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# **Functional Magnetic Nerve Stimulation:**

The development of a method of generation of explosive expiratory flows in the intubated patient through abdominal muscle stimulation.

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## **Abstract**

### **Functional Magnetic Nerve Stimulation: The development of a method of generation of explosive expiratory flows in the intubated patient through abdominal muscle stimulation.**

A voluntary cough is an explosive expiratory manoeuvre where the larynx is closed during the early expiratory phase. Subsequent opening of the larynx generates high peak flows to facilitate the removal of mucus and inhaled material from the large airways.

The objective of the thesis was to explore the mechanics of a voluntary cough and develop a surrogate voluntary cough with application to the intubated critical care patient.

The thesis developed an understanding of voluntary cough mechanics through a variety of laboratory and clinical models. A modification of the classic Starling Resistor demonstrated that during a peak expiratory flow (PEF) manoeuvre, the addition of a surrogate larynx produced a significant reduction in the time to develop a peak flow, 0.2 to 0.04 seconds.

In clinical trials of the surrogate larynx, cough mechanics were compared with a PEF. A large rise in esophageal pressure ( $P_{es}$ ) ( $118\text{cmH}_2\text{O} \pm 14\text{cmH}_2\text{O}$ ) was a signature of a voluntary cough when compared with  $P_{es}$  during a PEF ( $66\text{cmH}_2\text{O} \pm 9\text{cmH}_2\text{O}$ ). The addition of a surrogate larynx during a PEF created an elevation in  $P_{es}$  and rapid rise in peak flow, comparable to a voluntary cough. Observation of the transdiaphragmatic pressure ( $P_{di}$ ) suggested that thoracic muscles contribute to the elevation in  $P_{es}$  during a voluntary cough.

Though gastric pressure is applied as a surrogate marker of abdominal pressure, the validity of this was confirmed in a clinical trial when compared with actual abdominal pressure recorded with a laparoscope.

The surrogate cough model considered for application to the critical care subject was the application of functional magnetic nerve stimulation of the abdominal muscles in intubated patients during sedation or anaesthesia. The development of this model needed to consider the deleterious effects on the force of muscle contraction following

anaesthesia with Propofol, and the potential for abdominal muscle stimulation to provide the force driving a voluntary cough. A clinical trial observed a reduction in twitch strength of 14% - 28%, following magnetic nerve stimulation of the phrenic nerve with Propofol anaesthesia. The magnitude of the effect of the abdominal muscles upon expulsive manoeuvres was also considered. In a clinical trial, spinal anaesthesia, with the loss of abdominal muscle function, diminished maximum expiratory pressure compared with baseline value ( $P = 0.003$ ), with no observed reduction in maximum inspiratory pressure.

Cough function in subjects following a laryngectomy observed the changes in  $P_{es}$  during a volitional cough. The objective was to observe if the rise in  $P_{es}$  may or may not be related to laryngeal closure. The observations were that the volitional "cough" generated a large elevation in thoracic pressure with (145cmH<sub>2</sub>O) that exceeded the maximum abdominal pressure (126cmH<sub>2</sub>O), but there was no rapid rise in time to peak flow. The latter could be reversed with the addition of a surrogate larynx.

Testing of the surrogate cough model in anaesthetised subjects demonstrated the potential of the model to reproduce some elements of a voluntary cough. However, the expiratory flow generated was limited even in the presence of a surrogate larynx. The surrogate larynx confirmed that it supports the rapid rise in expiratory flow but does not promote a rise in thoracic pressure.

Some elements of the thesis objective were realised. A voluntary cough bears similarities to a forced expiratory flow manoeuvre. Thoracic muscles are actively recruited to support the rise in esophageal pressure characteristic of a voluntary cough. Laryngeal closure does not support the elevation in thoracic pressure but shortens the time to peak flow improving the force generated.

The complex pattern of expiratory muscle recruitment observed during a voluntary cough is not easily reproducible through magnetic nerve stimulation of the abdominal muscles. The mechanics of delivery of a surrogate cough applying magnetic nerve stimulation is perhaps too complex to have practical application to intensive care respiratory physical therapy. The thesis developed a model of pressure and flow generation of a voluntary cough that could have application to the development of alternative physical therapy techniques. In particular a surrogate larynx may find

practical applications to subjects following a laryngectomy or in critical care where the normal larynx is bypassed by an endotracheal tube.



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## **Chapter 1: Introduction**

Cough is a vagally mediated, defensive airway reflex consisting of a modified respiratory act aimed primarily at generating the high flow velocities required for removal of mucous or any other foreign body from the lower respiratory tract(Fontana and Lavorini, 2006). The essence of cough mechanics is an explosive expiratory manoeuvre where the glottis is closed during the initial expiratory effort. The sequences of events are(McCool, 2006):

- An initial deep inspiratory effort
- A forced expiratory effort against a closed glottis. This is demonstrable as a rise in pleural or intrathoracic pressure or a surrogate measure of these indices.
- Subsequently the glottis opens, releasing the pressure head with a sudden exhalation demonstrated as a rapid rise in flow. The flow is described as a supramaximal flow(Figure 1), where the peak flow achieved is greater than the peak flow achieved during a peak expiratory flow manoeuvre.

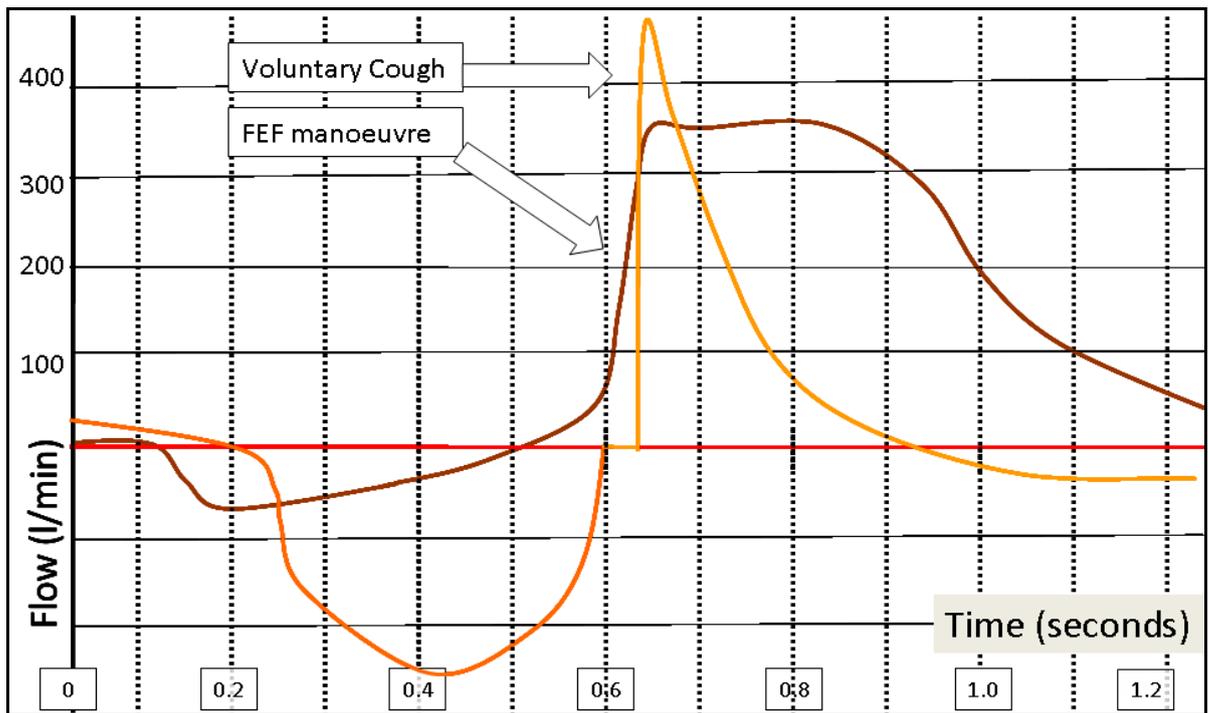


Figure 1. Schematic diagram comparing flow traced for a Forced Expiratory Flow (a) and voluntary cough. Flow trace copied from actual flow traces. Features to note

- Laryngeal closure interrupting cough flow at 0.6 seconds with a duration of about 0.03 seconds.
- Rapid rise in expiratory cough flow with glottic opening
- Final peak cough flow exceeding the peak of a FEF manoeuvre.

The initial cough effort may be followed by subsequent cough efforts or a “cough train”. An inspiratory effort may or may not precede each subsequent cough effort in the train.

The objective of a cough is the removal of inhaled material from the upper airways. This material may be native mucous or foreign material unintentionally inhaled from the pharynx or aspirated from the digestive tract.

The voluntary cough is but one element of protective mechanisms that are designed to maintain clear respiratory passages and allow the free movement of air, the other dominant element being the mucociliary escalator.

The voluntary cough may be compromised when:

- The volume of material to be removed overwhelms the ability of the cough mechanism.
- There is failure of some element of the laryngeal function that is sufficient to compromise the voluntary cough. Examples include laryngeal dysfunction in motor neurone disease or bulbar dysfunction following a brain stem cerebrovascular accident.
- There is generalised neuromuscular weakness that prevents the development of adequate pleural pressure or there is failure to co-ordinate the laryngeal elements of the cough mechanism.
- Through airway manipulation associated with anaesthesia and intensive care, and or the use of pharmacological nervous system depressants the cough mechanism is compromised.

When considering the patient receiving critical care respiratory support, the absence of an effective voluntary cough has several implications;

- A failure of voluntary cough through exhaustion, neuromuscular compromise(Suarez et al., 2002) or other factors that compromise voluntary cough mechanics will lead to respiratory compromise that may ultimately lead to respiratory failure.
- Compromise of a voluntary cough through endotracheal intubation, sedation, ventilation and paralysis will compromise normal cough mechanics leading to tracheal secretion retention.
- Restoration of normal respiration, extubation and recovery relies upon the presence of sufficient respiratory muscle function to support spontaneous ventilation and a voluntary cough to prevent the build up of tracheobronchial mucus that may ultimately lead to extubation failure.

Therefore, restoration and maintenance of tracheobronchial clearance will enable management and recovery from critical care(Ciesla, 1996). A failure to restore voluntary cough function is a predictor of extubation failure(Smina et al., 2003) and death on the critical care unit(Smina et al., 2003).

The current solution to the challenge of maintaining tracheobronchial toilet is through the application of respiratory physical therapy techniques (McCool, 2006) such as manual hyperinflation, chest percussion and cupping. A surrogate cough mechanism, applicable to the intubated ventilated patient, could complement current supportive respiratory therapy techniques.

The objective of this study is therefore, to develop an alternative respiratory therapy technique that harnesses spontaneous voluntary cough mechanics. The development of a surrogate cough mechanism requires an understanding of the mechanics of a voluntary cough. The introduction will review the mechanics of a voluntary cough, the mechanics of other forced expiratory manoeuvres and compare and contrast these manoeuvres with a voluntary cough. The introduction will examine clinical and bench models of a voluntary cough and consider which elements of a voluntary cough could be incorporated into a surrogate cough model that would have application on intensive care.

## **Chapter 2: Background**

A voluntary cough is an explosive expiratory manoeuvre where the glottis is closed during the initial expiratory effort. Subsequent opening of the glottis generates a supramaximal flow spike that is greater than the maximum generated during a peak expiratory flow manoeuvre (see below). An attempt to reproduce the mechanics of a voluntary cough requires an understanding of the relationship between the pressure and flow generated and the timing of the changes. However, the mechanics of a voluntary cough are less well described in particular the role of laryngeal closure. Therefore, though there are differences in the pressure/ flow profile of a FVC manoeuvre when compared with a voluntary cough (Figure 1) (Sivasothy et al., 2001), a review of the mechanics of the a FVC manoeuvre may realize significant physiological and mechanical elements that govern forced expiratory respiratory mechanics.

### **Forced Expiratory Flow Physiology**

A forced expiratory flow manoeuvre, a peak flow or a forced vital capacity manoeuvre are expiratory manoeuvres where, following a full inspiration, the participant forcefully blows out (Bongers and O'Driscoll, 2006). In the case of a forced

vital capacity manoeuvre the expiratory manoeuvre is complete when residual volume is reached. During a peak flow manoeuvre the measurement recorded is only that of the peak flow following a sharp exhalation. Though there are differences in the peak flows achieved with a forced expiratory flow and a forced vital capacity manoeuvre, these are of little clinical significance(Wensley et al., 2000) when considering the mechanics of flow.

The maximum flow achieved with either manoeuvre is limited through mechanisms that lead to collapse of the small airways(Goldberg et al., 2001). The peak flow limitation is described as an effort independent mechanism, which describes the fact that the peak flow cannot be raised even when a greater effort is applied. The time to achieve the peak flow during a peak flow manoeuvre is about 35mseconds(Knudson et al., 1974), with a volume acceleration of about  $300\text{l}\cdot\text{sec}^{-2}$ . The airway collapse begins sooner at low lung volumes than at high and as a result peak flows are achieved sooner at low than at high volumes(Knudson et al., 1974). The elements of the expiratory flow mechanics will be considered in more detail.

### **Effort Independence**

A Maximum Expiratory Flow Volume Manoeuvre (MEFV) is a forced expiratory manoeuvre(Figure 2). The test is performed following a deep inspiration and expiring to residual volume. The recorded values are dependent upon lung mechanics and the respiratory musculature. The curve depicting the MEFV, is a graphic reproduction of the manoeuvre and depicts air flow rate as a function of forced expired vital capacity, and demonstrates a reduction in flow as a function of lung volume(Abboud et al., 1995).

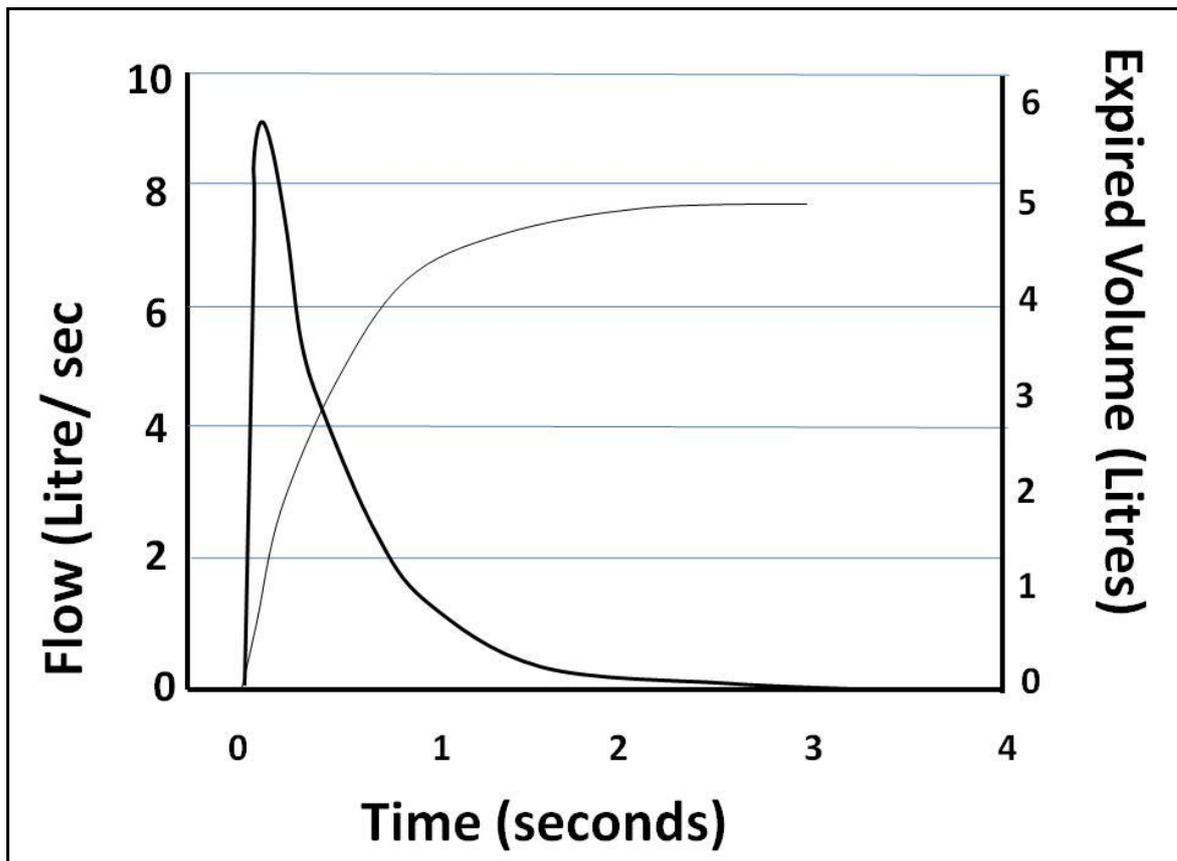
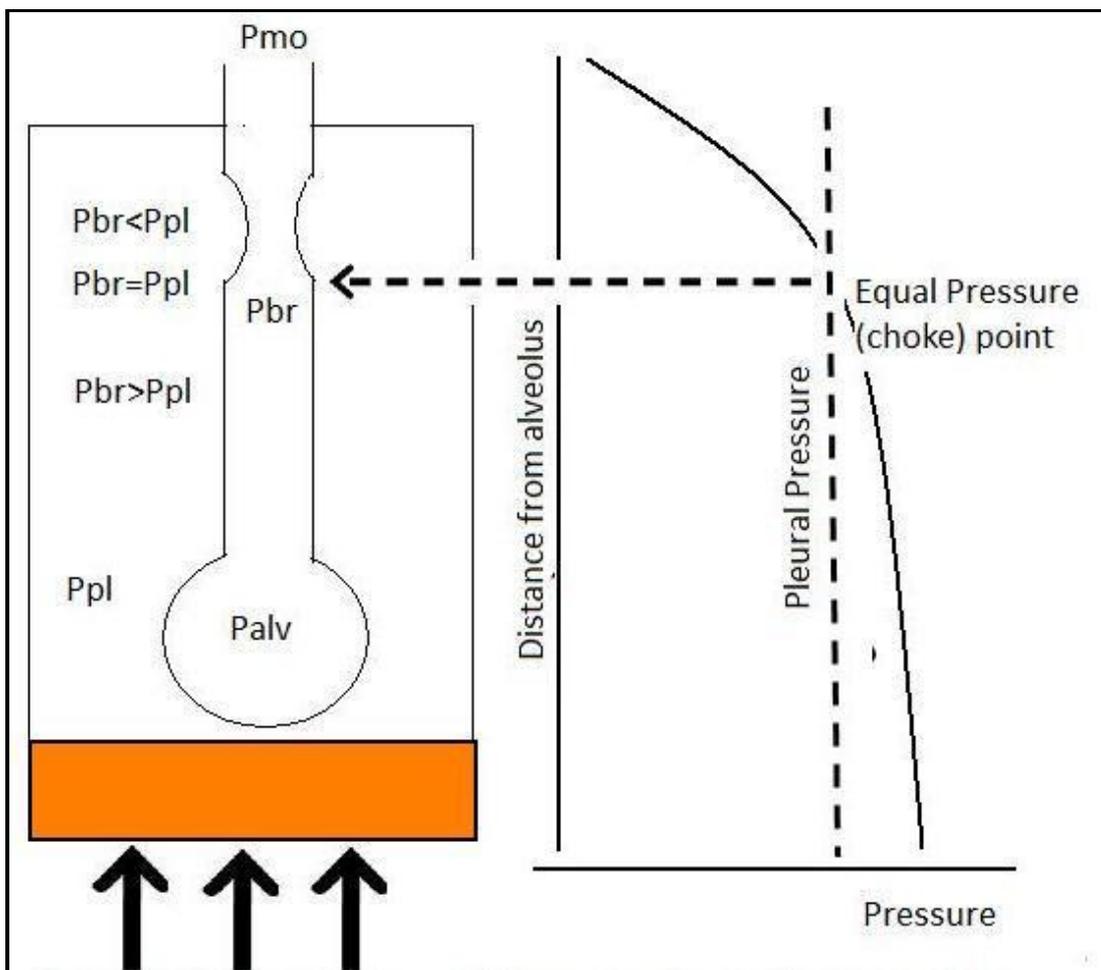


Figure 2. Maximum Expiratory Flow / Time and Flow / Volume Curves for a maximum expiratory flow volume manoeuvre (Personal Data).

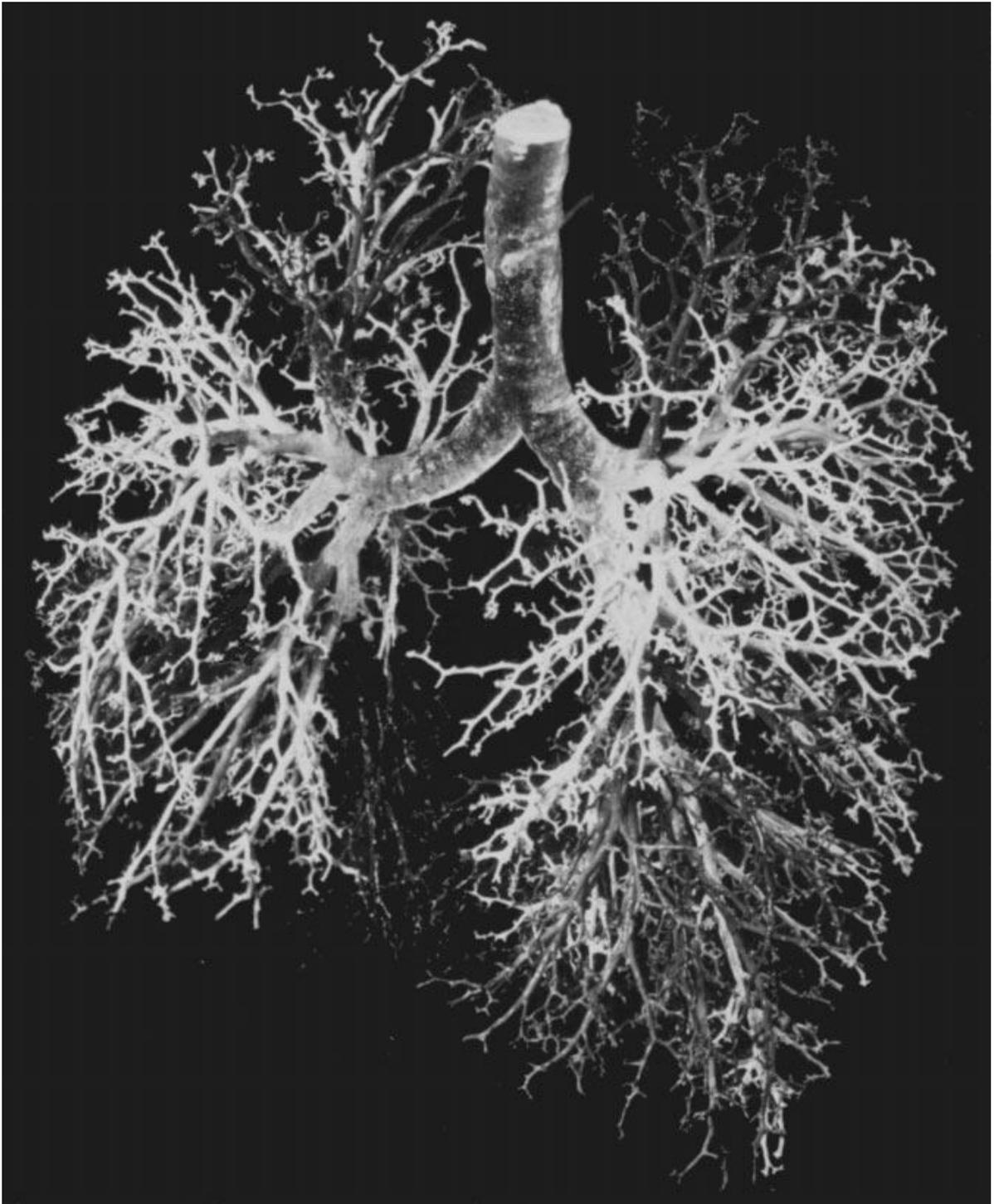
Models of the MEFV(Hyatt, 1983) manoeuvre consider the flow along the respiratory passages as arising upstream (*i.e. at the distal airways*) and flowing downstream (*i.e. to the large airways and trachea*). Flow will develop when the upstream pressure exceeds the downstream pressure. However, the respiratory passages are flexible and the forces that develop the upstream pressure also act to collapse the walls of the respiratory passages. The maximum flow achieved is therefore limited by the collapse of the large airways and the term *effort independence*(Tantucci et al., 2002, Dawson and Elliott, 1977) was coined by Mead to describe this phenomena. Mead described the position along the respiratory passages where airway wall collapse develops as the “*equal pressure point*” (*EPP*). The EPP(Figure 3) is a dynamic phenomenon that is related to the interplay of pleural pressure ( $P_{pl}$ ) and airway pressure ( $P_{aw}$ ) across the airway wall ( $P_{tm}$ ). During forced expiration there is a rise in  $P_{pl}$ , such that initially it rises from sub atmospheric to atmospheric. At this point the

EPP would be located at the airway opening. However, the rigidity of the laryngeal structures maintains the patency of the airway. Elevation of the Ppl beyond atmospheric shifts the EPP upstream, causing collapse of the trachea and large airways(Olsen et al., 1967). The location of the EPP varied with the lung volume at the commencement of the MEFV manoeuvre. That is at 70% lung volume, the EPP was at the level of the intrathoracic trachea(Macklem and Wilson, 1965, Pedersen et al., 1982, Begis et al., 1988), below 70% the EPP moved upstream as far as the lobar bronchi(Mead et al., 1967, Dawson and Elliott, 1977, Smaldone and Smith, 1985). Though the rigidity of the trachea resists collapse, the posterior muscular elements are known to herniate when exposed to a positive Ptm(Olsen et al., 1967, Teng et al., 2008, Walsh et al., 1995). At lung volumes above 70% of Total Lung Capacity (*TLC*), it is possible that the maximum flow achieved is effort dependent. That is collapse of the air passages is less likely to develop.



**Figure 3. Schematic Diagram illustrating the development of a choke point during a forced expiratory manoeuvre. Alveolar pressure ( $P_{alv}$ ) declines along the airway ( $P_{br}$ ) to reach zero at the mouth ( $P_{mo}$ ). Near the mouth, pleural pressure ( $P_{pl}$ ) exceeds  $P_{br}$  and a choke point develops.**

At lung volumes below 70% the site of airway collapse moves upstream (Pedersen et al., 1982) as far as the ninth generation as described by Weibel (Green et al., 1974) (Figure 4). However airways beyond the ninth generation, using Weibel's model, by virtue of their large number and the large collective area they present are unlikely to contribute to the measured airway resistance, unless expiratory manoeuvres are performed at very low lung volumes. This equates to airways smaller than 0.8 – 1mm internal diameter (Green et al., 1974).



**Figure 4. Cast of the human airway tree from the trachea extending out to the terminal bronchioles. Weibel estimated 20 bifurcations from trachea to alveoli. The alveoli have been trimmed away to make the airway tree more easily visible.**

### Airway Wall Oscillation

Dawson and Elliott(Dawson and Elliott, 1977) have further contributed to the concept of flow limitation through the development of the airway wall wave speed concept to explain the effort independent plateau on the forced expiratory flow curve. They considered the development of waves along the flexible portions of the airway walls. They showed that the flow developed cannot exceed the speed of wave propagation along the flexible wall of the airway. These waves arise from the interaction of the radial force of the elastic wall and the axial inertial force of the fluid. It has been argued that attempts to force fluid through flexible tubes at speeds greater than the wall wave speed would compromise the balance of forces across the tube wall. This model of flow limitation further developed the idea that the airway walls are flexible and respond to pressure across the wall in a dynamic manner. The dynamic motion of tube walls has been described by physicists and engineers, and is a feature of many biological systems(Grotberg and Jensen, 2004).

It was observed that stiffening the model airways increased the flow rate achieved, with comparable upstream pressure(Dawson and Elliott, 1977). This may be of clinical significance when later considering the supramaximal flow achieved during a cough manoeuvre.

### The Starling Resistor

Bench models reproducing the dynamics of flow along flexible airways have been developed. The most used laboratory model is that of the Starling resistor(Knowlton and Starling, 1912)(Figure 5). A flexible rubber tube (*Penrose tube*) acts as the airway(Figure 6) and the effects of pressure and flow variation can be observed. The observation of flow in flexible airway models has contributed to the concepts of wave speed and pressure waves, but these models have not been incorporated into models of cough mechanics, or specifically models of how laryngeal closure influences pressure and flow dynamics.

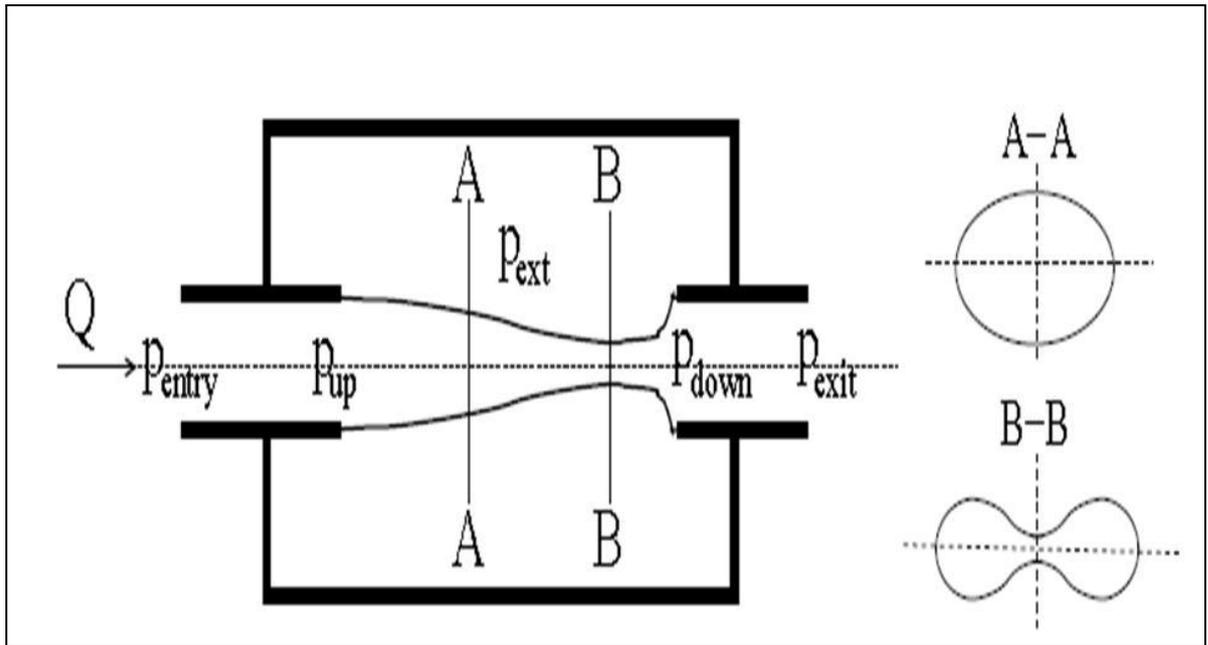
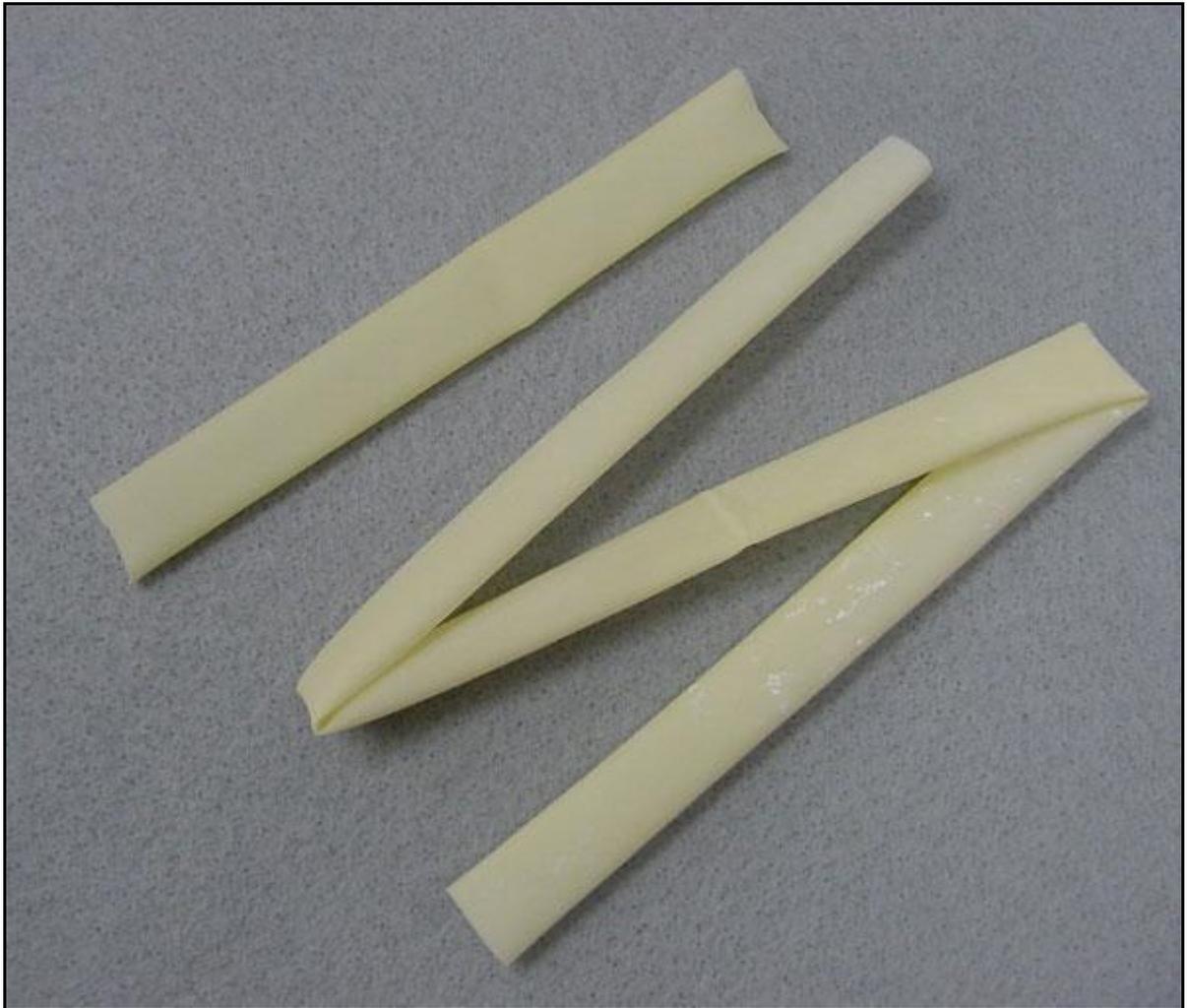


Figure 5. Sketch of Experimental Set-Up for Starling Resistor model of flow limitation. Cross section of tube at A-A and B-B.



**Figure 6. Natural rubber round, Penrose drain tube with regular smooth walls.**

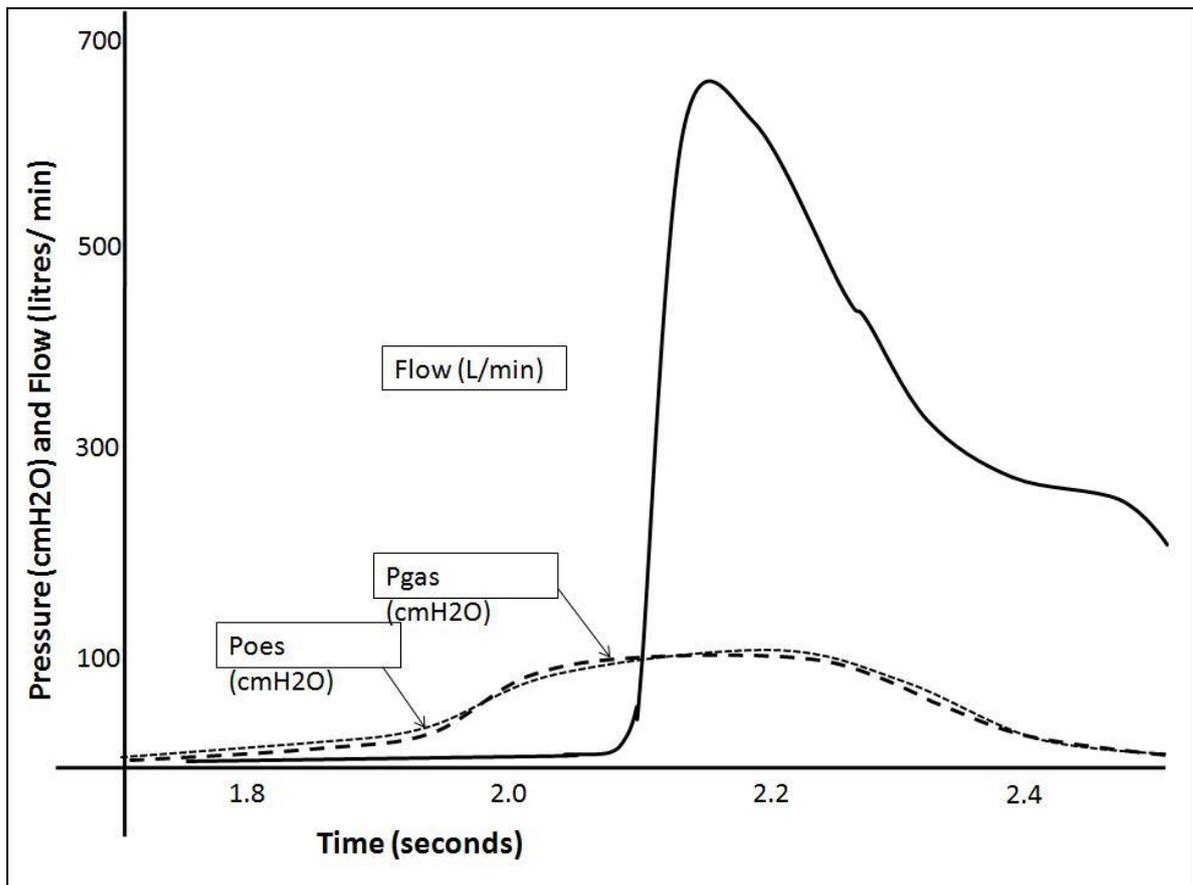
Though the Penrose tube adapted by Starling for his resistor is not comparable to the semi rigid structure of the trachea and large airways, the mechanics of expiratory flow limitation described in the Starling resistor, are observed in more complex tracheal models and supported by clinical observation. For example, Webster(Webster et al., 1985) and Walsh(Walsh et al., 1995) developed an artificial trachea with a latex membrane over a metal frame. Suction applied to the downstream end of the apparatus mimicked a forced flow manoeuvre. Flow limitation was observed as flow increased, with large wall oscillations downstream of a choke point. Aljuri(Aljuri et al., 1999, Aljuri et al., 2006) also observed flow limitation, in the excised trachea of humans, dogs

and sheep. The Penrose tube model, is therefore an acceptable model of flow mechanics, and this study will adapt the Starling resistor to investigate cough mechanics.

### **Voluntary Cough Mechanics**

A voluntary cough is a cough developed without mechanical or chemical provocation of the larynx or airway structures. Previous cough research has distinguished between the dynamics of a voluntary cough and that provoked by mechanical stimulation of the airways or inhalation with a noxious substance such as capsaicin or citric acid(Lavietes et al., 1998, Addington et al., 2008, Tatar et al., 1994, Piirilä and A.R.A., 1995). That is, the rise in Intra Abdominal Pressure (IAP), the peak flow and cough intensity has been identified as dependent upon the stimulus that provokes a cough(Tatar et al., 1994). The objective of this research is to understand the mechanics of a voluntary cough and to develop methods to reproduce those mechanics in anaesthetised subjects. Though the individual elements of a voluntary or provoked cough may differ with regard to the pressures and flows realised(Tatar et al., 1994), the relationships between flow, esophageal pressure, time and closing and opening of the larynx are comparable (Piiirila and Sovijarvi, 1995).

The prior discussion concerning the maximum expiratory flow manoeuvre makes clear that large airway collapse at the EPP limits the peak flow achieved. The peak flow achieved during a voluntary cough is however, greater or “supramaximal”(Ross et al., 1955) than achieved during a maximum expiratory flow manoeuvre. This observation requires consideration to explain the elements of a voluntary cough that are able to overcome the large airway collapse. The individual elements that make up a voluntary cough(Pennock, 1992) can be considered as(Figure 7):



**Figure 7. Voluntary cough demonstrating flow and pressure profile (Personal Data)**

### Inspiratory Phase

1. An inspiratory phase results in a large intake of air, up to 2.5 litres(McCool, 2006).

### Expiratory Phase

2. The subsequent forced expiratory phase has two elements(Pennock, 1992).
  - a. The initial expiration, lasting 0.1 - 0.2 seconds, occurs against a closed glottis(Pennock, 1992). There is contraction of the abdominal muscles with a volume reduction of the abdomen and an expansion of the thoracic volume(Pennock, 1992).

- b. Opening of the glottis leads to the next phase with rapid expulsion, over 0.5 seconds, of the up to 2.5 litres of air(Ross et al., 1955). Pleural pressures during the expulsive phase are 100 – 200mmHg, with maximum expiratory flow rates exceeding that of a maximum expiratory flow manoeuvre. The rapid exhalation corresponds to a contraction of the volume of the abdomen and thorax(Pennock, 1992).
3. The end of the expiratory phase may be followed by a subsequent short inspiration, and a further cough effort. This is described as a cough train(Hsu et al., 1994, Pennock, 1992), with each cough commencing at a lower lung volume than that preceding.

The features of a voluntary cough that set it apart from the maximum expiratory flow manoeuvre are

- A reduced time to reach peak flow
- The peak flow achieved is greater than achieved by a comparable maximum expiratory flow manoeuvre.
- The peak flow develops in advance of the peak pressure achieved.
- A maximum oesophageal pressure ( $>100\text{cmH}_2\text{O}$ ) and abdominal pressure that is greater than achieved by a maximum expiratory flow manoeuvre(Loudon and Shaw, 1967).

The peak pressure achieved contributes to dynamic compression of the large and medium airways. The rise in intrathoracic pressure contributes to a reduction in luminal diameter(Franklin and Janker, 1938). The consequence is an increase in velocity and an improvement in the expulsion of mucus downstream. However the increase in downstream resistance is less in a voluntary cough than during a maximum expiratory flow manoeuvre. By implication, this suggests that the transmural forces acting across the large and medium size airways are balanced in favour of the maintenance of the lumen in contrast to the airway collapse that typifies a maximum expiratory flow manoeuvre(Loudon and Shaw, 1967).

A variety of clinical and laboratory cough models, have been developed to expound an understanding of the physics responsible for gas flow in a voluntary cough.

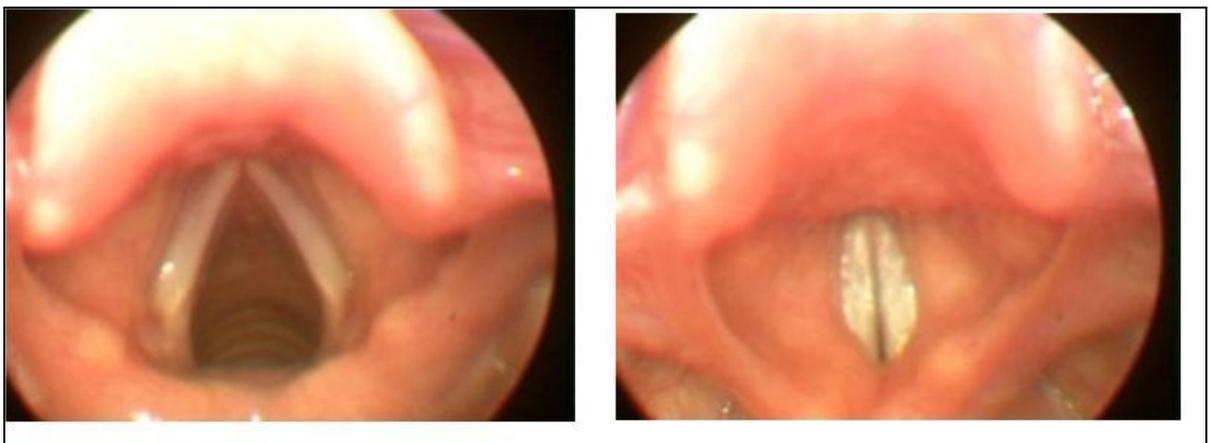
## **Cough Modelling**

An appreciation of the dynamics of forced expiratory manoeuvres can be gained by examining clinical and non-clinical or laboratory models. With respect of a voluntary cough, many of its features are comparable to a forced expiratory flow manoeuvre, and many features of the latter manoeuvre can be extrapolated to a voluntary cough.

An effective cough may be dependent on the generation of high linear velocities and interaction between flowing gas and mucus in the airways(Chang, 2006). A review of those various models of a voluntary cough could potentially indicate the key features that facilitate mucus removal from the large airways and thus need to be incorporated into a surrogate cough model.

### **Clinical Cough Models**

At the start of the cough manoeuvre, the glottis is clearly closed (Figure 8). Opening of the glottis will trigger a rapid rise in expiratory flow to a maximum(Figure 7).



**Figure 8. Photograph of vocal cords open and closed (Images taken from otolaryngology department, Sheffield).**

Therefore in a simplistic model if the glottis were replaced by a shutter valve, and a maximum expiratory effort were made against the shutter valve prior to its opening, the

resulting flow-time curve might be expected to be comparable to a voluntary cough. Knudson observed that the flow-time curve for the shutter valve expiratory manoeuvre, described as a triggered transient flow, generated a peak expiratory flow in excess of that seen during a normal maximum expiratory flow manoeuvre<sup>(Knudson et al., 1974)</sup>. Mead also observed that in contradistinction to a very simple shutter valve model of a voluntary cough, laryngeal opening was not instantaneous, but occurred over a period(Knudson et al., 1974) of 0.025 – 0.03 seconds. These clinical observations support the paradigm that vocal cord closure and then opening is responsible for the enhanced expiratory flows observed during a voluntary cough. In addition, vocal cord function during a voluntary cough probably goes beyond a shutter valve mechanism if controlled abduction occurs. The resistance to expiratory flow developed through incomplete vocal cord closure may be sufficient to prevent the fall in transmural pressure seen during a MEFV manoeuvre with the additional resistance elevating the airway pressure sufficiently to move the EPP to distal airway elements, whose impact upon the flow time curve is limited.

Baier(Baier et al., 1977) also observed that vocal cord adduction contributed to an increase in airway resistance during forced flow manoeuvres and voluntary coughs. Vocal cord dysfunction contributes to cough dysfunction in subjects with motor neurone disease(Chaudri et al., 2002). Therefore, the development of a surrogate cough needs careful consideration of cough dynamics and in particular the role of the larynx.

### **Voluntary cough compromise**

A voluntary cough requires the co-ordinated action of abdominal and thoracic muscles, the larynx and functioning airways. Compromise of any part of the mechanics of a cough may prejudice the effective removal of airway mucus. Observation of patients with compromise of cough mechanics will determine the relative roles of the constitutive elements and contribute to the development of surrogate cough mechanisms. The absence or compromise of a voluntary cough is a feature of acquired or inherited neuromyopathies(Chaudri et al., 2002, Szeinberg et al., 1988, Park et al., 2010), strokes, cervical spine trauma, bulbar palsy and other disorders of laryngeal and bulbar function, inherited and acquired respiratory diseases such as chronic airflow

limitation, emphysema, cystic fibrosis etc. Sedation and anaesthesia, and in particular where artificial respiratory support is augmented will compromise cough function through sedation, muscle paralysis and bypass of vocal cord mechanics.

Diseases that limit the force generated, such as muscular dystrophy demonstrate a reduction in peak flow generated (Szeinberg et al., 1988). The muscle relaxant curare when given to normal subjects, reduces the dynamic compression of airways during a voluntary cough similarly reducing the peak flow generated (Arora and Gal, 1981). Chronic airflow limitation compromises peak flows through reduction in airway diameter (Tiddens et al., 1996, Moretti et al., 1997). Patients with motor neurone disease and bulbar dysfunction are unable to generate a supramaximal flow spike (Chaudri et al., 2002). The conclusion is that generation of the supramaximal flow spike is dependent upon the totality of the mechanics of a voluntary cough, and not limited to one particular action. The investigation of a voluntary cough mechanics through a bench model will enable an observation of the role of the individual elements of a cough.

### **Cough and the action of the respiratory muscles:**

**Overview:** A voluntary or reflex cough requires the complex co-ordination of many of the muscles involved in respiration and expulsive manoeuvres. A normal cough results from a high pressure gradient developing between the intrathoracic airways and the mouth (Arora and Gal, 1981, Addington et al., 2008). The closure of the larynx during early expiration is believed to contribute to the high intrathoracic pressures developed when compared with a forced expiratory flow manoeuvre, where the larynx is open throughout the expiratory phase. The rapid shortening of the expiratory muscles of the chest and abdomen facilitates the development of the high intrathoracic pressure. Therefore, the relative contributions and actions of the muscles groups involved needs to be considered if the mechanics are to be reproduced.

**Abdominal Muscles:** The anterolateral muscles of the abdominal wall (*Rectus Abdominus*, *External Oblique*, *Internal Oblique* and *Transversus Abdominus*) participate in a wide variety of expulsive manoeuvres. It is well known that each of these muscles may exhibit a specific or characteristic activity pattern during different

behaviours. The co-ordinated contraction of these muscles (Bolser et al., 2000b) generates a rise in abdominal pressure to over 100mmHg (Addington et al., 2008, Bolser et al., 2000b). Bolser demonstrated that all four anterolateral abdominal muscles are simultaneously and vigorously activated in a similar fashion during the cough reflex. The pressure generated by the abdominal muscles is greatest in the prone or head up position compared with the supine or recumbent position.

**Chest Muscles:** The intercostal muscles are generally regarded as being inspiratory (De Troyer and Estenne, 1988). However, the mechanics of the chest wall and the inspiratory muscles (*internal and external intercostals, levator sternae and transversus thoracis*) are complex and depend upon the orientation of the ribs and recruitment of the intercostals muscles (De Troyer et al., 2005). The mechanical effect of the individual intercostals muscles demonstrates a topographic distribution from caudad to cephalad and dorsal to ventral (Taylor, 1960). Muscles with the greatest mechanical advantage are preferentially activated during the respiratory cycle (Gandevia et al., 2006). Further the individual muscle groups cannot simply be ascribed an inspiratory or expiratory action; rather their action upon the rib cage needs to be considered in relation to the orientation of the rib cage. Neither the internal intercostals, nor external intercostals can be considered to be purely inspiratory or expiratory. The activation of the intercostal muscles is coordinated to deliver the optimum mechanical advantage for the lowest energy expenditure (Legrand et al., 1996, De Troyer and Wilson, 2000, Gandevia et al., 2006).

The complexity of the co-ordinated activation of thoracic muscles during expulsive efforts does not obviously lend itself to reproduction of action through neuroaxial electrical or magnetic nerve stimulation. In contrast, abdominal muscle recruitment is observed during expulsive efforts and the abdominal muscles act as a single unit with expiratory function (Bolser et al., 2000a). Therefore, spinal cord stimulation may recruit sufficient abdominal muscles to support an expulsive effort, albeit, less effective than would be the case with recruitment of the chest wall muscles.

**Diaphragm:** The diaphragm is predominantly, an inspiratory muscle. However, the diaphragm may be recruited during non-respiratory, expulsive efforts characterised by large swings in abdominal pressures (Al-Bilbeisi and Mc, 2000, DePalo et al., 2004). These manoeuvres include weight lifting and sit-ups. Through diaphragm contraction the transmission of abdominal pressure to the thorax is minimised, thereby reducing the negative haemodynamic effects of marked elevations in thoracic pressure (Gandevia and McKenzie, 1985, DePalo et al., 2004, Tomori and Widdicombe, 1969). However, where the diaphragm is paralysed, thoracic pressure swings are exaggerated during expulsive efforts unless the glottis remains open (Bolser et al., 2000b). Compromise of the cough effort is demonstrable where diaphragm paralysis is demonstrated (Gharagozloo et al., 1995).

**Larynx:** The action of the intrinsic laryngeal muscles has been observed in anaesthetised dogs (Sant'Ambrogio et al., 1997). The action of the laryngeal muscles varies according to the phase of the cough, which in this case was initiated by direct stimulation of the carina. During the inspiratory phase the posterior cricoarytenoid and the cricothyroid muscle were active. The former muscle abducts and separates the vocal folds, the latter muscle elongates the vocal cords. During the early expulsive phase the thyroarytenoid, and arytenoidus muscles are active bringing the vocal folds together. Cricothyroid activity is also seen. This phase is associated with a rise in intra-thoracic pressure. The recruitment of the laryngeal abductors, posterior cricoarytenoid and cricothyroid indicates the onset of the expulsive phase. The pressure flow relationship in the upper airways is alinear, and turbulence develops in the large airways at high flows. However, turbulence in the trachea is less than predicted when the glottis is included in pressure flow models (Baier et al., 1977). Modifications of glottic aperture during high flow manoeuvres may reduce the development of turbulent flow and improve peak flows generated.

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**Artificial Stimulation of Expiratory Muscles and Application to the Development of a Surrogate Cough.**

The artificial stimulation of voluntary muscles can be achieved through electrical activation of the muscle(DiMarco et al., 2005a), the motor nerve(Glenn and Phelps, 1985), the spinal cord(DiMarco et al., 2005b) or the motor cortex(Pascual-Leone et al., 1994, Day et al., 1989). Respiration has been achieved through both phrenic nerve and intercostal muscle stimulation(DiMarco, 2005). The latter has been achieved through electrical or magnetic nerve stimulation of the spinal cord or phrenic nerve(DiMarco et al., 2005a). That the diaphragm is the principal muscle of inspiration, simplifies the mechanics involved. Whereas forced expiratory manoeuvres involve multiple diverse muscle groups, generating variable forces and timings and therefore may require more complex stimulation paradigms to reproduce those mechanics.

The expiratory muscles may be stimulated through electrical stimulation of the abdominal muscles via abdominal surface electrodes(Stanic et al., 2000), posterior surface electrodes(Butler et al.) or epidural implanted electrodes(DiMarco et al., 2006). These techniques have been applied to patients with high spinal cord injury to augment expiration and a voluntary cough(Gollee et al., 2008). However, electrical stimulation is a less attractive option for the awake or weaning critical care patient where awareness of discomfort limits application, and implantation of spinal cord electrodes is impractical.

Magnetic nerve stimulation of the expiratory muscles is a pragmatic solution to the reproduction of cough mechanics through abdominal muscle stimulation. It has the advantages of being non-invasive able to generate supramaximal stimulation and with recent developments in magnetic nerve stimulators, functional stimulation profiles can be generated.

Magnetic stimulation applies Faraday's law, which states that, whenever a magnetic field changes, an electric field is induced. This induced electric field, if of adequate amplitude and duration, may generate sufficient current to stimulate peripheral nerves. In recent years, investigators have used magnetic stimulation to evaluate the

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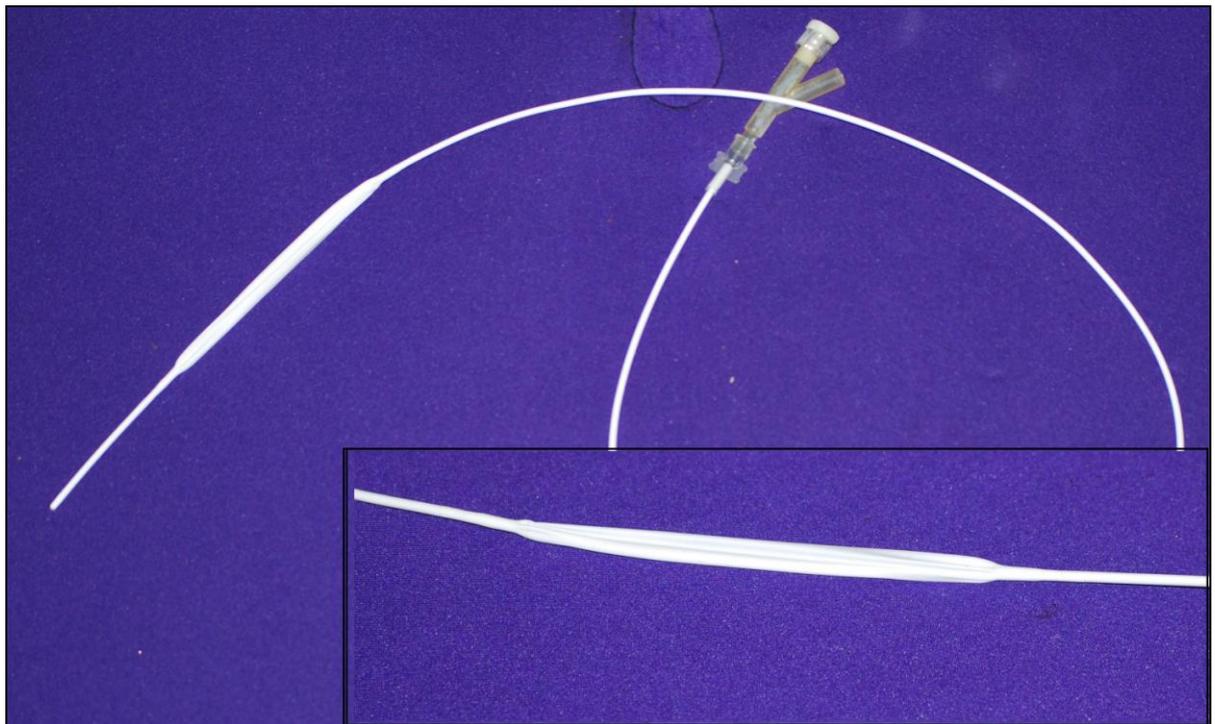
respiratory system by stimulating the phrenic nerves(Mills et al., 1996), thoracic spinal nerves, and the cortex. Magnetic stimulation is not as painful, when compared with surface electrical stimulation, does not require direct physical contact with the patient, and can be applied outside the clothing. Magnetic nerve stimulation may stimulate several nerve roots through one stimulator coil, when compared with surface electrical or epidural implants.

Recent technological developments in magnetic nerve stimulators also allow the delivery of prolonged stimulation protocols. These include stimulators delivering biphasic or repetitive supramaximal stimuli with a frequency up to 100Hz for up to 2 seconds. The thesis will explore the potential of functional magnetic nerve stimulation to develop effective expiratory muscle contraction.

## **Chapter 3: Measurement Methods**

### **Oesophageal and Gastric Pressure**

Gastric pressure ( $P_{ga}$ ), esophageal pressure ( $P_{es}$ ) and transdiaphragmatic pressure ( $P_{di}$ ) were measured using commercially available 10cm balloon-tipped catheters (Figure 9), 110 cm in length ((*Ackrad Laboratories, Cranford, New Jersey, USA*)), positioned according to methods described below. The esophageal balloon material is PVC (Polyvinyl chloride), radiation stable, with 70 A Durometer hardness. The material is 0.007 inches thick with a thickness tolerance of  $\pm 0.002$  inches. The manufacturer recommends the addition of 1.0 ml of air into the deflated balloon prior to measurement.



**Figure 9. 10cm Oesophageal Balloon Catheter with balloon (Inset) (Ackrad Laboratories, Cranford, New Jersey, USA).**

The balloon catheter was attached to the pressure transducer via a 100cm polyvinyl catheter, 1mm internal diameter. A three-way tap was placed at the transducer end of the balloon/ catheter set up, so that the balloon could be inflated and deflated. The pressure recording system for the balloon catheters consisted of a transducer amplifier (*143PC03D Honeywell control systems limited, Bracknell, Berkshire, England*). The flow and pressure signal was digitised using an analog to digital converter and passed through a signal sampler sampling at 200Hz. The signal was subsequently recorded and viewed in real time using customized Labview Software (*National Instruments, California, USA*). The transducer amplifier system were calibrated prior to each experiment by zeroing at room pressure and 100mmHg using a standard graduated mercury manometer.

Gastric (*Pga*) and Oesophageal (*Pes*) pressure was measured via two balloon catheters placed per nasally or orally into the stomach(Figure 10) and mid third oesophagus respectively. Confirmation of placement in the stomach was the presence of a positive pressure deflection during inspiration and manual palpation(Figure 11) and an absence of cardiac pulsation(Benditt, 2005)(Figure 12). Confirmation of placement of the oesophageal catheter is through the dynamic occlusion test described by Milic Emmili and later modified by Baydur(Baydur et al., 1982, Milic-Emili et al., 1964a). In this test the subject makes inspiratory and expiratory efforts against a closed airway. Equivalence of mouth pressure (*Pmo*) and *Pes* over a range of pressures during respiratory effort is believed to ensure the accuracy of the *Pes* measurement(Figure 13).

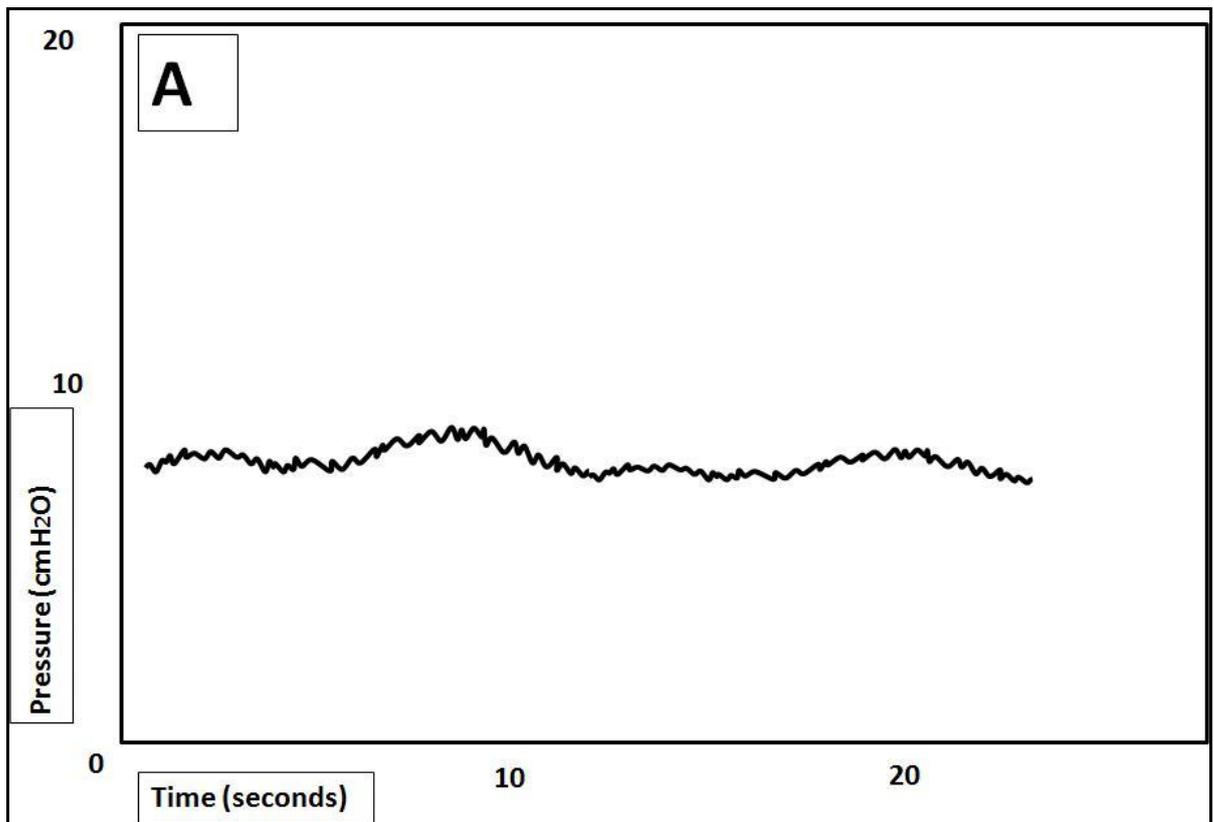


Figure 10. Balloon Catheter Pressure Trace recording intragastric Pressure at 8cmH<sub>2</sub>O.

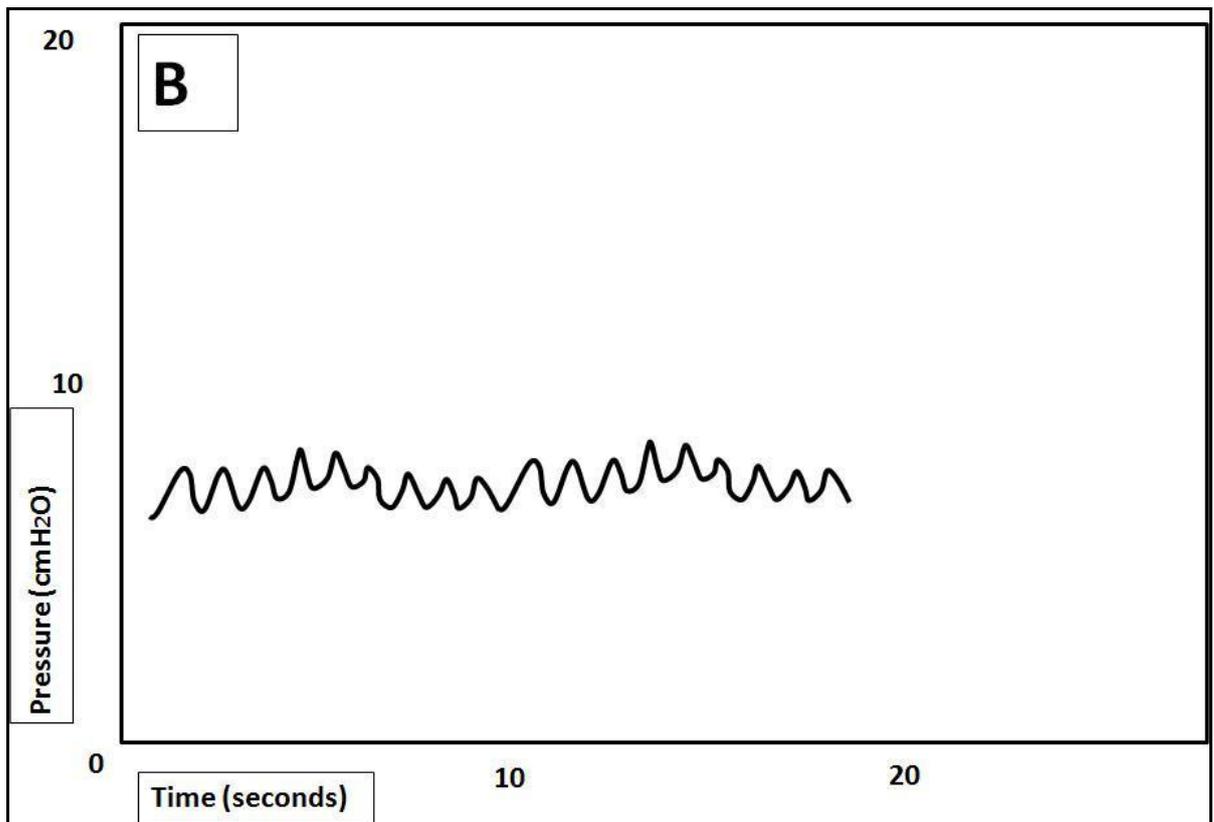


Figure 11. Balloon Catheter Pressure Trace recording sharp upswings in gastric pressure associated with manual compression of the abdomen.

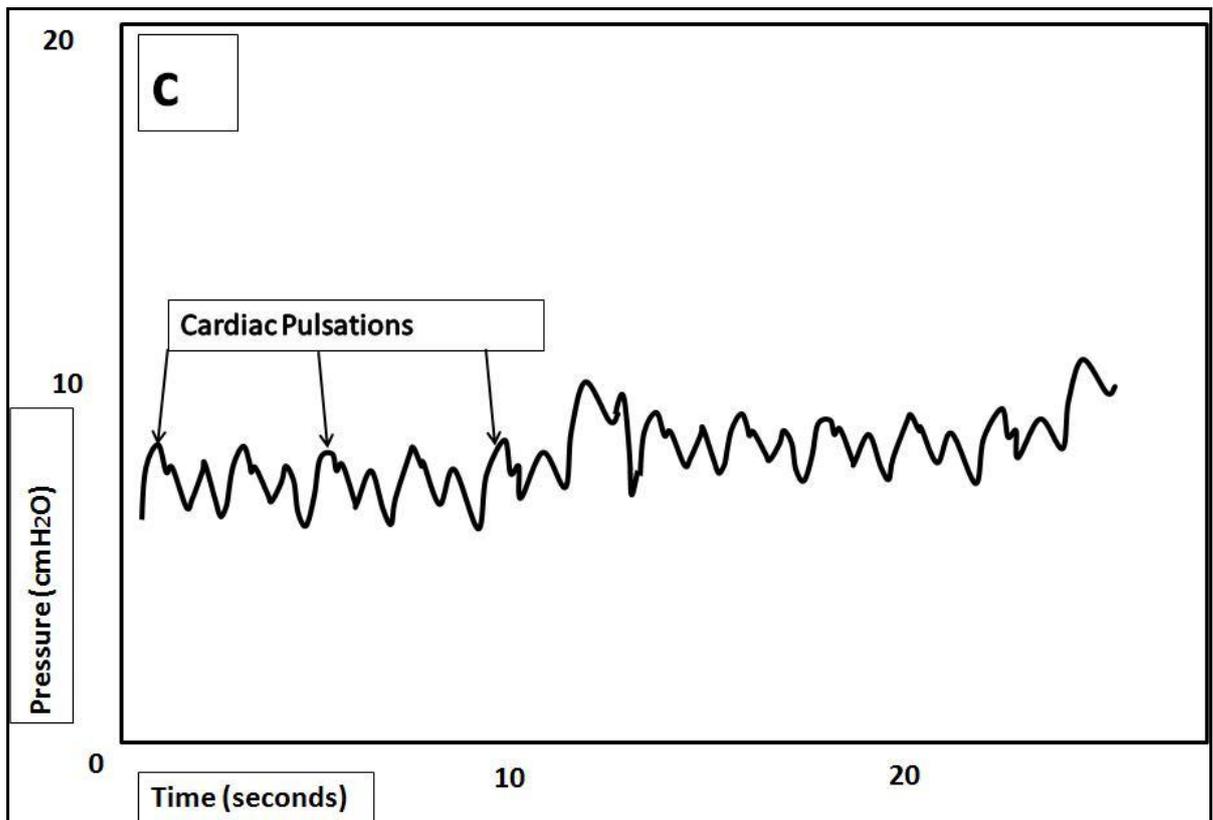
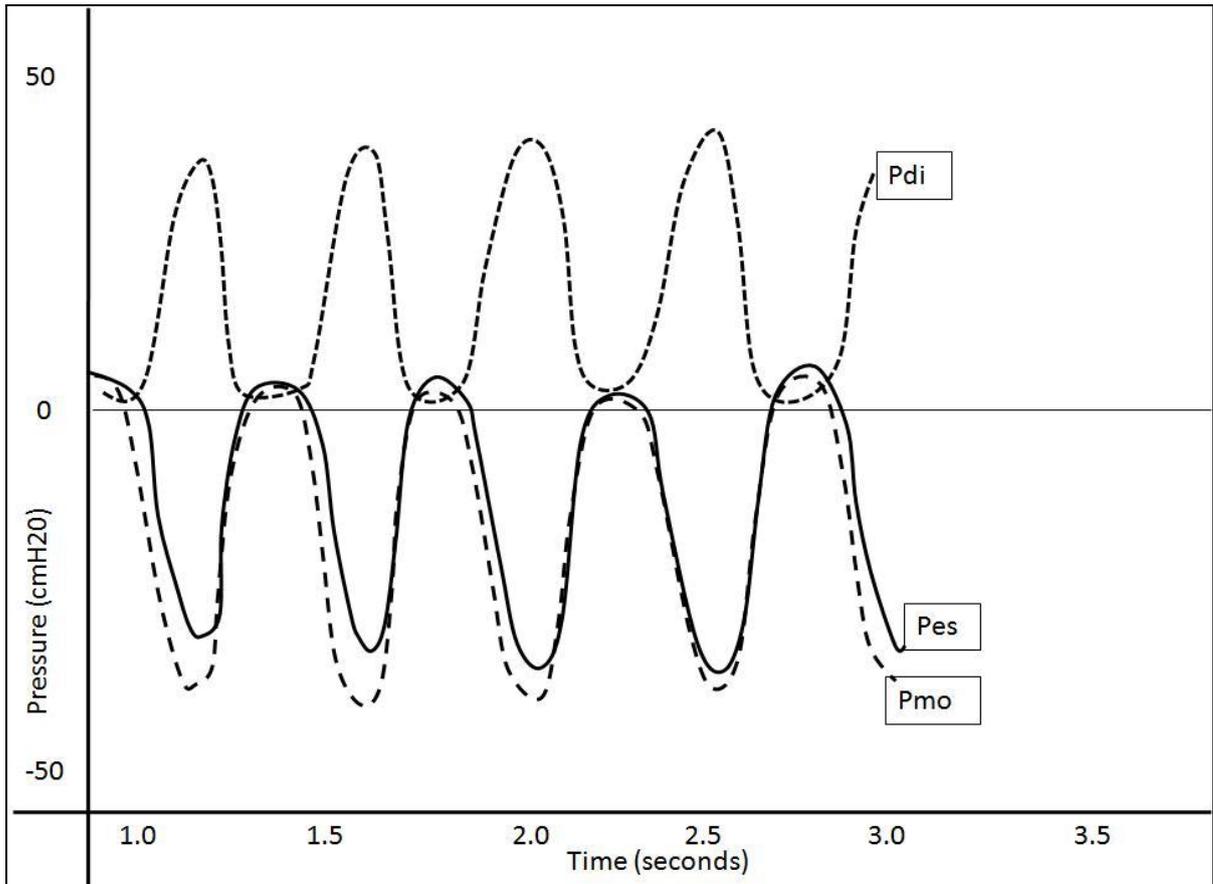


Figure 12. Balloon Catheter Pressure Trace recording cardiac pulsations associated with mid-oesophageal placement. Images acquired during gastric pressure study.

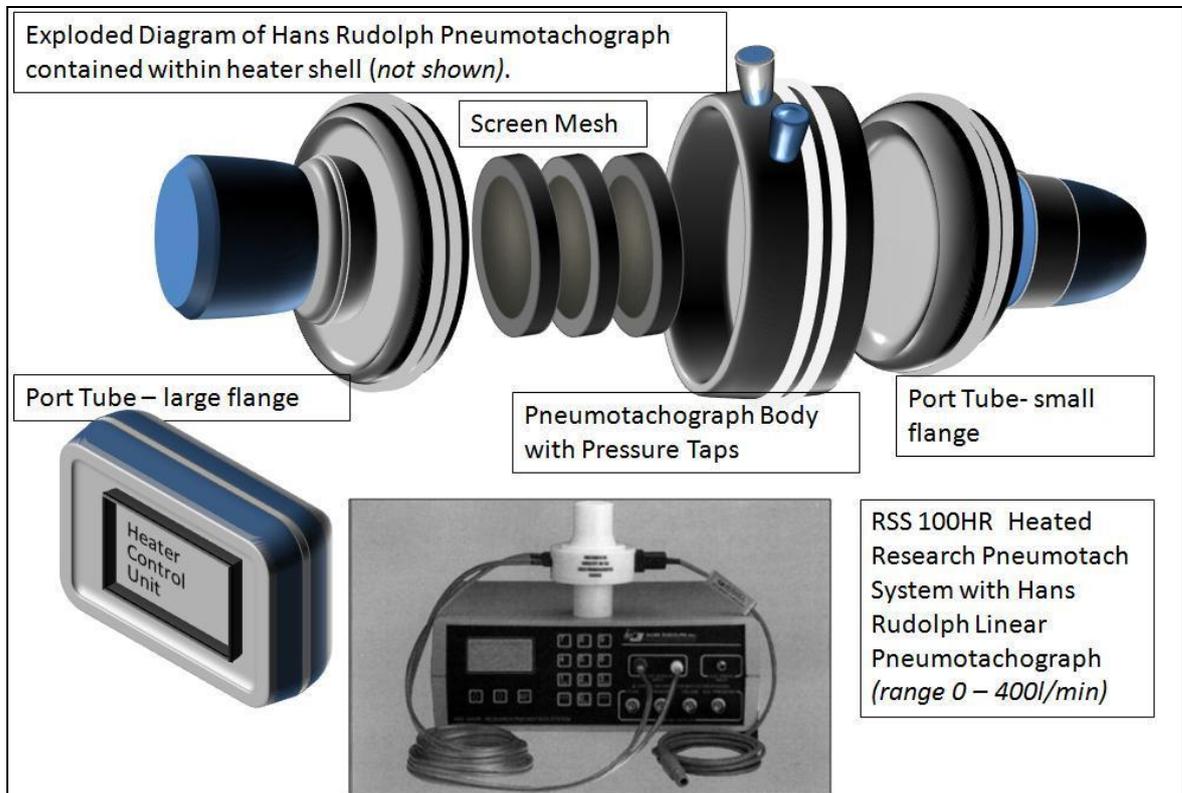


**Figure 13.  $P_{es}$  and  $P_{mo}$  pressure changes during confirmation of correct placement of oesophageal catheter during occlusion method described by Baydur and Milic-Emili.**

### Respiratory flow Measurement

Respiratory flow was measured with a heated screen type pneumotachograph (*Hans Rudolph* linear to  $0 - 400\text{l}\cdot\text{min}^{-1}$ )(Figure 14). Volunteer subjects sat quietly and comfortably. Each wore a nose-clip and breathed *via* a wide-bore mouthpiece into an open circuit comprised of the pneumotachograph and a two-way valve. The flow signal was obtained from a bidirectional transducer, amplified, and fed to an A-to-D converter). The signal was digitized at 200 Hz and then transmitted to a computer. The data processing program (*Labview, National Instruments, California, USA*) was used to

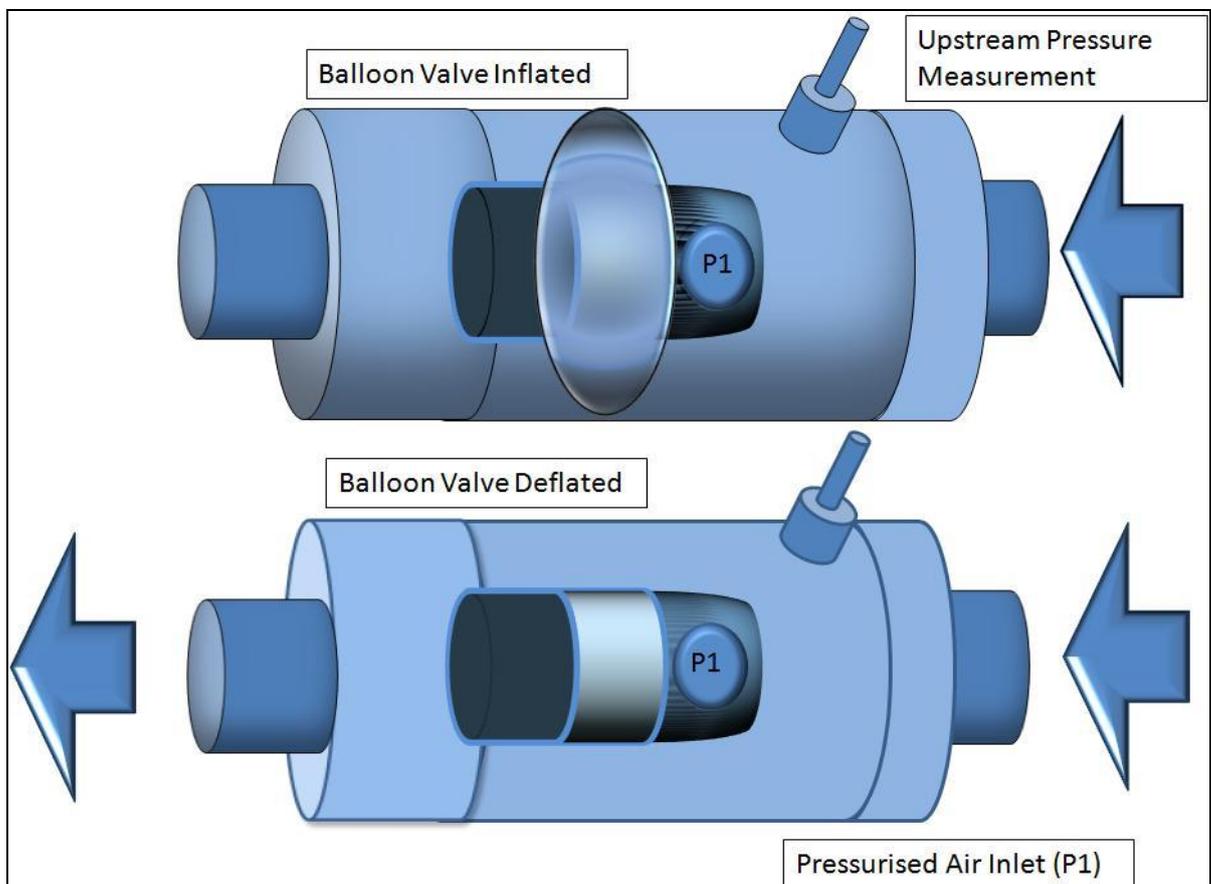
display and record the flow signal on a desktop computer running Windows operating system.



**Figure 14. Exploded Assembly image of Hans Rudolph Pneumotachograph.**

## Balloon Valve (Surrogate Larynx)

An air driven balloon valve was purchased from the clinical engineering department at the Brompton Hospital (Figure 15). The valve consisted of a cylinder (internal diameter, 29 mm); within the cylinder an occluding balloon (Serial No. 9308, Hans Rudolph Inc.) was mounted. The balloon could be rapidly inflated (by compressed air) and deflated. The controlling circuitry for the valve was arranged so that it could be inflated by the operator at the end of the inspiratory phase; the valve was automatically opened and kept open once the mouth, gastric or oesophageal pressure reached a predetermined pressure level. The valve was intended to act as a surrogate larynx for several studies. The pressure level at which the valve would open was determined for each subject during the volunteer studies or peak expiratory flow. For the experiments where the subjects were not conscious, the pressure level was preset at a level estimated to represent 40cmH<sub>2</sub>O.



**Figure 15. Schematic Diagram of air driven balloon valve provided by the clinical research team at the Brompton Hospital. The upper figure demonstrates the valve inflated. A change in upstream acting as the trigger to valve deflation, lower figure.**

### **Methods: (Normal Subjects)**

The clinical studies described in subsequent sections, used either healthy normal subjects or patients admitted to the Royal Hallamshire Hospital for surgical procedures. The healthy, normal subjects were recruited from within the department of anaesthesia and surgical sciences. All subjects were non-smokers. The subjects were well motivated and familiar with respiratory manoeuvres. All had normal pulmonary function tests. None had acute or chronic cardiopulmonary or neuromuscular diseases. A complete description of the volunteers is provided in appendix. All respiratory manoeuvres were evaluated with subjects in the seated position. Subjects performed the cough manoeuvres with a large-bore (2.5cm) rubber mouthpiece to prevent leaks.

### **Methods: Clinical Subjects**

All subjects involved in clinical trials were having anaesthesia as part of an elective surgical procedure. No additional anaesthetic techniques were performed to accommodate the trial. Patients were only intubated where clinical need dictated. All participants provided informed consent prior to inclusion in the trial. For the magnetic nerve stimulation trial patients were not paralysed, and control of ventilation was maintained with Remifentanyl. This potent opioid is able to suppress respiratory muscle function during general anaesthesia.

### **Methods: Non Clinical**

The laboratory studies are described in each study. However, the methods for pressure and flow measurement were comparable to clinical testing.

### **Respiratory Function Tests in volunteers.**

Respiratory function testing was performed on volunteer subjects where applicable. The volunteer subject's age, height and weight were recorded. Forced vital capacity (FVC), FEV1, and the FEV1/FVC ratio and PEFr were obtained using spirometry in the standing position. In accordance with the recommendations of the American Thoracic Society (1995), a minimum of three trials was obtained, subjects used nose clips, the highest results were used and the tests were carried out at standard room temperature and pressure. Predicted normal results were taken from published tables of normal results.

### **Maximum Expiratory Pressure**

Maximum expiratory pressure (MEP) was measured at total lung capacity against a closed three way tap valve that allowed the airway to be closed (Black and Hyatt, 1969). Mouth pressure was recorded as described previously. A standard mouth piece was used to prevent leaks during the test. A nose clip was used during testing to minimise leaks. Subjects were asked to breathe in to a maximum and then breathe out forcefully. Maximal pressures were read visually and had to be maintained for at least 1 second. The procedures were repeated 5 – 10 times and subjects were encouraged to persevere until reproducible maximum values could be achieved. Results were expressed in cmH<sub>2</sub>O and as a percentage of predicted normal values

### **Maximum Inspiratory Pressure**

Maximum Inspiratory pressure (MIP) was recorded with a maximum inspiratory effort against a closed valve, via a flanged mouth piece (Hautmann et al., 2000, Black and Hyatt, 1969, Volianitis et al., 2001). All manoeuvres were made with the subject standing or seated cowboy style on a chair. The subject commenced

inspiration following a slow expiration to residual volume. A small hole in the system was preventing closure of the glottis during inspiration and a nose clip was used in all efforts. The subjects were asked to sustain a maximal inspiratory effort for 2–3 s. The procedures were repeated 5 – 10 times and subjects were encouraged to persevere until reproducible maximum values could be achieved. Results were expressed in cmH<sub>2</sub>O and as a percentage of predicted normal values

### **Voluntary Cough Manoeuvre**

For the volunteer subjects, each cough manoeuvre was performed in the upright position, or seated cowboy style across a chair. A flanged mouth piece minimised leaks. Subjects were instructed to inspire to total lung capacity. Subjects were instructed to cough forcefully and verbal encouragement was given to help the subjects perform maximally. The trials which did not represent the subjects' maximum effort, according to their subjective feeling, were discarded. The Maximal pressure and flows were read visually and procedures were repeated up to 10 times.

### **Magnetic Nerve Stimulation**

Magnetic stimulation was performed using a Magstim (*Magstim Co. Ltd, Whitland, Dyfed, UK*) with a circular 90 mm coil. Inspiratory and expiratory pressures were instantaneously monitored on a computer screen. The stimulation was triggered at the end of a subject's normal tidal breath or following a deep inspiratory effort. The subjects were not prewarned of the delivery of the stimulation. To find the optimal site for magnetic stimulation of the lumbar or thoracic spine nerve roots in both normal subjects and patients the coil was placed over a spinous process. The coil was then moved up and down the lumbar or thoracic spine in the midline until the maximum response was obtained at 80% power output. Having found and marked the optimal site for stimulation, the volunteer subject would be rested for 20 minutes to avoid twitch potentiation. TwPdi was then measured at 100% Magstim output as the mean of five twitches performed at least 30 seconds apart.

The authors were concerned about the potential for trauma to anaesthetised volunteers during magnetic nerve stimulation, were the housing of the coil to be damaged. A rigid plastic housing was therefore developed to embrace the 90mm Circular coil. Heating of the coil was however magnified and the coil would shut down when it reached a maximum temperature. This did not limit stimulation during testing of the anaesthetised subjects.

### **Data and Statistical Analysis**

Statistical analysis was performed on SPSS 15 for Windows (*SPSS, Chicago*). Standard statistical tests, including simple and multiple variable regression analysis and Student's t-test for unpaired and paired data, were performed.

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## **Chapter 4: Characteristics of flow in rigid and collapsible tubing: Development of a Starling resistor with application to the investigation of Cough Flow Mechanics**

### **Introduction**

Almost all vessels carrying fluids within the body are flexible, and interactions between the internal flow and wall deformation often underlie a vessel's biological function or dysfunction. Such interactions can involve a rich range of fluid mechanical phenomena. For example, the flow of air along the flexible airways is limited by the pleural pressure generated and the transmural deforming pressure in the large airways which tends to collapse the bronchi and limits the peak expiratory flow generated. The maximal flow generated during a forced expiration is then limited by both airway collapse and the local wave speed (Aljuri et al., 1999). However, the maximal flow generated during a voluntary cough exceeds that generated during forced expiration (Laviertes et al., 1998). No explanation is available for the mechanisms that underlie the differences in fluid mechanics between a forced expiration and a voluntary cough.

Simple fluid mechanics along rigid tubes with smooth walls are governed by the Hagen - Poiseuille ( $Q = \pi R^4 / 8\mu l \times (p_1 - p_2)$ ) equation which predicts the flow of gas through a tube of rigid sides (Sutera, 1993). However, the pattern of flow through the large airways where the tube walls are irregular with deformable sides, where the flow is not constant and flow is influenced by the presence of fluid lined walls requires more complex mathematical models (Aljuri et al., 1999). Prediction of flow through mathematical or computer modelling needs to be supported with physical testing.

Collapsible tubes have long been used to demonstrate the flow limitation observed in respiratory function measurements (Bertram, 2008). Typically these involve

a flexible Penrose tube of 5 – 25cm length held between rigid tube ends. The Starling resistor, a model of flow in flexible tubes, was developed in 1912(Knowlton and Starling, 1912). The Starling resistor allows observation of the effect of a transmural pressure on flow induced tube wall oscillation and enabled the development of the wave speed theory to predict the observation of flow limitation(Dawson and Elliott, 1977, Knowlton and Starling, 1912). Increasingly sophisticated models have been developed that have modelled the rigid C-like cross section of the trachea and its branching conduits(Webster et al., 1985). The impact of laryngeal closure and opening has not previously been investigated in a model. The objective of this study is to develop a model that reproduces elements of a voluntary cough. These are:

1. The variable transmural pressure that reflects the upstream pressure and
2. The effect of closing and opening of a downstream shutter valve on the pressure and flow generated.

The original Starling resistor was modified to develop these two elements. The flow and pressure relationship in the cough model could then be observed under a variety of conditions to define the importance of each element in developing a supramaximal flow.

Experimental studies have previously demonstrated that forced expiratory flow through flexible tubes generates a rich variety of non-uniform, chaotic tube wall oscillations. System configurations will impact upon the pressure/ flow measurement errors(Grenvik et al., 1966). Therefore, the initial experiments will seek to compare our own findings with published data and confirm that the fidelity of the flow and pressure measurement. These confirmatory observations will support the reliability of any new findings of our cough model.

## Methods

### Model 1: The pressure and flow relationship in a rigid tube.

Pressure and flow along a rigid corrugated tubing (6mm diameter and length 30cm) was observed. The air flow was generated from a pressurised air cylinder developing flows from 0 – 200l/min. The pressure was recorded at the upstream end of the tubing (Figure 16). A mesh type pneumotachograph was installed at the upstream end of the apparatus and flow was recorded. Flow and pressure were recorded using the equipment previously described.

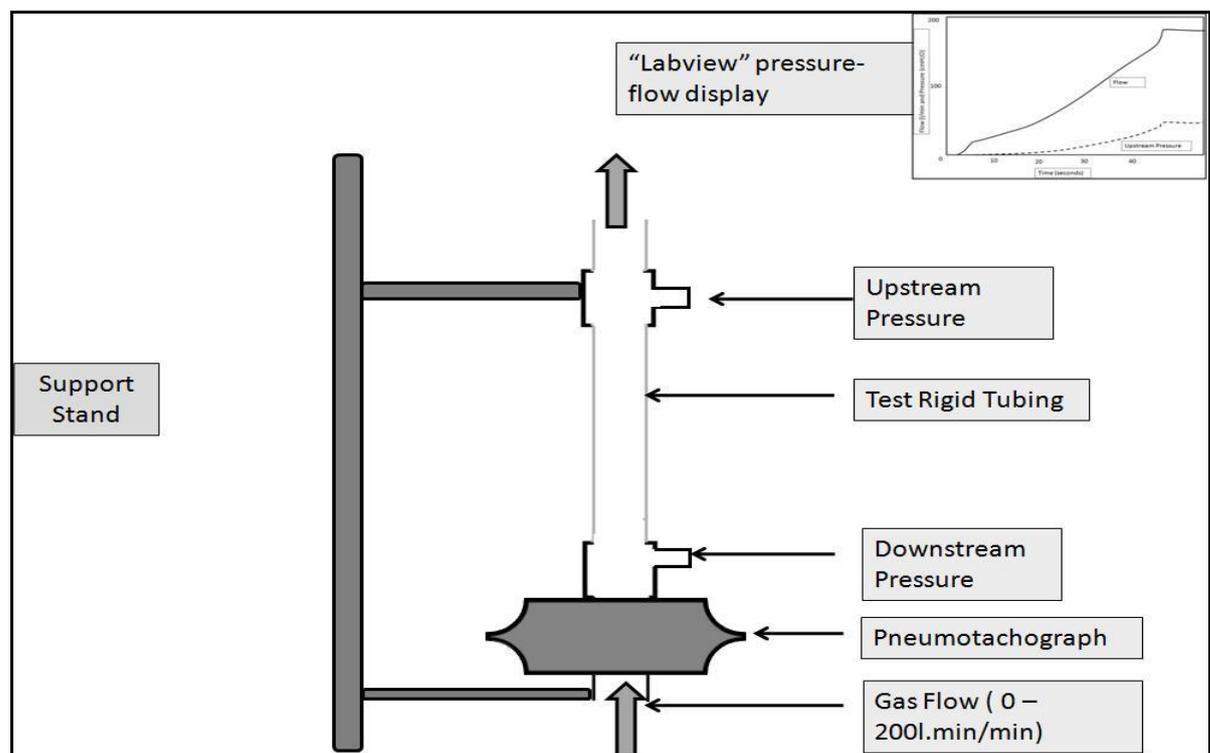


Figure 16. Schematic diagram illustrating measurement of pressure and flow in rigid and flexible penrose tubing.

### Model 2: The pressure and flow relationship in a flexible tube.

A 400mm long rubber Penrose tube of uniform properties was cannulated at each end with rigid tube (12.5mm outside diameter) and tied to minimise leakage. The

proximal (*downstream*) end was attached to the gas outlet port of an air cylinder. The attachment consisted of a semi-rigid hose from the gas outlet. The distal end of the hose was attached to a rigid tube. The gas flow was adjusted at the gas cylinder. Flow was measured upstream by the pneumotachograph previously described. A 0.7mm diameter side tap with a 200cm polyethylene catheter formed a gas tight fit was attached to both rigid downstream and upstream ports. These ports enabled the measurement of pressure at the upstream and downstream ends of the Penrose tubing using the pressure recording apparatus previously describes(Figure 16). Airflow was generated from a pressurised air cylinder developing a flow from 0 – 200l/min. The procedure was repeated ten times

**Model 3: The pressure and flow relationship in a flexible tube: effect of differences in tube length.**

Model 2 was adapted to observe the effect of change in the length of a Penrose tube. A pressure-flow curve was created by steadily changing the flow through various collapsible Penrose Tubes. All Penrose tubes were of a fixed diameter of 10mm and a variable length (of 5, 10, 15 and 20cm. The pressure drop across the collapsible tube ( $\Delta P$ ) versus the flow rate ( $Q$ ) was recorded. The flow was generated from a pressurised air cylinder and the flow was recorded with a pneumotachograph as in previous experiments. The study was repeated five times for each tube length and the mean pressure and flow value calculated

**Model 4: The effect of a downstream shutter valve.**

The air driven balloon valve (*described in the methods section*) was placed at the downstream end of the apparatus. Closure and opening of the valve was controlled manually and the pressure and flow were recorded as in previous studies. The objective is to observe the impact of temporary downstream occlusion upon the peak flow developed and the time to develop the peak flow during a peak expiratory flow manoeuvre. Preceding the peak flow three volunteers from the department of Anaesthetic Sciences were instructed to inhale as deeply as possible and to blow

forcefully into the mouthpiece until their lungs were empty (Bongers and O'Driscoll, 2006). The measurement was repeated 10 times with the valve open throughout the measurement period and ten times with the valve initially closed but triggered to open with the development of a downstream pressure of 30cmH<sub>2</sub>O. The analysis considered the difference in time to peak flow, the peak flow and the pressure difference along the flexible tube using an ANOVA with a p value < 0.05 considered significant.

### **Model 5: The Modified Starling Resistor**

The Starling Resistor was modified to represent the variable transmural pressure mechanics of a forced expiratory manoeuvre. The collapsible Penrose tube is maintained at a constant length and a constant cross-sectional area at each of its ends because it is held between two rigid tubes. (1.25 cm OD, 0.94 cm ID) that were 60 cm apart. The surrounding enclosure, a transparent chamber, could be sealed or opened through a removable lid. In the open state the surrounding pressure is the same as that of the external pressure. In the closed state the external pressure reflects upstream pressure through a small leak in the upstream rigid tube connector. This is in contrast to the normal Starling resistor where the external pressure is fixed through an external manual pump.

Preliminary observations of the effect of a peak flow manoeuvre performed through the "cough box" were gathered. Three volunteers from the department of Anaesthetic Sciences were coached to perform a peak expiratory flow manoeuvre via the modified Starling resistor. Measurements were observed of the peak flow achieved, the pressure difference along the Penrose tube and the time to achieve the peak flow. The flow, pressure and time values were observed in the presence and absence of a downstream surrogate larynx as described previously. The shutter time for the larynx was set at 0.3 seconds and the pressure to open was set at 30cmH<sub>2</sub>O.

The analysis compared the difference in time to peak flow, the peak flow and the pressure difference along the flexible tube using an ANOVA with a p value < 0.05 considered significant.

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**Model 6: Flow Pressure changes in an Ovine Trachea**

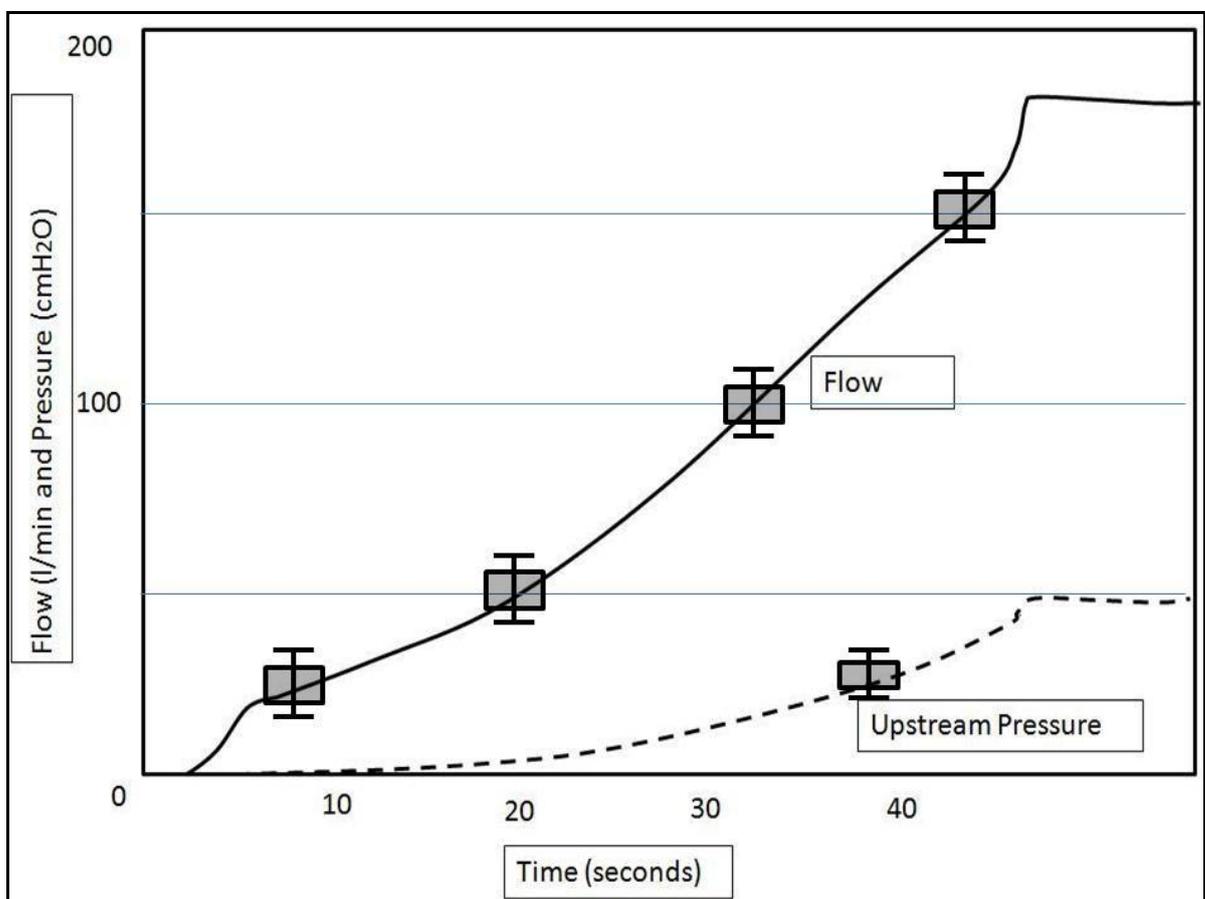
An ovine trachea replaced the flexible Penrose tubing in the modified starling resistor. The ovine trachea was sourced from a local abattoir. The trachea was cleaned from surrounding tissues and kept refrigerated at 5°C and used within three days. The ovine trachea was sealed to the plastic male connections of the testing apparatus with acrylic glue. The largest possible diameter connector was used that was able to effect an airtight seal. The seal was confirmed with the absence of bubbles when placed under water when air was driven through the apparatus. A flow pressure profile was generated in the absence and presence of a downstream shutter valve triggered to open when the downstream pressure reached 30cmH<sub>2</sub>O as described in the previous study.

**Analysis:** All Experiments were repeated a minimum of 10 times. The data was stored and reviewed using the customised Labview software previously described. The SPSS 15 statistics software analysed the final data and produced the final graphical summaries. Analysis measured the mean and standard deviation where applicable.

**Results:**

**Model 1: The pressure and flow relationship in a rigid tube.**

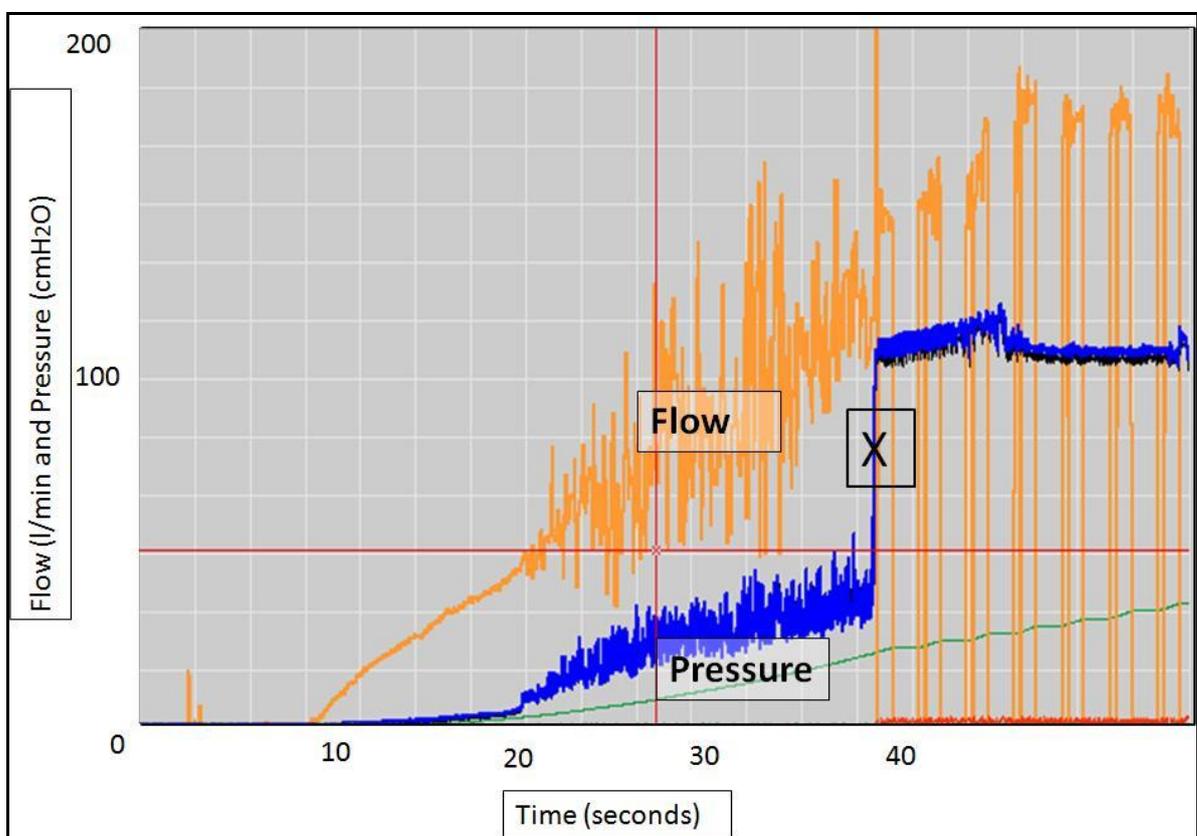
The study observed a clear linear relationship between the upstream pressure and the flow along the rigid tubing. There was no disturbance in the pressure-flow trace, and no tube wall motion was evident(**Figure 17**).



**Figure 17. Relationship between Downstream Flow and Upstream Pressure along rigid tubing. Box plots indicate 25<sup>th</sup> and 75<sup>th</sup> percentile (the box) and minimum and maximum values (whiskers).**

### Model 2: The pressure and flow relationship in a flexible tube.

The flow and pressure relationship for the Penrose tubing is displayed (Figure 18). There is a clear disturbance of flow and pressure with an increase in flow. This is demonstrable through the large swings in pressure and flow. At position X there is an abrupt increase in pressure and this was evident through a sudden dilation of the Penrose tubing upstream of the obstruction. The flow continues after point X with the upstream pressure now elevated.



**Figure 18. Flow and Pressure along Penrose Tubing. Point X demonstrates large rise in downstream pressure with airway collapse**

The tube wall oscillation was audible with observation of intermittent ballooning and collapsing of the tube walls. Tube wall oscillation finally led to destruction of the tube walls. This observation was observed each time the experiment was repeated. The sharp upstroke in pressure along the tube at X was reached at a comparable flow value

for each successive experiment. It is unclear why the intermittent flow cessation was not mirrored by large swings in pressure.

**Model 3: The pressure and flow relationship in a flexible tube: effect of differences in tube length.**

The magnitude of the difference between the upstream and downstream pressure ( $\Delta P$ ) is a measure of tube wall oscillation increasing the resistance to flow. The graph(Figure 19) demonstrates that tube wall oscillation is present in all tubes 5 – 20cm, demonstrated as a rise in pressure along the tube beyond a flow of 50l/min. Comparison of the difference between the change in pressure along the tube at a given flow for each tube length demonstrates no significant difference ( $p = 0.96$ ). These findings were confirmed with each successive repetition of the study.

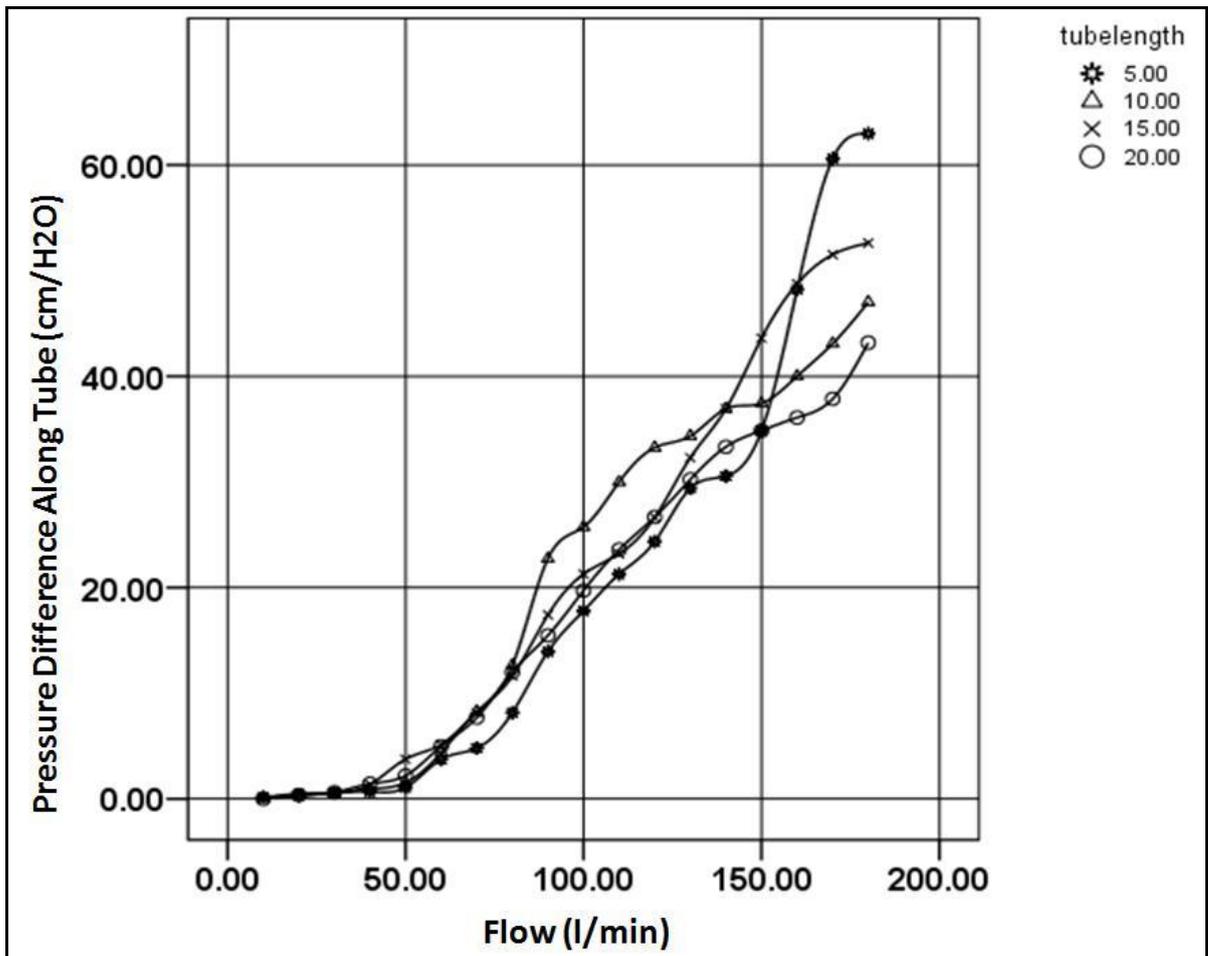


Figure 19. Scatter Plot of Flow vs. Pressure along a Penrose tube for various tube lengths. The data points represent mean values of pressure.

**Model 4: The effect of a downstream shutter valve.**

The introduction of the downstream shutter valve altered the flow dynamics with a rapid rise to a peak flow, a peak flow developed that was greater than that observed in the steady state preceding valve occlusion(Figure 20). There followed a rapid decline in flow to zero before return to steady state flow (Figure 20). The results of the impact of the distal shutter valve are illustrated(Figure 21), with both flow( $p = 0.01$ ) (Figure 22), differential pressure at the time of the peak flow ( $p < 0.001$ ) and time to achieve a peak flow ( $p = 0.03$ ) achieving statistical significance.

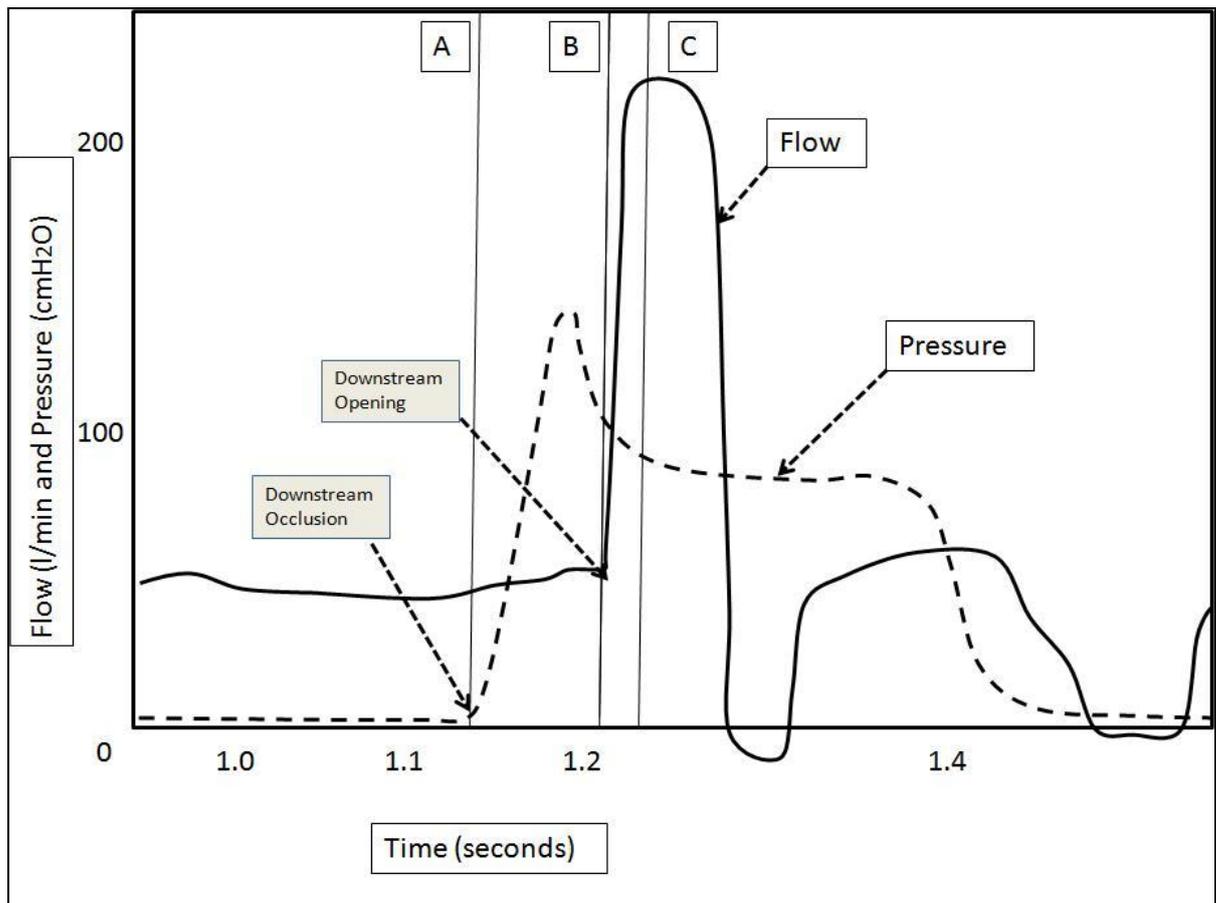


Figure 20. Demonstration of effect of temporary downstream occlusion upon pressure-flow dynamics along Penrose tubing. Note the elevation in pressure with onset of airway occlusion (A), the development of flows in excess of steady state following airway opening (B) and the short rise time to develop a supramaximal flow (C). It is not clear why the upstream pressure declines prior to valve opening. This is not observed in physiological recordings of a voluntary cough. There is a fall to zero flow before flow resumes.

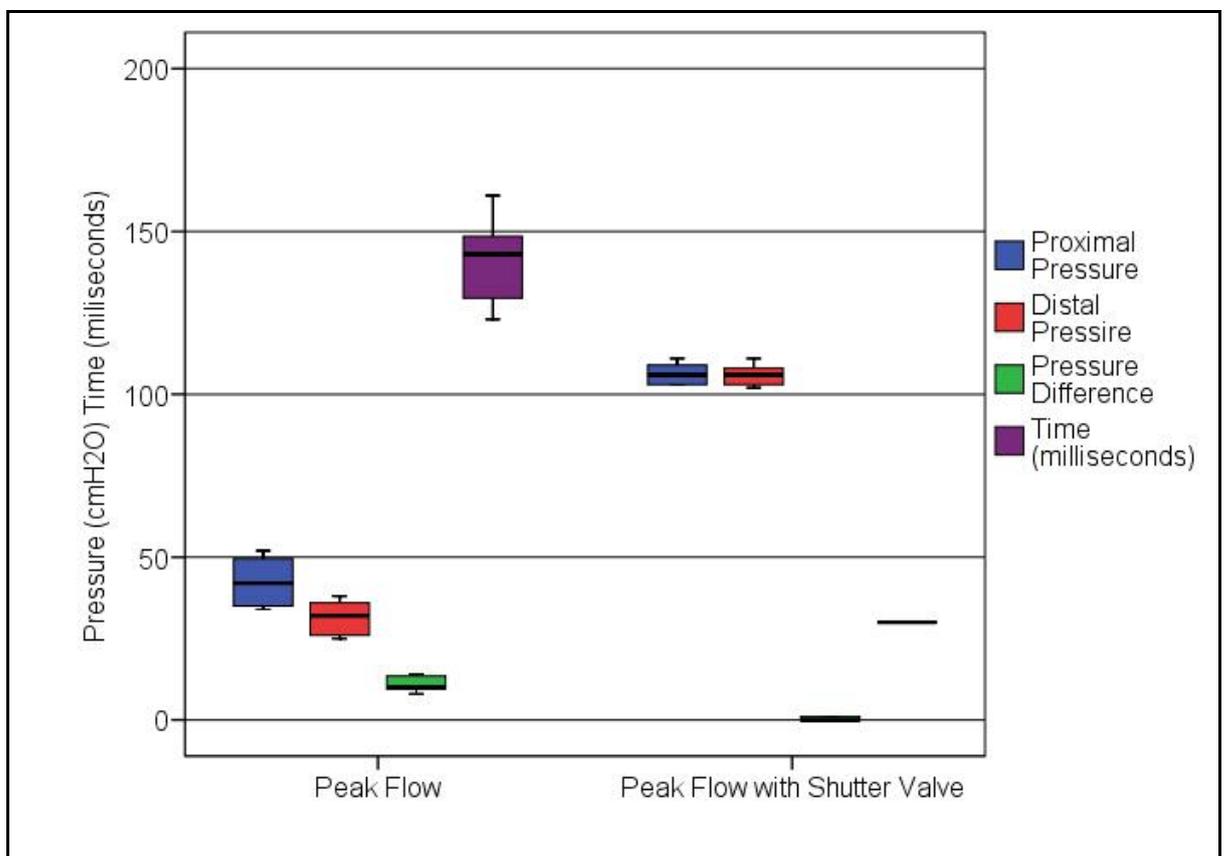
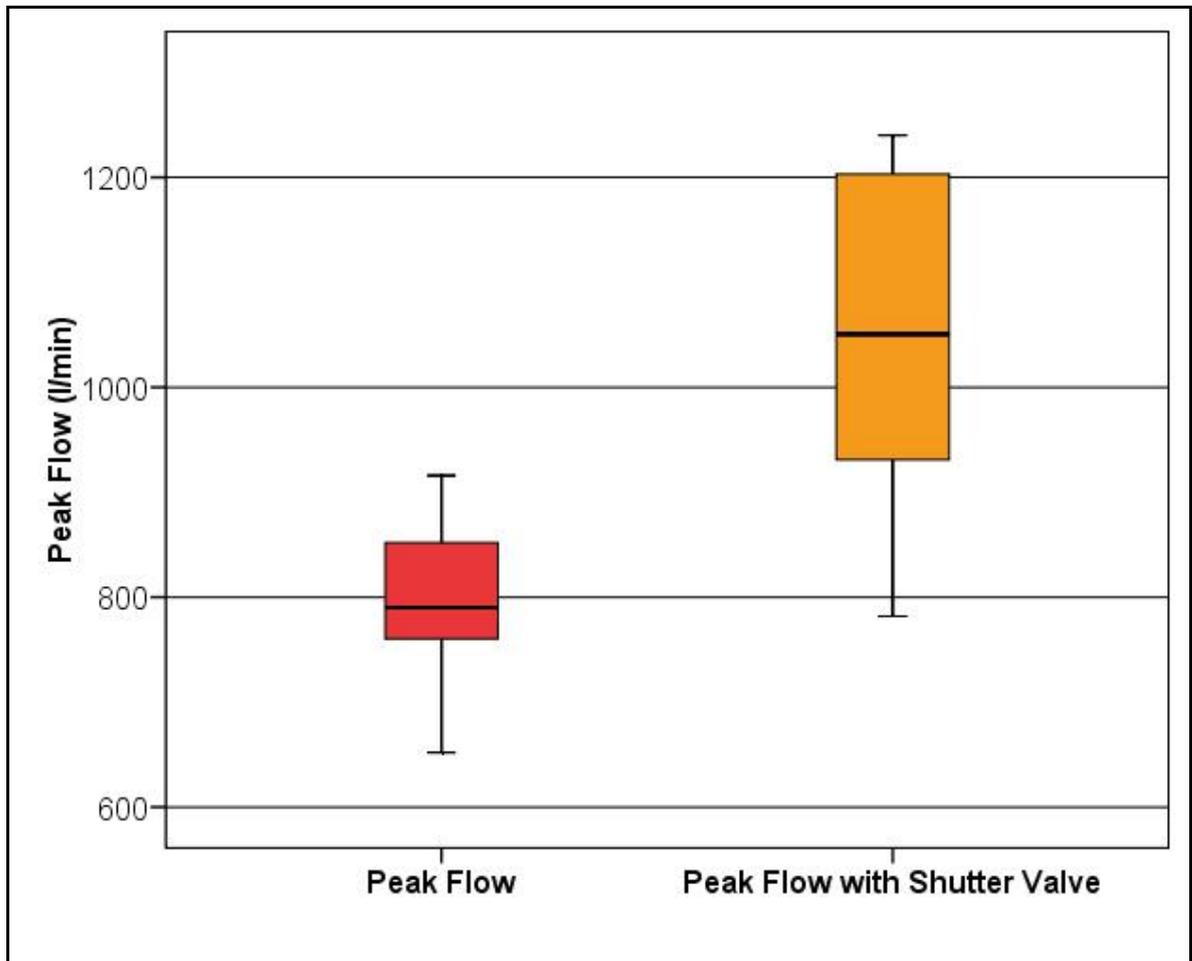


Figure 21. Boxplots describing effect of the addition of a shutter valve upon flow in flexible tube model. The time (milliseconds) to develop the peak flow is reduced and the pressure difference along the Penrose tube is elevated.

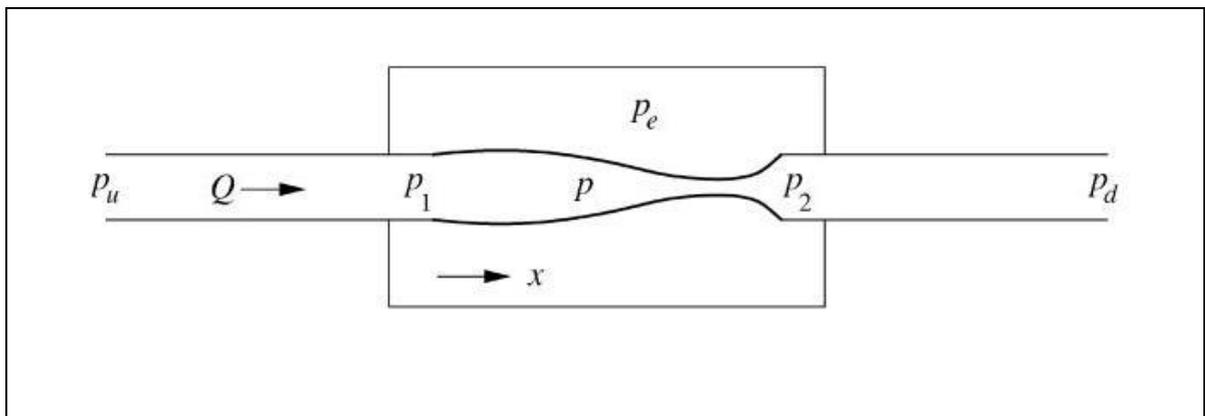


**Figure 22. Boxplots describing effect of the addition of a shutter valve upon flow in flexible tube model. The peak flow achieved is elevated with the addition of a downstream shutter valve.**

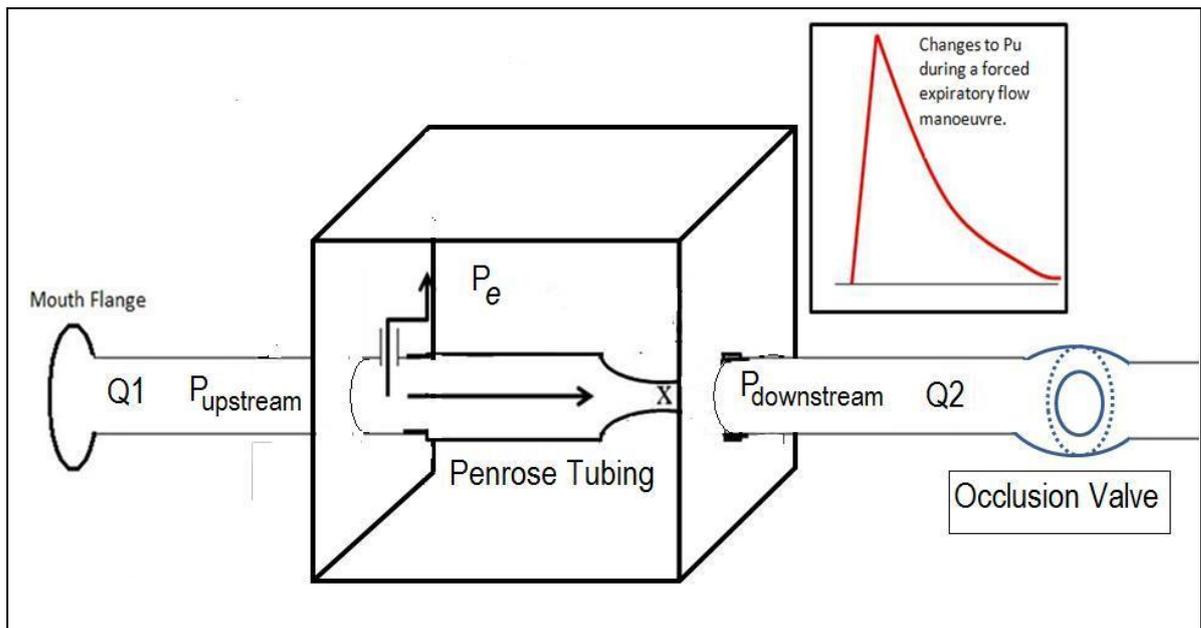
**Model 5: Starling Resistor Modification – the “cough box”.**

The original Starling Resistor Model developed a fixed transmural pressure, through an elevation in  $P_e$ , set by the operator (Figure 23). The Starling resistor is known to develop large-amplitude self-excited oscillations of great complexity. The Starling

resistor has been applied to the prediction of flow limitation during peak flow manoeuvres, but the design constraints may limit prediction of supramaximal flow generation during a voluntary cough. The modification developed and reported here in the “cough simulation box” attempts to reproduce more closely the pressure flow dynamics during a voluntary cough. The compressive pressure ( $P_e$ ) is now related to the upstream driving pressure through a small upstream leak (Figure 24). Downstream airway collapse will lead to an elevation in upstream pressure that will open the downstream end. However, the external compressive force will also rise tending to collapse the downstream segment again. The effect upon flow of the pressure oscillation across the tube is observed in this model.



**Figure 23. A Starling Resistor: a collapsible tube is mounted between two rigid tubes and is enclosed in a chamber held at pressure  $p_e$ . Flow with volume flux  $Q$  is driven by the imposed pressure drop  $p_u - p_d$ .**



**Figure 24. Modified Starling Resistor ("cough box):** Upstream flow ( $Q_1$ ) is directed into the Modified Starling resistor. A proximal leak allows the generation of a pressure within the box ( $P_e$ ) that is related to the upstream pressure ( $P_{upstream}$ ). A choke point ( $x$ ) develops when the  $P_e$  exceeds the pressure within the tubing. A downstream occlusion valve allows observation of the effect of temporary valve closure on flow and pressure dynamics.

The effect of the addition of the surrogate larynx was to change the flow, pressure and time to develop peak flow (Figure 25)(Figure 26). The difference in the measured values demonstrates the time to achieve a peak flow was reduced and the pressure difference along the Penrose tube ( $P < 0.001$ ) was reduced prior to the valve opening. There was no difference in the peak flow developed.

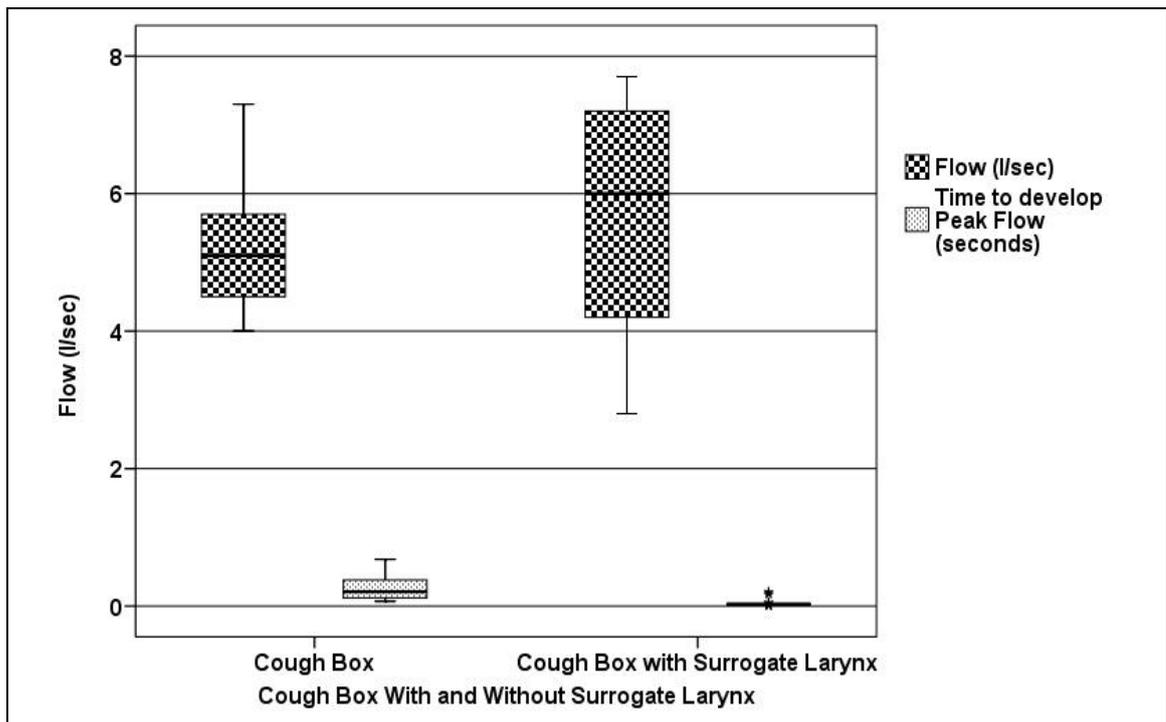


Figure 25. A forced Expiratory Flow Manoeuvre using the Modified Starling Resistor. Box Plots demonstrating changes in Peak Flow and Time to achieve peak flow when a surrogate larynx is added.

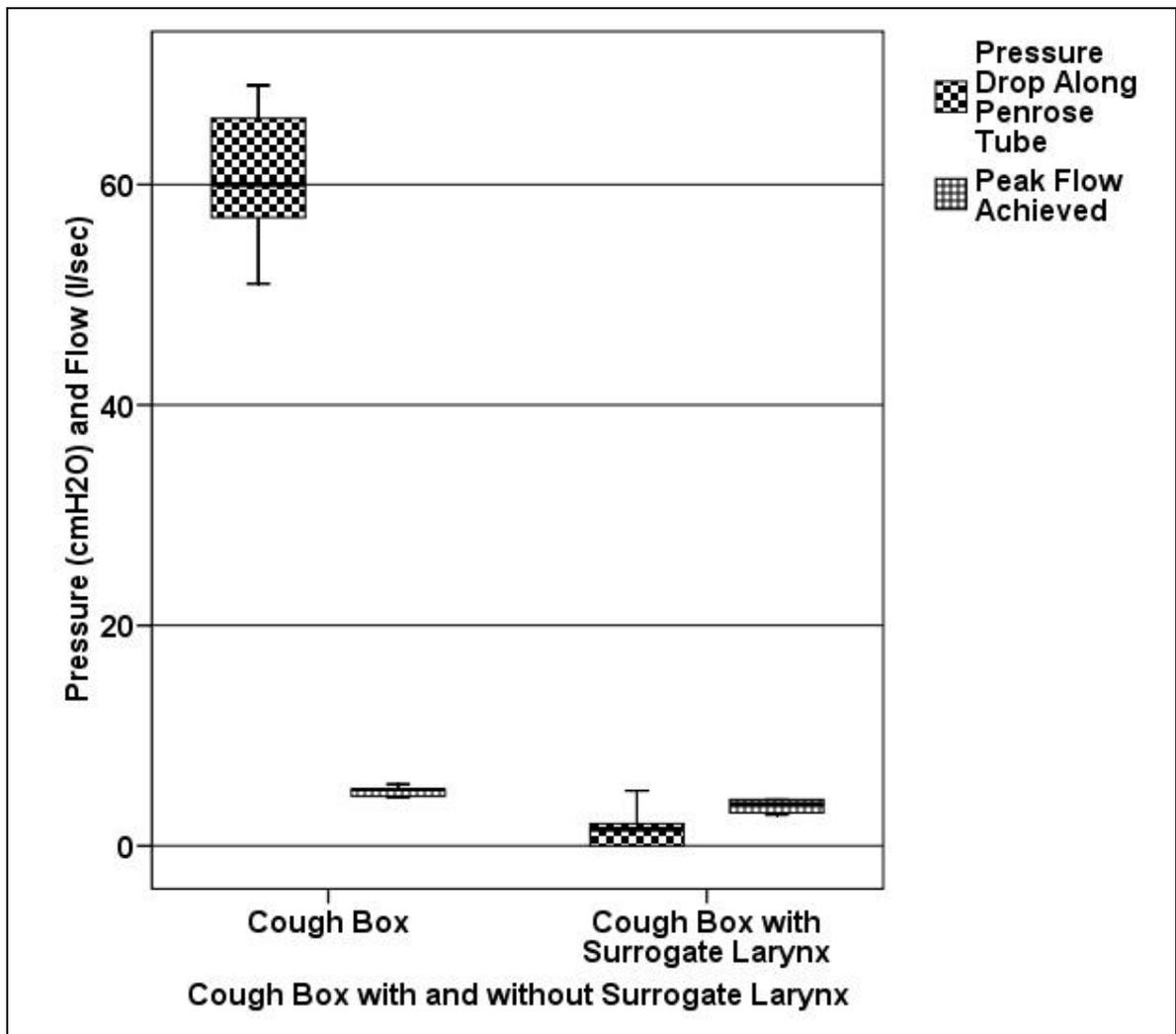
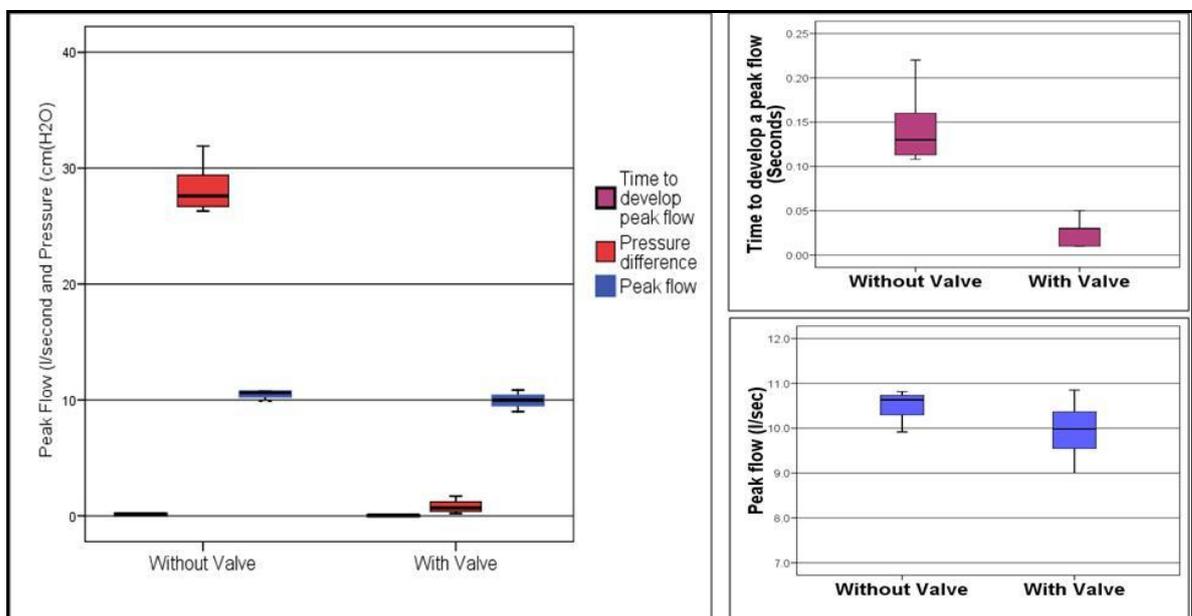


Figure 26. Peak Expiratory Flow Manoeuvre performed using the modified Starling Resistor: Effect of surrogate larynx upon the pressure drop along the Penrose Tube and the peak flow achieved. (The flow units are in l/second to enable both flow and pressure to be represented in the same chart.)

**Model 6: Flow Pressure changes in an Ovine Trachea**

A series of peak expiratory flows demonstrated the pressure changes along the ovine trachea. The values are represented in graphical format(Figure 27) The graph suggests that airway collapse has created a pressure difference along the ovine trachea. Analysis demonstrates that the pressure difference along the ovine trachea and the time to develop a peak flow is significant ( $p < 0.001$ ). There was no statistical difference in the measured peak flow ( $p = 0.2$ ).



**Figure 27. Ovine Trachea Mounted within Modified Starling Resistor: Effect of peak flow manoeuvre on pressure difference along trachea, peak flow achieved and time to develop the peak flow. The peak flow and time to develop peak flow data is depicted separately to allow the differences to be displayed clearly.**

### Discussion

The data presented develops a model for investigation of the forces responsible for the development of a supramaximal flow during a voluntary cough. With rigid tubing, flow and pressures are directly related, with a rise in upstream pressure leading to a rise in measured flow (Sutera, 1993). In contrast the pressure and flow relationship of flexible tubing is more complex and reflects the development of self induced tube wall oscillations (Grotberg and Jensen, 2004, Katz et al., 1969b).

The Starling resistor, with a fixed external tube wall pressure has previously demonstrated the effort independence of a forced expiratory flow manoeuvre with flow limitation (Katz et al., 1969a). The Starling resistor modifications considered the effect of a variable external tube pressure related to upstream driving pressure and temporary downstream occlusion.

The pressure and flow observations reported compare with those observed during a voluntary cough. The time to achieve a peak flow is rapid when flow is interrupted by a downstream valve (surrogate larynx). The pressure difference along the tube at the time of the peak flow is reduced with the introduction of the surrogate larynx. The absence of an upstream/ downstream pressure difference may support the development of a supramaximal flow. In contrast to a voluntary cough manoeuvre, the modified Starling resistor did not realise a consistent increase in peak flow. It is possible that the force developed during a voluntary cough is augmented beyond that of a forced expiratory flow manoeuvre through mechanisms not measured in this study (De Troyer et al., 2005).

The Penrose tube, though frequently adopted as a surrogate model for the airways, is not comparable to the trachea and primary bronchi with their semi rigid cartilaginous rings. However, large airways do collapse to a fraction of their resting cross sectional area (Kamm, 1999) during a forced expiratory manoeuvre (Holzhauser and Lambert, 2001), and this was demonstrated in the observations of flow along the ovine trachea. Though direct observation of tracheal compression was not observed, it

could be surmised that a reduction in diameter developed through the observed development of a pressure difference along the trachea during the forced flow manoeuvre. This pressure difference was reversed with the inclusion of temporary downstream occlusion, though again this model did not demonstrate an increase in peak flow.

### **Conclusion**

The cough box is a practical model to observe the pressure flow dynamics of a forced flow or voluntary cough manoeuvre. The inclusion of a downstream valve also reproduces some elements of the flow pattern of a voluntary cough. Further observations of the pressure flow dynamics during forced expiratory flow and voluntary cough with this model will support the development of a surrogate cough. The following study will determine the respiratory mechanics associated with a forced expiratory flow manoeuvre and a forced expiratory flow manoeuvre with a surrogate larynx. This will further develop the model for application in a surrogate cough.

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## Chapter 5: The Modified Starling Resistor and the pressure flow dynamics as applied to a voluntary cough.

### Introduction

The *Hagen-Poiseuille law* is the physical law concerning the voluminal laminar stationary flow of incompressible uniform viscous liquid through a cylindrical tube with the constant circular cross-section(Sutera, 1993). The equation indicates that a change in  $\Delta P$  will produce an equal change in flow (Q). If this relationship is applied to a forced expiratory flow manoeuvre, the expectation is the description of a linear plot. However, the contextual application of this relationship does not allow for factors that mitigate this linear relationship(Zach, 2000). The flow-pressure relationship for the peak expiratory flow manoeuvre has been previously described as linear up to the point of maximal flow achieved.

The plateau of the pressure flow curve (*effort independent*) is a result of negative transmural pressure (*with respect to the inside*) across flexible central airways leading to their collapse. This dynamic obstruction to flow within the respiratory passages has been labelled as a *flow limiting segment*(Smaldone and Messina, 1985) or *choke point*. Model airways confirm that at maximum flow there is collapse of the airway(Walsh et al., 1995) due to the balance of forces across the airway wall being positive with respect to the inside(Gavriely et al., 1989).

However, the peak flow achieved during a voluntary cough is supramaximal exceeding the flow limitation of a PEF manoeuvre(Lavietes et al., 1998). Early closure of the larynx during forced expiration sets a voluntary cough apart from a PEF. The impact of early laryngeal closure upon the gastric and oesophageal pressure is not described. The objective of this study is the application of the modified Starling

Resistor to model the pressure and flow dynamics in the large airways during a PEF prefaced by downstream valve closure.

### **Methods:**

Pressure flow data was obtained from 5 non-smoking volunteers who were familiar with respiratory function studies. All were staff members of the department of anaesthesia and surgical sciences at Sheffield University. No volunteer reported respiratory or neurological problems that may compromise the study. This data was collected as part of another study regarding cough mechanics, and informed consent was collected from all subjects. Lung function studies were measured for each volunteer.

Each subject was seated, cowboy style on a chair. The subjects were provided with a flanged mouthpiece to perform the various respiratory manoeuvres, and a nose clip to prevent nasal flow leaks.

Respiratory gas flow was recorded with a Hans Rudolph pneumotachograph. Oesophageal and gastric pressures were recorded using an oesophageal balloon catheter inserted into the mid third oesophagus and stomach. Mouth pressure was recorded at the mouth piece using the recording apparatus described earlier. All data was interfaced with the pressure and flow display and recording apparatus previously described.

Volunteers were instructed to perform a series of variable effort forced expiratory flow manoeuvres from total lung capacity. This generated an envelope or perimeter to produce a pressure/ flow relationship comparable to that described by Fry and Hyatt earlier.

For each manoeuvre the peak oesophageal pressure and peak flow data was recorded and used to complete the data analysis.

Data was analysed and graphics generated using SPSS version 13 software. A flow against pressure graph was generated for each subject and an  $R^2$  value calculated.

**Protocol 1: Pressure - Flow relationship for a Forced Expiratory Flow Manoeuvre.**

Each volunteer sat quietly on a chair. The volunteers held a flanged mouth piece between their teeth attached to a heated, mesh type, differential pressure, pneumotachograph (*Hans Rudolph inc. Kansas, USA*) recording flow. The pneumotachograph was calibrated according to the manufacturer's instructions using a three litre syringe prior to each study.

Oesophageal pressure was used as a surrogate measure of pleural pressure. The oesophageal balloon catheter was placed via a nostril into the mid oesophagus according to the description of Baydur (Baydur et al., 1982), where maximum negative pressure upon inspiration was recorded. The balloon was inflated according to the manufacturer's instructions with 1ml of air.

Gastric pressure was used as a surrogate marker of intra-abdominal pressure. The balloon catheter was passed into the stomach via a nostril to 60 – 70cm according to the manufacturers marking. Confirmation of position was through observation of the difference in pressure compared with the oesophageal balloon. Pressure rises with abdominal palpation provided additional confirmation of correct positioning.

Mouth pressure was recorded via a 200cm polyvinylchloride catheter connecting the mouth piece to a pressure transducer. The data for flow and pressure was recorded in real time using equipment previously described. The flow and pressure data were visible to the volunteer.

Subjects were coached to blow out hard from TLC, varying the intensity of their effort with each expiratory effort. After each subject appeared to have mastered this task, a series of at least 40 forced expiratory manoeuvres were recorded. During this series, subjects were encouraged to blow out either "gently", "with moderate strength", or "as hard as you can" until a sufficient number of expiratory efforts for analysis was recorded. Each subject performed at least 40 such manoeuvres allowing the development of an envelope or perimeter of the flow against pressure curve

**Protocol 2: Pressure - Flow relationship for a Voluntary Cough.**

Protocol 2 mirrored the methods of Protocol 1 with measurement of oesophageal, gastric and mouth pressures, flow and time to develop peak flow. Subjects were coached to cough repeatedly from TLC, varying the intensity of their effort with each cough. After each subject appeared to have mastered this task, a series of at least 40 coughs were recorded. During this series, subjects were encouraged to cough either "gently", "with moderate strength", or "as hard as you can" until a sufficient number of coughs for analysis was recorded. Each subject performed at least 40 separate cough manoeuvres from the maximum to minimal effort allowing the development of an envelope of the pressure/ flow relationship comparable to that of protocol 1.

**Analysis:** We surmised for the purpose of the analysis that though the peak oesophageal pressure did not always develop at the same time as the peak of the flow, the oesophageal pressure was the driving force and therefore the peak pressure was the closest measure of that force. Therefore the analysis measured the relationship between peak oesophageal pressure ( $P_{esPeak}$ ) and peak flow ( $PEF_{cough}$ ). Data interpretation involved measuring the relationship between the pressure flow data using scatter plots and calculating the  $R^2$  value.

**Results:**

The respiratory function tests for the group, (*PEF, FVC, and FEV<sub>1</sub>*) were within the normal range(Figure 28).

Subject	Gender	Age	Weight	Height	BMI	PEFR	FEV1	FVC
1	♀	55	55	1.6	21.5	365	2.6	3.4
2	♀	39	75	1.7	26.0	264	2.5	3.2
3	♂	56	68	1.7	23.5	673	4.1	5.3
4	♂	38	73	1.7	25.3	692	4.3	5.5
5	♂	46	110	1.8	34.0	747	3.5	4.5

**Figure 28. Summary of Study Participants - demographics and respiratory function tests**

**Protocol 1: Forced Expiratory Flow Manoeuvre.**

The linear pressure flow relationship for a forced expiratory flow manoeuvre observed. The graphical results for subject 4 are reproduced below. The pressure flow relationship is linear for both oesophageal(Figure 29), gastric(Figure 30) and mouth(Figure 31) pressure. A linear relationship is maintained for oesophageal and gastric pressure and expiratory flow for all 5 subjects tested(Figure 32).

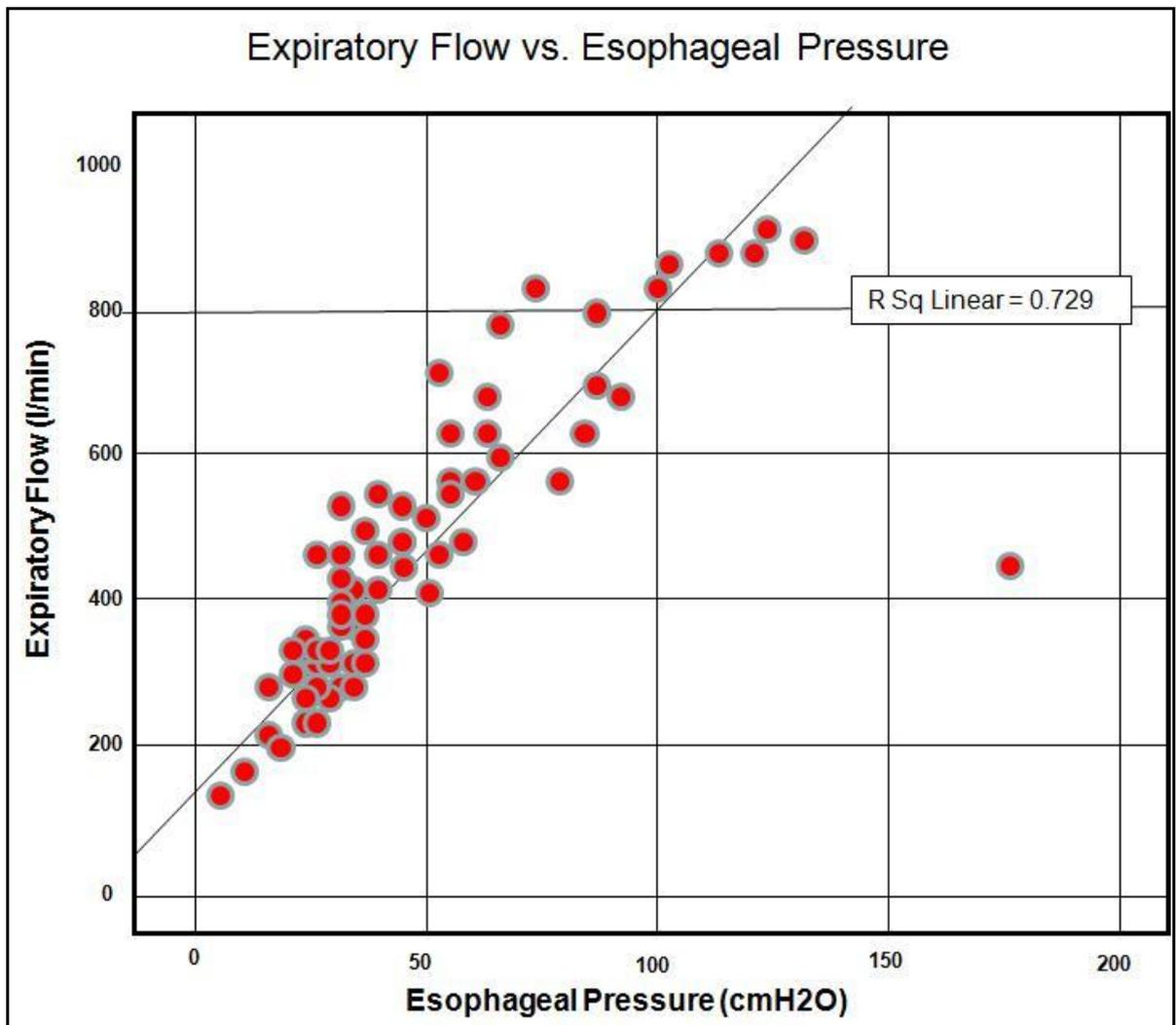


Figure 29. Oesophageal Pressure and Flow relationship for a forced expiratory flow manoeuvre for subject 4.

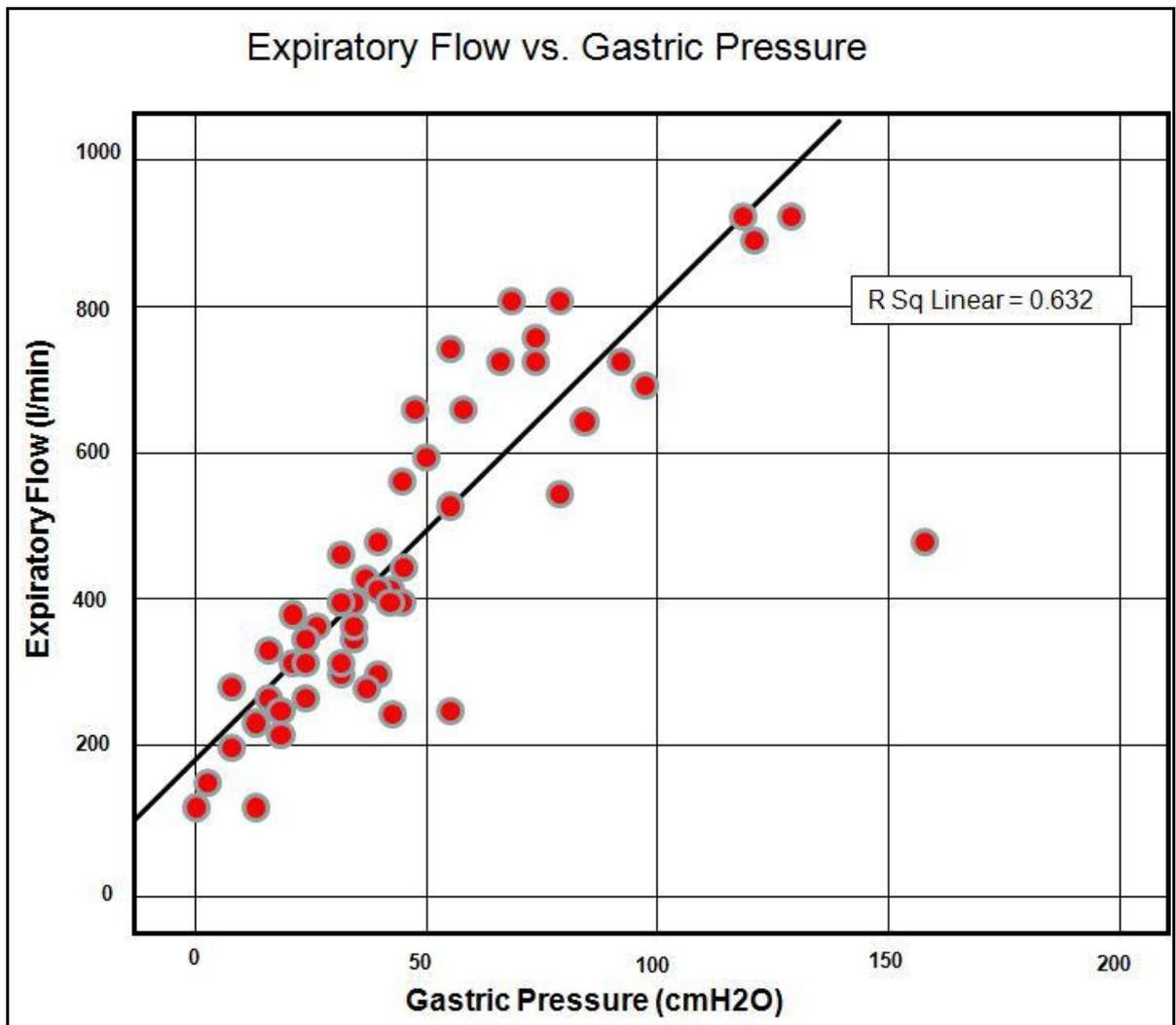


Figure 30. Gastric Pressure and Flow relationship for a forced expiratory flow manoeuvre for subject 4

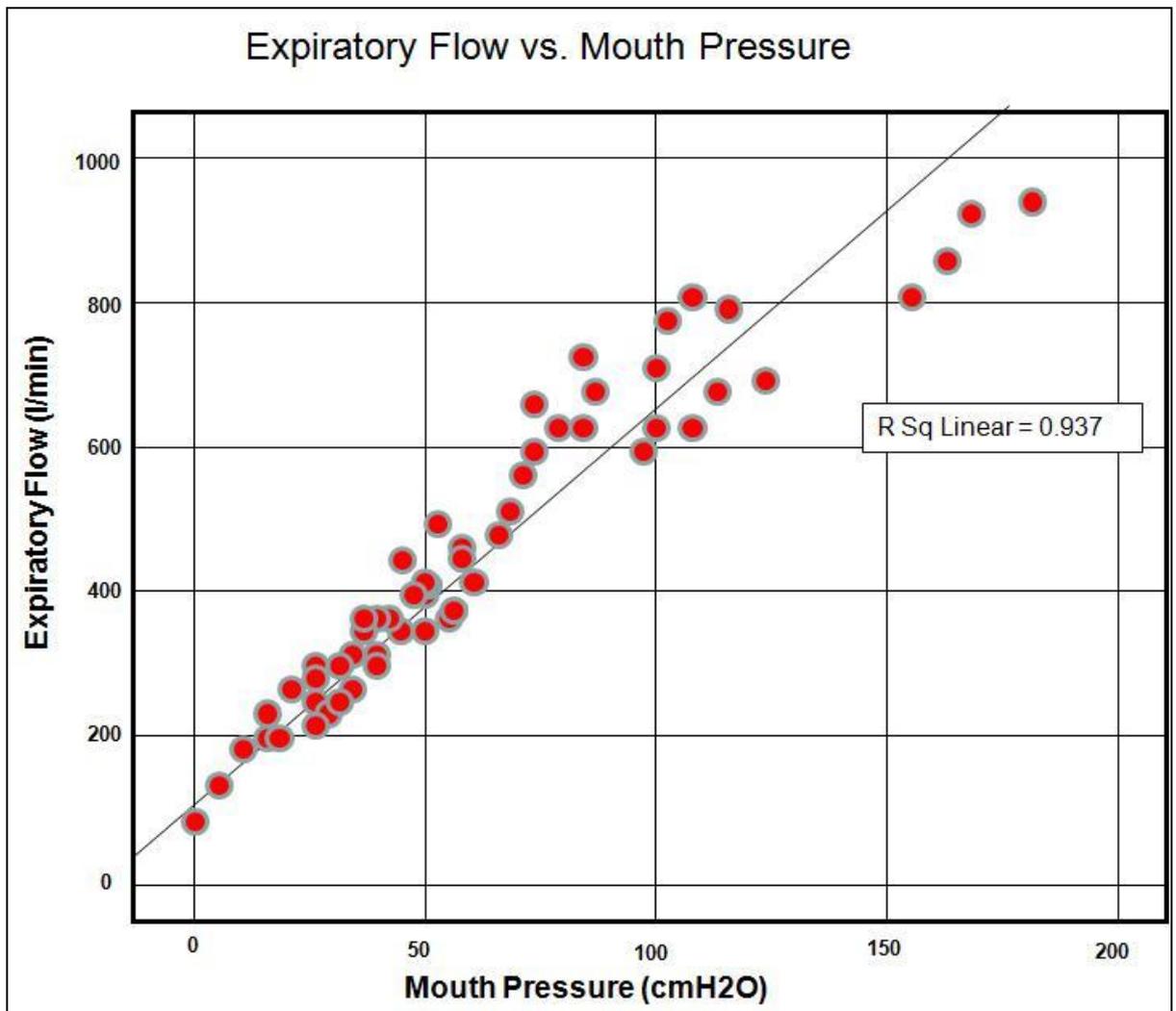


Figure 31. Pressure and Flow relationship for a forced expiratory flow manoeuvre:  
Subject 4.

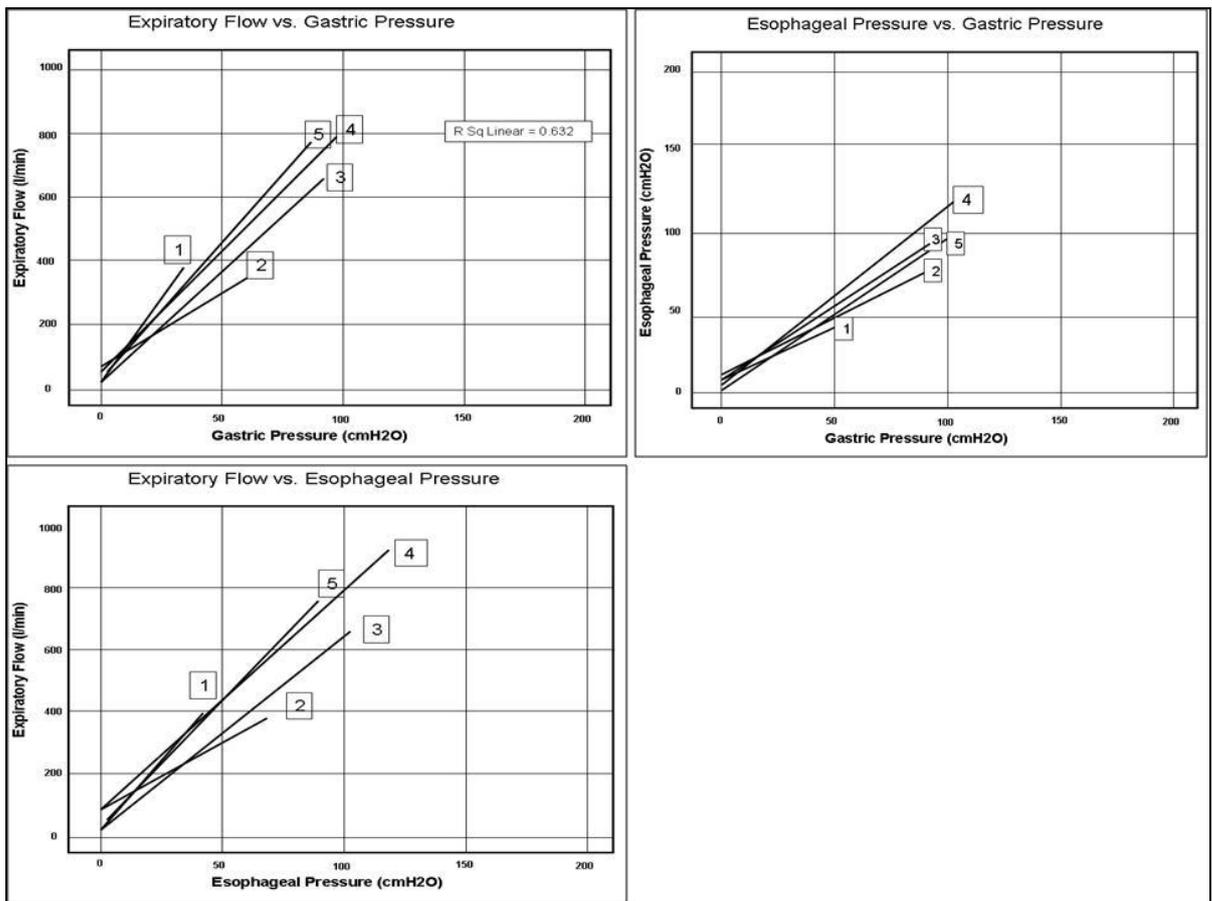


Figure 32. Summary Graphics demonstrating relationship of esophageal, gastric and expiratory flow for 5 test subjects. The linear relationship is maintained for all subjects to a maximum expiratory flow.

**Protocol 2: Pressure/ flow relationship of a voluntary cough.**

The pressure flow plots for a voluntary cough (subject 4) are illustrated below. There is a linear relationship between oesophageal ( $P_{es}$ ) and gastric pressure ( $P_{ga}$ ) (Figure 33) which was apparent for all subjects tested. For all subjects tested, there is no apparent pressure flow relationship between  $P_{es}$  and flow(Figure 34) or  $P_{ga}$  and flow(Figure 35). The absence of a relationship between gastric/ esophageal and expiratory flow is present in all 5 subjects tested. There is a linear relationship between  $P_{Mouth}$  measured once expiratory flow has commenced and peak flow developed during a voluntary cough(Figure 36) and this is also demonstrated for all 5 test subjects.

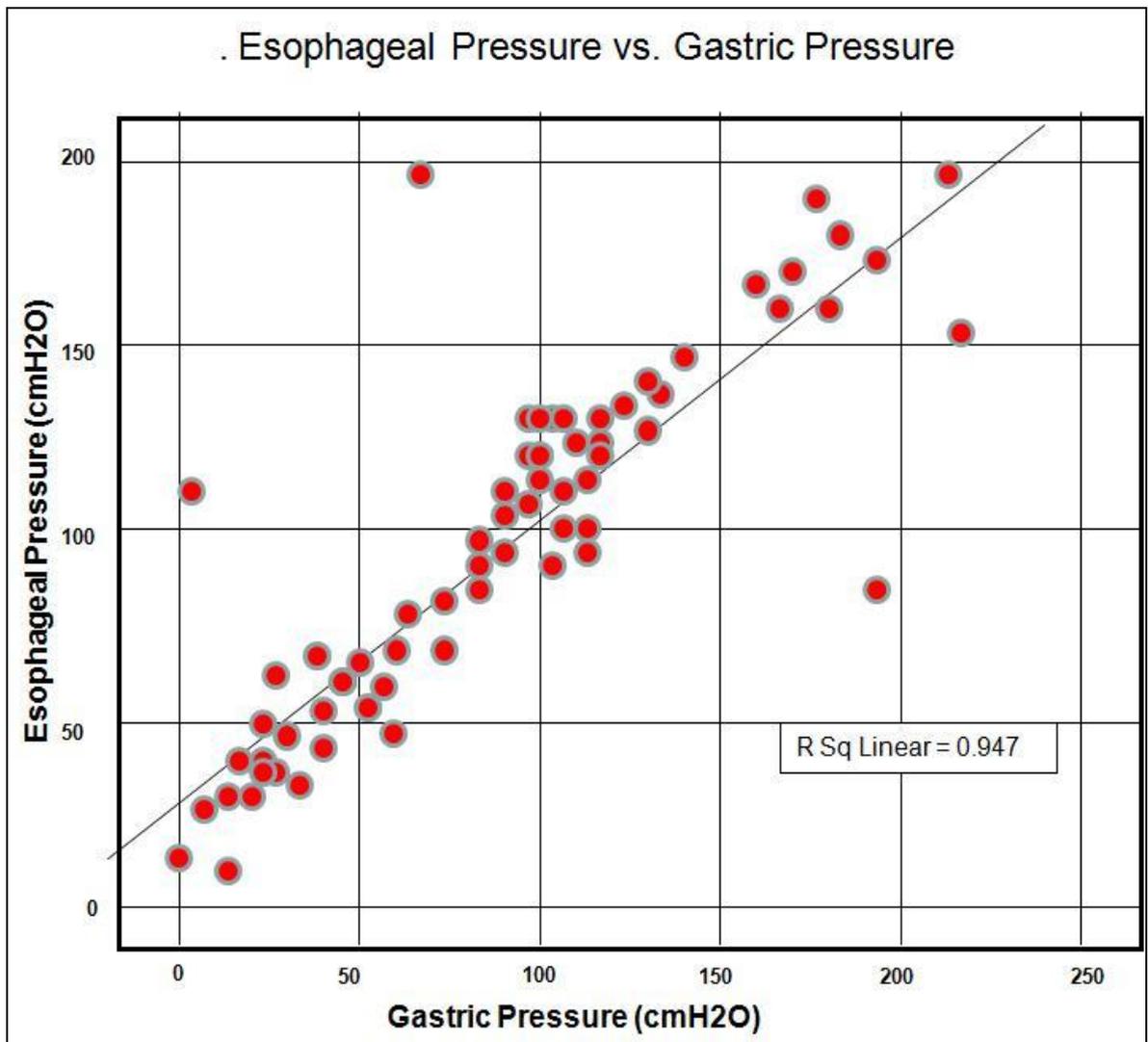


Figure 33. Scatter Plot demonstrating relationship between gastric pressure and esophageal pressure for a voluntary cough. A line of best fit demonstrates a strong positive correlation (Subject 4).

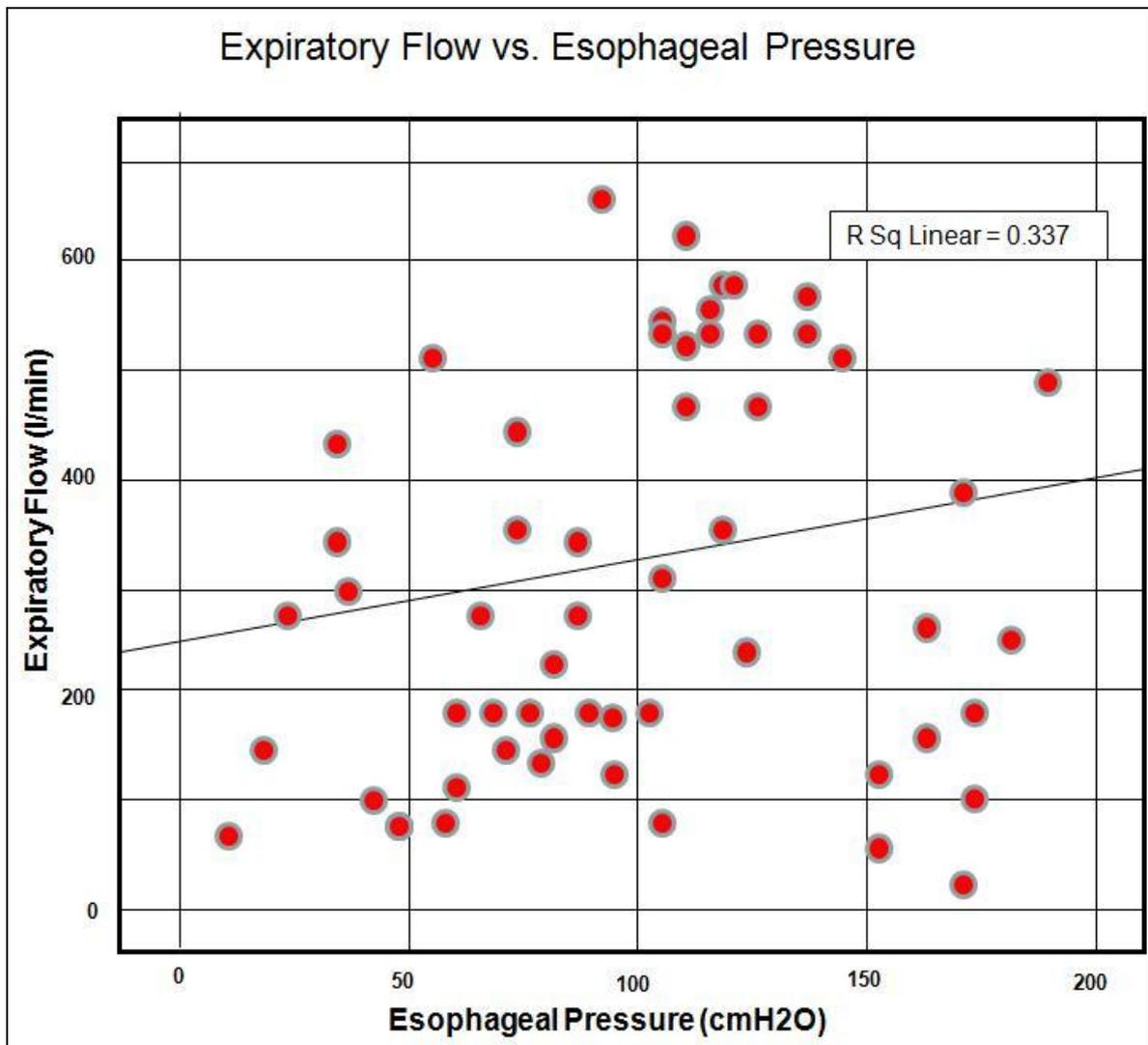


Figure 34. Scatter Plot demonstrating relationship between esophageal pressure and peak expiratory flow for a voluntary cough. A line of best fit demonstrates a weak positive correlation (subject 4).

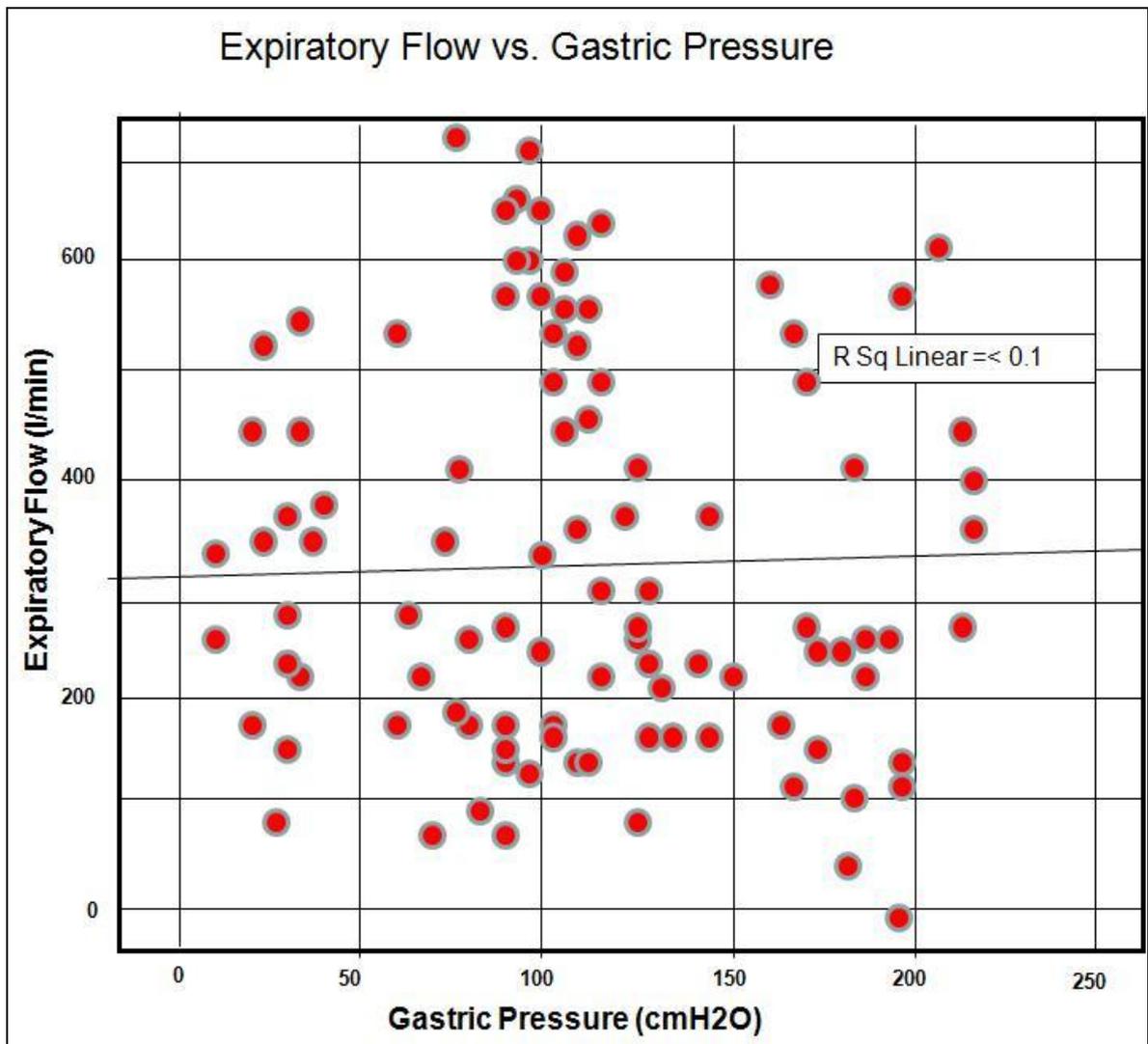
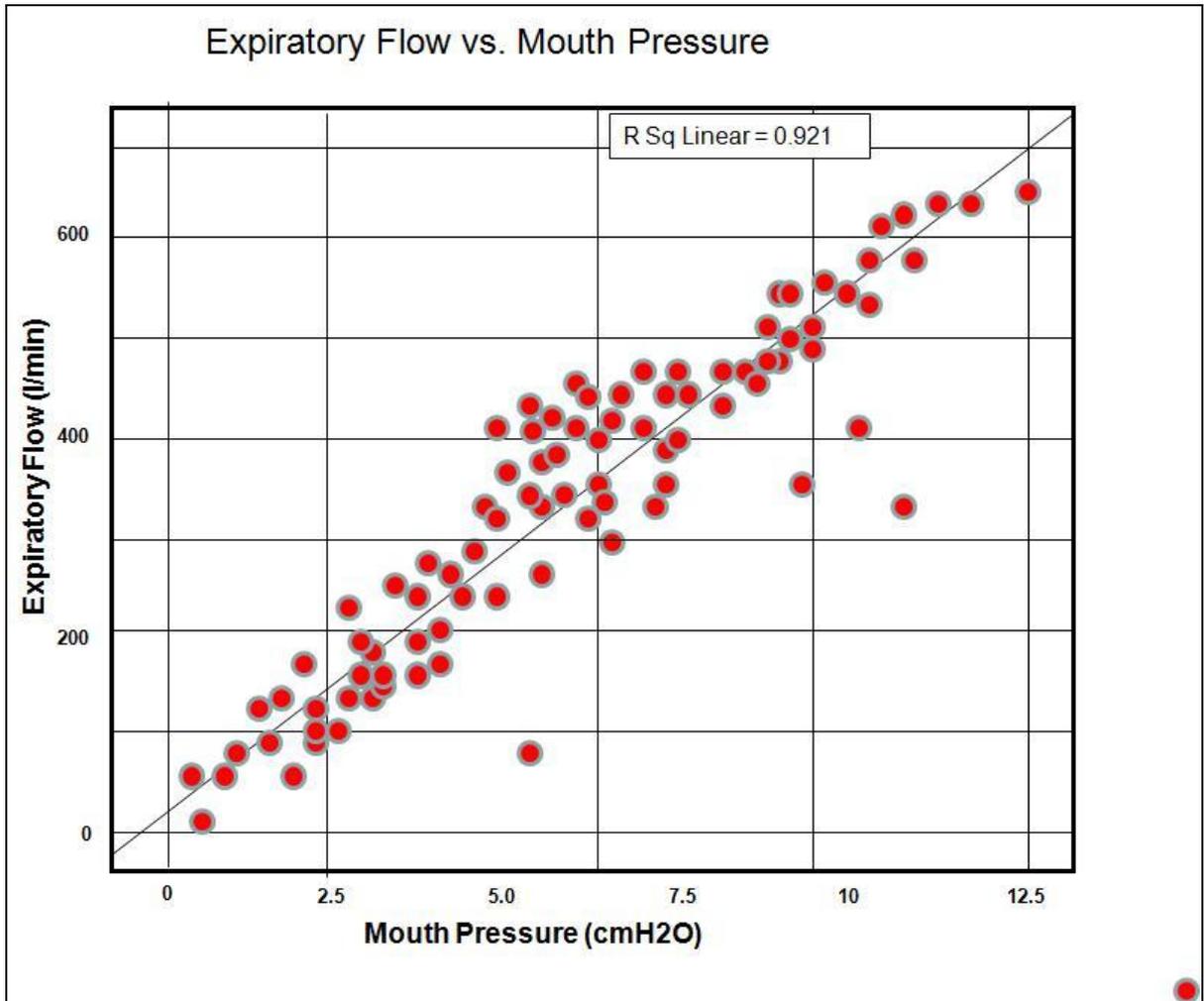


Figure 35. Scatter Plot demonstrating relationship between gastric pressure and peak expiratory flow for a voluntary cough. A line of best fit demonstrates a weak positive correlation (Subject 4).



**Figure 36. Scatter Plot demonstrating relationship between mouth pressure and peak expiratory flow for a voluntary cough. A line of best fit demonstrates a strong positive correlation (Subject 4)**

An analysis comparing the pressure and flow achieved during a voluntary cough and a forced expiratory flow demonstrate important differences. The box plots below demonstrate that the pressure, flow (Figure 37) was greater for a maximum voluntary cough and the time peak flow (Figure 38) achieved was shorter for a voluntary cough than for a maximum FEF. An ANOVA indicated that these differences were significant, and a post hoc analysis demonstrated that  $P_{es}$ ,  $P_{gas}$  and peak flow values were different ( $p < 0.05$ ).

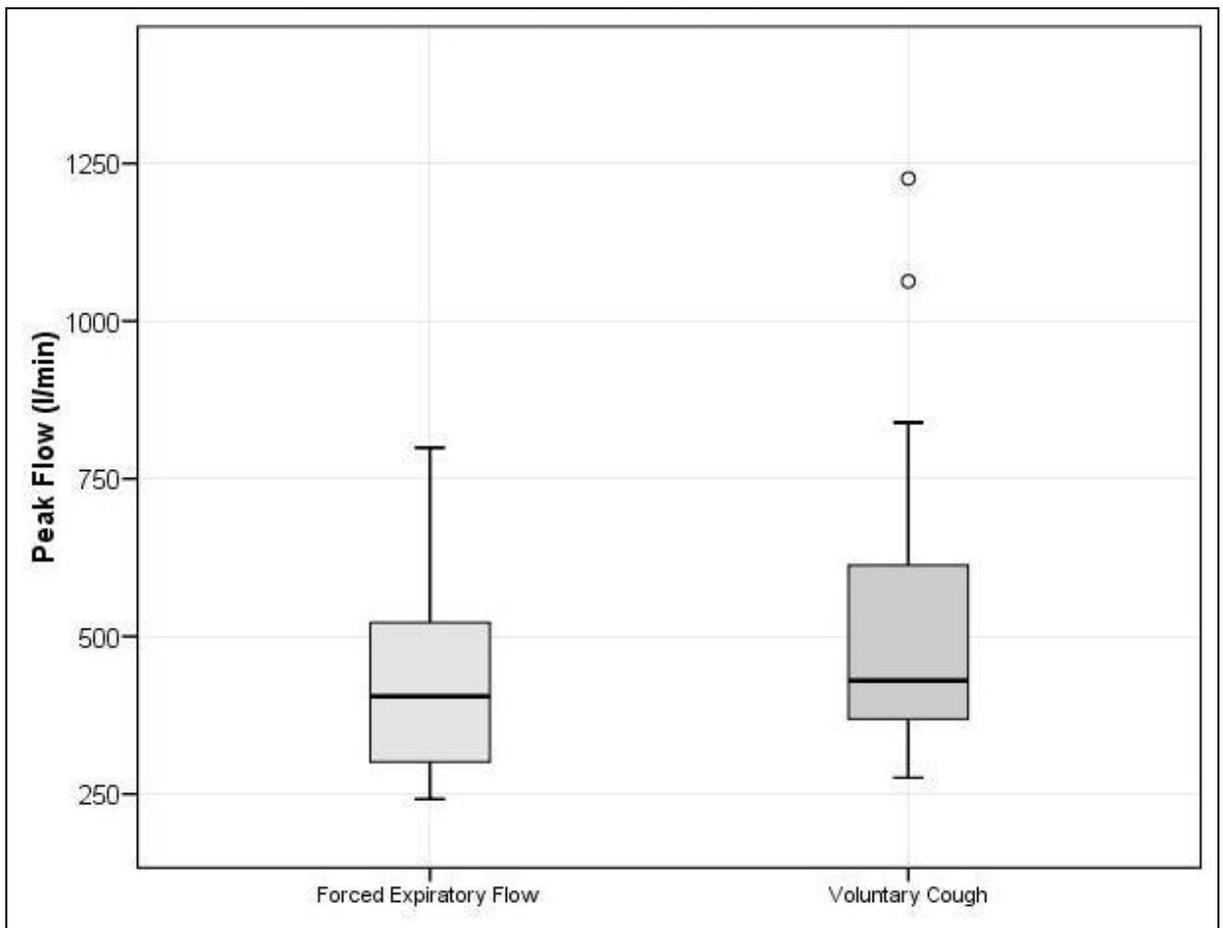
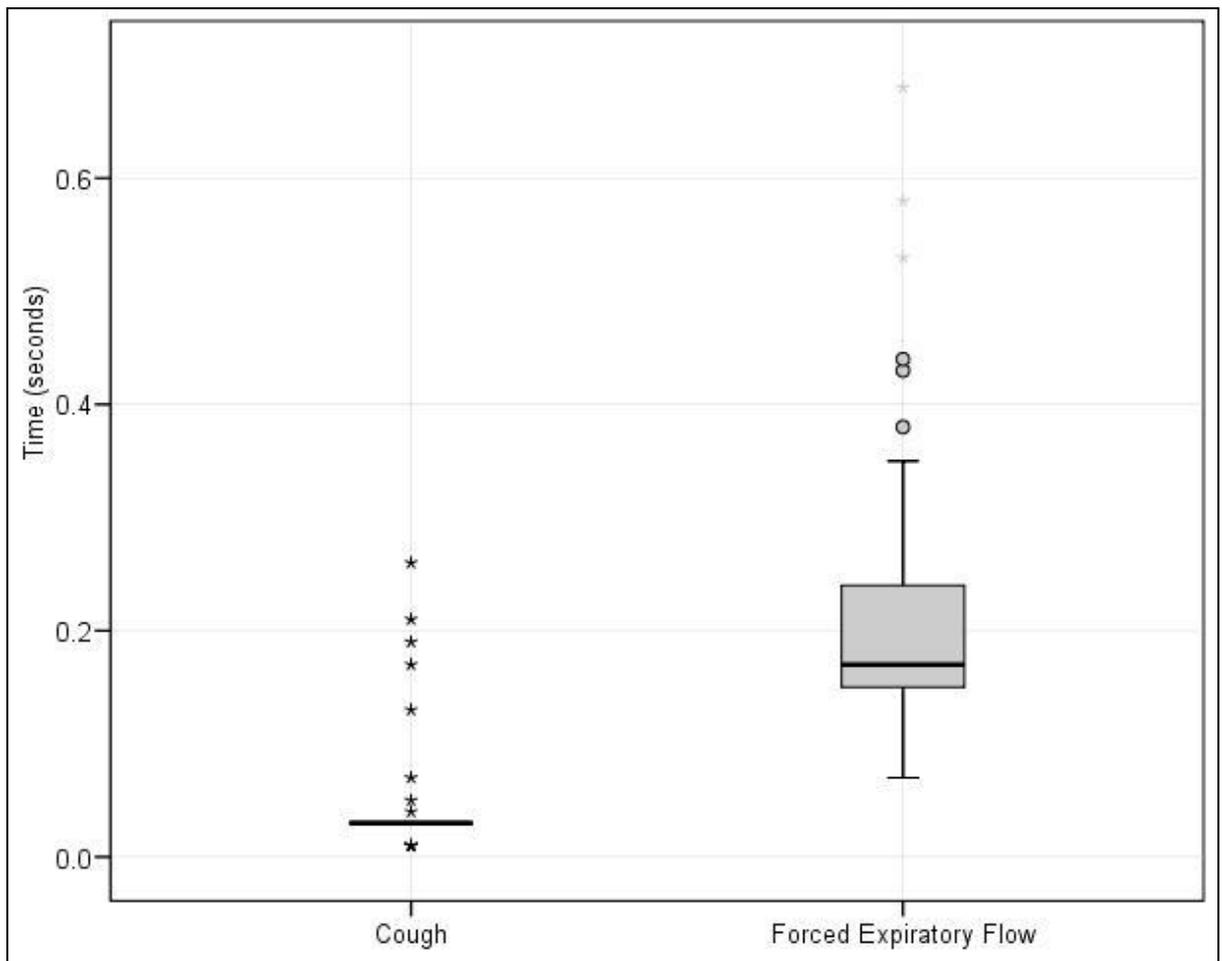


Figure 37. Box Plot demonstrating differences in peak flow between a forced expiratory flow and voluntary cough manoeuvres for all test subjects.

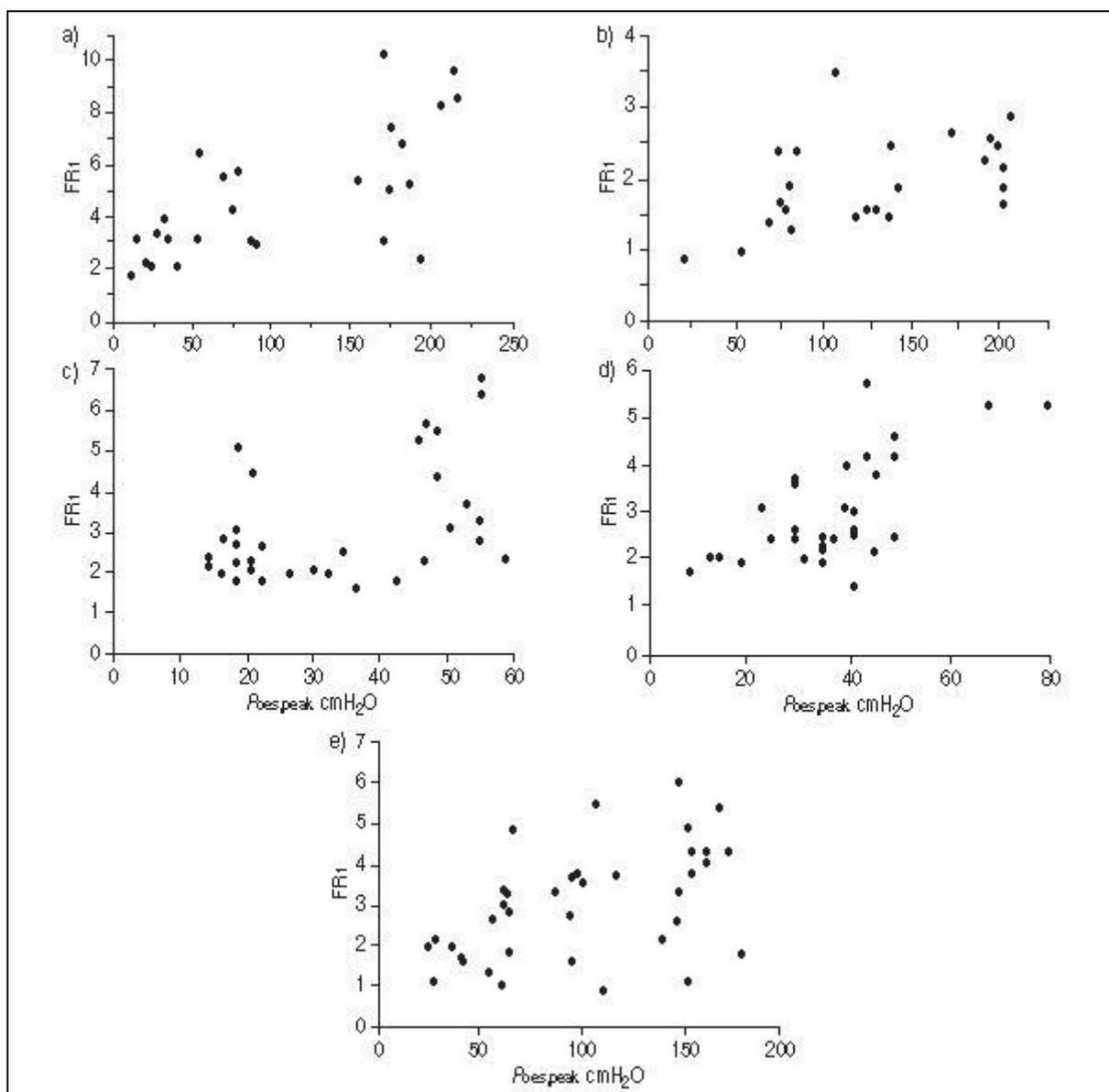


**Figure 38. Box Plot demonstrating difference in time to achieve peak flow for a Voluntary Cough or a Peak Flow Manoeuvre for all test subjects.**

### Discussion

The results confirmed the findings of Fry(Fry, 1958) and Hyatt(Hyatt and Wilcox, 1963) that a linear relationship exists between the pressure generated in either the thorax ( $P_{es}$ ) or abdomen ( $P_{gas}$ ) and the peak flow developed. However, it is well described that there is a maximum expiratory flow, beyond which an increase in pressure will not generate an increase in expiratory flow. This is described as the effort independent part of the pressure flow curve(Wilson et al., 1980). It is surmised that large airway collapse is responsible for the limitation to a further increase in expiratory flow(Fry, 1958). However, a voluntary cough is able to achieve a peak flow in excess of a forced expiratory flow manoeuvre, a “supramaximal flow”, therefore does the data from our observations of voluntary cough mechanics provide an explanation for this.

The pressure-flow relationship for a voluntary cough is demonstrated. As with a forced expiratory flow manoeuvre, there is a linear relationship between oesophageal and gastric pressure. In contrast to a forced expiratory flow manoeuvre, a rise in oesophageal or gastric pressure does not demonstrate a strong positive correlation to the peak expiratory flow generated. Though it is intuitive that flow will not occur in the absence of a pressure difference and that an elevation in that pressure difference will lead to an increase in flow, there are factors responsible for the generation of cough flows that are not accounted for by these simple observations. The observation that for each subject, peak oesophageal pressure was unrelated to the peak flow generated during a voluntary cough was also observed by Lavietes(Lavietes et al., 1998)(**Figure 39**), though no explanation was offered.



**Figure 39. Lavietes demonstrating absence of relationship for esophageal pressure and peak expiratory flow during a voluntary cough. (Airway dynamics, oesophageal pressure and cough. Eur Respir J 1998; 11: 156–161)**

An explanation for the difference between the two expiratory manoeuvres is that early glottic closure during a cough allows the development of intrathoracic pressures in excess of that seen during a PEF. Sudden glottic opening then generates a brief expiratory flow spike. Knudson's observation of the origin of supramaximal flows concluded that the volume expired was accounted by the dynamic compression of the bronchial tree (Knudson et al., 1974). These observations were confirmed by Ohya

observing forced expiratory flow against a shutter valve(Ohya et al., 1989). During laryngeal closure, the bronchial tree is subject to the compressing force of pleural pressure. The length of the compressed segment and the amount of compression will be dependent on airway wall compliance and lung size. These authors did not observe the higher pleural pressure generated during a voluntary cough when compared with a forced expiratory flow manoeuvre. The role of the thoracic muscles in expiration has been reviewed recently. It is possible that a voluntary cough is able to recruit thoracic muscles to generate an additional pressure that is additive to the dynamics generated by the glottic closure. These observations do not refute or confirm this, but cough mechanics could be maintained even in the absence of abdominal muscle paralysis, but would be compromised with thoracic muscles compromise.

The implication of these observations is that the mechanics of flow observed during a voluntary cough and a forced expiratory flow manoeuvre are not comparable. Some of the difference may be a consequence of the higher intrathoracic pressures generated during early expiration. Distension of the elastic components of the large airways may store potential energy that upon glottic opening contributes to the generation of supramaximal flows. The relationship between flow and pressure therefore involves several components that can only be estimated(Knudson et al., 1974) and were not measured in this study.

The study observed that the time to develop a peak flow is reduced for a voluntary cough manoeuvre (*0.04 seconds +/- 0.05*) compared with a FEF manoeuvre (*0.21 seconds +/- 0.13*) implies that the acceleration of the gas is greater during a voluntary cough. If Newton's second law of motion (**F = Mass x Acceleration**) is considered with respect to a voluntary cough. The acceleration would represent the rate of change of velocity of the gas expired and mass the volume of air expired. The force then generated by the moving air will have a significant impact on the force applied to mucus lining the airway wall. If Knudson(Knudson et al., 1974) estimates that the mass of air expired is increased slightly and the acceleration is elevated then the increase in force will be considerable within the large airways where cough is known to be most effective. The effect would be an effective downstream movement of airway mucus and or inhaled matter.

It is not clear from these observations if an absence of laryngeal closure would compromise normal cough mechanics to make it ineffective. Attempts to reproduce cough mechanics will need to consider which cough elements contribute to the efficiency of a voluntary cough.

**Comment**

Propofol and other sedatives produce a dose related decrement in the contractility of voluntary muscles. The surrogate cough model is dependent upon the force developed through magnetic nerve stimulation of the abdominal muscles. The reduction of force may negatively impact the airway pressure generated when the model is applied to the sedated critical care patient. The objective of the subsequent study is to provide a measure of the decrement in muscle force likely when magnetic nerve stimulation is applied in the presence of Propofol.

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## **Chapter 6: The effect of Propofol on airway pressures generated by magnetic stimulation of the phrenic nerves**

### **Introduction**

Anaesthesia reduces resting lung volume and changes the position of the chest wall and the diaphragm. This may in part be due to inhibition of the central or peripheral nervous system (PNS) or a direct action on the respiratory muscles, leading to a fall in strength. However, the effect of anaesthetic agents on pressures generated during stimulation of the respiratory muscles via the PNS has not been investigated in humans.

Measurement of the pressure change at the mouth during supramaximal magnetic stimulation of the phrenic nerves (TwPmo) allows a non-invasive assessment of the airway pressures that can be generated by the diaphragm (Hamnegaard et al., 1995). A comparison of the pressures generated before and after induction of anaesthesia can therefore be made.

In normal conscious subjects TwPmo mirrors twitch oesophageal pressure (TwPes), which is generated when the diaphragm is stimulated (Hamnegaard et al., 1995). Therefore, a change in TwPmo reflects the percentage change in diaphragmatic contraction or twitch transdiaphragmatic pressure (TwPdi) that is producing it, even though we do not know the twitch gastric pressure (TwPgas) component of TwPdi.

Unfortunately, the resting position of the diaphragm also affects the maximal force of contraction. If the diaphragm becomes more stretched as lung volume decreases, it can generate a greater TwPdi or resulting TwPmo, for a given stimulus. The effect that changes in lung volume have on diaphragmatic contractility has previously been described (Smith and Bellemare, 1987, Hubmayr et al., 1989). Hamnegard described the relationship between twitch pressures produced using cervical magnetic stimulation of the phrenic nerves (CMS) and lung volume (Hamnegard et al.,

1995). Further related work using bilateral magnetic stimulation of the phrenic nerves from an anterior approach has examined the relationship of posture and lung volume to twitch amplitude. This allows an approximate correction to be made to twitch pressure amplitude for the effect of lung volume changes seen during anaesthesia in the supine position.

We are able to assess more precisely the functionally important change in airway pressure generated by diaphragmatic contraction, which is the contribution of the diaphragm to the pressure driving inspiration at the mouth. If the drop in airway pressure produced by stimulation of the diaphragm is reduced by propofol this could have implications for patients weaning from respiratory support. Therefore, our primary aim was to determine if propofol affected the change in airway pressure produced by supramaximal single twitch stimulation of the diaphragm.

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## **Methods and materials**

### **Subjects**

Patients were excluded if they had a history of acute or chronic airways obstruction. Thirteen patients scheduled for elective surgical procedures under general anaesthesia were studied. Eleven using twitch pressure measured at the mouth and a further two subjects using oesophageal and gastric balloon catheters. They were ASA grade I-II, aged 20-74 (nine male, six female). Three further subjects were excluded from the study: One subject, because of difficulties gaining an adequate seal during pressure measurements, and two other subjects, because we achieved inadequate phrenic nerve stimulation. The study was approved by the local ethics committee and conducted within the principles of the Helsinki declaration. All subjects gave written, informed consent.

### **Equipment**

The change in airway pressure during diaphragmatic contraction was measured by a differential pressure transducer range  $\pm 180$  cmH<sub>2</sub>O (*Honeywell, Calif., USA*) connected to the mouthpiece, amplified and passed to a PC running LabView 4 software (National Instruments, Austin, Tex., USA). In the case of the patients with balloon catheters, pressures were measured using identical transducers. The change in lung volumes with anaesthesia was recorded using an 8- l dry spirometer (SensorMedics, Calif., USA) substituted for the breathing bag in an anaesthetic circle system, which contained a CO<sub>2</sub> absorber.

### **Diaphragmatic strength measurement**

Diaphragmatic strength is conventionally assessed by electrically stimulating the phrenic nerves. We used magnetic stimulation because it is easier to position consistently and is more comfortable for the awake patient (Hamnegard et al., 1996). On contraction the diaphragm descends, decreasing the intra-thoracic and intra-pleural

pressure, whilst increasing the intra-abdominal pressure. This elevates the differential pressure across the diaphragm, known as twitch transdiaphragmatic pressure (TwPdi), which is the difference between twitch gastric pressure (TwPgas) representing abdominal pressure and twitch oesophageal pressure (TwPoes) representing pleural pressure.

Conventionally the TwPoes and the TwPgas are measured directly with balloon catheters, which are passed per nasally. Unfortunately, the technique is quite invasive and only two patients were prepared to go ahead with this. In these two subjects one catheter was positioned in the stomach and the other in the lower third of the oesophagus (Milic-Emili et al., 1964b), using the technique described by Baydur (Baydur et al., 1982). Care was taken to ensure the change in oesophageal pressure and mouth pressure during the Baydur manoeuvre was as close to identical as possible in the supine position. Therefore, TwPmo was employed in the remaining 13 subjects.

The ratio of TwPoes to TwPgas has been shown to change when subjects move between the supine position, reclining at 45 degrees and sitting up at 90 degrees to the horizontal (Koulouris et al., 1989). However, providing the same posture is maintained throughout the experimental procedure, TwPoes and therefore TwPmo will still be proportional to the diaphragmatic contraction producing them (Hamnegard et al., 1995). Therefore any change in TwPmo will reflect the same percentage change in TwPdi.

TwPmo only reflects the effect of diaphragmatic contraction if the glottis is open, maintaining a continuous air passage from the mouth into the upper airway and the chest. Therefore, a gentle spontaneous inspiratory or expiratory effort is required immediately before the phrenic stimulation to ensure the airway is maintained patent.

To make a recording, the mouthpiece is closed at the end of a normal expiration. In order to allow a small inspiratory flow sufficient to maintain glottic patency during the inspiratory effort, a small leak is preserved via a 4-cm long/1-mm diameter tube attached to the closed mouthpiece. When the gentle inspiratory effort begins there is a drop in the airway pressure. As this reaches  $-3 \text{ cmH}_2\text{O}$ , the computer triggers a pair of

linked magnetic nerve stimulators (Magstim, Whitland, Dyfed, Wales), which energize the two 43-mm mean diameter double coils stimulating the phrenic nerves simultaneously.

To minimise potentiation, subjects were asked to rest quietly, in a supine position, for 20 min before the measurements, avoiding talking or vigorous respiratory efforts. Potentiation is the process by which muscles that have recently contracted, have an augmented contraction in response to a further twitch stimulation. This phenomenon lasts for 20 min after a period of activity (Wragg et al., 1994) and is greater the harder the muscles have worked. Fortunately, single twitches have minimal impact on twitch amplitude.

### **Experimental protocol**

Patients were premedicated with lorazepam (1-2 mg) 1-2 h prior to the study. Although, the effect of lorazepam on twitch height is unknown, the pre- and during propofol measurements were only minutes apart and so any difference in impact on relative twitch height were thought to be negligible between the two measurements.

Two sets of phrenic nerve stimulation were performed in the supine position; one prior to and one after induction of anaesthesia. In each set, stimulations were repeated five times, avoiding any leaks, with the mouthpiece valve fully closed during stimulation, while maintaining a patent airway, leading to smooth undistorted pressure changes. Prior to induction, patients were asked to attempt to inhale gently through the mouthpiece, which had been temporarily closed at the end of expiration. On inspiration the fall in pressure within the mouthpiece, triggered the magnetic stimulators and the change in airway pressure (TwPmo) was recorded. Simultaneously, skin surface diaphragmatic electromyogram EMG recordings were amplified using a Magstim Neurosign 100 and passed to the computer.

Anaesthesia was then induced with the patient breathing through a well-fitting facemask onto which the pressure transducer mouthpiece had been attached. This was attached to the closed-circle system. No further fresh gas was added until breathing had

been re-established after induction in order to measure the change in resting end expiratory position (REEP). The 8-l volume of the spirometer bellows was sufficient to ensure that the inspired oxygen remained adequate throughout the recording. Changes in REEP with induction of anaesthesia were later estimated from the spirometer tracings, to the nearest 100 ml, using the method described by Bergman(Bergman, 1982). After adequate spirometer recordings had been made fresh oxygen was introduced from the common gas outlet of the anaesthetic machine.

Hamnegard et al.(Hamnegard et al., 1995) showed a linear reduction in the TwPdi (5.3 cmH<sub>2</sub>O/l) with increasing lung volume. TwPmo reflects the change in oesophageal pressure (TwPoes) produced by diaphragmatic contraction, showing a linear reduction with increasing lung volume 5.6 cmH<sub>2</sub>O/l. TwPgas is relatively little affected by changes in lung volume. BAMPS produces results comparable to CMS, showing a linear reduction in TwPdi of 5.9 cmH<sub>2</sub>O/l, TwPoes of 4.9 cmH<sub>2</sub>O/l and TwPgas 0.6 cmH<sub>2</sub>O/l in the supine position. We used 4.9 cmH<sub>2</sub>O/l to correct TwPmo for changes in REEP.

Anaesthesia was induced and maintained with propofol by Target Controlled Infusion initially set to achieve a plasma level of 6 µg/ml, adjusted depending on the response of the subject(Swinhoe et al., 1998, Turtle et al., 1987). Once breathing was re-established under propofol anaesthesia a second set of measurements of TwPmo was made using the same technique.

To confirm that the phrenic nerves were being stimulated supramaximally, a further set of phrenic stimulations were performed with the patients stable under anaesthesia. Recordings of TwPmo were made in nine patients and EMG in seven, while randomly varying the output of the magnetic stimulators (to encompass all of the following settings 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100% of maximum). Five TwPmo and EMG recordings were made at each power setting.

**Results**

Details of the subjects are shown below (Figure 40). We determined whether we could achieve supramaximal stimulation of the phrenic nerves. TwPmo and the EMG amplitude produced by the range of stimuli were normalized to allow comparison between the patients. The TwPmo or EMG amplitude produced at the stimulus intensity of 100% was taken to be the 100% TwPmo or EMG amplitude for that patient and then compared with the response at differing stimulus intensities.

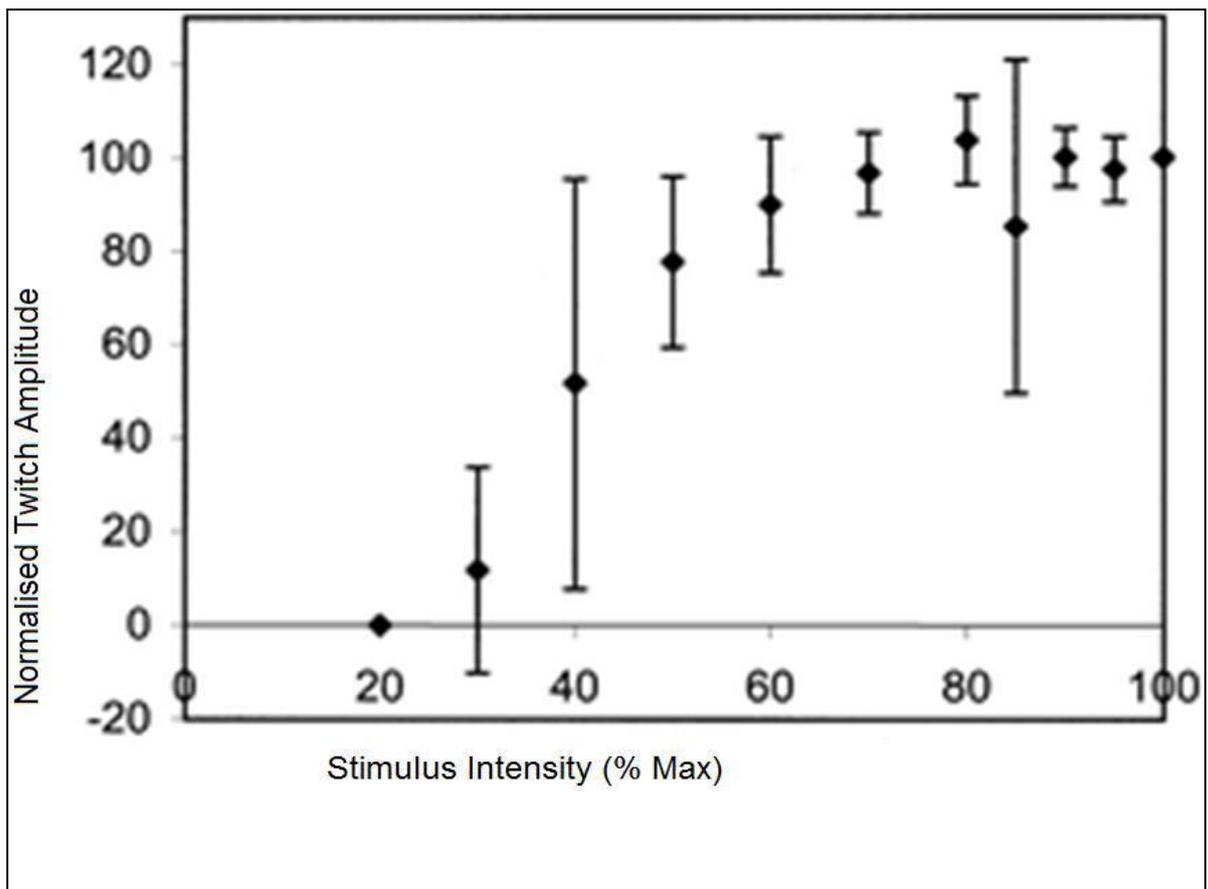
Subject No.	Age Years	Sex	Height cm	Weight kg	FVC (l)	FEV1 (l)	Proposed operation
1	26	F	157	60	3,4	2,9	Dental extraction
2	71	M	178	69	3,9	3,2	TURT
3	62	M	178	89	3,3	2,8	TURP
4 <sup>a</sup>	29	M	183	94	4,6	2,8	Herniorraphy
5	20	M	185	72	5,4	4,8	Perc. Nephrolithotomy
6	53	M	175	84	3,9	3,0	Herniorraphy
7	33	F	163	59	2,8	2,3	Biopsy of skin lesion
8	25	F	167	60	3,5	2,9	Cystoscopy
9	55	M	180	80	6,4	3,9	Cystoscopy
10	52	M	171	74	5,9	3,6	Cystoscopy
11	39	F	159	71	3,3	2,8	Laparoscopy
12 <sup>b</sup>	27	F	150	56	3,3	2,8	Dental extraction
13 <sup>b</sup>	74	M	179	76	3,6	3,0	Cystoscopy
SD	19	F: 5	11	12	1,1	0,6	
Mean	44	M: 8	171	73	4,1	3,1	

**Figure 40. The characteristics of the subjects. (TURP transurethral resection of prostate, TURT transurethral resection of bladder tumour)**

**a) FEV1 difficult in subject 4 due to hernia, but no history of lung disease**

**b) With oesophageal and gastric balloon catheters**

(Figure 41) and (Figure 42) show the normalised TwPmo and EMG amplitude for the group, as the output of the magnetic stimulator is varied. This demonstrates a plateau phase followed by a fall in response at lower outputs, confirming the output of the magnetic stimulator was sufficient to achieve a supramaximal response.



**Figure 41. The mean and standard deviation of twitch pressure measured at the mouth normalised as a percentage of the pressure generated with 100% stimulus power, compared to percentage of maximum magnetic stimulus applied**

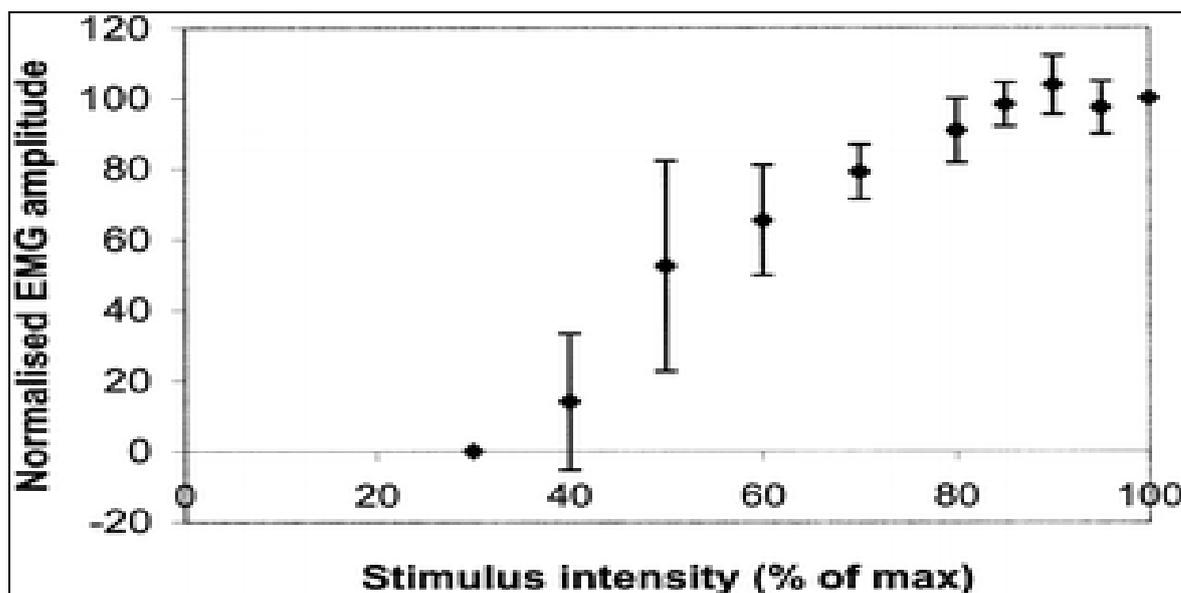


Figure 42. The mean and standard deviation of EMG amplitude normalised as a percentage of the EMG amplitude generated with 100% stimulus power, compared to percentage of maximum magnetic stimulus applied

Lung volume fell immediately following induction of anaesthesia with Propofol. There was a mean reduction in REEP of 0.3 l (SD 0.2) (Figure 43).

Patient number	1	2	3	4	5	6	7	8	9	10	11	Mean	SD
Pre-TwPmo (cmH <sub>2</sub> O)	14,9	17,7	11,3	18,1	9,8	16,8	23,3	24,1	14,3	14,3	16,9	16,5	4,4
Post-TwPmo (cmH <sub>2</sub> O)	13,1	18,8	11,3	19,0	7,0	11,8	20,5	17,4	9,7	13,2	14,1	14,2	4,3
?Post-TwPmo corr*	13,1	15,8	8,9	17,5	6,1	11,8	19,5	16,0	8,7	11,7	13,1	12,9	4,1
REEP Change l	0,0	0,6	0,5	0,3	0,2	0,0	0,2	0,3	0,2	0,3	0,2	0,3	0,2
% fall in TwPmo	12,6	-6,0	0,2	-0,5	28,3	29,6	12,2	27,8	32,2	7,7	16,6	14,2	14,0
% fall in TwPmo corr*	12,6	10,6	21,8	3,1	38,3	29,6	16,4	33,9	39,0	18,0	22,4	23,3	11,7
Pre-EMG		170,4	100,2	294,4	156,4	144,2	214,4	324				200,6	82,0
Post-EMG		209,3	128,8	291,3	169,8	137,5	206,4	264,5				201,1	61,2
% fall EMG		-22,8	-28,5	1,1	-8,5	4,6	3,7	18,4				-4,6	16,5

Figure 43. Changes in twitch mouth pressures and EMG with propofol anaesthesia. (corr\* corrected for changes in lung volume)

To investigate the effect of Propofol on the diaphragm and TwPmo, statistical analysis was performed using a paired *t*-test and one-sample *t*-test. Each patient acted as their own control for readings taken before and after induction of anaesthesia. Mean TwPmo fell from 16.5 cmH<sub>2</sub>O to 14.2 cmH<sub>2</sub>O: a mean fall of 2.3 cmH<sub>2</sub>O ( $P=0.01$ , 95% CI 0.7 to 4.0 cmH<sub>2</sub>O). This represents a fall of 14.2% ( $P<0.01$ ). If we look at the figures corrected for change in lung volume, mean TwPmo fell from 16.5 cmH<sub>2</sub>O to 12.9 cmH<sub>2</sub>O: a mean fall of 3.6 cmH<sub>2</sub>O ( $P<0.001$ , 95% CI 2.2 to 5.0 cmH<sub>2</sub>O) or 22.3% ( $P<0.001$ ).

The two subjects studied with balloon catheters demonstrated a fall of TwPdi of 18% and 20%, respectively, or 26% and 28% corrected for volume(Figure 44).

Subject		Pre	Post	Post-corr*	% change	% corr*
<b>12</b>	TwPdi	15,3	12,6	11,4	-18,1	-25,8
	TwPes	13,7	10,8	9,8	-21,3	-28,4
	TwPgas	2,1	2,1			
	REEP change	0,2				
<b>13</b>	TwPdi	15,4	12,3	11,1	-20,0	-27,7
	TwPes	14,6	11,1	10,1	-23,7	-30,4
	TwPgas	3,2	2,9			
	REEP change	0,2				

**Figure 44. Changes in the two subjects studied with balloon catheters. (corr\* corrected for changes in lung volume)**

### Discussion

We have found that during Propofol anaesthesia, there is a reduction in the inspiratory pressure, measured at the mouth, which is produced by a supramaximal single stimulation of the phrenic nerves causing maximal twitch contraction of the diaphragm. A study in dogs during Propofol anaesthesia(Fujii et al., 1999) detected a fall in TwPdi of 10% to 20%. Volatile anaesthetic agents have also been found to reduce diaphragm contractility in some animal studies(Veber et al., 1989, Ide et al., 1990, Kochi et al., 1990), but not all(Ide et al., 1992).

Most previous studies of the effect of anaesthetic agents have investigated transcranial stimulation, where the effect of the agents are concentrated on the brain and CNS(Kalkman et al., 1992, Kalkman et al., 1991). However, halothane has also been shown to act on muscle cells increasing cytosolic free calcium and inhibiting Na<sup>+</sup>/H<sup>+</sup> exchange in L6 muscle cells(Klip et al., 1990).

A decrease in respiratory muscle strength may explain the fall in lung volume that is seen immediately after induction of anaesthesia. Bergman found a fall in resting end expiratory volume 30 s after induction, stabilising at a lower level after another 1545 seconds(Bergman, 1982). Some of this volume change may also be due to other factors(Etsten and Li, 1955), such as movement of blood into the thorax during spontaneous breathing or out during mechanical ventilation(Krayer et al., 1987, Hedenstierna et al., 1985). However, results so far are extremely variable.

EMG studies, have shown a reduction in tone of the rib cage muscles(Drummond, 1987). There is evidence that tonic activity in the scalenes, sternocleidomastoids and, to a lesser extent, the intercostals is abolished by thiopentone(Drummond, 1987), although tonic activity has not been found in the parasternals(Warner et al., 1996, Warner et al., 1995, Warner and Warner, 1995). Following initial conflicting radiological studies, computerised tomography has shown a cephalad displacement of the diaphragm on induction of anaesthesia(Reber et al., 1998).

The size of the fall in lung volume has been investigated. Spens(Spens et al., 1996), used inductive plethysmography, while supporting the spine to reduce skeletal

movements and found a fall in rib cage volume of 307 ml after induction of anaesthesia with propofol. Previous studies have detected a reduction in REEP of 189-285 ml (Bergman, 1982, Rutherford et al., 1994). These values are close to our findings. Nitrogen washout produced higher figures of 600-700 ml (Krayner et al., 1987), possibly due to absorption atelectasis.

TwPmo pressure has been shown to reflect TwPdi in awake normal subjects (Kalkman et al., 1992). A given percentage change in TwPmo is due to an equivalent percentage change in TwPdi or diaphragm strength, even if we don't know the exact value of TwPdi. We can usually say this, because the ratio of TwPoes to TwPgas and TwPoes to TwPdi remains constant for an individual in a given posture and lung volume. Indeed, the average between occasion coefficient of variation for the ratios of TwPoes/TwPdi and TwPgas/TwPdi when studied in normal subjects every 2 months for 10 months is 8.7% and 6.6%, respectively. The within occasion average variabilities are 6.5% and 4.4%

When lung volume changes in normal conscious subjects, TwPdi changes depending on the stretch being applied to the diaphragm. If we look closely at what is happening to its components, we find TwPoes changes, so altering TwPdi, but TwPgas remains little changed over a wide range of volumes (Hamnegard et al., 1995) and TwPmo or the equivalent TwPoes, makes up most of TwPdi when supine. Knowledge of the split between TwPgas and TwPoes could allow us to make an estimate of TwPdi and then apply a correction for the effect of changes in lung volume.

What is currently unknown is whether anaesthesia, as well as changing TwPoes and TwPgas because of alterations in lung volume, also produces more complex effects on the ratio between these two components that make up TwPdi, because of any differing effects on chest wall, diaphragmatic, and abdominal wall tone. Changes in tone may alter the position of the points of origin and insertion of the relevant muscles. The fall in lower thoracic circumference will affect the diaphragm, but it is unclear if this has important different effects compared to a simple reduction in lung volume. This may mean if we try to correct for lung volume changes, then changes in TwPmo before and after anaesthesia will only approximate to the percentage changes in TwPdi.

Fortunately, the lung volume reductions are relatively small and so the impact of any extra effects on the results probably is not great, but may be another source of variability between subjects. Even if there is a different pattern that precludes an exact assessment of the percentage change in TwPdi, TwPmo will provide important information, by demonstrating how propofol alters the inspiratory pressures generated at the mouth during a supramaximal single twitch stimulation of the diaphragm. If our correction is close to being accurate, this would mean that there was a fall in diaphragmatic contractility for all the subjects.

The spontaneous effort used to trigger the stimulator is part of a normal breath and is not enough to potentiate the stimulated twitch. However, since the twitch will be superimposed on top of a very small spontaneous effort, part of the diaphragm is already contracting and so the stimulated twitch will have slightly lower amplitude than would have occurred if the diaphragm had been completely resting. However, this error remains constant before and during propofol anaesthesia, and therefore the results retain validity.

There is always a possibility that leaks from the facemask may occur and affect twitch pressure or lung volume recordings. The masks were well-fitting with a rigid frame, well-conforming rim, but low dead-space. The spirometer and an inline capnograph were watched closely for signs of loss of seal or airway obstruction. One experimenter was dedicated to the maintenance of the airway and ensuring the seal of the mask was complete. A leak was detected in one patient's mask and so this subject was excluded from the study.

Individuals may vary in response to propofol or there may be some deviation from the propofol target plasma level, although studies suggest the regime is effective in maintaining target levels to within 7% of the target (Swinhoe et al., 1998).

Supramaximal stimulation of the phrenic nerves can be difficult to achieve in clinical studies. Figures 1 and 2 demonstrate supramaximal stimulation even though the subjects are under anaesthesia. The lack of variability in the within occasion within individual data (mean TwPmo coefficient of variation preinduction 6.9% and during

propofol anaesthesia 4.3%, mean coefficient of variation of EMG amplitude preinduction 7.3% and during propofol anaesthesia 6.5%) fits well with the consistency expected with supramaximal stimulation(Mills et al., 1996). This may also suggest that consistent passage of pressure change from the lower airways to the mouth is occurring.

The between patient variability is greater. The 25th-75th centile range for the fall in twitch pressure is 12.6-33.9% when corrected for changes in lung volume. Therefore, there is variability between individual patients. This may be contributed to by any of the factors described above. Despite this the change seen with propofol is consistently a reduction in pressure.

We were unable to pass balloon catheters on most of our subjects because recruitment for these invasive procedures proved too difficult. Balloon catheters are the standard technique, but they too have problems. The oesophageal balloon catheter is normally passed per nasally until the pressure seen at the mouth during a gentle inspiration against a closed mouthpiece, equals the pressure change detected in the oesophagus by the catheter. A small amount of extra air in the balloon will initially help counter the compressing effect of the weight of the lungs and heart on the balloon catheter, but most studies have found supine posture makes balloon positioning difficult(Baydur et al., 1982). Once anaesthesia is induced the inward movement of the chest wall and the cephalad movement of the diaphragm will alter the relationship between pressure at the mouth and the balloon catheter in its set position. If atelectasis starts to occur this will produce additional local pressure transmission problems(Strandberg et al., 1986).

Electromyography of the diaphragm is an alternative, but it does not tell us about strength in a readily quantifiable way. Unfortunately, maintaining the same relationship between the position of the electrodes and the diaphragm with a change in lung volume is very difficult(Gandevia and McKenzie, 1986), although the use of an oesophageal array is more promising(Luo et al., 2000). We believe this change in position of the electrodes relative to the diaphragm as lung volume decreased explains why our EMG studies did not show a significant change due to propofol anaesthesia. However, once the initial lung volume change has stabilised, the amplitude of the EMG signal became

useful to confirm supramaximal stimulation, because little further change in lung volume occurred during the few minutes required to perform a ramp of stimuli needed to confirm supramaximal stimulation.

Magnetic stimulation is more consistent and rapid than electrical stimulation in patient studies, but may produce stimulation of other muscle groups that have little effect on pressure, but may distort surface EMG signals (Mills et al., 1996). Needle electrodes have been inserted (Hemmerling et al., 2001, Mills et al., 1995), but are invasive.

We normally consider the sedative effect of anaesthetic agents particularly on respiratory drive as being important potential problems during weaning. However, if agents do reduce diaphragm strength this may promote atelectasis by allowing cephalad movement of the diaphragm or inward movement of the chest wall, necessitating the application of increased PEEP. This fall in lung volume may increase work of breathing. The medical response to this may be to overcompensate with increases in pressure support and paradoxically to reduce respiratory muscle exercise and promote atrophy.

A reduction in respiratory muscle strength may be relatively unimportant in patients with normally compliant lungs and normal respiratory muscle strength, but respiratory muscle weakness may have contributed to the initial reason for ventilation, or may have developed during the critical illness. An additional 10-20% reduction in strength, together with increased work of breathing due to poor compliance may increase the likelihood of respiratory muscle fatigue and result in failure to wean from respiratory support. Therefore, when anaesthetic agents are selected as ICU sedatives, their effect on the respiratory muscles may be an important consideration.

The complex interrelationship between strength, lung volume, and mechanics of the chest wall, diaphragm, and abdomen mean that the assessment of the effect of propofol on the diaphragm is difficult. However, we have detected a fall in the pressure change produced in the airway by supramaximal single twitch stimulation of the diaphragm during propofol anaesthesia: a finding that deserves further investigation. We conclude

propofol does reduce the effectiveness with which diaphragmatic contraction produces changes in pressure in the airway.

**Comment**

The surrogate cough model developed in this thesis is dependent upon the recruitment of the abdominal muscles through magnetic nerve stimulation of thoracic nerve roots. The surrogate cough model assumes that the abdominal muscles are the dominant expiratory muscles. It is known that thoracic muscles are also involved in expiration, but it is not clear if they have a dominant role in forced expiratory manoeuvres. We sought to determine in the subsequent study if through abdominal muscle paralysis there was a significant decrement in expiratory pressure generated.

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## Chapter 7: The Impact of Spinal Anaesthesia upon Expiratory and Inspiratory Muscle Strength.

### Introduction:

Spinal anaesthesia is known to cause a reduction in peak expiratory flow (Gamil, 1989) respiratory frequency (Gauthier et al., 1992), peak expiratory flow (Harrop-Griffiths et al., 1991) (PEFR), forced expiratory volume (FVC) and forced expiratory volume in one second ( $FEV_1$ ). The apparent absence of respiratory compromise in normal subjects following spinal or extradural anaesthesia leads to spinal and extradural anaesthesia being advocated for patients with respiratory disease. It would however, be anticipated that spinal anaesthesia, through interruption of thoracic and lumbar spinal cord efferents, would produce changes in the force generated by respiratory muscles. In particular the loss of abdominal muscle tone may prevent the diaphragm, the principle muscle of inspiration, elevating its point of insertion in the lower ribs and in turn the whole rib cage during inspiration. It has previously been demonstrated that maximal expiratory ( $P_{\text{emax}}$ ) and inspiratory ( $P_{\text{imax}}$ ) pressure (Gal and Goldberg, 1981), are sensitive measures of respiratory muscle compromise when compared with FVC. That vital capacity is spared in the presence of mild or moderate respiratory muscle weakness is evidence of the ability of respiratory muscles to compensate (Gal and Goldberg, 1981). We hypothesized that  $P_{\text{emax}}$  and  $P_{\text{imax}}$ , would be a more sensitive indicator of the effect of spinal anaesthesia upon inspiratory and expiratory respiratory muscle function. We therefore observed the changes in  $P_{\text{emax}}$  and  $P_{\text{imax}}$  in 20 subjects following spinal anaesthesia.

**Methods:**

The institutional ethics committee approved the study and informed consent was obtained from each subjects. Twenty patients were recruited for the study that required spinal anaesthesia for surgery to the lower abdomen or legs(Figure 45). Maximal inspiratory and expiratory pressure was performed via a mouthpiece (*Morgan Medical*), with the nose occluded. Handgrip strength (*GS*) was used as an independent variable. Handgrip strength is unlikely to be influenced by lumbar spinal anaesthesia, and therefore acted as an indicator of changes in patient effort. Each test was repeated 6 times and the best value for each parameter (*MIP, MEP and GS*) was recorded. Patients were trained in the practise of MIP, MEP and GS on the day prior to surgery. All tests were performed with the patient in the supine position and were repeated at regular intervals. Spinal anaesthesia was performed using a 25G Whitacre needle at the L3/L4 interspace in all cases. The volume of 0.5% heavy bupivacaine introduced was determined by the anaesthetist performing the anaesthetic and was uninfluenced by inclusion of the patient in the study. The level of spinal anaesthesia was determined from the dermatomal level at which the subject could detect cold. Following spinal anaesthesia subjects were asked to repeat MIP, MEP and GS at intervals of ten to twenty minutes up to 3 hours.

Age (years)	Weight (Kg)	Height (m)	BMI	FEV <sub>1(l)</sub>	FVC (l)	Dose of Bupivacaine (ml)
64 (14)	77 (16)	1.7 (0.1)	25 (4)	2.2 (1)	3.2 (1.1)	2.5 (0.3)

**Figure 45. Details of study subjects. Values are mean (+/- SD)**

**Analysis**

SPSS (*Statistical Package for the Social Sciences*) was used for subsequent data analysis. We anticipated that the effect of spinal anaesthesia upon MIP and MEP would be greatest between thirty and sixty minutes. The values for MIP, MEP and grip strength at thirty and sixty minutes were therefore compared with the values measured at time zero. Student's t-test was used to measure the strength of the difference between these values and a p value less than 0.05 was taken to be significant.

### Results:

Data was collected on all twenty patients. (Figure 46) indicates the level of cutaneous analgesia achieved and the accompanying changes in MIP, MEP and GS(Figure 47). The cephalad level of anaesthesia reached T5 (range T3 – T8), as determined by the patients' ability to detect cold. There was no significant change in grip strength at the thirty-minute period ( $P > 0.3$ ). The reduction in MEP at thirty minutes was significant ( $P = 0.003$ ), whereas the change in MIP was not significant at the thirty-minute period ( $P = 0.09$ ), or the sixty-minute period.

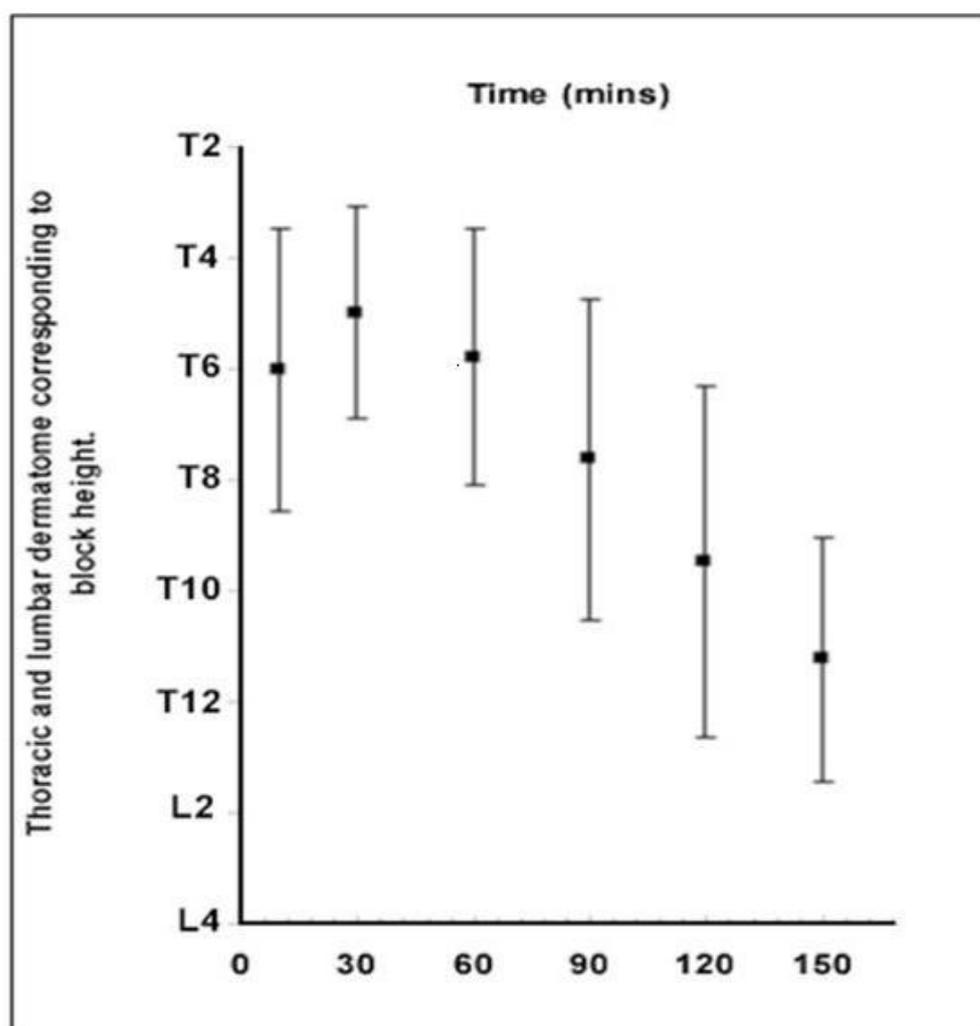


Figure 46. Upper level of cutaneous analgesia (+/- 1SD) achieved following spinal anaesthesia

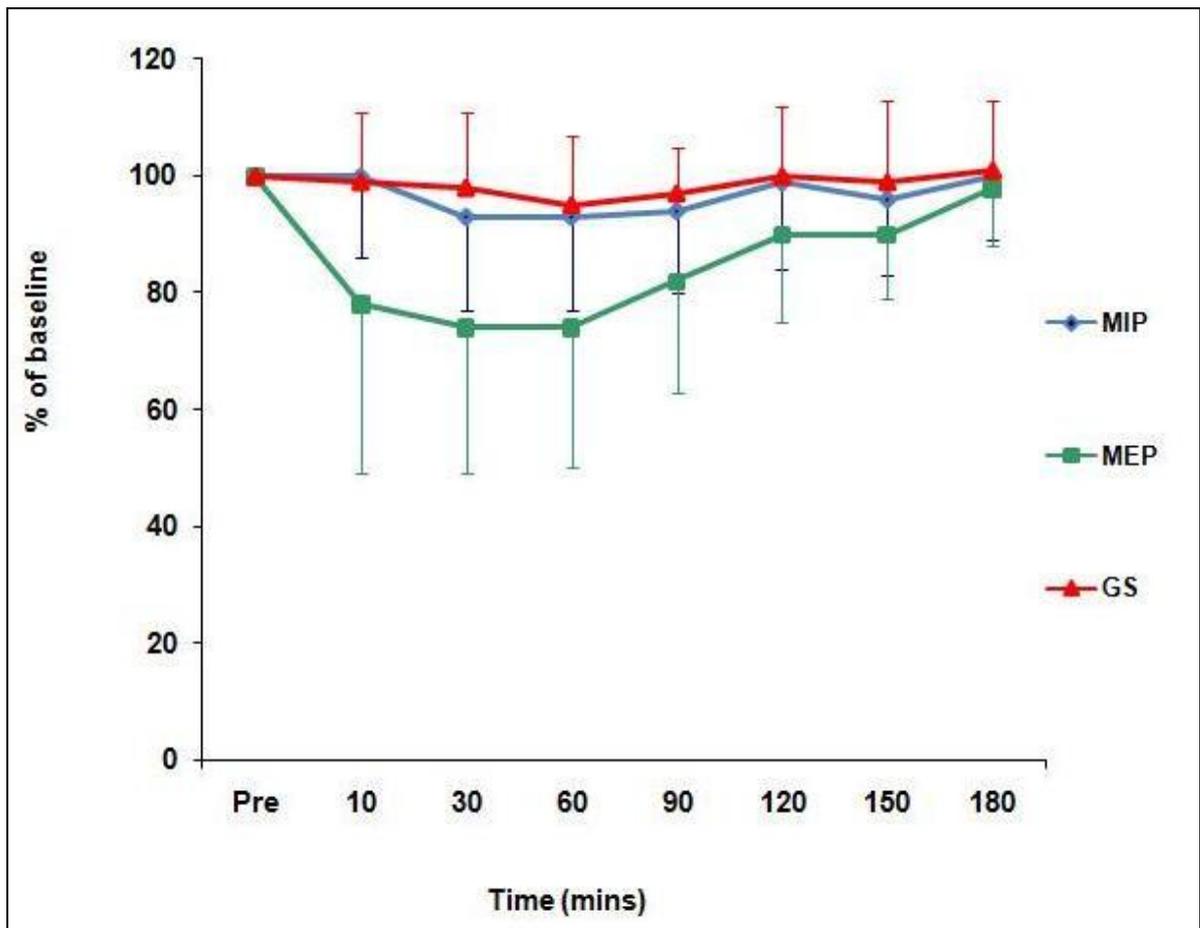


Figure 47. Upper level of cutaneous analgesia ( $\pm$  1 SD) achieved following spinal anaesthesia

### Discussion:

The principle muscles of expiration have a motor innervations originating in nerve roots within the thoracic and lumbar segments. The motor innervations for the diaphragm, the principal muscle of inspiration, originate in the cervical segments C3-C5. Interruption of motor innervations from thoracic or lumbar segments through either spinal cord injury or central neuroaxial blockade, will predominantly compromise expiratory muscle function(Estenne and Gorini, 1992). The degree of expiratory muscle compromise will be dependent upon the level of the blockade and the position of the patient. Previous papers have concentrated upon the effects of central neuroaxial block upon measures of expiratory function. However in the presence of respiratory muscle weakness, vital capacity manoeuvres are an insensitive measure of respiratory muscle weakness(Gal and Goldberg, 1981), when compared with measures of respiratory muscle strength. We therefore, observed changes in inspiratory and expiratory muscle strength using grip strength as an independent measure of patient effort.

Maximum grip strength was included in the study as an independent arbiter of effort. The absence of change in maximal grip strength suggests that the subjects were able to maintain enthusiasm and full effort during the study period. Changes in MIP and MEP, we can conclude, were a direct result of spinal anaesthesia and not a reduction in subject effort.

We observed significant reductions in maximal expiratory pressure following lumbar spinal anaesthesia, without significant reductions in maximal inspiratory pressure. These results could have several explanations. The level of cutaneous analgesia achieved in our subjects extended from T3 to T8. The level of motor block though not assessed was likely to be at least two dermatomes below the level of cutaneous analgesia(Freund et al., 1967). Therefore the temporary reduction in expiratory muscle strength can be explained because of the blockade of thoracic segments supplying the expiratory muscles.

The absence of significant changes in MIP in our subjects is surprising. Although the diaphragm is the principle muscle of inspiration, diaphragmatic contraction is mechanically coupled to movement of the rib cage(Goldman et al., 1976). Outward and upward motion of the lower and upper rib cage during inspiration requires the

coordinated activity of intercostal and parasternal intercostal muscles(Brichant et al., 1993). In the presence of spinal cord injury sparing the diaphragm(De Troyer, 1983) or spinal anaesthesia in infants(Pascucci et al., 1990) paradoxical inward motion of the upper rib cage has been noted. The inspiratory pressure generated by the diaphragm is dependent upon its resting length(Legrand et al., 1998). At end expiration, abdominal muscle activity, elevates the diaphragm in dogs, increasing its resting length(Warner et al., 1991). This may be important in patients with emphysema, who have a flattened diaphragm and hyperinflated chest. The flattened diaphragm is in a poor mechanical position to develop inspiratory pressure. Therefore, lumbar spinal anaesthesia, even in the absence of blockade of cervical nerve roots, might be expected to have some impact upon inspiratory pressure generation. The absence of significant inspiratory force reduction in our subjects following spinal anaesthesia could have several explanations. Functional reserve in the diaphragm(Pascucci et al., 1990, Brichant et al., 1993) and the inspiratory muscles(Warner et al., 1991) may accommodate for the reduction in activity of some accessory inspiratory muscles. Secondly, to allow measurement during surgery our study was performed with patients in the supine position. The weight of the abdominal viscera in the supine subject could displace the diaphragm cephalad at end expiration, reducing end expiratory thoracic volume and compensating for the loss of abdominal tone following spinal anaesthesia. Also in the presence of abdominal muscle paralysis the lower rib cage muscles can significantly elevate abdominal pressure and reduce end expiratory thoracic volume(Warner et al., 1991). However, abolition of activity of lower intercostal muscles as in a high spinal blockade, will reduce tidal volume(Brichant et al., 1993).

In conclusion, this study demonstrated that in healthy subjects there is no significant reduction in inspiratory muscle strength following lumbar spinal anaesthesia when used to provide analgesia for pelvic and lower abdominal procedures. The situation in emphysema remains to be determined. The reduction in expiratory muscle strength returns to normal three hours after the onset of spinal anaesthesia.

### Comment

This study demonstrates a fall in maximum expiratory pressure developed with neuroaxial block of the principal muscles of expiration. However the magnitude of the effect is unlikely to compromise respiration, and although cough function was not tested, it is likely that a cough can still be generated with this level of expiratory strength. The block extends to T5 but on average 80% of MEP is maintained. This could imply that the thoracic muscles, rather than the abdominal are able to contribute a major proportion of the expiratory effort. This could imply that stimulation of the abdominal muscles alone may generate insufficient force to drive a voluntary cough, and that the thoracic muscles could be the main source of the power for a voluntary cough. Nevertheless, other authors have had some success with lower thoracic stimulation to produce a surrogate cough paradigm (Lin et al., 1998c, Polkey et al., 1999) and so further investigation is worth pursuing.

As discussed previously, pragmatic and accurate measurements of voluntary and surrogate cough mechanics are required to compare the two models. Abdominal pressure measurement is currently provided through intermittent bladder pressure measurement. This is not practical when studying volunteers and does not provide continuous real time measurement. In contrast gastric pressure is a frequent surrogate measure of abdominal pressure in studies of respiratory physiology. The objective of the following study is to provide objective data confirming the relationship between abdominal and gastric pressure.

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## **Chapter 8: Intra-Abdominal Pressure Measurement - Validation of Intragastric Pressure as a Measure of Intra-Abdominal Pressure.**

### **Introduction:**

The combination of elevated abdominal pressure and the adverse physiological effects that develop has been termed *abdominal compartment syndrome (ACS)*(Malbrain, 1999). This condition may arise in the critical care patient because of sepsis(Cullen et al., 1989), pancreatitis(Schein and Ivatury, 1998, Cullen et al., 1989), gross ascites, bowel obstruction, megacolon(Birkhahn and Gaeta, 2000), abdominal trauma(Cullen et al., 1989, Ivatury et al., 1998) or retroperitoneal haemorrhage(Cullen and Eger, 1972). The diagnosis of ACS depends upon the demonstration of an elevated intra-abdominal pressure (IAP(Buscher et al., 2000)). As direct measures of IAP are impractical under most circumstances, a surrogate measure of IAP has been chosen. The homogenous transmission of pressure within the abdomen(Tzelepis et al., 1996) allows IAP to be estimated via either the bladder(Kron et al., 1984), rectum(Obeid et al., 1995) or stomach(Obeid et al., 1995). The technique of intravesical pressure measurement described by Kron(Kron et al., 1984) and Iberti(Iberti et al., 1987, Iberti et al., 1989) has been validated(Fusco et al., 2001) and remains the accepted surrogate measure of IAP for clinical use(Yol et al., 1998, Chiu et al., 1994). Despite modifications of the technique(Cheatham and Safcsak, 1998, Sugrue, 2002, Sugrue et al., 1996), intravesical pressure measurement is cumbersome to perform. Furthermore, as abdominal pressure is influenced by a number of factors including patient position, ventilation strategies(Burchard et al., 1985), bowel function and so on, a continuous real time recording of abdominal pressure is a worthwhile objective. Though continuous vesical pressure is commercially available, it has not enjoyed widespread popularity.

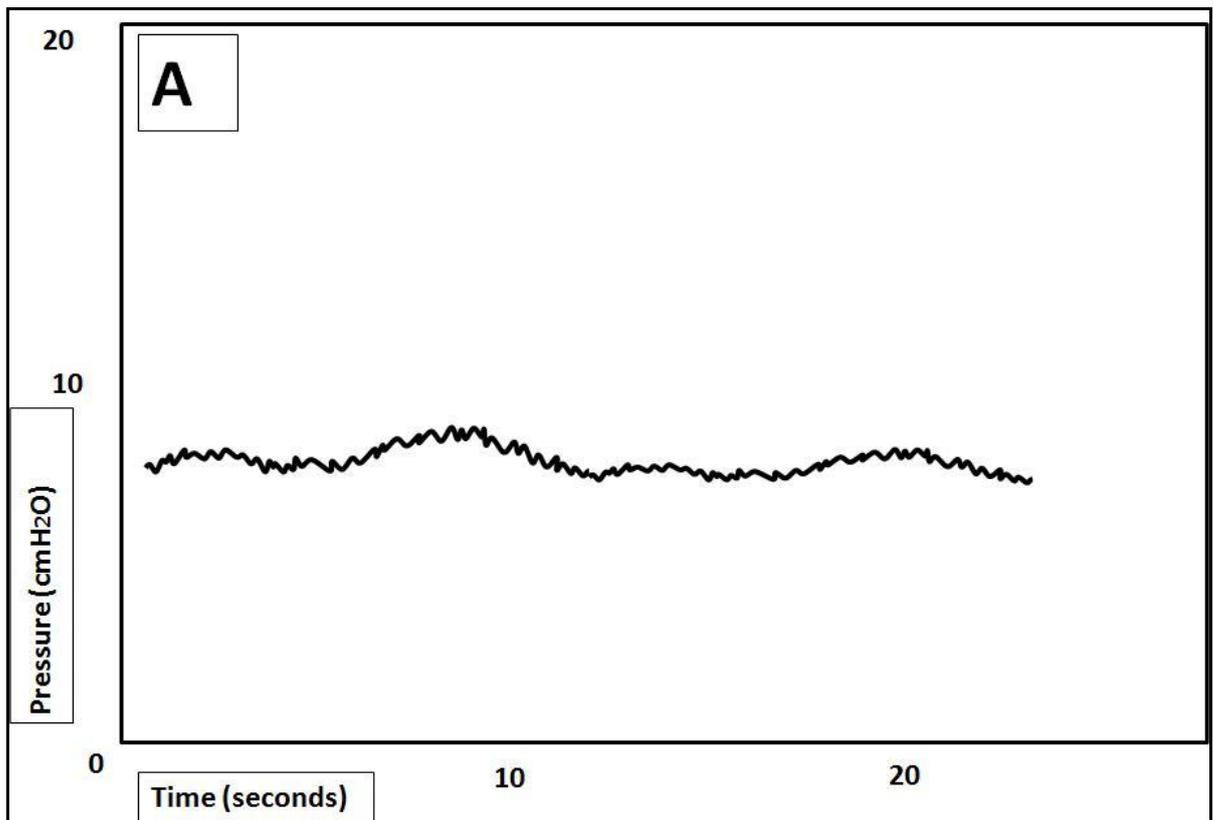
Though intragastric pressure (IGP) is commonly employed as a surrogate measure of IAP in respiratory research, evidence for the relationship between IGP and IAP is conflicting (Kron et al., 1984, Decramer et al., 1984). Previous attempts to measure the relationship between IGP and IAP in humans have often used the index measurement of IAP as that recorded either by the pressure monitor built within the high flow carbon dioxide insufflator during laparoscopy or intravesical pressure (IVP) when neither measure may reliably reflect IAP.

This study describes the relationship between IGP measured with a single use, commercially available, air filled balloon catheter and a direct recording of IAP during laparoscopic surgery.

### Material and Methods:

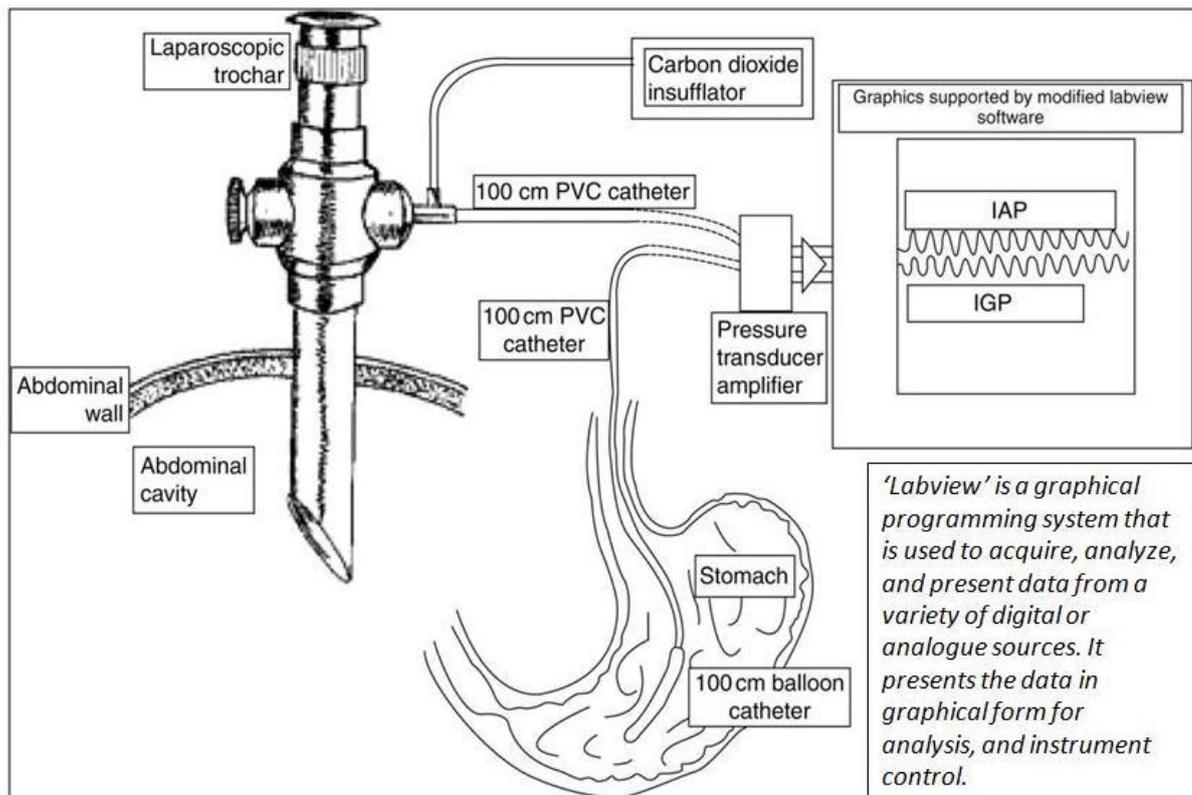
The institutional ethics committee approved the study. 29 female subjects, who provided written consent to participation in the study, were recruited. All subjects were to have laparoscopic surgery as part of gynaecological investigations. No subjects reported abdominal pathology that might compromise IGP measurement. All subjects received a general anaesthetic, with muscle paralysis, tracheal intubation and artificial ventilation. IGP was measured with an 80cm long polyvinyl chloride balloon catheter (*Ackrad Laboratories, Cranford, New Jersey, USA*) with a 10cm distal balloon(Figure 9). The balloon catheter was inserted orally to a depth of 60 – 70cm. Previous studies in our department in spontaneously breathing subjects have demonstrated that placement of the balloon catheter to this distance is sufficient to guarantee gastric placement.

Further confirmation of the position of the distal balloon in the stomach was through an observation of pressure swings with epigastric percussion and the absence of cardiac pulsations indicating oesophageal placement(Figure 48). The catheter was connected to the recording apparatus via a 100cm polyvinyl chloride catheter. The distal balloon was initially emptied by opening the three-way tap to the atmosphere during positive pressure ventilation. The balloon was subsequently inflated with 1ml of air from a 2ml graduated glass syringe. The patient, initially in the supine position, was placed in the Trendelenburg position to aid surgical visualisation of the pelvis. IAP and IGP were recorded in both the supine and Trendelenburg positions.



**Figure 48. Balloon Catheter Pressure Trace recording intragastric Pressure at 8cmH<sub>2</sub>O**

IAP was recorded via a 13mm laparoscopic trochar. A three-way stopcock was placed on the side port reserved for CO<sub>2</sub> insufflation. A 100cm polyvinyl chloride catheter was attached from the three-way tap to our independent pressure monitoring equipment. The three-way tap allowed the intermittent CO<sub>2</sub> insufflation and IAP pressure recording. The pressure indicated by the CO<sub>2</sub> insufflator was also noted. Bench top testing of this set up had previously indicated that there was no discrepancy between pressure measured at the side port of the trochar and that measured at the distal end of the trochar(Figure 49).

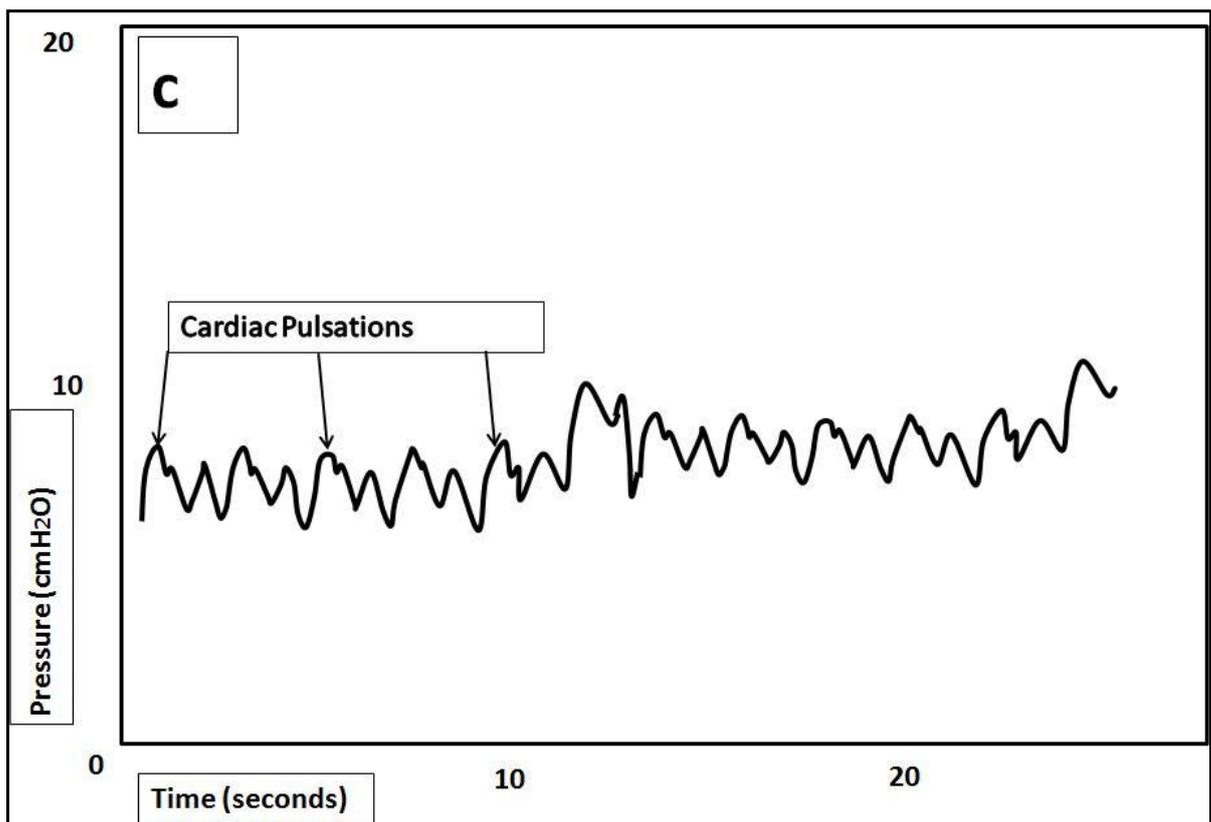


**Figure 49.** A schematic illustration of the IAP and IGP measurement. A three-way tap on the surgical trochar links the carbon dioxide insufflator and the pressure transducer recording IAP. Both IAP and IGP are recorded in real time using customised "Labview" software.

Abdominal insufflation pressure was set between 10 and 15 mmHg according to the requirements of the operator. The IAP and IGP were continuously recorded, and stored for later data analysis.

The recording equipment for IAP and IGP consisted of two-piezoresistive pressure transducers (*Honeywell, Morriston, New Jersey*), placed with the recording equipment on a portable bench next to the patient. These generated an analogue signal that was relayed via a data acquisition box (*National Instruments, SCB 68 series*), sampling at 1000Hz to an analogue/ digital converter (*National Instruments, NI DAQ series 6*). The digitised signal was recorded and viewed with customised software<sup>1</sup> (*Labview, National Instruments*) for real time display on a computer terminal (*RM PC520, RM, Abingdon Oxfordshire, UK*), running Microsoft Windows 98.

The pressure transducers were calibrated prior to each study. Though both the pressure transducers were placed at a convenient position on a portable bench and not at the level of the symphysis pubis as is classically described (Iberti et al., 1987), the error introduced by the difference in height is small in an air filled system, unlike that of a fluid filled system. Furthermore, the error in IGP would be of the same magnitude and in the same direction as that of IAP. Small amplitude pressure swings were noted in both the IAP and IGP traces. These were cardiac in origin and did not interfere with pressure measurement (Figure 50). Respiratory pressure swings from positive pressure ventilation were also present in both traces. IAP and IGP were taken at end expiration. High amplitude pressure swings were seen in the IAP trace only. These were a result of intermittent CO<sub>2</sub> insufflation and did not interfere with IAP measurement.



**Figure 50. Balloon Catheter Pressure Trace recording cardiac pulsations associated with mid-oesophageal placement. Images acquired during gastric pressure study**

*Statistical Analysis:* For each subject the difference between IAP and IGP was measured at 10 time intervals. A final total of 266 data sets for IAP and IGP in the Trendelenburg position and 259 in the supine position were available for analysis(Figure 51).

	Mean	One Standard Deviation	Range	Standard Error of the mean	95% confidence Interval (upper and lower boundary)
	Mean	One Standard Deviation	Range	Standard Error of the mean	95% confidence Interval (upper and lower boundary)
Weight (kg)	65.3	13.5	44 - 90		
BMI	25.6	5.3	17 - 39		
Baseline IGP (cmH <sub>2</sub> O)	9	3.1	5.1 - 15		
<b>Abdominal Pressure difference in Trendelenburg Position (n = 29, df = 258)</b>					
IGP - IAP Pressure	2.8	1.1	0.8 - 5.8	0.07	2.59 - 2.87
<b>Abdominal Pressure difference in Supine Position (n = 29, df = 265)</b>					
IGP - IAP Pressure	2.48	1.33	0.5 - 8.1	0.08	2.32 - 2.64
<b>Coefficient of Variation</b>					
IAP Supine	0.30				
IGP Supine	0.27				
IAP Trendelenburg	0.28				
IGP Trendelenburg	0.26				

**Figure 51. Descriptive Statistics for intra-abdominal pressure data**

Using the statistical software package (SPSS 15), a linear regression analysis will establish the relationship between the IAP and IGP. The calibration method and Bland Altman method were considered to demonstrate the strength of the relationship between IAP and IGP

### Results:

29 female subjects were recruited for the study. The mean age of subjects was 29 years (range 17-44), and mean body mass index was 26 (range 17 - 39). The balloon catheter was successfully inserted in all subjects. The basal IGP ( $9 \pm 3.1\text{cmH}_2\text{O}$ ) was recorded prior to commencement of surgery. There was a low correlation between IGP and BMI (Pearson's coefficient 0.381) with an  $R_2$  value of 0.14. IGP and IAP were recorded in all subjects in both the supine position and Trendelenburg position with 15' of head down tilt.

The  $\text{CO}_2$  insufflation was pulsed and produced sharp swings in IAP which was not observed by the intragastric balloon catheter(**Figure 52**)(**Figure 53**)(**Figure 54**). These were assumed to represent local rises in pressure within the trocar during the pulsed  $\text{CO}_2$  insufflation and were therefore ignored. The correct value for IAP was therefore taken when  $\text{CO}_2$  insufflation was absent and the IAP trace was stable.

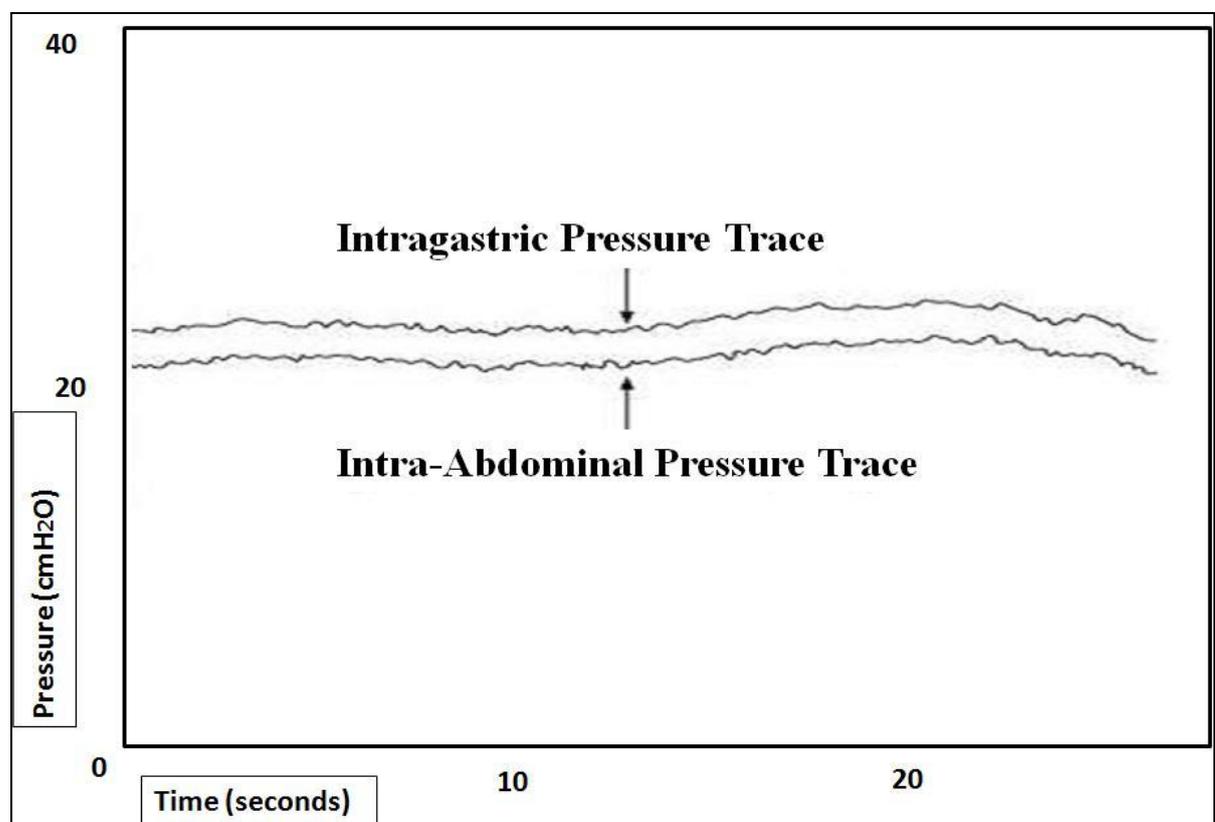


Figure 52. Typical IGP and IAP traces observed during the study. IGP is uppermost in all examples. (A) IGP and IAP: 21 and 19 cm H<sub>2</sub>O, respectively.

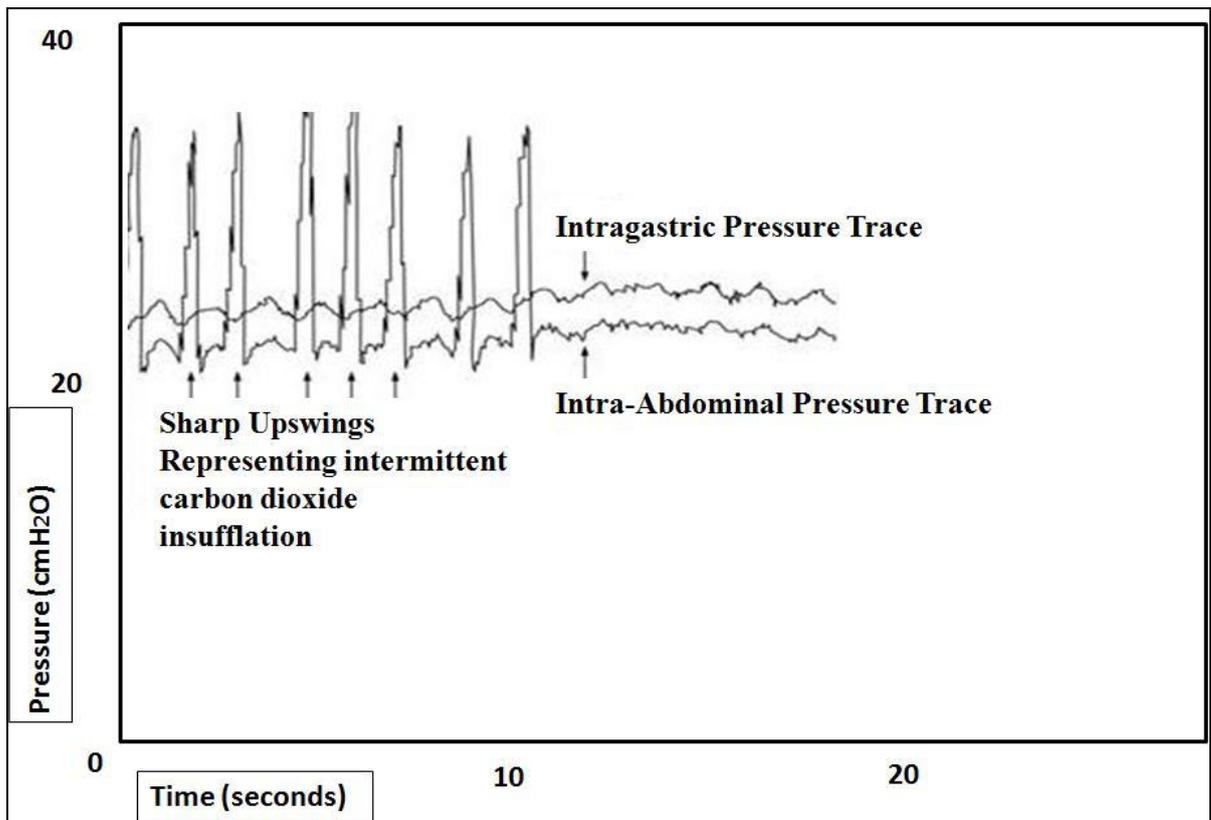
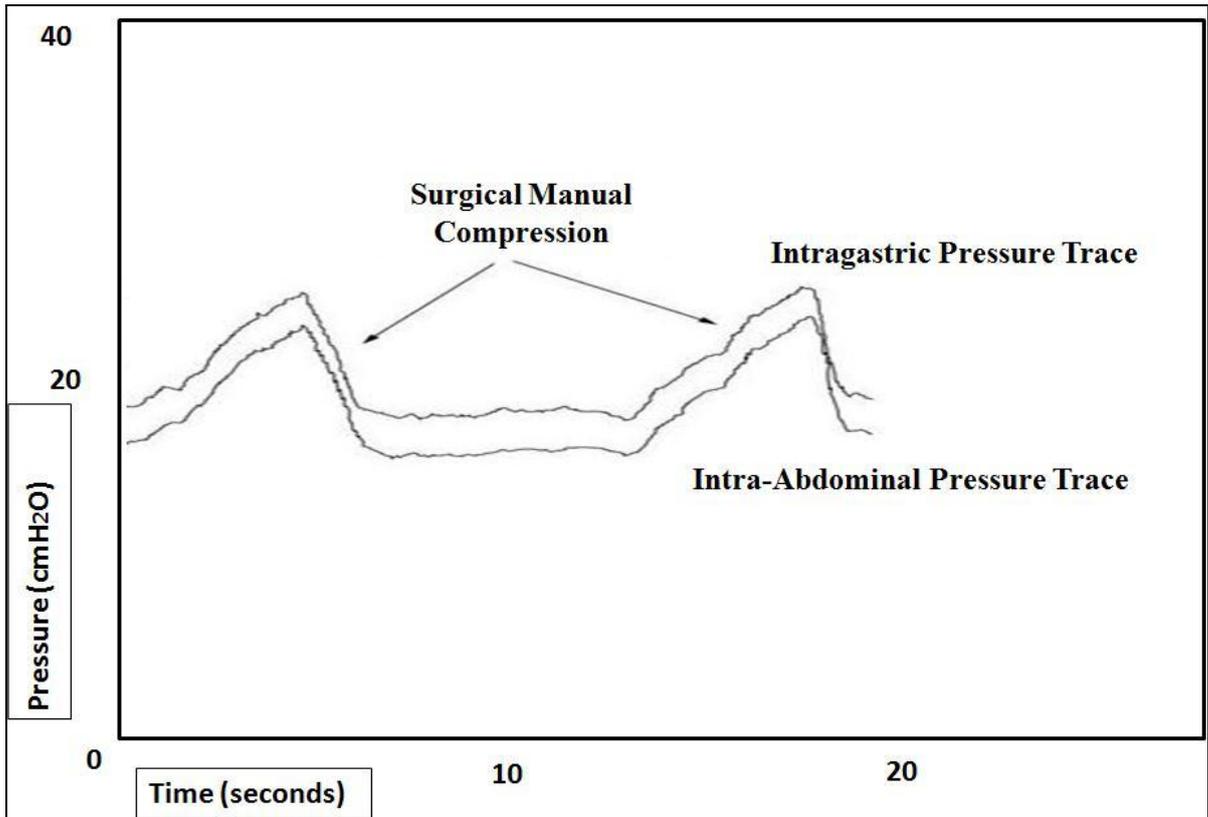


Figure 53. IAP trace with sharp upswings representing CO<sub>2</sub> insufflation. Note that the IGP trace does not reflect these pressure changes.

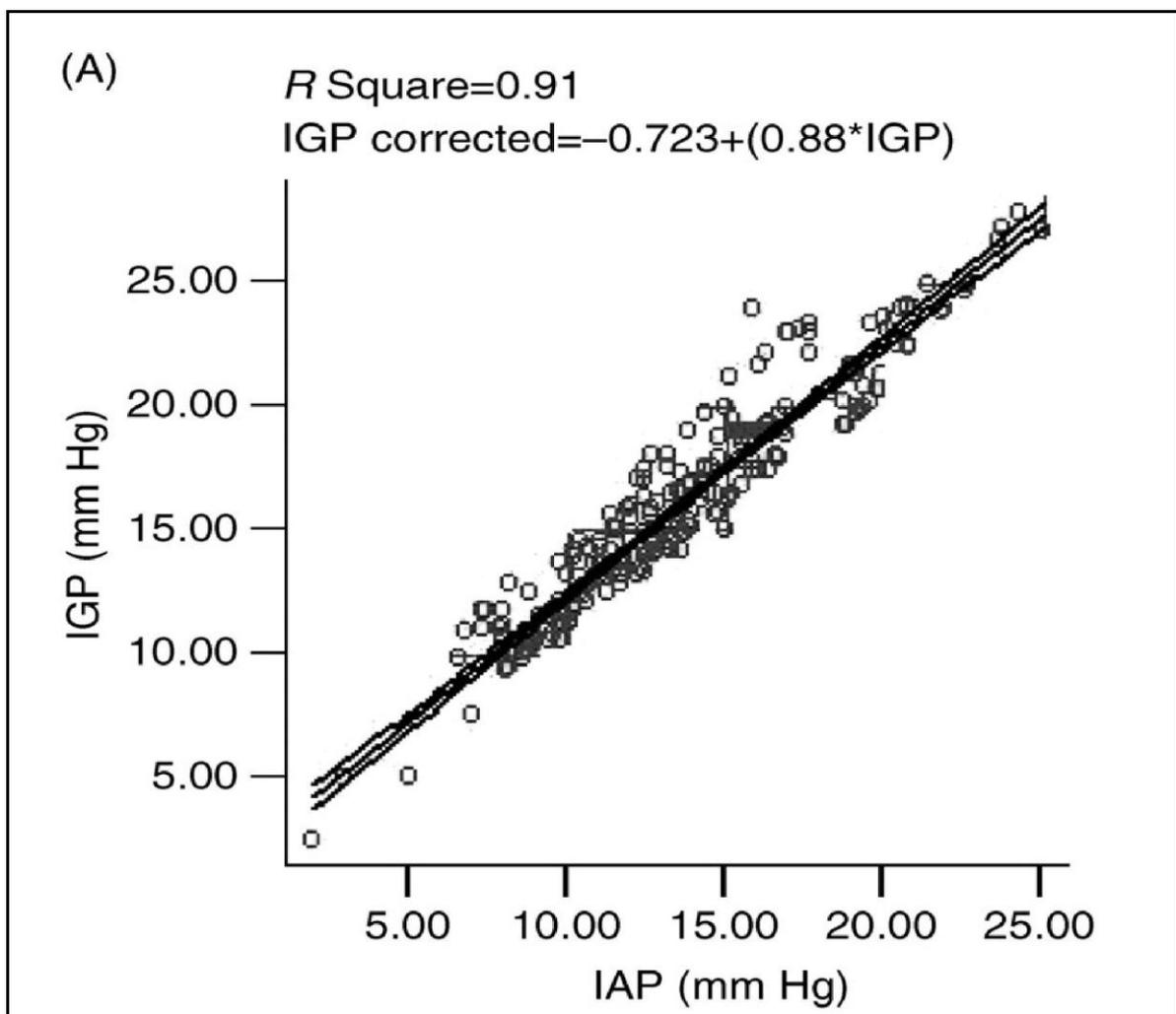


**Figure 54. Typical IGP and IAP traces observed during the study. IGP is uppermost in all examples. (D) Surgical manipulation causing sharp upswings in both IGP and IAP.**

During surgical palpation of the abdomen higher IAP's were seen. These sharp pressure swings were transient providing only transient data that was insufficient for statistical analysis. Given the risk of cardiovascular collapse, maintenance of these pressures for the benefit of the study was not considered.

From the data a scatter plot was drawn using IAP and IGP in the X and Y axis respectively(Figure 55)(Figure 56). The correlation coefficient in the Trendelenburg and Supine position was greater than 0.9. A linear relationship between IAP and IGP was then assumed and a line of best fit or regression line was drawn. A linear regression analysis calculated the values for the slope of the line and the intercept on the X axis. With these values, a new IGP could be calculated using the equation  $y = a + bx$ , where

'a' is the intercept, 'b' the slope and 'x' the IGP value. The calculated y value is called the corrected IGP (IGP<sub>c</sub>). A new regression analysis of IAP against IGP<sub>c</sub> demonstrated the intercept of the regression line is 0. Although not described when performing a calibration method, a Bland and Altman plot was drawn using IAP and IGP<sub>c</sub>. The graph demonstrates the expected error in IGP<sub>c</sub> compared to IAP in both the supine(Figure 57) and Trendelenburg position(Figure 58).



**Figure 55. The scatter plots demonstrates the regression analysis between IAP and IGP in the supine position. Lines indicate mean and 95% confidence intervals.**

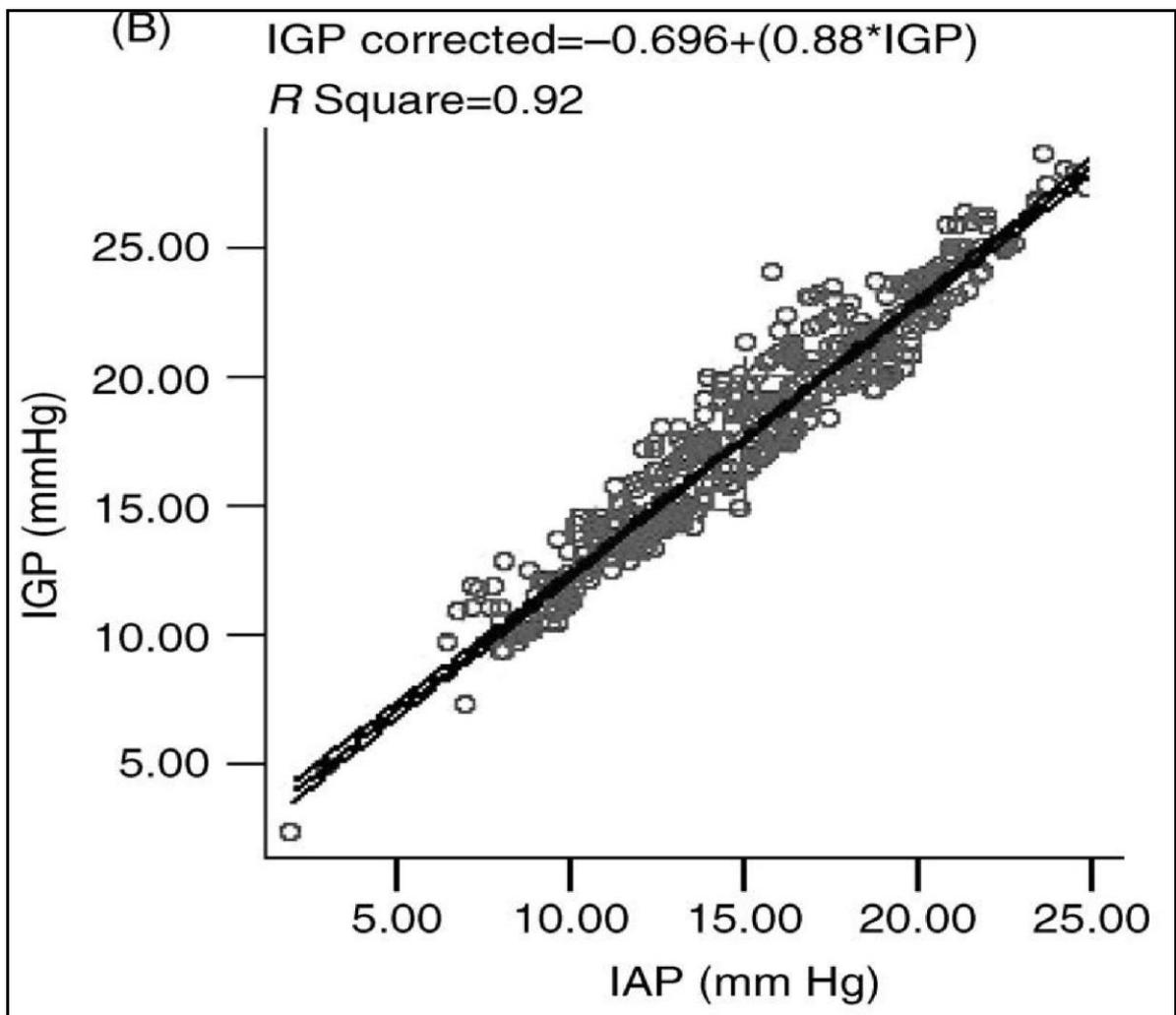


Figure 56. The scatter plots demonstrate the regression analysis between IAP and IGP in the Trendelenburg position. Lines indicate mean and 95% confidence intervals.

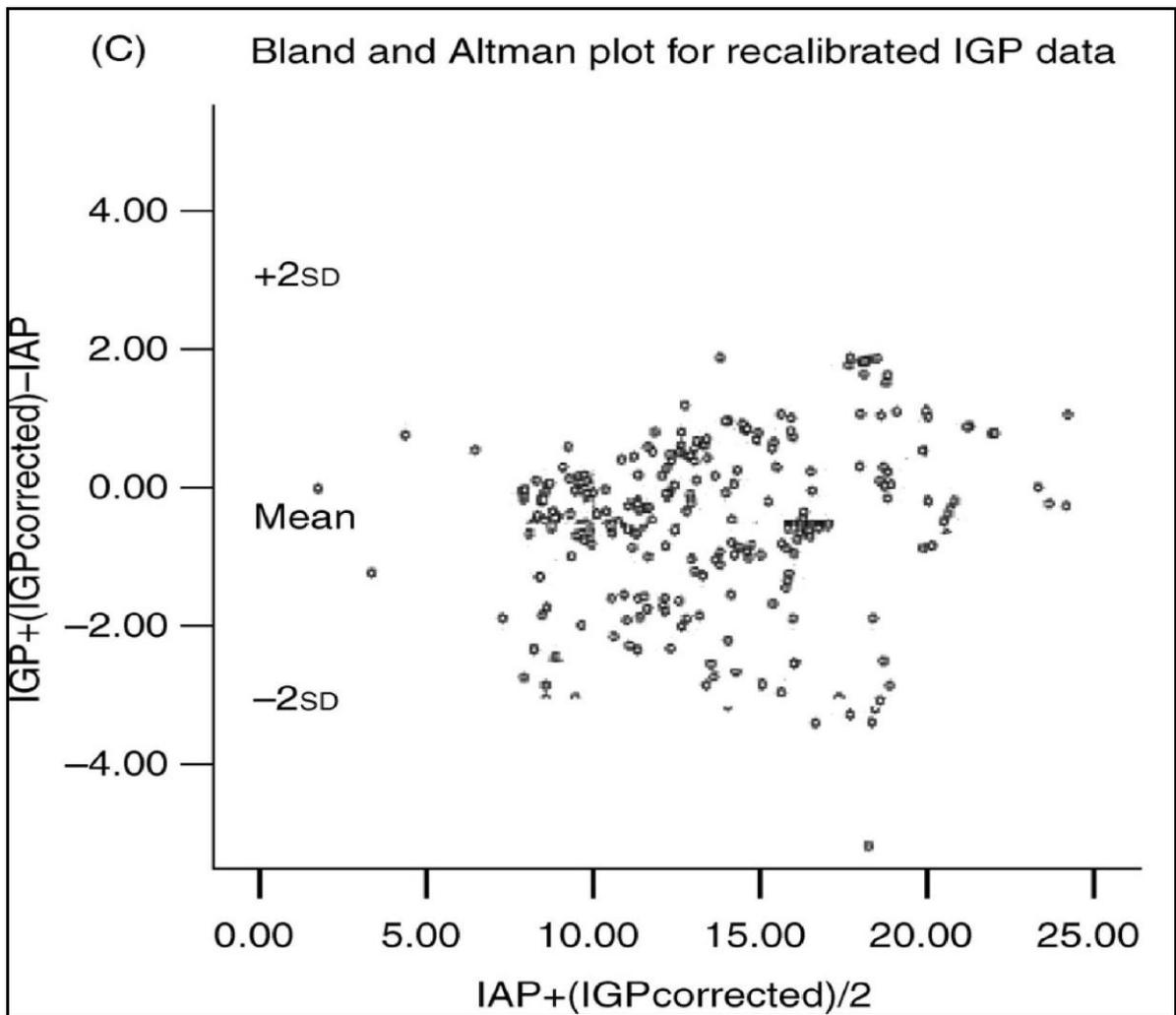


Figure 57. Bland and Altman plot demonstrating the strength of the relationship for IAP and IGP( with correction factor) in the supine position.

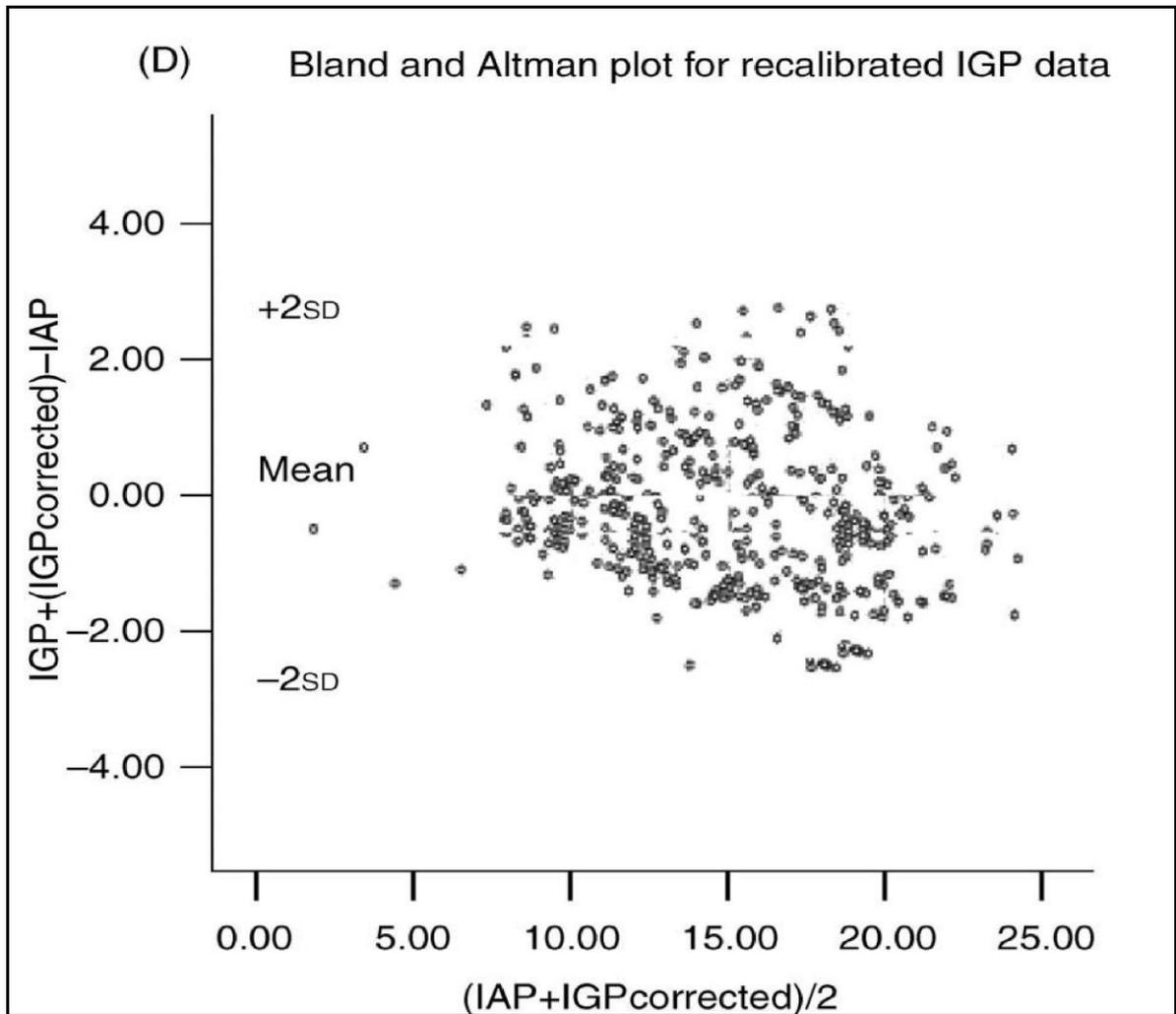


Figure 58. Bland and Altman plot for IAP and IGP (with corrections factor) demonstrating the strength of the relationship in the Trendelenburg position

### Discussion:

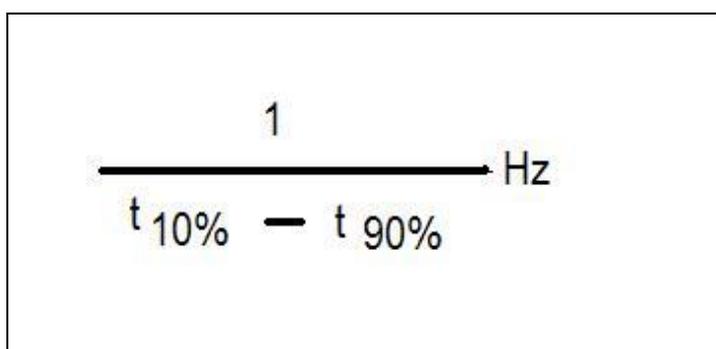
The sole use of females in our study was a practical decision given the large number of investigative laparoscopies performed in our institution. Confirmation of catheter placement in the stomach is normally achieved with subjects awake performing various inspiratory manoeuvres. We felt it unrealistic to expect naïve pre-operative volunteers to consent to passage of the balloon catheters whilst awake.

The BMI of our population may be greater than average that may lead to an elevated IAP; this is unlikely to influence our results, which was to estimate the difference between IGP and IAP. In line with previous studies(Sugerman et al., 1997), there was a low correlation between BMI and basal IGP in our female population.

An elevation of pressure greater than 25mmHg-30mmHg (32-39cmH<sub>2</sub>O), within the abdominal cavity will result in compromise of perfusion of visceral organs(Chiu et al., 1994, Richards et al., 1983, Gudmundsson et al., 2001). Persistence of the elevated pressure will result in death of the patient through renal, cardiac and respiratory failure and gut bacterial translocation(Malbrain, 1999). The management of ACS requires confirmation that the abdominal compartment pressure is elevated. Though IAP measured via the bladder(Yol et al., 1998) , may provide a reliable estimate of abdominal pressure, the failure to provide a continuous measure, is a potential flaw. This study demonstrates the relationship between IAP and IGP. When calibrated the discrepancy between IGP will lie within 2.6mmHg ( $\pm 2SD$  in the supine or Trendelenburg position) of the real value of IAP. Though previous studies had suggested that IVP reflected IAP(Kron, 1989, Gudmundsson et al., 2002, Fusco et al., 2001, Iberti et al., 1989), Johna(Johna et al., 1999), Fusco(Fusco et al., 2001) and Gudmundsson(Gudmundsson et al., 2002) have contested these findings. Johna(Johna et al., 1999) demonstrated that intra-vesical pressure was always positive, even when the IAP was zero. Gudmundsson(Gudmundsson et al., 2002) noted that the instillation of 50ml of saline into the bladder(Iberti et al., 1989) may lead to an increase in basal IVP. He proposed the instillation of only 10 – 15ml of saline prior to IVP measurement. Fusco(Fusco et al., 2001) also noted that the discrepancy between IVP and IAP

increased, with intravesical instillation of saline. Over the bladder volumes tested of 0 – 200ml, IVP was 3.8mmHg greater than IAP on average.

We are aware that the pressure measurement apparatus described in the methods section are not practical for clinical use. We therefore, considered the suitability of commercial pressure transducers currently used for arterial and central venous pressure measurement, as a suitable surrogate pressure transducer. With the distal port capped off they can be transformed into an air filled transducer system (*Figure 18.6*). The accuracy of the transducer can be determined through measurement of its frequency response, as described in previous articles (Buscher et al., 2000). Briefly, the test involves placing a latex balloon around the balloon catheter and inflating it to a pressure of 100cmH<sub>2</sub>O. The balloon is rapidly deflated through the application of a hot pin to the surface. The subsequent step change in pressure and the time for the system to record that step change indicates the dynamic response of the recording apparatus. The response reported is the inverse of the time taken for the pressure to fall from 90% to 10% of the maximum recorded (Figure 59). The dynamic response rate of our recording apparatus and the commercial pressure sensor was 16.3Hz ± 1.2 and 32.3Hz ± 2.2 respectively, demonstrating the greater response of the commercial transducer.



**Figure 59. Equation for Pressure System Evaluation or Pop Test**

The influence of the gastric mechanical activity (Collard and Romagnoli, 2001), intestinal ileus and enteral feeding may be of concern to clinicians considering using IGP in intensive care patients. The major migratory complex causes temporary

elevations of IGP and can be readily differentiated from the basal IGP through observation of the gastric pressure trace. Collard(Collard and Romagnoli, 2001) demonstrated that the frequency of gastric contraction increased with enteral feeding, but that these pressure waves were distinguishable from basal IGP. We have found no reports of the influence of intestinal ileus upon IGP. We realise that the application of IGP measurement as a standard surrogate measure of IAP, will need testing in the critical care area. Though the operator set the IAP delivered by the CO<sub>2</sub> insufflator to be between 10 and 15cmH<sub>2</sub>O (7.6 – 11.4mmHg), IAP recorded by our system was frequently higher. This reflects the additional IAP generated during surgical manipulation and compression of the abdomen (*figure 18.4*). Within a subject the relationship between IGP and IAP pressure was consistent. This was reflected by the small coefficient of variation. For diagnostic purposes, an IAP in excess of 25mmHg (30cmH<sub>2</sub>O) is considered diagnostic of ACS(Johna et al., 1999).

This study has demonstrated the close relationship between IGP and IAP. IGP monitoring is easy to perform, provides continuous monitoring allowing observation of the effects of prone ventilation, high levels of PEEP and other therapeutic manoeuvres. However, ileus, the effects of the major migratory complex and enteral feeding may compromise the accuracy of IGP measurement in the critical care patient. Follow up studies in critical care patients are necessary to validate the accuracy of IGP measurement. Nevertheless, the authors consider that the simplicity of IGP measurement should provide the impetus for establishment of routine IGP measurement in critical care. This could even be made routine by the production of a nasogastric tube with an attached pressure measuring balloon or port.

### Comment

Intragastric pressure as a surrogate measure of abdominal pressure was tested in subjects undergoing general anaesthesia. The initial subjects tested received nitrous oxide as adjunct to a volatile anaesthetic to provide general anaesthesia. However, nitrous oxide is a very soluble gas and is able to diffuse into other air filled spaces, increasing the volume of that space. The balloon of the oesophageal catheter is pervious

to nitrous oxide, and it was apparent that the pressure measurement was compromised by the nitrous oxide diffusion. The solution was to avoid anaesthesia where nitrous oxide was used, or recalibrate the oesophageal balloon at regular intervals. The objective of the subsequent study is to measure the impact of nitrous oxide upon the accuracy of the balloon catheter.

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## **Chapter 9: Air filled oesophageal balloon catheters: Nitrous Oxide diffusion as a potential source of error.**

### **Introduction:**

The blood gas partition coefficient of nitrogen and nitrous oxide is 0.013 and 0.46 respectively(Reinelt et al., 2002). That is nitrous oxide is 34 times more soluble in blood than nitrogen. This physical difference leads to the expansion of air filled cavities when nitrous oxide is used as an adjunct during general anaesthesia. The increase in volume and pressure caused by nitrous oxide diffusion has been reported for pneumothoraces, bowel(Reinelt et al., 2002), middle ear(Ostfeld et al., 1980), venous air emboli(Lockwood, 2002), dural and epidural air, endotracheal tube cuffs(Bernhard et al., 1978), Swan Ganz catheter balloons(Kaplan et al., 1981) and intraocular gas bubbles following retinal surgery. Air filled oesophageal balloon catheters have a distal air filled balloon, typically made of polyvinyl chloride. They are used for the objective assessment of respiratory mechanics through the measurement of oesophageal and gastric pressure. We were concerned that if used during general anaesthesia where nitrous oxide was used, there was a potential for the production of erroneous pressure recordings because of nitrous oxide diffusion into the balloon. We compared the pressure recorded by a balloon catheter in a semi-closed anaesthetic breathing circuit containing nitrous oxide compared with the pressure recorded from an open-ended catheter within the same system. If there was diffusion of nitrous oxide into the air filled balloon, this would produce a higher recorded pressure when compared with the open-ended catheter. The time course over which pressure and volume changes occurred would be observed.

### Methods:

A commercially available polyvinyl chloride balloon catheter (*Ackrad Laboratories*) was used in this study. The balloon was 10 cm long and the material was 60 $\mu$ m thick. The manufacturer recommends the addition of 1.0 ml of air into the deflated balloon prior to measurement. The balloon catheter was attached to the pressure transducer via a 200cm catheter. A three-way tap was placed at the transducer end of the balloon/ catheter set up, so that the balloon could be inflated and deflated.

**Pressure measurement:** The balloon catheter and open ended catheter recording system briefly consisted of a transducer amplifier (*143PC03D Honeywell control systems limited, Bracknell, Berkshire, England*), the amplified signal was digitized and passed through a signal sampler sampling at 200Hz. The signal was subsequently recorded and viewed in real time using customized Labview Software (*National Instruments, California, USA*). The transducer amplifier system were calibrated prior to each experiment by zeroing at room pressure and 100mmHg using a standard graduated mercury manometer.

**Balloon Compliance:** The compliance of the balloon catheter was calculated by adding 0.1 ml increments of air from complete balloon deflation, until 3 ml of air has been introduced into the balloon. The pressure was recorded for each increment. The test was repeated 10 times (Figure 60).

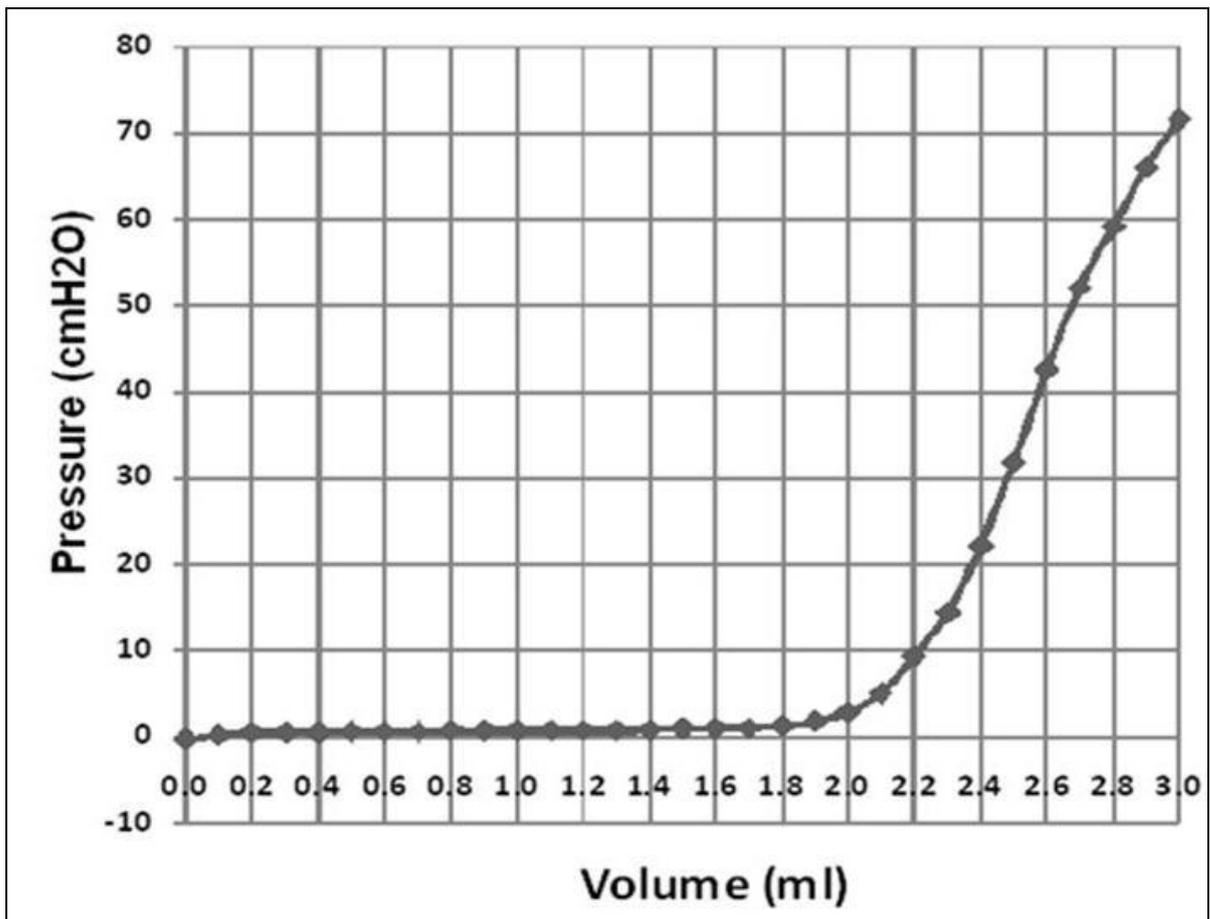


Figure 60. Compliance curve of esophageal balloon catheter

**Dynamic Response to a Step Change in Pressure:** To measure the response to a step change in pressure (Pettersson et al., 1986) the oesophageal balloon, connected to the pressure transducer via a 200cm catheter, was placed inside a latex balloon. The balloon was inflated to 100cmH<sub>2</sub>O ( $\pm 10\%$ ). As previous descriptions of the test (Pettersson et al., 1986) have demonstrated that the amplitude of the test impulse within the range of 52 - 156cmH<sub>2</sub>O has no influence upon the calculated final frequency, precision with the balloon inflation pressure was unnecessary. Exploding the balloon with a heated needle produced the step response in pressure. For comparison an open-ended 200cm catheter was also placed inside the balloon. The limiting frequency of the system is the time in seconds for the system to register the pressure drop from 90% to 10%. The limiting frequency was then calculated as for the open-ended and balloon catheter. The step change in pressure was measured with the oesophageal

balloon inflated to 0ml, 0.5ml, 1ml, 2ml, 2.5ml and 3ml. The test was repeated six times at each balloon volume.

**Nitrous Oxide Diffusion Set Up:** A 2 litre reservoir bag was attached, via a T-piece with a 3mm port, to the gas outlet of an anaesthetic machine (figure 2). The distal end of the balloon catheter and the distal end of a 200cm polyvinyl chloride catheter were placed through the 3mm port, into the 2-litre reservoir bag. The 3mm port was seal to prevent air loss. The reservoir bag was inflated with a nitrous oxide/ oxygen gas mixture delivered via the anaesthetic machine. The gas mixture was analysed using a Datex/ Ohmeda AS/3 monitor and the gas mixture maintained at 70% nitrous oxide and 30% oxygen. The reservoir bag pressure was maintained at 20cmH<sub>2</sub>O through control of the valve on the anaesthetic machine

The oesophageal balloon catheter was inflated with 1ml of air as per the manufacturer's instructions. Applying negative pressure via the 2ml syringe emptied the balloon. The three-way tap was then opened to allow the balloon to balance with atmospheric pressure. The 2ml graduated syringe was then applied to the three-way tap and the balloon inflated with 1ml of air. The pressure from the open ended catheter and the balloon catheter were measured. The pressure in the catheter balloon catheter and open-ended catheter were recorded at 5-minute intervals from 5 to 35 minutes. At the end of each five-minute interval the valve was opened and the bag deflated. The pressure in the balloon catheter and open-ended catheter were again recorded. This was repeated for each time interval of 5, 10, 15, 20, 25, 30 and 35 minutes. At the end of each period the gas in the balloon catheter was sampled and analysed using the Datex gas analyser. The presence or absence of nitrous oxide was recorded. The volume of air in the balloon at the end of each time interval was calculated from the compliance curve of the balloon catheter(Figure 60). The diffusion study was repeated 10 times.

**Results:**

**Nitrous oxide diffusion study:**

The recorded balloon pressure increased over the 35-minute period of the study (Figure 61). The difference between the open ended catheter and the oesophageal balloon catheter was calculated. Where the reference pressure was atmospheric ( $0\text{cmH}_2\text{O}$ ), the mean difference in recorded balloon pressure was  $0.0005\text{cmH}_2\text{O}$  at time zero and  $10.5\text{cmH}_2\text{O}$  (range  $0.5 - 14.1\text{cmH}_2\text{O}$ ) at 35 minutes. Where the reference pressure was  $20\text{cmH}_2\text{O}$ , the mean difference in balloon pressure was  $0.04\text{cmH}_2\text{O}$  at time zero and  $0.89\text{cmH}_2\text{O}$  (range  $0.4 - 2.3\text{cmH}_2\text{O}$ ) at 35 minutes. Where the reference pressure was atmospheric, the estimated final balloon volume taken from the oesophageal balloon compliance curve was  $2.1\text{ml}$  (range  $1 - 2.2\text{ml}$ ).

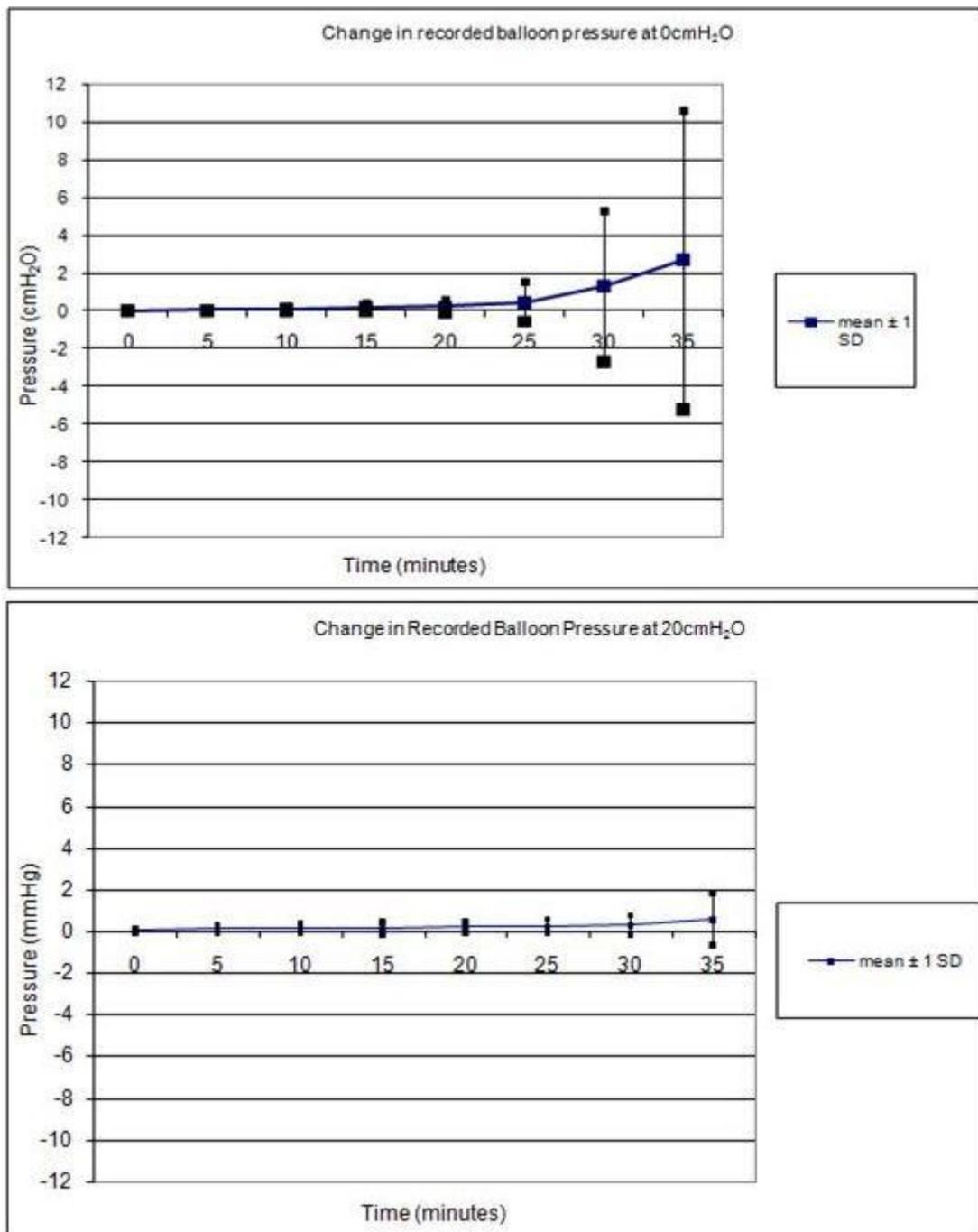


Figure 61. Changes in balloon volume with exposure to nitrous oxide. The magnitude of the error is greater when the actual pressure is 0cmH<sub>2</sub>O than when the actual pressure is 20cmH<sub>2</sub>O.

### Discussion:

Gas permeation through a porous membrane is a diffusion mechanism. The diffusion rate is a function of the size of the molecule, the pressure of the gas and the thickness and nature of the porous membrane. Gas permeation can be summarised as a diffusion coefficient (Marx et al., 1996). The rate of change of an air filled cavity is a product of the rate of gas diffusion into the cavity and the compliance of the limits of the cavity. This study clearly demonstrates that pressure within the distal balloon of the study catheter increased within an atmosphere containing nitrous oxide. Several published respiratory studies have used oesophageal balloon catheters during exposure of the catheter to nitrous oxide (Fauroux et al., 2002, Higgs et al., 1983). The diffusion of nitrous oxide into the balloon catheters could influence the result, and may explain the contradictory conclusions of some studies (Hoshi et al., 2002, Fauroux et al., 2002). It has been clearly demonstrated that nitrous oxide diffuses into the bowel (Reinelt et al., 2002) and will diffuse through the balloon catheter material (Marx et al., 1996). This in vitro study, establishes that measurement errors from the balloon catheter develop if the balloon is exposed to an atmosphere of nitrous oxide for twenty minutes or more. However, discrepancies in pressure recording from the balloon catheter are sometimes apparent after five minutes. The discrepancy in pressure recording is greater when the actual pressure is 0 cm H<sub>2</sub>O compared with 20cmH<sub>2</sub>O. The dynamic response is compromised only when the limits of the balloon compliance are reached, 2ml in the case of the balloon catheter tested. This study did not measure the rate of rise of balloon volume with time with the catheter placed in the stomach. Though the volume change may be slower than our in vitro study, as nitrous oxide needs to diffuse from the blood into the stomach to effect a gastric balloon catheter, previous authors have identified the rapid diffusion of nitrous oxide into the bowel (Reinelt et al., 2002). Measurement errors are a potential cause of discrepancy, and need to be considered, particularly where there are discrepancies between studies (Hoshi et al., 2002, Fauroux et al., 2002). As this study demonstrates, balloon catheter errors relating to nitrous oxide diffusion, take some time to develop. Refilling the distal balloon, prior to data recording should avoid this potential problem.

**Comment**

The subsequent study has two objectives;

Firstly, the inclusion of a gastric balloon catheter as a surrogate measure of IAP has not been applied in a clinical trial. This trial will observe the application of IGP during a clinical trial, and if gastric mechanics and misplacement of the balloon catheter compromise IAP measurement.

Secondly, it is anticipated that the surrogate cough model will have application to subjects in either supine or prone positions. The effect of prone positioning on abdominal pressure will have implications for the surrogate model where an elevation in IAP is the force driving the surrogate cough.

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## **Chapter 10: Intra-abdominal Pressure: The effect of the prone position.**

### **Introduction:**

The prone position has been proposed to improve oxygenation in adult respiratory distress syndrome. The mechanisms involved are a reduction in venous admixture and more homogenous regional lung inflation. However, not all patients demonstrate improvements in oxygenation and changes in the compliance of the thoracoabdominal cage has been observed to differentiate between responders and non responders (Pelosi et al., 1998).

Patients in the prone position in critical care are typically placed on air displacement mattresses with additional pelvic and chest support to limit the rise in intra-abdominal pressure (IAP) (Michelet et al., 2005). Lumbar spinal surgery requires a limitation of the lumbar lordosis to improve surgical access and a reduction in IAP that would otherwise increase venous drainage through the epidural veins. Surgical support frames for lumbar surgery are designed with these constraints in mind. However, differences in body habitus may compromise satisfactory patient positioning and impair chest or abdominal compliance (Park, 2000). The impairment of chest and abdominal compliance may also relate to frame type and positioning (Palmon et al., 1998).

The primary objective of this study was an observation of the impact of the prone position for lumbar surgery on abdominal pressure. The secondary objective was the observation of the performance of gastric pressure measurement as a surrogate measure of abdominal pressure.

### Methods:

19 subjects undergoing elective surgery to the lumbar spine were entered into the study. All subjects gave their informed consent, and the study was granted approval by the local research ethics committee. Following induction of anaesthesia, a balloon catheter was placed per-oral into the stomach. Confirmation of placement was through direct visualisation of tube passage into the oesophagus, passage of the catheter to 70cm from the incisors and visible pressure waves with gastric palpation. The technical aspects of gastric pressure recording have been described in previous studies. Gastric pressure was recorded in the supine position for one minute. The subjects were then placed in the prone position, using either the Montreal Mattress or the Wilson frame. The choice of prone positioning support system was the responsibility of the operating surgeon, and the choice was not influenced by inclusion of the patient in the study. The gastric pressure was again recorded in the prone position for one minute at intervals of 30 minutes during surgery. Following completion of surgery and return to the supine position, gastric pressure was recorded again.

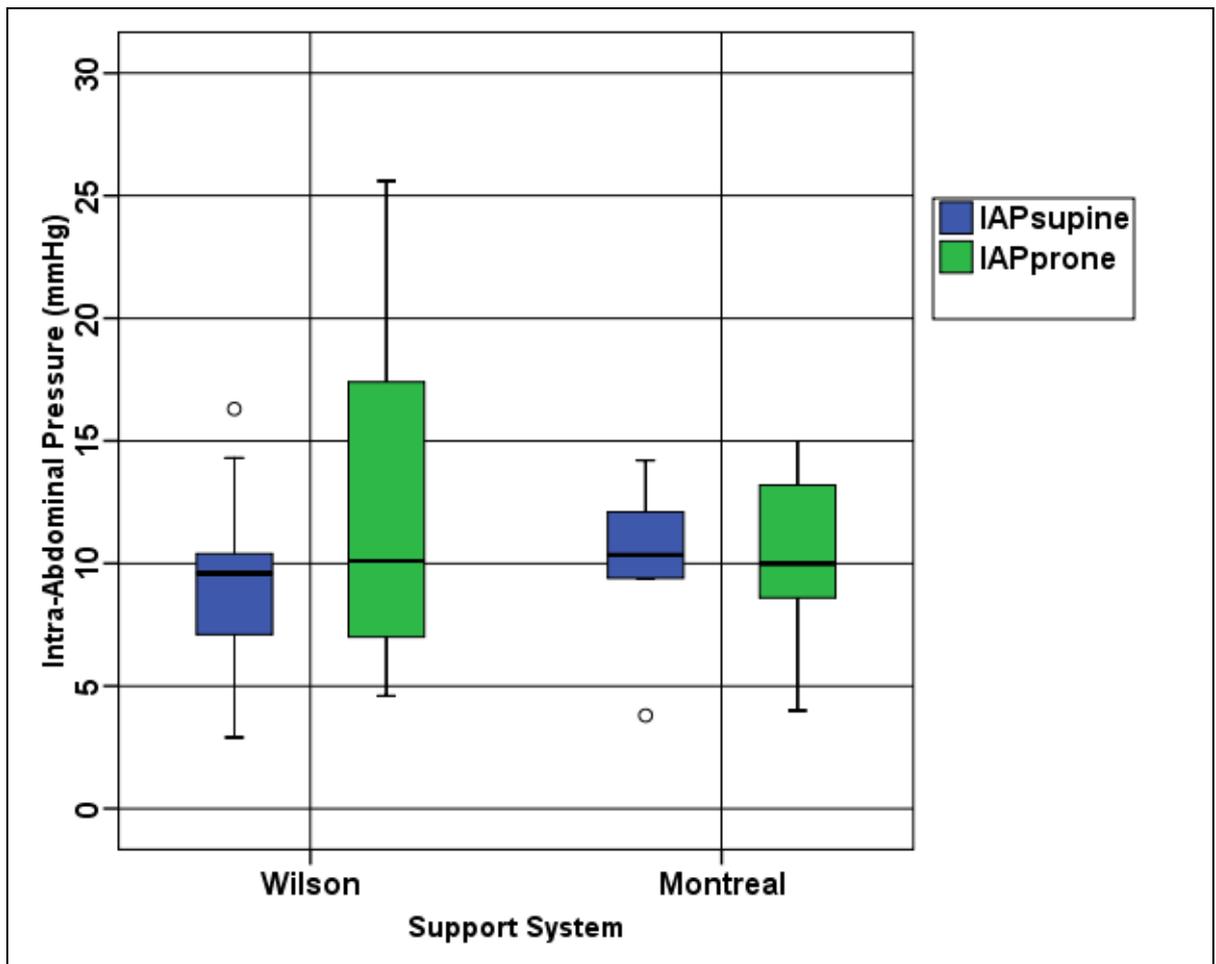
SPSS version 15 was applied to the statistical analysis and production of graphical data. Student's t test compared the difference between the two groups. A p value <0.05 was considered a significant difference. Regression analysis measured the strength of the relationship between abdominal pressure and other measured factors.

**Results:**

19 Subjects completed the study and the demographics are summarised in (Figure 62). When considering all patients in the supine position(Figure 63), the intra-abdominal pressure was 9.5mmHg (+/- 3.3). Turning prone(Figure 63) the IAP rose to 11.7mmHg (+/- 6.1). This difference was not significant (P = 0.23).

<b>Male</b>	<b>12</b>
<b>Female</b>	<b>7</b>
<b>ASA I/II/III</b>	<b>10/8/1</b>
<b>Age (years)</b>	<b>46 +/- 14</b>
<b>Weight (kg)</b>	<b>78.8 +/- 16.8</b>
<b>Montreal Mattress</b>	<b>6</b>
<b>Wilson Frame</b>	<b>13</b>

**Figure 62. Patient Demographics. Values indicate actual value or mean value (+/- 1SD)**



**Figure 63. Box plots demonstrating IAP in the supine and prone position for the Wilson frame and Montreal mattress**

There was no relationship between IAP in the supine position and body weight ( $r^2 = 0.009$ ) (Figure 64). There was a weak relationship between IAP in the prone position and body weight ( $R^2 = 0.38$ ) (Figure 65).

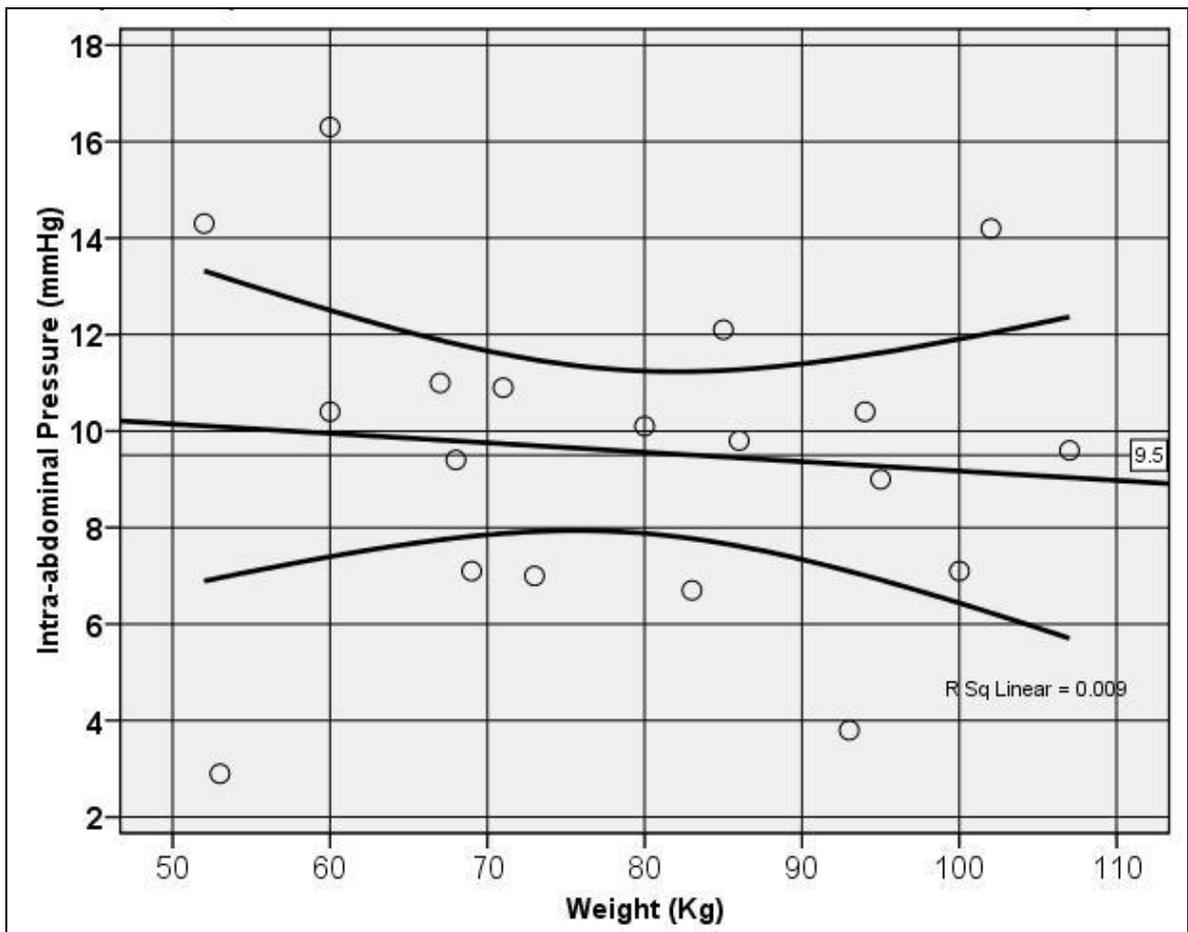


Figure 64. Scatter Plot demonstrating relationship between Weight and IAP in the supine position (mean line and correlation line with 95% confidence interval)

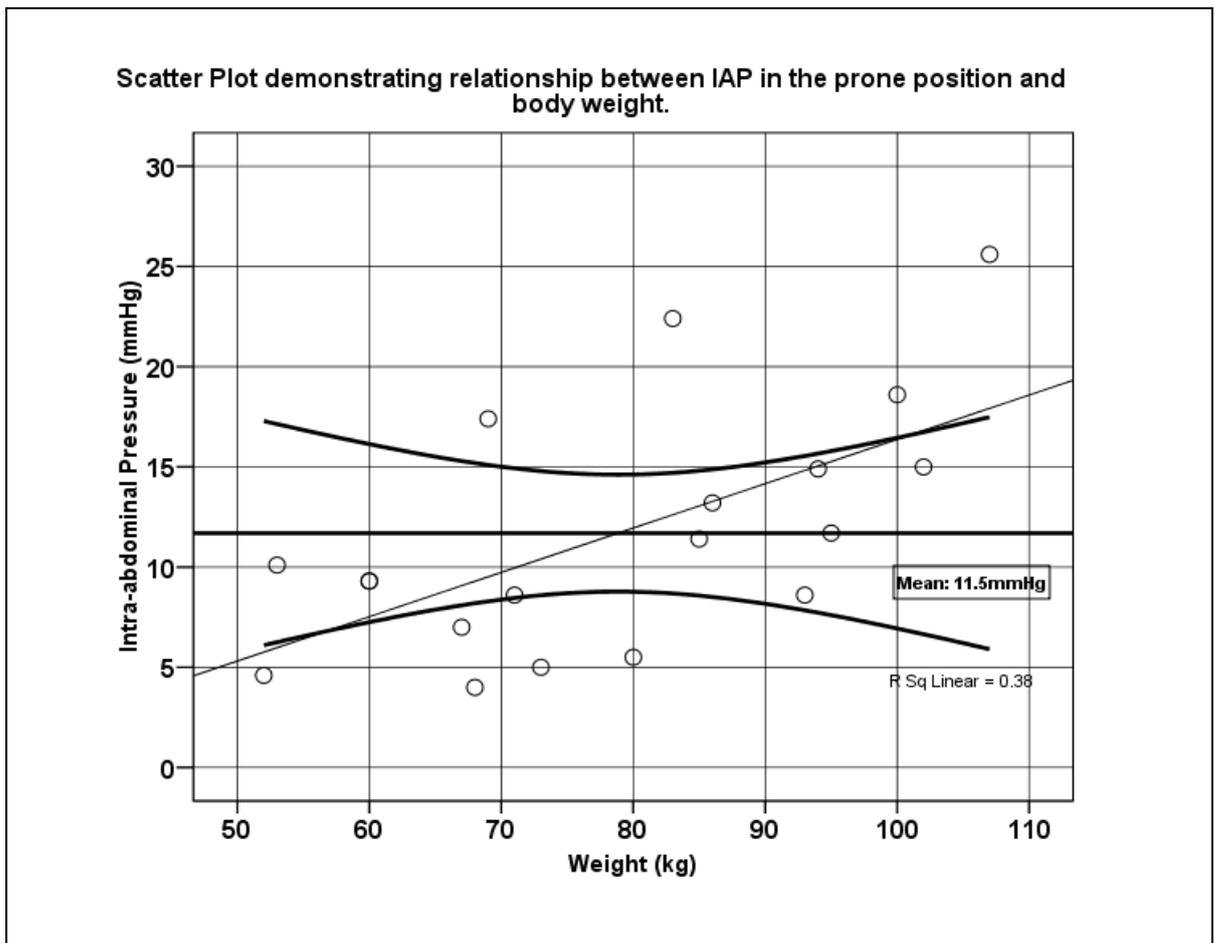


Figure 65. Scatter plot demonstrating relationship between patient weight and IAP in the prone position.

### Discussion:

Intuitively an increase in body weight should lead to an increase in IAP. This study indicates that in the supine position there is no relationship between IAP and body weight. This is confirmed (Sugerman et al., 1997, Whitson and Ikramuddin, 2008, Noblett et al., 1997) by previous research. An elevation of IAP in the obese patient is a function of the direct mass effect of the abdominal viscera. A relationship has been established between sagittal abdominal diameter and IAP (Lambert et al., 2005, Sugerman et al., 1997), but no such relationship is demonstrable for IAP and BMI or body weight (Sugerman et al., 1997, Lambert et al., 2005).

Turning the patient into the prone position causes a non-significant rise in IAP when compared with the supine position. Previous studies have confirmed that with the appropriate support the potential rise in IAP can be avoided by a well designed supporting mattress (Michelet et al., 2005).

In the prone position this study demonstrated a weak association between IAP and body weight. Though this is intuitive, it has not previously been described. This may suggest that the Wilson frame and Montreal Mattress were not intended for use in the obese patient and the abdomen is compressed rather than dependent, with the weight distributed over the pelvis and upper body.

The prone position is frequently applied to the critical care patient. The prone position allows aeration of previously dependent lung units, and leads to an improvement in compliance and oxygenation. The prone position does not lead to an elevation in IAP with appropriate support. However, in the presence of poor support, or central obesity, a rise in abdominal pressure is likely. This would lead to a cephalad movement of the diaphragm, a rise in thoracic pressure and compromise mechanical ventilation. Gattinoni (Gattinoni and Protti, 2008) has argued that the prone position is not ideal for all patients requiring mechanical ventilation for respiratory failure. Continuous gastric pressure measurement may provide useful adjunct information for managing patients in the prone position, particularly where improvement in respiratory indices is not immediately forthcoming.

We have previously demonstrated that gastric pressure is a surrogate of IAP. This study confirms that gastric pressure has a practical application for the real time measurement of IAP during surgery and by association would have practical application in the critical care unit. It may well be that patients who show an elevation in gastric pressure may not benefit from being placed in the prone position and if the pressure increase is great, they may develop abdominal compartment syndrome with resulting organ dysfunction.

**Comment**

Previous studies have sought to determine the impact of a surrogate larynx upon respiratory mechanics during a voluntary cough. The subsequent study seeks to determine the modification of respiratory mechanics during a voluntary cough in the absence of a larynx. Our results suggest that laryngeal closure may not be responsible for the augmentation of the pressure within the thorax during early forced expiration. This study seeks to clarify the mechanics responsible for thoracic pressure elevation.

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## **Chapter 11: Flow and Pressure dynamics of a voluntary cough in the laryngectomee: an observational study.**

### **Introduction**

The larynx in humans has become adapted for vocalization with a narrowing above the trachea creating a choke point, a low position in the neck behind the tongue, and a capacious pharynx facilitating phonation (Negus, 1954). However, the function of the larynx in animals, birds and reptiles is subsumed for other functions such as vomiting, hiccupping, swallowing, postural adjustments, as a protective valve during diving (Bartlett, 1989) and coughing. Vocalisation is facilitated through modifications of the trachea in birds or adaptations of the pharynx in mammals (Lindsay and Clayton, 1986). Consequently, though modifications of the larynx support complex vocalization in humans (Fitch and Reby, 2001), its removal may compromise respiratory functions beyond speech, in particular the expulsive efforts associated with a voluntary cough.

A voluntary cough is characterized by temporary occlusion of the larynx during early expiration, providing an environment that supports the development of a supramaximal expiratory flow. A supramaximal expiratory flow is a peak expiratory flow that exceeds that developed during a forced expiratory flow (Ackerstaff et al., 1995, Ackerstaff et al., 1999). A laryngectomy would therefore, be expected to compromise normal cough function. However, following a laryngectomy, patients report satisfactory clearance of upper airway secretions (Ackerstaff et al., 1999) through adaptive coughing mechanisms (Fontana et al., 1999). These cough adaptations in the laryngectomee are not well described. The primary objective of this study is to describe the pressure and flow dynamics of the “adaptive cough” manoeuvre in the laryngectomee.

In a supplementary experiment, an expiratory valve was developed to reproduce the mechanics of laryngeal closure and opening during a voluntary cough. We explored the impact this surrogate larynx may have upon the pressure/ flow dynamics of a forced expiratory manoeuvre when compared with the adaptive cough in the laryngectomee.

### Methods

The institutional ethics panel passed the study and all subjects gave prior consent. 12 subjects, 2 female and 10 male were recruited from an outpatient clinic. Each subject had a heavy smoking history prior to laryngectomy for carcinoma of the larynx. The laryngectomy was performed several months prior to testing (*mean duration 64 months, range 18 – 144 months*). All subjects had a definitive tracheal stoma, and Provox voice prosthesis. All subjects had desisted from smoking following surgery and none had evidence of recurrence at the time of study. The majority of subjects (*10 of 11*) reported no subjective compromise of cough function.

**Pressure and Flow Measurement:** A commercially available 10cm balloon catheter (*Ackrad Laboratories, Cooper Surgical, Inc. Trumbull, CT*) was used in this study. The balloon material is PVC (Polyvinyl chloride), radiation stable, with 70 A Durometer hardness. The material is 0.007 inches thick with a thickness tolerance of +/- 0.002 inches. The manufacturer recommended the addition of 1.0 ml of air into the deflated balloon prior to measurement. The balloon catheter was attached to a pressure transducer (*see below*) via a 100cm polyvinyl catheter. A three-way tap was placed at the transducer end of the balloon/ catheter set up, so that the balloon could be inflated and deflated.

The pressure recording system for the balloon catheters consisted of a transducer amplifier (*143PC03D Honeywell control systems limited, Bracknell, Berkshire, England*). The flow and pressure signal was amplified, digitised and passed through a signal sampler, sampling at 200Hz. The signal was subsequently recorded and viewed in real time using customized Labview Software (*National Instruments, California, USA*). The transducer amplifier system were calibrated prior to each experiment by zeroing at room pressure and 100mmHg using a standard graduated mercury manometer.

Gastric ( $P_{gas}$ ) and Oesophageal ( $P_{es}$ ) pressures were measured via balloon catheters placed per nasally into both the stomach and mid third oesophagus. Transdiaphragmatic pressure ( $P_{di}$ ) was recorded as an index to represent the pressure generated by the diaphragm (Chieveley-Williams et al., 2002) and is calculated as the difference between  $P_{es}$  and  $P_{gas}$  ( $P_{di} = P_{es} - P_{gas}$ ).

Respiratory flow was measured with a screen type pneumotachograph (*Hans Rudolph*).

**Respiratory Function Tests:** Pulmonary function testing was performed via an extra-tracheal device. To achieve an effective seal between the tracheal stoma and the measuring devices, the cuff of a tracheostomy tube (*Portex, Smiths Medical International, UK*) was inflated with 10ml of air and placed within the tracheal stoma. The size of the tracheostomy tube (*7.0, 8.0 or 9.0 mm internal diameter*) selected was the largest size that would prevent audible air leakage during a peak expiratory flow manoeuvre.

All respiratory functions tests were performed 5 - 10 times according to the tolerance of the subject. Prior to formal testing, each subject performed a number of practise attempts at each of the respiratory manoeuvres until they were comfortable with the apparatus and felt that they could perform the manoeuvres satisfactorily.

Maximal inspiratory ( $MIP$ ) and expiratory pressure ( $MEP$ ) provided estimates of respiratory muscle strength. During coughing subjects were instructed to cough both at the end of normal tidal breath (*FRC cough*) and following a deep inspiration (*TLC cough*).

**Mechanical Cough Reproduction:** To reproduce the mechanics of glottic function during a voluntary cough, we constructed a valve to reproduce the mechanics of the glottis. The valve consisted of a cylinder (*internal diameter, 29 mm*); within the cylinder an occluding balloon (*Serial No. 9308, Hans Rudolph Inc.*) was mounted. The balloon could be rapidly inflated (*by compressed air*) and deflated. The controlling circuitry for the valve was arranged so that it could be inflated by the operator once the subject achieved relaxation at the end of the inspiratory phase; the valve was automatically opened and kept open using elevation in gastric pressure as a signal. The subject was instructed to take a shallow (*from FRC*) or deep inspiration (*from TLC*); the occluding valve was closed at the end of the inspiratory effort. The subject was then instructed to perform a forced expiratory maneuver. The occluding valve was triggered to open at a gastric pressure of 40cmH<sub>2</sub>O and the pressure/ flow mechanics at the tracheostomy were recorded.

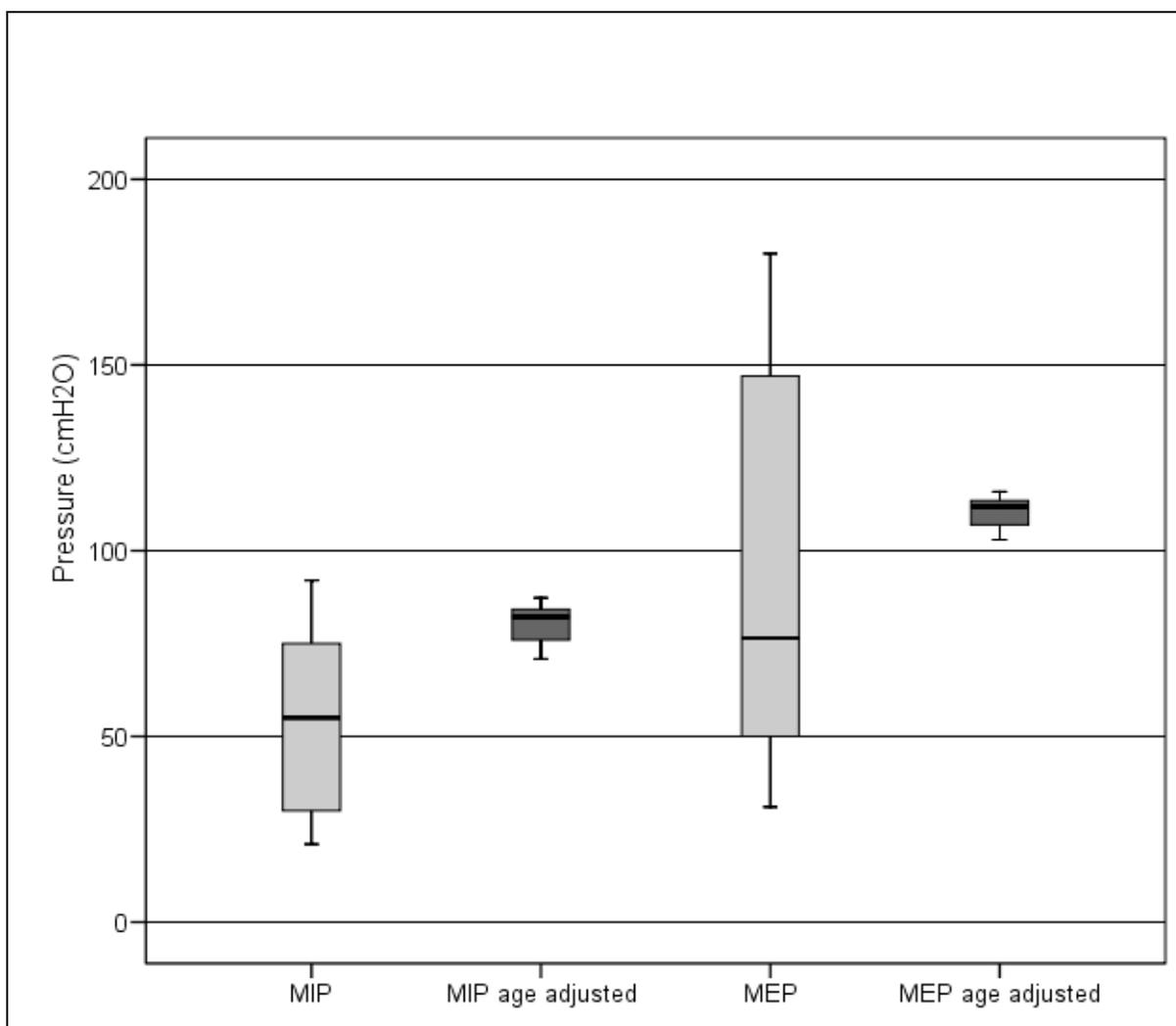
**Non-Volitional Measurement of Diaphragm Strength:** Twitch transdiaphragmatic pressure (*TwPdi*) was measured through cervical magnetic nerve stimulation (Luo et al., 1998) performed using a Magstim 200 (*Magstim Co. Ltd, Whitland, Dyfed, UK*) with a circular 90 mm coil. The coil was placed over the spinous process of C7. During stimulation, subjects were seated in a chair with the neck flexed. Stimulation was performed, following a rest period to limit potentiation, at relaxed end expiration with the abdomen unbound. TwPdi was then measured at 100% Magstim output as the mean of five twitches performed at least 30 seconds apart.

**Analysis:** SPSS (*version 15*) statistics package was used for statistical analysis and production of graphical material. Mean, median and range values were calculated for each subject. Student's t test (*two samples*) and ANOVA (*three or more samples*) was used to compare differences between samples. Where a difference was observed between three or more samples, a Bonferroni correction was applied. The level of significance was taken as a p value <0.05.

### Results:

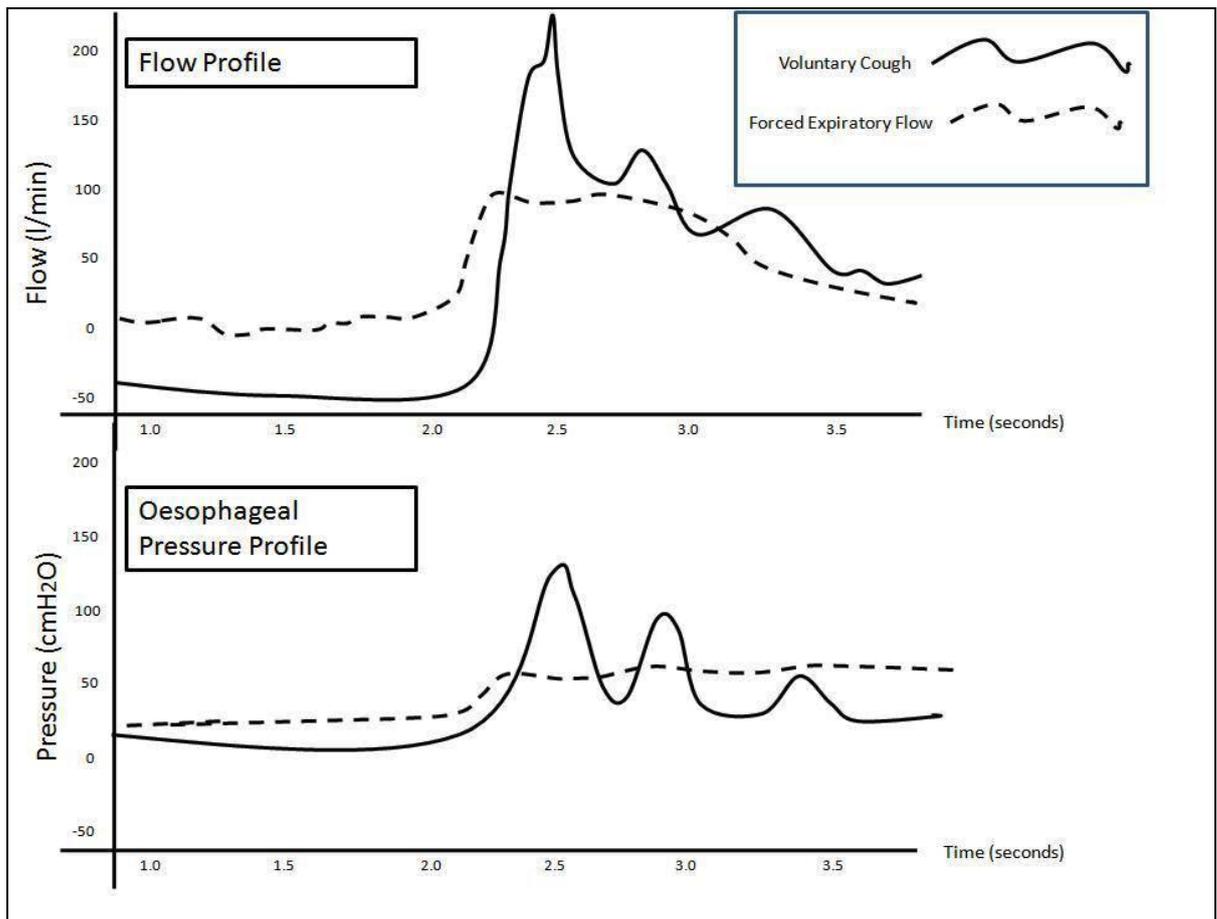
The mean age of the subjects was 67 years (range 60 – 74). All subjects had received a laryngectomy for laryngeal carcinoma between 18 and 144 months prior to testing (*mean 64 months*). No subject reported a diagnosis of chronic respiratory disease prior to laryngectomy, and only one subject reported respiratory compromise following surgery. One subject considered that his cough was ineffective; the remaining 11 subjects denied an impaired voluntary cough. In one subject the oesophageal and gastric balloons would not pass and only flow was measured.

**Respiratory Muscle Strength:** The Mean Expiratory and Mean Inspiratory Pressure was 65cmH<sub>2</sub>O ( $\pm$  46) and 47cmH<sub>2</sub>O ( $\pm$  22) respectively. Normative values for MIP and MEP were calculated for the test subjects (Neder et al., 1999). A boxplot (Figure 66) represents actual and calculated maximal respiratory pressures. The difference between the measured and calculated values for MIP is significant ( $p = 0.009$ ), but is not so for the MEP ( $p = 0.332$ ).



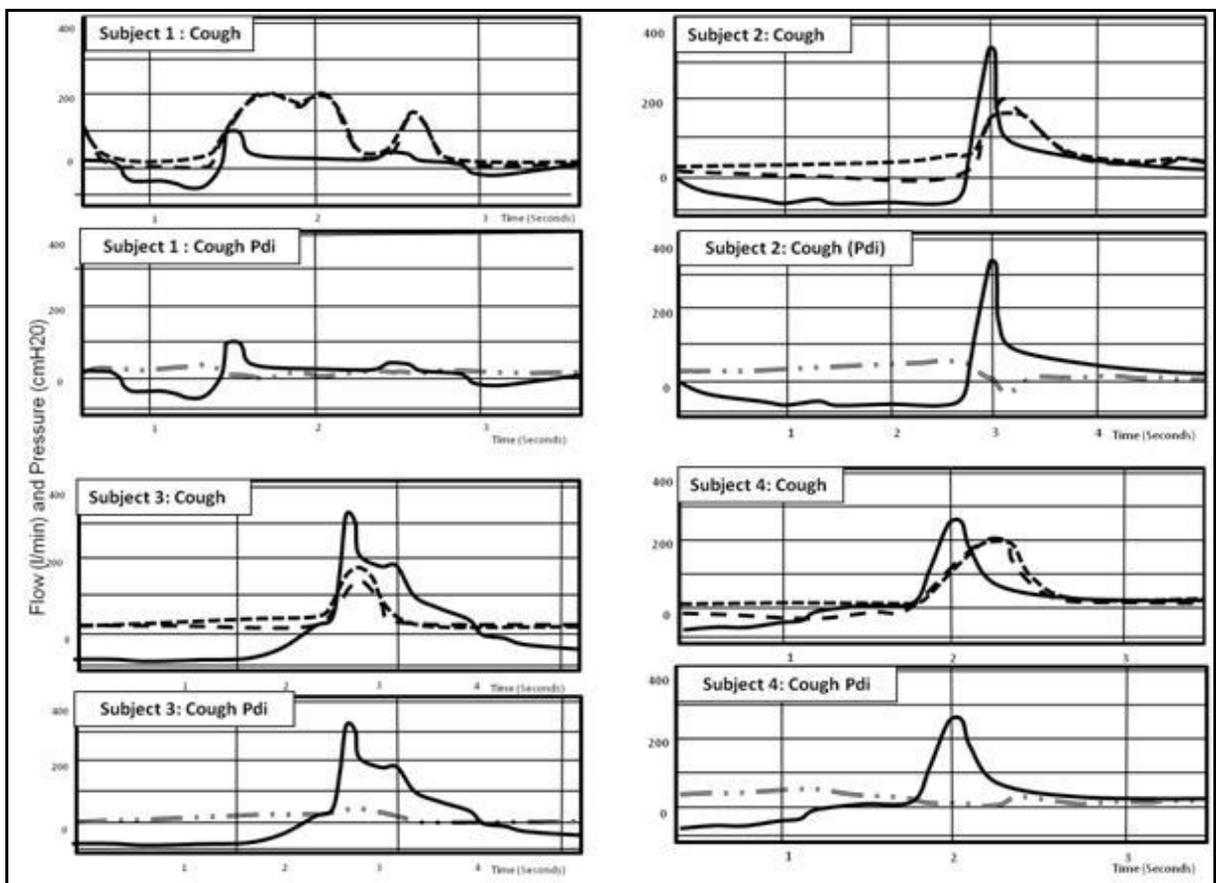
**Figure 66. Boxplot illustrating MIP and MEP for test subjects compared with calculated age adjusted normal values**

**Comparison of Forced Expiratory Flow and Voluntary Cough:** The subjects were asked to perform both a forced expiratory flow manoeuvre and a voluntary cough. (Figure 67) illustrates the pressure profile for a forced expiratory flow manoeuvre in a laryngectomee, when compared with that of a voluntary cough in the same subject. The graph suggests that the absence of a larynx does not compromise the development of a rise in esophageal pressure where it is seen to exceed that of a forced expiratory flow manoeuvre.

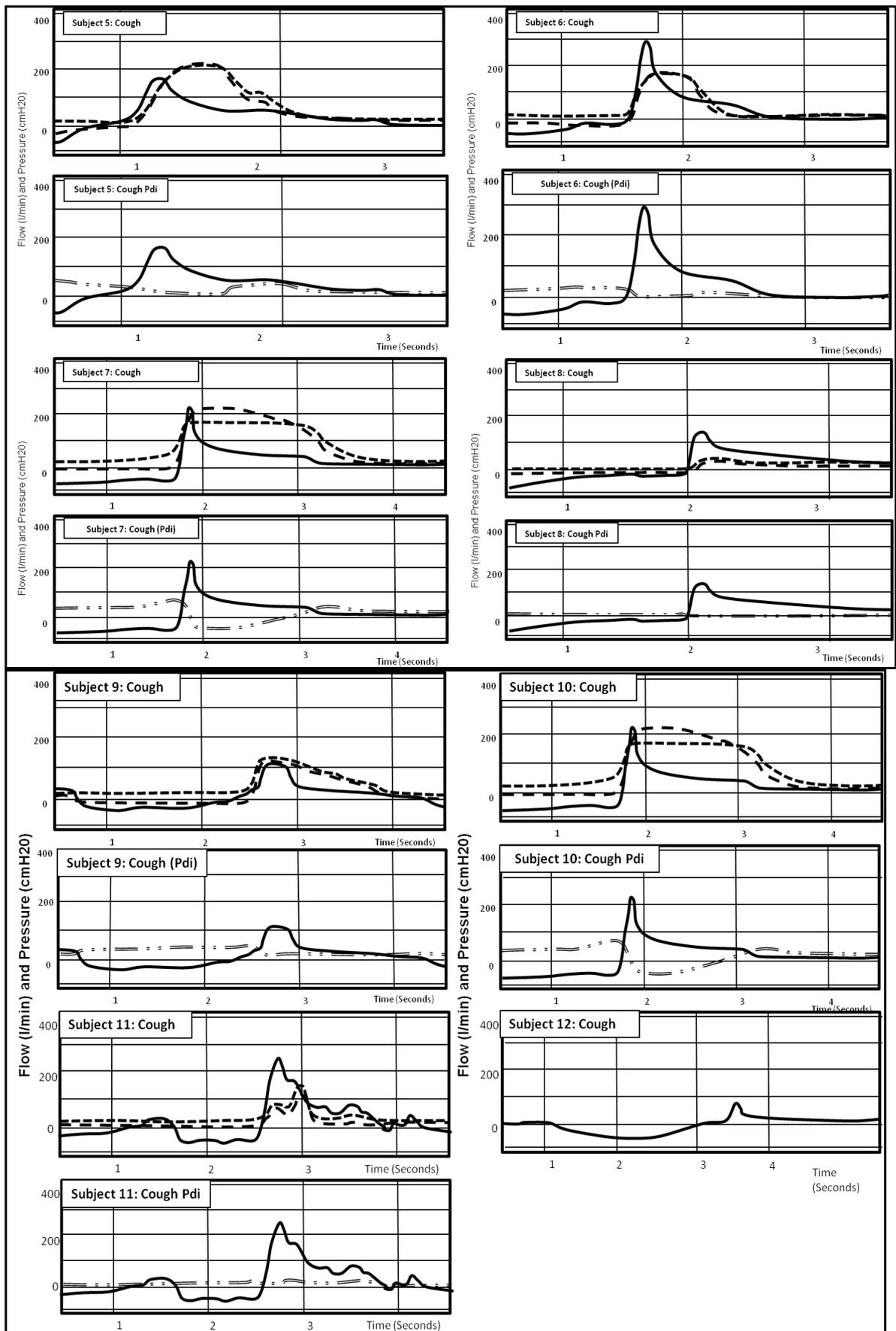


**Figure 67. Comparison of flow and Esophageal Pressure profile for a forced expiratory flow manoeuvre (Dashed Line) and a voluntary cough (Solid Line) in a laryngectomee. Flow and pressure profiles are taken from the same subject**

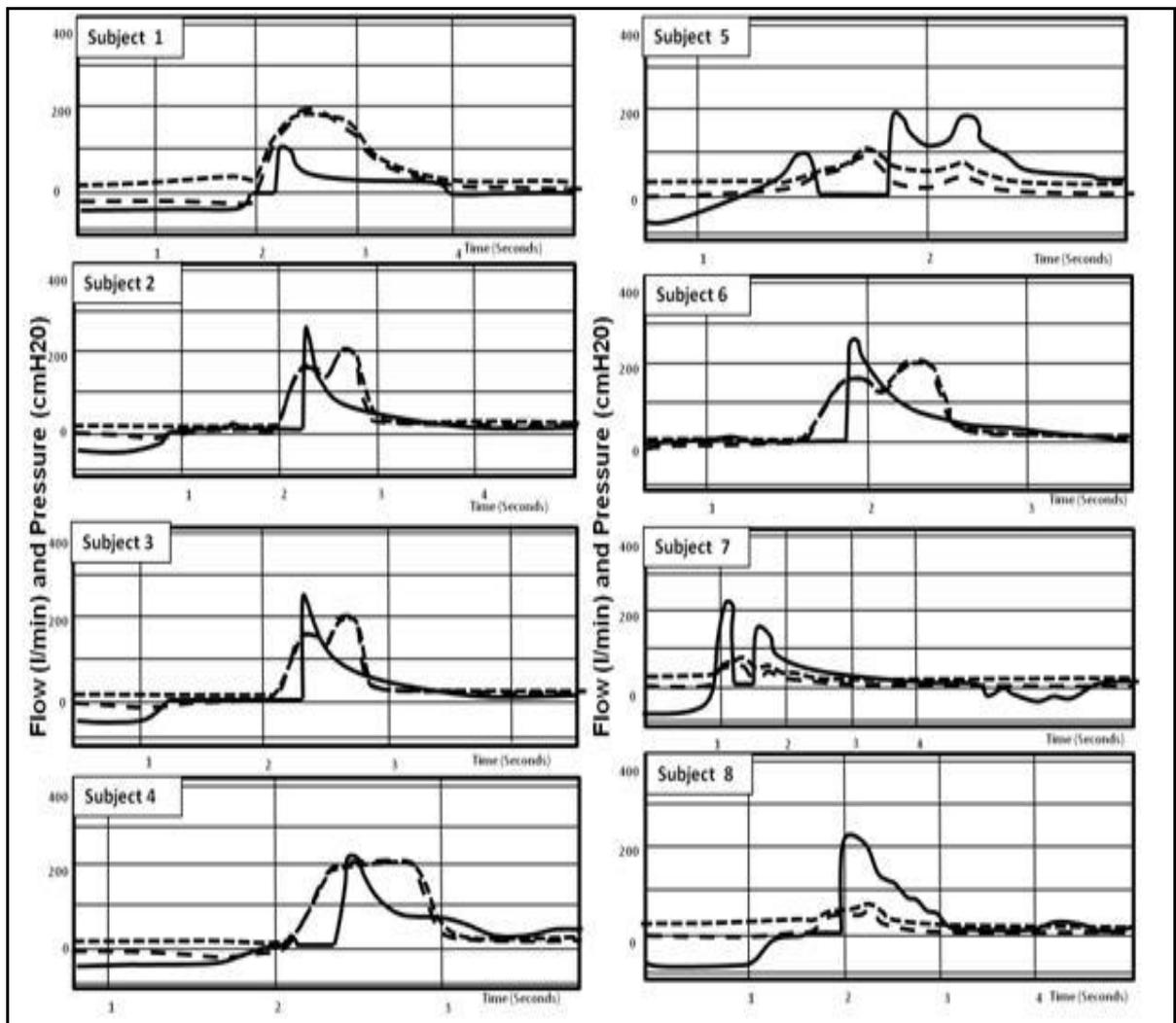
**Adaptive Cough Dynamics:** (Figure 68) illustrates the dynamics of the adaptive cough in each of the study subjects. The pressure and flow curves demonstrate the simultaneous relationship between the pressure and flow diagram. The  $P_{es}$  is seen to approach or exceed 200cmH<sub>2</sub>O in the majority of subjects. The Pdi/ flow curves illustrate the relative contribution of the abdominal and thoracic pressure generation during the adaptive cough. In subjects 2, 7 and 10 the Pdi trace falls below zero pressure demonstrating the dominance of esophageal pressure, and in subjects 1, 3, 4, 6 and 8 the Pdi falls to zero demonstrating an equal contribution of thoracic and abdominal pressure.



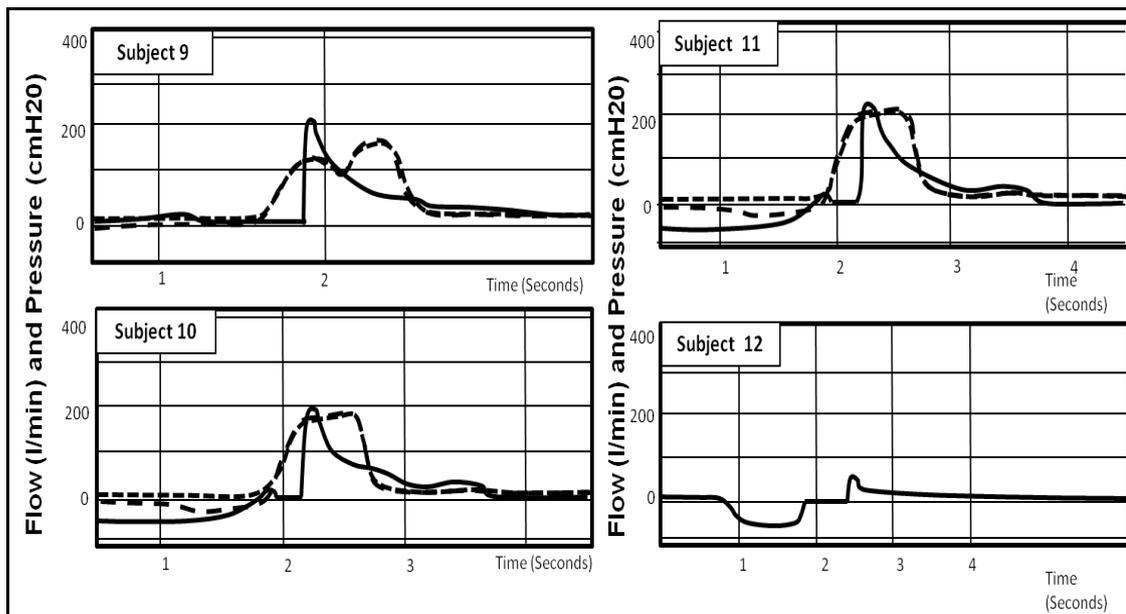
**Figure 68.** Flow, Pressure and Pdi profile for the adaptive cough for the twelve subjects. The flow (l/min), oesophageal pressure (cmH<sub>2</sub>O) and gastric pressure (cmH<sub>2</sub>O) are presented separately. Where  $P_{es}$  and  $P_{gas}$  cannot be distinguished, they have followed the same line and only one can be observed.  $P_{es}$  approaches or exceeds 200cmH<sub>2</sub>O in most subjects.



**Surrogate Cough Dynamics:** (Figure 69) illustrates the impact of the surrogate larynx on the flow and pressure profile of a voluntary cough in the study subjects. Co-ordination of the valve closure presented practical difficulties and is demonstrated by the failure to close the valve at the onset of the expiratory manoeuvre. The surrogate cough demonstrates a reduction in the time to develop a peak flow, which compares favourably with the dynamics of a voluntary cough in an individual with a functioning larynx.



**Figure 69.** Flow and Pressure profile for the surrogate cough for twelve subjects. The flow (l/min), oesophageal pressure (cmH<sub>2</sub>O) and gastric pressure (cmH<sub>2</sub>O) are presented separately from the flow (l/min). Opening of the expiratory valve leads to a rapid rise in expiratory flow. Failure to co-ordinate valve opening with expiration is evident in subject 5, 7.



The table(Figure 70) illustrates the mean values for peak flow, Pes, Pgas and Pdi for a cough developed with a prior deep inspiratory effort (*Cough from TLC*) and a forced expiratory flow maneuver with the addition of the surrogate larynx. Statistical analysis (*ANOVA with Bonferroni correction*) demonstrates that there is no significant difference between the measured values for a cough from TLC and the surrogate cough, except for the time to achieve peak flow, where the addition of the surrogate larynx reduces the time to peak flow ( $p < 0.001$ ).

Cough Type	Pes (cmH <sub>2</sub> O) (mean Value)	Pgas (cmH <sub>2</sub> O) (mean Value)	Pdi	Peak Flow (l.min <sup>-1</sup> )	Time to peak flow (seconds)
Cough from TLC	145 (65)	121 (49)	24.2 (30)	226 (85)	0.26 (0.17)
P value	1	1	1	1	<0.001)
Cough from TLC with surrogate valve	156 (68)	126 (54)	29.8 (31)	191 (61)	0.07 (0.07)

**Figure 70. Changes in the measured values during a voluntary cough from TLC and a Forced expiratory flow with the introduction of a surrogate larynx. There are non-significant differences in all the values measured. The exception is the time to develop a peak flow which shows a significant reduction.**

The addition of a valve that opened in response to a rise in gastric pressure changed the nature of the flow pattern with a shorter rise time (*0.07 seconds ± 0.07*). There was not the expected increase in peak flow, but there was a small increase in P<sub>es</sub> and P<sub>gas</sub>. These differences were not however, statistically significant.

**Diaphragm Strength:** Estimation of diaphragm strength through measurement of magnetic phrenic nerve stimulation was possible in 5 subjects only. Two subjects did not have balloon catheters inserted and 5 subjects declined further testing. Mean TwPdi was 13.3 cmH<sub>2</sub>O ( $\pm$  4.0 cmH<sub>2</sub>O). This is within the range reported with TwPdi reported in previous studies of subjects with chronic obstructive pulmonary disease(Polkey et al., 1996, Wanke et al., 1994, Similowski et al., 1991).

### Discussion:

The observation of the abdominal (Pga), oesophageal (Pes) and diaphragmatic (Pdi) pressures during a cough manoeuvre in the laryngectomee, demonstrates that the absence of early laryngeal closure does not appear to compromise the development of an elevation in Pes. Pes >100cmH<sub>2</sub>O during a maximum expulsive manoeuvre such as a cough is within the range previously reported (Gandevia et al., 1992) for normal subjects. The Pes is also greater than expected for subjects with chronic pulmonary disease performing a maximum expiratory manoeuvre (Marin et al., 1999).

The Pdi trace falls to zero or below in several subjects. The implication of this observation runs counter to current assumptions that the rise in thoracic pressure is a consequence of a rise in abdominal pressure creating a cephalad movement of the diaphragm. The expiratory function of the internal intercostal muscles of the chest wall is described in a recent review (De Troyer et al., 2005). Co-activation of both expiratory thoracic muscles and abdominal muscles would amplify the thoracic pressure rise seen in a voluntary cough. Though closure of the larynx is frequently assumed to support the elevation in thoracic pressure seen in the early expiratory phase of a voluntary cough, the thoracic pressure rise observed in this study suggests an alternative function of laryngeal closure during a voluntary cough.

The explanation may be observed through the impact of the surrogate larynx on the flow profile of the forced expiratory manoeuvre. The time to develop a peak flow demonstrates a significant reduction. The impact of this flow change would be an increase in the force generated during a voluntary cough according to Newton's second law of motion:

$$\text{Force} = \text{Mass} \times \text{Acceleration.}$$

That is if the mass of air expelled is comparable when comparing a forced expiratory flow and the surrogate cough manoeuvre, then the reduced time to develop peak flow would see a significant increase in the force generated.

A critique of the study may consider that adaptation of a tracheal stoma to facilitate the measurement of respiratory function in the laryngectomee is a compromise that may limit the accuracy of the respiratory function tested in this study. Fortunately, pulmonary function testing in the laryngectomee is not a novel technique and previous studies have confirmed that an extra-tracheal airway device permits pulmonary function testing and that these tests are reliable and consistent (Ackerstaff et al., 1993, Hess et al., 1999).

Synchronisation of the expiratory valve closure required manual closure of the valve at the commencement of the forced expiratory flow manoeuvre. This contributed to failure to synchronise consistently (*figure 4*) Automation of the valve closure in combination with valve opening may optimise the peak expiratory flow profile.

The impact of laryngectomy does not therefore prevent the rise in oesophageal pressure, but compromises the rapid rise to peak flow. Thus a voluntary cough in the laryngectomee will be limited, but not ineffective. This is supported by previous studies that following a laryngectomy there is an increase in the frequency of coughing (Braz et al., 2005) and an increase in sputum production (Togawa et al., 1980, Hess et al., 1999).

**Conclusion:**

The role of the larynx during a voluntary cough was previously presumed to allow the development of a high thoracic pressure during the forced expiratory effort against the closed glottis. This study throws that premise into doubt suggesting that the role of laryngeal closure is through development of a flow profile with a steep rise to peak flow. The introduction of the surrogate larynx reproduces the flow profile seen in a normal subject

The absence of the larynx will therefore compromise the efficiency of a voluntary cough. The functional impact of an ineffective cough mechanism would be a greater reliance upon the mucociliary escalator to clear tracheal secretions, more frequent activation of involuntary coughing through the usual mechanisms, an increase in peripheral airway mucus plugging and perhaps a greater tendency to develop lower respiratory tract infections. The laryngectomised patient requires continuing support to avoid declining pulmonary function with stomal humidifiers, physiotherapy and medical treatment of obstructive pulmonary disease. Future developments in expiratory valves may support a surrogate larynx and limit the chronic respiratory complications.

**Comment**

The quantitative determination of the recruitment of abdominal or thoracic muscles is through an observation of the transdiaphragmatic pressure (Pdi). The Pdi is widely used for research on inspiratory muscle strength as Pdi is a qualitative measure of the force of diaphragm contractility. The diaphragm is not an expiratory muscle, and the Pdi is not a measure of diaphragm recruitment during forced expiratory manoeuvres. The subsequent study sought to determine the dynamics of the Pdi during forced expiratory manoeuvres and if the recruitment of expiratory thoracic muscles can be observed.

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## **Chapter 12: Tension Developed by the Diaphragm during Forced Expiration and Coughing.**

### **Introduction**

The simultaneous measurement of oesophageal and gastric pressures was developed in order to analyse the relative contribution of thorax, abdomen, and diaphragm to the mechanical behaviour of the respiratory system (Agostoni and Rahn, 1960). The thoracic and abdominal pressures are typically measured with a balloon catheter placed in the mid esophagus ( $P_{es}$ ) and the stomach ( $P_{gas}$ ). The quantitative difference between the thoracic and abdominal pressure is a measure of the force developed across the diaphragm during inspiration, or  $P_{di}$ , where  $P_{di} = P_{gas} - P_{es}$ . Diaphragm activation during inspiration creates a negative thoracic pressure and this is reflected as a positive  $P_{di}$ .

Observation of diaphragm tension during expiratory manoeuvres is less well described. During a forced expiratory manoeuvre the  $P_{di}$  will reflect the relative contribution of the expiratory muscles of the abdomen and chest. It is known that diaphragm contraction during some forced expiratory or expulsive manoeuvres may limit transmission of pressure from the abdomen to the chest (Filippelli et al., 2001), perhaps to protect thoracic viscera from large pressure swings. The  $P_{di}$  during forced expiration is therefore positive, reflecting the dominance of abdominal muscle contraction. Similar changes in  $P_{di}$  during other forced expiratory manoeuvres have been observed (Gandevia et al., 1992, Al-Bilbeisi and Mc, 2000). The objective of this observational study of transdiaphragmatic pressure during a forced expiratory flow manoeuvre and a voluntary cough was to describe the relative contribution of thoracic and abdominal muscles to the flow developed.

### Methods

We studied 6 normal individuals whose anthropometric and functional respiratory characteristics (*PEFR*, *MIP*, *MEP*) were measured. All subjects were familiar with pulmonary function techniques. The study data formed part of other studies observing between cough and forced expiratory flow manoeuvres. The studies were approved by the institutional Ethics Committee, and informed consent was obtained from each subject.

### Lung Mechanics

Each volunteer sat quietly on a chair. The volunteers held a flanged mouth piece between their teeth attached to a heated, mesh type, differential pressure, pneumotachograph (*Hans Rudolph inc. Kansas, USA*) recording flow. The pneumotachograph was calibrated according to the manufacturer's instructions using a three litre syringe prior to each study.

Esophageal pressure (*Pes*) was used as a surrogate measure of pleural pressure. The esophageal balloon catheter was placed via a nostril into the mid esophagus according to the description of Baydur (Baydur et al., 1982), where maximum negative pressure upon inspiration was recorded. The balloon was inflated according to the manufacturer's instructions with 1ml of air.

Gastric pressure (*Pgas*) was used as a surrogate marker of intra-abdominal pressure. The balloon catheter was placed into the stomach via a nostril to 60 – 70cm according to the manufacturers marking. Confirmation of position was through observation of the difference in pressure compared with the esophageal balloon. Pressure rises with abdominal palpation provided additional confirmation of correct positioning.

Transdiaphragmatic pressure (*Pdi*) was derived from the signals of *Pgas* and *Pes* according to the equation  $Pdi = Pgas - Pes$ .

The data for flow and pressure was recorded in real time using equipment previously described. The flow and pressure data were visible to the volunteer.

During the forced expiratory efforts, subjects were coached to blow out hard from TLC. After each subject mastered the task, a series of at least 5 forced expiratory maneuvers were recorded.

During the cough efforts, subjects were coached to cough out hard having previously taken a maximum inspiration. After each subject had mastered the task, a series of at least 5 cough efforts were recorded.

**Analysis:**

Data are presented as means  $\pm$  1 SD. Differences between values were tested by Student's paired *t*-test. The ratio of  $P_{es}/P_{gas}$  for each subject provides an estimate of the relative contribution of each element to the driving pressure. The maximum value for  $P_{di}$  also describes the tension origin of the driving force for the forced expiration. A qualitative account of the  $P_{di}$ ,  $P_{es}$  and  $P_{gas}$  was evaluated.

### Results:

Pulmonary function was within the normal range in all subjects(**Figure 71**). The Pdi for a forced expiratory flow manoeuvre demonstrated that the pattern of recruitment of abdominal muscles and thoracic muscles of a forced expiratory flow or a voluntary cough demonstrated high intraindividual similarity but interindividual variation. Considering the 6 subjects observed, two patterns were observed. The first, observed in four subjects, is dominated by a rise in Pgas and smaller rise in Pes. This generates a positive Pdi(**Figure 72**). The second sees a greater rise in Pes generated a slight negative deflection in Pdi(**Figure 73**)

Subject	Gender	Age	Weight	Height	BMI	PEFR	FEV1	FVC
1	♀	55	55	1.6	21.5	365	2.6	3.4
2	♀	39	75	1.7	26.0	264	2.5	3.2
3	♀	56	68	1.7	23.5	673	4.1	5.3
4	♀	38	73	1.7	25.3	692	4.3	5.5
5	♀	46	110	1.8	34.0	747	3.5	4.5
6	♀	38	60	1.6	23.4	432	2.5	3.2

**Figure 71. Summary of Study Participants - demographics and respiratory function tests**

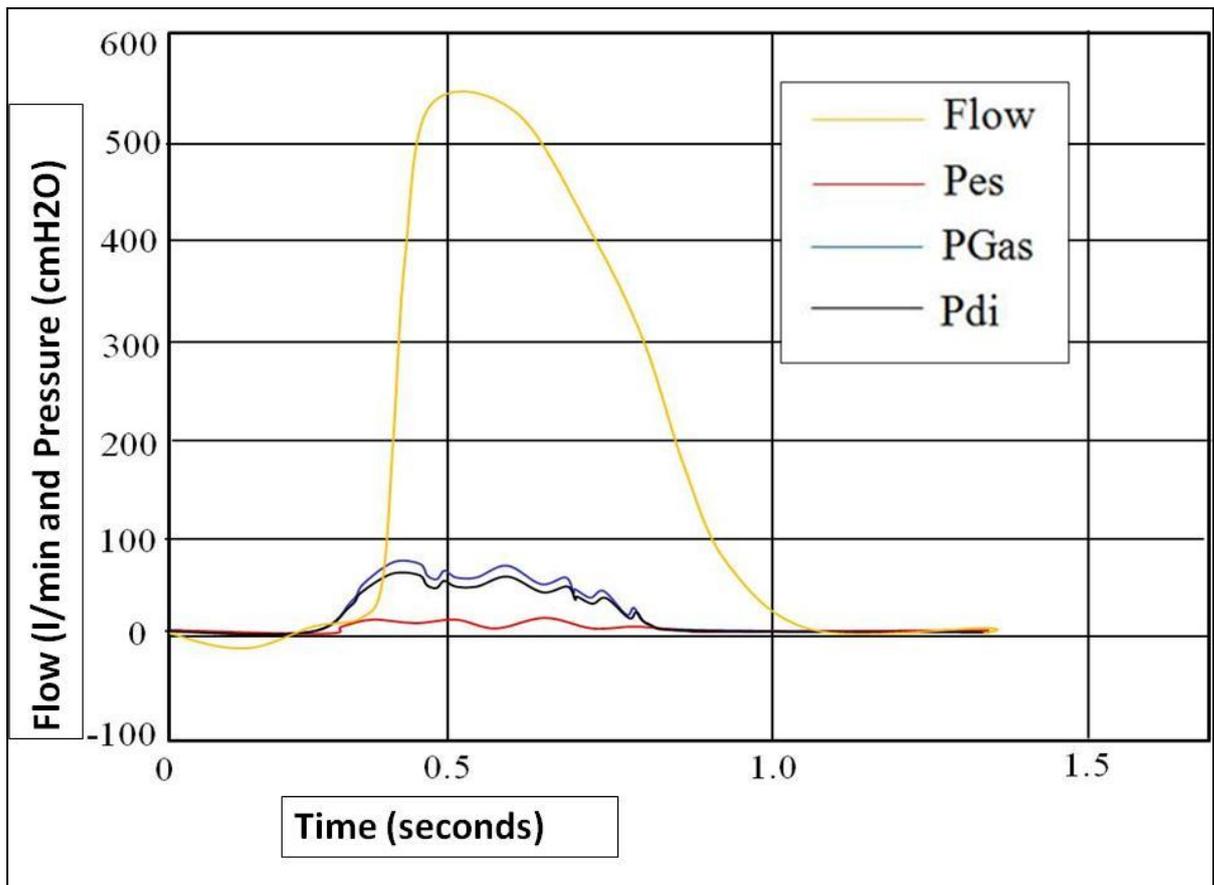
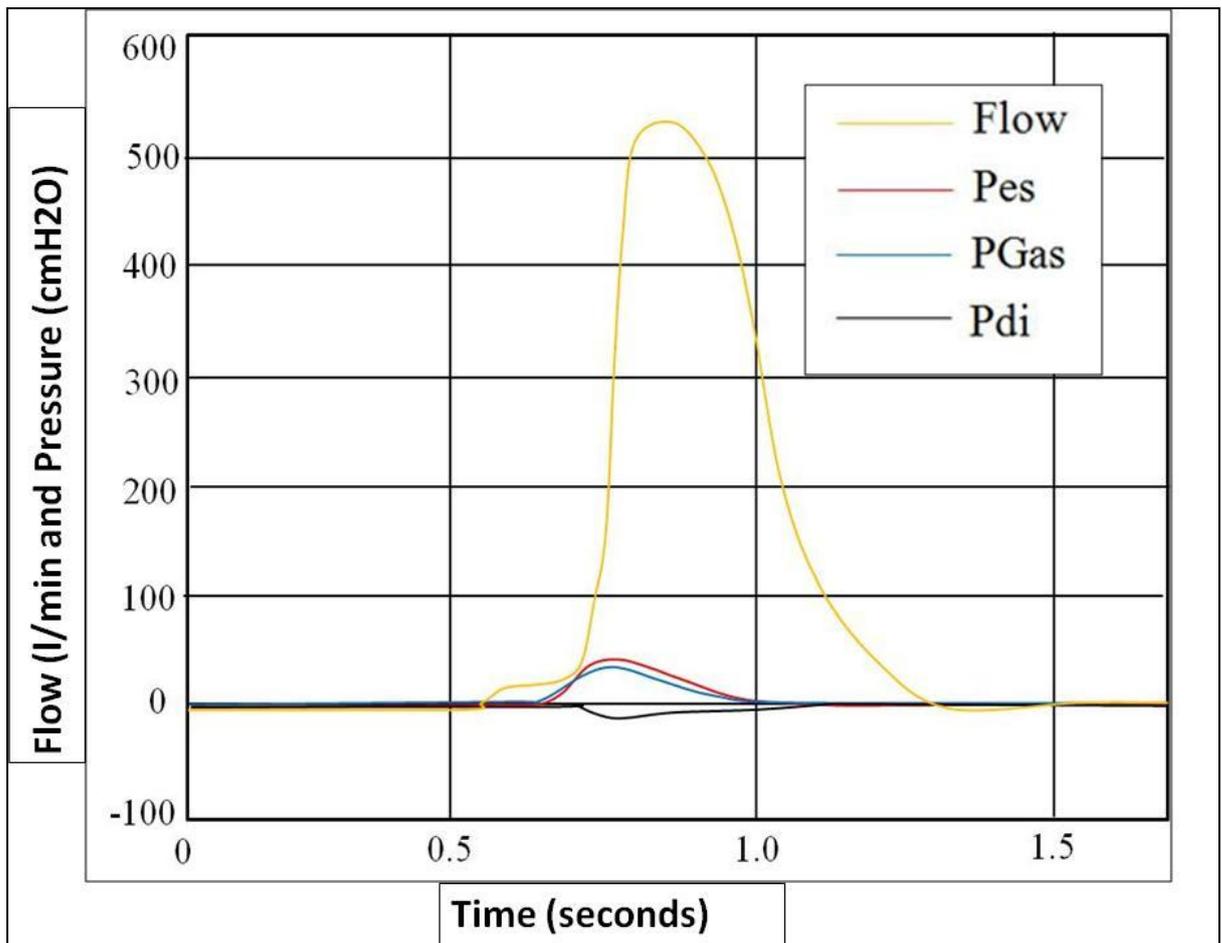
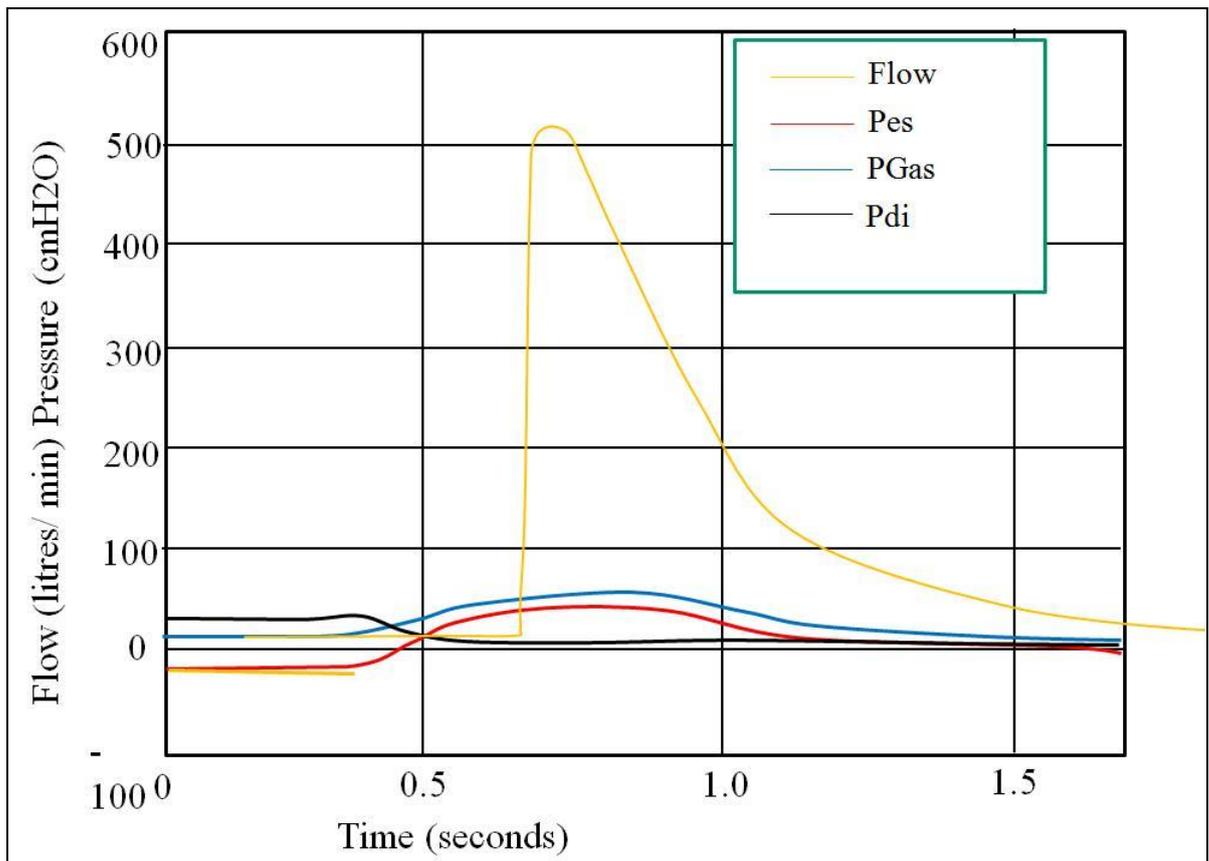


Figure 72. Pressure Flow Profile of a forced expiratory flow maneuver for Subject 1 demonstrating a positive deflection of the Pdi trace

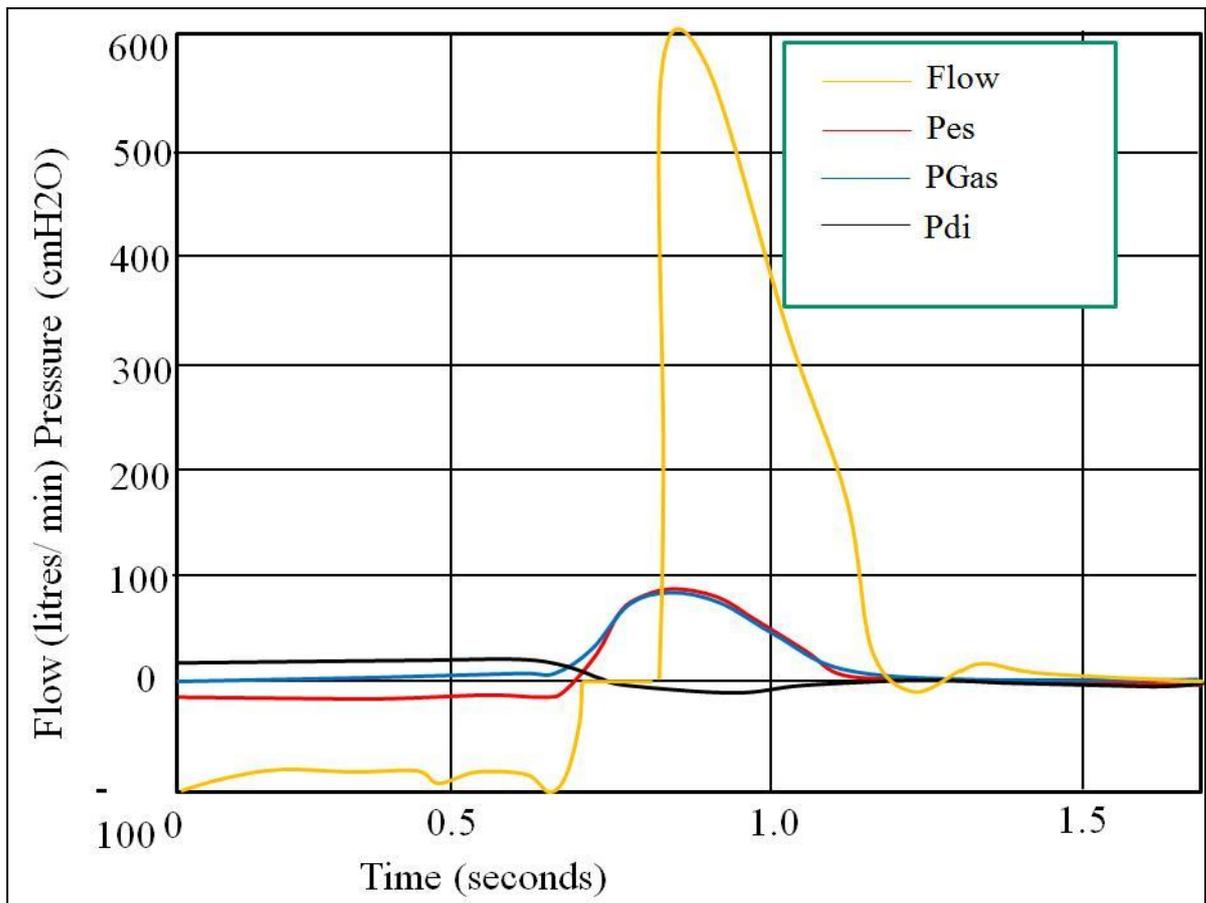


**Figure 73. Pressure Flow Profile of a forced expiratory flow manoeuvre for Subject 2 demonstrating slight negative deflection in Pdi**

During maximal coughing manoeuvres there were qualitative differences between subjects that are typified by the two images below. In both cases there is a rise in both Pgas and Pes. In (*four subjects*) there is a rise in Pes less than Pgas generating a small positive deflection in Pdi(Figure 74) or in the remaining subjects the Pes is greater than the Pgas generating a negative deflection in the Pdi trace(Figure 75).

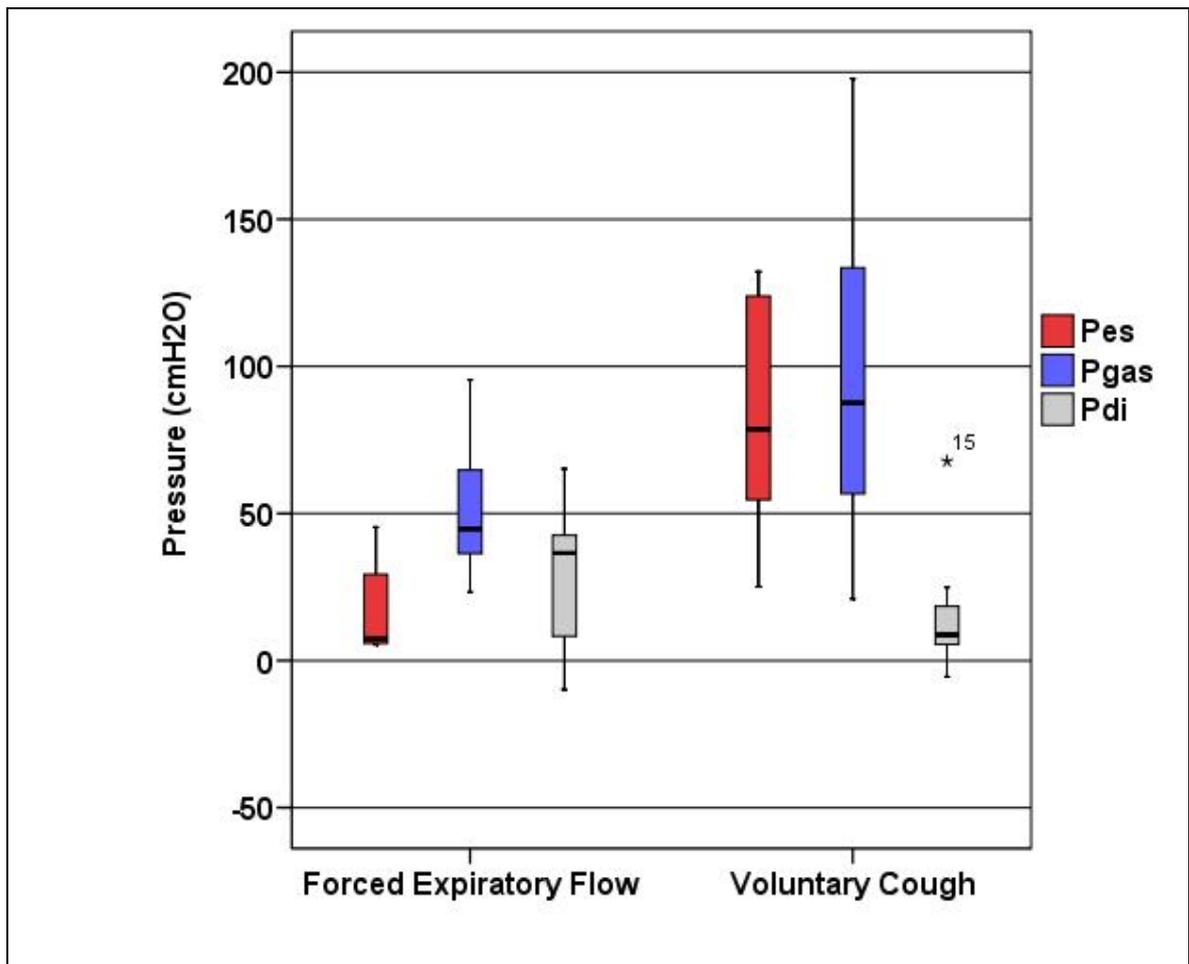


**Figure 74. Pressure and flow profile of a voluntary cough demonstrating rise in gastric pressure in excess of esophageal pressure with a positive Pdi**



**Figure 75. Pressure and flow profile of a voluntary cough demonstrating rise in pleural pressure in excess of gastric pressure**

Analysis (ANOVA) of the peak Pes, Pgas and Pdi observed for all subjects demonstrates a difference between the two manoeuvres, voluntary cough and forced expiratory flow. There is a significant difference between the Pdi ( $P = 0.04$ ) and the Pes ( $P < 0.001$ ), but no statistical difference between the Pgas ( $P = 0.114$ ). The analysis is summarised in the boxplot (Figure 76)



**Figure 76. Box and Whisker Plot of Peak Pressure achieved for a Peak Expiratory Flow Manoeuvre and a Voluntary Cough. Values represent smallest and largest values at ends of whiskers, lower quartile (Q1), median (Q2), upper quartile within the box**

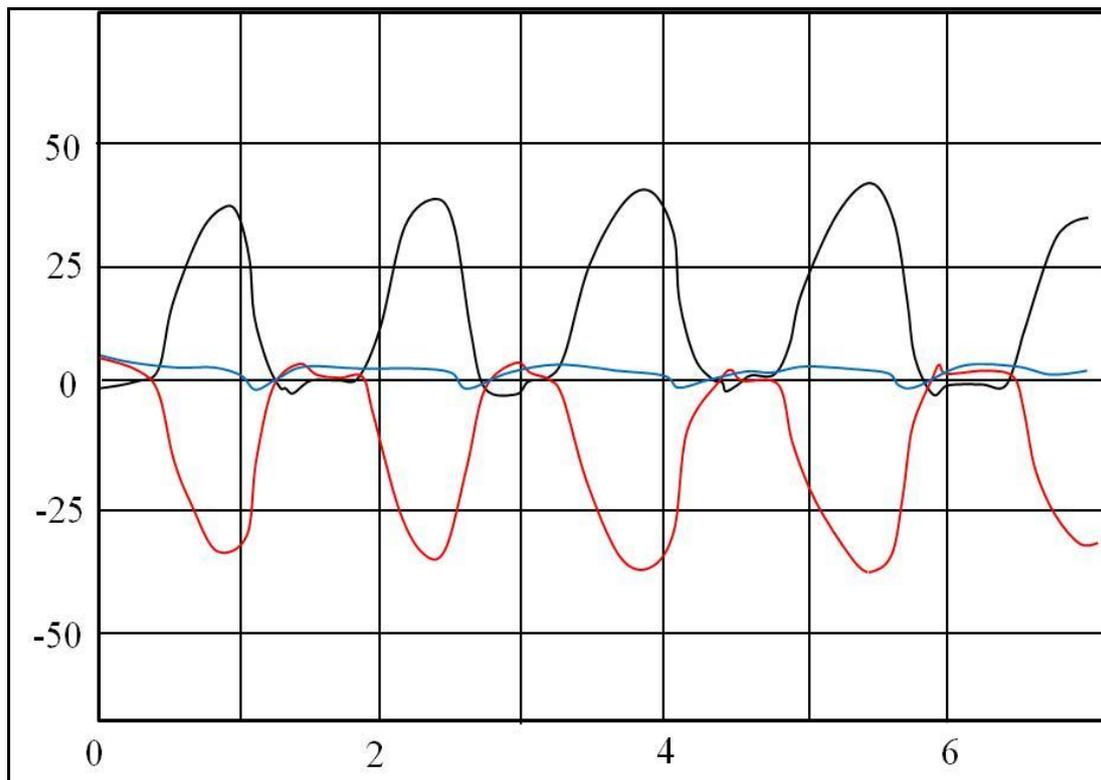
## **Discussion**

Our results demonstrate that there are interindividual differences between the patterns of thoracic and abdominal muscle recruitment for a forced expiratory flow manoeuvre and a voluntary cough. Though we have not quantified the contribution of the various muscle groups to the expiratory manoeuvres, we can make qualitative statements about the mechanics of the pressure generation.

The rise in  $P_{es}$  suggests that the thoracic muscles may contribute to the development of pressure driving a forced expiratory flow. In some cases the  $P_{es}$  exceeds the  $P_{gas}$  reflected by a fall in  $P_{di}$  below zero. In other subjects, the rise in  $P_{gas}$  dominates the pressure generation, with little or no thoracic pressure generation. These two patterns of muscle recruitment are reproducible within an individual.

During a voluntary cough the pattern of respiratory muscle recruitment was qualitatively and quantitatively different when compared with the forced expiratory flow. In all individuals there is strong contribution from the thoracic muscles, demonstrated by a larger rise in  $P_{es}$ , in addition to the recruitment of the abdominal muscles. However, the thoracic or abdominal pressures generated demonstrated two patterns where either  $P_{gas}$  or  $P_{es}$  was dominant reflected by a positive or negative deflection in  $P_{di}$ .

Interindividual differences in respiratory muscle recruitment were observed by de Troyer during forced inspiratory manoeuvres against a closed airway (Figure 77). Differences in the contribution of thoracic and abdominal muscles during expiratory manoeuvres have not been described previously.



**Figure 77. Forced Inspiration against a closed valve demonstrating development of diaphragm tension as a positive inflection in Pdi recording.**

Abdominal muscle activation will create an environment to support expiratory or expulsive manoeuvres. Conversely, intercostal muscle activation will support inspiration. However, intercostal muscles are known to contribute to expiration(De Troyer et al., 2005), and the Pdi observed may not accurately reflect diaphragm tension(De Troyer and Estenne, 1981).

The diaphragm though predominantly a muscle of inspiration(Figure 77), diaphragm tension during forced expiratory manoeuvres is described. Examples include weight lifting where it may limit the pressure transmission to the chest and thoracic viscera and stabilize the lumbar spine(Hodges and Gandevia, 2000). During inspiration the simultaneous measurement of abdominal and pleural pressure provides an index of the tension developed by the diaphragm through a positive inflection in the Pdi trace(Figure 77). In the absence of diaphragm tension, such as following phrenic nerve palsy, the Pdi will reflect the absence of tension and remain zero. However, unless

diaphragm activation is directly measured, the simultaneous measurement of Pes and Pgas will not indicate if the diaphragm is a passive or active participant during an expiratory manoeuvre (Macklem, 1985). Therefore, these observations reported neither exclude nor include diaphragm activation developing during forced expiration, but they do indicate that the rise in Pes observed is not a direct consequence of a rise in abdominal pressure, but caused in part through activation of expiratory thoracic muscles.

The implication of these observations to the reproduction of cough mechanics is that a rise in thoracic pressure is common to all subjects. The thoracic pressure is dominant in some individuals. The expiratory action of intercostal muscles is a complex interplay between the mechanics of the rib cage and the pattern of intercostal muscles activated. It is not possible to selectively activate those portions of the intercostal muscles that have an expiratory action with current magnetic nerve stimulator models. Surrogate forced expiration through magnetic or electrical stimulation of lower thoracic nerve roots will only partially recreate the mechanics of a voluntary cough, though it may be sufficient to support airway toilet and thereby reduce respiratory tract infections in subjects with a compromised cough through compromised respiratory function.

### **Comment**

It has been determined that both abdominal and thoracic muscles are, at least in part, responsible for the elevation in thoracic pressure that determines the voluntary cough strength. We have also determined that a voluntary cough flow profile is dependent upon the opening and closing of a larynx or an appropriate substitute. The next study sought to determine if a surrogate cough in sedated patients through high frequency stimulation of the abdominal muscles was practical with potential application to critical care.

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## **Chapter 13: Stimulation of Cough in Man through High Frequency Thoracic Magnetic Nerve Stimulation**

### **Introduction:**

A normal cough requires the co-ordinated activity of the abdominal and thoracic muscles to generate high intra-abdominal and thoracic pressures. The high peak expiratory flows are a direct result of these high pressure attained. Compromise of a normal cough leads to retention of bronchial secretions, microbial colonisation of the respiratory system and pneumonia. Therefore the ability to clear these secretions using something approaching a normal cough would be a major help. However there still would be situations where weakness made this technique ineffective. Cough compromise develops in the presence of inadequate muscle strength, bulbar palsy with laryngeal dysfunction or iatrogenic cough inadequacy through the use of sedative drugs or mechanical respiratory support. Cough in the critical care subject may in addition be compromised through critical illness and critical illness myoneuropathy, sedation and muscle paralysis to facilitate mechanical ventilation. Clearance of bronchial secretions is then achieved through a combination of tracheal suction and respiratory physical therapy.

Magnetic nerve stimulation realises stimulation of the spinal nerves through the application of a rapidly changing magnetic field applied to the surface of the back. Magnetic nerve stimulation is tolerated by awake subjects, does not require direct physical contact with the patient, and can be applied outside the clothing. Recent developments in high-speed magnetic stimulation have the potential to develop functional expiratory muscle stimulation. Application of this technique to subjects following spinal cord injury has been explored. We speculated that the technique could have application to the critical care patient.

Some elements of an FMS protocol with application to a surrogate cough, have been investigated by ourselves (unpublished data) and other groups. This study will observe the effect of FMS upon proxy markers of surrogate cough effectiveness. The

markers observed are Pgas, Pes, the time to develop a peak expiratory flow and the maximum peak expiratory flow achieved. The objective of this clinical study is the observation of these proxy markers when an FMS protocol is applied to awake subjects, and compare these observations with comparable markers in a voluntary cough.

### **Methods:**

A 130mm circular magnetic nerve stimulator produced by the Royal Hallamshire Hospital Medical Physics Department was used to generate the nerve stimulation. The construction of a repetitive magnetic nerve stimulator needs to consider two technical difficulties. That is the energy to repeatedly charge and discharge the capacitor is greater than can normally be drawn from the mains electric supply. Repetitive stimulation of a coil will lead to a rise in coil temperature. The first problem is solved through the use of multiple booster packs to achieve a stimulation frequency of 25Hz over 0.5 seconds (Polkey et al., 1999). The latter problem uses an automatic cut off as coil temperature rises.

We were concerned about coil distortion or fracture with the coil placed behind the subject with the patient supine. This was resolved with the development of an opaque Perspex case. Though this prevented coil distortion, it compounded coil warming through the insulating properties of the Perspex.

### **Subjects:**

Five subjects were recruited for this study (*Appendix 3: Subjects 3, 4 5 8 and 10*). All subjects were familiar with respiratory function tests. None reported respiratory or neurological disease that may compromise study results. The optimum stimulation protocol that achieved the largest rise in Pes, Pgas and Expiratory Flow had been previously identified was achieved with the axis of the stimulating coil over the spinous process of T11.

### **Oesophageal, Gastric and Mouth Pressure Measurement:**

After topical anaesthesia of the nasal mucosal with lignocaine, subjects were instructed to pass two balloon catheters through the nares into the stomach. Final

correct placement of the balloon catheters in the stomach and mid-oesophagus is achieved using the method described by Baydur (Baydur et al., 1982). Mouth pressure is recorded via a 200cm catheter connected at the mouthpiece. A three-way tap at the mouthpiece occludes the airway. With the airway occluded the subject is asked to breathe in and out. When the phase difference between oesophageal and mouth pressure is zero the oesophageal balloon catheter is fixed to the nares and the balloon catheter length at the nose recorded.

### **Expiratory Flow Measurement:**

A Hans Rudolph Screen type, heated pneumotachograph, measured expiratory and inspiratory flow. The data was displayed together with the pressure data using the customised software (*Labview, (National Instruments)*)

### **Magnetic Coil Stimulation Technique and Surrogate Cough:**

A high frequency magnetic nerve stimulator powered a 130mm coil (*Sheffield Royal Hallamshire Hospital, Department of Medical Physics*), at 25Hz for 0.5 seconds. The point of stimulation was considered the midpoint of the coil. The axis of the coil was placed over the spinous processes of T11. This level was previously demonstrated to provide the largest rise in  $P_{gas}$ . The subjects rested cowboy fashion on a chair. Subjects were instructed to breathe quietly and avoid unnecessary movements to minimise twitch potentiation. Nerve stimulation was initially at 50% of maximum power output of the magnetic nerve stimulator, and then increased to a level that was tolerated by the subject. The cough was initiated at relaxed end expiration as judged by the level of  $P_{es}$ .

### **Voluntary Cough:**

All subjects performed a voluntary cough following a maximum inspiration following the magnetic nerve stimulation testing. The physiological values of  $P_{es}$ ,  $P_{gas}$  and flow were recorded.

### Results:

When the measured values  $P_{es}$ ,  $P_{gas}$  (Figure 78) and Flow (Figure 79), developed through rapid rate stimulation at T11 are compared with a voluntary cough, it is clear that the difference is significant ( $P < 0.001$ )

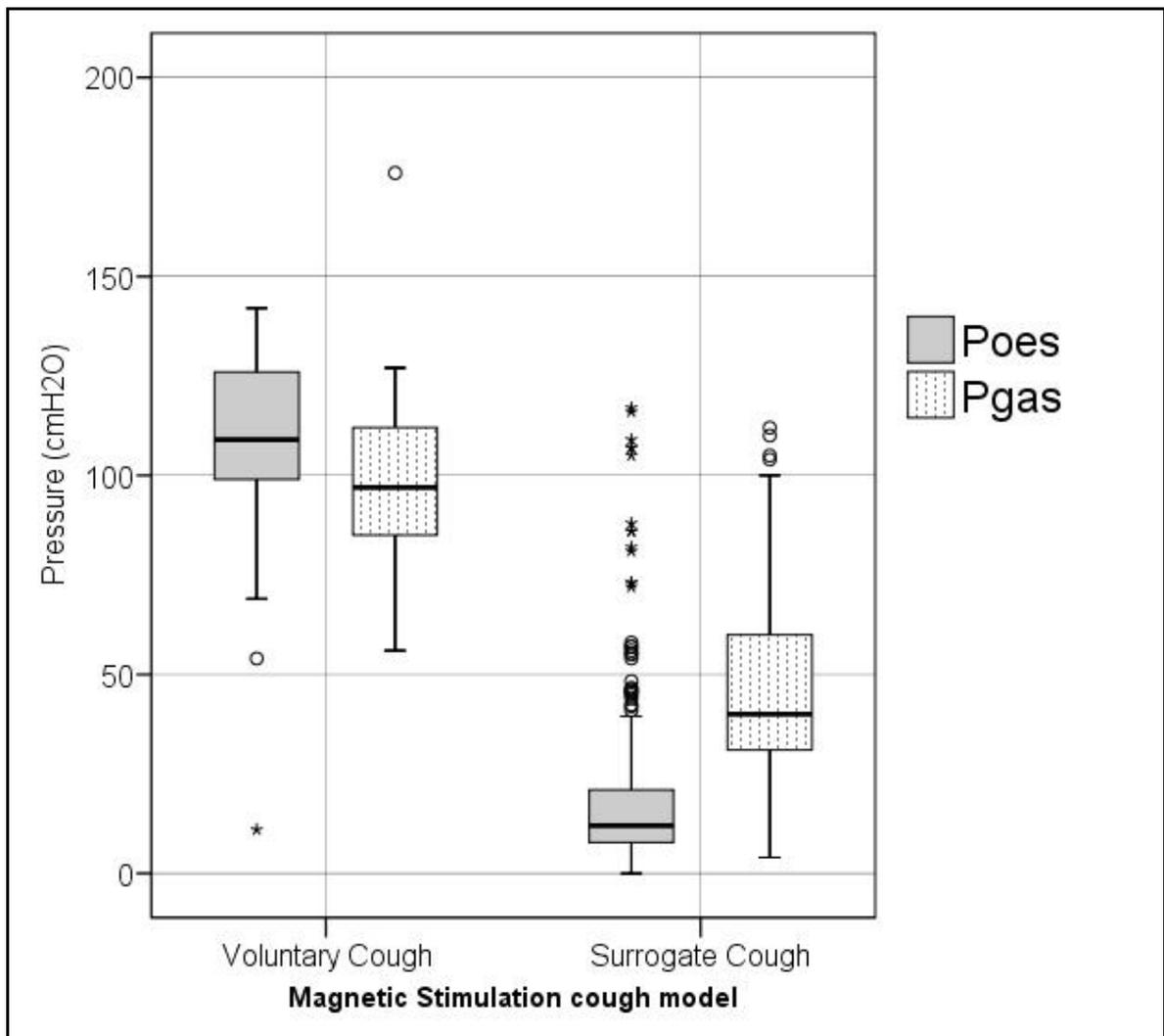
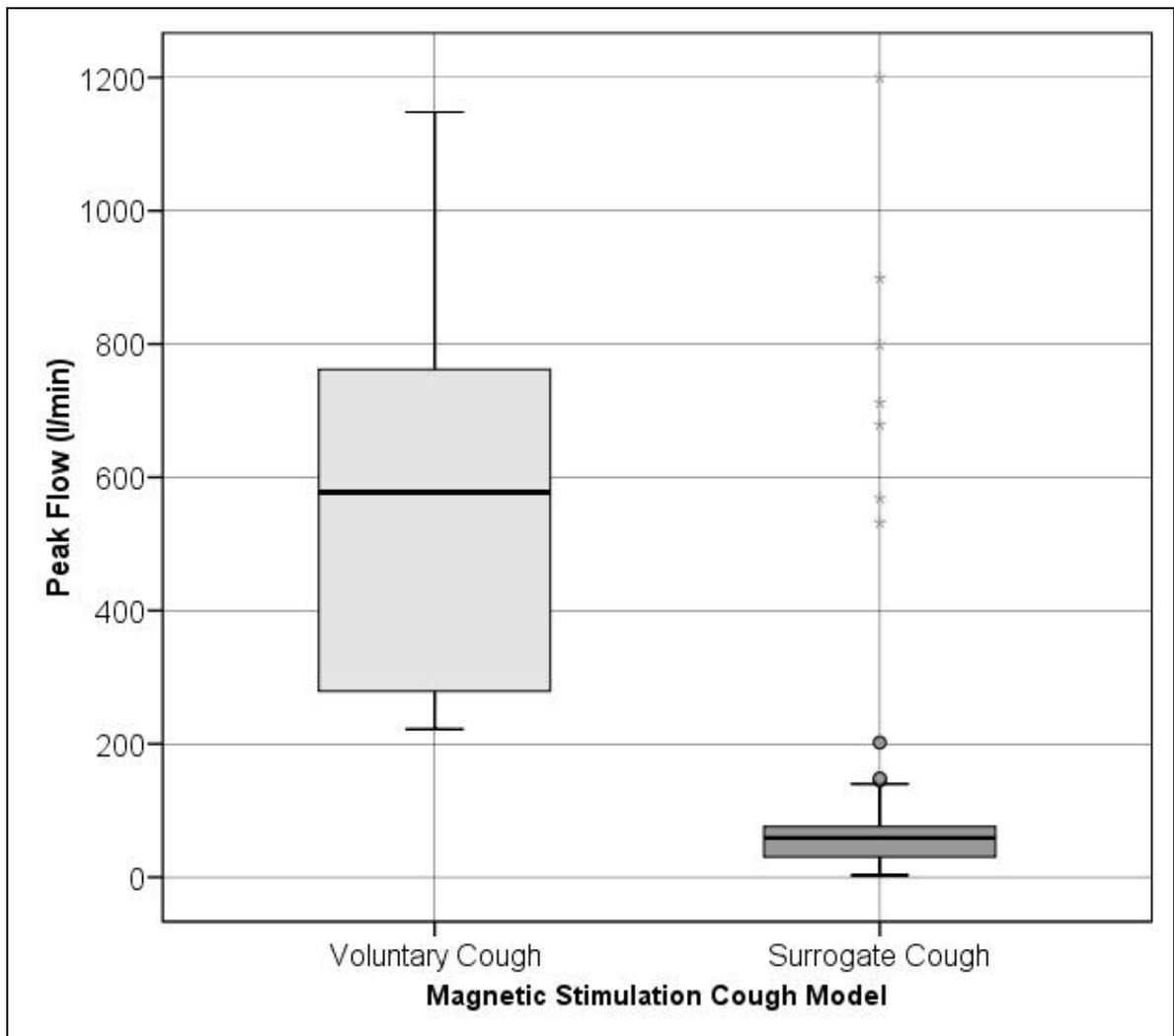


Figure 78. Boxplots demonstrating difference in  $P_{oes}$  and  $P_{gas}$  generated following magnetic nerve stimulation at T11 when compared with the values for a voluntary cough. The outliers indicated by open circles and an asterisk represent values of more than 1.5 and 3 box lengths beyond the end of the box.



**Figure 79. Boxplots demonstrating comparison of peak flow developed during a surrogate and voluntary cough. Open circles and stars represent moderate and extreme outliers.**

### Discussion:

Previous reports of the magnitude of the effect of thoracic magnetic nerve stimulation upon peak expiratory airflow had been promising (Kyroussis et al., 1997). Kyroussis and colleagues (Kyroussis et al., 1997) observed the effect of single twitch magnetic nerve stimulation using a 90mm round coil upon gastric pressure with the centre of the coil over the T10 spinous process. Subjects were six healthy volunteers from the department. The gastric pressure generated was  $35\text{cmH}_2\text{O} \pm 3.5$  with subjects in the supine position. This compares to  $100\text{cmH}_2\text{O}$  or more generated by subjects during a voluntary cough (personal data). In a follow up experiment, Kyroussis used paired magnetic nerve stimuli with a stimulus interval of one – 100Hz. Six healthy subjects from the department were again the subjects of the study. The maximum gastric pressure generated was  $74\text{cmH}_2\text{O}$  compared with a gastric pressure of  $212 \pm 21\text{cmH}_2\text{O}$  generated by the same volunteers during a voluntary cough.

Singh et al. (Singh et al., 1999) explored the effect of high frequency magnetic nerve stimulation with a 137cm round coil and a stimulation protocol of variable intensity, 20Hz for 2 seconds. He measured expiratory pressure against an occluded valve. Spinal stimulation over the T7 to T11 produced the highest expiratory pressure, with a mean of  $76\text{cmH}_2\text{O}$  compared with a maximum voluntary expiratory pressure of  $115\text{cmH}_2\text{O}$ . Neither oesophageal pressure, expiratory flow, nor abdominal pressures were measured, so no comparison could be made with voluntary cough efforts. Singh commented that voluntary effort by test subjects is a potential confounding variable. Subjects were asked to avoid voluntary efforts, but our experience suggests that it is difficult to prevent even in the experienced test subject. Our results must temper those original findings.

The discomfort of high frequency magnetic nerve stimulation of the abdominal muscles is not insignificant and use of the rapid rate stimulator with a power output greater than 70% is poorly tolerated by awake subjects. In addition, an unpleasant stimulus is likely to generate a reflex response, which following stimulation, may be a sharp exhalation. The magnitude and direction of this response is unclear, and without removal of this reflex through general anaesthesia, the actual effect of rapid rate

stimulation will not be realised. Even, where this technique of spinal cord stimulation has been applied to subjects with high C-Spine injuries, it is unclear whether spinal reflexes may prevent objective measurement of the true effect. An inspection of the results suggests peak “cough” flows or around 200 – 300l/min were achieved. It is unclear if this would be of a sufficient magnitude to be functional and aerolise and remove tracheobronchial secretions. Further work to ascertain the magnitude of the true effect of abdominal muscle stimulation is essential prior to considering this technique as a routine application for subjects with spinal cord injury or sedated for management on critical care.

**Conclusion:**

The model for a surrogate cough depends upon the achieving an elevation of abdominal pressure of a magnitude comparable to a voluntary cough. This would provide a driving force for a rise in thoracic pressure and an expiratory flow spike. This was not realised in preliminary testing of a cough model. The rise in  $P_{es}$ ,  $P_{gas}$  was not comparable to a voluntary cough, and the “cough” peak flow developed was diminished as a consequence. However, other authors have continued to develop the model of abdominal muscle stimulation through surface electrical or magnetic nerve stimulation. Therefore, it is not clear that a surrogate cough will have little effect when applied to the anaesthetised subject, and deserves testing in this environment.

The role of the early laryngeal closure and the improvement in force generated has not been considered in previous surrogate cough models. Combination of the abdominal muscle stimulation with a surrogate larynx may improve the measured values of the surrogate cough. This will be explored in a later study.

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## **Chapter 14: Abdominal Muscle Magnetic Nerve Stimulation - A surrogate cough in the anaesthetised subject**

### **Introduction**

Through sedation, ventilation and intubation, critical care leads to compromise of the respiratory defence system and the development of respiratory infections(*Chastre, 2005*). Respiratory physical therapy supports the removal of tracheobronchial secretions through manual hyperinflation(*Denehy, 1999*), chest wall percussions (*Gosselink, 2006*) gravity-assisted drainage and chest wall vibrations(*Jelic et al., 2008*). Though these techniques may reduce colonisation and subsequent infection of the respiratory system, they are not a surrogate for a voluntary cough. If a practical surrogate cough could be developed, it may limit tracheobronchial secretion retention and subsequent infection.

Previous studies have considered the development of an artificial cough in patients with a spinal injury(*DiMarco et al., 2006*) or chronic motor neuropathies(*Sivasothy et al., 2001*). Electrical stimulation of the abdominal muscles in subjects with tetraplegia improves cough peak flow(*Gollee et al., 2007*), but electrical stimulation uses implanted epidural electrodes and is not practical for the critical care patient. Magnetic nerve stimulation of the abdominal muscles may reproduce cough mechanics in awake volunteers(*Lin et al., 1998c*). However, anaesthesia has a significant impact on the compound muscle action potential generated through magnetic(*Schmid et al., 1992*) or electrical nerve stimulation, with a reduction in the compound muscle action potential being related to the dose of anaesthetic and the agent(*Zhang et al., 2009, Kawaguchi et al., 1996*).

The technical aspects of a surrogate cough have not previously been applied to the anaesthetised subject. A surrogate cough has previously been developed following an inspiration by awake volunteers(*Lin et al., 1998c*) or at end expiration(*Polkey et al., 1999*). It would seem appropriate to commence stimulation following a deep

inspiration, and for the initial expiratory effort to occur against a closed valve. These technical demands have not previously been applied to the anaesthetised subject, and our observations in the laryngectomy group have demonstrated the difficulties of synchronising the individual elements of the voluntary cough.

The primary objective of this study was to observe the expiratory flows generated by abdominal muscle stimulation in anaesthetised, intubated subjects. A secondary objective was to observe the practical effect of an artificial larynx upon the cough flows generated and consider the difficulties of synchronising the individual elements of a surrogate cough.

### Methods

14 subjects having elective surgery were recruited for participation in the study (Figure 80). The study was passed by the local ethics committee and all subjects provided voluntary consent. No subject reported abdominal pathology, had received previous abdominal surgery or reported acute or chronic respiratory disease. All subjects were non-smokers. Target controlled intravenous anaesthesia (TCI) was applied to all subjects using Remifentanyl (*Minto Model*) and Propofol (*Marsh model*). Following induction of anaesthesia no subject received muscle relaxants until the conclusion of the study where indicated. All subjects were intubated with a size 8.0mm (*female subjects*) or 9.00mm (*male subjects*) endotracheal tube. All subjects were subsequently ventilated (*volume control*), with the end tidal CO<sub>2</sub> maintained at or near to 4.5kPa.

Gender	Age(years)	Weight	Height(cm)	Height(m)	BMI	PEF	FEV	FVC
Female	80	100	152	1.5	44	250	1.46	1.79
Male	26	104	180	1.8	32	410	2.64	3.12
Female	44	66	170	1.7	23	409	2.20	2.60
Male	74	74	170	1.7	26	460	2.08	2.42
Male	79	82	165	1.65	30	460	2.05	2.36
Male	34	65	180	1.8	20	413	2.35	2.80
Female	56	66.5	155	1.55	28	397	1.98	2.30
Male	66	92	170	1.7	32	452	2.24	2.60
Male	66	80	150	1.5	36	406	1.96	2.24
Male	65	85	165	1.65	31	438	2.15	2.49
Female	57	65	140	1.4	33	367	1.81	2.07
Female	60	60	150	1.5	27	392	1.86	2.16
Female	39	60	160	1.6	23	378	2.08	2.46
Male	41	67	170	1.7	23	404	2.22	2.63

**Figure 80. Summary data for study population**

A 90mm round coil (*Magstim Company*) protected by a bespoke plastic jacket was positioned with the axis of the coil over the spinous process of T11. The jacket prevented damage to the windings during stimulation, and reduced the potential for accidental electrocution of the subject if the plastic housing of the winding were

damaged. A high frequency stimulator was set to 60% power and stimulus duration 0.5 seconds.

$P_{es}$  and  $P_{gas}$  were measured via balloon catheters placed per orally. Verification of correct positioning was through abdominal palpation (*gastric balloon*) and visible cardiac pulsation (*oesophageal balloon*). In the anaesthetized subject the Baydur method is not applicable.

Expiratory flow was measured with a heated mesh type pneumotachograph (*Hans Rudolph*). This was calibrated with a 3litre syringe prior to each study.

The action of the larynx was reproduced with a balloon valve that has been described previously. Briefly, the valve consists of perspex housing with male and female ends to connect with respiratory equipment. An inflatable cuff is contained within the housing, with rapid inflation provided by an air cylinder. The valve is triggered to open or close through an electronic trigger. In this case the trigger was a rise in gastric pressure. The  $P_{gas}$  to trigger valve opening was arbitrarily set at 20cmH<sub>2</sub>O.

$P_{es}$ ,  $P_{gas}$ ,  $P_{di}$  and flow signals were measured and recorded as previously described.

### **The Artificial Cough:**

All subjects were supine, and an absence of spontaneous ventilator activity was noted on the displayed end tidal CO<sub>2</sub> trace. Following a manual inspiration (600ml tidal volume) the “larynx” was manually closed (*appendix 4*). The functional magnetic nerve stimulation was applied. The rise in  $P_{gas}$  triggered the opening of the “larynx”. The study was repeated 5 times in the absence and presence of the “larynx”.

### **Statistical Analysis**

SPSS version 15 was used for the statistical analysis and graphical representation of results. Results were reported as mean +/- 1 standard deviation. Students T test and ANOVA compared the differences between the two groups of artificial cough (with and without the use of a surrogate larynx).

**Results:**

All subjects completed the study. The  $P_{es}$  trace failed to record in one subject. The functional magnetic nerve stimulation produced an elevation in  $P_{gas}$  and  $P_{es}$ . When the larynx was included in the respiratory circuit, the rise in  $P_{gas}$  triggered opening of the valve in all cases. However, the rise in  $P_{gas}$  and  $P_{es}$  was limited when compared with data previously collected from other volunteers performing a voluntary cough (**Figure 81**)(**Figure 82**). Analysis observing the magnitude of the difference for the values measured demonstrates that the addition of the surrogate larynx produces a significant difference in  $P_{es}$  ( $p = 0.03$ ) and flow(**Figure 83**) and time to develop a peak flow ( $p < 0.001$ )(**Figure 84**) but no statistical difference in  $P_{gas}$ . An observation of the boxplot demonstrates that the direction of the difference in  $P_{es}$  and  $P_{gas}$  is similar to that of the peak flow when comparing the two surrogate cough models with and without a surrogate larynx(**Figure 85**).

Cough Type		$P_{es}$	$P_{gas}$	Flow	Time to Peak Flow
Without Larynx	Mean	18.9	26.2	40.9	0.12
	1 SD	9.1	12.8	32.1	0.08
With Larynx	Mean	23.6	27.2	75.0	0.03
	1 SD	12.9	10.5	39.6	0.02
Voluntary Cough	Mean	54.8	44.8	598	0.03
	1 SD	13.9	15.1	137	0.01

**Figure 81. Summary results for study population. The results demonstrate a difference in  $P_{es}$  , flow and time to peak flow when a surrogate cough with a without a larynx are compared. These values are all exceeded when compared with a normal voluntary cough.**

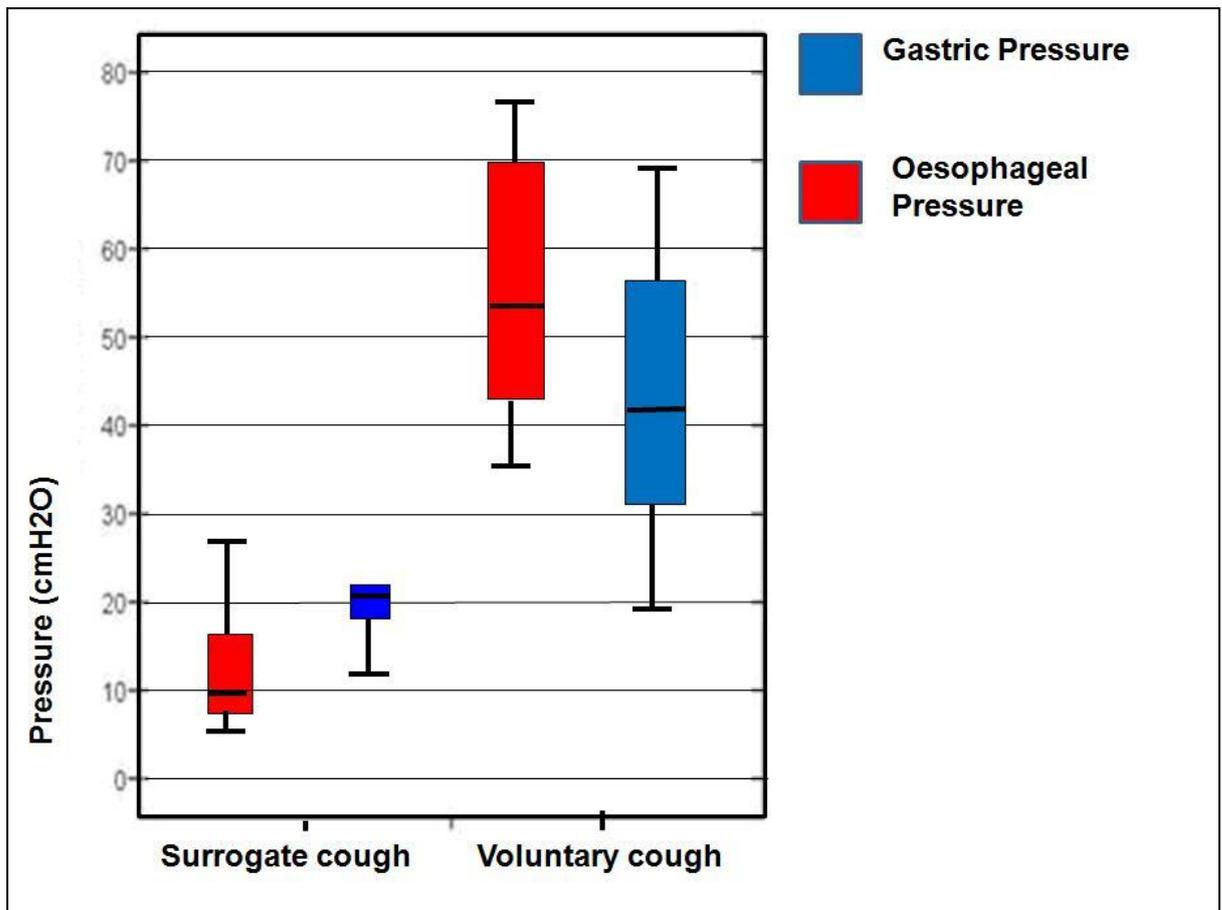
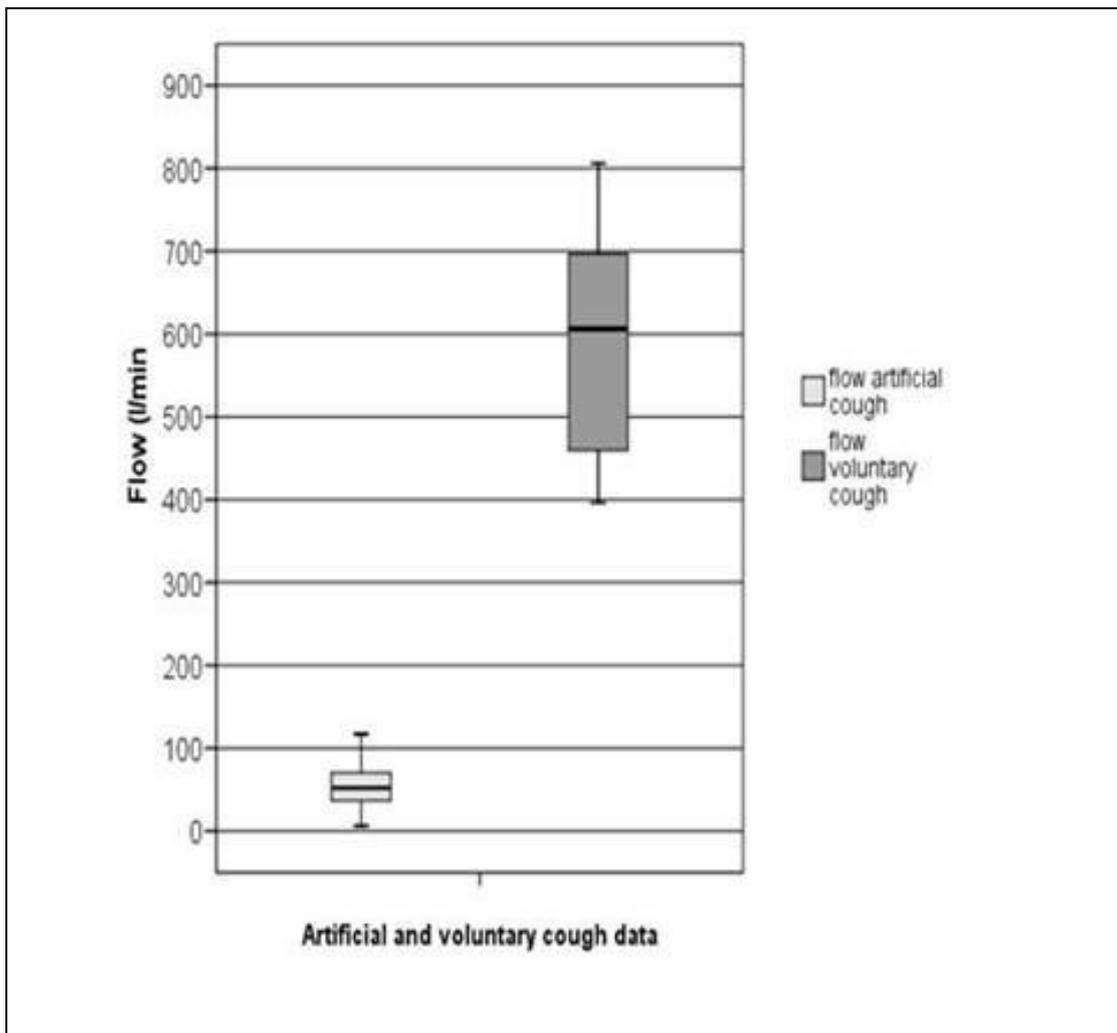


Figure 82. Box Plots demonstrating difference between maximum  $P_{es}$  and  $P_{gas}$  for a surrogate or voluntary cough. There is a difference in both the magnitude and the direction of the pressure differences. The  $P_{es}$  is greater than  $P_{gas}$  in the surrogate cough and this difference is reversed in the surrogate cough.



**Figure 83. Box Plots demonstrating difference in flow between and artificial and voluntary cough. The surrogate peak flow is much reduced compared with a voluntary cough.**

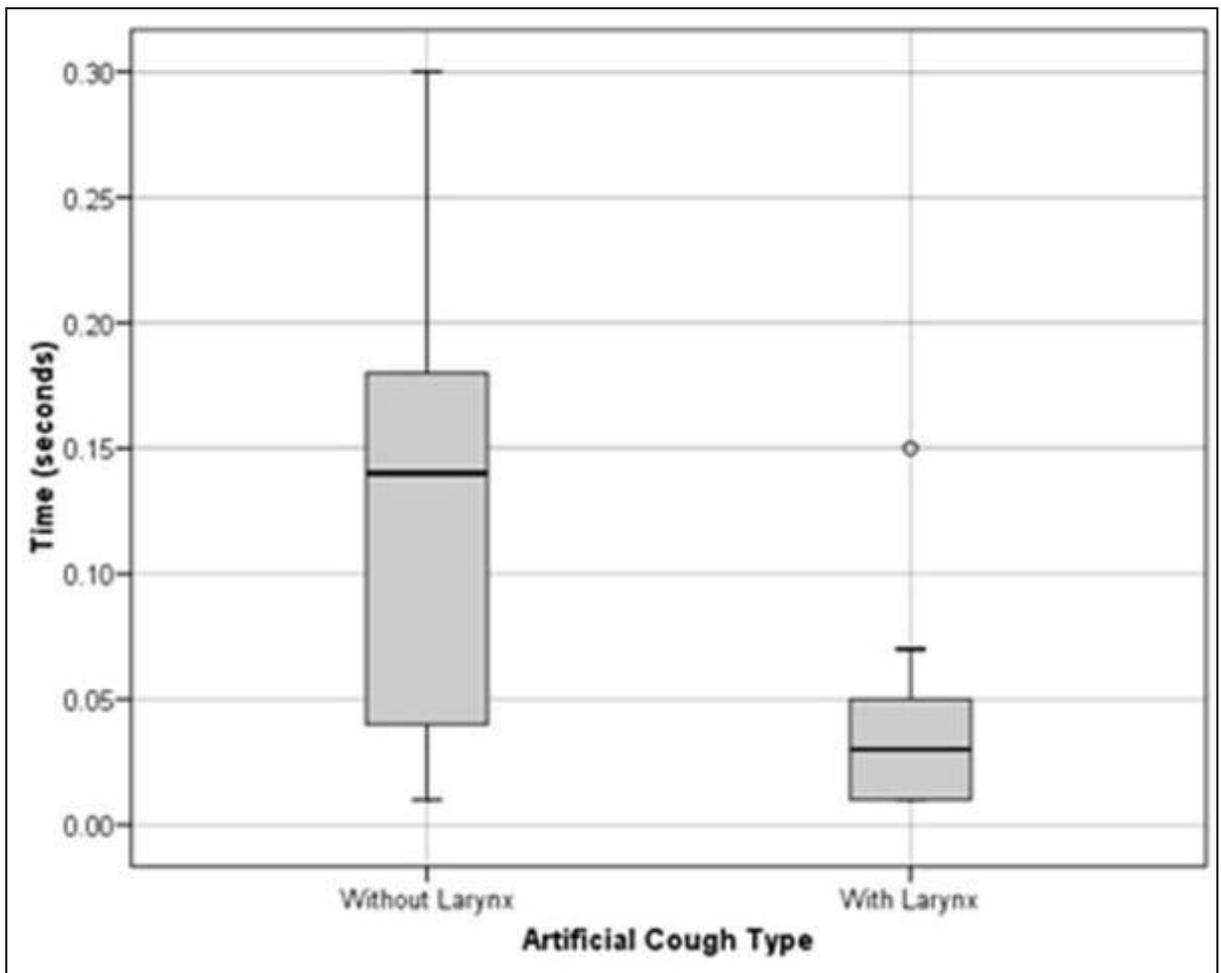


Figure 84. Boxplots demonstrating time to peak flow for a simulated cough with and without a surrogate larynx

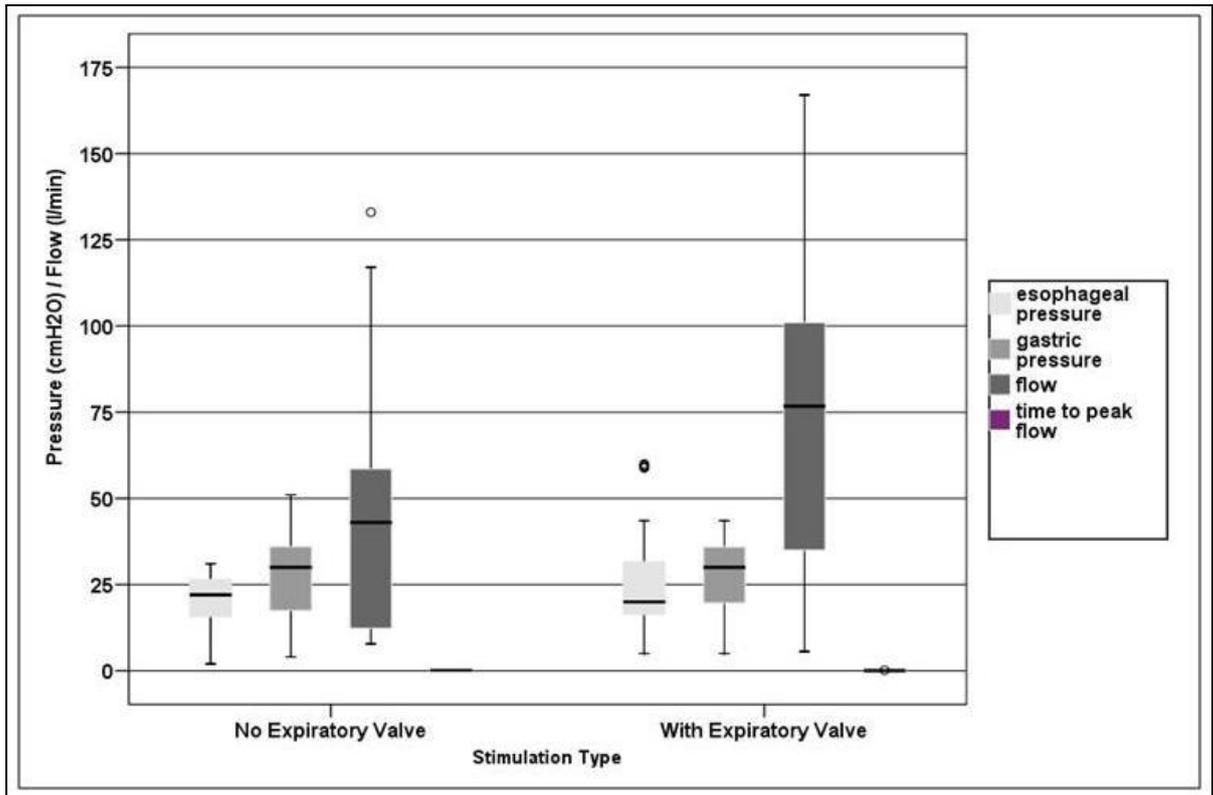


Figure 85. Boxplots demonstrating Pgas, Pes and flow data for simulated cough with and without surrogate larynx

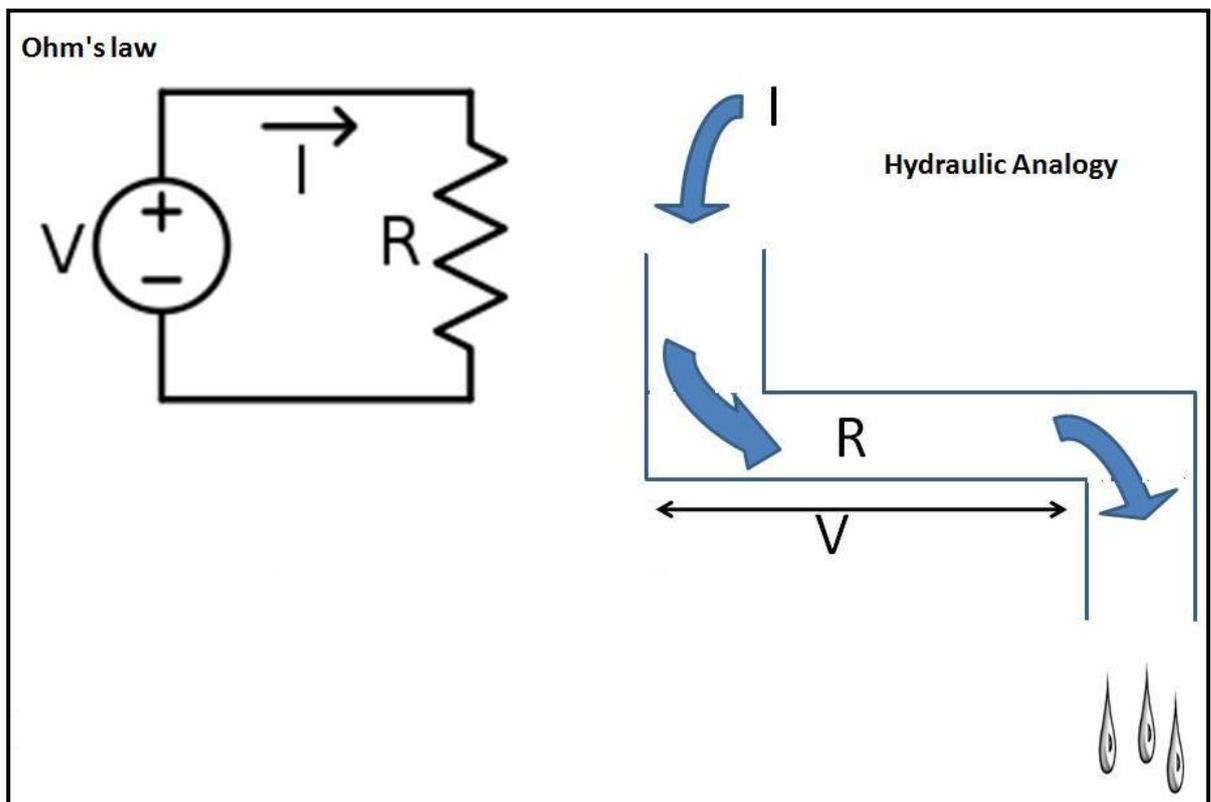
### Discussion:

The original objective of this study was to develop an artificial cough for application in the critical care unit. The paradigm for the development of a surrogate cough was that activation of the abdominal muscles would elevate IAP. IAP elevation would cause a cephalad movement of the diaphragm and a rise in thoracic pressure (Addington et al., 2008). The rapid rise in both IAP and thoracic pressure would support a forced expiratory flow (Man et al., 2003), comparable to a voluntary cough. This paradigm had been applied in previous studies using electrical activation of the abdominal muscles in subjects with spinal cord injury (Stanic et al., 2000, DiMarco et al., 1995), direct anterior electrical surface stimulation of the abdominal muscles (Lee et al., 2008), or magnetic nerve stimulation of the abdominal muscles in normal subjects (Lin et al., 1998c, Kyroussis et al., 1997). Closure of the larynx during the initial expiratory effort is a constant feature of an expiratory effort. The inclusion of a surrogate larynx in this study, allowed observation of the magnitude of its effect upon peak expiratory flow and time to develop peak expiratory flow.

The findings from this study are that magnetic nerve stimulation of the abdominal muscles during anaesthesia fails to realise the abdominal pressure that develops during a voluntary cough. The much reduced rise in abdominal pressure impacts upon the subsequent rise in thoracic pressure through the measured  $P_{es}$ . The consequence of these two limitations is that the expiratory flow developed is not comparable to a voluntary cough as measured in previous studies. However, the inclusion of the surrogate larynx does confirm that temporary closure of the “larynx” reduces the time to develop a peak flow.

The study findings also suggest that this model of a voluntary cough demonstrates that a rise in IAP is not successful at driving a rapid rise in thoracic pressure. This finding is in contrast to the assumptions that lie behind the generation of thoracic pressure elevation. Previous attempts to augment a voluntary cough or develop a surrogate cough models have relied upon the development of a large pressure differential between the large airways and the mouth. A large pressure difference, it is argued, will generate a high expiratory flow. This is the hydraulic analogy of Ohms Law ( $I = V/R$ ) that gas flow is a result of the sum of the pressure difference between

two points and the inverse of the resistance of the channel through which the gas flows(Figure 86). Thus, the objective of physical respiratory therapy techniques is to increase the upstream pressure through intermittent chest compression.



**Figure 86. Comparison of Ohms Law and Hydraulic Analogy applies to electrical circuits and states that the current (i) through a conductor is directly proportional to the potential difference or voltage (v) across the two points and inversely proportional to the resistance (R) between them.**

Commercial cough augmentation devices(Bach, 1993, Homnick, 2007, Winck et al., 2004) increase the differential pressure through both a positive pressure insufflation followed by a rapid reduction in downstream pressure, the exsufflation(Figure 87). The exsufflation may generate an expiratory flow of  $2.7 - 7.5l.sec^{-1}$  (Marchant and Fox, 2002). This compares with a voluntary cough of up to  $20l.sec^{-1}$  (Homnick, 2007).



**Figure 87. The "respironics" cough assist mechanical insufflator-exsufflator.**

However, a voluntary cough involves more complex hydromechanics than can be simply described by Ohms law, and this includes dynamic changes in tube diameter, and the development of an airway pressure in excess of that achieved during a forced expiratory flow manoeuvre. The rapid elevation of intrathoracic pressure that precedes the expiratory component of a voluntary cough will have two effects.

An elevation in intrathoracic pressure will cause dynamic airway compression of the large downstream airways(Hyatt, 1959). As flow is inversely related to the fourth power of the radius of the tube (*Hagen-Poiseuille law*), the expiratory flow will be magnified, when compared with the less vigorous exhalation during a forced expiratory flow manoeuvre.

The rapid acceleration of the gas flow that follows vocal cord opening, generates a large force as demonstrated by Newton's second law of motion(Hyatt, 1959).

Newton's second law of motion describes the relationship between the acceleration of a mass and the force generated. That is  $Force (F) = Mass (m) \times acceleration (a)$ .

A voluntary cough generates a rapid rise in flow, or acceleration over the first 0.03 seconds. Compare this with a forced expiratory flow manoeuvre where the flow reaches a maximum in 0.2 seconds (Abboud et al., 1995).

By the two mechanisms described, a brief supramaximal flow is developed, in excess of that developed during a forced expiratory flow manoeuvre (Hyatt, 1959), expiratory flow is limited as a result of dynamic airway collapse. It is apparent therefore from the preceding discussion that the distinguishing feature of a voluntary cough manoeuvre is that early expiratory laryngeal closure allows the development of *supramaximal* airway pressures that subsequently provides the driving force for the *supramaximal expiratory flow* that is the sine qua non of a voluntary cough. Simulation of a voluntary cough needs therefore to reproduce these two elements:

- **Elevation of intrathoracic pressure**
- **Early expiratory flow obstruction to allow the development of a supramaximal airway pressure and airway compression.**

The abdominal and thoracic muscles appear to demonstrate a mechanical coupling that would allow the elevation in abdominal pressure to drive an elevation in thoracic pressure. This premise has been applied by several previous authors developing a surrogate cough model in both normal volunteers and subjects with a spinal injury.

### **Mechanical Coupling of abdominal and thoracic muscles:**

The premise that abdominal muscle stimulation could generate a rise in intrathoracic pressure needs to be considered in the light of the experimental data.

Changes in abdominal pressure, intrathoracic pressure and thoracic volume will influence the pressure and flow generated during various expiratory manoeuvres. Abdominal and thoracic muscles demonstrate, along with all voluntary muscles, a length tension relationship. That is, an increase in muscle length, beyond a maximum,

will compromise the tension that can be developed with the imposition of a stimulus to muscle contraction. Previous studies have developed this concept with electrical and magnetic nerve stimulation of the abdominal muscles with some success. However, these subjects were awake human volunteers with or without spinal cord injury. We confirmed these previous studies with preliminary observation in awake subjects using a variety of stimulation protocols of both upper and lower thoracic nerve roots. The initial observation was that, abdominal and thoracic pressure elevation had the potential to provide the airway pressure changes necessary to drive a surrogate cough. However, this patient study demonstrated that this is may not be the case, and indeed in the absence of any involuntary responses to abdominal muscle stimulation, abdominal and thoracic pressure elevation is poor.

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## **Chapter 15: Conclusions**

The objective of this thesis was the investigation of the mechanics of a voluntary cough and the development of a surrogate cough with application to the intensive care unit patient.

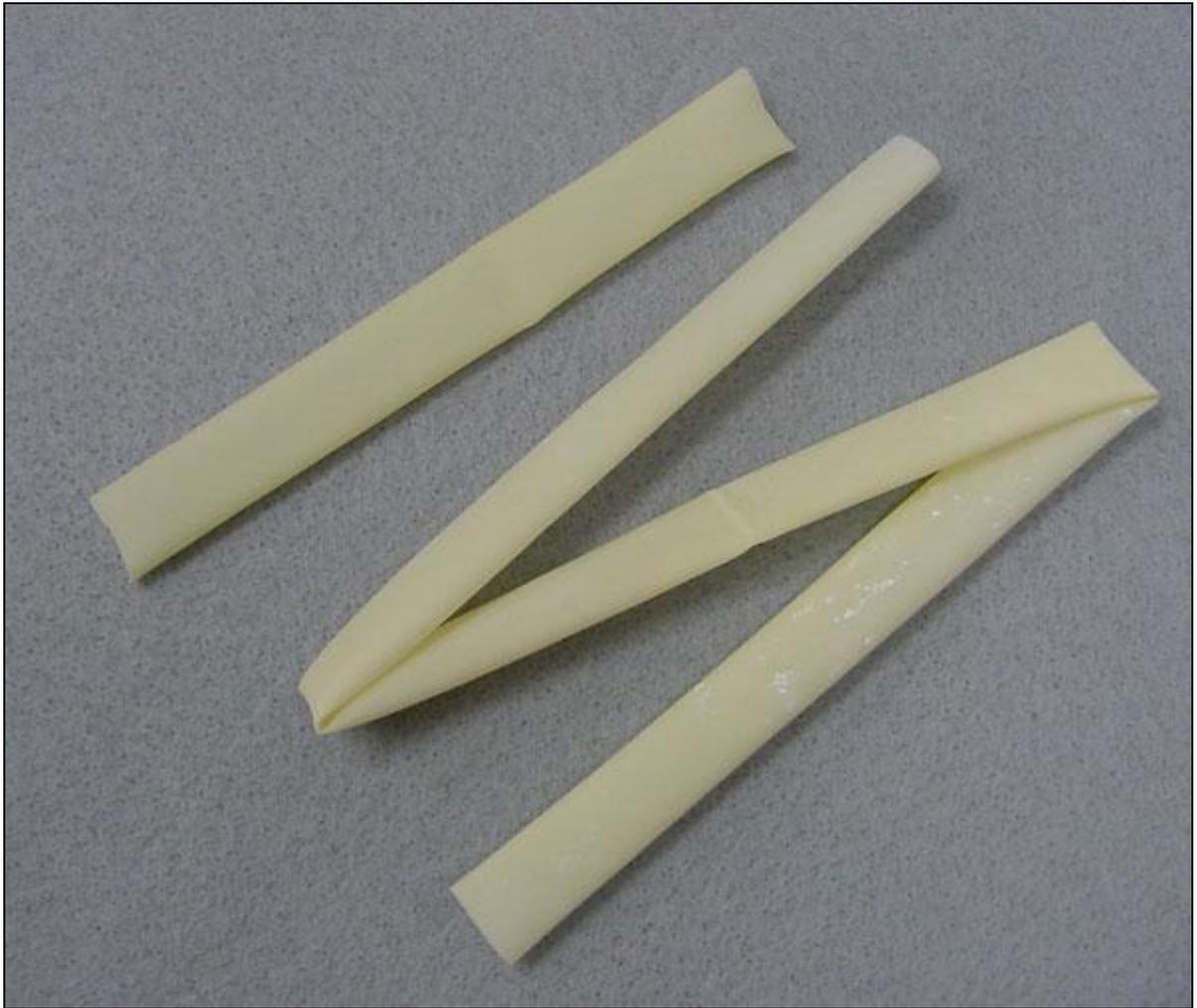
Cough mechanics are incompletely understood, in particular the mechanics that lead to the development of a supramaximal flow, or a flow that exceeds the maximum developed by a forced expiratory flow manoeuvre. Knudson considered that the supramaximal flow spike was a consequence of the emptying of large airways that were compressed by a rise in thoracic pressure during the occluded expiratory phase of a voluntary cough (Knudson et al., 1974, Sala et al., 1996, Sharpey-Schafer, 1953). It has been assumed that expiration against a closed glottis is responsible for the development of the rise in thoracic pressure. The rise in thoracic pressure is in turn responsible for the dynamic large airway compression. Clinical paradigms to support this premise have not been developed. The development and interrogation of a cough model was therefore considered appropriate to inspect the validity of this model.

The Starling resistor<sup>1</sup> is a model widely used for the investigation and observation of airflow along tubes with flexible walls. The model incorporates a flexible walled tube or Penrose (Figure 88) tube<sup>2</sup> contained within a chamber with a fixed pressure. However, the fixed transmural pressure is not comparable to forced expiratory manoeuvres. During forced expiratory manoeuvres, transmural pressure is variable and related to the upstream driving pressure. The downstream larynx will also modify flow mechanics where early laryngeal closure may amplify the upstream pressure developed.

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<sup>1</sup> The **Starling resistor** was invented by English physiologist Ernest Starling and used in an isolated-heart preparation during work which would later lead to the "Frank–Starling law of the heart".

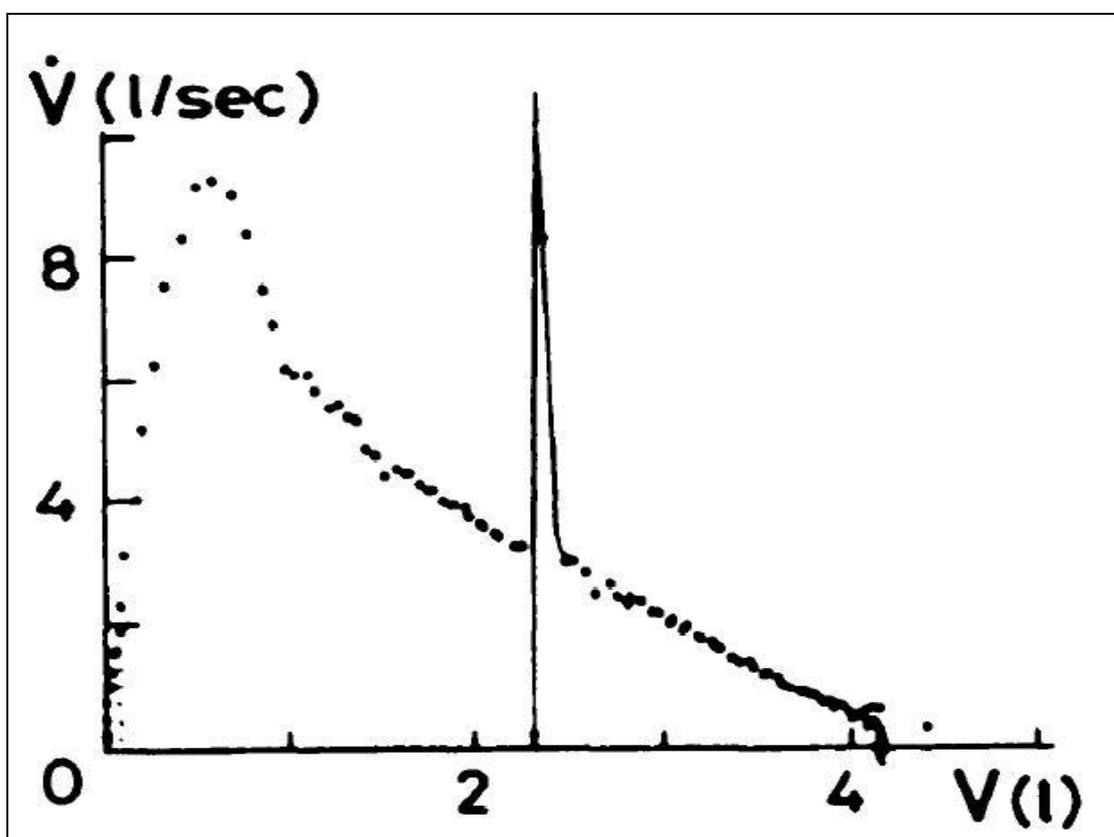
<sup>2</sup> A **Penrose drain** is a surgical device placed in a wound to drain fluid. It consists of a soft rubber tube placed in a wound area, to prevent the build up of fluid. It is named for the American gynecologist Charles Bingham Penrose (1862–1925).



**Figure 88. Soft rubber Penrose drains, named after the American gynaecologist Charles Bingham Penrose.**

Therefore, modifications of the traditional Starling resistor were developed to model the mechanics of forced expiratory and voluntary cough manoeuvres. A variable external pressure within the chamber, related to the upstream driving pressure was added. Secondly, a surrogate larynx was added downstream. The magnitude and direction of these modifications was observed during forced expiratory flow manoeuvres. This model observed that the addition of a surrogate larynx with brief closure during early expiration allowed the development of flows in excess of the maximum observed during a forced expiratory flow. Furthermore, the larynx affected a very rapid rise to the supramaximal flow, or an amplification of the airflow acceleration. This was also observed by Ohya during temporary interruption of a forced

expiratory flow(Ohya et al., 1989)(Figure 89). The objective of a cough is the removal of inhaled foreign material and large airway secretions. The dynamic interaction between the gas flow in the large airways and the downstream movement of fluid lining the airways is dependent upon the velocity of the gas flow, the wall material, the viscosity of the fluid and the Reynolds number. In addition the external compressive force will invaginate the posterior wall and enhance the aerosolization of fluid lining the walls(Coburn, 1972). An increase in velocity and acceleration of airflow will increase the force upon the fluid lining the wall(Grotberg, 2001). Development of a surrogate cough model would need to consider the significance of these effects.



**Figure 89. Flow Time curve demonstrating supramaximal flow spike following brief temporary downstream interruption of airflow during a maximum expiratory effort. From Ohya et al, 1989.**

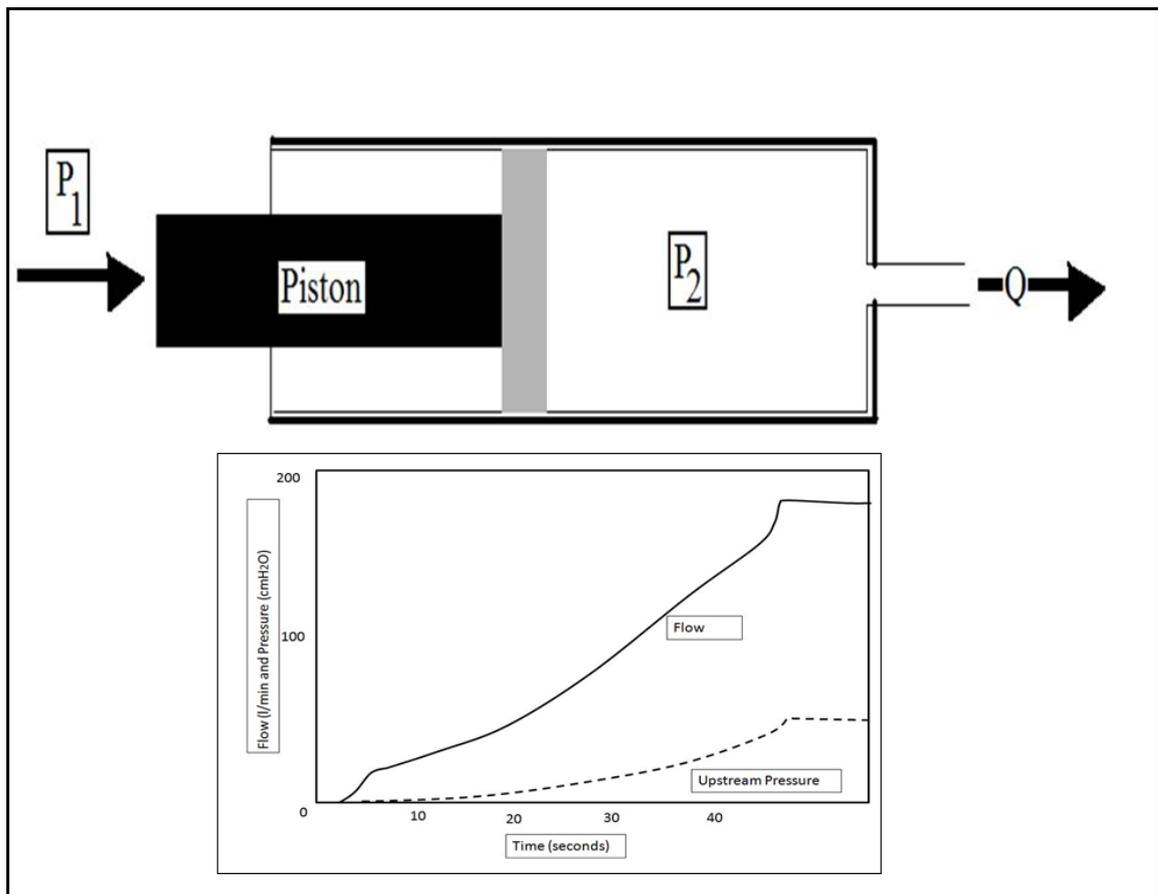
The paradigm that led to the surrogate cough model developed in this thesis, that is stimulation of thoracic nerve roots lead to a contraction of abdominal muscles and an elevation in abdominal pressure, is one that has been considered and investigated by

others (DiMarco et al., 2006, Lin et al., 1984, Kyroussis et al., 1997, Jaeger et al., 1993, Lin et al., 1998a, Polkey et al., 1999, DiMarco et al., 2009a, DiMarco et al., 2009b, Linder, 1993, Spivak et al., 2007, Zupan et al., 1997). This cough paradigm involves some assumptions:

- An elevation in abdominal pressure through contraction of the abdominal muscles will lead to an elevation in abdominal pressure.
- Abdominal pressure elevation can be realised through either surface electrical stimulation, direct spinal cord stimulation or magnetic nerve stimulation of the spinal nerve roots or spinal cord.
- Elevation of abdominal pressure cause cephalad movement of the diaphragm and thoracic pressure elevation, or a surrogate marker such as oesophageal pressure.
- The rapid elevation in thoracic pressure will develop a rapid expiratory flow spike, which will be comparable to that seen in a voluntary cough.

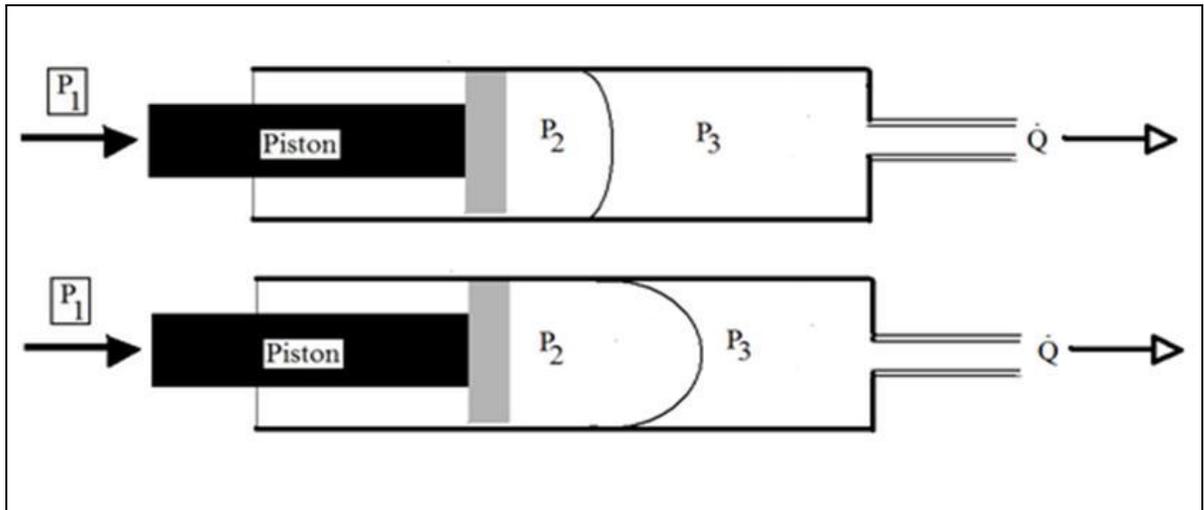
This “*surrogate cough*” paradigm developed proposes elevation of abdominal pressure as the principal driving force that subsequently leads to an elevation in thoracic pressure and the expiratory supramaximal flow spike.

The observation of changes in  $P_{es}$ ,  $P_{gas}$  and  $P_{di}$  in this thesis raises questions about the assumptions of this cough paradigm. Consider the forces contributing to a voluntary cough represented as a piston. A force applied to the piston, generates a rise in pressure within the barrel of the pneumatic pump, driving the air out (**Figure 90**). A change in the force applied to the piston will alter the flow ( $Q$ ). The pressure/ flow plot will be linear, assuming a Newtonian fluid mechanics apply.



**Figure 90. Schematic representation of one compartment surrogate cough model. Flow and Pressure plot demonstrating direct linear relationship (Personal data).**

Modification of the model to include a flexible membrane dividing the chamber into two, better represents the abdominal and thoracic cavities (Figure 91). Because of the realities of fluid mechanics, and the laws of thermodynamics, energy will be lost to move the air from the chamber at  $P_3$ . If the pressure were recorded within the first and second chambers, it would be expected that  $P_2$  would be greater than  $P_3$ . The relationship between the driving pressures  $P_1$ ,  $P_2$  or  $P_3$  and flow ( $Q$ ) would still be linear.



**Figure 91. Schematic diagram illustrating two compartment model for surrogate cough. The piston elevates pressure in compartment (P2) that moves the diaphragm. The subsequent elevation of pressure in the second compartment (P3) generates the expiratory flow (Q).**

Considering this cough model applied to the concept of a voluntary cough. The expiratory muscles of the abdominal wall are represented by the piston driving ( $P_1$ ), expiratory muscle activation will elevate pressure in the abdomen ( $P_2/P_{gas}$ ). A rise in  $P_{gas}$  elevates the diaphragm leading to a rise in pressure in the second compartment ( $P_3/P_{es}$ ). Pressure across the diaphragm ( $P_{2(gas)} - P_{3(es)}$ ) would be positive. An expiratory flow spike is subsequently generated; the rate of rise and the peak flow being related to the force applied, and a pressure/ flow plot would be linear.

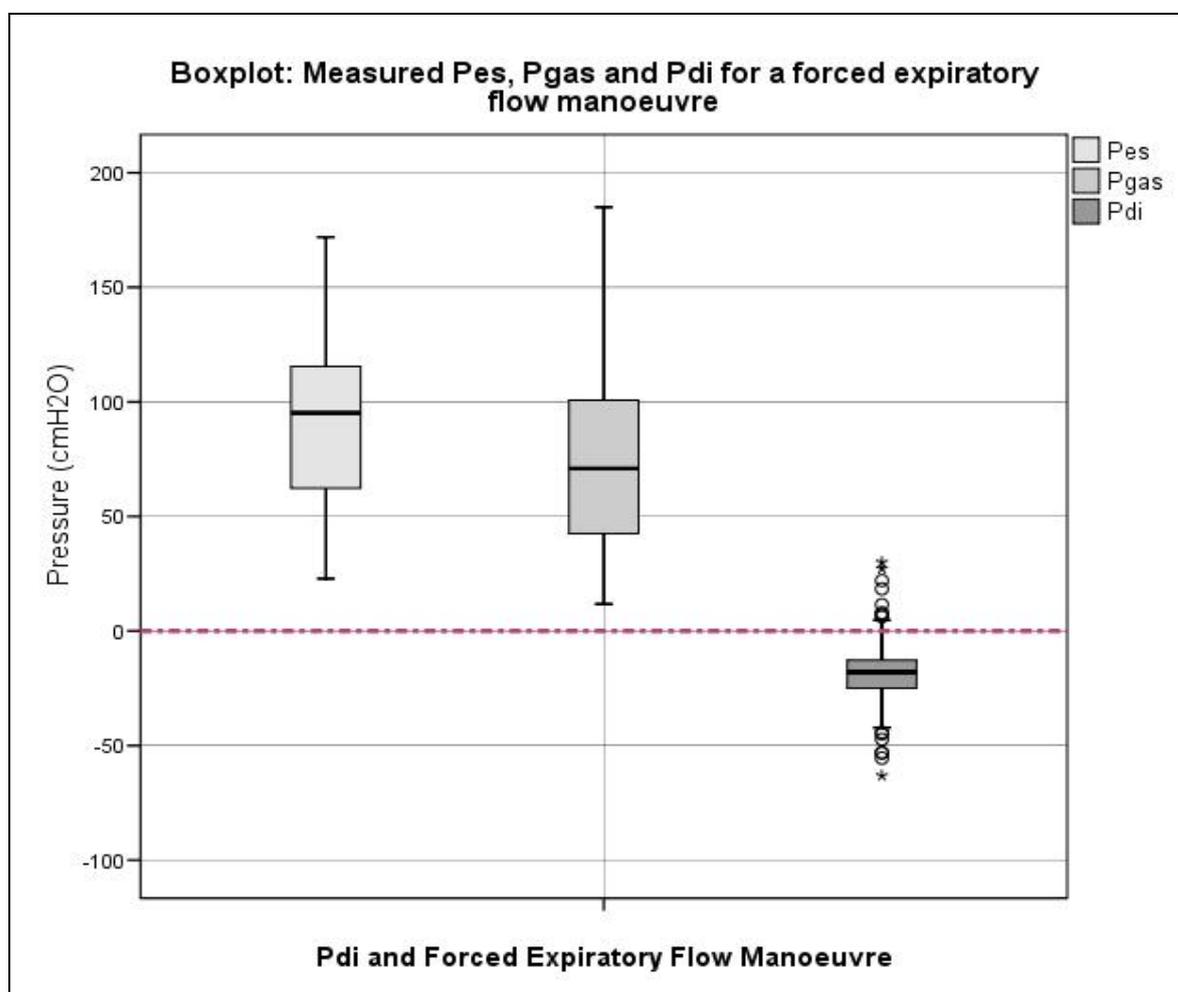
The  $P_{di}$  is the measure of the difference between  $P_{gas}$  and  $P_{es}$ . If the schematic piston model were correct, the  $P_{di}$  would be positive ( $P_{di} = P_{gas} - P_{es}$ ). However,  $P_{di}$  was developed as a measure of diaphragm contractility during inspiration. Is it therefore an appropriate measure applicable to expiratory manoeuvres?

This was considered in chapter 12, “Tension Developed by the Diaphragm during Forced Expiration and Coughing”. During forced expiratory manoeuvres, the  $P_{di}$  will reflect the difference between pleural and abdominal pressure. The diaphragm is not mechanically placed to take part in expiration and tension in the diaphragm would limit the transfer of pressure between the abdomen and chest, as suggested by some authors.

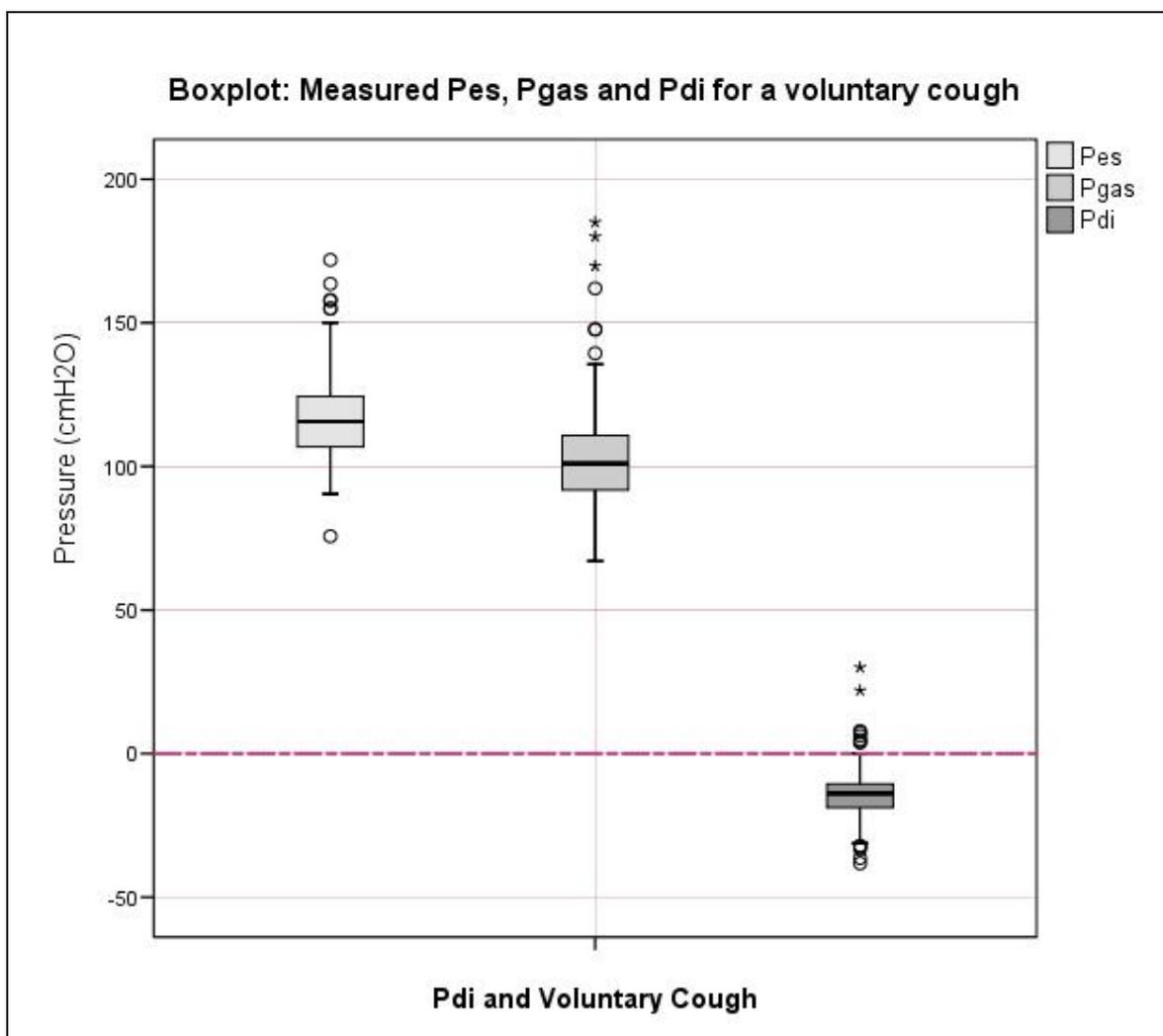
Our observation that pleural pressure exceeds abdominal pressure in some

subjects supports the paradigm that the intercostal muscles may be acting as expiratory muscles.

Further analysis of the data from the peak flow and cough comparison study demonstrates the negative  $P_{di}$  during both forced expiration (Figure 92) and voluntary cough (Figure 93). In addition the pressure/ flow plot is not linear with respect to a voluntary cough in contrast to that of a forced expiratory flow manoeuvre. The implications of these observations are that the schematic piston model is not applicable to a voluntary cough, that is abdominal muscle contraction does not explain all the dynamic observations of a voluntary cough.

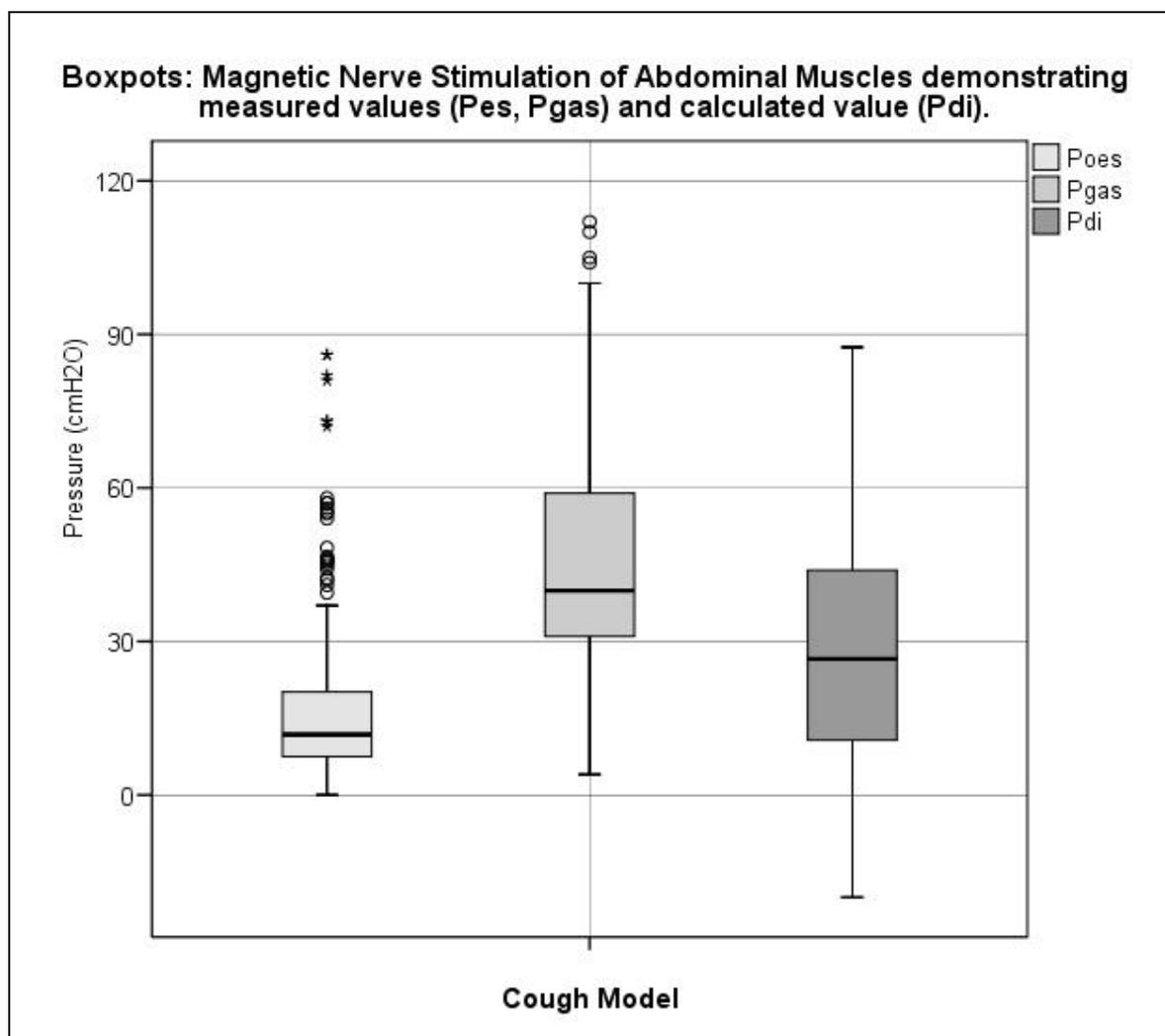


**Figure 92. Boxplots from forced expiratory flow study demonstrating negative Pdi**



**Figure 93. Boxplots from voluntary cough study demonstrating negative Pdi**

The studies do demonstrate a balance between the  $P_{es}$ , and  $P_{gas}$  suggesting that the mechanics generating the rise in  $P_{es}$  are also acting on  $P_{gas}$ , albeit to a lesser extent. In contrast the measured  $P_{di}$  during abdominal muscle magnetic nerve stimulation is positive (Figure 94) reflecting the dominance of abdominal pressure in our surrogate model.



**Figure 94. Box plots from Surrogate (Magnetic Stimulation) cough demonstrating weakly positive  $P_{di}$**

Are these observations reproduced in other clinical trials? Kyroussis(Kyroussis et al., 1997) in a trial on awake volunteers, described  $P_{gas}$  changes following thoracic magnetic nerve stimulation of about 80cmH<sub>2</sub>O with a subsequent peak flow of about 200 – 300l/min. Zupan(Zupan et al., 1997) observed the effect of surface electrical stimulation of abdominal muscles in 13 tetraplegic subjects but did not measure the dynamics of the model, but focused on the improvement in respiratory function. Lim(Lim et al., 2007) studied electrical surface and magnetic nerve stimulation of abdominal muscles in healthy volunteers. The  $P_{es}$  of the former was about 10cmH<sub>2</sub>O and  $P_{gas}$  about 30cmH<sub>2</sub>O. Lim also noted that the  $P_{di}$  was positive.

The absence of the combined measurement of  $P_{es}$  and  $P_{gas}$  with the simultaneous calculation of  $P_{di}$  in many studies of a surrogate cough limits the ability to relate voluntary cough dynamics with the surrogate models. In the absence of robust physiological data for a surrogate cough is there sufficient evidence to support the continued investigation of abdominal muscle stimulation.

This study suggests that magnetic nerve stimulation of the abdominal muscles in anaesthetized subjects appears to be unable to reproduce the elevation in  $P_{es}$  observed with a voluntary cough. This in part explains the small expiratory flow generated. The impact of anaesthesia upon the magnitude of the force developed may in part explain these observations. The negative impact of anaesthesia has been previously observed in studies of phrenic nerve stimulation(Zhang et al., 2009).

However, other authors have continued to develop the surrogate cough model in normal and tetraplegic subjects(DiMarco et al., 2009a, DiMarco et al., 2009b, Lim et al., 2007). DiMarco reported the effect of electrical nerve stimulation in 9 tetraplegic subjects(DiMarco et al., 2009a, DiMarco et al., 2009b). Electrical stimulators were implanted at three sites (T9, T11 and L1). Implanted electrodes are able to stimulate two nerve roots above and below the site of implantation. The combined stimulation of three electrodes would therefore achieve nerve root activation from T7 – L3. A biphasic stimulus of variable pulse width, with variable amplitude, frequency and pulse width was observed. The stimulator was used for 30 seconds to 10 minutes, and up to 3 times per day and activated by either a carer or the subject. Activation of 2 or 3 electrodes, at either site, generated a peak expiratory flow exceeding 600 l/min and an airway pressure exceeding 200cmH<sub>2</sub>O in some subjects. Following testing the stimulation setting was adjusted to achieve a maximum flow and pressure. Objective follow up of respiratory symptoms demonstrated a significant reduction in problems related to airway secretion retention and a reduced incidence of respiratory tract infections.

Stanic(Stanic et al., 2000) observed the effect of surface electrical stimulation upon 6 normal subjects, and 6 tetraplegic subjects. Stanic only measured the tidal volume following stimulation, but found a significant increase in tidal volume and total

ventilation in both the normal subjects and those with spinal cord injury. No other measures of respiratory dynamics or pressures were made, so these cannot be assessed.

Lin(Lin et al., 1998b) observed the effect of magnetic nerve stimulation on  $P_{\text{mouth}}$  and expiratory reserve volume (ERV), in 12 normal volunteers. Lin concluded that functional magnetic nerve stimulation of the abdominal muscles is able to generate pressure equal or greater than voluntary Maximum Expiratory Pressure (MEP) and that there is a significant change in ERV. Again,  $P_{\text{gas}}$ ,  $P_{\text{es}}$  and flow were not measured and so there was no assessment or judgment of the dynamics of magnetic nerve stimulation. The flow – time curves reported, were of insufficient detail to allow determination of the flow pattern. However, previous experience suggests that a forced expiration where the glottis is open throughout is unlikely to achieve the velocity and acceleration seen during a voluntary cough.

As few studies have measured  $P_{\text{es}}$ ,  $P_{\text{gas}}$ ,  $P_{\text{di}}$ , peak flow and time to peak flow a comparison with the dynamics of a voluntary cough is not possible. Nevertheless, the evidence supporting the efficacy of abdominal muscle stimulation provided by DiMarco, in subjects with spinal cord injury is compelling(DiMarco et al., 2006, DiMarco et al., 2009b). Direct electrical nerve stimulation of the abdominal muscles reduced the number of respiratory complications. In the absence of early, brief closure of a downstream expiratory valve, DiMarco and others have not reproduced the dynamics of a voluntary cough. Rather, the expiratory muscle activation described by these authors is best described as a “*huff*”, a respiratory physical therapy technique applied to the management of subjects with cystic fibrosis, chronic airflow limitation(Badr et al., 2002) and other chronic respiratory diseases. A huff is akin to a forced expiratory flow maneuver, where the glottis remain open throughout the expiratory phase(Fink, 2007), and though it is not a cough, there is evidence that it is an effective method to remove large airway secretions and reduce respiratory complications in spinal injury patients? Unfortunately, implanted spinal cord electrodes are not a practical model to apply to the critical care patient.

Electrical activation of the abdominal muscles has demonstrated that a surrogate cough need not reflect all elements of a voluntary cough to be effective. Therefore,

considering the critical care patient, are their elements of a voluntary cough that could have practical application to the development of a surrogate cough.

### Voluntary Cough and the Larynx

A common feature of surrogate cough models and respiratory physical therapeutic manoeuvres designed to enable removal of respiratory secretions is an absence of a surrogate larynx. Comprehensive reviews of the role of the larynx in a voluntary cough (Sant'Ambrogio, 1996, Bartlett, 1989) do not consider the mechanics of the larynx or the effect of a variable downstream orifice upon airflow in the large airways. However, this study data suggests that the larynx is likely to contribute to the removal of large airway secretions?

A review of comparative physiology can often illuminate biological conundrums, and in the case of the larynx it can aid in an understanding of the original design and function (Bartlett, 1989). Though a comprehensive review of the larynx across species is beyond the focus of the thesis; it is notable that the larynx may control respiration in some species. For example, inspiration in amphibians and lung fish is achieved through forcing air from the mouth through the larynx and subsequently closing the glottis to prevent air leak. Expiration is achieved through opening the glottis and allowing the lungs to empty. This "*oral force pump method*" of inspiration is limited by the volume of the oral cavity, but the advantage to the diving reptile is they can remain under water for prolonged periods. Laryngeal adaptation in mammals allowed continuous tidal breathing and the larynx providing protection against aspiration and regulates the resistance to airflow during inspiration and expiration. The regulatory respiratory role of the larynx therefore precedes the role of phonation achieved in higher mammals (Bartlett, 1989). The larynx therefore developed as an organ supporting expiration which may also contribute to the fluid mechanics that support airway secretion clearance during a voluntary cough. Would a surrogate larynx also contribute to the effectiveness of a surrogate cough?

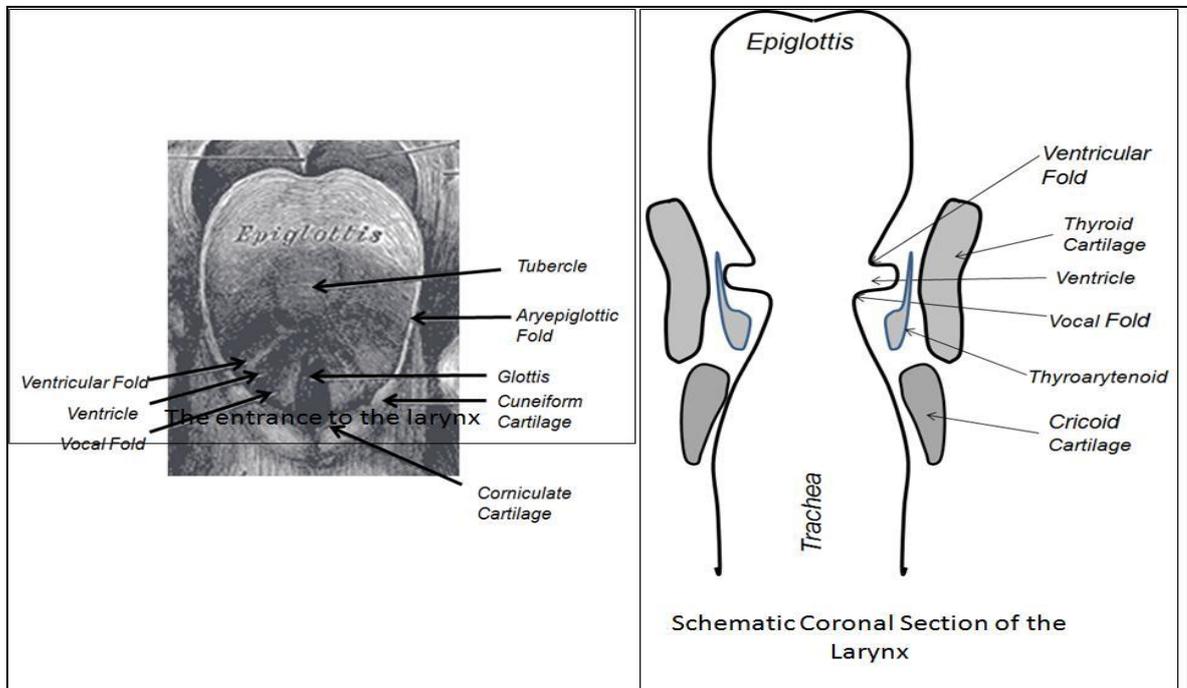
The studies presented, observed the effect of a surrogate larynx upon forced expiratory flow along a flexible tube (*a modified Starling resistor*). The observations concluded that early laryngeal closure leads to an elevation in upstream pressure with an increase in peak flow and a much reduced time to develop peak flow (Suleman et al., 2004) or an enhanced cough acceleration. As discussed, Newton's Second law, ( $F = m \times A$ ) the implication is that the enhanced acceleration creates a mechanical advantage to upper airway clearance of secretions. It is expected cough performance in the absence of a larynx or a dysfunctional larynx will be compromised. Does the literature support this assertion?

Murty (Murty et al., 1991) observed the cough intensity in subjects following a laryngectomy, and though he observed there was a decrease in the time to achieve a peak cough flow, the peak flow achieved was comparable to that achieved by normal subjects with a larynx. He concluded that laryngeal closure is not essential for cough function.

Fontana observe coughing in laryngectomised patients (Fontana et al., 1999). He recorded abdominal EMG activity, peak flow and time to peak flow in both reflex coughing and coughing in response to inhaled fog. Fontana observed a reduction in peak flow compared with a control group, a reduction in the time to achieve peak flow, and a reduction in the intensity of abdominal muscle activation. Fontana speculated that the reason for the reduction in time to peak flow was a consequence of the open stoma prevented compression of air during the normal compressive phase of a voluntary cough. Isometric contraction during the compressive phase places the expiratory muscles at a mechanical advantage in subjects with a functioning larynx. This compares with those where the larynx is absent where muscle shortening occurs during the "compressive phase". Fontana concluded that laryngectomy may lessen cough efficiency and contribute to the development or sustainability of chest infections (Fontana et al., 1999, Chellini et al.).

Laryngeal opening during the expulsive phase is not an all or nothing phenomena and there is a control of the laryngeal inlet size (Yanagihara et al., 1966, Green and Howell, 1959) (Figure 95). The potential implication of the larynx providing a variable

orifice during the expulsive phase of a voluntary cough, is the promotion of an increase in airflow velocity(Woodson, 1996) through a narrowed orifice.



**Figure 95. Coronal Section of larynx demonstrates tapering outline of the trachea as it approached the glottis. The glottis is a variable orifice entrance to the larynx. The larynx may be able to alter airflow dynamics through variations in the glottic aperture**

Though not considered by previous authors, consideration also needs to be given to the shape of the larynx. The larynx is not a straight sided cylinder interrupted by an occlusion valve. Rather, it is a gradually tapering orifice, interrupted by a variable orifice valve. This design will impact upon the fluid dynamics, particularly the supramaximal flows associated with a voluntary cough. In addition we observed that a tapering connector at the distal end of the modified Staring Resistor limited the tube wall vibrations associated with flow limitation.

The reduction in time to achieve peak cough flow has been previously observed(Yanagihara et al., 1966). Therefore, although the impact of a laryngectomy will compromise those aspects of flow described by Fontana above and in addition:

- The absence of a variable orifice reduces cough flow velocity.
- The removal of the tapered larynx may compromise flow dynamics and increase tube wall vibration.

Therefore it is likely that the voluntary cough achieved by the laryngectomee, when compared with a normal individual, will be less effective. Effective mucus expectoration could be achieved through an increase in the frequency of coughing (Ackerstaff et al., 1995), and this was reported by our volunteers in the study of cough flow dynamics following a laryngectomee.

These studies therefore support the inclusion of a surrogate larynx in the development of a surrogate cough model.

### **Surrogate Cough Modelling**

Electrical and Magnetic nerve stimulation have been demonstrated to develop an increase in abdominal pressure that can elevate thoracic pressure and create an expiratory flow spike. DiMarco (DiMarco et al., 2006) has demonstrated that this surrogate cough model is able to improve airway toilet, and reduce respiratory tract infections in subjects with cervical spine cord injury.

These studies are at odds with our observations in anaesthetised subjects where abdominal muscle activation was unable to elevate abdominal pressure or generate significant expiratory flow. The conclusion may be that either

1. There was a flaw in our study design.
2. Magnetic nerve stimulation in awake subjects, with and without spinal cord damage elicits involuntary reflexes that promote a rise in abdominal pressure.
3. Electrical nerve stimulation through implanted epidural electrodes is better able to activate the abdominal expiratory muscles.

However, even were direct electrical magnetic nerve stimulation able to provide an adequate surrogate “cough”, are the abdominal muscles the principal expiratory muscles during tidal forced expiratory manoeuvres. If this were not the case, is there

evidence to support the development of a stimulation protocol of the upper thoracic nerve roots

During tidal breathing it is assumed that expiration is achieved through relaxation of the thoracic and abdominal muscles, allowing the rib cage to relax back to its resting position (Kenyon et al., 1997). The abdominal muscles (*Transversus Abdominus*, *internal oblique*, *external oblique* and *rectus Abdominus*) assist expiration through compression of the abdominal contents, cephalad displacement of the diaphragm, and a reduction in thoracic volume. *Transversus Abdominus* is the dominant expiratory muscle at rest. The fibres of *Transversus Abdominus* extend circumferentially around the abdomen, and are able to constrict the abdominal contents, more effectively than the other abdominal muscles.

A regional variation in the activation of the four abdominal muscles, during expiratory manoeuvres, has been described (Strohl et al., 1981, Bolser et al., 2000b, Misuri et al., 1997). During active expiration and coughing, *Transversus Abdominus* (TA) activity is dominant. TA has its origin along the inner surface of costal cartilage of the lower six ribs and is innervated by nerve roots with their origin at T7 – T11. The bulk of TA is in the upper abdomen, with a thinner aponeurosis in the lower abdomen. Contraction of TA will develop force along the direction of its fibres that is from the central linea semilunaris to the iliac crest. The role of the external oblique (EO), internal oblique (IO) and Rectus Abdominus (RA) appear to have a lesser role in expiratory activity and serve to support the torso during lifting. During forced expiratory activity there is thickening and shortening of the TA, whereas there is no thickening or shortening of the RA or EO (Misuri et al., 1997). There is a close relationship between the rise in abdominal pressure ( $P_{gas}$ ) and the increase in thickness of TA. Furthermore the velocity of TA shortening during coughing is 5 fold greater during forced expiratory efforts when compared with breathing at rest. However, the mean length of muscle shortening developed was comparable (van Lunteren et al., 1991).

During tidal breathing, there is ventral displacement of the upper abdomen (De Groote et al., 1997). This would imply that expiration would lead to a dorsal displacement of the abdomen. Again the fibre orientation of TA makes it a likely candidate for this displacement.

So far the literature implicates the abdominal muscles in expiratory activity, but the influence of the abdominal muscles is more complex than has been suggested by reports supporting abdominal muscle stimulation. Given the complexity of abdominal muscle activity during expiratory respiratory manoeuvres, it is likely that the role of the intercostal muscles is similarly complex.

The observations reported in this thesis of voluntary cough mechanics, implies that recruitment of intercostal muscles may be essential to the generation of supramaximal expiratory flow. However, the recruitment of chest wall muscles to support expiratory function has proven difficult with magnetic nerve stimulation. Is this apparent contradiction explicable upon review of the action of the intercostal muscles?

The intercostal muscles are generally regarded as being inspiratory(De Troyer and Estenne, 1988). However, the mechanics of the chest wall and the inspiratory muscles are complex and depend upon the orientation of the ribs and recruitment of the intercostals muscles(De Troyer et al., 2005). The intercostals muscles form two incomplete, thin layers that span the intercostal spaces. In addition, there are two smaller muscles *levator costae* and *triangularis sterni*. The former is a thin muscle that fans out from the transverse process and inserts into the caudal rib below. The latter lies ventrally and spans from the sternum inserting into the inner surface of the 3<sup>rd</sup> to 7<sup>th</sup> ribs ventrally.

The mechanical effect of the individual intercostals muscles demonstrates a topographic distribution from caudad to cephalad and dorsal to ventral(Taylor, 1960). Muscles with the greatest mechanical advantage are preferentially activated during the respiratory cycle(Gandevia et al., 2006). Further the individual muscle groups cannot be ascribed an inspiratory or expiratory action; rather their action upon the rib cage needs to be considered in relation to the orientation of the rib cage. Neither the internal intercostals, nor external intercostals can be considered to be purely inspiratory or expiratory. The activation of the intercostal muscles is coordinated to deliver the optimum mechanical advantage for the lowest energy expenditure(Legrand et al., 1996, De Troyer and Wilson, 2000, Gandevia et al., 2006).

This complex topographic arrangement of inspiratory and expiratory muscles is supplied by the intercostal nerves. The neural drive coordinating the activity of intercostal muscles to gain the most mechanical advantage is dependent upon the respiratory cycle and the spatial orientation of the rib cage (Hodges et al., 1997). The intercostal muscles with the largest mechanical advantage are preferentially activated during breathing at rest and activity. The selective neural drive even extends to selective activation of muscles within the same group (Iscoe, 1998). The preferential activation of intercostal muscles during explosive expiratory efforts is also described. It is clear that stimulation of the spinal cord above T7 would not provide the normal stimulation subtleties developed by normal subject. However, all the abdominal muscles support expiration, though selective individual abdominal muscle recruitment is observed. Therefore, spinal cord stimulation below T7, is likely to recruit the abdominal muscles and support an expulsive effort, albeit, less effective than would be the case with recruitment of the chest wall muscles.

### **The Diaphragm and Forced Expiratory Effort**

The diaphragm is clearly an inspiratory muscle. However, the diaphragm is recruited during non-respiratory activities where large swings in abdominal pressures develop (Al-Bilbeisi and Mc, 2000, DePalo et al., 2004). These manoeuvres include weight lifting and sit-ups, where the glottis is closed during the effort, limiting transmission of abdominal pressure to the thorax and stabilising the spine during lifting efforts (Gandevia and McKenzie, 1985, DePalo et al., 2004, Tomori and Widdicombe, 1969). These reports demonstrate a mean abdominal pressure of 210 cmH<sub>2</sub>O. The rise in oesophageal pressure is not though matched by a comparable rise in oesophageal pressure (DePalo et al., 2004). This may suggest the diaphragm is limiting large pressure swings in the abdomen perhaps to limit adverse hemodynamic changes associated with large thoracic pressure swings (Fontana and Lavorini, 2006). Thoracic pressure swings are exaggerated where the diaphragm is paralysed and is less so if the glottis remains open during the expulsive effort (Bolser et al., 2000b). Compromise of the cough effort is demonstrable where diaphragm paralysis is demonstrated.

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## **Conclusion**

These studies have modelled the mechanics of a voluntary cough and observed

- The mechanics of a forced flow manoeuvre are not comparable to the mechanics of a voluntary cough.
- The larynx has a significant role in the development of an environment that supports the forced expulsion of air from the large airways.
- The intercostal muscles play a significant role in the development of a pleural pressure rise.
- The stimulation of the abdominal muscles through surface magnetic nerve stimulation does not reproduce the mechanics of a voluntary cough, but does generate a weak expiratory flow.
- The combination of a surrogate larynx to the cough model improves the flow dynamics with an reduced time to generate a peak flow.
- The measurement of Pdi during forced expulsive manoeuvres may not reflect activity within the diaphragm and should be viewed with caution.
- Further development of the surrogate cough model could consider more pragmatic models to generate high peak flows.

## Appendices

### Appendix 1: Physiological Data for normal recruits

A total of thirteen subjects (6 female/ 7 male) were recruited for the physiological studies. All subjects were from the department of anaesthetics and the university department of anaesthetic and surgical sciences and were familiar with respiratory function tests. None had a history of respiratory or neurological disease that may compromise data interpretation or performance during the studies. The subjects recruited for each study are indicated in table 2.

**Table 1: Physiological Indices for study recruits.**

Data is given as mean ( $\pm 1$  SD).

Age	Weight (kg)	Height (m)	BMI	PEFR (l/min)
40.0 (10.8)	70.2 (14.2)	1.7 (0.1)	25.5 (3.8)	508.6 (159)

**Table 2: Summary of Study Participants - demographics and respiratory function tests**

Subject	Gender	Age	Weight	Height	BMI	PEFR	FEV1	FVC
1	♀	55	55	1.6	21.5	365	2.6	3.4
2	♀	39	75	1.7	26.0	264	2.5	3.2
3	♀	56	68	1.7	23.5	673	4.1	5.3
4	♀	38	73	1.7	25.3	692	4.3	5.5
5	♀	46	110	1.8	34.0	747	3.5	4.5
6	♀	38	60	1.6	23.4	432	2.5	3.2
7	♀	29	70	1.7	25.7	300	4.1	5.3
8	♀	60	80	1.6	31.3	460	2.7	3.5
9	♀	32	60	1.7	20.8	356	3.2	4.1
10	♀	30	70	1.7	24.2	560	4.2	5.4
11	♀	31	72	1.6	28.1	657	4.0	5.2
12	♀	32	64	1.6	25.0	575	3.1	4.0
13	♀	34	55	1.6	21.5	531	2.9	3.7

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