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to

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Respiratory Muscle Strength and Ventilatory Failure in Neuromuscular Diseases – Myotonic Dystrophy and Motor Neurone Disease

From Research Conducted in the Department of Respiratory Medicine

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ABSTRACT

This thesis has explored the use of pulmonary function tests, sleep studies, volitional and nonvolitional respiratory muscle strength assessment techniques in the evaluation of patients with neuromuscular diseases. I have particularly concentrated on patients with myotonic dystrophy and motor neurone disease, which comprised the largest group of patients apart from Duchenne muscular dystrophy, referred for assessment to Glasgow Respiratory units with expertise in non-invasive ventilation.

In a group of 20 myotonic dystrophy (MyD) and 5 subjects with MND, I went on to establish that spirometry remains a useful basic tool. Supplemented with mouth pressures, we can derive useful information regarding global respiratory muscle strength. Additional routine evaluation of static lung volumes and diffusion capacity did not add in useful information that would be useful in routine clinical care.

It is well known that sleep worsens respiratory failure. The use of screening sleep studies in assessing patients with neuromuscular diseases remains debatable. 25 subjects with MyD and 12 with MND were studied. Routine sleep studies did not seem to add any useful information that could not be predicted from the daytime pulmonary function tests apart from 12% of MyD patients where it was useful in identifying nocturnal respiratory disturbance.

However it is debatable whether treating these abnormalities affects prognosis in the long term.

There has been significant contribution to our understanding of respiratory muscle strength in various circumstances such as in children and intensive care setting with the introduction of magnetic phrenic nerve stimulation technique. After establishing the methodology at the laboratory, in a group of 10 patients with myotonic dystrophy, we found this to be useful in providing nonvolitional diaphragm strength. It would be immensely useful in this group as mouth pressures are frequently reduced due to facial muscle weakness. We showed that underestimation of respiratory muscle strength using volitional methods is common in MyD [Mean (sd) Sniff Pdi of 67.1(30.7)cm H_2O vs bilateral Tw Pdi of 17.1(9.4) cm H_2O]. BAMPS was also a useful daytime marker of nocturnal respiratory disturbances and low Tw Pdi identified 75% (3 out of 4) subjects with sleep related breathing disorder during daytime. Repeat volitional and nonvolitional tests 4-6 months' apart confirmed stable respiratory muscle strength.

Lastly, I studied patients with motor neurone disease. This group had severe respiratory muscle weakness even at the outset with marked symptoms. Non-invasive ventilation improved symptoms in its users. Interestingly, we found that the inspiratory and expiratory positive airway pressures required for these patients were significantly lower compared to patients with hypoventilation due to obesity and post-polio syndromes.

ACKNOWLEDGEMENTS

I would like to begin by thanking all the patients and volunteers who gave up their valuable time for my studies even though to many it was of no direct benefit. I am indebted to my supervisor Dr Kanti Patel for providing me with such a great opportunity and for his guidance, kindness and enthusiasm throughout the two and half years of research. I am grateful especially for his initial guidance on the framework of projects and for his constant encouragement during a difficult task of setting up the Respiratory Muscle Laboratory at Gartnavel General Hospital. I would like to thank Prof Neil Thomson for his guidance and being a constant source of encouragement within the Department of Respiratory Medicine. I am particularly grateful to Dr Steve Banham for his support even after I left Glasgow, his moral support and the helpful hints to aid my thoughts and discussions.

My most gratitude should go to Dr Mike Polkey at Royal Brompton Hospital, London for making an arduous task of setting up a laboratory from scratch seem easy. His inspiration, clarity of thoughts and zest for knowledge has influenced me greatly even in his physical absence at Glasgow and will remain with me for life. My sincere thanks to the Research Fellows at Royal Brompton Hospital especially to Annabel Nickol, Ewen Ross, Nick Hopkinson, Mark Dayer and Nick Hart for being at the other end of the phone line or email no matter what time of the day it was to sort all my obstacles during initial days of the lab work.

I would like to thank Dr Alison Wilcox, Dr Douglas Wilcox and Dr Richard Petty for supporting my projects and reviewing drafts of results and presentations. My sincere gratitude to Donald Smith at Southern General Hospital, Ian Tullis at Strathclyde University and David Gaffney at Gartnavel

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Lastly I would like to thank Mrs Jess Peter for creating the perfect atmosphere to work and I am particularly grateful for her kindness throughout my stay in Glasgow. As ever, I would like to thank my family once again for supporting me through another walk of life.

DECLARATION

I am the sole author of this thesis and I have personally consulted all the references that I have included. I undertook the work in the Department of Respiratory Medicine at Gartnavel General Hospital, Glasgow, under the supervision of Dr K R Patel.

This thesis has not been submitted to a higher degree previously.

LIST OF ABBREVIATIONS

A-P	Antero posterior
ATPS	Ambient temperature and pressure, saturated with water vapour
BAMPS	Bilateral Anterior Magnetic Phrenic Nerve Stimulation
BMI	Body mass index expressed as kg/m^2
BTPS	Body temperature and pressure, saturated with water vapour
CO_2	Carbon dioxide
DI	Desaturation index
DRG	Dorsal Respiratory Group Neurones
EMG	Electromyogram
ERV	Expiratory Reserve Volume
ES	Electrical Stimulation
ESS	Epworth Sleepiness Scale Score
FEV_1	Forced Expiratory Volume in 1 sec
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
H^+	Hydrogen ion concentration
HAD	Hospital Anxiety and Depression scale score
HCO_3^-	Bicarbonate ion concentration
IC	Inspiratory Capacity
IRV	Inspiratory Reserve Volume
KCO	Carbon Monoxide Transfer coefficient
MIP	Maximal Inspiratory Pressure
MEP	Maximal Expiratory Pressure
MND	Motor Neurone Disease
MVC	Maximal Voluntary Contraction
MyD	Myotonic Dystrophy
NMD	Neuromuscular Diseases
NREM	Non Rapid Eye Movement Sleep
O_2	Oxygen
PaO_2	Partial Pressure of Oxygen in the arterial blood
PAO_2	Alveolar Partial Pressure of Oxygen
$PaCO_2$	Partial Pressure of Carbon Dioxide in the arterial blood
Pdi	Transdiaphragmatic Pressure
pH	Logarithm of the reciprocal of H^+
Pmo	Mouth pressure
Poes	Oesophageal Pressure
Pgas	Gastric Pressure
QoL	Quality of Life
RAR	Rapidly Adapting Pulmonary Stretch Receptor
REM	Rapid Eye Movement Sleep

RV	Residual Volume
SAR	Slowly Adapting Pulmonary Stretch Receptor
SE	Sleep Efficiency
SpO_2	Oxygen Saturation as measured by pulse oximetry
SNIP	Sniff Nasal Inspiratory Pressure
SRBD	Sleep Related Breathing Disorders
Ti	Inspiratory time
Ti/Ttot	Inspiratory time normalised for total respiratory cycle
TLC	Total Lung Capacity
TLCO	Transfer factor for carbon monoxide
Tw	Twitch
VE	Ventilation per unit time
VRG	Ventral Respiratory Group Neurones
VT	Tidal Volume

LIST OF FIGURES

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VII. Presentations/Abstracts generated:

1. Respiratory muscle strength assessment in neuromuscular diseases – Respiratory unit meeting at Gartnavel General Hospital - 2002.

2. Ventilation in neuromuscular diseases – Respiratory unit meeting at Gartnavel General Hospital – 2003.

3. Audit on non-invasive ventilation at Gartnavel General Hospital – Scottish Thoracic Society Meeting – December 2002.

4. Invasive respiratory muscle strength assessment in Myotonic dystrophy – Presentation at Scottish Thoracic Society Meeting – November 2003 - Recipient of Methven prize.

5. Ventilation in Myotonic Dystrophy update – Presentation at Department of Neurology at Glasgow Muscle Group Meeting, Southern General Hospital – May 2004.

6. Volitional and nonvolitional respiratory muscle strength assessment in myotonic dystrophy – American Thoracic Society meeting – Poster session – May 2004.

7. Sleep Studies in Neuromuscular diseases – British Thoracic Society meeting – Oral presentation – December 2004.

Publications:

1. Sleep Studies in Myotonic Dystrophy – Accepted for publication in 'Chronic Respiratory Disease' journal (in press) – October 2006.

CHAPTER I

INTRODUCTION

1.1 CONTROL OF VENTILATION

Ventilation is an essential aspect of life and depends primarily on O_2 consumption and CO_2 production within the tissues. It is normally controlled by a combination of central rhythm generator, mechanical and chemical stimuli with input from higher central nervous system structures (1). Both involuntary and automatic/voluntary controls operate in humans. Other main components of the respiratory system include the lungs and the respiratory pump comprising of respiratory muscles and chest wall. This thesis has explored the methods used to assess respiratory muscles in normal people and subjects with neuromuscular disorders, particularly those with myotonic dystrophy (MyD) motor neurone disease (MND)

HIGHER CORTICAL CENTRES:

Electrical stimulation of many cortical areas (especially limbic area) in animals has revealed them to be inhibitory to ventilation. However certain motor and pre-motor areas are excitatory (1). Cortical impulses interact with medullary neuronal network as well as spinal cord via corticobulbar and corticospinal tracts respectively.

CENTRAL RHYTHM GENERATOR (fig 1.1.1):

The central rhythm generator controls the rate and depth of breathing with feedback from peripheral counterparts. Respiration is initiated by a complex interaction of neuronal aggregates in medulla and pons. The **medulla** contains two dense bilateral neuronal aggregations – **i) Dorsal respiratory group** (DRG) neurones situated in the dorsomedial medulla, in association with the ventrolateral nucleus of the solitary tract. These

neurones are predominantly inspiratory in nature and interact with the ventral group via the collaterals.

ii) Ventral respiratory group (VRG) neurones lie in the ventrolateral medulla in association with retrofacial nucleus, nucleus ambiguous and nucleus retroambigualis. Neurones in association with retrofacial nucleus are mostly expiratory and form a group called 'Bötzinger complex' that has been shown to inhibit few DRG neurones and phrenic motor neurones. The neuronal output from both these groups is carried in the ventral and dorsal columns of the spinal cord to phrenic and intercostal motor neurones and thereby to diaphragm and intercostal muscles. Commonly known pneumotaxic centre is located in the **dorsolateral pons** in association with nucleus parabrachialis medialis and this region is thought to play an important role in switching between the inspiratory and expiratory phases of respiration. Lumsden described the rostro-caudal organisation of the mammalian neural network in an anaesthetised cat back in 1923 (2). He was also the first to coin the term 'apneusis' that represented prolonged inspirations approaching spasms along with brief expiratory efforts after combined bilateral vagotomy and pneumotaxic centre lesion. The brainstem centres predominantly control automatic respiration.

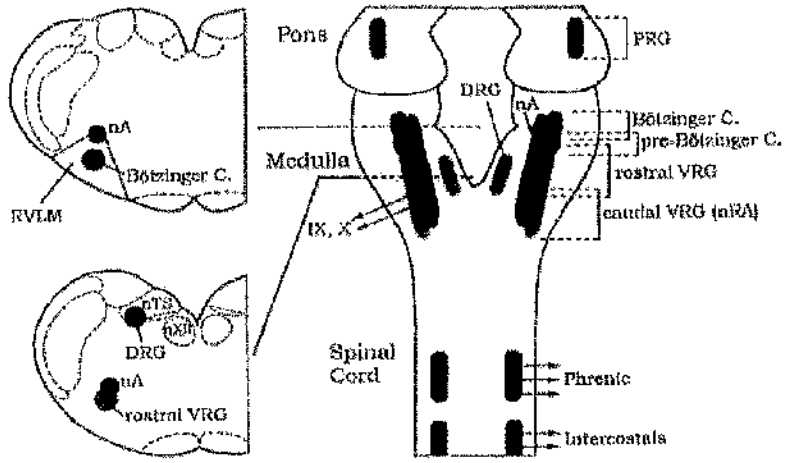


Fig 1.1.1: Pontine, medullary and spinal cord respiratory neuronal aggregations schematically depicted from a dorsal view (right) of the brain stem and spinal cord. Also shown (left) are transverse sections of the medulla at the corresponding levels indicated by the solid and dashed lines on the right. C = complex; DRG = dorsal respiratory group; IX = 9th (glossopharyngeal) cranial nerve; nA = nucleus ambiguus; nRA = nucleus retroambigualis; nTS = nucleus of the tractus solitarius; nXII = 12th (hypoglossal) cranial nerve nucleus; PRG = pontine respiratory group; RVLM = rostral ventrolateral medulla; VRG = ventral respiratory group; X = 10th (vagus) cranial nerve. (Reproduced and modified with permission from Duffin J, Ezure K, Lipski J. Breathing rhythm generation: Focus on the rostral ventrolateral medulla. *News in Physiol Sci* 1995;10:133-140).

GENETIC INFLUENCES:

Recent studies have identified molecular switches that operate at early embryonic stages to develop brainstem respiratory rhythm generator (3). This has been demonstrated in chick embryos. Most of these studies are still in infancy but the gene microarrays and proteomics now used to address cell signalling are likely to shed more light (3).

NEUROMECHANICAL INPUT:

Although resting alveolar ventilation is predominantly set by chemical stimuli, mechanoneural receptors can modify ventilatory pattern. Their exact role especially the relation between structure and function in humans is yet to be defined. The receptors known to-date include (4-6):

i) **SLOWLY ADAPTING PULMONARY STRETCH RECEPTORS (SAR)** – are located in close proximity to the smooth muscle cells of both extra and intrathoracic lower airways with vagal afferents. They are stimulated by increase in the lung volume. For instance if the lung volume is held at end inspiratory level, a reduction in respiratory rate occurs predominantly by prolongation of the expiratory phase [Inflation reflex of Hering Breuer – first described in 1868 (7)]. This reflex is apparent in newborns and adults under general anaesthesia when tidal volumes over 800ml are used. A reduction in the activity of these receptors with lung deflation stimulates inspiratory onset (Deflation reflex). This may contribute to the tachypnoea that occurs in atelectasis.

ii) **RAPIDLY ADAPTING PULMONARY STRETCH RECEPTORS (RAR/Irritant receptors)** – are concentrated near the carina and central bronchi, also with vagal afferents. They are fewer in number compared to SARs and are associated with airway epithelium. Mechanical or chemical stimulation (with histamine or prostaglandins) of RAR generates cough reflex (8).

iii) **C-FIBER ENDINGS** – are attached to unmyelinated vagal afferent fibres and are found close to the pulmonary capillaries [where they are called type J (juxtapulmonary capillary) receptors (9), first described by Paintal in 1969] and the bronchi in proximity to bronchial circulation. They are stimulated by endogenously produced substances (10) such as histamine, prostaglandins, bradykinin, serotonin and may have a role in asthma, pulmonary venous congestion and pulmonary embolism (10). They are also stimulated by lung hyperinflation.

iv) **NEUROEPITHELIAL BODIES** – situated at the bifurcation of small bronchi are thought to act as sensors of hypoxia and thereby increase ventilation (11).

CHEMICAL CONTROL OF BREATHING:

Breathing can be altered by variation in blood chemistry. The **peripheral chemoreceptors** are located in the aortic and carotid bodies. The aortic bodies lie near the aortic arch and carotid bodies close to the carotid bifurcation on either side of the neck. Aortic bodies, though active in infancy and childhood, are relatively dormant in adulthood (12). The carotid bodies consist of two kinds of cells – type I/glomus/chief cells that sense hypoxia and type II/sheath/sustentacular cells, their function being uncertain. The sensory nerve endings from carotid bodies join the sensory fibres of carotid baroreceptors to form the carotid sinus nerve, the cell bodies of which lie in the

petrosal sensory ganglion of the glossopharyngeal nerve. They also contain autonomic nerves to regulate blood flow. The main neurotransmitter released in response to hypoxia is dopamine although other neurotransmitters have been implicated. Afferent input from these receptors leads to the release of the excitatory amino acid glutamate centrally (13) that increases ventilation. The peripheral chemoreceptors are complex sensors receiving high blood flow relative to their size and respond to changes in both arterial pH and partial pressure of oxygen (PaO_2). Hypoxia and acidity interact and are more than additive in their combined influence to increase the chemoreceptor discharge and thereby ventilation. The partial pressure of carbon dioxide ($PaCO_2$) also stimulates these chemoreceptors, though to a lesser extent, but can have an effect due to its influence on pH. Denervation of the peripheral chemoreceptors leads to 12-20% reduction in ventilation and the $PaCO_2$ increases by 5-10mm Hg [0.7-1.3 kPa] (14). The **central chemoreceptors** located near the ventrolateral surface of the medulla oblongata sense H^+ concentration in the local environment. The ventilatory response to acute rise in $PaCO_2$ is predominantly due to central chemoreceptors. CO_2 increases the H^+ concentration in the extracellular fluid that bathes the chemoreceptors. Small alteration in H^+ concentration within the brain interstitial fluid leads to marked changes in the ventilation. For the same arterial pH change, rise in ventilation is greater for respiratory acidosis than that due to metabolic origin, as the blood brain barrier is more permeable to CO_2 compared to HCO_3^- due to its lipid solubility (15) and hence the effect of respiratory acid-base disturbance is much more immediate. The stimulatory effect of hypercapnia is offset by compensatory renal retention of bicarbonate and a concomitant increase in ECF and CSF bicarbonate, which buffer hydrogen ions. This takes 48-72 hours to develop.

The cholinergic activity of the respiratory neurones is high with central acidosis, the effect being exerted via the muscarinic - M1 and M3 receptors and it has been shown that increased ventilation due to salicylates is a function of this cholinergic system (16). Beta-adrenergic agents also have stimulatory effect on central ventilation. On the other hand, alpha-adrenergic agents inhibit the cholinergic system and thereby reduce ventilation (17).

The central rhythm generator and the sensors act on respiratory muscles, the effectors to move air in and out of the lungs. Fig 1.1.2 schematically summarises the control of breathing at the different levels involved.

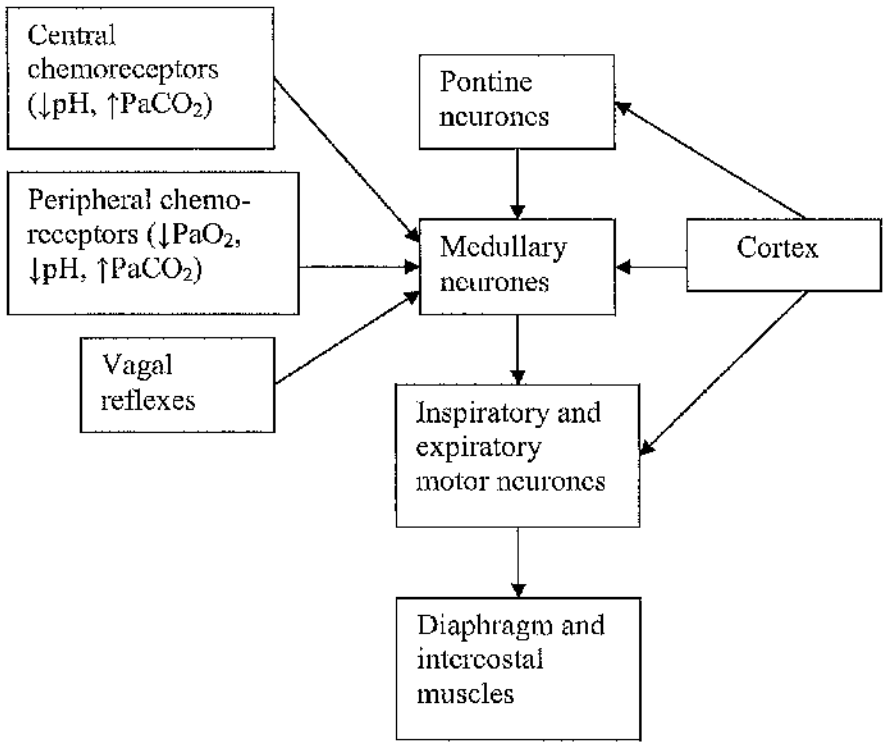


Fig 1.1.2: Schematic Representation - Control of Breathing.

VENTILATORY DRIVE:

The ventilatory drive measures the response in ventilation per minute. A major drawback to the methods used to measure drive is that they depend on normal lungs, respiratory muscles and chest wall mechanics. The commonly used methods include **Hypoxic** and **Hypercapnic Ventilatory Responses**. In the physiological range of $PaCO_2$, the minute ventilation rises linearly with rise in $PaCO_2$. The slope of this line is normally 2-5 L/min/mmHg $PaCO_2$ [15-37.5 L/min/kPa $PaCO_2$ (fig 1.1.3)]. A reduced slope indicates decreased ventilatory drive. About 15% of the population have reduced response to CO_2 with ventilation increasing by only 1 L/min/mmHg $PaCO_2$. They are at increased risk of ventilatory failure in the presence of additional burdens to the respiratory system such as obesity and chronic obstructive lung disease (18,19,20).

The change in ventilation to falling PaO_2 follows a hyperbolic curve (fig 1.1.4). On the other hand, if plotted against oxygen saturation this remains a linear relationship. Hypoxic ventilatory response largely assesses the integrity of peripheral chemoreceptors with some evaluation of the central input. Ventilation increases sharply once PaO_2 is less than 60 mm Hg (8 kPa). Since hypoxic drive is rather modest when $PaO_2 > 60$ mm Hg, it is generally the carbon dioxide response that maintains normal ventilation at sea level. Once PaO_2 is about 40mm Hg (5.3kPa), ventilation increases to 3-6 times the resting value. In patients who have depressed hypoxic drive, invariably some reduction in hypercapnic ventilatory response will be noted. Genetic influences, age, anaesthetic agents and sedatives all affect the range of measured ventilation (21,22).

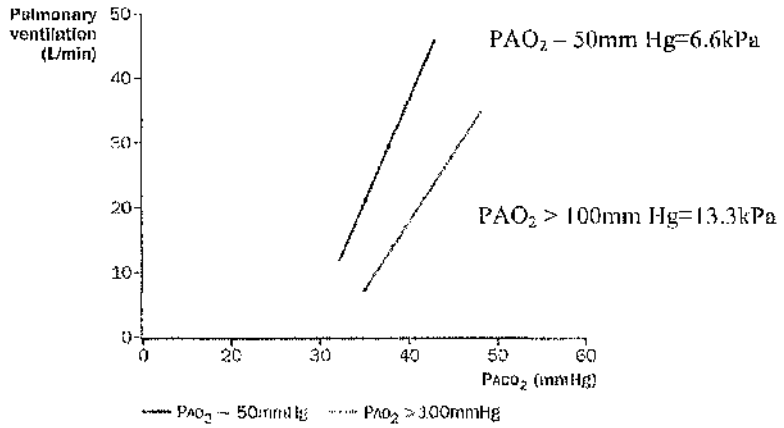


Fig 1.1.3: Ventilatory response to inhaled CO_2 at two different levels of alveolar partial pressure of oxygen (PAO_2). The slope increases with additional low PAO_2. Modified and reproduced with permission from Harcourt Publishers Ltd.- 'Comprehensive Respiratory Medicine'- Albert, Spiro, Jett eds 2001 - Section 1: Structure and Function – Culver B H.

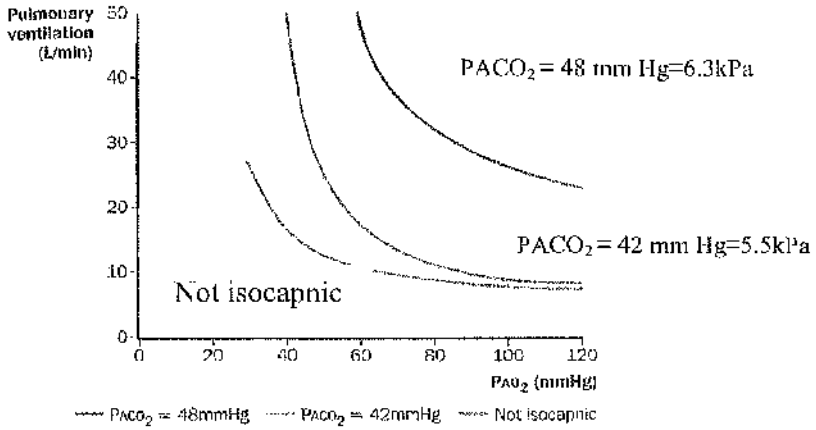


Fig 1.1.4: Hypoxic Ventilatory Response. Non-linear increase in ventilation in response to reduced PAO_2. Response is enhanced in presence of hypercapnia. Modified and reproduced with permission from Harcourt Publishers Ltd.- 'Comprehensive Respiratory Medicine'- Albert, Spiro, Jett eds 2001 - Section 1: Structure and Function – Culver B H.

An attempt to measure the drive in patients with lung or chest wall disease has led to the development of **$P_{0.1}$ technique**. This is an inspiratory pressure developed against a

transiently closed shutter during the first 100 msec of a tidal breath. It has been suggested that within this time, mechanical status of the respiratory system does not influence the force generation and the occlusion is too short to alter respiration voluntarily (23). $P_{0.1}$ technique can also be used to assess ventilatory response to hypoxia and hypercapnia. The accuracy of this technique needs to be established as there is significant overlap between normal subjects and patients with lung disease but $VE/P_{0.1}$ (the ratio of resting ventilation to mouth occlusion pressure ie., output/input) has been shown to be a valid discriminator between normal and disease states (24). However, some people may find the occlusion uncomfortable and maximal rate of change of oesophageal pressure ($\Delta Poes/\Delta t$) over 100ms of inspiration will give another measure of central respiratory drive (25).

In absence of serious mechanical impediment to ventilation, **$PaCO_2$ level above the normal range (37-43mmHg or 4.9-5.7kPa)** at sea level in itself reflects low respiratory drive.

Electromyogram (EMG) studies of respiratory muscles: The slope of moving time average of the diaphragm EMG is a reliable measure of neural inspiratory drive (26). However diaphragm EMG response to CO_2 rebreathing does not increase as much as $P_{0.1}$. This may be due to recruitment of intercostal muscles or enhanced contractility of the diaphragm itself in presence of increased load (27).

In conclusion, a given ventilatory drive for a subject should be interpreted in the context of the integrity of lungs, chest wall and respiratory muscles.

1.2 SLEEP AND RESPIRATION

To sleep; perchance to dream: ay, there is the rub - William Shakespeare
(Hamlet III, i, 65-68)

Haldane in 1905 noted that breathing ceased altogether if $PaCO_2$ level was extremely low and there was no need to breathe (28). But Fink et al in 1963 observed this to be true only if the subject was asleep or anaesthetised but not if awake (29). This has given origin to the so called 'wakefulness drive' although the exact nature and location of this stimulus remains unclear.

Many changes occur during sleep. For instance, there is reduced metabolism by 10-25% with decreased oxygen consumption; hormonal secretory patterns change and body temperature decreases. Most are functions of the brain tissue, thought to be restorative in nature, but still there are some features that associate respiration and sleep in a unique way.

RESPIRATORY DRIVE:

There is functional overlap between the neurones that regulate sleep and those that control respiration. Also, sleep related breathing disorders (SRBD) arise from sleep-dependent changes and this is supported by the fact that most people with SRBD tend to have normal breathing whilst awake, at least in the initial stages of the disease. Eucapnic hypoxic ventilatory response is reduced both in normal males and females and in both non rapid eye movement (NREM) and rapid eye movement (REM) sleep (30). Low ventilatory drive as assessed by chemosensitivity during sleep results in lesser activity of

the upper airway dilator muscles as compared to the diaphragm and this again predisposes to upper airway collapsibility.

UPPER AIRWAY:

Nasal and pharyngeal resistances increase during sleep (31,32). The narrowing of the pharyngeal lumen may be restricted to few segments such as at the level of the palate or in the portion of the pharynx posterior to the tongue. The upper airway collapsibility seen in obstructive sleep apnoea is also confined to these sites (33). The upper airway during sleep is thought to behave like a Starling resistor (34). High upper airway resistance or increased driving pressure across the segments (either due to high pressure applied to highly compliant airway or the pressure difference generated due to the hypotonic pharyngeal muscles) predisposes the upper airway to collapse.

LOWER AIRWAY:

During sleep there is reduced alveolar ventilation due to fall in the central respiratory drive, reduction in respiratory motor output, increased upper airway resistance due to hypotonia of the pharyngeal muscles and blunted protective reflexes. Laryngeal and lung resistance do not change in sleep. Lung volumes decrease only slightly in healthy non-obese individuals but the changes will be greater in the obese. As a result of all these factors, nocturnal $PaCO_2$ rises mildly even in normal people (35-37).

During NREM sleep, there is reduced ventilation and in fact there is evidence of increased work of breathing in the form of increased activity of intercostals and the

diaphragm which maintains the lung volumes only slightly less to that of the upright posture (38).

The REM sleep as first described by Aserinsky and Kleitman in 1953 (39) stresses the respiratory system in interesting ways. REM sleep comprises of phasic REM associated with bursts of rapid eye movement and tonic REM, between the bursts. The distinction is better appreciated in animal studies than in humans where the eye movement densities tend to be widespread during REM sleep. The tidal volume is aimed to be maintained as in NREM sleep but with greater excursions of the diaphragm activity and marked suppression of the chest wall muscles. However the relative hypercapnia and failure to compensate the resistive loads could well result in reduced tidal volume (40). Breathing tends to be more irregular, shallow and rapid especially during phasic REM. The breathing pattern during REM sleep is summarised in fig 1.2.1 (41).

In conclusion, sleep tests the efficiency of the respiratory system and the ventilatory indices.

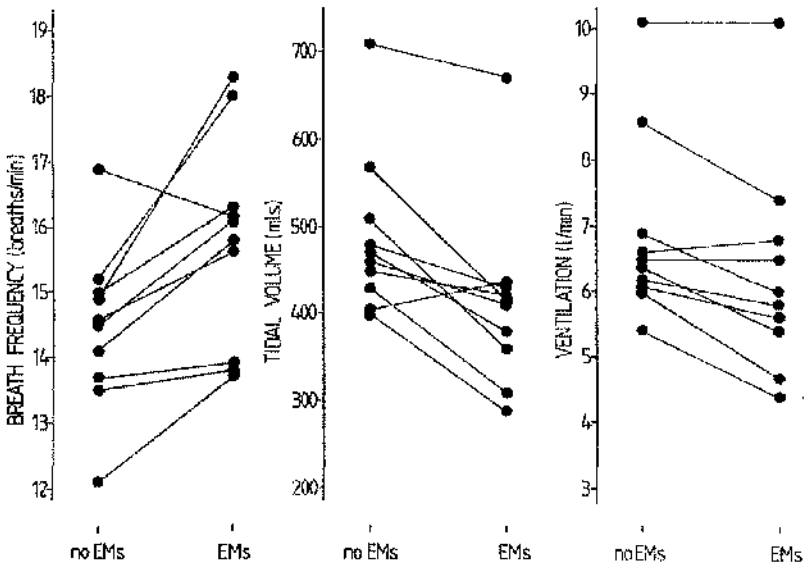


Fig 1.2.1: This experiment in 10 normal men showed that during eye movements (EMs), there was significant increase in the breathing frequency predominantly due to reduction in expiratory time; Tidal volume and minute ventilation fell in comparison to periods of sleep without eye movements (Adopted with Permission from - Gould G A, Gugger M, Molloy J et al. Breathing pattern and eye movement density during REM sleep in humans. *Am Rev Respir Dis* 1988;138:874-877).

1.3 RESPIRATORY MUSCLES IN HEALTH

It was believed for a long time that the diaphragm is the only muscle of breathing. Galen identified that intercostal and other accessory muscles played an important role in breathing (42). Though Leonardo da Vinci made the analogy between breathing and a pair of bellows, it was only in early 1900s that John Mayow described the mechanics of breathing in a greater detail (43). Hutchinson quantified the respiratory muscle strength for the first time (44).

Structurally and functionally respiratory muscles are skeletal muscles and their function is to displace the chest wall rhythmically to pump air in and out of the lungs. Just like the other muscles, they are composed of fibres, a number of which will be innervated by a single motor neurone to form a motor unit. The fibres merge with the connective tissues distally and each is surrounded by a membrane system, which also extends between the bundles of myofibrils that comprise a muscle fibre. In turn, each myofibril consists of bundles of interdigitating thick and thin filaments of actin and myosin. These protein molecules form the basis of the contractile apparatus within the muscles. Acetylcholine released from the motor end plate of the motor neurone leads to depolarization of the muscle cell membrane causing release of calcium. The calcium uptake by the protein molecule, troponin, leads to cross bridge formation between actin and myosin molecules and the relative movement of the two molecules causes shortening of the myofibril. The process of cross bridge formation and release is driven by conversion of adenosine triphosphate to diphosphate.

The force generated within the skeletal muscles is related to the length of the muscle at the time of stimulation (force-length relationship), the speed of muscle contraction (force-velocity relationship), the frequency of stimulation (force-frequency relation) and the integrity of the contractile apparatus.

Force-length relationship:

The optimal length for maximal force generation is the resting length of the muscle (45). As lung volume increases toward TLC the force generating capacity is reduced.

Force-velocity relationship:

The more rapidly a muscle shortens, less is the tension that can be achieved (46). The velocity of shortening is best estimated in physiological studies by measuring the rate of airflow and it is the speed of muscle contraction that determines the maximal airflow in normal subjects (47). It is also possible to assess the velocity of shortening by measuring the rate of contraction of the muscles, which can be estimated by quantifying the time to peak pressure (48).

Force-frequency relationship:

The muscle contraction elicited by a single stimulus is a twitch (Tw). The force generated by a muscle increases as the frequency of stimulation increases until a tetanic contraction is induced at high levels of stimulation (49). The repetitive stimulations allow little time for relaxation of the muscle between contractions and this results in a summation of the contractions and a resultant increase in force development (50). The tetanic plateau of the

force-frequency curve occurs in the respiratory muscles between 50 and 100Hz (51,52). For maximal force generation in respiratory muscles a stimulation frequency of approximately 100Hz is required.

The upper airway muscles, diaphragm, chest wall muscles and abdominal wall muscles are individually dealt with in my thesis bearing in mind that they normally work together in a coordinated manner. The interrelationship between the thoracoabdominal movements and the respiratory muscle contraction is posture dependent. For instance, in upright posture due to gravity, abdomen is distended and abdominal muscles are lengthened. On assuming a supine posture there is reduction in anteroposterior diameter with variable change in lateral diameter (53). Therefore the length of the abdominal muscles decreases. Cephalad diaphragmatic movement in supine posture increases the A-P and lateral diameter of the rib cage and thoracic expiratory muscles are put at an advantage.

UPPER AIRWAY MUSCLES:

The upper airway is a complex conglomeration of bones, muscle bundles and mucosal structures in a narrow space (fig 1.3.1). Though upper airway muscles are not strictly called 'respiratory muscles' their pre activation prior to diaphragm contraction is required to stabilise the upper airway. Loss of pre activation of these muscles is important in the pathogenesis of obstructive sleep apnoea hypopnoea syndrome (54). As upper airway collapsibility is commoner in patients with neuromuscular diseases, I have discussed important functions of upper airway muscles here. The muscles comprise those of external nares, oral cavity, soft palate, pharynx and larynx. Though phasic activity of

genioglossus muscle can be recorded during wakeful state, it is masked by the pronounced tonic activity. Tonicity is reduced during sleep and phasic activity becomes easier to pick up. Phasic inspiratory activity during quiet breathing can also be demonstrated in alae nasi, tensor veli palatini and the vocal cord abductors.

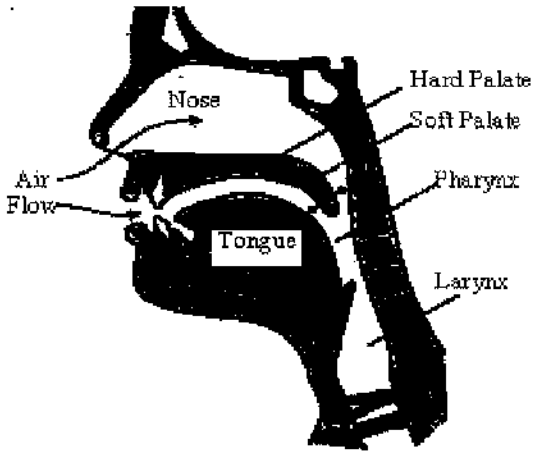


Fig 1.3.1: Upper airway: Adopted and modified from 'Snoring and Sleep Apnoea Syndrome': Hilton M F.

DIAPHRAGM:

Diaphragm is a thin musculotendinous structure in which muscle fibres radiate from a central tendon. It is the main inspiratory muscle and accounts for 70% of inspiratory effort during tidal breathing (55). The **crural (or vertebral)** portion arises from the ventrolateral aspect of the first three lumbar vertebrae and the aponeurosis of arcuate ligaments. The **costal** portion inserts on the xiphoid process of the sternum and the upper margins of the lower six ribs. The costal fibres are closely apposed to the inner aspect of the lower rib cage forming the 'zone of apposition'. Phrenic nerves originating from the third, fourth and fifth cervical segments form the motor supply of the muscle. The

anterior or sternal part of the diaphragm is preferentially innervated by axons from motoneurones in the cranial end of the phrenic motor column; lateral or costal fibres, by axons from the middle of the column and the crural fibres from the caudal end of the column. The internal mammary, intercostals and phrenic arteries supply the diaphragm with extensive anastomoses within the arterial network. Most of the venous drainage is through the inferior phrenic vein, which drains into the inferior vena cava. Though the heart muscle receives more blood supply than that of the diaphragm both during rest and exercise, the percent increase in blood flow to the diaphragm is higher in comparison to other organs during exercise (56).

Action:

Diaphragm contraction results in outward displacement of the anterior abdominal wall, caudal movement of the upper ribs and expansion of the lower rib cage circumference. The reduction in cross sectional area of the upper rib cage is due to the effect of negative pleural pressure as it has been shown to be abolished by introduction of bilateral pneumothoraces in animal experiments followed by diaphragm contraction (57). Hence diaphragm has inspiratory action on the lower rib cage and expiratory action on the upper rib cage. The expansion of the thoracic cavity in the craniocaudal axis reduces the pleural pressure and depending on whether the airways are open or closed, lung volume increases or alveolar pressure falls. The inspiratory action also depends on the lung volume. Towards TLC, the zone of apposition disappears, diaphragm muscle fibres lay transversely and this effect makes the diaphragm expiratory. Inspiratory activity of the diaphragm results in part from the force the muscle applies due to its insertions [referred

to as the 'insertional forces'] (58) and also to 'appositional forces' (59, fig 1.3.2). During breathing, the change in pressure in the pleural recess between the apposed diaphragm and the rib cage is almost equal to the change in abdominal pressure. i.e., pressure in the pleural recess rises supporting the view that the rise in abdominal pressure gets transmitted through the apposed diaphragm to expand the lower rib cage.

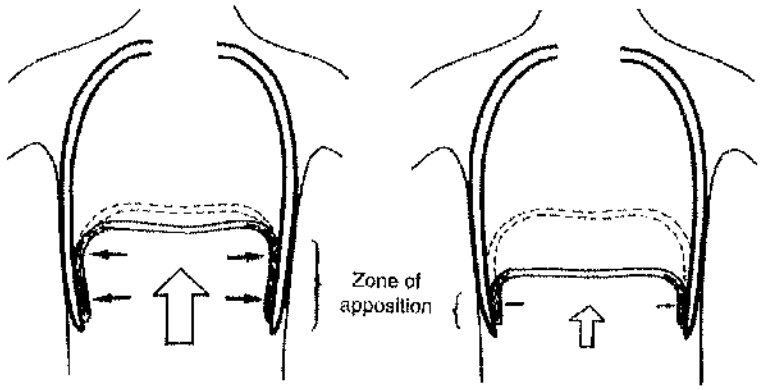


Fig. 1.3.2: When the abdominal resistance (open arrow) is high, zone of apposition remains significant throughout inspiration and there is considerable expansion of the lower rib cage. If the abdominal resistance is low (right panel), diaphragm descends more, zone of apposition is reduced and the inspiratory activity of the diaphragm on lower rib cage is less pronounced. (Reproduced with permission from Respiratory muscle function - André de Troyer in Respiratory Medicine ed., Brewis, Corrin, Geddes, Gibson - Saunders 1995).

Based on the myosin heavy chain isoform skeletal muscle fibres are classified as slow 1 (fatigue resistant), fast 2A (intermediate fatigue resistance), fast 2X and fast 2B (easily fatiguable). Type 2B is not expressed in human muscle (60). The muscle fibres comprising the diaphragm show predominance of fatigue resistant type. About 50% are slow fibres, which have high oxidative and low glycolytic capacity and bear small fibre size with numerous capillaries. The high aerobic capacity of these fibres makes them fatigue resistant. About 20% fibres are type 2A that have high oxidative and glycolytic

capacities. The remaining 30% are type 2X fibres, which have low oxidative and high glycolytic activity and are susceptible to fatigue (61). The intercostal muscles also show a high proportion of slow fibres. However the slow/fast nature of these fibres is not fixed and can be modified by training, hypoxia, age, disease states and pharmacological agents (62,63). For instance in rabbit diaphragm it has been shown that during tachypnoea, there is shift in recruitment from slow to fast muscle fibres (64,65). Drugs such as steroids and beta agonists can alter the density and types of fibres. Chonic use of beta agonists has shown to result in hypertrophy of fast fibres and switch from slow to fast fibre types. In murine models of muscular dystrophy shift from fast to slow fibre types is evident (1 and 2A fibres).

RIB CAGE MUSCLES:

The chest wall consists of the ribcage and the abdomen separated by the diaphragm. The movement of the ribs in humans is shown in fig 1.3.3. The **external intercostal** muscles extend from the tubercles of the ribs dorsally to the costochondral junctions ventrally, with their fibres orientated obliquely caudal and ventral from the rib above to the rib below.

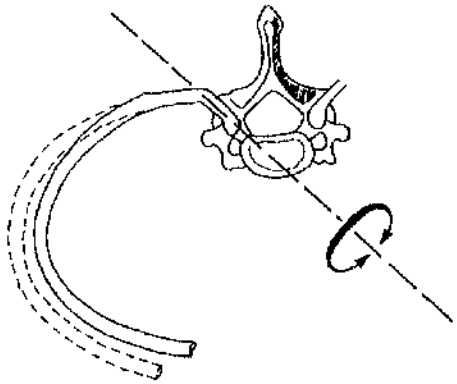


Fig 1.3.3: Movement of the ribs in man: The ribs rotate around the axis of the neck (heavy broken line) and rotation increases anteroposterior and transverse diameters of the rib cage (dotted line). (Reproduced with permission from Respiratory muscle function - André de Troyer in Respiratory medicine ed., Brewis, Corrin, Geddes, Gibson - Saunders 1995).

The **internal intercostal** muscles on the other hand extend from the angles of the ribs dorsally to the sternocostal junctions ventrally with the fibres running obliquely caudal and dorsal from the rib above to rib below. The fibres are particularly thick between the sternum and the chondrocostal junctions and they are called as **'parasternal intercostals'**. The parasternal intercostals act directly on the rib cage expanding it in anteroposterior and lateral diameters. Along with the diaphragm they form the primary muscles of inspiration. Nerve supply to all the intercostal muscles is through the intercostal nerves. External and parasternal intercostals are most active during inspiration and the internal intercostals during expiration. The contribution of external and internal intercostals to tidal breathing is small.

Scalene muscles are in three bundles running from the transverse processes of the lower five cervical vertebrae to the upper surface of the first two ribs. Scalene muscles are

innervated by the lower five cervical segments. Though traditionally classified as the accessory muscles of respiration, scalene muscles contract in normal humans with the diaphragm and the parasternal intercostals during inspiration (66). Contraction of the scalene muscles results in expansion of the upper rib cage.

OTHER ACCESSORY MUSCLES OF RESPIRATION:

Sternocleidomastoid, pectoralis minor, trapezius, erector spinae, serrati have predominantly postural functions but assist inspiration during increased requirements. The clavicular portion of the pectoralis major assists expiration when the requirement is high as in paralysis of the abdominal muscles due to spinal cord injury.

Triangularis sterni (Transversus thoracis) is a flat muscle deep to the sternum and parasternal intercostals supplied by the intercostal nerves. Though inactive during resting breathing, it contracts during voluntary or involuntary expiratory efforts such as laughing, coughing and speech.

ABDOMINAL MUSCLES:

Muscles within the anterior abdominal wall are the chief expiratory muscles. Transversus abdominis, internal oblique, external oblique and rectus abdominis have important respiratory function apart from their work as rotators and flexors of the trunk. On contraction, they pull the abdominal wall inwards increasing the abdominal pressure and move the diaphragm cranially reducing the lung volume. Secondly, they pull the lower ribs caudally deflating the rib cage thereby aiding expiration. They also have an

inspiratory effect by equalising the pressure in the pleural recess to that in the abdomen thereby raising the lower rib cage as discussed above. At end expiration they relax, causing passive descent of the diaphragm aiding inspiration. It has been shown that in healthy subjects, phasic expiratory contraction occurs when the demand on the inspiratory muscles increases as in exercise (67). The tonic contractions of these muscles in standing posture makes the diaphragm longer at the onset of inspiration and prevents over-shortening during expiration. In accordance with the length-tension characteristics of the muscle, diaphragm capacity to generate pressure is thus enhanced.

In conclusion, pharyngeal dilators, diaphragm and the rib cage muscles work in a coordinated fashion to aid tidal breathing. Accessory muscles of respiration contribute during periods of increased demand such as exercise.

1.4 RESPIRATORY MUSCLE STRENGTH ASSESSMENT

The recent developments with regard to measuring pulmonary mechanics have focussed on patients with unexplained breathlessness, neuromuscular diseases and patients who are difficult to wean from ventilators. Measurement of respiratory muscle strength forms an important part of assessment in these groups of patients.

Symptoms of Respiratory Muscle Weakness:

Mild to moderate respiratory muscle weakness can be asymptomatic unless there is an additional load on the respiratory system such as superadded infection, airflow obstruction or pulmonary fibrosis. Most common symptom is breathlessness on exertion (68,69). Associated limb muscle weakness may mask this disabling symptom (70). As the disease progresses, dyspnoea may occur at rest signifying imminent respiratory failure. With marked respiratory muscle weakness, nocturnal hypoventilation ensues with sleep fragmentation resulting in unrefreshed sleep, excessive daytime sleepiness, tiredness, poor concentration and memory. Hypercapnia causes cerebral vasodilatation that could result in throbbing, especially morning headaches when $PaCO_2$ may be greatest.

Unilateral diaphragm weakness is usually asymptomatic. However patients with severe unilateral diaphragm weakness can develop ventilatory problems following an anaesthetic or experience dyspnoea with supine posture, bending or immersion in water (71). With bilateral diaphragm paralysis subjects are likely to experience orthopnoea or dyspnoea on exertion.

Weakness of expiratory or bulbar muscles results in difficult speech, failure to clear secretions or aspiration culminating in recurrent lower respiratory tract infections (72).

Signs of Respiratory Muscle Weakness:

Physical examination may reveal signs that suggest the underlying aetiology for the respiratory muscle weakness. There may be gross wasting of the muscles, which is better appreciated in the neck accessory muscles than the intercostals. Associated myotonia, fasciculations, absent or exaggerated deep tendon reflexes, sensory disturbances could also help in localising the level of lesion within the nervous system.

During initial stages of the disease examination may be normal. With progression of respiratory muscle weakness, tachypnoea at rest manifests with reduced tidal volume. This rapid shallow breathing is an adaptation to lower the elastic work of breathing but increases the dead space ventilation. This is thought to be a response to the imbalance between the strength and the load on the respiratory system (73,74).

Diaphragm Paralysis:

Selective diaphragm weakness results in compensatory increase in the activation of inspiratory rib cage muscles. The fall in pleural pressure gets transmitted across the flaccid diaphragm so that the abdominal pressure falls and there is paradoxical inward movement of the abdomen with inspiration, opposing the lung inflation (71). This is usually better appreciated in supine posture, more pronounced when the weakness is severe (maximal transdiaphragmatic pressure < 30 cm H_2O) and occurs when there is still

adequate extradiaphragmatic upper chest wall muscle strength. If the ribcage muscles are predominantly involved there may be paradoxical thoracic inward movement during inspiration (75). Rarely both the patterns may be apparent in the same individual at different times and this has been termed 'respiratory alternans'. It is postulated that this may be a central mechanism to avert fatigue in different groups of muscles.

Laboratory Assessment:

Normally comparing the motor nerve input of the muscle to the force and movement developed within it assesses its function. Since the length-tension relationship of the respiratory muscles alter with different body postures, the usual methods to assess strength in limb muscles can not be routinely applied to the respiratory muscles.

ELECTRICAL ACTIVITY: Needle electromyography can be performed for accessory muscles of respiration such as the sternocleidomastoid and scalenes. Oesophageal electrode has been used successfully to assess diaphragmatic activity. Since diaphragm, intercostals and abdominal muscle lie close to pleural and peritoneal cavities, surface electrodes are the preferred choice to measure electrical activity routinely in these muscles. Anterolateral chest wall is commonly used to measure diaphragm surface EMG, as there are relatively few external intercostal fibres in the region. However the signals are affected by the activity of internal intercostals and possibly abdominal muscles. Use of oesophageal electrodes avoids this interference. EMG signals can be integrated to provide quantitative estimate of contraction. Spectral analysis on the other hand is a useful non-invasive measure of muscle fatigue.

MECHANICAL ACTIVITY: Since respiratory muscle contraction results in force generation, the subsequent pressure changes measured in vivo provide quantification of their strength (76). Transpulmonary, transthoracic, transabdominal and transdiaphragmatic pressure measurements, all provide useful information regarding the respiratory muscle activity.

Full Lung Function Tests:

Commonly measured lung volumes in the respiratory laboratories are depicted in fig 1.4.1.

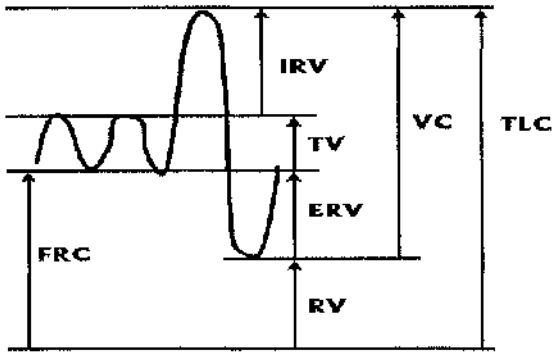


Fig 1.4.1: Shows different lung volumes.

Monitoring vital capacity (VC) is simple and useful for repeated measurements as in impending respiratory failure due to Guillain-Barré syndrome. Supine vital capacity falls less than 10% (mean 7.5%, SD ± 5.7%) of that due to sitting values in normal people (77). Again this is due to the loss of gravity assistance to diaphragm descent but this has no functional consequence. A greater than 25% fall in supine vital capacity suggests

significant diaphragm weakness. However it is a volitional test and a non-specific marker of respiratory muscle weakness. Also VC can be completely normal in mild to moderate weakness. In later stages of respiratory muscle dysfunction, FVC has been shown to be a better predictor of morbidity (78).

Some studies have shown increased FEV_1 and mid expiratory flow rates (79, 80) and this is generally attributed to patent airways at lower driving pressure maintaining higher flow rates. TLC and FRC tend to be reduced when there is significant weakness. Residual volume (RV), if high, suggests significant expiratory muscle weakness. Diffusion analysis usually yields low carbon monoxide diffusion capacity (TLCO) with normal or raised transfer coefficient (KCO) suggesting normal diffusion within the alveoli available for gas exchange, in keeping with extrathoracic restrictive defect. Though conventional methods are used to measure lung volumes, computed tomography to reconstruct three-dimensional images of thorax or magnetic resonance imaging can also be used.

Flow volume loops:

Sometimes even when the vital capacity is within the normal range the appearance of the flow volume loop can indicate underlying respiratory muscle weakness (fig 1.4.2). Characteristically it shows delayed peak of the expiratory limb, abrupt drop of the forced expiratory flow near the residual volume, blunting of the inspiratory and expiratory limbs (81). In distinction to normal forced expiratory flow volume curve, the peak flow as well as the terminal segment after FRC is effort-dependent. Upper airway dysfunction can also become apparent on flow volume loops. Flow oscillations are commonly seen in patients with clinically evident bulbar dysfunction. If incorrect scaling is used, observer can misinterpret the data to represent upper airway obstruction. Most labs use the ATS

standard of plotting 2L/s flow against 1L of volume to avoid this error (82). Flow volume loops however are not useful to compare variations between individuals and have not been tested in population screening for neuromuscular diseases.

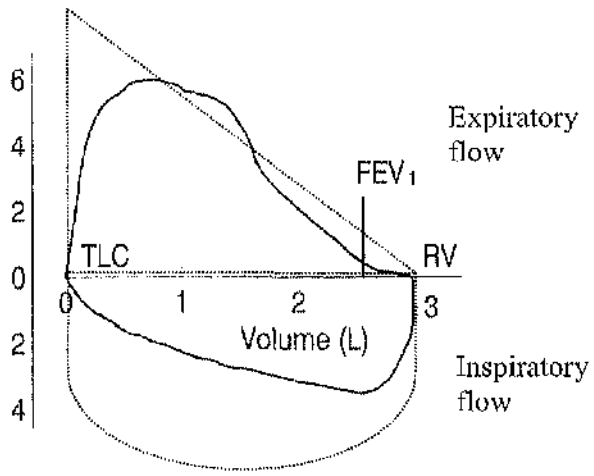


Fig 1.4.2: Flow volume loop showing respiratory muscle weakness
Modified and reproduced with permission from Harcourt Publishers Limited; Lung function tests: Physiological principles and clinical applications, 1999; Eds Hughes J M B, Pride N B.

Mouth Pressures:

Static inspiratory and expiratory pressures are commonly measured using mouth pressure meters. They give an assessment of the global respiratory muscle strength. The pressures generated tend to be higher with a tube mouthpiece in normal people compared to flanged mouthpiece but the perioral leaks are likely to be higher using a tube mouthpiece (83). The values though wide are well established (84-86) and tend to be higher in males compared to females. The values decline with age. As with any volitional test, obtained values are dependent on subject motivation and effort, which partly explains the wide range of reported normal range. A low value can be difficult to

interpret as this could either be due to poor effort or true muscle weakness. On the other hand normal values can be difficult to differentiate from mild respiratory muscle weakness. The pressures generated depend on the lung volume at which the test is performed. Maximal inspiratory pressure is usually measured from FRC or RV and the maximal expiratory pressure from TLC. Some people do find the forceful manoeuvres difficult and sniff tests will be useful in that instance. If maximal inspiratory pressure (MIP) is reduced, **sniff nasal inspiratory pressure (SNIP)** measured from FRC will be useful to detect any significant respiratory muscle weakness. A value of SNIP over 70 cmH_2O usually excludes significant respiratory muscle weakness. The basis for a SNIP test is that the pressure within the alveoli closely relates to the nasal pressure when the airway is occluded. Hence it becomes unreliable in presence of nasal anatomical abnormalities or pulmonary fibrosis where the pleural pressure transmission is not uniform. Ideally SNIP should be less than MIP considering the force-velocity and force-length aspects of skeletal muscles. However SNIP is often greater than MIP because (i) many subjects find sniffing to be an easier manoeuvre and hence muscle recruitment is likely to be better. (ii) Diaphragm EMG activity is higher during sniff than MIP. (iii) Diaphragm length appears to be more favourable to generate pressure during initiation of a sniff than a maximal inspiratory manoeuvre. It is generally recommended that SNIP and MIP be used as complementary tests in the assessments of inspiratory muscle strength.

If oesophageal and gastric balloon catheters are inserted, **sniff oesophageal pressure (sniff Poes)** will become a useful indicator of inspiratory muscle strength with values >

70 - 80 cm H_2O being normal. It has the added advantage that it is not altered by imperfect pressure transmission within the respiratory system as in chronic obstructive lung disease. It has higher maximal pressures compared to SNIP, narrower range of normal values and better reproducibility (87). **Transdiaphragmatic pressures (Pdi)** can also be measured if specific diaphragm assessment is required. Sniff Pdi >100 cm H_2O signifies good diaphragm strength. If sniff Pdi is reduced or subjects are unable to perform voluntary manoeuvre phrenic nerve can be stimulated electrically or magnetically to obtain twitch Pdi. An unpotentiated unilateral Tw Pdi > 10cm H_2O and bilateral Tw Pdi > 20cm H_2O generally excludes significant diaphragm weakness.

Cough gastric pressure (Cough Pgas) provides another useful measure of expiratory muscle strength. It is more reproducible than MEP and normal values have recently been reported – 214.4(42.2) for normal males and 165.1(34.8) cm H_2O for females (88).

(Normal values have been adopted from Respiratory Muscles - J Moxham in Hughes and Pride eds. Lung function tests: Physiological principles and clinical applications 1999).

Imaging:

Chest X Ray:

Unilateral or bilateral elevated diaphragms may be apparent due to weakened diaphragm. Lung volumes may appear smaller but this will be difficult to differentiate from poor inspiratory effort. Sensitivity is high in that the condition is unlikely if diaphragm weakness is absent. However the specificity of chest X ray to diagnose unilateral hemidiaphragm paralysis is only in the range of 0.44 (89).

Fluoroscopy:

Fluoroscopic examination during an inspiratory manoeuvre such as submaximal sniff in an upright position from FRC will be useful in some patients. False positive results are significant with this. Alexander et al (90) showed that 6% of normal subjects have the inspiratory cranial hemidiaphragm motion usually considered diagnostic of hemidiaphragm paralysis because of abdominal muscle relaxation.

Ultrasound:

Ultrasound examination is radiation free and can reveal the paradoxical upward movement of the paralysed diaphragm during inspiration but again this may only be appreciated in the supine posture. In upright posture this can be compensated by assistance of gravity. Another useful measure will be the thickness and the degree of shortening during inspiration as a chronically paralysed diaphragm has an atrophic appearance and does not thicken during inspiration (91).

In summary, significant respiratory muscle weakness can exist with minimal symptoms and signs. Therefore high degree of clinical suspicion along with appropriate tests will be required to detect the problem early.

1.5 RESPIRATORY MUSCLES IN NEUROMUSCULAR DISEASES

It appears logical to think that any progressive neuromuscular disease eventually affects the respiratory muscles if not already so at the outset. Respiratory muscle weakness contributes to significant morbidity and mortality in patients with neuromuscular diseases. Respiratory muscle weakness and/or fatigue is responsible for dyspnoea, reduced exercise tolerance, nocturnal oxygen desaturation and prolonged weaning from mechanical ventilation associated with NMD. This is not a universal manifestation as mitochondrial myopathy (92) can present with marked diaphragm fatigability with relatively well-preserved mouth pressures. Ventilatory failure in this instance is because of the inability to sustain respiratory efforts and it has been showed that exercise limitation occurs sooner in comparison to normal controls (93). Inspiratory muscle weakness results in progressive decline in vital capacity, restrictive lung defect and eventually hypercapnic respiratory failure. Expiratory muscle weakness results in retention of secretions, impaired cough and thereby recurrent respiratory tract infections, which eventually contribute to reduction in vital capacity. If bulbar involvement coexists as in MND, aspiration episodes tend to be more frequent. In presence of underlying lung disease symptoms manifest early. Reduced drive is exaggerated in neuromuscular diseases with associated blunting of arousal threshold and reduced respiratory muscle activity (94). The disproportionate loss of upper airway muscle tone poses additional load especially during REM sleep when there is maximal muscle hypotonia (95,96) resulting in recurrent upper airway collapses and sleep fragmentation.

Sleep disordered breathing manifests as nocturnal oxygen desaturations, hypopnoeas, obstructive, central apnoeas and hypercapnia that occurs initially during REM sleep (97). Though sleep disordered breathing can develop early in the course of the disease it is not always apparent from daytime clinical assessment. However the pattern and severity of the sleep related breathing disorder could sometimes be inferred from daytime lung and respiratory muscle function tests (98).

It has been shown that even during episodes of upper respiratory tract infection, VC, MIP and MEP reduce significantly in NMD and transient hypercapnia is evident in few patients (99). This does not occur in normal people and highlights the delicate balance of the respiratory muscles in NMD. Duration of NMD and nutritional state of the patient has not been shown to predict the respiratory muscle weakness (100). Though there is no correlation between the respiratory muscle strength and the peripheral muscle weakness, the distribution of weakness and the type of NMD can determine the way in which respiratory muscles are compromised.

Since diaphragm is the main inspiratory muscle, its weakness in NMD warrants special mention. With unilateral diaphragm paralysis, VC has been shown to be reduced by 20-25% even in the upright posture and PaO_2 may fall in the supine posture mostly due to increase in the closing volume and compression of the basal segments of the lung on the affected side (101,102). With bilateral diaphragmatic paralysis, there is increased respiratory rate with reduced tidal volume at rest and alveolar hypoventilation during sleep (103). Ventilation perfusion mismatch occurs in the decubitus posture (104), which

contributes to arterial hypoxaemia. Unusual phasic activity during REM has been shown to occur in patients with motor neurone disease (MND) with severe diaphragm weakness and this may well be an adaptive mechanism of the respiratory pump (105).

To conclude, in neuromuscular diseases, respiratory muscles function at a lower capacity and the altered peripheral mechanics with or without depressed respiratory drive increases the load on them. Some of the changes noted such as tachypnoea and accessory muscle recruitment may well be adaptive mechanisms to combat the increased load but in most instances respiratory failure ensues with daytime hypercapnia, although the timescale is variable in different conditions.

1.6 VENTILATORY FAILURE IN NMD

Though neuromuscular diseases form a heterogeneous group of diseases, ventilatory failure (defined as $PaO_2 < 8$ kPa and $PaCO_2 > 6$ kPa) commonly occurs in many patients. It often occurs as a terminal event. Ventilatory failure can occur even in the absence of underlying pulmonary pathology. Associated respiratory muscle weakness and sleep disordered breathing tend to be important contributors to the onset of respiratory insufficiency. Respiratory muscle weakness may be apparent at the time of initial diagnosis though this is not universal. In proximal myopathy, it has been shown that hypercapnia is common when respiratory muscle strength is <30% predicted and VC <55% predicted (106).

In NMD, problems with ventilation can arise from involvement of the brain, brainstem nuclei, spinal motoneurones, defective neuromuscular transmission or reduced respiratory muscle force generation. Neuronal abnormality within the brain could either be due to anatomical lesion or abnormal metabolic responses to common ventilatory stimuli. Normal response to hypoxia and hypercapnia includes increase in tidal volume (VT) with little change in the respiratory rate (f). In NMD, resting breathing pattern can often be abnormal and there may be low VT and high f response to hypoxic or hypercapnic stimuli. Though defective central control could result in this, often the peripheral mechanics due to respiratory muscle weakness will account for this. The specific problem of assessing drive in presence of weak muscles is discussed in section 1.8.1.

Table 1.6.1: Classification of NMD that compromise ventilation depending on the primary level affected.

Muscles	Neuromuscular Junction	Neurogenic	Others
Dystrophies	Myasthenia gravis	MND/ALS	Drugs
Myopathies	Tetanus	Poliomyelitis	Metabolic
Connective tissue disease	Snake Bite	Guillain Barré Syndrome	
(SLE, polymyositis)	Botulism	Phrenic nerve palsy	
COPD	Sepsis	(surgery, trauma, carcinoma)	
Chronic heart failure		Stroke	
Kyphoscoliosis		Parkinson's Disease	
		Multiple sclerosis	
		Spinal cord injury	

Nocturnal hypoventilation especially during REM sleep is a recognised initial manifestation. By the time patients are symptomatic, when non-invasive ventilation is introduced, ventilatory failure tends to be established with daytime hypercapnia. The recognition of symptoms such as breathlessness may be delayed, as exercise tends to be limited due to associated muscular weakness. Hence high clinical suspicion with supportive laboratory assessments will be needed to identify patients at risk of developing ventilatory failure. This is increasingly important as evidence shows the benefit of non-invasive ventilation in these conditions by prolonging survival, improving quality of life and blood gas parameters.

With mild to moderate respiratory muscle weakness, ventilatory drive is increased and results in hyperventilation. Hence in early stages arterial blood gas analysis will reveal normal pH and reduced $PaCO_2$. However PaO_2 and alveolar-arterial (A-a) gradient remains normal unless there is compromise within the lung parenchyma. With progression, nocturnal rise in $PaCO_2$ and eventually daytime hypercapnia ensues (107).

In essence, there is a combination of reduced drive, increased load and decreased capacity which initially manifests as hypoventilation during REM sleep and in later stages with daytime hypercapnia and progression of symptoms. The contribution of these three factors in the pathogenesis of ventilatory failure can be different depending on the underlying actiology. For instance respiratory drive tends to be well preserved in Duchenne muscular dystrophy but impaired in many patients with myotonic dystrophy. The extent and progression of respiratory insufficiency is also variable depending on the underlying NMD. NIV at present is being offered depending on the local availability, expertise and financial assistance provided for such services. NIV is likely utilised better if respiratory muscle strength assessments are carried out at regular intervals as patients have time to develop an understanding of the progression of the disease and proposed interventions. At present symptoms and arterial blood gas parameters remain pivotal in evaluation of these patients to plan appropriate management.

1.7 SHOULD RESPIRATORY MUSCLE STRENGTH BE ASSESSED IN NMD?

It can be argued that vital capacity in conjunction with arterial blood gas analysis alone provides enough clinical information that would assist in planning the required medical intervention. That poses the question: Is it really necessary to measure respiratory muscle strength in NMD? In established ventilatory failure, VC and blood gases may well be sufficient to plan further management. However, with the advent of the newer genetic modalities/screening many NMD patients are being diagnosed in early/asymptomatic stages of the disease. At the same time research has started to unravel the frequency with which respiratory problems occur in these patients in greater detail. The involvement of inspiratory and expiratory muscles can differ between the diseases and mode of intervention will also be different. There is increasing awareness amongst both patients and medical professionals regarding the benefits of inspiratory muscle assists in the form of non-invasive ventilators and expiratory aids such as insufflator – exsufflator devices (108). Although myopathy can result mostly from fatigability in the presence of normal mouth pressures as in mitochondrial myopathy, commonly neuromuscular diseases tend to present with low mouth pressures. VC can be entirely normal in mild to moderate respiratory muscle weakness and awake blood gases are usually normal in earlier stages of the disease. Hence it would be essential to have formal assessment of respiratory muscle strength to provide better care for NMD patients. I will now describe the background work on the respiratory assessment in Myotonic dystrophy and Motor neurone disease (the two main conditions I studied).

1.8 REVIEW OF LITERATURE ON MyD AND MND

1.8.1 Respiration in MyD – What we already know:

MyD is the commonest adult muscular dystrophy that exhibits the phenomenon of genetic anticipation occurring at younger age and in more severe form with successive generations. It affects 1 in 8000 persons worldwide. There are over 750 patients within Scotland. At present in the West of Scotland with around 280 patients, it is estimated that one to two affected family members are missed with the existing screening programme (personal communication, Dr Wilcox, Scottish Muscle Network, 2004). There is emerging evidence of the benefit with NIV in respiratory failure due to myotonic dystrophy in terms of symptoms and blood gas parameters. However the NIV compliance has been shown to be lower than in a group of age and sex matched post poliomyelitis patients requiring NIV (109).

Myotonic dystrophy type I results from unstable expansion of the trinucleotide (CTG) repeats on the long arm of chromosome 19 (19q13.3). The size of the trinucleotide repeats in the normal population varies from 3-30. Greater than 40 CTG repeats is associated with myotonic dystrophy (110). All the patients I studied belonged to type I myotonic dystrophy (MyD) group. MyD usually presents during second or third decade of life with myotonia, generalised progressive muscle weakness, characteristic facial appearance of ptosis and frontal balding, cataracts, diabetes mellitus, gonadal atrophy and neuropsychiatric disturbances (111). The median survival at present extends only to fifth - sixth decade of life. The main causes of death include cardiac conduction defects and

respiratory complications. Approximately half the deaths are related to respiratory complications in the form of pneumonia or respiratory failure. Generally four disease types have been recognised - late onset (mild), adult onset (classical), childhood and congenital (112). The implications I have discussed mostly concentrate on the classical variety of the disease.

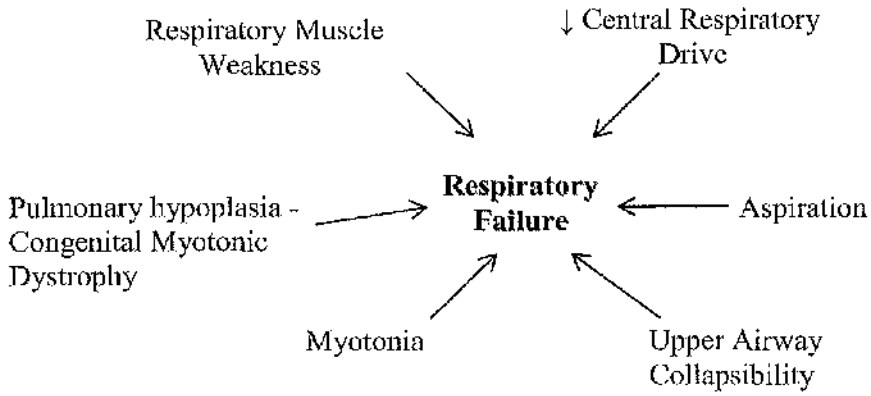


Fig 1.8.1.1: Schematic presentation of factors that affect ventilation in Myotonic Dystrophy

The complex interaction between the various parameters is yet to be completely understood and may vary between individuals of the same family. As in other neuromuscular diseases due to restricted activity symptoms of respiratory muscle weakness can be masked till later in the course of the illness. Sleep complaints are prevalent even in absence of nocturnal respiratory disturbance. It has been shown that patients with excessive daytime sleepiness report greater hypnagogic hallucinations and pain associated with nocturnal awakenings (113).

Respiratory Drive:

As a direct measure of respiratory centre output is not clinically possible, many other physiological parameters are used as a surrogate of this drive. Irregular breathing pattern at rest during wakefulness (114,115) has been described mostly with increased respiratory rate and reduced tidal volume. It has been postulated that input from the chest wall receptors might be enhanced in presence of myotonia thereby leading to tachypnoea though conclusive evidence is lacking. Respiratory muscle weakness in itself and/or altered peripheral respiratory mechanics could account for this. In addition, abdominal muscle recruitment as evidenced by EMG activity tends to be higher in these patients during resting breathing. In association with expiratory muscle weakness this may well contribute to abnormal breathing pattern and increased work of breathing (116). Duty cycle (determined by Ti/Ttot that represents the inspiratory-phase fraction of the respiratory cycle. Ti = inspiratory time, Ttot = total duration of the respiratory cycle) and central inspiratory drive [measured as tidal volume (VT)/Inspiratory time (Ti)] have been shown to be well preserved compared to normal controls.

Occlusion pressure ($P_{0.1}$) is either normal or slightly higher than in control subjects at rest which suggests normal resting central drive in few patients (117). However this has to be interpreted with the knowledge that $P_{0.1}$ represents only a small fraction of the total muscular pressure generated for the tidal volume and is independent of the maximal pressure limitation reached in the latter half of inspiration. This may well explain why only a group of patients studied show abnormal drive. Another interpretation is that 'measured normal drive' in the face of respiratory muscle weakness may be

inappropiately low to maintain alveolar ventilation. Reduction in pulmonary compliance results in greater pressure generation to produce the same level of ventilation.

It has been shown in 12 patients that moderately severe global respiratory muscle weakness does not influence ventilatory response to hypercapnia or the perception of inspiratory effort [MIP 43.1(17.2) cm H_2O vs 123(15.2) cm H_2O in normal controls] (118). This is in contrast to earlier studies, which had shown depressed ventilatory response to chemical stimulation. It appears that patients with normal $PaCO_2$ retain sensitivity to CO_2 stimulation (119). Since there is no direct correlation between CO_2 retention and the hypercapnic ventilatory response (114), it is likely that additional factors apart from respiratory muscle weakness per se operate. One such hypothesis suggests that disordered afferent information from the affected muscles could impair the function of the respiratory centre. When there is significant respiratory muscle weakness and altered pulmonary mechanics, the central neural drive may not be translated into alveolar ventilation due to 'neuro mechanical uncoupling' and this may well be the reason for reduced slope of HCVR.

Central mechanisms may play a key role in this as well. In support is the study in a small group of myotonic dystrophy patients where the densities of the neurones in dorsal, ventral central medullary nuclei and sub trigeminal medullary nucleus have been shown to be reduced. All these subjects had abnormal hypercapnic ventilatory response and central hypoventilation in comparison to normal controls and patients without

hypoventilation (120). Another factor being the frequent occurrence of central apnoeas in MyD (121).

Pulmonary function tests:

Restrictive spirometry is commonly apparent in later stages of the disease. Vital capacity declines as the respiratory muscle weakness progresses. Total lung capacity (TLC) tends to be reduced. Residual volume (RV) is usually normal. If RV is high this usually signifies expiratory muscle weakness. Maximal voluntary ventilation (MVV) can either be in the normal range or reduced. When MVV is limited it usually is associated with hypoxaemia at rest (122).

Respiratory muscle strength:

Mouth pressures tend to be reduced. MEP tends to be more impaired than MIP. Associated facial muscle weakness interferes with the Valsalva and Muller manoeuvres and thereby underestimates the strength using these non-invasive tests. Table 1.8.1.1 gives a summary of the mouth pressures and % predicted vital capacity in Myotonic Dystrophy patients available in the literature.

Table 1.8.1.1: Results expressed as mean (SD)/mean [SE]. Mouth pressures expressed in cm H_2O.

Authors - year	n patients/ controls	MIP - MyD	MIP - controls	MEP- MyD	MEP- controls	% Pred FVC
Scrisier et al-1982	19/20	<50	>90	<50	>110	-
Jammes et al-1985	10	23(10.3)		39.7(23.1)		75.9(14.2)
Cirignotta et al-1987	8	44.5(10)	-	-	-	75.19(18.9)
Gilmartin et al-1991	7/7	48.1	94.4	37	102.7	71.1
Bogaard et al-1992	17	44.3[4.3]	-	19.6[1.4]	-	74.7[4.6]
Bégin et al- 1997	62*	55(23)	-	64(20)	-	64(14)
Ugalde et al-2001	10/10	50.9(27.8)	>100.8(35.8)	63.3(20.5)	>126.1(29.2)	80.6(13.7)

*Patients with mild to moderate proximal weakness according to Muscular Disability Rating Scale, which comprised the largest group of patients Bégin et al studied.

It appears that the severity of respiratory muscle weakness usually does not significantly correlate with either the pulmonary function variables or clinical severity. Significant reduction in static mouth pressures can occur even when the vital capacity and the arterial blood gases remain within the normal range. Sniff Pdi measurements have been studied in MyD but to date nonvolitional diaphragm strength using BAMPS has not been routinely assessed in this group.

Sleep in Myotonic Dystrophy:

Respiratory failure worsens during sleep. Nocturnal desaturations and upper airway collapsibility are far more frequent in MyD than in other neuromuscular diseases with similar degree of respiratory muscle weakness (123). Sleep disruption is encountered even in patients without obstructive apnoeas or hypopnoeas. Reduced sleep efficiency (ratio of total sleep time to time in bed), reduced total sleep time, increased percentage of stage 1 and reduced slow wave sleep, frequent wakenings at night are commonly seen. Increased stage 1 sleep is not consistently reported and in the studies, which have reported this, the result may well be due to the 'first night effect' in the sleep laboratory (124).

Non-invasive ventilation (NIV) is an efficient tool not only to relieve symptoms of hypoventilation, improve blood gas parameters in neuromuscular and chest wall diseases (125-129) but also to improve quality of life and prolong survival in its users (130-132). Optimal time for introducing NIV can be difficult to identify in individual patient setting and often sleep studies are used for early identification of 'patients at-risk' as it is well

established that nocturnal sleep abnormalities precede daytime hypercapnia. It is also widely known that sleep worsens the respiratory impairment in chronic neuromuscular diseases (97,133). The usefulness of screening sleep studies however is debatable as nocturnal measurements are poor predictors of survival. It has also been shown that sleep and nocturnal respiratory parameters correlate poorly (134).

Excessive daytime sleepiness:

Excessive daytime sleepiness, which is out of proportion to nocturnal events, is commonly reported in this group of patients. Multiple sleep latency test carried out in 6 patients were normal and no sleep onset rapid eye movements (REM) have been recorded (135) though other investigators have noted diurnal and nocturnal sleep onset REMs (136). A central sleep control defect could account for excessive sleepiness in these patients.

Myotonia:

Myotonia of the respiratory muscles has been demonstrated using fluoroscopy and electromyogram using intramuscular electrodes (137). Myotonia can also be observed on invasive respiratory muscle strength assessment where slow decay of the transdiaphragmatic pressure tracings is apparent during sniffs (138). Myotonia is a rare occurrence during tidal breathing but has been shown to occur more frequently at higher levels of ventilation and this may well be a contributor towards reduced ventilatory response to chemical stimuli. Myotonia of the respiratory muscles means that greater diaphragmatic pressure has to be generated for each inspiration and this may in itself

reduce the fatigue threshold of the diaphragm. Myotonia can induce dyspnoea in two ways. Firstly, by placing the inspiratory muscles in an unfavourable length – tension relationship. Secondly, an enhanced reciprocal inhibition on spinal motoneurones supplying intercostal muscles can result in abnormally active expiratory intercostal muscles with reduced activity of inspiratory muscles. Such inhibition in limb muscles is compensated by increased activation of supraspinal centres but the compensation in respiratory muscles is less well understood. There are isolated case reports in the literature that suggest improvement in breathlessness after antimyotonic therapy such as procainamide (138) though there are no long term studies in this regard. Also associated side effects of these drugs make longer-term use difficult.

Aspiration:

Associated cardiac sphincter malfunction along with delayed gastric emptying (139) can lead to episodes of aspiration resulting in recurrent lower respiratory tract infections requiring antibiotics. Acute respiratory insufficiency can be precipitated post operatively after a general anaesthetic due to aspiration.

Anaesthesia and Myotonic Dystrophy:

It has been shown that central depressive agents such as thiopentone delivered as an aerosol exaggerates the abnormal breathing pattern in Myotonic dystrophy (140). Good preoperative assessment can help prevent many of the complications. Ideally short acting non-depolarising neuromuscular junction blockers (e.g. atracurium or vecuronium) should be used so as to avoid need for neostigmine. Opiate use should be minimised and

sedative premedications avoided. Aspiration is a potential problem to be anticipated. Post operatively patients should be monitored in high dependency units with monitoring of oxygen saturation, avoiding sedation and constant watch out for evidence of infection. Chest physiotherapy should be prompt to avoid respiratory complications.

In summary, myotonic dystrophy patients have significant abnormalities on static mouth pressure assessments even when the muscular disability is only minimal. These patients frequently have facial muscle weakness and hence low mouth pressures obtained during routine testing needs to be interpreted with caution. However normal lung function tests and mouth pressures would be helpful in excluding significant respiratory muscle weakness. A combination of reduced strength, increased load and probably low central ventilatory drive at least in a subset of patients eventually results in chronic hypercapnia. Aspiration and general anaesthesia in unsuspected patients are the likely sources of acute respiratory insufficiency in the present day. Central stimulating drugs such as modafinil and its evidence-based use in myotonic dystrophy may well help to understand certain central features of the disease and thereby open up new therapeutic avenues alongside NIV.

1.8.2 Respiration in Motor Neurone Disease – what we know:

Amyotrophic lateral sclerosis (ALS) is the commonest type of adult-onset motor neuron disease (MND). ALS involves both upper and lower motor neurones and presents as an idiopathic, progressive degeneration of anterior horn cells and their associated neurons resulting in progressive muscle weakness, atrophy, and fasciculations. The disease was first described in 1869. ALS is named for its underlying pathophysiology. Amyotrophy refers to the atrophy of muscle fibres, which are denervated as their corresponding anterior horn cells degenerate. Lateral sclerosis refers to hardening of the anterior and lateral columns of the spinal cord as the motor neurons in these areas degenerate and are replaced by fibrous astrocytes (gliosis). Annual incidence of ALS is 1-2 per 100,000 population. In a year, approximately 100 new patients with ALS are assessed at the Department of Neurology, Southern General Hospital that covers the Greater Glasgow Health Board region (verbal communication Dr R K H Petty, 2004). ALS may occur at any age, but peak age of onset is 55-75 years. Eventually, all deaths directly caused by ALS result from respiratory complications (141,142). This occurs primarily from progressive respiratory muscle weakness and hypercapnic respiratory failure. In patients with bulbar weakness, aspiration of secretions or food may occur and precipitate pneumonia resulting in further respiratory compromise. Mean duration of ALS from onset to ventilator dependence or death is 2-4 years. Most patients who opt for ventilatory support die within 5 years of diagnosis, but a small percentage (8-22%) survive 10 years.

Pulmonary Function Tests:

Restrictive defect on lung function testing is common due to associated respiratory muscle weakness. Most patients at presentation tend to have abnormal lung function test even in absence of symptoms. Rate of decline in VC tends to be around - 3.5%/month (143). The decline is steeper in patients who die early.

Respiratory Muscle Strength:

Respiratory muscle weakness is present in most patients with ALS at the time of diagnosis. SNIP is sensitive to pick up mild weakness and is a good predictor of progressive decline in muscle strength. It is easy to perform even in advanced disease (144). In a study of 81 patients including those with bulbar involement, SNIP has been shown to have greater predictive power for the presence of hypercapnia compared to all the noninvasive tests including vital capacity (145). In those without bulbar involvement, sniff Pdi had the greatest predictive power in this study. However, in patients with bulbar involvement, none of the tests of respiratory muscle strength predicted hypercapnia and other investigators have also reported difficulty in reliably assessing strength in these patients.

Sleep and Motor Neurone Disease:

REM sleep abnormalities precede daytime hypercapnia as in any other neuromuscular disease. Patients who are known to have diaphragmatic weakness as assessed during the daytime are particularly prone for this. The duration of REM sleep has been shown to be reduced in patients with diaphragm dysfunction. Obstructive apnoeas and hypopnoeas are almost never seen in ALS.

Arterial Blood Gases:

Venous bicarbonate and chloride have lately evoked interest (146) providing prognostic information regarding the respiratory status of these patients. This has opened avenues for domiciliary monitoring of MND patients. However it should be noted that this is only a useful marker of severe nocturnal hypoventilation and/or established hypercapnia and provides no useful information in early stages of the disease. Measurement of VC and mouth pressures is far more likely to provide such information in the initial stages.

In summary survival in MND is compromised by progressive respiratory muscle weakness leading to hypercapnic respiratory failure. Timely intervention with NIV has been shown to improve symptoms, survival and quality of life (130-132). Hence appropriate measures of respiratory muscle strength form an important assessment tool in these patients.

1.9 PURPOSE OF THE STUDY

Various parameters of respiratory function such as vital capacity, sniff nasal inspiratory pressure are helpful in assessing the progression of the underlying disease and respiratory muscle weakness. But no single entity has been shown to predict the onset of ventilatory failure or mark the presence of underlying hypercapnia in this group of patients. Recently, bilateral anterior magnetic phrenic nerve stimulation (BAMPS) has been shown to be a useful nonvolitional way of assessing diaphragm strength. BAMPS has not been studied in MyD group and largely remains a research tool in patinets with MND. Identification of factors that would identify onset of ventilatory failure early would help in timely intervention with non-invasive ventilation and thereby improve quality of life and survival. The purpose of my research was:

1. To evaluate the role of routine pulmonary function tests and sleep studies in MyD and MND.
2. Evaluate the magnetic phrenic nerve stimulation technique in patients with MyD and MND as volitional tests can underestimate respiratory muscle strength.
3. To correlate the results of volitional and nonvolitional tests to assess respiratory muscle strength in MyD and MND.
4. To assess the relationship between peripheral and respiratory muscle strength, if any.

Most NMD patients are evaluated in clinics with the use of volitional assessment tools. Associated facial muscle weakness and/or bulbar dysfunction can be a confounding factor in these circumstances. The main objective of my research was to address the

benefits of nonvolitional tests in preference to volitional tests in assessing respiratory muscle strength, if any. MyD and MND patients formed the two main groups of patients referred for respiratory assessment to our clinics and the studies were carried out in them.

I will now describe the materials used and the way the equipments were calibrated prior to each study.

CHAPTER 2

MATERIALS AND GENERAL METHODOLOGY

2.1 SUBJECT RECRUITMENT

Normal control subjects included staff from the respiratory laboratory and medical doctors from the respiratory wards at Gartnavel General Hospital.

Patients referred from the Departments of Neurology at Southern General Hospital, Medical Genetics Department at Yorkhill Hospital, Department of Respiratory Medicine at Gartnavel General Hospital and Glasgow Royal Infirmary were approached to take part in my studies. A Neurologist or a Medical Geneticist had evaluated all the patients and the diagnosis was confirmed by molecular genetics, muscle biopsy and/or electrophysiological studies where necessary.

Inclusion criteria: Patients with diagnosis of

1. Myotonic Dystrophy (MyD)
2. Motor Neurone Disease (MND)

Exclusion criteria:

1. Epilepsy
2. Neurosurgery with history of aneurysmal clips, cochlear implants
3. Cardiac pacemakers (147) or implanted defibrillators
4. Associated major cardiovascular or other respiratory conditions such as symptomatic airways obstruction or pulmonary fibrosis
5. Pregnancy

2.2 ETHICS APPROVAL

Ethical permission for each study was obtained from the Glasgow West Ethics Committee prior to commencement of the studies. Written information was given to all the subjects and written informed consent was obtained prior to the studies from all participants.

2.3 EQUIPMENT USED

2.3.1 Spirometry

Spirometers have come a long way since Hutchinson first described their use with a simple water sealed device (44). They form the basic screening tool in all respiratory laboratories for assessment of respiratory diseases. Vitalograph (fig 2.3.1.1) spirometer was used in my studies. This used Fleisch pneumotachograph for air flow measurements (accuracy ± 15L/sec, Maximal recordable volume 8L) and flow was integrated to give lung volumes. Subjects wore noseclip. Measurements were taken with the 'open circuit method'. Subjects took a breath to maximal inhalation, then inserted the mouthpiece into the mouth with good seal from the lips around it and then blew out and continued exhalation to the end with continuous encouragement. FEV_1, FVC and supine VC were routinely measured. For values to be reproducible, proper attention to technique was given. Best of 3 efforts was taken and the variability of the values obtained between the efforts had to be < 5%. Reference values were taken from Quanjer et al (149). Inter and intra observer variation tends to be less marked in computerised analysis. The variability has been well studied in a large epidemiological study for diagnosis of COPD by Spanish investigators (150). Amongst seven investigators, intraindividual coefficient of variation was about 4% for FEV_1, FVC and FEV_1/FVC and interobserver coefficients of correlation were 0.99 for FEV_1 and FVC measurements and 0.958 for FEV_1/FVC (151). This amount of variablility is generally considered acceptable in research studies. Quality control data was maintained in the laboratory for the duration of the study.

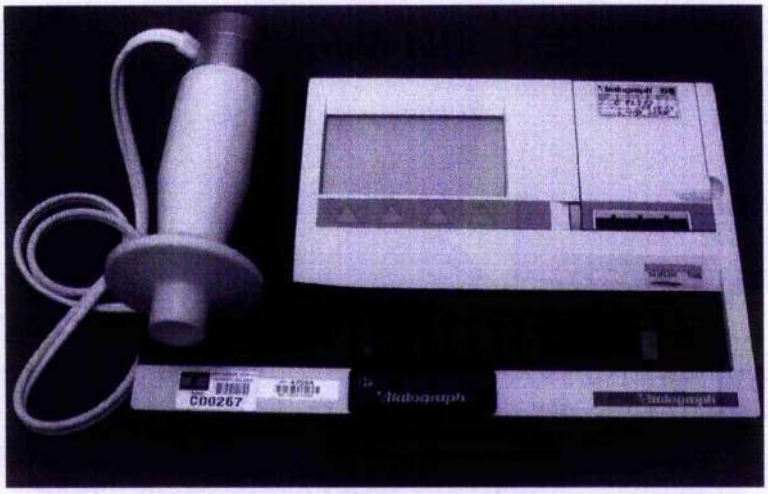


Fig 2.3.1.1: Vitalograph spirometer.

2.3.2 Transducers and Amplifiers: (Fig 2.3.2.1)

Fig 2.3.2.1: Transducer module (on the right) attached through a universal interface module to the MP 150 recording system (on the left).

The pressure transducers measure a pressure applied to one or both sides of their diaphragm. All the pressure measurements were made using a 4-channel pressure module built by the Biomedical Engineering Department at the South Glasgow Hospitals NHS Trust. It was designed to be added on to the Biopac MP 150 system through which all the recordings were carried out. The pressure ranges built in were within the estimate of clinical usage (+ 350 cm H_2O). All the signals were pre amplified, electrical signals passed through an analog-digital (A-D) board to be recorded using the MP 150 system.

Linearity of the pressure transducers (measuring Pmo, Poes, Pgas) was checked against Bio-Tek pressure meter (BIO-TEK instruments Inc, Winooski, VT, USA) as shown in fig 2.3.2.2.

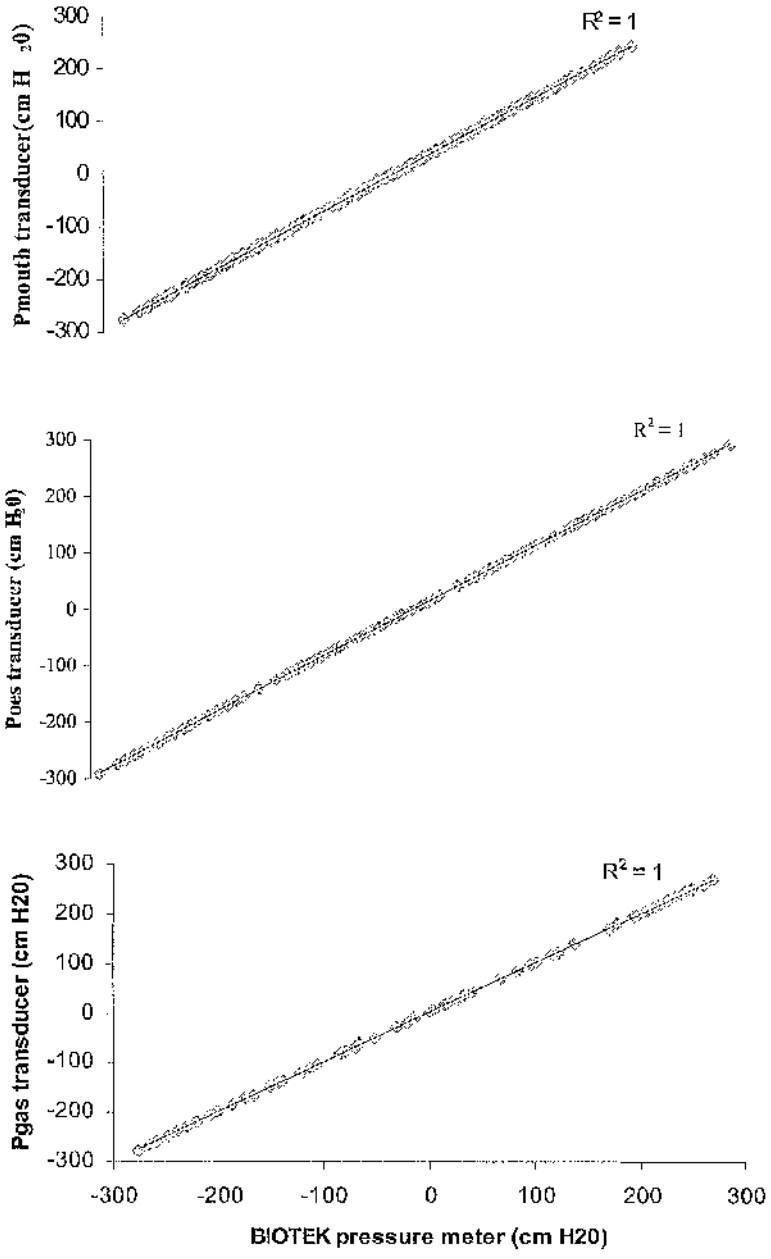


Fig 2.3.2.2: Shows the pressure transducers to be linear over -250 to +250 cm H_2O pressure that is well within the clinically measured range.

2.3.3 Mouth Pressure Equipment:

Static Inspiratory and Expiratory Mouth Pressures:

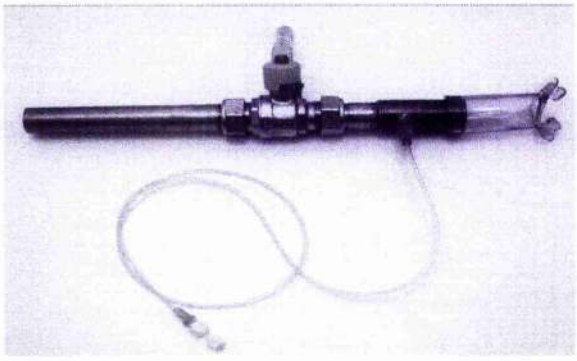


Fig 2.3.3.1: Modified cylinder with attached flanged mouthpiece to measure mouth pressure.

Mouth pressures were measured using a cylinder with a modified three way valve system (fig 2.3.3.1) while each subject was seated comfortably and wore a nose clip. The stem was 31.5cm in length with an internal diameter of 2.3cm. A small hole (diameter 2mm) was created proximal to the occlusion that could temporarily be created using the 3-way valve. This was to prevent cheek pressures from buccal contraction contributing towards measurements during the expiratory manoeuvres and to keep the glottis open during inspiratory efforts (86). The subject held the metal cylinder in his hand and performed the inspiratory/expiratory manoeuvre by keeping the flanged mouthpiece tightly sealed between the lips to prevent any perioral leaks. Since associated facial muscle weakness is commoner in the group of subjects I studied, flanged mouthpiece was used. Patients were also encouraged to support their cheeks with the other hand to minimise leaks. Assistance was given to hold the metal cylinder in those patients who were unable to do so on their own. The metal cylinder was connected through rubber tubing to the pressure

transducer-amplifier system. The normal values were established for our laboratory (appendix I and II). The values were averaged for the first second from initiation of the effort to obtain the sustained pressure for one second (fig 2.3.3.2 & fig 2.3.3.3). Subjects were given constant encouragement to obtain maximal effort to sustain for about 2 sec. They could visualise their effort on the computer screen. Best of 4 to 6 efforts was taken as the value of maximal inspiratory (MIP) and expiratory pressure (MEP). If the last measurement obtained was the highest, further measurements were carried out.

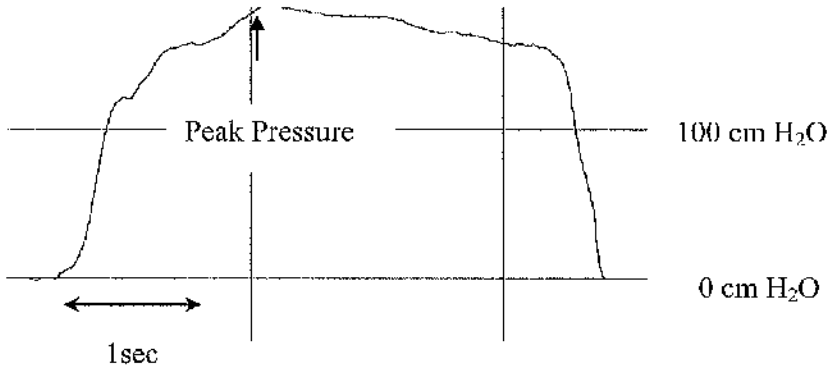


Fig 2.3.3.2: A typical MEP measurement.

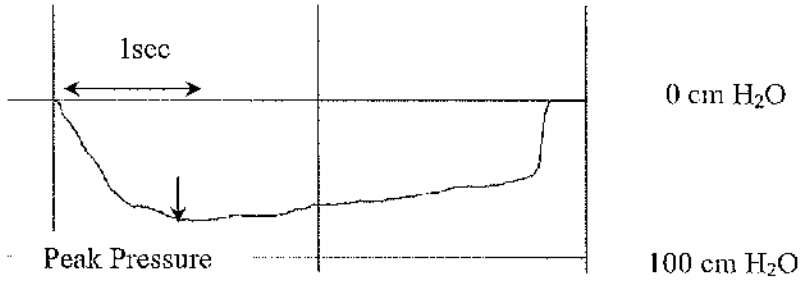


Fig 2.3.3.3: A typical MIP measurement.

Ringvist et al have shown that the highest maximal expiratory pressures were obtained at greater than 70% of TLC and the highest maximal inspiratory pressures were at volumes

less than 40-50% of TLC (86). As per convention, MIP was measured from RV and MEP from TLC.

Pressure measured at the mouth (Pmo) is a combination of respiratory muscle pressure (Pmus) and the elastic recoil of the lungs and chest wall (Prs). At FRC Prs is zero and hence Pmo = Pmus and that is the advantage of measuring mouth pressures from FRC as the negative recoil pressure of the respiratory system is excluded. However MIP was measured from RV in these studies when Prs may be approximately -30cm H_2O. At MEP measured at TLC, again Prs can be up to + 40 cm H_2O (152). The advantage of MEP measured from TLC is that expiratory muscles are at optimal length to generate force. Many studies done to date normally have not taken into account the contribution of Prs and this usual convention was followed in my experiments.

In my studies, MIP $\leq$ 80cm H_2O, MEP $\leq$ 90cm H_2O and SNIP $\leq$ 70cm H_2O were considered to be significantly reduced on the basis of available literature and the normal values obtained in our lab (appendix I,II).

Sniff Nasal Inspiratory Pressure: (fig 2.3.3.4)

Fig 2.3.3.4: SNIP measured with the nasal bung made of dental impression material, connected through a tubing to the pressure transducer.

SNIP is a non-invasive measure of sniff Poes. It is characterised by an increase in the lung volume with distortion of the chest wall. It often reflects inspiratory muscle strength better than MIP. However studies have shown that level of agreement between SNIP and MIP is low (153) and hence these measurements are likely to be complementary rather than substitutive. SNIP was measured through a nasal bung occluding one nostril whilst short sharp sniff manoeuvre was performed through the other. The nasal bung was made from dental impression material. It was connected to the pressure transducer through a 96 cm polyethylene catheter (internal diameter 1.3mm). Measurements were made in sitting posture from RV and best of 4-6 sniff efforts were taken as the maximal SNIP. Each sniff manoeuvre was separated by 30 sec. Subjects were given constant encouragement and were allowed to view their effort on the computer. The total duration of the effort should have been less than half a second to be suitable for analysis.

2.3.4 Balloon Catheters (fig 2.3.4.1)

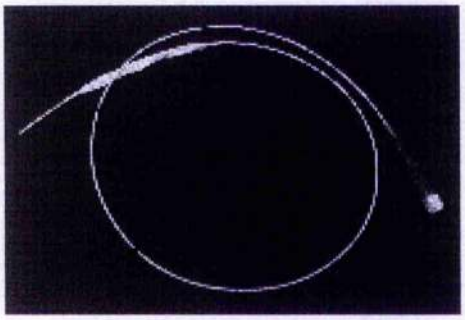


Fig 2.3.4.1: Oesophageal balloon catheter.

Liquid filled catheters (154) and catheter mounted microtransducers, fibreoptic sensors can all be used for the measurement of the oesophageal pressure. Balloon catheter system was used in my studies (155). Ackrad Laboratories, Cranford, manufactured the set I used. This radio opaque latex-free set contained an 86 cm closed end catheter with a 9.5 cm balloon with an uninflated circumference of 1cm placed 5cm proximal to the catheter tip. The internal diameter of the catheter was 1.3mm and the exterior was 2mm. At the distal end within the balloon were 4 parallel placed holes. There was a stylet with Y connector to aid placement of the catheter. Two catheters were inserted through the nose after application of 10 to 15 ml 2% lignocaine gel (Biorex Laboratories, London, UK) to the nostril. Once the catheters were advanced to the hypopharynx, swallowing of the catheters was aided by sipping cold water through a straw. Most subjects tolerated this reasonably well. Both catheters were passed to the stomach, the position confirmed by positive deflection on the pressure tracings during inspiration. Then one of the catheters was withdrawn to the oesophagogastric junction – which was identified by the

change in pressure tracing to negative deflection. The catheter was withdrawn by a further 10 cm so that the balloon was positioned in mid oesophagus. The stylet from the catheter was then removed. Most subjects felt the tubes to be more tolerable once the stylet was removed. The catheters were secured with tape. All subjects were instructed not to eat or drink anything until numbness subsided to avoid aspiration. Studies have shown that the Poes and Pgas represent pleural and abdominal pressures respectively (156,157) and the resultant arithmetic difference between them, Pdi, remains the gold standard for measuring diaphragm contractility.

The catheter was then connected to the pressure transducer-amplifier system through the extension tubes (96 cm in length and internal diameter 1.3 mm) provided with the catheter set via a 3-way stopcock to allow patients to move their heads freely. With the stopcock open to an attached 10 ml syringe, all the air from the balloon was evacuated by pulling back on the plunger and then allowing the plunger to return to a non-vacuum position. About 5 ml air was injected to smooth out folds within the balloon. The oesophageal balloon was inflated leaving behind 0.5 ml air and the stomach balloon with 2 ml of air. The volume of air was decided depending on the available literature and the pressure volume characteristics of the balloon as carried out in our laboratory (fig 2.3.4.2).

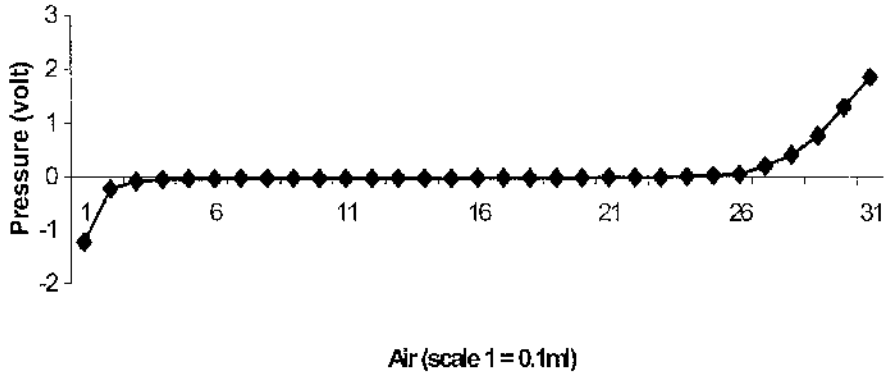


Fig 2.3.4.2: Pressure volume characteristics were determined at atmospheric pressure after the balloon was emptied and increments of 0.1 ml volume air was added with a syringe and the pressure was recorded after each incremental addition. The pressure volume curve of the balloon catheter system at atmospheric pressure was flat between 0.4 – 2.4ml of air; ie., there was only negligible change in balloon pressure when air was added in this range. Outside the body the balloon required 0.4 ml of air to restore pressure to zero.

The positions of the balloon catheters were confirmed by measuring the mouth pressure whilst the subject took a slow inspiration against a closed shutter (158). The position was considered satisfactory if the mouth and oesophageal pressures were parallel. After positioning the balloon catheters, tracheal artefact was looked for. Valsalva and Müller manocuvres normally provide only a small lung volume change when glottis is open and the airway is obstructed beyond the pressure tap for mouth pressures. Then the pressure difference from the mouth to oesophagus approximates transpulmonary pressure and any pressure change will also be small. If upper part of balloon was placed behind the proximal trachea, transpulmonary pressure changes will be marked by larger increase during Valsalva manoeuvre and decrease during Müller manocuvre. This is due to

impingement of the trachea against the oesophagus. During Valsalva manoeuvre, trachea is pulled away from the oesophagus making oesophageal pressure change to be in a more negative direction. During Müller manoeuvre the trachea is forced against the oesophagus causing oesophageal pressure to increase markedly. If this artefact was present the oesophageal pressure would change with head position, extension causing negative deflection and flexion positive. Finally, the position was adjusted to minimise cardiac pulsations (159).

Oesophageal spasm can occur nearer to TLC and peristaltic waves lasting for 2-5 sec were monitored for. The peristaltic waves tend to be more frequent when the balloon is in the lower oesophagus and during swallowing and before mealtimes (160).

'Pop test' (161, fig 2.3.4.3) was used to measure the response time of each catheter – connecting tube – transducer –amplifier - recorder system. The balloon catheter was placed in a larger pressurised condom (pressure was raised by insufflation of air via a cylinder). The pressure was maintained at 100 cm H_2O and a square wave fall in pressure was created by bursting the condom with a red hot needle. 90-10% decay time (Dt) for pressure was 0.019 sec. The frequency response of the system used in my thesis was calculated using the equation $Fr = (3*Dt)^{-1}$. ie., $(3*0.019)^{-1} = 17.5$ Hz.

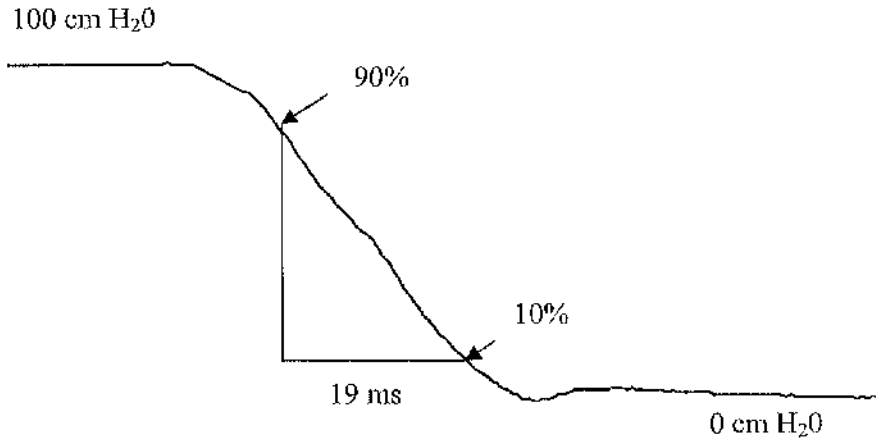


Fig 2.3.4.3: Frequency response of the system.

A static in vitro test of the balloon transducer amplifier computer system was also conducted by comparing the pressure inside a sealed glass bell jar (fig 2.3.4.4) measured directly with bio-tek meter with that obtained using the transducer-amplifier-computer connected to balloons containing 0.5 and 2 ml air. The pressure changes were linear and accurate over -200 to −250 cm H_2O (fig 2.3.4.5).

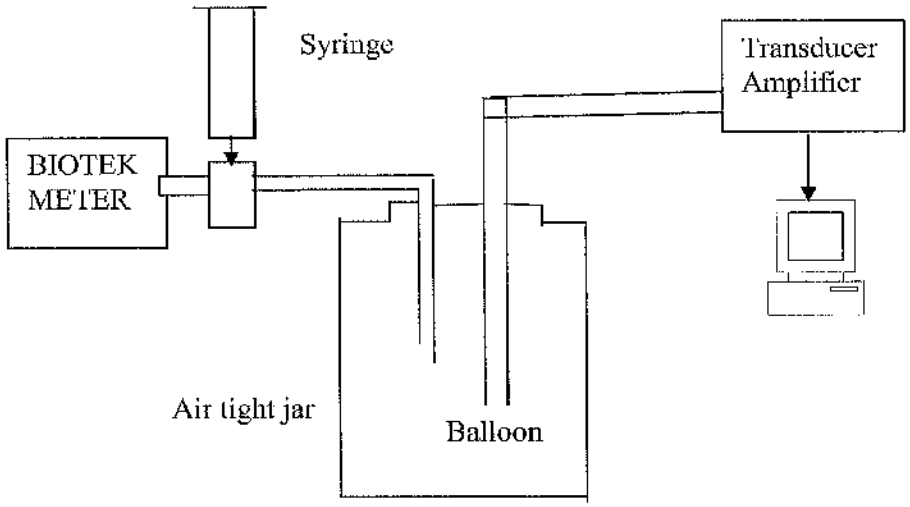


Fig 2.3.4.4: Schematic representation of in vitro test of the balloon transducer amplifier computer system.

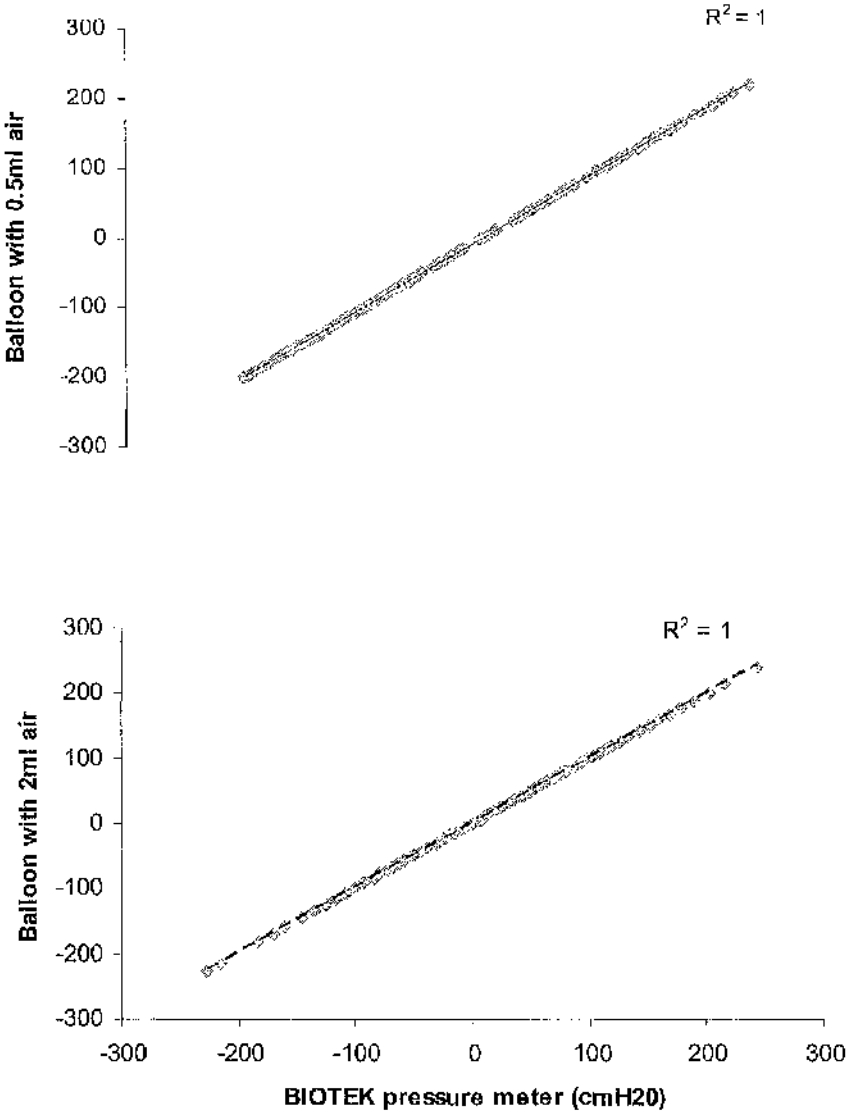


Fig 2.3.4.5: In vitro test of balloon transducer amplifier computer system.

2.3.5 Magnetic Phrenic Nerve Stimulation

Duchenne introduced the technique of phrenic nerve stimulation. However quantification of the diaphragm contraction was not carried out till 1970's (162). Unilateral or bilateral percutaneous phrenic nerve stimulation can be carried out by creating an electric current via bipolar electrodes placed over the anterolateral aspect of the neck (163). Until recently electrical stimulation (ES) of the phrenic nerve was the preferred choice to study the electrical activity of the diaphragm. It is a highly skilled technique and not used routinely in clinical practice. The stimulation can be painful and finding the nerve root with the electrode, which is crucial, can be time consuming. When the values are low, it is difficult to be certain if the stimulation was submaximal. All these factors contribute to the widely reported normal range of TwPdi with ES –> 8.8-33 cm H_2O. More recently magnetic phrenic nerve stimulation has been shown to be useful to study the electrophysiological properties of the respiratory muscles, diaphragm in particular. The advantage of this technique is that it is relatively painless, precise localisation of the nerve is not required as with ES and it has also been used successfully in intensive care settings.

Introduction to Magnetic Stimulation: Michael Faraday in 1831 first described electromagnetic induction at the Royal Institution of Great Britain. He wound two magnetic coils on an iron ring and found that whenever the coil on one side was connected to a battery, electrical current passed through the coil on the other side. A change in the magnetic field from the first coil induced a current in the second coil. With time it has been realised that if sufficient primary current exists the iron ring can be

dispensed with as it only improved the coupling efficiency (fig 2.3.5.1). This forms the basis of non-invasive magnetic peripheral nerve stimulation in clinical practice. Polson et al produced the first magnetic stimulator capable of peripheral stimulation and recorded the muscle evoked potential (164). The intense magnetic fields created by stimulation penetrate clothing, soft tissue and bone to reach neural tissue. They preferentially activate the larger fibres, avoiding smaller fibres that mediate pain (165).

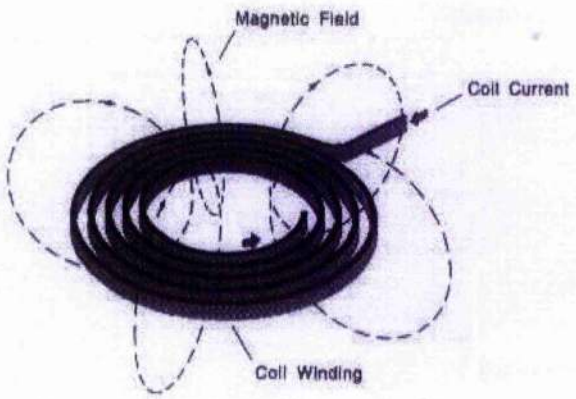


Fig 2.3.5.1: Magnetic Stimuli created by passing strong electrical current through a coil of wire (Reproduced with permission from Reza Jalinous – Guide to magnetic stimulation).

The magnetic nerve stimulators consist of two distinct parts: a high current pulse generator and a stimulating coil (fig 2.3.5.2). Magstim 200 stimulator (Magstim Company Limited, Whitland, Dyfed, Wales) was used in my study. The high current pulse generator produces magnetic pulses with field strengths of 1 tesla and pulse duration of 1msec (manufacturer's information). Although the energy released is small, the duration of discharge is short and hence the power (energy/unit time) is considerable. When a magstim receives a trigger input signal, the stored energy in the capacitor is

discharged and transferred to the stimulating coil that contains wound insulated copper coils in a plastic case.

Fig 2.3.5.2: Magstim stimulators with figure of 8 coils.

The discharge switch contains an electronic device called thyristor which conducts current in only one direction. Magstim 200 thus being monophasic has reduced heat dissipation in the coil and fewer stimulus artefacts.

The stimulating coil used was a 70 mm double coil (butterfly or figure of 8) in which the current induced was maximal directly under its centre where the two windings meet. The current flow in one is opposite to the flow in the other which may explain the site of maximal current.

Cervical magnetic phrenic nerve stimulation: Similowski et al (166) reported this technique to assess nonvolitional diaphragm strength in 1989. The stimulation is carried out by placing a circular 90 mm coil over the spinous process of C7 whilst the neck is in a flexed position to allow bilateral stimulation of the phrenic nerve roots.

Bilateral anterior magnetic phrenic nerve stimulation (BAMPS) was employed in my study as it is more likely to be supramaximal (167) compared to the cervical approach and also the contribution from ribcage muscle contraction towards TwPdi is less (168). Supramaximal stimulation implies that a further increase in stimulus intensity does not result any further increments in tension generation. Stimulations were carried out on subjects in a seated position after at least 20 min of rest to avoid twitch potentiation (169). The two coils were placed on either side of the neck at the posterior border of the sternocleidomastoid muscle at the level of the cricoid cartilage in sitting posture. The two Magstim 200 stimulators were connected so they fired simultaneously and at least 30 sec was left between stimulations. Each subject received 4 to 6 stimulations. Stimulations were done at end expiration, which was verified by careful observation of the oesophageal tracing (170). Previously researchers have used abdominal binding but this can markedly increase TwPdi although not have any effect on sniff Pdi (171). The abdomen was unbounded in my studies.

Whilst doing off-line calculation of the tracings, particular attention was paid to the quality of the twitches. Only twitches with a peak within 200m sec from the stimulation were included for analysis. Twitch responses where the Poes varied more than 1 cm H_20

immediately prior to the realisation of the twitches were ignored. So were the stimulations performed during swallowing or oesophageal peristalsis.

It has been shown that postprandial state increases TwPdi substantially (172) and I had asked all my subjects not to eat anything for at least 2 hours prior to arriving for the tests.

Table 2.3.5.1: Summary of the differences between electrical and phrenic nerve stimulation (173):

	Electrical Stimulation	**Magnetic Stimulation**
Stimulation Technique	Stimulates phrenic nerve selectively	Stimulates phrenic nerve as well as cervical nerve roots
Technical Expertise	Necessary	Not necessary
Associated Pain	+	Relatively painless
Poes	-	Higher than with ES
TwPdi	8 - 33 cm H_2O	Narrower range

Transdiaphragmatic pressure (Pdi), the difference between Pgas and Poes represents the force generated by the diaphragm (174). Poes and Pgas were measured directly and Pdi was calculated in real time by the online subtraction of Poes from Pgas.

Magnetic stimulus applied end expiration

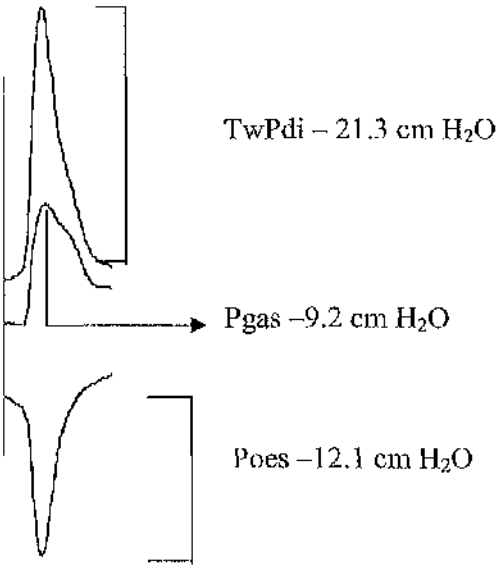


Fig 2.3.5.3: A typical pressure tracing following magnetic phrenic nerve stimulation.

2.3.6 Pneumotachograph for flow measurements (Fig 2.3.6.1)

Fig 2.3.6.1: Hans Rudolf heated pneumotachometer.

Hans Rudolf heated pneumotachometer (model 3700 series) was used in my studies to make all the flow measurements. The principle involves gas flow across two fixed resistors and a transducer measures the pressure drop from one end to the other and this is proportional to the gas flow as long as the flow is laminar. A heater was used to minimise condensation of the expired gas on the element. The flow signal was integrated to obtain tidal volume measurements. The flow measurements were mostly used to calculate the dynamic compliance of the lung.

2.3.7 Compliance of the Lung

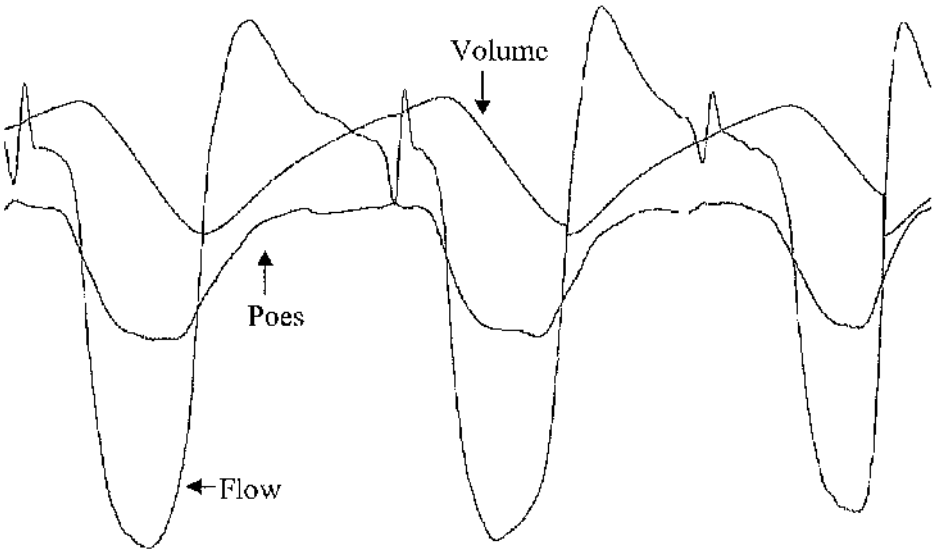
Compliance of the respiratory system is a measure of the distensibility of the lung. It is the inverse of the elasticity or the elastic recoil. The total compliance of the respiratory system is a combination of the compliance due to that of the lung and the chest wall. Since they are in parallel, they can all be linked by the equation,

$$\frac{1}{\text{Total Compliance}} = \frac{1}{\text{Compliance of the lung}} + \frac{1}{\text{Compliance of the chest wall}}$$

Total compliance in a normal person at FRC is about 0.1L/cm H_2O and that of the lung and chest wall about 0.2 L/cm H_2O.

The compliance of both lungs together will be additive as they run parallel.

Dynamic compliance of the lung was measured in my studies and this represents the pressure volume characteristics during tidal breathing. At low breathing frequencies, dynamic compliance is usually equal to the static compliance. In patients with increased resistance to air flow at higher breathing frequencies, the ratio of dynamic to static compliance falls below unity.



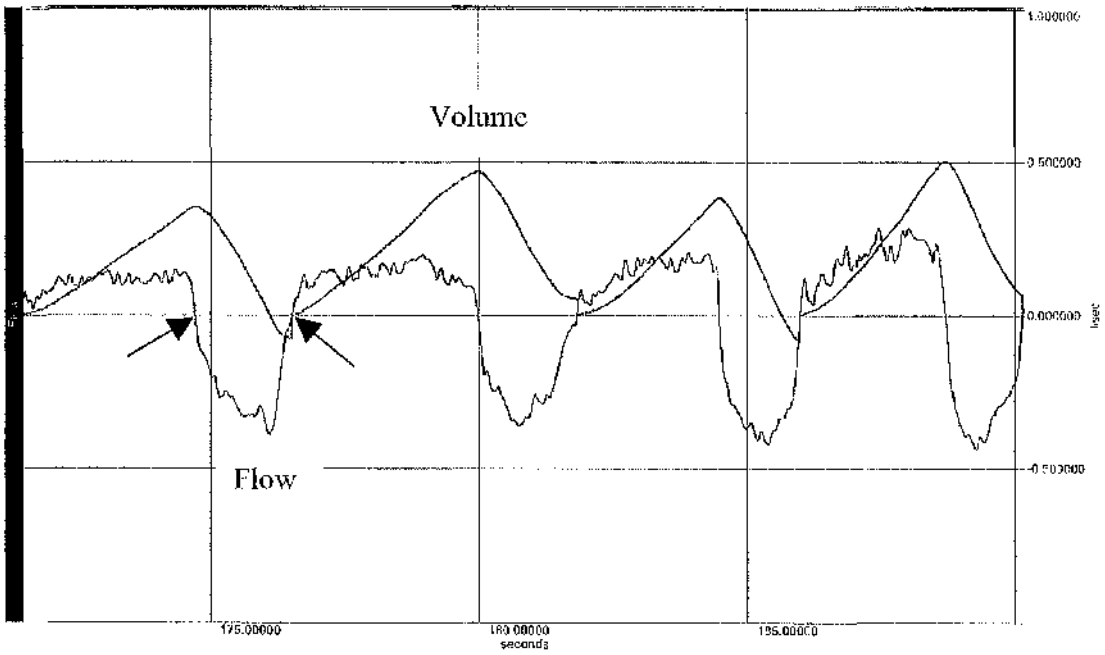


Fig 2.3.7.1a: The dynamic compliance was calculated by dividing change in volume by change in Poes at points of zero flow and by averaging 5-15 consecutive breaths.

Fig 2.3.7.2b: Represents the raw graph demonstrating points of zero flow (block arrows). Difference in the direction of the integrated volume depicted in the figures is due to change of flow in the flow head of the pneumotachograph.

Since dynamic compliance is frequency dependent, comparative measurements were matched for respiratory rate (175).

2.3.8 Strain Gauge for Quadriceps Strength Assessment

Dynamometers are commonly used to measure muscle strength although the variability of these tools is quite high (176). Any measurement of muscle force assessment are affected by the type of the equipment used, knee flexion angles and underlying disease condition. Since motor neurone disease can affect muscle groups patchily, peripheral muscle strength was not assessed in subjects with this condition.

A strain gauge system on a T piece was used in my studies to assess quadriceps muscle strength. The strain gauge was connected through a pre-stretched cord to an ankle band. Subjects were tested in lying posture and were asked to pull hard against the cord (fig 2.3.8.1). 5 to 10 attempts were made for each subject and the maximal value was taken as the maximal voluntary contraction (MVC) of the quadriceps muscle.

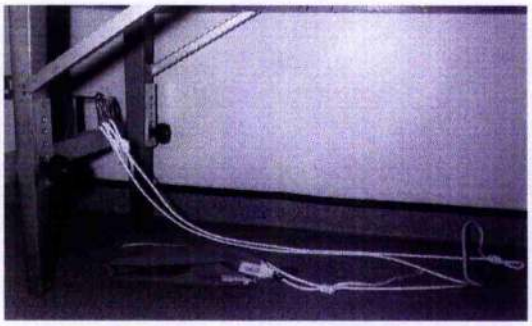


Fig 2.3.8.1: Strain gauge system used to measure peripheral muscle strength.

Linearity of the strain gauge system was checked (fig 2.3.8.2).

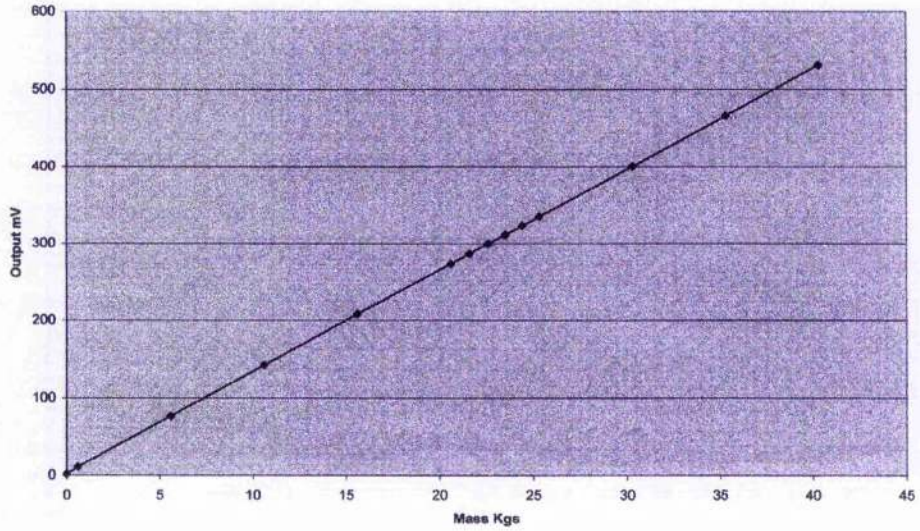


Fig 2.3.8.2: Demonstrates linearity of the strain gauge system at a gain of 100, which was used for study purposes.

2.4 Calibration of the Equipment

Electrical equipments require time to warm up during which the output from the transducers and amplifiers can drift. To obtain accurate signals able to discriminate small changes, all equipment was regularly calibrated. I used the two-point calibration system recording a zero signal (at atmospheric pressure) and a signal at one extreme of the range measured prior to each study.

The spirometer was calibrated using a three-litre syringe (with an accuracy of ± 15ml, Vitalograph Ltd, Buckinghamshire, England, UK) and a two-point calibration technique with zero as the baseline point and three litres as the actual value. The variability had to be < 3% to be acceptable.

The pressure transducer-amplifier system was calibrated prior to each study using the portable DPM III Universal biometer (BIO-TEK instruments Inc., Winooski, VT, USA). Atmospheric pressure (defined as 0) was used as one value and the other value was obtained by creating either a negative (for transducer measuring Pmo/MIP/SNIP) or positive (for transducer measuring MEP/Pgas) pressure using a 10ml syringe in a closed circuit with the transducer and the biometer. The universal biometer, flow meters of the air regulator and the Platon rotameter were checked for accuracy using the Timiter Calibration Analyser (series RT-200, Timiter Instrument Corportaion, Lancaster, PA – fig 2.4.1) on a periodical basis (every 6 months).

Fig 2.4.1: Timiter series calibration analyser.

The pneumotachograph was calibrated with flows in both inspiratory and expiratory directions. Airflow was generated via a pressurised air cylinder and controlled by a rotameter (Paton flow control, Basingstoke, UK and this covered flow range from 0.06 to 100 L/min air). Calibration was carried out at ambient temperature, again using the 2-point system.

The strain gauge system used to measure MVC was calibrated using two known weights (0kg, 25kg) prior to each study.

CHAPTER 3

INDIVIDUAL EXPERIMENTS AND RESULTS

3.1 Pulmonary Function Tests in MyD and MND

3.1.1 Hypotheses:

1. Simple spirometry needs to be supplemented with mouth pressures to give better picture about underlying respiratory muscle weakness in MyD and MND.

2. Routine measurement of full pulmonary function tests would be useful in monitoring these patients.

3.1.2 Study Design:

In 20 MyD and 5 MND patients we evaluated dynamic lung volumes, relation between FEV_1 and FVC, correlation between FVC, TLC, RV, diffusion capacity and mouth pressures (MIP≤80cm H_2O and MEP≤90 cm H_2O were considered to be significantly reduced). There were 4 patients without any particular respiratory symptoms (2 with MND and 2 with MyD) and the remaining 21 had disturbed sleep pattern, excessive sleepiness, breathlessness on exertion and tiredness when directly enquired.

All patients attended the respiratory laboratory in the morning to minimise the diurnal effect on pulmonary function testing (177). Height and weight were recorded to obtain body mass index [BMI in kg/m^2 = weight in kg / height in m^2] (178). Epworth sleepiness scale score was obtained (179, appendix III). Twenty patients underwent lung volume measurement using the Medisoft HYPAIR Compact Helium dilution technique. Five patients had body plethysmography in place of Helium dilution technique using Pulmolink system (Medisoft 5500 model with EXPAIR software). This can give higher

values for FRC (thoracic gas volume) as it takes into account any trapped gas. This was used due to technical problems with Helium dilution technique on the day patients attended the laboratory. Sitting/standing VC and supine VC were measured with a Vitalograph spirometer (Bucks, UK).

3.1.3 Technical outline:

Helium Dilution Technique (180): Subjects breathed through a closed circuit, a gas mixture containing insoluble Helium (14% He, 24.5% oxygen balanced with nitrogen). During rebreathing CO_2 was absorbed and oxygen added continuously to maintain constant overall volume of the system. Normally He equilibration is taken to be complete when the concentration of He is < 0.02% over 30sec.

FRC was calculated from the formula:

$$V_i * F_1He = V_2 * F_2He$$
$$= (V_1 + FRC + VD) * F_2He$$

$$FRC+VD = \frac{V_1(F_1He - F_2He)}{F_2He}$$ L.ATPS (which is converted to BTPS).

Where V_1 - Known volume of the gas mixture
F_1He - Initial fractional concentration of He
F_2He - Equilibration concentration of He
VD - Dead Space (of the equipment + anatomical dead space)

At the end of the procedure subjects took a deep breath in to give inspiratory capacity IC.
FRC+IC = TLC.

The **body plethysmograph** employs Boyle's law, which states that for a closed container at constant temperature, the pressure times the volume is constant. The subjects sat in the 'box' and breathed through a mouthpiece. The tubing from this contained a sidearm connected to a pressure transducer to measure mouth pressure. At relaxed end expiration, mouth and alveolar pressure equals atmospheric pressure (P_1). V_1 is the unknown FRC. A second pressure monitor measured box pressure. Pneumotachograph was used to measure airflow. Once a normal breathing pattern was established the operator closed the shutter in the airway at the end of normal expiration. The subjects took a breath in against the closed airway. Here the chest continued to expand and box pressure increased because of the volume of air in the box decreased by the amount the patient's chest volume increased (ΔV). The true box volume which is the volume of the plethysmograph minus the volume occupied by the patient can not be easily determined and hence the plethysmograph was calibrated with the patient in it by injecting known volumes of air into the plethysmograph and determining the increase in pressure.

$$P_1 * V_1 = P_2 * V_2$$

$$= (P_1 - \Delta P) * (V_1 + \Delta V)$$

$$V_1 = P_1 * \Delta V / \Delta P$$

Product of $\Delta V \Delta P$ is ignored as the value tends to be very small.
ΔV is a function of the change in the box pressure that can be measured easily.
ΔP – Change in the mouth pressure (P_1) after full inspiration.
P_1 – Initial mouth pressure at end expiration, which is the barometric pressure.
V_1 – Represents the thoracic gas volume at end expiration.

Carbon monoxide Diffusion Capacity (TLCO) was measured using single breath technique (181). Subjects breathed rapidly from RV to TLC via a reservoir bag containing a mixture of 0.28% CO + 9% He + 19% O_2 balanced with nitrogen. The

breath was held for 10sec at maximal inspiration and then a rapid and complete exhalation was made. The rate of transfer of CO (kCO) was measured at full lung inflation and was corrected for the haemoglobin concentration (182). TLCO was calculated as the multiple of kCO and alveolar volume divided by the barometric pressure (Pb).

3.1.4 Results:

There were 8 former and 1 current smoker in the group. Subject details and lung volumes are summarised in Tab 3.1.4.1-3.1.4.4. Results are expressed as mean (95% CI).

Table 3.1.4.1 Patient subgroups:

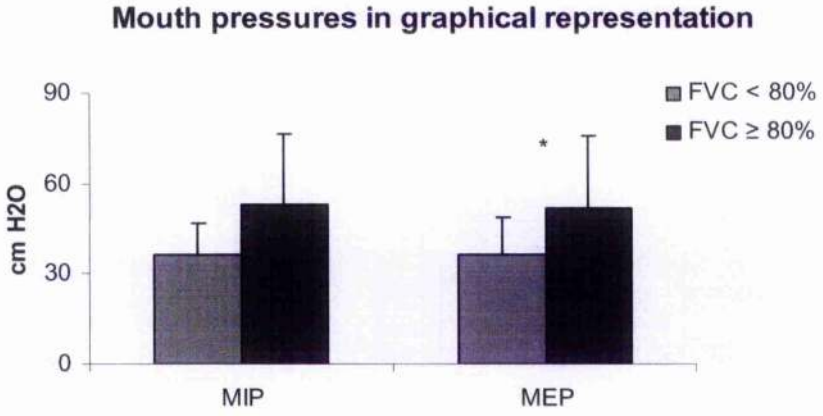
	Patients with reduced FVC < 80% n = 14	**Patients with normal FVC ≥ 80% n = 11**
	Male:Female	Male:Female
MyD	6:5	5:4
MND	3:0	1:1

Table 3.1.4.2 Demographic details:

	Patients with reduced FVC < 80% n = 14	**Patients with normal FVC ≥ 80% n = 11**
Age (years)	44.5 (38.7-50.3)	41.1 (34.6-47.6)
ESS	9.1 (6.8-11.3)	13.1 (10.7-15.5)
Body Mass Index (kg/m^2)	27.8 (24.5-31.2)	25.4 (23.8-27.0)

Table 3.1.4.3 Dynamic Lung Volumes: * $p < 0.05$

	Patients with reduced FVC < 80% n = 14	**Patients with normal FVC ≥ 80% n = 11**
% Predicted FEV_1	59.0 (51.9-66.1)	94.2 (86.2-102.2)*
% Predicted FVC	59.3 (52.8-65.9)	94.2 (86.2-102.2)*
FEV_1/FVC	101.7 (99.7-103.6)	95.4 (89.9-100.9)
% fall in supine VC	11.7 (7.5-15.9)	6.7 (4.1-9.2)



*p = 0.048

Fig 3.1.4.1: Mouth pressures in MyD and MND. Though both MIP and MEP tended to be reduced, only MEP showed a significant trend in subjects with FVC < 80% predicted.

Table 3.1.4.4 Static Lung Volumes:

	Patients with reduced FVC <80% n = 14	**Patients with normal FVC ≥ 80% n = 11**	**p value**
% Predicted FRC	81.3 (66.2-96.4)	102.8 (93.1-112.5)*	0.013
% Predicted ERV	51.7 (44.4-59.1)	115.6 (97.1-134.1)*	0.0001
% Predicted RV	107.4 (85.3-129.5)	94.4 (81.4-107.3)	0.62
% Predicted TLC	75.7 (66.6-84.9)	97.7 (92.3-103.1)*	0.007
% Predicted TLCO	68.6 (63.3-73.8)	84.1(76.7-91.4)*	0.02
% Predicted KCO	109.9 (99.2-120.6)	92.2 (82.6-101.8)	0.10

* $p < 0.05$

Correlation between static, dynamic lung volumes and mouth pressures is depicted in Fig 3.1.4.2 to 3.1.4.8.

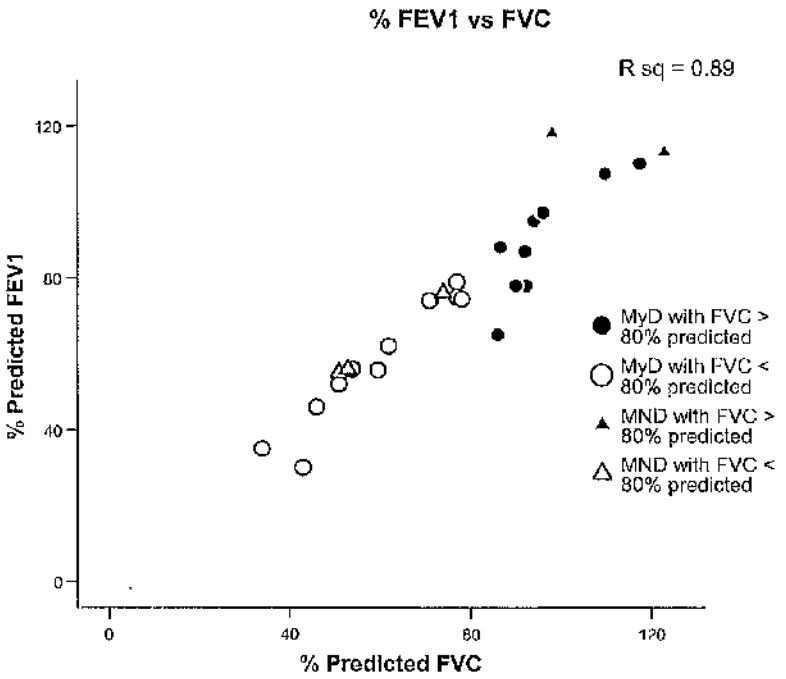


Fig 3.1.4.2: Correlation between FEV_1 and FVC.

Only two patients who were previous smokers had FEV_1/FVC ratio < 80% predicted. Otherwise the reduction in FEV_1 tracked closely to that of FVC (fig 3.1.4.2) showing the well described restrictive defect. Though the percent supine fall in supine vital capacity was higher in patients with low MIP and FVC, this did not reach statistical significance.

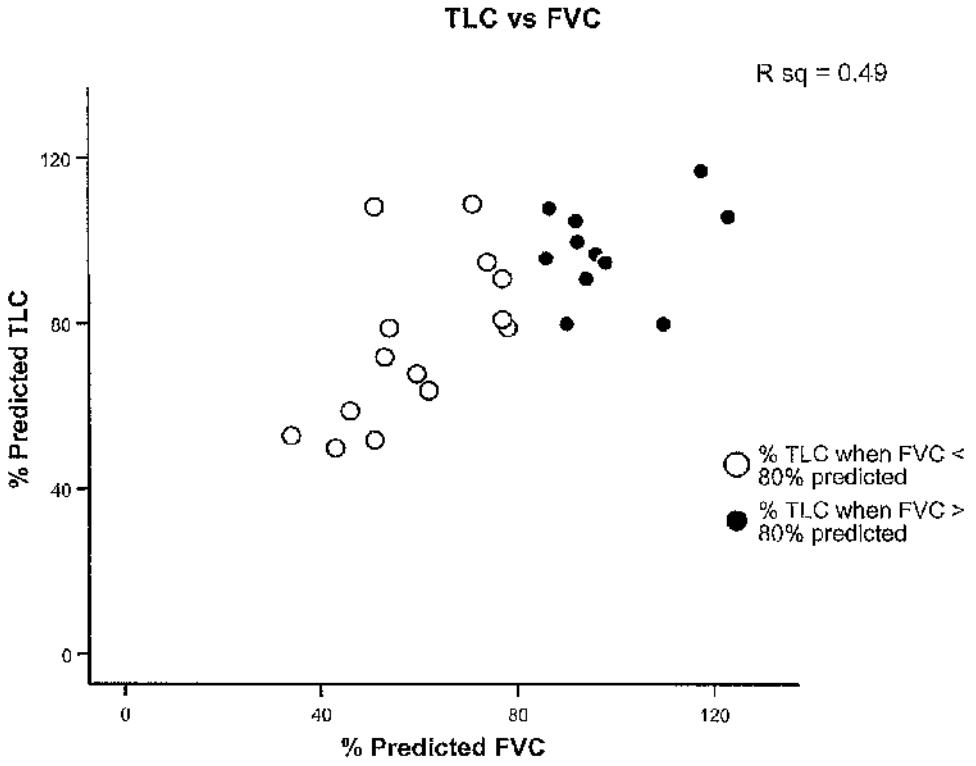


Fig 3.1.4.3: Correlation between FVC and TLC ($r=0.7$, $p<0.05$). There were 2 patients with TLC > 100% predicted when FVC was reduced. One was a patient with MND with significant smoking history and FEV_1/FVC ratio was < 80% signifying airflow obstruction. The other subject was one with MyD with 10 pack year history of smoking but the spirometry was restrictive in nature. This patient had lung volume estimation by body plethysmograph.

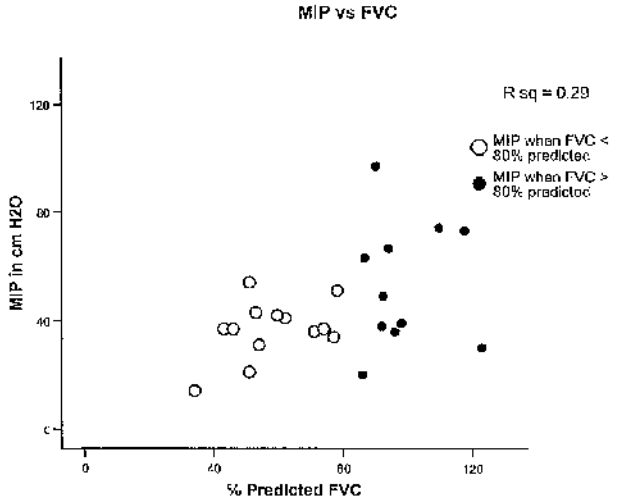


Fig 3.1.4.4: Correlation between FVC and MIP ($r=0.54$, $p<0.05$). This graph demonstrates low values of MIP even when FVC is within the normal range.

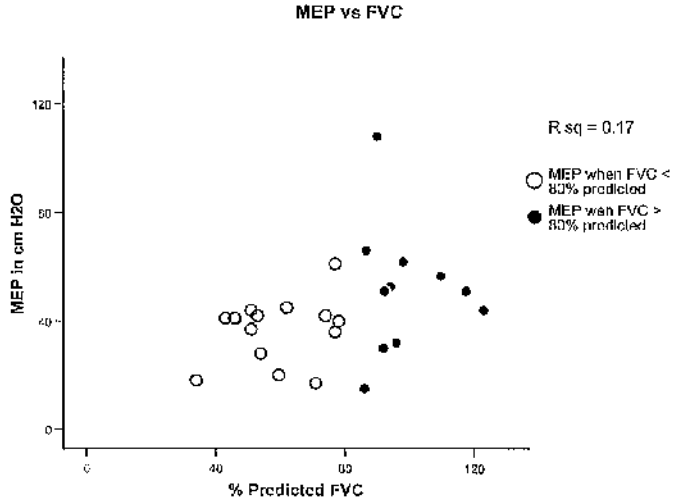


Fig 3.1.4.5: Correlation between FVC and MEP ($r=0.42$, $p=0.0005$). Again, there is a scattter but this graph highlights that MEP as with MIP is reduced in a group of patients when the FVC is within the predicted range.

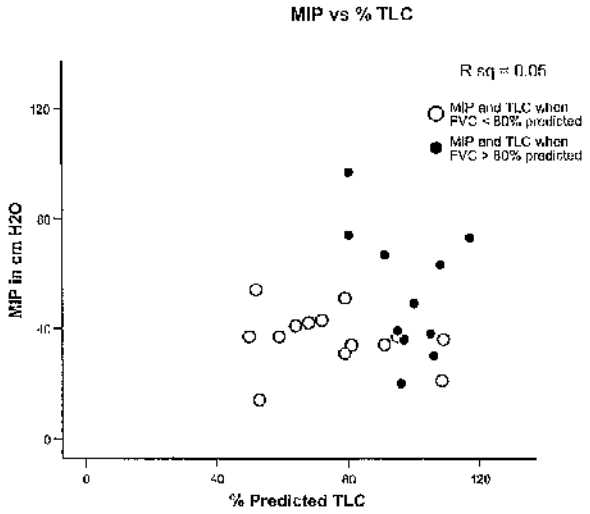


Fig 3.1.4.6: Correlation between TLC and MIP (r=0.23, p=0.27). The scatter around the axis was greater compared to the relation between FVC and MIP (weaker correlation). Again there were patients with normal TLC with reduced mouth pressures as seen with FVC.

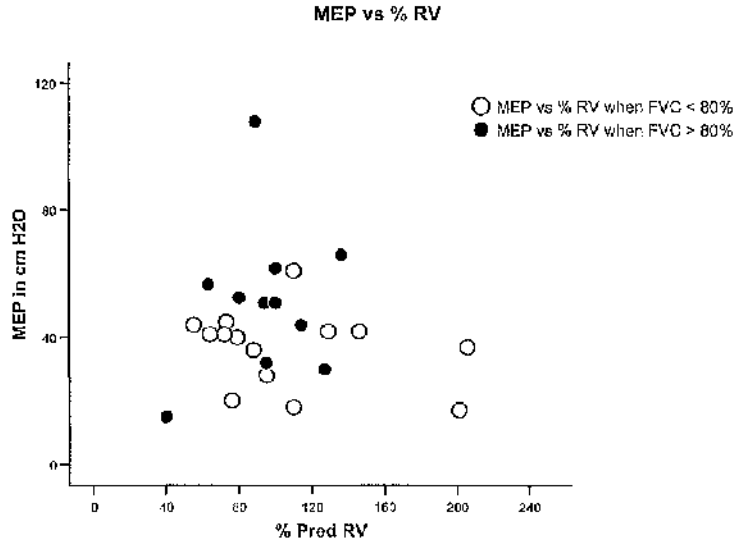


Fig 3.1.4.7: Correlation between RV and MEP (r=-0.2, p=0.4).

In 10 out of 11 patients (90.9%) with normal FVC, MIP and/or MEP were reduced suggesting significant inspiratory and/or expiratory muscle weakness. The ratio of % RV/TLC correlated significantly with percent predicted RV (r=0.4, p=0.02), as a measure of air trapping, which is an indirect evidence of expiratory muscle weakness. However correlation between MEP and %RV, %RV/TLC and % ERV was weak.

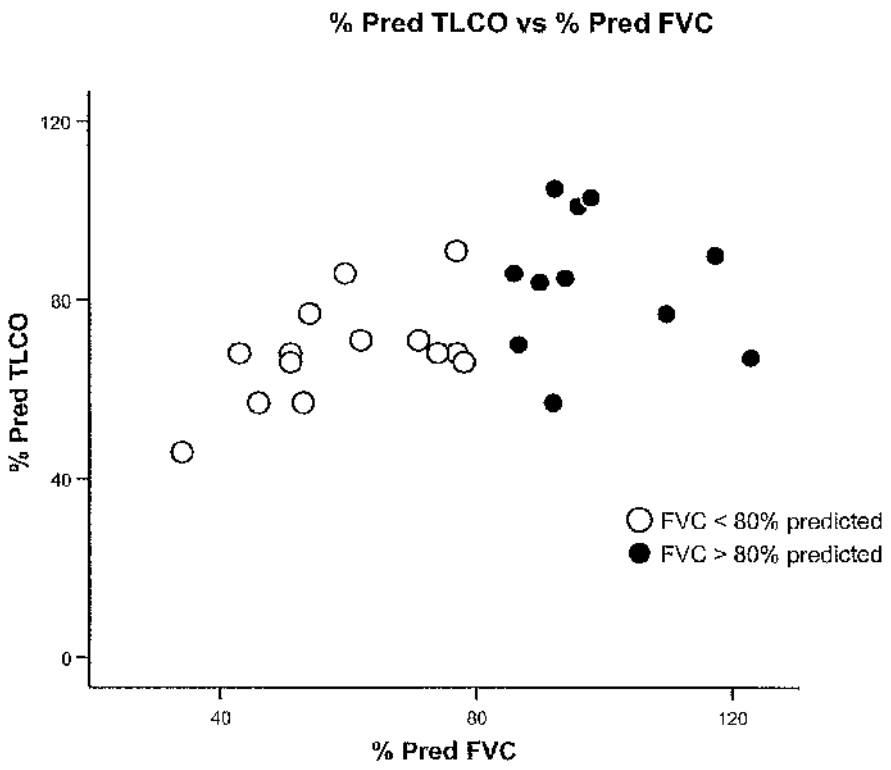


Fig 3.1.4.8: Correlation between FVC and % TLCO (r=0.53, p=0.006). There were 4 patients (36.7%, 3 with MyD and 1 with MND) with reduced % TLCO when FVC was preserved. Mouth pressures were invariably reduced in these patients.

Correlation between FVC and KCO again was not strong though significant (r=-0.47 and p=0.02).

3.1.5 Discussion:

In our group of MyD and MND patients with minimal symptoms, 56% showed reduction in both FVC and mouth pressures. However 90.9% of patients with preserved vital capacity showed reduced mouth pressures. Vital capacity was a good marker for TLC, FRC, ERV and TLCO. MEP correlated poorly with residual volume. This study reiterates the importance of basic spirometry to provide useful information at the outset in the assessment of this group of patients. MIP, MEP values were quite reduced in spite of ensuring adequate seal during the procedure and making certain that there were no leaks within the system. Again this is supported by the values obtained for 'normal subjects' within our laboratory using the same methodology (appendix I,II). The relation between FVC and MIP is curvilinear (183) and hence the fall in mouth pressure precedes lung volume change. This could partly explain the significant number of patients with low mouth pressures and preserved FVC and also highlights the importance for measuring mouth pressures along with simple spirometry in this group of patients. There is a great between- and within individual variation for mouth pressures and this could contribute to the low values of MIP and MEP with reasonably preserved FVC in our group of patients. Thirdly, use of flanged mouth piece gives lower and more variable values compared to a tube mouth piece especially in patients with buccal muscle weakness (184) which would contribute to low mouth pressures in our patients.

Static lung volumes and diffusion capacity did not yield any further information that could not be predicted from baseline spirometry. For routine monitoring this also avoids

neuromuscular disease patients to come into the laboratory for detailed assessments. Simple spirometry and mouth pressures carried out either in the outpatient clinics or at home by trained staff provides useful information that could guide further management of patients with neuromuscular and chest wall disorders. It used to be thought that respiratory muscle weakness is associated with reduced TLCO and increased KCO showing the well described 'extra pulmonary restriction'. However in a landmark study by Hart et al (185), relation between lung volumes, respiratory muscle weakness and diffusion capacity was explored. It was shown that the KCO varies depending on the volume and extent of inspiratory/expiratory muscle involvement and in combined weakness KCO was even normal or reduced indicating abnormalities of lung parenchyma or vasculature. There were patients with reduced TLCO and KCO in our group of patients but as invasive respiratory muscle tests were not carried out, a closer examination of this relationship was not possible.

It is generally accepted that < 25% fall in supine vital capacity is a marker of significant diaphragm weakness. In our group of patients, even in the face of severe reduction in MIP this was an uncommon event. This suggests that the sensitivity of supine vital capacity is quite weak and if clinically indicated, further tests of diaphragm strength should be carried out to confirm the diagnosis. However in this set of studies, SNIP or Pdi measurements were not carried out. This is further discussed in chapter 5.1.

3.1.6 Conclusions:

It was noted that mouth pressures were low in patients even when their FVC and TLC were within the predicted range and this supports our hypothesis that 'mouth pressures should always supplement routine lung function tests in assessment for respiratory muscle weakness'. No extra information was gathered by routine monitoring of static lung volumes and diffusion capacity.

The difficulty remains for the clinician to determine whether low mouth pressures/volitional tests equate to 'true reduction in respiratory muscle strength' and this is explored in further experiments.

3.2 Sleep Studies in MyD and MND

3.2.1 Hypothesis:

1. Routine sleep studies would help to identify a group of MyD and MND patients with significant SRBD early that would benefit from interventions such as NIV.

Our secondary aims were to

i) Identify common symptoms of presentation.

ii) Define the prevalence of SRBD in our group of patients.

iii) Relate daytime pulmonary function tests to nocturnal parameters.

iv) Identify the practicality of different sleep study systems.

3.2.2 Study Design

Number of patients: 37

Table 3.2.2.1: Patient characteristics.

	MyD n=25 (15 Male:10 Female)	**MND n=12** (11 Male:1 Female)
Age (years)	40.0 (35.9-44.1)	59.2 (45.1-73.2)
BMI (kg/m^2)	26.1 (22.8-29.3)	24.5 (21.2-27.7)
ESS	11.0 (8.8-13.2)	4.6 (2.9-6.3)

Patients should have had at least one symptom suggestive of respiratory muscle weakness or nocturnal hypoventilation to be included in the study. They were specifically asked

about daytime sleepiness, breathlessness, orthopnoea, easy fatigability, snoring, apnoea, disturbed sleep, morning headaches and recurrent lower respiratory tract infections.

All the patients were asked to complete the Epworth Sleepiness Scale (ESS) as a measure of sleepiness (179, appendix III). They subsequently underwent full polysomnography or overnight oximetry in hospital followed by assessment of spirometry, supine vital capacity, mouth pressures (MIP $\leq$ 80cm H_2O, MEP $\leq$ 90cm H_2O and SNIP $\leq$ 70cm H_2O were considered to be significantly reduced) and awake arterial blood gases in the morning. Patients who preferred not to come into the hospital were called into the Respiratory Laboratory to have lung function tests and were given a wrist pulse oximeter to take home for overnight monitoring.

Dynamic lung volumes were measured using a spirometer (Vitalograph; Bucks, UK) and reference values taken from the European Community for Steel and Coal (149). Maximal Inspiratory pressure (MIP) was measured from total lung capacity and Maximal Expiratory pressure (MEP) from residual volume according to standard criteria (152,186).

Polysomnography: Sixteen-channel polysomnography (Sensormedics Alpha or Alice 3 v1.2) was carried out in 20 subjects (18 MyD and 2 MND) and that included electroencephalogram (EEG), electrooculogram, chin electromyogram (EMG), airflow (3 port thermistor), electrocardiogram (ECG), respiratory movements of chest and abdomen

(using inductance plethysmography), microphone to identify snoring and pulse oximetry. EEG (C4-A1, C3-A2) was used to score awakenings and sleep stages according to standard criteria (187). Computer scoring was reviewed by an experienced technician and rescored manually if required. Sleep efficiency (SE) was derived as the ratio of total sleep time (TST) to time in bed. An apnoea was defined as reduction in airflow to ≤ 30% from baseline associated with 4% reduction in oxygen saturation (SpO_2) or complete cessation of flow lasting at least 10 sec. A hypopnoea was scored when the airflow reduced to ≤ 50% from baseline associated with 4% drop in SpO_2. An apnoea was considered to be obstructive when the thoracic or abdominal movements were present and central when these movements were absent. An experienced technician scored all the events manually. Patients were classified to have significant upper airway collapsibility when the apnoea-hypopnoea index or respiratory disturbance index (RDI) was ≥15 events/hour. Nocturnal hypoxaemia of SpO_2 ≤ 90% lasting > 30% of the night is normally considered for long-term oxygen therapy in chronic lung diseases (188). ACCP guidelines in 1999 (189) suggested considering NIV in symptomatic neuromuscular disease patients nocturnal desaturation of ≥ 88% lasted 5 min or longer. There is considerable variation in recommendations regarding significant nocturnal desaturation.

Overnight oximetry: Nocturnal pulse oximetry was carried out at home using Minolta pulsox (Sampling frequency: one in every 5 sec) 3i model (fig 3.2.2.1). Patients were encouraged to use it for at least 5-6 hours on the day of the study. Mean overnight oxygen saturation and time spent below SpO_2 of 90% were recorded. Desaturation index (DI) was taken to be significant when episodes of 4% or greater SpO_2 drop lasted 10 sec

and the frequency was ≥15 events/hour. 7 MyD and 10 MND subjects were assessed with nocturnal pulse oximetry.

Fig 3.2.2.1: Minolta pulse oximeter.

SRBD definition for the purpose of the study:

SRBD consisted of upper airway collapsibility (RDI/DI ≥ 15events/hr), persistently low baseline SpO_2 (≤ 90%), lasting for greater than 10 min. at a stretch, REM state hypoventilation and/or daytime hypercapnia.

3.2.3 Results

Prevalence of excessive daytime sleepiness as assessed by Epworth sleepiness scale (ESS > 11) was highest in MyD patients (37%). The main symptoms for referral included tiredness and excessive sleepiness in MyD (67%), breathlessness in MND (76%). Sixteen patients (43.2%) assessed had significant sleep disordered breathing. Symptoms of apnoeas, snoring and disturbed sleep were more prevalent in the SRBD group. However orthopnoea and breathlessness was not a feature even in patients with daytime hypercapnia.

Myotonic Dystrophy subgroup:

Table 3.2.3.1: Baseline patient characteristics. Patients with SRBD tended to be older and had higher BMI in comparison to non-SRBD group, though this was not statistically significant.

	SRBD group (n=9)	**Non-SRBD group (n=16)**
Age (years)	43.1 (35.7-50.5)	38.8 (33.3-44.2)
BMI (kg/m^2)	28.4 (23.8-33.0)	24.6 (20.0-29.2)
ESS	10.6 (6.7-14.4)	12.3 (9.3-15.2)

Table 3.2.3.2: Summary of the daytime lung function tests and nocturnal parameters in MyD.

	SRBD group (n=9)	**Normal overnight study group (n=16)**
% Predicted FEV_1	68.0 (44.4-91.6)	74.3 (65.3-83.3)
% Predicted FVC	71.5 (49.4-93.6)	79.1 (70.6-87.7)
% fall in supine FVC	11.4 (4.5-18.3)	7.8 (4.2-11.5)
RDI/DI (events/hour)	22.8 (8.8-36.8)	2.7 (0.4-5.0)*
Time spent < 90% (min)	79.9 (50.1-109.7)	6.2 (1.8-10.7)*
Mean overnight SpO_2	90.6 (89.9-91.3)	93.8 (92.5-95.0)*

*$p < 0.05$ and significantly different in comparison to SRBD group.

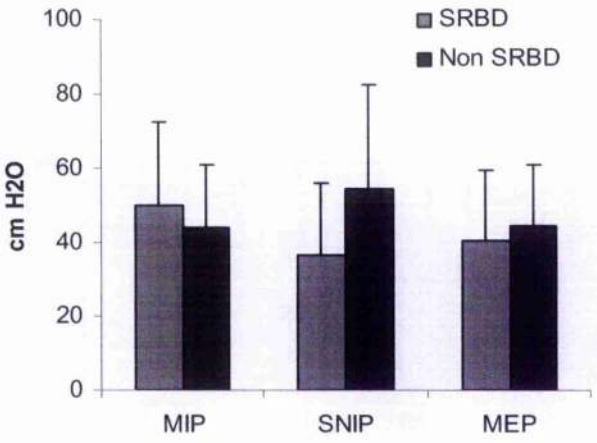


Fig 3.2.3.1: Graph showing the non-invasive respiratory muscle strength (Error bars reflect the 95% CI) in the two different groups. As with the percent-predicted FVC there was tendency to have lower mouth pressures in SRBD group. But the differences between the two groups were not statistically significant.

Correlation between FVC and mouth pressures was weak ($r = 0.4$ with MIP, $p=0.08$, $r = 0.5$ with SNIP and $r = 0.6$ with MEP, $p=0.18$). However for the whole group FVC correlated well with arterial pCO_2 ($r=-0.7$, $p<0.05$). It was of interest to note that three subjects (out of nine) with SRBD had normal predicted FVC and three patients (out of 16) had < 60% predicted FVC and did not have SRBD. Thus the positive predictive value of FVC < 60% for predicting underlying SRBD (sensitivity) would be 67% and specificity (FVC > 60% excluding SRBD) would be 85%. Correlation between FVC and RDI was also weak at 0.3 ($p=0.16$). Incidence of upper airway collapsibility was higher in patients with low mean overnight oxygen saturation. Daytime $PaCO_2$ was higher in SRBD patients [mean 6.3 (0.9) kPa vs 5.8 (0.3) kPa in non SRBD] though this did not reach statistical significance.

Table 3.2.3.3: Sleep stages in Myotonic Dystrophy in 18 subjects who underwent PSG.

Statistically there were no significant differences between the various sleep stages within the two groups.

	Patients with SRBD (n = 8)	**Patients without SRBD (n = 10)**
TST (min)	285.1 (219.3-350.9)	322.3(290.6-353.9)
SE (%)	79.0 (67.8-90.1)	73.7(69.5-77.9)
% Stage I	24.1(14.0-34.2)	26.7(18.1-35.4)
% Stage II	40.7(30.7-50.8)	34.3(29.0-39.6)
% Stage III	9.8(5.8-13.9)	20.2(11.7-28.7)
% Stage IV	3.1(0.3-5.9)	3.9(2.0-5.7)
% REM	15.0(7.3-22.7)	9.0(0.4-11.6)

There was predominance of lighter stages of sleep in comparison to slow wave sleep in myotonic dystrophy patients. In 3 out of the 7 patients with compromised nocturnal oxygenation, this could not be predicted from any of the daytime tests. ESS was normal in two of these patients and the patient with sleep apnoea had only mildly elevated ESS at 12. FVC was normal in all the three patients though MEP was reduced more than MIP, which is known to occur in MyD. The common sleep abnormalities noted in these patients included central sleep apnoea (1 patient) and nocturnal hypoventilation (2 patients). A sleep tracing of a patient showing REM hypoventilation is shown in fig 3.2.3.2.

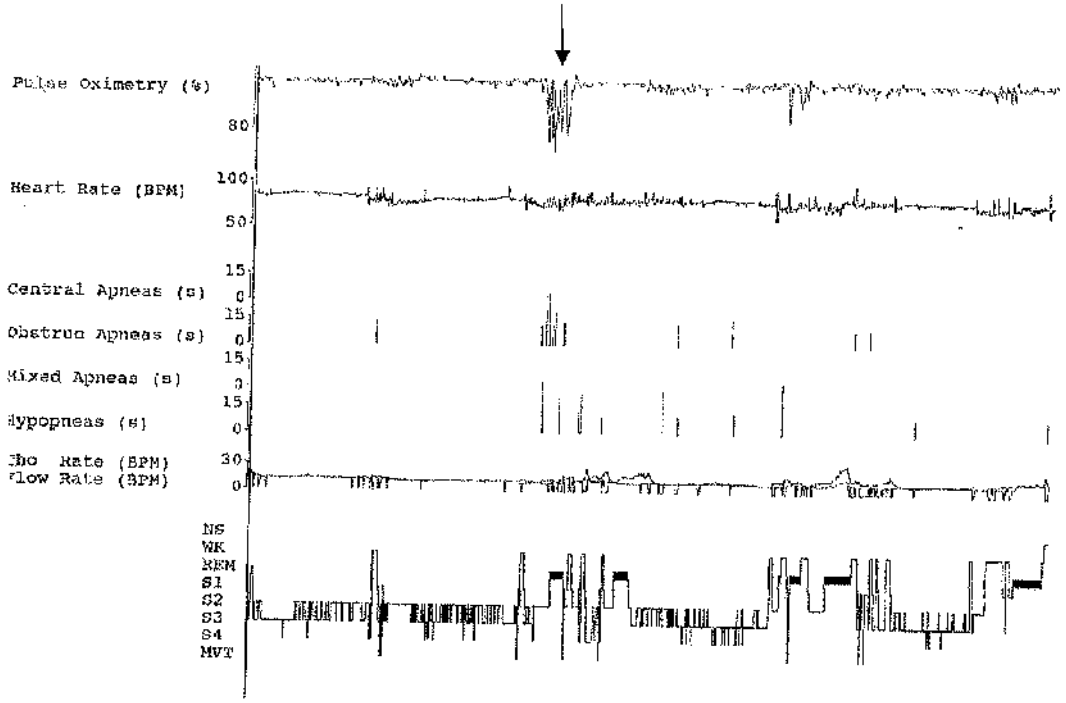


Fig 3.2.3.2: REM hypoventilation.

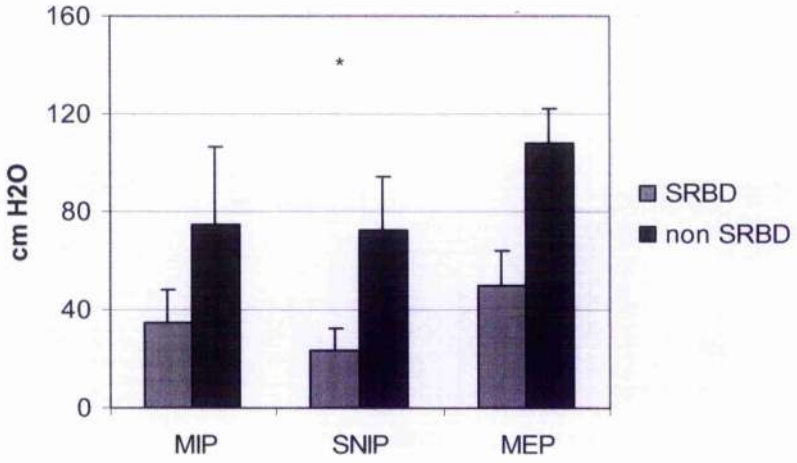
MND subgroup:

Table 3.2.3.4: Baseline Characteristics. Results in mean (95% CI).

	SRBD group (n=7)	**Non-SRBD group (n=5)**
Age (years)	64.1(55.4-72.9)	52.2(35.2-69.2)
BMI (kg/m^2)	25.3(21.4-29.2)	28.1(26.0-30.2)
ESS	5.0(3.4-6.6)	4.2(3.8-4.6)

Table 3.2.3.5: Differences between the two subgroups.

	SRBD group (n=7)	**Normal overnight study group (n=5)**
% Predicted FEV_1	67.3(49.4-85.2)	75.3 (37.6-113.0)
% Predicted FVC	67.2 (45.9-88.6)	72.7 (47.2-98.1)
% fall in supine VC	17.6 (0.5-34.7)	4.0 (-1.0-9.0)*
RDI/DI (events/hour)	2.0 (1.1-5.0)	0.6 (0-2.0)
Time spent < 90% (min)	39.7(6.0-73.3)	6.2 (4.6-9.1)*
Mean overnight SpO_2	90.8(89.5-92.2)	95.6(94.6-96.6)*



*p<0.05

Fig 3.2.3.3: Mouth pressure difference between SRBD and non-SRBD group. Though MIP and MEP showed downward trend in SRBD group, SNIP was significantly different.

In most patients with motor neurone disease, overnight monitoring did not reveal any additional information that could not be predicted from their symptoms, daytime lung function assessment and blood gas analysis. In the two patients who had PSG, this was useful only to identify sleep macro architecture. Correlation between mouth pressures and FVC was weak (MIP vs FVC r=0.6, p=0.2, MEP vs FVC r=0.4, p=0.08, SNIP vs FVC r=0.6, p=0.2). The correlation between percent predicted FVC and RDI was also weak (r=-0.2, p=0.15). There was significant correlation between FVC and $PaCO_2$ at r=0.8, p=0.03.

3.2.4 Discussion

In neuromuscular diseases it is sometimes difficult to determine how much the nocturnal events contribute to daytime symptoms. Though nocturnal events precede daytime symptoms and blood gas abnormality, their occurrence can be difficult to predict from daytime measurements. Often in neuromuscular diseases, symptoms of respiratory muscle weakness can be delayed due to reduced mobility and the associated peripheral muscle weakness may in fact mask any concomitant respiratory symptoms. Facial muscle weakness can also underestimate mouth pressures and hence when reduced their interpretation becomes difficult. Daytime hypercapnia is a late event. In presence of symptoms and normal blood gases, therefore, often sleep studies are resorted to. To date there is no conclusive evidence of benefit with routine monitoring. This study adds data to the existing evidence. However it also identifies a group of myotonic dystrophy patients with significant nocturnal disturbance, albeit small (12% of myotonic dystrophy patients) that will be missed if only mouth pressures, spirometry and arterial blood gases are employed for assessment. Generally it is known that patients with neuromuscular diseases run into complications when FVC < 40-50% of the predicted (190). Hence, 3 patients with myotonic dystrophy in our patient population with normal FVC and significant SRBD merit further discussion. This may well be related to the differences in muscle groups affected. Since diaphragm function was not specifically measured in this group, it will be interesting to see in further studies if such a scenario is due to predominantly affected diaphragm with sparing of the other respiratory muscles. Does it really matter if we do not identify these patients as it is well known that compliance with NIV in MyD patients is not as good as in other neuromuscular diseases? (109). It is

debatable, as the experience with NIV in MyD is still in its infancy. Myotonic dystrophy patients are known to have neuropsychiatric and cognitive impairment and it will also be interesting to see if this solely contributes to the non-compliance. Since more of these patients are likely to be assessed for NIV in the future it is worth trying to identify the subgroup of patients who will benefit from it. There is emerging evidence that NIV does improve daytime blood gases in MyD patients (109).

A critique of our methodology is that there was no clear distinction between patients who underwent in-hospital sleep studies and those in their own homes. This was entirely dependent on patient preference, taking into account the distance to travel, mobility and willingness. Unattended studies are likely to underestimate the occurrence of respiratory events especially in the presence of respiratory muscle weakness and it is also well known that obstructive events can be underscored as central events when using non-invasive respiratory movement analysis techniques (191,192). Those who were admitted for polysomnography were assessed on a single night and the lower percentage of slow wave sleep observed could well be attributed to the 'first-night' effect.

We acknowledge that DI and RDI are not directly comparable and that our chosen index of $\geq$ 15 events/hour is a high threshold for SRBD in general. However, since sleep breathing therapies are usually instituted when SRBD is marked (109) and the sampling rate of the pulse oximeter used would have high specificity at this level to pick up desaturations (148), we opted to use this threshold value for RDI/DI. These factors could have contributed to a smaller proportion of SRBD patients being identified in our group.

Nocturnal pulse oximetry has recently been shown to be useful to detect early desaturations during overnight monitoring in motor neurone disease (193). This study adds further evidence that home monitoring with overnight oximetry may be a useful tool in selected group of patients with neuromuscular diseases. It is well known that REM hypoventilation precedes more prolonged desaturations during the night and total reliance on overnight oximetry is likely to miss this group of patients. Eight out of seventeen patients (47%) in the pulse oximetry group had home study. It was technically feasible in all of them and patients did not report any problems with its use. Simplicity of the technique makes it an attractive option especially for some chronic neuromuscular diseases where patients are reluctant to come into hospital. The data available on Duchenne muscular dystrophy in this regard can also be applied to other neuromuscular diseases (194).

3.2.5 Conclusions

Prevalence of SRBD was 43.2% in symptomatic individuals referred for assessment in our clinic. Common symptoms of presentation included excessive sleepiness and tiredness in MyD and breathlessness in MND. Correlatioon between daytime measurements (FVC, MIP, SNIP, MEP) and nocturnal events (RDI/DI) was poor. It was feasible to carry out nocturnal oximetry in both MyD and MND patients with 36.8% of studies detecting significant SRBD (vs 50% detected on the PSG).

Routine sleep studies did not add any further value in comparison to daytime measurements apart from 3 patients (12% MyD) who would be missed if only daytime studies were relied on. Of all the non-invasive tests, FVC correlates best with daytime hypercapnia. Detailed sleep studies seem best utilised as targeted investigation in patients with multiple symptoms that raise suspicion of nocturnal hypoventilation and/or upper airway collapsibility with normal awake arterial blood gases. Certainly it was commoner in older and heavier individuals though statistical significance was not reached in our study.

3.3 Respiratory Muscle Strength in Myotonic Dystrophy (MyD)

With this background we went on to:

1) Review retrospectively all the MyD patients that had attended our respiratory units.

2) Evaluate the volitional and nonvolitional respiratory muscle strength in patients with MyD.

3.3.1 Five-year case note review

As a preamble to my studies, we undertook retrospective case note review of all the 40 myotonic dystrophy patients that could be traced who attended the two Respiratory units at Gartnavel General Hospital and Glasgow Royal Infirmary over the last 5 years. Time to clinic referral from the onset of respiratory symptoms was variable (0-72 months). Twenty-one patients required ventilatory support for symptomatic respiratory failure, nocturnal hypoventilation or upper airway collapsibility. Fifteen received bilevel pressure support and six continuous positive airway support.

Table 3.3.1.1: Differences between patients that required NIV and those who didn't.

	Patients requiring NIV	**Not requiring NIV**
Patient number	21	19
Age, years	42.0(14.1)	40.4(12.1)
Epworth Sleepiness Scale at presentation	13.4(3.9)	12.3(6.4)
Body Mass Index (BMI) kg/m^2	33.7(8.7)	24.8(4.3)*
% predicted FEV1	63.9(22.7)	74.0(15.0)
% predicted FVC	65.8(25.0)	79.9(16.2)
MIP (cmH_2O)	37.4(19.3)	41.4(15.7)
MEP (cmH_2O)	34.1(14.6)	40.3(14.5)
Obstructive Sleep Apnoea (RDI ≥15/hr) (patient number)	14	2
Mean overnight oxygen saturation (%)	90.6(4.4)	93.7(3.1)*

Results in mean (SD). * $p<0.05$

With this review, it was apparent that Myotonic Dystrophy patient who later required NIV had lower FVC and maximal expiratory/inspiratory pressures at presentation but this did not reach statistical significance. The mouth pressures in both the groups were lower than predicted normal and hence difficult to conceptualise the level at which this compromised ventilation the most. Interestingly, those who went on to require NIV had a significantly higher BMI. Compliance with NIV was universally poor.

3.3.2 Hypotheses:

1. Volitional tests underestimate respiratory muscle strength in MyD.

2. Nonvolitional tests would be better at identifying patients with significant SRBD.

3. There would be a correlation between respiratory muscle strength assessed by BAMPS and peripheral muscle strength.

3.3.3 Study Design

A group of 10 normal subjects and 10 patients with MyD took part in this study. Study measurements were carried out on two occasions 4-6 months apart in the Respiratory Muscle Laboratory at Gartnavel General Hospital.

Visit 1:

1. Obtain written informed consent.

2. Eligibility check with particular attention to symptoms and mode of confirmation of underlying diagnosis.

3. All subjects were examined to categorise their muscular impairment scale (195, Appendix V).

Grade 0: No muscular impairment
Grade 1: Minimal signs
Grade 2: Distal weakness
Grade 3: Mild Proximal weakness
Grade 4: Severe proximal weakness

Muscular disability rating scale (MDRS) is a five-point rating scale, based on manual testing of 11 muscle groups and has been validated in many studies. It is thought to be

helpful in establishing the natural history of the disease and to define groups of patients with similar level of disability.

4. Complete the following questionnaires:

Epworth Sleepiness Scale Score (ESS) – to assess daytime sleepiness (Appendix III, 179).

The ESS is a widely used eight-item questionnaire that measures the subjective sensation of recent sleepiness. Subjects are asked to rate how likely they are to fall asleep, as opposed to just feeling tired, in eight specific quiet or relaxed situations. The scale runs from zero (unlikely to fall asleep in any of the eight relaxed situations) to 24 (high chance of falling asleep in all eight situations).

The Short Form 36 Health Survey Questionnaire (SF 36) - as a measure of general well being and functioning (196, Appendix IV).

The SF-36 is a widely used and validated questionnaire that measures QoL in health-related states and conditions. This instrument does not contain questions related directly to the effects of sleep disorders but instead has questions that focus on QoL in general rather than in relation to any specific disease. The SF-36 produces a profile of eight dimensions of health status

(i) limitations in physical activities because of health problems

(ii) limitations in social activities because of physical health problems

(iii) limitations in usual role activities because of physical health problems

(iv) bodily pain

(v) general mental health

(vi) limitations in usual role activities because of emotional problems

(vii) vitality

(viii) general health perceptions

However two summary scores can be extrapolated from these 8 dimensions: a physical and a mental component summary. The SF-36 has been used in many studies involving different medical conditions and hence was used in my study. The question scores on each variable can be summed and transformed to a scale from 0 to 100 (from worst health to best health apart from the pain score which is the reverse) (197).

Hospital Anxiety and Depression Score (HAD) (198, Appendix VI) – to assess psychological aspects.

This questionnaire analysed the severity of underlying anxiety and depression. The questionnaire contains seven items reflecting anxiety and seven reflecting depression. (Of the seven depression items five reflect aspects of reduction in pleasure response). Each item was answered by the patient on a four point (0–3) response category so the possible scores ranged from 0 to 21 for anxiety and 0 to 21 for depression. A score of 0 to 7 for either subscale was regarded as being in the normal range; a score of 11 or higher indicated presence of the mood disorder and a score of 8 to 10 being just suggestive of the presence of the respective state.

5. Baseline pulmonary function test - to include Forced Expiratory Volume in 1 sec and Forced Vital Capacity

6. Lying and standing vital capacity

7. Oxygen Saturation Assessment

8. Arterial Blood Gases if $SpO_2 \leq 92\%$ or awake arterial blood gases in all patients who underwent in-patient polysomnography.

9. Respiratory Muscle Strength was assessed using volitional tests such as MIP, MEP, SNIP and sniff transdiaphragmatic pressure after placement of oesophageal and gastric balloon catheters. MIP $\leq$ 80cm H_2O, MEP $\leq$ 90cm H_2O and SNIP $\leq$ 70cm H_2O were considered to be significantly reduced. Peak MIP and MEP were also recorded as there are studies which have shown that they may be easier to obtain and equally reliable in subjects (199). Non-volitional respiratory muscle strength was measured using bilateral anterior magnetic phrenic nerve stimulation technique to obtain twitch transdiaphragmatic pressure.

10. Peripheral muscle strength was assessed by maximal voluntary contraction of the quadriceps muscle. Quadriceps strength was measured in the dominant leg.

11. Dynamic Compliance of the respiratory system was calculated during a period of quiet breathing through a heated pneumotachograph as the ratio of difference in tidal volume to change in the oesophageal pressure.

12. Patients were booked in for either overnight oximetry or full polysomnography if not done before or subjects had symptoms of excessive daytime sleepiness, sleep disturbances or ESS over 11.

- to obtain information on sleep quality by analysing time spent in different stages of sleep as defined by electroencephalographic (EEG) criteria
- to assess episodes of desaturation defined as a drop in SpO_2 by 4%
- to exclude associated sleep apnoea hypopnoea syndrome

Visit 2: 4-6 months later subjects were reassessed with:

1. Review of Symptoms

2. Questionnaires

3. Pulmonary Function Tests, Lying and Standing VC

4. Oxygen saturation ± arterial blood gas assessment

5. Respiratory muscle strength assessment – volitional and nonvolitional

6. Assessment of peripheral muscle strength

3.3.4: Results

10 normal subjects (6 men, 4 women) and 10 patients with myotonic dystrophy (6 men, 4 women) took part in this study. 6 patients had no physical disability as assessed by MDRS, 2 had minimal signs, 1 with distal weakness and 1 other with mild proximal weakness. They were all ambulatory. Demographics are summarised in table 3.3.4.1.

Table 3.3.4.1: Demographic details.

	Normal subjects n = 10 (6M:4F)	**MyD patients n = 10 (6M:4F)**
Age (years)	30.1(5.2)	37.2(9.8)
Body mass index (kg/m2)	24.3(3.1)	27.5(5.4)
Epworth sleepiness scale	5.8(3.4)	16.1(4.0)*

Results in mean (SD). * $p<0.05$

Symptom Evaluation:

The common symptoms patients with myotonic dystrophy presented included tiredness (90%), excessive sleepiness (70%) and disturbed sleep mostly due to snoring (40%). Considering Epworth sleepiness scale score > 11 as significant 90% of the patients studied were hypersomnolent during the daytime.

Questionnaires:

The SF-36 results are summarised in Tables 3.3.4.2.

Table 3.3.4.2: SF-36 scores in normal and MyD subjects.

	Normal subjects n = 10	**MyD subjects n = 10**
Physical Functioning	93.9(13.2)	52.5 (25.2)*
Role-Physical	94.4(16.7)	90.6(26.5)
Role-Mental	92.6(22.2)	87.5(24.8)
Social Functioning	80.2(15.5)	52.8(16.5)*
Mental Health	84.4(9.0)	64.0(12.1)*
Energy	78.9(13.6)	40.0(10.0)*
Pain	92.6(9.6)	59.7(20.9)*
Health Perception	73.3(12.5)	43.8(10.9)*

Results presented as mean (SD). * = $p < 0.05$.

Compared to normal subjects, MyD patients had lower scores in all the components of SF-36. However it was interesting to note that role limitations due to physical and emotional problem scores though lower in MyD patients did not reach statistical significance in comparison to normal subjects. When subgroups of MyD patients were looked at, statistically there were no differences in any of the 8 components of SF-36 between patients with normal nocturnal parameters and those with significant respiratory disturbance during the night (table 3.4.4.3).

Table 3.3.4.3: SF-36 scores in subgroups of MyD patients.

	MyD subjects with normal nocturnal parameters n = 6	**MyD subjects nocturnal desaturators n = 4**
Physical Functioning	62.0(22.5)	36.7(24.7)
Role-Physical	100.0(0.0)	75.0(43.3)
Role-Mental	86.7(29.8)	88.9(19.2)
Social Functioning	57.8(18.3)	44.4(11.1)
Mental Health	62.4(15.1)	66.7(6.1)
Energy	39.0(12.9)	41.7(2.9)
Pain	66.7(20.8)	48.1(17.0)
Health Perception	49.0(8.2)	35.0(10.0)

On the HAD scale, MyD patients had significantly higher scores compared to normal individuals with the mean anxiety score of 7.9(4.5) {vs 3.3(1.6) in normals} and mean depression score of 10.4(4.6) {vs 3.2(1.7) in controls}.

Pulmonary Function Tests:

Looking at basic spirometry (fig 3.3.4.1), there was no significant difference between the predicted FEV_1 and FVC for the whole group between the normal subjects and patients with myotonic dystrophy though there was tendency in the MyD group to have lower values.

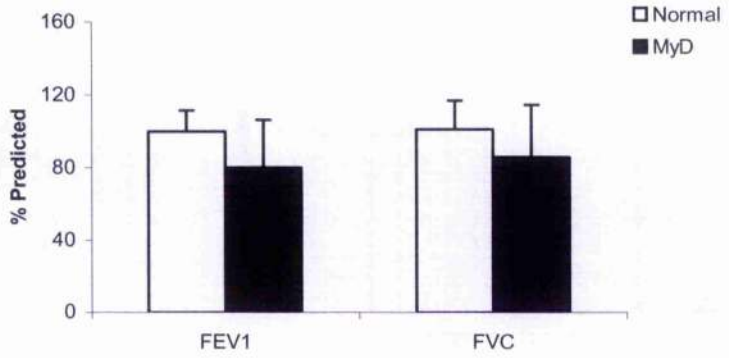
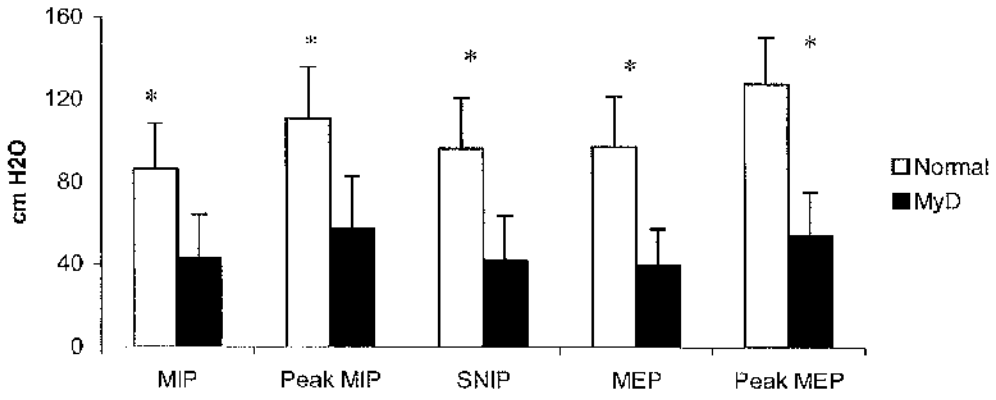


Fig 3.3.4.1: Baseline spirometry between the normal subjects and patients with myotonic dystrophy. Error bars reflect SD for the group.

However looking at the mouth pressures (fig 3.3.4.2), both inspiratory and expiratory pressures were markedly reduced in MyD group. MEP tended to be more reduced than MIP. Correlation between FVC and MIP, MEP was good in the MyD group [fig 3.3.4.3 and fig 3.3.4.4 ($r=0.7$, $p=0.02$)]. Within the normal subjects, however, the correlation between mouth pressures and FVC was not significant.



*p < 0.05

Fig 3.3.4.2: Mouth pressure differences between normal subjects and patients with MyD.

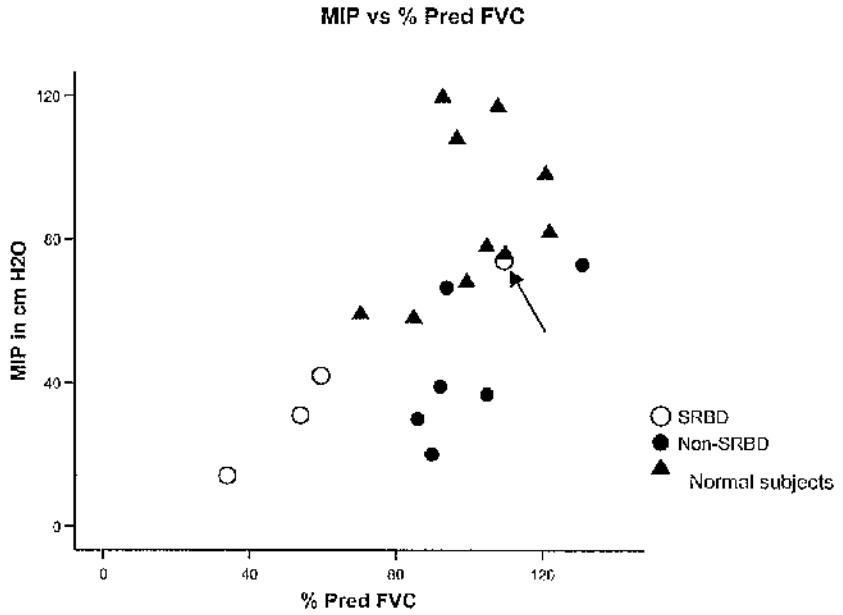


Fig 3.3.4.3: Correlation between FVC and MIP in MyD (r=0.7, p=0.022). This graph also highlights an interesting patient who has normal FVC and reasonably preserved MIP who has significant SRBD (arrow).

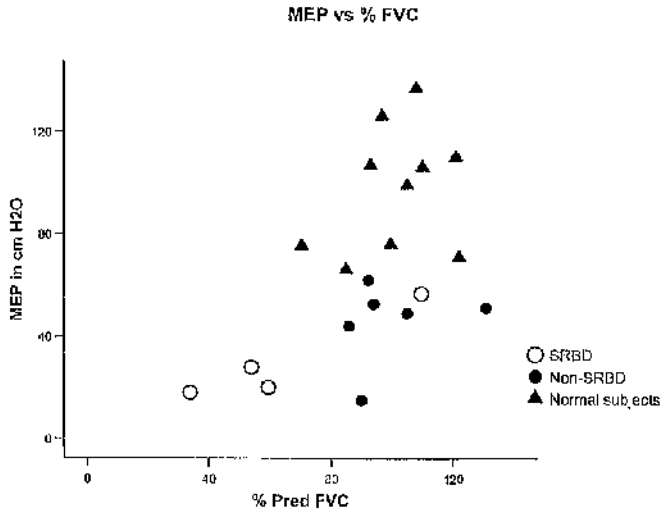


Fig 3.3.4.4: Correlation between FVC and MEP in MyD (r=0.7, p=0.021).

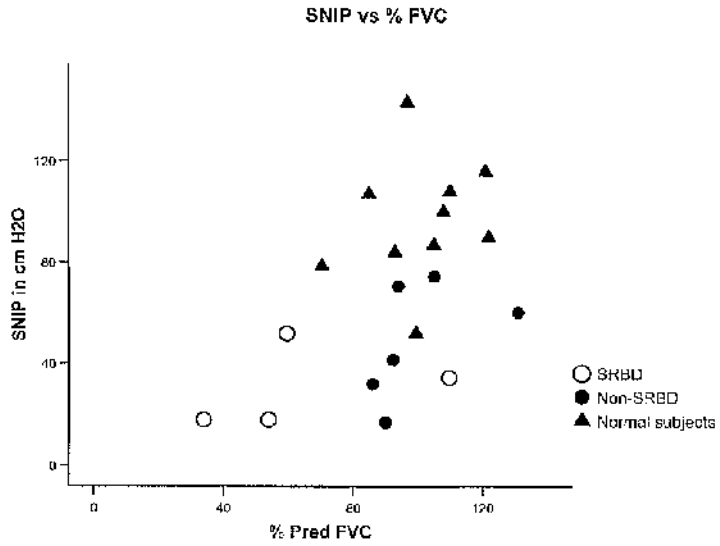


Fig 3.3.4.5: Correlation between FVC and SNIP for the whole group (r=0.5, p=0.02).

Table 3.3.4.4: Invasive respiratory muscle strength between normal subjects and MyD patients.

	Normal n = 10	**MyD n = 10**
Sniff Poes (cm H_2O)	80.5 (9.1)	57.3 (26.3)*
Sniff Pdi (cm H_2O)	89.5 (24.2)	67.1(30.7)
Right TwPdi (cm H_2O)	11.2 (2.9)	5.4 (1.8)
Left TwPdi (cm H_2O)	12.6 (3.3)	8.1(3.6)
TwPdi (cm H_2O)	25.0 (6.4)	17.1(9.4)
Cough Pgas (cm H_2O)	140.6 (43.4)	105.3 (41.7)
Dynamic compliance ($L.cmH_2O^{-1}$)	0.19 (0.10)	0.11 (0.06)*

* $p < 0.05$

In comparison to normal subjects, MyD patients had generally lower transdiaphragmatic and cough gastric pressures. However in the group we studied only the sniff Poes and the dynamic compliance was significantly lower in MyD patients. Hence we looked at how patients with significant nocturnal disturbances matched with those who had normal sleep pattern and overnight oxygen saturation (table 3.3.4.5, fig 3.3.4.3).

Table 3.3.4.5: Differences between patients with significant nocturnal respiratory disturbance and those with normal overnight oxygen saturation.

	Patients with SRBD n = 4 (3M:1F)	**Patients without SRBD n = 6 (3M:3F)**	**p value**
Age (years)	40.2(8.4)	35.2(10.9)	0.45
Body mass index (kg/m^2)	32.8(2.3)	24.8(4.1)*	0.02
Epworth sleepiness scale	15.5(2.4)	16.6(5.2)	1.00

* $p < 0.05$

Patients with significant SRBD (mean oxygen saturation ≤ 90%, upper airway collapsibility defined as apnoea hypopnoea index ≥ 15 events/hour, REM hypoventilation and/or awake hypercapnia) were older though not significantly. Excessive daytime sleepiness was a feature of MyD patients even in absence of significant nocturnal respiratory disturbance. Body mass index was significantly higher in patients with nocturnal desaturation. However the correlation between BMI and RDI/DI was weak (r=-0.1).

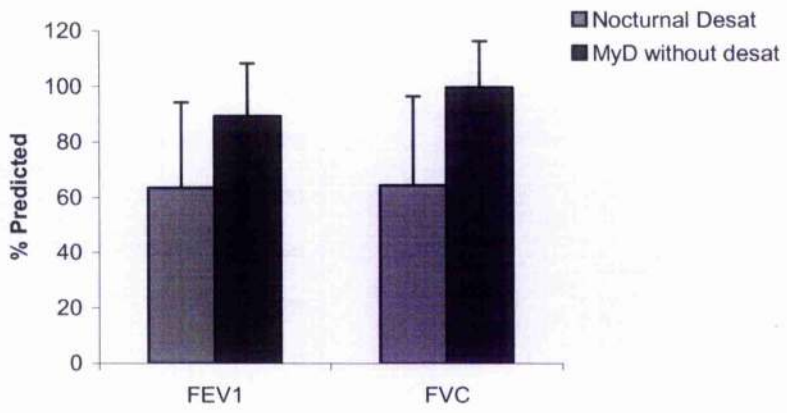


Fig 3.3.4.6: Spirometry in MyD patient subgroups.

Though there was tendency for patients with nocturnal desaturation to have lower FVC, this was not statistically significant and this may well be a reflection of the sample size. The same was true for supine vital capacity as well and the percent fall in supine VC was 12.6(9.1) in patients who had significant nocturnal desaturation, compared to a fall of 6.2 (4.9)% in the MyD subgroup that didn't desaturate.

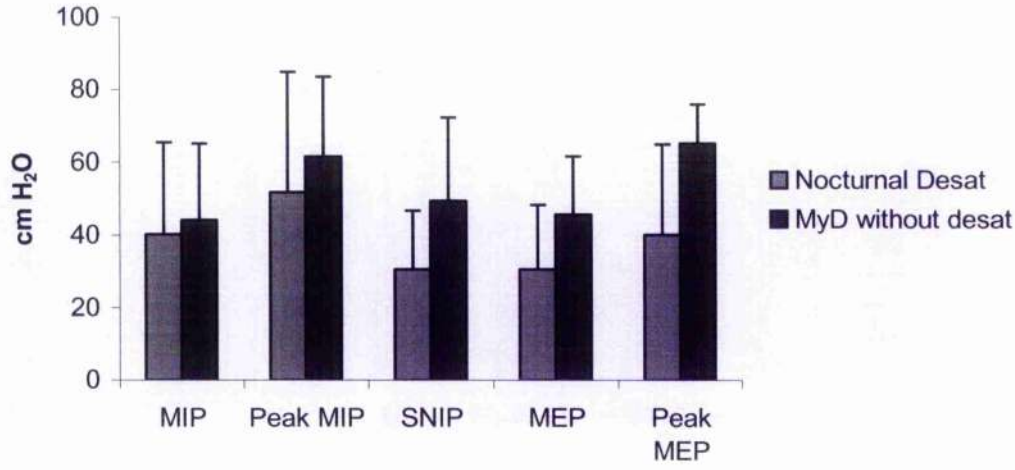


Fig 3.3.4.7: Differences in mouth pressures between the MyD subgroups.

There was tendency of SNIP, MEP and peak MEP to be lower in patients who had significant nocturnal desaturation. However these were not statistically significant between the subgroups.

Table 3.3.4.6: Invasive respiratory muscle strength between the subgroups.

	Patients with SRBD n = 4	**Patients with normal overnight oxygen n = 6**
Sniff Poes (cm H_2O)	48.1(29.6)	63.5(24.6)
Sniff Pdi (cm H_2O)	50.0(35.4)	78.6(23.5)
Right TwPdi (cm H_2O)	3.6(0.6)	6.4(1.3)*
Left TwPdi (cm H_2O)	4.8(2.7)	10.1(2.4)†
Bilateral TwPdi (cm H_2O)	8.7(6.2)	22.6(6.6)*
Cough Pgas (cm H_2O)	100.0(46.2)	108.8(42.5)
Dynamic compliance ($L.cmH_2O^{-1}$)	0.08(0.02)	0.13(0.07)

* $p < 0.05$; $^{\dagger} = 0.07$

There was tendency in MyD patients who had nocturnal disturbances to have lower sniff Poes and Pdi values though statistically this wasn't significant. However bilateral TwPdi was a good descriminator of the two subgroups. Paralysed diaphragm as seen on oesophageal and gastric pressure tracings of one of the patients with low Pdi is shown in fig 3.3.4.7.

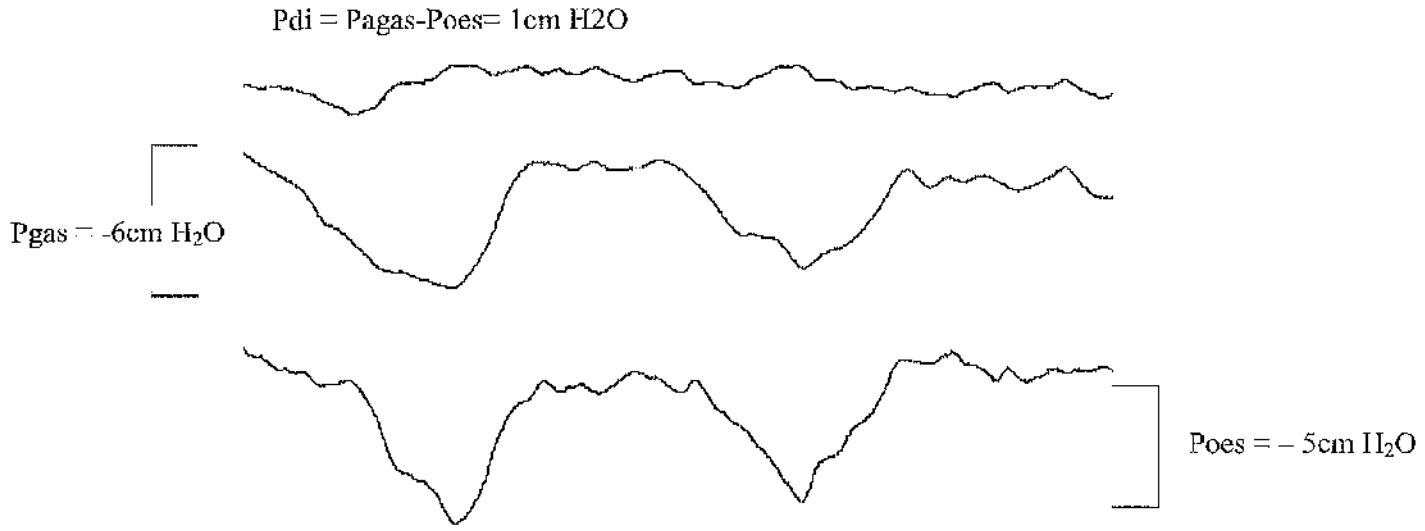


Fig 3.3.4.8: Diaphragm paralysis as evident on oesophageal and gastric pressure tracing (GainX5).

Correlation between volitional and non volitional tests are now explored.

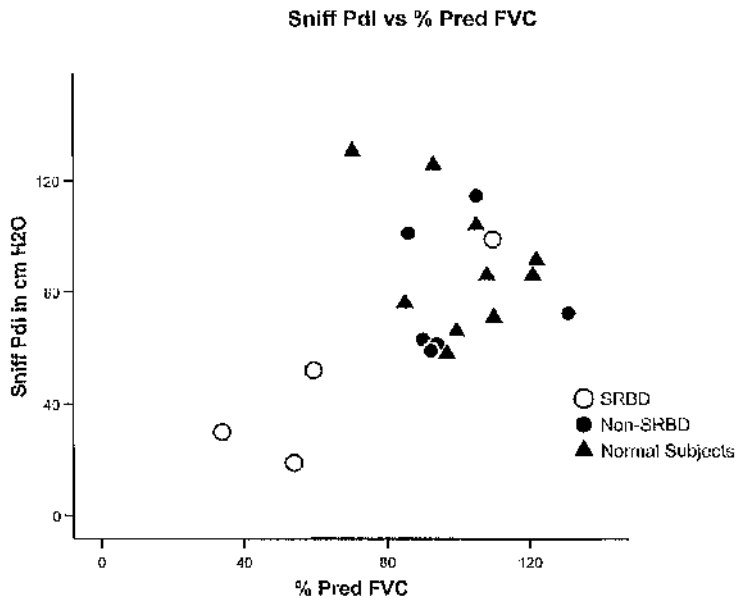


Fig 3.3.4.9: Correlation of sniff Pdi and FVC (r=0.45, p=0.04).

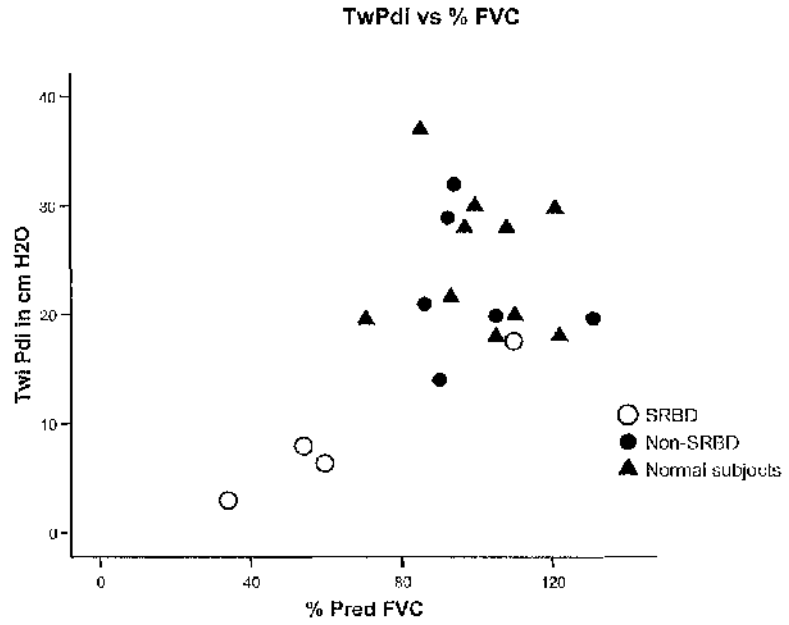


Fig 3.3.4.10: Relation between FVC and TwPdi (r=0.5, p=0.01).

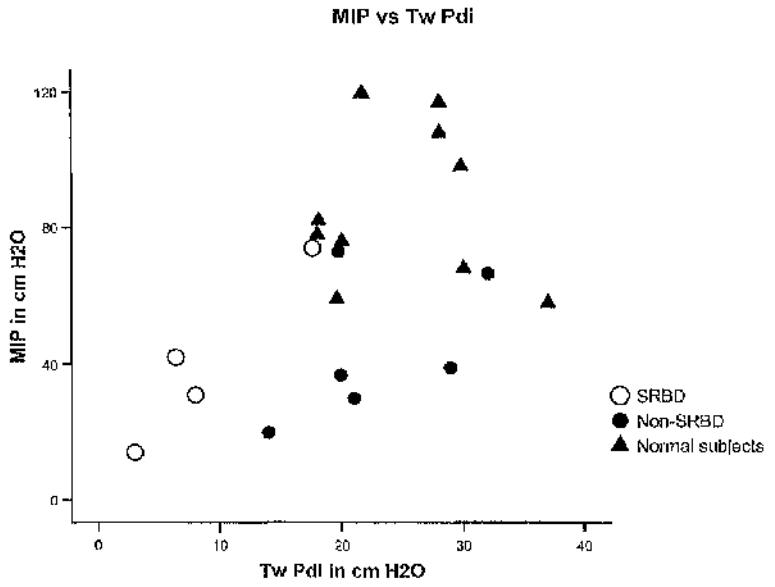


Fig 3.3.4.11: Relation between MIP and TwPdi (r=0.5, p=0.02 for the whole group).

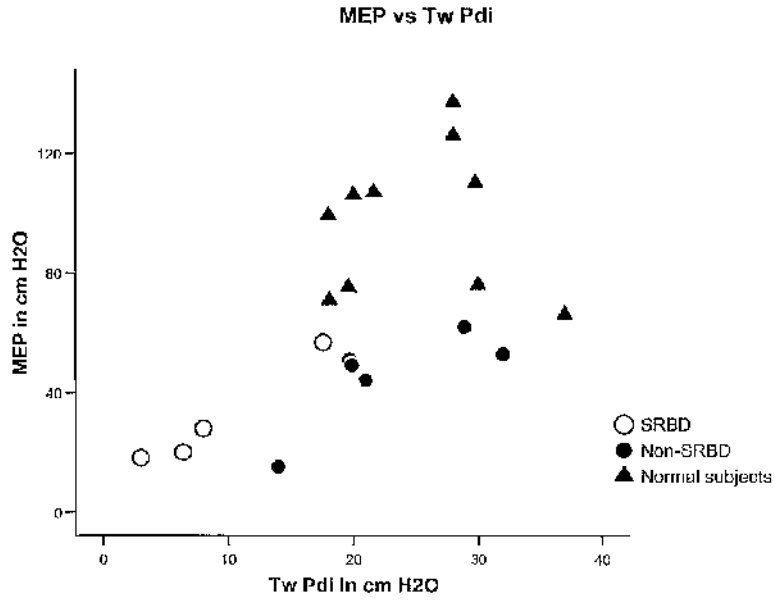


Fig 3.3.4.12: Relation between TwPdi and MEP (r=0.58, p=0.007).

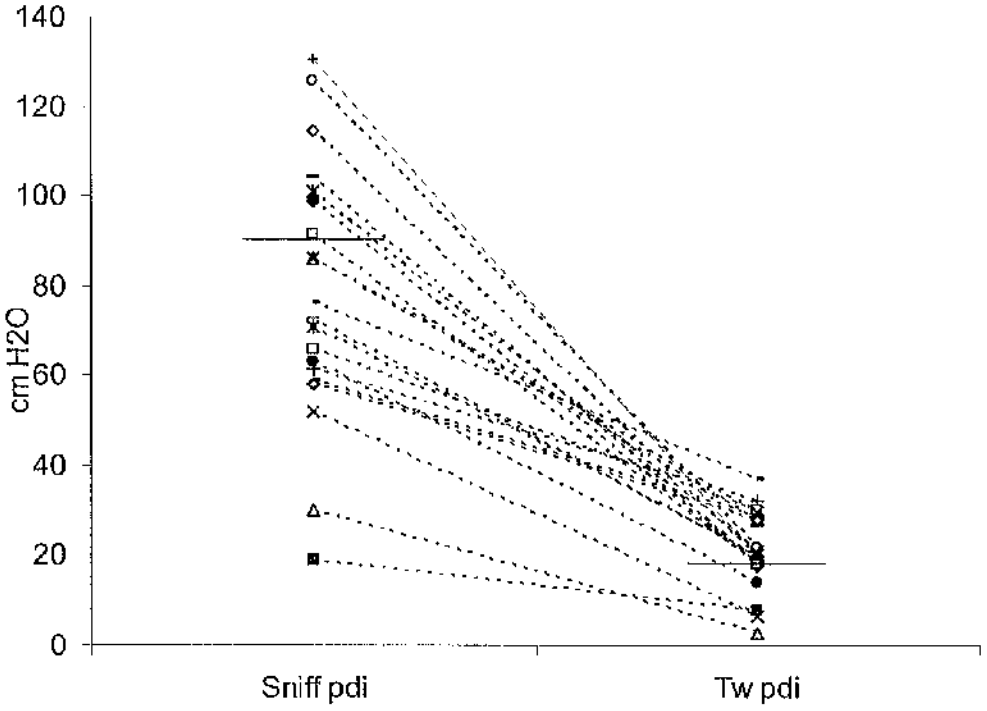


Fig 3.3.4.13: Relation between Sniff and Tw Pdi. This clearly demonstrates the superiority of Tw Pdi results in assessing diaphragm strength. Solid lines stand for 89.5cm H_2O for sniff Pdi (recorded mean value for normal subjects) and 20 cm H_2O on bilateral Tw Pdi. There were subjects who would be classified to have weak diaphragms on sniff Pdi who had normal Tw Pdi. The reasons for slightly lower than expected sniff Pdi for the group are explored in the discussion.

3 normal subjects and all the MyD subjects had MIP < 80cm H_20. 4 normal and 7 MyD subjects had lower than the expected sniff Pdi. All the normal subjects had TwPdi > 18 cm H_2O and 3 MyD subjects had low TwPdi. Only considering sniff Pdi, 55% of the group would have been thought to have low diaphragm strength. However, only 15% of the group actually had reduced strength as assessed by Tw Pdi.

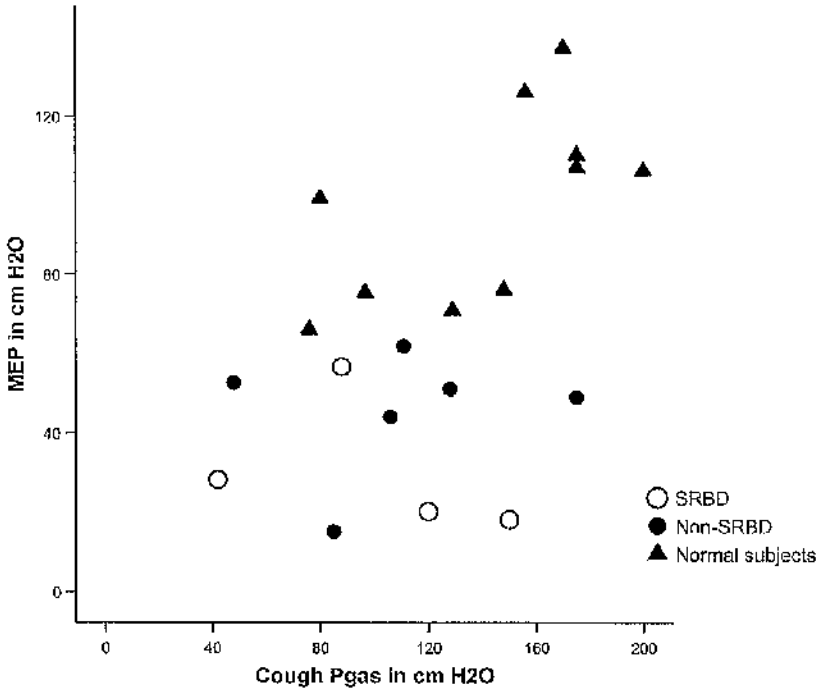


Fig 3.3.4.14: Correlation between MEP and Cough Pgas (r=0.5).

Though the strength of correlation was strong between invasive and non invasive tests for the whole group, they were not significant to differentiate SRBD and non SRBD group.

Sleep and arterial blood gas analysis:

Only the MyD patients had overnight monitoring. Three patients did not wish to come into the hospital and hence home overnight oximetry was carried out on them using Minolta pulse oximeter. They were specifically asked to make a note of the time they went to bed, awakening time and also about the subjective quality of sleep on the study night. The rest of the patients (n=7) underwent full polysomnography in hospital. All the three subjects who had overnight oximetry had a mean oxygen saturation of 96% on air. It was interesting to note that all these 3 subjects had TwPdi within the normal range. The polysomnographic data are summarised in table 3.3.4.7.

Table 3.3.4.7: Polysomnography in Myotonic Dystrophy patients (n=7).

	Mean (SD)
TST (min)	295.1 (121.3)
SE (%)	79.0 (14.6)
Stage I (%)	25.1 (14.0)
Stage II (%)	35.7 (20.8)
Stage III (%)	15.8 (6.7)
Stage IV (%)	7.1 (8.2)
REM (%)	15.0 (12.7)

Generally lighter stages of sleep (stages I, II) were noted to be higher than in the normal range though we did not control for the first-night effect. This was irrespective of whether the patients had significant nocturnal desaturation or upper airway collapsibility that could account for the disrupted sleep architecture.

Four out of the 10 subjects had significant upper airway collapsibility or evidence of hypoventilation. Two of them had obstructive sleep apnoea with nocturnal desaturation [(mean $SpO_2 \leq 90\%$ on air(tracing shown in fig 3.3.4.15)], one had central sleep apnoea [31 events/hour (fig 3.3.4.16)] and the other had severe nocturnal hypoventilation with mean $SpO_2 = 87\%$ and raised awake CO_2 levels.

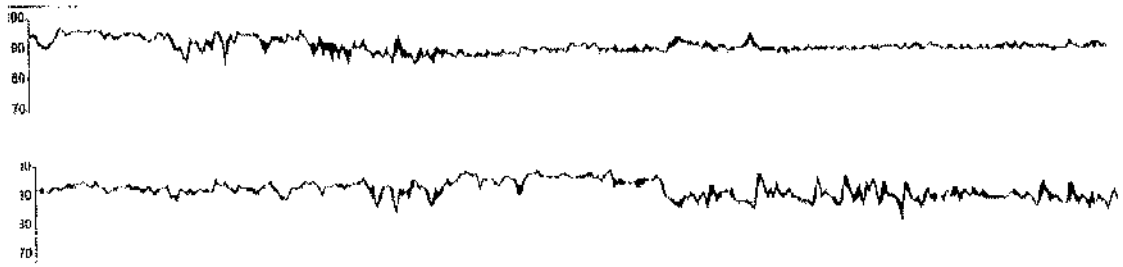


Fig 3.4.4.15: Shows nocturnal hypoventilation with initial SpO_2 in low 90s and as the night progresses there is progressive drift in the baseline with associated brief desaturations associated with increased heart rate (not shown) suggesting underlying sleep apnoea.

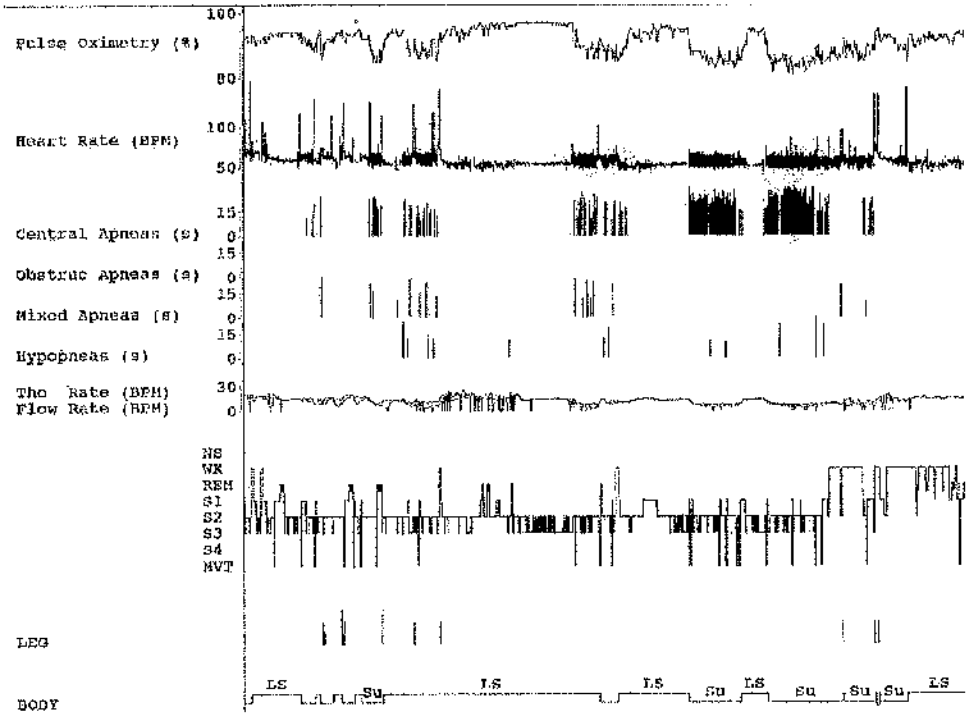


Fig 3.3.4.16: Polysomnographic data in a patient with central sleep apnoea.

Arterial blood gas analysis revealed mean PaO_2 of 10.2(2.1) and $PaCO_2$ of 6.3(0.9) for the MyD group. As could be expected, the correlation between $PaCO_2$ and HCO_3^- was significant (r=0.6, p=0.04). The correlation between $PaCO_2$ levels and bilateral TwPdi was also good at r=-0.7, p=0.04 (fig 3.4.4.17) as was that with FVC (r=-0.7, p=0.03).

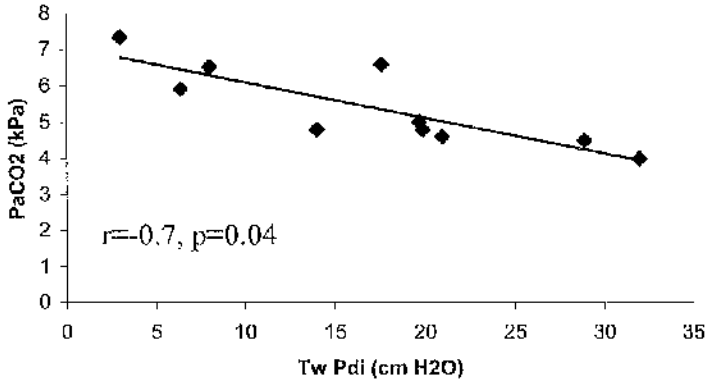


Fig 3.3.4.17: Correlation between $PaCO_2$ and Tw Pdi.

One patient with central sleep apnoea had normal FVC, minimally reduced mouth pressures and normal sniff Pdi (98.9 cm H_2O). His bilateral TwPdi was minimally reduced at 17.6cm H_2O. This patient highlights the complex interaction between various factors that result in ventilatory failure in MyD (fig 1.8.1.1).

When considered in combination on a linear regression model, hypercapnia was significantly predicted by FVC and Tw Pdi (p=0.019) but not by Sniff Pdi or the mouth pressures.

Peripheral Muscle Strength:

Maximal voluntary contraction of quadriceps was 40.9 (9.9)kg in normal subjects and 32.8 (13.8)kg in MyD subjects. In patients with nocturnal disturbance MVC was lower at 30.4(11.4) in comparison to 34.4(16.0) in patients who had normal nocturnal oxygen levels. However this trend was not statistically significant. The correlation between general muscle weakness as assessed with MDRS and MVC quadriceps was only weak (r=-0.3, p=0.3).

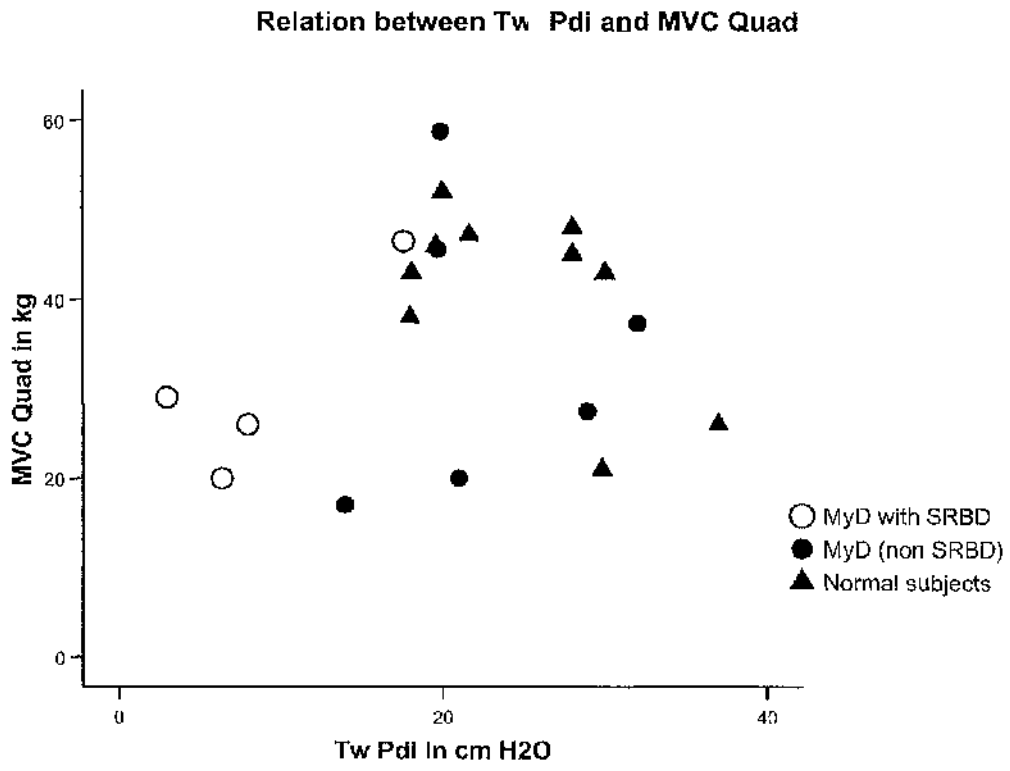


Fig 3.3.4.18: Relation between peripheral muscle strength as assessed by MVC quadriceps and nonvolitional diaphragm strength (r=0.4, p=0.4). There was no significant correlation in the variables either in normal individuals or in MyD subjects.

Analysis of repeat tests in 4-6 months:

Only 9 normal controls and 7 in the MyD group attended for the repeat studies. There was no change in the MDRS scoring of any of the MyD subjects. Again the SF-36 scores were reduced in most of the domains compared to the normal subjects and HAD scores were higher suggestive of increased prevalence of mood disorders.

Table 3.3.4.8: Summarises the non-invasive pulmonary function tests in the normal and MyD subjects. Results given as mean (SD).

	Normal subjects I visit n = 10	**Normal subjects II visit n = 9**	**MyD subjects I visit n = 10**	**MyD subjects II visit n = 7**
% Pred FEV_1	103.7(6.5)	98.1(12.5)	77.4(25.5)	72.5(24.4)
% Pred FVC	105.9(12.4)	101.4(15.5)	83.4(28.3)	76.3(24.7)
% fall in supine VC	3.9(3.2)	2.4(2.4)	10.5(7.0)	15.2(13.3)
MIP in cm H_2O	89.4(22.1)	86.2(19.9)	42.5(20.4)	31.9(10.1)
Peak MIP-cm H_2O	114.2(24.2)	107.4(23.0)	57.2(26.1)	35.4(19.1)
SNIP in cm H_2O	98.5(25.1)	83.7(20.4)	41.9(21.7)	37.2(18.4)
MEP in cm H_2O	99.7(24.5)	98.1(20.5)	40.1(16.7)	46.9(17.4)
Peak MEP-cm H_2O	129.8(22.9)	126.0(24.6)	54.0(21.6)	51.6(20.5)

It appeared that there was significant decline in maximal inspiratory pressure in MyD patients during the second visit in association with fall in supine vital capacity. On reflection, this may well be related to the development of significant diaphragm weakness in the group that was studied. However analysing data for the 7 subjects from the initial visit, MIP was similar to the mean value obtained at the second visit [30.4(10.2) cm H_2O at the initial visit]. Fig 3.3.4.19, 3.3.4.20 summarise the volitional and non-volitional tests between the two visits.

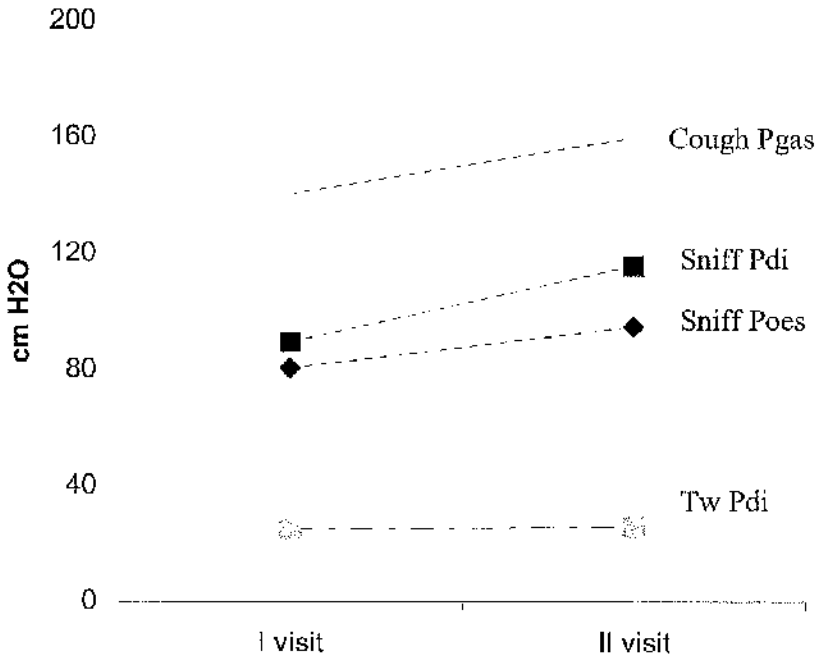


Fig 3.3.4.19: Volitioanl and Non-volitional respiratory muscle parameters in normal subjects. The slight increment noted in sniff Poes, sniff Pdi and cough Pgas could well be a learning effect and there was no significant difference compared to the I visit.

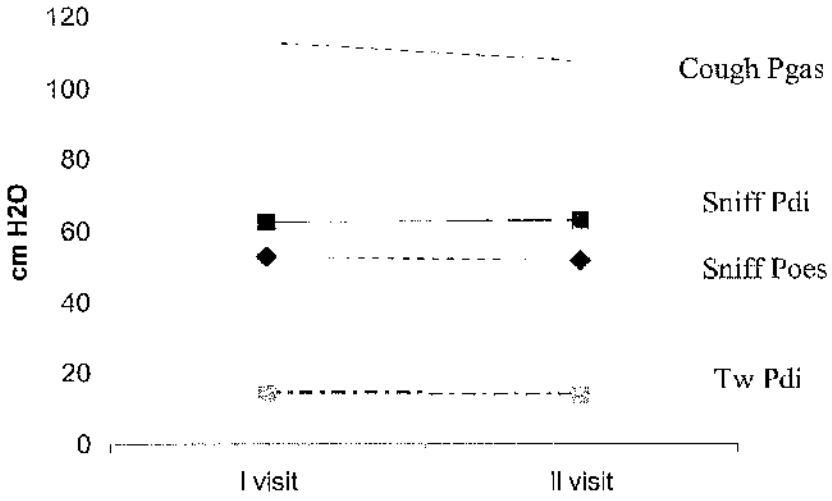


Fig 3.3.4.20: Volitional and Non-volitional respiratory muscle parameters between the two visits in MyD.

There was no statistical difference between the 2 visits in sniff or Tw Pdi and cough Pgas in either normal or MyD subjects. MVC quadriceps was also similar on the two occasions tested being 28.3(14.1)kg on the initial visit and 24.5(10.1)kg on the second visit in the 7 MyD subjects studied. Since the disease progression in patients with MyD is long, stability of the respiratory muscle strength assessment both by volitional and non-volitional tests in that period is quite reassuring.

Four subjects with sleep apnoea and/or hypoventilation were initiated on NIV. At II visit mean use of bilevel positive airway pressure ventilation (BIPAP) was only 2.4 hours/night and one patient had discontinued its use completely as he had no significant

symptomatic improvement. It was interesting to note that one patient with hypoventilation and daytime hypercapnia, who used NIV on a regular basis (Mean of 3.5hours use/night) had no change in her Tw Pdi on repeat testing (Tw Pdi of 8cm H_2O on both occasions).

3.3.5: Discussion

It appeared that most patients with MyD attributed their longstanding tiredness and sleepiness to their underlying myotonic dystrophy and none were aware that respiratory impairment could be a contributing factor for their symptoms. There is increasing effort from the medical profession to raise awareness of the various complications that can occur in MyD. Myotonic Dystrophy care card illustrates one such attempt (appendix VII). However treatment of respiratory complications has remained a challenge. The associated neuropsychiatric disturbances may make compliance with any kind of treatment difficult which especially applies to non-invasive ventilation. Many of the patients were particularly reluctant to attend clinics in the mornings and this may well be something to bear in mind while formulating care plans for these patients.

Assessment of QoL

MyD patients scored lower in most of the domains of SF-36 compared to normal and this stresses the implications the disease has on QoL. Though scores >11 are considered to be clinically relevant for the diagnosis of anxiety or depression on HAD scale, mean scores were less than this. However half the MyD group fulfilled the criteria for depression with

HAD score > 11. This was equally common in both subjects with SRBD and those without. There was no direct correlation of SF 36 or HAD scores with FVC, mouth pressures or $PaCO_2$. MyD patients with or without SRBD are significantly sleepy as assessed by ESS.

Volitional and non volitional respiratory muscle strength and their relevance to SRBD

We found bilateral anterior magnetic phrenic nerve stimulation technique to be a useful method to assess non-volitional respiratory muscle strength in patients with MyD. To our knowledge, this is the first time BAMPS has been tested this way in MyD. Patients tolerated the technique well and TwPdi provided a nonvolitional measure of diaphragm strength. As mouth pressures are invariably reduced, assessment of TwPdi could provide useful information as a daytime measure of nocturnal events in this group of patients (Identified 75% of patients with SRBD in the group). This is more likely to be of value in patients who perform volitional tests suboptimally. In two normal subjects the tests were repeated and the coefficient of variation in TwPdi value was noted to be 8% in between the occasions.

It was of interest to note that the sniff Poes, Pdi and TwPdi values we obtained in normal people were slightly lower than expected from other centres where these tests are carried out routinely. It was ensured that there was no apparent leak in the system. It is quite likely that our normal controls were physiologically at the lower end of 'normality' and hence the variation. It is known that for human diaphragm the ratio of single twitch to

maximal contraction is 0.23-0.24(200,201). It did not appear to be related to poor effort, as the values were consistent

and reproducible. The small number of subjects studied might have contributed to this effect as well.

Sleep studies were quite useful to provide the sleep architecture that could explain the disturbed sleep pattern. Only one patient with normal FVC, sniff Pdi and minimally reduced Tw Pdi at 17.6 cm H_2O had significant nocturnal disturbance in the form of central sleep apnoea and awake hypercapnia. His wife had noticed episodes of apnoeas prior to participating in the study. It is quite likely that this subject has an abnormal respiratory drive or disordred afferent input from the diaphragm that contributed to the SRBD. However, diaphragm EMG/respiratory drive was not directly measured in my studies. His resting breathing frequency was 16 breaths/min. His VT/Ti as a measure of drive was not significantly different to the group [Mean (sd) of 0.390(0.150)l/sec in normal subjects to 0.343(0.170)l/sec in MyD group]. There was also no difference in Ti/Tot between normal subjects and MyD subjects [0.417(0.062) vs 0.480(0.024) respectively].

Peripheral muscle strength

There was no direct correlation between the peripheral muscle strength (as assessed by MVC quadriceps) and measures of respiratory muscle strength including TwPdi. This suggests that peripheral muscle weakness has no direct relevance to respiratory muscle involvement in these patients. However none of the patients we tested had significant

proximal weakness and our results may well be due to this. Strength was measured in only one leg but all the subjects had been examined to ensure that there was no asymmetry of power in their legs. Non volitional assessment of strength (electrical or magnetic stimulation of the femoral nerve with EMG monitoring) was not carried out and hence it is not entirely clear whether MVC underestimates strength in MyD as volitional respiratory muscle tests do.

Again high BMI was associated with increased frequency of sleep related breathing problems. In future studies it would be interesting to see if weight loss has any impact on the nocturnal parameters. Dietary advice should probably be given to overweight MyD subjects especially in view of the associated adverse respiratory outcome.

Targeted sleep studies depending on the symptoms may well provide useful information in MyD. Certainly patients with multiple symptoms suggestive of respiratory muscle weakness, hypoventilation or upper airway collapsibility should be considered for nocturnal assessment especially if they are overweight. This is particularly important as one patient with near normal TwPdi did have SRBD at the outset. Our experience with NIV confirmed the well-recognised poor compliance with treatment in this group of patients.

3.3.6 Conclusions

1. Sniff Pdi taken as the gold standard for diaphragm strength can significantly underestimate Pdi in comparison to Tw Pdi assessed by BAMPS.

2. Though FVC correlated well with $PaCO_2$, it was not significantly different between paitents with SRBD and non SRBD. Tw Pdi, however, correlated well with hypercapnia and was a useful to identify MyD patients with SRBD. However, SRBD occurred in MyD inspite of both preserved FVC and diaphragm strength. In a symptomatic patient, even when TwPdi is normal, sleep studies should be considered for further evaluation.

3. Peripheral muscle strength as assessed by MVC quadriceps did not correlate with transdiaphragmatic pressure assessed by BAMPS or general muscle weakness.

3.4 RESPIRATION IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

3.4.1: Hypotheses

1. Serial monitoring of volitional tests of respiratory muscle strength would identify patients with SRBD.

2. Strength of correlation between respiratory muscle tests and SRBD is strong.

Our secondary aims were to

1) Define the prevalent symptoms of respiratory muscle weakness in MND.
2) Define the prevalence of bulbar symptoms.
3) Relate ALS- Functional rating scale (ALS-FRS) to respiratory muscle strength parameters.
4) To assess non invasive and invasive respiratory muscle strength in MND at an interval of 4 months.

3.5.2 Study Design:

1. Obtain written informed consent
2. Eligibility check with particular attention to symptoms and mode of confirmation of underlying diagnosis
3. Questionnaires

- Epworth Sleepiness Scale (appendix III, 179)
- ALS-Functional Rating Scale (appendix VIII, 202)

ALS-FRS is a physician generated estimate of the patient's degree of functional impairment and is evaluated by response to 10 questions regarding daily activities. Each

task is scored on a 5 point scale (0-4) with the sum to produce a score between 0 (worst) to 40 (best).

4. Baseline pulmonary function tests – FEV_1, FVC

5. Lying and standing vital capacity

6. Oxygen Saturation Assessment/ABG

7. Overnight home oximetry

8. Volitional respiratory muscle strength assessment using MIP, MEP, SNIP and sniff transdiaphragmatic pressures.

9. Non-volitional respiratory muscle strength assessment using BAMPS

3.4.3 Results

10 patients with MND participated in this study – 9 males, 1 female. All the 10 subjects had been commenced on riluzole. Mean age was 57.2(16.9) years.

Main symptom of referral included breathlessness (75%, 1/3rd of these subjects had orthopnoca), tiredness (50%), morning headache (20%). 33.3% of the patients studied had symptoms suggestive of bulbar involvement. Table 3.4.3.1 summarises the differences in baseline characteristics between visits I and II. One subject had died in the interim and one did not wish to come for the second visit in view of worsened mobility. There was significant weight loss within the group after 4 months of initial assessment. The prevalence of mood disturbances was higher during the II visit and the functional impairment more marked.

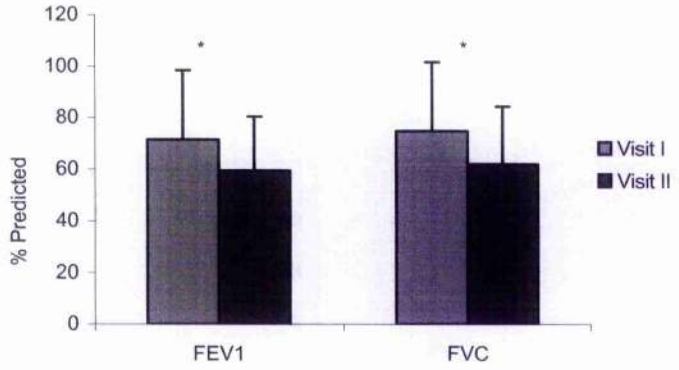
Table 3.4.3.1: Differences between I and II visits in baseline characteristics.

	I Visit n = 10	**II Visit** n = 8
Body Mass Index (kg/m^2)	25.0(5.0)	21.4(3.6)*
ESS	5.2(1.5)	6.4(1.6)
HAD - Depression	8.5 (2.9)	11.4(3.6)*
HAD - Anxiety	11.2 (3.4)	12.6 (3.2)
ALS – FRS score	36.2(2.8)	30.8(4.0)*

*$p < 0.05$

Pulmonary function tests:

There was one former cigarette smoker in the group. None of the subjects had obstructive spirometry at the outset. Either the values were normal or represented restriction in keeping with underlying respiratory muscle weakness. The percent fall in supine vital capacity was minimal even in the face of marked reduction in mouth pressures at 4.6(4.0) during the first visit and 10.6(6.2) at the second visit.



*p < 0.05

Fig 3.4.3.1: Basic spirometry between visits I and II.

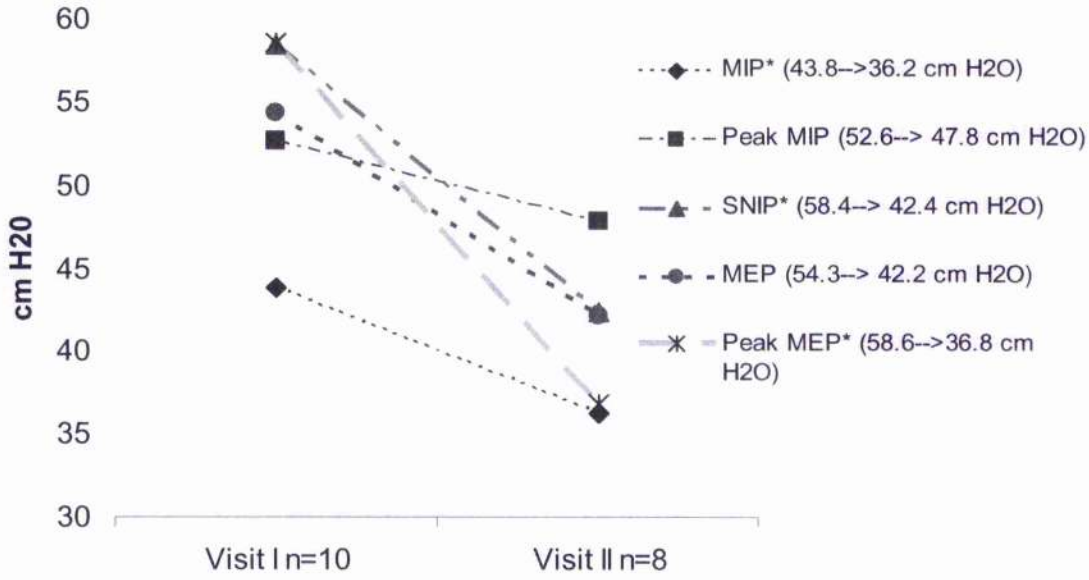


Fig 3.4.3.2: Summary of volitional respiratory muscle strength between the 2 visits.

The decline in MIP, SNIP and Peak MEP with time was statistically significant. However all the parameters showed decline suggesting progressive respiratory muscle weakness. The decline in body mass index during that time would have contributed to the reduction in mouth pressures in part. Patients with lower ALS – FRS scores showed greater reductions in mouth pressures (r=-0.4 MIP vs ALS-FRS score). However this was not statistically significant.

Three subjects underwent invasive respiratory muscle strength assessment and only two agreed for the repeat tests. None of these subjects had bulbar symptoms. In general, BAMPS confirmed severe diaphragmatic weakness in all the three subjects with further decline in the strength on repeat tests.

Mean MIP was 30.3(11.4), MEP 49.7(17.8) and SNP 29.8(15.8) for these 3 subjects. Sniff Poes was 28.0 (11.5), mean sniff Pdi 36(6.5) suggesting severe inspiratory muscle weakness. Bilateral TwPdi was also reduced to 5.5 (2.2) cm H_2O in keeping with severe diaphragm weakness. Again it was interesting to note that there was no significant correlation between percent supine fall in VC and TwPdi. Cough Pgas was also reduced with mean level of 46.3(19.5) H_2O suggesting significant expiratory muscle weakness.

Sleep and Arterial Blood Gas assessment:

All the subjects had overnight oximetry and arterial blood gas assessment during the daytime. Overnight oximetry showed mean SpO_2 level to be 90.6(4.2). Desaturation index was 16.2(9.6). Correlation between DI and FVC was non significant (r=-0.4). Mean PaO_2 for the group was 8.4(3.2) and $PaCO_2$ of 7.1(2.2). Though there was no significant correaltion between DI and mouth pressures, SNIP showed a trend towards significance when compared with time spent below SpO_2 of 90% (r=-0.7, p=0.048). Five subjects had daytime hypercapnia with established respiratory failure. Correlation between FVC and $PaCO_2$ was good (r=0.7, p=0.02).

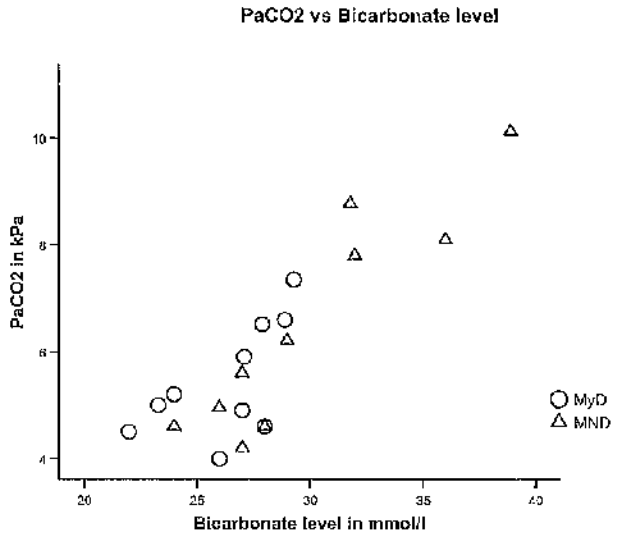


Fig 3.4.3.3: Correlation between $PaCO_2$ and bicarbonate level compared to MyD subjects from section 3.3. The correlation was higher in MND patients compared to MyD [r=0.6, p=0.048; R^2=0.661, p=0.038 in MyD group compared to r=0.917, p=0.00; R^2=0.835, p=0.003 in MND group]. The correlation between the two variables was high for the group [r=0.867(p=0.00), R^2=0.769(p=0.00)].

When all the variables were considered in combination (Tw Pdi not included due to small numbers), $PaCO_2$ was best explained by % FVC, SNIP and Peak MEP (p=0.06). It is quite likely that this failed to reach statistical significance due to the sample size.

3.4.4 Experience with NIV in the MND group

Six subjects were commenced on NIV following the initial assessment (5 had hypercapnic respiratory failure and 1 subject had severe nocturnal desaturation on oximetry). They all had NIV trial in hospital for at least one night. One opted not to continue with the treatment. This subject had severe respiratory muscle weakness without daytime hypercapnia and was commenced on NIV in view of symptoms and oximetry findings. Table 3.4.4.1 gives a summary of ABG pre and post NIV (overnight).

Table 3.4.4.1: ABG pre and post NIV.

	Pre NIV (n = 6)	**Post NIV (n = 5)**
PaO_2	7.6(2.8)	9.0(2.2)*
$PaCO_2$	7.1(1.9)	6.1(2.1)
HCO_3^{-1}	32.5(2.5)	33.1(2.8)
H^+	43.3(5.3)	42.6(3.8)

*p<0.05

At 4 weeks review, all NIV users noted symptomatic benefit. 2 subjects were using it for 15-18hours a day and 3 were using NIV overnight. Commonest problem was related to the mask. Interestingly we noted that all the patients required low inspiratory and expiratory positive airway pressures with mean IPAP of 10cm H_2O and EPAP of 6 cm H_2O. This was in contrast to 10 historical controls established on BIPAP with mean IPAP of 15.1(2.9) and EPAP of 9.5(2.7) cm H_2O.

3.4.5 Discussion

Patients with MND had more pronounced symptoms of respiratory muscle weakness at presentation and the weakness progressed rapidly in contrast to MyD patients during II visit. The symptomatic benefit with NIV was quite marked. However in this set of patients expiratory aids were not offered and routine measurement of peak cough expiratory flows was not carried out.

Respiratory muscle strength assessment revealed reduced mouth pressures and SNIP with rapid decline in both patients who went on to develop respiratory failure during the study period and those who did not (only one subject during the second visit at 4 months). Mortality within the group was also high with half of them succumbing to the disease in the 6 months of follow up. There was no significant difference in the rate of decline between patients who went on to NIV and those who didn't. Our sample size is small to assess this effect. Patients with bulbar symptoms did show the lowest SNIP values. Again due to the sample size, no clear conclusions can be drawn about the differences between bulbar group and those with predominantly limb involvement.

Basic spirometry, SNIP, overnight oximetry provided useful initial assessment tools for this group of patients. There is evidence on SNIP to predict survival (203) and hence its routine monitoring would be able to predict onset of SRBD. All the patients with FVC < 50% at the outset in our group went on to develop respiratory failure within 6 months. BAMPS was useful to provide quantitative diaphragm strength in this group of patients.

However it did not add any useful information for routine monitoring of these patients. Small sample size could have attributed to this result. In contrast to MyD patients, symptoms of respiratory muscle weakness and/or hypoventilation were more marked in MND patients and this was also useful marker of underlying SRBD.

It was interesting to note that inspite of significant weakness of global respiratory as well as diaphragm weakness, the fall in supine vital capacity was not high as could be expected. Certainly it was greatest in the patient with lowest Tw Pdi. This is again discussed in detail in section 5.1.

Since upper airway collapsibility is not a constant feature of MND, multi channel sleep studies are unlikely to be useful for routine clinical care. In our experience, overnight oximetry at home was welcomed by all the patients and provided information regarding overnight mean oxygen saturation and desaturation index that would guide further management.

3.4.6 Conclusions:

1. Our subject group was polysymptomatic for nocturnal hypoventilation with severe respiratoy muscle weakness even at the outset and this showed rapid significant decline on repeat testing at 4 months.

2. SNIP showed strong correlation with time spent below $SpO_2 < 90\%$. There was no significant correlation between mouth pressures and DI.

CHAPTER 4

DATA HANDLING AND STATISTICAL ANALYSIS

DATA HANDLING AND STATISTICAL ANALYSIS

All the data were stored on a computer in keeping with data protection act. Statistical analysis was carried out using a statistical software package (SPSS 14.0, SPSS Inc, Chicago, USA). Statistical significance was defined as $p<0.05$. Non-parametric statistics (Mann Whitney-U test) were used to compare the data between two groups. For variables measured in the same group on two occasions, Wilcoxon signed-rank test was used.

CHAPTER 5

CONCLUSIONS

I set out to explore the various methods of assessing respiratory muscle strength and identify predictors of ventilatory failure in neuromuscular diseases as daytime hypercapnia is a late event and tests that could predict onset of respiratory failure would be useful in day to day clinical practice. The degree of respiratory muscle weakness and its contribution to ventilatory failure is variable amongst different neuromuscular diseases. Hence interpreting different pulmonary function variables, mouth pressures, blood gas parameters in light of symptoms will be necessary to plan management in individual patient setting. Myotonic dystrophy and Motor neurone disease patients were studied in my research.

5.1 Critique of methods used

Subject selection:

It would have been ideal to study the full lung function tests, volitional tests of respiratory muscle strength, sleep studies followed by nonvolitional tests in a proportion of patients. Given the complexity of the disease studied, MyD and a rapidly progressive primary neurological disorder, MND, this did not turn out to be practical. Hence, patients who participated in the sleep studies subsection were different to the ones who consented to undergo the invasive tests. Studying more number of patients in MND group would have strengthened the data but again this did not prove to be practical.

Questionnaires:

ESS was originally developed for assessment of patients with primary sleep disorders (181) such as sleep apnoea and narcolepsy. It was not intended for primary assessment of

NMD patients. However it gives a very good indication of subjective sleepiness and has been shown to decrease after the initiation of NIV correlating with improvement in symptoms. Hence I used ESS in my studies. Though in the original study ESS score of ≥ 14 is considered significant, there are studies which have shown that patients are symptomatic even when it is lower. ESS > 11 has conventionally been used in our lab and this threshold was maintained throughout my studies.

Sleep Monitoring:

Overnight sleep studies have many problems on their own. Patients may not sleep well in the sleep lab and that would alter results obtained. Transcutaneous CO_2 analysis would have added in further information and given a clearer idea about nocturnal hypoventilation in our patients. However, this should not undermine the results of the current study as significant numbers of patients with SRBD (50% in PSG group and 36.8% in the overnight oximetry group studied) were picked up.

Volitional Respiratory Muscle strength:

It was observed that volitional muscle strength obtained for our cohort of subjects was lower compared to that reported in the literature (appendix I, II). Reasons for this are discussed in Section 3.3.5. Criteria for measurement was in accordance with other studies and great care was taken to ensure maximality of the procedure with constant verbal and visual encouragement to subjects. Also, it was ensured that SNIP and sniff Poes pressure tracings were identical during sniff Pdi manoeuvres. In view of this, absolute values of the mouth pressures, SNIP and sniff Pdi were used for analysis rather

than percent predicted values used in literature. Non-invasive measures of expiratory muscle strength such as peak cough expiratory flow rate was not evaluated in my studies and certainly this should be considered in clinical management of neuromuscular disease patients especially in view of emerging evidence of benefits of in-exsufflators.

Supine Vital Capacity

It was surprising that large falls in supine vital capacity (>20%) was a rarity in our subjects even when the Tw Pdi was low considering reported direct relation between fall in VC and nocturnal desaturation (97). Within the MyD group, percent fall in supine VC was 12.6(9.1) in SRBD group, compared to a fall of 6.2(4.9)% in the non-SRBD. Excluding the subject with SRBD who had normal FVC, the values for fall in supine VC were 12.3, 17, 21% which would be expected given the low TwPdi. Within the MND group, % fall in supine VC was rather low given the severity of diaphragm weakness at 4.6(4.0)% but this incremented to 10.6(6.2)% at the second visit as the weakness progressed. A contributing factor could be the altered diaphragm force-length relationship in supine position in our subjects. Certainly none of them had visible chest wall deformity that could explain this. Abdominal muscles prevent diaphragm to over-shorten during contraction and increased activity of these muscles has been shown in MyD. It is quite likely that this again altered the force-length relationship in the supine posture and contributed to our results. FVC estimates global respiratory effort and rib cage muscle contribution was not separately assessed in my studies. As supine VC is a relatively insensitive marker for diaphragm strength (though specific ie., if present highly suggestive of diaphragm weakness), it is quite likely that our group of patients had good

'extra-diaphragmatic inspiratory muscle strength' even when the Tw Pdi was low preventing supine fall in VC. Smaller size sample could also have prevented the differences from emerging.

Tw Pdi measurements:

BAMPS has been shown to be supramaximal for Tw Pdi assessment. This was confirmed in our lab in two normal subjects by varying the intensity of the Magstim stimulator output. Diaphragm EMG as an indicator of 'motor output' was not assessed in my studies. No evidence of myotonia was picked up during the study time in MyD group and hence it is unlikely to have contributed to the ventilatory impairment in our group of subjects.

Another potential problem in TwPdi measurement is that due to obesity especially in MyD which increases the abdominal girth. This in turn increases the impedance of abdomen and rib cage giving a higher Pdi measurement. Also, as baseline diaphragm activity can be high, twitch potentiation is a possibility and hence all the waveforms were visualised prior to analysis.

Peripheral muscle strength assessment:

As motor involvement in MND can be patchy, quadriceps strength was not assessed. MVC quadriceps values measured in the dominant leg were found to have no correlation to general muscle weakness as assessed by MDRS or diaphragm strength assessed by

TwPdi. However, nonvolitional measures of peripheral muscle strength were not used in my study.

5.2 Final Conclusions:

Pulmonary function tests in Myotonic dystrophy and Motor neurone disease:

Of all the routine pulmonary functions tests, basic spirometry still provides most useful information at the outset. This has to be supplemented with mouth pressures to identify subjects with respiratory muscle weakness in MyD and MND with 56% of those studied showing significant reduction in both spirometric values and mouth pressures.

Sleep studies in MyD and MND:

Screening sleep studies were useful to identify 12% of MyD subjects who would have been missed on routine spirometry and mouth pressures alone. Their targeted use in MyD patients particularly those with multiple symptoms of respiratory muscle weakness/nocturnal hypoventilation, who are overweight would help to pick up SRBD. Symptoms of respiratory muscle weakness (orthopnoea, morning headaches in particular) within MND group invariably revealed significant SRBD on overnight monitoring.

Volitioanl and Non volitional tests in MyD and MND:

We describe BAMPS as a useful technique to assess nonvolitional diaphragm strength in MyD for the first time. This also seems to be a daytime marker of SRBD in 75% (MyD group). Respiratory muscle weakness progression in MND is rapid with progressive symptoms and close monitoring of these patients will be needed. MyD subjects on the other hand, had stable muscle strength both by volitional and nonvolitonal methods after

6 months. No new symptoms of SRBD were reported at the second visit, when these tests remained stable.

Main conclusions in MyD:

- On linear regresssion, Tw Pdi and % predicted FVC proved to be the main predictors for daytime hypercapnia (p=0.019). Tw Pdi should be considered in patients with low volitional respiratory muscle strength.
- The positive predictive value of FVC<60% predicting SRBD (sensitivity) was 67% and specificity ie., >60% excluding SRBD was 85%. Hence these physiological tests should be interpreted in the light of symptoms as SRBD was seen with normal FVC, sniff Pdi and mildly reduced Tw Pdi. Further tests in the form of sleep studies and assessment of drive should be considered in this instance.
- On repeat tests at 6months, both volitional and nonvolitional tests were stable and this is reassuring at a clinical level, where MyD patients can be monitored with volitional tests for respriratory muscle strength if TwPdi at the initial visit is in the normal range.

Main conclusions in MND:

- Best correlates for hypercapnia in MND group were % FVC, SNIP and peak MEP, though just outside the level of significance ($p=0.06$) which is likely to be a reflection of the sample size.
- Serial monitoring is more crucial as respiratory muscle weakness progression was rapid. SNIP correlated with nocturnal desturation.
- Strong correlation between bicarbonate level and $PaCO_2$ strengthens the evidence for home monitoring patients with respiratory failure due to MND (146).

5.3 Future directions:

We hope to have added further insight into the physiology of respiration in MyD and MND. It has been shown that BAMPS can be used to dissociate upper airway muscles from the contraction of diaphragm (204). This has proved to be a useful technique to study upper airway dynamics in patients with sleep apnoea hypopnoea syndrome and assess response to continuous positive airway pressure therapy (205,206). Since it is well known that upper airway collapsibility occurs in MyD, feasibility of BAMPS opens up interesting avenues to study these patients during the daytime to gain insight into nocturnal events. This is especially important given the complexity of sleep studies, the behavioural aspects of MyD patients and their general unwillingness to seek medical attention or comply with treatment. Home monitoring with venous bicarbonate, given the correlation with $PaCO_2$ is another aspect that is worth exploring in these patients as is studying respiratory drive along with nonvolitional measures of diaphragm strength.

Due to the small number of patients that require specialised respiratory assessment it may be useful to identify regional centres which have expertise in carrying out both volitional and nonvolitional techniques of respiratory muscle strength assessment and provide useful advice on any problems encountered with non-invasive ventilation in the region. Certainly as in conditions such as chronic obstructive lung disease, home assessments including spirometry and sleep studies can be brought into practice and some of my studies have certainly shown the feasibility of these tests at home. A close collaboration between various specialists is paramount for the good clinical care needed for these patients including neurologists, medical geneticists, specialist nurses, physiotherapist, social worker, carer and the respiratory physicians. I do sincerely hope that all my work over the last 3 years has provided a foundation for a functional Scottish Neuro Respiratory Assessment centre in Glasgow with continued collaboration between the specialists.

I would like to conclude this thesis by providing a summary sheet that we found useful for the initial assessment and follow up of neuromuscular disease patients. This is currently being utilised at the respiratory laboratory in Gartnavel General Hosptial.

Neuromuscular Disease Assessment, Respiratory Unit, Gartnavel General Hospital

Diagnosis:

Duration:

Past History: **Smoking:** yes/no/ex

Medications:

Symptoms of Inspiratory muscle weakness:		**Duration:**
Breathlessness	☐	
Orthopnoea	☐	
Easy fatigability	☐	
Excessive daytime sleepiness	☐	
Choking at night	☐	
Snoring	☐	
Disturbed sleep	☐	
Witnessed apnoea	☐	
Morning headache	☐	
Cough	☐	

Symptoms of Expiratory muscle weakness/bulbar symptoms:

Recurrent chest infections	☐
Inability to clear secretions/cough	☐

Associated symptoms:

Swallowing Difficulty	☐
Wt Loss	☐
Speech problems	☐
Limitation of mobility	☐

Examination: (INITIAL VISIT)

Wasted respiratory muscles	☐
Accessory muscle use	☐
Paradoxical abdominal motion	☐
Normal chest expansion	☐
Additional sounds	☐

Ht: Wt: BMI: Epworth Sleepiness Scale: SpO_2:

	Value (L)	% predicted	Supine value (L)	%supine fall (VC)
FEV1				
FVC				

(> 25% fall in supine VC is strong evidence for diaphragm weakness – arrange sleep studies even if other indices normal)

	Value	**Normal values**
MIP (maximal inspiratory pressure)		>80 cm H_20
MEP (maximal expiratory pressure)		>90 cm H_20
SNIP (sniff nasal inspiratory pressure)		>70 cm H_20
Peak cough flow rate		>3L/sec (PEFR on the spiro)

ABG (if FVC < 50% predicted, symptoms of hypoventilation)

(non volitional diaphragm strength assessment to be considered if accurate diaphragm strength is sought and mouth pressures are low due to facial weakness)

Sleep Studies: (if FVC < 50%, symptoms of hypoventilation and PaO_2 >10, $PaCO_2$ < 6 kPa)

The current practice has been to obtain spirometry, mouth pressures a day prior to the clinic visit and if needed, overnight oximetry kit will be issued. If further sleep study (polysomnography) or full PFT (Eg., associated airflow obstruction or diffuse lung disease) is thought to be useful during the clinic visit, these will be organised as an outpatient.

Follow up: 6-12 months (stable patients)

3/12 (If respiratory muscle weakness progression unclear at the outset)

1-2/12 (Motor neurone disease/rapidly progressive muscle weakness on NIV)

Facilities available for self referral if symptoms develop, for early assessment and management.

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APPENDICES

I – Normal values established at our laboratory (24 male subjects)

	Age (yrs)	BMI (kg/m^2)	MIP (cm H_2O)	Peak MIP (cm H_2O)	SNIP (cm H_2O)	MEP (cm H_2O)	Peak MEP (cm H_2O)	FEV_1 (L)	% Pred FEV_1	FVC (L)	% Pred FVC	%drop in lying VC
	37	29.7	88.0	124.0	143.0	99.0	117.0	3.9	96.3	4.6	94.0	0.0
	30	25.1	68.0	86.0	52.0	76.0	148.0	4.6	100.0	5.5	100.0	1.8
	32	24.3	117.0	130.0	100.0	137.0	163.0	5.2	111.0	6.1	108.0	0.0
	27	23.2	98.0	126.0	116.0	110.0	126.0	5.5	112.0	7.1	121.0	0.0
	27	26.8	94.6	111.5	63.2	124.9	130.3	4.0	91.1	5.3	101.7	6.2
	35	30.2	76.0	84.0	108.0	106.0	124.0	4.5	105.0	5.7	110.0	1.1
	58	37.2	62.0	80.0	101.0	94.0	110.0	3.0	92.0	3.0	85.0	0.0
	44	32.5	97.0	118.0	112.0	144.0	160.0	2.8	79.0	3.6	79.0	0.0
	56	34.4	84.0	121.0	85.0	100.0	133.0	3.3	96.5	4.3	101.2	8.6
	40	33.4	112.0	161.0	132.0	128.0	177.0	4.0	94.7	4.9	93.9	1.8
	71	39.8	62.0	80.0	92.0	87.0	106.0	1.8	58.0	3.3	80.0	10.5
	49	31.9	57.0	99.0	65.0	69.0	81.0	2.8	84.0	3.6	89.0	5.0
	25	37.6	78.0	110.0	90.0	92.0	123.0	2.9	75.0	4.0	88.0	4.5
	47	32.0	84.0	105.0	106.0	140.0	189.0	2.8	94.0	3.4	95.0	0.0
	40	32.6	60.0	81.0	96.0	95.0	121.0	3.1	75.0	4.9	95.0	9.9
	46	34.8	99.0	101.0	60.0	147.0	160.0	3.4	88.0	4.9	105.0	6.1
	51	30.9	128.0	162.0	97.0	143.0	179.0	3.7	98.0	5.2	110.0	9.8
	48	31.9	123.0	147.0	10.0*	128.0	182.0	4.1	123.0	4.9	122.0	2.0
	35	26.2	122.5	154.0	46.3	123.9	183.0	3.7	87.6	5.7	111.0	2.4
	23	24.6	58.4	75.8	42.3	72.5	78.6	4.8	106.5	5.9	110.5	7.6
	19	19.2	59.1	82.3	78.5	75.3	109.5	3.1	72.1	3.5	70.5	0.0
	54	23.4	63.0	79.0	51.6	70.0	108.9	3.1	85.1	4.5	99.4	1.3
	24	26.0	79.2	95.9	67.2	131.9	157.8	4.3	97.2	5.7	110.7	2.3
	50	30.4	92.8	121.4	62.0	82.1	100.7	2.7	81.0	3.4	82.6	0.0
Mean	**40.3**	**29.9**	**85.9**	**109.8**	**82.3**	**107.3**	**136.1**	**3.6**	**91.7**	**4.7**	**98.4**	**3.4**
95% CI	**(35.1-45.6)**	**(27.8-32.0)**	**(76.8-95.0)**	**(98.9-120.7)**	**(69.8-94.8)**	**(96.8-117.9)**	**(123.0-149.3)**	**(3.3-4.0)**	**(85.9-97.5)**	**(4.3-5.1)**	**(93.1-103.8)**	**(1.9-4.8)**

Cross reference Koulouris et al, 1988 (n=11). MIP = 122.2±31.6 cm H_2O , MEP = 165.1±38.7 cm H_2O. Vincken et al, 1987 (n=46): MIP = 104.9(25.5) cm H_2O, MEP = 139.6 (37.7) cm H_2O. There were 2 current and 2 ex smokers within the group (highlighted in italics). *: Nasal obstruction on the day of test.

II – Normal values established for 14 female subjects at our laboratory

	Age (yrs)	BMI (kg/m^2)	MIP ($cm H_2O$)	Peak MIP ($cm H_2O$)	SNIP ($cm H_2O$)	Peak MEP ($cm H_2O$)	MEP ($cm H_2O$)	FEV_1 (L)	% Pred FEV_1	FVC (L)	% Pred FVC	%drop in lying VC
	21	25.6	108.0	136.0	143.0	126.0	145.0	3.0	102.0	3.3	97.0	2.0
	27	21.2	58.0	88.0	107.0	66.0	93.0	2.8	92.0	3.0	85.0	0.0
	33	22.7	78.0	116.0	87.0	99.0	113.0	3.1	101.0	3.7	105.0	6.0
	36	24.6	82.0	110.0	90.0	71.0	107.0	3.2	107.0	4.3	122.0	7.0
	31	17.9	65.1	76.4	92.8	78.2	89.2	2.4	75.1	2.9	77.5	4.5
	62	28.5	72.1	78.7	82.3	104.4	105.1	2.4	102.2	2.9	104.0	6.9
	68	29.6	68.0	74.0	90.0	86.0	94.0	1.7	91.0	2.5	100.0	1.2
	56	39.9	63.0	106.0	96.0	69.0	83.0	2.5	115.0	3.4	132.0	0.0
	54	33.3	93.0	119.0	128.0	78.0	106.0	2.2	103.0	3.1	121.0	0.6
	48	39.7	64.0	96.0	85.0	65.0	95.0	2.5	86.5	3.5	105.7	0.8
	48	33.6	58.0	79.0	67.0	68.0	95.0	2.8	108.0	3.5	115.0	4.6
	32	31.2	55.0	79.0	97.0	88.0	116.0	3.0	98.0	3.4	97.0	2.4
	53	32.8	95.0	116.0	95.0	83.0	98.0	2.8	119.0	3.4	123.0	5.6
	49	25.4	57.0	70.6	78.0	37.5	53.5	2.0	87.0	3.7	135.0	9.8
Mean	**44.1**	**29.0**	**72.6**	**96.0**	**95.6**	**79.9**	**99.5**	**2.6**	**99.1**	**3.3**	**108.5**	**3.7**
95% CI	**(36.7-51.5)**	**(25.5-32.4)**	**(63.4-81.2)**	**(85.1-107.0)**	**(85.3-105.8)**	**(69.0-91.0)**	**(89.0-110.0)**	**(2.3-2.8)**	**(92.8-105.2)**	**(3.1-3.5)**	**(99.6-117.4)**	**(2.0-5.3)**

All the subjects were non-smokers.

Cross reference Koulouris et al, 1988 (n=10). MIP = 85.6±24.4 cm H_2O, MEP = 117.2±31.6 cm H_2O .

Vincken et al , 1987 (n=60). MIP = 70.3±23.4 cm H_2O , MEP = 88.6±23.4 cm H_2O.

III- Epworth Sleepiness Scale

The Epworth Sleepiness Scale is used to determine the level of daytime sleepiness. Use the following scale to choose the most appropriate number for each situation.

0 = would *never* doze or sleep.
1 = *slight* chance of dozing or sleeping
2 = *moderate* chance of dozing or sleeping
3 = *high* chance of dozing or sleeping

Situation	***Chance of Dozing or Sleeping***
Sitting and reading	____
Watching TV	____
Sitting inactive in a public place	____
Being a passenger in a motor vehicle for an hour or more	____
Lying down in the afternoon	____
Sitting and talking to someone	____
Sitting quietly after lunch (no alcohol)	____
Stopped for a few minutes in traffic while driving	____
Total score	____

IV

THE SHORT FORM 36 HEALTH SURVEY QUESTIONNAIRE (SF-36™)

The following questions ask for your views about your health, how you feel and how well you are able to do your usual activities. If you are unsure about how to answer any questions please give the best answer you can and make any of your own comments if you like. Do not spend too much time in answering as your immediate response is likely to be the most accurate.

1. **In general**, would you say your health is:

(Please tick one box)

- Excellent ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐

2. **Compared to one year ago**, how would you rate your health in general now?

(Please tick one box)

- Much better than one year ago ☐
- Somewhat better than one year ago ☐
- About the same ☐
- Somewhat worse now than one year ago ☐
- Much worse now than one year ago ☐

3. **HEALTH AND DAILY ACTIVITIES**

The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

(Please tick one box on each line)

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b)	**Moderate activities**, such as moving a table, pushing a vacuum, bowling or playing golf	☐	☐	☐
c)	Lifting or carrying groceries	☐	☐	☐
d)	Climbing **several** flights of stairs	☐	☐	☐
e)	Climbing **one** flight of stairs	☐	☐	☐
f)	Bending, kneeling or stooping	☐	☐	☐
g)	Walking **more than a mile**	☐	☐	☐
h)	Walking **half a mile**	☐	☐	☐
i)	Walking **100 yards**	☐	☐	☐
j)	Bathing and dressing yourself	☐	☐	☐

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

*(Please answer **Yes** or **No** to each question)*

		Yes	No
a)	Cut down on the **amount of time** you spent on work or other activities	☐	☐
b)	**Accomplished less** than you would like	☐	☐
c)	Were limited in the **kind** of work or other activities	☐	☐
d)	Had **difficulty** performing the work or other activities (eg it took more effort)	☐	☐

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

(Please answer Yes or No to each question)

		Yes	No
a)	Cut down on the **amount of time** you spent on work or other activities	☐	☐
b)	**Accomplished less** than you would like	☐	☐
c)	Didn't do work or other activities as **carefully** as usual	☐	☐

6. During the **past 4 weeks**, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

(Please tick one box)

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

7. How much **bodily pain** have you had during the **past 4 weeks**?

(Please tick one box)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very Severe ☐

8. During the **past 4 weeks** how much did **pain** interfere with your normal work (including work both outside the home and housework)?

(Please tick one box)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

YOUR FEELINGS

9. These questions are about how you feel and how things have been with you **during the past month**. (For each question, please indicate the one answer that comes closest to the way you have been feeling).

(Please tick one box on each line)

	How much time during **the last month:**	**All of the time**	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
a)	Did you feel full of life?	☐	☐	☐	☐	☐	☐
b)	Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
c)	Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
d)	Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
e)	Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
f)	Have you felt downhearted and low?	☐	☐	☐	☐	☐	☐
g)	Did you feel worn out?	☐	☐	☐	☐	☐	☐
h)	Have you been a happy person?	☐	☐	☐	☐	☐	☐
i)	Did you feel tired?	☐	☐	☐	☐	☐	☐
j)	Has your **health limited your social activities** (like visiting friends or close relatives)?	☐	☐	☐	☐	☐	☐

HEALTH IN GENERAL

10. Please choose the answer that best describes how **true** or **false** each of the following statements is for you.

(Please tick one box on each line)

		Definitely true	**Mostly true**	**Not sure**	**Mostly false**	**Definitely false**
a)	I seem to get ill more easily than other people	☐	☐	☐	☐	☐
b)	I am as healthy as anybody I know	☐	☐	☐	☐	☐
c)	I expect my health to get worse	☐	☐	☐	☐	☐
d)	My health is excellent	☐	☐	☐	☐	☐

V - Muscular Disability Rating Scale

0 - No clinical impairment

1 – Minimal signs of weakness (ptosis, myotonia, facial or neck flexor weakness)

2 – Distal weakness (Weakness of muscles distal to extensors at elbow)

3 – Moderate proximal weakness (Grade 3/5, 4/5 motor power)

4 – Non ambulatory (Grade ≤ -3/5 motor power)

This has been tested for interrater reliability which is good. It is not recommended for use in short term therpeutic trials.

VI – HAD Scale – Scoring sheet

I feel tense or "wound up":	A
Most of the time	3
A lot of the time	2
Time to time, occasionally	1
Not at all	0
I still enjoy the things I used to:	D
Definitely as much	0
Not quite as much	1
Only a little	2
Hardly at all	3
I get a sort of frightened feeling as if something bad is about to happen:	A
Very definitely and quite badly	3
Yes, but not too badly	2
A little, but it doesn't worry me	1
Not at all	0
I can laugh and see the funny side of things:	D
As much as I ever could	0
Not quite as much now	1
Definitely not as much	2
Not at all	3
Worrying thoughts go through my mind:	A
A great deal of the time	3
A lot of the time	2
From time to time, not too often	1
Only occasionally	0
I feel cheerful:	D
Not at all	3
Not often	2
Sometimes	1
Most of the time	0
I can sit and feel relaxed:	A
Definitely	0
Usually	1
Not often	2
Not at all	3

I feel as if I am slowed down:	D
Nearly all the time	3
Very often	2
Sometimes	1
Not at all	0
I get a sort of frightened feeling like "butterflies" in the stomach:	A
Not at all	0
Occasionally	1
Quite often	2
Very often	3
I have lost interest in my appearance:	D
Definitely	3
I don't take as much care as I should	2
I may not take quite as much care	1
I take just as much care as I ever did	0
I feel restless as if I have to be on the move:	A
Very much indeed	3
Quite a lot	2
Not very much	1
Not at all	0
I look forward with enjoyment to things:	D
As much as I ever did	0
Rather less than I used to	1
Definitely less than I used to	2
Hardly at all	3
I get sudden feelings of panic:	A
Very often indeed	3
Quite often	2
Not very often	1
Not at all	0
I can enjoy a good book or TV or Radio Programme:	D
Often	0
Sometimes	1
Not often	2
Very seldom	3

VII – Myotonic Dystrophy Care Card

Myotonic Dystrophy and how it could affect your health.

Personality changes are often the main problem reported by families and can include lack of motivation, inertia, stubbornness and liking a set routine. This can lead to relationship problems with family, friends and at school or work.

Tiredness is very common and sometimes can be extreme. Sleeping during the day increases with age and sleep at night is often poor.

Muscle weakness is very variable and can range from mild to severe. It particularly involves the face and eyelids, jaw, neck, forearms and hands, lower legs and feet. It can affect **speech** and give lack of facial expression. Handwriting may start well but become a scrawl after a few lines.

Myotonia is a difficulty in relaxing a muscle after it has been contracted, e.g. after gripping something, it might be difficult to let go.

Heart problems can cause abnormal rhythm of the heart might require treatment. This can affect adults, even those without symptoms. Regular ECGs (heart tracings) of affected adults are advised to detect problems at an early stage.

Chest and breathing problems include chest infections. These may result from weakness of breathing muscles, including the diaphragm, or from food entering lungs as a result of choking. Inadequate breathing during the night might lead to disturbed sleep, snoring, difficulty waking, morning headaches and daytime sleepiness.

Digestive problems are common as the muscle throughout the digestive system may be affected. This may lead to: swallowing problems (which can also be a cause of food entering the lungs); pains in the bowels with constipation and diarrhea; soiling of underwear particularly when stressed or excited and occasionally enlargement of the large bowel. Gallstones, which can cause painful spasms after eating fatty food, can be a problem in myotonic dystrophy (even in young adults) and great care needs to be taken with any surgical treatment. Many patients have reported that medicines containing codeine cause severe constipation.

Eye problems include cataracts which cause blurring and dimming of vision. This may be the only problem caused by myotonic dystrophy, particularly in the first affected generation of a family. Droopy eyelids can cause a problem with reading and watching television. You should have regular checks at the optician and see a medical eye specialist if there is any concern.

Anaesthetics and surgery. Myotonic dystrophy can cause problems with your recovery after an operation when certain anaesthetic drugs are used. **Make sure the surgeon and anaesthetist know about your myotonic dystrophy before an operation.** They may wish to contact a specialist centre for advice. Carry this document or an Alert Card in your wallet or purse at all times, in case of an accident or emergency. **Anaesthetic guidelines are at: www.gla.ac.uk/muscle/dmanaesthesia.htm**

Other problems include: Diabetes, (ask to have your blood or urine sugar checked); male infertility; the muscle in the womb can be involved and lead to long difficult labour (possibly with bleeding afterward), and obstetric help may be required; the brain can be affected causing thinking and learning difficulty, especially when onset is in childhood.

Special difficulties in affected children: Muscle involvement can be more severe, especially when myotonic dystrophy is present at birth. Sometimes severely affected babies may live only a short time. However, if an affected baby survives infancy, parents and doctors are often surprised by the good progress the child subsequently makes but speech, educational and behaviour problems are common.

Inheritance: Other family members are frequently affected. It can affect and be passed on by both sexes, but affected mothers are more at risk of having a seriously affected baby than affected fathers. Genetic counselling is advised if genetic testing is being considered. Accurate genetic tests are possible: for healthy people who are at risk of developing myotonic dystrophy because they have an affected relative and in early pregnancy where one parent is affected.

Note: it is very unlikely one person would develop all these problems.

Fold 1

Fold 2

Fold 3

Further Information

Regional Muscle Clinic:
Address/contact details.

Myotonic Dystrophy Support Group:
a self help group, willing to provide support to families affected by Myotonic Dystrophy.
Tel: 0115 987 0080
Email: mdsg@tesco.net
Web: www.mdsguk.org

Muscular Dystrophy Campaign:
a charity funding medical research and support , including Family Care Officers, for people with neuromuscular conditions.
Tel: 0207 720 8055
Email: info@muscular-dystrophy.org
Web: www.muscular-dystrophy.org

Scottish Muscle Network:
information, regional and updated versions of the Card at: www.gla.ac.uk/muscle/dm.htm
Card enquiries and suggestions to:
d.e.wilcox@clinmed.gla.ac.uk

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Version 10.02 : 06/06/02

MEDICAL ALERT

The bearer of this card has **MYOTONIC DYSTROPHY**, a neuromuscular condition that may cause the following:

A. muscle weakness and stiffness.
B. extreme tiredness.
C. speech difficulties.
D. Adverse reaction to commonly used anaes-thetic agents.
E. Abnormal heart rhythm.

MYOTONIC DYSTROPH

CARE CARD

GP	ECG	Blood/urine glucose
	☑	☑

Optician	Family Care Officer
☑	

Occupational Therapist	Physiotherapist

Geneticist	Neurologist

Other specialists who might be able to help you, (or your child), with some of the problems of myotonic dystrophy include: anaesthetist, cardiologist, obstetrician, ophthalmologist, paediatrician, paediatric neurologist, physician, respiratory physician, social worker, surgeon and speech therapist.

Development of the Care Card:

The best management of myotonic dystrophy is difficult to assess because of the small number of patients compared to common disorders such as heart attacks. At the Scottish Muscle Network meeting in September 2000 the Myotonic Dystrophy Support Group voiced concern that the majority of their members did not have access to specialist clinics and the concept of a patient held Care Card was discussed. The MDSG then sponsored a meeting, in London in December 2000, of a multi-disciplinary team of 33 UK experts in the management of neuromuscular disorders. After local trials, the Care Card was appraised at a UK national meeting sponsored by the Muscular Dystrophy Campaign in Cambridge in March 2001. The Care Card was further developed at the 99th European Neuro Muscular Centre "Workshop on the management of myotonic dystrophy" in the Netherlands in November, 2001.

☑ **A number of Good Practice Points emerged from the development discussions and include:**

The diagnosis of myotonic dystrophy in an affected person should be confirmed by DNA testing.

Healthy adults at risk of inheriting myotonic dystrophy should be offered genetic counselling before DNA testing.

Healthy children, at risk of inheriting myotonic dystrophy, should be allowed to make their own decision about testing when they are adults and can consider implications for insurance, employment and having children.

Affected mothers, whose babies are at risk, should give birth in a specialist maternity hospital with access to a neonatal intensive care unit.

Affected adults should have an ECG and urine sugar checked every year and visit an optician for an eye test every 2 years.

Anaesthetists should seek advice before treating people with myotonic dystrophy, or their apparently unaffected relatives. Anaesthetic guidelines at:
www.gla.ac.uk/muscle/dmanaesthesia.htm

VIII - ALS Functional Rating Scale

A. Speech

4 - Normal speech processes

3 - Detectable speech disturbances

2 - Intelligible with repeating

1 - Speech combined with nonvocal communication

0 - Loss of useful speech

B. Salivation

4 - Normal

3 - Slight but definite excess of saliva in mouth; may have night time drooling

2 - Moderately excessive saliva; may have minimal drooling

1 - Marked excess of saliva with some drooling

0 - Marked drooling; requires constant tissue or handkerchief

C. Swallowing

4 - Normal eating habits

3 - Early eating problems - occasional choking

2 - Dietary consistency changes

1 - Needs supplemental tube feeding

0 - NPO (exclusively parenteral or enteral feeding)

D. Handwriting

4 - Normal

3 - Slow or sloppy; all words are legible

2 - Not all words are legible

1 - Able to grip pen but unable to write

0 - Unable to grip pen

E. Cutting Food and Handling Utensils

(patients without gastrostomy-feeding tube)

4 - Normal

3 - Somewhat slow and clumsy, but no help needed

2 - Can cut most foods, although clumsy and slow; some help needed

1 - Food must be cut by someone, but can still feed slowly

0 - Needs to be fed

Cutting Food and Handling Utensils(alternate scale for patients with gastrostomy)

4 - Normal

3 - Clumsy but able to perform all manipulations independently

2 - Some help needed with closures and fasteners

1 - Provides minimal assistance to caregiver

0 - Unable to perform any aspect of task

F. Dressing and Hygiene

4 - Normal function

3 - Independent and complete self-care with effort of decreased efficiency

2 - Intermittent assistance or substitute methods

1 - Needs attendant for self-care

0 - Total dependence

G. Turning in Bed and Adjusting Bed Clothes

4 - Normal

3 - Somewhat slow and clumsy, but no help needed

2 - Can turn alone or adjust sheets, but with great difficulty

1 - Can initiate, but not turn or adjust sheets alone

0 - Helpless

H. Walking

4 - Normal

3 - Early ambulation difficulties

2 - Walks with assistance

1 - Nonambulatory functional movement

0 - No purposeful leg movement

I. Climbing Stairs

4 - Normal

3 - Slow

2 - Mild unsteadiness or fatigue

1 - Needs assistance

0 - Cannot do

J. Breathing

4 - Normal

3 - Shortness of breath with minimal exertion (e.g. walking, talking)

2 - Shortness of breath at rest

1 - Intermittent (e.g. nocturnal) ventilatory assistance

0 - Ventilator dependent