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ARTP | Association for Respiratory Technology & Physiology

Inspire

INSIDE THIS ISSUE:

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FIRST WORD

VOLUME 18, ISSUE 3. DECEMBER 2017

Welcome to the December issue of Inspire and an early Merry Christmas to you all. There was a late surge of content for this issue, with articles (pages 8,15, 25, 36, 48) from those who were awarded ARTP bursaries to attend the recent ERS conference in Milan. Each of these were of high quality, covered a range of topics and allowed the author the opportunity for Continued Professional Development, plus the all-important networking. Further information about how you can obtain an ARTP bursary is available on the ARTP website and this is just one of the benefits of becoming a member.

Following from this, the life of ARTP is based around its members and it is important we communicate concerns, celebrate positive outcomes and even say hello (occasionally) to nearby hospitals. We have the forum, this journal, the website plus more but the ARTP Regional Co-ordinator, has provided a quick introduction to the ARTP Regional Groups, to encourage participation at a local level. Nationally, I recently attended the ARTP National Strategy Day meeting and found it a well attended, timely and informative update.

Another way we communicate is at conference and for January 2018 this is taking place in Brighton. So far as I am aware, the number of submitted abstracts exceeded previous totals and the standard was high, so plenty to look forward to come January. Thursday sees one of the traditional highlights, The P.K. Morgan Memorial Lecture, and I am grateful to the Morgan family for providing an introduction to this.

And talking about communication, we know that by nature social media such as Twitter are meant to be dynamic however in this issue we are going to try to give a flavour of what has been tweeted by @ARTP_News, amongst others, at the time of going to press (actually, someone named 'Meghan Markle' is trending a little ahead of ARTP at present, but sure it will pass!). At the very least it will provide some links to interesting articles but as usual please let me know, at inspire@artp.org.uk if you find this useful (or not). Finally there is a mildly diverting cryptic crossword with all clues lung function-related and no prizes at all on offer.

My thanks to all the contributors and the Editorial team for their reviews and assistance. I look forward to seeing you at Conference 2018.

Aidan Laverty

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A WORD FROM THE CHAIR

Dr. Karl Sylvester

ARTP Honorary Chair

Merry Christmas to all! Hopefully not too early but this will be the last Inspire until the New Year. Christmas is a time for Santa Claus and his sleigh travelling around the world at record speeds ensuring not a child is left without a present….well the good ones that is, so I hope you've all been good this year!

In ARTP we have our own Santa Claus crew, spreading the word globally and ensuring the quality standards we in ARTP adhere to are for all the world to learn and begin to use in their daily practice. We've had ARTP members travelling to Brussels for World COPD day, testing staff and visitors in the EU building, our very own Paul Burns teaching spirometry to healthcare professionals in Lahore, Pakistan and Vice-Chair Julie Lloyd and Prof Brendan Cooper travelling to Nepal to teach and assess healthcare professional as part of the European Spirometry Driving Licence. What a fantastic achievement for the name and standards of ARTP to

be represented on a global scale. What a gift for ARTP to give to the world, just like Santa. I hope in the next Inspire edition you will hear more of their exploits.

In regard to standards, for a while now ARTP have been offering spirometry training that involved a 2-day face to face taught course, a paper portfolio and usually a practical assessment in the students place of work. This has been very successful over the years with over 800 individuals now on the national spirometry register signed off as competent by ARTP professionals to perform and interpret quality assured diagnostic spirometry. Over the previous few years some of us have worked closely with other organisations such as BTS, PCRS and Department of Health to improve the performance of spirometry in all areas of practice. This came to fruition with the publication of the "Quality Assured Diagnostic Spirometry" document published a couple of years ago. This gave the impetus for all areas of practice that perform diagnostic spirometry to be appropriately trained and assessed and appear on the ARTP's national spirometry register. With the publication of this document and the support from organisations such as CQC who will recognise this as a requirement when they undertake inspections, the demand

for our training and assessment is expected to sky rocket. With the increase in numbers needing to be trained and assessed our current method of delivery just isn't fit for purpose and so has to be brought into the 21st century. For the past year certain individuals within ARTP have been working unbelievably hard to produce a training and assessment programme fit for purpose. This has been in collaboration with the Institute of Clinical Science and Technology (ICST) and will involve an online e-learning package, a half-day practical skills workshop, an online portfolio and a centralised practical assessment. This takes away the administrative demands that were often felt by accredited centres, with the majority now being centrally organised by ARTP. What we now need are individuals with the appropriate qualifications and experience to put themselves forward as trainers and assessors. If you are interested in being involved then please see here, find out more and sign up today.

You'll see in this edition of Inspire a number of publications from those successful in obtaining an ARTP grant to attend the European Respiratory Society congress meeting in Milan in September of this year. One of the perks of being an ARTP member is that you have access to these bursaries and we have the same for you to attend the ARTP conference in January. The 2018 conference is being held in the balmy, or is it 'barmy' location of Brighton and will be another event not to be missed. We have some exceptional keynote speakers this year; see the link for more information. We also have some surprises in store for those in attendance which we know you will enjoy. One of the highlights every year is the P. K. Morgan memorial lecture and I'm delighted that Patrick's son Patrick F. Morgan has written a piece for this Inspire just highlighting what an exceptional human being his father really was. A real inspiration for all of us in how to use your tenacity and drive to further the development of technology for patient benefit. Something I know we can all learn from.

I look forward to seeing all of you that can attend in 2018. It's a pleasure to meet and greet colleagues and give recognition to all the hardworking people through the awards ceremony on the Friday night. One addition this year is the inclusion of an Exhibitor's Reception on the Wednesday night which I hope you can attend too. All the exhibitors are a great support to ARTP and this is just a small thank you to them for their on-going backing.

Until next time...

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ARTP EDUCATION BURSARY

The Prevalence Of Previously Unrecognised Respiratory Pathology In Patients Attending For Cardiac Surgery.

Sara McArthur, J.Alastair Innes

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Background

The prevalence of unrecognised respiratory disease is high with current studies suggesting that less than one third of the predicted three million people in the UK with COPD currently have a diagnosis[1]. In NHS Lothian, patients attending for pre-operative elective cardiac surgery assessment perform spirometry and measurement of oxygen saturation as part of their day long assessment to ascertain fitness for surgery. Breathlessness and other respiratory symptoms have been noted in these patients but it is often unclear whether their symptoms are fully cardiac in origin or whether there is an underlying respiratory problem contributing to them.

A previous study from this Department[2] demonstrated that reduced FEV_1 strongly predicted increased length of stay and in-hospital mortality following cardiac surgery. The authors concluded that FEV_1 is a widely available measure of physiological health that may improve risk stratification of complex patients undergoing cardiac surgery and should be evaluated for inclusion in new prediction tools.

Identifying patients with unrecognised respiratory pathology would allow treatment to reduce risks for the patient, anaesthetist and surgeon.

Aim

To establish how many patients scheduled for cardiac surgery have previously unrecognised respiratory pathology on routine pre-operative spirometry.

Methods

A retrospective investigation was carried out to identify patients who had undergone spirometry and oxygen saturation measurements as part of their pre-operative visit to the Royal Infirmary in Edinburgh over a 12 week period.

Prior to spirometry, patients were asked questions about their smoking history, respiratory medications, any recent surgery and any contra-indications to performing the test.

Spirometry was carried out following the Association for Respiratory Technology and Physiology (ARTP) and local protocol standards (reproducibility between 100mls and a minimum of 3 forced manoeuvres and 2 relaxed manoeuvres) by either a clinical physiology assistant or a clinical physiologist. Forced expired volume in 1 second (FEV_1), forced vital capacity (FVC), relaxed vital capacity (VC), peak expiratory flow (PEF) and the ratio between FEV_1 and the best achieved vital capacity (FEV_1/VC ratio) were measured.

SpO_2 was measured via the finger ensuring the finger was well perfused, no nail varnish or false nails are applied, no tremor was noted (e.g. Parkinson's disease etc.) and a good quality signal was achieved.

Spirometry was then interpreted using the European Community of Coal and Steel (1993) predicted regression equations and deemed abnormal if FEV_1, VC or ratio were <1.65 standardised residuals (SRs) from predicted values.

All data were entered into an Excel spreadsheet and analysed.

Results

- **An initial 156 patients scheduled for cardiac surgery over a 12 week period (*25/10/2016-18/01/2017*) were assessed (Table 1). 4 patients were excluded; 1 unable to follow instructions, 1 had recent eye surgery and prolonged increased ocular pressure, 1 died before pre-operative assessment (comorbidities), 1 had incomplete data. This left a final n=152 patients included in the investigation (Figure 1).**
- **Mean Age (years)**= 67.3 **range=** 23.9-89.5
- **Mean BMI (kg/m²)**= 29.5 **range=**19-47
- **Sex (M/F)**: 98/54
- **Smoking History (Non-Smoker / Smoker / Ex Smoker):** 56/25/71
- **Mean Oxygen saturation,S_pO_2 (%)**=97 **range**=86-100

Operation Type	Number (n=)	Operation Type	Number (n=)	Operation Type	Number (n=)	Operation Type	Number (n=)
Aortic Root Replacement	1	AVR and Root Replacement	1	CABGx3 and AVR	3	Resection of yolk sac tumour from right pleural cavity and right upper lobectomy	1
Ascending Aorta Replacement	1	CABG	10	CABGx4	6	Sternal Wound	1
Ascending Aorta and Proximal Arch Replacement	1	CABG and AVR	11	CABGx4 and AF Ablation	1	TAVI	7
AVR	38	CABG and MVR	2	CABGx4 and AVR	1	TAVI and Ascending Root Replacement	1
AVR/CABG	1	CABGx2	14	CABGx5	1	TAVR/ ARR/CABG	1
AVR/MVR	1	CABGx2 and AVR	5	MVR	22	TVR	1
AVR and Ascending Root Graft	1	CABGx3	18	Sternal Wire Removal	1		

Table 1: Operation Type For All Patients (n=152). See appendix for abbreviations.

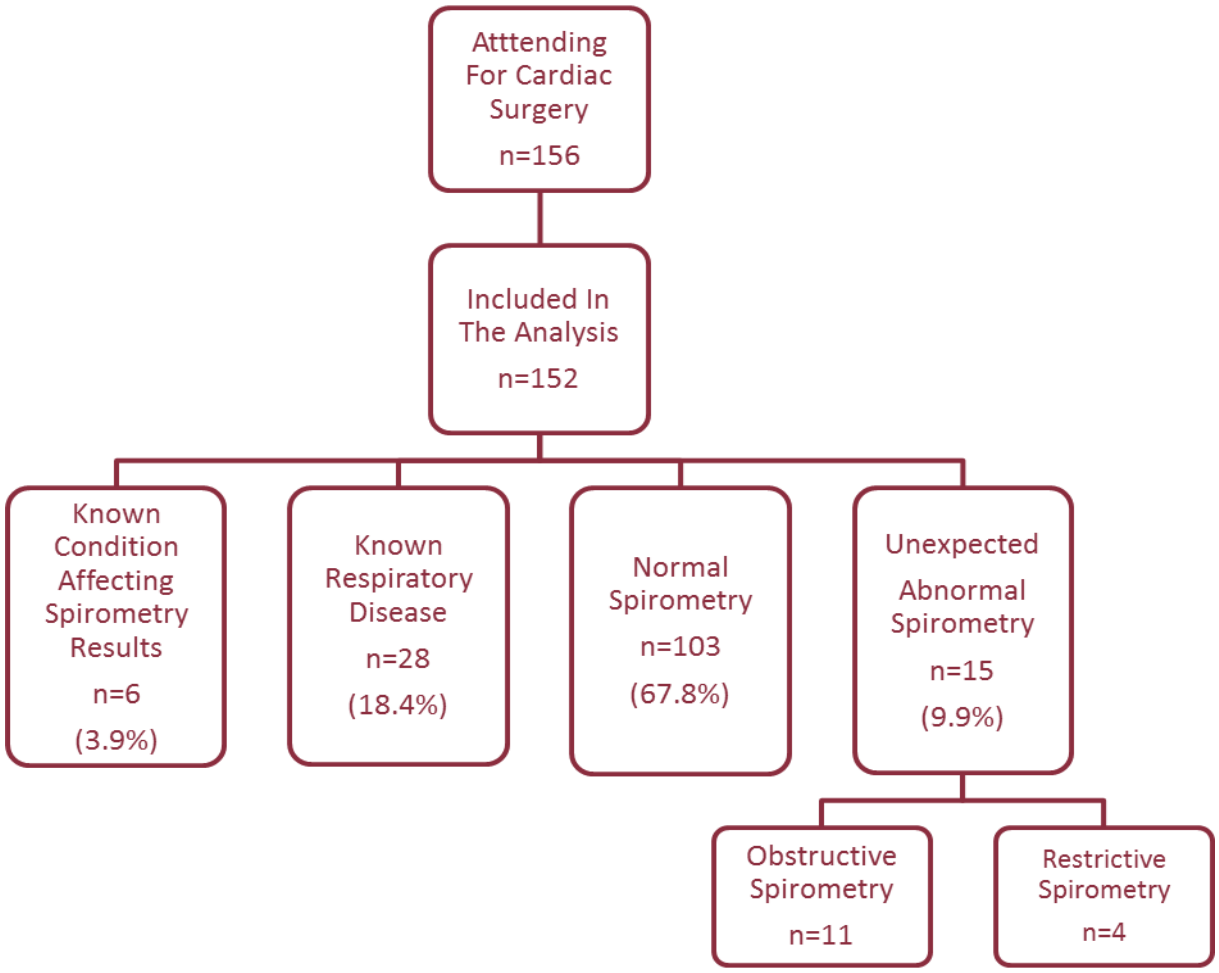

Figure 1: Synopsis Of Results

22.4% of this population have previously recognised conditions affecting spirometry, and another 9.9% had abnormal spirometry but without a previously known cause.

Known Condition Affecting Spirometry Results (**Table 2**)

- **n=6 patients with a previous medical history that may affect spirometry results**
- **Mean Age (years)=** 61.4 **range=**23.9-80
- **Mean BMI (kg/m2)=** 28 **range=**20-34
- **Sex (M/F):** 2/4
- **Smoking History (Non-Smoker / Smoker / Ex Smoker):** 5/0/1
- **Mean Oxygen saturation, S_pO2 (%)=**98, **range=**96-100

4 patients had normal spirometry, 1 had a mild obstructive ventilatory defect and 1 had spirometry suggestive of restriction

TB as child
Asbestos exposure
Mediastinal tumour/chemotherapy
Polymyalgia Rheumatica
Previous radiotherapy/chemotherapy
Left upper lobe apical mass

Table 2: Previous medical history that may affect spirometry results

Known Respiratory Disease (Table 3, Table 4)

- **n=28 patients with known respiratory disease**
- **Mean Age (years)=** 68.09 **range=** 31.6-84.5
- **Mean BMI (kg/m²)=** 31.5 **range=**19-47
- **Sex (M/F):** 17/11
- **Smoking History (Non-Smoker / Smoker / Ex Smoker):** 4/10/14
- **Mean Oxygen saturation, S_pO_2 (%):** mean=96 **range=**86-99

There were two patients that were noted to be deceased prior to their operation date.

As an oxygen saturation of 95% and above is generally considered normal[3] the patients in the known condition affecting spirometry results, abnormal spirometry and normal spirometry groups were essentially all normal (2 patients in the normal spirometry group had an S_pO_2 of 94% in air).

In the group of patients with known respiratory disease there were three patients that had an S_pO_2 of below 95% on air (94%, 93% and 86%). Interestingly the patient with the S_pO_2 of 86% was noted as deceased prior to their surgery date.

Respiratory Disease	(n=)	Respiratory Disease	(n=)
Asthma	8	COPD/Rheumatoid Arthritis	1
Asthma/COPD	2	Pleural Plaques	2
Asthma/Pulmonary Hypertension	1	Pulmonary Fibrosis	1
COPD	10	Pulmonary Hypertension	1
COPD/Pulmonary Fibrosis	2		

Table 3 : Types of respiratory disease

Interpretation	(n=)	Interpretation	(n=)
Low FEV_1 but VC and ratio normal	3	Moderate obstructive	1
Low VC	1	Moderate obstructive with low VC	1
Mild obstruction	11	Normal	6
Mild obstruction with a reduced VC	1	Suggestive of restriction	4

Table 4: Interpretation based on SRs

Normal spirometry

- **n=103 patients with normal spirometry**
- **Mean Age (years)=** 67.75 range= 26-89.5
- **Mean BMI (kg/m²)** =29.15 range=20-45
- **Sex (M/F):** 71/32
- **Smoking History (Non-Smoker / Smoker / Ex Smoker):** 39/13/51
- **Mean Oxygen saturations S_pO_2 (%):** mean=97 **range=**94-100

5 patients had a large ventilatory capacity

Unexpected Abnormal Spirometry

- **n=15 patients with unexpected abnormal spirometry**
- **Mean Age (years)=** 64.6 **range=** 45.8-78.6
- **Mean BMI (kg/m²)=** 29.2 **range=**20-39
- **Sex (M/F):** 8/7
- **Smoking History (Non-Smoker / Smoker / Ex Smoker):** 8/2/5
- **Mean Oxygen saturation S_pO_2 (%): mean=**97 **range=**95-100

11 patients showed a mild obstructive ventilatory defect

4 patients showed spirometry that was suggestive of restriction

Conclusion

Patients being assessed for pre-operative cardiac surgery have a 9.9% chance of having a previously unrecognised respiratory pathology.

22.4% of patients attending for pre-operative cardiac surgery have previously recognised conditions affecting spirometry or known respiratory disease.

Identifying occult respiratory disease in these patients allows us to undertake a respiratory review and to optimise their lung function prior to surgery using, for example, inhaled beta agonists in those with obstructive disease. It also forewarns the anaesthetist about possible underlying obstructive or interstitial disease, helping to minimise clinical risk.

References

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Appendix

Abbreviations:

AF Ablation:	Atrial Fibrillation Ablation
ARR:	Aortic Root Replacement
AAPA:	Ascending Aorta and Proximal Arch Replacement
AAR:	Ascending Aorta Replacement
ARG:	Ascending Root Graft
ARR:	Ascending Root Replacement
AVR:	Aortic Valve Replacement
CABG:	Coronary Artery Bypass Graft
CABGx2:	Coronary Artery Double Bypass Graft
CABGx3:	Coronary Artery Triple Bypass Graft
CABGx4:	Coronary Artery Quadruple Bypass Graft
CABGx5:	Coronary Artery Quintuple Bypass Graft
MVR:	Mitral Valve Replacement
SWR:	Sternal Wire Removal
TAVI:	Transcatheter Aortic Valve Implantation
TVR:	Tricuspid Valve Replacement

ARTP Article: Acknowledgement

The authors would like to acknowledge the Association for Respiratory Technology & Physiology (ARTP) for their generous support to attend the ERS congress Milan 2017 where this study was presented as a thematic poster.

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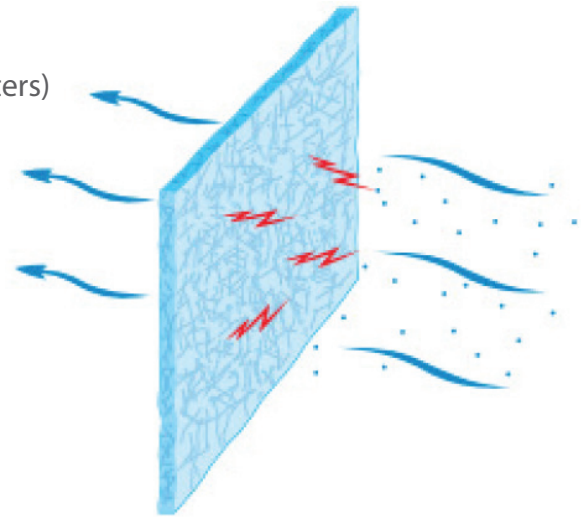

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ARTP EDUCATION BURSARY

Understanding Cystic Fibrosis; pathophysiology, diagnosis and treatment

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Introduction

Cystic Fibrosis (CF) is a multi-organ disease characterised predominantly by obstructive airways disease, gastrointestinal and urogenital abnormalities [1]. There are over 10,000 CF patients in the UK, and it is the most life-limiting autosomal recessive genetic disorder in Caucasians [1–5].

Given the heterogeneity of the disease, clinical presentation may occur within the first few days of life or as the disease progresses [6–8]. Typically, respiratory features manifest with chronic purulent sputum production, bronchiectasis and progressive, chronically variable airways obstruction, with increasing severity during periods of exacerbation [2]. Respiratory symptoms include dyspnoea, chest tightness and wheeze [8,9], and in advanced CF digital clubbing, cyanosis and abnormal chest shape may develop as a result of respiratory failure [8–10].

A wealth of research over the past century has led to advances in our knowledge and improvements in clinical management of CF [11,12]. Life expectancy has increased from a few months to a predominantly adult CF population with median survival of >50 years predicted for patients born in 2000 [11–13].

It is now well established that the pathophysiology of CF stems from a defective epithelial chloride channel known as the CF transmembrane conductance regulator (CFTR). CFTR dysfunction disrupts the normal salt and water transport across the airway epithelium and initiates a cascade of events including the production of excessively viscous mucus, bacterial colonisation, and inflammation leading to chronic airway injury [1,14]. Subsequent structural remodelling causes progressive irreversible airway obstruction and parenchymal destruction, leading eventually to respiratory failure, and premature mortality [14, 16, 19].

Pathophysiology

Our growing understanding of CF pathophysiology has enabled CF care to develop, improving prognosis and increasing life expectancy.

Abnormal mucus secretions were recognised early on as a distinctive feature of CF [18]. In the CF airway dehydration of the surface liquid due to reduced chloride secretion and sodium hyper-absorption causes excessively viscous mucus, ciliary dyskinesis and impaired mucociliary clearance [13, 16]. Accumulation of cellular debris and mucus hypersecretion due to upregulation of MUC gene expression further contribute to mucus plugging, which causes bronchiectasis and predisposes the airways to a vicious cycle of infection, inflammation and airway injury [21,22].

Given the ideal conditions created by mucus plugging, initial respiratory tract infections develop early and progress to chronic bacterial colonisation. An exaggerated and defective immune response further aggravates the airways by generating pro-inflammatory signalling and neutrophil recruitment [13–16]. The neutrophils release neutrophil elastase which destructs the elastin and fibronectin structure of the airway epithelium, and causes irreversible obstructive airways disease [9,14,23]. Hence a self-perpetuating cycle of infection, inflammation and epithelial injury ensues. Whether infection or inflammation comes first remains a topic of debate [13,25].

Repeated injury to the airway results in progressive destruction of the airway wall [21,23], and the resulting obstruction, gas trapping and hyperinflation alter pulmonary mechanics and increase work of breathing [9,19,21]. In advanced CF parenchymal damage reduces gas exchange, and leads to respiratory failure [21].

Family history of CF
Persistent respiratory tract bacterial colonisation
Chronic cough
Purulent sputum production (positive for pathogens)
Functional or radiological evidence of obstructive airways disease eg. Diffuse bronchiectasis
Nasal polyps
Finger clubbing
Gastrointestinal abnormalities including , pancreatic insufficiency, intestinal obstruction, hepatic or nutritional abnormalities
Salt loss syndrome
Obstructive azoospermia (adult males)

Table 1. Clinical manifestations of CF [9, 24]

In 1983 dysfunctional chloride transport was confirmed as the basic defect of CF[26], and subsequently the CFTR gene was identified and cloned [27,28]. CFTR is a cyclic AMP regulated epithelial chloride channel normally expressed at the apical membrane of the airway epithelium where it regulates the transport of water and ions [9,16,19]. Through both direct interactions and alterations in electrophysiological gradients CFTR determines the activity of other epithelial channels, including the Epithelial Na channel (ENaC) [2,10,16]. The CFTR gene is located on the 7q31.2 chromosome and as CF is an autosomal recessive disease, patients carry two defective copies [10]. Over 2000 CFTR mutations have been identified and classified according to their effect on CFTR production, expression, function and stability (**Figure.1**). There are exceptions to this classification, and due to the heterogeneity of CF and the potential impact of environmental factors and modifier genes, the genotype-phenotype relationship has only been identified for a discrete number of common mutations [1,2,9].

The precise relationship between CFTR dysfunction and lung injury is yet to be established [9,22]. The "*dehydration hypothesis*" is well-known throughout CF literature, and relates CFTR dysfunction to abnormal dehydration of the airway surface fluid due to reduced chloride secretion and increased sodium and water reabsorption [22,29]. Strong evidence to support this theory comes from electrophysiological studies which have demonstrated an increased transepithelial potential difference in CF epithelial cells [9]. The "*high salt hypothesis*" relates to the osmotic gradient created by the balance of epithelial CFTR and ENaC activity [16,29]. Evidence of increased nasal potential differences in CF patients compared to controls, and in-vitro studies which have demonstrated a higher transepithelial voltage and radio-labelled Na flow [29] suggest ENaC activity is upregulated in response to the CFTR dysfunction [16,18,29].

Diagnosis

Although there are classic clinical manifestations of CF (**Table.1**), 5-10% of cases present atypically [7], and epidemiological reports of survival data have identified missed and late diagnoses as a result [11]. Atypical CF may present with symptoms concurrent with differential diagnoses such as alternative obstructive airways diseases, immune deficiency, chronic kidney disease, connective tissue disorders, and Young's syndrome [7,30]. Given the wide spectrum of CF presentations and genotype-phenotype relationships, there is need for comprehensive diagnostic investigations [9,31].

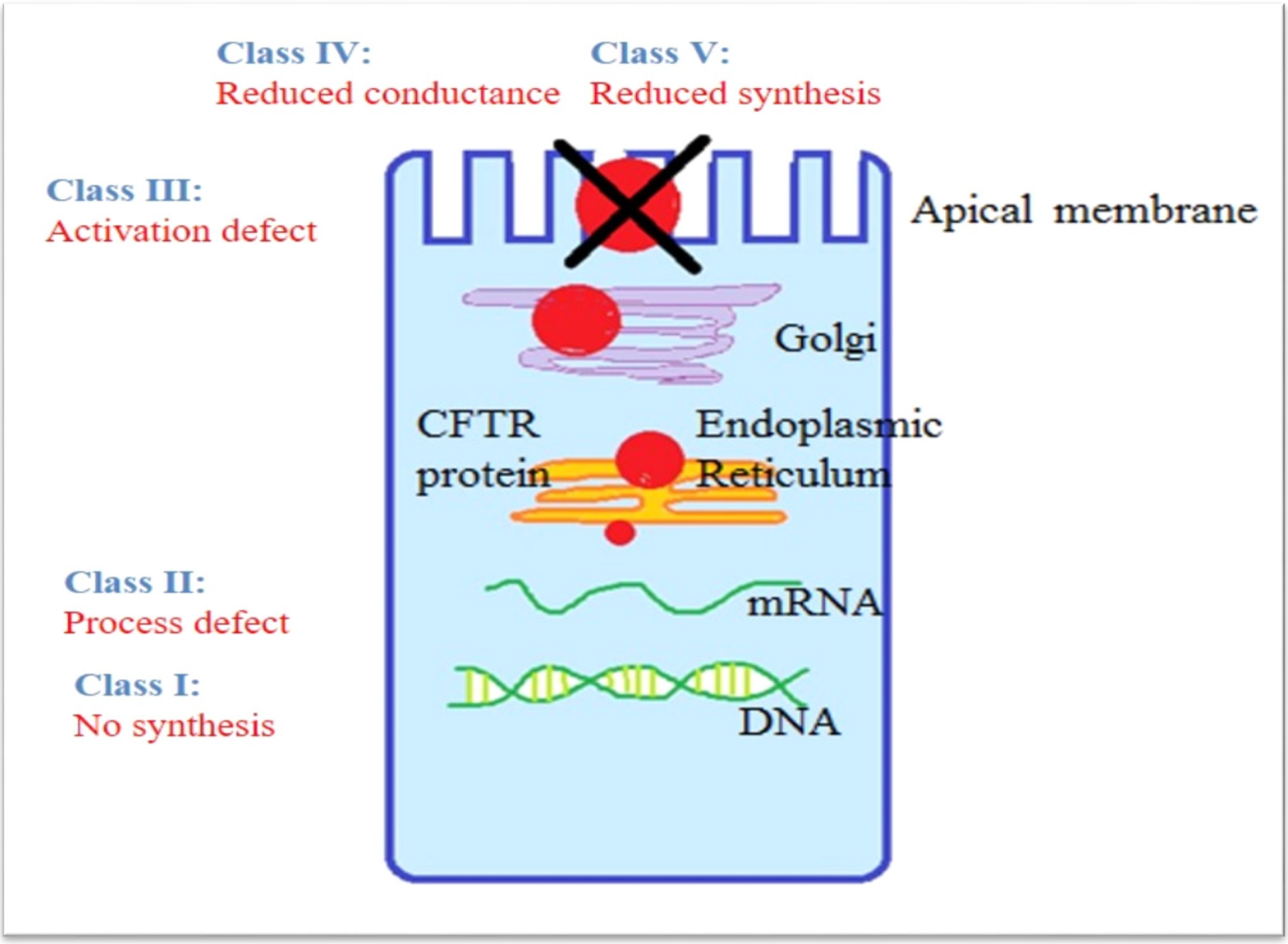

Figure 1. Classification of CFTR mutations

Class I mutations disrupt synthesis of CFTR, resulting in no production of the protein, eg. G542X.

Class II mutations disrupt the processing of CFTR, resulting in a mis-folded protein which is then degraded by proteases, eg. F508del.

Class III mutations disrupt activation and opening of CFTR at the apical membrane, eg. G551D.

Class IV mutations disrupt CFTR conductance at the apical membrane, eg. D1152H.

Class V mutations cause reduced synthesis of CFTR, eg. D1152H.

Class VI mutations disrupt CFTR membrane stability, eg. Q412X

Newborn screening programme

Early and rapid diagnosis aids faster administration of treatment and improves prognosis [8,24]. Screening programmes can help to prevent delayed and missed diagnoses, as well as reducing the severity of the disease and burden and cost of care [2,12]. The newborn screening programme (NBS) involves an immune reactive trypsin assay in combination with DNA analysis for common CFTR mutations [6,10]. The tool has 90-95% sensitivity [7], and a randomised control trial (RCT) of NBS demonstrated a significant and sustained improvement in nutritional parameters versus controls [9]. However, given the potential for false positive and negative results, specialist clinical judgement and interpretation are essential, and further diagnostic tests are required to confirm diagnosis [24].

Sweat test

Elevated sweat chloride level was recognised as a distinguishing feature of CF in 1953 [7,18], and today it is still recommended by current guidelines as the gold standard for clinical diagnosis [6,7]. Pilocarpine ionotophoresis is used to stimulate sweating from the forearm and the chloride concentration is measured [6–8]. Sweat chloride concentrations > 60 mmol/l on repeated tests are highly supportive of a CF diagnosis, and <30mmol/l imply CF is unlikely. Intermediate levels of 30-60mmol/l may indicate atypical CF which should be confirmed using DNA analysis [7,10].

DNA Analysis

The discovery of the CF gene in 1989 was pivotal to increasing our understanding of the disease pathophysiology and approaches to management [18]. For a definitive diagnosis in atypical CFTR presentation two copies of a CF mutation must be identified [10], whereas in classic presentation a single mutation is sufficient to confirm diagnosis [6]. Genotyping can differentiate CF from primary ciliary dyskinesia, a genetic condition also characterised by impaired mucociliary clearance [30].

Routine DNA analysis screens only for common CF genotypes, therefore a problem arises for approximately 10% of patients who carry a rare or unidentified mutation [7]. Hence, CF diagnosis must still be considered in patients with otherwise classic features but no identifiable CF mutation [6,32]. Over 2000 CF mutations have been identified, the clinical spectrum of symptoms is diverse, and the genotype -phenotype relationship is yet to be fully established [33]. Where definitive diagnosis remains unclear due to intermediate sweat chloride results and atypical clinical presentation, measurements of transepithelial nasal or intestinal potential differences may be useful [34].

Management of lung disease in CF

Historically, CF care focused on management of downstream effects specifically improving mucus clearance and treating infection and inflammation, but today CF care is evolving and the focus is now on restoring function of the defective CFTR [20,35].

Despite these advances, current guidelines still centre around traditional "*pillars of treatment*"; infection control, specialist multi-disciplinary care, mucus clearance and antibiotic treatment for infection [18,24,36]:

Mucus clearance

Mucus clearance is a fundamental aspect of CF management. Physiotherapy techniques include postural drainage, clapping [18,37], breathing techniques and adjuncts such as positive expiratory pressure and oscillating devices [37–40]. These techniques improve forced expiratory volume in 1 second (FEV_1) and mucus clearance [41,42], and should be supported with mucolytic therapy [36,37]. Longitudinal studies have demonstrated that Recombinant human deoxyribonuclease (RhDNase) improves FEV_1 and forced vital capacity (FVC), and reduces the number of exacerbations [37]. However only 1/3 patients will benefit from RhDNase, therefore despite their lower efficacy, osmotic agents such as nebulised hypertonic saline and dry powder Mannitol are recommended as an alternative or complimentary mucolytic therapy [43,44].

Antibiotics

Given the susceptibility of CF patients to common pathogens, antibiotic therapy remains central to their management [45]. Chronic, prophylactic treatment for S.Aureus can suppress infection [2,8], however it is not recommended due to the associated increased risk of methicillin-resistant Staphylcoccus aureus (MRSA) and Pseudomonas aeruginosa (P.aeruginosa) [24]. In contrast there is strong evidence to support maintenance use of inhaled Tobramycin for P.aeruginosa, and large randomised control trials have demonstrated improved FEV_1 and reduced infection and hospital admission rates [46–48]. However, antibiotic resistance and production of biofilms remain a major challenge, and strict infection control procedures are implemented by specialist CF centres in recognition of patient-patient infection transmission [18,49–51], given the implications of infection on lung function, potential transplant listing and mortality [50].

Macrolide antibiotics target both infection and the exaggerated immune response [19]. As highlighted by a recent Cochrane review and current guidelines, there is a wealth of evidence to demonstrate that chronic use of Azithromycin therapy significantly reduces lung function decline and exacerbation rates by 50% [52].

Emerging treatments

In 2015 the CF gene was successfully cloned, transferred and expressed in an airway epithelial cell [53], and early findings from a phase IIB randomized control trial of gene therapy demonstrated a small but significant reduction in FEV_1 decline at 12 months (3.7%, p=0.046) [53–55]. These findings are promising; however further evidence is required to support routine gene therapy and gene delivery systems need development [53,56].

Recent advances in research have led us to a new era of individualised small molecule CF therapy which targets the underlying CFTR defect, and restores function (**Table.2**).

A randomised control trial of the CF potentiator Ivacaftor demonstrated that patients treated with Ivacaftor had a significantly higher mean increase in FEV_1% predicted from baseline (10.6%), and a 55% reduction in exacerbations compared to controls [57]. The improvement in lung function is a result of altered mechanical properties [58], and is a significant advancement on any previous CF therapies. These findings have been confirmed by further trials; subsequently Ivacaftor is now licensed and recommended for use in the 5% of CF patients with the G551D mutation [20,24,59,60]. Furthermore, there is early evidence Ivacafor could also increase function of non-G551D gating mutations [31,55].

The development of the CFTR corrector Lumacaftor shows potential for the treatment of the class II F508del mutation, which accounts for approximately 67% of all CF mutations [20]. Although initial trials found no benefit when patients were treated with this therapy alone, a phase II trial of combined Lumacaftor and Ivacaftor revealed a significant increase in FEV_1 (6%) compared to controls ($p<0.01$) [20]. Furthermore, in two recent phase III trials, combination therapy reduced the number of infective exacerbations by 30-39% [62]. However, cell-based studies have revealed unexpected drug interactions [63], and it is yet to be approved for use in the UK [64].

Similarly, development of treatments which target class I mutations are on the horizon (**Table.2**) [31], and have shown promise in phase II trials [61].

Small molecule drug	Function/mechanism	Target CFTR defect
CFTR potentiators **Eg. Ivacaftor**	Increase CFTR channel open time, therefore increasing channel conductance.	Class III G551D mutation (5% of all CF mutations)
CFTR correctors **Eg. Lumacaftor**	Increase cellular processing and trafficking of CFTR proteins to the apical surface.	Class II mutations eg. F508del (67% of all CF mutations)
Read- through agents **Eg. Ataluren**	Induce ribosomal read-through of nonsense mutations during mRNA translation, thus rescuing protein synthesis.	Class I mutations eg. G542X (9% of all CF mutations)

Table 2. Novel small molecule therapies [8, 45]

Conclusion

This article discusses the clinical presentation, pathophysiology, diagnosis, and management of obstructive airways disease in CF. Advances in research using cell-based and animal models, have contributed to our growing understanding and improved management approaches to this complex disease. Ongoing research aims to better define genotype-phenotype relationships, improve CF standards of care and encourage pharmaceutical development [65]. The introduction of gene therapy and novel small molecule drugs offer huge potential for the future of CF patients, and although further research is needed, life expectancy is predicted to continue to rise.

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ARTP EDUCATION BURSARY

An Overview of Occupational Asthma: Definition, Diagnosis and Treatment

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INTRODUCTION

Occupational asthma (OA) is caused by exposure to airborne irritants, allergens, or sensitising agents in the workplace and accounts for 10-25% of all cases of adult-onset asthma [1,2,3]. OA is distinguished from work-exacerbated asthma (WEA) where symptoms of pre-existing or concomitant asthma are worsened by occupational exposure [4]. OA is then divided into the subgroups of immunologic or sensitising OA (sOA), acute irritant induced asthma (IIA) and irritant induced asthma with latency (L-IIA) (**Figure 1**)[5]. OA and WEA are both considered forms of work-related asthma (WRA).

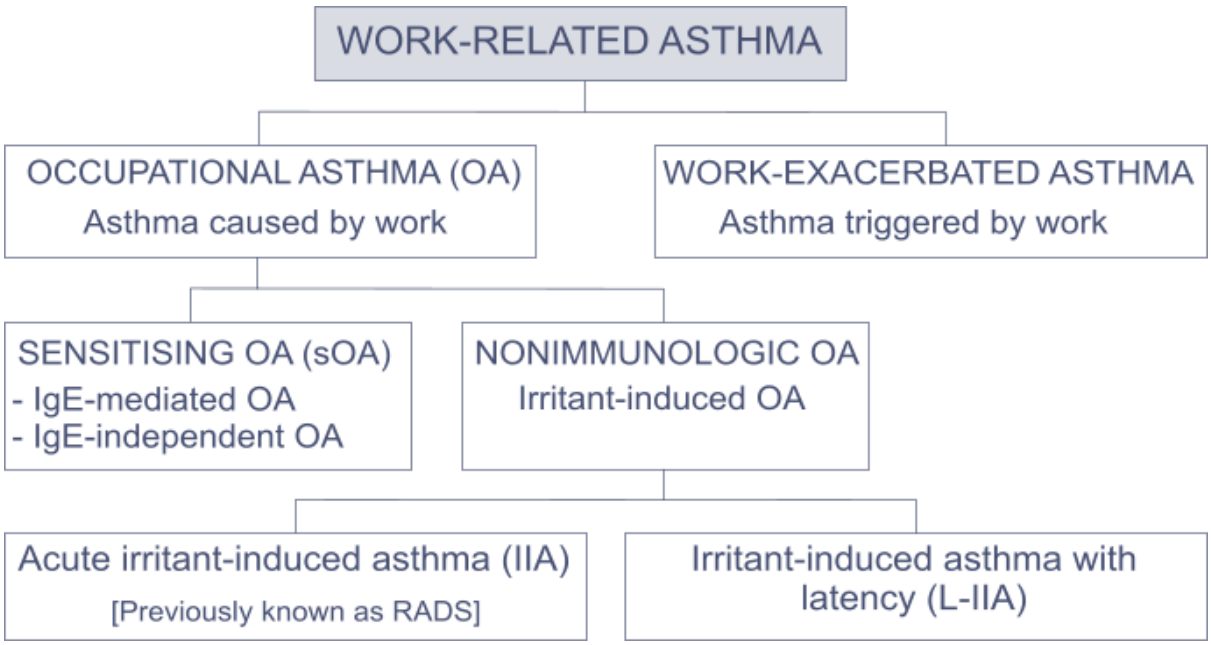

Figure 1 : Types of work-related asthma (adapted from Muñoz et al. 2014). OA: occupational asthma, IgE: immunoglobulin-E, RADS: reactive airways dysfunction syndrome.

A diagnosis of sOA requires a clear association of asthma symptoms that worsen during working days and improve on weekends and vacation periods. Immunological studies, pulmonary function testing, including serial peak expiratory flow (PEF), and specific and non-specific bronchial challenge testing are used in confirming the diagnosis [5,6]. There is a latent period before symptoms present that can range from weeks to years and sOA usually has an allergic or hypersensitivity mechanism [7].

Definition of OA

There is no universally accepted definition of OA, which may be due to the heterogeneity of the disorder. However, there is consensus regarding several aspects of the disease. Definitions for OA focus around three key points: i) airway hyperresponsiveness / variable airflow limitation; ii) a clear distinction of work-relatedness; and iii) no pre-existing asthma underlying symptoms. Muñoz et al. (2014)[5] described OA as "*variable airflow limitation and/or hyperresponsiveness and/or inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace*".

Differentiation between types of OA requires investigation into the agent that caused symptoms and the clinical features presented. **Table 1** contains a nonsological method to classify OA phenotype. Typically, IIA involves a sudden onset following exposure whereas sOA has a latent period between exposure and symptom development.

	OA		
	Immunological (sOA)	**Non-immunological (IIA)**	**WEA**
Mechanisms	IgE-mediated (HMW agents and some LMW agents) Unknown (most LMW agents)	Acute toxic injury from single (RADS) or multiple high-level exposures	Agents with irritant properties
Clinical features	Latency period	Sudden onset No latency period (RADS)	Work-related asthma symptoms
Evidence of casual relationship	Demonstration of specific IgE by skin testing, in-vitro assays or SIC.	Inference from temporal relationship between exposure and onset of asthma	Exclusion of OA
Objective diagnosis	Measurement of airway obstruction, responsiveness, and inflammation at work and away from work. Serial PEF SIC	Measurement of airway obstruction and responsiveness after the accidental exposure(s)	Measurement of airway obstruction, responsiveness, and inflammation at work and away from work.
Outcome	Improvement on removal from exposure; often with persistent hyperresponsiveness	Improvement on removal from exposure; often with persistent hyperresponsiveness	Unknown

OA: occupational asthma, WEA: work-exacerbated asthma, IgE: immunoglobulin-E, HMW: high-molecular weight, LMW: low-molecular weight, RADS: reactive airways-dysfunction syndrome, SIC: specific inhalation challenge, PEF: peak expiratory flow.

Table 1 : Nonsological classification of work-related asthma adapted from Bernstein et al (2013)[8], and Vandenplas & Malo (2003)[9].

Impact

The cost of asthma is estimated to be $5.8 billion per annum in the US [10], with an estimated cost of $1.6 billion for work-related asthma [12]. In the literature, the impact of asthma is subdivided into direct and indirect costs. Direct costs are listed as medicines, hospital admissions and professional time required (e.g. consultations, nursing, social support). Indirect costs are listed loss of productive work by the patient, by the patient's family, and loss of productive work by the patient due to early retirement or premature death. WRA is associated with a 10-fold greater direct cost per patient than non-WRA in the year before and after diagnosis [12]. There is a significant risk of unemployment in patients that develop OA, with an increased risk for women, industry workers, those with severe asthma or a lack of higher education [13]. Quality of life in patients with WRA is affected and a review of psychological distress in occupational asthmatics concluded that the data available suggest that OA is associated with increased rates of depression and anxiety [14].

Agents

sOA: Sensitisation can be caused by high molecular weight (HMW) agents such as flour, amylase, wood dust and latex, or certain low molecular weight (LMW) agents such as isocyanates [15]. Isocyanates are the most common agents identified as the cause of sOA [16].

IIA: The most frequently reported agents that cause IIA (in a single-dose RADS form) are cleaning materials, chemicals otherwise not specified (nos), chlorine, solvents nos, acids, bases, oxidizers nos, smoke nos, and diesel exhaust [17]. The workers at risk are chemical processors, engineers, electricians, manufacturers, transport or construction workers, health or scientific professionals [18].

L-IIA: L-IIA constitutes a small subset of occupational asthmatics. Burge et al [19] identified 127 patients with this form of OA from the SHIELD database. SHIELD is a voluntary reporting scheme in the West Midlands where occupational and chest physicians notify details of OA cases. The proposed causative agents in these patients were welding fumes, diesel exhaust, building dust and cement, aluminium casting, chlorine and chloramines, acids, bleach, ammonium chloride, coal dust, cigarette smoke, and caustic soda.

DIAGNOSIS

A diagnosis of OA requires a relationship to be established between exposure in the workplace and asthma symptoms. This can be accomplished by monitoring of airflow limitation in relation to working time and time away from work, or airflow limitation following exposure to specific workplace substances. It must be determined that symptoms are a result of workplace exposures, and then distinction needs to be made between exacerbation of pre-existing asthma and new onset OA. **Figure 2** shows the process of determining the form of asthma present.

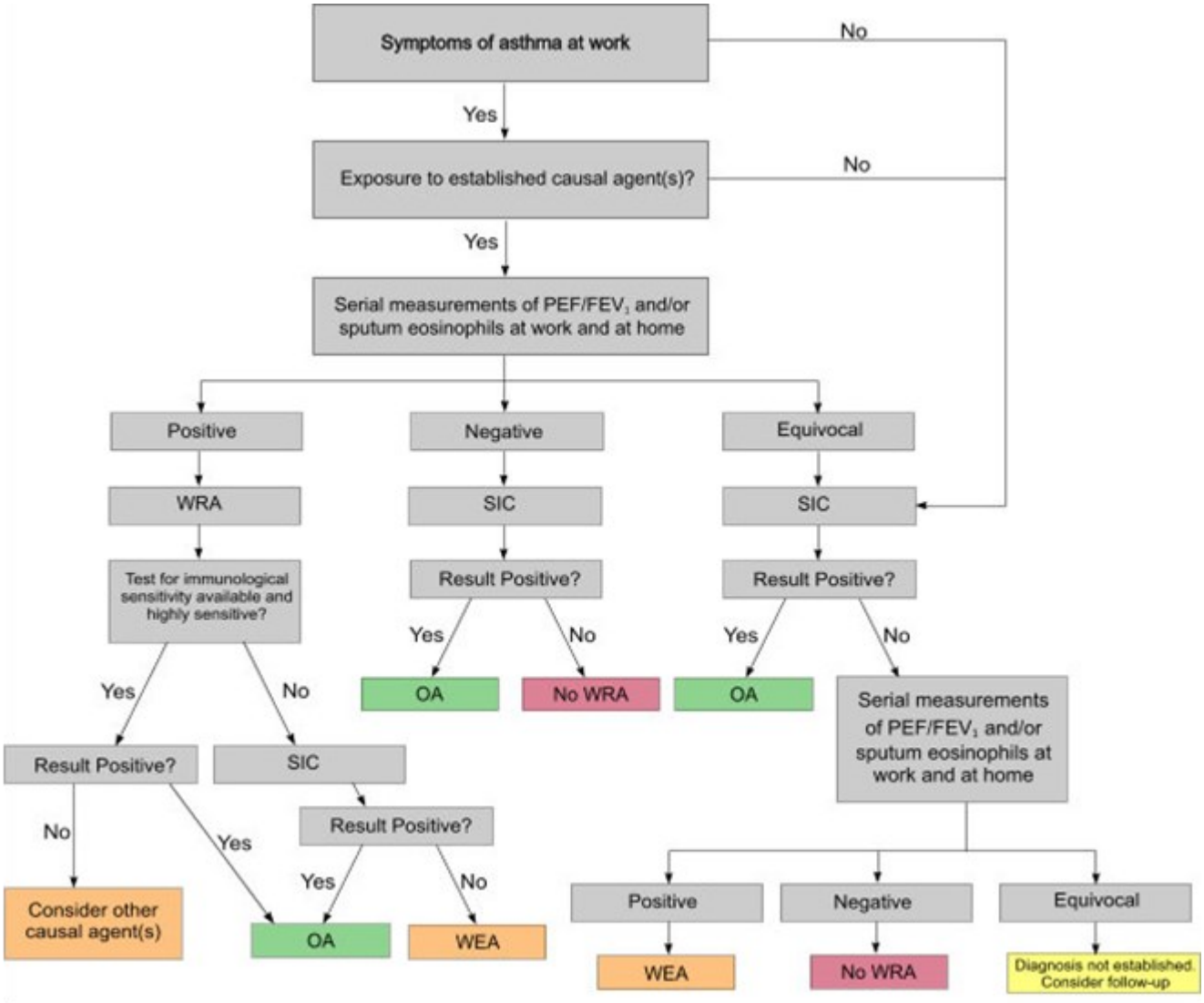

Figure 2. Algorithm for the diagnosis of occupational asthma adapted from Muñoz et al (2014). *OA: occupational asthma, WRA: work-related asthma, WEA: work-exacerbated asthma, SIC: specific inhalation challenge, PEF: peak expiratory flow, FEV_1: forced expiratory volume in 1 second.*

Peak Expiratory Flow (PEF)

PEF is a reproducible and simple measurement of pulmonary function that can be used to determine airflow limitation. It can be effectively utilised to determine the work-relatedness of asthma symptoms. This can be achieved by comparing mean PEF values when at work and away from work [20], and by observing diurnal variation of PEF at work and away from work [21]. Interpretation of results can involve visual analysis by experts, statistical analysis or computer based analysis. A systematic review of serial PEF measurements in the diagnosis of OA by Moore et al [22] found a sensitivity of 82% and specificity of 88%. However, serial PEF analysis demands that a patient produces PEF every 2 waking hours. This labour-intensive technique is effective in assessing the work-relatedness of asthma, but may not be feasible for the long-term study of OA disease progression.

Specific Inhalation Challenge (SIC) and FEV_1

Forced expiratory volume in 1 second (FEV_1) is a marker of disease severity and a predictor of long-term outcome – therefore it is a useful prognostic marker. FEV_1 declines with age at a rate of 22 ml/year in non-asthmatics and 38 ml/year in asthmatics with symptoms not related to occupational exposure [23]. Workers that remain exposed to the causative agent show a rapid FEV_1 decline. Anees et al. [24] determined that FEV_1 decline in workers with various forms of OA (of which >80% were sOA) before removal from exposure was 100 ml/year and a year after exposure was 26 ml/year. The study also revealed that there was an initial step-up period of ~12 ml in the first year. There is no data to determine whether there is a difference in FEV_1 decline pre- and post-exposure between workers with sOA and L-IIA.

In the diagnosis of OA, serial measurements of FEV_1 are made during a specific inhalation challenge [25]. This technique is considered the gold standard for the diagnosis of sOA [5,6]. The test involves repeatedly exposing the patient to the presumed causative agent. The challenge test aims to replicate the environment the patient would be exposed to at work in terms of duration and concentration. A positive test is defined as causing a decrease in $FEV_1 \geq 15\%$ from baseline [35].

Non-Specific Bronchial Challenge Tests

Non-specific bronchial challenge tests are aimed at determining the presence or severity of non-specific bronchial hyperresponsiveness (NSBHR). NSBHR is an excessive narrowing of the airways in response to a physical or chemical stimulus that would typically not produce bronchospasm [27]. NSBHR is a common feature of asthma and it is measured by inhalation of a pharmacological stimulus that acts on the airway smooth muscle (e.g. methacholine, histamine [28]. The key outcome is the dose of the substance that provoked a 20% drop from baseline FEV_1 – known as the PD_{20}.

These challenge tests can be used in the diagnosis of OA by making NSBHR measurements whilst exposed in the workplace and then after at least a week away from exposure. It has been shown that a 3.2 fold decrease in reactivity when not exposed (the upper 95% confidence limit for the between day reproducibility of the test [29] has a moderate sensitivity (48%) and specificity (64%) for diagnosing occupational asthma [30].

Induced-Sputum Analysis

Sputum analysis involves inducing expectoration after administration of increasing concentrations of inhaled hypertonic saline solution [31]. The sputum produced is analysed for concentrations of non-squamous cells. Eosinophils are the primary cell identified as a marker for inflammation in asthma[32]. This technique has been shown to produce reliable measurements in normal subjects and asthmatics [33] and is an effective method to assess airway inflammation in asthma [34].

TREATMENT AND PROGNOSIS

A diagnosis of OA is associated with a poor outcome. As mentioned previously, OA is associated with a significant economic impact and reduction in quality of life. There are several systematic reviews focused on ideal treatment and the benefit of reducing/ceasing exposure to causative agent. The data regarding prognosis is broad. The challenge for a systematic review of OA is the inherent heterogeneity of the disease. It is plausible that the prognosis of OA is specific to the form of the disease, severity, or causative agent. Furthermore, disease severity may play a role in response to treatment and therefore long-term prognosis.

Reducing exposure

The most effective treatment recommended to patients with sOA is cessation of exposure to the substance [4,35]. Cessation of exposure may be feasible to some workers where moving to a different role in the business is an option. However, a cessation of exposure may mean unemployment in certain occupations. The recommendation to avoid exposure rather than reduce exposure in sOA is based on two clinical findings:

i) Persistent exposure in sensitised patients can aggravate the airway obstruction and non-specific bronchial hyperresponsiveness leading to irreversible airways remodelling, and can potentially cause fatal exacerbations[36];

ii) Avoidance of exposure improves non-specific bronchial hyperresponsiveness in relation to the duration of exposure cessation [37]. This finding is independent of whether symptoms of asthma persist after removal from exposure.

IIA is typically the result of one accidental high-concentration exposure to an irritant agent. It is not clear whether cessation of exposure is of benefit; the worker should never have been exposed to that concentration and therefore repeating that exposure would be detrimental regardless. Whether continued low-level exposure exacerbates asthma is not determined. Malo et al [38] showed that positive NSBHR continued in 73% of workers re-tested after being away from exposure for a mean of 13.6 ±5.2 years.

L-IIA is not well documented and the outcome regarding cessation versus reduction in exposure has not been assessed. The long-term prognosis of L-IIA is not known to differ from sOA; Burge, Moore and Robertson [19] found the clinical characteristics of L-IIA and sOA to be indistinguishable despite the different mechanism of action.

Pharmacological intervention

Pharmacological intervention is not the recommended method of long-term treatment for OA at present time. Anti-asthma medications are used to control exacerbations or relieve symptoms. Patients are prescribed long-acting β2-agonists (LABA) and inhaled corticosteroids (ICS) to attenuate bronchial response to inhaled allergens, and a short-acting β2-agonist (SABA) to use when required [39]. If further control is needed, drugs like theophylline, leukotriene receptor antagonists, cromoglycate and antihistamines may help control symptoms [40]. The treatments for IIA are similar to those who suffered acute inhalational injury with anti-asthma medication provided to relieve symptoms [41].

CONCLUSION

Occupational asthma is a prevalent and debilitating form of the disorder that accounts for a large proportion of adult asthma. Accurate diagnosis of the condition can require specialised testing in the form of specific-inhalation challenges. In regards to treatment and prognosis, there is substantially more research concerned with the sensitising form of occupational asthma than the irritant-induced forms of occupational asthma. The most effective treatment for occupational asthma of a sensitising nature is to cease exposures in the workplace, but it is less clear what is most effective in irritant-induced occupational asthma.

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ARTP EDUCATION BURSARY

Outpatient initiation of domiciliary non-invasive ventilation in chronic stable hypercapnic respiratory failure

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INTRODUCTION

BTS guidelines outline the use of non-invasive ventilation (NIV) in acute hypercapnic respiratory failure[1]

Clinical consensus suggests that to effectively commence NIV in chronic hypercapnic respiratory failure admission with monitoring of nocturnal gas exchange is required[2]

In low risk competent patients, local services titrate NIV pressures in a single outpatient session, discharge with home NIV (Lumis ST-A 150; ResMed) the same day and use remote monitoring (Airview®; ResMed) to assess and guide patient concordance with therapy.

Aim

The aim is to retrospectively review the local process of NIV initiation in a single outpatient session relative to treatment efficacy, and patient concordance.

Method

$PaCO_2/PaO_2$ are compared across the pathway in relation to baseline. Baseline is obtained immediately before NIV; post-titration following 30 – 60 minutes on prescribed NIV pressures. Post-trial are obtained at the first follow up appointment, and corrected following any secondary changes to NIV pressure prescription. NIV concordance is compared to thresholds observed in the literature (≥5 hrs/day).[3] NIV concordance is assessed at 30 days, and 90 days. Long term oxygen therapy (LTOT) is managed within BTS guidelines[4] where clinically appropriate.

Data are presented as mean ± standard deviation or median and range where stated otherwise. Paired t-test has been used to identify statistically significant changes in contrasted metrics. Hypercapnia is defined as $PaCO_2$ > 6.0kPa, and improvements are expressed in relation to normal ranges of $PaCO_2$ (4.67 - 6.00kPa). Blood gases were measured by obtaining arterialised capillary earlobe samples

Results

Cohort

15 patients underwent NIV titration between January 2016 and June 2017 (**Table 1**). All patients consented to long term NIV. One patient died in the first month (not associated with NIV or respiratory failure) – this data has been withdrawn from the findings. Median time until post trial and corrected measurements was 38.5 and 66.5 days, respectively. Average pressures were 18.8±4.3 and 8.7±4.5cmH2O, for IPAP and EPAP respectively. Mean median mask leak was 1.8l/m (±3.6).

Table 1. Patient characteristics

n:	15
age (y):	64 ±9.0
Male:	6 (40%)
BMI (kg/m^2):	42.4 ±10.2
Baseline PCO_2 (kPa):	7.45 ±0.7
LTOT:	10 (67%)
Previous CPAP/NIV:	8 (53%)
Diagnosis:	
COPD:	9 (60%)
Obesity:	11 (73%)
OSA:	7 (47%)
Chest wall:	3 (20%)
Diaphragm dys.:	1 (7%)

Treatment Concordance

At 90 days, 6/14 patients did not meet the threshold for adequate concordance (**Table 2**). Average usage in non-concordant individuals was 4.0±0.8hrs/night, compared to 7.3±1.5hrs/night in concordant individuals. Compared to the first 30 days, concordance showed a tendency for improvement in the subsequent 60 days (95% CI -0.03 – 1.52; p=0.058). There was no difference when comparing usage between individuals who were naïve to CPAP/NIV and those who were not (95% CI -4.53, 1.52; p=0.30).

Table 2. Patient concordance

Usage first 30 days (hours/day):	5.0±2.6
Usage 30 – 90 days(hours/day:	5.8±2.1

Hypercapnia

Table 3 and **Figure 1** show changes in blood gases prior to and following NIV. $PaCO_2$ decreased significantly (-1.01kPa) when comparing baseline (7.40kPa±0.74) and corrected (6.39kPa±0.53) measurements (95% CI -1.35, -0.66; p=<0.001). 2 individuals had normal $PaCO_2$ following NIV treatment. Median reduction of $PaCO_2$ was 1.15kPa (0.02 – 1.63kPa) in those (n=4) with significant residual hypercapnia (>6.66kPa). **Figure 2** shows the frequency of residual hypercapnia following the NIV treatment period. Improvement in hypercapnia was noted in 12 individuals (median reduction: 1.14kPa [0.56-1.71kPa]). No improvement in $PaCO_2$ was observed in 2 individuals (+0.02kPa and +0.19kPa, respectively); both individuals were non concordant.

Table 3. blood gases (n=14)

Baseline $PaCO_2$	7.40 ±0.74
Post titration $PaCO_2$	6.81 ±0.90* p=0.018
Post trial $PaCO_2$	6.56 ±0.86* p=<0.001
Corrected $PaCO_2$	6.39 ±0.53* p=<0.001
Baseline PaO_2	7.48 ±1.36
Post titration PaO_2	7.86 ±0.86
Post trial PaO_2	8.22 ±1.01
Corrected PaO_2	8.35 ±1.00* p=0.028

* Significant difference relative to baseline

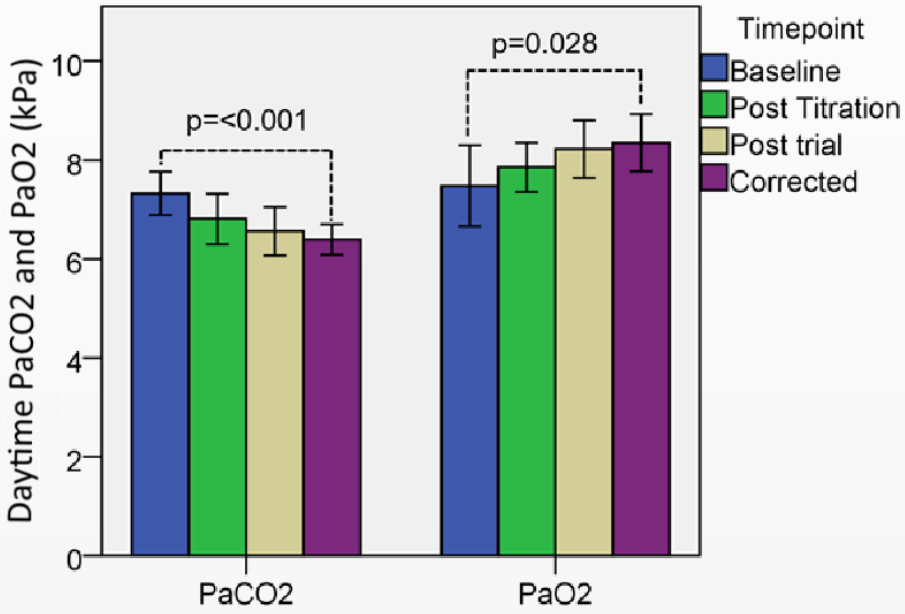

Figure 1. Change in PCO2 and PO2 over the NIV treatment period

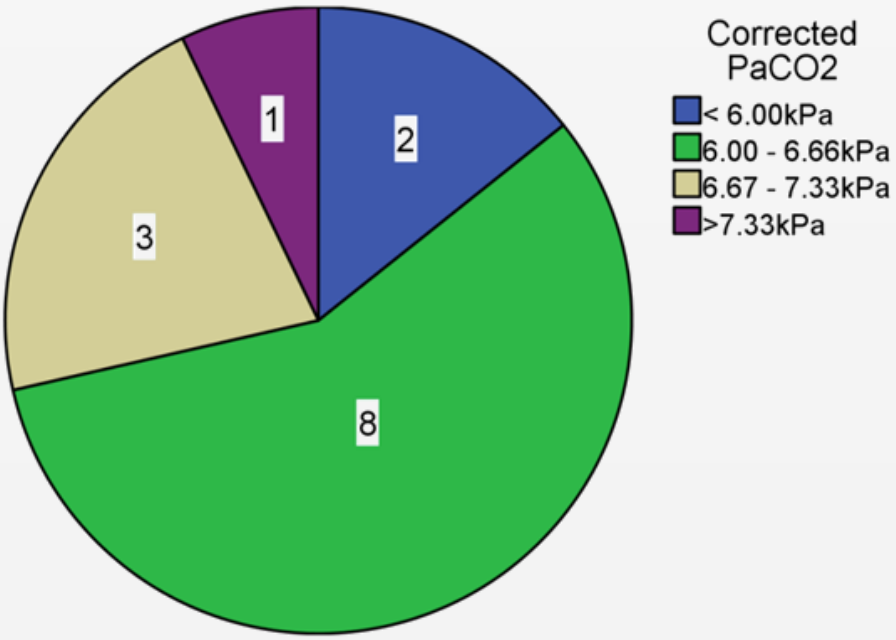

Figure 2. Residual hypercapnia following NIV

Oxygen

Following NIV, optimal oxygenation (≥8.0kPa in LTOT patients, and ≥7.4kPa in non LTOT patients) was achieved in 10/14 patients. Post NIV trial, 3/10 patients no longer required LTOT (PaO_2 on air = ≥7.4kPa). 4 individuals on LTOT were suboptimally oxygenated (median: 7.67kPa [7.27-7.94])

CONCLUSION/DISCUSSION

This method of commencing NIV shows improvement in daytime blood gases in the majority of individuals (12/14). 10/14 individuals had no or slight hypercapnia ($PaCO_2$≤6.66kPa) following domiciliary NIV trial; 3/4 individuals with residual significant hypercapnia still had good improvement compared to baseline measurements. Normalisation of $PaCO_2$ is desirable, but only 2 of the group achieved this. Whilst NIV concordance was not as high as expected in a significant proportion of the cohort (6/14), only two of these individuals had no improvement in $PaCO_2$.

Further research

Further metrics to consider are changes in nocturnal gas exchange, symptoms, control of sleep disordered breathing, health related quality of life measures (e.g. Severe Respiratory insufficiency questionnaire, SRI[5]) and reduction in the likelihood of admission.

Further research could include comparing a cohort of inpatient set up patients with single/multiple night admission, to a cohort set up using the process outlined above; in addition, identifying whether higher intensity NIV would improve hypercapnia further, but maintain concordance/ tolerance

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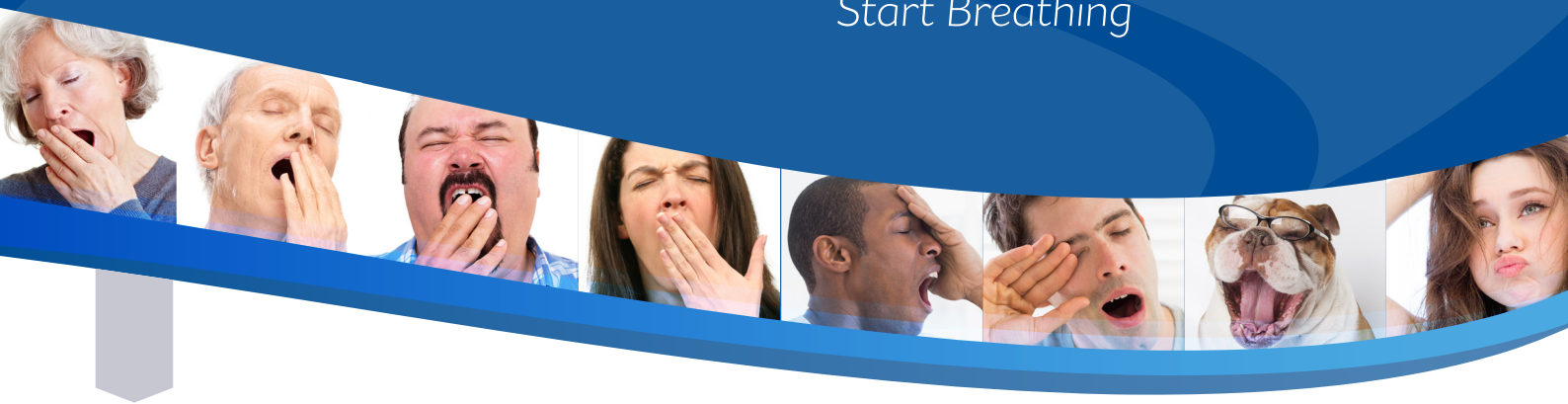

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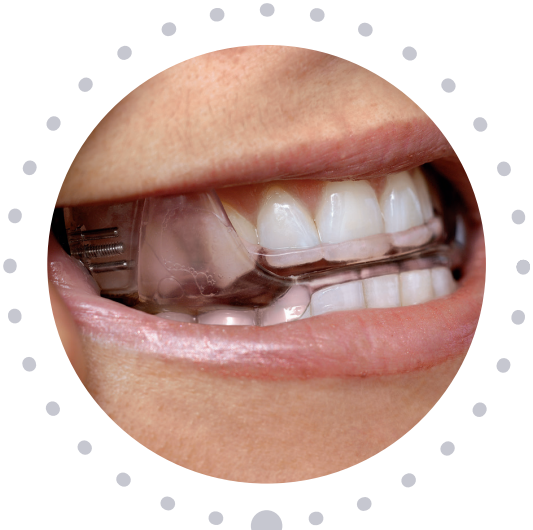

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ARTP GROUPS AND REGIONAL MEETINGS

The meetings are held in order to maximise communications between ARTP and membership to share timely information and findings. It is important for us that we not only keep you all up to date with the most relevant information but also hear from you and understand how all of our members feel about the topical issues that are affecting us all.

The topics discussed are not pre- set, the content is driven by those who attend, they range from local issues to national issues, whatever you want to share with your professional neighbours (within reason of course). This shared information may help us all to run a smooth service and do our jobs to the best of our ability.

We all need to gather evidence for our CPD so being involved in organising meetings, presenting for a meeting or taking the minutes of the meeting or just attending can all be used as part of our professional development.

It's good to step away from our daily routine and catch up with our neighbours, it can be fun!

The regions are; West Midlands, Trent, South West, South Central, Northern, Yorkshire, North West, London, South East, Home Counties, East, South Wales, North Wales and Northern Ireland.

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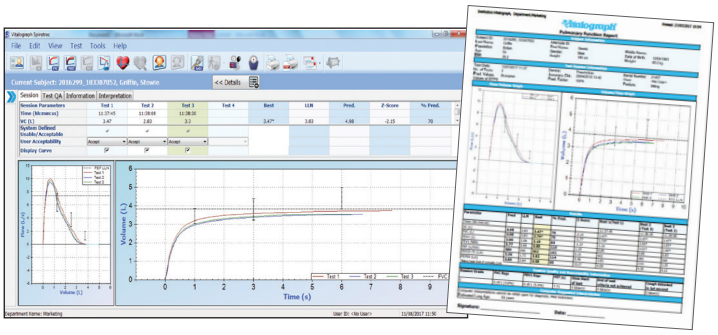

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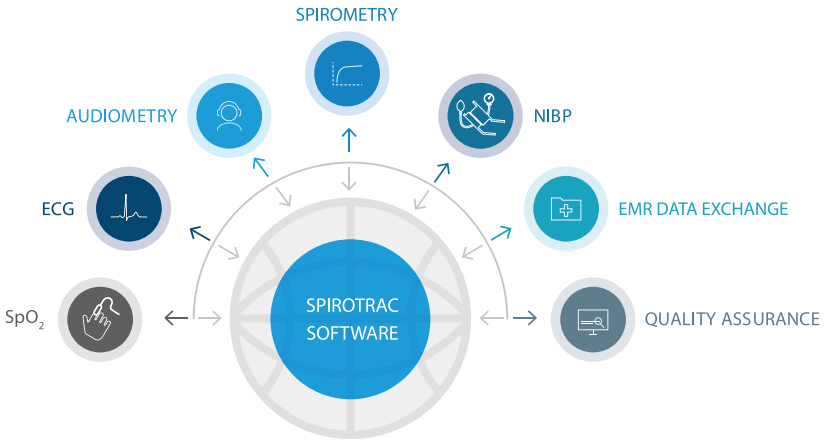

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National Strategy Day for Leaders in Respiratory/Sleep Physiology

York Racecourse, Monday 30th October 2017

Aidan Laverty, Great Ormond Street Hospital, London

Session One (ARTP Sleep)	Vicky Cooper
CPAP certification	Alan Moore
AASM Interscorer and other elements	Adrian Kendrick
Registration for Sleep Physiologists	Brendan Cooper and Trefor Watts
DVLA Update	Brendan Cooper
Session Two (ARTP Education)	
ARTP Professional Examinations Update	Sandra Davis and Helen Purcell
ARTP Spirometry Process and Register	Vicky Moore
Session Three (Standards)	Ian Cliff
Remote monitoring	Ed Parkes and Richard Glover
Testing Times	Andrew Pritchard
IQIPs: what's new and what's next	Ian Cliff
Session Four	Karl Sylvester
ARTP/BTS Session—ARTP Survey results	Karl Sylvester
Update on Patient Group Directives	Julie Lloyd

The great and the good (and others) turned out for this full day session at an atmospheric venue surprisingly near to the centre of York. This is a concise update on what I gleaned from the meeting so any inaccuracies are down to me.

First of all, **Alan Moore** spoke about the technical standards required for CPAP and it appeared that basically there were not any. If an NIV device did not meet your standards then you need to discuss with each company individually. A study in Germany tested 4 x CPAP and 1 x AutoPAP device and found only a 50% success rate in the devices meeting their technical specifications. Alan mentioned BAREMA

(www.barema.org.uk), the Association for Anaesthetic and Respiratory Device Suppliers, as an organisation that is seeking to standardise specifications..

Adrian Kendrick spoke about interscorer testing with regards to sleep studies – how do we ensure that each physiologist will score a study in the same way—the Interscorer Reliability (ISR)? Adrian discussed the American Academy of Sleep Medicine (AASM) (https://aasm.org/) interscorer system, which he said worked out cheaper than setting up such a system yourself, once you factor in the time required. Using AASM he sets aside one hour per week for staff to perform ISR.

Prof. Brendan Cooper & **Trefor Watts** talked about some of the "*appalling*" findings of the Francis report and listed several ways in which Clinical Physiologist actions could result in their being struck off the register, be it RCCP, AHCS etc. Their websites do not make it clear to the patient what to do if they have a complaint about a member of the profession. It was mentioned that RCCP have applied for Professional Standards Authority (PSA) accreditation and that the PSA currently provide a useful tool wherein a patient can check if their healthcare practitioner is registered.

Brendan ran through the latest DVLA advice for medical professionals on assessing fitness to drive, which you can read at https://www.gov.uk/guidance/miscellaneous-conditions-assessing-fitness-to-drive#excessive-sleepiness--including-obstructive-sleep-apnoea-syndrome.

The afternoon session began with **Sandra Davies** (Sandra.Davies4@wales.nhs.uk) and **Helen Purcell** discussing the different levels of Individual Record of Clinical Practice (IRCP) available – be they associate or practitioner level. Sandra advised we look at the 'ARTP-BTS National Assessments' section on the ARTP website, mentioned there were currently no examination centres in London and made a plea for more examiners to put themselves forward.

Vicky Moore talked about Spirometry accreditation. ELearning is available now and by 2021 all practitioners must be accredited. Train the Trainer dates to aid in this are To Be Confirmed.

Ed Parkes and **Richard Glover** spoke about remote monitoring of NIV. They mentioned the rise of Electronic Patient Records (EPR) and the potential of this being a potentially useful way to integrate adherence records but the jury is out at present as to how useful remote monitoring actually will be. A paper by Pinto (J Neurol Neurosurg Psychiatry. 2010 Nov;81 (11):1238-42) was mentioned and they stressed a need for research into Quality improvement methodology to show improved adherence.

Andrew Pritchard presented the results from the testing times survey which had a relatively good response rate and gave median times for many of the most common respiratory and sleep physiological investigations

undertaken by our services. This data was published in ARTP 'Inspire' Vol 18, 1, April 2017 and has been utilised by the workforce survey which was summarised later on in the day.

Ian Cliff's topic was Improving Quality in Physiological Services (IQIPS) accreditation scheme, which can admittedly be difficult because it is time-consuming. IQIPS is now under the auspices of the United Kingdom Accreditation Service (UKAS). To date, 178 centres across UK are ready to pursue accreditation of which 20 are denoted as respiratory or sleep. The process is now a 4-year cycle and evidence can be uploaded as the centre proceeds. It is endorsed by NHS England and by the CQC. The cost is an initial £500 + VAT PER ORGANISATION to access a traffic light system which assesses your readiness to proceed. This fee is refunded if the full process is subsequently followed. Full application costs £1500+VAT.

Karl Sylvester presented the ARTP survey results. The response rate was lower than the previous *2012* survey so there is work to do to improve this. It appeared from the survey that there is, in one worst case, a 100 week wait for a multichannel sleep study. On the flip side, one department listed itself as having 35 respiratory consultants and 20 Clinical Nurse Specialists.

Julie Lloyd talked about an update on Patient Group Directives (PGD), in particular Medicines management and specifically how rigorous the procedure needs to be for prescribing a bronchodilator. Julie mentioned that Clinical Physiologists are not under statutory regulation so currently cannot work under PGD. A case is being prepared for March 2019 which if approved will allow Clinical Physiologists and Scientists to be added to list of professions who can prescribe via PGD.

Images. A. Laverty

ARTP EDUCATION BURSARY

Specific inhalation challenge testing in the diagnosis of occupational asthma

Vicky C Moore (vicky.c.moore@heartofengland.nhs.uk)

Birmingham Heartlands Hospital, Heart of England Foundation Trust

INTRODUCTION

Occupational asthma accounts for approximately 9-20% of all adult asthma [1-3] and it is one of the most common occupational health issues. Several definitions for occupational asthma have been proposed, but presently there is no one internationally agreed definition. It is agreed, however, that the causal agent should be specific to the workplace [4-10]. One of the simplest ways to raise suspicion about whether a person's symptoms are work related is to ask "*do your symptoms get better on days away from work*" and "*do your symptoms get better on holiday*". It is important to ask this rather than whether the worker felt worse at work as many people have late reactions which do not begin until the work shift has ended. If a suspicion of occupational asthma is raised, the current best practise is to refer the worker to a specialist clinic for further investigations [11]. However, there can be a long delay between the first symptom and referral which means a poorer prognosis for the worker. It also makes the diagnostic procedure more difficult, for example if the patient's work tasks have changed before he/she is seen at the specialist clinic. It would therefore be preferable to start the diagnostic tests immediately when the suspicion of occupational asthma has arisen. Performing serial peak expiratory flow (PEF) measurements while the worker is at work and away from work can be used as a first-line diagnostic test, and can easily be implemented in primary and secondary care without specialist involvement. Respiratory physiologists could ask the questions about work related symptoms when performing lung function measurements on those referred with a diagnosis of possible asthma. Workers should be asked to complete 4 weeks of PEF measurements carrying them out every 2-3 hours from waking to going to bed every day. Interpretation of the results can be easily achieved through a freely available computer program called Oasys (occupational asthma system) from www.occupationalasthma.com. If particular logging meters are used, these directly download into the program. The Oasys system gives a variety of scores inferring the likelihood that the worker is showing a work-related effect [12-15]. Once suspicion is raised, or confirmation of a work-related effect found, then referral to a specialist centre is advised. The diagnosis given by a clinician affects the compensation that a worker can receive and should lead to removal from exposure to the causal occupational agent to achieve the best prognosis.

Specific challenge testing

If serial PEF measurements have not been obtained previously, these would be carried out by the specialist centre. The occupational asthma specialist would also take a detailed symptom and occupational history plus carry out tests for asthma such as reversibility assessments, exhaled nitric oxide measurements, non-specific challenge testing and in some cases specific inhalation challenge testing.

In some workers, where there is more than one potential causative agent, the agent is something new, or for prognostic reasons it is important to confirm the exact cause, specific inhalation challenge (SIC) tests will be performed. Specific inhalation challenge testing is considered to be the "*gold standard*" for occupational asthma diagnosis [16-19] and was first promoted by Pepys and colleagues for occupational exposures [20]. The test involves exposing the worker to a small amount of the likely causative agent(s) that they are exposed to in the workplace. It is usually performed in a dedicated laboratory and in a way that mimics the work exposure. For some allergens, solutions are available which can be nebulised (e.g. cow epithelium and metal salts). There is generally a lack of standardised methods for some agents, yet the method used is likely to have an impact on the results.

Specific inhalation challenge testing is time consuming, as only one allergen can be tested each day due to the occurrence of possible late reactions (anytime from 1 hour to 12 hours post exposure). Guidelines on how to perform SIC testing have been produced by an European Respiratory Society (ERS) taskforce[21]. **Figure 1** shows the SIC procedure for Birmingham, UK. Workers are generally admitted into hospital for the tests for 1 week. Non-specific bronchial reactivity measurements are carried out at the beginning and end of the week to see if an increase in reactivity has occurred (which would further confirm a positive test). Asthma treatment is stopped in line with normal rules for non-specific bronchial reactivity testing, the patient then ideally remains off treatment for the week of the challenge testing. The main reason for stopping treatment is to remove beta agonist and anti-muscarinic therapy. With most inhalers now being dual therapy (steroid plus bronchodilator), the stopping of inhaled steroids can mean the patient becomes very variable and therefore difficult to challenge, so a decision is made as to whether to keep these patients on inhaled steroids only throughout the challenge test, or combined medication at night only. The SIC is carried out in a small room that is $9m^3$ in size. Depending on the agent being tested and how it is used in the workplace, workers may tip the agent to create a dust, the agent may be heated for the worker to breathe in any fume, or the agent could be nebulised or painted/sprayed. The decision about which agents could be a problem comes from previous research and case studies in the area and known reactions that take place with certain products.

Pre-challenge: measurement of non-specific bronchial reactivity and FEV_1/PEF readings performed over 2 days away from work before the challenge (weekend before)

⇩

Day 1: Placebo challenge to either another agent that the worker is exposed to but is unlikely to be the cause, or an agent which has similar (physical) properties to the active challenge agent so can be administered in the same way but is unlikely to be an allergen. F_ENO measured pre and 24 hours post challenge.

⇩

Day 2-4: Active challenge administered in a similar way to how exposed at work. Start off with a low concentration (day 2), then if needed, increase the concentration/length of time exposed on subsequent days. Or, challenge to different agents each day. F_ENO measured pre and 24 hours post challenge.

⇩

General method: Each day, baseline FEV_1 measurements are made, and then the worker is exposed for up to 2 hours (depending on the agent) over 3 challenges. After each trip to the challenge chamber, FEV_1 measurements are performed. If the worker decreases by > 15%, they will not re-enter the challenge chamber. If they maintain their FEV_1, they will undergo all 3 challenges, then return to the laboratory to perform FEV_1 measurements every 5 minutes for half an hour, every 10 minutes for half an hour, then every hour until bed.

⇩

Analysis 1: Results are plotted in excel and checked before deciding what to do the following day. If the worker has at least 2 points ≥15% below their baseline FEV_1, this would constitute a positive test. If a small fall is seen, a greater exposure may be given the following day. If no response is seen, the next agent will be tested.

⇩

Analysis 2: If 2 points are below the lower limit of the 95% confidence interval for FEV_1 from pooled results of the rest/placebo days then this can also be used to constitute a positive test. Using this may mean workers do not need as big a fall as 15%.

⇩

Post-challenge: measurement of non-specific bronchial reactivity.

Figure 1. Flow diagram showing SIC procedure in Birmingham

Mechanism and Agents

The mechanism of how the agent affects the lungs is often not known, a few are known to be immunoglobulin E (IgE) mediated and specific IgE levels can then be measured in the blood. Material safety data sheets are gathered for all possible causative products and their specific agents assessed for sensitising potential. A group in Manchester at the Centre for Occupational and Environmental Health have produced a system which looks at the chemical structure of an agent and it's occupational asthma hazard potential [22]. This is very useful when "*drilling down*" into specific causative agents and trying to work out which could be more of an issue than others.

Workplace challenge testing

For exposures that are difficult to recreate in the laboratory setting e.g. welding or diesel fume exposure, a workplace challenge may be carried out instead. This would involve a specialist scientist/ physiologist going to the workplace environment and carrying out measurements on site rather than in the laboratory. This may happen over 2 or more days, the first day possibly being in an area of the workplace without the suspected causative agent and the subsequent days being spent in the workers normal environment. The drawback of this type of testing though is that other exposures will also be present thereby the specific cause is not easily found as is the case with serial PEF measurements.

Sensitivity and Specificity of SIC

The sensitivity and specificity of specific inhalation challenge tests are difficult to assess as SIC is considered to be the gold standard so there is no recognised reference to compare with. It is likely that false negative tests occur, for example due to exposing to a lower dose than experienced at work, exposing the worker to the incorrect causal agent, exposing them by a different method to that taking place at work (if it cannot be reproduced easily in the laboratory) [23] or if there has been a long time since the worker was last exposed to the agent. A number of authors have found some workers to have a negative specific inhalation challenge when other tests for occupational asthma are positive [24-28]. False positive reactions may also occur if too large a dose of an agent is given (irritant), or if a subject has severe non-specific bronchial reactivity [29].

CONCLUSIONS

Specific inhalation challenge tests require specialist input and are time consuming. They remain the gold standard test in the diagnosis of occupational asthma, but do not always elicit a positive outcome even when other physiological evidence of a work-related change in lung function has been found (often through serial PEF measurements). Making the diagnosis of occupational asthma early and acting on it gives the best outcome for the worker.

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The next ARTP Annual Conference is on Thurs 25th – Fri 26th January 2018 and we are returning to the Hilton Brighton Metropole.

Please Click Here for further details or for Registration.

We are thrilled to offer so many diverse sessions around the fields of Respiratory physiology and medicine, and believe we have put together an excellent selection of speakers. Here are some of the highlights:

PK Morgan Memorial Lecture, this year we are delighted to have Professor Peter Calverley, Professor of Pulmonary and Rehabilitation Medicine, from University of Liverpool

Extreme Physiology Session – From Ice to Dust: Extreme Medicine, Dr Mike Stroud

There are also specialist sessions on: Sleep, Paediatrics, Cardiopulmonary Exercise Tests, Pulmonary Rehabilitation, Cough

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The P.K. Morgan Memorial Lecture

The Guest Lecture at the annual ARTP Conference is named after my father, the late Philip Kenneth Morgan, to commemorate his distinguished work in the development and manufacture of cardiopulmonary devices.

Philip Kenneth Morgan
25th January 1927 – 26th August 2007

This prestigious lecture invites eminent speakers, who share Philip's passions, to speak on fascinating topics in the respiratory physiology field ranging from asthma in elite athletes, allergy, atopy, inflammation and bronchial challenge testing, to respiratory muscle assessment.

Previous Speakers

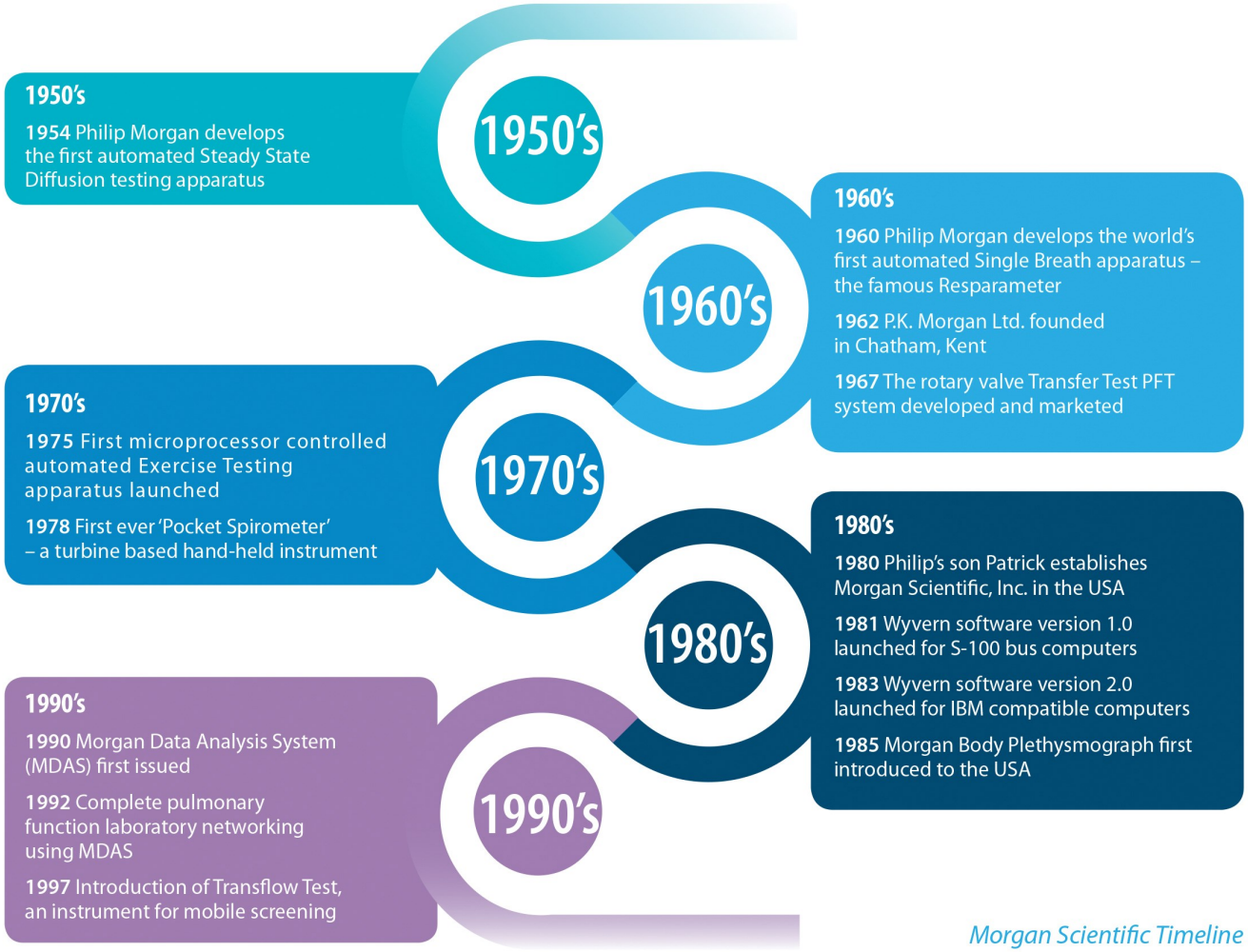
Year	Speaker
2008	**Dame Helena Shovelton,** BLF
2009	**Dr Kim Prisk,** University of California
2010	**Mr Patrick Morgan,** Boston USA & **Mr James Sullivan,** New York USA
2011	**Dr Paul Enright,** Tucson, Arizona USA
2012	**Dr Neil Martin,** Leicester
2013	**Professor Denis O'Donnell,** Ontario Canada
2014	**Professor John Moxham,** London
2015	**Dr Chris Corrigan,** London
2016	**Professor Mike Hughes,** London
2017	**Professor Sandy Anderson,** Australia

The January 2018 ARTP Annual Conference sees the 11th memorial lecture and is a good time to look back at the legacy of this distinguished man who gave so much to British respiratory medicine and helped to shape the pulmonary function test equipment we use today.

Philip Morgan was one of the founding fathers of British manufacturing in the field of pulmonary function diagnostics, from his early days at the Brompton Hospital to being a director of Godart- Mijnhardt Ltd before forming P.K. Morgan Ltd.

The invention of the Resparameter from the Medical Research Council in Llandough Hospital Penarth, provided the commercial realisation that enabled P. K. Morgan Limited to develop links throughout the UK and all over the world. At that time, the reliable measurement of carbon monoxide posed a serious challenge. Philip formed the Analytical Development Company Ltd (ADC) together with engineers in Hoddesdon, Hertfordshire to specialize in infra-red gas measurement techniques. ADC went on to lead the world in infra-red instruments used in both industrial and medical applications. In the 1970's P.K. Morgan were the first company to introduce microprocessors into a pulmonary function range. Philip continued to work closely with UK research to develop and introduce ideas such as the nasal airway resistance tester (NART), a project with Dr David Hughes and the Wellcome Research Laboratories, the Glasgow Vest Transducer (GVT) a UK alternative to the Respitrace, the Nebicheck a dosimeter developed in cooperation with Dr Reg Mills and Roger Carter, an X-ray Planimeter a collaboration with Dr David Denison at the Brompton Hospital and even a foray into the world of basal body temperature used in fertility monitoring through the World Health Organization.

The Resparameter developed into the highly popular Transfer Test Series that led the UK market through the 1970's, 1980's and 1990's. The Transfer Test USA was developed for the United States market where hundreds of instruments were sold during the 1980's. This success was followed by the introduction of the Transfer Test Benchmark along with the highly popular Body Plethysmograph and Exercise Test systems.



Morgan Scientific Timeline

Philip worked closely with The Brompton Hospital, The London Chest Hospital and Kings College Hospital. He also was instrumental in the formation of the ARTP together with Derek Cramer, Jane Jones and Len Smith.

Philip was always involving himself with new ideas, new approaches and technology, always trying to expand the development of respiratory medicine. In the mid 1990's the growing pressures of the Corporations that supply the medical markets showed the fact that inexpensive general instruments were taking over from any innovative instruments that placed the tools necessary for research back in to the hands of the Physiologist users. The push button technology was taking hold.

In response to the need to raise capital to fund further research Philip reluctantly allowed the company he had formed to be sold. He continued to work for the company until it became clear that the hoped for investment was not forthcoming, signalling the end of the company that was proud to carry the name 'P.K. Morgan'.

"Many of us will hold fond memories of Philip from his 'hands on approach' he would sell, install and service your instruments, train you in the correct use of the instruments and be there to advise you when you have the difficult subject that seems to defy the instruments abilities." Kevin Hogben

In 2010, I was honoured to be invited over to the UK to give the lecture in dedication to my father. I invited one of America's leading technologists, James Sullivan, to share the stage, because I wanted the ARTP to see the influence of my father's passion through transatlantic eyes.

In the early days of introducing P.K. Morgan products into America, it was quickly apparent that the quality and clinical background of the Morgan hardware was beyond equal. However, as computers quickly became the norm in respiratory function, it was also clear that a new emphasis on software was required.

Working with software engineers in Andover, Massachusetts and clinical partners at Massachusetts General Hospital (MGH) and Boston Children's Hospital, my own company, Morgan Scientific began developing a suite of pulmonary function software in 1981. This product, known to many as MDAS was sold back though P.K. Morgan Ltd around the world. In 1985, we completed the first ever hospital information interface at MGH sending results from the pulmonary lab directly into the billing systems and clinical data centres of the hospital. As our reputation grew in pulmonary function software, we were continually encouraged by my father to "stay closely allied with clinical centres".

This sound advice has remained with us ever since and we can proudly say that today our products continue to be infused with ideas from America's leading teaching hospitals.

The third generation of Morgan's now work to improve our products; Gareth Morgan is a PhD who works to expand our company in sales and clinical collaboration and Stuart Morgan leads software development.

In our testing area, we have a wonderful picture of my father that everyone admires; his steely blue eyes fix anyone who looks at the picture with a determination and pride that is unmistakable.

Thank you on behalf of all the Morgan Family for honouring someone we so admired and loved.

Patrick Morgan

Patrick F. Morgan

President

Morgan Scientific, Inc.

Matt Rutter

Alan Moore

Prof. Brendan Cooper

ON THE BLOWER

A brief OTB this issue as we managed to meet with some of you at the National Strategy Day and of course we shall see you soon, at ARTP conference 2018. Happy Christmas to our Manufacturers and thank you for your ongoing support.

We mentioned in a previous version of “On the Blower” that we would be relocating our office in Basingstoke where we would be better able to serve our customers as a pure-play “breathing company,” Vyaire Medical. I am pleased to say that this has now happened.

Moving forward telephone numbers will remain the same for the office support team and for your field customer support team. Our new address is;

Vyaire Medical
Waterside
Frog Lane
Mapledurwell
Basingstoke
Hampshire
RG25 2JR

Tel:	01256 388517 and 01256 388512
Email:	uk-respiratory-service@vyaire.com
	uk-respiratory-sales@vyaire.com
Website:	https://www.vyaire.com/uk/our-products/respiratory-care/cardio-pulmonary-diagnostics

I can also confirm that our new Vyaire RDx Training Centre will be up and running from early December 2017. Throughout the year we will look to host various training courses on our products and services that will give you the opportunity to be fully engaged, out with your place of work.

Additionally we would welcome everyone, to come along and learn about our various products and connectivity solutions whether you are an existing/prospective user or simply one with a keen interest in what latest technology we have to offer. We are extremely excited about our new Vyaire RDx Training Centre, and we hope that you will share the same enthusiasm by coming to visit us in the near future.

ADDED AIR

ARTP @ARTP_News Retweeted ERS publications @ERSpublications Nov 23

Pulmonary haemodynamics during exercise provides relevant information on the lung, pulmonary vessels and heart http://ow.ly/EBOF30fuHWY

Leeds Respiratory @RespNetwork Retweeted PCRS UK @PCRSUK Nov 20

Single spirometry or clinical respiratory symptoms alone are not enough for accurate COPD diagnosis - npjPCRM http://go.nature.com/2z2Nvdg @noelbaxter @stonny999 @ARNS_UK @lunguk

Leeds Respiratory @RespNetwork Retweeted Prof. Nicholas Hart @NickHartThorax Nov 20

Clinical diagnoses are based on probability...history (e.g. cough, sputum and wheeze), examination (e.g. prolonged expiratory phase and wheeze), simple investigations (spirometry) and advanced investigations (CT) increase the probability of a correct diagnosis of COPD...

Alex Perkins @physiologic_al Nov 11

Better and more responsive healthcare professional regulation is needed for #HealthcareScience @ARTP_News @ahcsuk @ClinPhys Have your say: https://consultations.dh.gov.uk/professional-regulation/regulatory-reform/ ...

ARTP Retweeted CHESTVerified account @accpchest Nov 11

End-diastolic pressure ratio may be marker for treatment response in patients w/ pulmonary hypertension. http://dx.doi.org/10.1016/j.chest.2017.05.008

Hannah syed @syed_hannah Nov 9

Great evening learning how to optimise inhaler technique in adults and children with nursing and pharmacy colleagues.

ARTP Retweeted @The_HCPC—Nov 8

The @DHgovuk is now consulting on regulation of medical associate professions in the UK http://bit.ly/2z2zmMO

ARTP Research Retweeted Lancet Respiratory @LancetRespirMed Nov 6

#RCT: FeNO as a predictor of response to ICS in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility

James Hull @Breathe_to_win Oct 16

Commuter thought for the day. Dispersion of #cough droplets in a rail carriage - 2 minutes! http://www.sciencedirect.com/science/article/pii/S036013231100093X ...

ARTP @ARTP_News Oct 31

Compared with TLCO alone, combined TLCO–TLNO measurement does not improve detection of PH in unselected SSc pts https://t.co/MpeHI08IKj

ARTP @ARTP_News Oct 31

Biological variability of lung clearance index is dependent on magnitude; % change is better for tracking patients https://t.co/DqX6RL8cK8

ARTP @ARTP_News Oct 31

Management of hypertension in OSA https://t.co/zHNtjN2toF

We HC Scientists @WeHCScientists Retweeted Team NUH Oct 30

We HC Scientists Great to see a #healthcarescience team get @nottinghamhospitals 'Team of the Week' award. Congrats to all in Lung Function @ARTP_News

Team of the Week are our colleagues in Lung function who support lots of different services. https://t.co/xcKjX7sY6U

"Air pollution in Victorian-era Britain – its effects on health now revealed" – http://theconversation.com/air-pollution-in-victorian-era-britain-its-effects-on-health-now-revealed-87208

An airway traffic jam: http://casereports.bmj.com/content/2017/bcr-2017-220514.full

Teaching science is good for you: http://casereports.bmj.com/content/2017/bcr-2017-220514.full

"Delhi suffers second smog crisis in 12 months, as wake-up calls go unheeded" – http://theconversation.com/delhi-suffers-second-smog-crisis-in-12-months-as-wake-up-calls-go-unheeded-87604

Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study
http://www.thelancet.com/journals/lanres/article/PIIS2213-2600%2814%2970034-7/fulltext

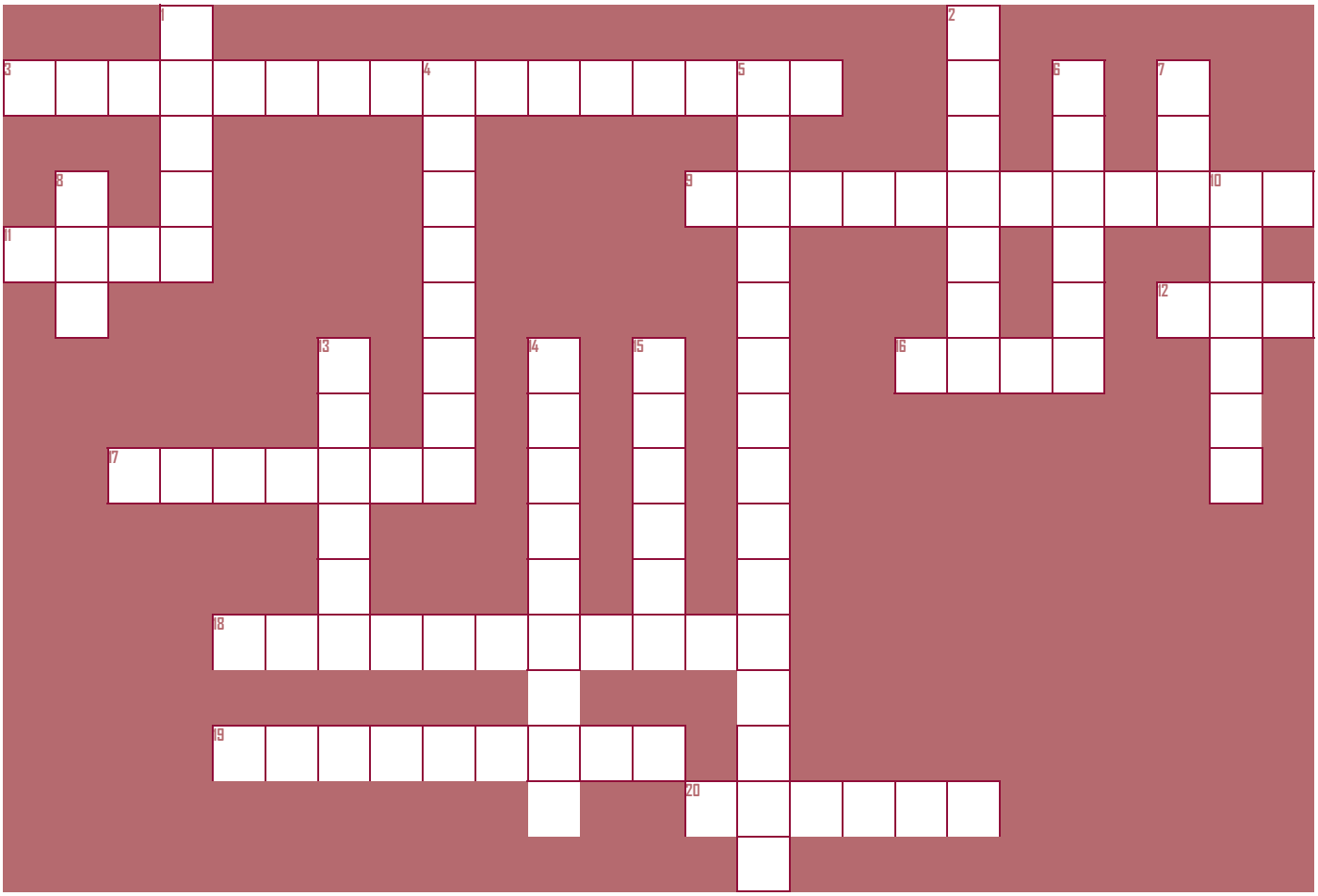
H1N1 Influenza (2015-2016): Critical Illness Outcomes in Vaccinated vs Unvaccinated Patients.
http://journal.chestnet.org/article/S0012-3692%2817%2931759-2/fulltext

Changes in lung function of CF infants could be reversible
https://www.ersnet.org/the-society/news/changes-in-lung-function-of-cf-infants-could-be-reversible-during-early-life?utm_source=ERS+newsletter&utm_campaign=3de046098a-ERS_Newsletter_32&utm_medium=email&utm_term=0_372fc3467c-3de046098a-46046233

Physical Activity and Fatigue in Patients with Sarcoidosis
https://www.karger.com/Article/Abstract/481827

Improving CPR Performance - Cardiopulmonary Interactions
http://journal.chestnet.org/article/S0012-3692(17)30883-8/fulltext

‘NO PRIZES’ CRYPTIC CROSSWORD



All answers related to lung function.

Answers to ‘No Prizes’, August 2017 issue:

Across.: 4. BRONCHUS, 6.TRANSFER, 9. POLLUTION, 10. BODY, 13. SPIROMETRY, 14. EXERCISE, 16. ASTHMA, 18. FIBROSIS, 21. ALVEOLI, 22. CPET, 23. LUNG, 24. COPD

Down:: 1. NITRIC, 2. SKIN, 3. PULMONARY, 5. NEBULISER, 7. EMPHYSEMA, 8. VOLUME, 11. MONOXIDE, 12. BETA, 15. INHALER, 17. TRACHEA, 19. SMOKING, 20. FLOW, 23. POOL

ARTP Association for Respiratory Technology & Physiology

CLUES

ACROSS

3 Could be new Latin facial growth chart flowmeter (16)

9 70s shoe style above puffers for spirometer type (5, 7)

11 The earth minus initial gravity for portion of lung (4)

12 Take the rise out of this curved bone (3)

16 This physical exercise flair regime is absolutely capital! (4)

17 Total hesitation by Germany's limits gives aversion (7)

18 Dosimeter at play measures height (11)

19 A heel clang might be difficult, especially if provoked (9)

20 God of Thunder near less usual implement to create cavity (6)

DOWN

1 Almost tug South East for sign of life (5)

2 Bits of continental beer mixed with hazel perhaps forms spinner (7)

4 Begging with this in hand in London reaches limit? (8)

5 Gets all boxed in with ghastly pop rhyme (15)

6 Rearranged trifle blocks out the nasties (6)

7 Surname of British musician, who sometimes measures inflammation (3)

8 First Order Transfer initially to measure respiratory mechanics (3)

10 Sounds like hanging around for something heavy (6)

13 Base of trachea found during motor car in a diversion (6)

14 It isn't hers, thanks, it's my provoking agent (9)

15 The tallness of alternative VIII? (6)