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FERNANDA MARIA VENDRUSCULO

# FISIOTERAPIA RESPIRATÓRIA, CAPACIDADE DE EXERCÍCIO E PREDIÇÃO DE MORTALIDADE EM PACIENTES COM FIBROSE CÍSTICA

Porto Alegre
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Tese de doutorado apresentada ao Programa de Pós-graduação em Pediatria e Saúde da Criança da Pontifícia Universidade Católica do Rio Grande do Sul para obtenção do título de Doutor em Saúde da Criança.

Orientador: Prof. Dr. Márcio Vinícius Fagundes Donadio

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*"Tudo parece impossível até que seja feito"*

*Nelson Mandela*

*DEDICATÓRIA*

*Ao meu Avô Ferdinando Luiz Caovilla (in memoriam) por todo orgulho que sempre demonstrou sentir por mim e pela minha profissão.*

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## RESUMO

**Introdução:** A fibrose cística (FC) é uma doença genética, multissistêmica, caracterizada pela perda progressiva da função pulmonar e obstrução das vias aéreas. Assim, a limitação ao fluxo aéreo e a hiperinsuflação dinâmica podem limitar a capacidade de exercício desses pacientes. Além disso, a capacidade de exercício têm se correlacionado com a sobrevida de crianças e adultos com FC.

**Objetivo:** Avaliar o efeito da fisioterapia respiratória sobre a capacidade de exercício e o papel do consumo máximo de oxigênio como preditor de mortalidade em pacientes com FC.

**Métodos:** Está tese está dividida em dois artigos. O artigo 1 foi um estudo piloto, prospectivo, randomizado e *cross-over* realizado em crianças com diagnóstico de FC, com idade >9 anos e >128 cm de altura. Foram realizadas duas visitas com um mês de intervalo, sendo uma com a realização da fisioterapia respiratória utilizando pressão expiratória positiva e drenagem autogênica, antes da espirometria, pletismografia e do teste de exercício cardiopulmonar (TECP), e outra sem a realização da fisioterapia respiratória. O TECP foi realizado no ciclo ergômetro com a utilização do protocolo de *Godfrey*. Todos os testes seguiram as recomendações internacionais. O artigo 2 consistiu em uma revisão sistemática e meta-análise, no qual foi realizada uma pesquisa *on-line* nas bases de dados *PubMed*, *Embase*, *LILACS* e *SciELO*. Foram incluídos estudos de coorte que avaliaram as taxas de mortalidade após medições do consumo máximo de oxigênio ($VO_2$pico) durante um TECP. A análise de qualidade dos artigos selecionados foi realizada com a escala *Newcastle-Ottawa*. O principal desfecho avaliado foi a mortalidade de pacientes com FC. Sempre que possível, e se apropriado, foi realizada uma meta-análise de efeito aleatório.

**Resultados:** No estudo 1 foram incluídos 12 pacientes com FC com média de idade de 12,83±1,85 anos, o índice de massa corporal em escore Z foi 0,08±0,82 e 75% deles apresentavam um alelo ΔF508. Não foram encontradas diferenças significativas no consumo máximo de oxigênio com a realização da fisioterapia respiratória. No entanto, houve uma diminuição significativa na ventilação minuto ($V_E$) e nos equivalentes ventilatórios para o consumo de oxigênio ($V_EVO_2$) e para a

produção de gás carbônico ($V_EVCO_2$) no limiar anaeróbico quando realizaram fisioterapia respiratória antes do TECP. A média da $V_E$ ($L.min^{-1}$) foi 26,67±5,49 *vs* 28,92±6,30 (p=0,05), $V_EVO_2$ ($L.min^{-1}$) foi 24,5±1,75 *vs* 26,05±2,50 (p=0,03) e $V_EVCO_2$ ($L.min^{-1}$) foi 26,58±2,41 *vs* 27,98±2,11 (p=0,03). No estudo 2 foram incluídos seis estudos de coorte, totalizando 551 participantes. Cinco estudos foram classificados com alta qualidade metodológica. Foram realizadas duas análises diferentes para avaliar a influência do $VO_2$pico sobre a mortalidade. A diferença total padronizada significativa entre as médias do $VO_2$pico nos grupos sobrevivente ou não-sobrevivente foi -0,606 (IC95%= -0,993 – -0,219; p=0,002). Além disso, os pacientes com menor $VO_2$pico foram associados a um risco de mortalidade significativamente maior (RR: 4,896; IC95%= 1,086 – 22,072; p=0,039).

**Conclusão:** Os resultados obtidos sugerem que a realização de fisioterapia respiratória antes do exercício pode levar a uma melhora da dinâmica ventilatória durante o exercício em pacientes com FC. Além disso, a revisão sistemática com meta-análise demonstrou que baixos níveis de absorção máxima de oxigênio estão associados a um aumento de 4,9 vezes no risco de mortalidade na FC, em um período de seguimento de 8 anos, indicando que o $VO_2$pico também pode ser uma importante variável de acompanhamento.

**Palavras-chave:** Fibrose Cística. Técnicas de Fisioterapia. Consumo de Oxigênio. Capacidade de Exercício. Mortalidade.

## ABSTRACT

**Introduction:** Cystic fibrosis (CF) is a genetic, multisystemic disease characterized by progressive loss of lung function and airway obstruction. Thus, airflow limitation and dynamic hyperinflation may limit exercise capacity of these patients. In addition, exercise capacity has correlated with survival in children and adults with CF.

**Objective:** To evaluate the effect of respiratory physiotherapy on exercise capacity and the role of maximal oxygen consumption as a predictor of mortality in CF patients.

**Methods:** This thesis is divided into two articles. Article 1 was a prospective randomised, cross-over pilot study performed on children diagnosed with CF, aged >9 years and >128 cm tall. Two visits were performed with one month of interval, one with respiratory physiotherapy using positive expiratory pressure and autogenic drainage, before spirometry, plethysmography and the cardiopulmonary exercise test (CPET), and another without respiratory physiotherapy. The CPET was performed on a cycle ergometer using the Godfrey protocol. All tests followed international recommendations. Article 2 consisted of systematic review and meta-analysis, in which an online search was performed in PubMed, Embase, LILACS and SciELO databases. Were included cohort studies that assessed mortality rates after maximal oxygen uptake ($VO_2$peak) measurements during CPET. The quality analysis of the selected articles was performed using the Newcastle-Ottawa scale. The main outcome evaluated was the mortality of CF patients. Whenever possible, and if appropriate, a random effect meta-analysis was performed.

**Results:** Study 1 included 12 patients with CF with mean age of 12.83±1.85 years, body mass index in Z score was 0.08±0.82 and 75% of them presented at least one allele ΔF508. No significant differences were found in maximal oxygen consumption with respiratory physiotherapy. However, there was a significant decrease in minute ventilation ($V_E$) and ventilatory equivalents for oxygen consumption ($V_EVO_2$) and for carbon dioxide production ($V_EVCO_2$) at lactate threshold when respiratory physiotherapy was performed prior to CPET. The mean $V_E$ ($L.min^{-1}$) was 26.67± 5.49 vs 28.92±6.30 (p=0.05), $V_EVO_2$ ($L.min^{-1}$) was 24.5±1.75 vs 26.05±2.50 (p=0.03) and $V_EVCO_2$ ($L.min^{-1}$) was 26.58±2.41 vs 27.98±2.11 (p=0.03). In study 2, six cohort

studies were included, totaling 551 participants. Five studies were classified with high methodological quality. Two different analyzes were carried out to evaluate the influence of $VO_2$peak on mortality. The significant standardized total difference between the $VO_2$peak averages in the survival or non-survival groups was -0.606 (95%CI= -0.993 – -0.219; p=0.002). In addition, patients with lower $VO_2$peak were associated with a significantly higher mortality risk (RR: 4.896; 95%CI= 1.086 – 22.072; p=0.039).

**Conclusion:** The results suggest that the performance of respiratory physiotherapy prior to exercise may lead to improved ventilatory dynamics during exercise in CF patients. In addition, the systematic review with meta-analysis has shown that low levels of maximal oxygen uptake are associated with an increase of 4.9 in the risk of mortality, in an 8-year follow-up period, indicating that $VO_2$peak could also be an important follow-up variable.

**Key words:** Cystic Fibrosis. Physiotherapy Techniques. Oxygen Consumption. Exercise Capacity. Mortality.

## LISTA DE FIGURAS

### TESE



### ARTIGO ORIGINAL 1



### ARTIGO ORIGINAL 2

## LISTA DE TABELAS

### ARTIGO ORIGINAL 1



### ARTIGO ORIGINAL 2

## LISTA DE ABREVIATURAS

| | |
|---|---|
| **ATS** | American Thoracic Society |
| **CFTR** | Cystic fibrosis transmembrane conductance regulator |
| **CPT** | Capacidade pulmonar total |
| **CRF** | Capacidade residual funcional |
| **CVF** | Capacidade vital forçada |
| **DA** | Drenagem autogênica |
| **ERS** | European Respiratory Society |
| **FC** | Fibrose cística |
| **FEF25-75%** | Fluxo expiratório forçado entre 25 e75% da capacidade vital forçada |
| **LA** | Limiar anaeróbico |
| **NOS** | Newcastle-Ottawa |
| **PA** | Pseudomonas aeruginosa |
| **PEP** | Pressão expiratória positiva |
| **RER** | Taxa de troca respiratória |
| **RV** | Reserva ventilatória |
| **SpO2** | Saturação transcutânea de oxigênio |
| **TECP** | Teste de exercício cardiopulmonar |
| **VCO2** | Produção de dióxido de carbono |
| **VE** | Ventilação minuto |
| **VE/VCO2** | Equivalente ventilatório para produção de gás carbônico |
| **VE/VO2** | Equivalente ventilatório para o consumo de oxigênio |
| **VEF1** | Volume expiratório forçado no primeiro segundo |
| **VO2pico** | Consumo máximo de oxigênio |
| **VR** | Volume residual |
| **VVM** | Ventilação voluntária máxima |

**SUMÁRIO**

## 1 INTRODUÇÃO

A fibrose cística (FC) é uma doença genética multissistêmica, caracterizada pela perda progressiva da função pulmonar, obstrução das vias aéreas e consequente limitação ao exercício (1). Assim, as complicações pulmonares são as principais responsáveis pelo aumento da morbidade e mortalidade desses pacientes (2). No entanto, com avanço no diagnóstico e tratamento da doença, a expectativa de vida está aumentando a cada ano e, segundo dados da *Cystic Fibrosis Foundation*, a sobrevida mediana no ano de 2015 foi de 41,7 anos (3).

A fisioterapia respiratória tem papel fundamental no tratamento desses pacientes, com o objetivo de diminuir a obstrução das vias aéreas e a limitação do fluxo aéreo e melhorar a distribuição da ventilação (4), além de prevenir o fechamento prematuro das vias aéreas, contribuindo para uma redução no aprisionamento aéreo (5) que podem levar a intolerância ao exercício. Dessa forma, é possível que a realização de fisioterapia respiratória antes da prática de atividade física possa melhorar a capacidade de exercício em paciente com FC.

O teste de exercício cardiopulmonar (TECP) é considerado o padrão ouro para avaliar a capacidade de exercício nesses pacientes e tem sido utilizado não apenas para acompanhar a evolução da doença (6), pois avalia o desempenho e a interação dos sistemas cardiovascular, respiratório e metabólico (7), como também para a prescrição de exercício físico (8). Além disso, estudos têm demonstrado associações entre a capacidade de exercício e sobrevida em pacientes com FC (9-11). Apesar disso, ainda não é claro o papel do consumo máximo de oxigênio como preditor de mortalidade na FC.

Desta forma, esta tese é composta pelo referencial teórico, objetivos, hipóteses e metodologias, além de dois artigos originais. O primeiro artigo foi intitulado “Airway clearance physiotherapy improves ventilatory dynamics during exercise in patients with cystic fibrosis: a pilot study” e teve como objetivo investigar se a realização da fisioterapia respiratória antes do teste de exercício cardiopulmonar resulta em aumento na capacidade de exercício. Já o segundo artigo apresentado nesta tese foi denominado “Peak oxygen uptake and mortality in cystic fibrosis: systematic review and meta-analysis” e teve o objetivo de avaliar a associação entre os níveis de consumo máximo de oxigênio e as taxas de

mortalidade em pacientes com FC.

# 2 REVISÃO DE LITERATURA

## 2.1 FIBROSE CÍSTICA

A FC é uma doença genética, crônica e progressiva, que causa manifestações clínicas em múltiplos órgão e sistemas do organismo (12). A incidência é maior na raça caucasiana, sendo que no Brasil estima-se que seja de 1:7576 nascidos vivos, porém apresenta diferenças regionais, com valores mais elevados nos estados da região Sul sendo de aproximadamente 1:5000 nascidos vivos (13). Já em países europeus, como no Reino Unido, a incidência aumenta para 1:2500 (14). Nas últimas décadas, devido ao avanço no diagnóstico e tratamento da doença, houve um aumento na expectativa de vida desses pacientes, e segundo dados da *Cystic Fibrosis Foundation*, a sobrevida mediana no ano de 2015 foi de 41,7 anos (3).

Essa doença é causada por mutações genéticas no braço longo do cromossomo 7, que codifica uma proteína reguladora transmembrana da fibrose cística (CFTR - *cystic fibrosis transmembrane conductance regulator*), responsável pelo transporte de cloro para o interior da célula (15). Já foram identificadas mais de 1800 mutações no gene CFTR, sendo que a mutação genética mais comum é o ΔF508, ocorrendo em cerca de 50 - 70% dos pacientes (16).

A presença de dois alelos com mutações no gene da FC provoca falta de atividade ou funcionamento parcial da CFTR, causando redução na excreção de cloro e água, além do aumento da eletronegatividade intracelular. Através deste processo, ocorre desidratação das secreções mucosas e aumento da viscosidade, causando obstrução dos ductos, acompanhada de infecção e consequente inflamação (17). As secreções das vias aéreas infectadas contêm proteases que destroem o tecido pulmonar, assim, as vias aéreas perdem a estabilidade e tendem a entrar em colapso, aprisionando ar e muco. Ainda, o colapso das vias aéreas periféricas menores resulta em áreas não homogêneas de distribuição da ventilação (18).

Uma ampla gama de micro-organismos está associada a infecções pulmonares em pacientes com FC. Lactentes e crianças pequenas estão mais susceptíveis de serem infectados por *Haemophilus influenzae* e *Staphylococcus*

*aureus*. Já em crianças mais velhas e em adultos, é mais provável que seja encontrada a colonização por *Pseudomonas aeruginosa* (PA) (19). A PA é o micro-organismo mais relevante associado à FC, aproximadamente 80% dos pacientes serão eventualmente infectados por este patógeno, resultando em deterioração clínica. Normalmente, a infecção crônica não ocorre no início da vida, desta forma, há um período de colonização intermitente até que o paciente desenvolva uma infecção crônica. No entanto, na infecção crônica, há um crescimento contínuo de PA que leva a um aumento da inflamação e juntamente com o dano causado pela própria bactéria são as principais causas de lesão do tecido pulmonar e da diminuição da função pulmonar (20).

A obstrução pulmonar progressiva e a destruição pulmonar resultam no desenvolvimento de bronquiectasias, estreitamento das paredes das vias aéreas e hiperinsuflação pulmonar, o que leva a um declínio progressivo na função pulmonar e a limitação ao exercício físico (1).

## 2.2 TRATAMENTO

Devido ao acometimento multissistêmico na FC, o tratamento desses pacientes deve ser realizado em um centro de referência especializado, com uma equipe multidisciplinar (21, 22). Essa equipe deve ser composta por pneumologistas, gastroenterologistas, fisioterapeutas, nutricionistas, enfermeiros, psicólogos, farmacêuticos e assistentes sociais (21). Desta forma, o tratamento consiste no controle das infecções pulmonares, na melhora da depuração das secreções brônquicas, na reposição enzimática e adequado aporte energético (23). Todos esses fatores influenciam na qualidade de vida dessa população, contribuindo para a diminuição da morbidade e mortalidade da doença (22).

## 2.3 FISIOTERAPIA RESPIRATÓRIA PARA DEPURAÇÃO DAS VIAS AÉREAS

Considerando a fisiopatologia da doença pulmonar na FC, a fisioterapia respiratória é parte fundamental no tratamento desses pacientes (24). De acordo com as diretrizes internacionais, a fisioterapia respiratória deve ser realizada rotineiramente por todos os pacientes (24, 25), com o objetivo de diminuir a

obstrução das vias aéreas e a limitação do fluxo aéreo e ainda melhorar a distribuição da ventilação através da mobilização e remoção das secreções (4). Existem diversas técnicas que podem ser utilizadas, sendo que cada uma delas apresenta vantagens e desvantagens, no entanto, não há evidências científicas que apontem superioridade de uma técnica em relação à outra (25). Historicamente, a fisioterapia respiratória consistia na combinação da drenagem postural com vibração e percussão do tórax (26), contudo, várias técnicas alternativas foram desenvolvidas com o objetivo de melhorar a eficiência e a autonomia dos pacientes (27), incluindo a pressão expiratória positiva (PEP) e a drenagem autogênica (DA).

A PEP consiste no uso de dispositivos que fornecem pressão expiratória positiva através de uma resistência expiratória que evita o fechamento prematuro das vias aéreas, contribuindo para reduzir o aprisionamento de ar no pulmão (5). Além de manter o fluxo de ar e a abertura das vias aéreas, a PEP promove o deslocamento proximal do muco, favorecendo a remoção de secreções (4). A respiração através da PEP induz um aumento temporário da capacidade residual funcional e uma maior interdependência entre os alvéolos (28), facilitando o fluxo ventilatório colateral e a abertura de vias aéreas colabadas (29). A PEP pode ser aplicada através da utilização de um bucal ou máscara facial juntamente com um resistor alinear ou do tipo *spring load* (linear). No caso da utilização de um resistor alinear, um manômetro deve ser inserido entre a válvula expiratória e o resistor para que se possa selecionar o nível apropriado da resistência expiratória, já que a resistência adequada é aquela que atinge uma pressão expiratória estacionária de 10 a 20 $cmH_2O$ (30).

Já a DA é uma técnica respiratória que utiliza diferentes volumes pulmonares para maximizar o fluxo expiratório e mobilizar secreções das vias aéreas distais. O mecanismo de depuração das vias aéreas é baseado em dois sistemas diferentes, o efeito da depuração ciliar e o efeito das forças de cisalhamento induzidas pela maximização do fluxo de ar (31). Essa técnica é realizada em três fases, incluindo uma fase de deslocamento das secreções das vias aéreas periféricas, através da realização de uma ventilação de baixo volume pulmonar, uma fase de coleta das secreções nas vias aéreas de médio calibre, através de uma ventilação de médio volume e uma fase de eliminação das secreções proximais das vias aéreas, através da realização de uma ventilação com alto volume pulmonar (32).

Existem poucos desfechos válidos, confiáveis e responsivos para avaliar as intervenções de depuração das vias aéreas na FC. Muitos pacientes apresentam radiografias de tórax, pontuação de escores clínicos e testes de exercícios normais. Além disso, alguns pacientes não produzem escarro, o que dificulta ainda mais a avaliação das mudanças após uma intervenção. Os desfechos comumente utilizados nos estudos já existentes sobre depuração das vias aéreas incluem a espirometria assim como o volume e o peso do escarro (33, 34). Contudo, são necessários mais estudos para identificar desfechos adequados para avaliar intervenções com depuração das vias aéreas. Além disso, estudos controlados randomizados de longo prazo são difíceis devido às questões éticas de retenção de tratamento e fatores de confusão de outras intervenções ao longo do tempo. Apesar disso, uma revisão da Cochrane foi capaz de mostrar que a fisioterapia respiratória, em comparação com a não realização de fisioterapia respiratória, teve um efeito em curto prazo no aumento do transporte de secreção (33).

## 2.4 LIMITAÇÃO VENTILATÓRIA AO EXERCÍCIO FÍSICO

A baixa capacidade de exercício tem sido relatada em crianças e adolescentes com FC e parece ser influenciada por vários fatores, incluindo a idade, o sexo, o estado nutricional, a massa muscular, a função pulmonar, a resistência e a força dos músculos respiratórios (10, 35).

A função pulmonar representa um importante fator de limitação progressiva ao exercício (36) devido ao aumento do trabalho respiratório causado pela obstrução das vias aéreas. Isso pode ser explicado pelo fato de que a realização de exercício exige um aumento ventilatório e a combinação de altas taxas respiratórias com a diminuição dos fluxos expiratórios podem resultar em um tempo expiratório insuficiente para expirar todo o ar inspirado, gerando o aprisionamento aéreo e a hiperinsuflação dinâmica (37). Além disso, o padrão ventilatório dos pacientes durante o exercício consiste em uma ventilação superficial relativamente rápida, com menos recrutamento alveolar, de modo que uma maior proporção de cada ventilação entra e sai do espaço morto, em vez de participar das trocas gasosas, podendo resultar em hipoxemia devido a alteração na relação ventilação/perfusão (38).

Há mais de 40 anos, Godfrey e Mearns (39) relataram a descoberta de que os indivíduos com FC apresentam um aumento no seu espaço morto fisiológico durante o exercício, desta forma, reduzindo o volume que está disponível para ventilação alveolar em cada ventilação (39). O resultado da obstrução das vias aéreas é que maiores fluxos de inspiração devem ser gerados para que a troca de gás continue de forma otimizada. Assim, é necessário um aumento no esforço muscular ventilatório para a mesma quantidade de ventilação (36, 40). Além disso, a limitação do fluxo aéreo pode promover a hiperinsuflação dinâmica e levar ao aumento do espaço morto no exercício e, assim, aumentar a ventilação para atingir uma determinada carga de trabalho (39). Os pacientes com FC apresentam uma ventilação minuto ($V_E$) maior, devido à presença do espaço morto fisiológico crescente no exercício, que aumenta com a gravidade da doença (37). Esses fatores, quando combinados, levam à limitação ventilatória no exercício em indivíduos com FC.

## 2.5 TESTE DE EXERCÍCIO CARDIOPULMONAR

O TECP é uma ferramenta importante na avaliação da capacidade funcional, limitação e determinação de níveis de aptidão física (41). Através dele pode-se identificar se a limitação ao exercício físico é de causa respiratória, cardiovascular, periférica ou devido a um descondicionamento físico (42).

Nos pacientes com FC, esse teste é considerado o padrão ouro para avaliar a capacidade de exercício, e tem sido utilizado não apenas para acompanhar a evolução da doença (10), pois avalia o desempenho e a interação dos sistemas cardiovascular, respiratório e metabólico (7), como também para a prescrição de exercício físico e avaliação de sintomas associados ao exercício (8), orientação quanto à prescrição de oxigênio (43, 44) e avaliação pré-transplante pulmonar (45, 46). Assim, segundo recomendação internacional, o TECP deve ser realizado anualmente nesses pacientes (42).

O teste pode ser realizado em uma esteira ou em um ciclo ergômetro, embora, na maioria das condições clínicas, como no caso da FC, o ciclo ergômetro é o equipamento de preferência, pois a esteira requer maior familiarização do paciente com o equipamento, mais espaço e um número maior de pessoas da equipe

disponível para a realização do teste (42, 47). Existem diferentes tipos de protocolos que podem ser utilizados para avaliar a aptidão física em doenças crônicas, contudo, os protocolos incrementais são mais amplamente utilizados na prática clínica (47). Apesar disso, ao escolher o protocolo mais adequado deve-se considerar a condição clínica e a faixa etária do paciente (48).

No caso da utilização de ciclo ergômetros os incrementos podem ser rápidos (a cada 1-3 minutos), tanto continuamente com incremento em rampa ou com incrementos súbitos em degraus, quanto lentos, a cada 3 minutos ou mais, em degraus (43). Protocolos rapidamente incrementais do tipo rampa parecem originar os melhores resultados para o TECP, todavia, protocolos em degraus de até dois minutos produzem respostas virtualmente indistinguíveis dos testes em rampa (49).

De acordo com as diretrizes do grupo europeu de exercício em FC, o TECP deve ser preferencialmente realizado no ciclo ergômetro, com a utilização do protocolo de *Godfrey* (42), que utiliza um incremento contínuo do tipo rampa, em que a carga de trabalho depende da altura do sujeito, iniciando e aumentando a cada minuto em 10 (<120 cm), 15 (120-150 cm) ou 20 W (>150 cm) (39). Esse protocolo tem sido amplamente utilizado em pacientes com FC (39) para avaliar as reações adversas ao exercício (40), o efeito de intervenções com exercício físico (41, 42) e associações entre a capacidade de exercício e outras variáveis como função pulmonar, atividade física, qualidade de vida e sobrevida (9, 50-52).

O parâmetro mais importante da capacidade de exercício é o consumo máximo de oxigênio ($VO_2$pico), definido como a maior absorção de oxigênio alcançada durante um único teste (8). No entanto, através do TECP se obtém dados de outras variáveis como a produção de dióxido de carbono ($VCO_2$), a $V_E$ e a taxa de troca respiratória (RER) (47). Além disso, é possível identificar o limiar anaeróbico (LA), uma variável utilizada na identificação do nível de condicionamento físico e prescrição da intensidade do treinamento físico, já que o descondicionamento resulta em uma eficiência reduzida da transferência e utilização de oxigênio em nível muscular e um LA precoce (53).

## 2.6 TESTE DE EXERCÍCIO CARDIOPULMONAR E A MORTALIDADE

Associações significativas têm sido relatadas entre a capacidade de exercício e a expectativa de vida em crianças (6) e adultos (9, 11) com FC. Nixon et al. (9) foi o primeiro a demostrar que o $VO_2$pico é um preditor independente de sobrevida em pacientes acompanhados por um período de 8 anos, sendo os que apresentavam um alto $VO_2$pico, com valor maior ou igual a 82% do previsto, demonstravam também uma maior taxa de sobrevida. Alguns anos depois, este achado foi replicado pelo estudo de Pianosi et al. (6) que mostrou uma associação do consumo de oxigênio com a mortalidade. Crianças que apresentavam um $VO_2$pico maior do que 45 $mL.kg^{-1}.min^{-1}$ apresentaram uma maior sobrevida em um seguimento de sete anos. Essa associação também foi encontrada em um seguimento de cinco anos em adultos com FC (11). Além disso, Leeuwen et al. (54) mostraram que uma baixa capacidade de exercício foi associada a uma maior taxa de mortalidade, a um declínio acentuado na função pulmonar e a um maior aumento nos níveis de IgG total.

## 3 JUSTIFICATIVA

Assim, considerando a fisiopatologia da doença pulmonar e a consequente limitação na capacidade de exercício, entende-se relevante investigar como as técnicas de depuração das vias aéreas podem influenciar o desempenho no exercício físico. Além disso, estudos têm demonstrado associações entre a capacidade de exercício e a sobrevida desses pacientes, no entanto ainda não está claro se o consumo máximo de oxigênio pode ser considerado um preditor independente de mortalidade. Dessa forma, um melhor entendimento sobre o tema pode potencialmente contribuir para melhorar a rotina de tratamento de pacientes com FC.

# 4 OBJETIVOS

## 4.1 OBJETIVO GERAL

Avaliar o efeito de uma sessão de fisioterapia respiratória sobre a capacidade de exercício e o papel do consumo máximo de oxigênio como preditor de mortalidade em pacientes com FC.

## 4.2 OBJETIVOS ESPECÍFICOS

- Investigar se a realização de uma sessão de fisioterapia respiratória antes do teste de exercício cardiopulmonar resulta em aumento na capacidade de exercício.
- Avaliar os efeitos de uma sessão de fisioterapia respiratória sobre as mudanças no consumo máximo de oxigênio, na ventilação minuto e nos equivalentes ventilatórios para consumo de oxigênio e para produção de gás carbônico no limiar anaeróbico e no pico do exercício.
- Avaliar, através de uma revisão sistemática e meta-análise de efeito randomizado, a associação entre os níveis de consumo máximo de oxigênio e as taxas de mortalidade em pacientes com FC.

## 5 HIPÓTESES

H1: A realização de uma sessão de fisioterapia respiratória antes do exercício pode melhorar a capacidade de exercício em pacientes com FC.

H2: O consumo máximo de oxigênio está associado com as taxas de mortalidade em pacientes com FC.

# 6 MÉTODO - ARTIGO ORIGINAL 1

## 6.1 DELINEAMENTO

Foi realizado um estudo piloto, prospectivo, randomizado, do tipo cross-over.

## 6.2 CRITÉRIOS DE INCLUSÃO

Foram incluídos pacientes com diagnóstico de FC, de ambos os sexos, com idade a partir de nove anos e altura >128cm, que realizavam acompanhamento regular na clínica de FC do *Royal Hospital for Sick Children* em Edimburgo, Escócia.

## 6.3 CRITÉRIOS DE EXCLUSÃO

Foram excluídas as crianças e adolescentes que apresentassem infecção crônica por *Burkholderia cepacia* e *Non-tuberculous mycobacterium abscessus.* Além disso, foram excluídos os pacientes que apresentassem, no dia dos testes, sinais indicativos de exacerbação pulmonar como febre, aumento da tosse e aumento da produção de escarro e aqueles que não conseguissem realizar um TECP máximo.

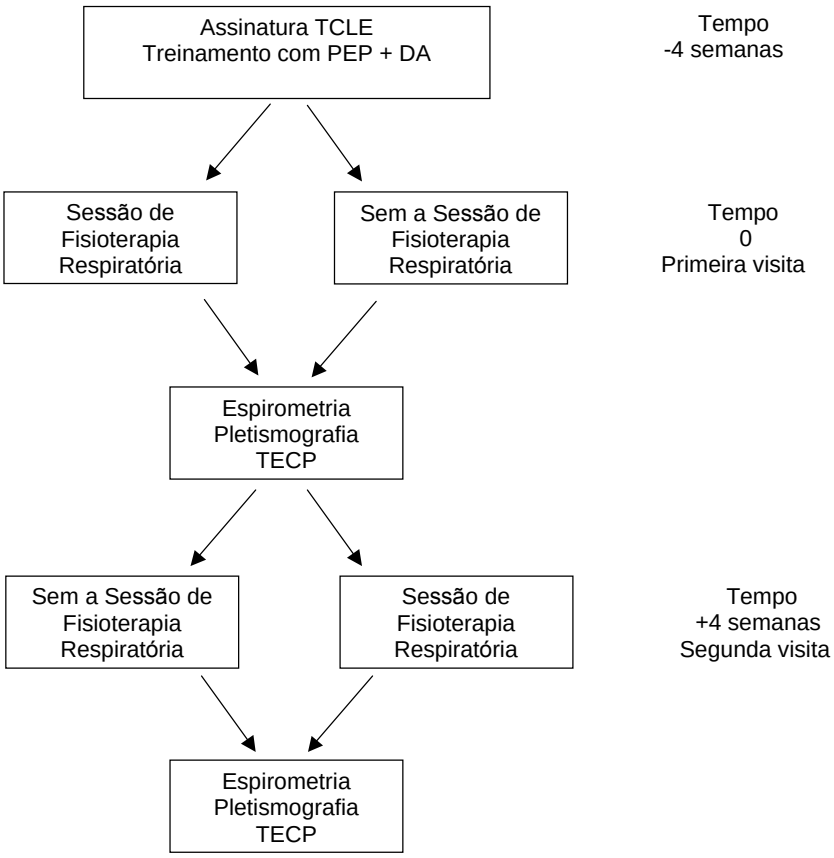
## 6.4 COLETA DE DADOS

Os testes de função pulmonar e os TECP foram realizados no laboratório de fisiologia respiratória do *Royal Hospital for Sick Children*. Além dos testes, foram coletados, em prontuário eletrônico, dados clínicos de cada paciente, incluindo o genótipo, a presença de colonização crônica por PA e insuficiência pancreática. A coleta de dados foi realizada no período de Janeiro/2015 a Outubro/2016. A equipe que executou e analisou os testes de função pulmonar e os TECP foi cegada quanto à realização ou não da fisioterapia respiratória.

## 6.5 DESENHO DO ESTUDO

Foram realizados dois TECP com um mês de intervalo - um com a realização de uma sessão de fisioterapia respiratória antes do teste e o outro sem a fisioterapia. Após o recrutamento e a assinatura do termo de consentimento livre e esclarecido, o uso padronizado das técnicas de PEP e DA foi ensinado a todos os participantes. Os pacientes foram randomizados para realizar a fisioterapia respiratória na primeira ou na segunda visita. A primeira visita foi após 4 semanas do treinamento da fisioterapia respiratória com a técnica padronizada, sendo a segunda realizada 4 semanas mais tarde. Os testes foram realizados na seguinte ordem: espirometria, pletismografia e TECP. Os pacientes foram orientados a não realizar a fisioterapia respiratória e as nebulizações no dia das visitas. O desenho do estudo é apresentado na Figura 1.

**Figura 1 - Desenho do estudo.**



## 6.6 FERRAMENTAS PARA AVALIAÇÃO

### 6.6.1 Avaliação antropométrica

A avaliação antropométrica foi realizada através da mensuração do peso e da altura em triplicata ou até a obtenção de dois valores idênticos. O peso foi obtido com os indivíduos em posição ortostática, com o mínimo de roupa, sem calçados, com o uso de uma balança digital (*Weymed, 500 series, H Faraday, London, England,* UK) previamente calibrada com precisão de 100 gramas. A altura foi obtida com os participantes descalços, com os pés em posição paralela, tornozelos unidos e braços estendidos ao longo do corpo (55), através de um estadiômetro portátil (*Harpenden Stadiometer, Holtain Limited, Crymych, Wales,* UK) com precisão de 1 mm. Para o cálculo do índice de massa corporal (IMC) absoluto foi utilizada a relação entre o peso em quilogramas e a altura em metros elevada ao quadrado ($Kg/m^2$) e para o cálculo do escore Z foi utilizado o programa *WHO Anthroplus* (56). Os dados foram apresentados em escore Z.

### 6.6.2 Sessão de fisioterapia respiratória

A sessão de fisioterapia respiratória foi realizada utilizando uma máscara de PEP juntamente com DA e foi orientada sempre pelo mesmo fisioterapeuta. A máscara PEP (*Astra Medical*) consistiu em uma máscara facial à qual estão conectadas uma válvula inspiratória e uma válvula expiratória. Na válvula expiratória foi conectado um resistor de orifício, para gerar uma pressão entre 10 a 20 cmH2O, e um manômetro, para verificar a pressão gerada (30).

Os participantes foram instruídos a sentar-se com as costas retas, e os cotovelos apoiados sobre uma mesa, foram então convidados a segurar a máscara contra o rosto com as duas mãos e inspirar com uma respiração em volume corrente através da máscara, realizando uma respiração abdominal. A DA foi realizada junto com a máscara de PEP, cada participante expirou em baixos volumes pulmonares e gradualmente foi aumentando o volume em três fases usando altas taxas de fluxo expiratório em diferentes volumes pulmonares para facilitar a depuração do muco (31,32). Os pacientes foram orientados a realizar uma expiração ativa, não forçada, contra a máscara, para gerar uma pressão entre 10-15 $cmH_2O$ medida pelo

manômetro (*Wells Pct Healthcare*, Suécia). Isso foi repetido por 15 respirações. A máscara foi então removida do rosto e o participante foi instruído a executar 2 *huffs* seguidos de tosse. Este procedimento foi repetido 4 vezes. A Figura 2 ilustra a utilização da máscara de PEP.

**Figura 2 - Utilização da máscara de pressão expiratória positiva**

6.6.3 Função Pulmonar

A espirometria foi realizada antes de cada TECP, com a utilização do *Jaeger Masterscreen PFT Pro* e seguiu as diretrizes da *American Thoracic Society* e *European Respiratory Society* (ATS / ERS) (57). Os pacientes foram posicionados em ortostase, sem o uso de clipe nasal (58) e foram orientados a realizar inspiração máxima seguida por uma expiração máxima, rápida e sustentada por pelo menos três segundos. Foram realizadas três manobras tecnicamente aceitável e duas reprodutível. Foram coletados os dados de volume expiratório forçado no primeiro segundo ($VEF_1$), capacidade vital forçada (CVF) e fluxo expiratório forçado entre 25% e 75% da CVF ($FEF_{25-75\%}$). Os valores da espirometria foram expressos em escore Z, utilizando-se dados de referência (59).

A pletismografia do corpo inteiro para mensuração dos volumes pulmonares (capacidade pulmonar total - CPT, capacidade residual funcional - CRF e volume residual - VR) foi realizada com o equipamento *Jaeger Masterscreen PFT Pro*. A

realização do exame e os critérios de aceitabilidade e reprodutibilidade seguiram as recomendações da ATS/ERS (60). O teste foi realizado com o paciente sentado, dentro da cabine fechada, em posição confortável, pés apoiados no chão, com o uso de clipe nasal e os lábios firmemente fechados ao redor do bocal. O paciente foi orientado a respirar calmamente até a estabilização do nível expiratório final. O *shutter* então se fechava automaticamente por 2-3 segundos enquanto o paciente realizava uma série de manobras de respiração curta (contra 0,5-1,0 Hz de resistência), com ambas as mãos sustentando as bochechas. Foram realizadas uma série de três a cinco manobras tecnicamente satisfatórias. Após, o *shutter* foi aberto para permitir a determinação do volume de reserva expiratório sendo que, posteriormente, o paciente inspirava até a CPT, e isso era seguido de uma manobra expiratória forçada na qual o paciente expiravam até o VR. Todos os volumes foram determinados sem o paciente retirar a boca do bocal. Foram realizadas, no mínimo, três manobras aceitáveis e reprodutíveis com uma variação menor do que 5%. Os dados foram expressos em escore Z (61).

### 6.6.4 Teste de exercício cardiopulmonar

Os pacientes realizaram os TECP em um ciclo ergômetro com freio eletromagnético (*Ergoline Viasprint 200, Ergoline, Blitz*, Alemanha) utilizando o protocolo de *Godfrey* (39) (Figura 3).

**Figura 3 - Teste de exercício cardiopulmonar no ciclo ergômetro.**

Durante o teste, os pacientes respiraram em uma máscara facial conectada a um pneumotacógrafo e linhas para coleta dos gases (*CareFusion* UK, Basingstoke, Inglaterra). Foram realizadas medidas respiração por respiração do $VO_2$pico, $VCO_2$, $V_E$ e RER. A frequência cardíaca também foi monitorada continuamente por um eletrocardiograma de 12 derivações, a pressão arterial foi medida em repouso, ao longo do teste (a cada 2 minutos) e durante a fase de recuperação ativa. A saturação periférica de oxigênio ($SpO_2$%) foi medida por um oxímetro de pulso colocado na orelha direita ou no dedo indicador direito.

O TECP apresentava quatro fases: (1) coleta de dados no repouso (3 a 5 minutos) - o paciente permanecia em repouso sentado no ciclo ergômetro até que as respirações se tornassem regulares e as medidas de trocas gasosas se estabilizassem; (2) ciclismo sem carga (3 minutos) - o paciente pedalava sem resistência (ergômetro ajustado para zero watts) mantendo uma cadência constante de 65rpm, realizando assim um aquecimento muscular; (3) teste de exercício incremental (8 a 12 minutos) - utilizando um protocolo de rampa predeterminado (39), o exercício foi realizado com uma carga de trabalho cada vez maior, sendo a taxa de trabalho aumentada minuto a minuto por 15w ou 20w mantendo uma

cadência a 65rpm; (4) fase de recuperação (4 minutos) - a resistência do ciclo ergômetro foi removida e o paciente continuou pedalando suavemente com uma cadência de 20-30rpm até que a frequência cardíaca retornasse ao valor basal.

Os seguintes critérios foram utilizados para avaliar se o teste de exercício foi "máximo": (1) uma frequência cardíaca máxima semelhante ao valor máximo teoricamente previsto, ou seja, 85% da frequência cardíaca máxima prevista pelo participante, onde a frequência cardíaca máxima prevista foi calculado através da fórmula 210 - (0,65 * idade) (62); (2) um $V_E$ máximo próximo ao alvo previsto; (3) um platô na absorção de oxigênio apesar de uma carga de trabalho crescente (ou seja, aumento final de $VO_2$ <200 mls.min$^{-1}$ para um aumento no trabalho de 5 a 10%); (4); RER > 1,03 (42); (5) incapacidade do participante de manter a cadência, apesar do encorajamento. No início e no final do TECP, os participantes foram convidados a classificar o grau subjetivo de dispneia e fadiga de membros inferiores usando a escala de Borg modificada.

A capacidade aeróbica máxima foi calculada como o $VO_2$pico nos últimos 30 s do teste e foi expressa corrigida quanto ao peso corporal (mL.kg$^{-1}$.min$^{-1}$). Foram também calculadas variáveis adicionais de interesse do TECP incluindo o equivalente ventilatório para consumo de oxigênio ($V_E/VO_2$) e o equivalente ventilatório para produção de gás carbônico ($V_E/VCO_2$). Os dados das variáveis TECP foram apresentados no LA e no pico de exercício. O LA ocorre em um ponto em que $V_E/VCO_2$ começa a subir enquanto $V_E/VO_2$ está caindo ou atingiu um platô (63). A reserva ventilatória (RV) foi incluída e definida como RV=ventilação voluntária máxima (VVM) - $V_E$pico / VVM x 100. A VVM foi estimada usando (27,7 x $VEF_1$) + (8,8 x $VEF_1$% previsto), que é citada como a melhor equação de predição de VVM em pacientes com FC, de 10 a 16 anos de idade (64).

## 6.7 ASPECTOS ÉTICOS

Este estudo foi aprovado pelo comitê de ética do *NHS Lotihan*, REC 14/NW/1270. Todos os responsáveis em concordância assinaram o Termo de Consentimento Livre Esclarecido e as crianças e adolescentes assinaram o termo de assentimento.

## 6.8 ANÁLISE ESTATÍSTICA

A normalidade dos dados foi avaliada através do teste de *Shapiro-Wilk* e como apresentaram uma distribuição normal, as variáveis contínuas foram apresentadas como médias e desvio padrão. As variáveis categóricas foram apresentadas em frequências absolutas e percentuais. Foi utilizado o teste *t* pareado para comparar variáveis com a realização da fisioterapia respiratória e sem a sessão de fisioterapia. Todas as análises e processamento de dados foram realizados através do programa SPSS versão 18.0 (*SPSS Inc*, Chicago, Illinois). Em todos os casos, as diferenças foram consideradas significativas quando $p \leq 0,05$.

## 7 MÉTODO - ARTIGO ORIGINAL 2

Esta revisão sistemática foi realizada seguindo as diretrizes do MOOSE (*Meta-Analysis of Observational Studies in Epidemiology*) (65) e os dados foram descritos de acordo com o PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) (66). O protocolo desta revisão foi registrado no *International prospective register of systematic reviews* (PROSPERO) e aceito sob o número CRD42016045759.

### 7.1 ESTRATÉGIA DE BUSCAS

Estudos foram identificados a partir da busca nas seguintes bases de dados: *Publisher Medline* (PubMed), *Elsevier Database* (Embase), Literatura Latino-americana e do Caribe em Ciências da Saúde (LILACS), *Scientific Electronic Library Online* (SciELO). Os termos usados foram (*Exercise Test OR Exercise Testing OR Cardiopulmonary Exercise Test OR Cardiopulmonary Exercise Testing OR Peak Oxygen Uptake OR Maximal Oxygen Consumption OR Exercise Tolerance OR Exercise Capacity*) *AND* (*Mortality OR Survival*) *AND* (*Cystic Fibrosis*). Não foram utilizados filtros. Uma busca manual foi realizada nas referências bibliográficas dos artigos selecionados, a fim de procurar publicações adicionais que fossem pertinentes ao estudo. As buscas foram realizadas em Março de 2017.

### 7.2 SELEÇÃO DE ARTIGOS

Dois autores (FMV e JSR) avaliaram independentemente os títulos e resumos dos artigos, selecionando assim os estudos a serem incluídos na revisão. Foram incluídos estudos de coorte cuja população fosse de indivíduos com FC e que avaliassem as taxas de mortalidade após as medidas de absorção de oxigênio durante um teste de exercício máximo. Foram excluídos artigos que não utilizassem as variáveis do teste TECP para predizer a mortalidade, artigos que avaliassem a mortalidade de pacientes na lista de transplante pulmonar, estudos de revisão, estudos de caso, modelos experimentais, resumos, cartas de resposta e editoriais, e publicações duplicadas, bem como aqueles que não cumprissem os critérios de

inclusão com base no rastreamento dos resumos ou texto completo dos artigos. Divergências sobre a adequação de estudos para inclusão na revisão foram discutidas e sanadas através de consenso. Um terceiro autor (MVFD) avaliou e resolveu as discrepâncias quando persistiu desacordo ou dúvidas entre os dois autores.

## 7.3 EXTRAÇÃO DOS DADOS

De cada um dos estudos selecionados foram extraídos os seguintes dados: título, nome do primeiro autor, ano da publicação, país de origem, língua da publicação, tipo de estudo, idade dos participantes, tamanho da amostra, tipo de equipamento utilizado, tipo de protocolo utilizado, duração do seguimento, $VO_2$pico, RV, $V_E/VO_2$ e $V_E/VCO_2$. Além disso, foram coletados os dados das variáveis do TECP e de outras variáveis que pudessem predizer a mortalidade de pacientes com FC. Quaisquer discrepâncias foram resolvidas por consenso entre os pesquisadores.

## 7.4 DESFECHO AVALIADO

O desfecho primário avaliado nessa revisão foi a mortalidade de pacientes com FC.

## 7.5 ANÁLISE DE QUALIDADE

A análise de qualidade dos artigos selecionados foi realizada individualmente por dois autores (FMV e JPHF) através da utilização da escala *Newcastle-Ottawa* (NOS) (67). A NOS atribui um máximo de nove pontos aos estudos de maior qualidade de acordo com os três parâmetros avaliados: seleção (quatro pontos), comparabilidade (dois pontos) e desfecho (três pontos). Assim, a qualidade geral do estudo foi definida como pobre (pontuação 0-3), razoável (pontuação 4-6) ou alta (pontuação 7-9). Os achados foram discutidos em conjunto com um terceiro autor (MVFD) e as discrepâncias ou dúvidas foram sanadas através de consenso.

## 7.6 SÍNTESE DOS DADOS E ANÁLISE ESTATÍSTICA

Quando possível e apropriado uma meta-análise de efeito randomizado dos estudos foi realizada. A diferença padrão entre as médias do $VO_2$pico entre o grupo sobrevivente e não sobrevivente foi realizada através da extração dos dados de média, tamanho da amostra e o valor do "p" de cada estudo incluído nessa análise. A associação do $VO_2$pico (alto/baixo) com a mortalidade foi calculada entre o grupo sobrevivente e não sobrevivente através da extração do risco relativo e do intervalo de confiança de 95% e/ou do número de eventos (morte) e o total de participantes em cada grupo, usando o modelo de efeito randomizado *DerSimonian-Laird*.

O *Forest plot* com o tamanho do ponto que reflete o peso de cada estudo utilizado foi representado graficamente nos resultados da meta-análise. O $I^2$ e teste de Q foram utilizados para quantificar o grau de heterogeneidade entre os estudos. Não foi possível avaliar o viés de publicação pelo teste *Egger's* devido ao pequeno número de estudos incluídos em cada análise. Todas as análises foram realizadas no *software Comprehensive Meta-analyses*.

## 8 CONCLUSÕES

Os resultados obtidos nesta tese demonstraram que a realização de uma sessão de fisioterapia respiratória antes do teste de exercício cardiopulmonar não aumentou o consumo máximo de oxigênio. No entanto, pode alterar os mecanismos ventilatórios levando a uma melhora da eficiência ventilatória, demonstrado pela diminuição da ventilação minuto ($V_E$) e dos equivalentes ventilatórios para consumo de oxigênio ($V_E/VO_2$) e para produção de gás carbônico ($V_E/VCO_2$) no limiar anaeróbico. Desta forma, essas adaptações podem favorecer o condicionamento físico alcançado através da realização de treinamento de exercício nesses pacientes. No entanto, o efeito da fisioterapia respiratória ainda deve ser explorado em estudos longitudinais.

Além disso, a revisão sistemática e meta-análise apresentada nesta tese mostrou que um baixo nível de consumo máximo de oxigênio está associado a uma maior mortalidade na FC, já que os pacientes com $VO_2$pico abaixo de 45 $mL.kg^{-1}.min^{-1}$ ou 82% do previsto aumentaram em 4,9 vezes o risco de um desfecho fatal. Isso indica que $VO_2$pico também pode ser uma variável de acompanhamento importante, além do $VEF_1$. Além disso, as comparações entre variáveis de capacidade aeróbica, $VEF_1$ e índice de massa corporal como preditores de mortalidade em FC precisam ser exploradas em estudos futuros.

Assim, os achados desta tese podem contribuir para um melhor tratamento dos pacientes com FC, considerando a importância da fisioterapia respiratória e seu efeito durante o exercício físico. Além disso, com o aumento da expectativa de vida torna-se cada vez mais importante o avanço no tratamento e a busca por ferramentas de prognóstico para um melhor acompanhamento desses pacientes.

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# APÊNDICES

## APÊNDICE A - ARTIGO ORIGINAL 1

### Airway clearance physiotherapy improves ventilatory dynamics during exercise in patients with cystic fibrosis: a pilot study

Submissão: Este artigo foi submetido para Archives of Disease in Childhood.

**ABSTRACT**

**Background:** Airflow limitation and dynamic hyperinflation may limit exercise capacity in cystic fibrosis (CF) patients. The aim was to investigate whether the undertaking of airway clearance physiotherapy (ACT) prior to cardiopulmonary exercise testing (CPET) results in improvements in exercise capacity.

**Methods:** A prospective randomised, cross-over pilot study was performed on children aged >9 years and >128 cm tall. Spirometry, plethysmography and CPET were performed on two separate occasions – one test with ACT prior to CPET and the other without.

**Results:** Twelve CF patients were included in the study with a mean(sd) age of 12.83(1.85) years. No significant difference in peak $VO_2$ was found between the tests. However, lower minute ventilation ($V_E$) and ventilatory equivalents ($V_EVO_2$ and $V_EVCO_2$) at lactate threshold (LT) were noted when ACT was undertaken prior to CPET. The mean(sd) $V_E$ ($L.min^{-1}$) at LT was 26.67 (5.49) vs 28.92(6.3) (p=0.05), $V_EVO_2$ ($L.min^{-1}$) at LT was 24.5(1.75) vs 26.05(2.5) (p=0.03) and $V_EVCO_2$ ($L.min^{-1}$) at LT was 26.58(2.41) vs 27.98(2.11) (p=0.03).

**Conclusions:** These pilot data suggest that ACT prior to exercise may lead to improved ventilatory dynamics during exercise in individuals with CF.

**Keywords:** cystic fibrosis, exercise physiology, physical therapy, exercise test

## 1. INTRODUCTION

Cystic fibrosis (CF) is a multi-system genetic disease, which may impact several organ systems.[1] In the lungs a cycle of persistent inflammation and infection leads to chronic infection, severe airway damage and consequent loss of respiratory function.[2] Thus, CF is characterized by progressive loss of lung function, with obstruction of the airways.[3]

Airway obstruction may occur in CF as a result of mucus within the airways and/or airways hyper-reactivity.[4] The result of this obstruction may be that greater inspiratory airflows must be generated in order for gas exchange to continue optimally such that an increase in respiratory muscle effort is required for the same amount of ventilation.[5, 6] Furthermore, airflow limitation may promote dynamic hyperinflation and lead to increased dead space on exercise, and thus increased ventilation to achieve a given workload.[7] CF patients may have a higher minute ventilation ($V_E$), due to the presence of an increasing physiological dead space on exercise, which increases with disease severity.[8] These factors, when combined together can lead to ventilatory limitation on exercise in subjects with CF.

Cardiopulmonary exercise testing (CPET) is considered the gold standard for assessment of physical fitness in CF patients.[9] The most commonly-reported parameter of aerobic exercise capacity is the peak oxygen uptake ($VO_2$peak), defined as the highest oxygen uptake attained during a single test.[10] However, other variables derived from CPET, including minute ventilation ($V_E$) on exercise, and the peak ventilatory equivalent ratios for oxygen uptake ($V_E/VO_2$) and carbon dioxide production ($V_E/VCO_2$), are important to evaluate ventilatory efficiency during exercise.[11] Submaximal exercise data, for example parameters measured at a subject's lactate threshold (LT) are also very valuable in assessing levels of conditioning.[12] The lactate threshold is the point at which anaerobic metabolism begins to predominate with exponentially increasing carbon dioxide production and accumulation of fatigue-related metabolites including lactate. These effects on musculoskeletal and respiratory mechanisms serve to limit exercise capacity after LT. Due to the volitional aspects of all exercise tests, there may be an argument that measures at LT are more reproducible than are peak data. Finally, significant associations have been reported between the exercise capacity and life expectancy

in patients with CF.[13-17] CPET provides detailed information on the the performance of a patient's lungs in combination with cardivascular and muscle systems, such that the test is an excellent way of monitoring clinical status and assessing response to disease and treatment.

When considering the pathophysiology of lung disease in CF, chest physiotherapy plays an important part in these patients' care.[18] Putative goals of airway clearance techniques (ACT) are to decrease airway obstruction and airflow limitation and to improve ventilation distribution as a result of mobilization and removal of airway mucus.[19] Moreover, ACT prevents premature airway closure, contributing to a reduction in air entrapment in the lung which minimises the development of dynamic hyperinflation.[20] There are several techniques that can be used, including positive expiratory pressure (PEP) and autogenic drainage (AD).[18, 21]

Given the mechanisms by which mucus retention within airways may lead to partial airway obstruction and increased dead space in those with CF, and the fact that dead space may be further impacted by dynamic hyperinflation on exercise, we hypothesise that the undertaking of ACT immediately prior to exercise may decrease airflow obstruction and enhance exercise performance. Thus, the aim of present study was to investigate whether the undertaking of ACT prior to CPET results in improvements in exercise capacity. A better understanding of how airway clearance techniques may influence exercise performance can potentially contribute to the daily life therapeutic management of CF patients.

## 2. METHODS

A prospective randomised, crossover pilot study was performed on children aged > 9 years and > 128cm tall that were attending CF clinic at the Royal Hospital for Sick Children, Edinburgh, UK. Patients who were chronically infected with *Burkholderia cepacia* and/or *Mycobacteriu abscessus* were excluded due to infection control considerations. Children and adolescents were not recruited to the study at times of CF chest exacerbation, but could later be approached at a time of stability. Data were collected from January 2015 to October 2016. The study had ethical

approval (REC 14/NW/1270). Assent was obtained from each participant along with informed consent from their parents.

### 2.1. Study Design

Two CPET tests were performed one month apart – one with ACT prior to CPET and the other without. Following recruitment and consent, subjects attended at least 4 weeks prior to the first CPET. Standardised ACT with PEP mask and AD was taught to all participants. Test 1 was performed after 4 weeks of undertaking ACT using the standardised technique, with Test 2 being undertaken a further 4 weeks later (correlating where possible with clinic visits).

Subjects were allocated randomly, by sealed envelope, to one of two orders of testing: a) ACT performed prior to first exercise test with no ACT undertaken prior to second test, and b) ACT performed prior to second exercise test with no ACT undertaken prior to first test. The study design is shown in Figure 1.

At each visit, subjects would first have an appointment with a physiotherapist (30 minutes) during which they would either have an ACT session or a 30 minute social conversation. All ACT session were performed by the same physiotherapist. The physiotherapy appointment would be immediately followed by an appointment with the respiratory physiology department (60 minutes) where spirometry followed by body plethysmography, followed by CPET would be performed. The schedule used at each visit is shown in Figure 2.

The respiratory physiology and medical staff that supervised the CPET and the individuals that analysed test data were blinded as to whether subject had undergone airway clearance physiotherapy before the test.

### 2.2. Anthropometric Measures

Body mass and body height were determined using an electronic scale (Weymed, 500 series, H Faraday, London, England, UK) and a stadiometer (Harpenden Stadiometer, Holtain Limited, Crymych, Wales, UK) respectively, in triplicate or until 2 identical values. Body mass index (BMI) was calculated as the body mass in kilograms divided by the square of the body height in metres. Data

were converted to standard deviation scores (z scores) using the program WHO Anthroplus.[22]

### 2.3. Airway Clearance Physiotherapy

Airway clearance physiotherapy was carried out using the PEP mask (Astra Medical) along with AD techniques. Participants were instructed to sit with back straight, and elbows resting on a table. They were instructed to perform a gentle relaxed breathing at tidal volume using abdominal breathing, about 5 breaths or until breathing appears relaxed. They were asked to hold the mask tight against face with both hands and inspire with normal sized breath (using abdominal breathing) through the mask. AD breathing was performed with the PEP mask in place ensuring each participant expired down to low lung volumes and gradually moved through the three-phased breathing regime using high expiratory flow rates at varying lung volumes to facilitate mucus clearance.[23-25] They were told that expiration should be slightly active (not forced) against the mask, to create a back pressure of between 10-15 $cmH_2O$ measured by manometer (Wells Pct Healthcare, Sweden).[26] This was repeated for 15 breaths. The mask was then removed from the face and the participant was instructed to perform 1 - 2 huffs followed by a cough. This procedure was to be repeated four times.

### 2.4. Lung Function

Spirometry was performed (Jaeger Masterscreen PFT Pro) prior to each exercise test. Three technically acceptable manoeuvres were performed and forced expiratory volume in 1 second ($FEV_1$), forced vital capacity (FVC), and forced expiratory flow between 25% and 75% of FVC ($FEF_{25-75\%}$) were recorded in accordance of the joint American Thoracic Society and European Respiratory Society (ATS/ERS) standards for spirometry.[27] Lung function values were expressed as Z-score using appropriate reference data.[28]

Whole-body plethysmography was performed also (Jaeger Masterscreen PFT Pro) enabling measurement of total lung capacity, (TLC), residual volume (RV) and calculation of RV/TLC ratio.[29] Tests were performed, and criteria of acceptability

and reproducibility were applied in accordance with American Thoracic Society/European Respiratory Society guidelines.[30] Whole-body plethysmography values were expressed as Z-score.[29]

### 2.5. Cardiopulmonary exercise testing

Subjects performed cardiopulmonary exercise testing on an electromagnetically braked cycle ergometer (Ergoline Viasprint 200, Ergoline, Blitz, Germany) using a modified version of the Godfrey protocol.[7] Subjects breathed into a full face mask connected to a pneumotachograph and sampling lines, using a calibrated metabolic cart (CareFusion UK, Basingstoke, England). Seat and handlebar height were identical for each test. The same mask was used for both tests by each subject.

Breath-by-breath measurements of oxygen uptake ($VO_2$), carbon dioxide production ($VCO_2$), minute ventilation ($V_E$), and respiratory exchange ratio (RER) were made. Heart rate (RR) was also monitored continuously by a 12-lead electrocardiogram, blood pressure was measured every 1-2 minutes at rest, throughout the test and during active recovery and transcutaneous oxygen saturation (SpO2%) was measured by a pulse oximeter placed on the right ear or on the index finger. Exercise was undertaken with a steadily increasing workload. Work rate was increased minute-by-minute by 15w or 20w maintaining a cadence at 65rpm.[7] The following criteria were used to assess whether an exercise test had been 'maximal', namely: 1) a maximal heart rate similar to the theoretically predicted maximal value i.e. >85% of the participant's predicted maximal heart rate, where predicted maximal heart rate is calculated as 210 – (0.65*age);[31] 2) a peak $V_E$ close to the predicted target;[32] 3) a plateau in oxygen uptake despite an increasing workload (i.e. final increase in $VO_2$ < 200 $mL.min^{-1}$ for an increase in work of 5 to 10%); 4) Respiratory Exchange Ratio (RER) >1.03;[9] 5) an inability of the participant to maintain cadence despite encouragement. At the beginning of the CPET and at the end subjects were asked to classify the subjective degree of dyspnea using the modified Borg scale.

Peak aerobic capacity was calculated as the $VO_{2peak}$ over the last 30 s of the test and was expressed corrected for body weight ($mL.kg^{-1}.min^{-1}$). Additional variables of interest from the CPET including the $V_E/VO_2$ and $V_E/VCO_2$ were also

calculated. CPET variables data were presented at lactate threshold (LT) and at peak exercise. AT LT occurs at a point where $V_E/VCO_2$ begins to rise whilst $V_E/VO_2$ is either falling or has reached a plateau. Breathing reserve was included and defined as BR= Maximal voluntary ventilation (MVV) - $V_{Epeak}$ / MVV x 100, where MVV was estimated using the 2003 prediction equations of Stein and colleagues.[32]

### 2.6. Statistical analysis

Data normality was assessed by the Shapiro-Wilk test, and, since they presented a normal distribution, the continuous variables were presented as mean and standard deviation (SD). Categorical variables were presented in absolute and percentage frequencies. Paired t-tests were used to compare variables between tests. All analysis and data processing were performed via SPSS program version 18.0 (SPSS Inc, Chicago, Illinois). In all cases, differences were considered significant when $p \leq 0.05$.

## 3. RESULTS

Eighteen subjects were recruited to the study. However, 4 subjects dropped out before the first test of the study and 2 patients were unable to adequately perform CPET (data unreportable). A total of 12 patients (6 boys/6 girls) completed the study with a mean age of 12.8±1.9 years. 75% (9) of the patients presented at least one allele F508del. Baseline characteristics of study subjects were presented on table 1.

Table 2 displays pulmonary function data with and without ACT having been performed before the tests. In general, results were within or close to the limits of normality. No significant differences were found with regard to whether physiotherapy had been performed prior to spirometry. There was however, a significant difference in mean(sd) FRC z score with ACT prior to plethysmography 0.12(0.53) compared to -0.23(0.70) without (p=0.01).

Variables evaluated at peak exercise and at LT during CPET with physiotherapy before and without physiotherapy are shown in Table 3. No significant difference in peak $VO_2$ was found between the tests. Mean(sd) $VO_{2peak}$ with ACT prior to CPET was 41.08(8.89) compared to 42.16(10.64) $mL.kg^{-1}.min^{-1}$ without prior

ACT (p=0.305). However, a significant decrease in minute ventilation ($V_E$) and in ventilatory equivalents ($V_EVO_2$ and $V_EVCO_2$) at LT was noted when undertaking ACT prior CPET. The mean $V_E$ ($L.min^{-1}$) was 26.67(5.49) vs 28.92(6.3) (p=0.05), $V_EVO_2$ ($L.min^{-1}$) was 24.5(1.75) vs 26.05(2.5) (p=0.03) and $V_EVCO_2$ ($L.min^{-1}$) was 26.58(2.41) vs 27.98(2.11) (p=0.03).

Finally, no statistical difference was found in MVV and BR when ACT was undertaken prior to CPET. Mean MVV with ACT was 96.15(23.38) and without was 94.23(26.94) (p=0.30). In addition, the mean of BR at LT with physiotherapy was 71.5(4.98) and without was 69.16(5.92) (p=0.10), and at peak exercise with ACT was 26.50(12.85) and without was 24.08(14.34) (p=0.62).

## 4. DISCUSSION

The study is a proof of concept study, demonstrating the potential for airway clearance physiotherapy techniques prior to exercise to improve exercise performance. Rather like the administration of a bronchodilator to an asthmatic shortly before exercise, this study provides physiological evidence that ACT may improve ventilator efficiency during exercise in individuals with CF.

A higher FRC is noted in the group who have undertaken ACT prior to plethysmography. It is known that positive end expiratory pressure (PEEP) can distend airways, increase FRC, with potential alterations in lung compliance and ventilation/perfusion matching,[33] and Van der Schans and colleagues [34] have reported a significant increase in FRC during the use of PEP physiotherapy. An altered breathing pattern, with decreased expiratory flow and an increased expiratory time, leading to a reduced exhaled volume, may be one explanation of why FRC increases.[35] The finding of higher FRC with prior ACT in this study may provide some supportive evidence for ACT using PEP and AD having similar effects on lung dynamics.

Differences in exercise physiology in subjects with CF are well-described.[36] Studies have demonstrated that $V_E$ in exercising CF subjects is elevated to levels above that expected in healthy individuals [32, 37, 38] such that exercising CF subjects may have reduced breathing reserve at the end of exercise. The altered

ventilatory mechanics are reported to reflect the increased dead space caused by limitations in airflow, and tend to parallel disease severity.[8, 38] In addition, ventilatory equivalents ($V_E/VO_2$ and $V_E/VCO_2$) are also indicators of dead space ventilation, and are indices.[11]

The reduction in $V_E$ at LT when ACT was undertaken prior to exercise–may suggest improved ventilatory mechanics following ACT. Furthermore, the lower ventilatory equivalent ($V_E/VO_2$ and $V_E/VCO_2$) measures at LT noted when ACT was undertaken prior to exercise suggests improved ventilatory efficiency with a lower minute ventilation per unit of oxygen consumed and carbon dioxide eliminated when compared to performing CPET without prior ACT. Mechanisms for lower $V_E/VO_2$ and $V_E/VCO_2$ measures could include relief of mucus obstruction and/or reduction in dynamic hyperinflation on exercise, each plausible as being directly impacted by ACT.

There are few valid, reliable, and responsive outcome measures to evaluate airway clearance interventions in CF. Many patients have normal chest X-rays, clinical scores, and exercise tests; moreover, some patients do not produce sputum, making it more difficult to assess changes after an intervention. Whilst the choice of outcome measure would depend upon the question being asked, commonly used outcomes in studies of airway clearance have included spirometry as well as sputum volume and weight,[39, 40] are needed further research to identify appropriate outcome measures to evaluate airway clearance interventions appears warranted, and to our knowledge, this is the first study demonstrating that a session of physiotherapy can improve ventilatory dynamics during exercise in CF patients.

It is perhaps unsurprising that no differences at peak exercise were noted, for $VO_{2peak}$ is a global measure of fitness that assimilates the interaction of lungs, cardiovascular system and also skeletal muscle conditioning.[41] Thus, a single session of physiotherapy although it might improve ventilatory dynamics and allow for an improved training response would be unlikely to alter $VO_{2peak}$.The ongoing use of ACT prior to physiotherapy as part of a training programme may however be associated with improvements in conditioning, and thus may impact peak exercise measures over time. Such a hypothesis would be worthy of consideration to test in future studies.

It is known that exercising around LT promotes a subjects endurance, improves conditioning and improves exercise performance.[12] Aerobic exercise programmes in CF that are designed to achieve a heart rate and/or $VO_2$ similar to that measured at LT are reported in published exercise training studies for example the Mukotrain study.[42] Therefore by reducing $V_E$ and improving ventilatory efficiency around LT, improvements in training and conditioning ability may ensue that provide advantageous exercise adaptation.

There are study limitations that are important to note. First, the small sample size makes it difficult to generalize the results of this study, and it is important to interpret the findings of our pilot study with caution. The sample size was limited by the study being undertaken in a single-centre, and requiring children to be old enough to reliably perform CPET. Secondly, we cannot evaluate the effect size of the physiotherapy because it was impossible for subjects to perform two maximal tests on the same day, with between test differences being confounded by the biological variability of the test itself. Furthermore, the fact that exercise itself promotes airway clearance would make it invalid to test our hypothesis with a second test on the same day. Finally, it remains to be further tested whether the significant differences in ventilatory dynamics that are reported at LT are of clinical significance, and whether they can be successfully exploited by incorporating ACT into exercise training programmes for individuals with CF.

## 5. Conclusion

These pilot data suggest that ACT prior to exercise may alter ventilatory mechanics and improve ventilatory efficiency in exercising CF patients. These are potentially favourable adaptations to exercise training for individuals with CF and are worthy of further exploration in larger, longitudinal studies.

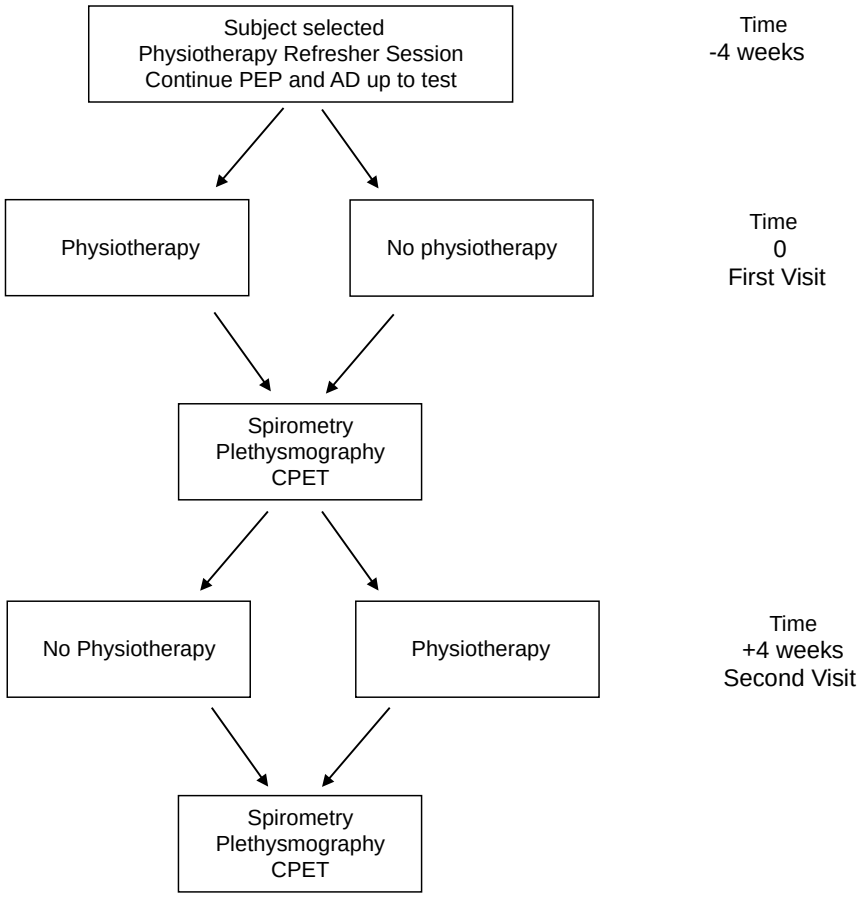


**Figure 1.** Flow chart of study design.

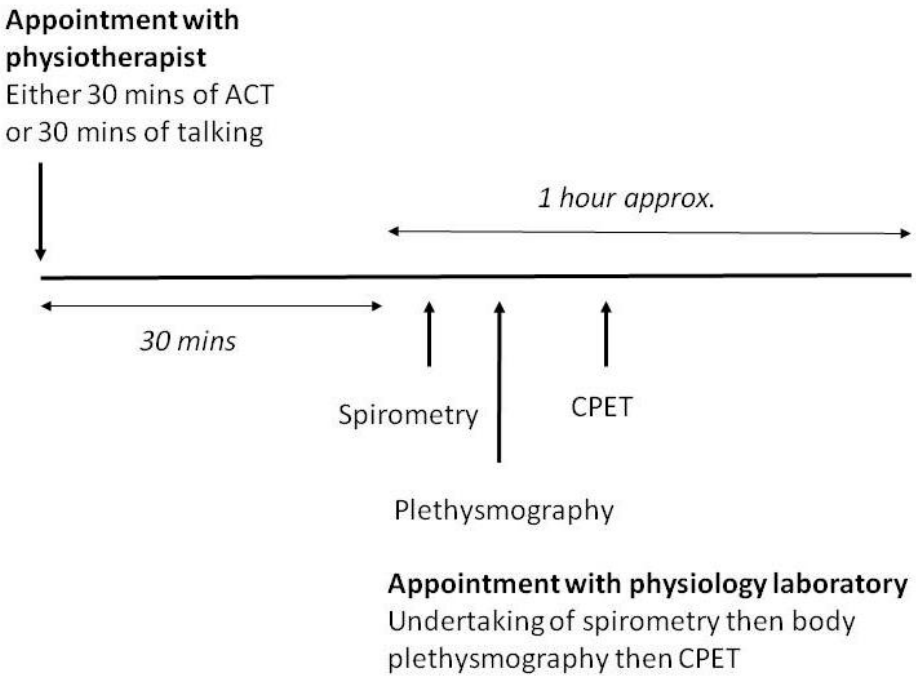


**Figure 2.** Order of ACT/placebo and tests.

**Table 1.** Baseline characteristics of study subjects (n=12)

| **Variables** | | **Range** |
|---|---|---|
| Demographic Characteristics | | |
| *Age (Years) | 12.83 (1.85) | 9.83 - 15.78 |
| Sex | 6 male/ 6 female | N/A |
| Anthropometry | | |
| *Weight (z score) | 0.06 (0.80) | 1.18 - 1.60 |
| *Height (z score) | -0.03 (0.50) | -0.84 - 1.15 |
| *BMI (z score) | 0.08 (0.82) | -1.08 - 1.60 |
| Chronic colonization | | |
| Pseudomonas aeruginosa, n (%) | 1 (8.33%) | N/A |
| Genotype | | |
| At least one allele F508del, n (%) | 9 (75%) | N/A |
| Pancreatic insufficiency, n (%) | 9 (75%) | N/A |

*Values expressed as mean(sd).

**Table 2.** Pulmonary function values with and without airway clearance physiotherapy (ACT) before the tests.

| | ACT prior to lung function | No ACT prior to lung function |
|---|---|---|
| **Spirometry (z score)** | | |
| FVC | -0.17 (0.97) | -0.33 (0.99) |
| $FEV_1$ | -0.51(0.76) | -0.71 (0.69) |
| $FEV_1$/FVC | -0.49 (1.01) | -0.62 (0.82) |
| $FEF_{25-75\%}$ | -0.52 (1.16) | -0.66 (1.06) |
| **Plethysmography (z score)** | | |
| TLC | 0.48 (0.65) | 0.35 (0.84) |
| FRC | 0.12 (0.53) | -0.23 (0.70) |
| RV | 0.18 (0.42) | 0.03 (0.55) |
| RV/TLC (absolute) | 26.75 (4.07) | 26.00 (3.74) |

FVC: forced vital capacity; $FEV_1$: forced expiratory volume in one second; $FEF_{25-75\%}$: forced expiratory flow between 25% and 75% of vital capacity; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume. Values expressed as mean (sd).

**Table 3.** Variables evaluated at peak exercise and at lactate threshold during CPET with and without airway clearance physiotherapy (ACT) before the tests.

| Variables evaluated | ACT prior to CPET | No ACT prior to CPET | Difference (95% CI) | p value |
|---|---|---|---|---|
| **At peak exercise** | | | | |
| $VO_2$ ($mL.kg^{-1}.min^{-1}$) | 41.08 (8.89) | 42.16 (10.64) | -1.08 (-3.29 to 1.13) | 0.31 |
| $V_E$ ($L.min^{-1}$) | 70.50 (20.55) | 70.33 (19.42) | 0.17 (-8.06 to 8.39) | 0.96 |
| $V_E/VO_2$ ($L.min^{-1}$) | 35.47 (5.64) | 35.12 (4.48) | 0.35 (-2.98 to 3.68) | 0.82 |
| $V_E/VCO_2$ ($L.min^{-1}$) | 29.82 (3.56) | 29.63 (2.28) | 0.19 (-1.62 to 2.00) | 0.82 |
| $V_T$ (L) | 1.49 (0.41) | 1.46 (0.42) | 0.03 (-0.08 to 0.14) | 0.59 |
| RER | 1.19 (0.09) | 1.18 (0.09) | 0.004 (-0.05 to 0.06) | 0.87 |
| HR (bpm) | 179 (14) | 182 (12) | -3.17 (-9.39 to 3.06) | 0.29 |
| RR ($breaths.min^{-1}$) | 48 (8) | 49 (8) | -1.0 (-6.9 to 4.9) | 0.72 |
| **At Lactate Threshold** | | | | |
| LT (%$VO_2$peak) | 59.83 (19.66) | 57.75 (12.21) | 2.08 (-5.57 to 9.73) | 0.56 |
| $VO_2$ ($mL.kg^{-1}.min^{-1}$) | 22.13 (4.63) | 23.05 (5.47) | -0.92 (-2.63 to 0.78) | 0.78 |
| $V_E$ ($L.min^{-1}$) | 26.67 (5.49) | 28.92 (6.30) | -2.25 (-4.55 to 0.05) | **0.05*** |
| $V_E/VO_2$ ($L.min^{-1}$) | 24.50 (1.75) | 26.05 (2.50) | -1.56 (-2.95 to -0.17) | **0.03*** |
| $V_E/VCO_2$ ($L.min^{-1}$) | 26.58 (2.41) | 27.98 (2.11) | -1.40 (-2.59 to -0.21) | **0.03*** |
| VT (L) | 0.91 (0.26) | 0.95 (0.31) | -0.04 (-0.15 to 0.08) | 0.50 |
| RER | 0.92 (0.07) | 0.93 (0.04) | -0.04 (-0.05 to 0.04) | 0.82 |
| HR (bpm) | 130 (12) | 128 (14) | 1.67 (-4.26 to 7.59) | 0.55 |
| RR ($breaths.min^{-1}$) | 30 (5) | 32 (5) | -1.5 (-4.33 to 1.33) | 0.27 |

ACT: airway clearance physiotherapy; CPET: cardiopulmonary exercise test; CI: confidence interval; $VO_2$: maximal oxygen uptake; $V_E$: minute ventilation; $V_E/VO_2$: ventilatory equivalent ratio for oxygen uptake; $V_E/VCO_2$: ventilatory equivalent ratio for carbon dioxide production; LT: Lactate threshold; $V_T$: tidal volume; RER: respiratory exchange ratio; HR: heart rate; RR: respiratory rate. Values expressed as mean (sd) unless otherwise stated, *p≤0.05

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## APÊNDICE B - ARTIGO ORIGINAL 2

### Peak oxygen uptake and mortality in cystic fibrosis: systematic review and meta-analysis

Submissão: Este artigo foi submetido para Respiratory Care.

**ABSTRACT**

**Background:** Aerobic fitness, as measured by maximum oxygen uptake ($VO_2$peak), correlates with survival in children and adults with cystic fibrosis (CF). The objective was to evaluate the effects of $VO_2$peak on mortality rates in CF subjects.

**Methods:** An online search in PubMed, Embase, LILACS and SciELO databases was conducted and cohort studies that assessed mortality rates after oxygen absorption measurements during a maximal exercise test were included. Data were extracted independently by two reviewers. The quality analysis of the selected articles was performed using the Newcastle-Ottawa scale. The main outcome evaluated was the mortality of CF subjects. Whenever possible, and if appropriate, a random effect meta-analysis was performed.

**Results:** Six cohort studies were included in this systematic review including 551 participants. Five studies were classified with high methodological quality. Two different analyses were carried out to evaluate the influence of $VO_2$peak on mortality. Total difference standardized mean between $VO_2$peak averages in the survival or non-survival groups was -0.606 (CI 95%=-0.993, -0.219, p=0.002). In addition, subjects with a lower $VO_2$peak had a significantly higher mortality risk (RR: 4.896, 95% CI=1.086 - 22.072, p=0.039) in an 8-year follow-up period.

**Conclusion:** Low levels of maximal oxygen uptake are associated with an increase of 4.9 in the risk of mortality in CF. This indicates that $VO_2$peak could also be an important follow-up variable measured, in addition to forced expiratory volume one second.

***Key Words**:* Cystic fibrosis, oxygen consumption, exercise capacity, exercise test, mortality

## 1. Introduction

Cystic fibrosis (CF) is a multisystemic genetic disease characterized by progressive loss of lung function and consequent limitation of aerobic fitness [1]. Although morbidity and mortality are still a major concern in the disease management, with advancement in the diagnosis and treatment, life expectancy is increasing each year and, according to data from the Cystic Fibrosis Foundation, the expected median survival in the year 2015 was 41.7 years [2]. Thus, as lung function is better maintained and aging of subjects increase, other comorbidities rise and there is a growing importance of factors such as preservation of aerobic fitness status [3].

In general, many factors have been associated with a worse prognosis in individuals with CF, among them sex [4], decline in lung function [4-7], number of exacerbations [6, 7], nutritional status [7-9], chronic colonization of the airways [10, 11] and maximal oxygen consumption ($VO_2$peak) [5, 11, 12]. It is known that the $VO_2$peak reduction is of multifactorial origin, since the mechanisms which limit aerobic fitness may be respiratory, cardiovascular and of peripheral muscles [13]. Thus, although forced expiratory volume in the first second ($FEV_1$) has still been cited as the best predictor of mortality in children and adults with CF [4, 11, 12], considering only pulmonary function as a disease progression marker may not identify other factors that lead to morbidity and mortality in these subjects. For that, aerobic fitness evaluation through the cardiopulmonary exercise test (CPET) seems to be a more comprehensive method [14].

CPET is considered the gold standard for evaluating aerobic fitness, and has been used not only to follow the evolution of the disease [15], since it evaluates the performance and interaction of the cardiovascular, respiratory and metabolic systems [16], but also for the prescription of physical exercise [17]. In addition, studies have shown the high reproducibility reproducibility of CPET for young [18] and adult [19] CF subjects, demonstrating a coefficient of variation of 9.3% and 6.9%, respectively. Moreover, the recent statement on exercise testing in CF recommended to perform CPET in individuals aged 10 years and older, as an important part of the annual review process [14].

Exercise intolerance due to hyperinflation and increased respiratory work caused by airway obstruction may be present as disease advances [20], although it is

increasingly common some paediatric subjects do not present dynamic hyperinflation during exercise. Aerobic fitness correlates with survival in children [12] and adults [5, 11] with CF. Nixon et al. [11] was the first to demonstrate that $VO_2$peak (<45 mL/kg/min) could be a predictor of survival in young individuals. Few years later, this finding was replicated by the study of Pianosi et al [12], showing that subjects with $VO_2$peak greater than 82% of predicted had better survival rate.

Thus, we hypothesized here that low levels of $VO_2$peak was an independent predictor of mortality in individuals with CF. Therefore, we performed a systematic review and quantitative meta-analysis of all available studies that reported the effects of maximum oxygen consumption on mortality rates in individuals with CF.

## 2. Methods

This systematic review was performed following the MOOSE guidelines (Meta-Analysis Of Observational Studies in Epidemiology) [21] and data were described according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes) guidelines [22]. The protocol of this review was registered in the International prospective register of systematic reviews (PROSPERO) and accepted under the number CRD42016045759.

### 2.1. Search strategy

Studies were identified from the following databases: Publisher Medline (PubMed), Elsevier Database (Embase), Latin American and Caribbean Literature in Health Sciences (LILACS) and Scientific Electronic Library Online (SciELO). The terms used were (Exercise Test OR Exercise Testing OR Cardiopulmonary Exercise Test OR Cardiopulmonary Exercise Testing OR Peak Oxygen Uptake OR Maximal Oxygen Consumption OR Exercise Tolerance OR Exercise Capacity) AND (Mortality OR Survival) AND (Cystic Fibrosis). No filters were used. A manual search was performed on the bibliographic references of the selected articles, in order to search for additional publications that were pertinent to the study purpose. The searches were conducted in March 2017.

### 2.2. Study selection

Two authors (FMV and JSS) evaluated independently the titles and abstracts of the articles, thereby selecting the studies to be included in the review. Cohort studies with CF individuals and that assessed mortality rates after oxygen uptake measurements during a maximal exercise test were included. Articles that did not use variables of the maximal exercise test to predict mortality, articles that assessed the mortality of individuals already on the lung transplant list, review studies, case studies, experimental models, abstracts, response letters, editorials and duplicate publications, as well as those that did not meet inclusion criteria were excluded after the analysis of the abstract or full text. Disagreements over the inclusion criteria of a particular study were discussed and resolved through consensus. A third author (MVFD) evaluated and resolved the discrepancies whenever disagreement or doubts between the two authors remained.

### 2.3. Data extraction

The following data were extracted from each of the selected studies: title, first author's name, year of publication, country of origin, language of publication, type of study, age of participants, sample size, type of equipment used, type of protocol used, duration of follow-up, $VO_2$peak, breathing reserve (BR), ventilatory equivalent for maximum oxygen consumption ($VE/VO_2$) and ventilatory equivalent for carbon dioxide production ($VE/VCO_2$). In addition, data from the variables of the cardiopulmonary exercise test and other variables that could predict the mortality of CF subjects were collected. Any discrepancies were resolved by consensus among the researchers. Moreover, whenever appropriate, an attempt to contact authors of the included studies was performed in order to request additional information.

### 2.4. Outcomes

The main outcome evaluated in this review was the mortality of CF subjects.

### 2.5. Quality analysis

The quality analysis of the selected articles was performed individually by two authors (FMV and JPHF) using the Newcastle-Ottawa scale (NOS) [23]. NOS assigns a maximum of nine points to the highest quality studies according to the three evaluated parameters: selection (four points), comparability (two points) and outcome (three points). So, the overall quality of the study was defined as poor (score 0-3), reasonable (score 4-6) or high (score 7-9). The findings were discussed together with a third author (MVFD) and the discrepancies or doubts were resolved by consensus.

### 2.6. Synthesis of data and statistical analysis

When possible and appropriate a randomized meta-analysis of the studies was conducted. The standard difference of the $VO_2$peak averages between the survival and non-survival groups was performed by extracting the average data, sample size and p-value from each study included in that analysis. The association of high or low $VO_2$peak with mortality was calculated between the survival and non-survival groups by extracting the relative risk and the 95% confidence interval and/or the number of events (death) and the total of participants in each group, using the DerSimonian-Laird randomized model.

Forest plots with the point size reflecting study weight were used to graphically represent the results of meta-analysis. The $I^2$ and Q test were used to quantify the heterogeneity's degree between the studies. It was not possible to evaluate the bias of publication by the Egger's test due to the small number of studies included in each analysis. All analysis were performed in the Comprehensive meta-analysis software.

## 3. Results

A total of 8698 articles were found with 3886 in Pubmed, 4787 in EMBASE and 25 in LILACS. Of these, 2786 were excluded because they were repeated in the databases used and 5906 because they did not meet the eligibility criteria of present study. Therefore, after the analysis of the full texts, six studies were included in this

review and four studies in the meta-analysis. Figure 1 shows the flowchart of the total articles found and the reasons for the exclusion of studies.

The selected articles included a total of 551 participants, and the sample size of each study varied between 28 and 149 subjects, with an average age ranging from 10 to 30.2 years and the follow-up time between 2.8 and 8 years (Table 1). Only two studies presented CFTR genotype classification, although no separate analyses were performed [9, 10]. All studies used the cycle ergometer to perform CPET. However, when evaluating the type of protocol, three [9-11] studies used the Godfrey protocol, two [5, 24] performed a ramp protocol and one study[12] used a step increment. Data of $VO_2$peak, BR, $VE/VO_2$ and $VE/VCO_2$ of each article are presented in table 2.

Regarding the overall methodological quality, five included studies [5, 9, 11, 12, 24] were classified with high quality, and two [5, 11] of these received the maximum score (9 points). On the other hand, only one article [10] was classified with reasonable quality and assigned 6 points. Table 3 presents the parameters evaluated in the NOS scale.

Table 4 shows the data of significant variables to predict mortality in CF subjects. $VO_2$peak was significant in five studies [5, 9-12] and BR in 1 study [9]. In the study by Nguyen et al. [24] only the arterial-alveolar oxygen gradient was significant. Regarding other variables analyzed, $FEV_1$ was significant in 5 studies, [5, 9, 11, 12, 24] body mass index (BMI) in 2 [9, 24] and the presence of *Pseudomonas cepacia* colonization was significant in one study [11]. In order to determine the influence of CPET variables on the mortality of CF subjects, three studies [9, 11, 12] used Cox Proportional Hazards and the other three used log rank test [10], multivariate logistic regression [24] and $\chi 2$ test [5].

### 3.1. Meta-analysis

Two different analyzes were carried out to evaluate the influence of $VO_2$peak on mortality in individuals with CF and 2 studies were included in each one. Figure 2A shows data from articles reporting differences between $VO_2$peak averages in the survival or non-survival groups. The $I^2$ analysis did not show heterogeneity between studies ($I^2$=0%, p=0.843). The total difference standardized mean was -0.606 (CI

95%=-0.993, -0.219, p=0.002), indicating that subjects in the non-survival group had a lower $VO_2$peak compared to the survivors.

In addition, subjects with a lower $VO_2$peak (<45 mL/kg/min or <82% of predicted) were associated with a significantly higher risk (RR: 4.896, 95% CI=1.086 - 22.072, p=0.039) for mortality. There was a small heterogeneity in the studies ($I^2$=31.56%, p=0.227) included in this analysis, although not significant (Figure 2B). It was not possible to generate funnel charts in the analyzes because of the small number of studies included.

## 4. Discussion

Low aerobic fitness has been reported in individuals with CF and is associated with several factors, including impairment of lung function [25], poor nutritional status [26], low muscle power [25], cardiac dysfunction [27], high level of inflammation [10] and physical deconditioning [25]. $VO_2$peak, defined as the maximum amount of oxygen that can be transferred and utilized during exercise, is the main parameter in the evaluation of aerobic capacity [17]. The data of the present systematic review and meta-analysis demonstrates that subjects with lower $VO_2$peak rates, that is, values below 82% of predicted or 45 mL/kg/min, increased by 4.9 the risk for a fatal outcome in an 8-year follow-up period, indicating that measurement of aerobic fitness could be a tool for prognosis in CF. Furthermore, the difference between means indicated that individuals in the non-survival group had a lower $VO_2$peak compared to the survivors. This association of oxygen consumption with mortality has also been described for individuals with chronic obstructive pulmonary disease [28, 29] and chronic heart failure [30, 31]. To our knowledge, this is the first meta-analysis that evaluated the association of $VO_2$peak with mortality in CF subjects.

Nguyen et al. [24] was the only study included that found no relationship between $VO_2$peak and mortality. They demonstrated that only alveolar-arterial gradient for oxygen at peak exercise was significantly associated with mortality. On the other hand, the remaining articles demonstrated an association between $VO_2$peak and mortality. However, other variables, including $FEV_1$ and BMI, were also significant in predicting mortality. A higher BMI has been associated with an increased likelihood of survival in CF subjects [7-9, 32], corroborating with data of

Nguyen et al. [24] and Hulzebos et al. [9]. Furthermore, $FEV_1$ has been considered the best predictor of mortality in CF subjects [4, 11, 12], including those on lung transplant lists [33]. According to Kerem et al. [4] individuals with $FEV_1$ below 30% of predicted should be referred for lung transplantation. Moorcroft et al. [5] showed that despite the correlation of $VO_2$peak with survival, $FEV_1$ is still the best indicator of prognosis. On the other hand, Pianosi et al. [12] demonstrated that the change in $VO_2$peak over time is more useful as a prognostic marker than the commonly used longitudinal decline in $FEV_1$. In addition, abnormalities in aerobic fitness in early disease in stable subjects may reflect changes that are not detected by spirometry, since Dodd et al. [34] have demonstrated that the correlation between thoracic computed tomography abnormalities and exercise limitation is stronger than the correlation between spirometry and BMI with exercise limitation. Thus, it is possible that $VO_2$peak is a better prognostic marker early in life, as compared to $FEV_1$, although further studies are needed to directly address that question.

Information obtained through CPET plays an important role in the care and follow-up of CF subjects, for its contribution to prognosis and functional information [17]. Thus, an annual follow-up of $VO_2$peak is relevant to identify individuals at risk for a worsening prognosis [14] and also those who may benefit from a more intense therapy [35], considering that aerobic fitness correlates with survival in children [12] and adults [5, 11] with CF. In addition, it is well-established that exercise increases $VO_2$peak, indicating its importance as a therapeutic tool that could influence prognosis [36]. The studies included in this systematic review and meta-analysis showed a variation in the follow-up time, ranging from 2.8 to 8 years. Considering that these are studies to evaluate mortality, a short follow-up time may be considered as a limitation, since it could influence this outcome. Also, it is already known that in CF the evolution of the disease is characterized by a decline in lung function and exercise limitation [1], highlighting the role of long-term follow-up periods in the evaluation of mortality rates.

Regarding CPET, all articles included performed the test on the cycle ergometer and used an incremental protocol, that is, with progressive increase of load in predetermined periods [17]. Several types of protocols have been used to evaluate physical fitness in individuals with chronic diseases, but there is no consensus as to the best protocol to be used in the clinical setting. In addition, protocols should vary depending on clinical condition and age range of the subjects

[37]. As for the variables of CPET reported, the included studies showed a large variability, which prevented us to include some articles in certain analyzes and to evaluate the influence of other variables such as ventilatory reserve data, $VE/VO_2$ and $VE/VCO_2$. A high breathing reserve index at the lactate threshold represents a reduction of the pulmonary mechanical reserve and was already reported as a predictor of mortality in individuals with CF waiting for lung transplantation [38]. In addition to this, $VE/VO_2$ measurement has also been shown to be important in predicting mortality [5, 9]. Despite the relevance of the analyzed variables, it is important to recognize that CPET is not widely available in CF centers and requires specific equipment and expert personnel to perform and interpret the test. On the other hand, increasing life expectancy and new therapeutic options are changing clinical presentation of CF and markers such as lung function are better maintained over time, highlighting the importance of other factors such as aerobic fitness. Thus, studies designed to evaluate the prognostic value of CPET as compared to nutritional status, lung function and other exercise tests are needed to further understand the role of aerobic fitness as a disease progression marker in CF.

Regarding the methodological quality of the studies included, in general, a high quality was found, since only one study [10] presented a reasonable classification according to the NOS, which strengthens the present systematic review and meta-analysis. In addition, the $I^2$ test in the analysis of the difference between means did not show heterogeneity and the relative risk analysis showed a low heterogeneity among the included studies, which may confirm the power of the analysis presented, despite the small number of articles.

One of the main limitations of this study is the small number of articles included in each analysis and the variability of the parameters evaluated. Due to the different presentations of data, only two articles were included in each of the analyses. This way, it was not possible to perform the funnel chart to evaluate publication bias of the studies. A short follow-up period, especially for a population of young children and adolescents, may also be considered a limitation in the evaluation of mortality. In addition, the lack of response when we tryied to contact authors of some studies [9-12] in order to request additional information on $VO_2$peak separately from individuals who survived and those who did not survive may be considered a limitation of present study.

## 5. Conclusions

The present systematic review and meta-analysis showed that a low level of peak oxygen uptake is associated with higher mortality in CF, as subjects with reduced $VO_2$peak increased by 4.9 the risk for a fatal outcome in an 8-year follow-up period. This indicates that $VO_2$peak could also be an important follow-up variable measured in addition to $FEV_1$. Moreover, comparisons between aerobic capacity variables, $FEV_1$ and BMI as mortality predictors in CF need to be further explored in future studies.

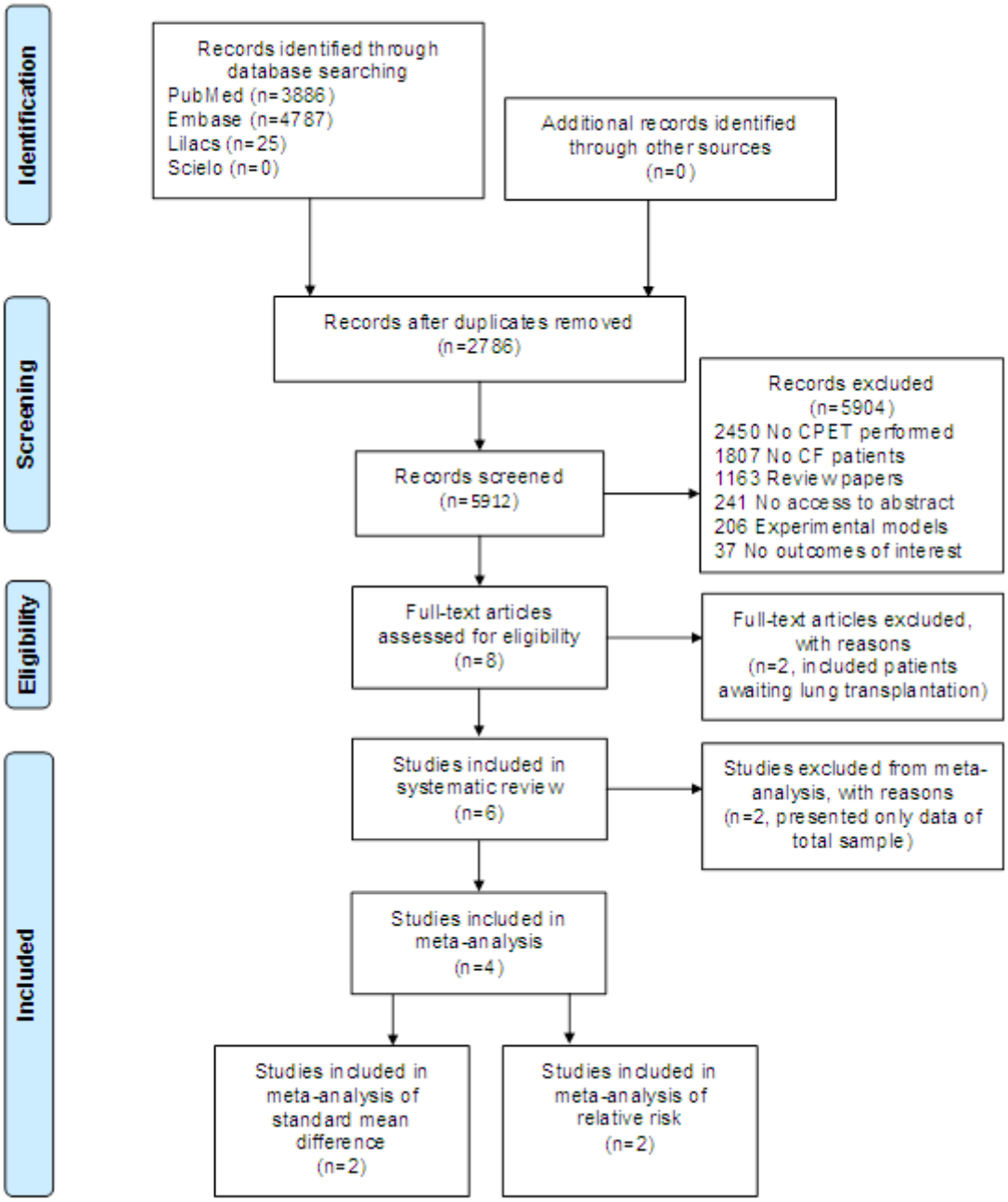


**Figure 1.** Flow diagram of screening and selection of studies included in the systematic review and meta-analysis.

**Table 1.** Main methodological characteristics of the studies.

| Author & Year | Country of origin | Type of cohort | Sample size | Age (years)* | Follow-up (years) |
|---|---|---|---|---|---|
| Hulzebos, 2014 | Netherlands | Prospective | 127 | 12.7 (11-14) | 7.5 |
| Leeuwen, 2012 | Netherlands | Prospective | 149 | 13.2 (12-13) | 2.8 |
| Nguyen, 2010 | France | Retrospective | 51 | 30.2 (16-67) | 3 |
| Pianosi, 2005 | Canada | Prospective | 28 | 10 (7-16) | 8† |
| Moorcroft, 1997 | United Kingdom | Retrospective | 87 | 19.8 (15-40) | 5 |
| Nixon, 1992 | United States | Prospective | 109 | 17 (7-35) | 8 |

*Mean (min-max); †Approximate value.

**Table 2.** Main results of cardiopulmonary exercise test variables of the studies included in the systematic review.

| Author & Year | Baseline $VO_2$ | BR | $VE/VO_2$ | $VE/VCO_2$ |
|---|---|---|---|---|
| Hulzebos, 2014 | 41.5±8.8 mL/kg/min 93.3±17.9 % | 0.25±0.1* | 37.4±6.8 | 32.3±5.4 |
| Leeuwen, 2012 | 41.4±8.8 mL/kg/min 96.2±18.2 % | - | - | - |
| Nguyen, 2010 | G1: 51.8±15.6 % G2: 66.1±20.7 % | 100.1±20.5† 74.5±21.3† | - | - |
| Pianosi, 2005 | 41.2 mL/kg/min | 0.92# | - | - |
| Moorcroft, 1997 | G1: 53.7 % G2: 66.6 % | - | G1: 38.7 G2: 32.4 | - |
| Nixon, 1992 | 35 mL/kg/min 70 % | - | - | - |

VO2: maximal oxygen uptake; G1: non survivor, G2: survivor; BR: breathing reserve at maximum exercise; VE/VO2: ventilatory equivalent ratio for oxygen; VE/VCO2: ventilatory equivalent for carbon dioxide; %: percent of predicted; *1-(VEpeak-MVV); †VEpeak (%) of MVV; #VEpeak/MVV.

**Table 3. Newcastle-Ottawa Scale (NOS) table: methodological quality of cohort studies included in the systematic review.**

| First author, publication year | Representativeness of the exposed cohort | Selection of the unexposed cohort[†] | Ascertainment of exposure[‡] | Outcome of interest not present at start of study | Control for important factor or additional factor[§] | Assessment of outcome | Follow-up long enough for outcome to occur[&] | Follow-up of cohort adequate | Total quality score |
|---|---|---|---|---|---|---|---|---|---|
| **Hulzebos, 2014** | * | * | * | * | * | * | * | * | 8 |
| **Leeuwen, 2012** | * | * | * | * | | * | | * | 6 |
| **Nguyen, 2010** | * | * | * | * | * | * | | * | 7 |
| **Pianosi, 2005** | * | * | * | * | * | * | * | * | 8 |
| **Moorcroft, 1997** | * | * | * | * | ** | * | * | * | 9 |
| **Nixon, 1992** | * | * | * | * | ** | * | * | * | 9 |

*A study could be awarded a maximum of one star for each item except for the item Control for important factor or additional factor. The definition/explanation of each column of the Newcastle-Ottawa Scale is available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm

[†]The category does not apply to the exposure investigated in the systematic review. Thus, all studies were equally graded.

[‡]Description of the ergometer and the protocol used.

[§]A maximum of 2 stars could be awarded in this item. Studies receiving one star: tested $FEV_1$ on a multivariate, univariate or mixed model analysis; two stars: tested 3 of the 4 variables (age, BMI, gender and chronic colonization by *Pseudomonas Aeruginosa* or *Burkholderia Cepacia*) in the models described previously.

[&]Cohort studies with a mean/median follow-up time longer or equal to 5 years (60 months) received one star; if the mean follow-up time was not clearly indicated: no star.

**Table 4.** Variables used as mortality predictors in patients with cystic fibrosis.

| Author & Year | Exercise capacity variables | Others variables |
|---|---|---|
| Hulzebos, 2014 | $VO_2$ peak/Kg (% pred): 2.96 (1.06-8.23)*<br>BR: 3.35 (1.19-9.48)* | $FEV_1$%: 17.84 (4.02-79.08)*<br>BMI: 8.11 (2.93-22.51)* |
| Leeuwen, 2012 | $VO_2$ max/kg (% pred) ≤ 80: 96.3% mortality†<br>$VO_2$ max/kg (% pred) > 80: 80.0% mortality | - |
| Nguyen, 2010 | $P(A\text{-}a)O_2$ peak: 0.794 (0.668-0.943, p=0.009)# | $FEV_1$%: 1.015 (0.904-1.139, p=0.798)#<br>BMI: 1.770 (1.070-2.930, p=0.026)# |
| Pianosi, 2005 | Peak $VO_2$ intercept: 0.910 (0.816-1.014, p=0.087)*<br>Peak $VO_2$ slope: 0.048 (0.005-0.430, p=0.007)* | $FEV_1$ intercept: 0.915 (0.868-0.964, p<0.001)*<br>$FEV_1$ slope: 0.008 (0.0003-0.210, p=0.004)* |
| Moorcroft, 1997 | $VO_2$ peak (cut-off 56%): 64% sensitivity and 72% specificity | $FEV_1$ (cut-off 55%): 91% sensitivity and 74% specificity |
| Nixon, 1992 | $VO_2$ peak % (≤ 58 vs ≥ 82): 3.2 (1.2-8.6, p=0.024)& | $FEV_1$% (≤ 50 vs ≥ 65): 1.1 (0.4-2.7, p=0.826)&<br>*P. cepacia* (present vs absent): 5.0 (2.6-9.5, p<0.001)& |

$VO_2$: maximal oxygen uptake; *Hazard ratio (95% CI); BR: breathing reserve; $FEV_1$: forced expiratory volume in 1 second; BMI: body mass index; †p=0.018; $P(A\text{-}a)O_2$: alveolar-arterial gradient for oxygen; #odds-ratio (95% CI); &relative risk (95% CI); *P. cepacia*: *Pseudomonas cepacia.*

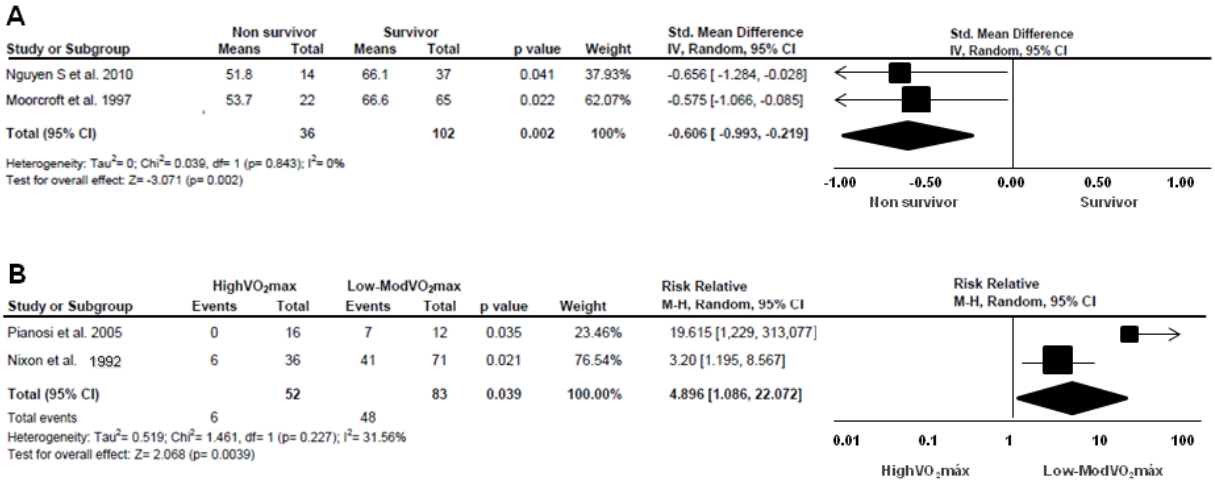


**Figure 2.** Meta-analysis of studies that reported mean difference in $VO_2$peak between survival or non-survival groups (A) and the association (risk relative; 95% CI) of $VO_2$peak (high vs. mod-low) with mortality (B). Low $VO_2$peak was considered when <45 mL/kg/min or <82% of predicted**.**

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# ANEXOS

# ANEXO A - APROVAÇÃO DO COMITÊ DE ÉTICA E PESQUISA

**Health Research Authority**
**National Research Ethics Service**

**NRES Committee North West - Lancaster**
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7109
Fax:0161 625 7919

28 October 2014

Dr Donald Urquhart
Consultant in Paediatric Respiratory and Sleep Medicine
NHS Lothian
Royal Hospital for Sick Children
Edinburgh
EH9 1LF

Dear Dr Urquhart

| | |
|---|---|
| **Study title:** | **Does the undertaking of a session of physiotherapy (PEP and Autogenic Drainage) prior to exercise improve exercise performance?** |
| **REC reference:** | **14/NW/1270** |
| **IRAS project ID:** | **160316** |

Thank you for your correspondence of 20 October 2014 , responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mrs Carol Ebenezer, nrescommittee.northwest-lancaster@nhs.net.

**Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

**Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

*Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.*

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

*Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of approvals from host organisations*

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

**Ethical review of research sites**

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

**Approved documents**

The final list of documents reviewed and approved by the Committee is as follows:

| *Document* | *Version* | *Date* |
|---|---|---|
| Covering letter on headed paper | | 01 August 2014 |
| Instructions for use of medical device | 1 | 01 August 2014 |
| Letters of invitation to participant | 2 | 02 October 2014 |
| Other | 1 | 02 October 2014 |
| Other [A6.1 Research Summary] | | |
| Participant consent form | 2 | 02 October 2014 |
| Participant consent form | 2 | 02 October 2014 |
| Participant consent form | 2 | 02 October 2014 |
| Participant information sheet (PIS) | 2 | 02 October 2014 |
| Participant information sheet (PIS) | 2 | 02 October 2014 |
| REC Application Form [REC_Form_01092014] | | 01 September 2014 |
| Research protocol or project proposal | 1.0 | 01 August 2014 |

| | | |
|---|---|---|
| Summary CV for Chief Investigator (CI) | | 29 January 2014 |
| Summary, synopsis or diagram (flowchart) of protocol in non technical language | 1 | 01 July 2014 |

**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**After ethical review**

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

**User Feedback**

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

**HRA Training**

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

| | |
|---|---|
| **14/NW/1270** | **Please quote this number on all correspondence** |

With the Committee's best wishes for the success of this project.

Yours sincerely

pp
**Dr Lisa Booth**
**Chair**

Email:nrescommittee.northwest-lancaster@nhs.net

| | |
|---|---|
| *Enclosures:* | "After ethical review – guidance for researchers" |
| *Copy to:* | *Ms E Dhouieb*<br>*Mrs Karen Haggart, Research and Development Department* |

University Hospitals Division

NHS Lothian

**Queen's Medical Research Institute**
**47 Little France Crescent, Edinburgh, EH16 4TJ**

FM/NM/approval

13 November 2014

**Research & Development**
**Room E1.12**
**Tel: 0131 242 3330**

**Email:**
**R&DOffice@nhslothian.scot.nhs.uk**

**Director: Professor David E Newby**

Dr Don Urquhart
NHS Lothian
Paediatric Consultant
Royal Hospital for Sick Children
Sciennes Road
Edinburgh
EH9 1LF

Dear Dr Urquhart

**Lothian R&D Project No:** 2014/0371

**Title of Research:** Does the undertaking of a session of physiotherapy (PEP and Autogenic Drainage) prior to exercise improve exercise performance?

**REC No:** 14/NW/1270

**Participant Information Sheet:**
Parent version 2 dated October 2014
Children version 2 dated October 2014

**Consent Form:**
Paediatric Assent version 2 dated October 2014
Paediatric Patient Version 2 dated October 2014
Parent/Carer version 2 dated October 2014

**Protocol:**
Research Proposal

I am pleased to inform you that this study has been approved for NHS Lothian and you may proceed with your research, subject to the conditions below. This letter provides Site Specific approval for NHS Lothian.

Please note that the NHS Lothian R&D Office must be informed if there are any changes to the study such as amendments to the protocol, recruitment, funding, personnel or resource input required of NHS Lothian.

Substantial amendments to the protocol will require approval from the ethics committee which approved your study and the MHRA where applicable.

Please inform this office when recruitment has closed and when the study has been completed.

I wish you every success with your study.

Yours sincerely

Fiona McArdle.

Ms Fiona McArdle
Deputy R&D Director

STA034

# ANEXO B - REGISTRO NO PROSPERO

**PROSPERO**
**International prospective register of systematic reviews**

NHS National Institute for Health Research

## Systematic review

### 1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Exercise capacity and mortality in cystic fibrosis: systematic review and meta-analysis

### 2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

### 3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

30/08/2016

### 4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

25/11/2016

### 5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review.

The review has not yet started: No

| Review stage | Started | Completed |
|---|---|---|
| Preliminary searches | Yes | No |
| Piloting of the study selection process | No | No |
| Formal screening of search results against eligibility criteria | No | No |
| Data extraction | No | No |
| Risk of bias (quality) assessment | No | No |
| Data analysis | No | No |

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

## 6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Miss Vendrusculo

## Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

## 7. * Named contact email.

Give the electronic mail address of the named contact.

fevendrusculo@hotmail.com

## 8. Named contact address

Give the full postal address for the named contact.

Rua Tomaz Gonzaga, 20/904. Boa vista, Porto Alegre, Brasil. CEP 9130480

## 9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+555192076664

## 10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Pontifícia Universidade Católica do Rio Grande do sul

## Organisation web address:

http://www.pucrs.br/

## 11. Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Miss Fernanda Maria Vendrusculo. PUCRS
Dr João Paulo Heinzmann Filho. PUCRS
Dr Márcio Vinícius Fagundes Donadio. PUCRS
Miss Juliana Severo da Silva. PUCRS
Dr Margarita Perez Ruiz. Universidad Europea de Madrid

## 12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

There is no funding involved.

## 13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

## 14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

## 15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

Are maximal oxygen consumption levels associated with mortality rates in individuals with cystic fibrosis?

## 16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

The following databases will be searched: PubMed, EMBASE, Lilacs and Scopus. A manual search will be performed in the reference lists.
Keywords: Exercise Test OR Exercise Testing OR Cardiopulmonary Exercise Test OR Cardiopulmonary Exercise Testing OR Peak Oxygen Uptake OR Maximal Oxygen Consumption OR Exercise Tolerance OR Exercise Capacity AND Mortality OR Survival AND Cystic Fibrosis
No filters were used.
Search dates: From August 2016 to October 2016.

## 17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

## 18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Cystic fibrosis is the most common autosomal recessively inherited disease in Caucasian populations. This multisystemic disease is characterized by impaired mucus clearance leading to chronic infective and inflammatory lung disease, nutritional malabsorption due to pancreatic insufficiency, and excessively salty sweat. These patients show a markedly reduced exercise tolerance which is a predictor of survival.

## 19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion criteria: individuals with a clinical diagnosis of cystic fibrosis (genetic or sweat test) able to perform a maximal exercise test.
Exclusion criteria: individuals with cystic fibrosis during exacerbation or hospitalization periods.

## 20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

The exposure to be studied is the maximal exercise test evaluating oxygen uptake, regardless of protocol or equipment used, in individuals with cystic fibrosis.

## 21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

No comparators or control apply to this case.

## 22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

We will include cohorts to evaluate mortality rates after oxygen uptake measures.

## 23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

## 24. * Primary outcome(s).

Give the pre-specified primary (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Mortality rates.

## Timing and effect measures

## 25. * Secondary outcome(s).

List the pre-specified secondary (additional) outcomes of the review, with a similar level of detail to that required for primary outcomes. Where there are no secondary outcomes please state 'None' or 'Not applicable' as appropriate to the review

None.

## Timing and effect measures

## 26. Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

From each of the selected studies, the following data will be extracted when described: title, first author's name, year of research, city of research, year of publication, language of publication, type of study, age, sample size, type of equipment, type of protocol, follow-up duration, maximal oxygen consumption, breathing reserve, ventilatory equivalent for oxygen and ventilatory equivalent for carbon dioxide.
Information collected will be saved in Microsoft EXCEL data sheet for later analysis. Three researchers will be involved and possible discrepancies will be resolved by consensus.

## 27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how

this will influence the planned synthesis.

The Newcastle–Ottawa Scale (NOS) will be used to evaluate study quality. The NOS assigns a maximum of nine points to studies of highest quality according to the following three quality parameters: selection (four points), comparability (two points), and outcome (three points). Each included study will be assessed by three reviewers and possible discrepancies will be resolved by consensus.

## 28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

The relationship between maximal oxygen consumption and mortality will be summarized by considering oxygen consumption as a continuous variable (by 1 mL/kg/min oxygen consumption increase). To compensate for potential between study heterogeneity, we will calculate a pooled HR using DerSimonian–Laird random-effect model. Forest plots with point size reflecting study weight will be used to graphically represent the results of the meta-analysis. The I-squared and Q test will be used to quantify the degree of heterogeneity among studies. Two different software packages for statistics will be used, REVMAN 5.2 and/or Comprehensive Meta Analyses.
Where meta-analysis is not possible or appropriate, studies will be synthesized as a narrative.

## 29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

None planned.

## 30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

### Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
Yes

Methodology
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Qualitative synthesis
No

Review of reviews
No

Service delivery
No

Systematic review
Yes

Other
No

## Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

## 31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

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## 32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Brazil

## 33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

## 34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

## 35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

The review will be published as a scientific article.

## Do you intend to publish the review on completion?

Yes

## 36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Cystic Fibrosis
Exercise Test
Mortality

## 37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

## 38. * Current review status.

Review status should be updated when the review is completed and when it is published.
Please provide anticipated publication date

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**International prospective register of systematic reviews**

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Review_Ongoing

## 39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

## 40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.


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