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Airway Clearance Techniques for Primary Ciliary Dyskinesia; is the Cystic Fibrosis literature portable?

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Educational aims

- To review the existing evidence for chest physiotherapy in paediatric PCD
- To discuss the differences between PCD and CF pertaining to mucus clearance
- To explore the appropriateness of extrapolating CF research to PCD chest physiotherapy practice

Future research directions

Greater understanding of the physiological differences between PCD and CF will increase understanding of how mucociliary clearance is facilitated and when it is impaired.

Knowledge of the effects and benefits of undertaking ACTs in PCD is needed, but as it would be unethical to withhold treatment for a randomised-controlled trial consideration will need to be given to study designs. Large PCD specific trials of pharmacological agents such as mucolytics are also required to quantify the 'true' risks and benefits for this population.

The potential impact of the European Task Force recommendations on practice, is keenly awaited.

Keywords: PCD, Chest Physiotherapy, Airway Clearance, CF,

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Abstract

Primary Ciliary Dyskinesia (PCD) is a rare inherited disease with impaired mucociliary clearance. Airway clearance techniques (ACTs) are commonly recommended for patients with PCD to facilitate mucus clearance, despite a lack of evidence in this group. Current physiotherapy practice in PCD is based on evidence extrapolated from the field of Cystic Fibrosis (CF). This paper focuses on the available evidence and outlines challenges in extrapolating evidence between the conditions for best clinical practice.

1.1

PCD

PCD is a rare, predominantly autosomal recessive condition in which ultra-structure abnormalities of ciliated cells cause impaired ciliary function (1). Impaired ciliary function results in changes across the body including situs abnormalities (dextrocardia, situs inversus totalis), chronic otitis media, sinusitis, rhinitis, subfertility, and the main focus of this review; impaired mucociliary clearance from the lungs (2). Normal ciliary function is essential to clear the respiratory tract from particles and organisms and in its absence, neonatal respiratory distress, a wet cough and persistent nasal discharge are commonly present. Unlike CF, PCD is generally not thought to reduce life expectancy, however in a North American cohort of patients >18 years, 38% of patients had respiratory failure (3). Centres diagnosing PCD use a range of methods including high speed video microscopy, transmission electron microscopy, immunofluorescence microscopy, nasal nitric oxide levels, and genetics which all have recognised limitations (4). In the absence of a single “gold standard” diagnostic method (5), even an experienced team using combination of diagnostic tools can often find inconclusive results making diagnosing PCD challenging (6).

1.2

Epidemiology

Prevalence of PCD in children aged 5-14 years to be between 0.33-0.5 per 10,000 across Europe (7); lower than the European prevalence of CF (0.74 per 10,000) (8). Variance in PCD prevalence rates may be true variance across different populations, illustrated by the unusually high prevalence of 4.4 per 10,000 amongst the Bradford Pakistani population (9). However, spurious variance may be due to under-diagnosis, with patients mis-diagnosed as idiopathic bronchiectasis or asthma in geographical areas with a lower awareness of PCD or under-diagnosis where availability of diagnostic services are limited (7). The age of diagnosis can vary with a median of 5.3 years across European paediatric centres (7) compared to a median 23.5 years, range 1-72 years in an adult specialist centre (10),

reflecting the challenge of diagnosis. Symptoms of a productive cough, rhinorrhea and otitis media can be common amongst healthy children, making the presence of situs inversus key in early diagnosis for the 50% patients with this feature of the disease (7). It is anticipated that prevalence, diagnostic and clinical data will become more detailed and reliable with the development of national and international registries.

1.3

PCD management

Links between early diagnosis, lower incidence of bronchiectasis and stable lung function have been established for over two decades (11) and later diagnosis has been associated with increased frequency of *Pseudomonas aeruginosa* colonisation and lower baseline lung function (FEV₁) (10). Once diagnosed, condition specific management can be commenced. A survey of paediatric PCD patients in European centres (including Turkey, Israel, Serbia and Estonia), conducted between 2007 and 2009, aimed to describe service organisation, diagnostic methods, treatment-options and long-term follow up (12). There was greater consistency in the methods used to diagnose PCD than the treatments used to subsequently manage patients and care seemed to mostly be de-centralised. Diagnostically, 90% had access to nasal or bronchial mucosal biopsies for patients suspected to have PCD, whereas for PCD management; the prescription of antibiotics for exacerbations was consistent (87.6% using routinely) but prophylactic antibiotic use was more varied (58% using sometimes). Variance was also seen across nebulised hypertonic saline (45.95% using sometimes), inhaled corticosteroids (69% using sometimes) and nebulised rhDNase (41.2% using sometimes). ACTs were more consistently recommended with 78% of centres prescribing these to all patients and 85% of PCD teams employing an integrated physiotherapist. Although the results of this survey were not published until 2012, data collection was undertaken in 2009, prior to publication of European Task Force proposals for diagnosis and management of children with PCD (5). These recommended specialist-centre care (either shared- or full-care), regular airway clearance (physiotherapy and exercise), and advised on antibiotic use (in acute airway infections, managing patients colonised with *Pseudomonas aeruginosa* and prophylaxis), anti-inflammatory strategies, exposure to smoke and pollutants and advised against the use of N-acetylcysteine. These recommendations were based on PCD evidence categorised by the task force as low level on the BMJ GRADE scoring system (13), evidence extrapolated from CF evidence or on expert opinion.

1.4

Airway Clearance Techniques (ACTs)

ACTs are a range of interventions which aim to facilitate clearance of mucus from the airways. These are typically advised by a physiotherapist across a range of conditions in which the normal physiological mucociliary escalator is unable to effectively clear the airways of the mucus produced. Physiologically ACTs aim to influence regions of ventilation, splint open small airways, access channels of collateral ventilation, optimise and bias airflow, manipulate the location of the equal pressure point and oscillate air within the airways. The skill and expertise of a physiotherapist involves identification of the barriers to the natural mucus clearance in an individual, then selecting and advising on application of appropriate ACTs to overcome or address the identified barrier. A benchmarking exercise of English Paediatric PCD Centres demonstrated the range of ACTs undertaken in this group including; positioning, manual techniques (percussion, vibrations), positive pressure adjuncts, breathing techniques, and oscillatory devices.

2.1

Physiotherapy evidence in PCD

Systematic review of the paediatric PCD literature in databases Medline, Embase, Cinahl and Amed found 375 studies using search terms which included variant terms of PCD and physiotherapy or ACTs. Of these 342 were excluded (62 duplications, 28 adult studies, 1 animal study and 252 which did not actually involve ACTs in PCD). Of the remaining 35 results, 18 comprised of guidelines, literature reviews, conference summaries or PCD overviews which were searched for relevant contents and references. Finally 4 case reports mentioned but did not focus upon ACTs, 3 studies focused on quality of life and 1 study had a mixed Bronchiectatic population and sub-group analysis was not undertaken. The 4 remaining publications pertaining to this area comprised of two studies on exercise (14-15), a discussion paper (16) and a study which specifically focused on the utility of high frequency chest wall oscillation (HFCWO) (17).

2.2

Evidence for ACTs in PCD

A randomised cross-over design was used to compare HFCWO with postural drainage percussion and vibrations (PDPV) in 12 positions performed by a physiotherapist (17). Twenty four paediatric PCD patients received one intervention for 5 days and after a 2-day washout period; they received the alternate intervention for 5 days, with patients randomly allocated to receive either manual techniques or HFCWO first. Outcomes included lung function and patient's reports of both comfort and perceived effectiveness of the

interventions. A significant improvement in lung function was seen following both interventions, but there were no significant differences when comparing interventions. Patients preferred HFCWO, however this finding must be interpreted with caution. Firstly, participants were in-patients for the PDPV period but at home for the HFCWO period. Hospitalisation can be disruptive and associated with times of active illness and this may have negatively biased patients against PDPV. Secondly, the patients may have been predisposed to prefer a new novel treatment. The generalisability of these findings may be limited as the sample had a much higher proportion of situs inversus totalis (91.7%) than the general PCD population.

2.3

Evidence for exercise in PCD

PCD consensus statements suggest regular exercise may assist secretion clearance and have a positive bronchodilation in PCD (2, 5). Again, there is a paucity of literature with only 2 studies pertaining to exercise in paediatric patients with PCD identified in the search. One study evaluated the effects of exercise and a 200µg dose of salbutamol on lung function in 12 paediatric PCD patients (14). The interventions of 8 minutes on a treadmill and a dose of salbutamol were given in succession with a rest period, concluding when Peak expiratory flow rate (PEFR) had returned to baseline, used as a washout period. It was reported that 10/12 participants had a better bronchodilator response to exercise than salbutamol, however as spirometry was only measured at the start and end of the assessment and not between the exercise and salbutamol, it is impossible to attribute the improvements to salbutamol alone. Additionally published data illustrates variable PEFRs during exercise with intra-subject increases and decreases from baseline in 8/12 of the group. Without a measure of cough frequency or secretion clearance, interpretation of the results becomes more equivocal. With 16 fast expiratory manoeuvres (PEFR) undertaken to collect data during the intervention, the process of data collection could have caused secretion movement, changes in airflow and fatigue. It is hypothesised that changes seen in spirometry and PEFR in this study are due to a combination of physiological changes and, importantly, secretion clearance.

Another study investigated exercise tolerance in PCD patients (15) using maximal cardiopulmonary testing, in 10 paediatric patients with PCD and 8 matched controls. They found reduced exercise capacity in the PCD patients compared to control (VO_{2peak} and increased VE/VCO₂ slope), which reached statistical significance in the 40% of the PCD sample who had low lung function ($FEV_1 < 85\%$). Whilst the sample size was small, the

clinical value of exercise testing in PCD for both assessment and to guide exercise advice can be considered. With physical and psychological benefits of exercise in children it is reasonable to recommend exercise to patients with PCD generally. However with an absence of evidence of the effects of exercise on mucus clearance, caution should be taken when recommending exercise in isolation for airway clearance.

3.1

Key differences between CF and PCD

With minimal evidence of the effectiveness of ACTs in PCD, practice is often based on evidence extrapolated from research in CF (18). Yet, there are notable differences in the pathophysiology, disease trajectory and symptoms of the two conditions (19) and it is important to consider differences between the conditions which may influence clinical application. PCD is often likened to CF, which is also an inherited condition in which mucociliary clearance is impaired. However in PCD the impairment of mucociliary clearance is primary and present from birth whereas in CF the mucociliary clearance impairment is secondary, possibly due to inflammation, and may be preserved at least initially (20): many patients with CF do not have respiratory symptoms at birth. As newborn screening for CF has successfully reduced the age of CF diagnosis to a median of 3 weeks (21), debates over whether to prescribe routine ACTs to asymptomatic infants with CF have become more common (22). These debates are arguably less relevant to PCD as, with symptoms from birth and commonly later diagnosis, commencing regular ACTs at the point of a confirmed or suspected diagnosis of PCD should be recommended.

In PCD, unlike CF, no correlation has been found between the most reliable measure of airway disease (high-resolution CT) and more routinely used measures (lung function and lung clearance index (LCI) (23). As routine CT's are not conducted due to risks, costs and accessibility this poor correlation makes the clinical identification of early signs of deterioration more challenging. LCI is more commonly abnormal than lung function in PCD, suggesting abnormalities develop in the distal airways prior to the proximal ones (24). When comparing PCD with CF it is hypothesised that there is a different ratio of proximal to distal airway disease with CF patients having a greater severity of proximal airway disease (23). In PCD a productive cough is usually present from birth leading families become accustomed to its presence and role in clearing secretions. It must be remembered that whilst an effective cough clearance mechanism is regularly observed in PCD, peripheral airway dysfunction exists preventing mobilisation of mucus from smaller airways (24).

3.2

Selection of appropriate ACTs

There are a number of interventions shown to be effective in CF which are widely applicable to PCD due to common physiological principles. Normal mucus clearance occurs through a combination of ciliary clearance and airflow forces shearing and mobilising mucus. This led to the development of Autogenic Drainage (AD) (25), which guides patients through the manipulation of lung volumes and airflows to move mucus from smaller to larger airways. With the absence of an effective ciliary beat, one of two key components in mucus clearance, it is logical to utilise the effects of airflow forces in PCD through the utilisation of AD. An alternative breathing-pattern-based ACT used in both PCD and CF, the active cycle of breathing technique (ACBT), aims to optimise ventilation by reducing ventilation asynchrony and mobilise mucus from smaller to larger airways before expectoration. As such, it is reasonable to consider either the ACBT or AD in patients with PCD, and with an element of concentration and understanding required, clinicians should advise patients on these on an individualised basis (26).

Positive expiratory pressure (PEP) devices in CF care have been shown to increase functional residual and total lung capacities (27) and would have similar applicability in PCD patients in accessing the channels of collateral ventilation and mobilising peripheral mucus. Oscillatory PEP devices cause vibrations of the airway walls, which in CF are used to alter mucus rheology and augment mucociliary clearance, in addition to the previously discussed benefits of standard PEP. All commercially available oscillatory devices (Acapella®, Flutter®, Cornet®, Aerobika®) provide oscillatory frequencies similar to normal ciliary beat frequency, which is thought optimal for secretion clearance (28). Ciliated cells show mechano-sensitivity, and stimulation of cultured cilia from healthy samples showed a temporary elevation in frequency ciliary beat and potentially increase mucus clearance (29). As ciliary beat is commonly slowed or absent in PCD, it is unclear whether the proposed effects of oscillatory devices would have a greater or lesser impact on mucociliary clearance in PCD. This is an important area for future investigation and raises the prospect of ACT prescription tailored to ciliary abnormalities in the future.

3.3

Optimisation of ACTs

The position in which patients undertake an ACT can be varied and positioning is commonly used alongside other ACTs to target areas of lung and optimise regional ventilation (30). Ventilation is usually greatest in the dependant regions of the lung; the lower lobes in sitting,

the lowermost lung areas in supine and the dependant lung in side lying (31). However caution should be taken when applying positioning principles as ventilation is thought to be highly variable even amongst healthy children (32). The location of bronchiectasis within the lung has been found to differ on CT scan of patients with PCD and CF. In CF, the distribution of bronchiectasis is seen mainly in the upper lobes, yet in PCD bronchiectasis is more commonly seen in the middle and lower lobes (33-35). It has been suggested that the relative sparing of the upper lobes in PCD may be due to the gravitational augmentation of secretion clearance from these areas (35). Thus clinicians may need to explore positioning options for patients with PCD, utilising CT scans to target focal areas and physiological based clinical reasoning to tailor ACTs for each individual and optimise their efficacy.

3.4

Consideration of mucus properties

In CF, impaired Cl⁻ and HCO₃⁻ secretion and increased epithelial Na⁺ absorption result in dehydrated mucus, which when compounded by the effects of inflammatory mediators make CF mucus understandably challenging to clear. Despite differing pathophysiology, mucus from PCD patients has been found to have similar biophysical and transport properties to CF mucus (18), with significantly higher interleukin-8 levels in PCD mucus than in CF mucus (18,20). Within CF, mucolytic dornase alpha (rhDNase) and osmotic agents such as nebulised hypertonic saline are recommended to assist with mucus clearance (36) and can be used as an adjunct to ACTs.

The potential risk of extrapolating evidence between conditions is illustrated by the evidence base for rhDNase. Studies in CF have shown improvements in lung function trajectories and rates of exacerbation with rhDNase (36). Yet conversely, a large high quality RCT in adults with idiopathic bronchiectasis found an increased frequency of exacerbations and a greater rate of decline in lung function with rhDNase compared to placebo (37). Whilst this has led to recommendation against the use of rhDNase in PCD (5) improvements in lung function have been found in a small number of PCD patients (38-39) reflecting the continued use of this costly and controversial mucolytic in some centres (12). With conflicting evidence from other conditions and a small PCD evidence base, larger scale trials are needed within PCD to inform and guide practice not only with rhDNase but with all pharmacological adjuncts to ACTs.

3.5

The impact of undertaking ACTs

Undertaking daily treatments such as ACTs are time-consuming and can be a considerable treatment burden for patients causing psychosocial implications. Within PCD, ACTs can serve as a cue that individuals might feel different to their peers and reminders of disease (40). Coughing is one of the most visible signs of abnormality in PCD, yet one of the essential elements of an effective ACT session. Coughing can be a stigma for patients with PCD and some children and young people cough suppress to conceal their disease (41). In this sense, ACTs can be a 'private' element of self-care. Clinicians and patients need to work together to balance the challenges of care with the benefits of maintaining quality of life in the future (42). It is hoped that the emergence of a PCD specific quality of life measure will help to understand the impact of treatments much more (43).

4.1

Future research directions

Greater understanding of the physiological differences between PCD and CF will add to understanding of how mucociliary clearance is facilitated and when it is impaired. Whilst it would be unethical to withhold ACTs from patients with PCD, randomised-controlled trials of their effects, knowledge of the benefits of undertaking daily time-consuming treatments is needed. Large PCD specific trials of pharmacological agents such as mucolytics are also required to quantify the 'true' risks and benefits for this population. The impact of European Task Force recommendations on practice, especially in aspects where practice was not in line with recommendations is keenly awaited.

4.2

Conclusion

In the absence of PCD-specific research, clinical practice must be based on the best available evidence and expert opinion. Knowledge and understanding transposed from studies in people with CF have provided the foundation on which PCD care has been built. However, there are fundamental physiological differences between the conditions and caution needs to be exercised prior to more comprehensive extrapolation. The lack of research in PCD populations is well recognised but it is hoped that the evidence-base will grow. At present, consensus supports the recommendation of ACTs to all patients with PCD. Exercise is recommended across the general population and should be encouraged in patients with PCD, however its utility as an airway clearance technique needs further evaluation. The clinical reasoning of treatments based on sound physiological principles sits within the scope of physiotherapy and regular physiotherapy reviews will ensure patients with PCD undertake effective ACTs.

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