

## Airway Clearance in Cystic Fibrosis: Is There a Better Way?

The pathophysiology of cystic fibrosis (CF) lung disease is initiated by dysfunction of the CF transmembrane conductance regulator protein, leading to dysregulation of the salt and water content of the airway surface liquid. Abnormal airway surface liquid compromises mucociliary clearance and airway defenses against infection. An exaggerated inflammatory response leads to an influx of large numbers of neutrophils, which subsequently necrose and release their intracellular contents, including deoxyribonucleic acid and filamentous actin, further increasing the viscosity and adhesivity of the airway secretions. The result of this ongoing cycle of chronic infection, inflammation, mucus plugging, and worsening airway obstruction is irreversible and diffuse bronchiectasis.

Physical airway-clearance therapies augment the mobilization and expectoration of secretions and have long been considered the cornerstone of therapy for the prevention and treatment of CF airway disease. A sufficient number of trials have been performed to provide moderately convincing evidence of the efficacy of airway-clearance therapy, even though most of the studies, when evaluated individually, had important methodological failings.<sup>1-3</sup> The challenges to designing a clinical trial to appropriately evaluate the effectiveness of airway-clearance-therapy modalities are multiple and have been previously reviewed.<sup>4,5</sup> A number of studies have attempted to address comparative effectiveness of various airway-clearance therapies, and while some have shown an apparent advantage of one over another, several meta-analyses have concluded that the overall literature shows no substantive advantage with any particular technique.<sup>1,2,5</sup> Given the poor patient adherence to any form of airway-clearance therapy,<sup>6</sup> it is likely that, in most cases, effectiveness (which describes the success of an intervention in actual clinical practice) will trump efficacy (which describes the ability of an intervention to work under ideal conditions). In order to optimize the effectiveness of ambulatory airway clearance in a chronic disease such as CF, it is essential to maximize adherence, and adherence seems to correlate best with patient satisfaction regarding the technique.<sup>7</sup> Given our current state of understanding, the most appropriate approach to choosing an airway-clearance therapy in CF is probably to provide patients and families with the complete menu of possibilities and let them choose which they find most satisfactory, given lifestyle considerations and

subjective impression of benefit, as well as the scant available objective evidence.<sup>8</sup>

High-frequency chest wall compression (HFCWC) is an increasingly popular airway-clearance therapy for patients with CF and other conditions with compromised airway clearance; HFCWC appears to be efficacious and it allows greater independence than traditional manual percussion and postural drainage.<sup>1,2</sup> There are several different commercial HFCWC devices, which differ in certain characteristics, such as transmitted waveform and recommended pressure/frequency settings. The potential importance of different HFCWC settings is typically overlooked by most practitioners and reviews,<sup>1,2</sup> but has been the subject of some preliminary study<sup>9,10</sup> and is anecdotally thought to be important by some CF respiratory therapists.<sup>11</sup>

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The paper by Kempainen and colleagues in this issue of *RESPIRATORY CARE*<sup>12</sup> reports on a clinical trial that compared the efficacy of a standard approach to HFCWC (relatively low pressure with a fixed mid-range frequency) to a more complex approach with varying higher pressures and frequencies (the so-called “Minnesota protocol”<sup>11</sup>) in patients with CF. The study team recruited 16 stable adults with non-severe CF lung disease followed at the University of Minnesota CF center, where they tend to prescribe the high-pressure HFCWC protocol, although only 6 subjects were able to verify that they used these settings at baseline prior to enrollment. Subjects were exposed, in a crossover manner, to a single-blinded (if that is possible) treatment of either higher pressure and varying frequency or lower pressure and fixed frequency HFCWC, and their expectorated sputum quantity and viscoelasticity were measured immediately after, along with pulmonary function tests (spirometry). The investigators found that sputum wet weight was increased with the higher pressure settings, but not sputum dry weight or viscoelasticity, and there was no difference in spirometry or the subjects’ report of comfort or perceived efficacy between the 2 approaches.

The implications of these findings for clinical practice are unclear. The HFCWC device is used chronically in a large heterogeneous group of patients (with CF or other conditions) to help slow the long-term progression of lung disease; this study compared the short-term impact of 2 HFCWC

protocols in a small homogeneous group of patients from a single CF center, and showed that the more complex protocol led to an apparently advantageous effect on a sputum measure of uncertain clinical consequence. The subjects' failure to discern any subjective difference in efficacy or comfort between the 2 approaches is important because these factors may affect adherence,<sup>7</sup> the major challenge to effectiveness of airway-clearance therapy,<sup>6</sup> and adherence is typically reduced when the treatment regimen is more complex.<sup>13</sup>

On the other hand, as pointed out by Kempainen et al, short-term study end points such as lung function may be insensitive for detecting differences in airway treatment modalities, and the impact of a very small improvement in secretion clearance detectable after just one airway-clearance treatment may be significantly amplified with many such treatments over time. If there is a better way to use an existing modality such as airway clearance, this is low-hanging fruit, and respiratory care clinicians would want to take advantage of it. Thus, while the results of this trial are of questionable clinical importance, and do not currently support the widespread adoption of the Minnesota protocol, they do suggest a possible advantage. The next step would be a larger multicenter long-term trial whose primary end points are patient-centered outcomes,<sup>14</sup> such as lung function, frequency of pulmonary exacerbations, and quality of life,<sup>15</sup> as well as adherence.

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