



Acoustic airway clearance devices: A systematic review of experimental and numerical studies

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ARTICLE INFO

Keywords:

Acoustic airway clearance devices (ACDs)
Muco-obstructive pulmonary diseases
High-frequency chest compression (HFCC)
High-frequency chest wall compression (HFCWC)
High-frequency chest wall oscillation (HFCWO)
Oral high-frequency oscillation (OHFO)

ABSTRACT

The global respiratory care devices market, including acoustic airway clearance devices (ACDs), is expected to experience a compound annual growth rate of 6.10 % from 2023 to 2030. However, there are a number of inconsistencies in the categorization and working frequency range from one discipline to another one. A better understanding of the mechanisms of action of these devices is therefore of prime importance in order for physicians, physiotherapists, scientists, and engineers to remain abreast of up-to-date studies in the field and specifically on the frequency range used. In the present review, we have categorized acoustic ACDs according to their working principles while reviewing their existing shortcomings in both experimental and numerical studies, thereby paving the way for future research directions. A total of 14 different ACDs are discussed, taking into account their working principle and frequency range, and classified as follows: mechano-acoustic devices, high-frequency chest wall compression (HFCWC), and high-frequency chest wall oscillation (HFCWO) for high-frequency chest compression (HFCC) and oral high-frequency oscillation (OHFO). Existing studies highlight that ACDs with HFCWC distinguish themselves from other devices by supplying compression in a homogeneous manner, allowing the delivery of both efficient and gentle therapy up to approximately 40 Hz. Notwithstanding, a stark difference in the working frequency range across the various devices was found and identified as a literature gap. Given that this difference arises from both experimental and numerical studies between the various disciplines, the studies are further classified according to their respective objectives, methodology and outputs to help readers quickly and straightforwardly locate the articles of interest for potential future investigations. The review also brings to light the interdisciplinary nature of ACDs, whereby numerical biomedical studies can actively assist experimental studies in terms of reproducibility and reliability, creating a digital twin of the human chest and its respective components.

1. Introduction

Bronchial mucus can obstruct the airways either because its physico-chemical properties render it too adhesive or due to its presence in excessive amounts [1]. An increase in mucus production in the bronchi and bronchioles coupled with a decrease in the ability to expectorate sputum is acknowledged as a hallmark of muco-obstructive pulmonary diseases [2,3]. Such pulmonary diseases were furthermore reported as the second and third most common cause of death in 1990 and 2019,

respectively [4]. It is one of the reasons explaining the compound annual growth rate in respiratory medical devices, which is expected to increase by 6.10 % from 2023 to 2030 [5]. Indeed, utilization of these devices has been shown to reduce rehospitalization and length of hospital stay [6]. Although acoustic airway clearance devices (ACDs) are used in most cases to facilitate expectoration during therapy, their actual effectiveness remains to be properly quantified. Hence, there is an unmet need for large prospective studies to properly assess the efficiency of mechanical airway clearance therapies [7]. With the advent of the Internet

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of Medical Things (IoMT), wearable smart devices are increasingly used to replace or supplement traditional physiotherapy (CPT) [8,9]. The main objective of ACDs is to help patients gain greater autonomy, allowing them to independently apply the respiratory therapy themselves whenever and wherever necessary [10,11]. The devices can be used to enhance breathing in patients with muco-obstructive pulmonary diseases such as chronic obstructive pulmonary disease (COPD), bronchiectasis, cystic fibrosis (CF), COVID-19, emphysema and asthma [12–14].¹

Over the years, ACDs have been classified in various manners, including intermixing working methods with the devices as well as taking into account the patient's activity during therapy, hence causing misunderstanding with regard to their classification from one study to the next. For example, Hristara et al. [15] categorized the devices as positive expiratory pressure (PEP), high-frequency chest wall oscillation (HFCWO), oral high-frequency oscillation (OHFO), intrapulmonary percussive ventilation (IPV), incentive spirometry (IS), Flutter®, Acapella®, and Cornet® devices. However, there is a mixture of information in this categorization with certain terminology such as PEP referring to the actual workings of the device and others referring to device names which deliver a type of airway clearance therapy. Homnick et al. [16], on the other hand, divided the devices and treatment techniques into two general categories, 'active' and 'passive', according to those necessitating substantial patient effort to administer and those requiring less effort. However, at the first glance, this subcategorization does not appear clear-cut or understandable in terms of either their usage or their type. Another study categorized these devices as PEP, airway oscillating, and mechanical percussive (MP) with external high-frequency chest compression (HFCC), high-frequency chest wall compression (HFCWC) and HFCWO devices [17]. This characterization may be misleading since all of these devices are aimed at creating airway oscillations, which was used as one of the classifications of these devices. Therefore, their mechanism of action still remains ill-defined since complex technical, methodological and statistical factors render the interpretation of data challenging [7,18] in addition to the applied frequency range.

The frequency range used by these devices for their categorization as high- and low-frequency remains an additional inconsistency. Different frequency ranges are determined for different scales from one study to another. For example, the frequency range in some instances is categorized as being low-frequency (under 100 Hz), middle-frequency (200–600 Hz), and high-frequency (600–1200 Hz) [43]. However, in another categorization, the range is determined by the "Goldman Triangle" [44], i.e. 6–11 Hz, 15 Hz, and 20 Hz for resonance frequency, low-frequency, and high-frequency, respectively. However, the operating frequencies of commercial devices used for both OHFO and HFCC differ quite significantly from these ranges, and vary between 2–300 Hz and 1–65 Hz, respectively as shown in Table 2 [19,20]. To overcome this inconsistency, it is necessary to review these devices by considering both the experimental and numerical studies, including multidisciplinary studies underpinning these various device types according to their working principles.

Experimental studies on the vibration response of ACDs are long-established and generally patient-based. Recently, these studies have increasingly focused on the physico-chemical properties of mucus and

their extreme variability [21]. Although the improvements in ACDs have paved the way for more in-depth experimental acoustic studies, by the latter 1950s [22], researchers recognized that the application of harmonic acoustic excitation from the mouth or onto the chest surface with the aid of an ACD constitutes an effective treatment [23,24]. Given that the main objective of the ACDs is to change the physico-chemical properties of mucus in order to facilitate expectoration, biomedical engineering studies have gained significant importance in quantifying mucus properties. For example, in healthy humans, mucin content represents 1 % by weight, with a total protein and glycoprotein concentration of approximately 2.5 % [25], increasing up to 5.6 ± 2.0 % by weight for patients with CF [26]. Hence, in recent years, experimental studies conducted by scientists and biomedical engineers have supported medical and physiotherapy research by measuring the viscoelastic, shear-thinning, and thixotropic properties of bronchial mucus [27–29]. While numerous frequency ranges were considered, experimental studies have generally been conducted in the under 100 Hz range [27,30], most of which have focused in the 5–20 Hz frequency range [19,31].

The advent of numerical biomedical studies, on the other hand, is more recent and has accelerated for five years. Whereas it is difficult to conduct experimental studies in a living patient with a muco-obstructive disease, numerical models can expand our understanding of both the vibration response of the body and the physico-chemical properties of the mucus [26,32]. To illustrate, computed tomography-based finite element model (CT-FEM) studies can increase both the reproducibility and accuracy of the results since they are based on an in vivo-derived modeled geometry [33] (see [34] for the entire body and [35,36] for the lungs). However, the mucus layer remains very small (0.10^{-5} m) even in diseased patients when compared to the whole human thorax. This multiscale issue makes it difficult to address the entirety of the problem with a single numerical solver. As a result, numerical studies focusing on the physio-chemical properties of mucus have gained increasing importance, and have been predominantly dedicated to the mucociliary transport mechanism by ciliated epithelial cells [37], the search for an optimum frequency [20,38], and the average velocity and instantaneous flow rate [30] for mucus mobilization. These studies can be used to enhance our understanding of relevant sound transmission phenomena, particularly in the field of biomechanics. As for the frequency range, in contrast to the many reported varieties and inconsistencies, in numerical studies, these are consistent with the latest experimental studies up to 100 Hz [34,35].

In light of the above, and given the lack of consideration of the different domains when performing complex categorizations together with the large multiplicity of working frequency ranges used, we hypothesized that a simple and well-defined categorization would provide greater clarity and address the wide frequency ranges by reviewing both experimental and numerical studies while taking into account multidisciplinary research. Therefore, in the present comprehensive review, the 14 most known ACDs are categorized into two main groups, namely OHFO and HFCC devices. OHFO is the transmission of sound generated at the mouth and its propagation through the airway, whereas HFCC creates vibrations from the surface of the chest wall and transmits the latter through the airways using two different specific techniques, HFCWC and HFCWO. The HFCWC technique involves a vibratory excitation mechanism located on a vest to vibrate the chest wall while HFCWO inflates and deflates the vest with oscillating pressure to create air-assisted vibrations. In addition to the categorization of the devices in an understandable and detailed manner, an additional novelty of this study is that both experimental and numerical acoustic studies are considered from a multidisciplinary perspective. It includes: (1) the vibration response of the thorax or internal organs and (2) the influence of transmission on the physico-chemical properties of bronchial mucus, thereby contributing to encompassing the viewpoints of medical professionals, physiotherapists, scientists, and engineers, with a primary focus on the most recent five-year literature.

¹ Abbreviations: ACDs, airway clearance devices; BCV, biphasic cuirass ventilator; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CPT, conventional physiotherapy; CT-FEM, computed tomography-based finite element model; FEV, forced expiratory volume; FEV1, forced expiratory volume in one second (FEV1); FVC, forced vital capacity; Freq, frequency (Hz); HFCC, high-frequency chest compression; HFCWC, high-frequency chest wall compression; HFCWO, high-frequency chest wall oscillation; IoMT, Internet of Medical Things; NEP, negative expiratory pressure; OHFO, oral high-frequency oscillation; PEP, positive expiratory pressure; PMC, peripheral mucus clearance; TMC, tracheal mucus clearance.

2. Literature search methodology

2.1. Preparatory search

A targeted search was first performed using MEDLINE, PubMed, Scopus, Web of Science, and Google Scholar to incorporate various disciplines from January 3, 2020 through August 16, 2024. The keywords were defined as *pulmonary therapy*, *HFCC*, *HFCWO*, *HFCWC*, *OHFO*, *mucus*, *mucus obstructive*, *COPD*, *cystic fibrosis*, and *acoustic pulmonary therapy*. This preparatory screening was further enhanced by assessing the reference lists of selected articles. The inclusion and exclusion of documents were achieved through a total of 5 rounds, each with specific criteria. The number and motives for the discarded articles at each round are provided in Fig. 1 and Table 1.

2.2. Content selection method

A total of 3532 documents were initially screened, including

conference papers, full-length articles, master's and doctoral theses, books, ACD user manuals, and patents, to evaluate both experimental and numerical studies. After eliminating duplicated documents, the initial search was shortlisted through totally 5 analysis rounds to 107 documents, consisting of 94 full-length articles, 5 books, 3 conference papers, 3 instruction manuals, 1 report, and 1 doctoral thesis. The search involved a time frame spanning more than 65 years up to August 2024, although most documents are from the last 5 years as a result of the increment in technical knowledge which has remarkably up-lifted IoMT and numerical studies, as well as improvements in experimental studies. In addition, research papers based on important aspects such as objectives, methods, and findings were categorized as an aid for locating them efficiently and straightforwardly. Fig. 2 presents the number of publications distributed over time between 1958 and 2024.

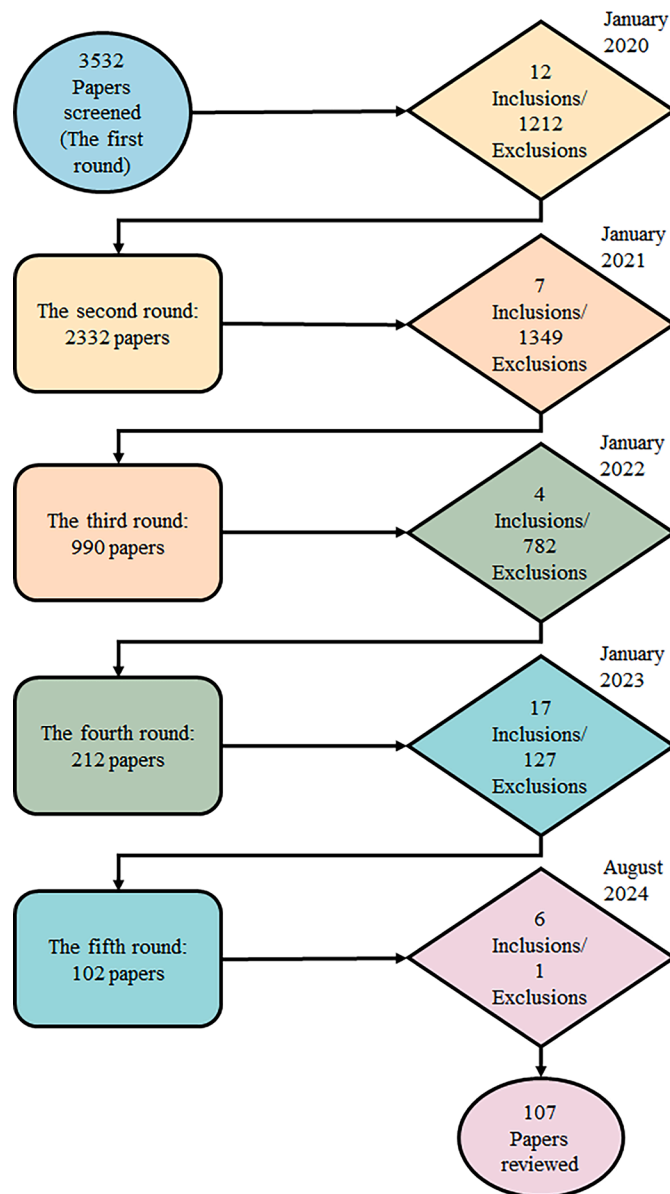


Fig. 1. The review journey with the number of included and excluded papers from January 2020 to August 2024.

*Inclusion and exclusion strategies are given in e-Table 1.

Table 1

Exclusion and inclusion strategies in the review process with the associated numbers of publications.

Search Round	Number of publications	Reason for exclusion	Number of excluded papers	Reason for inclusion	Number of included papers
Initial search and 1st round	3532	Duplicated studies Low-quality studies* No vulnerable population**	1025 144 43	Up-to-date [†] and reference checking [‡]	12
2nd round	2332	Non-pulmonary study Not specifically on OHFO or HFCC	566 783	Up-to-date [†] and reference checking [‡]	7
3rd round	990	Low-quality rehabilitation study*** Study predominantly concentrated on cilia	686 96	Up-to-date [†] and reference checking [‡]	4
4th round	212	Insufficient information on software and CT data (for the numerical studies)	59	Up-to-date [†] and reference checking [‡]	17
5th round	102	Insufficient information on the experimental set-up Changed with corresponding up-to-date comprehensive published work	68 1	Up-to-date [†]	6

* Studies with insufficient quantitative data related to the working frequency range were eliminated.

** Studies lacking information on sex, age, and physical diversity were eliminated.

*** Insufficient information related to data collation and boundary conditions were detected in experimental and numerical studies, respectively.

[†] Articles, including hot-published papers, over the last more than four years were actively reviewed.

[‡] All papers were reviewed by cross-checking their cited references. The references of the reviewed articles were included, even if not available in the source material.

All articles selected were in English language (no translations).

3. Acoustic airway clearance devices

3.1. Oral high-frequency oscillations

OHFO techniques are based on acoustic excitation at the mouth to create oscillations as illustrated in Fig. 3. These techniques are used in physiotherapy to promote pulmonary function [39] and are underscored in various surveys as the most preferable technique [40]. The most common OHFO devices are Flutter®, Simeox®, Aerobika®, Acapella®, PARI-OPEP®, Shaker®, RC Cornet®, and Lung Flute®.

Finding common attributes for comparing these devices remains nonetheless challenging with no particular device deemed superior to another [41,42]. For example, Santos et al. [41] compared the mechanical performance of the Flutter®, Shaker®, and Acapella® devices by measuring pressure amplitude, OPEP, and oscillation frequency. Poncin et al. [42] compared six different OHFO devices, namely Flutter®, Gelomuc®, Shaker®, PARI-OPEP®, Acapella®, and Aerobika® at 12 Hz or above and PEP ranging between 10 and 20 cm H₂O. Both groups concluded that all devices exhibited similar mechanical

performances, although Acapella® and Aerobika® required higher expiratory pressure to reach vibration response efficiency.

3.2. High-frequency chest compression

The working principle of HFCC lies in the creation of vibrations on the chest wall to clear secretions [27,43]. The frequency effect on the human chest wall was first documented, by McKusick [22] in 1958, whereas its role in mucus removal for patients with muco-obstructive pulmonary diseases was originally reported by Beck [44] in 1966. It has advantages over CPT in terms of sputum expectoration, stabilization or improvement of respiratory function, increasing airflow in low lung volumes, and has a positive effect on forced vital capacity (FVC) and forced expiratory volume (FEV) [45]. It contributes positively to not only tracheal mucus clearance (TMC) but also peripheral mucus clearance (PMC) [46]. HFCCs are categorized as HFCWC, HFCWO, and mechano-acoustic devices according to the working principle as illustrated in Fig. 3.

The well-known commercial brands of HFCWO devices are The

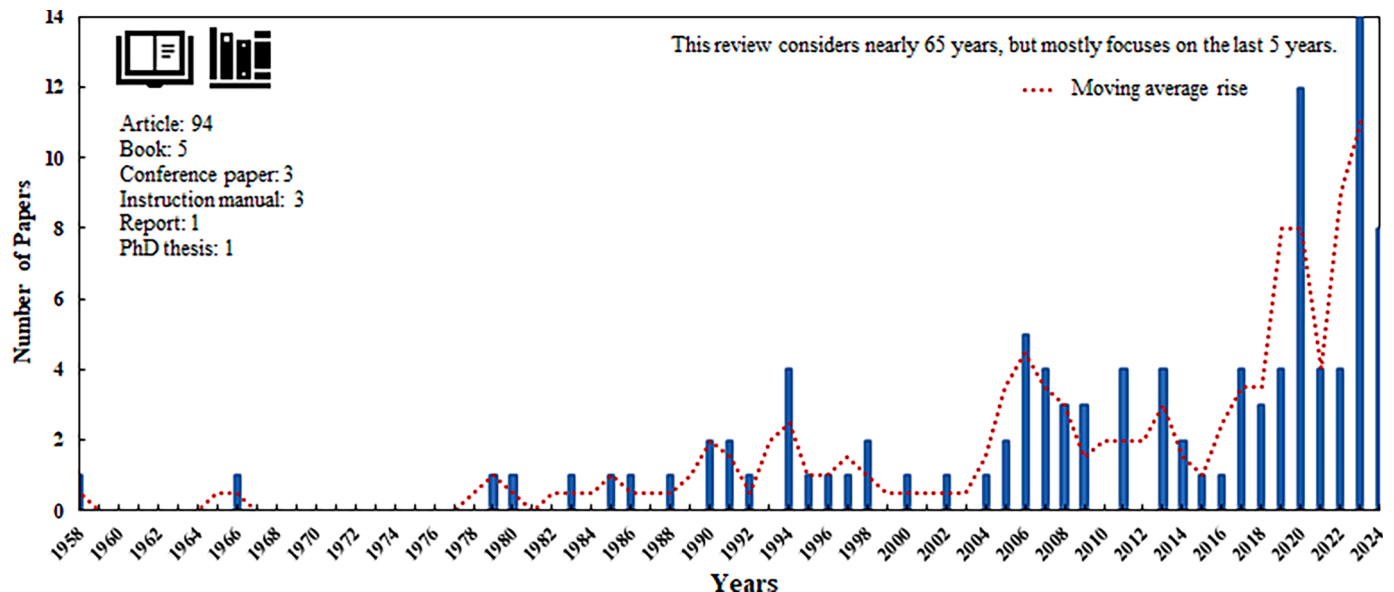


Fig. 2. Total number of papers included in this study according to the year of publication.

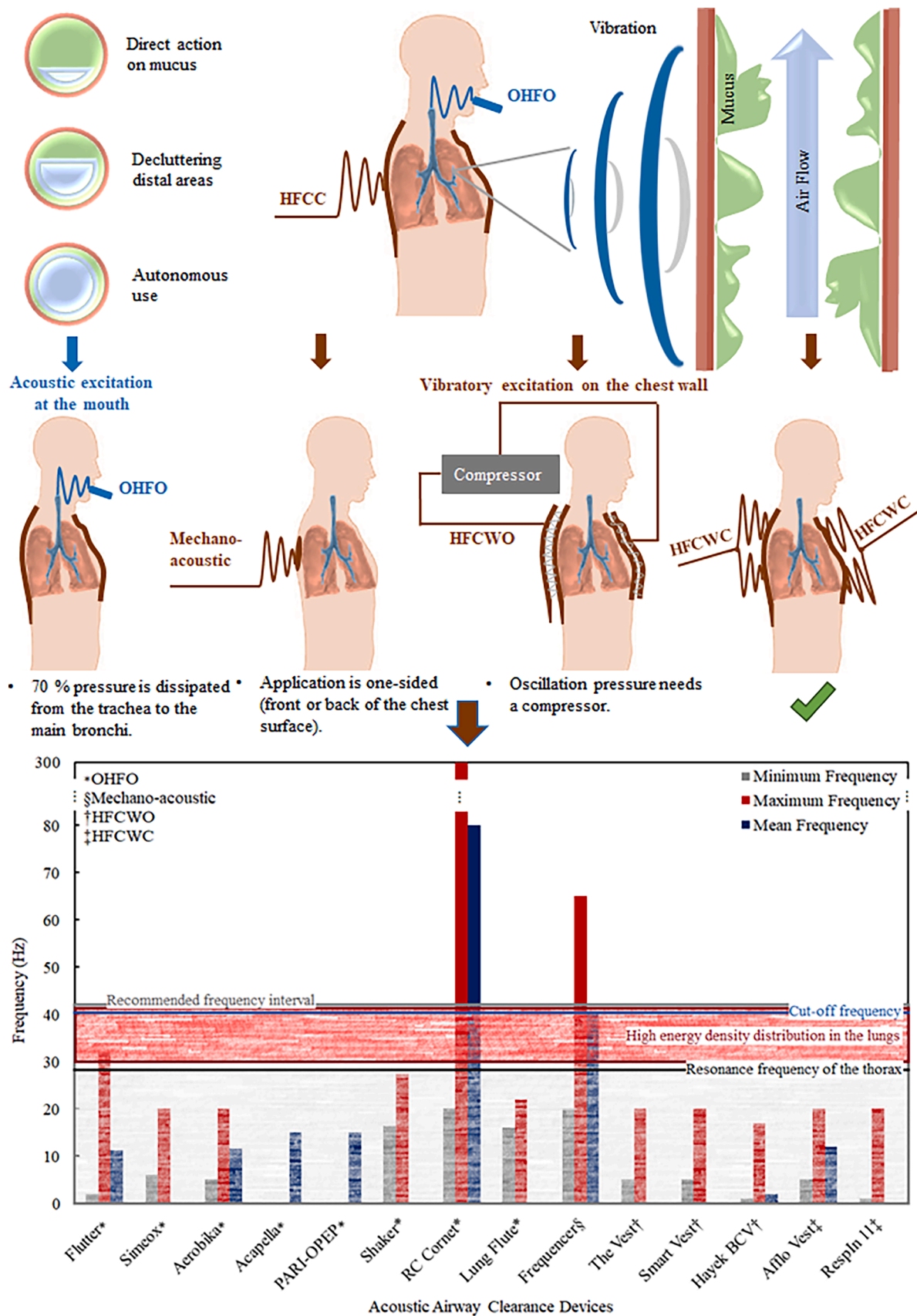


Fig. 3. Classification of ACDs according to their working principle and comparison in terms of the applied frequency range (prepared according to Table 2 and references [27,33,61]).

Vest®, Hayek® Biphasic Cuirass Ventilator (BCV) and Smartvest® which operate in the form of a wearable smart vest technology under a low-frequency range. Although HFCWO with BCV is commonly and effectively used in emergency medicine in combination with high-flow nasal oxygenation [47], one study conversely concluded that oscillating pressure may not enhance the effectiveness of HFCC therapy since oscillating pressure can reduce end-expiratory lung volume, which in turn may lead to a decrease in airway size and subsequent airway obstruction [48]. HFCWC is effective in enhancing both PMC and TMC [46] with the AffloVest® and RespIn 11 Bronchial Clearance System®, which operate up to approximately 20 Hz. Frequencer® is a mechano-acoustic device used in the 20–65 Hz frequency range and provides the best airway clearance therapy at 40 Hz [27].

3.3. Perspectives on airway clearance devices

Some studies have pointed out that acoustic ACDs provide 1.8 times higher mucus clearance in a single therapy session compared to conventional physiotherapy (CPT) [63]. However, other studies reported no evidence that one device is better than the other in transmitting the vibration response [64]. In terms of comfort, some patients preferred OHFO to HFCC [65] while others preferred the opposite [40]. Therefore, when comparing different ACDs, a comprehensive numerical model is necessary to impose equal conditions between each device and repeat the tests accordingly to avoid this choice-based source of confusion [33]. However, instead of results based on patient choice, a greater amount of measurable data and numerical calculations need to be considered such as a decrease in sputum production [66] and high acoustic pressure distribution from the applied source to the bronchioles [67]. When all methods were considered, HFCWC devices were found to be distinguishable in terms of increasing both PMC and TMC in a homogeneous manner in addition to enhanced treatment efficiency due to a uniform frequency supply. In addition, HFCWC was found to provide more mobility for patients with wearable small battery technologies [62].

4. Experimental acoustic studies

Experimental acoustic ACDs studies have long been established and associated with airway clearance as a vibration response, with numerous studies focused on determining the resonance frequency in order to provide the most efficient therapy [22,68,69]. These studies have recently been supported by biomedical engineering studies on the physico-chemical properties of mucus [27,28]. Table 3 provides a summary of the experimental studies on acoustic ACDs categorized according to their objective, applied frequency, subjects, method, conditions and outputs in chronological order. With regard to the frequency range, experimental studies are generally conducted below 100 Hz [27,30] and mostly focus on the 5 to 20 Hz range [19,31]. There is consensus among these studies as to the 40 Hz cut-off frequency because of lung-rib cage interactions [70] and as an appropriate frequency for the rheological properties of mucus [27].

4.1. Vibration response

The main challenge of experimental acoustic studies resides in the non-stationary nature of the vibrations and sound transmission in the human chest as well as the positioning of the acoustic ACDs, which are not easily repeatable [71]. The effectiveness of all these treatments varies according to each disease, although are of significant use in subjects with CF in both the pediatric and adult populations [72].

There are several experimental studies in the literature regarding the influence of vibration response on excessive sputum clearance in bronchial secretions [24,46,73]. In these studies, α , F , and P -values are the probability parameters used to obtain a statistical summary of the main effect, with group interactions of lung function defined as forced expiratory volume in one second (FEV1) and FEV1/FVC ratio that is equal to

or more extreme than the observed value under a specified statistical model such as the sample mean difference between two groups [74]. In addition to these parameters, oxygen saturation (S_pO_2) is also used as an assessment parameter for the comparison of airway clearance therapies [75].

Chest resonance frequency is contingent on a multitude of factors such as body mass index (BMI), the subject's mass, height, chest size, age, and sex [68,69]. In 1994, Goodwin [69] measured the average resonance frequency of the chest wall by applying frequencies between 0 and 100 Hz in 15 fully healthy subjects, yielding values of 25 Hz and 33 Hz for male and female volunteers, respectively. In 2006, Ong and Ghista [68] found chest resonance frequencies of 26.7 Hz and 27.8 Hz in a sample of 23 healthy male and female volunteers, respectively. In contrast, McKusick [22] previously reported respective resonance frequencies of 125 Hz, 150–175 Hz, and 300–400 Hz in men, women, and children. In addition to the above inconsistencies, different frequencies have been used for commercial devices investigated in the literature, including 15–50 Hz [68], 6.1 Hz [76], and 6–19 Hz [77]. With regard to oral sound excitation, 13 Hz and 10–28.5 Hz [41] were found as a resonance frequency for dogs.

In accordance with Table 3, low frequencies ranging up to 40 Hz are typically utilized for treating the human chest surface as they are known to have therapeutic effects on the chest area. On the other hand, frequencies below 25 Hz are applied for oral vibration tests. These tests are conducted to assess the vibratory sensation in the oral cavity, which can be useful in diagnosing certain medical conditions.

4.2. Physico-chemical properties of mucus

According to studies on the physico-chemical properties of mucus in healthy humans, mucin content is 1 % by weight with a total protein and glycoprotein concentration of approximately 2.5 % [25]. However, its rheological properties change according to the patient's disease [77]. The bronchial drainage function is a complex phenomenon directly linked to the thermophysical and rheological properties of the mucus layer coating the airways [28,29]. Lafforgue et al. [29] measured the rheological properties of a mucus simulant mimicking bronchial mucus under different disease settings in the range of 1 to 100 rad.s^{-1} . They also measured their density, surface tension, thermal diffusivity, and thermal conductivity as a function of temperature. Schieppati et al. [27] investigated the influence of frequency and amplitude on mucus viscoelasticity in-vitro. The authors concluded that a frequency of 40 Hz coupled with a 0.5 gL^{-1} NaCl rehydrated mucus lowers its viscosity and potentially facilitates its expectoration.

Given that parameters vary from one muco-obstructive pulmonary disease to another [78], it may be of valued interest to quantify the influence of oscillation frequency on the cohesive and adhesive failure of mucus, which has yet to be considered to date. Indeed, taking into account these changes could provide a much-needed contribution to the well-being of respiratory patients. The seminal study by Button et al. [79] accordingly demonstrated a direct relationship between airway clearance and the cohesive and adhesive failure of mucus in healthy subjects. The authors found that both adhesive and cohesive strengths are dependent on velocity (and thus shear force) and concentration, indicating that energy dissipation occurs within the mucus during coughing. However, the cohesion and adhesion of mucus under vibrations have yet to be quantified.

5. Numerical acoustic studies

Numerical simulations are crucial for eliminating external factors and ensuring consistent test conditions for devices in both HFCC- and OHFO-related biomedical engineering applications. In addition, the recent developments of IoMT have enabled the acceleration of CT-FEM studies by which researchers are able to illustrate the effect of an acoustic medical device on the human body [34] as well as on the lungs

[35,36]. In terms of numerical acoustic studies on physico-chemical properties of the mucus, coughing effect and mucociliary clearance by beating cilia at under approximately 20 Hz are the two main mechanisms for airway clearance in healthy patients [37], and likely one of the reasons of the many studies near this frequency. This, in turn, has led to an increasing number of studies on the optimum frequency for airway clearance [20,38] and on the generated average velocity and instantaneous flow rate of mucus [30]. These studies are listed in chronological order in Table 4 and are categorized according to their objective, applied frequency, geometry, method, conditions, and outputs. Numerical studies are generally conducted below the frequency range of 100 Hz [35].

5.1. Vibration response

The internal sound propagation in the human chest is non-stationary and poorly reproducible [71,94] and whose characteristics are dependent on multiple factors including the patient's health condition, age, sex, and physical geometric features. Numerical models can thus be used to enhance our understanding of relevant sound transmission phenomena. In addition to the material properties of the respiratory systems, CT data are necessary to generate accurate results from 3D numerical studies [20,35,95]. The Biot's theory for the human lungs and the Kelvin-Voigt model for both soft tissues and osseous regions are often applied in numerical studies to determine the material properties [96–98]. It is also essential to have a realistic, high-quality, and easily-simulated CT-FEM [33]. When comparing acoustic ACDs, the same conditions such as frequency range and the same patient should be taken into account simultaneously, which is nearly impossible. Nevertheless, according to a recent advancement, CT-FEM can provide numerically reliable and reproducible tests under the same conditions with different excitations, thus generating comparable outputs. Furthermore, it is an invaluable instrumental tool for putting together a scientific multidisciplinary puzzle as illustrated in Fig. 4.

In a recent study, CT-FEM was created to numerically test airway

clearance therapy, with the resonance frequency of the human thorax determined at 28 Hz [34]. The lung energy density distributions under HFCC were furthermore investigated within the 5–100 Hz range, whereby both kinetic and elastic strain energy density distribution peaks were observed to be below approximately 40 Hz [35,36]. These findings were supported by two different literature experimental studies for the resonance frequency [68,69] with the cut-off frequency found at 40 Hz as a result of lung-rib cage interactions [70]. However, a previous experimental study performed in 1958 contradicts these findings [22], thus warranting further studies addressing the persisting confusion surrounding the frequency range.

5.2. Physico-chemical properties

Mucus properties are dependent on the patient's health conditions [78,99] and change with respect to the frequency range, so it is hard to standardize them and serve as inputs to numerical studies. To illustrate that, over a given small airway segment, cilia may synchronize to beat uniformly in the periciliary fluid (with their tips in the mucus layer) at generally under 20 Hz [37]. However, Brunengo et al. [20,38] identified the optimum frequency for airway clearance as 6.5 Hz for RespIn 11 Bronchial Clearance System®. The authors further observed that in the frequency range between 3 Hz and 15 Hz, the amount of airflow at the mouth opening remained within 1 % of its maximum. Obembe et al. [30] recently found that vibration frequency affects the average velocity and the instantaneous flow rate. Using a constructed 2D model, they reported an improvement of 68 % in the mucus mobilized in the tube when the vibration frequency was increased by a factor of 2 (from 15 Hz to 30 Hz) and of 343 % when increasing the vibration frequency by a factor of 6 (from 15 Hz to 90 Hz). Recently, El Naser and Karayel [100] identified a significant trend in their numerical study, where increasing the frequency up to 30 Hz led to a pronounced decrease in mucus viscosity for oscillating ACDs. Moreover, their findings highlighted the importance of frequency-dependent behavior in optimizing applied vibrations for enhancing mucus clearance through adjustments in amplitude, pressure

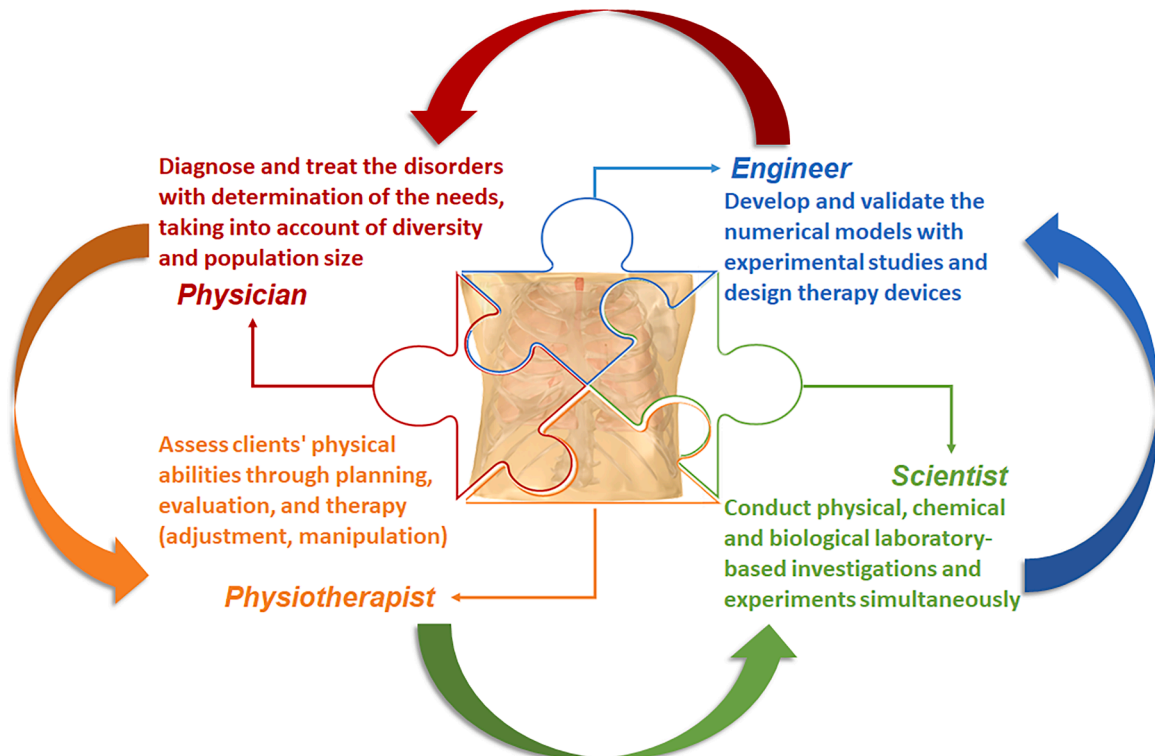


Fig. 4. Recommended interdisciplinary framework for future studies (visualization supported CT-FEM [33]).

differentials, fluid properties, and ciliary movements.

Given these discrepancies, it becomes clear that no direct correlation can be established between the numerical simulations and the experimental findings detailed in Section 4.2. This divergence is primarily attributable to the varying assumptions made, particularly regarding the presence or absence of ciliary activity and the insufficient modeling of mucus rheological properties, which exhibit considerable variation across different frequency spectra [27]. Furthermore, the influence of dynamic oscillatory forces on both nasal and pulmonary mucus properties was ignored. To illustrate that, the sputum in chronic obstructive disease is significantly more elastic and viscous compared to that in healthy individuals [101]. Furthermore, it changes according to the severity of the disease and other factors [102], but these effects have not been considered so far in the literature.

6. Discussions and perspectives on airway clearance devices

In order to facilitate a comprehensive comparative analysis, a bar chart was therefore developed incorporating a total of 14 different ACDs based on the applied frequency ranges as shown in Fig. 3 (see also Table 2). As it can be seen, there are inconsistencies in the frequency ranges used for both OHFO and HFCC, ranging from 2 to 300 Hz and 1–65 Hz, respectively [19,20]. Consequently, an accurate frequency range was only recommended when an agreement between experimental and numerical results was obtained for a gentle and effective therapy in the low-frequency range. For instance, the resonance frequency for the chest wall was found to be 26.7 Hz and 27.8 Hz in 23 healthy male and female volunteers, respectively [68] and supported numerically as 28 Hz with a male model [34]. Furthermore, the cut-off frequency was found to be 40 Hz due to lung-rib cage interactions [70], and the strong decrease in energy density distribution in the lungs above 40 Hz [35]. Furthermore, in light of both numerical experimental studies done in the recent five-year studies, an increase in the frequency range up to nearly 30–50 Hz was indicated as useful (see Tables 3, 4 and specifically references [27,35,36,100]). Therefore, although the diversity in BMI, weight, height, chest size, and disease severity (among other parameters) plays a crucial role in the effective applied frequency

range, it would appear that both experimental and numerical studies generally agree that a low-frequency range up to around 40 Hz is sufficient and effective as a gentle therapy.

As illustrated in Fig. 4, which presents a recommended interdisciplinary framework for future studies, the inconsistency in the frequency range used by acoustic ACDs can be further elucidated. This framework, supported by a visualization based on the CT-FEM model [33], underscores the importance of interdisciplinary research. Such studies may not only clarify the observed frequency variations but also promote collaboration across fields like medicine, physiotherapy, science, and engineering. This cross-disciplinary effort is essential for advancing the development and optimization of ACDs. With the help of numerical studies, mimicking the medical devices' effects can be accurately repeatable across tests so as to generate a digital twin of the human chest under vibrations by including organ geometry as well as the amount and rheologic properties of mucus. Implementing CT-FEM studies could hence foster enhanced collaboration among medical professionals, physiotherapists, scientists, and engineers, leading to significant benefits in ACDs.

7. Conclusions and perspectives

A number of studies are currently being conducted independently, leading to inconsistencies in the frequency range identified as the most appropriate for ACDs in the setting of muco-obstructive pulmonary diseases. This review provides a comprehensive point of view on the state of the art of the working frequencies used in acoustic ACDs, taking into account both experimental and numerical studies, with the aim of paving the way for future interdisciplinary studies, including medicine, physiotherapy, and engineering domains.

In a first instance, a total of 14 currently available ACDs for OHFO and HFCC were described according to their working principles and frequency ranges (Fig. 3 and Table 2). Despite numerous devices being described in the literature, many discrepancies remain both in the manner in which these are applied and the type of patients investigated. All of the devices were categorized herein and, to the best of our current knowledge, we conclude that HFCWC devices are unique as they provide

Table 2
Currently used modern acoustic ACDs.

Type	Name	Form	Freq. (Hz)	Working Principle	Ref.
OHFO	Flutter®	Hand-held portable	2–32 (mean 11.3 ± 1.5)	The fluctuation of pressure and airflow are triggered by a steel ball movement during expiration.	[49–51]
	Simeox®	pipelike device with OPEP	6–20	Pneumatic vibratory stimulus oscillations during expiration.	[1,52]
	Aerobika®	Electronic NEP device	5–20 (mean11.6 ± 2.2)	Pressure pulses are generated during exhalation.	[53–55]
	Acapella®	Hand-held portable device with OPEP	15.0 ± 3.7 (mean)	Using a counterweighted lever and magnet, PEP can be achieved. Exhaled gas generates air flow oscillations.	[51,53]
	PARI-OPEP®		15 (mean)	The vibratory movement of a ball generates oscillatory pressure when the patients exhale.	[42,56]
	Shaker®		16.41–27.48	During exhalation, resistance generates PEP along with airflow rates and oscillation frequencies.	[39,41]
	RC Cornet®		20–300 (mean 80)	PEP device operates using a latex-free hose, which creates oscillations by randomly striking the top and bottom of the tube, intermittently obstructing the flow.	[19]
	Lung Flute®		16–22	Tubular PEP device, with a plastic mouthpiece at one end, attached to a Mylar reed that flutters during use.	[2,57, 58]
HFCC	Frequencer®	Acoustic treatment with a mechano-acoustic device	20–65	An electro-acoustical transducer is used to create oscillatory sound waves, which cause vibrations on the chest wall.	[27,43]
	The Vest®	Wearable technology with HFCWO	5–20	Repeated inflation and deflation of the vest helps create oscillations of the thorax.	[59]
	Smart Vest®		5–20	The vest is inflated and deflated with a single hose, causing pulses of air that softly squeeze and release the thorax.	[60]
	Hayek® BCV		1–17	The device uses BCV technology that flattens the diaphragm down and creates negative pressure for the inspiratory phase.	[47,61]
	AffloVest®	Wearable mobile technology with HFCWC	5–20 (mean 12)	The device works with eight mechanical oscillating motors. They are engineered to target all five lobes of the lungs, front and back.	[62]
	RespIn 11 Bronchial Clearance System®		1 to 20 (per line)	The device controls the frequency and the intensity of the piston expansion in different lines, front and back, by focused pulse techniques. Two lines in the front and three lines in the back side can be powered alone or together.	[20]

Table 3
Experimental studies on acoustic ACDs.

Year	Objective	Freq. (Hz)	Subjects	Method	Outputs	Ref.
1983	Observation of the clearance of mucus in the trachea	3–17	9 dogs	HFCWO	HFCWO was effective in the 11–15 Hz range, with a peak at 13 Hz for mucus clearance.	[24]
1985	Investigation of the effects of oscillations on PMC and TMC	13	5 dogs	HFCWO with 0–150 cmH ₂ O	(1) 13 Hz with 100–120 cm H ₂ O significantly enhanced the PMC index in peripheral airways. (2) TMC rate at 13 Hz with 50 cmH ₂ O reached a plateau level. (3) 13 Hz with 50–60 cmH ₂ O significantly increased the PMC index.	[46]
1986	Effects of pressure oscillations in an air-filled cuff wrapped around the lower thorax	3.5–8	3 males and 2 females	HFCWO with 90–120 cm H ₂ O	(1) HFCWO at 3–5 Hz reduced spontaneous minute ventilation and maintained gas exchange. (2) 8 Hz and higher frequencies could be uncomfortable for patients.	[80]
1990	Development of a device to aid in mucus clearance	5–25	5 participants	HFCWO, 3.7–5.2 kPa and CPT	An average of 3.3 cc and 1.8 cc of mucus were collected during a therapy session based on HFCWO therapy and CPT, respectively.	[63]
1990	Determine the chest resonance frequency		6 mongrel dogs (4 male and 2 female)	OHFO	Resonance frequency was measured at 6.1 ± 0.9 Hz which was very close to the panting frequency (5.7 Hz) of the same dogs.	[76]
1991	Detection of the long-term effects of oscillation therapy	5–22	16 patients with CF	HFCWO	(1) The pre-HFCWO period predicted the FVC slope as -0.013 , which represents an average decline of approximately 5 % predicted FVC per year. (2) For the period during HFCWO therapy, the predicted FVC slope was 0.012 ($P < 0.001$).	[45]
1992	Determining whether the airway oscillations cause bronchoconstriction	10	8 asthmatic and 6 normal subjects	OHFO with 25 psi	The initial FEV and FVC were 3.4 ± 0.91 and 4.6 ± 1.01 with maximal drop observed at 60 min following vibrations (FEV and FVC 3.1 ± 1.11 and 4.3 ± 0.41 , respectively ($P > 0.05$)).	[81]
1994	Measurement of the thorax resonance frequency	0–100	15 volunteers	Mechano-acoustic	The resonance frequency was 25 Hz and 33 Hz for males and females, respectively.	[69]
1994	Comparison of HFCC and CPT	6–19	50 patients with CF	HFCC and CPT	There was no significant difference between HFCC therapy and CPT, although there was a significant improvement after both therapies in terms of weight gain, respiratory rate, S _p O ₂ , white blood cell count, and absolute neutrophil count in both groups within 7 and 14 days.	[82]
1995	Analysis of the effect of the Hayek Oscillator on humans	1–5	20 healthy volunteers	HFCWO	(1) The oscillator could ventilate individuals through chest wall oscillations at frequencies ranging from 1 to 3 Hz. (2) In a study of five of the twenty patients with respiratory failure, external HFCWO improved oxygenation by 16 % and reduced arterial carbon dioxide by 6 % when compared to intermittent positive pressure ventilation.	[83]
1996	Comparison of CPT with HFCWO therapy	6–19	15 male and 14 female CF patients	CPT and HFCWO	The mean wet expectorated secretions were 2.86 ± 4.0 g and 6.76 ± 9.7 g for CPT and HFCWO, respectively ($P < 0.001$). The mean dried weights were 0.26 ± 0.45 g and 0.74 ± 2.4 g for CPT and HFCWO, respectively ($P < 0.01$).	[77]
1998	Comparison of ACDs and CPT	8–16	14 patients with CF	OHFO, HFCWO, and CPT	The wet and dry sputum weights varied from 4.3 ± 1.2 g to 7.6 ± 3.1 g and from 0.14 ± 0.04 g to 0.41 ± 0.08 g, respectively. There were no significant differences among OHFO, HFCWO, and CPT in terms of wet and dry sputum weights. However, patients tended to choose HFCWO in terms of self-administration.	[84]
2004	Comparison of HFCC with a sine and triangle waveform pulses	5	8 patients with CF	HFCC	Approximately 75 % and 60 % of the vest pressure was attenuated within 2 ms for the triangle and sine waveform, respectively. More sputum was collected with the triangle waveform than with the sine waveform.	[85]
2006	Investigation of the resonance frequency	15–50	8 males and 13 females	Mechano-acoustic	The resonance frequency was measured at 26.7 Hz and 27.8 Hz in males and females, respectively.	[68]
2006	Test a novel HFCC device	25–40	22 individuals	Mechano-acoustic	The maximum amount of sputum was collected at 40 Hz with 50 % amplitude.	[43]
2008	Investigation of the external layer effect in CPT	2.5–10.5	5 males and 13 females	CPT with a sheet, and with a towel	The addition of a sheet or towel did not notably affect the force applied on the chest ($F = 0.6^a$, $P = 0.55^b$) and generated vibration ($F = 2.53^a$, $P = 0.09^b$).	[86]
2011	Comparison of the short-term effects of different ACDs	15–20	34 patients with CF	HFCWO and OHFO	(1) There was no significant difference between HFCWO and OHFO. (2) S _p O ₂ decreased after the treatments (98 ± 1.0 % versus 97 ± 1.2 %, $P < 0.001$). (3) Patients tended to choose OHFO.	[65]
2015	Measuring lung function using sound waves	5–20	Patients of different ages and sex	OHFO	Higher frequencies (> 20 Hz) travelled shorter distances (generally up to the large airways), while lower frequencies (< 15 Hz) travelled deeper into the lungs and reached the small airways and lung parenchyma.	[87]

(continued on next page)

Table 3 (continued)

Year	Objective	Freq. (Hz)	Subjects	Method	Outputs	Ref.
2017	Investigation of the thermo-physical properties of mucus in certain conditions	0.159	Synthetic mucus	Excitation directly applied on mucus	Density and thermal properties of the synthetic mucus were measured. They were formulated as a function of the temperature and the concentration of Actigum™.	[28]
2017	Measurement of the rate of early moderate-to-severe exacerbations and related costs	5–20 Hz	405 patients with COPD	OHFO	(1) 18.5 % of patients using Aerobika vs. 25.7 % of controls had a moderate-to-severe exacerbation, $P = 0.014$. (2) 13.8 % of patients with Aerobika vs. 19.0 % of controls had a severe exacerbation, $P = 0.046$. (3) Per-patient cost of moderate-to-severe exacerbations in the Aerobika group was 34 % lower than the control group, $P = 0.012$.	[88]
2018	Characterization of complete rheological properties of mucus in certain conditions	10 ⁻⁵ –100	Synthetic mucus	Excitation directly applied on mucus	(1) The viscoelasticity, viscoplasticity, shear-thinning, and thixotropy as a function of Actigum concentration were investigated. (2) The temperature dependence of the gel response was negligible in the 20–37°C range.	[29]
2019	Effect of the frequency range on the expectoration of excessive mucus	20–65	Synthetic mucus	Directly applied to mucus container	A frequency of 40 Hz coupled with a 0.5 g.L ⁻¹ NaCl rehydrated mucus, lowered its viscosity and rendered expectoration easily.	[27]
2019	Development of an ACD algorithm to examine the long-term effects	5–20	65 patients with bronchiectasis	HFCWC	Overall antibiotic usage was reduced annually for pre- and post-initiation as 2.5 ± 0.86 and 2.1 ± 0.92 , respectively, $P < 0.0001$.	[89]
2020	Measurement of the effectiveness of a mobile HFCWC	10–15	6 males and 3 females	HFCWC	The new mobile HFCWC device could be an effective option for CPT in terms of mobility and effectiveness with an overall improvement in the Brody index (57.71 ± 16.55 vs 55.20 ± 16.98 for mobile and standard HFCWC device, respectively, $P = 0.001$).	[10]
2020	Comparison of the clinical outcomes of OHFO devices	5–20	5029 patients with COPD	OHFO	(1) Patients with Aerobika were less likely to have severe breathing problems in 30 days and 12 months compared to those who used Acapella. (2) They also had fewer severe breathing problems within 12 months (0.7 vs. 0.9 per patient per year). (3) Aerobika users were less likely to be admitted to the hospital for any reason in 30 days (13.9 % vs. 20.3 %) and 12 months (44.9 % vs. 51.8 %) than Acapella users.	[31]
2020	Examination of the impact of Aerobika on patients	5–20	10 patients with COPD	OHFO	Generally, there were no significant alterations, except for a significant 2.88 % increase in determined specific airway volume after treatment.	[90]
2020	Comparison of OHFO devices	5–20	60 patients with COPD	OHFO	(1) FEV1 improved by 2.64 %, 8.92 %, and 10.49 % for patients with routine treatment, active cycle breathing technique treatment, and OHFO therapy, respectively. (2) FEV1/FVC and walking distance also improved in all patients. (3) Quality of life was improved in all patients.	[91]
2021	Verify the safety and compare the immediate effects of voiced high-frequency oscillation using different types of Shaker devices	15–40	15 women and 15 men healthy individual	OHFO	(1) 3 min of voiced OHFO with the New Shaker increases “fatigue when speaking” in both genders. (2) 5 min of voiced OHFO with the New Shaker reduces “voice failure” in women, while 3 min with the Shaker Plus reduces “dry cough” and “voice failure” in men.	[39]
2022	Development of a disposable OHFO device, with comparable mechanical performance to commercial devices	26	a healthy volunteer	OHFO	A mean pressure of 14.82 cm H ₂ O at a mean flow rate of 18.82 L/min generated an oscillation frequency of 26 Hz with an amplitude of 1.28 cm H ₂ O.	[92]
2023	Efficiency of Simeox in homecare treatment	20	8–17-year-old patients with CF	OHFO	20 Hz causes a significant drop in proximal airway obstruction with maximum expiratory flow at 75 % of FVC.	[1]
2023	Examine the impact of Aerobika	5–20	53 subjects	OHFO	Remarkable improvements in small airway resistance at 5–20 Hz were measured as early as 12 weeks of usage, with sustained improvement in lung function at 24 weeks.	[55]
2024	Testing the new prototype for HFCWO and comparing it with commercial VEST-205 device	5–20	Mannequin	HFCWO	(1) The prototype can maintain a vibration frequency of up to 14 Hz. (2) The pressure waveform with the prototype is similar to VEST-205 device at 8–12 Hz and 2–4 pressure intensity levels.	[93]

the gentlest therapy with the least side effects. Moreover, a low-frequency range of up to approximately 40 Hz appears to be adequate in providing an effective and gentle airway clearance.

Secondly, acoustic airway clearance experimental studies are long-established as listed in Table 3. In recent years, experimental physiotherapy studies have been expanded to include an engineering perspective. These studies now focus on the use of synthetic or real mucus to better understand its physico-chemical properties such as surface tension, thixotropic and shear-thinning behaviors under different settings mimicking ACDs.

Thirdly, the numerical studies pertaining to acoustic ACDs are listed in Table 4. Despite the fact the physico-chemical properties of mucus are clearly dependent on frequency, the numerical studies underpinning this mechanism of action are very few. We have highlighted that frequency-dependent realistic geometry and material properties play a key role in generating accurate results. Therefore, the medical imaging process, which has recently been used for CT-FEM, is critical in creating this realistic geometry.

We also identified the biggest technical gap, namely the difference between experimental and numerical studies, and suggested that 3D CT-

Table 4
Numerical studies on acoustic ACDs.

Year	Objective	Freq. (Hz)	Geometry	Method	Condition	Outputs	Ref.
2005	Analyze the respiratory airflow	5–21	1D	Electrical circuit analogue	HFCWO	Nonlinear characteristic of the respiratory system was simulated at 5, 15, and 20 Hz.	[103]
2011	Measurement of muco-ciliary transport in terms of the mean mucus velocity	3–20	2D	Projection method combined with the Immersed Boundary Method	Muco-ciliary transport	As the frequency increased, the mean velocity of the mucus layer also increased linearly.	[104]
2018	Detection of the mechanisms that facilitate gas exchange	10	3D	–	OHFO	(1) The exact location of gas transport mechanisms in the preterm infant at 10 Hz was with the low tidal volumes of 2.0 mlkg ⁻¹ . (2) Lung volume increased during the first four breaths and remained stationary thereafter.	[105]
2019	Examination of the thickness of the two layers of mucus and oscillating airflow	0–80	CT, 3D	ANSYS Fluent	OHFO	(1) The mere presence of the serous layer was found to increase mucus clearance by more than 15 %. (2) An oscillating flow enhanced clearance by up to 5 %.	[106]
2021	Effect of the idealized HFCWO manipulation on the lung model	1–20	2D	Numerically-generated air branches, Octave	OHFO with 200 Pa	Frequencies between 3 and 15 Hz maximized the airflow inside the airways with an optimal value at 6.5 Hz.	[20]
2022	Effect of boundary vibration on mucus mobilization	15–90	2D, Cylindrical Tube	A Newtonian and an Oldroyd-B fluid, COMSOL Multiphysics®	Mechanical oscillation in the bulk fluid	48 %, 57 %, and 343 % improvements in mucus mobilization were documented by optimizing the mean relaxation time, vibration amplitude, and vibration frequency, respectively.	[30]
2023	Study of variations in mucus velocity under varying conditions	15–30	2D	Mathematical model	Mucosal-based medical treatments	The shear stress levels were found as 2, 1, and 0.01 Pa during sneezing, coughing, and quiet breathing, respectively.	[107]
2023	Modeling of the human thorax under low-frequency range	20–60	3D human thorax CT-FEM	Repairment, COMSOL Multiphysics® 6.1	Mechano-acoustic	The generation of 3D human thorax CT-FEM methodology was acknowledged with the decision-making process and validation.	[33]
2023	Examination of lung behavior under HFCC	5–100	3D human thorax CT-FEM	Repairment, COMSOL Multiphysics® 6.1	Mechano-acoustic	The lungs exhibited 2 peaks for both kinetic energy and elastic strain energy densities at approximately 30 and 40 Hz.	[35, 36]
2024	Investigation of the vibrations acting in the axial, radial, and tangential directions on mucus clearance	0–30	1D	COMSOL Multiphysics v.5.4	HFCWO	Applied vibrations enhanced mucus clearance, providing changes in vibration amplitude and frequency, pressure differentials, fluid properties, and ciliary movements on the flow up to 30 Hz.	[100]
2024	Investigation of the resonance frequency of the thorax and its response	5–100	3D human thorax CT-FEM	Repairment, COMSOL Multiphysics® 6.1	Mechano-acoustic	Two apparent resonance frequencies at 28 Hz and 41 Hz were found. Thoracic and internal organ responses at low-frequency resonance were simulated.	[34]

FEM could help reduce these discrepancies. It might also be helpful to compare the different devices. For these reasons, we recommend that future studies take into account of the interdisciplinary aspects of airway clearance in muco-obstructive pulmonary diseases and potentially include both experimental and numerical studies. As an example of the latter, a frequency of up to 40 Hz is recommended in this review, based on various engineering and medical studies. Lastly, the inconsistency of the frequency range used by acoustic ACDs could be elucidated through interdisciplinary studies which, in turn, may facilitate cross-disciplinary collaboration between professionals in the fields of medicine, physiotherapy, science, and engineering.

Data availability

Data will be made available on request

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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