OPEN ACCESS Freely available online

Clinical Pediatrics: Open Access

Review Article

LCI as a Marker of Disease Progression in Saudi Paediatric CF Population?

Adnan Zafar*, Wadha Alotaibi and Khalid Al-Mobaireek

Department of Pediatric, King Fahad Medical City, Children Specialized Hospital, Riyadh, Saudi Arabia

ABSTRACT

Aims: Cystic fibrosis in children forms a significant disease burden in Saudi children. Due to lack of new-born screening, many patients are diagnosed relatively late. Disease surveillance by efficient monitoring measures is vital for halting disease progression. LCI (Lung Clearance Index) is commonly used in western world and is a very reliable toll in preschool as well as school going population. We reviewed at best available evidence to make local clinicians think about adopting this test.

Methods: We searched for comprehensive articles for LCI in preschool and school going children in PubMed. The quality appraisal and selection of the final two articles was selected by all three authors adopting CASP (Critical Appraisal Skills Program).

Results: Articles by Aurora et al. and Stanojevic et al. were selected for inclusion for this review.

Conclusions: LCI is a consistent method of monitoring lung health in cystic fibrosis children, particularly in preschool children. LCI is more sensitive than spirometry in detecting lung function abnormalities in patients with CF beyond infancy. It needs effort by clinicians from tertiary care centers to be adopted and implemented in CF centers in Saudi Arabia.

Keywords: Cystic fibrosis; Children; Lung function; Lung clearance index; FEV1

Abbreviations: CEV: Cumulative Expired Volume; CF: Cystic Fibrosis; CI: Confidence Interval; FEV1: Forced Expired Volume in First Second; FEF25-75: Mean Expiratory Flow between 25% and 75% of Forced Vital Capacity; FEF75: Flow Measured After 75% of Forced Vital Capacity has been Exhaled; FRC: Functional Residual Capacity; FRCpleth: Functional Residual Capacity derived from Plethysmography; FVC: Forced Vital Capacity; LCI: Lung Clearance Index; MBW: Multiple-Breath Washout; RV/TLC: Ratio of Residual Volume to Total Lung Capacity-Measure of Air Trapping; sRaw: Specific Airway Resistance; SBW: Single-Breath Washout; SD: Standard Deviation; SF6: Sulphur Hexafluoride; TLC: Total Lung Capacity; TO: Lung Volume Turnover (calculated as number of FRCs); VI: Ventilation Inhomogeneitys

INTRODUCTION

The incidence rate of cystic fibrosis in Middle East has been estimated to be 1 in 2000 to 1 in 5800 live births. It has remained elusive to determine precise incidence and prevalence rate of cystic fibrosis in Saudi Arabia [1]. According to survey by General Authority of Statistics in 2016; Saudi Arabia population is estimated at 31.7 million. If we project this figure, there will be at least 800–1000 cases of CF. The median survival was estimated to be from 10 to 20 years of age. It is vital to help these children in their journey of life, as with good control of the disease, these individuals can perform to their potential and live a content life.

Cystic fibrosis is a life limiting inherited condition. Of UK affected individuals with this condition, more than half will live past 41 years of age [2]. Reliable screening and early diagnosis are one salient defining element. Care in specialist centers and more intensive therapy have contributed to an increased median age of survival from 23 years in 2002 to 43.5 years in 2012 in the UK [3]. The overall impact on respiratory health is not as remarkable and

Correspondence to: Adnan Zafar, Department of Pediatric, King Fahad Medical City, Children Specialized Hospital, Riyadh, Saudi Arabia, Tel: 966539457695; E-mail: adnan157@gmail.com

Received: June 12, 2019, **Accepted:** June 26, 2019, **Published:** July 03, 2019

Citation: Zafar A, Alotaibi W, Al-Mobaireek K (2019) LCI as a Marker of Disease Progression in Saudi Paediatric CF Population?. Clin Pediatr OA 4:156.

progressive lung damage may be delayed but inevitably still occurs. This remains the major cause of morbidity and mortality in CF.

Most of the children appear well during the early years, but pulmonary inflammation, infection and structural changes start at early age and take toll as time passes by [4]. There are often no easily detectable markers of disease and by the time symptoms develop, irreversible damage may have occurred. Early infection and inflammation also seem to impact on future health, with evidence that lung function does not return to baseline after an exacerbation, even in infancy.

Which markers are most informative remains an area of contention and investigation in infants and young children and has practical and ethical hindrances? Age between 2 to 5 years is the silent period for lung function. Here we are faced up with a population where infant lung function is no longer feasible and spirometry technique is hard to master.

Background

In 1940, for the very first time, inert gas washout was defined, and this is a measure of gas mixing in the lung [5]. For infants and toddlers, multiple breath wash out is a method commonly employed as it is easy to perform during tidal breathing while the child is sedated. Otherwise a preschool may be distracted by watching TV. It involves measuring declining inert gas concentration in the lungs. For the purpose of accuracy, the tracer gas must be insoluble or minimally soluble in blood. Commonly used inert gases are hexafluoride (SF6), helium and resident nitrogen. Helium and SF6 are washed into the lungs until they are in equal concentration on both sides i.e. the supply and the lungs [6]. At this point, gas supply is disconnected at end-expiration. Washout is then recorded during tidal breathing until the gas reaches $1/40^{th}$ of the concentration [7]. For washout of nitrogen, no wash in period is required as this can be done by inspiring 100% oxygen. For older children, mouth piece is a useful device whereas for young ones, a mask is applied which is sealed.

Spirometry and plethysmography are most common adopted methods for monitoring lung pathophysiological decline in cystic fibrosis. It is important that real time flow volume and volume time loops are examined for quality control [8]. For the purpose of reporting, the largest values for volumes i.e. FEV1 and FVC must be reported even if they are from different man oeuvres and similarly the flows must be recorded where the sum of these volumes is the highest [9]. In experienced hands, spirometry can be reliably performed in 75% of preschool children. With age, the chances of accuracy increases [10].

In children with cystic fibrosis, its use has been limited due to inability and insensitivity to detect early changes. In such patients, large numbers will be required to detect any significant treatment effect [11]. Lung clearance index has now been used for many years to detect ventilation inhomogeneity. It is a numeric value which records the number of times, Functional Residual Capacity (FRC), must be turned over for an inert gas to reach an end concentration which is $1/40^{th}$ of initial value. In diseased state, the number of turnovers to reach the end point is increased. In mathematical terms, lung clearance index is cumulative expired volume divided by the functional residue capacity [12]. The normal value of LCI is constant and is less than 8 [13]. For use in clinical practise, guidelines and quality control measures are available. The equipment required is a fast gas analyzer [14]. The gold standard for measurement is mass spectroscopy. At present, it is mostly performed in specialist centers however commercial devices are being analyzed for validation. In the specialist centers, there is a high success rate i.e. 80% in sedated infants and preschool children [15]. The variability with in and across patients is greater in infants but the coefficient of variation in preschool children is 5.2% [16]. For older children, the value of LCI is independent of age. It is important to bear in mind that in infants, the upper limit of normal is higher. From a study which involved 497 subjects, reference values have been published for MBW with SF6 however these values are specific for tracer gas and device [17].

In Wisconsin neonatal screening project, 64 children with CF were followed over a time span of 16 years. Farrell et al. found that airway obstruction was a late presenting sign in CF children utilizing spirometry [18]. This study reported that decline of FEV1 occurs late in progression of CF lung disease. This finding agrees with who demonstrated reduced peripheral flows measured by LCI even in the presence of normal FEV1 indicating early substantial lung damage [19].

The insensitivity of FEV1 to detect early lung function decline can be explained by theoretical reasoning. Forced expiratory flow is an output of all airways and in early disease these airways with reduced airflow may be masked by healthy airways in terms of flows. One of the other important things to understand is that airway obstruction in CF children is due to intraluminal obstruction rather than airway wall disease as seen in asthma and hence a forced expiratory man oeuvre may dislodge the mucous. LCI has become increasingly a measurement of choice in the evaluation and monitoring of early changes in the lung in CF [20]. The recognition of the significance of LCI has come from large body of evidence showing that it is more sensitive than spirometry and plethysmography in detecting early involvement of peripheral airways in children and adolescents with CF [21]. Gustafsson studied 43 children with CF (aged 3 to 18 yrs.) and reported an elevation in LCI in half to two thirds of those with normal spirometry or RV/TLC values [20].

Evidence base

The articles which were considered as most appropriate for evidence after above search and looking through journals were as follows [22,23].

This was a 12 months longitudinal study. In this study, healthy controls were recruited from local schools and playgroups. Children between 2.5 and 6 years of age with a confirmed diagnosis of CF, and matched healthy control subjects were enrolled at three North American CF centres. Study visits were done at enrolment, 1 month (± 1 week), 3 months (± 2 week), 6 months (± 2 week), 9 months (± 2 week), and 12 months (± 2 week). MBW was performed with the Exhalyzer D. Enrolment was done while there were no symptoms of acute respiratory infection in the preceding 4 weeks. Symptoms were recorded and outcomes measured at all subsequent visits. The authors categorised the visits as stable, if no respiratory symptoms were present. Pulmonary exacerbation was defined as an increase in respiratory symptoms (e.g., cough) combined with clinicians' decision to treat with antibiotics.

There were 412 MBW measurements in preschool children with CF and 391 in healthy children. There was no relationship between LCI and age in healthy children; therefore, an age-independent upper limit of normal was defined a LCI value of 8.

This was observed in 67% of healthy children in the study. In

children with CF, LCI was higher in children with at least 2 previous hospitalizations or infection with *Staphylococcus aureus* [24].

The Intra Class Correlation Coefficient (ICC) in CF was larger than healthy controls (0.57), and this increased further when the analysis done for stable visits (0.71). This is down to changes in symptoms or clinical status of the participant. The association between LCI and FEVt z-score at each visit was low but statistically significant (enrolment: r=–0.30, p=0.02; 1 mo: r=–0.33, p=0.01; 3 mo: r=–0.51, p<0.001; 6 mo: r=–0.59, p<0.001; 9 mo: r=–0.51, p<0.001; 12 mo : r=–0.37, p<0.001). Mostly there was a discordance between LCI and FEVt z-score in children with CF. LCI values were above the upper limit of normal ("abnormal") and FEVt was above the lower limit of normal ("normal"). Authors observed inverse relationship between LCI and FEVt z-score. The authors concluded that no relationship between FEVt z-score and LCI may have been biased for several reasons. In this study, spirometry was not a primary outcome and when children were tired after MBW testing, spirometry was not performed due to difficulties with this age group [25].

This study like the previous one included preschooler (3-5 years) with CF and healthy control subjects. They underwent spirometry and multiple breath washout at preschool age (3-5) and later in school age (6-10). The primary outcome for subjects was LCI from multiple breath washout and FEV1 from spirometry. Secondary outcomes were FVC, forced expired volume at 0.75 s and 0.5 s (FEV0.75 and FEV0.5), and forced expiratory flow between 25% and 75% of expired volume (FEF25–75). Tests were performed in same laboratory for comparison of preschool and school age values [26]. Means were compared by t tests on each occasion. Z-scores were measured from reference equations for spirometry. The lower limit of normal defined as 1.96 z scores [27-29].

The results were either classified as normal or abnormal. The predictability of either spirometry or MBW to detect lung function decline was calculated by positive and negative predictive values. A true positive was an abnormal preschool test followed by abnormal school age test result [30]. A false positive was abnormal preschool followed by normal school age result. The primary analysis was whether the preschool test predicted consequent lung function decline. Forty-five healthy control children and 48 children with CF were recruited. Time interval between tests was 3.7 years (range, 1.3–6.6 yr). Thirty-five (73%) children with CF had abnormal LCI at preschool age, whereas only five children had abnormal FEV1 [31]. From the study, the positive predictive value of preschool LCI for predicting any abnormal school-age result was 94%, with a negative predictive value of 62%. For FEV1, positive predictive value of preschool values for depicting lung function decline was 100%, but negative predictive value was only 25% [32].

CONCLUSION

From a research perspective, relative inability of FEV1 to detect lung function decline in milder disease necessitates larges sample sizes to see benefit in interventional studies. This can be a cumbersome task for intervention in milder form of disease.

FEV1 may well be with in normal range (two standard deviations in these children) with abnormal LCI values. In such instances, for clinician, the pondering point is whether to increase or reduce treatment and this will have to rely on symptomology and microbiology which has its own pitfalls. The prospective value of LCI as an outcome measure has been supported by a series of cross-sectional studies, which have shown abnormal LCI in presence of normal FEV1.

For LCI to be validated as a marker for early disease, it is important to see an effect with intervention i.e. improvement or decline in LCI value with treatment. This can be then correlated with other markers of disease, i.e. clinical symptomology, microbiology, FEV1 and exercise tolerance. The clinical effect has been demonstrated in one longitudinal study based on clinically collected data, and this study suggested that LCI becomes abnormal earlier than FEV1. There is evidence from two other studies that in individuals with established disease, LCI values correlate with response to course of intravenous antibiotics.

Both these studies had subjects who had established lung disease.

Effect on health economics

The early detection of deterioration in lung function and institution of management strategies aimed at halting decline in lung function may reduce the economic burden of this illness. LCI is now known to predict early decline for many years. Cystic fibrosis impacts health care economics in a very important way. The economic health burden includes treatment as well as social burden. Annual total cost of care is €48,603 (ranging from €26,335 to €76,271 for patients without carers and with carers, respectively). Informal care, medications, acute hospitalizations, outpatient clinic appointments, primary health care visits and early retirement of individuals from jobs, all increase the health spending many folds.

Future research

There are further challenges for researchers to clinically utilize LCI as an outcome measure in early CF. There is a need for long term longitudinal studies, but this is obviously going to be cumbersome. It is important to demonstrate that on long term basis, regular LCI monitoring has better outcome for CF patients than using other conventional methods. This will increase its utility or regular basis rather than doing it annually in centres where it is available. Hopefully, there will be new cheaper devices which are also more robust. It is vital that they are validated to same standards. There are two developments which are worth mentioning. One is a system built around a modified photo acoustic gas analyzer and employed by the UK gene therapy consortium. The second is a modified ultrasonic flow meter system developed by a German group, and currently employed in a German multicenter trial. They have both been validated against mass spectrometer developed earlier by. They are promising for use in both pre-school and school age children.

Future direction will include conducting a multicenter randomized control trial and ideally this should be a double blinded trial. This has not been possible so far due to very few centers utilizing multiple breath washout to extract LCI, and then utilizing it as a disease outcome measure. This report compares two test methods and not a treatment effect therefore double blinding might not have had significant yield.

Secondly, for best comparative analysis of test method, test yield will be increased by doing both tests simultaneously for healthy controls and disease population.

CONFLICT OF INTEREST

None

DATA AVAILABILITY STATEMENT

The retrospective observational data used to support the findings of the study are available from the corresponding author upon request.

REFERENCES

1. Banjar H, Angyalosi G. The road for survival improvement of cystic fibrosis patients in Arab countries. Int J Pediatr Adolesc Med. 2015;2(2):47-58.
2. General Authority of Statistics. Riyadh, Saudi Arabia. 2015.
3. Cystic Fibrosis Trust Annual Review 2012/13. 2013.
4. Sly PD, Brennan S, Gangell C, De Klerk N, Murray C, Mott l, et al. Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. Am J Respir Crit Care Med. 2009;180(2):146-152.
5. Darling R, Cournand A, Mansfield J, Richards DW. Studies on the intrapulmonary mixture of gases. I. Nitrogen elimination from blood and body tissues during high oxygen breathing. J Clin Invest. 1940;19(4):591-59.
6. Van Beek EJ, Hill C, Woodhouse N, Fichele S, Fleming S, Howe B, et al. Assessment of lung disease in children with cystic fibrosis using hyperpolarized 3-Helium MRI: comparison with Shwachman score, Chrispin- Norman score and spirometry. Eur Radiol. 2007;17(4):1018-1024.
7. Bouhuys A, Van Lennep HJ. Effect of body posture on gas distribution in the lungs. J Appl Physiol. 1962;17(1):38-42.
8. Aurora P, Gustaffson P, Bush A, Lindblad A, Oliver C, Wallis C, et al. Multiple breath inert gas washout as a measure of ventilation distribution in children with cystic fibrosis. Thorax 2004;59(12):1068-1073.
9. Beydon N, Davis SD, Lombardi E. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med. 2007;175(12):1304-1345.
10. Aurora P, Bush A, Gustafsson, Oliver C, Wallis C, Price J. Multiple-breath washout as a marker of lung disease in preschool children with cystic fibrosis. Am J Respir Crit Care Med. 2005;171(3):249-256.
11. Duncan J, Arora P. Monitoring early lung disease in cystic fibrosis: where are we now? Breathe. 2014;10(1):34-47.
12. Horsley AR, Gustafsson PM, Macleod KA. Lung clearance index is a sensitive, repeatable and practical measure of airways disease in adults with cystic fibrosis. Thorax. 2008;63(2):135-40.
13. Kieninger E, Singer F, Fuchs O, Abbas C, Frey U, Regamey N, et al. Long-term course of lung clearance index between infancy and school-age in cystic fibrosis subjects. J Cyst Fibros. 2011;10(6):487-490.
14. Beydon N, Davis SD, Lombardi E. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med. 2007;15(175):1305-1345.
15. Lum S, Gustafsson P, Ljungberg H. Early detection of cystic fibrosis lung disease: multiple-breath washout versus raised volume tests. Thorax. 2007;62(4):341-347.
16. Aurora P, Bush A, Gustafsson, Oliver C, Wallis C, Price J. Multiple-breath washout as a marker of lung disease in preschool children with cystic fibrosis. Am J Respir Crit Care Med. 2005;171(3):249–256.
17. Lum S, Stocks J, Stanojevic S. Age and height dependence of lung clearance index and functional residual capacity. Eur Respir J. 2013;41(6):1371-1377.
18. Farrell PM, Li Z, Kosorok MR. Bronchopulmonary disease in children with cystic fibrosis after early or delayed diagnosis. Am J Respir Crit Care Med. 2003;168(9):1100-1108.
19. Tiddens H, Puderbach M, Venegas J, Ratjen F. Novel outcome measures for clinical trials in cystic fibrosis, Pediatric Pulmonology. 2015;50(3):302-315.
20. Gustafsson PM, Aurora P, Lindblad A. Evaluation of ventilation maldistribution as an early indicator of lung disease in children with cystic fibrosis. Eur Respir J. 2003;22(6):972-9.
21. Kraemer R, Blum A, Schibler A, Ammann RA, Gallati S. Ventilation inhomogeneities in relation to standard lung function in patients with cystic fibrosis. Am J Respir Crit Care Med. 2005;171(4):371-378.
22. Stanojevic S, Davis SD, Retsch-Bogart G, Webster H, Davis M, Johnson RC, et al. Progression of Lung Disease in Preschool Patients with Cystic Fibrosis. Am J Respir Crit Care Med.2017;195(9):1216-1225.
23. Aurora P, Stanojevic S, Wade A. Lung clearance index at 4 years predicts subsequent lung function in children with cystic fibrosis. Am J Respir Crit Care Med. 2011;183(6):752-758.
24. Stanojevic S, Davis SD, Retsch-Bogart G, Webster H, Davis M, Johnson RC, et al. Progression of Lung Disease in Preschool Patients with Cystic Fibrosis. Am J Respir Crit Care Med.2017;195(9):1216-1225.
25. Arora P. Editorial, Multiple breath inert gas wash out test and early cystic fibrosis lung disease. Thorax. 2010;65(5):373-374.
26. Robinson PD, Cooper P, Van Asperen P. Using index of ventilation to assess response to treatment for acute pulmonary exacerbation in children with cystic fibrosis. Pediatr Pulmonol. 2009;44(8):733-742.
27. Scrase E, Oliver C, Kozlowska W. Change in lung clearance index (LCI) following intravenous antibiotic intervention in children with CF. Eur Respir J. 2008;32:514s-515s.
28. Van Gool K, Norman R, Delatycki MB, Hall J, Massie J. Understanding the costs of care for cystic fibrosis: an analysis by age and health state. Value Health. 2013;16(2):345-55.
29. Angelis A, Kanavos P, Batisda J. Social and economic costs and health-related quality of life in non-institutionalised patients with cystic fibrosis in the United Kingdom. BMC Health Serv Res. 2015;15:428.
30. Horsley AR, Gustafsson PM, Macleod KA. Lung clearance index is a sensitive, repeatable and practical measure of airways disease in adults with cystic fibrosis. Thorax. 2008;63(2):135-40.
31. Fuchs SI, Buess C, Lum S. Multiple breath washout with a side stream ultrasonic flow sensor and mass spectrometry: a comparative study. Pediatr Pulmonol. 2006;41(12):1218-25.
32. Gustafsson PM, Aurora P, Lindblad A. Evaluation of ventilation maldistribution as an early indicator of lung disease in children with cystic fibrosis. Eur Respir J. 2003;22(6):972-979.