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Title: Ways to shorten the lung clearance index measurement I – Are three measurements needed?

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Body: Background Inert gas multiple-breath washout (MBW) derived lung clearance index (LCI) is a sensitive lung function parameter in subjects with mild cystic fibrosis (CF) lung disease, but rarely measured in clinical routine due to lack of available equipment and lengthy protocols. Using an available nitrogen (N₂) MBW setup (Exhalyzer D, Eco Medics, Switzerland) we assessed shortened N₂MBW protocols for LCI. Methods We determined whether the LCI from the 1st (LCI₁) and the mean LCI of the 1st and 2nd valid N₂MBW (LCI₂), respectively, are comparable to the averaged information obtained from three N₂MBW (LCI₃). We analyzed data of 33 school-aged children with CF and 10 controls performing triplicate N₂MBW. Results LCI₁, LCI₂, and LCI₃ differed significantly between healthy and CF children. LCI₁ and LCI₂ were strongly associated with LCI₃ ($R^2 = 0.98$ for both), took less time, and were of similar diagnostic value. Comparing LCI₁ and LCI₂ with LCI₃, mean (range) test duration was 2.2 (0.5-5.2), 6.6 (3.6-12.7), and 11.1 (8.0-17.1) min, and upper limits of normal LCI (8.3, 8.3, and 8.4) all correctly classified 71% of children, respectively. Bland-Altman analysis of LCI₁ and LCI₂ showed good agreement with LCI₃: Mean difference was -1.1% and -0.7%, limits of agreement were 6.8 to -9.0% and 5.9 to -7.3%, respectively. Conclusion In the current study population, the 1st LCI or the mean of the 1st and 2nd LCI take less time and predict the mean LCI of three N₂MBW within physiological measurement variability. Using less N₂MBW measurements seems promising for time-saving LCI measurement in clinical routine.