patients with asthma, chronic obstructive pulmonary disease, bronchiectasis, stroke and Parkinson's disease, with a documented high level of patient safety and no serious adverse events (15-25). The use of capsaicin for cough sensitivity testing is currently its only application in respiratory medicine and research. In a different application, capsaicin is utilized in topical analgesics for its neurotoxic and desensitizing properties (14).

Evidence in support of the hypothesis

Some data in support of the hypothesis are available from the author's previous research, in which 82 individuals with acute stroke underwent assessments of peak cough flow (PCF), an indicator of cough effectiveness (25,26).

Higher peak cough flow in reflex cough than volitional cough

PCF was assessed for both maximal volitional cough effort and capsaicin-induced reflex cough (25,26). A sub-group of 20 patients with weak volitional cough (mean PCF 220 L/min, SD 80) showed higher PCF during capsaicin-induced reflex cough than in maximal volitional cough (table 1). PCF of capsaicin-induced reflex cough was on average 184 L/min (SD 130) higher than PCF of subjects' maximal volitional cough effort. This suggests that capsaicin-induced reflex cough under such circumstances could be more effective in shifting excess respiratory secretions from the lungs into the oropharynx than volitional cough. These observed magnitudes of PCF of volitional and reflex cough also largely align with values of PCF that are thought to indicate the threshold for successful secretion clearance and which, depending on patient group and clinical scenario, range from 160 to 270 L/min (4,8,27,28)

INSERT TABLE 1 ABOUT HERE

The data shown in table 1 are from patient assessments, in which nebulized capsaicin was delivered in up to 12 rounds, starting at a concentration of 0.49 µMol/L and doubling in dose up to a maximum of 1,000 µMol/L. These are the same escalating concentrations used in the recommended standardized protocol for cough sensitivity testing (17). But while in cough sensitivity testing the aerosol is delivered during a single inspiration and timed to 1.2 seconds to ensure consistent dosage, stroke patients in the above study inhaled capsaicin for up to 60 seconds at each concentration. This is a relevant consideration for the proposed hypothesis. Midgren *et al*. observed in their study of capsaicin-induced cough in healthy humans (15) that subjects were able to continue breathing through 60 seconds of inhaling nebulized capsaicin, which was not possible with citric acid. Capsaicin therefore appears to lend itself to prolonged inhalation, which is an advantage for the application proposed here.

Cough augmentation through consecutive reflex cough bouts

It is suggested that the patient will inhale nebulized capsaicin at increasing concentrations through a facemask for 60 seconds at a time. When the threshold is reached, at which vigorous reflex coughs are elicited, it is envisaged that this will result in the cough pattern observed in the above study: a number of reflex coughs in rapid succession (observable in the cough flow-time trace as ‘cascades’ of reflex cough spikes) was followed by a deep inspiration, which in turn delivered more aerosol to the receptor sites and triggered a further reflex cough bout, and so on (figure 2). The physiological significance of this cough flow pattern is that during the first 'cascade' of reflex coughs the patient is likely to expel from their expiratory reserve volume, which increases the potential for the following inspiration to exceed the resting tidal volume, *i.e*. generate a greater pre-cough inspiratory volume for the following cough bout. Techniques for increasing pre-cough inspiratory volume are an important aspect of cough augmentation treatments (2,3,5,7,8), because greater inspiratory volume maximizes the potential for higher expiratory cough flow (29) and therefore effective secretion clearance. In addition, greater inspiratory volume bio-mechanically optimises the length-tension relationship of expiratory muscles and allows for higher intrathoracic pressure during the compression phase of cough (30). Figure 2 illustrates this effect in the cough flow trace of a stroke survivor with very weak volitional cough. In this example, the PCF of repeated maximal volitional cough efforts averaged 204 L/min, with a maximum of 276 L/min. In contrast, the PCF of repeated capsaicin-induced reflex coughs averaged 291 L/min, culminating in one particularly strong cough at 494 L/min PCF in the last of 4 cough bouts.

INSERT FIGURE 2 ABOUT HERE

Evidence against the hypothesis

As a potential limitation of the hypothesis, it may be considered that the proposed intervention is dependent on the integrity of the patient's cough reflex. Patients with diseases and conditions that impede the neurophysiology of reflex cough may therefore not show the hypothesized response of secretion clearance through capsaicin-induced reflex cough.

The main reflexogenic zones for cough are located in the larynx and the tracheobronchial tree, where capsaicin stimulates primarily unmyelinated C-fibres (6,16,31-33). Sensory afferents are conveyed via the superior laryngeal nerve and vagal afferents from the lower airways, and terminate in the tractus solitarii in the brainstem. From there, second-order neurons project extensively to the pontine and medullary respiratory centres. The efferent pathways of reflex cough lead via upper motor neurons to the spinal motor neurons supplying the inspiratory and expiratory muscles (effecting inspiratory and expiratory muscle action); via cranial motor neurons to the intrinsic laryngeal muscles (effecting co-ordinated glottis closing and opening); and via sympathetic and parasympathetic efferents to the smooth airway muscles (effecting bronchoconstriction) (18, 33,34).

Conditions causing structural and/or functional impairment of the cough reflex

Theoretically, any structural and/or functional impairment at any point of the cough reflex arc could lead to failure of the proposed intervention. For example, should there be decreased chemosensitivity to capsaicin or denervation of the sensory afferents, this could lead to an inability to elicit vigorous reflex cough bouts, even at the highest available concentration of capsaicin. Similarly, in conditions causing irreversible denervation and atrophy of respiratory muscles (*e.g.* motor neuron disease or cervical/thoracic spinal cord injury), it could be assumed that reflex cough is unlikely to be more effective for clearing secretions than volitional cough, as the (in)ability of the respiratory muscles to generate the necessary intrathoracic pressures would probably remain the same for both volitional and reflex cough. However, it may not be appropriate to reason deductively in this case, because current neurophysiological knowledge about reflex cough in humans derives mainly from animal models, and experimental evidence from human populations is rather limited (6,8,16,18).

Few studies have investigated reflex cough in those patient groups and under those circumstances that are relevant to the hypothesis presented here, for example in conditions that could be expected to disrupt cough sensory afferents (6). Smith and Wiles conducted a study in the 1990s (35), in which reflex cough sensitivity to capsaicin was assessed in 28 patients with different neurological diagnoses, including multiple sclerosis, encephalitis, motor neuron disorders, myopathy and myasthenia. Capsaicin was delivered in incremental concentrations from 7 to 2,000 µMol/L, and this was sufficient to elicit reflex coughs in all participants at an average concentration of 50.6 µMol/L. A comparison of cough sensitivity thresholds between those patients who, based on their diagnosis, were expected to have impaired pharyngeal or laryngeal sensory function and those that did not, did not show any difference in capsaicin responses. A more recent small study of 4 adults with traumatic brain injury showed that nebulized capsaicin at 200 µMol/L triggered reflex cough in all participants; although urge to cough and number of cough events were reduced in comparison with healthy norm reference values (36). The authors offer a discussion of the potential contributing factors, such as dampening of sensory inputs, central processing of these inputs, disrupted motor pathways, and/or peripheral muscle weakness and atrophy, including the possibility that surgical tracheostomy may have affected stimulus-induced cough in these individuals. In a similar vein, it has generally been assumed that lung transplantation leads to complete sensory and autonomic denervation of the airways, including loss of cough reflex. But recent observations indicate that with time there is the possibility of functional and structural restoration of reflex cough after lung transplantation (37).

Lower peak cough flow in reflex cough than volitional cough

With respect to PCF and effectiveness of reflex cough, Brandimore *et al*. (24) and Wheeler Hegland *et al*. (23) have investigated differences in respiratory kinematics and airflow between volitional cough and capsaicin-induced reflex cough. The authors examined various parameters in 25 healthy volunteers (24) and 20 patients with idiopathic Parkinson's disease (23). One finding, which is in conflict with, and therefore pertinent to the hypothesis presented here, is that in both groups of participants PCF of capsaicin-induced reflex cough was lower than PCF of volitional cough; and that in both studies about one fifth of participants did not respond to capsaicin. These findings may be explained by the fact that in these studies capsaicin was administered in one single dose (*i.e.* for one breath) and up to a maximum concentration of 200 µMol/L. Brandimore *et al*. emphasise that the method of elicitation of cough, whether reflex or volitional, results not only in neurophysiological differences, but also in kinematic and airflow differences (24). For the purpose of this hypothesis, it is therefore suggested that the contrary data presented above in support of the hypothesis can be explained by the difference in the administration of nebulized capsaicin (*i.e.* delivery of up to 1,000 µMol/L of capsaicin for up to 60 seconds at a time).

Attenuation of the cough reflex due to reduced level of consciousness

Lastly, some studies have examined reflex cough in patients with reduced level of consciousness. In their short report from 1994, Moulton and Pennycook (38) describe a sample of 76 patients admitted at the emergency department, who presented in a comatose state (Glasgow Coma Scale scores from 3 to 8) due to drug overdose, alcohol intoxication, head injury, post-ictal state, *etc*. The presence of cough reflex was assessed during airway management procedures such as suctioning, *i.e.* using a mechanosensory stimulus, and described as normal, attenuated or absent. While there were more observations of absent cough reflex in patients with lower levels of consciousness on the Glasgow Coma Scale, there were also patients in which cough reflex was present at the lowest level of consciousness (37). More recently, this study has been replicated in a larger sample of 208 patients admitted with trauma, poisoning, neurological and cardiorespiratory conditions, *etc*., and level of consciousness ranging from full (Glasgow Coma Scale score 15) to comatose (Glasgow Coma Scale score ≤8) (39). A higher proportion of attenuated and absent reflex cough was observed in patients with reduced level of consciousness; although about a quarter of comatose patients did exhibit a normal cough reflex. In the context of the hypothesis presented here, these findings are relevant in that they demonstrate that reflex cough is preserved in a proportion of individuals with reduced level of consciousness. However, in these studies cough was elicited by mechanosensory stimulation, and it may not be assumed that chemosensory stimulation with capsaicin would achieve the same outcome.

Testing the hypothesis

Literature searching

A thorough literature search was conducted in June 2016, and updated on an ongoing basis, using auto-alerts and manual re-runs. Electronic databases of indexed peer reviewed scientific journals (PubMed, CINAHL Plus, Embase, AMED, MAG Online Library, Web of Science, *etc*.), grey literature (NICE Evidence Search, OpenGrey), and registries of completed and ongoing clinical studies (NIHR Evaluation Trials and Studies portfolio, HRA/RES database of research summaries, ISCRTN registry, EU Clinical Trials Register, and ClinicalTrials.gov) were searched using relevant search terms. Of note, the search strategy also included the two commonly used alternative cough stimulants to capsaicin, citric and tartaric acid. Out of 3,792 results, 21 were reviewed in full-text, including recent systematic and narrative reviews of interventions for respiratory secretion management (7-9,28), and no evidence addressing the hypothesis was identified.

An applied and pragmatic experimental approach

The studies described above illustrate that there is limited experimental evidence available to answer the hypothesis deductively and based on existing neuro- and pathophysiological knowledge. Furthermore, the hypothesis applies to a scenario that clinicians approach with primarily problem-based clinical reasoning (*i.e*. addressing the problem of secretion retention and impaired airway clearance, against the background of the individual patient's medical diagnosis), as opposed to primarily diagnosis-based reasoning (*i.e.* focusing on the management of one particular medical diagnosis, against the background of its possible sequelae and problems). The hypothesis presented here is relevant to a variety of patient groups, and therefore it may be suggested that it should be understood as an applied clinical hypothesis (*i.e.* conceived and developed from observations in clinical practice and research), as opposed to a hypothesis that has been deduced primarily from (patho)physiological knowledge of one particular disease or condition. It follows that this should be reflected in the method of testing the hypothesis. It is therefore suggested that an applied and pragmatic experimental approach (*i.e.* trialling the proposed intervention in 'real life' clinical situations) is preferable over observational or experimental physiological studies, which may expand the theoretical knowledge base but are unlikely to yield data to verify or reject the hypothesis outright.

A Clinical Trial of an Investigational Medicinal Product (CTIMP)

The design of such an applied and pragmatic research approach could be modelled on the phases for development of new pharmaceutical products (40). From a regulatory standpoint, although the safety of nebulized capsaicin for the purpose of cough sensitivity testing in research has been well documented in the literature (20,21), the use of nebulized capsaicin in the application proposed here implies its use for curative purposes, and would therefore require development of the formulation according to procedures and regulatory standards for developing Investigational Medicinal Products (IMPs). To test the proposed application in the first instance, and corresponding to phase I of a Clinical Trial of an Investigational Medicinal Product (CTIMP), capsaicin-induced reflex cough could be trialled in a small number of patients, for example in a case series or cohort study design, with the main objective of establishing its safety and feasibility in this particular clinical context. Once safety and feasibility have been established, efficacy of the proposed intervention may then be investigated in a phase II pragmatic randomized controlled trial, leading on to a phase III trial to compare safety and effectiveness of the novel intervention against existing treatment modalities.

CONSEQUENCES OF THE HYPOTHESIS AND DISCUSSION

The hypothesis described here concerns NTS, a procedure that, although an important treatment modality in chest physiotherapy and respiratory care, presents a somewhat hidden area of clinical practice. This may account for the dearth of scientific publications and lack of research and development around NTS in the past.

Improved patient experience, commercial exploitation and health economic benefit

The proposed alternative to NTS has the potential to provide a convenient and safe non-invasive treatment modality for acute secretion retention and improve patient experience. As described above, this respiratory problem is not linked to any particular medical diagnosis. The intervention could therefore benefit neurologic, respiratory, geriatric, general medical and surgical patients, for example individuals with dysphagia and aspiration pneumonia, or patients who are deconditioned following a prolonged respiratory wean. This hypothesis also indicates the potential to re-purpose a known pharmaceutical substance (capsaicin) in a novel application, from which a number of possible consequences for health-economic impact may be considered. The potential for commercial exploitation, for example in developing a user-friendly capsaicin nebulizer 'kit', is obvious. In addition, the proposed intervention may provide a treatment option suitable for community settings. Due to safety considerations, NTS is rarely performed outside of hospital settings, but nebulized capsaicin could be applied, for example, in the community management of patients with recurrent episodes of hypersecretion and risk of acute secretion retention. This could deliver whole system savings through reduction of hospital bed days, in addition to improving patient comfort and convenience through offering an option for community management. Another possible consequence could be efficiencies in staff resources. As the clinical skill of administering nebulized capsaicin can be acquired and maintained more easily than NTS, savings could be realized through more efficient staff training and more widespread skill competency amongst members of physiotherapy or nursing staff, which could relieve more experienced and senior members of staff within a local health economy.

Conclusion

In conclusion, it is hypothesized that capsaicin-induced reflex cough could be used instead of NTS as a treatment for acute secretion retention in self-ventilating, non-intubated and non-tracheotomized patients. Some clinical data from a stroke trial are available to support the hypothesis, while some neuro- and pathophysiological considerations indicate potential limitations of the hypothesis. Because the hypothesis was conceived and developed based on observations from clinical practice and applied clinical research, it is suggested that a pragmatic and applied clinical research design is best suited to test the hypothesis.

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Figure 1. Placement of nasotracheal catheter for suctioning the tracheobronchial tree. Reproduced by the kind permission of Wolters Kluwer Health from Nettina SM. Lippincott Manual of Nursing Practice. 9th ed. London: Lippincott Williams & Wilkins. 2010. p. 233.

Figure 2. Cough pattern (flow-time trace) of a patient with stroke; (a) maximal volitional cough efforts showing 7 distinct cough spikes with mean (range) peak cough flow (PCF) of 204 L/min (113, 276); (b) capsaicin-induced reflex cough bouts showing 11 distinct cough spikes in 4 ‘cascades’ with mean (range) PCF of 291 L/min (203, 494).

Table 1. Comparison of peak cough flow of maximal volitional cough effort and capsaicin-induced reflex cough in 20 acute stroke patients. Data are from a subgroup of patients in a previous stroke trial (Kulnik et al, 2015).

Participant number*	Peak cough flow of maximal volitional cough effort (L/min)	Peak cough flow of capsaicin-induced reflex cough (L/min)	Difference (L/min)
01	129	414	285
06	254	347	93
07	271	329	58
15	319	500	181
20	170	400	230
22	176	512	336
24	395	559	164
25	255	306	51
26	77	579	502
27	237	504	267
34	269	410	141
42	167	194	27
43	333	371	38
46	131	433	302
49	200	336	136
51	232	419	187
58	285	319	34
67	184	557	373
71	116	314	198
76	206	276	70

* Participant number derived from original trial participant code