PROBLEM ASTHMA CLINIC

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COHORT OBSERVATIONAL STUDY OF THE UPPER AIRWAY AND BREATHING PATTERN

A thesis submitted to the University of Glasgow for the degree of MD

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Publications

The following publication and abstracts presented to learned societies have arisen from this thesis:

Publication

AE Stanton and CE Bucknall. Vocal cord dysfunction – a review. Breathe 2005; 2(1): 31 – 7.

Abstracts and Presentations to Learned Societies

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AE Stanton, GW McGarry, R Carter, CE Bucknall. The spectrum of upper airway problems in a problem asthma clinic – the role of the nose. ERJ 2004; 24(Supp 48): P1710 - Presented to the European Respiratory Society Annual Congress, Glasgow, September 2004 as a Poster Discussion

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List of Abbreviations

BCT	Breathing Control Therapy
BHT	Breath Hold Time
BTS	British Thoracic Society
DB	Dysfunctional Breathing
ENT	Ear, Nose and Throat
FEV_1	Forced Expiratory Volume in 1 second
FOT	Forced Oscillation Technique
FVC	Forced Vital Capacity
FVL	Flow Volume Loop
GRBAS(I)	Grade, Roughness, Breathiness, Asthenicity, Strain, (Instability) Score
HAD	Hospital Anxiety and Depression Questionnaire
HCT	Histamine Challenge Testing
MEF_{50}	Maximum mid-expiratory flow
MIF_{50}	Maximum mid-inspiratory flow
Mini-AQLQ	Mini-Asthma Quality of Life Questionnaire
NPV	Negative Predictive Value
NSS	Nasal Symptom Score
PAC	Problem Asthma Clinic
PCAQ	Perceived Control of Asthma Questionnaire
PET	Progressive Exercise Testing
PPV	Positive Predictive Value
RCP	Royal College of Physicians
RS	Reflux Score
R_e	Expiratory Airways Resistance

R_f	Respiratory Frequency
R_i	Inspiratory Airways Resistance
R_t	Total airways resistance
R_{int}	Interrupter resistance
R_{occ}	Occlusion Resistance
VCD	Vocal Cord Dysfunction
ENT	Ear, Nose and Throat
PPV	Positive Predictive Value
PAC	Problem Asthma Clinic
SLT	Speech and Language Therapy / Therapist
SNOT-22	Sino-Nasal Outcomes Test (22)
T_i	Inspiratory time
T_e	Expiratory time
V_{min}	Minute ventilation
VoiSS	Voice Symptom Score
V_t	Tidal Volume

Summary

The investigations reported in this thesis are observational studies of various aspects of the upper airway and breathing pattern in patients attending a Problem Asthma Clinic (PAC) based in a large city hospital. We hypothesised that Vocal Cord Dysfunction (VCD) would be present in a proportion of patients attending our clinic and that the Forced Oscillation Technique (FOT) would play a role in the non-invasive identification of this. In addition we explored the relationships between structural nasal, laryngeal and vocal pathology and symptoms, along with a detailed assessment of vocal morbidity by both patient reported (Voice Symptom Score – VoiSS) and Speech and Language Therapy assessment (GRBAS score) methods. We hypothesised further that a strategy of performing challenge testing with Histamine and Exercise challenge would be helpful in the diagnosis of VCD. Finally we proposed that patients felt to have dysfunctional breathing (DB) on the basis of Nijmegen scores would have different physiological measurements of breathing pattern to those not felt to have DB and that physiotherapist delivered breathing control therapy (BCT) would produce an improvement in Nijmegen scores and asthma related quality of life.

Firstly, the clinical characteristics of a cohort of 49 new-patient referrals to the PAC, along with interrelationships between psychological correlates of asthma (Hospital Anxiety and Depression (HAD), Asthma related quality of life (AQLQ), perceived control of asthma, hyperventilation (Nijmegen) score) are described. Of this cohort, 39 (79.6%) had definite evidence of asthma. There were statistically significant

correlations between baseline questionnaire scores, with the most convincing relationship seen between Nijmegen and HAD (Anxiety) ($r = 0.70$, $p = 0.006$). After 1 year attendance at the clinic, which included regular re-enforcement of self-management training, there were no differences seen in any questionnaire parameter.

Our first pilot study involved wide ranging assessment of the upper airway in 43 patients attending the PAC. We found no evidence of VCD, as classically described in current literature, but did find evidence of other structural and functional laryngeal abnormalities, nasal pathology and vocal morbidity. Laryngitis was the most frequent structural abnormality (15 patients). Functional abnormalities included glottic chink (5), phonating with false cords (5) and reduced cord mobility (2). Individual laryngopharyngeal symptoms were poor predictors of laryngeal pathology but symptom combinations increased the likelihood of any laryngoscopic abnormality. The lack of VCD identification prevented any conclusion being made regarding the role of FOT in VCD diagnosis. At nasendoscopy 22 patients had normal examination (median NSS 4), 8 had polyps (median NSS 5), 7 had deviated nasal septum (median NSS 4), 4 oedematous mucosa (median NSS 7) and 2 had other abnormalities. Individual nasal symptoms were poor predictors of individual nasal pathologies, but hyposmia was the best individual predictor of any abnormality (Positive Predictive Value (PPV) 80%). Combination of symptoms increased the likelihood of any nasendoscopic abnormality with obstruction, rhinorrhoea and hyposmia together having a PPV of 100%. Only 1 patient had evidence of laryngeal candidiasis, emphasising that dysphonia (in 13 patients as defined by SLT assessment) in patients with asthma is more complicated than may be initially assumed. VoiSS scores were

higher in patients with laryngeal abnormalities (median VoiSS 33 vs 22, 95% CI for difference 0.0, 21.0, p = 0.044) while GRBAS did not differ in this group.

Given the lack of positive identification of VCD in our pilot study, we investigated the role of challenge testing in VCD diagnosis by combined histamine challenge and progressive exercise testing. We recruited 9 patients we suspected this diagnosis as a co-existing factor with asthma to the study, 7 of whom completed the protocol. We found no evidence this diagnostic strategy was of value with no change in laryngeal appearance after either challenge in any patient.

We performed a more comprehensive observational survey of nasal symptomatology and nasal pathology to help determine the value of routine nasendoscopy in a problem asthma clinic by inviting as many patients with asthma as were attending the clinic to attend a simple study run in parallel with their attendance at the PAC. A control group of patients with COPD or Interstitial Lung Disease was used for comparison. This study suffered form poor recruitment rate in both groups (26 with asthma recruited versus 7 controls). We found proportionally more patients in the control group had any nasendoscopic abnormality (5/6, 83%) compared with the Asthma group (15/21, 71%), but only one in the control group actually required further ENT review for this in comparison with 11 out of 21 patients with asthma requiring further ENT review. Individual symptoms seemed to be better individual predictors of a general abnormality than in our pilot study and intriguingly the best individual predictor was " loss of smell or taste" (PPV 83.3%).

The other main component of this thesis addresses the issue of hyperventilation or dysfunctional breathing along with breathing pattern characterisation and investigation of the role of breathing control therapy in patients with asthma. 102 patients attending our clinic completed Nijmegen and Mini-AQLQ questionnaires. Patient with a positive Nijmegen score (n = 65, said to have evidence of dysfunctional breathing – "DB") were referred for breathing control therapy (BCT) and progressive exercise testing (PET) to seek confirmation of hyperventilation. We aimed to collect follow up questionnaire data at six months in both the group who received BCT and the group who did not (those with negative Nijmegen scores – "Non-DB"). We found a strong relationship between Nijmegen score and Mini-AQLQ ($r = -0.63$, $p < 0.001$) and a less strong relationship between level of asthma symptoms and Nijmegen scores ($r = 0.43$, $p < 0.001$) at baseline. There was poor agreement between Nijmegen identified hyperventilation and PET identified hyperventilation. Follow up data (available in 29 patients) showed no significant change in either of Nijmegen scores or Mini-AQLQ, after a moderate intensity intervention delivered by a specialist respiratory physiotherapist in parallel with attendance at the problem asthma clinic, although 8 patients had Nijmegen scores that fell to within the normal range and 9 also had clinically significant improvements in Mini-AQLQ. This data suggests that the Nijmegen questionnaire overestimates the prevalence of HVS, by wrongly attributing symptoms of poor asthma control to hyperventilation.

A subgroup of the above patients (n = 78; 31 DB, 47 Non-DB) underwent physiological assessment of breathing pattern. Data on inspiratory time (T_i), expiratory time (T_e), expiratory / inspiratory time ratio (T_e/T_i), Tidal volume (V_t) for each breath was available from each recording. Subsequently, minute ventilation

(V_{min}) and respiratory frequency (R_f) could be calculated. Other than a statistically significant difference observed was in the measurement of V_t (95% CI 0.01, 0.39, p = 0.044) there were no differences in between those with positive and those with negative Nijmegen Scores. Breath-to-breath variability for T_i, T_e, T_e/T_i and V_t also did not differ between the two groups. Follow up data subsequent to breathing control therapy (31 patients - 16 Non-DB, 15 DB) showed there was no significant difference at follow up from baseline measurement in any breathing pattern characteristic.

CHAPTER 1

REVIEW OF THE LITERATURE

1.1 Severe Asthma

There are a variety of patients with asthma who require input from secondary care. Such patients include those in whom initial diagnosis is not immediately apparent, those who have not responded to initial treatment in primary care and those recently discharged from hospital requiring further monitoring and self management training. There is then the group of patients who require long term management in specialist clinics with "Severe Asthma". While there are very good clinical indicators to define the severity of an acute exacerbation of asthma ([1]), it has been much harder to reach consensus on clear definition of "severe" asthma over the longer term. A multitude of labels have been given to this clinical entity for example chronic severe, severe persistent, difficult, difficult to control, treatment resistant. "Difficult Asthma" has been previously defined as "failure to achieve control when maximally recommended doses of inhaled therapy are prescribed" ([2]). It is clear however that a number of factors influence either patients' or doctors perception of severity of disease in addition to a particular level of treatment taken such as compliance, level of current symptoms, frequency of exacerbations, degree of airflow obstruction, bronchial hyper-reactivity, exhaled markers of airway inflammation and of course any aggravating factors. These factors may not necessarily correlate with each other, for example the patient who has frequent exacerbations but with minimal symptoms and lung function impairment in between may be on a high level of treatment to minimise such exacerbations. One simple, treatment based description of severity is to use the current British Thoracic Society (BTS) guidelines step wise approach, with BTS Step 4 or 5 representing severe asthma. The European Respiratory Society (ERS) Task force defines difficult / therapy resistant asthma as "asthma which is poorly controlled

in terms of chronic symptoms, episodic exacerbations, persistent and variable airways obstruction and a continued requirement for short acting beta agonists despite delivery of a reasonable dose of inhaled corticosteroids (≥ 2000 mcg/day beclomethasone, 1600 mcg/day budesonide or 1000 mcg/day fluticasone) +/- regular courses or a regular dose of oral corticosteroid" ([3]). Despite this there remains an argument for more specific definition of "asthma phenotypes" which could guide both clinical management and clinical research and which ultimately could be linked to genotype ([4]). An example of an asthma phenotype is that of the "brittle asthmatic", with two sub-types recognised ([5]). Type I brittle asthma is characterised by wide variations in peak flow (> 40% diurnal variation for > 50% of the time over a period of at least 150 days) despite therapy consisting pf at least 1500 mcg/day beclomethasone or eauivalent. Type II brittle asthma is characterised by sudden acute attacks without an obvious trigger on a background of well controlled asthma and apparent normal airway function. More recent work has attemped teasing out of different aspects of the severe asthma phenotype by comparing 163 patients with "severe asthma" with 158 controlled asthma, with principle findings being of female predominance and more neutrophilic inflammation the severe group ([6]). The definition of severe asthma (one asthma exacerbation in the last year despite treatment with ≥ 1200 mcg/day beclomethasone or equivalent) was different in this study to that of the ERS task force described above.

Due partly to difficulties in reaching consensus as to diagnostic criteria for severe asthma precise figures for its prevalence of are not available, but some hints come from survey data. 4.6% of 3373 patients with asthma had treatment consistent with severe asthma in an English community survey ([7]), and in a French survey of 4362

patients with asthma, 5.1% were on such treatment, 9% had an FEV1 < 60% predicted and 16-17% had continuous daily and frequent nocturnal symptoms([8]).

1.2 Vocal Cord Dysfunction

In asthma inflammation and obstruction in the lower airways manifests itself by the symptoms of wheeze and breathlessness. Involvement of the upper airway can produce symptoms which can be difficult to distinguish from those of asthma. In Vocal Cord Dysfunction (VCD) there is abnormal adduction of the vocal cords during respiration leading to airflow obstruction and symptoms which can mimic asthma. This condition has also previously been given the name of paroxysmal vocal cord motion, paroxysmal vocal cord dysfunction, paradoxical movement of vocal cords, episodic paroxysmal laryngospasm and irritable larynx syndrome ([9]). This condition continues to present both diagnostic and therapeutic dilemmas to respiratory physicians.

Epidemiology

True population figures for incidence and prevalence of VCD are not known. In a group of 1025 patients evaluated for exertional dyspnoea, 29 (2.4%) were found to have VCD ([10]). In a smaller study of 105 army recruits evaluated for dyspnoea 10 (9.5%) had VCD ([11]).

The incidence in patients with asthma has been explored in more detail but still remains unclear. One tertiary referral centre evaluated patients with *refractory* asthma and found 22 out of 132 (16.7%) to have VCD in addition to asthma ([12]). In one of the largest case series of 95 patients with VCD, 53 also had asthma ([13]). This case series also suggested a high incidence of psychiatric problems in patients with this

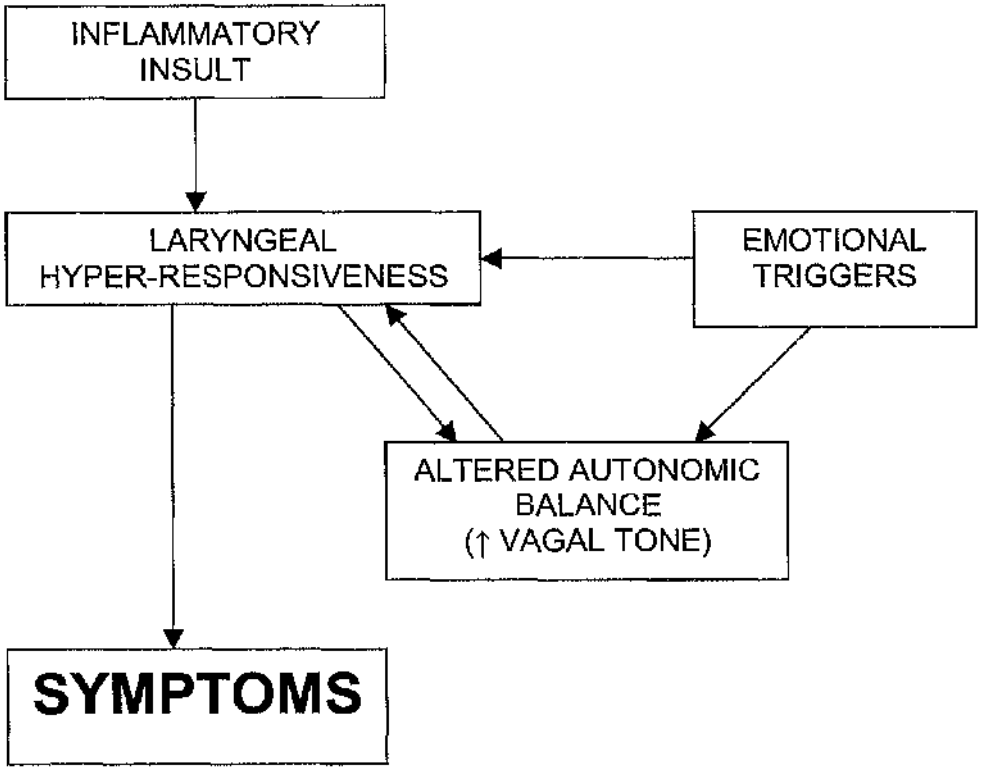
condition. In the 42 patients with pure VCD, 9 had had psychiatric hospitalisations, 73% had a major psychiatric disorder and 37% had a personality disorder. 38% of these patients also had a history of sexual, physical or emotional abuse. Similar degrees of psychiatric morbidity were found in those with VCD and asthma. Christopher ([14]) proposed that VCD is a form of conversion disorder, a view supported by Selner's small series ([15]). This is not however confirmed by later work ([16;17]). Newman's series ([13]) and a further series of 22 patients ([18]) suggest that this is typically a condition of younger females. Other case reports implicate occupationally inhaled irritants([16]), child abuse ([19]), brain-stem compression ([20]), cystic fibrosis ([21]), working in health care ([13;22]) and gastro-oesophageal reflux ([23]).

Pathophysiology

There is no clear consensus on how this condition arises. First of all the innervation of the larynx must be considered. Sensory information is transmitted via the vagus nerve to the medulla. A variety of other factors such as stress, emotion and ambient temperature also input to this part of the central nervous system. These may influence the motor outflow, also via the vagus. Consequently a base line autonomic balance can be said to exist ([24]). Ayres and Gabbott propose that this can become "imbalanced" by either laryngeal hyperresponsiveness (initiated by some form of inflammatory insult) or perhaps from a central stimulus such as ill-defined psychological factors (Figure 1 – adapted from Ayres ([24])). Morrison([25]) proposed a similar mechanism whereby the threshold for stimulating glottic spasm is lowered by chronic irritation of the larynx by gastro-oesophageal reflux. Such an imbalance may favour adduction of the vocal cords.

There remains the possibility that more than one of these factors may exist in any one patient and that depending on the persistence or degree of such factors, a vicious cycle encouraging persistence may be created. The ultimate result is of abnormal adduction of the vocal cords with creation of a characteristic posterior glottic "chink" visualised at laryngoscopy ([13;14;22]). This occurs during the respiratory cycle leading to upper airway obstruction and symptoms. This most commonly occurs during inspiration, but can also occur during expiration in addition or in isolation ([26-28]). Due to the variable nature of the factors described above, the symptoms are also variable.

Figure 1 – Vocal Cord Dysfunction - Proposed Pathogenesis



If laryngeal hyperresponsiveness is the basis of VCD, what provides the initial insult? This may be due to upper airway hyper-responsiveness occurring in association with the lower airway hyper-responsiveness of asthma. Bucca ([29]) demonstrated that histamine provocation testing could produce extrathoracic (upper) airway narrowing as measured by a 25% decrease in mid-inspiratory flow in 25 of 40 patients with episodic breathlessness with wheeze and / or cough. This extrathoracic airway hyperresponsiveness (EA-HR) was observed with or without lower airway bronchial hyperresponsiveness (BHR) as measured by a 20% fall in FEV_1 in response to histamine. Although laryngoscopy was only performed in 7 of these 25 patients, it is interesting that in addition to mucosal oedema and pharyngoconstriction, adduction of the vocal cords during forced inspiration was seen in all 7 of these patients. Five of the 15 patients who had no evidence of EA-HR also had laryngoscopy but with normal findings. This study did not state how many patients had asthma and so it is unclear if EA-HR was a phenomenon distinct from or part of the spectrum of asthma. The same group later showed that isolated EA-HR was responsible for asthma-like symptoms in 117 of a larger sample of 441 patients, but laryngeal examination was not undertaken in this study ([30]). EA-HR occurred in association with BHR in a further subgroup of 179 patients in this study. This raises the possibility that a reflex can be triggered by stimulation of pharyngo-laryngeal receptors independent of the lower airways, and this is supported by the finding of EA-HR in 72% of patients with sinusitis ([31]).

Other workers have suggested that stimuli such as acid reflux or inhaled irritants could initiate or contribute to laryngeal hyperresponsiveness. Perkner ([16]) described 9 patients from a cohort of 127 VCD patients with symptoms relating to irritant

exposure to ammonia and fumes from cleaning fluids. In this same group, 28 had symptomatic gastro–oesophageal reflux disease (GORD), but this was not defined objectively. In Powell's cohort ([18]), 19 of 22 patients had laryngoscopic changes suggestive of reflux disease. The relationship of GORD, and perhaps even more importantly laryngopharyngeal reflux disease to VCD has not been prospectively evaluated.

Clinical Features

Christopher ([14]) used the term Vocal Cord Dysfunction to describe five patients with dramatic episodes of wheezing, previously thought to have asthma. Further investigation demonstrated no objective evidence of asthma but each had marked flattening of the inspiratory limb of a flow-volume loop and characteristic laryngoscopic abnormalities. Other case reports ([32-38]) and the large series mentioned above have described the clinical features of VCD in detail. The patient may complain of wheezing, "noisy breathing", stridor, dyspnoea, cough or throat tightness. VCD has been shown to account for "choking" during athletic activities in patients previously felt to have exercise-induced asthma([39]). Because of these symptoms, asthma is commonly misdiagnosed, as several case reports describe, and the patients may have been on long term high dose steroids resulting in a Cushingoid appearance. Other clues to the diagnosis are inspiratory stridor heard over the trachea, the absence of typical asthma features (in particular BHR) and lack of response to conventional asthma therapy. If a patient is ventilated for presumed severe asthma and found to have normal inflation pressures, this would also suggest the diagnosis.

Examination may be unhelpful. Careful listening to patients breathing may reveal inspiratory stridor rather than expiratory wheeze, but the timing of abnormal vocal cord adduction can be inspiratory or expiratory. Similarly, pronounced inspiratory noise heard by auscultating over the trachea may help in some cases. As a result of profound upper airway obstruction, hypoventilation and therefore hypoxia can rarely occur and in some cases lead to intubation and mechanical ventilation ([35]).

Diagnosis

Perhaps the most significant problem in the diagnosis of VCD lies in the episodic nature of symptoms. Visualisation of the cords, with characteristic adduction of the anterior two thirds and creation of a posterior glottic chink during inspiration and /or expiration must be regarded as the gold standard of diagnosis ([13;16;23]). In between attacks, the cords may be normal. Other diagnostic tests detailed below can be helpful in suggesting VCD as a diagnosis.

Spirometry

Measurement of Forced Expiratory Volume in one second (FEV_1) and Forced Vital Capacity (FVC) are likely to be normal unless lower airway obstruction is present. FEV_1 is not a sensitive measure of extrathoracic airway narrowing([40]).

Measurement of flow-volume loops is more helpful if VCD is present. Truncation of the inspiratory limb is characteristic (although not specific for VCD) resulting in a Mid-expiratory flow / Mid-inspiratory flow (MEF_{50}/MIF_{50}) ratio exceeding 1.5 ([41]).

The Flow Volume Loop (FVL) may only be abnormal in about a fifth of asymptomatic patients ([13]). An atypical expiratory limb with abrupt drop and rise has been described ([36;42]) presumably due to expiratory VCD.

Estimation of mid-inspiratory flow (MIF_{50}) is a more numerical method of measuring extrathoracic airflow obstruction and in a small sample of patients, was shown to correlate well with mid-inspiratory glottis area measured laryngoscopically ([29]).

Specific Challenge Testing

Given the episodic nature of symptoms, if a particular precipitant can be identified, it would seem logical to attempt provocation testing to aid diagnosis. Selner ([15]) reported reproduction of symptoms with cooked corn in one VCD patient but also with placebo during food challenge in another patient initially felt to have symptoms related to egg products. In this latter patient methacholine also produced stridor. In Perkner's description of irritant-associated VCD, these were all diagnosed by laryngoscopy within 24 hours of exposure, but no formal challenge tests were subsequently performed ([16]).

Bronchial provocation tests

Methacholine and histamine are bronchoconstrictors that act directly on bronchial smooth muscle. The ability of histamine challenge to detect extrathoracic airway hyperresponsiveness has been discussed. It seems simplistic however to presume that upper airway obstruction demonstrated in this way will always be due to VCD. In

Newman's cohort ([13]), Methacholine challenge Testing (MCT) induced VCD in 9 of 12 subjects with normal laryngoscopy. Morris ([11]) demonstrated changes in inspiratory limbs of flow-volume loops in 4 out of 10 VCD patients with MCT but did not correlate these findings with laryngoscopy. There has only been one prospective evaluation of MCT in the diagnosis of VCD. In this study ([43]), 10 known VCD patients, 12 patients with exercise induced asthma (EIA) and 12 controls underwent laryngoscopy before and after MCT challenge testing. The findings in the 10 known VCD patients were as follows:

- 2 had VCD changes before and after MCT
- 2 had VCD changes induced by MCT
- 6 had no VCD changes, but 3 demonstrated truncation of the inspiratory limb of the FVL suggesting extrathoracic airway hyperresponsiveness.

In addition, 7 of the 10 patients had bronchial hyperresponsiveness with MCT. None of the control group or EIA patients developed VCD post MCT although 1 EIA patient developed inspiratory FVL flattening with MCT. This study highlights the importance of correlating any FVL abnormalities with laryngoscopic appearances.

Exercise Testing

Case reports have described VCD in association with exercise([44;45]). McFadden([39]) described 7 elite athletes who developed VCD during sporting competitions. Attempts were made to recreate symptoms by exercise testing. This was only successful in 3/7 patients (2 in treadmill and 1 by bicycle ergometry) with 3 further patients being examined after their individual sporting activity and the remaining patient positive by

hyperventilation testing. The diagnosis was made by laryngoscopy in only 3 of these patients with FVL used in the others. Interestingly MCT did not provoke symptoms in any of these patients. In the same study previously quoted by Morris([11]), 40 patients and 12 controls were evaluated for exertional dyspnoea. Progressive cardiopulmonary exercise testing with pre and post test laryngoscopy was performed in all patients. Two patients had evidence of VCD pre and post-exercise. Exercise provoked VCD in a further 8 patients, with the remaining 30 patients and 12 controls having no evidence of VCD. It is not clear how many of these patients had asthma although 6 of the VCD patients had BHR on MCT.

More recently, the use of continuous transnasal laryngoscopy during exercise has been described in the diagnosis of exercise induced laryngeal dysfunction in a group of patients predominantly with laryngomalacia, rather than VCD([46]). This technique may be helpful to clarify the role of challenge testing in the diagnosis of VCD in future studies.

Forced Oscillation Technique

The forced oscillation technique (FOT) uses small oscillating forces in the form of sound waves to measure the impedance (the opposition to flow of these forces) of the respiratory system. The input is usually applied via a mouthpiece through which the subject performs tidal breathing. Impedance and thence resistance are calculated from the mouth pressure and flow after the effects of breathing have been removed by signal processing. Its merits include the rapid acquisition of data and that it does not require maximum effort manoeuvres([47]). It is therefore easier for some patients to

perform than routine pulmonary function tests which involve forced manoeuvres. This may be particularly relevant for patients with suspected upper airway symptoms who anecdotally often have difficulty with these.

Although there are no published data on this technique in the clinical setting of VCD, Rigau mimicked VCD in a model using variable resistance to simulate normal respiratory anatomy and found that the changes in oscillatory resistance were in agreement with the degree of area reduction in the model ([48]). As with changes in the inspiratory limb of the FVL, changes in FOT measured resistance will not be specific for obstruction at the cords, but rather more of a reflection of upper airways obstruction in general.

Other methods of diagnosis

One case report([49]) demonstrated VCD by means of airway radiographs and fluoroscopy in a patient where laryngoscopy was not performed.

Zelcer([50]) has described abnormalities in Multidimensional voice programme analysis whereby VCD patients had differences in soft phonation indexes compared with normal subjects. One case of VCD has been reported under hypnotic suggestion([51]).

Treatment

There are no randomised controlled trials of any form of treatment for VCD. Evidence is limited to case reports and series describing the course of the condition.

The patients from Christopher's series were treated by a speech pathologist ([14]). They were taught to focus attention away from the larynx and inspiratory phase of breathing. Instead they were taught to concentrate on active expiration using anterior abdominal muscles and to relax oropharyngeal muscles. Short-term psychotherapy was also administered to these patients and they all experienced a reduction in frequency and severity of attacks. Selner emphasised the importance of thorough psychological assessment, and the prevalence of psychiatric morbidity is discussed above ([13;24]). This may not be appropriate in all cases and may be counterproductive in patients who have been dismissed as "mad" by doctors previously. Together with speech therapeutic strategies similar to those used for treatment of other voice disorders (such as laryngitis, hoarseness), Newman([13]) emphasises the importance of cessation of unnecessary medications, as patients mislabelled as asthma may often have been prescribed significant doses of inhaled or oral corticosteroids resulting in side effects. Powell also treated his group with speech therapy and psychological counselling as well as raising interesting questions about the role of anti-reflux therapy in cases where this can be implicated. More recently, Sullivan([52]) reported success of a speech therapy programme in 20 adolescent female athletes with VCD.

In the acute setting, a mixture of helium and oxygen (heliox) has been described as beneficial. Weir detailed dramatic results in 4 VCD patients([38]). The mechanism of

action of Heliox is likely to relate to the low density of such a gas mixture allowing improving flow of air through the adducted cords ([53]). Lisboa found varying degrees of increased inspiratory resistance in asthmatics compared with normal, which was corrected by breathing heliox ([54]). Such a benefit from heliox has been described in other patients with fixed upper airway obstruction ([55]).

Other therapies for which there is anecdotal evidence of benefit include intralaryngeal injection of botulinum toxin ([56]) and a portable facemask with adjustable resistance to inspiration but not expiration ([34]).

Conclusions – Vocal Cord Dysfunction

Recognition and description of vocal cord dysfunction have improved over the last two decades. Respiratory physicians are more aware of the possibility of VCD underlying or mimicking poorly controlled asthma and will consider the diagnosis in others with atypical asthma like symptoms. Visualisation of the cords during an attack of symptoms is the current gold standard for diagnosis. It may be that VCD represents one end of a spectrum of "upper airways dysfunction" in patients who have extrathoracic hyperresponsiveness with or without associated asthma. Important questions remain regarding epidemiology within the general and asthmatic populations as well as the pathological mechanisms underlying VCD. These questions are beyond the scope of our proposed investigation.

1.3 Voice Problems and Asthma

Bearing in mind the above discussion regarding vocal cord dysfunction and the fact that inhaled medication for asthma has the potential for direct effects on the larynx, it is reasonable to consider the effect asthma or its treatment may have on patients' voice. Up to 50% of patients taking inhaled corticosteroids may suffer from dysphonia which is usually reversible([57]). This is usually attributed to fungal infection or steroid-induced adductor myasthenia of the larynx([58]), although laryngoscopy or voice laboratory assessment may reveal more complicated abnormalities([59;60]) such as apposition abnormalities and cycle to cycle irregularity.

Much of the voice literature is focused on patients attending otolaryngology clinics and voice morbidity in patients with asthma has not been extensively studied. Baker found that half of 80 young adults with asthma or allergy had abnormalities in vocal quality (assessed by Speech and Language Therapists) ([61]). Studies assessing prevalence of voice problems in patients with asthma have concentrated on using patient administered questionnaires as the principle outcome measure. In a sample of 255 patients attending an asthma clinic, 88 (34%) reported voice "huskiness" and 40 (16%) reported "reduced power" ([58]). A more recent study found 169 / 280 (63%) patients attending asthma clinics complained of "voice disturbance" in general but this was not characterised further ([62]).

The presence of dysphonia is clearly important to patients, as recent work has demonstrated quality of life as measured by SF-36 questionnaire was significantly

impaired in dysphonic patients (attending an ENT clinic) without significant structural laryngeal disease in comparison to normals ([63]).

Assessment by Speech and Language Therapists (SLT) can include sophisticated perceptual, acoustic, aerodynamic and endoscopic methods to diagnose and plan treatment for voice disorders([64]). There are a number of protocols available for perceptual analysis of the voice, with the GRBAS scale the recognised gold standard tool for this in the UK([65]). With this method, overall Grade (Overall degree of voice deviance, G), Roughness (impression of irregular pulses or of low frequency noise, R), Breathiness (audible turbulent air leakage, B), Asthenicity (A), and Strain (S), is assessed on a 4-point scale by SLT to determine the degree of vocal impairment. Several studies have shown that there is reasonable inter-rater reliability in the use of this scale ([66-69]). A number of studies have shown that this scale can correlate with various objective acoustic measurements of voice([70;71]) but it is unclear how the degree of impairment as determined by SLT relates to patients' perceptions.

A number of instruments are available for the self assessment of voice quality, including the Vocal Handicap Index (VHI)([72]) and Voice Related Quality of Life (V-RQOL)([73]). The Voice Symptom Scale (VoiSS) is a 30 item questionnaire which has been thoroughly evaluated as a tool for the self assessment of voice quality ([74;75]). It consists of a total score with three robust subscales assessing voice impairment, emotional reaction and laryngopharyngeal symptoms (physical component). It has been extensively investigated and refined in over 800 subjects, its subscales have shown good internal consistencies and has been subjected to the most rigorous

psychometric evaluation([75]). There is no data in for any of the above instruments in studies of patients with asthma.

1.4 Nasal Disease and Asthma

An association between asthma and nasal disease has long been recognised. Epidemiological data for the prevalence of allergic rhinitis varies between surveys as well as geographically, and its coexistence with asthma has been found to be between 30% and 80%([76]). The impact of allergic rhinitis on asthma has been comprehensively documented ([77]). A postal survey of 4300 patients in Finland found a significantly higher incidence of allergic rhinitis in asthmatics than non-asthmatics (73.1 vs. 39.6%)([78]). The true incidence of nasal polyps is not known. Their prevalence in asthma has been found to be between 7 and 15% ([79]), with higher frequency in patients over 50 years. Aspirin-intolerant patients have a higher frequency again (36%)([80]).

It has long been debated to whether nasal inflammation and asthma are part of the same disease process and whether appropriate treatment of sinusitis can improve asthma symptoms or lung function. A recent review([81]) of studies examining the surgical treatment of sinus disease concluded that in general the influence on asthma is positive. However the benefits are largely subjective and there is large variation in the severity of asthma and extent of sinus disease in such studies. While treatment of allergic rhinitis in patients with co-existing asthma is recommended by current guidelines([1]), there is no evidence that this will specifically improve asthma control([82-85]).

Nasal symptoms are protean and occur commonly in asthmatic patients([86;87]). In a general population survey of 8469 subjects([88]), asthma (and also chronic

bronchitis/emphysema – CBE) was found to be more common in patients complaining of nasal symptoms than in the whole sample. Nasal symptoms were more frequent in asthmatics than those with CBE. In the group with self-reported asthma, there was a higher incidence of recurrent or permanent nasal symptoms (46%), compared with a general population incidence of recurrent nasal symptoms of 26%. It is not clear from these studies however how individual nasal symptoms relate to the likelihood of finding specific nasal pathology at nasendoscopy and in day to day clinical experience it is difficult to know which patients will benefit from seeing an ENT surgeon on the basis of their symptoms.

1.5 Hyperventilation and Dysfunctional Breathing Pattern

Hyperventilation is defined as breathing in excess of the body's metabolic requirements and results in a reduction in arterial pCO2, respiratory alkalosis and wide ranging symptoms([89]). The term "hyperventilation syndrome (HVS)", coined over 60 years ago described patients with hypocapnic symptoms and those of anxiety([90]) and is recognised as a complicating factor in those with severe asthma([5;91]). Despite this, however, there remains no clear consensus on the gold standard for diagnosis of HVS. Demonstration of a respiratory alkalosis by measurement of arterial blood gases will be of value during the attack, but will not always be helpful when assessing a patient in between episodes. The fact that a degree of hyperventilation may be or is commonly seen with symptomatic asthma further complicates the issue. It is also clear that some patients, who may not necessarily be hyperventilating, may have other breathing pattern abnormalities such as frequent sighing or irregularity of breathing([92]) which may manifest themselves as intermittent breathlessness or sensation of over-breathing which is perhaps best brought under the term "dysfunctional breathing"([93]).

It can be difficult to tease out the contribution of these different factors when patients report poorly controlled asthma and some patients may be mislabelled as having asthma because of atypical breathing symptoms. There is a need to identify the best way to diagnose and manage such patients.

The Hyperventilation Provocation Test (HVPT), in which patients voluntarily hyperventilate and, if HVS is present, should reproduce their symptoms along with

demonstrating a delay in the recovery of end-tidal CO2 concentration, has been proposed as the diagnostic test of choice([94-96]). The ability to accurately categorise patients by this test has been challenged recently with isocapnic over breathing recreating a similar amount of HVS symptoms([97;98]). Mental-load tests have also been reported to reproduce the HVS symptoms([99;100]). Furthermore, none of these studies have attempted to explore the role of this test in an asthmatic population. In clinical practice, progressive exercise testing is often employed to detect hyperventilation but there is no data on sensitivity or specificity in its detection of HVS in asthmatics.

The Nijmegen score is a 16-item questionnaire designed to identify patients with hyperventilation on the basis of frequency of symptoms such as "feeling tense", "short of breath" and "tingling fingers". This has been found to have a sensitivity of 91% and specificity of 95% in the diagnosis of HVS([101]) (using clinical diagnosis as the gold standard), but this has not been extensively validated in asthmatics. Some of the questions relate to typical asthma symptoms with the probability that this would tend to overestimate hyperventilation in this group.

There has been interest in recent years in using this questionnaire in patients with asthma to diagnose HVS. Thomas([102]) used the Nijmegen questionnaire to estimate the prevalence of dysfunctional breathing in a primary care sample of asthmatics and found that 63/219 (29%) scored positively. It is not clear however how many patients also had poorly controlled asthma. In a smaller hospital based survey of 76 patients 42% had evidence of hyperventilation as determined by Nijmegen and/or HVPT ([103]). The relative proportions of patients diagnosed by Nijmegen score and HVPT is not described in this abstract.

Following identification of dysfunctional breathing, patients are usually managed with relaxation techniques or breathing control therapy, however there is very little data confirming its efficacy in patients with asthma. Following identification of a group of patients with possible dysfunctional breathing (positive Nijmegen score) from a General Practice asthma cohort as described above, Thomas went on to conduct a randomised controlled trial of breathing retraining([104]). Patients with a positive score benefited in terms of health related quality of life scores 1 month after breathing retraining exercises compared to a control group with only improvement in activities domain significantly greater than controls after 6 months. The Nijmegen score of the study patients fell but the difference was only statistically significant at 6 months. There was very little change in asthma therapy in either group in this study during follow-up. The patients in this study had mild to moderate asthma and whether this can be extrapolated to cohorts in secondary care, with more severe disease has not been investigated. In another group of non-asthmatics with HVS, a 2-3 month programme of breathing control was found to improve Nijmegen scores([105]).

There has also been recent interest in the use of breathing training in patients with asthma. The Buteyko breathing technique (which addresses asthma symptoms rather than hyperventilation) reduced asthma symptoms and bronchodilator use compared with placebo in a randomised controlled trial of patients with symptomatic asthma and ongoing airflow obstruction ([106]). A recent review ([107]) confirmed that while there is no evidence that routine measures of lung function are improved, there is a general trend of improvement in quality of life measurements with this method.

There are no comparative data on the most effective form of breathing retraining nor which health care professional (physiotherapist, speech and language therapist) should administer it.

In addition to the above diagnostic tests for the clinical syndrome of HVS, the breathing pattern of the patient can also be assessed. Several methods exist for measuring this objectively. Using respiratory inductive plethysmography (RIP), rib cage movements can be analysed to calculate respiratory frequency, tidal volume and minute ventilation, mean inspiratory time and fractional inspiratory time([108]). Tobin recorded breathing pattern by RIP over a fifteen minute period (after ten minutes rest) in symptomatic asthmatics and found an increased tidal volume, minute ventilation and shortened fractional inspiratory time without an increase in respiratory frequency compared to non-asthmatics([109;110]). Asymptomatic asthmatics had no difference in their breathing pattern compared to normals.

The breathing pattern can be influenced by breathing through a mouth-piece. This has been shown to increase tidal volume([111-113]) and in one series decrease respiratory frequency([112]) compared to natural breathing monitored with an external device. However, although mean values change, the breath to breath variability does not change when breathing via a mouthpiece and nose-clip([108]). Measuring breathing pattern with the RIP device is however potentially too time-consuming to be of a practical use in an out-patient clinic setting and it is not entirely clear if these long sampling periods are important.

1.6 Psychological correlates of asthma

Although in the past asthma was considered primarily a psychological condition, experience with inhaled corticosteroids and other treatments over the past 40 years has emphasised the importance of airway inflammation, bronchial hyper-reactivity and smooth muscle spasm as key patho-physiological factors. Nevertheless, there is evidence of a role of psychological factors contributing to asthma morbidity.

Firstly, studies of fatal or near fatal asthma have found evidence of psychological factors present in such patients ([114-116]). In a population study of 95 cases of death due to asthma in Scotland over 3 years in the mid-1990's, retrospective questioning of patients' General Practitioner revealed presence of any psychological or social factor in 55 / 95 (58%) and specific depression in 10 / 95 (11%)([114]). Campbell examined characteristics of 154 patients who had suffered a near fatal attack of asthma and 80 who had died from asthma. 17% and 22% respectively had undergone psychological assessment, but the precise frequency of definite or even GP reported psychiatric caseness in this study is unclear ([115]). In a more detailed study of 77 patients with near fatal asthma, 33 (43%) scored positively on the General Health Questionnaire suggesting a co-existing psychiatric diagnosis([116]).

Clinic based studies have also examined this issue. Using the General Health Questionnaire to detect a psychiatric disorder, ten Brinke found 21 / 98 (21.4%) of patients with severe asthma scored positively ([117]). Another study also suggested that psychiatric caseness is more prevalent in brittle asthma compared with non-brittle asthma ([118]). In a group of 73 patients with asthma evaluated in a tertiary centre to

examine the factors predicting therapy resistant asthma (TRA), Heaney found 32 / 65 patients who attended for psychiatric interview had an ICD10 psychiatric diagnosis ([119]). Nascimento found 45 / 86 (52.3%) of asthma clinic patients had evidence of at least one anxiety disorder ([120]) while another survey found an increased prevalence compared to controls of panic disorder and agoraphobia ([121]).

Population based studies have shown disparate findings. Janson, in a random selection of 708 people (from an original random population sample of 3600), found no relationship between anxiety or depression and evidence of asthma (either self reported or by objective measures) ([122]). More recently however a large population based study found that, of the 7619 out of a possible 10,080 subjects, who participated in the study, there was a higher prevalence of psychological distress (17.9% vs. 12.2%), anxiety / depression (40.5% vs. 31.2%) and specific mental health conditions (16.2% vs. 10.8%) in 834 patients who had self reported asthma ([123]). The Kessler Psychological Distress Scale was used in this study, and no objective clarification of asthma was sought. Rimmington found that levels of anxiety and depression (measured by the HAD score) were related to levels of symptoms but not with measures of lung function ([124]).

It is therefore likely that asthma is associated with psychological morbidity and that such factors are more common in severe asthma and contribute to some asthma deaths.

The Hospital Anxiety and Depression scale (HAD) is a simple, self-assessment instrument to detect anxiety and depression in the outpatient setting ([125]). Patients are scored on 7 items for both anxiety and depression, each on a scale of 0 to 21. A score

of ≥ 11 is said to indicate definite anxiety or depression, with score 8 – 10 being borderline. Several studies have used this tool in the setting of an asthma clinic, which are discussed further with reference to our results in Chapter 2.

The Asthma Quality of Life Questionnaire (AQLQ) is a valid instrument with excellent measurement properties in terms of evaluation and discrimination of aspects of impairment of function, of most concern to patients with asthma ([126]). Four domains are assessed: symptoms, emotional function, environmental stimuli, and activities limitation. The AQLQ has 32 items and can be self administered. A shorter, 15 item version of this questionnaire, the "Mini-AQLQ" has been developed and validated ([127]). This also measures impairment in the aforementioned 4 functional domains. In the 9 week observational study where the instrument was validated, the Mini-AQLQ was administered with the full AQLQ and was found to have good reliability and responsiveness ([127]). The Mini-AQLQ is increasingly being used in clinical trials of asthma treatment to measure quality of life outcome ([128;129]). The minimal clinically important change is +/- 0.5 on the 7 point scale ([130]).

Self management programmes are an integral aspect of asthma management, and current guidelines advise this for all patients with asthma ([1]). Different patients may have differing perception of their ability to control their condition, and a specific questionnaire has been developed to measure an individual's level of perceived control of day to day asthma and exacerbations ([131]). In the validation study of the Perceived control of asthma questionnaire (PCAQ), greater perceived control was associated with greater asthma self efficacy (evaluated by a separate self-efficacy score) and better asthma-specific quality of life (measured by the Marks Asthma

Quality of Life Questionnaire). The authors hypothesised that asthma self management education might improve perceived control and asthma quality of life. This has not been extensively studied, but one recent study found PCAQ scores improved along with AQLQ scores following a behaviour modifying education programme to enhance self-management skills and promote behaviour change ([132]).

Aims of the Thesis

We hypothesise that a significant number of patients attending the PAC have co-existing upper airway problems contributing to ongoing symptoms. We wish to determine the precise nature of these diagnoses and the optimal diagnostic evaluation. We propose that breathing control for the treatment of dysfunctional breathing in our cohort of patients will improve asthma related quality of life and Nijmegen scores and that such therapy will influence physiological measurements of breathing pattern.

This thesis will therefore address the following primary research questions:

1 What are the clinical characteristics of the patients referred to the PAC? What proportion have definite asthma, what is their psychological profiling and is there any evidence this changes with treatment optimisation?

2 What is the spectrum of upper airway problems in a Problem Asthma Clinic? More specifically, what is the frequency of Vocal Cord Dysfunction and the role of the Forced Oscillation Technique in its diagnosis?

3 What is the degree of voice morbidity in the PAC, and how does perceived morbidity by the patient relate to assessment by an experienced Speech and Language Therapist?

4 How well do upper airway symptoms predict structural or functional abnormalities of the nasal cavity or larynx?

5 Is there a role for routine rhinoscopy in a problem asthma clinic?

6 What is the role of histamine challenge and progressive exercise testing in the diagnosis of Vocal Cord Dysfunction?

7 What are the breathing pattern characteristics of patients attending the PAC?

8 Do patients with asthma suspected of having dysfunctional breathing / Hyperventilation Syndrome (HVS) have a different breathing pattern from other patients?

9 Does breathing control training influence breathing pattern, Nijmegen scores and asthma related quality of life in patients with moderate to severe asthma?

CHAPTER 2

REFERRALS TO THE PROBLEM ASTHMA CLINIC

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CHARACTERISATION OF A NEW PATIENT COHORT

2.1 Introduction

With the background of recently published studies ([133;134]) detailing the systematic assessment of patients with asthma in tertiary centres, and to provide a context for the observational studies described undertaken, we aimed to describe the characteristics of a cohort of new patient referrals to a Problem Asthma Clinic. Referrals to the clinic come from a number of sources. Firstly, there are patients from local general practitioners felt to need management input from secondary care, many of whom have been uncontrolled on escalating asthma treatment as recommended by British Thoracic Society Guidelines. Some of these will require a relatively brief period of assessment and optimisation of therapy allowing discharge from clinic, whereas others will have more severe disease requiring more intensive assessment and management. "In-house" referrals consist of patients with a recent asthma exacerbation requiring a brief period of treatment optimisation while others with severe asthma will be referred by other respiratory consultants within Glasgow Royal Infirmary. Finally there are some patients referred form other respiratory units from the surrounding region.

The aims of assessment were firstly to confirm (or refute) the diagnosis of asthma and to identify any co-existing or alternative respiratory diagnoses. In addition we aimed to identify the extent of psychological aspects which might impact on management, or be influenced by treatment optimisation and to examine the relationships between them. The clinic strategy, in terms of asthma management, was to optimise symptom control through appropriate inhaled and other therapy and encourage patients with exacerbations despite this to self manage effectively. We hypothesised that such an

approach would have beneficial effects in terms of disease specific quality of life and level of perceived control of asthma.

2.2 Methods

All new patient referrals (sources as previously decribed in section 2.1) to the PAC over a 1 year period (August 2003 to July 2004) were studied. As well as history and examination, baseline Mini-Asthma Quality of Life Questionnaire (Mini-AQLQ)([127]), Nijmegen ([101]), Hospital Anxiety and Depression (HAD)([125]) and Perceived Control of Asthma Questionnaire (PCAQ)([131]) responses were collated (Appendix 1). We used the Mini-AQLQ because of concerns the full AQLQ would have over-burdened our patients. As shown in the clinic investigation protocol (Appendix 2), all patients who scored positively on the depression sub-scale of the HAD (≥ 11) were offered an appointment with a clinical psychologist. All patients scoring positively on Nijmegen (≥ 23) were referred for breathing control therapy with our respiratory physiotherapist. At initial clinic visit, all patients were asked to complete morning and evening PEFR diary until next seen (usually 2-4 weeks later). Full pulmonary function testing was arranged for all patients. If these tests did not confirm asthma, the next investigation depended on lung function. If post bronchodilator FEV_1 was <80% predicted, 2 weeks of prednisolone 30mg once daily was given with repeat PFT to determine best lung function and steroid responsiveness. If lung function was normal, with no bronchodilator reversibility demonstrated (and PEFR diary showed no significant (≤ 15%) diurnal variability) a histamine challenge was requested to determine presence or absence of bronchial hyper-reactivity.

Asthma treatment was adjusted according to current British Thoracic Society guidelines ([1]), based on symptoms and PEF readings where available. Patients who had persistent symptoms and / or sub-normal lung function during follow up were

referred for pH studies to determine presence and degree of gastro-oesophageal reflux disease (GORD) and also for ENT assessment, which was directed to either a laryngologist or rhinologist depending on whether laryngeal or nasal symptoms were prominent. Specialist respiratory physiotherapy input was offered if disproportionate breathlessness was a feature as noted above

After one year or at discharge from clinic, follow up data as illustrated in Appendix 3 along with repeat questionnaires were collected.

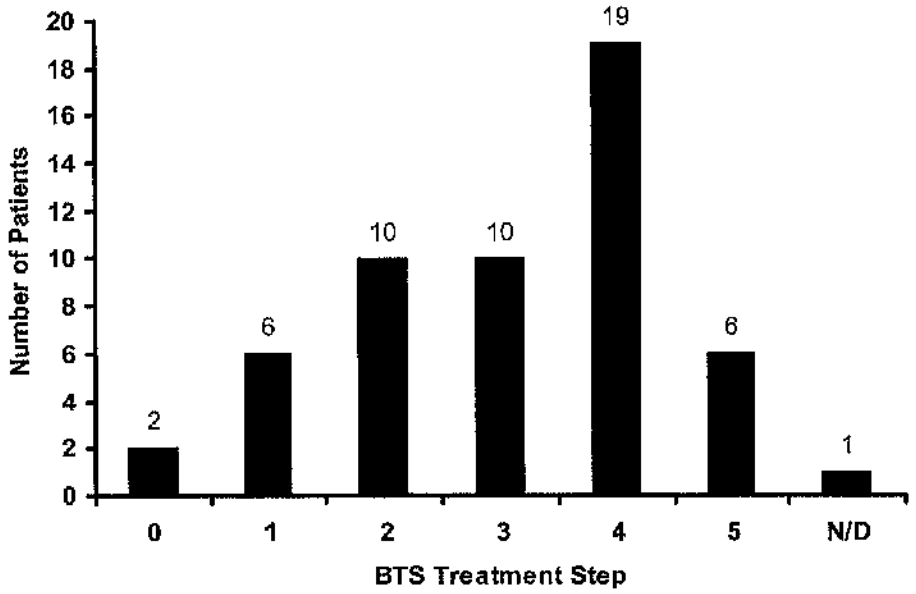
2.3 Results

Baseline Clinical Data

59 patients (19 male, 49 female) were referred to the PAC over the 1 year period described above. 10 did not attend on any occasion despite being sent further appointments with encouragement to attend. Of the remaining 49, 34 were female and 15 male with a mean (SD) age of 45.3 (16.7) years.

Baseline data were collected in 44 / 49 (89.8%) patients. In 22 of these patients prior objective evidence of asthma was available (7 with reversible airflow obstruction, 15 with variable PEFR). Smoking status was documented in 42 / 44 patients, with 19 never smokers, 14 ex-smokers and 9 (21%) current smokers. Pack year smoking history was recorded in 18 / 23 of the current or ex-smokers (mean 14.1 pack years). Baseline level of asthma treatment is shown in Figure 1. In 1 patient treatment was not documented.

Figure 2: Baseline level of asthma treatment (n= 44, N/D = Not Documented)



The exposure to oral corticosteroid (OCS) courses, A&E attendances and hospital admissions over the year prior to first clinic attendance are given in Table 1. Two patients had previously been admitted to ITU and 1 had been previously ventilated for acute asthma.

Table 1: Frequency of exposure to oral corticosteroid courses, A&E attendances and hospital admissions in year prior to clinic attendance

	Range	Median (IQR)	Mean (SD)
OCS courses	0 - 20	2 (0 – 4.5)	3.06 (3.61)
A & E Attendances	0 – 4	0 (0 – 1)	0.63 (1.8)
Hospital admissions	0 - 7	0 (0 – 1)	1.0 (1.41)

Baseline Questionnaire Data

Only 36 / 49 patients who attended filled out all 4 questionnaires completely. Data was available for Mini-AQLQ in 42, HAD in 43, PCAQ in 37 and Nijmegen in 43 patients. Baseline questionnaire results for all questionnaires and their relevant domains are shown in Table 2. As described in the Introduction, higher Mini-AQLQ indicates better asthma related quality of life, higher PCAQ indicates better level of perceived asthma control. Individual Mini-AQLQ domain scores are the mean of relevant responses and total Mini-AQLQ is the mean of all 15 responses. Higher HAD and Nijmegen scores are associated with greater levels of anxiety / depression symptoms and possible dysfunctional breathing symptoms respectively. All parameters were normally distributed.

Table 2: Baseline Mini-AQLQ, HAD, PCAQ and Nijmegen scores

QUESTIONNAIRE		RANGE	MEAN (SD)
Mini-AQLQ Domain (all range 1 – 7), n = 42	Symptom	1 – 6.8	3.33 (1.31)
	Environment	1.33 – 7.0	4.08 (1.55)
	Emotion	1.0 – 7.0	3.31 (1.35)
	Activities	1.0 – 7.0	3.93 (1.52)
	Total Mini-AQLQ	1.33 – 6.2	3.63 (1.23)
HAD, n = 43	Anxiety (0 – 21)	0 – 20	8.98 (4.74)
	Depression (0 – 21)	1 – 16	6.70 (3.83)
PCAQ (11-55), n = 37		22 – 47	33.24 (5.91)
Nijmegen (0 – 64), n = 43		1 – 53	23.49 (10.89)

17 /43 (39.5 %) patients scored positively on the anxiety subscale of the HAD and 7 (16.3 %) positive on the depression subscale. 23/43 (53.5 %) patients had positive Nijmegen scores.

The relationships between each questionnaire are shown in Table 3. All correlation coefficients are Pearson correlations, given the normal distribution of all parameters.

Table 3: Inter-relationships between questionnaire scores

Questionnaire		Correlation Coefficient, p value
Mini-AQLQ vs.	Nijmegen	-0.57, $p < 0.001$
	HAD (Anxiety)	-0.42, $p = 0.006$
	HAD (Depression)	-0.52, $p < 0.001$
	PCAQ	0.71, $p < 0.001$
Nijmegen vs.	HAD (Anxiety)	0.70, $p < 0.001$
	HAD (Depression)	0.57, $p < 0.001$
	PCAQ	-0.30, $p = 0.07$
PCAQ vs.	HAD (Anxiety)	-0.33, $p = 0.049$
	HAD (Depression)	-0.41, $p = 0.012$

Although all except one of the above correlation reached statistical significance, Figures 3a- 3i demonstrate that the relationships appear much stronger for some parameters. In particular, Nijmegen had a very strong relationship with the anxiety component of HAD. The relationships for PCAQ with HAD and Nijmegen were less convincing, although that with Mini-AQLQ was very strong.

Follow Up Clinical Data

1/10 who never attended over the 12 months was subsequently admitted with acute asthma and had good documented evidence of peak flow variability, consistent with a diagnosis of asthma. In many cases follow up data was recorded through case note review rather than at the appropriate time point 1 year from initial clinic attendance, due to variable attendance at clinic. It was not possible to collect any follow up data

for 2 patients. Of the 49 patients who did attend the clinic on at least one occasion, 39 (79.6%) were found to have a definite diagnosis of asthma. Table 4 illustrates the frequency of various diagnostic features (best objective evidence of asthma available) of these 40 patients (including the 1 patient admitted with acute asthma).

Table 4: Best objective evidence of asthma available at follow up.

BEST OBJECTIVE EVIDENCE	NUMBER OF PATIENTS
PEFR Variability (≥ 15%)	9
Airflow obstruction with Bronchodilator Reversibility	24
Bronchial Hyper-reactivity on Histamine Challenge	2
Trial of oral corticosteroids showing reversible airflow obstruction	5

In the 10 patients who had no objective evidence of asthma, 1 patient attended the clinic but never attended for relevant investigation and 9 had objective evidence of alternative diagnoses:

- COPD (5 patients – all with irreversible airfow obstruction and all with smoking history of over 20 pack years)
- Gastro Oesophageal Reflux Disease (GORD) (2 patients with clinical diagnoses supported by laryngoscopic signs of reflux and improvement with anti-reflux treatment. Both failed to attend for pH studies)

- GORD and Bronchiectasis (1 patient with abnormal pH study and HRCT evidence of bronchiectasis)
- Hyperventilation (1 patient – demonstrated on progressive exercise testing)

Co-morbidity in those with definite asthma

10 / 39 with definite asthma had evidence of respiratory co-morbidity, as follows:

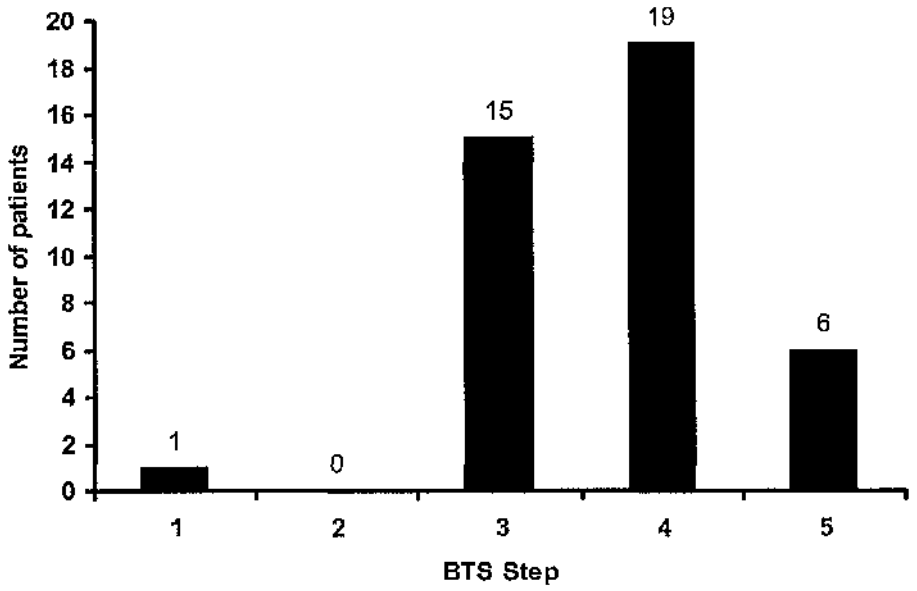
- hyperventilation / dysfunctional breathing pattern (5 patients) which was diagnosed on the basis of combination of Nijmegen scores and specialist physiotherapy assessment,
- allergic bronchopulmonary aspergillosis (2 patients (elevated total IgE, positive aspergillus precipitans, CXR infiltrates improved with steroids), 1 also with HRCT evidence of bronchiectasis),
- sub-pleural fibrosis on HRCT (presumed UIP, 1 patient),
- probable COPD component (1 patient with only minor bronchodilator reversibility (3%) and 10 pack year smoking history)
- tracheal tumour (1).

11 / 39 (28%) were referred for ENT assessment (9 rhinological, 2 laryngological assessment). Of the 2 referred for laryngeal assessment, 1 had normal appearances and 1 had evidence of mild chronic laryngitis. In terms of nasal disease, significant pathology was identified in 7 patients - nasal polyps (3), rhinitis (2), sinusitis (1) and deviated nasal septum requiring further treatment (1). Gastro-oesophageal reflux (GORD) was suspected in 13 patients, on the basis of ongoing wheeze and /or reflux

symptoms, and these were referred for pH studies. Only 1 of these patients attended and significant GORD was identified and treated. HRCT scans were not routinely requested to look for bronchiectasis.

Level of asthma treatment at follow up is shown below (Figure 4). In 8 patients the level of treatment was not documented. Of the 37 patients with known treatment level at baseline and follow up, 3 were up 2 BTS treatment levels, 8 were up 1 treatment level, 8 were down one, 1 was down two and 1 final patient down 3 treatment levels.

Figure 4: Level of asthma treatment at follow up (n = 41)



Lung Function

Data on best lung function was available for 42 patients. This is shown in Table 5. Spirometric values are post-bronchodilator.

Table 5: Best available lung function

Parameter	Range	Mean (SD)
FEV_1 (litres)	0.84 – 4.1	2.30 (0.94)
FEV_1 (% predicted)	30 - 119	80.4 (24.9)
FEV_1/FVC	30 - 86	66.7 (12.3)
Bronchodilator reversibility (% of baseline FEV_1, n = 22)	10 - 86	31.8 (20.9)

Self Management

19 / 40 patients with confirmed asthma had a self-management plan in place, of whom 8 were felt to be self managing effectively, as judged from their reported management of interval exacerbations.

Follow Up Questionnaire Data

Follow up data for all 4 questionnaires were only complete for 12 patients, although Mini-AQLQ was completed in 17, HAD in 18, PCAQ in 14 and Nijmegen in 16 patients. The most frequent reason for this was non-attendance at the clinic by the time follow up data was due for collection, either due to prior discharge of failure to attend. Time restraints on patients' part when filling in questionnaires accounted for incomplete data in 6 patients. Table 6 illustrates the available follow up questionnaire scores. As with baseline data, all parameters were normally distributed. Table 6 also demonstrates that there were no differences between any parameters at follow up compared to baseline (Mann-Whitney U-tests). 7 / 17 with Mini-AQLQ data at

baseline and follow up showed a clinically significant improvement of > 0.5 points. It is not possible to make definite comments from our data on features that distinguished this sub-group from the whole cohort. There was no significant change in level of asthma treatment (1 patient had gone from BTS step 5 to step 4 treatment), 2 had GORD, 1 had ABPA, and 4 were felt to be self managing effectively.

Table 6: Available follow up questionnaire data.

QUESTIONNAIRE		RANGE	MEAN (SD)	95% Confidence Interval for difference compared to baseline
Mini-AQLQ Domain (all range 0 – 7), n = 17	Symptom	1.0 – 7.0	3.42 (1.71)	-1.0, 0.80
	Environment	2.0 – 7.0	4.0 (1.48)	-0.67, 1.67
	Emotion	1.67 – 7.0	3.84 (1.69)	-1.33, 0.67
	Activities	1.0 – 7.0	3.81 (1.82)	-1.50, 1.25
	Total Mini-AQLQ	2.0 – 7.0	3.73 (1.55)	-0.87, 0.87
HAD, n = 18	Anxiety (0 – 21)	0 – 17	8.06 (5.06)	-4.00, 4.00
	Depression (0 – 21)	0 – 14	6.0 (4.41)	-3.00, 4.00
PCAQ (11-55), n = 14		28 – 44	35.57 (5.43)	-7.00, 3.00
Nijmegen (0 – 64), n = 16		10 – 42	23.75 (10.70)	-8.00, 5.00

Even in the small subgroup of patients who had clear self-management plans in place and for whom baseline and follow up Mini-AQLQ and PCAQ were available (n= 10 for Mini-AQLQ, n = 7 for PCAQ) , there were no differences at follow up (95% CI's

for difference compared to baseline -1.67, 0.67 for Mini-AQLQ, -9.0, 2.0 for PCAQ). 5 / 10 of these patients with Mini-AQLQ data had a clinically significant ($\geq$ 0.5) improvement in their Mini-AQLQ.

Figure 3a: Mini AQLQ (Total) vs Nijmegen

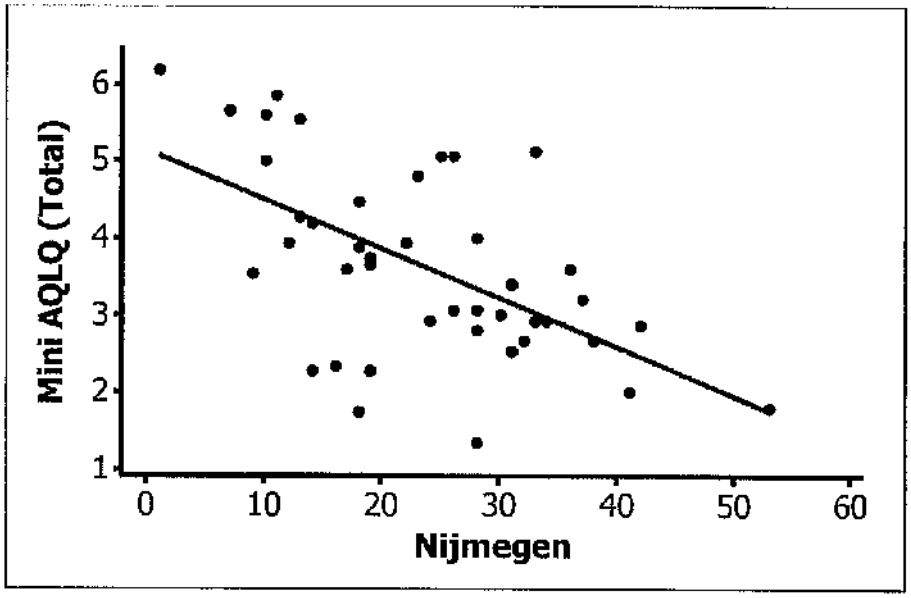


Figure 3b: Mini-AQLQ (Total) vs. HAD (Anxiety)

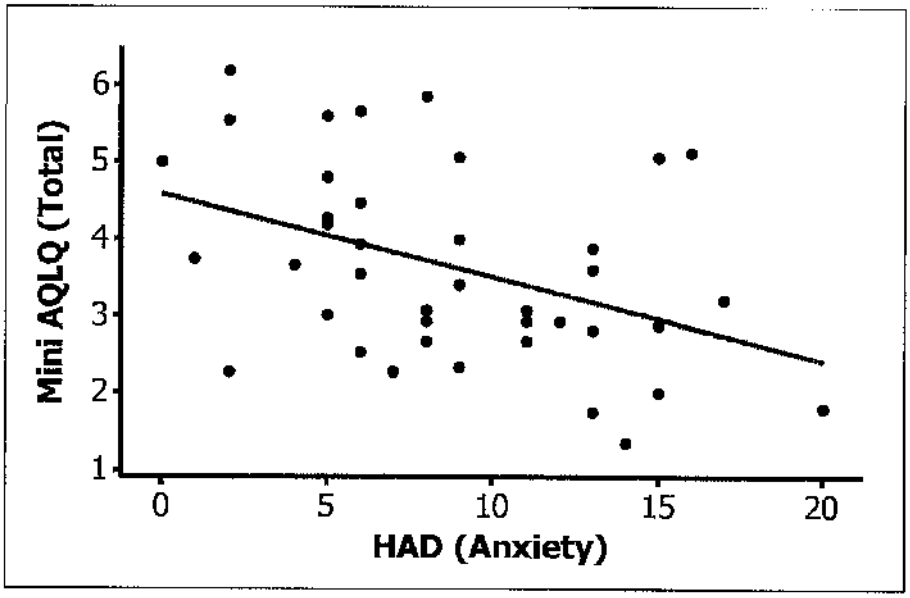


Figure 3c : Mini-AQLQ (Total) vs HAD (Depression)

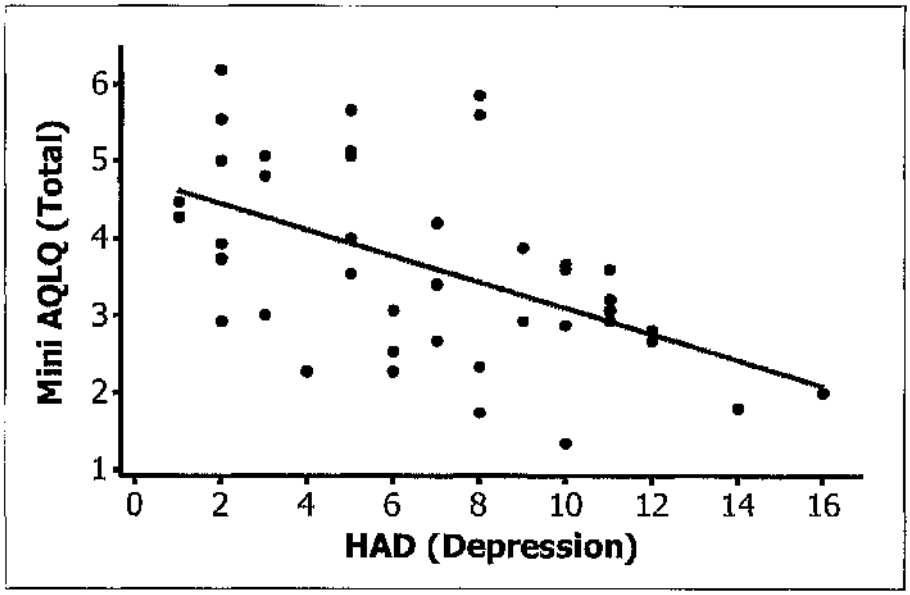


Figure 3d: Mini-AQLQ (Total) vs PCAQ

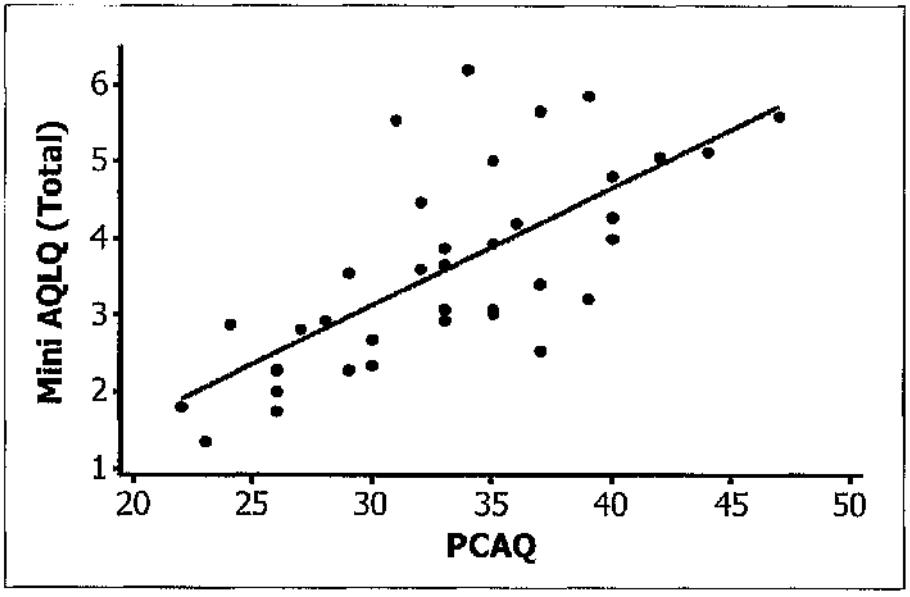


Figure 3e – Nijmegen vs HAD (Anxiety)

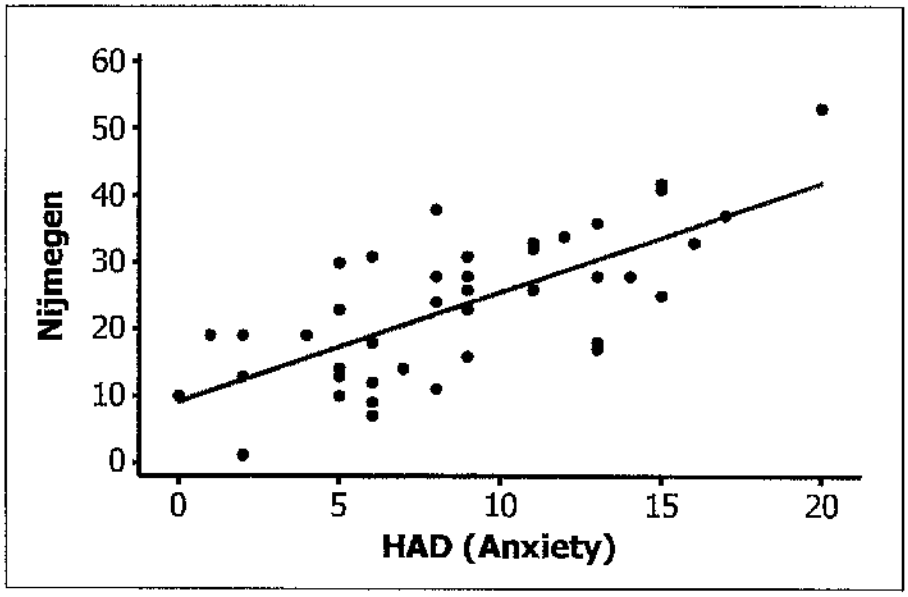


Figure 3f – Nijmegen vs HAD (Depression)

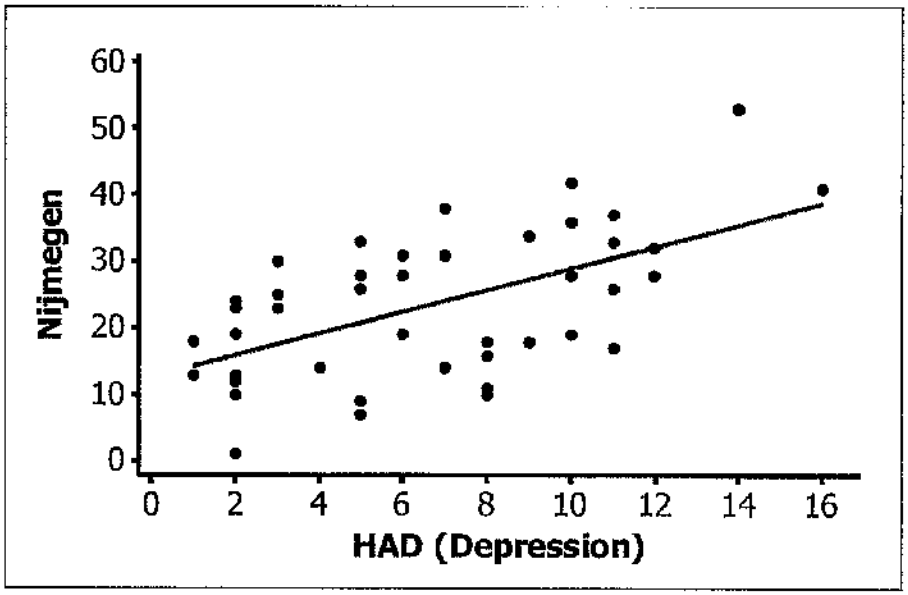


Figure 3g – Nijmegen vs PCAQ

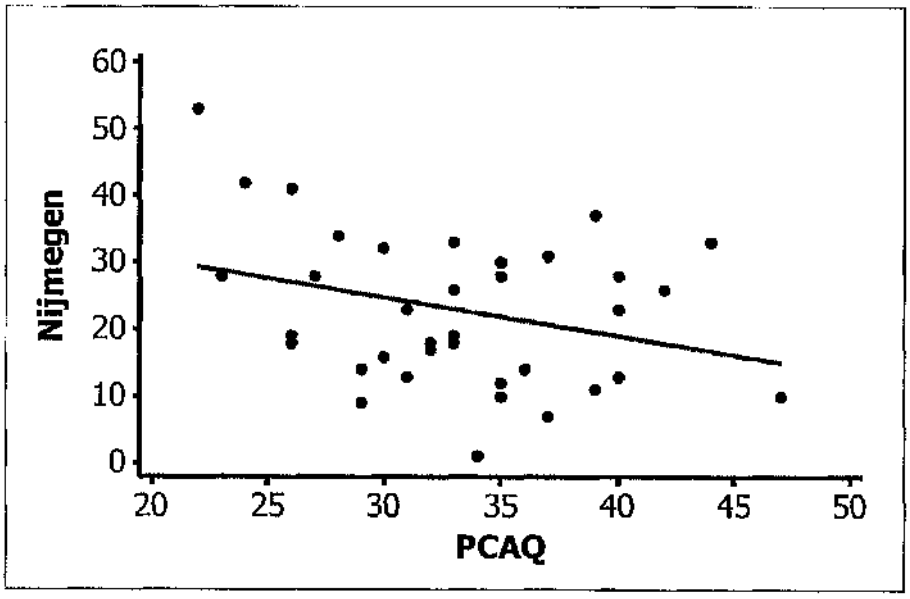


Figure 3h: PCAQ vs. HAD (Anxiety)

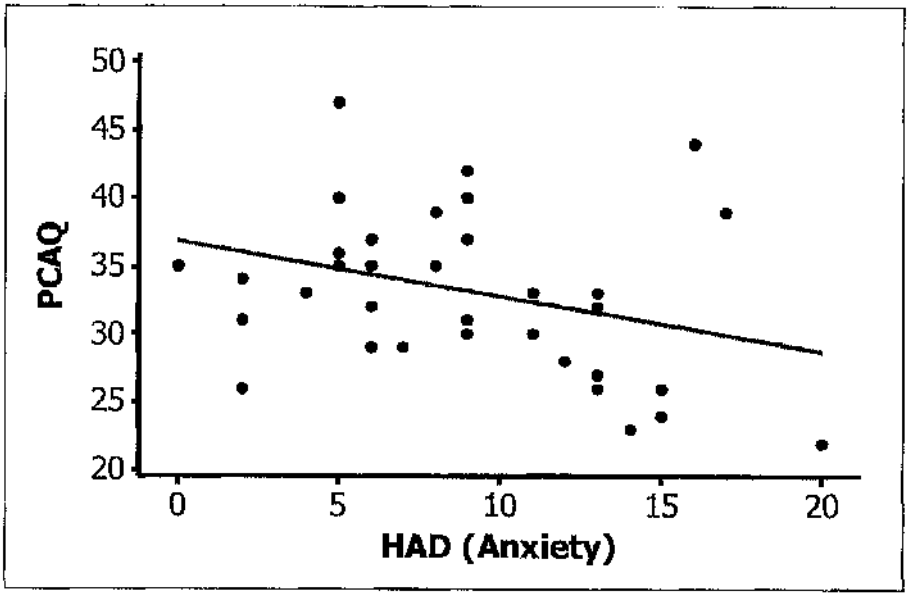
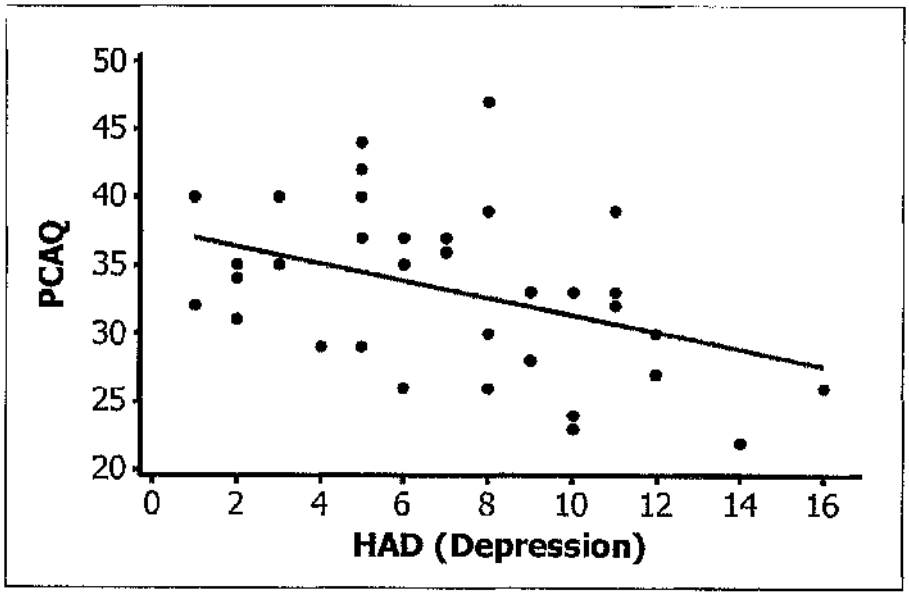


Figure 3i: PCAQ vs. HAD (Depression)



2.4 Discussion

We have described a variety of characteristics of patients referred to a Problem Asthma Clinic for assessment and treatment optimisation. The primary aim of assessment is to establish or refute the diagnosis of asthma, in order to avoid (potentially further) unnecessary treatment and direct attention elsewhere if a different diagnosis is made. In 9 / 49 (18%) we found no evidence of asthma and confirmed an alternative diagnosis. Furthermore 10 of the 39 (26%) patients with definite asthma had evidence of an additional diagnosis. Although these findings may under-represent other diagnoses, since we selectively targeted investigations such as pH studies to those with persisting symptoms after asthma treatment optimisation, they shed light on the day to day reality of patients attending a problem asthma clinic.

In the study by Robinson et al ([134]), 12 / 100 patients referred to a tertiary centre with difficult asthma were found not to have asthma (most frequently COPD) and those who did have asthma frequently had co-existing problems, especially rhinosinusitis (40 patients). Additional respiratory diagnoses in those with asthma were however less frequent (6 patients, most frequently bronchiectasis).

Heaney's study ([133]) examined factors predictive of therapy resistant asthma in 73 patients with asthma out of 86 originally referred for evaluation and 25 / 73 (34%) had evidence of respiratory co-morbidity, similar to our 26%.

It is not surprising that the level of treatment for the group did not change greatly, although individuals in whom co-morbid factors were identified and appropriately

treated experienced significant reductions in asthma therapy, particularly in the use of oral corticosteroids.

18/49 (36.7%) patients at follow up were documented as having a self management plan (SMP) in place. The clinic protocol aimed to ensure all patients spent time with the clinic asthma specialist nurses to discuss self management skills, over a number of clinic visits. Clinical experience tells us that some patients are more receptive to this than others, this being influenced in part by the likelihood of exacerbations, rather than persistent symptoms.

We suspected GORD was a common co-existing problem in this patient group on the basis of reported symptoms, and the poor attendance for confirmatory pH studies (1 / 13 requests) prevents further comment in this cohort. In a cohort from the same clinic seen over a more prolonged time period, GORD has been found to be a significant issue in asthma patients with persistent symptoms, after treatment optimisation. In this larger group, only 7 of 47 patients referred failed to attend for pH study (15%), with 18 having no evidence of GORD (38%) and 22 having GORD proven (47%) (Dr CE Bucknall, personal communication). The inter relationship of these two common conditions and the impact of one on the other remains an area of controversy ([135]) which still requires further systematic investigation. Clinical experience confirms the existing literature, showing that some patients experience major improvements in asthma symptom levels and reduction in asthma treatment requirements when GORD is abolished, and this was the rationale underpinning this aspect of the clinic protocol.

Our baseline questionnaire data demonstrated the frequent occurrence of anxiety (17 / 43 (39%) and depression 7 / 43 (16%). Varying frequencies of anxiety and depression have been found in other studies using the HAD, which may relate to the asthma population being studied. In Janson's study which looked more widely at respiratory symptoms in relation to anxiety and depression, 708 patients from a general population of 3600 completed HAD, with frequencies of 16% for anxiety and 22% for depression in the 108 patients with doctor diagnosed asthma ([122]). Bosley found a complex interaction between various psychological parameters and compliance with asthma medication, but in the 72 patients studied (all on at least BTS step 3 treatment), respective frequencies of HAD positive anxiety and depression were 25% and 4.2% ([136]). In a further study of 114 primary care patients with asthma where only 30% were on BTS step 3 treatment or above (52% on BTS step 2), relative frequencies were 34% and 10% ([124]). The population studied by Heaney to predict therapy resistant asthma were evaluated thoroughly for psychiatric morbidity ([119]). HAD scores were collected for all 73 patients with asthma (34 classified subsequently as therapy resistant asthma – TRA) and 65 attended for psychiatric assessment. In the TRA and non-TRA groups, mean Anxiety scores were 10.7 and 11.2 respectively and depression scores 7.5 in both groups. These seem comparable to our results (mean anxiety 9.0, depression 6.7). Heaney found 32 / 65 patients who attended for psychiatric interview had an ICD10 psychiatric diagnosis, only 6 of whom had had this identified previously. Positive and negative predictive values, using a cut off of 11 on the HAD were 74% and 73% respectively for all psychiatric diagnosis and 67% and 89% for depressive illness. We are not able to comment on the accuracy of this strategy in our cohort, not having any gold standard psychiatric assessment, but from Heaney's experience it is likely that we missed some cases of depression. A number

of patients defaulted from clinical psychologist attendance, although there were notable examples of individuals who benefited greatly.

We found a statistically significant correlation between HAD scores for both anxiety and depression and Mini-AQLQ. Figures 1b and 1c however do show quite a spread of data within this relationship. This data is consistent with other studies which have demonstrated correlation between HAD and measures of asthma related quality of life ([124;137]). Similarly, the relationship found between Mini-AQLQ and PCAQ is consistent with data from the validation of the PCAQ ([131]) and also later work ([132]) which found a reasonable relationship with Mark's Asthma Quality of Life Questionnaire.

Nijmegen scores also correlated with Mini-AQLQ (-0.57, $p < 0.001$) and there was a very strong relationship seen between Nijmegen and HAD (Anxiety) (0.70, $p < 0.001$), perhaps reflecting the close relationship between symptoms assessed as related to dysfunctional breathing on the Nijmegen questionnaire and those related more generally to heightened awareness of bodily sensations as part of generalised anxiety.

Although statistically significant, the relationships between HAD / PCAQ and Nijmegen / PCAQ are not particularly convincing as illustrated by Figures 1g-i.

It is disappointing that we only were able to collect follow up questionnaire data in 18 patients and that this was incomplete in 6 cases. Heaney ([133]) also observed a significant default rate in his clinic population. We did not demonstrate a change in any parameter (in particular Mini-AQLQ or PCAQ) in this small number with

complete data. We did not mail questionnaires to patients who were not in attendance at the clinic or who had defaulted from attendance following earlier visits, as we felt the lack of information on current treatment and symptoms levels would have acted as an unquantified confounding variable.

In the subgroup with clear self management plans in place again we found no significant differences in Mini-AQLQ or PCAQ scores. We measured PCAQ specifically to assess its usefulness as a tool for judging benefit from self management. Given the small number of patients (n = 7) who had baseline and follow-up PCAQ and a SMP, it is difficult to comment on this further.

As discussed earlier there is only limited data available for PCAQ in the literature. In a non-randomised observational study, PCAQ was found to improve by a mean of 4.8 points 3 months after completing a comprehensive asthma education and self management programme ([132]). This compares with a median change of -2 in our patients, (95% CI -7, 3 – Table 6). Unlike the Mini-AQLQ however, the minimal clinically important change in score has not been determined.

In summary this description of a cohort of new referrals to a problem asthma clinic illustrates the importance of seeking objective clarification of asthma. Our observational data is consistent with other reported cohorts and confirms the frequency of psychological issues in patients with asthma. We have examined the relationships between different psychological correlates of asthma. This data has been used to adjust our clinic protocol (Appendix 4) and provides further information on the use of such questionnaires as screening tools for problems which may not be

immediately apparent in the busy clinical setting. Further details of particular aspects of this patient group's co-morbidities are described in greater detail in subsequent chapters.

CHAPTER 3

THE SPECTRUM OF UPPER AIRWAY PROBLEMS IN A PROBLEM ASTHMA CLINIC

3.1 Introduction

The purpose of this study was to examine the upper airway in patients attending the PAC. Patients were enrolled in a pilot study involving laryngeal, physiological, nasal and vocal assessment. As detailed in the Aims of the Thesis, there were a number of specific questions we set out to answer with this study. For purposes of clarity, the results and their discussion have been divided into (1) Laryngopharyngeal Assessment; (2) Physiological Assessment; (3) Vocal Assessment and (4) Nasal Assessment.

Firstly we aimed to identify the frequency of VCD in our clinic population. The relationship between upper airway symptoms and structural or functional abnormalities of the larynx was then explored.

We wished to evaluate the Forced Oscillation Technique in VCD diagnosis along with a thorough physiological assessment of the upper airway. We hypothesised that airway resistance in inspiration would correlate with upper airway obstruction, such as occurs in VCD.

The aim of the vocal assessment aspect of the study was to characterise the vocal quality along with the laryngeal appearances above and to relate this to patients' and SLT perception of vocal morbidity. A secondary aim was to assess the local inter-rater reliability of the GRBAS scale among SLTs.

The purpose of the nasal assessment arm of the study was to characterise the spectrum of nasal symptomatology and nasendoscopic abnormalities in patients attending the PAC. We sought to examine the predictive value of key symptoms for abnormalities.

3.2 Methods

All patients attending the PAC were eligible for inclusion. Initially 121 letters of invitation to take part in the study were sent to patients attending the clinic. If no response was obtained, attempts were made by telephone or when being seen at clinic to reiterate our invitation. Additional patients (who did not receive a letter) were invited to participate from the clinic. 60 patients (17 of whom subsequently withdrew) agreed to take part in the study and therefore 43 patients were ultimately included in the protocol which was approved by North Glasgow University Hospitals NHS Trust Local Research and Ethics Committee (REC Reference Number 03RE002 / 03RE008). The protocol involved attendance on a single afternoon. All patients gave written informed consent for their participation in the study. Assessments were made in the following order: Baseline data / physiological assessment, vocal assessment, nasal / laryngopharyngeal assessment.

Baseline data

Level of current treatment and symptoms of asthma morbidity([138]) were recorded using the Royal College of Physicians (RCP) 3 symptom score (days and nights affected by asthma symptoms, and days of limited activity due to asthma over the previous seven days, giving a score ranging from 0 to 21).

Forced oscillation technique (FOT)

Forced oscillometry was measured using the machine designed by Birch([139]) following the practice described in recent guidelines.([47]) In brief, the subject performed tidal breathing through a mouthpiece with nose occluded and cheeks supported for two separate periods of one minute. A bias flow of 0.25L/s of air was fed into the breathing circuit to minimise re-breathing. Impedance was measured using a single sinusoidal excitation frequency of 5Hz and calculated from the flow and pressure waveforms using the method based upon power spectra adapted for within-breath analysis.([140]) Only the real part of the impedance value, resistance, was used in this study. This was low pass filtered to remove biological noise using a Butterworth 8-pole filter with a cut-off frequency of 5Hz. In line with current guidelines,([47]) data from the first 30 seconds of each recording was discarded, to allow the patient time to get used to the mouthpiece. In addition to an average value over all the breaths (R_t), separate values were obtained for the inspiratory (R_i) and expiratory (R_e) phases by averaging over the relevant part of the respiratory cycle. Data from each sampling period was used to give the overall value for each phase.

Pulmonary Function Testing

Standard spirometry and flow volume loops were measured using a body plethysmograph. This was performed after FOT. Measured variables included Forced Expiratory Volume in 1 second (FEV_1), Forced Vital Capacity (FVC), maximum mid-inspiratory and expiratory flow (MIF_{50}, MEF_{50}) and MEF_{50}/MIF_{50} ratio. All pulmonary function tests were performed to the guidelines of the British Thoracic Society and

Association of Respiratory Technicians and Physiologists.([141]) Predicted normal values were determined using the European Community for Steel and Coal equations for all variables.([142])

In addition to FOT measured airways resistance, Occlusion resistance (R_{occ}) was also measured as a further measure which has been shown to be helpful in the assessment of airway calibre. This has otherwise been termed interrupter resistance (R_{int})([143-145]) This was performed using the body plethysmograph and the method of Van Altena and Gimeno.([144]) All measurements were carried out with the subjects seated with the neck slightly extended; the cheeks and pharynx were not supported during the measurements. During tidal breathing, a shutter closes automatically within 10ms after peak expiratory flow and stays closed for 100ms. Mouth pressure was estimated by linear back-extrapolation of the post occlusion signal. R_{occ} was calculated by dividing mouth pressure by flow at the time of occlusion. The value of R_{occ} was calculated as a mean value of 5 sequentially obtained satisfactory measurements during expiration.

Vocal Assessment

Patients completed the 30-item self administered VoiSS questionnaire (Appendix 5). Voice recordings were then performed in a soundproof booth housed within the Otolaryngology department. Recordings were made using digital tape recorder and digital audio tape (DAT). Patients were asked to speak approximately 10 to 15 cms away from the microphone. They were asked to give a few seconds of simple spontaneous speech (name, how they got to hospital that day, what they had for dinner

and watched on TV the previous evening) before reading the standard "Rainbow passage"([146]). These recordings were made in the presence of one of 2 independent observers who were not involved in any further data analysis.

Digital audio tapes of the patients' recordings were transferred on to two compact discs (CDs). Each CD had every patient's recording, randomised, with anonymised personal details and in a different order. Each patient's recording therefore corresponded to an individual track on each CD. A master list was kept with the track numbers linked to patient names which was not seen by the raters.

The raters were three experienced SLT's familiar with the GRBAS scale. Raters graded the patients' voices according to the GRBAS score with a further assessment of fluctuations in voice quality (Instability - (I)) ([147]). Each subscale was assessed on a 4-point scale of 0-3 to determine the degree of vocal impairment. Each CD was listened to and independently rated by the same 3 experienced Speech and Language Therapists at least 7 days apart. Every patient therefore had their voice scored by the same 3 SLT observers on 2 occasions.

Mean values for each GRBAS(I) subscale for each patient were calculated from the 6 scores. Total GRBAS scores were calculated using the means of each subscale with the exception of the Instability component, as this is not in widespread use.

The VoiSS questionnaires were scored according to the total score and the 3 subscales of voice impairment (15 items, score range 0 - 60), emotional reaction (8 items, score

range 0 - 32) and physical symptoms (7 items, score range 0 - 28). A higher score indicates greater vocal morbidity.

Laryngopharyngeal Assessment

Patients were independently reviewed by a Consultant Otolaryngologist (Mr K MacKenzie) who was blinded to the severity of the asthma and results of above physiological evaluation. Patients were asked about a range of laryngopharyngeal symptoms and were asked to rank their symptoms. In addition we recorded a score from 3 symptoms felt to represent reflux – abnormal sensation at the back of the throat, throat clearing and abnormal taste each graded 0-3 (none, mild, moderate, or severe), giving a maximum reflux score (RS) of 9. Laryngoscopy using a flexible fiberoptic laryngoscope was performed following topical application of local anaesthesia, co-phenylcaine®, to the nose and nasopharynx. The assessment of the larynx was based on structure and function. Laryngeal appearance was noted with the mobility of the vocal cords on phonation, inspiration and expiration.

Nasal Assessment

Patients were independently reviewed by a Consultant Otolaryngologist (Mr GW McGarry) who was also blinded to the severity of asthma and results of above physiological evaluation. Nasal symptoms were recorded - obstruction, congestion, hyposmia, rhinorrhoea, sneezing, epistaxis, or other identified symptom, graded as

none (0), mild (1), moderate (2), severe (3), giving a maximum nasal symptom score (NSS) of 21. Standard 4mm 30 degree Rod Lens endoscopy was performed after topical decongestion and anaesthesia with co-phenylcaine®

Statistical Analysis

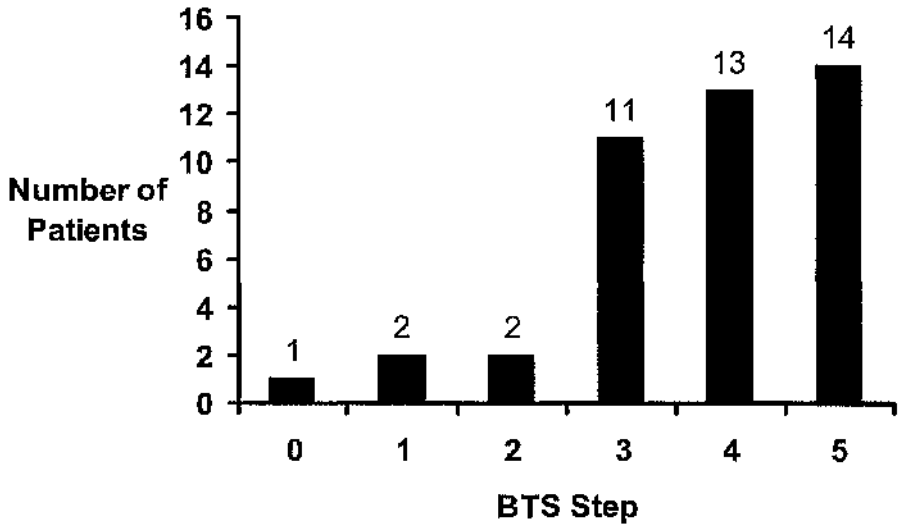
2 sample t-tests were used to compare unpaired interval data. Mann-Whitney U tests were used to compare unpaired sets of nominal data. Minitab (version 14) statistical software was used for these calculations. Sensitivity, specificity, positive and negative predictive values were calculated using conventional methods.([148]) Inter- and intra-rater reliability coefficients were calculated using the methods of Generalisability Theory ([149]). Bootstrap methods were used to construct 95% confidence intervals (CIs) for all reliability estimates, based on 10,000 bootstrap samples from the 43 patients ([150]).

3.3.1 Results – Baseline Characteristics

43 patients were recruited, 14 male, 29 female, aged from 23 – 78 years, median 43 years. Case notes were reviewed to determine how secure the diagnosis of asthma was in each case. We found that 34 (79%) of patients had prior objective evidence of asthma (16 bronchodilator reversibility, 2 bronchial hyper-reactivity, 2 bronchodilator reversibility and bronchial hyper-reactivity, 13 significant peak expiratory flow rate variability and one with an improvement in FEV1 of $\geq$ 20% following a trial of oral corticosteroids). Of the remaining 9 patients, 4 gave only a good clinical history of asthma in the presence of normal lung function when measured and the final 5 patients had no definite evidence of asthma.

27 patients were on BTS Step 4 treatment([1]) or above (any treatment combination including more that low dose inhaled corticosteroids and a long acting beta agonist) (Figure 5).

Figure 5: Baseline level of asthma treatment

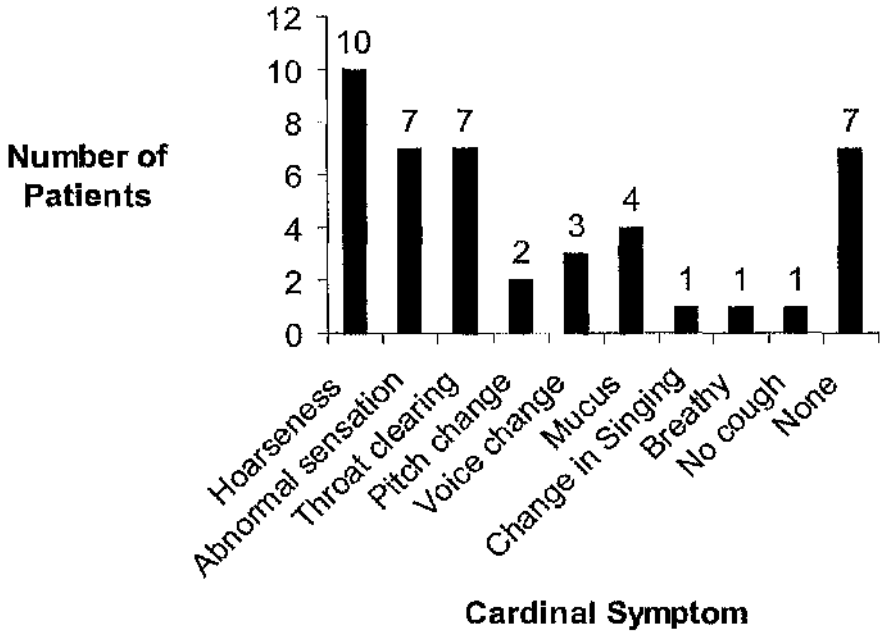


Patients displayed the full range of RCP asthma morbidity scores (0 – 21, a higher score indicates more severe symptoms) with a mean score of 10.6 (SD 7.7). These bore no relation to degree of airflow obstruction as determined by % predicted FEV_1 ($r = -0.28$, $p = 0.073$).

3.3.2 Laryngopharyngeal Assessment

18 different laryngopharyngeal symptoms were reported by the study cohort, ranging from 0 to 14 (mean 6.5). The most frequent cardinal symptom was hoarseness (10), with a total of 20 (47%) patients acknowledging a change in their voice when asked directly. Only 7 patients reported no cardinal laryngeal symptom (Figure 6).

Figure 6: Cardinal Laryngopharyngeal symptom reported



Reflux scores ranged from 0 to 7, median (IQR) 3 (1-5).

There was a mild correlation between RS and asthma symptoms (RCP score, $r = 0.34$, $p=0.026$), although both varied widely. There was no relationship with lung function (FEV_1, $r = -0.17$).

Structural and functional abnormalities identified at laryngoscopy are shown in Table 7.

Table 7: Laryngoscopic findings

Normal **structure**	25 Patients	Normal **function**	31 Patients
Abnormal structure	18 (42%)	Abnormal function	12 (28%)
• Mild/mod/severe laryngitis	• 10/4/1	• glottic chink	• 5
• Miscellaneous*	• 3	• phonating with false cords	• 5
		• reduced cord mobility	• 2

17 patients had normal appearances. The 3 miscellaneous abnormalities were abnormal arytenoids (1), vocal cord polyp (1) and pharyngeal narrowing (described in detail later). Only 1 patient had laryngeal thrush evident in addition to mild laryngitis.

Symptoms varied widely in those with a normal larynx (RS range 0-6, median 3). Laryngitis, defined as diffuse reddening and swelling of the glottis consistent with an inflammatory process, was the most frequent structural abnormality (10 mild, 4 moderate and 1 severe). One patient had upper airway narrowing identified by laryngoscopy in the form of a thickened base of tongue and narrow pharyngeal inlet (confirmed as benign on MRI). 12 patients had functional laryngeal abnormalities as shown above. No patient had "classic" appearances of VCD of inspiratory adduction of the cords associated with glottic chink formation.

Relationship between laryngeal symptoms and structure

We examined the predictive value of the "reflux symptoms" of abnormal sensation, abnormal taste and throat clearing for laryngoscopic features of reflux. For the purposes of this analysis each symptom was defined as either present or absent, rather than grading the severity of symptoms. Symptoms were analysed individually and in combination, comparing those who had any degree of every symptom in combinations tested, with those having no symptoms in the combination. This showed that neither individual nor groups of "reflux" symptoms were good predictors of laryngoscopic signs of reflux (Table 8).

Table 8: Predictive value of reflux symptoms for laryngoscopic signs of reflux.

SYMPTOM / SYMPTOM COMBINATION	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Abnormal Sensation	66.6	32.1	64.3	34.5
Abnormal taste	53.3	67.9	73.1	47.1
Throat clearing	80	32.1	75	38.7
Abnormal sensation + Abnormal taste (23 patients)	66.6	50	70	46.1
Abnormal sensation + throat clearing (26 patients)	75	50	81.8	40
Abnormal taste + throat clearing (31 patients)	88.9	27.3	85.7	33.3
All 3 "Reflux" Symptoms (19 patients)	83.3	46.1	85.7	41.7

We also determined the predictive value of symptoms for any structural or functional abnormality, including hoarseness and voice change (since these were the most frequent symptoms). These results are shown in Table 9 and suggest that combinations of laryngeal symptoms are better predictors of any laryngeal abnormality than specifically laryngitis.

Table 9: Predictive value of laryngeal symptoms for functional or structural abnormality in general (including laryngitis).

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Abnormal Sensation	73.1	41.2	50	65.5
Abnormal taste	51.9	81.5	50	82.4
Throat clearing	80.7	41.2	58.3	67.7
Hoarseness	42.3	29.4	25	47.8
Change in Voice	31.5	70.6	54.5	76.2
Voice change + abnormal taste (n = 23)	66.7	90.1	71.4	88.9
Voice change + throat clearing (n = 27)	86.7	58.3	77.8	72.2
Voice change + abnormal sensation (n = 33)	71.4	58.3	53.8	75
Voice change + hoarseness (n =27)	75	81.7	69.2	85.7
Voice change + hoarseness + abnormal taste (n = 16)	88.9	100	87.5	100

13 (30%) patients had management changed on basis of examination - 7 were referred for Speech therapy, 4 had a change in therapy for laryngitis and 2 underwent further ENT evaluation.

3.3.3 Results – Physiological Assessment

In one patient we were unable to obtain adequate spirometry or FOT data, with inadequate FOT and inspiratory FVL data obtained in a further 2 patients.

FEV_1 (% predicted) ranged from 1.11 (31% predicted) to 4L (137% predicted). 15 patients had an FEV_1 of ≤ 80% predicted, and 20 patients had an FEV_1/FVC ratio of < 70%.

The values for airway resistance determined by FOT and R_{occ} are illustrated in Table 10 (all were normally distributed).

Table 10: Airway resistance measured by Forced Oscillation Technique (n=40)

	Range (kPa/l/s)	Mean (kPa/l/s) (SD)
Inspiratory Resistance (R_i)	0.14 – 0.90	0.43 (0.17)
Expiratory Resistance (R_e)	0.19 – 1.16	0.50 (0.22)
Total Resistance (R_t)	0.17 – 1.05	0.47 (0.19)
Occlusion Resistance (R_{occ})	0.19 – 0.74	0.4 (0.12)

There are no clear data on the normal reference range for FOT measured airways resistance, but this probably lies in the region of 0.25-0.31kPa/l/s ([47]). 31 (72%) of our patients had values of R_t above this level. 32 (80%) patients had R_{occ} values over 0.3 kPa/l/s, which is the generally accepted upper limit of normal.([144])

The relationship between each component of FOT measured airways resistance and spirometric measurements which can suggest upper airway narrowing are shown in Table 11. Pearson Correlation Co-efficients were calculated given all parameters were normally distributed. Additionally, the relationships between FOT and R_{occ} and FEV_1 are shown.

Table 11: Pearson Correlation Coefficients of FOT with spirometric measures of upper airway obstruction (MIF_{50}, MEF_{50}/ MIF_{50}), R_{occ} and FEV_1.

	R_i	R_e	R_t
MIF_{50}	-0.14, p = 0.406	-0.26, p = 0.109	-0.23, p = 0.152
MEF_{50}/ MIF_{50}	-0.44, p= 0.004	-0.24, p = 0.14	-0.32, p = 0.041
R_{occ}	0.55, p < 0.001	0.66, p < 0.001	0.65, p < 0.001
FEV_1	-0.49, = 0.001	-0.42, p = 0.007	0.47, p = 0.002

We copared the values obtained for R_t, R_i and R_{occ} obtained in the patients who were found to have functional abnormalities at laryngoscopy with the normals, in the 40 patients with contemporaneous physiological data. These results are shown in Table 12.

Table 12: Ranges and mean (SD) values of R_t, R_i and R_{acc} subdivided by functional appearance at laryngoscopy (n = 40).

Functional status		R_t (kPa/l/s)	R_i (kPa/l/s)	R_{acc} (kPa/l/s)
Normal (29)	Range	0.17 – 1.05	0.14 – 0.90	0.19 – 0.74
	Mean (SD)	0.48 (0.20)	0.44 (0.18)	0.40 (0.21)
Glottic chink (5)	Range	0.31 – 0.66	0.24 – 0.55	0.33 – 0.48
	Mean (SD)	0.45 (0.13)	0.40 (0.16)	0.40 (0.06)
False cord phonation (4)	Range	0.29 – 0.65	0.29 – 0.64	0.26 – 0.47
	Mean (SD)	0.44 (0.16)	0.44 (0.16)	0.37 (0.09)
Reduced cord mobility (2)	Range	0.34 - 0.53	0.34 – 0.35	0.26 – 0.59
	Mean (SD)	0.43 (0.14)	0.35 (0.00)	0.44 (0.21)

All patients with glottic chinks had values of R_t and R_{acc} which are higher than previously reported normal values([47;144]) as indeed had many of those with normal laryngeal appearances. There were no statistically significant differences observed between any of the groups according to functional abnormalities in terms of any of the above physiological parameter (2 sample t-tests). There was also no difference in MEF_{50}/MIF_{50} between any of these groups.

There were 4 patients who were evaluated by ENT on a different day from their physiological evaluation. Given that we are unable to make any claim about the validity of FOT in the diagnosis of VCD it was felt appropriate to include their results for analysis of the relationship between all the physiological parameters discussed above.

3.3.4 Results – Vocal Assessment

The VoiSS scores are shown in Table 13. There was no relationship between VoiSS score and current inhaled corticosteroid dose ($r = 0.23$, $p = 0.117$).

Table 13: VoiSS questionnaire scores.

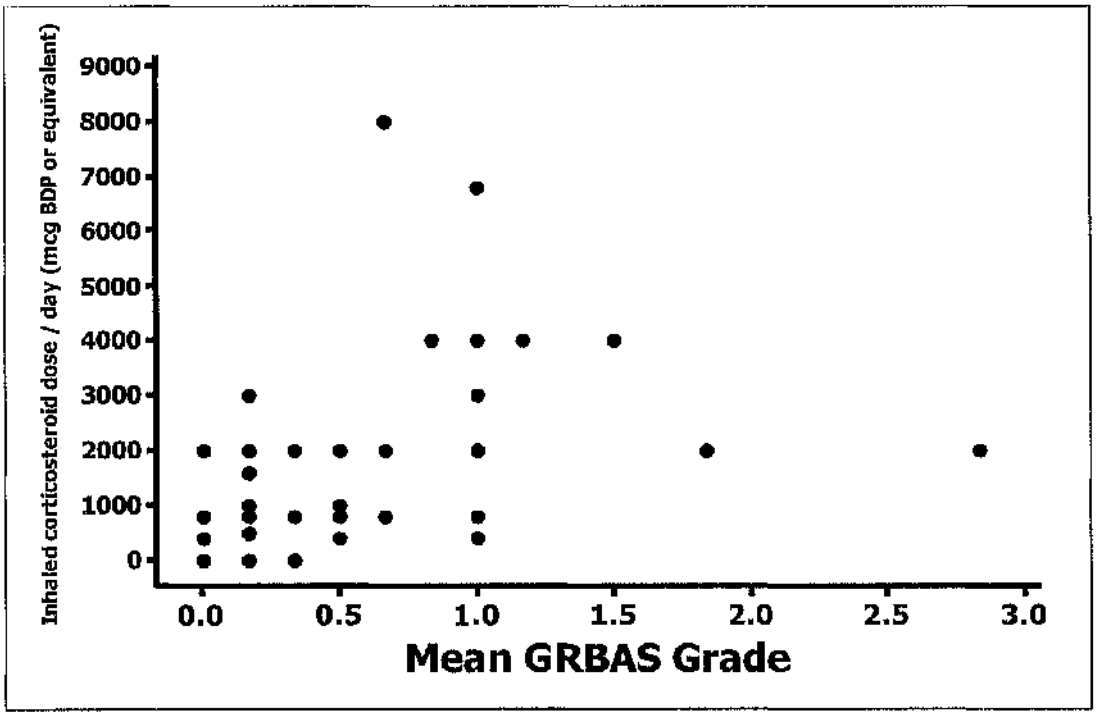
	Range	Mean (SD)	Median (IQR)
Total score	3 – 83	30.5 (18.5)	26 (16-40)
Impairment	0 – 47	15.7 (11.2)	16 (7-20)
Emotional Reaction	0 - 21	3.1 (5.3)	0
Physical Symptoms	3 – 27	11.0 (4.9)	10 (7-14)

The mean of the 6 GRBAS(I) assessments (2 from each reviewer) for each patient was calculated to give their final GRBAS(I) scores (Table 14). A GRBAS Grade of $\geq$ 1 is recognised as definitely abnormal, and 13 / 43 (30.2%) patients had this. A statistically significant correlation was observed between GRBAS Grade and inhaled corticosteroid dose (Spearman $r = 0.56$, $p < 0.001$, Figure 7).

Table 14: Mean GRBAS(I) scores

GRBAS(I) Subscale	Range	Mean (SD)	Median (IQR)
Grade	0 – 2.83	0.59 (0.57)	0.50 (0.17-1.0)
Roughness	0 – 2.5	0.88 (0.49)	0.83 (0.5-1.17)
Breathiness	0 – 2.17	0.43 (0.53)	0.33 (0-0.5)
Asthenicity	0 – 1.5	0.27 (0.36)	0.17 (0-0.5)
Strain	0 – 2.83	0.62 (0.57)	0.50 (0.17-1.0)
Instability	0 – 1.83	0.24 (0.38)	0.17 (0-0.33)
Total GRBAS	0.33 – 10.83	2.79 (2.1)	2.0 (1.25-3.83)

Figure 7: Relationship between inhaled corticosteroid dose and GRBAS Grade (BDP = Beclomethasone dipropionate) (Spearman r =0.56, p<0.001).



The group with normal appearances had lower median VoiSS scores than those with any abnormality demonstrated at laryngoscopy, as shown in Table 15. The mean GRBAS Grade did not differ between these 2 subgroups. However when the sub-

groups with functional or structural abnormalities were analysed seperately, the group with functional abnormalities were found to have higher mean GRBAS subscale scores in all but Roughness and Strain (Table 16). Full breakdown of VoiSS subscales and GRBAS related to laryngoscopic findings of structural or functional abnormalities are shown in Table 16.

Table 15: VoiSS and GRBAS Grade scores depending on laryngoscopic appearances

Laryngoscopic findings	**VoiSS**		**GRBAS Grade**	
	Range	**Median**	**Range**	**Median**
Normal structure and function (n = 17)	4 – 46	22	0 – 1.0	0.34
Abnormal structure OR function (n = 26)	3 – 83	33	0 – 2.8	0.67
95% CI for difference vs. normals	0.0, 21.0, p=0.044		-5.0, 0.0, p = 0.15	

Table 16: VoiSS subscales and GRBAS related to laryngoscopic findings of structural or functional abnormalities

	Functional Abnormality					Structural Abnormality				
	Absent		Present		p-value	Absent		Present		p-value
	Mean (SD)	median (IQR)	Mean (SD)	median (IQR)		Mean (SD)	median (IQR)	Mean (SD)	median (IQR)	
Impairment	14.7 (11.4)	14 (5-19)	18.3 (10.7)	18 (11.5-26)	NS	13.9 (10.0)	13 (5-19)	18.3 (12.5)	16 (10.8-25)	NS
Emotional Reaction	3.5 (5.8)	0 (0-6)	2.1 (3.7)	1 (0-2.75)	NS	1.8 (3.3)	0 (0-2)	4.9 (6.9)	1 (0-9.25)	NS
Physical Symptoms	11.7 (5.3)	11 (9-15)	8.9 (3.3)	9 (6.25-10.75)	NS	10.4 (4.7)	10 (7.5-13)	11.7 (5.3)	11 (7-16.25)	NS
Total	30.5 (20.0)	25 (16-40)	30.6 (14.7)	32 (19-39.75)	NS	26.7 (13.6)	25 (16-37.5)	35.8 (23.0)	30 (21-49)	NS
Grade	0.45 (0.56)	0.17 (0.17-0.68)	0.94 (0.44)	1.00 (0.68-1.13)	**0.0015**	0.58 (0.49)	0.50 (0.17-1.00)	0.60 (0.68)	0.50 (0.17-0.71)	NS
Roughness	0.82 (0.52)	0.83 (0.50-1.17)	1.04 (0.36)	1.00 (1.0-1.29)	NS	0.83 (0.46)	0.83 (0.42-1.17)	0.95 (0.53)	1.00 (0.79-1.17)	NS
Breathiness	0.31 (0.48)	0.17 (0.00-0.33)	0.72 (0.56)	0.50 (0.33-1.00)	**0.0043**	0.39 (0.47)	0.33 (0.00-0.42)	0.47 (0.62)	0.25 (0.00-0.75)	NS
Asthenicity	0.18 (0.26)	0.00 (0.00-0.33)	0.51 (0.48)	0.42 (0.17-0.83)	**0.0154**	0.25 (0.37)	0.00 (0.00-0.50)	0.31 (0.36)	0.17 (0.00-0.50)	NS
Strain	0.55 (0.60)	0.33 (0.17-0.67)	0.81 (0.47)	0.75 (0.38-1.29)	NS	0.61 (0.47)	0.50 (0.25-1.00)	0.64 (0.70)	0.42 (0.17-0.79)	NS
Instability	0.19 (0.36)	0.00 (0.00-0.17)	0.39 (0.40)	0.25 (0.17-0.5)	**0.0335**	0.23 (0.26)	0.17 (0.00-0.33)	0.27 (0.51)	0.00 (0.00-0.33)	NS
Total	3.00 (2.90)	1.83 (1.17-4.50)	5.18 (2.67)	4.5 (3.42-7.00)	**0.0062**	3.55 (2.57)	2.67 (1.25-5.83)	3.69 (3.53)	2.42 (1.50-4.50)	NS

The Spearman Rank correlations between the median GRBAS(I) rating and the VoiSS score and subscales are shown below in Table 17. Non significant p values are not shown.

Table 17: Correlations between VoiSS and GRBAS(I)

		VoiSS Subscale			
		Total	Impairment	Emotional	Physical
GRBAS(I)	Grade	0.24	0.33 (p=0.034)	0.28	0.05
	Roughness	0.08	0.15	0.09	-0.09
	Breathiness	0.40 (p=0.008)	0.43 (p=0.004)	0.38 (p=0.013)	0.06
	Asthenicity	0.47 (p=0.002)	0.43 (p=0.004)	0.33 (p=0.032)	0.15
	Strain	0.25	0.30 (p=0.05)	0.26	0.21
	Instability	0.18	0.21	0.14	0.10
	Total GRBAS	0.34 (p=0.027)	0.38 (p=0.012)	0.32 (p=0.036)	0.13

Relationship between GRBAS / VoiSS and laryngoscopic appearances

VoiSS and GRBAS score predicted laryngoscopic abnormality equally (Table 18). A total VoiSS score of 30 was chosen as cut-off scores because of its relationship with the median total VoiSS score for the study group. A Grade of ≥ 1 on the GRBAS scale is recognised as identifying significant vocal morbidity and was therefore used as the cut off for this analysis. GRBAS data in Table 5 is presented as mean (SD) sensitivity, specificity, NPV and PPV from the 6 assessments each patient had.

Table 18: Predictive value of GRBAS and VoiSS for any laryngoscopic abnormality

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
GRBAS Grade ≥ 1 (mean (SD) of 6 SLT scorings)	57.1 (10.7)	59.8 (11.4)	50.1 (6.5)	68.7 5.8)
VoiSS ≥ 30	53.8	70.6	50	73.7

SLT Rater Reliability

The full breakdown of both inter and intra-rater reliability for the whole study group is shown in Table 19. As demonstrated, the Total GRBAS scores show good overall agreement for inter-rater reliability at 78.1% and excellent agreement for overall intra-rater reliability at 81.8%. However, this level of agreement is not sustained across the individual categories. Grade fairs best at an overall 64.7% for inter-rater reliability and 69.6% for intra-rater reliability. Asthenicity stands out as achieving the lowest inter-and intra-rater reliability at 43.4% and 49.6%, respectively. The level of reliability is not statistically different on the two occasions with the exception of improved agreement in the assessment of Instability on the second occasion. When examining the scores of the individual raters, it seems that Rater 3 achieves a high degree of consistency, dipping no lower than 62.3% across all categories. Rater 1, by comparison, appears much less consistent between the two scoring occasions with a low of 24.5% for Asthenicity. Rater 2 lies in the middle of the other two raters and seems to be consistently more reliable than Rater 1 with the exception of the GRBAS

Strain category. There only appears to be a statistically significant difference in intra-rater reliability between Rater 3 and Rater 1 in Asthenicity.

Separate analyses were undertaken for inter- and intra-rater reliability in respect of the GRBAS(I) categories for subjects with any laryngeal abnormality or with laryngeal abnormality as opposed to no observed laryngeal abnormality (Tables 20 and 21). This showed intra-rater reliability was significantly better in Grade assessment for patients with any laryngeal abnormality than those with normal appearances (78.8% versus 47.3%%, 95% CI for difference 6.2, 59.1). In all other categories (except Roughness) there was only a trend seen towards improved inter and intra-rater reliability with no other statistically significant differences observed. Examining the differences for patients with functional abnormalities (versus none), there is a general trend to improved inter and intra-rater reliability for patients with functional abnormalities but a statistically significant difference was only observed for intra-rater reliability in Strain assessment.

Table 19: Inter-rater and Intra-rater reliability for GRBAS(I) assessment

Estimate (Bootstrap 95% CI)	Inter-Rater Reliability (%)				Intra-Rater Reliability (%)						
	Overall	Occasion 1	Occasion 2	Difference	Overall	Rater 1	Rater 2	Rater 3	Differences		
				O_2-O_1					R_1-R_2	R_1-R_3	R_2-R_3
Total Score	78.1 (66.6, 88.2)	79.1 (68.3, 84.7)	80.6 (64.7, 93.4)	1.6 (-13.0, 12.6)	81.8 (68.5, 90.6)	75.8 (54.6, 86.1)	80.1 (56.3, 95.2)	87.3 (66.7, 95.6)	-4.3 (-27.7, 19.3)	-11.4 (-32.8, 3.8)	-7.2 (-26.8, 15.1)
Grade	64.7 (45.7, 82.4)	59.8 (41.1, 77.2)	71.2 (48.0, 89.0)	11.4 (-5.9, 27.0)	69.6 (51.4, 85.1)	54.7 (29.3, 72.8)	69.1 (41.4, 91.1)	82.4 (52.5, 96.3)	-14.5 (-43.5, 13.6)	-27.7 (-50.2, -1.4)	-13.2 (-42.7, 15.3)
Roughness	45.3 (29.4, 61.7)	40.1 (21.6, 58.5)	47.1 (27.9, 65.4)	7.0 (-12.9, 23.3)	56.3 (41.1, 73.1)	41.5 (16.1, 64.0)	61.4 (35.9, 82.4)	62.3 (44.8, 76.5)	-19.9 (-49.3, 13.4)	-20.8 (-46.3, 2.9)	-0.9 (-31.2, 19.6)
Breathiness	52.8 (32.5, 69.4)	53.9 (34.0, 67.0)	52.8 (27.1, 74.4)	-1.1 (-25.3, 18.2)	62.4 (44.6, 74.5)	48.7 (27.8, 71.1)	68.1 (34.6, 90.3)	69.2 (40.6, 82.6)	-19.4 (-49.7, 13.3)	-20.4 (-43.1, 10.9)	-1.1 (-34.4, 27.0)
Asthenicity	43.4 (26.9, 63.4)	50.8 (25.7, 68.5)	47.5 (25.5, 70.5)	-3.3 (-27.1, 27.6)	49.6 (29.7, 69.5)	24.5 (0.0, 61.1)	31.0 (0.0, 74.5)	67.8 (39.3, 84.7)	-6.5 (-34.9, 23.0)	-43.3 (-72.7, -7.6)	-36.8 (-72.3, 7.9)
Strain	54.4 (35.7, 75.4)	58.2 (42.4, 71.6)	51.8 (25.9, 79.6)	-6.4 (-28.9, 13.5)	68.7 (52.2, 85.1)	73.2 (51.8, 84.5)	58.6 (23.3, 88.6)	74.9 (52.5, 93.3)	14.6 (-19.1, 50.7)	-1.7 (-31.5, 23.9)	-16.3 (-56.2, 6.0)
Instability	50.5 (24.7, 76.9)	35.4 (13.5, 64.1)	65.9 (28.7, 87.7)	30.5 (13.9, 52.7)	72.2 (52.7, 85.3)	70.1 (46.2, 84.3)	74.7 (0.0, 100.0)	75.5 (29.4, 100.0)	-4.6 (-45.9, 74.6)	-5.4 (-43.8, 29.5)	-0.8 (-64.6, 100.0)

Table 20: Inter-rater and Intra-rater reliability depending on presence or absence of any laryngoscopic abnormality

Estimate (Bootstrap 95% CI)	Inter-Rater Reliability			Intra-Rater Reliability		
	Any Abnormality		Difference	Any Abnormality		Difference
	Yes	No	(Yes – No)	Yes	No	(Yes – No)
Total Score	79.2 (62.3, 90.2)	73.7 (63.2, 84.2)	5.5 (-15.4, 25.6)	84.6 (66.9, 92.9)	73.7 (60.2, 86.3)	10.8 (-9.2, 30.2)
Grade	67.8 (42.7, 85.4)	47.3 (27.2, 67.3)	20.5 (-9.1, 54.3)	78.8 (61.0, 89.5)	47.3 (26.6, 69.3)	31.5 (6.2, 59.1)
Roughness	45.3 (21.0, 69.5)	50.9 (20.5, 71.1)	-5.6 (-40.5, 36.6)	60.0 (37.9, 80.3)	57.3 (37.5, 75.9)	2.7 (-27.8, 34.4)
Breathiness	54.7 (29.7, 72.1)	39.8 (5.5, 74.3)	14.9 (-34.0, 52.3)	66.7 (47.1, 77.8)	43.6 (3.5, 82.2)	23.1 (-20.5, 65.3)
Asthenicity	46.3 (25.4, 68.1)	29.0 (0.0, 46.9)	17.3 (-11.1, 54.8)	56.3 (31.7, 76.2)	29.0 (0.0, 48.1)	27.3 (-2.0, 66.1)
Strain	57.1 (32.0, 81.2)	49.4 (28.3, 72.9)	7.7 (-26.0, 43.9)	70.2 (45.9, 88.8)	67.8 (49.3, 80.4)	2.4 (-25.2, 32.0)
Instability	56.3 (20.4, 82.6)	26.8 (0.0, 56.5)	29.5 (-21.8, 67.8)	78.5 (56.8, 90.2)	47.4 (25.0, 70.1)	31.2 (-3.7, 59.0)

Table 21: Inter-rater and Intra-rater reliability depending on presence or absence of functional laryngoscopic abnormality

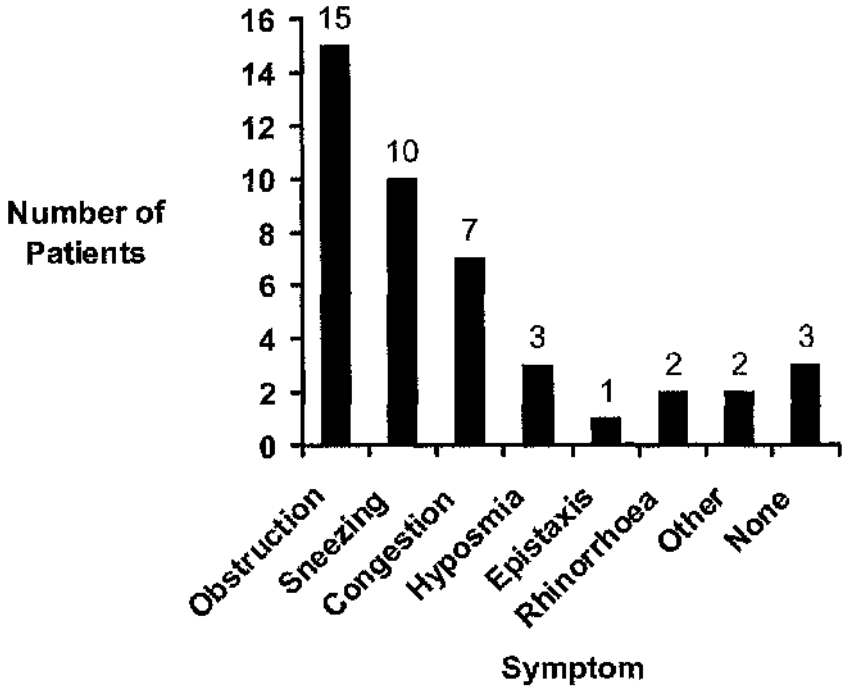
Estimate (Bootstrap 95% CI)	Inter-Rater Reliability			Intra-Rater Reliability		
	Functional Abnormality		Difference	Functional Abnormality		Difference
	Yes	No	(Yes – No)	Yes	No	(Yes – No)
Total Score	80.7 (61.8, 91.3)	66.1 (40.8, 79.6)	14.6 (-8.2, 59.1)	84.1 (66.4, 94.0)	70.8 (36.9, 87.8)	13.3 (-10.4, 59.6)
Grade	65.3 (34.2, 87.4)	49.2 (19.7, 72.7)	16.0 (-21.7, 68.8)	65.7 (34.0, 88.7)	68.3 (45.1, 82.4)	-2.5 (-37.0, 42.9)
Roughness	51.0 (29.3, 68.1)	23.9 (0.0, 57.1)	27.0 (-15.9, 57.8)	58.6 (37.8, 78.0)	46.3 (20.0, 74.9)	12.2 (-23.8, 46.9)
Breathiness	54.3 (24.9, 77.1)	41.0 (1.8, 63.8)	13.3 (-25.4, 64.1)	58.6 (27.8, 76.3)	61.3 (26.8, 79.2)	-2.7 (-36.1, 39.8)
Asthenicity	30.3 (9.2, 60.4)	50.8 (27.1, 75.2)	-20.5 (-55.9, 14.9)	44.9 (22.3, 69.6)	54.4 (23.7, 78.4)	-9.5 (-45.5, 28.2)
Strain	61.1 (34.5, 82.2)	35.8 (16.7, 66.6)	25.3 (-9.9, 60.0)	79.3 (62.8, 91.6)	35.8 (12.0, 63.6)	43.5 (13.2, 72.6)
Instability	60.2 (7.9, 85.8)	41.3 (4.8, 62.1)	18.8 (-35.0, 76.2)	73.6 (43.3, 90.3)	63.6 (14.3, 82.5)	10.0 (-24.5, 78.5)

3.3.5 Results – Nasal Assessment

Nasal Symptoms

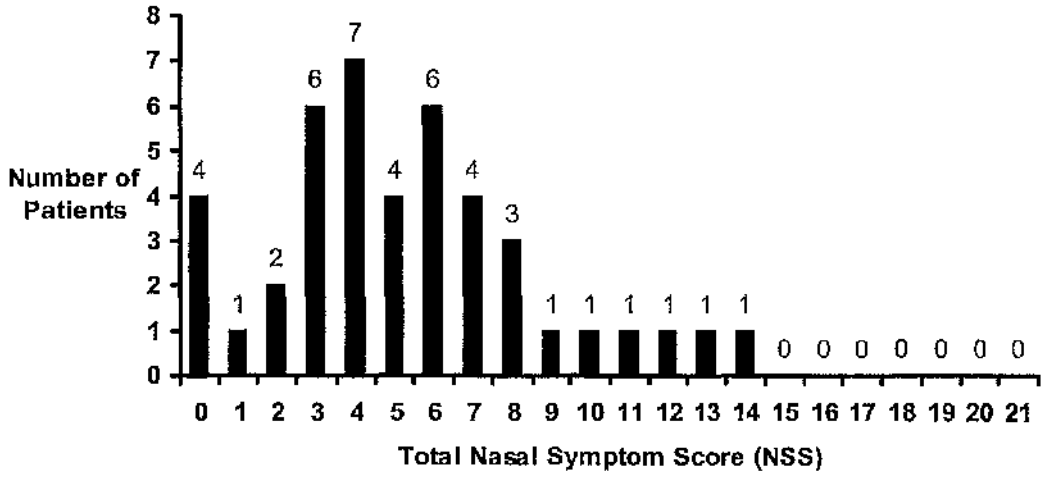
Obstruction was the most common cardinal symptom (15 patients, Figure 3). Three patients reported no cardinal nasal symptoms.

Figure 8: Cardinal nasal symptom reported.



The distribution of Nasal Symptom Scores (NSS) is shown in Figure 9.

Figure 9: Distribution of total Nasal Symptom Score (NSS).

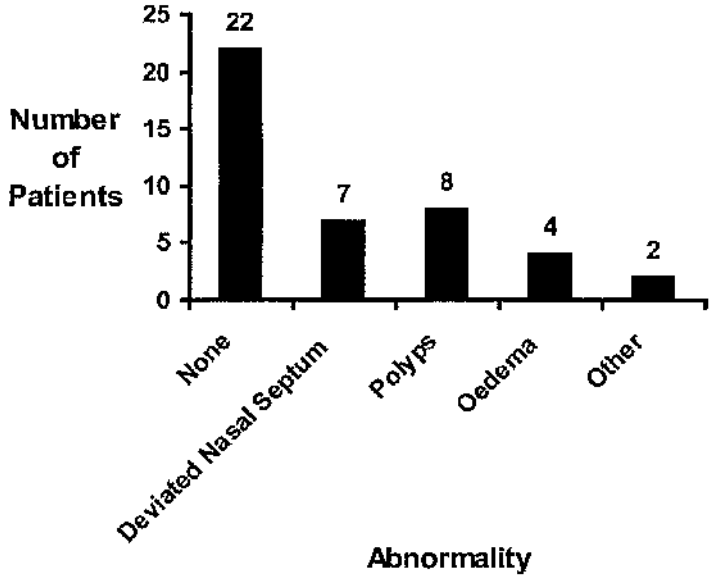


Median NSS was 5.3 (range 0-14) for the whole group. The NSS of the 12 patients taking nasal medication (10 were taking topical nasal steroids and 2 were taking antihistamines) at the time of the study was marginally higher than those who were not on nasal medication (medians of 6 and 4 respectively, p = 0.046 by Mann-Whitney U test, 95% confidence interval for difference -0.001 to –5). There was no correlation between NSS and severity of asthma symptoms (measured by the RCP score, r = -0.05) or FEV_1 (r = 0.01).

Nasendoscopy findings

Structural abnormalities at nasendoscopy were much less frequent than symptoms. Findings at nasendoscopy are shown in Figure 5. The two "other" findings were vestibulitis (1) and accessory sinus ostia (1, not thought to be pathological).

Figure 10: Nasendoscopy findings.



The NSS of patients with oedema and polyps were higher (Medians of 7 and 5 respectively) than those with normal nasendoscopy and deviated nasal septum (DNS) (both with medians of 4) but none of these differences reached statistical significance.

Initial analysis was performed to determine how well individual symptoms predicted the finding of any abnormality or the specific abnormalities of polyps or DNS for the whole study group. The results for predicting any abnormality are shown in Table 22. This indicates that individual nasal symptoms apart from hyposmia were poor predictors of any nasal abnormality (results for individual nasal pathologies were unremarkable and are shown separately in Table 23).

Table 22: Prediction of any nasal pathology by individual symptom.

SYMPTOM	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
OBSTRUCTION	57.1	45.5	52.6	50
SNEEZING	61.9	36.4	50	48.1
CONGESTION	76.2	31.8	58.3	51.6
HYPOSMIA	57.1	86.4	67.9	80
RHINORRHOEA	57.1	59.1	59.1	57.1

Table 23: Prediction of nasal pathology by individual symptom.

SYMPTOM		Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
OBSTRUCTION	POLYPS	62.5	45.7	84.2	20.9
	DNS	28.5	38.9	73.7	8.3
	ANY ABNORMALITY	57.1	45.5	52.6	50
SNEEZING	POLYPS	62.5	37.1	81.3	18.5
	DNS	42.9	33.3	75	11.1
	ANY ABNORMALITY	61.9	36.4	50	48.1
CONGESTION	POLYPS	71.4	23.8	33.3	61
	DNS	71.4	27.7	83.3	16.1
	ANY ABNORMALITY	76.2	31.8	58.3	51.6
HYPOSMIA	POLYPS	62.5	71.4	89.2	33.3
	DNS	28.6	63.9	82.1	13.3
	ANY ABNORMALITY	57.1	86.4	67.9	80
RHINORRHOEA	POLYPS	62.5	54.3	86.4	23.8
	DNS	57.1	52.8	86.4	19
	ANY ABNORMALITY	57.1	59.1	59.1	57.1

Further analysis of combinations of symptoms was then undertaken. This involved looking at smaller groups of patients, comparing those who had any degree of every symptom in combinations tested, compared to those with no symptoms in the combination. These results are shown in Table 24, indicating combinations of nasal symptoms which are strongly associated with nasendoscopic abnormality.

Table 24: Predictors of nasal pathology by groups of symptoms

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Congestion & Hyposmia (21 patients)	76.9	75	66.7	83.3
Rhinorrhoea & Hyposmia (21 patients)	66.7	91.7	78.6	85.7
Obstruction & Hyposmia (24 patients)	60	88.9	57.1	90
Congestion, Rhinorrhoea & Hyposmia (11 patients)	66.7	80	66.7	80
Obstruction, Rhinorrhoea & Hyposmia (12 patients)	80	100	87.5	100
Obstruction & Congestion (27 patients)	78.6	30.7	57.1	55
Obstruction & Rhinorrhoea (22 patients)	71.4	53.3	80	41.8
Rhinorrhoea & Congestion (24 patients)	83.3	50	77.8	58.8
Rhinorrhoea, Obstruction & Congestion (14 patients)	80	44.4	80	44.4

7 patients with structural abnormalities had a change in their management on the basis of the nasal findings - 5 patients were started on topical nasal steroids, one was given

topical antibiotic ointment and one was listed for surgery for grossly deviated nasal septum.

3.4.1 Discussion – Laryngopharyngeal Assessment

We studied the upper and lower airway of patients attending a problem asthma clinic, having a broad range of severity, in terms of FEV_1, symptom scores and BTS treatment step. Most of these patients had definite asthma. Our inability to attract consecutive patients to this study limits the generalisability of our findings, but this was a pilot study and nevertheless provides some important findings for further investigation.

Firstly, we did not identify the "classic" appearances of VCD (inspiratory cord adduction with associated glottic chink) in any of the 43 patients examined. Although true population figures for incidence and prevalence of VCD are not known, we might have expected to identify this in at least some patients, given the range of asthma severity and symptoms, previous clinical suspicions and prevalence rates of another tertiary referral centre([12]). In Denver 22/132 (16.7%) of patients with *refractory* asthma were found to have VCD in addition to asthma. It is known that asthma is very common in association with VCD, with co-existing asthma in 53/95 cases in one large case series of VCD patients ([13]).

We did however identify 12 patients with some form of functional abnormalities at laryngoscopy. Although not strictly meeting the currently accepted VCD definition, in the absence of any otherwise accepted term, it seems reasonable to suggest that a spectrum of "upper airways dysfunction" exists, encompassing a variety of functional abnormalities, which may at one end include "classic" VCD. Although we did not have a control group, and selection bias has to be considered, the frequency of these

abnormalities confirms our prior suspicion of reasonable prevalence of upper airway problems in our clinic population.

All laryngoscopies were performed by a single observer so that although consistency has been achieved, the impact of recognised inter-observer variability in the reporting of laryngoscopic findings cannot be assessed in this study.

We found some correlation between degree of "reflux" related laryngeal and of asthma symptoms, perhaps mirroring the difficulty which doctors as well as patients may have, of differentiating between the upper and lower airways. Lung function showed no relationship with either laryngeal or asthma symptoms. The lack of relationship between asthma symptoms and FEV_1 highlights the need to identify other coexisting problems in patients with problem asthma. Although we did not objectively assess the degree of either gastro-oesophageal or laryngo-pharyngeal reflux in our patients, the symptoms we defined as "reflux" symptoms have been shown to be strongly associated with laryngo-pharyngeal acid reflux ([151]). We do however acknowledge that the reflux score used in this study has not been validated. Other than the study by Belafsly,([152]) which validated a reflux symptom index in 25 patients, no other validated questionnaire for **laryngo**pharyngeal reflux disease is available. The association between this entity and asthma is much less well defined than the large body of work looking at asthma and gastro-oesophageal reflux disease ([153-155]). Laryngo-pharyngeal acid reflux may provide the initial stimulus for VCD ([24]).

Structural abnormalities at laryngoscopy were less common than symptoms and the degree of symptoms varied widely in patients with endoscopically normal larynges.

These pilot data suggest that specific laryngeal symptoms are poor predictors of laryngeal reflux. Although the negative predictive value of the absence of all 3 reflux symptoms (85.7%) was much better than their positive predictive value (41.7%) (Table 8), symptoms were better predictors of any laryngoscopic abnormality, with abnormal taste the best individual predictor. Combination of symptoms increased the likelihood of any laryngoscopic abnormality, an observation which may be of value in deciding on the utility of ENT assessment. This data suggests that prospective evaluation of such scores in correctly identifying laryngeal pathology is indicated.

3.4.2 Discussion - Physiological Assessment

Since VCD was not identified, we cannot draw any conclusions about the utility of FOT in diagnosing this. Currently, the gold standard for diagnosis rests with direct visualisation of the cords and we were hopeful that a non-invasive method of assessing the upper airways physiologically would provide a further method of diagnosis. Performing laryngoscopy when the patient with VCD is asymptomatic is often normal (26 out of 95 patients in Newman's series([13])) and this may be the reason we did not identify any cases. Challenge testing to identify VCD has been explored,([15;39;43]) and discussed in Chapter 1, but its precise role is not clear and is investigated further in Chapter 5.

In any event, the 12 patients who had some other forms of functional abnormality at laryngoscopy did not however have measurable differences in their physiology as measured by R_t, R_i R_{exc} or MEF_{50}/MIF_{50}. There were 6 patients enrolled in the study who had clinical suspicion of a substantial upper airway contribution to symptoms, one of whom (who had pharyngeal / base of tongue thickening demonstrated) had had VCD documented during a previous symptomatic episode. Only one of these 6 patients had a functional abnormality at laryngoscopy (glottic chink) and four had laryngitis.

FOT has the potential to be a non-invasive tool to identify upper airway narrowing. It has been known for some time that measurements of inspiratory flow are superior to FEV_1 for the diagnosis of upper airway obstruction([40]). Limitation of the inspiratory limb of the FVL has been well documented with VCD ([13;14;22;39]). With the FOT technique, it is possible to separate the airway resistance into expiratory and

inspiratory components and we postulated that inspiratory resistance might provide a clue to the diagnosis.

Previous work in patients with fixed upper airflow obstruction in the form of tracheal stenosis ([156]) demonstrated a clear correlation between FOT measurements and stenosis diameter, with less correlation between diameter and FEV_1. In addition, Rigau ([48]) mimicked VCD in a model using variable resistance to mimic normal respiratory anatomy and found that the changes in oscillatory resistance were in agreement with the degree of area reduction in the model. There is also evidence from sleep literature that FOT is helpful in the identification of upper airway narrowing ([157;158]).

Our data suggest that airway narrowing in general is reflected by R_i. Our inability to demonstrate VCD in the resting state of any of our patients prevents further conclusions being drawn.

We also looked at the relationship between the inspiratory part of FOT measured resistance and MIF_{50} since MIF_{50} (albeit in a small group of patients) has been found to correlate well with mid-inspiratory glottic area ([29]). R_i did not correlate well with MIF_{50} in this study ($r = -0.14$). Although there was a reasonable correlation between R_i and MEF_{50}/MIF_{50} ($r = -0.44$, $p = 0.004$), R_i (along with R_e and R_t) correlated well with FEV_1. This makes it difficult to postulate that R_i would have been a sensitive marker of upper airway obstruction, were we to have identified it.

There was a very strong relationship between resistance measured by FOT in both parts of the respiratory cycle (R_t) and that measured by R_{occ}, although resistance measured by R_{occ} was generally less than that measured by FOT (mean R_t 0.469 kPa/l/s vs. mean R_{occ} of 0.396 kPa/l/s, p = 0.04 for difference by 2 sample t-test), as has been observed previously ([159]). The good relationship between FOT and FEV_1 supports FOT as a further technique for objective assessment of airflow obstruction which may be useful in those unable to perform forced expiratory manoeuvres ([47]).

3.4.3 Discussion – Vocal Assessment

We have identified that voice morbidity is a problem in our clinic population. While other studies have investigated the frequency of voice problems in patients with asthma ([58;62]), these used self-administered questionnaires only to identify voice problems. Our study is novel, since it included a comprehensive vocal assessment by patient (VoiSS), SLT (GRBAS) and ENT specialist (direct visualization of the larynx). Although data from a control group would have strengthened our findings, this was a pilot, hypothesis generating study and further evaluation of VoiSS and or GRBAS in an asthmatic cohort should take this into account. Our analysis of the inter-relations of VoiSS, GRBAS and laryngeal appearance are not affected by these considerations.

The VoiSS has been extensively investigated and refined in over 800 subjects and its subscales have shown good internal consistencies, in contrast to self administered questionnaires used in earlier studies in patients with asthma ([58;62]). Although there are other instruments available for the self assessment of voice quality such as the Vocal Handicap Index (VHI) and Voice related Quality of Life (V-RQOL), we chose VoiSS because it has been extensively investigated, has been derived from a UK population and has been shown to reflect vocal morbidity and associated pharyngeal symptoms ([74,75]). There are no VoiSS data in patients with asthma. Our patients' scores are less abnormal than those of 144 functional dysphonics and 145 patients with structural laryngeal pathology (mean total scores of 43.3 and 46.5 respectively) ([75]). The GRBAS scores from this study are not readily comparable to those reported elsewhere as these have been reported differently (for example using a visual analogue scale) ([160]) or reported to determine inter-rater reliability ([66]).

Higher VoiSS scores were associated with laryngeal pathology (Table 15). We did not evaluate quality of life (either in general or asthma-specific) in this study but the emotional domain of the VoiSS may reflect this. Dysphonia has been shown to adversely affect patients' quality of life, ([63]) and in a different study, self rated voice quality was significantly related to a range of personality, psychological distress and quality of life measures ([161]). The contribution which dysphonia makes to impaired quality of life in patients with asthma merits further exploration.

As well as investigating the relationship between VoiSS responses and laryngoscopic findings, we have also shown a relationship between specialist GRBAS scoring and self reporting of symptoms by patients using VoiSS seen previously (Mr K MacKenzie – personal communication of data submitted for publication). Since GRBAS "Grade" is a summary measure of voice deviance, the observed relationship with the Impairment domain of VoiSS was expected. There were also weak positive correlations between other GRBAS subscales and total GRBAS with VoiSS. The lack of relationship between the Physical component of VoiSS and GRBAS was expected as this VoiSS subscale assesses non-vocal laryngopharyngeal symptoms. Murry ([162]) found a moderate correlation between total GRBAS score and voice related quality of life (V-RQOL) scores (a 10 item self administered questionnaire). There was no breakdown of the relationship with individual GRBAS subscales in that study, and it is these, rather than the total score which are pertinent to clinical practice. Our study therefore adds to the evidence that patients' perception of vocal morbidity relates to that of an experienced observer. Specialist, labour intensive GRBAS Grade was also no better than VoiSS at predicting laryngoscopic abnormality (Table 18). For these

reasons, we therefore believe that further validation of the VoiSS as a screening test for patients with vocal morbidity in the asthmatic population is warranted.

There was a low incidence of laryngeal thrush (1 patient) suggesting that dysphonia should not immediately be attributed to this. Lavy also found a low incidence of candidiasis in a group of asthmatics complaining of dysphonia (4 out of 22 patients) but found a number of other laryngoscopic explanations for symptoms (mucosal changes, apposition problems and supraglottic hyperfunction) ([60]).

As a secondary aim to the study we investigated our local SLT reliability in using the GRBAS score. Some authors have been able to report very high levels of reliability for the GRBAS scale. For example, Murry and colleagues have described reliability coefficients in a voice-disordered population, ranging from 0.88 for Strain to 0.98 for Grade and, in a normal population, of 0.99 for all GRBAS categories([162]). Reliability of GRBAS in the present instance has been shown to be fairly robust for Total scores, both on an inter-rater and on an intra-rater basis. These scores, however, are not in common clinical use and probably have little clinical relevance. More commonly, Grade is extracted as a measure of overall severity and has been generally reported as showing best levels of agreement([66;69;160]). By comparison our raters achieved a rather modest 64.7% for inter-rater reliability and 69.6% for intra-rater reliability for GRBAS Grade. It is not clear whether experience in using GRBAS would account for these differences. We found a tendency to improved reliability when the study group was split into patients with any and subsequently functional laryngeal abnormalities which has been demonstrated in a population of smokers([163]), but the converse (improved reliability in judging voices of normal subjects) has also been seen([164]).

In conclusion, we have demonstrated laryngeal structural and functional abnormalities occur in significant proportions of patients attending a problem asthma clinic and that this is associated with significant differences in self reported VoiSS, but not in the more labour intensive GRBAS screening tool. Very few patients were found to have fungal infection as a result of use of inhaled corticosteroids and we suggest that vocal morbidity should not be attributed to this without positive evidence. We have confirmed the positive correlations between VoiSS scores, and our gold standard measurement, GRBAS total and subscales, suggesting that they are measuring similar attributes. This pilot study suggests that VoiSS is a useful screening tool in our population, but further work is required, as is comparative data for normal subjects.

3.4.4 Discussion – Nasal Assessment

We have studied nasal symptoms and endoscopic findings in a broad range of patients with asthma. There were no strict inclusion or exclusion criteria for this study as the principle aim was to characterise the spectrum of nasal symptomatology and nasendoscopic abnormalities in patients attending an asthma clinic in an observational fashion. As previously discussed we felt this would produce results that would be more generalisable to routine practice. We have shown that nasal symptoms are common in our asthmatic patients in keeping with previously published work.([86;87]) Nasal symptoms were very frequently reported on direct questioning in our small group (40/43, 93%), with any degree of rhinorrhoea reported by 18/43 (42%) but selection bias was probably contributing to this.

Structural abnormalities at nasendoscopy were less common than symptoms. There were 7 patients whose management was changed on the basis of the nasal examination, and their NSS ranged form 4 to 14 (median 6). Although higher than the median NSS for the remaining 36 patients (median of 4), this difference did not reach statistical significance.

To our knowledge, no previous study has looked at the predictive value of nasal symptoms for the finding of nasendoscopic abnormalities. We were not using a previously well validated questionnaire, but rather a simple scoring system of none, mild, moderate or severe to grade a range of common nasal symptoms which is easily applicable to an out patient clinic consultation. Our results show individual nasal symptoms are poor predictors of nasal pathology, with hyposmia having the best

individual predictive value for abnormality (PPV of 80%). Combinations of symptoms increased the predictive value with every patient complaining of obstruction, rhinorrhoea and hyposmia having a nasendoscopic abnormality. The choice of specific symptom combinations was based on their individual predictive values and frequency as cardinal symptoms. Combinations which did not include hyposmia had improved sensitivity but reduced specificity. These pilot data suggest that the threshold for ENT referral should be lower when the patient complains of a symptom complex including hyposmia, as the likelihood of finding an abnormality is much higher. Furthermore, concurrent hyposmia, obstruction and rhinorrhoea should be seen as an indication for ENT referral. The validity of this observation and possible impact of adequate treatment of nasal and sinus disease on upper airway hyper-reactivity is worthy of further study.

CHAPTER 4

THE VALUE OF ROUTINE RHINOSCOPY IN AN ASTHMA CLINIC

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A PROSPECTIVE STUDY

4.1 Introduction

As we demonstrated in the nasal aspect of our pilot study, nasal symptomatology is more prevalent than structural nasal pathology and that hyposmia was the best individual symptom predictive of structural nasal abnormalities. We therefore wanted to perform a more comprehensive observational survey of nasal symptomatology and nasal pathology to help determine the value of routine nasendoscopy in a problem asthma clinic by inviting as many patients with asthma as were attending the clinic to attend a simple study run in parallel with their clinic attendance. With this study, we also sought to characterise more accurately the relationship between nasal symptoms and disease on this occasion by means of a previously validated questionnaire, the Sino-Nasal Outcomes Test (SNOT) and to determine if the predictive values of nasal symptoms for structural abnormalities were similar using this tool to our pilot data. Given that in our pilot study we included patients only from the PAC (most of whom had objective evidence of asthma) and consequently cannot be sure whether these symptom predictors are applicable to patients with asthma specifically, we tested the hypothesis that nasal symptoms and pathology would be more common in patients with asthma by comparison with a non-asthmatic respiratory cohort. Since then, nasal symptoms have been reported to be common in patients with COPD ([165]).

Sino-Nasal Outcomes Test (SNOT)

The SNOT is an instrument which exists in several forms. It originated in the larger (31 item) Rhinosinusitis Outcome measure which has been shown to be a valid tool in the assessment of rhinosinusitis related health status and quality of life ([166]).

Subsequently, studies have confirmed that shorter versions of this questionnaire are suitable for such an assessment and we chose the SNOT-22 rather than other shorter versions ([167;168]) as it includes questions about nasal obstruction or loss of smell / taste. As was shown with our pilot study, these symptoms seem to be very important in the prediction of nasendoscopic abnormalities and we therefore felt it was necessary to include these in this study.

4.2 Methods

This study was run in parallel with patient attendance from two out patients clinics. The first group of patients were recruited from the Problem Asthma Clinic and were invited to attend if they had prior definite documented evidence of asthma and had not taken part in our pilot study. The second group (Control group) of patients were recruited from a separate respiratory clinic (Dr MC Cotton) running in the same clinic area and were invited to attend if they had definite evidence of Chronic Obstructive Pulmonary Disease or Interstitial Lung Disease (ILD), but had no evidence to suggest underlying asthma. All such patients were given patient information leaflets and gave written informed consent for their inclusion in the study which was approved by North Glasgow University Hospitals NHS Local Research and Ethics Department (Project Number 03RE007). Initially we collected baseline data on degree of asthma symptoms, level of medication and spirometry in the patients with asthma. This aspect of the protocol was later abandoned as we felt this extra time required with study patients was compromising our ability to recruit adequate numbers to the study. Study patients were asked to complete the SNOT-22 questionnaire (Appendix 6) and to attend the ENT clinic after their attendance in the Respiratory clinic area. They were asked not to tell the ENT clinic which specific clinic (i.e. PAC or General Respiratory Clinic) they had attended to allow the ENT doctor to be blinded to the patients' respiratory diagnosis. Furthermore ENT were not aware of patients treatment (for respiratory disease or otherwise) prior to their review. Nasendoscopy was performed as previously described by one of two doctors; G W McGarry (Consultant ENT surgeon) or S Robertson (Specialist Registrar, ENT). If any further ENT review was

needed, this was arranged accordingly. Therefore patients did not need to attend hospital on any separate occasions purely for the purposes of the study.

4.3 Results

Patient Recruitment

A significant hurdle we faced in the running if this study was recruitment to the study. We ran this study on every Wednesday afternoon when there was an ENT clinic running as well as both Respiratory clinics, following Research and Development approval of our study on 9th January 2004 until the end of December 2004. The average number of patients attending the PAC is around 14 each week, non-attendees at the clinic are not infrequent (usually 2 - 3 per week) with some patients attending more frequently than others. 43 patients had been included in the pilot study and were therefore not eligible to take part. Over the course of running this study, 79 patients with asthma attending the PAC were asked to take part. 45 refused and 8 were unable to give informed consent (unable to read Patient Information Sheet due to lack of reading glasses was most frequent reason given for this). 26 patients with asthma were enrolled, but 5 of these did not attend for ENT review leaving only 21 with complete questionnaire and nasendoscopic data.

Recruitment of control patients proved even harder with only 7 (4 with COPD, 3 with ILD) recruited for this group.

In the Asthma group (10 male, 16 female), the mean age was 45.3 years (range 14 – 81), and in the control group (5 male, 2 female), the mean age was 71 years (range 61 – 88).

SNOT-22 Scores

Each item in the SNOT-22 scores between 0 and 5 with a higher score indicating greater degree of impairment. The mean score for each domain (nasal symptoms (8 items), physical symptoms other than nasal symptoms (4 items), functional impairment 7 items), emotional impairment (3 items)) is then calculated, along with the Total score being expressed as the mean of all 22 responses.

SNOT-22 scores are summarised in Table 25. With the exception of the physical domain, patients with asthma scored statistically significantly higher than control patients on the SNOT-22. In the Asthma group, patients scored higher in the nasal symptom domain than the physical (symptoms other than nasal) domain (95%CI for difference 0.50, 1.25, p = 0.0002 by Mann-Whitney U-test).

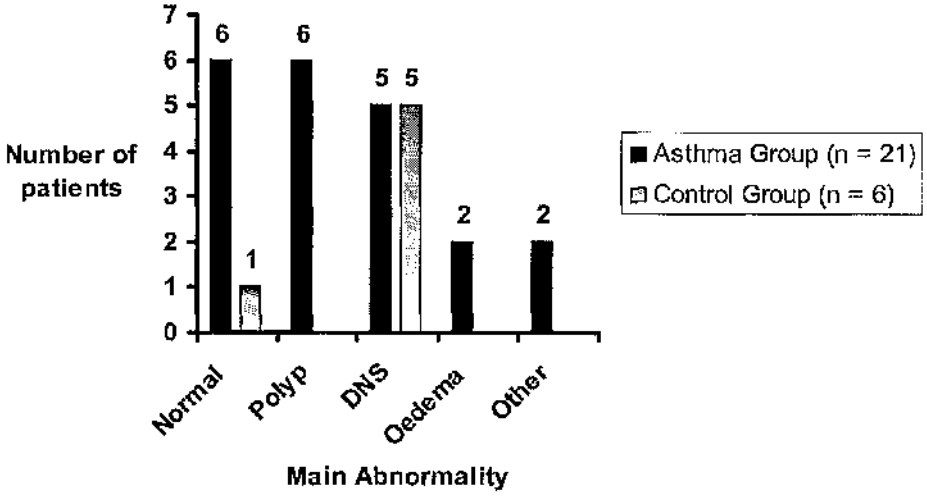
Table 25: SNOT-22 scores. Results are expressed as median (IQR), confidence intervals calculated by Mann-Whitney U-test

	SNOT-22 DOMAIN				
	Total	Nasal	Physical	Functional	Emotional
Asthma group (n = 26)	1.46 (1.14 – 2.15)	1.25 (0.88 – 2.25)	0.25 (0.0 – 0.88)	2.57 (1.14 – 3.32)	1.67 (0.25 – 2.42)
Control Group (n = 7)	0.5 (0.32 – 0.96)	0.5 (0.13 – 1.25)	0.0 (0.0 – 2.0)	0.43 (0.29 – 1.29)	0.0 (0.0 – 0.33)
95% CI for ifference, p -value	0.18, 1.64 p = 0.017	0.00, 1.50 p = 0.041	-0.500,0.50 p = 0.55	0.286,2.714 p = 0.02	0.00, 2.33 p = 0.009

Nasendoscopic Findings

5 of the patients in the Asthma group, and 1 in the control group did not attend for ENT review. The main abnormalities found at nasendoscopy are shown in Figure 11.

Figure 11: Distribution of nasendoscopic abnormalities (DNS = Deviated Nasal Septum).



The "Other" findings were crusting turbinate (1) and septal ulcer (1). On the basis of the ENT findings, 11 of the 15 patients in the Asthma group with abnormalities were recommended further ENT review (2 of whom were already known to ENT), with 5 being commenced on nasal steroid and 1 listed for septoplasty for deviated nasal septum. Only 1 of the patients from the control group required further ENT review for DNS.

The SNOT-22 scores for the Asthma Group according to whether specific nasendoscopic abnormalities were found are shown in Table 26. There were no statistically significant differences observed in either the Total SNOT or nasal

symptom domain scores in groups with nasendoscopic abnormalities compared to those with normal appearances. Furthermore, there were no differences seen when the 11 patients who required specific treatment or follow up of their findings were compared to the remaining patients (95% CI's for difference -1.45, 0.27 (Total SNOT), -0.75, 1.00 (Nasal SNOT).

Table 26: Total SNOT and Nasal SNOT scores according to nasendoscopic abnormalities.

NASENDOSCOPIC FINDING	**MEDIAN SNOT – TOTAL (IQR)**	**95 % CI FOR DIFFERENCE vs. NORMALS**	**MEDIAN SNOT - NASAL SCORE (IQR)**	**95 % CI FOR DIFFERENCE vs. NORMALS**
NORMAL (n = 6)	2.0 (1.31 – 2.62)	------	1.81 (0.78 – 3.15)	-----
POLYPS (n= 6)	1.21 (0.88 – 2.35)	-1.55, 0.82	1.94 (1.34 – 2.71)	-1.25, 1.50
DNS (n = 5)	0.55 (0.18 – 2.04)	-2.23, 0.50	0.63 (0.44 – 1.00)	-2.62, 0.12
OTHER (N = 4)	1.98 (1.46 – 2.53)	-1.86, 0.95	1.31 (1.16 – 2.03)	-2.00, 0.88
ANY ABNORMALITY (n = 14)	1.31 (0.64 – 2.13)	-1.59, 0.50	1.25 (0.88 – 2.00)	-1.75, 0.63

Predictive value of nasal symptoms

The sensitivity, specificity, negative and positive predictive values for the prediction of any nasendoscopic abnormality by each individual symptom from the nasal domain of SNOT-22 (Asthma Group) are shown in Table 27. This analysis was possible using data from the 21 patients in this group who attended for ENT review as per study protocol. Further analysis was performed to look at the combined value of SNOT items to predict abnormalities and this is shown in Table 28. This second analysis involved looking at smaller groups of patients, comparing those who had scored positively in all of the items tested with those scoring "zero" in all items tested.

Table 27: Predictive value of nasal domain SNOT-22 items for finding any nasendoscopic abnormality.

NASAL SYMPTOM	SENSITIVITY (%)	SPECIFICITY (%)	NPV (%)	PPV (%)
Need to blow nose	73.3	33.3	33.3	73.3
Sneezing	73.3	33.3	33.3	73.3
Runny Nose	66.7	33.3	28.6	71.4
Nasal Obstruction	64.3	33.3	28.6	69.2
Loss of Smell / Taste	66.7	66.7	44.4	83.3
Cough	93.8	0	0	75
Post Nasal Discharge	40	33.3	18.2	60
Thick Nasal Discharge	60	50	33.3	75

Table 28: Predictive value of combination of nasal domain SNOT-22 items for finding any nasendoscopic abnormality (Symptom combinations with PPV ≤ 75% are not shown).

NASAL SYMPTOM COMBINATION	SENSITIVITY (%)	SPECIFICITY (%)	NPV (%)	PPV (%)
Need to Blow Nose + sneezing (n = 12)	90	33.3	50	81.80
Need to Blow Nose + Loss of Smell / Taste (n = 10)	88.9	50	50	88.9
Sneezing + Post-nasal discharge (n = 12)	50	75	42.8	80
Sneezing + Loss of Smell / Taste (n = 12)	90	33.3	50	81.8
Runny Nose + Loss of Smell / Taste (n = 11)	77.8	50	33.3	87.5
Nasal Obstruction + Loss of Smell / Taste (n = 12)	70	33.3	25	77.8
Loss of Smell / Taste + Post Nasal Discharge (n = 10)	5.6	50	20	83.3
Loss of Smell / Taste + Thick Nasal Discharge (n = 16)	66.7	60	42.9	80
Runny Nose + Nasal Obstruction + Loss of Smell / Taste (n = 10)	75	50	33.3	85.7
Need to Blow Nose + Loss of Smell / Taste + Post Nasal Discharge (n = 6)	83.3	100	50	100

4.4 Discussion

Our primary aim with this study was to determine the value of routine rhinoscopy in a problem asthma clinic. Clearly with the small numbers we recruited to this study we cannot make a firm conclusion regarding this. Our hope was that by running the study in parallel with patients' attendance at the clinic, this would have aided recruitment by not requiring the patients to attend the hospital on a separate day. Despite this, our recruitment rate was poor. Our initial protocol included a short interview with the patient to determine degree of asthma symptoms, level of therapy and measurement of lung function by spirometry. In our pilot study we did not show any relationship between degree of nasal symptoms and asthma symptoms or lung function. Given this and that in the initial few weeks of running the study it became clear that this was taking too long from the patients' point of view, we felt collecting this data would not be productive, and was not necessary in answering our primary aim. Although dropping this aspect of the protocol did help in the running of the study slightly, it remained difficult to recruit sequential patients to the study and thus we are unable to answer the primary research question. We had designed this study in the hope of reducing any potential selection bias which we feel may have accounted for the high prevalence of nasal symptomatology in the pilot study. It could be argued that this may have been more of a problem with this protocol given that there were proportionally less patients in the Asthma group with normal nasendoscopic findings (6/21, 29%) compared to our pilot study (22/43, 51%).

We feel that this study has however confirmed that nasal symptomatology is common in our clinic population and that structural nasal disease is not uncommon. The SNOT

questionnaire addresses more than simple nasal symptoms and it is clear that the items assessing functional and emotional impairment may be influenced by asthma as well as any co-existing nasal disease. In the small group we studied, no statistically significant difference in nasal symptom domain scores was seen in patients with either specific or general nasendoscopic abnormalities.

Another aim of the study was to compare the spectrum of nasal symptomatology and disease with a non asthmatic respiratory cohort. We chose patients attending a general respiratory clinic running alongside the PAC because again we felt this would aid recruitment of this control group and since it would not require a separate attendance on account of the study. Furthermore, this had the benefit of blinding ENT to the respiratory diagnosis of the patient. It is not clear however if widening our appeal to other general respiratory clinics and therefore asking patients to return on a separate day would have helped recruitment in this group. We chose to target patients with diagnoses of COPD and ILD as we felt these would be the most appropriate control group. Although we found that patients in the control group had statistically significantly lower scores on all but the physical domain of SNOT, we feel the clinical relevance of this is uncertain given the much smaller number in the control group. Recent work in a cohort of patients with COPD ([165]) found that nasal symptoms were common but there is a paucity of other data in this area. This group of 65 patients had a mean total SNOT-20 score of 1.24 in comparison to our group's median total SNOT-22 of 0.5.

There were proportionally more patients in the control group with a nasendoscopic abnormality (5/6, 83%) compared with the Asthma group (15/21, 71%) probably

reflecting selection bias within the control group. Only one in the control group actually required further ENT review for this in comparison with 11 out of 21 patients with asthma requiring further ENT review. No further conclusions can be drawn from our data given the small number of recruited patients.

Lastly we sought to establish if the predictive value seen with nasal symptoms, either lone or in combination in our pilot study would be demonstrated using items from the SNOT-22. No firm conclusions regarding this can be made due to the smaller sample size in this study. The fact that individual symptoms (Table 27) seemed to be better individual predictors of a general abnormality than in our pilot study is not surprising given the much higher prevalence of nasendoscopic abnormalities in this study. However it is intriguing that the best individual predictor was the item asking about loss of smell or taste (PPV 83.3%), with hyposmia found to have PPV of 80% previously. The smaller numbers in groups with symptom combinations again make definite conclusions impossible although it is noteworthy that symptom combinations including the item "loss of smell or taste" were associated with greater likelihood of finding a nasendoscopic abnormality.

In conclusion, for the primary research question to be answered, the larger number and higher proportion of clinic attendees which needed to be studied to determine the true role of routine rhinoscopy in an asthma clinic was not achieved. Our data has failed to answer this question. This data does however add to our local evidence that not everyone with a nasal problem will necessarily volunteer symptoms prompting referral for ENT evaluation. Whether a validated instrument such as the SNOT adds more practical information regarding nasal symptomatology than a simple scoring

system as was used in our pilot study (Chapter 3) is not clear and further work to evaluate these two tools together in the same patients together with nasendoscopy is warranted.

CHAPTER 5

THE ROLE OF PROGRESSIVE EXERCISE TESTING AND HISTAMINE CHALLENGE IN THE DIAGNOSIS OF VOCAL CORD DYSFUNCTION (VCD)

5.1 Introduction

Although we found evidence of a range of functional laryngeal abnormalities in our pilot study (Chapter 3), we did not identify any patients with classical appearances of VCD. Given this and prior studies which have discussed the separate role of methacholine([11;43]) and exercise challenge testing([39]) in VCD diagnosis, we therefore sought to establish if a strategy of performing histamine challenge and progressive exercise testing in patients suspected of having VCD was of diagnostic value. We also evaluated FOT in this protocol to determine if it had the potential to provide a non-invasive alternative to laryngoscopy.

5.2 Methods

Patients attending the PAC were invited take part in the study on the basis of two inclusion criteria:

- VCD was suspected on clinical grounds
- Patients with objective evidence of asthma who had persisting breathless and wheeze despite moderate doses of inhaled corticosteroids and long acting bronchodilators (Step 3 of British Thoracic Society treatment guidelines([1])).

Patients who would have been unable to undertake histamine challenge or progressive exercise testing because of severe asthma or any other reason were excluded from the study. All invited patients were given patient information sheets about the study. Those willing to take part gave written informed consent for their inclusion in the protocol which was approved by North Glasgow University Hospitals NHS Trust Research and Ethics Committee (Project Number 03RE005).

The following measurements were made on the study visits.

Visit 1

Baseline Data

Current asthma treatment and symptoms of asthma morbidity([138]) were recorded using the Royal College of Physicians (RCP) 3 symptom score (days and nights affected by

asthma symptoms, and days of limited activity due to asthma over the previous seven days). 24 hour monitoring of oesophageal pH and manometry, off all acid suppressing therapy, was requested in all patients.

Forced oscillation technique (FOT)

Forced oscillometry was performed as previously described (Chapter 3.2).

Standard Pulmonary Function Testing

Standard spirometry and flow volume loops were measured using a body plethysmograph as described in Chapter 3.2. Occlusion resistance (R_{occ}) was also measured as previously described.

Baseline Laryngoscopy

Laryngoscopy using a flexible fibreoptic laryngoscope was performed by a single observer (Mr K MacKenzie) following topical application of local anaesthesia, co-phenylcaine, to the nose and nasopharynx. The assessment of the larynx was based on structure and function. Laryngeal appearance was noted with the mobility of the vocal cords on phonation, inspiration and expiration. This observer was blinded to all clinical details of the patients.

Histamine Challenge Testing

In accordance with ATS guidelines([169]), patients inhaled increasingly concentrated solutions of histamine (starting at 0.03 mg/ml, doubling on subsequent inhalations up to a maximum concentration of 16 mg/ml) via a nebuliser. Each dose was administered over two minutes. FEV_1, MEF_{50}, MIF_{50} MEF_{50}/MIF_{50} ratio, R_{occ} and FOT were repeated after each inhalation as described above, with FOT being measured over only one 1-minute sampling period. The test was stopped once the patient's FEV_1 dropped by $\geq 20\%$ from baseline. 2.5 mg of nebulised salbutamol was then administered to relieve bronchospasm.

Post-Challenge Laryngoscopy

Immediately after histamine challenge, the patient underwent repeat laryngoscopy as described above but without instillation of further local anaesthetic.

Visit 2

Baseline physiological parameters were recorded as described above. Laryngoscopy was not repeated at this stage.

Progressive Exercise testing

Symptom-limited exercise tests were performed using an electrically braked bicycle ergometer (SECA Cardiotest 100, Salford, England). The patients were initially

monitored for two minutes whilst seated at rest, to obtain baseline values, then asked to exercise for as long as possible until symptomatic limitation. A standard 12-lead electrocardiogram was displayed throughout the procedure. During the first two minutes of exercise, no additional load was applied. Thereafter, the work load was increased by 10-25 watts, depending on the individual patient, every minute until symptomatic limitation. Throughout each test, minute ventilation (V'E), oxygen consumption (V'O2) and carbon dioxide (V'CO2) were measured breath by breath by on-line ventilation and expired gas analysis (MedGraphics CPX-D) and the ventilatory anaerobic threshold on exertion was calculated by the curve fitting method using a plot of V'O2 against V'CO2 ([170]). These results are not reported however as the primary aim of performing the exercise test was to determine if VCD was precipitated.

Post-exercise evaluation

FEV_1, MEF_{50}, MIF_{50} MEF_{50}/MIF_{50} ratio, R_{occ} and FOT were repeated as described above (with a one minute sampling period for FOT was used) before laryngoscopy was performed as described above.

Other Study Visits

Given the variable nature of VCD, we also attempted to identify VCD by encouraging patients to attend during an attack of typical symptoms so that laryngoscopy could be undertaken at that time. All study patients were asked to contact AES (by radiopage via the hospital switchboard number given with the patient information sheet) in the

event of an exacerbation of symptoms so that prompt laryngoscopy could be performed in our hospital's ENT casualty clinic. This facility was available during office hours Monday to Friday.

5.3 Results

9 patients agreed to take part in the study, but one was excluded completely on account of poorly controlled asthma with an FEV_1 of 0.821 (48% predicted) at baseline. Of 8 subjects therefore, there were 2 males and 6 female with a median age of 46 (range 37 – 79 years). All subjects had asthma with clinical features to suggest VCD (upper airway noise with or without intermittent choking). 4 patients were on BTS Step 5 level of treatment (taking a mean daily dose of 11.5mg oral prednisolone). Of the remaining 4 patients two were on BTS Step 4 and two on BTS step 3. Mean (SD) RCP symptom score was 10.4 (9.3), range 0 - 21 (21 being maximum possible score).

Baseline FEV_1 ranged from 1.34 to 3.48 litres, mean (SD) of 2.39 (0.70) litres, equating to 59 to 106 % predicted, mean (SD) 86.8 (16.8). FEV_1/FVC ranged from 50 – 85, mean (SD) 70.4 (11.6).

4/8 patients undertook oesophageal pH monitoring (the other 4 declined to attend for this). 3/4 patients who attended had abnormal oesophageal acid exposure (AOE) (% time pH < 4 (normal being up to 4.5%) ranged from 13.8% to 67.6%, mean 37.3%).

Laryngoscopy findings

No patient was found to have evidence of VCD at baseline. Following histamine (n = 8) and exercise testing (n = 7) VCD was not precipitated in any patient. In terms of

laryngeal structure, at baseline 5 / 8 patients had mild chronic laryngitis (including all 3 patients with documented AOE) with the remaining 3 having normal appearances. All 8 patients had normal laryngeal function. There was no discrepancy between baseline and post challenge findings recorded. No study patient contacted us to arrange laryngoscopy during an acute attack of typical symptoms of breathlessness.

Physiological Evaluation – 1 – Histamine Challenge testing

Baseline and post histamine challenge physiology data are shown in Table 29. No change in the appearance of the inspiratory limb of the flow-volume loops, performed at each stage of the histamine challenge, was seen in any patient. Data on MEF and MIF 50 were lost in a computing system accident. Histamine PC_{20} ranged from 0.02 to 3.12 mg/ml, mean (SD) 1.13 (1.18).

Table 29: Physiology data before and after histamine challenge. Data are expressed in Mean (SD). Confidence Intervals for difference calculated by paired t-tests.

VARIABLE	Baseline	Post Histamine challenge	95% CI for difference compared to baseline
FEV_1 (l)	2.39 (0.70)	1.7 (0.56)	0.45, 0.80, $p < 0.001$
R_{occ} (kPa/l/sec)	0.34 (0.07)	0.55 (0.13)	-0.30, -0.12, $p = 0.001$
R_t (kPa/l/sec)	0.42 (0.15)	0.66 (0.18)	-0.40, -0.08, $p = 0.01$
R_e (kPa/l/sec)	0.46 (0.16)	0.66 (0.18)	-0.38, -0.03, $p = 0.027$
R_i (kPa/l/sec)	0.41 (0.17)	0.69 (0.16)	-0.45, -0.12, $p = 0.005$
MEF_{50} (l/min)	2.40 (1.38)	******	******
MIF_{50} (l/min)	4.14 (1.38)	******	******

There was a statistically significant correlation between FEV_1 and R_i ($r = -0.69$, $p = 0.041$), but none between FEV_1 and R_{occ} (-0.56, $p = 0.116$), R_t ($r = -0.64$, $p = 0.063$) or R_e ($r = -0.58$, $p = 0.101$).

Resistance measured by FOT during each part of the respiratory cycle increased in parallel during histamine challenge (Figures 12, 13 and 14, each line representing 1 patient), with the largest percentage changes being seen in R_i (mean % increase of 108.6% for R_i versus 65% for R_e)

Figure 12: Total Airways Resistance (R_t) during Histamine challenge

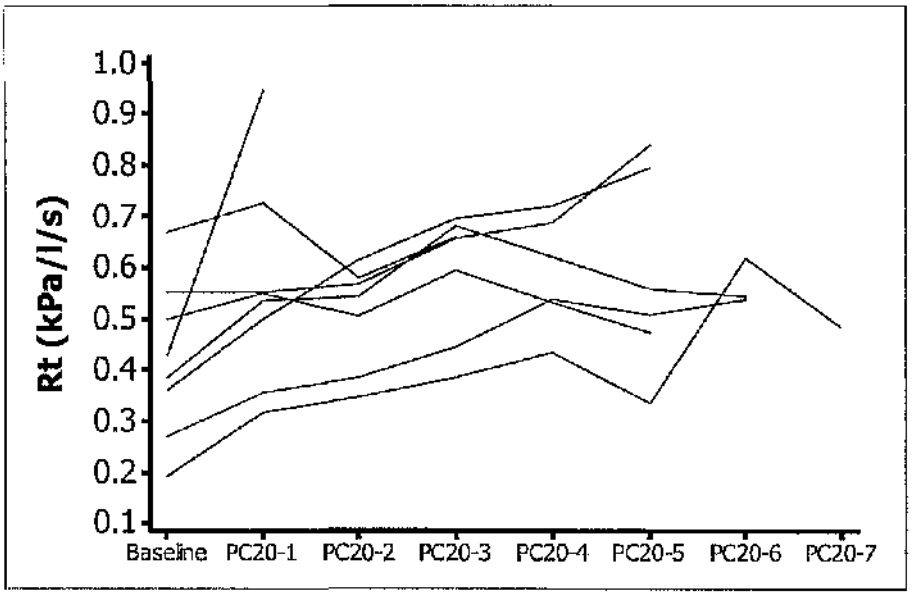


Figure 13: Expiratory Airways Resistance (R_e) during Histamine challenge

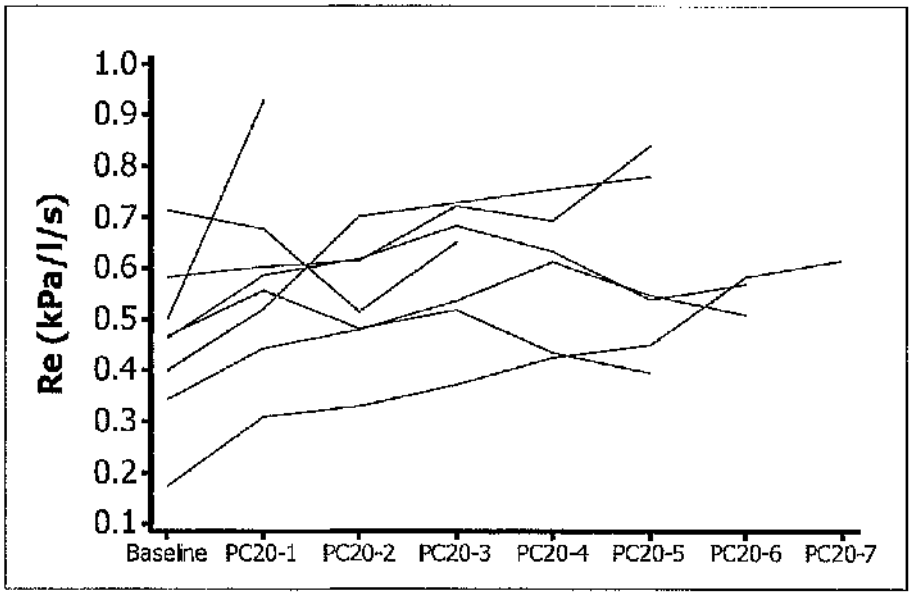
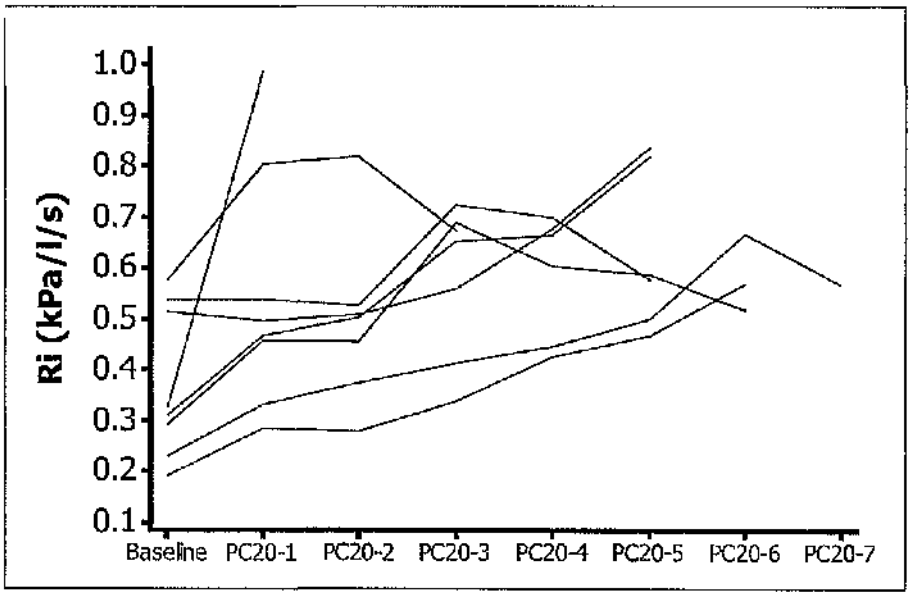


Figure 14: Inspiratory Airways Resistance (R_i) during Histamine challenge



Physiological Evaluation – 2 – Progressive Exercise Testing

There was no significant difference observed between baseline physiology measurements before exercise testing and histamine challenge testing (Paired t-tests). Baseline and post exercise testing physiology data are shown in Table 30 (n = 7). There was no evidence of truncation of the inspiratory limb of the flow-volume loop seen following exercise in any patient. As these results show, there was no evidence of any intra or extrathoracic airway narrowing demonstrated with exercise challenge with the recognised bronchodilatation following exercise being documented by FOT measurements, but not spirometry. VO_2 max ranged from 7.4 to 16.6 mls/kg/min, mean 11.4 (36.9 to 71.2 % predicted, mean 52.0)

Table 30: Physiology data before and after exercise challenge. Data are expressed in Mean (SD). Confidence Intervals calculated by paired t-tests.

VARIABLE	Baseline	Post Exercise Testing	95% CI for difference compared to baseline
FEV_1 (l)	2.52 (0.49)	2.66 (0.75)	-0.43, 0.14, p = 0.26
R_{occ} (kPa/l/sec)	0.38 (0.08)	0.38 (0.10)	-0.06, 0.05, p = 0.86
R_t (kPa/l/sec)	0.51 (0.18)	0.29 (0.10)	0.05, 0.39, p = 0.021
R_e (kPa/l/sec)	0.54 (0.18)	0.37 (0.10)	0.03, 0.32, p = 0.023
R_i (kPa/l/sec)	0.46 (0.18)	0.25 (0.09)	0.04, 0.40, p = 0.025
MEF_{50} (l/min)	2.72 (1.05)	2.65 (1.13)	-0.05, 0.19, p = 0.21
MIF_{50} (l/min)	4.67 (0.18)	5.12 (1.36)	-0.81, 0.11, p = 0.11

5.4 Discussion

The primary aim of our study was to determine the diagnostic value of challenging patients, in whom we suspected VCD as a contributing factor to their symptoms, with histamine and exercise. We did not identify a single case of VCD following either challenge in 7 patients, or following histamine challenge in a further patient. Clearly the small numbers included in our protocol have resulted in an underpowered study, but the negative results, as well as the intensive nature of the protocol, made further recruitment increasingly difficult. It is also unfortunate that none of our patients made use of the facility to have laryngoscopy at the time of an attack of symptoms. This would have been the gold standard to compare the negative results of challenge testing with in our study.

Estimating the appropriate number needed for this study is difficult due to the uncertainty of estimates of the true incidence and prevalence of VCD. Different studies have found prevalence ranging from 2.4% ([10]) to 9.5% ([11]) in samples of 1025 and 105 respectively with the latter study made use of challenge testing. VCD has been found to co-exist with asthma in 22 out of 132 (16.7%) patients, although this was from a tertiary referral centre with a particular interest in VCD ([12]). Given these figures we suspect we have a number of patients with VCD attending our clinic, and therefore likely to be included in our sample. In all patients recruited to the study, the suspicion of VCD arose from upper airway noise evident when seen in clinic with (4 patients) or without choking.

It is well recognised that examining patients in the resting state is frequently non diagnostic and studies which have looked at methacholine and exercise testing have suggested this will improve the diagnostic yield of VCD. Despite Newman's case series describing how methacholine challenge can unmask VCD in some patients([13]), there has only been one prospective evaluation of methacholine challenge in VCD diagnosis([43]). In this study however, the patients in whom the challenge was positive were already known to have VCD, with only 2 of 10 such patients developing VCD post MCT. There were 12 patients with exercise induced asthma and 12 control patients also evaluated in that study none of whom developed VCD following MCT. This may therefore overestimate the usefulness of MCT in VCD diagnosis if the test is applied to a cohort of people with only suspected, rather than proven VCD. Our negative findings, albeit in a small cohort suggest that challenge testing is not a useful diagnostic strategy in this situation.

As well as direct visualisation of the cords we performed detailed physiological assessment during and after histamine and exercise challenge. The literature describing upper-airway hyperresponsiveness (or extra-thoracic airway hyperresponsiveness, EA-HR) resulting in upper airway narrowing as a phenomenon that can occur in isolation or associated with lower airway hyperresponsiveness has been discussed in detail in Chapter 1. This has been defined as a 25% decrease in mid-inspiratory flow during histamine challenge([29;30]). Perkins([43]) found flattening of the inspiratory limb of the flow-volume loop during histamine challenge in the absence of VCD. We did not demonstrate any changes in the inspiratory limb of the FVL during either our histamine or exercise challenges. We are however unable to clarify precisely whether MIF_{50} changed significantly during histamine challenge as

this data was lost. Therefore we cannot quantify extra thoracic airway reactivity in our study group. Following exercise testing however there was no evidence of any extra-thoracic airway narrowing.

Measurements of airways resistance (Forced Oscillation Technique (FOT) and R_{occ}) were used as further assessments of airway physiology because we hypothesised that, as in our pilot study (Chapter 3) if VCD was identified, the possibility of compartmentalising airways resistance between inspiration (R_i) and expiration (R_e) might provide non-invasive diagnostic information. We also planned to compare FOT derived measurements of airways resistance with R_{occ}, if VCD had been identified. As VCD was not identified we cannot make any further comment on this but it is worth noting that R_i increased in parallel with R_t and R_e during histamine challenge. The observed rise in R_i which was proportionately greater than the change in R_e during HCT raises the possibility either that we were observing a subtle form of EA-HR, although no definite changes in the inspiratory FVL were seen, or that lower airways narrowing in inspiration is a contributing factor to these patients' "noisy breathing".

We used histamine rather than methacholine because the former is available locally to us. Both agents are bronchoconstrictors that act directly on bronchial smooth muscle and although different molecules, the rationale for their use is similar. We gave patients nebulised bronchodilator immediately after the histamine challenge test and before performing laryngoscopy as, we felt it would be unethical not to abrogate the lower airway response promptly. There is no reason to believe that any paradoxical movement of the cords, if produced, would be abolished by beta-agonists, particularly when a common theme in case series of VCD is the lack of symptomatic response to

anti-asthma therapy. No such paradoxical movement was seen at laryngoscopy, or suggested, prior to nebulised salbutamol, by any change in flow volume loops. Logistically it was impossible to perform laryngoscopy in the same room as the histamine challenge or exercise test, and the patients had to be transported (by chair after histamine challenge) 200 yards to the ENT department from the Pulmonary Function Lab.

In conclusion, in a small sample of patients with asthma in whom VCD was suspected, a strategy of undertaking histamine and exercise testing was of no diagnostic value in any patient. As far as we are aware our study is the first to prospectively evaluate both investigations in patients suspected of having VCD. For the time being, direct visualisation of the vocal cords at laryngoscopy at the time of symptoms remains the gold standard for VCD diagnosis, despite the logistic difficulty which this often imposes.

CHAPTER 6

AN OBSERVATIONAL INVESTIGATION OF DYSFUNCTIONAL BREATHING AND BREATHING CONTROL THERAPY IN A PROBLEM ASTHMA CLINIC

6.1 Introduction

It is increasingly recognised that dysfunctional breathing (or hyperventilation syndrome) can be an important co-existing factor in patients with asthma([5;91]). As discussed in Chapter 1, potential diagnostic instruments have not been extensively validated in patients with asthma.

This chapter describes attempts to identify dysfunctional breathing in our cohort of patients with moderate to severe asthma and to monitor the effect of breathing control therapy, delivered by a specialist physiotherapist. The measurement of physiological aspects of breathing pattern are discussed separately in Chapter 7.

6.2 Methods

All patients attending the PAC over a 5.5 month period who were being assessed using our standard protocol (Chapter 2), were included in this data set (new and existing patients). Baseline data on current treatment and current symptoms of asthma morbidity were recorded using the RCP score (as previously described) ([138]). Case notes were reviewed to determine the basis for patients' diagnosis of asthma. Patients Nijmegen and Mini-AQLQ responses were reviewed and all patients who had a Nijmegen score $\geq$ 23 were reviewed by the Respiratory Physiotherapy Specialist (PV), assessed for their individual requirement for breathing control therapy (BCT) and referred for progressive exercise testing. There were some occasions where the Physiotherapy Specialist was not present at the out-patient clinic, and in these circumstances, a separate out-patient review was arranged.

Assessment of Breathing Pattern and Breathing Control Therapy (BCT)

Patients with a score $\geq$ 23 on their Nijmegen questionnaire were reviewed by a specialist physiotherapist with experience in breathing control (Mrs Pamela Vaughn, PV). Breathing pattern, including rate, depth and location and end inspiratory and expiratory breath holding times were assessed. Data on inspiratory breath hold time (in seconds) at end of inspiration at initial visit and subsequent follow up visits were collected (measured manually).

The possible relationship between asthma and over-breathing was discussed with the patient, followed by re-education of any specific components of patients' breathing

pattern which were identified as being dysfunctional (tidal volume, flow rate or respiratory rate). The breathing cycle was broken into 3 phases – relaxed tidal inspiration, passive expiration to tidal volume and active effort to reach expiratory reserve with encouragement for a natural pause of a few seconds before the next inspiratory phase. Forced inspiratory or expiratory movements were discouraged as these were felt likely to reinforce or precipitate dysfunctional breathing pattern and therefore symptoms. Nasal breathing, to maximise conditioning of air reaching the lungs was encouraged. Patients were encouraged to practise the new breathing pattern 6-8 times per day for 10 minutes at a time initially. Once learned, the new breathing pattern was advised during sitting, standing, walking and activities which would provoke breathlessness. This approach represents standard physiotherapy practice.

After the initial assessment, patients who required further intensive input were identified. These patients tended to be those who were unable to establish good abdominal breathing pattern or were unable to sustain an expiratory pause for more than 3 consecutive breaths. They were offered weekly outpatient review for 4 weeks followed by physiotherapy review coinciding with subsequent asthma clinic appointments. All patients were therefore followed up at subsequent clinic appointments.

Progressive Exercise Testing

Symptom-limited exercise tests were performed using an electrically braked bicycle ergometer (SECA Cardiotest 100, Salford, England). The patients were initially monitored for two minutes whilst seated at rest, to obtain baseline values, then asked to exercise for as long as possible until symptomatic limitation. During the first two minutes of exercise, no additional load was applied. Thereafter, the work load was increased by 10-25 watts, depending on the individual patient, every minute until symptomatic limitation. Throughout each test, minute ventilation (V'E), oxygen consumption ($V'O_2$) and carbon dioxide ($V'CO_2$) were measured breath by breath by on-line ventilation and expired gas analysis (MedGraphics CPX-D). An ECG recording was made throughout the test. The ventilatory anaerobic threshold on exertion was calculated by the curve fitting method using a plot of $V'O_2$ against $V'CO_2$.([170]) The dead space to tidal volume ratio (V_D/V_T) and alveolar-arterial oxygen gradient ($A\text{-}aO_2$) was computed from mixed expired gas concentrations and blood gas analysis (Chiron Diagnostics Rapid Lab 855) using an arterialised ear lobe capillary sample. The blood samples were obtained at rest and at peak exercise with the gas exchange values calculated using standard equations.([171]) Trans-cutaneous pCO_2 was also measured throughout the procedure.

Follow Up

Nijmegen and Mini-AQLQ responses, in addition to breathing pattern parameters were collected on review of all patients attending the clinic at approximately 6 months follow up in the clinic where available. Some patients had been discharged by this

time point, and others defaulted. We were looking for a long term effect from this intervention and judged this to be an appropriate time to collect outcome data.

Statistical Analysis

Spearman rank correlations were used to examine relationships between parameters when one or both were non-normally distributed. Pearson correlations were used to examine relationship between normally distributed parameters. Baseline questionnaire data in groups divided according to Nijmegen scores were compared using Mann-Whitney U tests. Follow up questionnaire data was compared to baseline with Mann-Whitney U tests. All data was analysed using Minitab (Version 14) statistical software.

6.3 Results

Baseline Data

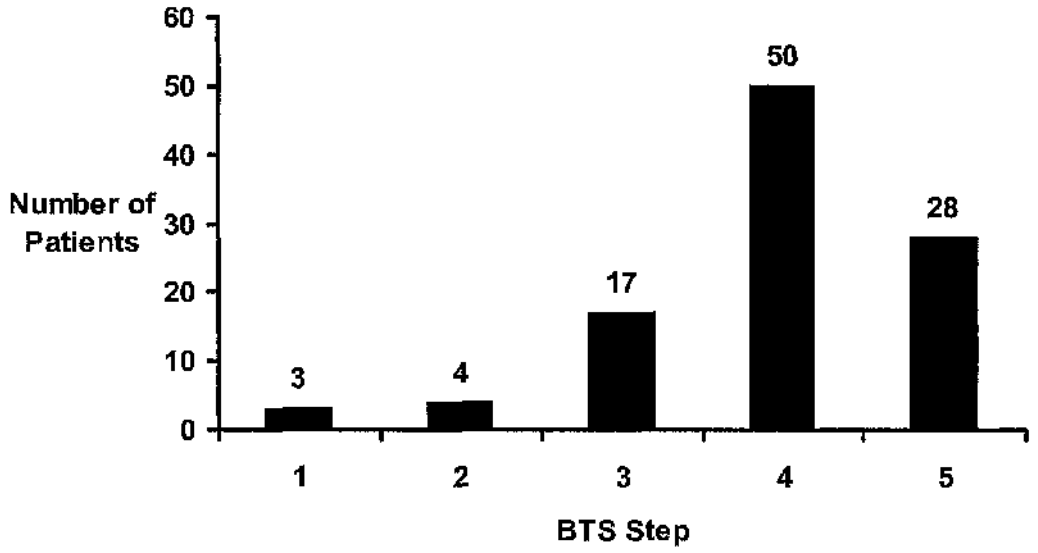
111 patients were assessed over a 5.5 month period. 9 had previously seen the Physiotherapy Specialist for BCT and so were excluded from analysis. There were 72 females (71%) and 30 males. The average age (range) was 48 (13.5 – 83) years. Case notes were reviewed to determine best objective evidence of asthma available for each patient (Table 31).

Table 31: Basis of Asthma Diagnosis in study population (n = 102)

BEST OBJECTIVE EVIDENCE AVAILABLE	NUMBER OF PATIENTS
Bronchodilator reversibility >12%	52
Bronchial Hyper-reactivity (BHR)	8
PEFR variability	19
Steroid trial	1
Good clinical history only	11
No objective evidence	11

The range of asthma treatment of the study group at baseline is shown in Figure 15.

Figure 15: Level of treatment of study group.



28 patients were taking long term oral corticosteroids (range 5mg – 30mg per day, median 10mg).

Patients reported the full range of RCP asthma morbidity scores (0 – 21, with a higher score indicating more severe symptoms) with a median score of 14 (IQR 3.8 - 21). There were 8 patients who did not have complete RCP symptom score data at baseline.

Baseline Nijmegen and mini-AQLQ scores for the whole study population are shown in Table 2. The mean (range) overall Mini-AQLQ score for the cohort was 3.30 (1.07 – 6.93) and mean (range) Nijmegen score for the cohort was 26.4 (1 – 61). Maximum Nijmegen score is 64, with a score ≥ 23 defining hyperventilation in non asthma patients. All parameters were normally distributed. The study group was separated

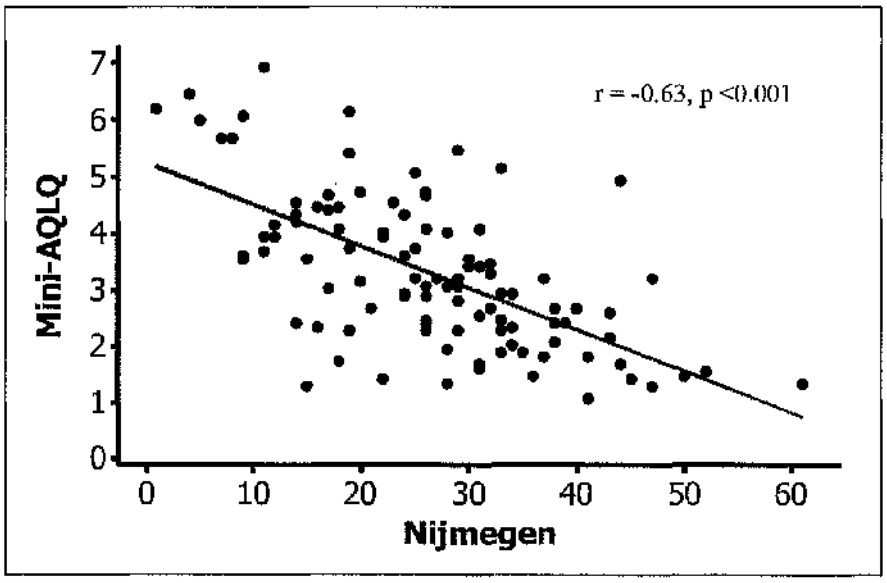
into two groups, on the basis of a Nijmegen score < 23 (described as having no evidence of dysfunctional breathing syndrome (No DB)) or ≥ 23 (those with evidence of dysfunctional breathing (DB)). Only the latter group received breathing control therapy and were referred for progressive exercise tests (PET) to confirm the presence of inappropriate hyperventilation. It was felt to be out-with the scope of our standard clinic protocol to perform PET in the Non-DB group. Due to pressure on our lung function laboratory, those patients who did not attend PET were not offered a further appointment unless they contacted the department to re-schedule their PET. There were significant differences between groups for total Mini-AQLQ scores (Table 32) and all Mini-AQLQ domains.

Table 32: Baseline Questionnaire Data: Nijmegen and Mini-AQLQ scores (DB = Dysfunctional Breathing).

VARIABLE		RANGE	MEAN (SD)	95% CI for difference between No-DB and DB, p-value)
Mini-AQLQ (Overall)	All Patients (n = 102)	1.07 – 6.93	3.30 (1.36)	0.87, 1.87 $p < 0.0001$
	No DB (n = 37)	1.27 – 6.93	4.12 (1.43)	
	DB (n = 65)	1.07 – 5.47	2.83 (1.07)	
Mini-AQLQ (Symptom Domain)	All Patients (n = 102)	1.00 – 6.80	3.11 (1.40)	0.8, 2.00, $p < 0.0001$
	No DB (n = 37)	1.00 – 6.80	4.01 (1.53)	
	DB (n = 65)	1.00 – 5.40	2.60 (1.03)	
Mini-AQLQ (Environment Domain)	All Patients (n = 102)	1.00 – 7.00	3.43 (1.64)	0.33, 2.00, $p = 0.004$
	No DB (n = 37)	1.33 - 7.00	4.12 (1.82)	
	DB (n = 65)	1.00 – 6.67	3.03 (1.40)	
Mini-AQLQ (Emotional Domain)	All Patients (n = 102)	1.00 - 7.00	3.27 (1.56)	0.33, 1.67, $p = 0.01$
	No DB (n = 37)	1.00 - 7.00	3.84 (1.66)	
	DB (n = 65)	1.00 – 6.00	2.94 (1.42)	
Mini-AQLQ (Activities Domain)	All Patients (n = 102)	1.00 - 7.00	3.44 (1.63)	1.00,2.25, $p < 0.0001$
	No DB (n = 37)	1.25 - 7.00	4.45 (1.64)	
	DB (n = 65)	1.00 – 6.75	2.87 (1.33)	
Nijmegen	All Patients (n = 102)	1 – 61	26.4 (11.5)	******
	No DB (n = 37)	1 – 22	14.5 (5.4)	******
	DB (n = 65)	23 – 61	33.2 (7.9)	******

The overall Mini-AQLQ score and each domain (symptoms, environment, emotional and activities, data not shown as relationships very similar) correlated well with the Nijmegen scores, as shown in Figure 16.

Figure 16: Relationship between Nijmegen and Mini-AQLQ (overall score)



Nijmegen scores varied widely across the range of RCP symptom scores (Figure 17), although a statistically significant correlation was observed (Spearman Rank r = 0.43, $p < 0.001$). There was a better relationship between RCP symptom score and Mini-AQLQ (Spearman Rank r = -0.69, $p < 0.001$, Figure 18).

Figure 17: Relationship between level of asthma symptoms and Nijmegen score

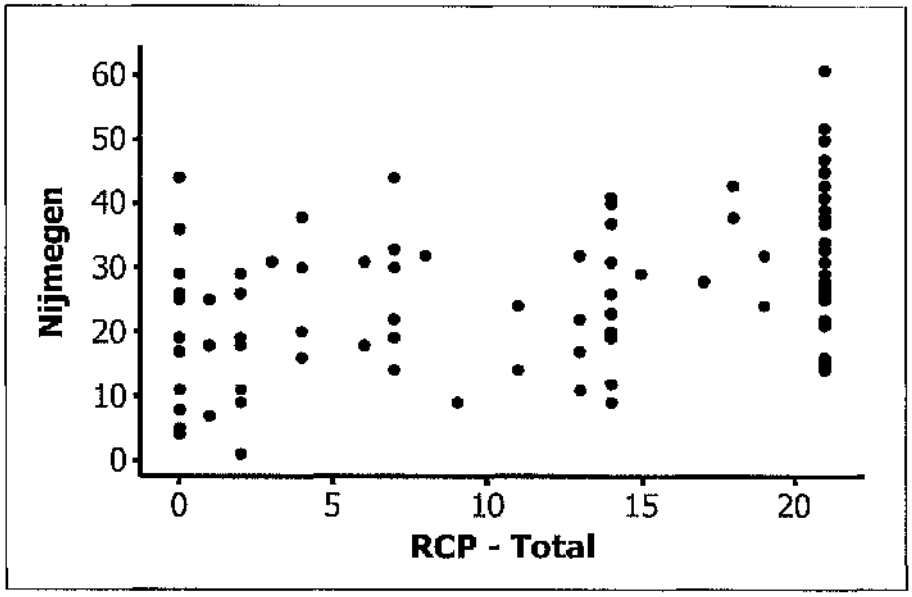
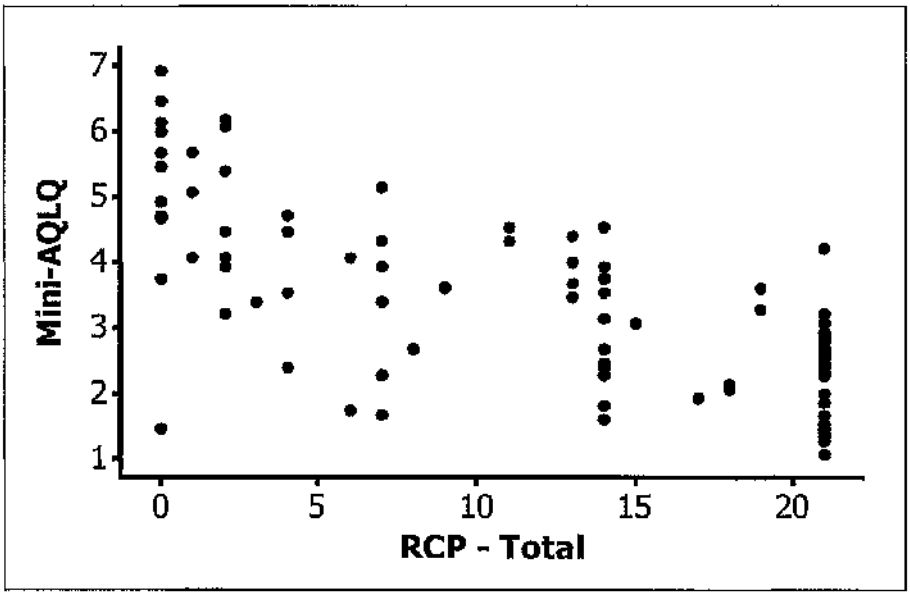


Figure 18: Relationship between level of asthma symptoms and Mini-AQLQ



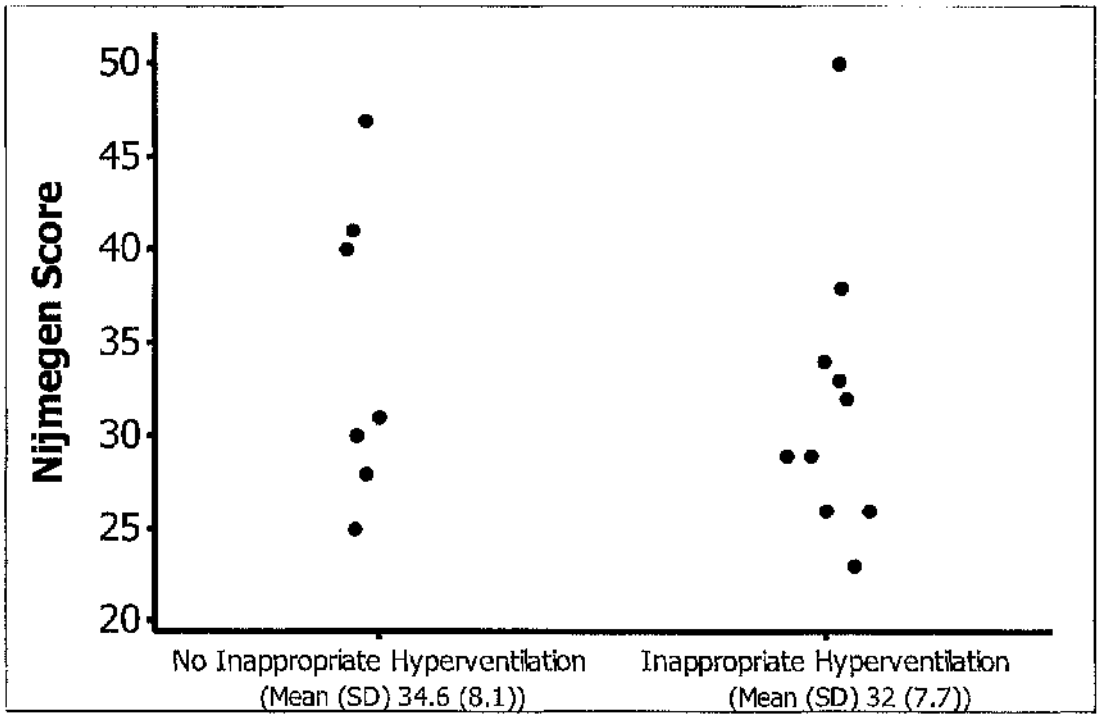
Progressive Exercise Testing (PET)

Of the 65 patients with positive Nijmegen scores, 21 (33%) had a co-morbidity which made progressive exercise testing impossible. Of those able to undertake PET (42), 24 (57%) attended for this investigation. 7 patients were unable to complete this investigation due to wheeze (4) or locomotor problems (3). 17 PETs were therefore undertaken.

Mean (SD) VO_2 Max attained was 11.5 (4.6) mls/kg/min, representing mean (SD) 44.4 (14.9) % predicted values. All patients had a $VE/VCO_2 > 30$ (range 34-73, mean (SD) 47.6 (9.1) indicating an elevated ventilatory response. In order to assess whether this was inappropriate, we looked at changes in trans-cutaneous p_aCO_2 during the test. A fall of trans-cutaneous p_aCO_2 to < 35 mmHg or by > 10% from baseline was defined as indicating inappropriate hyperventilation and 10/17 patients (59%) displayed this.

There was no difference in Nijmegen scores of those patients with and without evidence of inappropriate hyperventilation on PET. This data is shown with the scatter of Nijmegen scores, in Figure 19.

Figure 19: Nijmegen scores for patients completing PET (n = 17), subdivided by the finding of no inappropriate hyperventilation and inappropriate hyperventilation.



Physiotherapy assessment and attendance for Breathing Control Therapy (BCT)

All 65 patients who scored positively on the Nijmegen questionnaire were assessed by a specialist respiratory physiotherapist as outlined above, and offered breathing control therapy. 9 patients did not attend BCT at any given time with the remaining 56 patients being reviewed on a median (range) of 3 (1-15) occasions. 8 patients were seen once only.

Follow up data

Follow up questionnaire data was available for mini-AQLQ in 46 patients (17 No DB, 29 DB) and Nijmegen scores in 44 (15 No DB, 29 DB), at an average (SD) 186 (23) days. 1 patient with a positive baseline Nijmegen score completed follow up questionnaires but had not attended BCT and so was excluded from analysis. The most frequent reasons for missing data were prior discharge from the clinic or failure to attend around the desired follow up of 6 months after baseline data collection; time restraints on the patients' part when attending the clinic was a further contributing cause.

The results are grouped according to the baseline Nijmegen score (Table 33), with only those having baseline and follow up scores included. 95% Confidence intervals were calculated (Mann-Whitney U tests) for the difference between baseline and follow up scores (also shown in Table 33), and demonstrate no significant difference in either overall Mini-AQLQ (or any separate domain, data not shown) or Nijmegen scores in either No DB or DB groups.

Table 33: Follow up Mini-AQLQ and Nijmegen scores (DB = Dysfunctional Breathing).

VARIABLE		RANGE	MEAN (SD)	95% C.I. FOR DIFFERENCE FROM BASELINE
Nijmegen	DB (n = 29)	14 – 49	29.7 (9.3)	-1, 9
	No DB (n = 15)	6 – 32	18.5 (7.3)	-9, 2
Mini-AQLQ (Overall)	DB (n = 29)	1.20 – 5.33	3.04 (1.07)	-0.87, 0.33
	No DB (n = 17)	1.27 – 6.27	4.22 (1.47)	-1.33, 1.00

Although there were no significant differences between baseline and follow up Nijmegen scores in either group, there were 8/29, 28% of patients in the DB group whose Nijmegen scores fell into the normal range following BCT. There was no significant difference in level of asthma symptoms following BCT compared with baseline in this subgroup of patients (RCP score, 95 % CI for difference -9, 12 (Mann-Whitney U-test).

There were 9 / 29 (31%) of the patients who received BCT and completed follow up data who had a clinically significant improvements in Mini-AQLQ and this was observed in 6 / 17 (35%) of those without evidence of DB.

In the 17 patients who completed PET, follow up Nijmegen and Mini-AQLQ were available in 5 of the 10 patients shown to have inappropriate hyperventilation on PET

and 3 of the 7 not shown to have inappropriate hyperventilation. At follow up there was no difference seen in either parameter (Figures 20 and 21).

Figures 20 and 21: Available Baseline and follow up Questionnaire data for patients who had PET (n = 8, 3 no inappropriate hyperventilation (labelled No PET HVS), 5 inappropriate hyperventilation (labelled PET HVS), Nij = Nijmegen). Mann-Whitney U-tests show no significant differences in any group.

Figure 20

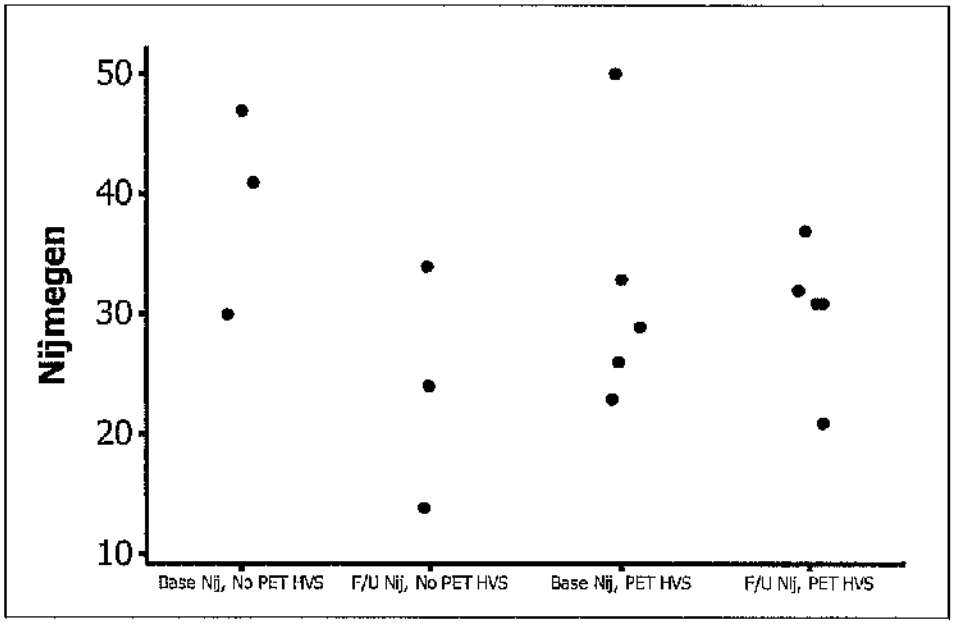
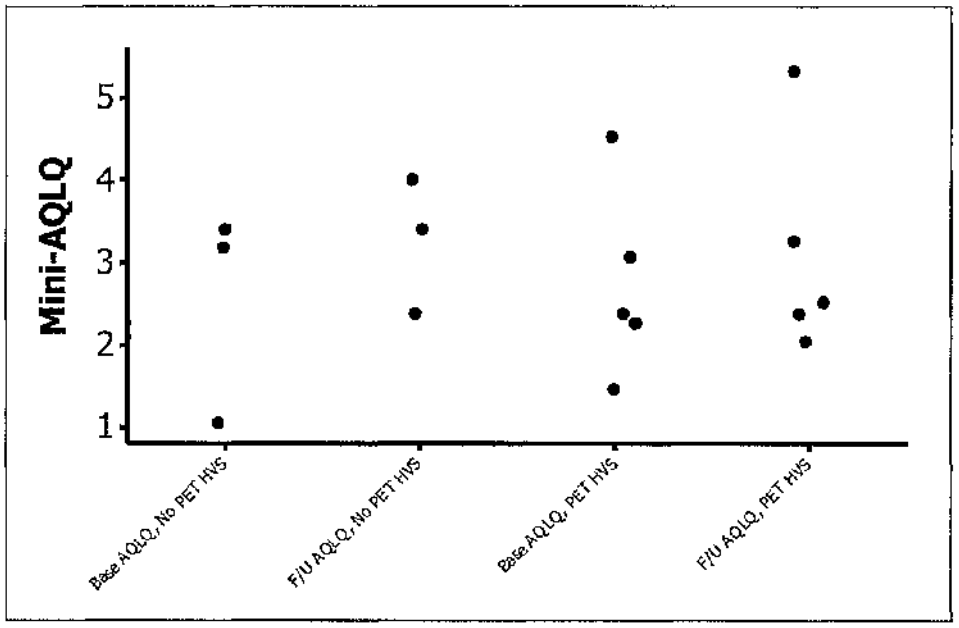


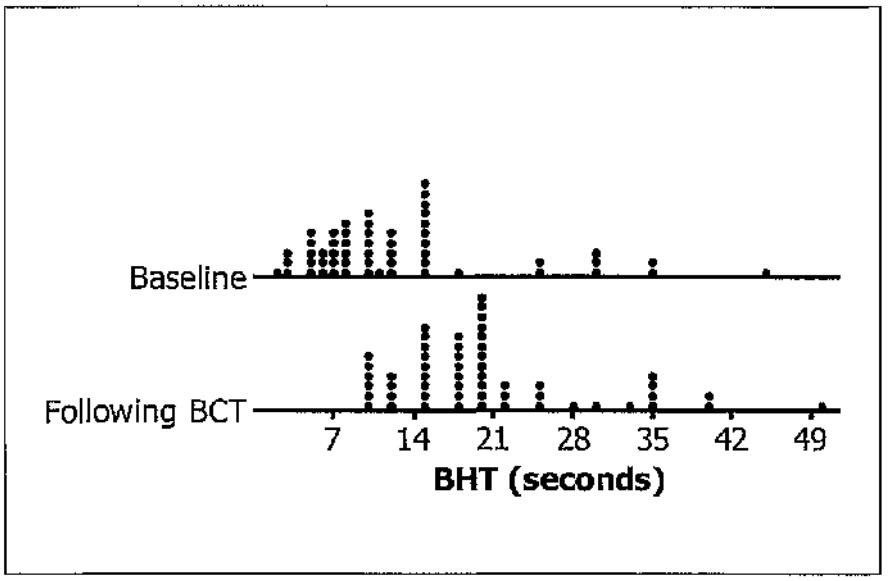
Figure 21



Global physiotherapy assessment of efficacy of BCT

Inspiratory breath hold times (BHT) were improved in all patients following BCT from median (IQR) of 10 (7 – 15) seconds at baseline to 20 (15 – 22) seconds at follow up (95% CI -10, -5, $p < 0.001$ by Mann-Whitney U-test, Figure 22, $n = 55$).

Figure 22: Inspiratory breath hold times (BHT, seconds) at baseline and at follow up



Following BCT, global assessment of compliance and benefit was made by PV. This was a subjective assessment, but was done with the knowledge of all objective measurements, including breath hold times and Nijmegen scores beforehand and afterwards. 7 / 29 patients who attended and had follow-up data were felt to have complied well and benefited from BCT. These patients had a mean (SD) fall in Nijmegen score of 5.1 (7.5).

There were 8 patients whose Nijmegen score fell to less than 23. Only 3 were included in the subgroup identified above, as having complied well and benefited from BCT suggesting regression to the mean. Median BHT improved from 15 to 21 seconds in this subgroup (95% CI for difference -13.01, 0.0, p =0.049). All but 1 also had an improvement in Mini-AQLQ (range -0.27, 2.93, mean (SD) 0.96 (0.99)), and 5 had > 0.5 improvement in total Mini-AQLQ score with improvements in all 4 AQLQ

domains and no significant difference in level of asthma symptoms (median RCP score of 8 at baseline and follow up).

6.4 Discussion

In collating and analysing these data from as complete as possible a cohort of patients attending a problem asthma clinic, we have described the range of symptoms, quality of life and Nijmegen scores in a group, most of whom (78%) have objective evidence of asthma and most (76%) were on BTS step 4 or 5 asthma therapy. This analysis shows the impact on quality of life and the distribution of Nijmegen scores, which in a normal population would suggest dysfunctional breathing. Analysis of the inter-relationships between symptoms and quality of life measures shows that Nijmegen responses and RCP symptom scores relate closely to Mini-AQLQ, although Nijmegen scores correlated less well with RCP symptom scores, raising the possibility that Nijmegen questions are assessing a different aspect of patients' experience.

We attempted to identify patients with dysfunctional breathing in order to provide breathing control therapy, with a dedicated respiratory physiotherapist usually present at the clinic and able to work with patients in a time-efficient manner (for both parties). We defined dysfunctional breathing by Nijmegen score, but sought to confirm the presence of inappropriate ventilation by progressive exercise testing. Some of the Nijmegen questions relate to typical asthma symptoms with the possibility that dysfunctional breathing would thereby be over-estimated in this group.

Evidence suggesting Nijmegen scores have a role on the diagnosis of dysfunctional breathing has been discussed but in Thomas' study ([102]) objective evidence of asthma was not detailed, with patients selected on the basis of a clinical diagnosis and receiving a prescription for bronchodilator therapy. In the subsequent randomised

controlled trial of BCT however, most patients (28/33) had objective evidence of asthma.([104])

The lack of a gold standard makes objective study of this phenomenon difficult and highlights the importance of global assessment by a specialist therapist as a further method of assessment.

Using the standard definition, based on Nijmegen score, to identify DB, our baseline data shows a high prevalence of this (65/102, 64%) in this cohort of patients with asthma. This is a higher frequency than in cohorts quoted above, which may reflect a higher prevalence of DB in patients with more severe disease (77 of 101 patients were on BTS Step 4 treatment or above) but may also be due to the Nijmegen questionnaire overestimating the prevalence of DB, by wrongly attributing symptoms of poor asthma control to dysfunctional breathing. In keeping with this interpretation, we found a significant relationship between level of asthma symptoms, using a numerical version of the RCP symptom score, with symptoms rated over the previous week, and Nijmegen scores ($r = 0.43$, $p < 0.001$). We found a stronger relationship between Nijmegen and Mini-AQLQ than between asthma symptom score and mini-AQLQ, raising the possibility that Nijmegen is measuring the perceived impact of symptoms, and thus, some aspect of asthma related quality of life.

We sought to confirm the presence of inappropriate hyperventilation by Progressive Exercise Testing. In the identification of this we considered a fall of trans-cutaneous pCO_2 to < 35mmHg or by > 10% from baseline in patients displaying an elevated ventilatory response to show inappropriate increased ventilation. There has been no

prior validation of this definition, but we felt this was reasonable. This was seen in 10 out of the 17 patients (59%) in whom we had PET data. Given that neither Nijmegen nor PET can be regarded as a gold standard, is not clear whether the lack of agreement between Nijmegen-identified DB and PET-identified inappropriate hyperventilation is explained by poor specificity of the Nijmegen or poor sensitivity of PET. From the scatter plot of Nijmegen scores in those with and without inappropriate hyperventilation on PET (Figure 19) it is clear that increasing the threshold Nijmegen score, in patients with asthma would not impact on this, if PET is considered the gold standard. Clearly it would have been interesting to look at PET findings in those with negative Nijmegen scores, but this would have been out-with the scope of our normal clinic protocol. Finally, it is important to note that the low attendance rate for PET limits the generalisability of these findings.

The second part of this observational study involved assessing the effect of breathing control therapy on Nijmegen and mini-AQLQ scores. We observed no significant differences in Nijmegen or mini-AQLQ scores (either total or separate domain scores) after BCT in either group, with Nijmegen scores in particular showing evidence of regression to the mean.

There was a subgroup of 8 patients with a clinically coherent pattern of changes, whose Nijmegen scores fell into the normal range. In this subgroup, breathing control may have had a positive impact, since parallel changes in pharmacotherapy are unlikely to have had this effect. It is however also possible that parallel and unrelated change in these patients' psychological state had an impact on both breath hold times and quality of life.

The possibility that Nijmegen is measuring aspects of quality of life is suggested by the 7 patients who were felt to have complied well and benefited from BCT on subjective assessment, without any improvement in Nijmegen scores. Another pointer to the lack of specificity of the Nijmegen questionnaire in this population is the lack of any relationship between Nijmegen score and documented inappropriate hyperventilation on PET (Figure 19). Perhaps we are, as busy clinicians in the early 21st century, identifying abnormal breathing pattern as a physical symptom, rather than as part of a syndrome of psychological distress.

Thomas's data discussed already ([104]) can be interpreted as showing a non specific effect of breathing retraining which had a greater initial impact on asthma related quality of life than Nijmegen scores. We did not seen similar trends in either Mini-AQLQ or Nijmegen scores.

We used the Mini-AQLQ in our study because we felt its brevity was more suited to the clinic setting than the full AQLQ ([126]). We found similar proportions of patients with and without DB who had significantly improved ($\geq$ 0.5) Mini-AQLQ scores (9/29, 31% and 6/17, 35%) Our study design makes it difficult to draw firm conclusions from this but certainly it does not suggest a definite treatment effect.

Inspiratory breath hold times (BHT) were measured by our physiotherapist delivering BCT. There are no published data supporting this as a diagnostic method for DB, and our routine use in the assessment of patients with suspected DB and subsequent monitoring is based on anecdote. One small study found lower BHT in a group of patients with symptoms suggestive of hyperventilation compared to controls ([172]). The

fact that all patients had an improvement in their BHT suggests a lack of specificity of BHT as a good outcome measure in the treatment of DB, but clearly the lack of BHT data in the group who did not receive BHT and lack of any other gold-standard outcome measure for comparison makes this purely speculative.

We had a huge loss to follow-up in both DB and Non-DB groups which was very disappointing. The potential confounding effect of this has to be acknowledged. The reasons for non-attendance is not clear, and it may be that the non-attendees had improved but one can only be speculative here. We did not feel it was appropriate to send out repeat questionnaires to those who did not attend as this would have been outwith the scope of our clinic protocol.

Clearly there are different methods of delivering breathing retraining. We judged the intervention we used to be applicable to normal clinic practice and likely to be sufficiently intensive to produce benefits, but this has not been confirmed, by these observational results. Patient compliance may have limited our ability to influence deeply ingrained patterns of behaviour. Most Buteyko courses are more intensive, but of shorter duration that the intervention we used, which was undertaken by a specialist respiratory physiotherapist in parallel with clinic attendance in order to maximise the chance of patients attending and completing this. Our data show no evidence that this strategy was successful and suggest that any formal RCT assessment of breathing control in this setting would need to be highly specific in terms of identification of patients likely to benefit, more intensive in nature and in the measurement of outcomes, since it is illogical to expect long term benefit if no short term advantage is identifiable. In such an RCT, it would also be important to compare a psychological

intervention with breathing retraining, as well as having a control group, in order to test the specificity of any observed effect.

In summary this observational study has increased our understanding of two aspects of patients with moderate to severe asthma, as judged by having persistent symptoms despite high levels of treatment. Firstly, we have a better understanding of the range of Nijmegen, RCP symptom and mini AQLQ scores and the strong relationships which exist between these scores suggesting that they are measuring related phenomena. We have shown only a loose relationship between Nijmegen score and inappropriate hyperventilation measured by PET. Our second observation is that a moderate intensity breathing retraining programme, undertaken in parallel with patients' normal clinic attendance had no benefit overall, with the pattern of benefit seen in subgroups raising the possibility that this intervention may not have had a specific physiotherapeutic effect. This will be useful in planning an RCT to address this issue, although we have also identified the problem caused by the lack of a gold standard method of identifying dysfunctional breathing in patients with asthma, which is likely to hamper its further study, until this issue is definitively addressed.

CHAPTER 7

BREATHING PATTERN IN PATIENTS WITH DYSFUNCTIONAL BREATHING AND THE EFFECT OF BREATHING CONTROL THERAPY

7.1 Introduction

Very little is known about physiological characteristics of breathing pattern in patients with asthma felt to have dysfunctional breathing. In parallel with identification of dysfunctional breathing (DB) in our cohort of patients with moderate to severe asthma, we aimed to characterise their breathing pattern. We hypothesised that patients with DB would have differences in physiological parameters of breathing pattern compared to "normals" and monitored this to determine if breathing control therapy had any effect on physiological parameters of breathing pattern.

This study represents an additional arm of the study described in Chapter 6.

7.2 Methods

Patients were entered into this analysis as described in Chapter 6. We were using the Forced Oscillation Technique (FOT) at the time in the PAC as a routine non-invasive method in the assessment of airway calibre, which was often helpful in guiding asthma management. It was then possible to extrapolate various physiological parameters of breathing pattern at a later date.

Patients performed FOT on the same day as completing Nijmegen and Mini-AQLQ questionnaires as described in Chapter 6. FOT was performed as described in Chapter 3.

Following acquisition of the raw data (Acq*Knowledge*® (Version 3.7.0) Software), processing by Matlab (Version 6.1) allowed data from each recorded breath to be imported into a Microsoft Excel spreadsheet. Data on inspiratory time (T_i), expiratory time (T_e), expiratory / inspiratory time ratio (T_e/T_i), Tidal volume (V_t) for each breath was available from each recording. Subsequently, minute ventilation (V_{min}) and respiratory frequency (Rf) could be calculated. The average value of airway resistance over all the breaths (R_t), was obtained. This was used as a marker of airway calibre, rather than forced manoeuvres such as FEV_1. The mean values for each breathing pattern parameter were calculated from both sampling periods. Again, in line with current guidelines([47]), data from the first 30 seconds of each recording was discarded, to allow the patient time to get used to the mouthpiece.

Breath to breath variability was measured by determining the standard deviations of T_i, T_e, T_e/T_i and V_t for each patient during the sampling period. Since V_{min} and Rf were calculated using data from the whole sampling period, these standard deviations for these parameters were not available.

Follow Up

Data on physiological parameters of breathing pattern collected on review of all patients at approximately 6 months follow up in the clinic where available. Since we sought a long term effect from this intervention, we judged this to be an appropriate time to collect outcome data.

Statistical Analysis

Baseline breathing pattern data was grouped according to Nijmegen score positivity and compared using 2 sample t-tests. Paired t-tests were used to compare follow up breathing pattern data to baseline. All data was analysed using Minitab (Version 14) statistical software.

7.3 Results

Baseline Physiological Characteristics of Breathing Pattern

FOT was performed in 78 / 102 patients on the same day as completing the questionnaires (76% of whole study group). 31 had Nijmegen scores ≤ 22 (Non-DB) and 47 scored ≥ 23 (DB). Baseline data is demonstrated in Table 34, with the study group separated according to their Nijmegen scores. The only statistically significant difference observed was in the measurement of Tidal Volume (V_t) (95% CI 0.01, 0.39, $p = 0.044$).

Table 34: Baseline Physiological Characteristics of Breathing Pattern (78 patients)

VARIABLE	Non-DB (n = 31)		DB (n = 47)		95% C.I. FOR DIFFERENCE
	RANGE	MEAN (SD)	RANGE	MEAN (SD)	
Inspiratory Time (T_i, seconds)	0.57 – 4.39	1.57 (0.70)	0.55 – 3.40	1.40 (0.53)	-0.10, 0.45
Expiratory Time (T_e, seconds)	0.75 – 7.15	2.29 (1.17)	0.82 – 4.85	2.03 (0.84)	-0.19, 0.72
T_e / T_i	0.67 – 1.89	1.44 (0.25)	0.88 – 2.44	1.48 (0.35)	-0.18, 0.11
Tidal Volume (V_t, litres)	0.25 – 2.65	1.05 (0.53)	0.38 – 1.74	0.85 (0.32)	0.01, 0.39
Minute Ventilation (V_{min}, Litres/minute)	5.78 – 31.94	16.60 (6.23)	6.80 – 26.71	15.38 (4.85)	-1.29, 3.72
Respiratory Frequency (R_f, breaths/minute)	5.2 – 38.0	17.4 (6.31)	7.4 – 38.8	19.2 (6.4)	-4.79, 1.10
Respiratory resistance (R_i, kPa/l/s)	0.20 – 1.06	0.52 (0.24)	0.22 – 0.95	0.47 (0.16)	-0.04, 0.14

Breath to Breath Variability

As described above, we were able to assess breath to breath variability for Ti, Te, Te/Ti and Vt by calculating the Standard Deviation over the two FOT sampling periods. The results are shown in Table 35. Analysis by 2 sample t-tests confirmed there was no difference between the Non-DB and the DB group in any parameter.

Table 35: Breath to Breath Variability

VARIABLE		RANGE	MEAN (SD)	MEDIAN (IQR)	95% CI FOR DIFFERENCE
SD - T_i	Non-DB (n = 31)	0.037 - 1.08	0.19 (0.19)	0.14 (0.09 - 0.25)	-0.06, 0.09
	DB (n = 47)	0.043 - 0.59	0.18 (0.12)	0.14 (0.10 - 0.21)	
SD - T_e	Non-DB (n = 31)	0.071 - 0.96	0.29 (0.20)	0.24 (0.16 - 0.34)	-0.10, 0.11
	DB (n = 47)	0.08 - 1.49	0.28 (0.24)	0.21 (0.14 - 0.34)	
SD - T_e/T_t	Non-DB (n = 31)	0.05 - 0.50	0.19 (0.10)	0.17 (0.12 - 0.25)	-0.10, 0.02
	DB (n = 47)	0.05 - 0.66	0.23 (0.15)	0.20 (0.14 - 0.29)	
SD - V_t	Non-DB (n = 31)	0.03 - 0.37	0.14 (0.08)	0.10 (0.08 - 0.20)	-0.01, 0.05
	DB (n = 47)	0.05 - 0.32	0.12 (0.06)	0.10 (0.07 - 0.15)	

Follow up Data

We were able to reassess breathing pattern in 31 patients (16 Non-DB, 15 DB). There were a number of reasons for the drop-out, the most frequent being non-attendance at clinic around the desired follow up point of 6 months after baseline data collection. Another less common reason was time restraint on the patients' part when attending the clinic.

Follow up breathing pattern data is shown in Table 36. There were no statistically significant differences in any breathing pattern characteristic measured at follow up between the Non-DB and the DB group (data not shown). Again, as with baseline data there was no difference in airway calibre as measured by R_t between the two groups at follow up (95% CI -0.09, 0.18 by 2-sample t-test). As demonstrated in Table 36, there was no significant difference at follow up from baseline measurement in any breathing pattern characteristic.

Table 36: Breathing Pattern Follow up data

VARIABLE		RANGE	MEAN (SD)	MEAN (SD) CHANGE FROM BASELINE	95% C.I. FOR DIFFERENCE FROM BASELINE
Inspiratory Time (T_i, seconds)	**Non-DB (n = 16)**	0.95 – 3.72	1.66 (0.64)	-0.01 (0.38)	-0.19, 0.22
	DB (n = 15)	0.76 – 2.44	1.54 (0.40)	-0.02 (0.37)	-0.19, 0.23
Expiratory Time (T_e, seconds)	**Non-DB (n = 16)**	1.56 – 5.34	2.40 (0.99)	-0.05 (0.84)	-0.39, 0.50
	DB (n = 15)	1.29 – 5.35	2.56 (1.05)	0.16 (0.5)	-0.434, 0.12
T_e / T_i	**Non-DB (n = 16)**	1.09 – 1.98	1.45 (0.27)	-0.00 (0.30)	-0.16, 0.16
	DB (n = 15)	1.16 – 2.33	1.65 (0.38)	0.05 (0.30)	-0.22, 0.11
Tidal Volume (V_t, litres)	**Non-DB (n = 16)**	0.53 – 2.01	1.01 (0.39)	-0.12 (0.35)	-0.07, 0.31
	DB (n = 15)	0.45 – 2.02	1.04 (0.36)	0.02 (0.27)	-0.17, 0.13
Minute Ventilation (V_{min}, Litres/minute)	**Non-DB (n = 16)**	8.04 – 31.22	15.98 (6.41)	-1.13 (5.33)	-1.71, 3.97
	DB (n = 15)	7.50 – 24.13	15.94 (1.77)	-0.45 (4.55)	-2.07, 2.97
Respiratory Frequency (R_f, breaths/minute)	**Non-DB (n = 16)**	6.7 – 22.1	16.37 (4.45)	-0.33 (3.84)	-1.72, 2.37
	DB (n = 15)	7.7 – 29.31	15.97 (4.90)	-1.34 (3.79)	-0.76, 3.43
Respiratory resistance (R_t, kPa/l/s)	**Non-DB (n = 16)**	0.22 - 0.98	0.50 (0.20)	-0.06 (0.13)	-0.01, 0.13
	DB (n = 15)	0.22 – 0.80	0.45 (0.18)	-0.01 (0.10)	-0.04, 0.06

Breath to breath variability for Ti, Te, Te/Ti and Vt was assessed at follow up as described above and compared to baseline values (paired t-tests). As can be seen in table 7 there were no differences seen at follow up in either group in any parameter.

Table 37: Breath to Breath Variability - Follow up data

VARIABLE		RANGE	MEAN (SD)	MEAN (SD) CHANGE FROM BASELINE	95% C.I. FOR DIFFERENCE FROM BASELINE
SD - T_i	Non-DB (n = 16)	0.06 - 0.43	0.18 (0.10)	0.02 (0.19)	-0.08, 0.12
	DB (n = 15)	0.09 - 0.65	0.18 (0.14)	0.00 (0.17)	-0.10, 0.10
SD - T_e	Non-DB (n = 16)	0.09 - 0.49	0.25 (0.13)	0.01 (0.19)	-0.09, 0.11
	DB (n = 15)	0.10 - 0.51	0.28 (0.12)	-0.03 (0.15)	-0.11, 0.05
SD - T_e/T_i	Non-DB (n = 16)	0.07 - 0.41	0.17 (0.09)	0.01 (0.15)	-0.07, 0.09
	DB (n = 15)	0.07 - 0.38	0.20 (0.09)	0.03 (0.14)	-0.05, 0.10
SD - V_t	Non-DB (n = 16)	0.03 - 0.27	0.12 (0.08)	0.00 (0.08)	-0.04, 0.05
	DB (n = 15)	0.05 - 0.34	0.13 (0.08)	-0.03 (0.1)	-0.08, 0.03

7.4 Discussion

In the 78 patients in whom we had complete breathing pattern data there was no discernable difference between the groups in any parameter. The difference in tidal volume (V_t) between the Non-DB and DB group only just reached statistical significance (95% CI - 0.0056 - 0.39, p = 0.044). However there were no further statistically differences in other breathing pattern parameters between the two groups, so the clinical significance of this observation is doubtful. Additionally we looked at breath to breath variability for inspiratory and expiratory time, expiratory/inspiratory time ratio and tidal volume, with the hypothesis that patients with dysfunctional breathing would display more variability in their breathing pattern. As demonstrated in Table 4 there was no such difference observed. This may be due to the variable nature of any abnormalities in breathing pattern in patients with DB and since our sampling periods were brief. We measured breathing pattern using data available from FOT recordings. FOT is primarily used for the measurement of airways resistance and can be especially useful in the assessment of airways calibre in patient who have difficulty performing forced expiratory manoeuvres. With this technique the patient is asked to take normal tidal breaths while breathing through a mouthpiece and wearing a nose clip. Unsurprisingly, breathing pattern can be influenced by such apparatus. Breathing through a mouth-piece has been shown to increase tidal volume([111-113]) and in one series decrease respiratory frequency([112]) compared to natural breathing monitored with an external device. However, although mean values change, the breath to breath variability does not necessarily change when breathing via a mouthpiece and nose-clip ([108]). With this in mind we still felt our method of breathing pattern

measurement would be valid, given we were looking to identify between group (and after BCT, within group) differences.

Several other methods exist for measuring breathing pattern objectively. Using respiratory inductive plethysmography (RIP), rib cage movements can be analysed to calculate respiratory frequency, tidal volume and minute ventilation, mean inspiratory time and fractional inspiratory time ([108]). Tobin recorded breathing pattern by RIP over a fifteen minute period (after ten minutes rest) in symptomatic patients with asthma and found an increased tidal volume, minute ventilation and shortened fractional inspiratory time without an increase in respiratory frequency compared to non-asthmatics([109;110]). Asymptomatic patients with asthma had no difference in their breathing pattern compared to normals. Measuring breathing pattern with the RIP device would have been too time-consuming in the out-patient clinic setting of our study and it is not entirely clear if these long sampling periods in comparison with two sampling periods of 1 minute (with the last 30 seconds from each used for analysis) used in our study are important in determining differences not just in individual parameters, but in any breath to breath variability.

The second phase of our observational study involved assessing the effect of breathing control therapy. This was done in an uncontrolled manner reflecting the normal clinical management of patients in our clinic. In the patients in whom we were able to obtain follow up measurements of breathing pattern, we observed no difference compared to baseline in the patients who had attended BCT in either individual parameters or in breath to breath variability. Also the group who did not attend BCT showed no change. It may be that the sampling method used in our study

is not sensitive enough to pick up any changes, if indeed any effect was ever going to be produced in these parameters with BCT. As far as we are aware, there are no prior studies that have examined the effect of breathing control therapy on physiological parameters of breathing pattern in patients with asthma. One study which evaluated the effect of breathing therapy in 92 patients with DB alone found mean values of inspiratory and expiratory time and tidal volume increased following treatment([105]).

In conclusion we found no evidence that measuring breathing pattern with the forced oscillation technique was helpful in discriminating between Nijmegen identified DB and non-DB, with no evidence of any differences in baseline physiological aspects of breathing pattern. These parameters were unchanged following a moderate intensity breathing retraining programme, undertaken in parallel with patients' normal clinic attendance.

Conclusions

We have studied a number of aspects of the upper airway and breathing pattern in a cohort of patients attending a Problem Asthma Clinic and to place these studies in context we have described a New Patient cohort seen over a 12 month period. Here we found the proportion of definite asthma comparable to other reported series and also similar levels of co-morbidities or alternative diagnoses.

Firstly, we were disappointed not to identify Vocal Cord Dysfunction as classically described, but despite potential selection bias, we did confirm a range of functional and structural laryngeal abnormalities in our pilot study. There were no detectable differences in measurements of airway calibre in the patients with abnormalities, although the wide variation found suggests using the Forced Oscillation Technique may not be specific in the identification of glottic narrowing such as occurs in VCD. We subsequently found a strategy of performing challenge testing in the form of lab based exercise testing and histamine challenge testing was of not diagnostic value, but in only a small group of patients. Until further larger studies can be performed, visualisation of the vocal cords during an attack of suggestive symptoms remains the gold standard for the diagnosis of VCD.

We explored the relationship between upper airway symptoms and presence of structural laryngeal and nasal abnormalities and found groups of symptoms which have better predictive values for abnormality, which is pertinent to routine clinical practice. Vocal morbidity was found to be a problem which should not be immediately attributed to laryngeal candidiasis, and is clearly a complicated issue in

patients with asthma. Assessment tools originally developed for use in an otolaryngological setting appear to be able to shed some light on this area.

The issue of dysfunctional breathing continues to present difficulties in diagnosis, and while we found no evidence of overall benefit from our routinely delivered breathing control therapy in our observational study (in terms of questionnaire parameters, or in any physiological measurements), the lack of well validated diagnostic instruments and outcome measures will continue to hamper further work in this field. Further research should target these issues.

We have observed relationships between Nijmegen and Mini-AQLQ which suggests the former may be measuring quality of life in patients with asthma.

While we have found negative answers to some of our primary research questions, our observational data has provided valuable insights into this complicated area of asthma management, which will be helpful in the planning of further investigation in such areas.

Firstly the inter-relationships between the questionnaire scores (HAD, Mini-AQLQ, Nijmegen, PCAQ) need to be further explored, for example using factor analysis with the data from our cohort baseline questionnaires. The correlations we observed suggest different questionnaires may be measuring similar attributes. In particular the very close relationship between Nijmegen scores and HAD (Anxiety) raises important questions about the approach to treatment of dysfunctional breathing. While we found no evidence of overall benefit from our physiotherapy delivered breathing control, it

may be that in the patients who do seem to derive benefit, this may be no different or better than from a psychological intervention such as cognitive behavioural therapy (CBT). If a method can be validated to identify dysfunctional breathing in patients with asthma (for example using a modified Nijmegen with some physiological evidence of dysfunctional breathing) then entering patients into a randomised controlled trial of CBT would be of great interest.

Secondly, a closer investigation of the VoiSS in patients with asthma is warranted, in particular whether higher VoiSS correlates with objectively defined gastro-oesophageal reflux by pH studies. If so, further investigation of its role as an outcome measure in the treatment of reflux with appropriate therapy should be undertaken.

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APPENDIX 1

NEW PATIENT QUESTIONNAIRE

GRI ASTHMA CLINIC QUESTIONNAIRE - NEW PATIENTS

We would be most grateful if you could spend a few minutes completing this questionnaire.

Your answers will help us in the long-term management of patients attending the asthma clinic.

Thank you for your time.

NAME:_____ DATE:_____

SECTION 1

Please complete *all* questions by circling the number that best describes how you have been during the *last 2 weeks as a result of your asthma.*
In general, how much of the time *during the last 2 weeks* did you:

		All of the time	Most of the time	A good Bit of the time	Some of the time	A Little of the time	Hardly Any of the time	None of the time
		1	2	3	4	5	6	7
1	Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
2	Feel bothered by or have to avoid DUST in the environment?	1	2	3	4	5	6	7
3	Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
4	Feel bothered by COUGHING?	1	2	3	4	5	6	7
5	Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
6	Experience a feeling of CHEST TIGHTNESS or CHEST HEAVINESS?	1	2	3	4	5	6	7
7	Feel bothered by or have to avoid CIGARETTE SMOKE in the environment?	1	2	3	4	5	6	7
8	Have DIFFICULTY GETTING A GOOD NIHGHT'S SLEEP as a result of your asthma?	1	2	3	4	5	6	7
9	Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
10	Experience WHEEZE in your chest?	1	2	3	4	5	6	7
11	Feel bothered by or have to avoid going outside because of							

WEATHER OR AIR POLLUTION?

How limited have you been during the last 2 weeks doing these activities as a result of your asthma?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
12 STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
13 MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
14 SOCIAL ACTIVITIES (such as talking, playing with ets/children, visiting friends/relatives)	1	2	3	4	5	6	7
15 WORK RELATED ACTIVITIES (tasks you have to do at work, OR if you do not work, tasks you have to do most days)	1	2	3	4	5	6	7

SECTION 2

Doctors and nurses are aware that emotions play an important part in most illnesses. If your doctor or nurse knows about these feelings they will be able to help you more.
This questionnaire is designed to help your Doctor or Nurse know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Do not take too long over your replies: your immediate reaction to each item will probably be more accurate than a long though-out response.

Tick only one box in each section

I feel tense or wound up
- most of the time ☐
- a lot of the time ☐
- time to time, occasionally ☐
- not at all ☐

I still enjoy the things I used to enjoy
- definitely as much ☐
- not quite as much ☐
- only a little ☐
- hardly at all ☐

I get a sort of frightened feeling as if something awful is about to happen
- very definitely and quite badly ☐
- yes, but not too badly ☐
- a little, but it does not worry me ☐
- not at all ☐

I can laugh and see the funny side of things
- as much as I always did ☐
- not quite as much now ☐
- definitely not so much now ☐
- not at all ☐

Worrying thoughts go through my mind
- a great deal of the time ☐
- a lot of the time ☐
- from time to time but not too often ☐
- only occasionally ☐

I feel cheerful
- not at all ☐
- not often ☐
- sometimes ☐
- most of the time ☐

I can sit at ease and feel relaxed
- definitely ☐
- usually ☐
- not often ☐
- not at all ☐

I feel as if I am slowed down
- nearly all the time ☐
- very often ☐
- sometimes ☐
- not at all ☐

I get a sort of frightened feeling like "butterflies in the stomach
- not at all ☐
- occasionally ☐
- quite often ☐
- very often ☐

I have lost interest in my appearance
- definitely ☐
- I don't take so much care as I should ☐
- I may not take quite as much care ☐
- I take just as much care as ever ☐

I feel restless as if I have to be on the move
- very much indeed ☐
- quite a lot ☐
- not very much ☐
- not at all ☐

I look forward with enjoyment to things
- as much as I ever did ☐
- rather less than I used to ☐
- definitely less than I used to ☐
- hardly at all ☐

I get sudden feelings of panic
- very often indeed ☐
- quite often ☐
- not very often ☐
- not at all ☐

I can enjoy a book or radio/ tv programme
- often ☐
- sometimes ☐
- not often ☐
- very seldom ☐

SECTION 3

For each of the following statements, please tick the box for the most appropriate response

		STRONGLY AGREE	AGREE	NEUTRAL	DISAGREE	STRONGLY DISAGREE
1	I can reduce asthma by staying calm and relaxed					
2	Too often, my asthma just seems to hit me out of the blue					
3	If I do all the right things, I can successfully manage my asthma					
4	I can do a lot of things myself to cope with my asthma					
5	When I manage my personal life well, my asthma does not affect me as much					
6	I have considerable ability to control my asthma					
7	I would feel helpless if I couldn't rely on other people for help when I'm not feeling well from asthma					
8	No matter what I do, or how hard I try, I just can't seem to get relief from my asthma					
9	I am coping effectively with my asthma					
10	It seems as though fate and other factors beyond my control affect my asthma					
11	Asthma is controlling my life					

SECTION 4

Please mark with a tick how often you suffer from the following complaints:

	NEVER	RARE	SOMETIMES	OFTEN	VERY OFTEN
CHEST PAIN					
FEELING TENSE					
BLURRED VISION					
DIZZY SPELLS					
FEELING CONFUSED / DISORIENTATED					
FASTER OR DEEPER BREATHING					
SHORT OF BREATH					
TIGHT FEELING IN CHEST					
BLOATED FEELING IN STOMACH					
TINGLING FINGERS					
UNABLE TO BREATHE DEEPLY					
STIFF FINGERS OR ARMS					
TIGHT FEELING ROUND MOUTH					
COLD HANDS OR FEET					
HEART RACING (PALPITATION)					
FEELINGS OF ANXIETY					

Thank you for taking the time to fill in this questionnaire.

Please hand it to the nurse when you are finished.

APPENDIX 2

PROBLEM ASTHMA CLINIC PROTOCOL – 2003

GRI/Stobhill Hospital Problem Asthma Clinic

Strategy:

1. Does this patient have asthma?
2. What is their current psychological profile and history of use of resources?
3. Which combination of associated/aggravating factors does he/she have? (poor compliance, allergy, acid reflux, upper airway/sinus, hyperventilation, vocal cord dysfunction, depression)
4. What is the treatment needed to optimise control? (asthma and any aggravating/associated conditions)
5. Do they need to learn to self manage (those with acute admissions or poor control after Rx optimisation)? Are they (subsequently) self managing effectively?
6. Is there any change in psychological profile and use of resources after this process has been?

New patient Clinic attendance

asthma nurse gives out questionnaires, checks BP, inhaler and PEF technique, takes blood for random glucose, total IgE and RASTs to common allergens (HDM, pollen, cat, dog, aspergillus), FBC (eosinophils), U&E, LFTs

Self completed questionnaires (HAD, PCAQ, mini-AQLQ, Nijmegen,)*

- **Give to AS**

Clinical evaluation, inc review of questionnaires – if Nijmegen positive (>/=23)– book PET and refer for breathing control (physio)

Complete new patient summary sheet and checklist

Start 2 week PEF diary

FOT

Book PFT for 2 weeks hence (phone lung lab), to coincide with next clinic appointment

First review (2 weeks)

Review & consideration of need for trial of steroids for best function (if FEV1 <80%)

Full PFTs, skin tests, flow volume loop before clinic attendance

Review of PEF diary and PFTs:

- Prednisolone 30mg daily for two weeks if FEV1<80%
- Optimise inhaled therapy if lung function normal, depending on current therapy and level of symptoms/PEFs
- If uncontrolled, and PEFs/PFT normal – proceed to histamine challenge

Continue PEF monitoring and diary card

Arrange further appointment accordingly

Second Review

Review of those on steroid trial with repeat PFTs to determine need for prolongation of trial; if lung function now normal, optimise inhaled/oral asthma therapy depending on residual symptoms and PEF levels/variability

IDENTIFY PATIENTS AT THIS STAGE AS GREEN OR ORANGE STREAM

Green stream patients (normal lung function and well on inhaled Rx)– self management training and monitor/adjust asthma Rx , aiming to discharge when stable for 3 months. Repeat questionnaires before discharge

Orange stream (Step 4 or more **or** persistent symptoms **or** subnormal PFTs):

- **Continue to optimise therapy,** if asthma confirmed (guided by degree of sputum eosinophilia – induced sputum – Physio will do this at clinic)
- Sinus CT/ ENT evaluation (esp nose and vocal cords)
- Oesophageal and pharyngeal pH monitoring, off PPI

- Dexa scan
- PET and PC20 (once best function achieved)
- Review of therapy to include PPI (with repeat pH monitroing **on Rx**), bisphosphonates, breathing control (with repeat Nijmegen score), S&L therapy, nasal steroids/antihistamines/consideration of need for surgery (repeat ENT evaluation) as appropriate, depending of results of investigations

- **Self management training**, if persistent exacerbations or symptoms

- **repeat PFTs & questionnaires when assessment complete and patient stable**

Change running of clinic so there are 3 streams –
Red (New) patient – seen by anyone, discussed with CEB
Orange - those with poorly controlled asthma, requiring full evaluation (seen by CEB or AS).
Green - seen by CEB or rotating SHO and discussed
Identify different streams with sticker on front of casenotes.

Christine E Bucknall
Consultant Respiratory Physician
14th August 2003

APPENDIX 3

COHORT FOLLOW UP DATA SHEEET

GRI ASTHMA CLINIC

PATIENT LABEL

COHORT FOLLOW UP DETAILS

Date

Definite Asthma Diagnosis Yes ❑ No ❑

Basis of Asthma Diagnosis

Variable Symptoms	❑	. (if only reason – justify)
Variable PEF	❑	
AFO with BD reversibility	❑	% BD reversibility _____
Histamine Challenge	❑	
Steroid Trial	❑	

Respiratory co-morbidity

COPD	❑
Bronchiectasis	❑
GORD	❑
Basis of diagnosis	_____
Other	_____

Current Therapy

BTS Step ____

Detail _____

Best Lung Function

Date_____

FEV1 _____(%pred)

FVC _____

Ratio _____

Degree of BD reversibility (%)_____

Self management plan in place? Yes ❑ No ❑

Is patient self-managing effectively? Yes ❑ No ❑

APPENDIX 4

PROBLEM ASTHMA CLINIC PROTOCOL - 2006

GRI Problem Asthma Clinic January 2006

Does this patient have objective evidence of asthma?

- **BD reversibility documented?**
- **Good quality PEF chart variability?**
- **PC 20 in keeping with asthma (< 2mg/ml, but not an absolute)**
- **Raised FEno?**

→ If no objective evidence of asthma, what about alternative diagnoses?

If asthma confirmed, are symptoms all due to asthma?

If asthma confirmed:

- has Rx been optimised?
- Is compliance an issue?
- Inhaler technique?
- Self management plan?
- Using SMP effectively? (review handling of recent exacerbation)
- Side-effects from Rx? (BP, glucose, osteoporosis) Are these being adequately managed?

GORD – Don't know/no/yes
If yes, has this been abolished?
What dose of PPI required to abolish?

Dysfunctional breathing – DK/no/yes
If yes, basis of diagnosis
Benefit from Rx?
Using breathing control effectively?

Any indication of Vocal cord Dysfunction – DK/no/yes
Details

Allergic Broncho-pulmonary Aspergillosis?

Total IgE? (not more that 6 monthly, maybe less)
Itraconazole/LFTmonitoring?

Physio input

Psychological/psychiatric issues – DK/no/yes
Details of management strategy

Upper airway evaluation:
No symptoms
Normal
Abnormal – detail, inc management .

Bronchiectasis?
Physio input

APPENDIX 5

VOICE SYMPTOM SCORE - VoiSS

The VoiSS- Voice Symptoms Scale

Your Name.....

Your Date of Birth.....

Today's Date...../...../.....

Please circle one answer for each item
Please do not leave any blank items

1.	Do you have difficulty attracting attention?	Never	Occasionally	Some of the time	Most of the time	Always
2.	Do you have problems singing?	Never	Occasionally	Some of the time	Most of the time	Always
3.	Is your throat sore?	Never	Occasionally	Some of the time	Most of the time	Always
4.	Is your voice hoarse?	Never	Occasionally	Some of the time	Most of the time	Always
5.	When talking in company do people fail to hear you?	Never	Occasionally	Some of the time	Most of the time	Always
6.	Do you lose your voice?	Never	Occasionally	Some of the time	Most of the time	Always
7.	Do you cough or clear your throat?	Never	Occasionally	Some of the time	Most of the time	Always
8.	Do you have a weak voice?	Never	Occasionally	Some of the time	Most of the time	Always
9.	Do you have problems talking on the telephone?	Never	Occasionally	Some of the time	Most of the time	Always
10.	Do you feel miserable or depressed because of your voice problem?	Never	Occasionally	Some of the time	Most of the time	Always
11.	Does it feel as if there is something stuck in your throat?	Never	Occasionally	Some of the time	Most of the time	Always
12.	Do you have swollen glands?	Never	Occasionally	Some of the time	Most of the time	Always
13.	Are you embarrassed by your voice problem?	Never	Occasionally	Some of the time	Most of the time	Always
14.	Do you find the effort of speaking tiring?	Never	Occasionally	Some of the time	Most of the time	Always
15.	Does your voice problem make you feel stressed and nervous?	Never	Occasionally	Some of the time	Most of the time	Always
16.	Do you have difficulty competing against background noise?	Never	Occasionally	Some of the time	Most of the time	Always

Please Turn Over ⇒

VoiSS

Please circle the correct answer for each item
Please do not leave any blank items

17.	Are you unable to shout or raise your voice?	Never	Occasionally	Some of the time	Most of the time	Always
18.	Does your voice problem put a strain on your family and friends?	Never	Occasionally	Some of the time	Most of the time	Always
19.	Do you have a lot of phlegm in your throat?	Never	Occasionally	Some of the time	Most of the time	Always
20.	Does the sound of your voice vary throughout the day?	Never	Occasionally	Some of the time	Most of the time	Always
21.	Do people seem irritated by your voice?	Never	Occasionally	Some of the time	Most of the time	Always
22.	Do you have a blocked nose?	Never	Occasionally	Some of the time	Most of the time	Always
23.	Do people ask what is wrong with your voice?	Never	Occasionally	Some of the time	Most of the time	Always
24.	Does your voice sound creaky and dry?	Never	Occasionally	Some of the time	Most of the time	Always
25.	Do you feel you have to strain to produce voice?	Never	Occasionally	Some of the time	Most of the time	Always
26.	How often do you get throat infections?	Never	Occasionally	Some of the time	Most of the time	Always
27.	Does your voice 'give out' in the middle of speaking?	Never	Occasionally	Some of the time	Most of the time	Always
28.	Does your voice make you feel incompetent?	Never	Occasionally	Some of the time	Most of the time	Always
29.	Are you ashamed of your voice problem?	Never	Occasionally	Some of the time	Most of the time	Always
30.	Do you feel lonely because of your voice problem?	Never	Occasionally	Some of the time	Most of the time	Always

Thank you for completing this questionnaire
Have you remembered to circle one response for each item?

For Office use:

Total VoiSS= .....

Impairment: 1, 2, 4, 5, 6, 8, 9, 14, 16, 17, 20, 23, 24, 25, 27 (max 60) = ...

Emotional: 10, 13, 15, 18, 21, 28, 29, 30 (max 32) = ...

Physical: 3, 7, 11, 12, 19, 22, 26 (max 28) = ...

APPENDIX 6

SINO-NASAL OUTCOMES TEST

(SNOT-22)

Below you will find a list of symptoms and social/emotional consequences of your nasal disorder. We would like to know more about these problems and would appreciate your answering the following questions to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems as they have been over the past <u>two weeks</u>. Thank you for your participation.

A. Considering how severe the problem is when you experience it and how frequently it happens, please rate each item below on how "bad" it is by circling the number that corresponds with how you feel using this scale →	No problem	Very mild problem	Mild or slight problem	Moderate problem	Severe problem	Problem as bad as it can be	Most important items (5)
1. Need to blow nose	0	1	2	3	4	5	☐
2. Sneezing	0	1	2	3	4	5	☐
3. Runny nose	0	1	2	3	4	5	☐
4. Nasal obstruction	0	1	2	3	4	5	☐
5. Loss of smell or taste	0	1	2	3	4	5	☐
6. Cough	0	1	2	3	4	5	☐
7. Post-nasal discharge	0	1	2	3	4	5	☐
8. Thick nasal discharge	0	1	2	3	4	5	☐
9. Ear fullness	0	1	2	3	4	5	☐
10. Dizziness	0	1	2	3	4	5	☐
11. Ear pain	0	1	2	3	4	5	☐
12. Facial pain/pressure	0	1	2	3	4	5	☐
13. Difficulty falling asleep	0	1	2	3	4	5	☐
14. Wake up at night	0	1	2	3	4	5	☐
15. Lack of a good night's sleep	0	1	2	3	4	5	☐
16. Wake up tired	0	1	2	3	4	5	☐
17. Fatigue	0	1	2	3	4	5	☐
18. Reduced productivity	0	1	2	3	4	5	☐
19. Reduced concentration	0	1	2	3	4	5	☐
20. Frustrated/restless/irritable	0	1	2	3	4	5	☐
21. Sad	0	1	2	3	4	5	☐
22. Embarrassed	0	1	2	3	4	5	☐

B. Please tick the most important items affecting your health (maximum of 5 items).....↑