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Review

Is the raised volume rapid thoracic compression technique ready for use in clinical trials in infants with cystic fibrosis?☆

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Abstract

The European Cystic Fibrosis Society Clinical Trial Network (ECFS-CTN) has established a Standardization Committee to undertake a rigorous evaluation of promising outcome measures with regard to use in multicentre clinical trials in cystic fibrosis (CF). The aim of this article is to present a review of literature on clinimetric properties of the infant raised-volume rapid thoracic compression (RVRTC) technique in the context of CF, to summarise the consensus amongst the group on feasibility and answer key questions regarding the promotion of this technique to surrogate endpoint status.

Methods: A literature search (from 1985 onwards) identified 20 papers that met inclusion criteria of RVRTC use in infants with CF. Data were extracted and tabulated regarding repeatability, validity, correlation with other outcome measures, responsiveness and reference values. A working group discussed the tables and answered 4 key questions.

Results: Overall, RVRTC in particular forced expiratory volume in 0.5 s, showed good clinimetric properties despite presence of individual variability. Few studies showed a relationship between RVRTC and inflammation and infection, and to date, data remains limited regarding the responsiveness of RVRTC after an intervention. Concerns were raised regarding feasibility in multi-centre studies and availability of reference values.

☆ Take home message: Since early respiratory interventions are needed to improve outcome in infants with cystic fibrosis, standardization and implementation of the RVRTC technique are needed before RVRTC can be used as primary outcome in clinical trials.

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Conclusion: The ECFS-CTN Working Group considers that RVRTC cannot be used as a primary outcome in clinical trials in infants with CF before universal standardization of this measurement is achieved and implementation of inter-institutional networking is in place. We advise its use currently in phase I/II trials and as a secondary endpoint in phase III studies. We emphasise the need for (1) more short-term variability and longitudinal 'natural history' studies, and (2) robust reference values for commercially available devices.

Keywords: Infant pulmonary function; Cystic fibrosis; Clinical trials; Surrogate outcome; Clinimetric properties; Raised volume rapid thoracic compression

Contents

1. Introduction

With the increasing availability of newborn screening (NBS) for cystic fibrosis (CF), there is a current focus in the CF community on developing and evaluating endpoints for clinical trials, especially in the early stages of CF lung disease (reviewed in [1]). The European Cystic Fibrosis Society Clinical Trial Network (ECFS-CTN) has established a Standardization Committee to undertake a rigorous evaluation of promising outcome measures with regard to use in multicentre clinical trials in young children with CF.

CF lung disease starts in early life and associates airway remodelling to bacterial infection and inflammation, resulting in an obstructive ventilatory defect which can be observed by lung function testing. Therefore, sensitive tools are needed to evaluate respiratory status in infants and guide interventions to improve respiratory outcome. Previous multicentre early intervention clinical trials have used ventilatory parameters as a secondary endpoint e.g. the raised volume-rapid thoracic compression (RVRTC) technique, or lung clearance index (LCI) [2–5]. RVRTC appeared to be a promising tool to monitor early lung disease in CF infants.

Pulmonary function test performance is particularly difficult from 0 to 3 years due to the lack of cooperation of the child. The RVRTC technique allows infant lungs to be inflated to near vital capacity (VC) by applying an inspiratory pressure to the airways through a face mask during inspiration followed by a rapid thoracic compression (RVRTC) manoeuvre applied through a jacket, at the end of the inflated inspiration (so called 'pump up and squeeze' technique). It measures volume and flow measurements during compression, such as: a) Forced expired volume in 0.4 or 0.5 s ($FEV_{0.4}$, $FEV_{0.5}$), b) Mean forced expiratory flow between 25 and 75% of FVC ($FEF_{25–75}$) and c) Forced expiratory flow at 75 or 50% of FVC (FEF_{75}, FEF_{50}) similar to spirometric forced flow-volume loops in older children [6,7].

In the early 2000s, following a joint effort by the American and European Respiratory Societies, raised volume forced expiration measurements were standardized [8] and implemented in centres around the world [8–11]. The current manuscript summarises information on the RVRTC technique as an endpoint of infant pulmonary function in CF, states recommendations by the ECFS-CTN to achieve standardization of this technique and lists further studies needed.