CHAPTER

33

Mechanisms of Exercise Limitation in Cystic Fibrosis: A Literature Update of Involved Mechanisms

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33.1 INTRODUCTION

Nearly two decades ago, Nixon et al. [1] reported a significant association between the exercise capacity of young Cystic Fibrosis (CF) patients and survival over 8 years [1]. Nowadays, physical training to increase or maintain exercise capacity is implemented in the usual care package offered to most patients with CF. In addition, clinicians encourage patients with CF to perform physical exercise to develop age-appropriate fitness and to maintain physical fitness in order to preserve or enhance: (1) exercise capacity, (2) muscular endurance and strength, (3) normally developed and retained bone mineral density, (4) a good posture, and (5) maintain or improve mobility of the chest wall (*International Physiotherapy Group for Cystic Fibrosis, 2009*).

An immediate aim for the young patient is to maintain a similar level of exercise in comparison with peers and friends. This is likely to influence self esteem and the type of everyday life activities. The aim of rehabilitating dysfunction is to strive to regain what has been lost (*International Physiotherapy Group for Cystic Fibrosis, 2009*).

Nevertheless, exercise capacity in patients with CF is limited, which seems to have a multifactorial cause [2,3]. If there is a possible relationship between CF genotype and some measures of exercise capacity, the mechanisms remain to be determined [3,4]. It seems that there is an interrelationship between lung function, muscle mass, energy expenditure, respiratory and/or skeletal muscle function, and exercise capacity in patients with CF [5]. The pathophysiology of reduced lung function and reduced muscle mass are known to be the most important factors leading to exercise limitation [6–8].

The exact mechanisms leading to exercise limitation in patients with CF are still a question of debate. The objective of this literature review was to give an overview of which cardiorespiratory and metabolic determinants are known to play a role in the limited exercise capacity in patients with CF. Progressive insight in the possible cardiorespiratory and metabolic limiting factors might be helpful (1) to understand the physiological mechanisms, and (2) for providing appropriate therapeutic interventions such as exercise training in patients with CF.

33.2 METHODS

33.2.1 Study Identification

We searched Medline, EMBASE, and CINAHL for studies about limiting factors in exercise capacity in patients with CF. We used no restriction in time period. The search strategy included the terms "Cystic Fibrosis" AND "Exercise Capacity" OR "exercise tolerance" OR "exercise performance" AND "limiting factor" OR limitation. The databases were searched for the terms in title, abstract or both. Titles and abstracts of search results

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were screened for eligibility. The search strategy and search results are available in supplemental appendix I.

33.2.2 Study Inclusion

Studies were eligible for inclusion if they: (1) were available as full article (no posters or congress abstracts were included), and/or (2) reported effects of interventions on exercise capacity in patients with CF, and/or (3) reported associations between exercise capacity and possible limiting variables in patients with CF.

We used no design and methodological quality threshold; the language restriction was English.

33.2.3 Data Extraction

One author (MW) selected potentially eligible studies for inclusion by abstract and full articles. Reference lists from selected studies were screened for further eligible studies meeting the inclusion criteria.

33.3 RESULTS

The search retrieved 38 articles of which 18 met all the inclusion criteria. Screening the reference lists of these articles revealed an extra 49 articles meeting the inclusion criteria articles of various methodological qualities and study characteristics. No meta-analysis could be performed due to the heterogeneity in interventions, outcomes, and associations described in the included studies (Figure 33.1).

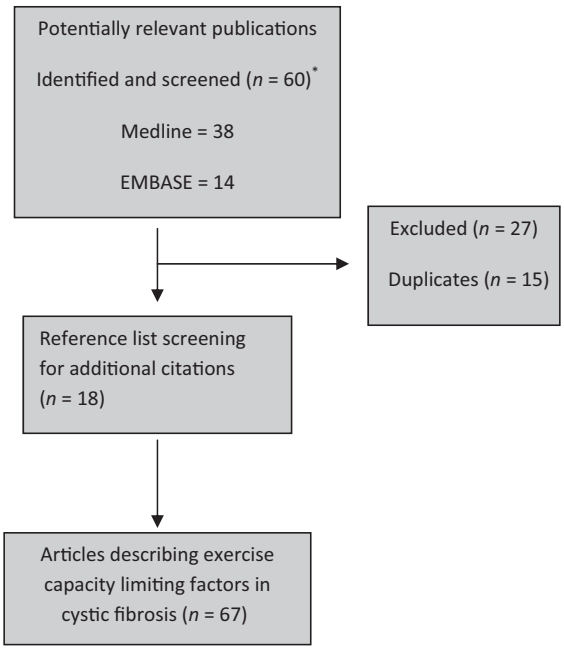

FIGURE 33.1 Result literature search.

33.4 VENTILATORY PARAMETERS

33.4.1 Ventilatory Constraints

Whether (mechanical) ventilatory constraints contribute to limited exercise capacity has traditionally been evaluated by the ventilatory reserve, which reflects the relationship of peak minute ventilation (VE_{peak}) at maximal exercise to the estimated maximal voluntary ventilation ($MVV = 35 \times FEV_1$ (L/min)) [9]. When the minute ventilation (VE) exceeds the arbitrary border of 70% of MVV, a ventilatory limited exercise capacity is suggested [9]. Furthermore, exercise dyspnea, assessed by the Borg scale, which is closely related to the level of ventilation as expressed by the VE/MVV ratio, was found to have an influence on exercise performance [10]. However, ventilatory demand and ventilatory capacity are dependent on multiple factors as lung function, anatomical dead space ventilation, respiratory muscle function, and ventilatory control [9]. Furthermore, Moorcroft et al. [11] found that VE/MVV exceeded the 70% border only in severe patients with CF ($FEV_1 < 40\%$ of predicted), suggesting that ventilatory factors only contribute to exercise limitation in severe disease state [11,12]. Furthermore, medicinal effective bronchodilation in ventilatory-limited patients with moderate CF (FEV_1 58 ± 17% of predicted) [13] and antibiotic therapy [14] showed no effect on exercise capacity, suggesting that the subjects in the studies were not truly ventilatory limited or that the primary determinant of ventilatory limitation may not be bronchoconstriction alone [13,14]. Additionally, increasing deadpsace (VD) during exercise to volitional exhaustion in mild patients with CF (FEV_1 76 ± 8% of predicted) did not induce changes in cardiopulmonary exercise parameters or subjective measures of exhaustion. This suggests that these mild patients still have an adequate ventilatory reserve to overcome added VD and implies that mild patients with CF are not primarily ventilatory limited [15]. Additionally, a group of patients with CF followed longitudinally had an annual decline (2.7% of predicted) in lung function (FEV_1) and exercise capacity (decrease of VO_{2peak} 0.162 mL/min kg per month) only when FEV_1 fell below 80% of predicted [16]. This indicates that ventilatory constraints play a role in limiting exercise capacity in a more progressive disease state.

Although lung function at rest, as determined by the FEV_1 or inspiratory capacity, was a longitudinal and cross-sectional determinant of exercise capacity [6,8,10,16–18], it seems that the presence of static hyperinflation (ratio between residual volume and total lung capacity (RV/TLC) > 30% after bronchodilator) in adolescents with CF by itself does not strongly influence ventilatory constraints during exercise. This could suggest that static hyperinflation is only a slightly stronger

predictor of exercise capacity than the FEV_1 (% of predicted), which only reflects the degree of airflow obstruction and does not account for ventilatory mechanisms at maximal exercise as dynamic hyperinflation [19]. Thin and coworkers [20] have shown that wasted ventilation depends on a higher VD and on the ventilatory pattern during exercise, specifically, a high breathing frequency and a low tidal volume [20].

Furthermore, in contrast to other work [21], lung function independent measurements such as severity of bronchiectasis, sacculations, and abscesses are shown to be independent predictors of exercise capacity in patients with CF. Some authors have noted stronger correlations between exercise capacity and CT findings than between exercise capacity and FEV_1 or body mass index [22,23].

33.4.2 Exercise-Induced Hypoxemia

Progressive lung disease in CF, which involves thick, dehydrated, mucus-impairing airway mucociliary clearance, predisposes the patient to recurrent bronchial infections, inflammation, and airway obstruction [24,25]. As a consequence, lung disease in CF develops from bronchiolitis to bronchitis, and eventually to bronchiectasis [26]. During exercise in the presence of severely impaired pulmonary function (FEV_1 % of predicted $31.1 \pm 12.4\%$), an increased physiological VD and arterio-venous shunting results in ventilation-perfusion mismatching, contributing to the development of hypoxemia [27]. Additionally, CF patients are reported to have a reduced alveolar membrane diffusion capacity (DLCO) at rest [28,29], and also a limited, exercise-induced increase in DLCO [29]. During exercise, pulmonary blood flow increases, which is not adequately met by an increased DLCO in the study of [29], leading to a drop in O_2 saturation. The authors suggested that this limitation in increasing DLCO in the alveoli is the consequence of a reduction in alveolar ventilation during exercise.

A Cochrane review about O_2 therapy for patients with CF pointed to evidence of modest enhancement of exercise capacity and duration with O_2 supplementation, especially in participants with more advanced lung disease [30,31]. O_2 supplementation was accompanied by a lower VE_{peak} and HR_{peak}, suggesting that decreasing or preventing exercise induced hypoxemia might prevent the occurrence of cardiac or ventilatory constraints as the primary limiting factors [31]. Further, the major findings of a study by McKone et al. [32] in moderate to severe adult patients with CF indicate that stressing the respiratory system with added dead space impairs exercise capacity (exercise duration to voluntary exhaustion) with no change in VE_{peak} and the peripheral measured O_2 saturation, suggesting that exercise was limited by the ventilation reaching its maximal capacity. Supplemental O_2 with added dead space caused a small improvement in exercise capacity with an increase in VE_{peak}. These results suggest that arterial hypoxemia is a limiting factor during maximal exercise in adult patients with CF by decreasing O_2 availability to exercising muscles or inducing the sensation of dyspnea associated with arterial hypoxemia [32]. Furthermore, hypoxemia is a partial explanation for the observed slowed oxygen uptake kinetics in the skeletal muscle in patients with CF [33].

33.5 MUSCLE FUNCTION

33.5.1 Muscle Weakness

Compared with healthy controls, reduced peripheral muscle strength has been found in patients with CF [34–39], which was found to be significantly correlated with BMI and FEV_1 [34,35]. Moreover, peripheral muscle strength was even lower when corrected for fat free mass (FFM) and was found to be of contractile origin [39]. However, although the systemic inflammation in patients with CF is suggested to be related with reduced muscle force [37], it does not seem to be an independent predictor of respiratory and limb muscle strength [40].

Whether inspiratory muscle weakness is present or not in CF patients, remains controversial. Inspiratory muscle strength, as reflected by PI_{max}, is found to be relatively well preserved [41] or even higher compared with healthy peers [38] in stable adult patients with CF, although there is a relationship (r .370; $p < 0.05$) between the loss of inspiratory muscle work capacity and FFM. On the other hand, other studies found lower PI_{max} values in patients with CF [42,43]. Furthermore, loss of FFM [41] and hyperinflation [44] are associated with the loss of diaphragm muscle strength. The higher PI_{max} values were ascribed to a conditioning effect on the inspiratory muscles, as WOB is increased in patients with CF [38]. In addition, inspiratory muscle endurance may be reduced in CF patients and is strongly related to exercise dyspnea. However, inspiratory muscle endurance limitation was independent of nutritional status, ventilatory obstructive defect, pulmonary hyperinflation, inspiratory muscle strength, or maximal exercise capacity [45].

Hence, as it is still questionable whether inspiratory muscle training can improve exercise capacity [46], the role of inspiratory muscle weakness alone as a limiting factor in exercise capacity in patients with CF remains unclear. On the contrary, unloading the inspiratory muscles by overnight, noninvasive ventilation in hypercapnic patients with CF showed improvement in exercise capacity compared with placebo-controls, suggesting that a nocturnal reduction in the WOB might lead to improved exercise capacity during the day [47].

This finding might still indicate a role of the inspiratory muscles in limiting exercise capacity in patients with CF.

33.5.2 CF Specific Mitochondrial Dysfunction

Compared with healthy controls, study findings indicate that the efficiency of oxidative work performance of skeletal muscle in patients with CF is reduced by 19–25% [48]. A decrease in mitochondrial function secondary to clinical or nutritional factors may be the explanation for this finding [48]. However, until 2010, the CFTR had not been shown to be expressed in human skeletal muscles. Recently, the expression of CFTR has been demonstrated in human skeletal muscle, and its localization in the sarcotubular network [49,50]. Additionally, using ^{31}Phosphorus magnetic resonance spectroscopy, recent literature showed a slower phosphocreatine (PCr) recovery time after 90 s of intense exercise in patients with CF and in patients with primary cilliary dyskinesia [51]. This points towards a possible intrinsic abnormality in mitochondrial oxidative metabolism; however, currently there is no firm evidence available [33,48,52–54]. Furthermore, as similar exercise physiology has been found between patients with CF and non-CF bronchiectasis [54], it is still questionable if the possible mitochondrial impairment may be CF specific or suggestive of a nonspecific effect of chronic systemic inflammation, as present in patients with CF and primary cilliary dyskinesia [51]. In conclusion, it remains unclear whether an intrinsic abnormality in muscle energy metabolism is present in CF [3,54], or whether the exercise physiology of CF skeletal muscles is hampered due to impaired O_2 delivery to these muscles [34,52].

33.5.2.1 Oxidative versus Glycolytic Energy Metabolism

Boas et al. [55] investigated aerobic and anaerobic exercise capacity in children with CF ($n=25$, FEV_1 92.5 ± 17.1% of predicted), children with asthma ($n=22$, FEV_1 100.3 ± 17.7% of predicted), and healthy controls ($n=23$, FEV_1 110.1 ± 8.3% of predicted). They found a similar aerobic and anaerobic exercise capacity among the three groups; however, children with CF used a lower percentage of their VO_{2peak} during each phase of anaerobic exercise testing. They applied mathematical modeling on the exercise data in order to clarify this result, which, compared to children with asthma and healthy controls, suggests the preferential use of the phosphocreatine/adenosine triphosphate (PCr/ATP) and glycolytic energy systems compared with oxidative pathways. In addition, Klijn et al. [6,8] reported a higher anaerobic power output normalized for FFM in patients with CF and moderate lung disease ($n=19$, FEV_1 62.9 ± 14.2% of predicted) than in patients with CF and mild lung disease ($n=20$, FEV_1 99.2 ± 10.6% of predicted). Their results indicate that with progressive lung disease, there is a shift from oxidative to glycolytic energy metabolism during exercise. In children with asthma, it was suggested that reduced aerobic capacity might be compensated for by a maintained or even enhanced anaerobic capacity [56], leading to enhanced CO_2 production during exercise. This phenomenon could explain the higher respiratory exchange ratios (VCO_2/VO_2) at rest and during submaximal exercise in patients with CF [3,48,52].

33.5.3 Nutritional Status

CF has detrimental effects on the patient's nutritional status and thereby induces malnutrition. Malnutrition can lead to the loss off body fat and FFM with muscle mass as the main part of it [57]. For instance, diaphragmatic performance declines as nutritional status, evaluated on the basis of BMI, decreases [44]. Indeed, peak anaerobic capacity [7,58], maximum work capacity [59,60] and, to a lesser extend, aerobic capacity [6,8,59] are found to be related with FFM. Additionally, low FFM is associated with the observed lower peak heart rate [57] and stroke volume (SV) [61] at maximal exercise in patients with CF, which is explained by the lower muscle mass performing the work leading to a decreased cardiovascular load [42] and output [61].

33.6 CARDIAC CONSTRAINTS

More than 20 years ago, a decreased SV was found in malnourished patients with CF [61], which might have been caused by the occurrence of both right and left ventricular dysfunction during stress, without clinical signs or symptoms [62]. However, this impaired SV was indirectly measured using the Fick equation, and thus could not provide distinction in involvement of right ventricular (RV) or left ventricular (LV) dysfunction [61].

A postmortem study showed evidence of RV hypertrophy of 70% in children with CF [63]. Florea et al. [64] and Ionescu et al. [65] confirmed the presence of significant RV systolic and diastolic dysfunction in clinical-stable and nonclinical-stable patients with CF. This RV dysfunction may be caused by pulmonary hypertension, secondary to chronic hypoxemia [66,67], by the chronic inflammation as present in patients with CF [65] or by ventilatory mechanics as airflow limitation, leading to increased intrathoracic pressure [66]. Contrary to what was previously suggested, a decreased SV during exercise could not be ascribed to hyperinflation of the thorax [54]. The increase in the intrathoracic pressure caused by the thoracic hyperinflation would limit the extent to which the Frank-Starling mechanism could be recruited to maintain SV in the face of an increased RV afterload

[66]. This lower SV could not be compensated for by an increase in heart rate, resulting in impaired blood flow to the lungs [54].

Overall, secondary RV enlargement develops in a proportion of patients with CF via pulmonary hypertension and pulmonary vascular remodeling. The exact prevalence of subclinical RV dysfunction in the population is unknown, but prognosis is poor once RV failure is evident [68]. Although involvement of LV dysfunction in patients with CF remains subject to debate [64,69,70], there is evidence for involvement of LV dysfunction [68]. This LV dysfunction could be caused be a regional LV myocardial perfusion deficit due to hemodynamic changes secondary to pulmonary hypertension and RV hypertrophy. A dysfunctional LV seems not to be of major importance in mild disease state, but, next to other previously mentioned factors, may become clinical evident in more progressive disease state in patients with CF, where a LV dysfunction could limit cardiac output during exercise [71].

33.7 CONCLUDING REMARKS

In patients with mild-to-moderate disease, nonpulmonary factors, as muscle mass and muscle function, predominate in limiting exercise capacity [11,12]. In more severe patients with CF ($FEV_1 < 40\%$ of predicted), ventilatory (mechanical) constraints and hypoxemia become more important determinants. However, in any state of progression of CF, none of these factors are the main limiting factor, suggesting that other factors, such as a possible CF specific muscle defect, and/or systematic inflammation, independent of the severity or progression of CF, are attributing to exercise limitation. This might result in specific, unique individual combinations of factors that limit exercise capacity in separate patients with CF.

33.8 CLINICAL IMPLICATIONS

The unique, individual combinations of factors that limit exercise capacity in patients with CF would implicate that exercise training in each patient should focus on different goals and indications. These indications are not only interindividual dependent, but are also dependent on disease progression and exercise induced limitations. These distinctive, interindividual characteristics require detailed cardiopulmonary exercise testing prior to the initiation of exercise training in order to provide the patients with CF with safe training recommendations [72].

In a less severe, mild to moderate disease state of CF, when nonpulmonary factors predominate in limiting exercise capacity, the focus of exercise training should emphasize prevention of the deterioration of lung function by focusing on optimizing chest mobility and airway clearance techniques [73]. Furthermore, general training programs should focus on peripheral muscle function according to the general ACSM Guidelines for exercise testing and prescription. (*ACSM Guidelines for exercise testing and prescription*.)

When ventilatory limitations become predominant, besides optimizing chest mobility and airway clearance techniques, the focus should be decreasing WOB by inspiratory muscle training [74]. Additionally, local peripheral muscle oxidative capacity could be stabilized or even improved by more intermittent, local, peripheral muscle training as high-intensity interval training (HIT), with less burden on the ventilatory system [75,76].

As stated in the Cochrane review about exercise training for cystic fibrosis, the benefits obtained from physical training may be influenced by the type of training. Further research is needed to understand the (physiological) benefits of exercise programs in people with cystic fibrosis, and the relative benefits of the addition of aerobic versus anaerobic versus a combination of both types of physical training to the care of people with cystic fibrosis [77]. Overall, there should be no such form of "one size fits all principle" in patients with CF, and tailored care should be the policy in the domain of exercise training.

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