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LARYNGOLOGY: UPDATE ON DYSPHAGIA (H STARMER AND A RAMEAU, SECTION EDITORS)

A Primer on Hypotussic Cough: Mechanisms and Assessment

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Abstract

Purpose of Review This narrative review introduces key elements of cough neural control, function, dysfunction, and measurement for physicians and speech-language pathologists. Its goal is to guide integrated approaches to the assessment of cough and facilitate differential diagnosis of cough dysfunction among people with dysphagia.

Recent Findings Research has shown that cough and swallow dysfunction have high co-occurrence, especially in neurodegenerative populations. Both sensory and motor components of cough dysfunction can be evaluated using high and low-tech equipment (e.g., handheld peak flow meters). The evaluation of cough function is vital given the known benefit of targeted dystussia treatments for people with dysphagia.

Summary Intact airway protection requires both functional swallowing and cough. However, clinicians report that objective cough evaluations are not commonly included in assessments of airway protection. This review provides an overview of cough neurobiology, describes its measurement, and presents case vignettes to illustrate the benefits of integrating cough assessments into clinical settings.

Keywords Dystussia · Hypotussic cough · Dysphagia · Peak flow meters · Airway protection · Aspiration pneumonia

Introduction

A cough is an airway protective mechanism that serves to expel material from the upper and lower airways to ensure pulmonary clearance and health [1]. Hypotussic, or down-regulated cough, refers to the inability to adequately sense or effectively remove aspirate material that enters the airway, resulting in a high risk of aspiration pneumonia [2–6]. Aspiration pneumonia is a serious consequence which can lead to increased healthcare costs, decreased quality of life, increased mortality rates, and other adverse health outcomes [2–4, 7–13]. Aspiration pneumonia risk is also particularly high in the presence of disordered swallowing, which exists at the opposite end of the continuum of airway protection from cough [1, 9, 11, 14–19]. Many individuals with swallowing disorders, or dysphagia, are at risk for aspiration and demonstrate decreased sensitivity to detect foreign material that errantly enters the airway, also known as "silent" aspiration [18, 20–22]. Additionally, many individuals with dysphagia exhibit a reduced ability to cough effectively to expel foreign material from the airway, even when sensation is present [23–25]. When the sensory or motor components of cough are impaired in the presence of impaired swallowing function, aspirate is repeatedly introduced into the

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respiratory system and is unable to be removed, contributing to uncontrolled colonization of bacteria [26–28]. Therefore, it is of critical importance that clinicians who work with individuals at risk for dysphagia understand when it is appropriate to refer, evaluate, and treat these individuals for impairment of sensorimotor cough function.

At present, many clinicians who treat individuals with dysphagia report limited education related to cough [29•]. In fact, over 97% of speech-language pathologists (SLPs) surveyed in a recent study reported an interest in learning more about cough assessment [29•]. Therefore, the aim of this review is to provide a basic introduction to cough function, describe its neurobiology in both healthy and disordered cough, and focus on the implementation of cough assessments in clinical practice. We will then conclude this review with case vignettes to exemplify how cough assessments may facilitate differential diagnoses in airway protection deficits and impact dysphagia management.

The cough literature frequently categorizes cough behaviors as either voluntary or reflex. These labels are important to understand theoretically and are relevant for clinical practice and cough research. Voluntary cough is initiated on command (e.g., after a verbal cue to cough), whereas reflex cough is triggered in response to stimulation of the airway [22, 30•, 31, 32]. There are a variety of external or endogenous stimuli which can trigger a reflex cough, one of which is the introduction of aspirate into the airway. Reflex cough can also be stimulated by aerosolized materials inhaled into the airway, which is how reflex cough is typically studied in research settings. Despite these labels, reflex and voluntary cough behaviors do not always exist as discrete entities. It is known that there is some degree to which individuals can sense and potentially even modulate cough behaviors [33]. This also relates to an important feature of reflex cough, known as the “urge to cough” or UTC. The UTC is the intensity of a person’s perception of a cough-inducing laryngeal or tracheal stimulus and can contribute to the ability to either up or down-regulate the cough response [33–37]. For example, if a subject perceives a faint airway irritant, they might have the choice to either produce a strong cough, stimulate a throat clear, or suppress a response altogether. However, if a subject feels a strong laryngeal irritant, this may result in a reflex cough response that is more difficult to modulate or suppress.

Neurological Control of Cough

Cough is a behavior which typically involves the coordination of afferent laryngeal sensory mechanisms and efferent cortical, subcortical, and brainstem activation systems. Two types of neurons facilitate the transfer of somatosensory cough information: mechanoreceptors and chemoreceptors [38]. Mechanoreceptors, which are primarily located in the distal airways (i.e., lungs and bronchi), respond to mechanical pressure, specifically touch-like stimuli. They are often described as “cough receptors,” “irritant receptors,” or “rapidly adapting mechanoreceptors.” Chemoreceptors, on the other hand, are primarily located in the proximal airways (i.e., trachea and main bronchi). These neurons include slow-conducting unmyelinated C-fibers that selectively respond to chemical stimuli, such as capsaicin (a tussigenic, or cough-provoking, stimulus) [39, 40]. Chemoreceptors respond to different types of stimuli depending on the afferent pathway and are responsible for inducing cough via the jugular afferent pathway [41].

Brainstem Processing of Reflex Cough

Airway protective reflexes are first sensed through the stimulation of laryngeal and tracheobronchial irritant receptors as well as vagal inputs through pulmonary stretch receptors [42, 43]. Polysynaptic pathways responsible for the integration of afferent input and sequencing of the respiratory pump motor patterns exist in the caudal medullary raphe nuclei [42]. This pathway connects to dorsal (DRV) and ventral respiratory groups (VRG), which in turn have mutual interactions with several brainstem regions [42, 44]. Specific regions of the medulla and pons have been identified as key areas of the brainstem responsible for controlling the magnitude of respiratory muscle activation to produce a cough [42, 45, 46].

Central and Subcortical Control of Reflex Cough and Voluntary Cough

Studies have demonstrated that a UTC always precedes the activation of a reflex cough, and a UTC can be detected at lower thresholds than stimuli that would prompt reflex cough responses [34]. The UTC sensation is a process dependent on both discriminative (i.e., discrete components such as location) and affective (i.e., emotional) processing. This multifactorial process includes the integration of respiratory afferent information, respiratory motor drive, affective state, attention, experience, and learning [34, 35, 37, 47].

In conscious humans, respiratory afferent information associated with a UTC typically ascends from the brainstem to the cortex for higher-order processing prior to efferent motor output of reflex cough [35]. Brain regions including the orbitofrontal cortex, supplementary motor area, insula cortex, anterior midcingulate cortex, and cerebellum have been associated with the activation of an UTC [48]. Two unique pathways have been proposed in relation to the cortical and subcortical integration of UTC afferent pathways; however, it is generally understood that there is overlap and integration [41, 45, 49, 50]. Jugular or superior afferent pathways receive inputs from the proximal airways and then project to the paratrigeminal nucleus of the brainstem [51]. These then continue to the primary sensory cortex and are important in the perception of UTC [50]. Nodose or inferior afferent pathways first project to the nucleus tractus solitarius of the brainstem [34, 49]. From there, nuclei project to the orbitofrontal cortex, cingulate cortex, and other limbic regions [41, 48]. This pathway is important for many aspects of the sensorimotor cough response following airway irritation [50]. Subcortically, structures such as the cerebellum and basal ganglia are also involved in controlling the coordination, timing, amplitude, and force of movement, which plays an important role in the production of cough [41, 52–54].

Conceptually, voluntary and reflex cough represent similar rapid expulsive pulmonary clearing behaviors. However, research now supports distinct cortical pathways for these two cough archetypes [45, 55]. In contrast with reflex cough, which can occur solely through brainstem control, neuronal activation of voluntary cough activates desire motivational pathways [35]. These are primarily accessed through cortical and subcortical pathways, and include areas of the motor cortex, premotor cortex, supplementary motor area, insula, anterior and mid-cingulate cortex, ventral and dorsomedial thalamus, inferolateral sensorimotor cortex, and the striatum [44, 52].

Peripheral Motor Control of Cough

The production of an effective cough requires precise coordination across three distinct motoric phases: inspiration, compression, and expulsion [56]. In the inspiration phase, there is contraction of the external intercostal muscles, which brings the rib cage upward and outward, resulting in expansion of the thoracic cavity. This action results in a reduction in lung pressure, allowing up to 2.5 L of air to fill the lungs [57]. In the compression phase, the vocal folds are firmly pressed in the closed position through adduction of the laryngeal cricoarytenoid and transverse arytenoid muscles [57]. The internal intercostals also contract, and this motion is followed by the contraction of the abdominal muscles, which push against the diaphragm. The compression phase results in the generation of subglottic pressure of 100 mmHg or more, which is necessary to produce an effective cough response [57, 58]. In the third phase (expulsion), there is a sudden glottal opening followed by continued dynamic compression of the intra-thoracic region. Air velocity during this third expulsive phase can reach speeds of 75 to 100 miles per hour [57].

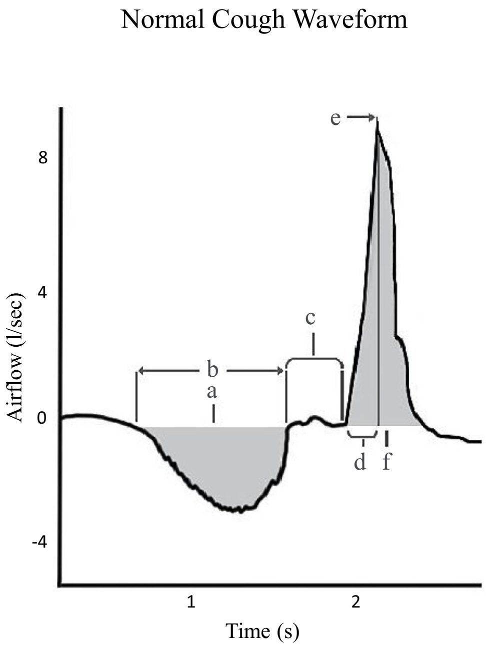
There are important physiologic differences between reflex and voluntary cough. For example, healthy adults typically initiate voluntary cough responses at higher lung volumes than reflex cough. Voluntary coughs are also associated with higher expulsive phase airflow rates (i.e., peak expiratory flow rate or PEFR; "e" in Fig. 1) [59]. Additionally, expiratory muscles tend to be activated sooner than accessory muscles during voluntary cough, whereas reflex cough demonstrates simultaneous activation of expiratory and accessory muscles and greater overall muscle activation for shorter periods of time [59].

In addition to the differences between reflex and voluntary cough, there are also functional and physiological differences between single and sequential coughs. This is notable because a reflex cough commonly forms a pattern including a sequence of expulsive cough events or a cough epoch [56]. While single coughs have been found to be effective at expelling debris from the upper airway, sequential coughs are more effective than single coughs at removing material from the lower airways [58, 60, 61]. This phenomenon is due to the dynamic compression that is generated during sequential cough production, which results in a reduction in the area of the tracheobronchial lumen and a subsequent increase in the velocity of airflow at the site of compression [60, 61].

Cough Measurement and Assessment

An effective cough response requires intact sensory and motor function as well as precise coordination of neural and peripheral mechanisms in order to effectively eject foreign material from the airway. Therefore, clinicians should consider both motor and sensory aspects when comprehensively evaluating cough. Several objective and patient-reported cough data can be obtained to measure cough sensorimotor function.

A subjective perceptual cough assessment is a widely used strategy that can be conducted as part of a clinical swallow evaluation [29•]. With this type of assessment, a patient would be asked to cough following a cue (e.g., "cough as if something went down the wrong pipe") [30•]. Cough effectiveness could then be subjectively described using words such as "weak" or "abnormal" [29•, 62]. However, recent research has demonstrated that perceptual ratings of cough effectiveness have only moderate interrater reliability [62, 63]. It is unclear whether this is because perceptual cough information is too inconsistent to be used as a proxy for objective measures, or because clinicians lack a universal rating system and training curriculum. In either case, the pitfalls of unstructured perceptual cough ratings highlight the need for more objective approaches to cough measurement.



Label	Cough Phase	Measurement	Abbreviation	Definition
a	Inspiration	Inspiratory volume	IV	The amount of air inspired prior to a cough
b		Inspiratory phase duration	IPD	The time from beginning of air intake to the closure of the glottis
c	Compression	Compression phase duration	CPD	The time from the closure of the glottis to re-opening of the glottis for the beginning of the expulsive phase
d	Expulsion	Peak expiratory flow rise time	PEFRT	The time from the start of the expulsive phase to the moment of maximum or peak expiratory flow
e		Peak expiratory flow rate	PEFR	The airflow rate at the maximal point in the cough episode
f		Cough expired volume	CEV	The total volume of expired air during the cough epoch
$\frac{e}{d}$		Cough volume acceleration	CVA	A measure derived from dividing PEFR by PEFRT

Fig. 1 A cough waveform is frequently used to represent and measure cough airflow parameters related to the cough phases of inspiration (**a** and **b**), compression (**c**), and expulsion (**d**–**f**) via spirometry. In this graph, the y-axis represents the airflow velocity measurement in liters per second, while the x-axis represents time in seconds. As one breathes in for the inspiratory phase, the graph slopes in the negative direction, indicating airflow into the lungs. During the compression phase, the waveform slope should become relatively flat, representing no change in airflow rate. Then, as the expulsive phase begins, the waveform slopes in the positive direction rapidly arriving at a peak. The peak then quickly returns to baseline as a breath is returned to the lungs after the cough is completed

Cough Airflow Measurements

Spirometry is the gold standard for lung function measurement. It can be used to provide quantitative data on the strength and coordination of various cough components (Fig. 1). A spirometry setup includes a pneumotachograph, which can be outfitted onto a facemask that covers the subject's nose and mouth. This then is connected via tubing to hardware for data acquisition and software to visualize the cough airflow. Unfortunately, cost and lack of portability remain barriers to the collection and analysis of spirometry data in most clinical practices which assess and treat dysphagia.

Fortunately, research has supported the use of handheld peak flow meters in place of the gold standard pneumotachograph, with no statistical differences found in mean peak cough airflow [22, 64]. Cough peak flow rates can be obtained with small analog or digital peak flow meters without significantly affecting reliability [22, 64]. These devices are cost-effective, portable, and easy-to-use. They provide a single numeric data point: PEFR ('e' in Fig. 1). This objective measure of cough strength has been found to be correlated with the ability to clear aspirated material from the airway [30•]. Obtaining PEFR has the potential to be a robust clinical tool, as objective data can be compared to normative ranges in healthy adults and tracked over time to examine disease progression or improvement with treatment [65, 66].

Reflex Cough Testing

The assessment of reflex cough typically involves administering cough-inducing, or tussive, agents to assess reflex cough sensory and motor integrity. These tussive agents are airway irritants, and they can be aerosolized and delivered to the airway in measured concentrations. In the case of hypotussic cough evaluation, these tussive agents are typically meant to imitate aspiration [67]. To obtain these measurements, a nebulizer, dosimeter, and compressor can be utilized in-line with a spirometry system. The nebulizer and compressor work to create and administer specific concentrations of aerosol particles, while a dosimeter can be used to time its delivery with inspiration [68]. Tussive agents that are most frequently used include capsaicin or citric acid [69]. When assessing reflex cough, key outcomes often include the presence or absence of a cough to a particular concentration of tussive agent (i.e., indicative of an intact sensory response), as well as cough airflow outcomes of interest (e.g., the strength of the motor response). Interestingly, even something as simple as the presence or absence of a cough reflex has been shown to be difficult for experienced clinicians to judge based on audiovisual information alone [62]. Therefore, there is a need for clear guidelines and training if this type of testing is to be adopted in a clinical setting.

Cough reflex testing (CRT) is a specific approach to the assessment of reflex cough which has garnered significant research and clinical interest. This type of measurement can be used to determine the lowest amount of tussive stimulus that elicits a consistent cough reflex [35, 69, 70]. CRT measurements can either be obtained to find the natural cough threshold at the lowest stimulus dose, or to find the threshold at which cough can no longer be suppressed [37, 71]. This is clinically relevant because research has found that lowered cough reflex thresholds are associated with a higher aspiration risk for individuals with dysphagia [2]. Additionally, CRT has been found to improve the sensitivity of instrumental assessments of swallowing to identify individuals at risk for silent aspiration [72, 73]. For this reason, it has become increasingly incorporated in clinical dysphagia care in countries such as New Zealand, Australia, Japan, and the UK [74, 75]. For a full description of a CRT protocol, see Wallace et al. [76•]. However, there is still work that needs to be done in comparing cough reflex thresholds across patient populations, and to understand how this can be used to guide clinical dysphagia practices [69, 74, 77•, 78, 79].

While understanding cough reflex thresholds across a variety of patient populations is important to further our understanding of cough sensitivity and aspiration risk, in the United States this type of testing is largely limited to research settings. This is in part due to the high cost associated with this equipment, as well as the lack of familiarity with cough measurement in the United States in general [29•]. However, a cheaper and more portable form of delivery can potentially be achieved with a portable or handheld nebulizer device. Some research on handheld nebulizers has revealed reliable cough thresholds in healthy controls as well as those at risk for aspiration [67, 80–82]. Additionally, using aerosolized solutions of distilled water (e.g., fog) in cough reflex testing can offer an appealing option for facilities with restrictions on other forms of tussigenic stimulation, though some studies have shown measurement variability with fog, potentially due to differences in nebulizer output [82–84]. Research is ongoing to develop the ideal methodology for a sensitive, specific, and feasible reflex cough assessment protocol that will be widely accessible in the United States.

Instrumental Assessments of Swallowing

Cough effectiveness can also be assessed during instrumental assessments of swallowing. When airway invasion occurs, patients can be asked to assess their UTC using a modified Borg CR10 scale [85]. This will provide information about whether the patient is sensing the aspirate or penetrant but are not responding effectively or whether they do not perceive the airway invasion at all. The UTC can also be used to assess the perception of cough inducing stimuli during reflex cough testing. Additionally, the effectiveness of a reflex cough or voluntary cough following airway invasion can be assessed by utilizing the penetration-aspiration scale (PAS) or visual analysis of swallowing efficiency and safety (VASES) outcomes to report changes in laryngeal residue from before to after the cough [86, 87].

Clinical Case Vignettes

Here, we briefly summarize the literature on hypotussic cough in three key clinical populations: amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and head and neck cancer (HNC). Clinical case vignettes will highlight the assessment of different cough profiles within a variety of clinical settings and the integration of these findings into a comprehensive airway protection (i.e., dysphagia and dystussia) management plan.

Clinical Case Vignette 1: Amyotrophic Lateral Sclerosis (ALS)

ALS is a neurodegenerative disease of the upper motor neurons of the cortex, and the lower motor neurons of the brainstem and spinal cord which results in global weakness [88, 89]. At disease onset, this corresponds with more focal weaknesses in the limbs or as bulbar symptoms, but the progressive course continues to global weakness. Mortality in ALS is primarily due to pneumonia-related complications resulting in respiratory failure [90]. Relatedly, it is known that individuals with bulbar ALS are at greater risk for airway protection impairments including dysphagia and dystussia [64, 91].

A 55-year-old female with a 1-year history of bulbar-onset ALS presents to an interdisciplinary clinic appointment. She consumes an unrestricted regular diet with thin liquids at home. The patient has recently lost around 30 lb and reports fatigue during meals as well as difficulty swallowing liquids. As a part of the interdisciplinary evaluation, the patient completes a cough evaluation with a handheld peak flow meter. The patient's maximum PEFR out of 5 trials is 2 L/s, which is associated with an increase in risk for airway invasion in the ALS population (PEFR < 3.97 L/s) [31]. Additionally, this value is well below thresholds which has been determined to promote cough clearance of aspirate material in a heterogenous group of individuals with neurodegenerative diseases. For example, clinically meaningful cutoffs for effective airway clearance in the literature are values greater than 3.23 L/s [30•].

Clinical Takeaways

Low-tech and cost-effective evaluation of cough with a handheld peak flow meter can serve to identify patients at risk for airway invasion, distinguish patients whose cough is too weak to clear aspirate material, and serve as a baseline measure to track changes in cough due to disease or treatment.

Clinical Case Vignette 2: Parkinson's Disease (PD)

PD is a neurodegenerative disorder involving the loss of dopaminergic neurons in the substantia nigra pars compacta [54]. The substantia nigra pars compacta is one of several circuits of the basal ganglia, and the progressive reduction of dopaminergic neurons in this brain region contributes to bradykinesia (e.g., slowness of movement) and increased muscle tone (e.g., rigidity), which are common symptoms of PD that affect movement timing and amplitude [41, 54, 92, 93]. These impairments also contribute to the high prevalence of dysphagia and dystussia in PD, likely due to sensory and neuromotor changes [20, 32, 70, 94–96]. It is also well-documented that individuals with PD are known to underreport dysphagia due to these sensory impairments [97].

A 65-year-old male with a 5-year history of PD and dysphagia presents to an SLP clinic for a comprehensive evaluation of airway protective function. An instrumental assessment of swallowing identifies consistent aspiration of thin liquids without a cough response and with blunted UTC. When cued to perform a voluntary cough to clear the aspirate material, the patient's cough is ineffective. The patient's maximum PEFR out of 5 trials is 3.5 L/s, which is associated with increased risk of airway invasion in PD (PEFR values of < 7.49 L/s are associated with penetration, while values < 5.24 L/s are associated with aspiration) [30•, 32, 70, 94, 96]. However, the patient's maximum expiratory pressure (MEP) is adequate at 120 cm H_2O [98].

Clinical Takeaways

In this individual with PD, the comprehensive evaluation of airway protection revealed the presence of airway invasion in the context of disordered cough. Specifically, cough function was ineffective in clearing airway invasion, UTC was blunted, PEFR was low, but MEP was adequate. Given the results of the evaluation, the patient's diagnosis, and likely pathophysiology of dysfunction, future treatment should target both swallowing and cough. Specifically, improved perception of cough stimuli and enhanced coordination of cough with cough skill training should be considered for this patient [99•, 100•, 101•].

Clinical Case Vignette 3: Head and Neck Cancer (HNC)

Physiological changes in HNC are mainly peripheral in nature [102]. The extent of these changes may depend on adjuvant therapies including radiation, chemotherapy, or surgery. Acute and long-term toxicities associated with airway protection deficits in HNC include pain, edema, salivary changes, fibrosis, and mucositis [17, 103–110]. Emerging research in cough testing has demonstrated that sensory changes in the upper airway can contribute to reduced sensation of penetrated and aspirated material [25].

A 70-year-old male patient with a diagnosis of HNC presents to a laryngology clinic. This patient has recently completed primary chemoradiation treatment for a posterior lingual mass. The patient reports no difficulty swallowing solids or liquids during meals but has had pneumonia recently. The ENT completes an examination which reveals increased post-radiation fibrosis of the oral and pharyngeal structures. The ENT refers this patient to SLP services. During this patient's SLP visit, PEFR trials with a handheld peak flow meter reveal cough inefficiency with a maximum peak flow value of 4.0 L/s across 5 trials. MEP is also found to be inadequate at 45 cmH_2O. Research has demonstrated that peak flow values less than 6.3 L/s and MEP values less than 100.8 cm H_2O are associated with aspiration risk in the head and neck cancer population [25]. Further swallowing assessment is planned to follow this initial cough assessment, given these findings as well as the clinical history of repeated pneumonia.

Clinical Takeaways

The pathophysiology of HNC and its associated treatments including chemoradiation can contribute to reduced force and range of oropharyngeal structures, which can impact both swallow safety and cough effectiveness. Treatment approaches such as expiratory muscle strength training may be an appropriate option to consider for these patients [111].

Conclusions

This narrative review aims to provide clinicians with a framework for the neurobiology of cough as well as how the measurement of sensorimotor cough function can be assessed with a variety of equipment and measurement approaches. Clinically, increasing the utilization of structured assessment of cough sensation and motor function can help to identify and treat disordered airway protection across a variety of populations at risk for dysphagia. Additionally, it is beneficial for allied providers, including referring physicians, to understand ways in which SLPs can offer cough assessment and treatment with the goal of reducing the incidence of aspiration pneumonia and improving the health and quality of life in patients with dysphagia.

Declarations

Conflict of Interest Dr. Troche reports the following: *Financial*: Salary — employment — Teachers College, NIH/NINDS — grant, and MedBridge Inc. — Royalty — Consulting. *Non-financial*: Dysphagia Research Society — professional — board membership, and Journal of Speech Language and Hearing Research — editorial board member. The other authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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