Experimental Physiology – *Research Paper*

Co-ordination of spontaneous swallowing with respiratory airflow and diaphragmatic and abdominal muscle activity in healthy adult humans

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Co-ordination of breathing and swallowing is essential for normal pharyngeal function and to protect the airway. To allow for safe passage of a bolus through the pharynx, respiration is interrupted (swallowing apnoea); however, the control of airflow and diaphragmatic activity during swallowing and swallowing apnoea are not fully understood. Here, we validated a new airflow discriminator for detection of respiratory airflow and used it together with diaphragmatic and abdominal electromyography (EMG), spirometry and pharyngeal and oesophageal manometry. Co-ordination of breathing and spontaneous swallowing was examined in six healthy volunteers at rest, during hypercapnia and when breathing at 30 breaths min^{-1}. The airflow discriminator proved highly reliable and enabled us to determine timing of respiratory airflow unambiguously in relation to pharyngeal and diaphragmatic activity. During swallowing apnoea, the passive expiration of the diaphragm was interrupted by static activity, i.e. an 'active breath holding', which preserved respiratory volume for expiration after swallowing. Abdominal EMG increased throughout pre- and post-swallowing expiration, more so during hyper- than normocapnia, possibly to assist expiratory airflow. In these six volunteers, swallowing was always preceded by expiration, and 93 and 85% of swallows were also followed by expiration in normo- and hypercapnia, respectively, indicating that, in man, swallowing during the expiratory phase of breathing may be even more predominant than previously believed. This co-ordinated pattern of breathing and swallowing potentially reduces the risk for aspiration. Insights from these measurements in healthy volunteers and the airflow discriminator will be used for future studies on airway protection and effects of disease, drugs and ageing.

(Received 20 November 2008; accepted after revision 12 January 2009; first published online 12 January 2009)
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Disturbances in breathing and swallowing interfere with quality of life and may cause aspiration with subsequent increased morbidity and mortality (Langmore *et al.* 2002; Butler *et al.* 2007). The oral, pharyngeal and oesophageal phases of swallowing each show distinct synchronized sequences of events (Jean, 2001), and co-ordination of breathing and swallowing is vital for safe passage of a bolus because the route for air and nutrients is partly shared. Methodological difficulties and differences between species have caused controversies over the precise co-ordination of breathing and swallowing in humans despite extensive studies (Paydarfar *et al.* 1995; Saito *et al.* 2002; Hiss *et al.* 2003; Martin-Harris *et al.* 2003, 2005; Perlman *et al.* 2005).

Breathing and swallowing are controlled by the interaction of neuronal groups co-localized in the brainstem (Dick *et al.* 1993; Saito *et al.* 2002; Ertekin & Aydogdu, 2003). This central neuronal control, combined with local anatomical conditions and sensory input from the pharynx, permit safe and directed passage of air, liquids and solids. Factors primarily thought to influence breathing (e.g. arterial partial pressure of CO_2) affect swallowing (Nishino *et al.* 1998; Sai *et al.* 2004), and changes in pharyngeal function (dysphagia due to

DOI: 10.1113/expphysiol.2008.045724

anatomical disorders or disease) affect breathing patterns (Nilsson *et al.* 1997; Hadjikoutis *et al.* 2000; Butler *et al.* 2007; Terzi *et al.* 2007). Breathing and swallowing are thus deeply intertwined.

Diaphragmatic EMG recordings are often considered to be the gold standard for registration of respiratory activity. However, for correct interpretation of the co-ordination of breathing and swallowing and to consider the risks of inhalation and aspiration of pharyngeal content, measurements of respiratory airflow may be superior. With this approach, it becomes vital to determine exactly when inspiratory and expiratory airflow start and stop before and after a swallowing manoeuvre. In human studies, this has been difficult using traditional equipment, such as a nasal pressure transducer, because respiratory air may not flow solely through the nose, other equipment used and patient position may disturb readings, and swallowing in itself may cause artefacts and make interpretation difficult. It is possible that methods with low sensitivity have led to misinterpretations of how breathing and swallowing are co-ordinated. We therefore developed a new technique using a bidirectional gas flow discriminator, which distinctly determines the presence and direction of airflow with high accuracy and resolution in time, regardless of respiratory route.

This study investigates the complex activities during breathing and spontaneous swallowing and their precise temporal relationship in healthy adults. We validated the new, more sensitive and exact methodology for detection of respiratory airflow, and used it together with conventional methods in a multimodal approach to simultaneously register respiratory phase patterns, diaphragmatic and abdominal muscle activity, spirometry and swallowing. This enabled a detailed analysis of the co-ordination of spontaneous saliva swallows and breathing at rest and during hypercapnia.

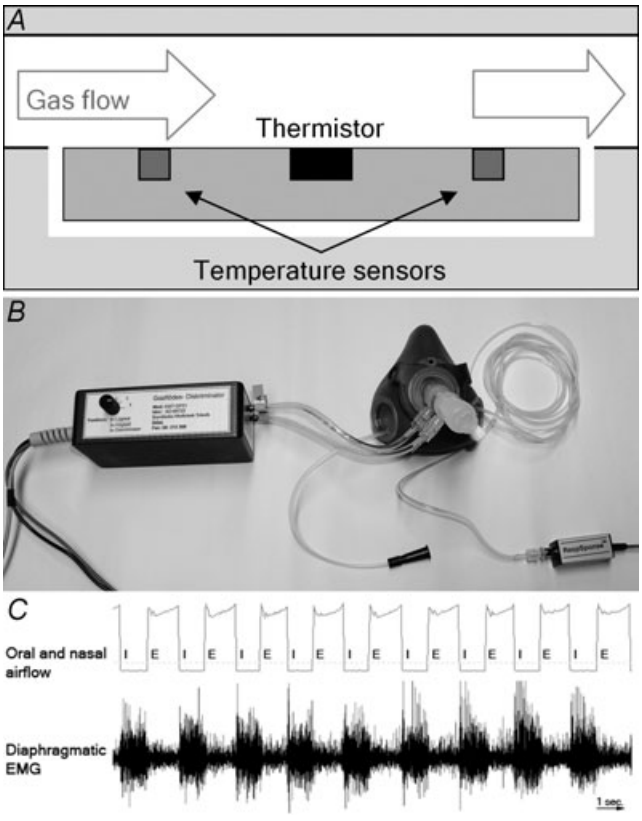

Figure 1. The bidirectional gas flow discriminator
Schematic illustration of the interior of the bidirectional gas flow discriminator (*A*). Applied to the face mask (*B*), oral and nasal airflow was recorded. For method validation, the bidirectional gas flow discriminator readings were compared with diaphragmatic EMG at a voluntary high-frequency respiration rate of 30 breaths min^{-1} as directed by a metronome (normocapnia; *C*) and during breathing at normo- and hypercapnia. Inspiration (I), expiration (E).

Methods

Ethical approval and study population

This study conforms to the standards of the Declaration of Helsinki and was approved by the Regional Ethics Committee on Human Research at the Karolinska Institutet, Stockholm, Sweden. Six healthy volunteers were included (3 female and 3 male; aged 21–35 years) after obtaining written informed consent. Subjects were unmedicated non-smokers without any history of dysphagia, gastroesophageal reflux disease or surgery to the pharynx, oesophagus or larynx.

Respiration

A bidirectional gas flow discriminator (ASF1430, Sensirion AG, Staefa, Switzerland), originally a mass flow integrator designed for industrial purposes, was remodelled to fit the breathing circuit of a face mask and for simultaneous sampling with manometry and EMG recordings (Fig. 1). The bidirectional gas flow discriminator detected respiratory airflow by dual temperature-compensated thermistors (CMOSens®, Sensirion AG, Staefa, Switzerland) with an internal flow integration time of 5 ms according to the manufacturer. The signal was first digital-to-analog converted, then digitized and sampled (Polygraph™, SynMed, Stockholm, Sweden) together with nasal pressure, pharyngeal and oesophageal manometry signals and the diaphragmatic and abdominal electromyography (EMG). Connected to the face mask, the bidirectional gas flow discriminator was used to detect the presence or absence of respiratory airflow through the mouth and/or nose as well as direction of flow, i.e. inspiration and expiration. The duration of inspiration, expiration and apnoea was measured. In addition, the time difference between detection of inspiratory airflow and diaphragmatic EMG activity was

measured and used for validation of the bidirectional gas flowmeter.

A nasal pressure transducer (RespSponse™, SynMed) was also introduced through the face mask and inserted into one of the nostrils as a supplementary monitor of the direction of respiratory airflow.

A tailor-made face mask with sealed passages for three catheters and transducers was tightly fixed over the nose and mouth using rubber bands. The mask was connected to a breathing circuit (Engström 2024, Stockholm, Sweden) with a dead space of 90 ml, allowing for minimal rebreathing. From measurements by a spirometer (D-lite™, Datex-Ohmeda AS/3™, GE Medical Systems, Madison, WI, USA), inspiratory and expiratory tidal volumes (in millilitres) were calculated.

Electromyography was used to record diaphragmatic and abdominal muscle activity. For diaphragmatic EMG, a concentric bipolar transcutaneous needle electrode (DNC™ 37 × 0.46 mm, Medtronic, Copenhagen, Denmark) was inserted between the eighth and ninth costae at the left midclavicular line and was manually held in place by one of the examiners. Abdominal EMG was recorded by a transcutaneous silver electrode with a small hook at the tip (1512A-M wire electrode needle set, Life-Tech® Inc., Stafford, TX, USA) inserted subcostally into the right rectus abdominis muscle and firmly taped to the skin. Surface reference and earth electrodes were placed on the torso. The EMG signals were duplicated, amplified and filtered (5 Hz to 10 kHz; Keypoint®, Medtronic, Copenhagen, Denmark). The first pair of analog signals was digitized using the Polygraph™ (Polygram®, SynMed) for analysis in relation to manometry and respiratory airflow and, owing to a maximal sampling frequency of 128 Hz (Polygraph™), the other pair of analog signals was digitized at 5000 Hz and recorded on a computer for analysis of amplitude (Axon Instruments Digidata 1320A, Axon Clampex and Clampfit 8.0, Molecular Devices, Sunnyvale, CA, USA). During analysis, diaphragmatic EMG amplitude was normalized (ratio) to inspiratory amplitude before swallowing (set to 1.0) and to expiratory amplitude after swallowing (set to 0.0). Abdominal EMG activity was analysed visually without systematic measurements of amplitude.

Swallowing

A manometry catheter with four solid-state pressure transducers 2 cm apart and response time 8 ms (Konigsberg Instruments, Pasadena, CA, USA) was introduced through one nostril and placed in the pharynx as described previously (Olsson *et al.* 1995; Eriksson *et al.* 1997). The catheter was placed with the transducers at the tongue base (TB), the pharyngeal constrictor muscles (two transducers) and the upper oesophageal sphincter (UES). For oesophageal manometry, the catheter was placed with the proximal sensor in the UES and the following three placed distally in the upper and mid parts of the oesophagus. The manometry signals were amplified, digitized and sampled at 128 Hz (Polygraph™).

Study protocol

Readings from the bidirectional gas flow discriminator were compared with diaphragmatic EMG for method validation. The time difference between onset of diaphragmatic inspiratory EMG activity and detection of inspiratory airflow by the bidirectional gas flow discriminator was measured in 10 breaths in each volunteer at normocapnia, hypercapnia and a preset respiratory rate of 30 breaths min^{-1}.

Co-ordination of breathing and swallowing was explored with volunteers placed supine with a 45 deg head-up tilt. The facemask, catheters, transducers and diaphragmatic and abdominal EMG electrodes remained in the same position throughout the study period of approximately 2 h. Signals of oral and nasal airflow, nasal air pressure, diaphragmatic and abdominal EMG and pharyngeal manometry were sampled at 128 Hz and recorded simultaneously with spirometry (Fig. 2). Subjects were studied while breathing air (normocapnia) and while breathing air with the addition of 5% CO_2 (hypercapnia). Recordings were made of steady-state periods of 10 min at normocapnia followed by 5 min at hypercapnia. In both conditions, subjects were allowed to swallow saliva spontaneously and were not given any instructions on how to swallow. Thereafter, at normocapnia, subjects were asked to breathe at a rate of 30 breaths min^{-1} for 30 s, as directed by a metronome. Finally, the manometry catheter was moved into the oesophagus, and respiration and spontaneous saliva swallows were recorded during a 5 min period of normocapnia. Respiratory rate and spontaneous swallowing frequency were calculated. Vital parameters, including heart rate, blood pressure and peripheral oxygen saturation, were monitored continuously, as well as end-tidal CO_2 (Datex-Ohmeda Cardiocap®/5, GE Medical Systems, Madison, WI, USA).

Statistics

During normo- and hypercapnia, the mean value of five swallows was calculated for each parameter and each volunteer. Results are presented as medians and ranges. Wilcoxon rank test was used for analysis of differences between normo- and hypercapnia. The time differences between diaphragmatic inspiratory EMG activity and detection of inspiratory airflow by the bidirectional gas flow discriminator were made using ANOVA for

repeated measures and are presented as individual mean values ± S.D. and median values with 95% confidence intervals (CI) for the group. Statistica™ 7.1 (Statsoft® Inc., Tulsa, OK, USA) was used for statistical analysis. $P < 0.05$ was considered significant.

Results

The bidirectional gas flow discriminator proved to be accurate and reliable (Fig. 1). During normocapnia at rest, the median time difference between detection of inspiratory airflow and diaphragmatic EMG activity was 42 ms (CI, 37–48 ms; Table 1). This time difference was reproduced in the 10 measurements in each individual and did not change when the respiratory rate was increased to 30 breaths min^{-1}. During hypercapnia, the difference between the methods decreased to 35 ms (CI, 32–39 ms; $P = 0.028$). Owing to frequent disturbances and artefacts, the nasal pressure recordings were difficult to interpret adjacent to swallowing, even for discrimination between inspiration and expiration (Fig. 2) and were therefore not used for further analysis.

Table 1. The bidirectional gas flow discriminator readings compared with diaphragmatic EMG for method validation

Volunteer	Normocapnia (ms)	Hypercapnia (ms)	Normocapnia, 30 breaths min^{-1} (ms)
1	52 ± 15	36 ± 8	55 ± 8
2	40 ± 16	36 ± 12	37 ± 11
3	38 ± 14	34 ± 11	44 ± 16
4	41 ± 22	41 ± 7	39 ± 14
5	42 ± 21	34 ± 10	42 ± 10
6	42 ± 20	31 ± 10	36 ± 11
Median	42	35*	41

The time differences (ms) from onset of inspiratory diaphragmatic EMG activity to onset of inspiratory airflow as detected by the bidirectional gas flow discriminator are presented as means ± S.D. of 10 breaths in each individual (*$P < 0.05$ *versus* normocapnia and 30 breaths min^{-1}).

There was no significant difference in the swallowing frequency during normocapnia

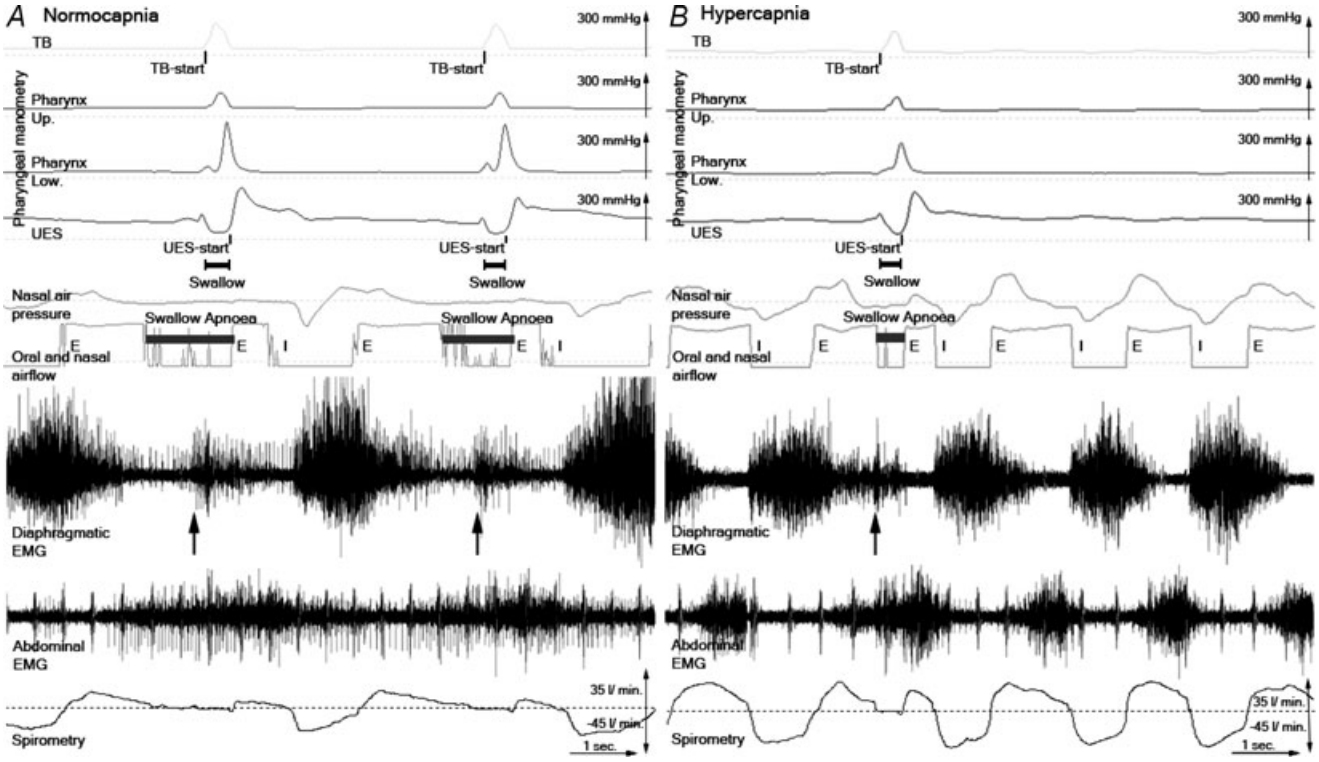

Figure 2. Registrations of pharyngeal manometry, nasal air pressure, oral and nasal respiratory airflow by the bidirectional gas flow discriminator, diaphragmatic and abdominal EMG and spirometry
Recordings of two swallows at normocapnia (*A*) and one swallow at hypercapnia (*B*). The swallows presented show the respiratory phase pattern E–E (inspiration–expiration–swallow–expiration). The start of pharyngeal swallowing was defined as the start of pressure rise at the tongue base (TB-start) and the end as the point in time when the upper oesophageal sphincter started to contract (UES-start). The duration of pharyngeal swallowing is marked with a horizontal bar (Swallow). Swallowing apnoea was detected by the respiratory airflow discriminator as an oscillating signal, representing zero airflow. Diaphragmatic activity during swallowing apnoea is marked with arrows (↑). Pharyngeal manometry was recorded at the tongue base (TB), upper/lower level of the pharynx (Pharynx Up./Low.) and upper oesophageal sphincter (UES). Inspiration (I), expiration (E).

[1.1 (0.5–2.6) swallows min^{-1}] compared with hypercapnia [1.6 (0.4–2.6) swallows min^{-1}; $P = 0.753$]. The median respiratory rate increased significantly during hypercapnia from 10.4 (6.6–14.2) to 12.6 (10.7–25.9) breaths min^{-1} ($P = 0.028$), and end-tidal CO_2 concentrations increased from 4.8 (4.6–5.3) to 6.1 (5.8–6.3)% ($P = 0.028$). Vital parameters were normal and stable throughout the experiment.

Respiratory phase patterns

A total number of 81 and 52 swallows were recorded at normo- and hypercapnia, respectively. Two respiratory phase patterns were detected: inspiration–expiration–swallow–expiration (E–E) and inspiration–expiration–swallow–inspiration (E–I). During normocapnia, 93% of swallows were preceded and followed by expiration (E–E), and this pattern was found in all volunteers. Swallowing was followed by inspiration (E–I) in 7% of swallows, a pattern detected in two of the six volunteers. During hypercapnia, 85% of swallows showed the E–E pattern and 15% the E–I pattern. Again, E–E patterns were present in all volunteers while E–I patterns persisted in the same two volunteers as during normocapnia. No swallows were preceded by inspiration, either at normocapnia or during hypercapnia.

The start of pharyngeal swallowing was defined as the start of pressure rise at the tongue base (TB-start; Fig. 2). This event was chosen because it represented the first sign of pharyngeal swallowing that was easily detected visually and showed stability in the temporal order of events. The end of pharyngeal swallowing was defined as the time point when the upper oesophageal sphincter started to contract (UES-start; Fig. 2).

Respiratory phases in swallows with the E–E pattern

The E–E pattern was by far the predominant pattern and therefore swallows with this pattern were chosen for an in-depth analysis of co-ordination of breathing and swallowing. For each volunteer, five swallows from the normocapnic period and five swallows from the hypercapnic period were analysed. To avoid selection bias, swallows were taken for analysis from every second minute during the 10 minute period of normocapnia, and from each minute during the 5 minute period of hypercapnia. If no swallow was recorded during a particular period, the swallow closest to this period was chosen.

There was no significant difference in durations of inspiration and expiration preceding swallowing during normocapnia and hypercapnia in swallows with the E–E pattern ($P = 0.173$ and $P = 0.116$, respectively; Table 2). Inspiratory and expiratory tidal volumes before swallowing were 709 (491–860) and 376 (89–687) ml, respectively, at normocapnia, increasing to 933 (565–1302) and 636 (388–1088) ml at hypercapnia ($P = 0.046$). The corresponding inspiratory and expiratory diaphragmatic EMG amplitude ratios were 1.00 and 0.87 both at normo- and hypercapnia ($P = 0.753$; Table 3). There was no detectable abdominal EMG activity during inspiration in any of the volunteers at any time point during the study period. However, during expiration before swallowing abdominal EMG activity was recorded in three of six volunteers at normocapnia, while it was seen in all volunteers at hypercapnia.

The time period of swallowing apnoea was divided into pre-swallowing apnoea, pharyngeal swallowing apnoea and post-swallowing apnoea. The duration of swallowing apnoea at normocapnia was 1338 (910–1754) ms, decreasing to 822 (524–1148) ms at hypercapnia ($P = 0.028$). The duration of pre-swallowing apnoea was generally longer than that of post-swallowing apnoea and decreased during hypercapnia ($P = 0.046$), while no effect was detected on post-swallowing apnoea (Table 2). Hence, the temporal positioning of pharyngeal swallowing was assymetrical, occurring in the latter part of swallowing apnoea at normo- but not at hypercapnia.

During swallowing apnoea, we found a consistent increase in diaphragmatic EMG. This EMG pattern was distinctly different from the pattern of inspiration and was present during both normo- and hypercapnia in all volunteers and all analysed swallows (Fig. 2*A* and *B* and Table 3). This diaphragmatic activation always preceded TB-start, and the peak activity occurred simultaneously with the start of pharyngeal swallowing. The diaphragmatic EMG activity then gradually decreased throughout pharyngeal swallowing, reaching a minimum at the start of post-swallowing expiration. This is presented schematically in Fig. 3. The duration of the diaphragmatic activity during swallowing apnoea was decreased during hypercapnia ($P = 0.028$; Table 2). The corresponding EMG ratios were unchanged (Table 3). The time difference between the start of diaphragmatic EMG activity during swallowing apnoea and TB-start decreased during hypercapnia ($P = 0.028$; Table 3). Notably, during hypercapnia, the onset of diaphragmatic EMG activity during swallowing apnoea often occurred simultaneously with the onset of swallowing apnoea (Fig. 2*B* and Table 2). In all volunteers and all swallows at normo- and hypercapnia, swallowing apnoea started prior to the pharyngeal phase of swallowing and ended after (Fig. 4*A* and Table 2). Thus, at normocapnia, the oesophageal phase of swallowing occurred when respiration was already resumed. The rostro-caudal wave of oesophageal muscle contractions reached the sensor placed 2 cm below the UES 496 (40–926) ms after the end of swallowing apnoea (Fig. 4*B*).

Table 2. Durations of respiratory phases in swallows with the E–E pattern (inspiration–expiration–swallow–expiration)

			Swallowing apnoea					
Volunteer	Inspiration (ms)	Expiration before swallowing (ms)	Pre-swallowing apnoea (ms)	Pharyngeal swallowing apnoea (ms)	Post-swallowing apnoea (ms)	Expiration after swallowing (ms)	Time from onset of diaphragmatic activity to onset of pharyngeal swallowing (ms)	Diaphragmatic activity during swallowing apnoea (ms)
Normocapnia								
1	2770	2232	246	616	48	2894	154	1412
2	1742	1668	384	520	190	1420	122	1180
3	1478	1420	400	508	404	1372	256	1148
4	2982	1948	570	608	576	516	246	1304
5	3352	1460	890	502	168	1086	432	1350
6	2188	1550	528	512	404	1048	254	1144
Median	2479	1609	464	516	297	1229	250	1242
Hypercapnia								
1	1716	1286	256	564	54	1430	140	1216
2	1000	926	26	426	72	432	26	906
3	1722	1480	64	486	120	902	64	1016
4	3046	1754	254	578	316	498	128	1119
5	3116	1542	106	488	230	1100	100	1008
6	1873	1404	118	504	198	598	110	1038
Median	1798	1442	112*	496*	159	750*	105*	1027*

$n = 60$ swallows; *$P < 0.05$ *versus* normocapnia.

Table 3. Diaphragmatic EMG activity (ratios) in swallows with the E–E pattern (inspiration–expiration–swallow–expiration)

			Swallowing apnoea				
Volunteer	Inspiration	Expiration before swallowing	Pre-swallowing apnoea	Pharyngeal swallowing apnoea	Post-swallowing apnoea	Expiration after swallowing	Diaphragmatic activity during swallowing apnoea
Normocapnia							
1	1.00	0.96	0.52	0.50	0.40	0.33	0.52
2	1.00	0.87	0.75	0.83	0.86	0.38	0.78
3	1.00	0.89	0.75	0.75	0.65	0.56	0.74
4	1.00	0.77	0.42	0.46	0.44	0.42	0.44
5	1.00	0.87	0.55	0.49	0.42	0.32	0.62
6	1.00	0.85	0.71	0.76	0.96	0.50	0.85
Median	1.00	0.87	0.63	0.62	0.55	0.40	0.68
Hypercapnia							
1	1.00	0.86	0.75	0.62	0.52	0.39	0.69
2	1.00	0.90	0.68	0.73	0.66	0.35	0.73
3	1.00	0.84	0.75	0.70	0.69	0.59	0.70
4	1.00	0.88	0.36	0.38	0.29	0.25	0.39
5	1.00	0.81	0.51	0.37	0.39	0.26	0.43
6	1.00	1.07	0.40	0.78	0.43	0.28	0.71
Median	1.00	0.87	0.60	0.66	0.48	0.31	0.70

$n = 60$ swallows.

The duration of expiration after swallowing decreased during hypercapnia ($P = 0.046$; Table 2), while expired tidal volumes were unaffected, being 222 (41–701) and 187 (157–521) ml at normo- and hypercapnia, respectively. We found no difference in diaphragmatic EMG activity during expiration after swallowing at normo- and hypercapnia (Table 3). At normocapnia, abdominal EMG activity was increased during expiration after swallowing in all volunteers but not after all swallows, more commonly seen when swallowing occurred late in the expiratory phase. At hypercapnia, abdominal EMG activity was increased during expiration after

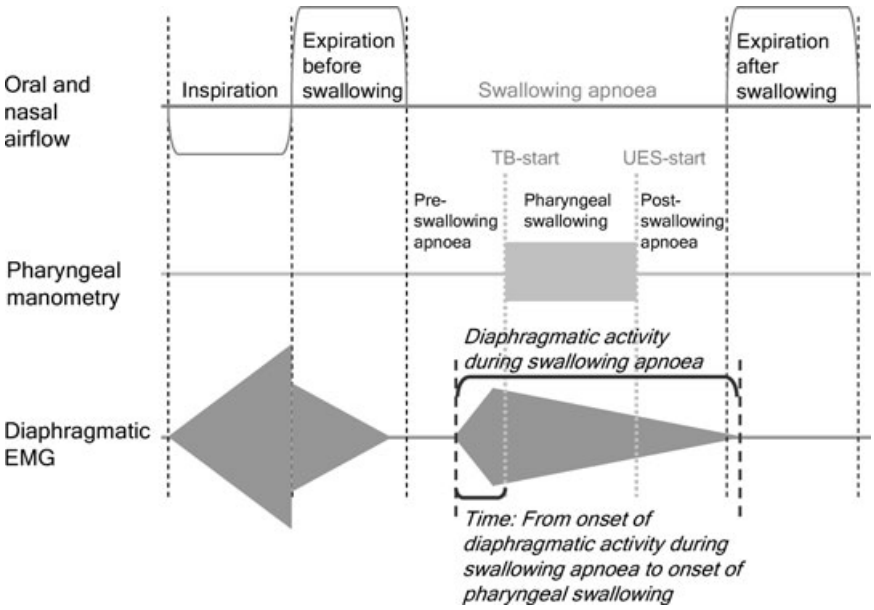

Figure 3. Schematic diagram of a swallow preceded and followed by expiration (E–E pattern) and the diaphragmatic activity during swallowing apnoea
The time from the onset of diaphragmatic activity during swallowing apnoea to the onset of pharyngeal swallowing was measured and is marked in the figure. The start of pharyngeal swallowing is defined as the start of pressure rise at the tongue base (TB-start) and the end of pharyngeal swallowing is defined as the start of pressure rise at the upper oesophageal sphincter (UES-start).

swallowing in all volunteers and in almost all swallows (Fig. 2*B*).

Discussion

This is the first study that uses the bidirectional gas flow discriminator to investigate the co-ordination of breathing and spontaneous swallowing in humans. The high-resolution measurements and the multimodal approach enabled a detailed characterization of previously unknown co-ordination of events.

When considering the risks for inhalation and aspiration of pharyngeal content during swallowing, it is crucial to know more precisely when inspiratory

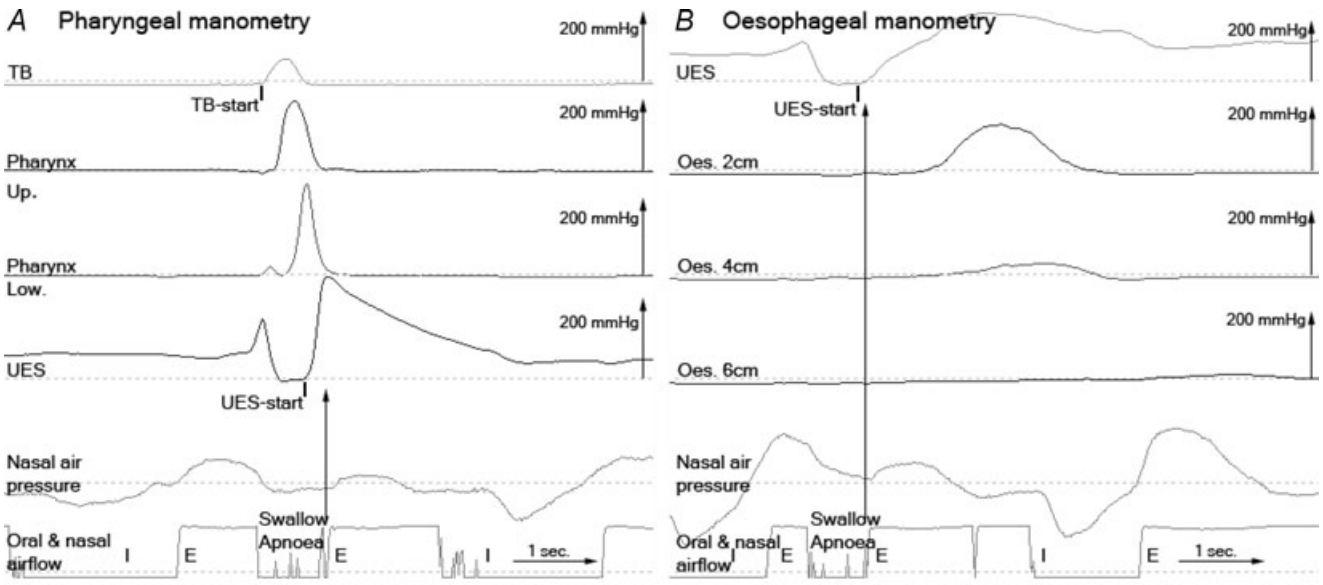

Figure 4. Pharyngeal and oesophageal swallowing and swallowing apnoea
One swallow preceded and followed by expiration (respiratory phase pattern E–E). Recordings of pharyngeal (*A*) and oesophageal manometry (*B*), nasal air pressure and oral and nasal airflow by the bidirectional gas flow discriminator. The end of swallowing apnoea is marked with arrows (↑). The start of pharyngeal swallowing is defined as the start of pressure rise at the tongue base (TB-start) and the end of pharyngeal swallowing as the start of pressure rise at the upper oesophageal sphincter (UES-start), which also defines the start of the oesophageal phase of swallowing. Pharyngeal manometry was recorded at the tongue base (TB), upper/lower level of the pharynx (Pharynx Up./Low.) and upper oesophageal sphincter (UES). Oesophageal manometry was recorded at 2, 4 and 6 cm below the UES. Inspiration (I), expiration (E).

and expiratory airflow start and stop. Using traditional equipment, such as a nasal pressure transducer, it may be difficult to determine the transition from apnoea to inspiration or expiration, especially adjacent to swallowing, when the signal may be unstable and show artefacts (Fig. 2). The bidirectional gas flow discriminator provides a new opportunity to determine, during the circumstances of breathing and swallowing studies, the timing and direction of airflow with a much greater accuracy. The time lag between the onset of diaphragmatic EMG activity and the start of inspiratory flow registered by the bidirectional gas flow discriminator probably results from a combination of biological and methodological delay, since diaphragmatic EMG reasonably should precede the onset of inspiratory flow. The shorter time difference during hypercapnia is most likely to be due to the increased respiratory drive, where a more forceful contraction of the diaphragm results in a quicker start of high initial airflow. Considering the response time of the manometry catheter and the bidirectional gas flow discriminator, the combined resolution for co-ordination measurements was 128 Hz, or 8 ms, which should be sufficient for a comprehensive analysis (Tarrant *et al.* 1997).

Central regulation of breathing and swallowing is deeply intertwined, since neurons in the brainstem are active both during respiration and swallowing (Saito *et al.* 2002). Saito and co-workers detected phrenic nerve activity during swallowing in rats, and in humans inspiratory effort without airflow has been termed 'swallow breath', 'Schluckathmung' and 'obstructed breathing' (Atkinson *et al.* 1957; Vantrappen *et al.* 1958; Wilson *et al.* 1981; Grelot *et al.* 1992; Shaker *et al.* 1992; Oku *et al.* 1994). In the present investigation, we demonstrate the result of the phrenic nerve activity described by Saito *et al.* (2002) as a characteristic diaphragmatic EMG pattern during swallowing apnoea to our knowledge never described in humans before. This pattern was distinctly different from that of an inspiration and did not produce airflow. We call this 'active breath holding', and speculate that this represents central control of breathing which aims to ensure that respiration has stopped before pharyngeal swallowing and that a significant proportion (in our study approximately 200 ml) of the tidal volume is 'put on hold' by the activated diaphragm, only to be expired at the end of swallowing apnoea. During normocapnia, the start of swallowing apnoea sometimes preceded the increase in diaphragmatic activity during swallowing apnoea. This happened if swallowing apnoea was caused by passively reached zero airflow rather than by active breath holding by the diaphragm.

Swallowing apnoea starts before glottic closure and is, therefore, not of mechanical origin (Ren *et al.* 1993) but controlled by the brainstem (Nishino & Hiraga, 1991; Martin *et al.* 1994; Hiss *et al.* 2003; Charbonneau *et al.* 2005; Martin-Harris *et al.* 2005). In contrast, the end of swallowing apnoea correlates well with laryngeal opening (Martin-Harris *et al.* 2005) and in the present investigation occurred at the transition from the pharyngeal to the oesophageal phase of swallowing. We believe that this is beneficial, since respiration can safely be resumed when the bolus has passed the pharynx and the laryngeal inlet. Expiratory airflow after swallowing may help clear the laryngeal inlet from bolus remnants and, thereby, prevent aspiration. In the present study, we show two active mechanisms which potentially promote post-swallowing expiratory airflow. The first mechanism is active breath holding, which preserves lung volume above the functional residual capacity (FRC). This static diaphragmatic activity decreased towards the end of swallowing apnoea. Relaxation of the diaphragm with lungs inflated above FRC would cause a positive subglottic airway pressure as found by Gross *et al.* (2003, 2006) and subsequent expiratory airflow when the glottis is reopened. Second, in contrast to animal studies (Oku *et al.* 1994), we found that abdominal EMG activity increased during swallowing apnoea and continued through post-swallowing expiration, with the highest activity being registered just before the next inspiration, i.e. when lung volume approached FRC. This would also contribute to a positive subglottic pressure and increase expiratory force in an active expiration. In agreement with this, we found a burst of abdominal EMG activity during post-swallowing expiration in swallows occurring very late in the expiratory phase.

A face mask was used for spirometry recordings, a validated technique which generates reproducible measurements (Wohlgemuth *et al.* 2003). The predominance of swallows initiated in the expiratory phase in the present study was even greater than found by others (Hiss *et al.* 2001; Martin-Harris *et al.* 2003). However, in some swallows (approximately 4%), the expiration preceding swallowing was very brief and could easily be missed if registrations had not been performed with as high accuracy. Stimulation of the sensory superior laryngeal nerve in the rat has been shown not to trigger swallowing during inspiration, but immediately before or after (Saito *et al.* 2002), and it has been proposed that the E–E pattern is preventive of aspiration (Paydarfar *et al.* 1995). We found no swallows preceded by inspiration and only a few swallows followed by inspiration in two of the volunteers. The E–I swallows occurred with lung volumes close to FRC which could imply that these volunteers trigger swallowing later during the expiratory phase due to weaker sensory input or higher threshold to trigger swallowing and that they simply run out of air for post-swallowing expiration. After some of the E–I swallows, we also found abdominal EMG activity suggesting 'expiration' with failure to produce airflow. However, the number of analysed swallows was too

limited for definite conclusions about these more unusual patterns.

While E–E remained the most common respiratory phase pattern during hypercapnia, there was a tendency to an increased frequency of swallows followed by inspiration, a finding supported by previous studies (Nishino *et al.* 1998). In a majority of swallows during hypercapnia, the beginning of swallowing apnoea coincided with the increased diaphragmatic EMG activity during swallowing. It may be that this active breath holding is of greater importance to ensure swallowing apnoea when respiratory drive is increased. In support of this, the duration of pre-swallowing apnoea was shorter and pre-swallowing expiration was interrupted more abruptly at a higher flow rate during hypercapnia. In contrast, the duration of post-swallowing apnoea was very similar in normo- and hypercapnia, suggesting that opening of the glottis is closely related to the end of the pharyngeal phase of swallowing. The duration of post-swallowing expiration was shorter during hypercapnia than normocapnia but volumes were similar. This supports the hypothesis on sensory feedback loops that modulate respiration and aim for a certain airway pressure or lung volume before the start and end of swallowing apnoea. In concordance, others have suggested that changes in swallowing frequency and respiratory phase patterns are not caused by CO_2 *per se*, but by inhibitory lung volume-related reflexes (Kijima *et al.* 1999, 2000; Sai *et al.* 2004).

Conclusion

A highly accurate airflow discriminator enabled us to determine respiratory airflow unambiguously in relation to pharyngeal and diaphragmatic activity in humans. For the first time in humans, we found specific diaphragmatic and abdominal muscle activity in the apnoeic period during swallowing, which promoted expiratory airflow after swallowing. Our results indicate that swallowing during the expiratory phase of breathing may be even more predominant than previously believed. This co-ordinated pattern of breathing and swallowing potentially reduces the risk for aspiration. Insights from these measurements in healthy volunteers and the use of the airflow discriminator may serve as a foundation for future studies on airway protection and effects of disease, drugs and ageing.

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Acknowledgements

The authors would like to thank Dr Jonas Persson MD for excellent EMG recording, Elisabeth Fabian for technical assistance, Mikael Gehlen and Mats Dehlin for technical support and finally Anette Ebberyd for skilful technical assistance and general support. The work was supported by Swedish Research Council for Medicine (K2008-53X-13405-09-3), Karolinska Institutet Research Grants, Stockholm County Council, Swedish Society for Anesthesia and Intensive Care Medicine, and Karolinska Institutet Travel Grants.