ORIGINAL PAPER

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Involuntary cough is superior to voluntary cough for identifying stress urinary incontinence

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Introduction Voluntary cough (VC) and the laryngeal expiration reflex (LER) provoke stress urinary incontinence (SUI). The aim of this article is to analyze the effectiveness of these stimuli on the timing of urinary leaks.

Material and methods Urodynamic testing using pressure catheters was performed on 123 subjects with history of SUI. The LER was triggered using the induced reflex cough test (iRCT). Each subject was tested with VC and LER and leaked with one or both stimuli. The occurrence and timing of leaks were recorded.

Results The peak and average intra-abdominal pressures were 16–19% greater for LER compared to VC. Of the 123 subjects, LER caused leak in 118 (96%), VC in 71 (58%) and both in 66 (54%). For LER compared to VC, leak was more likely to occur during or immediately after the first expiratory effort. The electromyogram for VC and LER were similar.

Conclusions The iRCT reliably initiated the LER and triggered SUI more effectively than VC. During VC, the smooth muscle of the internal urethral sphincter (IUS) starts to contract during inspiration, and constriction of the IUS continues into the expiratory phase; this increased urethral tonicity would lessen the likelihood of SUI. We refer to this as the inspiration closure reflex (ICR). With LER the inspiration would not take place, and the first expiratory effort would be against a non-constricted IUS, making leak more likely. Our findings disprove the pressure transmission theory. The internal and external urethral sphincters may both increase urethral closure pressure and resistance.

Key Words: cough ‹› stress urinary incontinence ‹› urethra ‹› urodynamics

INTRODUCTION

The laryngeal expiratory reflex (LER) provides involuntary neurological protection of the upper airway and prevents significant aspiration of food, fluid or medication into the lungs. The LER can be elicited by an inhalation of a nebulized 20% tartaric acid solution [1]. The LER and voluntary cough (VC) have distinctly different neurophysiological mechanisms [2–4]. VC is defined as an event that starts with an inspiratory effort that leads to lung inflation, followed by a forced expiration initially against a closed glottis [5]. Subjects are usually instructed to "take a deep breath in and then cough". The LER lacks this initial inspiration [2–4]. Stimulation of the induced reflex cough test (iRCT) triggers an abrupt series of expiratory events ('cough epoch'), which clears the upper airway of potential noxious stimuli, i.e. food or fluid. This neurological event mimics that seen with temporary aspiration of food or fluid into the supraglottic region of the larynx. Abrupt reflex coughing or sneezing often precede leakage of urine in women, who may have stress urinary incontinence (SUI).
We hypothesize that the neurological differences between VC and LER provocation might have different potencies in causing urinary leakage in subjects with

SUI. The distinction between VC and LER as provocative tests in patients with the primary complaint of SUI has not been reported.

MATERIAL AND METHODS

After institutional review board (IRB) and United States Food and Drug Administration (USFDA) approval and informed consent, 123 female subjects between the ages of 18 and 75 were enrolled. This study is a cohort of a ten site, double-blinded, crossover, randomized control trial that was approved by the FDA. All subjects had demonstrated urinary leakage, i.e. SUI, during either VC or LER maneuvers or both. Cystometrogram with surface electromyogram (EMG) was performed using a Lumax TS Pro with disposable bladder and rectal fiber-optic catheters, and pelvic floor EMG (Cooper Surgical Trumbull, CT). Using sterile technique, the calibrated bladder catheter was placed and secured to the subject's thigh. With continuous dual-channel recording, the subject's bladder was filled slowly with sterile water until 200 ml had been introduced.

For VC, the subjects were asked to take a deep breath and then give a strong cough; this was repeated a minimum of three times. Each cough effort may have consisted of several coughs. The VC responses were recorded on the urodynamic (UD) system. The LER was tested using the iRCT, which used a jet nebulizer (Pari®, Starnberg, Germany) to deliver a concentration of 20% L-(+)-tartaric acid dissolved in 0.15 mM sterile NaCl solution (Nephron Pharmaceuticals, Orlando, FL). The jet nebulizer was activated with 50 PSI from a portable oxygen tank that produced an average droplet diameter of 1–2 μm or smaller. The dose per inhalation was 5.8 mg tartaric acid. The subject was asked to exhale completely while the nostrils were pinched closed. The nebulizer mouthpiece was placed in the mouth, and the subjects sealed the mouthpiece with their lips during the brisk inhalation. The LER normally consists of an immediate series of expiratory efforts, a 'cough epoch'. During VC and LER, the intravesicular pressure, rectal pressure and pelvic EMG were simultaneously recorded for all subjects [6]. The order of VC and LER was randomized. The examiner wore noise-canceling headphones and was blinded to the type of cough being tested by a screen. Timing of every urinary leakage observed was marked on the record by the examiner with an electrical switch. Small, unidentified delays between leaks and the examiner's leakage marks on the tracings were noted for VC and LER.

Analysis of the intra-abdominal pressure (IAP) response. Graphs from the original UD assessments were digitized (10 samples/sec) for both VC and LER, and the intra-abdominal pressures (IAPs) generated during the cough were quantified. Each cough epoch was analyzed throughout its duration. Positive deviation from baseline IAP defined the start of the cough epoch. The end of a cough epoch was noted on the UD tracing when the IAP returned to approximate baseline levels. A graphic recording of pressure with vertical timelines was used to determine the peak IAPs (maximum intravesicular or rectal pressure during each expiratory cough effort, cmH_2O), the mean IAP (over the period of the expiratory cough efforts, cmH_2O), the durations of the cough epochs, the number of IAP peaks, and the peak values for each cough epoch. The area under the curve (AUC) values were derived from each cough epoch by the numerical integration of intravesicular or rectal pressure over time using Boole's rule [7]. In this study, AUC is a product of pressure and time, expressed as $cmH_2O \cdot s$.

Vertical lines were added to the records to identify particular timings; those in red indicated leak. Student's paired T-test was used for parametric analysis, and McNemar's test for nonparametric analysis using SPSS (Statistical Package for the Social Sciences) statistical software (version 10.0.5). Pressure and latency values are stated as means ±standard deviation (SD).

RESULTS

Analysis of the 123 subjects showed that mean values of peak and average IAP were 19% and 16% greater respectively during the LER than with VC (Table 1). For AUCs, those with LER were 54% greater than for VC, reflecting the longer duration of the epochs. Figure 1 illustrates the response of a subject, who leaked with LER but not VC. The peak IAPs were 131.7 and 138.3 cmH_2O. The average IAPs were 61.6 and 55.7 cmH_2O. The AUCs were 159 and 362 $cmH_2O \cdot s$ for the VC and the LER, respectively. In Figure 1, only the LER caused leak, which occurred during the first expiratory phase.

To compare leak latencies between VC and LER, we analyzed the results for the 66 subjects, who had SUI with both stimuli. Thus, each subject had matched tests. We measured the total number of expiratory efforts and leaks for each VC and LER stimulus. For VC, the mean number of leaks was 2.52 ±1.24, and for LER 4.63 ±1.69 (+84%, $P < 0.005$). With matched pairs, 42 subjects had more leaks with LER than VC; 5 had more for VC than LER; and 19 had equal number of leaks ($P < 0.005$). The mean number of expiratory efforts for VC was 4.15 ±1.45 and for LER was 6.48 ±2.65 (+56 %, $P < 0.005$). The mean expiratory efforts correspond well with AUC: VC 564 ±408, LER 843 ±534 $cmH_2O \cdot s$ (+49%, $P < 0.005$) (Table 1).

Compared to VC, the LER caused 84% more leaks and 56% more expiratory efforts.

For all 66 subjects who leaked with both tests, the latency from the start of the first expulsive phase of VC or LER to the leak was longer with VC than with LER in 45 (68%) subjects. For 17 (26%) subjects, there were longer latencies for LER than for VC, and 4 (6%) subjects had equal latencies. The mean leak latency time for LER was 3.78 ±3.21 sec and for VC 5.26 ±4.15 sec ($P < 0.005$). Similar values and statistical significances were obtained when the results of all 123 subjects were analyzed.

Analysis of the records suggested that this timing difference was related mainly to leak during or immediately after the initial expulsive efforts of the VC and LER. To assess this possibility, we further analyzed the records of all 123 subjects. The LER induced SUI in 118 (96%), VC in 71 (58%) and both in 66 (54%) subjects (Table 1). There was a significant difference ($P < 0.005$) with early leak in the first expulsive phase occurring more frequently with LER than with VC. The pelvic EMG recordings for VC and LER were similar during expiration and indicated somatic motor responses.

Figure 2 shows tracings of a subject with moderate to severe SUI, who leaked with both tests. For VC and LER respectively, the peak IAPs were 122.4 and 85.8 cmH_2O. The average IAPs were 52.1 and 34.5 cmH_2O. The AUCs were 449 and 404 $cmH_2O \cdot s$. Although the VC pressure values were greater than those for LER, the VC leak occurred after the expiratory efforts, and the LER leaks occurred early in the first compressive phase of the first and subsequent epochs. Latencies were 3.0 sec for VC and 0.5 sec for LER.

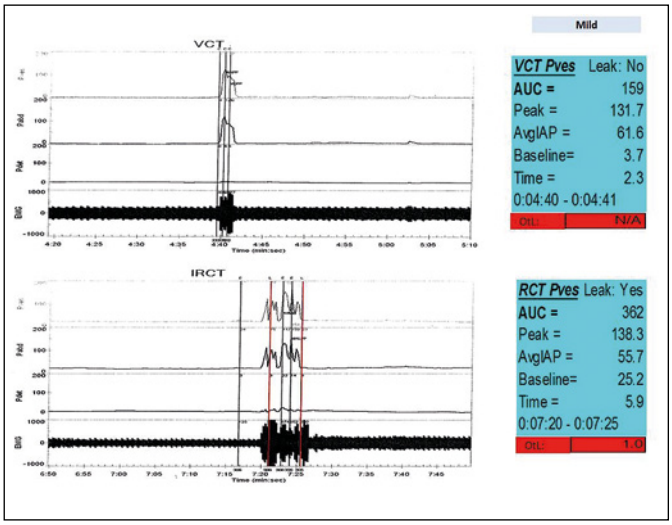

Figure 1. *Records of voluntary cough (VC) (above) and laryngeal expiratory reflex (LER) (below) in a subject. Traces from above down: intravesicular pressure, intra-abdominal (rectal) pressure, pressure in the detrusor muscle, pelvic floor electromyogram (EMG), time marks in seconds. The vertical lines are timing and signal marks, those in red signal leaks of urine. The panels on the right indicate the measured variables. In the upper record VC consisted of a single expiratory effort, and there was no urinary leak. In the lower record the LER consisted of several expiratory efforts and two leaks (red vertical lines), the first occurring just after the first expiratory phase. Note that the peak and average intra-abdominal pressures (IAPs) were very similar. The pelvic EMG demonstrated somatic motor activation with expiration.*

VCT – voluntary cough test; AUC – area under the curve; Avg IAP – average intra-abdominal pressure; VC – voluntary cough; LER – laryngeal expiration reflex; EMG – electromyogram; IAPs – intra-abdominal pressures

Table 1. *Voluntary cough (VC) and laryngeal expiration reflex (LER) peak and average intra-abdominal pressures (IAPs) and areas under the curve (AUCs) in 123 subjects who responded with leak to VC or LER or both (first two columns). Values are means ±standard deviations (SDs). The fourth row sums the results for all subjects. When considering all subjects (whether or not leak occurred), mean peak IAP, mean average IAP, and mean AUC were all higher for LER than with VC. The percentage increase for LER relative to VC with all 3 of these parameters is shown in row 5. The average responses with LER were greater than those with VC. *P <0.01 for LER compared with VC*

Leak Response		N	Peak IAP (cmH_2O)		Average IAP (cmH_2O)		AUC ($cmH_2O \cdot s$)	
VC	LER		VC	LER	VC	LER	VC	LER
+	+	66	141.4 ±25.6	165.6 ±33.1*	50.3 ±17.2	58.4 ±14.3*	564 ±408	843 ±534*
+	-	5	117.6 ±25.7	124.7 ±47.0	43.3 ±18.5	64.2 ±15.3	668 ±331	379 ±186
-	+	52	125.5 ±20.7	154.8 ±21.3*	44.4 ±14.9	50.2 ±15.3*	582 ±268	987 ±421*
Total		123	133.7 ±25.4	159.3 ±29.8*	47.5 ±17.2	55.2 ±14.8*	576 ±352	885 ±473*
				+19%*		+ 16%*		+54%*

VC – voluntary cough; LER – laryngeal expiration reflex; IAPs – intra-abdominal pressures; AUCs – areas under the curve; SDs – standard deviations; IAP – intra-abdominal pressure; AUC – area under the curve

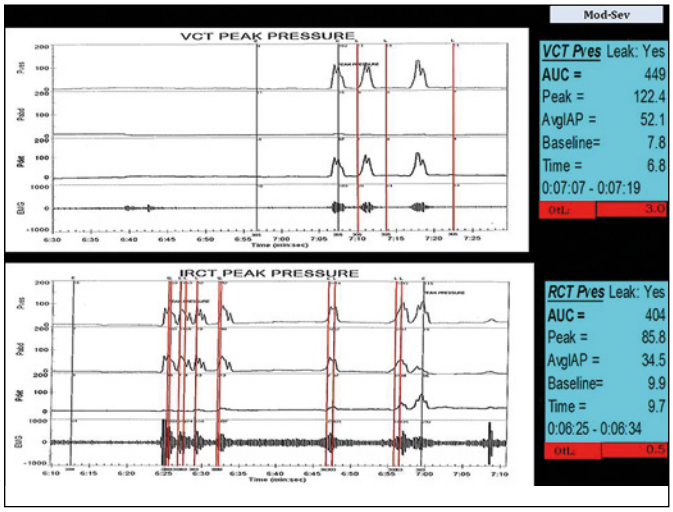

Figure 2. *In the upper record voluntary cough (VC) caused three expiratory efforts, and three leaks, the first occurring about 4 seconds after the start of the first expiratory effort. In the lower record, expiration reflex caused 5 leaks during the first epoch, the first occurring about 1 second after the start of the first expiratory phase. Note that the peak and average pressures were greater with VC than laryngeal expiration reflex (LER). Note also that the rectal catheter was displaced giving a pressure result of zero, thus the 'detrusor pressure' reflects the intra-abdominal pressure (IAP). The pelvic electromyogram (EMG) demonstrated somatic motor activation with expiration.*

VCT – voluntary cough test; EMG – electromyogram; iRCT – induced reflex cough test; AUC – area under the curve; AvgIAP – average intra-abdominal pressures; RCT Pres – reflex cough test pressure; VC – voluntary cough; LER – laryngeal expiration reflex; IAP – intra-abdominal pressures

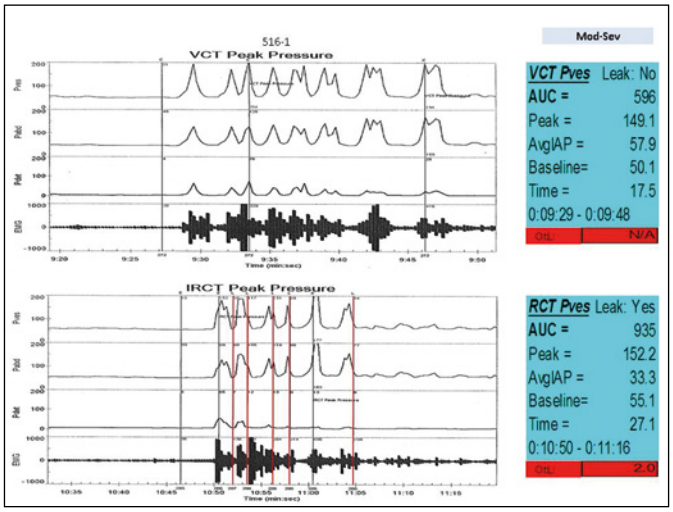

Figure 3. *Demonstrates a moderate-severe stress urinary incontinence (SUI) subject that did not leak on voluntary cough (VC) despite multiple frequent cough efforts. In contrast LER causes repeated leaks, during most of the expirations, despite average IAPs being less for LER compared to VC. The pelvic EMG demonstrated somatic motor activation with expiration. Used with permission.*

VCT – voluntary cough test; AvgIAP – average intra-abdominal pressures; RCT Pres – reflex cough test pressure; AUC – area under the curve; EMG – electromyogram; SUI – stress urinary incontinence; VC – voluntary cough; LER – laryngeal expiration reflex; EMG – electromyogram

Figure 3 (records as in Figures 1 and 2) demonstrates a moderate-severe SUI subject that did not leak on VC despite multiple strong cough efforts. Although the average IAPs were less for LER than VC, LER caused repeated leaks.

DISCUSSION

The LER caused significantly more leaks and had an earlier onset in the expiratory event than VC. This finding indicated that using the LER to stimulate an involuntary cough reflex identified subjects with SUI more reliably than VC provocation. The SUI results suggest neurophysiologic differences in the urethral function for the VC and LER events.

The differences in IAPs cannot explain the increased occurrence of leaks in the first expiratory phase of LER compared with VC. The latency of the LER from a laryngeal stimulus to abdominal muscle contraction is about 20 msec in humans and cats [8, 9]. This is too rapid to permit the smooth muscle of the urethral sphincter to contract during the first expiratory effort of the LER. However, VC latency from the start of the inspiratory phase to the expiratory effort is usually about 1 second [5], which would allow contraction of the IUS smooth muscle, which continues into the following expiratory phase, and prevents urinary leakage. In women with SUI, the number of leaks depends on fatigue of the striated muscles of the pelvic floor and the external urethral sphincter (EUS) [10]. Whether the smooth muscle of the IUS also shows fatigue has not been studied, but fatigue is not a property typical of smooth muscle. The LER does not appear to allow the IUS to have a latent closure phase, because there is no significant inspiration during the expiratory cough epoch.

In vitro smooth muscle preparations have slow latencies (100s of msec, or sec) from nerve stimulation to muscle contraction and subsequent relaxation [11, 12]. In vivo induced contraction of the IUS may require a few hundred milliseconds to reach peak and the same to reach trough baseline [13]. In VC, the IUS contracts 200–400 msec before abdominal pressure starts to increase, i.e. during the inspiratory phase of VC [14, 15]. In the sneeze of rats and cats, which mimics VC in that it consists of an initial inspiration followed by a strong expiration, the IUS

starts to contract before abdominal pressure increases [16, 17]. Kamo et al. demonstrated that a spontaneously breathing rat, with an open abdomen, had a mid-urethral pressure elevation with inspiration during sneeze without significant mid-IUS pressure elevation from the expiration [17]. The open abdomen would not allow pressure transmission to the IUS as the cause of the IUS pressure elevation.

The pressure transmission theory (PTT) states that a rise in abdominal pressure compresses and closes the urethra [18]. The PTT has been subtly applied in varying forms by the 'hammock hypothesis' [19]. Pressure transmission cannot explain the rise in mid-urethral pressure prior to a voluntary cough [16, 20]. The PTT does not agree with other reports which calculated that a significant increase in IAP would be required to physically stretch the urethral wall [21]. The findings in this report also dispute the PTT.

Petros and Ulmsten recorded greater pressure inside the urethra than outside during a mid-urethral sling operation performed under local anesthesia (Table 2) [22, 23]. Petros et al. emphasized that closure was a consequence of raised intra-urethral resistance, not pressure (Poiseuille's Law), and that halving the radius (r/2) increases the expulsion force required by a factor of 16 [24].

The inspiration closure reflex (ICR) may represent the neurophysiological control mechanism, in part, for the generation of the smooth muscle IUS resting maximal urethral closure pressure (MUCP) measurement in UD testing with quiet breathing. The neurological mechanism leading to the resting MUCP data, which is much studied and reported in the literature, is unclear. Mid-IUS closure pressure elevation preceding quiet respiratory muscle activation disputes a pressure transmission wave from the abdomen as the cause of the MUCP [20].

The pelvic floor EMG did not appear to activate during the inspiration phase in any of the subjects tested, but activated during the cough epochs as a somatic motor response. This indicates that the pelvic floor muscles are not reflexively activated in the preparatory phase prior to an LER or VC elevated IAP event. This indicates that an MUCP's origin is not from pelvic floor or EUS skeletal muscle activation, during quiet breathing, but more likely from autonomic mid-IUS smooth muscle closure.

If respiration activates the intrinsic sphincter closure events, it would seem logical that it could be an extension of the Hering-Breuer respiratory reflex driven by pulmonary vagal afferents [20, 25]. The relationship of respiration and the ICR activating intrinsic smooth muscle sphincters requires further study.

Table 2. *Demonstrates increased pressure inside the urethra compared to outside with the vagina intact with voluntary cough. This supports closure mechanisms elevating the pressure inside the urethra*

Patient	Outside bladder (T_1)	Inside bladder (T_2)	Outside urethra (T_1)	Inside urethra (T_2)
ER	30.00	26.00	18.00	23.00
KW	22.00	20.00	4.00	10.00
PB	75.00	73.00	40.00	60.00
TH	70.00	65.00	80.00	100.00
MF	22.00	19.00	24.00	45.00
Mean	44.00	41.00	33.00	47.60

*T1 is positioned outside the organ, and T2 inside the organ

Testing the LER is under the review of the FDA and should not be used clinically until approved. Measurement of the LER, by summation of the involuntary cough epoch, may help standardize SUI identification and add information regarding the severity. The indications for LER testing, including the measurement of airway protection status, are promising for routine patient care [26].

Our hypothesis is, therefore, that in VC, the IUS increases tonicity and contracts in preparation for a voluntary IAP elevation; and that the subsequent expiratory effort is against this increased sphincter tonicity, so that SUI is less likely. This neurological mechanism would not apply to the involuntary LER. In this respect, the LER tests the native state of sphincter tone and mimics the neuromuscular events prevalent in many SUI subjects.

CONCLUSIONS

This report shows that the iRCT reliably initiated the LER, which was a more effective method for demonstrating SUI than VC, in subjects with SUI complaints. VC inspiration appears to neurologically increase the tonicity of the IUS, and this increased resistance prevents or limits the demonstration of urinary leaks characteristic of SUI. The rapid neuromuscular LER event does not activate the ICR. Urinary incontinence with the LER may occur so that urine loss can be greater even at lower abdominal pressures compared to VC.

CONFLICTS OF INTEREST

Disclosure Drs. Addington, Stephens and Miller have a stock interest in Pneumoflex Systems, Inc. These authors were not compensated for this study. The data is part of an FDA application by Pneumoflex Systems LLC, ClinicalTrials.gov Identifier: NCT00801203.

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