Rethinking physical exercise training in the modern era of cystic fibrosis: a step towards optimising short-term efficacy and long-term engagement

Running Title: Rethinking physical exercise training in CF

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Abstract

Exercise is considered as an important component of the package of care delivered to people with cystic fibrosis (pwCF). However, despite the well-known short-term physiological and psychological benefits, training effects are heterogenous and the transfer of structured exercise programs to the daily life of pwCF is challenging. Training concepts and strategies developed over the last decades must be adapted to consider the aging population of pwCF with associated comorbidities, and also a new generation of young pwCF that are healthier than ever. In the present review we propose a new framework for optimising the choice among available exercise training procedures and we provide a theoretical and scientifically justified rationale for considering and testing new exercise training modalities. We propose a multidisciplinary approach, considering various physiological, psychological and logistical factors, with the aim to increase effects of exercise training and build positive long-term exercise behaviour.

Keywords: cystic fibrosis., aerobic training., resistance training., physical fitness., exercise preferences., CFTR modulator

1 - Introduction: why we should rethink physical exercise training in CF?

Physical exercise training is commonly viewed as an important cornerstone of care for people with cystic fibrosis (pwCF). Exercise is intended to increase health-related physical fitness measures, which in turn impact quality of life [1] and survival [2-5]. Moreover, exercise can serve as an adjunctive therapy for airway clearance [6, 7] and exert benefit on the various co-morbidities that make up the multisystem disease burden of CF. Finally, exercise is relatively inexpensive and is usually considered as more pleasant compared to other health-related interventions. However, despite these commonly accepted benefits supporting the concept of "Exercise is Medicine" in chronic diseases [8], including CF [9], things are far from being simple.

In the most recent Cochrane review investigating the beneficial effects associated with physical exercise training in pwCF, the authors found only limited evidence of benefit from 15 studies with low-to-moderate methodological quality [10]. In practice, it is indisputable that short-term benefits can be obtained with well-structured exercise programmes at the group level. However, it is just as apparent that training effects are heterogeneous at an individual level, such that many pwCF do not obtain clinically meaningful positive effects in physiological and/or patient-reported outcomes. In fact, notably because of the low prevalence and incidence of CF compared to many other chronic respiratory disorders, most exercise training studies in CF are small-sized despite having wide inclusion criteria, often mixing children and adults, with a broad range of disease severity [10]. Although some training components may appear adapted to individuals' physiological capabilities (*e.g.* aerobic training intensities based on gas exchange threshold determined by cardiopulmonary exercise testing (CPET)), it is likely that most training components may not be adequately individualised according to both physiological and psychological characteristics of the individuals. Another important related issue is the maintenance of the benefits associated with an exercise training programme in the long-term. Although some studies included follow-up periods at the end of training (*e.g.* from 3 to 18 months; [11-13]), the factors promoting the transfer from well-structured and (partially) supervised exercise training programmes to enhanced physical activity (PA) behaviour are unknown in pwCF and most likely differ between individuals.

In theory, individualised exercise training (*i.e.* individualisation of all components, comprising the type, intensity, duration and frequency of training) based on appropriate and regular individual evaluations, would be necessary to maximise the benefits in the short-, medium- and long-term. In practice, we are still some way off this ideal situation. Two important reasons are the lack of consideration of (1) psychological and physiological responses to acute exercise and (2) barriers to long-term engagement in habitual PA and exercise, in the design and implementation of exercise training programmes in pwCF.

The rationale for choosing a type of training modality and its associated parameters (*e.g.* intensity) is usually based solely on quite general physiological recommendations, which are often not specific to pwCF. For instance, aerobic training is widely utilised in exercise programmes in CF because of its well-known effects on cardiorespiratory fitness. A standard session consists of 30-45 min of cycling at a constant metabolic intensity corresponding to ~60-80% of peak heart rate or peak oxygen uptake ($\dot{V}O_{2peak}$) or heart rate around the first ventilatory threshold [10, 14] - training intensities that are typically determined from CPET [15]. While such testing and training modalities may be adapted for most individuals from a physiological perspective, this may not be the case from a psychological point of view. As yet, no studies consistently have evaluated affective responses and enjoyment associated with these procedures in pwCF. Poor enjoyment and negative affective response for a given exercise modality may alter short-term motivation and immediate engagement in the training session, but also the ability to engage in subsequent long-term regular PA [16-19]. These issues may be of particular concern in pwCF and notably in those with more advanced disease as they may exhibit unique affective responses during physical exercise due to factors such as dyspnoea [20]. A given exercise training programme with a high potential in terms of physiological benefits may thus be ineffective in the medium-long term in some pwCF due to negative psychological responses. Such psychological responses to exercise most likely vary from one person to another and may not be easily predictable, requiring direct measurements.

Another important gap in the CF literature is the paucity of data about the physiological factors that may predict the success of exercise training. Very little is known in CF regarding the interaction between ventilatory limitation and muscle loading during an acute session of a given exercise modality, which may be a key factor underlying exercise training efficacy. For instance, following the principle of muscle overload, reports in people with chronic obstructive pulmonary disease (COPD) have shown that those developing significant muscle fatigue following an acute exercise training session were more prone to obtain positive physiological and psychological benefits following an exercise training programme [21, 22]. It is important to note that optimal muscle loading is hard to predict and is not only driven by training intensity, emphasising the need to directly measure these acute muscle adaptations to exercise at the individual level. Such findings, if they turned out to be transferable to some pwCF (*e.g.* those with more severe disease), may provide opportunity for the development of new strategies aiming to increase the overload imposed on skeletal muscles, while keeping tolerable ventilatory demands/sensations.

Beyond the aforementioned psychological responses to acute physical exercise, there is increasing evidence that pwCF may have several other barriers impeding long-term engagement in PA, with their relative influence varying according to age and disease severity [23]. However, those barriers are still often ignored in the initial design of many exercise training programmes. This is not helped by the absence of any widely accepted recommendations regarding PA and exercise training for pwCF that rigorously consider the potential differences between children, adolescents and adults with varying clinical presentations. Such issues are becoming more and more important with the considerable improvements in survival observed in the past two decades [24] and the expected further substantial increase in the near future owing to highly-effective CFTR modulator therapies [25, 26]. Proposing the same exercise training programmes for adolescents and adults made sense in the past when most pwCF were under the age of 30 years. There is now, however a growing cohort of older adults aged >40 years [27, 28], some with specific comorbidities [29] and new psychosocial factors modulating PA behaviour that must be factored into the design of exercise training programmes, whilst younger pwCF are healthier than ever with further improvements in health status anticipated as a result of new therapies. The combination of over-nutrition and improved CFTR function promotes weight gain, thus increasing the risk of overweight and obesity in pwCF [30], paralleling the observed obesity trends within the general population. It is therefore important to adapt training concepts and strategies developed in the young people over the last decade in order to improve several health and skill-related physical fitness measures and prepare for the physical demands of regular sports practice for pwCF [31]. The setting where the training programmes take place may be pivotal in regard to barriers and facilitators to PA in pwCF. This is a very timely consideration given the expansion of telemedicine, with an urgent need to evaluate the feasibility and efficacy of various remote exercise training procedures in both youth and adults with CF.

The aim of the present review is to provide a novel theoretical framework for facilitating choice among existing training programmes for pwCF as well as incorporating innovative training procedures that are tailored to an individual. This approach is multidisciplinary and considers various physiological, psychological and logistical factors, with the aim being to optimise training short-term efficacy and long-term engagement.

2 - Preliminary considerations: why habitual physical activity should be supplemented with physical exercise training in CF

The terms "exercise" and "PA" are still used somewhat interchangeably despite distinctions between these terms being defined almost 40 years ago (*e.g.* [32]). In this review, we will use the term "PA" to designate all PA categories, inclusive of formal exercise. The terminology "habitual PA" will refer to incidental PA, exclusive of formal exercise.

Similar to the general population, children and adults with CF are encouraged to adopt a physically active lifestyle. However, the volume of PA required for this population as well as the balance between habitual PA and the exercise component of PA are not clear. Many studies have measured PA levels in pwCF over a short period of time using questionnaires or accelerometry [33, 34]. The rationale for the recommendation of achieving normal PA levels for pwCF has been based on previous studies showing the efficacy of formal exercise training programmes at improving markers of health-related physical fitness. For instance, $\dot{V}O_{2peak}$ determined from CPET is considered the gold standard measure of physical fitness in CF. This is in part supported by the fact that $\dot{V}O_{2peak}$ reflects the integrated functioning of multiple organs, which is intuitively relevant in a multi-system disease such as CF. In practice, $\dot{V}O_{2peak}$ is also a key marker of prognosis and survival in CF [2, 3, 35] and PA interventions should thus be tailored in part to improve or prevent decline in $\dot{V}O_{2peak}$. However, it is well-known that improving markers of cardiorespiratory fitness such as $\dot{V}O_{2peak}$ is not an easy task and often requires very specific modalities from a formal exercise training programme [10]. There are currently no widely accepted PA guidelines specifically adapted for pwCF. Hence, some studies dealing with PA in CF (see [33] for a recent systematic review) used guidelines adapted from the general population such as the World Health Organization (WHO) (*e.g.* "at least 150 minutes of moderate to vigorous intensity PA throughout the week" for adults) or a minimal number of steps per day (*e.g.* achieving 10'000 steps daily). Although the achievement of these guidelines is important to obtain some fundamental health benefits, they may not be enough specific to address the marked reductions in outcomes such as $\dot{V}O_{2peak}$ observed in some individuals. Studies often report PA levels in pwCF according to the time spent in each intensity levels (*e.g.* light, moderate and vigorous), without stratifying for the PA category (*i.e.* habitual PA *vs.* scheduled exercise) or considering the specificity of the activity (*e.g.* whole body *vs.* isolated muscle exercise) and the specific associated goal (*e.g.* increasing limb muscle strength) [33]. It is likely that reaching "normal" PA levels based on a purely quantitative indicator (*e.g.* 10'000 steps per day), in the absence of tailored bouts of exercise, may not be adequate to address the reductions in some specific markers of physical fitness. Such intuitive assumptions are further supported by the only weak (or even absent) correlations between global quantitative indicators of PA and some important markers of physical fitness in CF (*e.g.* quadriceps strength, six-minute walking distance, $\dot{V}O_{2peak}$ [36, 37]).

Thus, it is obvious that habitual quantitative PA recommendations (*e.g.* a given number of steps) must be supplemented with more individualised bouts of planned exercise in individuals with CF exhibiting deficiencies in some specific physical fitness outcomes. While formal supervised programmes (*e.g.* aerobic training) may indeed be necessary to improve a given marker of physical fitness (*e.g.* $\dot{V}O_{2peak}$) in some individuals, it is unrealistic to hope maintaining a high adherence with the initial "strict" version of the programme on a long-term basis. Hence, beyond short-term physiological efficacy, it is just as important to foresee the potential of a given training programme for being incorporated in the daily life of pwCF. In other words, it is fundamental to anticipate for a more scalable version of the programme, taking into considerations as many enablers of positive PA behaviour as possible.

3 – Selection of physical exercise training modalities

3.1 Aerobic training and/or resistance training? Preliminary considerations

Aerobic training is cornerstone of exercise rehabilitation programmes in most chronic diseases. Aerobic training is versatile and can act simultaneously on different systems (*e.g.* respiratory, cardiovascular, metabolic and musculoskeletal). Aerobic training may lead to significant improvements in both submaximal and maximal exercise capacity in pwCF [10], reduces the sensation of breathlessness [38] on exercise, and positively impacts quality of life [39]. Aerobic training may also improve ease of sputum expectoration [40] and is a recommended adjunctive therapy for airway clearance [6]. However, this form of training has only limited effects on improving limb muscle atrophy and strength which may be important for many pwCF [41], potentially limiting exercise capacity and the ability to engage in PA.

Resistance training aims to increase muscle mass, strength, and local muscle endurance. Resistance training is often performed under a "strength" or "weight" training modality in CF, consisting in performing sets of repetitions at a fixed percentage of maximal load (*e.g.* 1-repetition maximum; 1-RM) for the same exercise focusing on a specific muscle group (*e.g.* 3 sets of 6 repetitions at 70-80% 1-RM on a bench press to increase chest strength). This form of training has been shown to increase the strength of various muscle groups in both children and adults with CF [10, 41]. However, resistance training alone has only limited effect on cardiorespiratory fitness and is less efficacious (compared to aerobic training) at improving global fitness outcomes such as $\dot{V}O_{2peak}$ [42, 43].

Considering these elements, it is intuitive to recommend a combination of concurrent aerobic and resistance training in CF, to maximise benefits in terms of both cardiorespiratory fitness and muscle strength. Swisher et al. [14] recommended in adolescents and adults with CF, beyond habitual PA, to perform aerobic training at least 3 times per week (ideally 60 minutes daily) with an intensity of at least 70% of maximal heart rate, as well as formal resistance training 2-3 times per week, targeting both limb and trunk muscles (1-3 sets of 8-12 repetitions at 70-85% 1-RM). Whilst such a recommendation for combined training may be "ideal" from a physiological perspective, such an exercise commitment faces several barriers, limiting its incorporation in the daily life of most pwCF.

On one hand, we must pursue the research effort to increase the time pwCF are willing to dedicate to exercise training. As we will argue in the next sections, there are many physiological, psychological and logistical aspects that can be modulated to facilitate the incorporation of both forms of training as part of the daily life of pwCF. However, we must bear in mind that the lack of time due to competing priorities is an important barrier to PA in pwCF. Many pwCF already have a time-consuming treatment regime [44], and some also have to deal with the burden of decreased life expectancy and an increased pressure to achieve milestones (education, career, relationships) within a shortened lifespan [45]. Therefore, although high volumes of both resistance and aerobic training modalities may be achieved during short-duration supervised programmes, it is unlikely that pwCF will adopt such formal programmes for a lifetime. Pragmatically, one must ascertain where a pwCF sees exercise in terms of priority and work with the pwCF to find the best balance between aerobic and resistance training, *e.g.* in a fixed available time per week, can replacing some sessions of aerobic training with resistance training permits to increase muscle strength while still preserving meaningful positive effects on cardiorespiratory fitness.

From a purely physiological point of view, the adjustment of the volume of resistance training that can be substituted for aerobic training may be best based on the degree of the initial limb muscle weakness. However, the measurement of limb muscle function is absent in many CF centres. As compared to other forms of exercise testing (*e.g.* CPET [15]), limb muscle testing has received little attention in this population [46]. It is too early at present to accurately adjust the volume of required resistance training based on appropriate individual limb muscle testing; it seems essential in the meantime to highlight the potential for early detection of limb muscle abnormalities in CF. The proposed approach implies reasoning in terms of subgroup of individuals that may share common basic demographic and clinical characteristics. This is essential not only to guide future research but also to facilitate the understanding of the future exercise training recommendations for both pwCF and healthcare providers, based on well identified characteristics such as the age profile of the patients. Such an approach is also supported by the fact that, beyond physiological considerations, various logistical and psychological factors should be considered in the balance between aerobic and resistance training but also in the manner to perform both training modalities. These factors, acting as potential barriers or facilitators to the implementation of a given training strategy, may greatly vary across the lifespan and should thus be considered differently between children and adults with CF.

3.2 Resistance training: age matters

At some point along the course of their disease, pwCF may enter into a downward spiral of physical deconditioning. A possible entry mechanism, particularly in those with greater disease severity, is disengagement in vigorous PA to prevent unpleasant symptoms such as breathlessness, pain, fatigue or embarrassment related to sputum production [23, 47, 48]. The resulting lack of activity, coupled with various factors predisposing to myopathy (*e.g.* corticosteroid use [49], proinflammatory state [50]) may lead to various structural and metabolic changes within the skeletal muscles [41] which, in turn, reinforce symptoms (*e.g.* breathlessness) and discourage exercise, prompting further deconditioning. While exercise training is indicated to break this negative spiral, this may become much more challenging as the disease progresses and symptoms worsen, further fueling this vicious cycle. For these reasons, it is essential to promote exercise in the very early stages of the disease, before individuals' symptoms and their exacerbation become an insurmountable barrier. The aforementioned concepts and assumptions are exemplified in **Figure 1,** depicting a conceptual model which compares changes in neuromuscular function in pwCF across the lifespan, according to different PA behaviours.

3.2.1 Children with CF: the importance of early integrative neuromuscular training

One of the best ways to exercise at a young age is to be involved in sports (both recreational and/or competitive). Many sports can be performed at school and in sports clubs from a young age. Sport can act positively on both neuromuscular and cardiorespiratory fitness and is certainly one of the best modalities to promote a positive perception of PA and "normality" (i.e. one of the most important modulator of PA behaviour in young pwCF [23, 51, 52]). This may result in increased value attributed to PA, which is essential to build positive long-term PA behaviour and sustainable high PA levels in adulthood. This may ultimately promote long-term health benefits, notably through avoiding or delaying the entrance into the spiral of deconditioning **(Figure 2**). With recent improvements in therapeutics, children with CF are healthier than ever, and almost all will be physically able and should be encouraged to reach the WHO guidelines for PA (notably targeting vigorous activities through regular sport participation at school and in sports clubs), without requiring formal specific exercise programmes (*e.g.* cycle ergometry aerobic training, see section 3.3). However, optimal participation in sport is already facing many barriers in the general population, contributing to the fact that more than 80% of school children (11-17 years) do not meet WHO PA guidelines [53]. Beyond traditional barriers shared with the general youth population which can be reinforced in children with CF (*e.g.* competing priorities/lack of time), many of them may accumulate various specific psychological and physical factors favouring sport avoidance. Two of the most common barriers to exercise are non-normality and embarrassment [23], which can be consecutive to the inter-related influences of poor physical fitness and self-efficacy. In many young pwCF, pulmonary function is now near normal (*e.g.* CF Foundation reported a median FEV_1 %pred of 94% in 9,411 pwCF aged 6 to 17 [54]) and is expected to further increase in the era of highly-effective CFTR modulators. Pulmonary factors are thus unlikely to contribute to reduced physical fitness and self-efficacy in the actual generation of children with CF. Despite nutritional improvements over the last decades, height and weight percentiles remain below those of the general population [54]. Some children with CF may still exhibit growth retardation [55] and delayed puberty [56]. Moreover, fat free mass depletion is still prevalent in children with CF [57]. This may contribute to poorer neuromuscular skills, physical self-efficacy and body image, when comparing to healthy peers at a given chronological age. Neuromuscular skills affected can include jumping, sprinting and throwing which are paramount for most school-age sports. The resulting sports avoidance can be further reinforced by parental overprotection and/or negative belief toward early training.

In healthy children, the development of neuromuscular skills can be initiated early in age, by targeting specific neural and structural adaptations according to the stage of maturation (i.e. prepubertal, pubertal and post-pubertal) [31]. This refers to the concept of "integrative neuromuscular training" (INT), with progression and precautions carefully adjusted according to the individual's training age [31]. INT encompasses a wide range of training modalities and goals, aiming to improve muscle mass and strength but also various fundamental neuromuscular skills. INT is thus inclusive of resistance training (and the so-called "strength" or "weight" training components) but also aims to develop several basic movement skills (*e.g.* agility, coordination, speed) with the aim to increase general preparedness for sport. There is no obvious physiological rationale for discouraging an early initiation of INT in the contemporary young CF population. In fact, we postulate that early training of neuromuscular abilities can be a vital trigger to increase sports participation at young age in CF, by building positive body image and optimal neuromuscular capacities **(Figure 2)**. This may help to bridge the small gap that may exist with their healthy peers, increasing in turn the ability to "keep-up" with them. This is of particular importance as social comparison has been reported as an important modulator of PA in young pwCF [52, 58]. Moreover, early INT may minimise the risk of athletic injuries [31] which may be a further disruptive event that may cumulate with hospitalisation.

Weight training is feasible and can increase muscle strength in children with CF [42, 59, 60]. The feasibility and efficacy of training other basic neuromuscular skills (*e.g.* jumping and sprinting) is supported by a scarce literature in youth with CF [11]. Beyond short-term physiological improvements, further studies should determine whether INT (*i.e.* combining weight training with fundamental movement skills development), initiated early in age and appropriately supervised, can increase psychological modulators of PA (*i.e.* physical self-efficacy, body image), and, eventually, whether gaining confidence in their own abilities promote children's long-term engagement in sports. Initial programming and progression must be flexible according to the stage of maturation (that should be evaluated, using tools such as peak height velocity and Tanner staging [61, 62], and preferred over chronological age) and the individual's training age **(Figure 2)**. Exercise counselling providers can get inspiration from the recent recommendations regarding INT in the general youth population [63-65] which individualise training prescription (*i.e.* dose and type) according to maturational status, allowing appropriate transfer to the youth CF population considering their potential growth retardation and delayed puberty. These prescriptions should of course consider potential sex differences along the puberty timeline. There is a lack of data on the effects of resistance training between young males and females with CF, and whether it should be applied differently. Although never specifically investigated in CF, one may expect specific barriers (*e.g.* competing interests, body image) and lower participation in early resistance training in young girls with CF compared to boys. However, it is intuitive that training of neuromuscular fitness must not be overlooked in young girls with CF for different reasons. The impact of hormones (*i.e.* estrogen [66]), among other factors, on chronic respiratory infections and overall disease progression has been suggested to translate into worse outcomes for females, compared to males with CF [67, 68] with potential deleterious consequences for skeletal muscle function. This may explain, at least in part, why young and physically active girls with CF exhibit alterations in skeletal muscle metabolism, and have reduced leg strength despite similar muscle mass compared to age-matched controls [69]. Such results are generally not observed in studies with balanced sex distribution [70] or in those that predominantly focus on males [71-73]. As proposed earlier, decreased neuromuscular abilities at young age may negatively influence PA and sports participation, which are generally lower in girls compared to boys with CF [74-76]. Considering these elements and the absence of sex-specific training responses and adaptations [74], it seems particularly relevant to encourage early initiation of INT in young girls with CF.

3.2.2 Adults with CF and increased disease severity: settings priorities

Many adults with CF of the current generation exhibit limb muscles abnormalities [41]. With advancing age, pwCF may indeed accumulate several factors acting negatively on both limb muscle mass and function. These may include increased rates of hospitalisation and symptoms (*e.g.* increased dyspnoea with the progressive decline in lung function), or long periods of immobilisation pre- and post-transplant, causing muscle deconditioning. Lack of time/competing priorities may also increase when moving into adulthood (*e.g.* combination of family and professional life considerations), prompting physical inactivity [23, 77]. Prevalence of anxiety and depression also increase from adolescence to early young adulthood in pwCF [54, 78], remaining elevated in older adults [54]. Although still poorly documented in CF, it is well known that a complex relationship exists between mental disorders and PA behaviour, and that both depression and anxiety-related symptoms may hinder people to engage in exercise training programmes [79]. The prevalence of other factors and conditions (*e.g.* oxidative stress [80], CF-related diabetes [54]) potentially promoting skeletal muscle dysfunction can also increase with age in pwCF. As a result of prolonged survival, these considerations will be relevant to an increasing number of pwCF in the near future.

The relative influence of limb muscle abnormalities on exercise tolerance and basic activities of daily living is thus expected to increase substantially with advancing age, with the gap between pwCF and healthy people becoming evident from about age 25-30 years **(Figure 1)**. Increasing neuromuscular fitness is thus still of high priority in adults with CF, but not for the same reasons. While in children with CF the emphasis should be put on the development of broad neuromuscular abilities through the mastering of various fundamental movement skills to promote sports participation (see section 3.2.1), most adults of the current generation should prioritise preservation of muscle mass and strength. Of course, CF adults with advanced training age and mild disease profile should continue as much as possible to practice sports-specific anaerobic drills. On the other hand, learning and mastering complex anaerobic movement patterns may be perceived as too effortful and time-consuming for adults who did not engaged early in INT/sports during childhood. Moreover, working muscle function through whole-body specific anaerobic workouts (*e.g.* involving sprints and/or multi-jump repetitions) may be increasingly complicated with advancing age, especially in those with moderate/severe disease profile, due to multiple factors (*e.g.* increased dyspnoea, CF bone disease related osteoarticular issues). The priority should thus be set on improving local muscle strength with movements requiring lower technicality, while keeping ventilatory requirements tolerable. Traditional strength training using guided weight machines (*e.g.* guided bench press, leg extension machines) may thus be recommended, targeting large upper and lower muscles groups (see [14] for examples of strength training sessions in pwCF).

However, strength training with costly machines that have large space requirements may not be adapted for home-based training, which is an important alternative in CF. For instance, exercising at home allows to eradicate the problems of cross-infection when exercising with other pwCF in indoor environments. Home-based training using web-based technologies may be a useful training modality and alternative in light of the current sanitary situation, as shielding against COVID-19 had a negative impact on PA levels among pwCF [81]. Overall, it can be anticipated that home-based training will become an even more popular training modality in the growing era of telemedicine and has the major advantage that pwCF can engage in group-based exercises together. Investigating whether resistance training with minimal resources can improve muscle strength remains to be specifically investigated in pwCF. For instance, several recent studies conducted in COPD have demonstrated the efficacy of elastic band resistance training at improving the strength of several muscle groups [82-85], with equal gains compared to conventional weight training [82, 85]. The efficacy of such portable and low-cost resistance training strategy, which can possibly be supervised remotely, remain to be investigated in pwCF.

Neuromuscular electrical stimulation (NMES) is another portable and relatively inexpensive strategy to improve limb muscle strength, with several studies demonstrating its efficacy in COPD, notably in those who are the most debilitated [86]. NMES has only received very little attention in CF, despite very promising results published few years ago showing its usefulness in pwCF with advanced lung disease [87]. NMES may be of particular interest in CF individuals unable to perform a full conventional resistance training programme and its feasibility and efficacy should particularly be tested in situations prone to rapid and substantial muscle deconditioning (*e.g.* repeated hospitalisations, pre and post lung transplant). For instance, in adults with CF, quadriceps strength was found to be 17% lower at hospital admission for acute pulmonary exacerbations than at convalescence [88]. Another study found a strong correlation between individual changes in quadriceps strength during exacerbation and daily time spent in activities of at least moderate intensity in adults with CF [89], highlighting the importance of early exercise initiation during hospitalisation to minimise the decline and promote recovery of physical fitness. In the absence of specific recommendations regarding the "best training modality" during pulmonary exacerbations in pwCF, and as respiratory symptoms may be an important barrier to optimal engagement in traditional exercise training modalities (*e.g.* weight and aerobic training), training modalities associated with a limited ventilatory load like NMES might be of particular interest during and after acute exacerbations in this population. Other strategies eliciting reflex muscle contractions like whole body vibration (WBV), performed during static or dynamic exercises, might also be of interest. Randomised controlled trials demonstrated the feasibility and the efficacy of WBV on exercise capacity in people with COPD hospitalised for treatment of pulmonary exacerbations [90] and in lung transplant recipients [91]. Positive effects on exercise capacity are sought to be mediated by both improvements in muscle function and balance performance [92], suggesting WBV a potentially interesting training modality for older adults with CF, notably those with severe lung disease and musculoskeletal and postural deficits. Two small pilot studies showed positive effects of WBV on lower-limbs muscle power in adults with CF [93, 94], warranting further controlled trials. Exercise training modalities which can be used in pwCF and their respective advantages and disadvantages are summarised in **Table 1.**

In summary, improving neuromuscular fitness in CF is important at any age but individual motives for training and preferential training methods likely evolve across the lifespan. In young pwCF, priority should be given to the development of basic neuromuscular skills aiming to increase the general preparedness for sport and for developing long-term positive PA behaviours. With increasing age and disease severity, it becomes essential to prevent the loss of muscle mass and strength with conventional weight training, which may possibly be substituted by specific training strategies (*e.g.* NMES) if indicated.

3.3 Aerobic training: time to rigorously consider individual's preferences

Aerobic training predominantly aims to increase cardiorespiratory fitness. Under its formal modality, aerobic training is usually performed in pwCF using continuous exercise at moderate intensity, including activities such as cycling, walking or jogging [10]. In practice, aerobic training usually elicits heart rate ≥ 60-70% peak heart rate for a total duration of at least 20-30 min. Some sports (*e.g.* team sports) may also fulfill this criterion and could thus be considered as a means of maintaining or increasing cardiorespiratory fitness (see section 3.2.1 and **Figure 2**). No studies to date evaluated sports participation/intensity in pwCF with objective assessments and stratifications based on demographic and disease severity markers. However, using accelerometers, several studies reported reduced levels of moderate-to-vigorous PA in both children and adults with CF [36, 95, 96]. Moreover, in the largest survey to date addressing sports participation in pwCF (n=403) [97], only 12.6% and 23.1% reported participation in team and individual sports, respectively, compared to 41.2% for traditional endurance activities (*e.g.* recreational walking, cycling, swimming, running). Altogether, these data suggest reduced participation in sports among pwCF. While we propose some strategies to increase sports participation in youth with CF (see section 3.2.1), some barriers may not possibly be overcome, notably in adults with more severe disease, and thus, more formal aerobic training should also be considered in some specific subgroups. Then, two important questions must be answered: where and how?

Aerobic training (excluding the sports component) can be performed in various indoors and outdoors settings. In pwCF, there is no direct evidence for claiming the superiority of one setting compared to another. However, the setting can influence the nature and level of initial supervision, which is an important factor to consider for optimising the effects of aerobic training. In-person supervision in a clinical setting is essential to set initial aerobic training intensity based on appropriate testing (*e.g.* CPET, see [15, 98] for specific recommendations) and ascertain the feasibility of a given session, while giving confidence to pwCF in their physical abilities. In-person supervision is also important to ensure familiarisation with training intensity/safety indicators (*e.g.* heart rate, oxygen saturation, perceived exertion) in view of achieving autonomy in aerobic training procedures. However, beyond this mandatory educational period, close in-person supervision is not always required in the mid-long term, especially if it restricts pwCF in their choice of training modalities and their ability to exercise regularly. In fact, remote online and offline (*e.g.* transfer of heart rate recordings after a given number of sessions) monitoring may allow to perform aerobic training in various settings (*e.g.* at home, outdoors) without direct in-person supervision. A recent small study conducted in children with CF (n=10) confirmed the feasibility of a remote training programme including aerobic training bouts (controlled by heart rate monitors), using streamed sessions from a telemedicine platform [99]. These online and offline means of remote supervision are particularly adapted for most aerobic training modalities which often require less technical execution compared to some specific resistance training modalities and may thus be sufficient to allow safe training sessions in individuals with prior experience. Many ongoing trials are currently investigating the use of digital technologies to promote and supervise physical exercise in pwCF (see [100] for a recent review summarising some of these trials) and their results will be crucial to determine the best technologies and the challenges remaining in their implementation and guide future research in the rapidly growing area of exercise and telemedicine.

In view of the variety of settings, levels of supervision and types of aerobic training, it is essential to keep individuals' preferences central when guiding the choice of training modality and environment, with the aim of increasing training feasibility, eliciting positive affects and enjoyment and thus reducing the rate of drop out. If such considerations also apply for resistance training, they are particularly relevant for traditional aerobic training modalities which often suffer from a "boring" reputation. Evaluating exercise preferences in a rigorous and repeated manner at the individual level seems particularly relevant in CF regarding the very large heterogeneity in the disease profile (*i.e.* age and severity), the increased number of barriers to exercise [23] and the acute changes that punctuate the disease (*e.g.* hospitalisation, start of a new treatment), which all make exercise preferences hard to predict and highly variable along the time course of the disease. Unfortunately, although recent tools can help in identifying barriers and facilitators to PA at the individual level in pwCF ([101] so far only available in French language), no instruments are yet available to specifically evaluate exercise preferences in pwCF. While it is an important research goal for the near future, it is still possible in the meantime to use some general items from scales validated in other diseases, like the Stroke Exercise Preference Inventory (SEPI, [102]). Some items relative to supervision (*e.g.* "I like a trained instructor to supervise my exercise") and settings (*e.g.* "I like to exercise outdoors") are easily transferable to pwCF. Some items (*e.g.* “I like to exercise at home”, […] “to exercise with family and friends”, […] “to watch TV during exercise”) may also help in the choice of incorporating distinctive modalities such as active video games, in the aerobic training package of pwCF. Some active video games can elicit exercise intensities equivalent to ~70% peak heart rate in pwCF [103] and 6-weeks of home-based active video games training improved various indicators of physical fitness in youth with CF [104]. As mentioned earlier, it is important to consider exercise preferences as a rapidly evolving concept, which thus need to be reassessed on a regular basis. This may be particularly true for the youngest CF individuals who may discover various exercise modalities on a very short-time frame, and a given preferred modality at a given moment (*e.g.* a specific active video game) may lose its appeal in the next few weeks/months.

Another crucial issue regarding aerobic training is the chosen intensity. Most studies involving pwCF in previous decades used moderate intensity continuous training (MICT; *e.g.* [59, 60, 87, 105, 106]). However, some recent studies demonstrated the feasibility and efficacy of aerobic high-intensity interval training (HIIT) in CF adults with moderate and severe lung disease [107-109]. Aerobic HIIT consists in repetitive short bouts of high intensity interspaced by periods of active recovery **(Table 1)**. A recent small randomised, controlled trial demonstrated that HIIT was as efficacious as MCIT at improving aerobic capacity in adults with CF [110]. Beyond physiological efficacy and health-related feasibility issues (*e.g.* impossibility to complete a full session of MICT for some individuals with severe lung disease [107]), it is also essential to consider individual preferences and tolerance, which are strong predictors of future PA behaviours [18], in the choice of aerobic exercise intensity. Sawyer et al. [108] used audio-recorded semi-structured interviews to evaluate tolerance and enjoyment associated with HIIT sessions. However, the data were derived from a small sample (seven CF adults), without comparison with MICT. In fact, findings from various healthy and clinical populations revealed large inter-individual differences regarding preference and tolerance (*e.g.* affects and enjoyment) for a given intensity [18, 111-113]. For instance, using an aerobic training modality that is often used in CF (*i.e.* 30-min of cycling at 60% of estimated $\dot{V}O_{2peak}$), Van Landuyt et al. [114] found that about half of the young adult participants experienced a progressive improvement in affective balance while the other half reported a progressive deterioration. Such variability is highly anticipable in pwCF considering the wide spectrum of CF disease severity. While it will be important to directly monitor affects and enjoyment during and following a given exercise modality using dedicated generic tools (see section 4.2), it would be very valuable to obtain an *a priori* identification of individuals with a particular affinity toward a specific exercise intensity with the practical aim to guide initial aerobic training prescription. Ekkekakis et al. [113] developed and established the psychometric properties of the Preference for and Tolerance of the Intensity of Exercise Questionnaire (PRETIE-Q). Although it will be important in the future, notably for research purposes, to ascertain the psychometric integrity of the PRETIE-Q in the CF population (notably for young children as the PRETIE-Q has been developed and validated from a young adult population), it is intuitive that the generic nature of the items (*e.g.* “When I exercise, I usually prefer a slow, steady pace”, “Low-intensity exercise is boring”) make them directly usable in CF rehabilitation settings to help individualising aerobic training prescriptions.

A last important consideration regarding aerobic training is its ability to be used as an adjunctive therapy for airway clearance. In this specific circumstance, formal aerobic training in specific settings (*e.g.* home, physiotherapy centre) may be a time effective strategy serving a dual purpose (i.e. increase cardiorespiratory fitness while reducing the time spent to daily airway clearance therapy) **(Figure 2).** Whether exercise can replace chest physiotherapy has recently been acknowledged as one of the top ten research priorities in CF [115]. Several studies investigated acute effects of exercise (alone or in combination with physiotherapy interventions) on sputum properties in pwCF [40, 116-118], using moderate intensity aerobic exercises (walking or cycling) performed for 20-30 minutes. For instance, treadmill exercise at 60% of $\dot{V}O_{2peak}$ improved sputum hydration [40]. However, it is of note that the exercise modalities used in these studies may not elicit positive affective responses and low-activation displeasure (*e.g.* boredom) may alter long-term adherence. If aerobic exercise is ultimately intended to be used daily as a replacement of other airway clearance techniques, then it is essential to offer diversity in exercise modalities, considering individuals' preferences. Consequently, future trials should investigate whether other aerobic training modalities such as HIIT can improve patient-reported ease of sputum expectoration and sputum properties (*i.e.* viscoelasticity) in pwCF. If acute effects are proven, the next important step will be thus to compare the long-term effects of these strategies (*e.g.* HIIT *vs.* MICT), with the ultimate goal to modulate exercise prescription for airway clearance purposes considering individuals affinity toward a specific exercise modality/intensity.

In summary, numerous training modalities, performed in various settings, can improve cardiorespiratory fitness in pwCF. Beyond potential physiological efficacy, the choice is ideally guided by individual preferences in regard to the type of training and training intensity.

3.4 Specific considerations in the era of CFTR modulators

3.4.1 Current knowledge regarding the effect of CFTR modulators on physical fitness

The last decade has witnessed the emergence of CFTR modulator therapies targeting the underlying cause of CF with substantial improvement of several clinical outcomes in individuals with specific CFTR mutations [25, 26, 119-122]. The extent to which these health benefits have translated to exercise ability has been poorly studied to date. Case series have evaluated the effect of CFTR modulators on exercise tolerance (*e.g.* [123-126]). Saynor et al. [123] and Savi et al. [124] reported large improvements in $\dot{V}O_{2peak}$ in individual patients following short-term (12 weeks) of Ivacaftor [123], and longer term (2 years) of Lumacaftor/Ivacaftor [124] treatments. Conversely, Quon et al. [126] did not observe any improvement in endurance time during a symptom-limited constant load cycle performed at 80% of peak work rate in eleven adults with CF following 1-month of Lumacaftor/Ivacaftor treatment. Comparisons between the few reports [123-126] are limited by the sample size, type and duration of modulator treatment, and exercise testing modality. Moreover, all share the drawback of not being placebo-controlled. Two recent placebo-controlled, randomised studies evaluated the effect of CFTR modulators on $\dot{V}O_{2peak}$. Edgeworth et al. [127] in a randomised, placebo-controlled, double-blind, cross-over design, investigated the effect of 28-day of ivacaftor *vs.* placebo on $\dot{V}O_{2peak}$ in twenty adults with CF carrying the G551D mutation. Despite large improvement in resting pulmonary function, $\dot{V}O_{2peak}$ was unchanged. Even more recently, Wilson et al. [128] did not find any improvement in $\dot{V}O_{2peak}$ after 24 weeks in pwCF receiving Lumacaftor/Ivacaftor (n=34) *vs.* placebo (n=36). These observations echo the old but still relevant findings of Oelberg et al. [129] showing that $\dot{V}O_{2peak}$ was still drastically reduced (*i.e.* 45 ± 4%pred) in CF following bilateral lung transplantation, further confirming that ventilatory factors are far from being the sole driver of exercise intolerance in CF and indirectly highlighting the importance of skeletal muscle factors (see [41] for review). In practice, although further larger long-term studies are clearly needed (notably for testing the effects of the novel triple combination of Elexacaftor/Tezacaftor/Ivacaftor on various health-related physical fitness measures), it seems obvious from the three largest aforementioned studies [126-128] that CFTR modulator therapy alone is not efficacious to adequately address all the mechanisms underlying exercise intolerance in pwCF. While it cannot be excluded that CFTR modulators may slightly improve some markers of skeletal muscle function (*e.g.* increase in handgrip and knee flexion strength but unchanged knee extensors strength after 3 months of ivacaftor treatment [130]) notably through improved nutritional status, or even improve some intrinsic muscle metabolic defects, it is clear that addressing most of the abnormalities in the skeletal muscles of pwCF and preventing/slowing down their intensification will still require appropriate exercise training modalities (see previous sections and **Table 1**). This is particularly the case for adults with advanced lung disease who accumulate since many years various factors acting negatively on both skeletal muscle structure and function [41]. Future studies should evaluate the efficacy of combining CFTR modulator therapy with structured exercise training programmes including both markers of aerobic (*e.g.* $\dot{V}O_{2peak}$) and neuromuscular (*e.g.* limb muscle strength) fitness as well as patient-reported outcomes.

3.4.2 PA levels and exercise intentions following initiation of CFTR modulator therapy

At first glance, it seems intuitive that initiation of CFTR modulator therapy may induce positive changes in PA intentions and behaviour. Self-reported PA levels were unchanged after 1-month of lumacaftor-ivacaftor treatment in adults with CF [126]. Savi et al. [124] reported increased mild-intensity but not moderate to vigorous intensity PA in three adults with CF after two years of Lumacaftor/Ivacaftor. These preliminary data underline that it is too early to conclude on changes in habitual PA and scheduled exercise patterns following initiation of a new CFTR modulator therapy. It is however timely to propose some speculations in this beginning era of highly effective CFTR modulator therapy, with the aim to provide directions for future exercise counselling and research.

The direction of changes (if any) in PA/exercise patterns should depend on the efficacy of the CFTR therapy at improving lung function and associated symptoms and at reducing rates of pulmonary exacerbations. For instance, those benefiting from large improvements in lung function, reduction in dyspnoea and lower rates of pulmonary exacerbations may be more willing to engage in various daily life activities on a regular basis and thus increase at least mild intensity PA. Whether these health benefits will translate into a higher participation in specific bouts of vigorous-intensity exercise (which are required to improve outcomes such as $\dot{V}O_{2peak}$) is uncertain, and may depend, beyond physiological health issues, on previous psychological experience regarding physical exercise. Those who developed an intrinsic motivation regarding some vigorous exercise modalities in the past may see the sudden increase in their health status as a wonderful opportunity to perform these activities with the same intensity as they were able to do several months/years ago and to regain the feelings of enjoyment and personal accomplishment associated with them. However, it is essential to keep in mind that improvement in respiratory function may not transfer to equal changes in physical fitness following initiation of CFTR modulator therapy. Thus, while one may initially feel more able to complete some high-intensity exercise bouts, these latter can be challenging for the unprepared musculoskeletal system, potentially leading to muscle damage and even injuries which may be disruptive and constitute a first negative experience regarding vigorous exercise following treatment initiation, potentially impacting future exercise intentions and long-term PA behaviour. Several clinical trials observed creatine kinase (CK) elevations at various time-points during CFTR modulator treatment [26, 122, 131, 132], in some cases warranting treatment interruption or discontinuation. Middleton et al. [26] reported that elevated CK levels in the group treated by Elexacaftor/Tezacaftor/Ivacaftor were often associated with exercise. While increase in serum CK levels is a well-known indirect marker of muscle damage which may occur to various degrees following different exercise modalities ([133, 134]), it is unclear whether elevated CK levels observed following CFTR modulator therapy were only related to acute exercise or rather reflect a specific adverse drug effect that is potentiated by exercise. Beyond potential acute undesired physiological responses, negative emotions may also be triggered in some individuals during vigorous acute exercise (see section 4), especially in those unaccustomed / disaccustomed to high exercise intensities. In practice, considering the above-mentioned elements, it is even more important in these circumstances conductive to immediate engagement in vigorous exercise modalities to respect progressive overload to exercise with the ultimate goal of converting this acute engagement in vigorous exercise into a long-term positive PA behaviour.

While some individuals may have positive exercise intentions following initiation of CFTR treatment, others may be more reluctant to engage in vigorous exercise on a regular basis. It is possible that those who mainly considered physical exercise as a burdensome necessity for several years, without gaining specific enjoyment and satisfaction from it, may rather disengage from the most vigorous exercise modalities, considering that these latter are no longer a mandatory requirement in view of their currently improved health condition. In these circumstances, the first priority should be to promote a more intrinsically motivated PA, considering exercise preferences in terms of settings, modality and intensity as the main factor that should guide exercise prescription. Of course, while putting the emphasis on exercise preference is important at any stage along the course of the disease (see section 3.3), this may be particularly relevant in the context of CFTR modulator therapy in those initiating a new treatment, with the aim to take benefits of improved health status to instill the basis of a new intrinsically-motivated PA behaviour.

3.4.3 CFTR modulators and exercise: some considerations for the future

It is important to remember that we still only have limited evidence regarding long-term changes associated with CFTR modulator therapies, particularly for health-related physical fitness outcomes and especially when started early in life. It is thus uncertain to what extent these new treatments will change exercise tolerance and thus exercise training strategies in the next decades for the future generation of children and adults with CF. It can be anticipated that most children with CF will continue to have lung function within normal values. Moreover, considering the early promising results regarding improved nutritional status in young pwCF with some CFTR modulator therapy (*e.g.* body weight gain; [130, 135]) one can expect than many more CF children will reach normal anthropometric status at school age. The negative scenario depicted in **Figure 2** and detailed in section 3.2.2 (*i.e.* delayed growth/altered nutrition favouring poor self-efficacy and poor-delayed neuromuscular skills, exacerbating feelings of non-normality and embarrassment which are two fundamental barriers to sports practice) may thus concern less children in the next decade. Overall, young pwCF may perceive less barriers to early optimal sports participation in both recreational and competitive context, which should favour the emergence of a positive PA behaviour, increasing the likeliness to translate to sustainable high PA levels in adulthood **(Figure 2)**.

However, it is important to point out that the absence of specific physiological limitations at young age is not a guarantee of optimal engagement in PA. The modern society has created environments favouring physical inactivity in various settings, including schools, workplaces, home, and public spaces. As previously mentioned, many children without chronic diseases fail to meet WHO guidelines for PA, and the lack of activity becomes much more apparent with the entry into adolescence [136]. Moreover, it is well recognised that low PA levels in adolescence favour sedentary and physical inactivity behaviours in young adulthood [137]. Sedentary behaviour in adults is now recognised as an independent risk factor for many adverse health outcomes [138], including increased cardiometabolic risk, making lack of PA a major public health concern. Because of increasing incidence of over-nutrition and improved medical therapy, overweight and obesity are becoming more common in pwCF as early as in pubertal age [139]. As CFTR modulator therapy will become imminently available at an early age, the next generation of youth with CF may be at increasing risk of obesity (see [30] for a recent review summarising how improving CFTR function may modulate energy balance and weight gain), paralleling the general population. Physical exercise may thus play a pivotal role in preventing and managing obesity and the associated metabolic complications. Determining whether young pwCF of the next generation will share the same barriers to habitual PA and exercise as the general population or whether still specific barriers will remain or new will emerge is an important future research question. It will be important to anticipate the likely changes in the value attributed to PA, which is an important modulator of exercise intentions and behaviour [23]. If preventing and delaying deterioration of respiratory symptoms was (and is still) an important reason to exercise in many young pwCF, this may be less true going forward, considering that many more will have normal lung function, even at adult age. However, care providers and patients' families must be aware that triggering early positive PA behaviour will remain of high priority even in children with preserved nutritional status and lung health, with the new main goal of preventing cardiometabolic complications that may arise at an early age.

Moreover, with increasing age, other extrapulmonary sequelae which are more prevalent at older ages, such as CF-related diabetes (affecting about half of pwCF older than 40 years; [140]) and CF bone disease (e.g. osteopenia and osteoporosis; [54, 141]), will concern even more pwCF. New barriers to PA that were not clearly identified in previous reports [23] may be more frequently reported in the future (e.g. lack of knowledge regarding how exercise may modulate blood sugar control), requiring specific counselling. More research to determine how CFRD may specifically impact exercise tolerance [142] is also warranted with the aim to better individualise exercise strategies in those affected by this comorbidity. New strategies such as downhill walking/running, thought to be osteogenic [143, 144] (and also having the advantage of generating higher muscular stress with lower cardiorespiratory requirements compared to conventional endurance exercises [145]), would deserve specific attention, notably in the growing cohort of older adults with CF (see also section 4 and **Table 1**) and in pre- and post-transplant rehabilitation.

In summary, while CFTR modulator therapy can contribute to improvements in physical fitness, it may, as a stand-alone therapy, not be sufficient to adequately address all the mechanisms underlying exercise intolerance in pwCF. Regular exercise remains a priority in the multidisciplinary care of pwCF, and improved health status should be viewed as a good opportunity to develop new exercise intentions and behaviours. As increased life expectancy may be associated with increased prevalence of extrapulmonary complications, it is timely to develop and test new training modalities.

4 - Testing of physical exercise training modalities

Testing a given exercise modality which is intended to be used repeatedly in a training programme is an important (yet largely overlooked in pwCF) determinant of training efficacy. First because acute psychological responses to exercise such as affect and enjoyment are well known predictor of exercise adherence and future physical activity behaviour [146, 147]. Second, because muscle loading during an acute exercise session may predict improvements in health-related outcomes following a training programme [21, 22].

4.1 Acute psychological responses

One difficulty when assessing some psychological outcomes in pwCF is the absence of tools specifically validated in this population. It is the case for instance for studies which investigated fatigue, depression or anxiety in pwCF and used questionnaires for which psychometric properties where not available in CF at the time of the studies (*e.g.* [48, 78, 148, 149]). However, the use of generic items, showing extensive reliability and validity data in various chronic diseases over a large age range are often sufficient to justify the use of these scales, which will always remain better than simply ignoring these symptoms on the sole argument that no CF-specific scales are available. These observations apply for PA enjoyment which has been scarcely investigated in pwCF. For instance, Del Corral et al. [104] evaluated the enjoyment associated with active video games in children with CF using a simple 0-5 Likert scale.

The Physical Activity Enjoyment Scale (PACES) [150] is a widely validated 18-item scale which can be used to assess enjoyment associated with a given exercise modality. The generic nature of the items makes them usable in various contexts and populations, including young and old healthy people, children with asthma or overweight-to obese adults [111, 151-153]. This scale was able to discriminate enjoyment between two different exercise modalities (*e.g.* MCIT *vs.* HIIT) [154, 155], or between different versions of a given modality (e.g. 60-s *vs.* 120-s intervals for HIIT modality) [152]. As enjoyment is considered as an important motive for PA in both children and adults with CF [19, 23, 156], future studies should evaluate acute enjoyment associated with a given training modality using dedicated tools like PACES.

Beyond enjoyment, it might also be interesting to assess affective responses to exercise which may impact immediate engagement and motivation in the training session, but also long-term engagement in PA [17, 18]. In people with chronic respiratory disorders, negative affective responses to exercise may be consecutive to ventilatory abnormalities and thus encompass some qualitative dimensions of dyspnoea (*e.g.* dyspnoea-related anxiety, distress, fear, [157]). No studies to date investigated the affective dimensions of dyspnoea elicited by exercise in pwCF. However, as it has been recently reported that even CF adults with only mild lung disease may exhibit unique sensory dimensions of dyspnoea during CPET (*e.g.* sensations of chest tightness, unsatisfied inspiration) [20], it is anticipated that many pwCF will exhibit specific affective patterns during exercise, notably those with severe lung disease. It is also important to note that the affective responses to exercise are not only determined by respiratory sensations, and other simple generic scales, like the feeling scale and the felt arousal scale, are required to investigate the full “affective space” (*i.e.* high/low activation pleasure/displeasure, referring to sensations like energy, distress, calmness, boredom, e.g. [18]). While it is well documented in various populations that pleasure is often reduced for high exercise intensities, there is a large inter-individual variability for intensities around the gas exchange threshold [18], which are frequently used in pwCF. The relationship between training modality/intensity and affect is thus hard to predict at the individual level, justifying direct measurements.

Moreover, it has been reported in various populations that exercise may be better tolerated from a psychological perspective (*e.g.* better affective valence) when the intensity is self-selected rather than imposed (see [18] for a review). Most exercise training studies in CF used imposed training intensity, for instance using a constant metabolic intensity expressed as percentage of peak heart rate or $\dot{V}O_{2peak}$ [10]. It would be thus of value to test the tolerance and long-term acceptability of a training programme including self-regulated bouts of exercise. Beyond the potential advantage of stimulating the sense of autonomy and control and eliciting better affective responses, such modality may be practical to set training intensity when CPET is not available. It is of note that children with CF are able to use ratings of perceived exertion derived from the Children’s OMNI Scale to regulate both treadmill and cycle exercise intensity [158]. The use of such scales on long-term training programs remains to be investigated in pwCF.

In practice, considering enjoyment and affective responses to exercise in pwCF might be useful to guide the choice between two exercise strategies for use in the long-term (*e.g.* MCIT *vs.* HIIT), especially in the absence of an a priori preference regarding a given training component (*e.g.* exercise intensity (see section 3.3)). Such considerations are relevant in real-life rehabilitation settings **(Figure 2)** but also for research purposes, and measuring these responses during a feasibility trial and/or pilot testing might be particularly relevant before considering testing the efficacy of a given exercise strategy in a long-term randomised controlled trial.

4.2 Acute physiological responses

As mentioned earlier, there is a large inter-individual variability regarding training effects in pwCF and unfortunately many individuals do not obtain large benefits following a short- or medium-term exercise training programme, which is in turn not encouraging to engage in an active lifestyle. One of the main reasons is the absence of sufficient muscle loading during a training session. This was confirmed in chronic respiratory disorders by a study showing that people with COPD who developed acute contractile fatigue (*i.e.* reduction of quadriceps potentiated twitch elicited by magnetic femoral nerve stimulation ≥15%) after a representative acute exercise session where those obtaining the larger improvements in exercise tolerance and quality of life after a 3-month program, compared to the 'non-fatiguers' [21].

Several reasons may explain why a sufficient training stimulus is not reach and why a given individual with chronic respiratory disorders may not develop significant contractile fatigue following a training session (see [159] for a recent review). For instance, people with chronic respiratory disorders may have important ventilatory limitations during specific exercise modalities (*e.g.* during running in pwCF with moderate to severe lung disease), impeding to reach exercise intensities and durations compatible with sufficient muscle loading. Adults with CF with moderate to severe lung disease were able to develop significant muscle fatigue following a CPET despite ventilatory limitation [160]. However, it is unclear whether contractile fatigue develop during exercise training sessions of longer duration but lower intensities. It is important to note that even if precise modalities are specified for a given training session (*e.g.* cycling for 30 minutes targeting the intensity of 70% of peak heart rate measured during a CPET [42]), there is always a flexibility regarding both the intensity and the total duration based on individuals symptoms, which can thus modulate the level of contractile fatigue induced by the session. For instance, in the study by Selvadurai et al. [42] children with CF were allowed to stop cycling before the required 30 min if their perception of dyspnoea reached 7 on a 0-10 scale. This issue is particularly relevant if using self-regulated exercise modalities (see section 4.2). Some participants may produce adequate metabolic intensities when self-selecting exercise intensity (*e.g.* based on a rating of perceived exertion, as proposed by Higgins et al. [158] in children with CF). However, in some individuals the self-selected intensity may be too low to generate positive adaptations. This might be particularly the case in individuals unaccustomed to self-regulate their intensity with specific scales. If inadequate intensities may sometimes be obvious and easily detected during a supervised training session, this may not be always the case, especially for a multimodal training session comprising different types of exercise. In these specific situations, measuring the muscular stress induced by the whole training session is important to identify non-fatiguers. This will allow to prevent enrolling them in a long-term ineffective training program and thus modifying the prescription and proposing new alternatives at an early stage.

Investigating muscle fatigue induced by a specific acute exercise may also offer a rationale for the use of new training modalities. For instance, it has been shown in people with COPD that a bout of downhill walking exercise generated higher muscular stress (i.e. higher decrease in quadriceps potentiated twitch elicited by magnetic femoral nerve stimulation) with lower cardiorespiratory requirements compared to level walking [161]. Downhill walking, which has never been investigated in pwCF, may thus be an attractive alternative in this population, especially for older adults with severe lung disease. While the training stimulus offered by downhill walking may not be sufficient in younger and healthier CF individuals, the use of negative slope may increase the ability to run, which is particularly interesting for individuals unable to run on level ground due to early ventilatory limitation and dyspnoea. Beyond its potential of eliciting adequate muscle loading, giving the opportunity to run by means of slight negative slope may be adapted to stimulate the feeling of "normality" (*e.g.* exercising like their healthy peers), which is an important motive for exercise in pwCF [23]. Sections of downhill walking/running can also be performed in outdoor natural environment, which may be beneficial for various psychological outcomes (see [162] for a systematic review).

Femoral magnetic nerve stimulation is well-tolerated by pwCF and sensitive to detect changes in muscle state (*e.g.* over the course of a muscle fatigue protocol [72] or after intravenous antibiotics therapy for an exacerbation [89]). However, this technique requires costly equipment and trained investigator and may thus not be adapted to daily-life rehabilitation settings and may also be hard to implement in multicentre clinical trials. A promising lead for the future is the use of user-friendly app allowing valid assessment of muscle power (*e.g.* MyJump [163], Sit To Stand [164]), which may thus be used to evaluate the muscular stress induced by a training session of a given exercise modality (*e.g.* assessment of pre-post changes in vertical jump performance which is a sensitive marker of exercise-induced muscle fatigue [165]).

5 – Conclusion

In conclusion, we suggest to promote exercise quality and specificity rather seeking the sole achievement of quantitative PA guidelines. Young pwCF should be encouraged to train their neuromuscular abilities at an early stage, with the aim of overcoming barriers to sports participation and favouring long-term positive PA behaviours (Figure 2). Formal aerobic exercise modalities might preferentially be considered in young pwCF under specific circumstances (*i.e.* if barriers to sports participation are still insurmountable and/or if used as an adjunctive therapy for airway clearance). In adults with CF with elevated training age and mild disease profile, the authors believe it is important to recommend the pursuit of the complementary association between INT and sports practice. In those with more advanced disease, priority could be given to the prevention of rapid loss in basic health-related physical fitness measures (*e.g.* muscle strength), and more formal supervised exercise modalities may be necessary. In the absence of a clear consensus regarding the "best training modality" in CF for both resistance and aerobic training, it is essential to also consider individual preferences in the choice of exercise modalities to optimise exercise adherence. Preferences ideally address different types of exercises in different settings (*e.g.* hospital-based combined aerobic-weight training with machines/ergometers *vs.* home-based mixed training with minimal equipment) and exercise intensity, notably for aerobic training (*e.g.* MICT *vs.* HIIT). Finally, with the ultimate aim to move toward fully individualised training prescriptions, future studies may thoroughly investigate acute psychological and physiological responses elicited by the training sessions.

Whenever possible, all these general suggestions should be progressively adjusted/improved according to the results of the future exercise trials. Throughout this review we provided some priorities for exercise training studies that should be tested in the future. In general, exercise training studies are difficult to conduct in CF, particularly those that require long-term interventions in multicentre settings. Masking participants to their allocation in randomised trials is impossible with potential undesirable consequences for control group participants. Recruitment of participants into exercise trials is not only a challenge when targeting healthy people [166], but becomes more difficult when working with pwCF due to time commitments dedicated to other therapies. In the following, we provide some methodological suggestions to be considered when planning and designing an exercise trial with pwCF that might considered be useful for researchers new to the field:

- Consider involving stakeholders, patient representatives, and pwCF and use their input when designing a study.
- Do not only consider individual factors (*e.g.* exercise preferences, goals) as determinants of PA but also interpersonal (*e.g.* friends, family), and environmental factors (*e.g.* accessibility) when planning a trial [167].
- Choose patient-relevant outcomes that are valid, reliable, and responsive, and ideally for which a meaningful change and/or a minimal important difference is known.
- Choose one primary study endpoint and perform the sample size calculation on the basis of the primary hypothesis.
- Provide an attractive intervention for control group participants and/or offer them access to training once the trial is completed in order to avoid contamination and excess drop-out rates during the trial [168].
- Whenever possible, mask outcome assessors to avoid measurement bias.
- Consider a feasibility trial and/or rigorous pilot testing, paying particular attention to acute physiological and psychological responses associated with a given training modality.

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Thomas Radtke: Conception of article, Writing- Original draft preparation, Reviewing and Editing.

Figures legends and Table notes

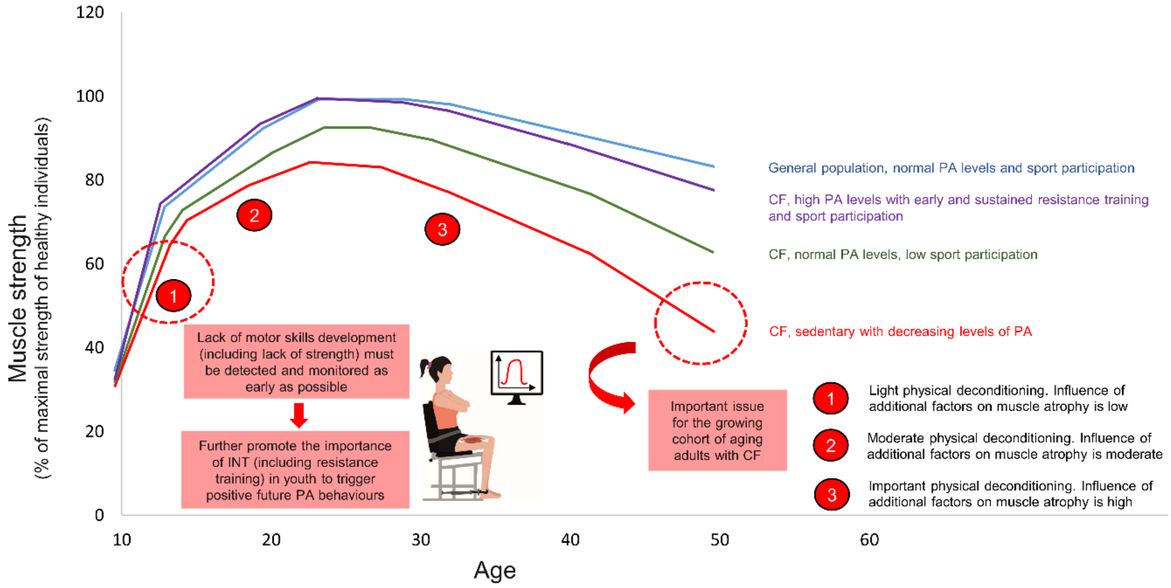

Figure 1. *Conceptual model showing hypothetical changes in muscle strength in people with cystic fibrosis (CF) across the lifespan, according to different profiles of physical activity behaviours.* Three profiles are depicted and compared to the general population exhibiting normal PA levels and sports participation. The global trend of age-related changes in muscle strength in the general population is derived from relevant literature [169-171]. The conceptual model is adapted and modified with permission from [172]. INT: integrative neuromuscular training; PA: physical activity.

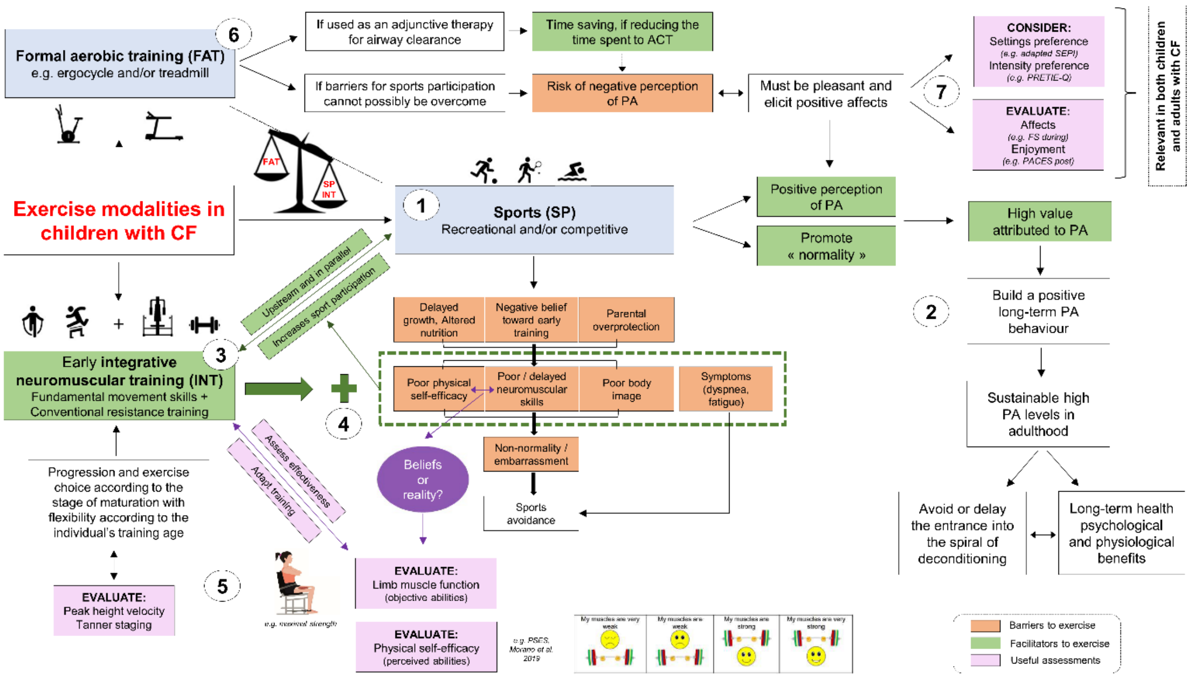

Figure 2. *Factors to consider for optimal exercise counselling in people with cystic fibrosis (CF).* Children with CF should be encouraged to engage in sports (1) to develop a positive long-term physical activity (PA) behaviour (2). Early engagement in integrative neuromuscular training (INT) (3) may help increasing preparedness for sport by acting positively on several potential barriers (4). Various evaluations (5) can be used to guide training programming. Formal aerobic training (FAT) (6) might be best applied under specific circumstances and programming should be guided by individual preferences (7). See text for details. B/W icons are designed by Freepik (https://www.freepik.com/) and from Microsoft Office. The The physical self-efficacy scale (PSES) is adapted from [173] distributed under Creative Commons CC-BY 4.0. The image depicting strength assessment is adapted with permission from [172]. ACT: airway clearance technique; CF: cystic fibrosis; FS: Feeling Scale; PACES: Physical Activity Enjoyment Scale; PRETIE-Q: Preference for and Tolerance of the Intensity of Exercise Questionnaire; SEPI: Stroke Exercise Preference Inventory; SP: Sports.

Table 1. *Exercise training modalities in people with cystic fibrosis (CF).* 1RM: 1 repetition maximum; 5 RM: 5 repetitions maximum; CRF: cardiorespiratory fitness; NF: neuromuscular fitness; $\dot{V}O_{2peak}$: peak oxygen uptake; Wmax: maximal aerobic power.

Exercise training modality	Example of use in CF		Predominant target	Preferential settings: home vs. other	Potential for live remote supervision	Main Pros	Main Cons
Conventional weight training	Santana Sosa et al. 2014	3 sets of 7 exercises (upper and lower limbs, 1× 12-15 rep per exercise), 50% of baseline 5RM	NF	other	low	best modality to improve both lower and upper limb muscle strength	may not be adapted for all prepubertal CF individuals; large space requirements; may require costly machines
Anaerobic training	Klijn et al. 2004	3 sets of 5 anaerobic exercises (30-s duration, including sprints, ball transfer etc…) 90-s recovery between exercises, 5-min between sets	NF	other	medium	adapted to improve anaerobic performance; may be particularly relevant in children	only few data in CF; may not be sufficient alone to improve limb muscle strength; may not be the priority for some CF adults
Integrative neuromuscular training	not yet specifically investigated	N/A	NF	other	low	cumulate the benefits of anaerobic and conventional weight training; can be indicated to increase general preparedness for sport in youth	never specifically tested in CF; require lengthy familiarization/supervision; time-consuming; may be hard to perform in adults with low training age
Elastic band resistance training	not yet specifically investigated	N/A	NF	home	high	cost effective strategy to increase limb muscle strength; can be performed in multiple settings	never specifically tested in CF; efficacy to be proven vs. conventional weight training
Neuromuscular electrical stimulation	Vivodtzev et al. 2014	30 min, both quadriceps, 35 Hz, 7-s contraction 10-s relaxation, intensity increased according to tolerance throughout the session	NF	home	high	positive effects on limb muscle strength; can be performed in multiple settings; an alternative when standard exercise training cannot be performed	only very few data in CF; may not be as efficacious as conventional weight training to increase limb muscle strength; may not be adapted to build a positive long-term physical activity behaviour

Whole-body vibration	Rietschel et al. 2008	3 x 3 min sessions twice a day, vertical vibration (frequency 20-25 Hz, peak-to-peak amplitude 0.6 mm)	NF	both	high	potential positive effects on limb muscle strength and posture; an alternative when standard exercise training cannot be performed	only very few pilot data in CF; likely not as efficacious as conventional weight training to increase limb muscle strength; may not be adapted to build a positive long-term physical activity behaviour
Sports	N/A*	N/A*	CRF and NF	other	low	relevant strategy to promote normality and build positive physical activity behaviour; can act positively on both CRF and NF	many barriers to overcome for optimal sports participation; barriers and benefits are sports categories dependant; barriers increase with age and disease progression
Active video gaming	Del Corral et al. 2019	30-60 min Nintendo Wii™, game EA SPORTS™ ACTIVE 2 (involves running, squats, lunges, and bicep curls)	CRF and NF	home	high	may be particular pleasant and fun for some individuals; may elicit cardiorespiratory responses compatible with CRF improvements	requires initial physiological testing of a given game; ↑ total screen time (may alter sleep quality); unknown adherence for a given game on the long-term
Aerobic HIIT	Sawyer et al. 2020	10-min cycling, [30-s work (intensity ≥ 80% Wmax) 30-s recovery] ×10	CRF	other	medium	great time efficiency; feasible in severe CF individuals; an alternative for those finding aerobic training at continuous moderate intensity boring	only few data in CF; need to identify the best protocol (e.g. ratio work : rest); may elicit negative affective responses in some individuals
Aerobic training at continuous moderate intensity	Beaudoin et al. 2016	20-40 min walking, jogging, cycling or elliptical trainer, intensity = 60%VO_{2peak}	CRF	both	medium	easy control of intensity; well-known positive effects; can serve as airway clearance therapy	monotony may alter long-term engagement; may not be always feasible in severe CF individuals
Downhill running	not yet specifically investigated	N/A	CRF and NF	other	low	offers the possibility to run (↑ normality) with lower ventilatory requirements; prone to positive psychological adaptations / great adherence if performed in natural environment; may be of interest for bone health	never tested in CF; requires a specific environment

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