

The Role of the Hering-Breuer Deflationary Reflex in the Control of Spontaneous Human Respiration

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Abstract — The application of engineering control theory to biological systems is a challenge. Often, in initial engineering models or designs of systems to exert control over a certain aspect or part of a biological system, other control loops may be in operation within the biological system that are not accounted for. When the operation of such unconsidered *hidden loops* reveals themselves, this presents an opportunity to expand knowledge of biological control systems. A complimentary pair of reflexes involved in respiration was described by Hering and Breuer in 1868. Since that time, the manifestation of these reflexes has been controversial. In a recent group of studies seeking to apply an open-loop control system to assist or restore ventilation by electrically stimulating abdominal muscles, unexpected experimental results led to a more thorough study of the potential presence of the Hering-Breuer deflationary reflex in adult human subjects. This paper describes experiments in which abdominal compression (both manual and by electrical stimulation of abdominal muscles) provide evidence supporting the presence of the deflationary reflex control loop in adult human subjects. The results can be utilized to develop a comprehensive model of the human respiratory system considering both chemical and mechanical feedback.

Index Terms — respiration, reflex, control, electrical stimulation.

GLOSSARY OF SYMBOLS AND ABBREVIATIONS

EEV:	End Expiratory Volume
ECG:	Electrocardiogram
EMG:	Electromyogram
DEMG:	Diaphragmatic EMG
f:	Frequency of respiration
FESAM:	Functional Electrical Stimulation of Abdominal Muscles
FRC:	Functional Residual Capacity
IAPR:	Intermittent Abdominal Pressure Regulation
IPPV:	Intermittent Positive Pressure Ventilation
MV:	Mechanical Ventilation

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MinV:	Minute Ventilation
SCI:	Spinal Cord Injury
sd:	Standard Deviation
T_{tot.cond}:	Time Duration of a single breath; if specified, experimental condition is normal or compressed
V_T:	Tidal Volume

I. INTRODUCTION

To exert control over a system, knowledge of the system behavior is required. The application of control theory relies on dynamic models, i.e., the mathematical description of the system to be controlled. Modeling and control developed for technical systems were commonly and successfully applied in many biological applications. As soon as biological systems have to be controlled, e.g., by a medical device aimed for medical intervention and treatment, a model of the physiological plant can be very helpful. With the underlying physiological mechanisms rather complex and very often only poorly understood, quantitative modeling of these systems is a challenge. A number of classic texts deal with the topic of control in biological systems [1, 2, 3].

Experimental investigations aimed to reveal system properties can only partially shed light on the underlying mechanisms depending on the experimental paradigm applied, while relevant subsystems may remain obscure. These *hidden loops* very often account for unexpected phenomena, or worse, undesired hazardous performance of the technical control systems of medical devices, when operation conditions do not match the assumptions the model is based on. A good example of possible problem is the plausible utilization of a model of human walking based only on experimental observations of cyclic level walking; yet, aiming to describe a stumbling event. In the case of stumbling, reflex activity will take action to prevent the person from falling, and the model cannot predict this biological response, as it is obscured under "normal" walking conditions; it is a *hidden loop*. In these cases, additional experiments with modified paradigms are necessary to reveal the *hidden loops*, and very often, appropriate experimental protocols are difficult to find to reliably isolate the effects in question. However, if identified appropriately, these findings cannot only be used

to improve control of the system investigated, but also to increase knowledge of the physiological processes.

This paper is concerned with the human respiratory system, in particular, with control mechanisms of the respiratory system. When individuals stop breathing, immediate medical attention is required. Some of the earliest attempts to restore ventilation were first reported by Silvester and Howard [17,18]. In each of these reports, ventilation was restored by a technique based on manual compression of abdomen and lower thorax. This method remains in use for emergency resuscitation to the present. The treatment of choice in most cases of respiratory failure is mechanical ventilation (MV). There are a wide variety of commercially available ventilators [19]. The most common type of ventilator produces intermittent positive pressure ventilation (IPPV) by inflating the lungs with an external pump. Air is either supplied by a mask, leaving the patient unable to speak, or by endotracheal or tracheostomy tubes, the latter requiring surgical opening of the trachea. Ventilators typically operate in an open-loop manner, i.e., tidal volume and respiratory rate are preset by an experienced physician, and remain constant.

Existing mathematical models of the respiratory system mainly consider blood gas concentrations of carbon dioxide, oxygen, and the hydrogen ion concentration measured by chemical receptors as relevant inputs for the regulation of respiration [1,2]. In some models, lung stretch receptors are modeled as a source of feedback to respiratory centers in the brain (e.g. Fig. 15.6 of [3]). In addition to the chemical regulation of respiration, these stretch receptors signal the expansion of the lungs, and provide inhibitory feedback to the inspiratory drive signal, thus inhibit activity of the main inspiratory muscles, the diaphragm, and the intercostals. The role of abdominal muscles is to support expiration, they normally remain inactive during quiet breathing, where expiration is passive due to elastic recoil of the rib cage. Fig. 1 displays the mechanism described.

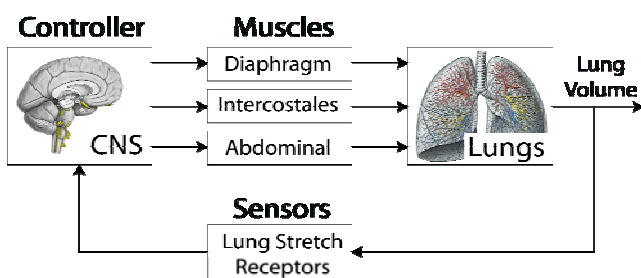


Fig. 1: Block diagram showing the presumed neurological pathways involved in the HB reflex. Inspiratory muscles are the diaphragm and the intercostals. Abdominal muscles are active in forced expiration only. During quiet, eupneic breathing, expiration is passive by elastic recoil of ribcage and abdomen.

Another existing, less common clinical technique for ventilation assistance, very relevant to this paper, is intermittent abdominal pressure respiration (IAPR) [20]. Although it may at first seem counterintuitive, IAPR

produces ventilation by assisting expiration rather than inspiration. An abdominal corset is lined with an elastic inflatable bladder. Upon inflation by an external pump, the abdomen is compressed, causing the diaphragm to rise, and expiration is forced. When the bladder is rapidly deflated, the diaphragm and abdominal contents fall as the result of gravitational action and elastic recoil, resulting in a passive inspiration with the advantage of avoiding unphysiologic positive pressure ventilation. There were at least two commercially available devices, the *Exsufflation belt* and *Pneumobelt* [21,22].

In patients with preserved but reduced ability to breathe, e.g. in high level spinal cord injured (SCI) patients, ventilation only needs to be assisted to increase the minute ventilation (MinV, the volume of air inhaled per minute). To avoid cumbersome mechanical ventilation, one of the authors, Jaeger with collaborators suggested functional electrical stimulation of abdominal muscles (FESAM) to assist or restore respiration, applying the same principle as in IAPR. Stimulation of abdominal muscles is triggered by natural expiration determined by the patient's natural breathing rate. Abdominal contraction yields a deflation of the lungs and reduces functional residual capacity (FRC, the volume remaining in the lungs at the end of expiration). In consequence, tidal volume (V_T , the volume inhaled during one breath) is increased, as well as MinV. The advantages are of economic, physiologic and ergonomic nature: patients use their own muscles to breathe in a physiologic manner (as opposed to mechanical IPPV); bulky mechanical ventilators can be avoided, as well as the need of a tracheostomy.

There have been two previous studies of using FESAM. In the first study, feasibility was assessed in nine neurologically intact subjects. A breath-by-breath analysis showed that both tidal volume and the frequency of respiration could be increased during periods of FESAM [23]. Minute ventilation was increased, but also an unexpected increase in respiratory rate could be observed. This study reported a mean respiratory rate of 16.0 1/min (sd=3.9) during normal breathing, 18.6 1/min (sd=4.9) during FESAM, and 18.4 (sd=5.0) during manual compression of the abdomen, using the experimenter's hands to compress the abdomen. The change in respiratory rate was found to be statistically significant.

A second follow-on study explored enhancing ventilation in six neurologically intact subjects and five subjects with SCI who had levels of injury between C4 and C7. Here, pulmonary ventilation was augmented predominantly due to an increase in tidal volume in both groups. The average increase in tidal volume during FESAM for the neurologically intact group was 350 ml while in the SCI group it was 220 ml. The FESAM caused active volume decreases in both the lower thorax and upper abdomen which together appears to be the mechanism behind the increases seen in tidal volume [24]. However, the average respiration rate increased from 15.8 breaths/minute to 18.5, again being statistically significant.

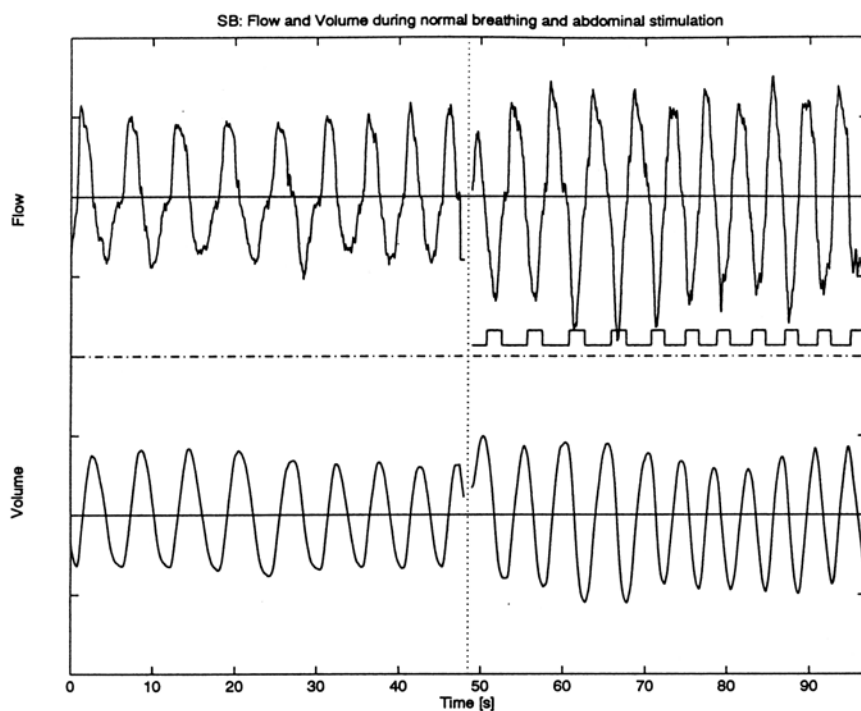


Fig. 2: Data from a single subject showing flow and volume versus time under normal quiet breathing (left side) and breathing with FESAM. The digital trace indicates that stimulation is being applied.

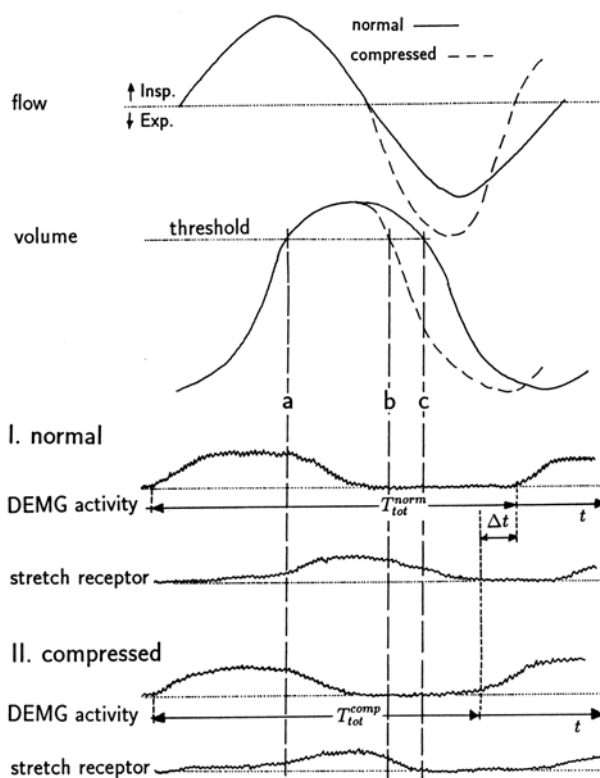


Fig 3: Theoretical traces of air flow, volume, EMG activity of the diaphragm, and lung stretch receptors for a normal breath and a breath in which abdominal compression was applied. Note that stretch receptor firing terminates earlier, which presumably leads to earlier DEMG onset in the compressed case.

We repeated these experiments with 3 SCI and 2 neurologically intact subjects using FESAM triggered by expiratory flow assessed by a pneumotach flow meter.

A custom built microprocessor controlled stimulator delivered pulse trains of 1.4 s duration. The pulse amplitude was set to produce the desired level of muscle contraction (pulse amplitude settings were between approximately 50-100 mA). The pulse repetition rate was 50 pulses per second, pulse width was linearly modulated from 25 μ s to 300 μ s over the 1.4 s delivery period.

To illustrate these FESAM experiments, Fig. 2 presents raw data from a single subject with SCI showing flow and volume versus time under normal quiet breathing on the left side of the figure, and breathing with the open-loop stimulation system operating on the right side of the figure. The digital trace added on the right side indicates that stimulation is being applied. It can be seen from the figure that both rate and tidal volume are

increasing when the stimulation is applied. The five subjects showed an average increase in respiratory rate of 129.6 ± 16.6 %, which is consistent with the two other previous studies [23,24].

The increase in respiratory rate, found in all studies, was not expected. As we deflated the lungs by FESAM or manually in synchrony with the natural breathing rate of neurologically intact subjects and SCI patients, the observed earlier onset of the following inspiration remains unclear, and might be caused by a *hidden loop*.

The assumed mechanism is shown in Fig. 3. During quiet breathing, contraction of inspiratory muscles, mainly the diaphragm, causes an influx of air (flow, upper trace) and inflates the lungs (volume, 2nd trace). With increasing lung volume, stretch receptors in the lungs increasingly discharge (4th trace). These stretch receptors have an inhibitory effect on inspiration, being transmitted to the respiratory centers of the CNS via vagal afferent pathways. In response, diaphragmatic activity decreases (Fig. 3, 3rd trace at vertical line a) and finally ceases. Expiration, due to elastic recoil in quiet breathing, empties the lungs. With stretch receptor discharge decreasing, the inspiratory drive is reestablished and causes the diaphragm to contract again, leading to the next inspiration (Fig. 3, vertical line c). If expiration is forced manually or by FESAM (Fig. 3, 5th and 6th trace, and vertical line b), inspiratory drive can build up earlier, thus, the onset of the next inspiration occurs earlier (by Δt in Fig. 3).

In 1868, Hering and Breuer investigated the role of the vagus nerve in respiratory control, and reported the existence of inflationary and deflationary reflexes of the lungs. In dogs, cats and rabbits under opiate anesthesia [4, 6], they expanded and compressed the lungs above/below a threshold, and observed a spontaneous expiration, and inspiration, respectively. The deflationary reflex could only be elicited if the lungs were emptied below functional residual capacity, FRC. These responses vanished after vagotomy, therefore Hering and Breuer concluded that vagal afferents transmitted the stimuli. The immediate response excluded chemical stimuli as a cause, since changes in blood chemistry would take longer to be detected by the respiratory center.

To date, relatively few studies investigated the Hering-Breuer (HB) reflexes in different species including human subjects [7-16]. The existence of these two reflexes is generally acknowledged to be present in animals and newborn infants. There is evidence for the persistence of the reflexes beyond the neonatal period, but it is commonly believed that they are very weak or absent in adults. Previous studies mostly focused on the inflationary HB reflex, and there is a gap of knowledge about the deflationary HB reflex. Only four publications could be found in which the deflationary HB reflex was investigated. The methods to achieve lung deflation were airway suction (application of negative pressure), or chest compression with an inflatable jacket. The only study that tried to demonstrate the deflationary reflex in adults, using chest compression, was not successful [10]. The HB reflexes are assumed to play a protective role to prevent the lungs from hyperexpansion and collapse, however, the existence in adult humans remains controversial.

In this paper, we will present a series of experiments that provide evidence the observed increase in breathing rate is due the deflationary HB reflex. These observations are relevant to the development of comprehensive models of the respiratory system, which can be used for the design of controllers for artificial ventilation devices, such as classical mechanical ventilators, as well as devices based on FESAM.

II. METHODS

It has to be proved that the earlier onset of inspiration, responsible for the increase in respiratory rate after forced expiration, is due to an inspiratory effort originating from the central respiratory center, and not due to the mechanical properties of ribcage and abdomen. Therefore, monitoring the airflow into the lungs only, as done in the FESAM experiments, is not sufficient. Ideally, inspiratory drive would be assessed as the neural activity in the inspiratory centers of the CNS, or the peripheral *N. phrenicus*, innervating the diaphragm. As this is not possible non-invasively, muscle activity of the diaphragm is chosen as an

indicator of central inspiratory drive, measured as diaphragmatic EMG.

Experimental Setup and Protocol

The experimental setup is depicted in Fig. 4. In preparation for the experiments, subjects had to swallow a "pill electrode" [25] which enabled measurement of diaphragmatic EMG (DEMG). The electrode was positioned close to where the esophagus is passing the diaphragm so that the signal showed the strongest DEMG activity. Airflow at the mouth was measured with a standard pneumotach. Signals from both the pill electrode and pneumotach were amplified, pre-filtered, and sampled at 1000 Hz. Data were stored on the PC's hard drive for off-line post-processing and evaluation. In the lower trace of Fig. 4 showing raw DEMG data, strong artifacts from the heart, the electrocardiogram (ECG), can be seen as bold vertical structures.

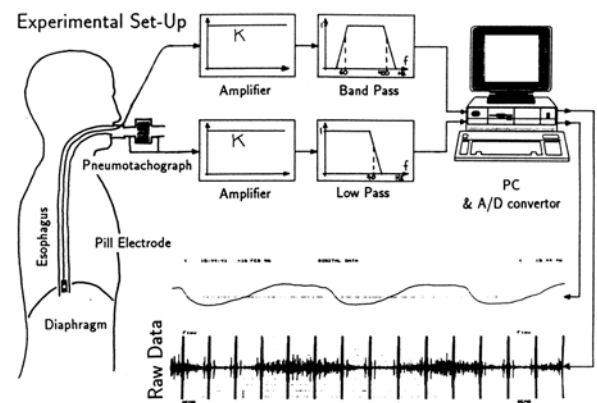
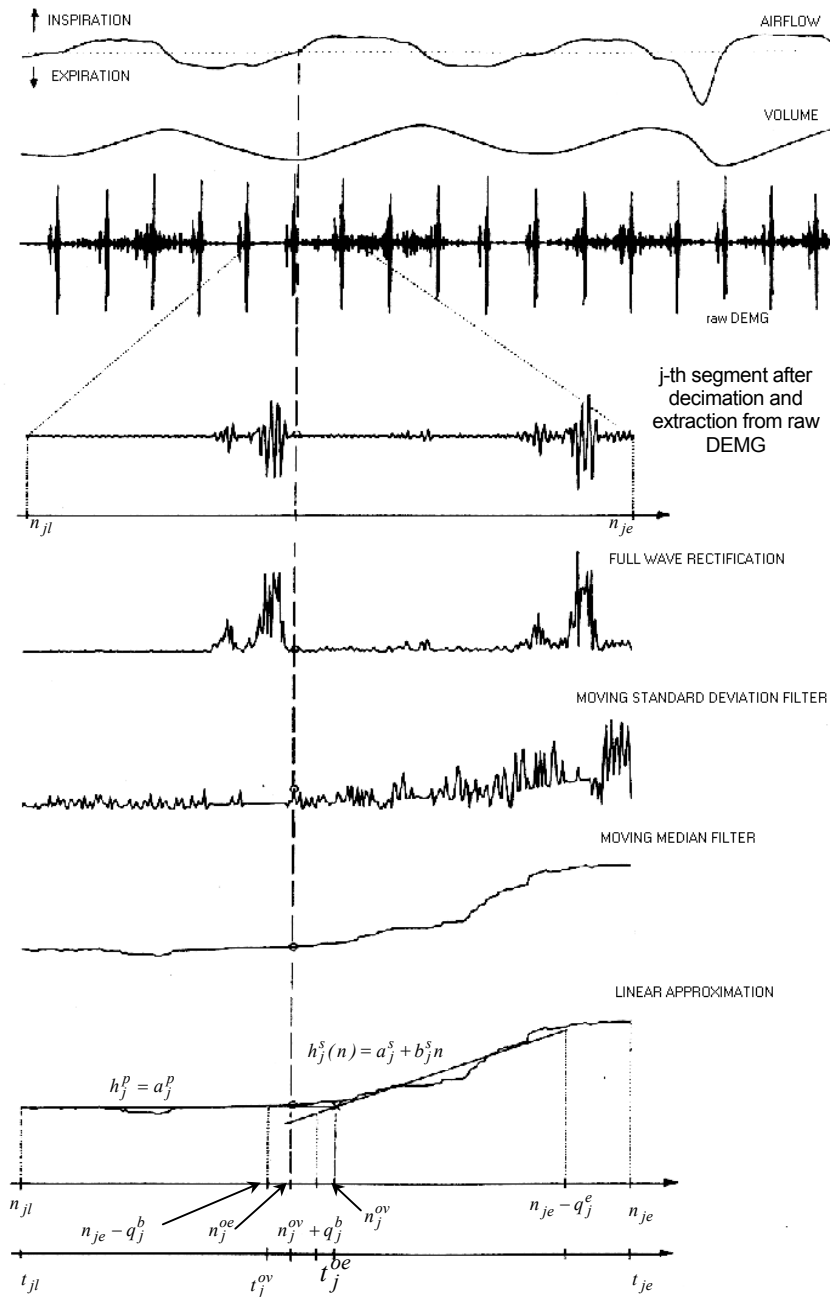


Fig. 4: Experimental setup of the Pill Electrode Experiments. Measured are diaphragmatic EMG from a pill electrode swallowed by the subject, and airflow at mouth with a pneumotach (flow meter). Signals are pre-filtered, A/D converted, and stored on a PC hard disk for off-line post-processing.

The experiments were performed only in neurologically intact subjects, compression of the abdomen was performed manually. The main purpose of these experiments was to acquire electromyographic data from the diaphragm to determine if the neural control system was actually commanding a post-compression breath earlier than would have been seen if no compression would have been applied. Five neurologically intact male subjects (mean age = 28.4 yrs.) were studied while standing in an upright position supported by a wall at their back. All subjects were asked to be relaxed and breathe quietly. The vision of the subjects was blocked so that they could not see the experimenter who would use his hands to apply brief forceful manual compressions of the abdomen in a randomized manner, while monitoring the airflow on a chart recorder, to ensure that all compressions were applied in expiration. The compression was always sufficiently short so as to be over prior to the onset of the next inspiration. The influence of conscious reactions was reduced by telling the subjects not to react to the applied compressions, which physiological



[1] Fig. 5: Filtering procedure applied to every breath to remove ECG artifact and automatically determine DEMG-based onset of inspiration.

and psychological studies have proven to be effective [27]. In addition, classical music was played via head phones to distract the subject from the experiments.

The intermittently applied manual compression resembles a Heimlich maneuver, although performed by far weaker. The Heimlich maneuver is a method to dislodge food or other material from the throat of a choking patient, in which the abdomen is forcefully compressed above the navel. If the compression is applied every breath, on the one hand, an adaptation might occur and would modify the results. On the other hand, the increased ventilation would alter the

blood chemistry, and the results might then be due to a combination of reflexive and chemical responses of the respiratory system. Isolation of the contribution by the postulated HB reflex would then be difficult, and rather speculative. Therefore, it was decided to compress the abdomen intermittently in neurologically intact subjects, allowing three to five normal breaths between compressions in an attempt to keep the blood gas concentrations constant.

Signal Processing

To remove artifacts from ECG, and automatically calculate the DEMG-based onset time of inspiration, raw DEMG signal is subjected to signal processing [26]. Since main energies of ECG and DEMG spectra do overlap, standard linear filtering techniques did not yield satisfactory results. Therefore, a novel ad-hoc filtering technique had to be developed. The procedure is depicted in Fig. 5.

For each breath, DEMG sequences are extracted consisting of 45% of the previous expiration and 55% of the following inspiration, based on the volume-based onset of inspiration. As only the low frequency contents of DEMG are of interest, the sequences are low-pass filtered at 100 Hz and decimated to a sampling rate of 200Hz. Each DEMG sequence is then full wave rectified. A moving standard deviation filter is moved over the sequence, and every sample exceeding 4σ is set to the mean value of the current window. This step is sufficient to remove most of the R-wave of ECG. To remove the

remaining R-wave spikes, a zero-phase moving median filter is applied. In both filters, the window width of 255 ms was chosen to be wider than twice the width of the R-wave. The segment of each sequence preceding the volume-based onset except the last 200 ms is assumed to contain zero diaphragm activity, thus, approximated by a horizontal straight line with offset being the median of this segment. The segment succeeding the volume-based onset except the first 200 ms is approximated by a straight line, as early DEMG is assumed to increase linearly. Offset and slope are calculated by linear regression. Finally, DEMG-based onset

is determined by calculating the intersection point of the two straight lines.

III. RESULTS

A total of 98 min of airflow and DEMG data was recorded during experimental sessions. The data contained 1127 breaths, in 247 of them a manual compression of the abdomen was applied during expiration. Calibrated integration of the flow signal revealed a deflation of the lungs by 400-600 cm³ due to the manual compression. Since an earlier onset of inspiration corresponds to a decrease in duration of the previous, compressed breath, the postulated earlier onset after manual compression was demonstrated by comparing total cycle durations of compressed breaths, $T_{tot,comp}$, with those of non-compressed normal breaths, $T_{tot,normal}$. A typical sequence of two normal breaths followed by a compressed breath is shown in Fig. 6. In the upper trace, air-flow is displayed. Positive values indicate inspiration. During the third expiration, at approx. $t = 26$ s, expiratory flow is constant for around 250 ms, then the forced expiration by manual compression can be seen. Immediately after the manual compression, the next inspiration occurs. In comparison to the two previous breath durations (avg. $T_{tot,normal} = 3.883$ s), the duration of the compressed breath is almost one second shorter ($T_{tot,comp} = 2.978$ s).

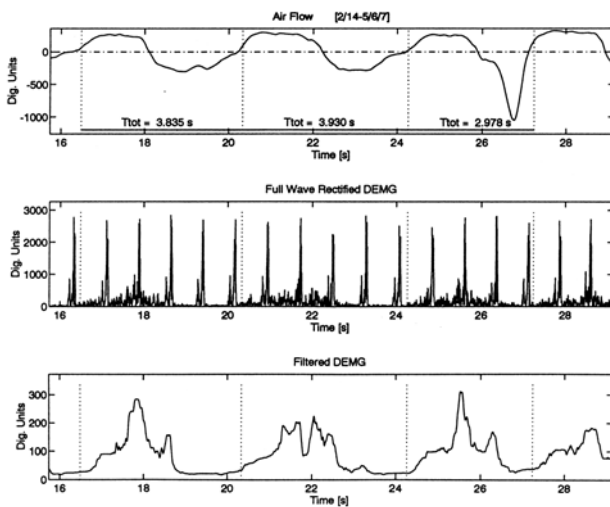


Fig. 6: A sequence of two normal breaths followed by a compressed breath of subject B. Inspiratory flow is positive. Onset of inspiration occurs immediately after the manual compression applied at $t = 26.3$ s.

Figure 7 shows the distributions of normal, non-compressed and compressed breathing cycle durations from one subject. The difference in duration of compressed (solid) and normal breaths (dotted bars) is clearly discernible, the slight skewness towards longer durations of the non-compressed breaths has been observed in all subjects, and may be in part attributed to sporadic occurrence of swallowing.

Results of all 5 neurologically intact subject are depicted in Table 1. The average cycle duration of compressed breaths, $T_{tot,comp}$, was reduced to 78.6% of the duration of normal, uncompressed breaths, $T_{tot,normal}$, ranging from 70.6% to 81.3%. Significance of results was determined by a two-tailed Student t -test for each subject separately, as mean respiratory rate differed significantly between subjects.

A Lilliefors-test was performed to justify the application of the Student t -test. The t values satisfied a $p < 0.001$ for all subjects. In addition, a non-parametric statistical evaluation using the Wilcoxon Rank-Sum Test (Mann-Whitney U)

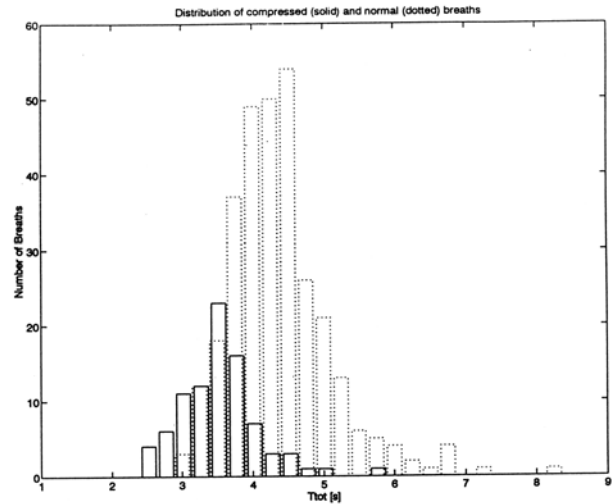


Fig. 7: Histogram of subject A showing distributions of T_{tot} for normal quiet breathing (dotted bars) and breaths in which abdominal compression (solid bars) was applied. Note the clear shortening of T_{tot} for compressed breaths.

was performed in the event that the data were truly not normally distributed, and yielded significance as well. Comparing the mean cycle duration T_{tot} of two normal breaths preceding a compressed breath with the duration of the compressed breath on the whole set of data of all subjects consistently revealed an average ratio of 0.783. These "Pill Electrode Experiment" results correspond to an increase in respiratory rate of about 128%, and are of the same magnitude found in the FESAM experiments.

IV. DISCUSSION AND CONCLUSIONS

A very mechanistic view describes reflexes as involuntary and unconscious, predictable, uniform, and definite responses of the organism to specific stimuli that have been sensed. The diaphragm itself is known to be poor in muscle spindles and a stretch reflex mediating the momentary state of the diaphragm, which would evoke a contraction of the diaphragm in response to an upward movement caused by the compressed abdominal contents, is unknown. The possibility that the earlier onset of DEMG in the pill electrode experiments is not due to a reflex, but to conscious response to the applied compression is not

Subject	age	N_{norm}	$T_{tot, norm}$	N_{comp}	$T_{tot, comp}$	$T_{tot, comp} / T_{tot, norm}$	t	non-par
A	46	307	4.384 (0.728)	88	3.503 (0.549)	0.799	10.5*	+
B	22	249	3.442 (0.450)	57	2.798 (0.447)	0.813	9.8*	+
C	21	60	9.156 (1.571)	26	7.232 (1.029)	0.790	5.7*	+
D	25	163	4.198 (0.536)	47	3.229 (0.394)	0.769	11.5*	+
E	28	101	8.166 (2.098)	29	5.765 (1.391)	0.706	5.8*	+
All		880		247		0.786		

Table 1: Data of neurologically intact subjects A-E. Age in years; N_{norm} : number of normal, uncompressed breaths; $T_{tot, norm}$: mean (sd) duration of uncompressed breaths; N_{comp} : number of compressed breaths; $T_{tot, comp}$: mean (sd) duration of compressed breaths; ratio of $T_{tot, comp}$ vs. $T_{tot, norm}$; t: Student t value, *: $p < 0.001$; non-par: result of non-parametric Wilcoxon Rank-Sum test of significance.

supported by the observed increase in respiratory rate results from the experiments with SCI individuals. These subjects were complete quadriplegics, and the only intact afferents known to be relevant in the respiratory system are the vagus nerves. A conscious response to sensations of the applied lung deflation by electrical stimulation of the abdominal muscles thus can be excluded. As these experiments were conducted with both neurologically intact subjects and subjects with SCI, it is difficult to imagine the observed effects in total absence of the deflationary HB reflex. However, manual compression of the abdomen was applied to neurologically intact subjects in this present study, and contribution from conscious sensations cannot be totally excluded. On the other hand there is only a small chance that conscious reactions exclusively contributed to the observed increase in respiratory rate. The deflation of the lungs in the present study was accomplished by compression of the abdomen, a method different from all previous studies on the HB reflexes. At first sight, the different methods (negative pressure deflation, chest compression, manual abdominal compression, and compression by electrical stimulation of abdominal muscles) are equivalent. Each method is deflating the lungs, and the deflation of the lungs is modifying stretch receptor discharge that elicits the HB reflexes.

From this point of view the question why the results of the present study clearly suggest the presence of the deflationary HB reflex in adults, which previous studies failed to, is still unanswered. A closer look at different ways of deflating the lungs might reveal, why our novel method was able to elicit the HB reflex. It can be assumed that in previous methods the lungs were deflated evenly across their whole volume, with both negative pressure or chest compression by an inflatable jacket. Abdominal compression, however, pushes the abdominal contents up against the diaphragm, which itself is pushed up and, in the first moment, compresses the lower parts of the lungs only, until the change in volume is leveled across the whole extent of the lungs after a delay determined by the mechanical properties of lung tissue, chest and abdomen. This heterogeneous lung deformation might be sufficient to locally decrease stretch receptor discharge, which reduces vagal feedback significantly enough for the central

inspiratory drive to initiate the next inspiration. Nevertheless, this concept would require a selective sensibility to local lung deflation rather than to total averaged lung volume, represented by integrated vagal activity. Signals from receptor organs, transmitted by afferent neural pathways, projected to efferent motor neurons via mono- or polysynaptic spinal connections, or supraspinal connections, may serve some adjustive or protective purposes.

In fact, there was and still is controversy as to how to define a reflex. As there is variable facilitating and inhibiting influence to any spinal synaptic junction from higher regions, reflexive responses are not uniform, can often be voluntarily modified, and can sometimes even be consciously influenced.

The experiments in this present study revealed that the next onset of inspiration occurred sooner, the earlier the compression was applied after the onset of expiration. Clark and von Euler [28] observed that the inspiratory HB reflex was elicited as soon as a volume threshold was exceeded in experiments with cats. In this case, the threshold for an inflating pulse to terminate inspiration was higher during early inspiration, and decreased with progressing inspiration. A similar, dynamic threshold operating in the deflationary HB reflex has not been described previously.

Our observations may be due to the fact, that the earlier the deflationary threshold was reached the earlier the next inspiration could follow, rather than a dynamic threshold. It is conceivable that the compressions were powerful enough to deflate the lungs below the threshold at any point of time during expiration, and a dynamic threshold, if present at all, did not play any significant role.

Extreme care was taken to apply the compression during expiration to prevent spurious results. If compression had been applied during late inspiration, it had been possible that the deflation was not terminating inspiration and was not inducing expiration, and the current inspiration would have been continued after the deflation. What then looked like an earlier onset of the next inspiration would have

rather been the continuation of the current, interrupted inspiration.

In summary, this series of experiments has presented strong evidence that the deflationary HB reflex is present and can be evoked in human adults. A novel way to elicit this reflex was developed (by abdominal compression), which seems to be more successful than previously described and applied methods. The usage of a swallowable pill electrode allowed recording intraesophageal DEMG as a measure of central respiratory drive. An ad-hoc filtering method was designed to successfully remove ECG artifacts from the DEMG signal using statistical median and standard deviation operations. The onset detection algorithm linearly approximated the rise of DEMG activity and was able to find the onset of inspiration very reliably.

The data of this study clearly support the hypothesis that manual compression of the abdomen hastened expiration, and resulted in the earlier onset of the next inspiration. However, we acknowledge that these results oppose the current opinion, that the HB reflex are weak or absent in adult human individuals. The conclusion drawn by some of the previous studies that the inability to demonstrate the HB reflexes at the same time excludes the influence of lung volume related feedback in the control and regulation of respiration is questionable. The protective role of the HB reflex might have been replaced to a certain extent by other mechanisms, e.g., closing of the glottis, but it is difficult to think of a respiratory control mechanism that operates without information on the state of the lungs. Based on the significant results of this study, it is suggested that the mechanisms that manifest themselves in what is commonly referred to as HB reflexes are present in adult human individuals, although the HB reflexes themselves, as a pronounced manifestation in response to a externally imposed stimulus, might be obscured, or weaker and more difficult to elicit than in animals and newborn infants.

Based on the results obtained, more investigations are required to quantitatively describe the properties of this revealed *hidden loop*. Then, it will be possible to design quantitative models of the respiratory system including chemical and mechanical feedback loops that can be utilized to design controllers, e.g., for assisted ventilation by FESAM.

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