Mucociliary Clearance and the Saccharin Test: Reference Values for a Young Adult Portuguese Population

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Abstract

Introduction: Mucociliary clearance (MCC) is a major defense mechanism of the respiratory airways. We aimed to determine Nasal Mucociliary Clearance Time (NMCT) reference values for the Portuguese population using the Saccharin Test (ST).

Methods: Observational, cross-sectional, descriptive study, including 97 participants, aged 18 to 35 years old, 68 females and 29 males, 19 smokers and 78 non-smokers. NMCT, gender and smoking habits were analyzed.

Results: NMCT mean value was 25.4 ± 12.1 minutes (range 9 to 68 minutes). Mucociliary hypomotility threshold for this population was 38.6 minutes ("slow movers"). No significant differences were observed between genders or according to smoking habits.

Conclusion: This study validates the use of the ST in the Portuguese population. The diagnostic utility of this test for clinical practice and scientific investigation as an inexpensive and easy method is undisputable. The interpretation of ST using these reference values may contribute for further research on disorders linked involving MCC impairment.

Keywords: Mucociliary Clearance; Saccharin Test; Portuguese population; Reference Values

Abbreviations

BMI – Body Mass Index

CBF – Ciliary Beat Frequency

CF – Cystic Fibrosis

COPD – Chronic Obstructive Pulmonary Disease

ENT – Ear, Nose and Throat

MCC – Mucociliary Clearance

NMCT – Nasal Mucociliary Clearance Time

NO – Nitric Oxide

PCD – Primary Ciliary Dyskinesia

SPSS – Statistical Package for Social Sciences

ST – Saccharin Test

Introduction

The upper respiratory tract, comprising the nose and paranasal sinuses, and the lower airways share a similar mucosal lining.(1) During normal breathing, the extensive epithelium of the respiratory tract between the nose and the alveoli is exposed to a large burden of inorganic and organic particulate and gaseous material with potentially nefarious effects.(2,3) The ability of respiratory mucosal surfaces to effectively eliminate foreign particles and pathogens depends, not only on the volume and composition of the airway mucus and periciliary fluid and its viscoelastic properties, but also on ciliary activity and regular regeneration of mucus/periciliary airway fluids. (3,4,5) The mucociliary clearance (MCC) is an innate first-line defense mechanism of the upper and lower airways against noxious stimuli in the environment.(1,4-6) Cilia in the respiratory tract beat in a synchronized manner to propel both mucus and trapped substances to the pharynx. (7) MCC disruption, whether acquired or inherited, predisposes to acute and chronic infections of the nose, paranasal sinuses and lower airways.(8)

Numerous ultrastructural defects or anomalies of the classical “9+2” structure of respiratory epithelial cilia have been associated with ciliary dyskinesia (9) and consequent mucociliary dysfunction. (2) Several disorders, such as primary ciliary dyskinesia (PCD), cystic fibrosis (CF), asthma, chronic obstructive pulmonary disease (COPD)(10) and bronchiectasis are known to affect MCC, mostly negatively, with different underlying mechanism from one pathology to another.(11) PCD refers to a group of heterogenous genetic pathologies featuring permanent ubiquitous ultrastructural and/or functional abnormalities of mobile cilia (12), associated with respiratory distress in term neonates, chronic otosinopulmonary disease, male infertility, and organ laterality defects in ~50% of cases.(13–15)

The ‘‘single airway’’ model is an important concept in chronic respiratory disease.(3) That assumption supports the fact that, in many cases, disrupted mucociliary may contribute to the pathophysiology of both sinonasal and lung diseases.(4) A wide variety of approaches to ameliorate impaired clearance were developed.(7)

The standardization of techniques to measure MCC in humans and the studies performed in patients with airway diseases linked to an impaired MCC, namely PCD, have yielded considerable knowledge about the role of ciliary activity in MCC, as well as the identification of many mutations affecting the cilia. (10) Early diagnosis of a disrupted MCC, although challenging, is an essential prognosis factor in PCD. (12) Many PCD patients, however, remain undiagnosed or misdiagnosed until bronchiectasis develop as a consequence of chronic airway infections, well into adulthood.(16) To date, only limited studies have addressed management of PCD (13) and the

impact of an early diagnosis on the patient's outcome and quality of life is yet to be investigated. (15)

New diagnostic tests are increasingly being introduced along with refinement of pre-existing ones (15). However, no single "gold standard" reference test is defined to diagnose PCD. The range of methods used to study this process explains the discrepancies found in published results for MCC. (17) Besides, most techniques are time consuming and expensive (and therefore not widely available), namely nasal nitric oxide (NO) measurement, isotopic MCC, ciliary cell culture, high-speed video-microscopy analysis, transmission electron microscopy, genotyping and immunofluorescence of the ciliary proteins.(13,17)

The evidence of a good correlation between tracheobronchia and nasal mucociliary clearance allows the use of inexpensive and easy tools to assess and measure the Nasal Mucociliary Clearance Time (NMCT), as the saccharin clearance test.(6,8) The Saccharin Test (ST) is considered the most useful test to assess mucociliary activity in the clinical practice and scientific investigation.(18) It is performed by depositing a particle of saccharin on the nasal mucosa with no need for sophisticated equipment, and causing the participant no discomfort. (8) Once the particle dissolves in the mucus, it becomes a moving spot of fluid (19), due to mucociliary activity, travelling through the entire nasal cavity, finally reaching the oropharynx. The time when the participants have the first taste of sweetness is recorded and it will represent their NMCT, which will provide information about the mucociliary function.(19) It represents the upper and lower respiratory tract mucociliary transport velocity.(4) Even though such tests depend on a participative factor, a prolonged transit time is considered to be highly indicative of impaired mucociliary clearance (4,8), making it an sensible and reliable initial diagnostic test in case of suspicion of PCD.(18)

Several studies associated several factors with an impairment of ciliary function, including aging, gender, external aggressions as environmental pollutants, smoking and respiratory infections (5,8,11) Notwithstanding, none has a sufficiently broad and accurately stratified sample to allow firm conclusions to be drawn. In addition, they focus on the comparison of a healthy control group of individuals and those afflicted by disrupted MCC associated disorders, namely PCD and CF, not stratifying by those impairing factors.(8)

Enhanced knowledge of the MCC would help us diagnose mucociliary diseases. But the interpretation of an observed value stresses that reference values are provided.(20) Concerning the Portuguese population, it is crucial to develop a study with a sample size of healthy individuals large enough to define the limits of normal NMCT using the ST.

The aim of this study is to determine reference values of NMCT for a healthy young adult Portuguese population using the ST. Furthermore, we try to associate NMCT and putative co-factors such as gender and smoking habits.

Population and Methods

Study Design:

Observational, cross-sectional, descriptive study.

Participants:

Ninety-seven consecutive participants with a mean age of 23.0 ± 2.6 years old were included. All participants were tested with the ST and completed a questionnaire (Annex 1) on health behaviours, including smoking habits, recent respiratory infections, comorbidities, contact with environmental pollutants and allergies, frequency of respiratory and ear, nose and throat (ENT) symptoms and disorders, chronic medication, surgical history, history of nasal trauma or face and neck radiotherapy and family history of ciliopathies.

The exclusion criteria included age below 18 years and above 35 years, respiratory or nasal symptoms within the preceding 2 weeks, active infections, diagnosis of primary ciliary dyskinesia, bronchiectasis, cystic fibrosis, valvular heart diseases, and bleeding disorders (9), major septal deviation, history of nasal trauma (4), history of radiotherapy of the face and neck, and history of substance abuse.

The study included smokers and non-smokers. We considered non-smokers all the individuals who never had smoking habits, according to the questionnaire answers, and those who have not smoked for 5 or more years.

The study protocol was approved by the Faculty of Medicine, University of Coimbra ethics committee (Annex 2) and was in accordance with the Declaration of Helsinki. All volunteers provided written informed consent before participating. (Annex 3)

Data Collection:

The method used to measure the NMCT was the ST, described by Anderson et al., (19) and modified by Rutland and Cole in 1980. (5) Under direct vision, a 1mm sodium saccharin particle was placed on the medial surface of the inferior nasal turbinate.(21)

The participants were studied in an environment free of dust and breeze, in the same posture and instructed not to sniff, sneeze, cough, smoke, eat or drink during the test. (6,8) Participants were asked to maintain normal ventilation. The ST result was the time interval between placing the saccharin and the moment the participant first perceived reported the sweet taste. It was recorded to the nearest minute and the test was considered completed. (8)

Data Analysis:

The statistical analysis of the questionnaire information was performed using Statistical Package for Social Sciences program (SPSS Inc, Chicago, Illinois, USA) version 24. The analysis included descriptive statistics (mean, standard deviation, minimum and maximum values) and percentile distributions for NMCT, gender, age, weight and smoking habits. Frequency tables and histograms were drawn separately in relation to each variable mentioned above. Mann-Whitney U test was used to investigate possible associations between the NMCT and gender, and smoking habits, asthma and weight.

Results

The study included 97 participants (70.1% women and 29.9% men), aged 18 to 35 years (mean 23.0 ± 2.6 years). Descriptive statistics for age, weight and BMI (Body Mass Index) are presented in Table 1 and descriptive statistics for NMCT according to gender and in participants with smoking habits, asthma, allergic rhinitis, rhinosinusitis and taking chronic medication is shown in Table 2. The distribution of age is shown in Figure 1. Among the participants, the non-smokers account for 80.4% and 19.6% are active smokers.

Table 1. Descriptive Statistics for Age, Weight and BMI

	Mean±SD	Median	Minimum	Maximum
Age	23±2.6 (years)	23	18	35
Weight	62.6±11.1 (Kg)	60	42	99
BMI	22.1±2.6 (Kg/m²)	21.6	17.3	30.9

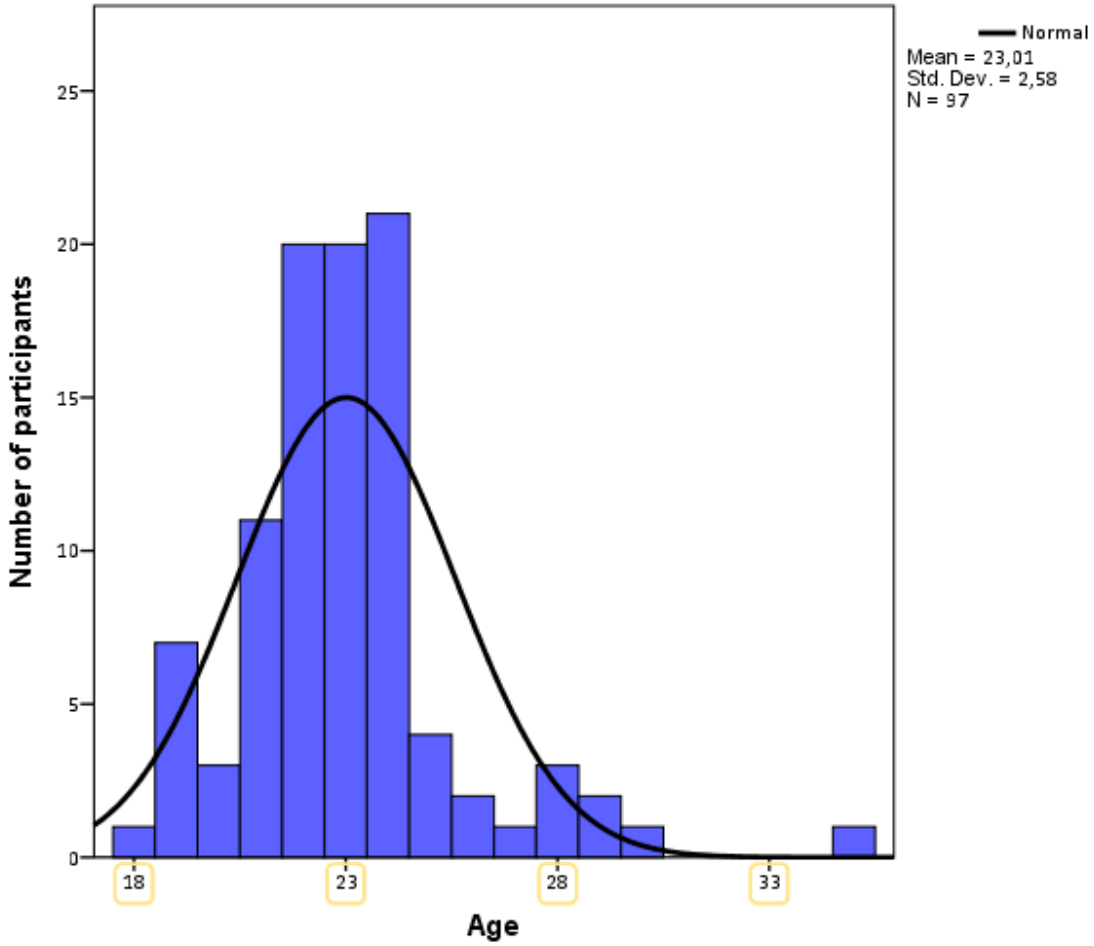
BMI – Body Mass Index; Kg – Kilograms; Kg/m² – Kilogram per square meter; SD – Standard Deviation

Table 2. Descriptive Statistics for NMCT according to gender and in participants with smoking habits, asthma, allergic rhinitis, rhinosinusitis and taking chronic medication

		NMCT			
	N	Mean±SD	Median	Minimum	Maximum
Gender	68 FEMALES	25.5±12.4	23	9	67
	29 MALES	25.2±12.5	23	10	68
Smokers/	19	24±14	24	10	68
Non-smokers	78	24.6±11.6	23	9	67
Asthma/	9	25.2±8.5	26	14	41
Non-asthma	88	25.4±12.4	23	9	68
Allergic rhinitis/	27	25±11.5	23	10	61
Non-allergic rhinitis	70	25.5±12.4	23	9	68
Rhinosinusitis/	11	25.9±14.8	22	13	61
Non-rhinosinusitis	86	25.3±11.8	23	9	68
Chronic medication/	41	24±10.7	23	12	67
No chronic medication	56	26.3±13	24	9	68

NMCT – Nasal Mucociliary Clearance Time; N – Number; SD – Standard Deviation

Figure 1. Age distribution of the participants

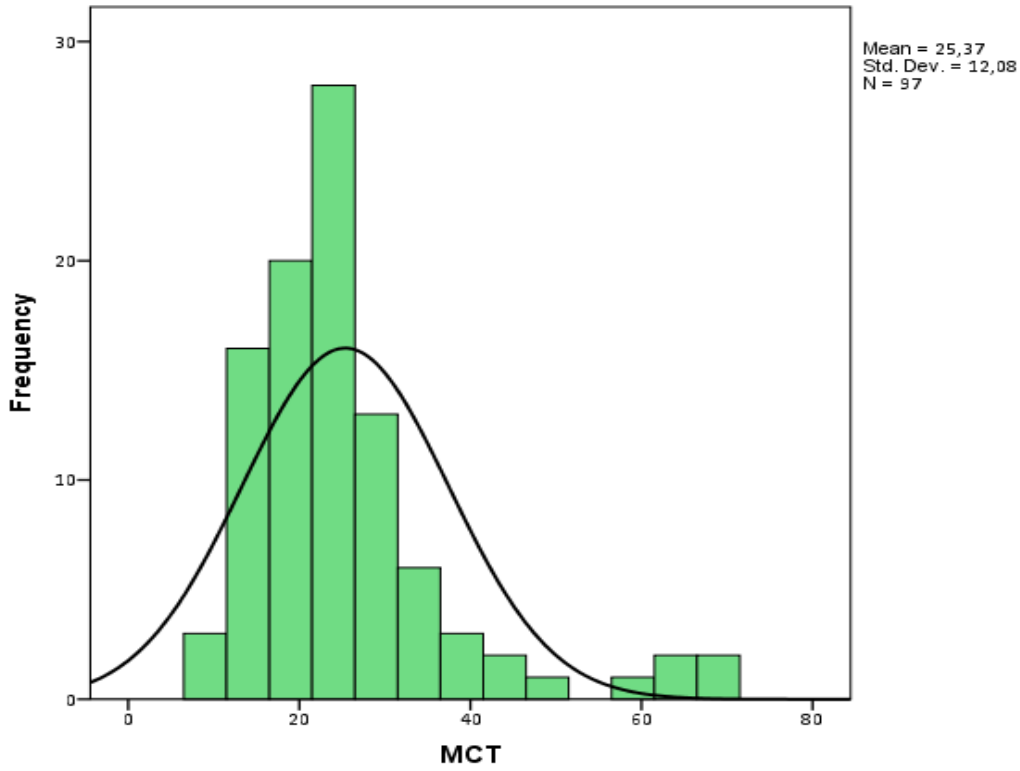


Subtitle: Std. Dev. - Standard Deviation; N - Number

Descriptive Statistics for NMCT

The average NMCT was 25.4 ± 12.1 (range 9-68 minutes)]. The 10th percentile of NMCT was 13 minutes and the 90th was 38.6 minutes (Table 3 and Figure 2).

Figure 2. NMCT values distribution of the participants



The histogram shows the distribution of nasal mucociliary transport time values in the sample. MCT – Mucociliary Clearance Time; Std. Dev – Standard Deviation; N – Number.

Table 3. Descriptive Statistics of NMCT for the population

		MCT
N	Valid	97
Mean		25,37
Median		23
Std. Deviation		12,08
Minimum		9
Maximum		68
Percentiles	25	19
	50	23
	75	29

Table 3. MCT – Mucociliary Clearance Time

NMCT and Gender

The NMCT in males was 25.2± 11.4 minutes and in females was 25.5±12.4 minutes ((p=n.s.).

NMCT and Smoking Habits

The NMCT in smokers was 24.0± 11.6 minutes and in non-smokers 24.6±14.0 minutes (p=n.s.).

NMCT and Weight

Overweighted individuals represent 13.4% of our study population. The NMCT in overweight (BMI>25 kg/m²) participants was 22.8±10.6 minutes. In the normal weight population the NMCT was 25.7±12.3 minutes (p=n.s.)

NMCT and Asthma

Asthmatics consist of 9.3% of our study population. The NMCT in asthmatic participants was 25.2±8.5 minutes and in non-asthmatic participants was 25.4±12.4 minutes (p=n.s.).

NMCT and Allergic Rhinitis

Participants with allergic rhinitis account for 27.8% of the population. The mean value of NMCT in participants with allergic rhinitis is 25±11.5 minutes and in participants who do not report to have allergic rhinitis is 25.5±12.4 minutes (p=N.S.).

“Slow Movers”

The participants with NMCT values higher than 38.6 minutes (>p90), were considered “slow movers”. Table 4 summarizes the results we obtained by analyzing the characteristics of the so called “slow movers”.

Table 4. Analysis of the “slow movers” characteristics

	Normal	Slow movers (>p90)	Difference (p-value)
Gender	61♀(69.3%); 27♂(30.7%)	7♀(77.8%); 2♂(22.2%)	NS
Asthma	8 (9.1%)	1 (11.1%)	NS
Allergic Rhinitis	24 (27.3%)	3 (33.3%)	NS
Overweight	12 (13.6%)	1 (11.1%)	NS
Rhinosinusitis	9 (10.2%)	2 (22.2%)	NS

P90 – 90th percentile; NS – Not Significant

Discussion

The NMCT mean value found for our population was 25.4±12.1 minutes. The 10th percentile of NMCT was 13 minutes and the 90th percentile was 38.6 minutes, which defines the upper normality in our population. Plaza Valía P et al (8) found a mean value of NMCT for the Spanish population between 10 and 29 years of 15±6.2 minutes and between 30 and 49 years of 15.7±7 minutes. These values are smaller probably because they were more restrictive about their exclusion criteria, not including chronic nasal or respiratory disease, acute respiratory tract disease in the 6 weeks prior to the test, altered taste, smokers and those receiving pharmacotherapy that might influence mucociliary clearance. Dülger et al (21) found a mean value of NMCT for a non-smoking Turkish population (between 18 and 65 years) of 9 minutes. Once again, they excluded all the subjects who presented asthma, COPD as well as nasal allergies. Their population was also smaller than ours, consisting of 35 individuals. Besides, they have a much older population and the role of aging in MCC in not thoroughly clear yet. Ho et al (9) studied the NMCT in a non-smoking Chinese population ranged from 11 to 90 years. They divided the population according to age groups. In the group of participants whose ages ranged from 21 to 30 years, they found a mean value of NMCT of 9.8±5.1 minutes. However, the group included only 26 individuals, which may explain the discrepancies.

Analysis of MCC provides grounds for suspected diagnosis of certain diseases as PCD, CF, asthma, COPD (10) and bronchiectasis and help assess courses of treatment and prognosis.(8,11) Besides, through the innumerous techniques available, the role of ciliary activity in MCC is becoming more and more clear and many mutations affecting the cilia are now known. (10)There is a broad sample of techniques that enable the study of MCC, namely NO measurement, isotopic MCC, ciliary cell culture, high-speed video-microscopy analysis, transmission electron microscopy, genotyping and immunofluorescence of the ciliary proteins.(13,17)

The ST is overall the most advantageous test as the easiest, most affordable and innoquous *in vivo* technique that allows the measurement of NMCT.(21,22)

Regardless of the standardization applied when performing the test NMCT presents oscillations amongst healthy individuals. “Slow movers” represent healthy individuals with a prolonged NMCT. In our population, 9,3% of the participants corresponded to the so called “slow movers”, which was considered for those who presented a NMCT value higher than our 90th percentile (38.6 minutes). Having a prolonged NMCT does not necessarily mean that the patient is afflicted by a ciliary dyskinesia. However, it may render those individuals more susceptible to respiratory infections as inhaled particles, some of them noxious, are slowly removed from the respiratory tract. This may induce a secondary ciliary dyskinesia as a consequence of acute and chronic inflammatory changes in the airways. We are not able to draw a pattern for our study population concerning the “slow movers” sample. However, 4 of them reported frequent respiratory

symptoms, such as nasal obstruction, mucoid or mucopurulent nasal discharge, sneezing and dry cough associated with a history of rhinosinusitis. Moreover, 1 of the slow movers had asthma, 3 had allergic rhinitis, 2 were smokers with a smoking load of five and four cigarretes per day, and 1 was overweight (Body Mass Index (BMI)>25 kg/m²).

Age

Our sample was composed by young Portuguese university students with (18 to 35 years old). We chose a young population to avoid the physiological effect that aging has on MCC, that includes impaired MCC and increased frequency of ciliary ultrastructural anomalies (9). On the other hand, the elderly become more predisposed to respiratory infections due to decreased elasticity of extracellular matrix, loss in respiratory muscle power and decline in humoral immunity (9). As said, respiratory infection may lead to secondary ciliary dyskinesia development and consequently to MCC progressive deterioration. However, it has the side effect of preventing us from drawing any conclusions about the influence of aging on ciliary function. In fact, just a few studies on the topic have been published and most of them are not representative of the general healthy population as they include respiratory disease patients, and therefore were inconclusive for the general population. (9) The results obtained by Yager et al.(23) indicate that ciliary beat frequency (CBF) decreases with increasing age. But probably due to small sample size, data was not considered significant.(11)

Gender

Numerous studies focusing on how the pulmonary parameters are influenced by factors as age, sleep, exercise and the environment, led also to the conclusion that the male and female respiratory system have dimorphic differences determined by the sex hormones (24). However, the following investigations over this particular association raised contradictory observations. If on the one hand Svartengren et al (**25**) and Armengot et al (**26**) observed that the NMC was faster in females when compared to men, on the other no correlation between NMCT and gender was reported by others. (8, 24, **27)**

The confluence of multiple other factors, such as the contact with pollutants, history of allergies, respiratory disease, chronic medication, past ENT surgery, overweight, may mitigate the gender influence on the NMCT. The effect of gender on NMCT would, in this scenario, be less pronounced when compared to more significant, co-existing variables.

Smoking Habits

In our population, in spite of having a slightly prolonged NMCT, smokers did not show a significant difference when compared to the non-smokers, possibly due to the small number of smoking participants included. Therefore, in disagreement with other studies in the literature (21,**28,29,30**) smoking did not associate with prolonged MCC time. It is known that smoking impairs the viscoelastic properties of mucus through ciliostatic effects and that smokers are prone to functional and inflammatory changes in nasal and lower airways in correlation with their smoking history.(21) Several studies showed that the mucociliary transport was more severely degraded in older and longer smoking history (**28**). The lack of similar evidence in our study can be explained by the fact that our population was young and also because that none of the smokers included in this study was a long-term tobacco smoker. (22)

Asthma and Allergic Rhinitis

Bronchial asthma is characterized by inflammatory changes of the bronchial mucosa accompanied by an increase in tracheobronchial secretions (31). Therefore, one might speculate that there is a mucociliary transport deterioration in progress. In our population, the participants with asthma represent 9.3%. Asthmatics did not show a significant difference when compared to the non-asthmatics, possibly due to the small number of smoking participants included.

In our population, 27.8% of the participants reported to have allergic rhinitis. In a stable phase of allergic rhinitis, there is, also, a significant delay of the mean values (31). In our population, it was found no significant difference between participants with allergic rhinitis and those without it.

Weight

We also analysed a possible association between prolonged NMCT with overweight. For that reason we calculated the BMI for the participants. Individuals are considered to be overweight if their BMI>25 kg/m², which in our sample, was noted in 13.4% of the participants. No significant difference was ascertained while comparing the NMCT values in the overweight participants and the ones with a BMI within the limits of normal. In fact, the percentage of overweight participants is narrow, which may explain this finding.

Limitations

Although the sample size was considered adequate for the Portuguese population, it is difficult to draw conclusions for co-factors groups. Because we wanted a representative population, we included individuals with history of allergic rhinitis, asthma, rhinosinusitis, diabetes mellitus and hypothyroidism, prone to affect MCC. However, significant abnormal values were not found in said participants.

In addition, the method chosen to assess NMCT, despite being the easiest and most accessible, might not be as sensitive and specific as the most complex ones. (8)

Further Research

To allow comparisons between studies, evidence based international standards for conduct of diagnostic tests and reporting of results is needed.(17) However, supplementary investigation is mandatory before assessing the usefulness of each therapy in the broad array of different diseases. In addition, many questions concerning the structural interaction between cilia and the mucus layer remain unanswered.(10) Furthermore, regarding PCD, the specific genes defects underlying conditions are yet to be determined. Further knowledge within this field might enhance the development of therapies aimed at correcting chronic defects of mucociliary clearance.(7) In spite of the striking progress in the understanding of PCD over the last years, the collaborative efforts of many scientists from different fields will be required.(10,15)

Further research aiming to elucidate the mechanism(s) underlying the slowing of ciliary beat and development of ciliary ultrastructural defects with aging (9) is hoped to be translated into more available and effective clinical care, thereby slowing the progressive decline in pulmonary function.(8,16)

Therefore, it is clear that studies with wider and larger samples are required to pursue further investigation on the subject. Moreover, regarding the Portuguese population, there is no comparative study on healthy individuals *versus* those afflicted by disorders known to affect NMCT, namely CF or PCD.

Conclusion

NMCT consists of a reliable index of the respiratory system mucociliary function that is part of the tracheobronchial tree defense mechanism against nefarious external aggressions. It can be measured by the ST, which is the most useful test in clinical practice, because it is inexpensive, widely available and easy to carry out.

In our population, the NMCT mean value is 25.4 minutes with a standard deviation of 12.1 minutes. NMCT was not prolonged in smokers and male individuals. This study may be the foundation for further research in the Portuguese population, or worldwide, providing the reference grounds for comparative studies between healthy individuals and ones afflicted by disorders known to affect MCC, as PCD and CF. Besides, it can enhance management algorithms destined to assess and treat these conditions in a more uniformed and efficient way.

Conflicts of Interest

The authors declare that there are not potential conflicts.

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ESTUDO – VALIDAÇÃO DO TESTE DA MOTILIDADE CILIAR POR SACARINA PARA A POPULAÇÃO PORTUGUESA NORMAL

Data de preenchimento do questionário:___/___/____(dia/mês/ano) Local_____

- Idade:_____anos
- Sexo:_____
- Qual a sua profissão/ocupação? _____
- Peso e altura:_____
- Está grávida?_____
- Fuma?_____
- É ex-fumador?_____
- Se sim, há quantos anos deixou de fumar?_____
- Se sim, durante quantos anos fumou?_____
- Quantos cigarros fuma/fumava por dia (em média)?_____
- As pessoas com quem vive fumam ao pé de si?_____
- Tem contacto frequente com poeiras?_____

Especifique:_____

- Tem contacto frequente com fontes poluentes?_____

Especifique:_____

- Tem contacto frequente com aerossóis?_____

Especifique:_____

- Tem contacto com animais?_____

Especifique:_____

- Tem frequentemente algum dos sintomas seguintes?

Tosse?_____

Se sim, seca? Com expetoração? Durante o dia? Durante a noite?
_____

Expetoração?_____

Falta de ar?_____

Pieira?_____

Obstrução nasal?_____

Se obstrução nasal, é **dos dois "lados"**?_____

Se obstrução nasal apenas de um lado, é **sempre do mesmo lado**?_____

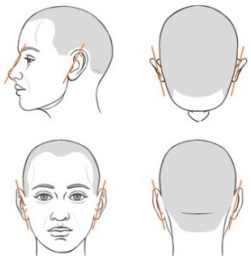
Corrimento nasal?_____

Se corrimento nasal, de que **cor** é o corrimento?_____

Prurido nasal?_____

Crises de espirros?_____

Dores de cabeça?_____



Se dores de cabeça, **em que zona** da cabeça?(assinale na imagem)

Alterações do olfato?_____

Alterações do paladar?_____

- Teve alguma infeção aguda do trato respiratório nas 6 semanas anteriores à realização deste teste?_____
- Há quanto tempo?_____
- Alguma vez lhe foi diagnosticado por um médico:

1.Rinite alérgica____

2.Rinossinusite____

3.Asma____

4.Asma na infância____

5.DPOC ou "bronquite"____

6.Fibrose quística____

7.Outra doença respiratória – atual ou passada_____

8.Otites de repetição____

9.Deficiências da imunidade____

- Está a fazer algum tratamento por via nasal?_____

  Se sim, qual?_____

- Está a fazer tratamento para uma doença respiratória crónica (incluindo nariz, sinusite, brônquios, pulmões)?_____

Se sim, qual?_____

- É atualmente seguido em ORL?_____

Porquê?_____

- No passado, já foi seguido em ORL?_____

Porquê?_____

- Alguma vez foi submetido a cirurgia ORL – nariz, boca, faringe, etc?_____
  Se sim, quando?_____

  Se sim, porquê?_____

- Tem história de traumatismos nasais?_____
- Tem história de radioterapia da face/cabeça?_____
- Outras doenças que tenha – **especifique:_____**
- Faz alguma medicação crónica/habitual?_____

Se sim, qual?_____

- Nasceu de parto prematuro?_____
- Com quantas semanas de gestação?_____
- História familiar de:

1.Discinésia ciliar primária_____

2.Fibrose quística_____

3.Asma_____

4.“Bronquite”_____

5.Outras…_____

Obrigada pela sua colaboração.

Annex 2 – Ethics Committee Approval

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FMUC FACULDADE DE MEDICINA
UNIVERSIDADE DE COIMBRA

COMISSÃO DE ÉTICA DA FMUC

Of. Refª **135-CE-2018**
Data 26 / 11 /**2018**

C/C aos Exmos. Senhores
Investigadores e co-investigadores

Exmo. Senhor
Prof. Doutor Duarte Nuno Vieira
Director da Faculdade de Medicina de
Universidade de Coimbra

Assunto: Pedido de parecer à Comissão de Ética - Projeto de Investigação autónomo (refª CE-132/2018).

Investigador(a) Principal: João Carlos Ribeiro

Co-Investigador(es): Vitória Silva de Melo, Frederico Regateiro e Isa Elói

Título do Projeto: ***"Validação do teste da motilidade ciliar por sacarina para a população portuguesa normal".***

A Comissão de Ética da Faculdade de Medicina, após análise do projeto de investigação supra identificado, decidiu emitir o parecer que a seguir se transcreve:

"Parecer favorável não se excluindo, no entanto, a necessidade de submissão à Comissão de Ética, caso exista, da(s) Instituição(ões) onde será realizado o Projeto".

Queira aceitar os meus melhores cumprimentos.

O Presidente,

Prof. Doutor João Manuel Pedroso de Lima

HC

SERVIÇOS TÉCNICOS DE APOIO À GESTÃO - STAG • COMISSÃO DE ÉTICA
Pólo das Ciências da Saúde • Unidade Central
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Tel.: +351 239 857 708 (Ext. 542708) | Fax: +351 239 823 236
E-mail: comissaoetica@fmed.uc.pt | www.fmed.uc.pt

FORMULÁRIO DE INFORMAÇÃOE CONSENTIMENTO INFORMADO

TÍTULO DO PROJECTO DE INVESTIGAÇÃO: Validação do teste da motilidade ciliar por sacarina para a população portuguesa normal

PROTOCOLO Nº

PROMOTOR (Entidade ou pessoa(s) que propõe(m) o estudo)	Vitória Silva de Melo, Faculdade de Medicina da Universidade de Coimbra
INVESTIGADOR COORDENADOR	João Carlos Ribeiro
CENTRO DE ESTUDO	Faculdade de Medicina da Universidade de Coimbra
INVESTIGADOR PRINCIPAL	João Carlos Ribeiro
MORADA	Praceta Mota Pinto, 10º piso, ORL
CONTACTO TELEFÓNICO	916442199

NOME DO DOENTE
(LETRA DE IMPRENSA) _____

É convidado/a a participar voluntariamente neste estudo por pertencer a população portuguesa jovem (idade entre 18 e 35 anos), saudável e não fumadora.

Este procedimento é chamado consentimento informado e descreve a finalidade do estudo, os procedimentos, os possíveis benefícios e riscos. A sua participação poderá contribuir para obtenção de valores padrão sobre o tempo de clearance mucociliar nasal na população portuguesa e melhorar o conhecimento sobre distúrbios de motilidade nasociliar.

O Investigador ou outro membro da sua equipa irá esclarecer qualquer dúvida que tenha sobre o termo de consentimento e também alguma palavra ou informação que possa não entender.

Depois de compreender o estudo e de não ter qualquer dúvida acerca do mesmo, deverá tomar a decisão de participar ou não. Caso queira participar, ser-lhe-á solicitado que assine e date este formulário. Caso não queira participar, não haverá qualquer penalização nos cuidados que irá receber.

1. INFORMAÇÃO GERAL E OBJETIVOS DO ESTUDO

Estudo realizado no âmbito de Tese de Mestrado, por uma aluna do 6º ano do Mestrado Integrado em Medicina da Faculdade de Medicina da Universidade de Coimbra (FMUC) e sob a orientação do Prof. Dr. João Carlos Ribeiro, Otorrinolaringologista do Centro Hospitalar e Universitário de Coimbra (CHUC) e do Prof. Dr. Frederico Regateiro, Imunoalergologista do Centro Hospitalar e Universitário de Coimbra, ambos Professores Auxiliares Convidados da Faculdade de Medicina da Universidade de Coimbra.

Este estudo foi aprovado pela Comissão de Ética da Faculdade de Medicina da Universidade de Coimbra (FMUC) de modo a garantir a proteção dos direitos, segurança e bem estar de todos os participantes, constituindo prova pública da mesma.

A finalidade desta investigação é aferir valores de referência do tempo de *clearance* mucociliar nasal (TCM) para a população portuguesa normal, não fumadora, jovem (entre os 18 e os 35 anos de idade), recorrendo ao teste da sacarina, tendo em linha de conta o género e a idade dos indivíduos selecionados. Para o efeito, selecionar-se-ão algumas turmas práticas dos diferentes ciclos de estudos do Mestrado Integrado em Medicina da Faculdade de Medicina da Universidade de Coimbra. Submeter-se-ão, previamente, todos os participantes a um questionário direcionado para avaliação de variáveis relacionadas com o objeto do Estudo.

Trata-se de estudo observacional descritivo, isto é, de acordo com as variáveis em estudo (TCM, idade e género) e após introdução de partícula de sacarina no corneto inferior de uma das cavidades nasais do indivíduo, registar-se-á o tempo (em minutos) que o mesmo demora a sentir o sabor doce. Analisar-se-ão os resultados obtidos como um todo, calculando média, mediana e limites superior e inferior do normal. Através destes e de cálculo de percentis, traçar-se-ão os valores de referência pretendidos, permitindo, ainda, deteção de valores anormalmente baixos de TCM.

2. PROCEDIMENTOS E CONDUÇÃO DO ESTUDO

2.1. Procedimentos

O Estudo será executado com recurso a questionários com questões fechadas e orientadas para avaliação de variáveis que possam interferir diretamente com a motilidade nasociliar e, por conseguinte, dar origem a desvios significativos do valor padrão de tempo de *clearance* mucociliar nasal. Depois do preenchimento deste questionário, será realizado o teste da sacarina para medição do tempo de *clearance*.

2.2. Duração

O preenchimento do questionário e a realização do teste da sacarina tem a duração de alguns minutos (sempre inferior a uma hora).

2.3. Tratamento de dados/ Randomização

Será, posteriormente, realizada a análise estatística dos dados provenientes da resposta ao questionário, assim como dos valores de tempo de *clearance* mucociliar nasal resultantes do teste da sacarina a fim de obter valores padrão para a população portuguesa jovem, saudável e não fumadora. Para além disso, desvios significativos serão discutidos à luz das respostas ao questionário para ponderar realização de estudos comparativos subsequentes e poderão fornecer novas informações que complementem o conhecimento acerca do diagnóstico de discinesia ciliar.

3. RISCOS E POTENCIAIS INCONVENIENTES PARA O DOENTE

Sem riscos. O preenchimento do questionário, bem como a realização do teste da sacarina levam alguns minutos.

POTENCIAIS BENEFÍCIOS

Este estudo tem a vantagem de estudar a diabetes gestacional e permitir um melhor conhecimento do seu impacto psicológico. Além disso, a informação que será recolhida irá contribuir para alertar os profissionais de saúde para a importância de rastrear, acompanhar e tratar a ansiedade, stress ou depressão associadas ao diagnóstico de diabetes gestacional, melhorando a qualidade de vida materna.

4. NOVAS INFORMAÇÕES

Ser-lhe-á dado conhecimento de qualquer nova informação que possa ser relevante para a sua condição ou que possa influenciar a sua vontade de continuar a participar no estudo.

5. TRATAMENTOS ALTERNATIVOS

Não se aplica neste estudo.

6. SEGURANÇA

Será garantida a confidencialidade e anonimato dos participantes. Não será submetido a nenhuma intervenção prejudicial, apenas será solicitada resposta a um questionário e realização do teste da sacarina que é indolor e sem compromisso da sua segurança. Nenhum outro procedimento será solicitado posteriormente.

7. PARTICIPAÇÃO/ ABANDONO VOLUNTÁRIO

É inteiramente livre de aceitar ou recusar participar neste estudo. Pode retirar o seu consentimento em qualquer altura sem qualquer consequência para si, sem precisar de explicar as razões, sem qualquer penalidade ou perda de benefícios e sem comprometer a sua relação com o Investigador que lhe propõe a participação neste estudo. Ser-lhe-á pedido para informar o Investigador se decidir retirar o seu consentimento.

O Investigador do estudo pode decidir terminar a sua participação neste estudo se entender que não é do melhor interesse para a sua saúde continuar nele. A sua participação pode ser também terminada se não estiver a seguir o plano do estudo, por decisão administrativa ou decisão da Comissão de Ética. O médico do estudo notificá-lo-á se surgir uma dessas circunstâncias, e falará consigo a respeito da mesma.

8. CONFIDENCIALIDADE

Os seus registos manter-se-ão confidenciais e anonimizados de acordo com os regulamentos e leis aplicáveis. Se os resultados deste estudo forem publicados a sua identidade manter-se-á confidencial.

Ao assinar este Consentimento Informado autoriza este acesso condicionado e restrito.

Pode ainda em qualquer altura exercer o seu direito de acesso à informação. Tem também o direito de se opor à transmissão de dados que sejam cobertos pela confidencialidade profissional.

Os registos que o identificarem e o formulário de consentimento informado que assinar serão verificados para fins do estudo pelo promotor e/ou por representantes do promotor, e para fins regulamentares pelo promotor e/ou pelos representantes do promotor e agências reguladoras noutros países. A Comissão de Ética responsável pelo estudo pode solicitar o acesso aos seus registos para assegurar-se que o estudo está a ser realizado de acordo com o protocolo. Não pode ser garantida confidencialidade absoluta devido à necessidade de passar a informação a essas partes.

Confidencialidade e tratamento de dados pessoais

Os dados pessoais dos participantes no estudo, incluindo a informação de saúde recolhida como parte do estudo serão utilizados para condução do estudo, designadamente para fins de investigação científica relacionados com a patologia em estudo.

Ao dar o seu consentimento à participação no estudo, a informação a si respeitante, designadamente a informação clínica, será utilizada da seguinte forma:

1. O promotor, os investigadores e as outras pessoas envolvidas no estudo recolherão e utilizarão os seus dados pessoais para as finalidades acima descritas.
2. Os dados do estudo, associados às suas iniciais ou a outro código que não o (a) identifica diretamente (e não ao seu nome) serão comunicados pelos investigadores e outras pessoas envolvidas no estudo ao promotor do estudo, que os utilizará para as finalidades acima descritas.
3. Os dados do estudo, associados às suas iniciais ou a outro código que não permita identificá-lo(a) diretamente, poderão ser comunicados a autoridades de saúde nacionais e internacionais.

4. A sua identidade não será revelada em quaisquer relatórios ou publicações resultantes deste estudo.
5. Todas as pessoas ou entidades com acesso aos seus dados pessoais estão sujeitas a sigilo profissional.
6. Ao dar o seu consentimento para participar no estudo autoriza o promotor ou empresas de monitorização de estudos/estudos especificamente contratadas para o efeito e seus colaboradores e/ou autoridades de saúde, a aceder aos dados constantes do seu preenchimento do questionário, para assegurar o rigor dos dados que lhe dizem respeito e para garantir que o estudo se encontra a ser desenvolvido corretamente e que os dados obtidos são fiáveis.
7. Nos termos da lei, tem o direito de, através de um dos médicos envolvidos no estudo/estudo, solicitar o acesso aos dados que lhe digam respeito, bem como de solicitar a retificação dos seus dados de identificação.
8. Tem ainda o direito de retirar este consentimento em qualquer altura através da notificação ao investigador, o que implicará que deixe de participar no estudo/estudo. No entanto, os dados recolhidos ou criados como parte do estudo até essa altura que não o(a) identifiquem poderão continuar a ser utilizados para o propósito de estudo/estudo, nomeadamente para manter a integridade científica do estudo, e a sua informação médica não será removida do arquivo do estudo.
9. Se não der o seu consentimento, assinando este documento, não poderá participar neste estudo. Se o consentimento agora prestado não for retirado e até que o faça, este será válido e manter-se-á em vigor.

10. COMPENSAÇÃO

Este estudo é da iniciativa dos investigadores e, por isso, se solicita a sua participação sem uma compensação financeira para a sua execução, tal como também acontece com os investigadores e o Centro de Estudo. A participação será voluntária e não haverá prejuízos assistenciais ou outros caso não queira participar ou abandonar o estudo a qualquer momento.

11. CONTACTOS

Se tiver perguntas relativas aos seus direitos como participante deste estudo, deve contactar:

Presidente da Comissão de Ética da FMUC,
Azinhaga de Santa Comba, Celas – 3000-548 Coimbra
Telefone: 239 857 708
e-mail: comissaoetica@fmed.uc.pt

Se tiver questões sobre este estudo deve contactar:
(Vitória Silva de Melo, Quinta do Pinhô, lote 23, 3500-020 - VISEU,
contacto:965424988, e-mail: vitoriasmelo94@hotmail.com)

NÃO ASSINE ESTE FORMULÁRIO DE CONSENTIMENTO INFORMADO A MENOS QUE TENHA TIDO A OPORTUNIDADE DE PERGUNTAR E TER RECEBIDO RESPOSTAS SATISFATÓRIAS A TODAS AS SUAS PERGUNTAS.

CONSENTIMENTO INFORMADO

De acordo com a Declaração de Helsínquia da Associação Médica Mundial e suas atualizações:

1. Declaro ter lido este formulário e aceito de forma voluntária participar neste estudo.
2. Fui devidamente informado(a) da natureza, objetivos, riscos, duração provável do estudo, bem como do que é esperado da minha parte.
3. Tive a oportunidade de fazer perguntas sobre o estudo e percebi as respostas e as informações que me foram dadas.

   A qualquer momento posso fazer mais perguntas ao médico responsável do estudo. Durante o estudo e sempre que quiser, posso receber informação sobre o seu desenvolvimento. O médico responsável dará toda a informação importante que surja durante o estudo que possa alterar a minha vontade de continuar a participar.
4. Aceito que utilizem a informação relativa ao preenchimento do questionário no estrito respeito do segredo médico e anonimato. Os meus dados serão mantidos estritamente

confidenciais. Autorizo a consulta dos meus dados apenas por pessoas designadas pelo promotor e por representantes das autoridades reguladoras.

5. Aceito seguir todas as instruções que me forem dadas durante o estudo.
6. Autorizo o uso dos resultados do estudo para fins exclusivamente científicos e, em particular, aceito que esses resultados sejam divulgados às autoridades sanitárias competentes.
7. Aceito que os dados gerados durante o estudo sejam informatizados pelo promotor ou outrem por si designado.

   Eu posso exercer o meu direito de retificação e/ ou oposição.
8. Tenho conhecimento que sou livre de desistir do estudo a qualquer momento, sem ter de justificar a minha decisão e sem comprometer a qualidade dos meus cuidados médicos. Eu tenho conhecimento que o médico tem o direito de decidir sobre a minha saída prematura do estudo e que me informará da causa da mesma.
9. Fui informado que o estudo pode ser interrompido por decisão do investigador, do promotor ou das autoridades reguladoras.

Nome do Participante _____

Assinatura : _____ ***Data:*** _____/_____/_____

Nome de Testemunha / Representante Legal: _____

Assinatura: _____ ***Data:*** _____/_____/_____

Confirmo que expliquei ao participante acima mencionado a natureza, os objetivos e os potenciais riscos do Estudo acima mencionado.

Nome do Investigador: _____

Assinatura: _____ ***Data:*** _____/_____/_____