Insignificant Difference of Mucociliary Clearance in Middle-Aged and Elderly Patients

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Abstract: Aging has always been assumed to have negative effect on mucociliary clearance, but studies are in fact limited. Nasal mucociliary clearance (NMC) is a mirror image of bronchial clearance. This study aims to evaluate the difference of NMC, measured by saccharin test, in middle-aged (40-59 years) and elderly (>60 years) patients which are the most common age groups in our clinical settings. It is a cross-sectional study involving middle-aged (n=18) and elderly (n=12) patients. Smokers and patients having respiratory symptoms were excluded. Data of age, sex, history of diabetes, malignancy, forced vital capacity (FVC), forced expiratory volume in one second (FEV1)/FVC ratio, and saccharin transit time were taken. There is no significant difference in baseline characteristics, except FVC. Saccharin transit time (STT) was not statistically different between middle-aged and elderly patients (11.9+5.8 vs 12.8+6.3 mins, p=0.696). A patient with Bechet's disease had abnormally prolonged STT (26.13 mins). With this patient excluded, history of malignancy was the only factor associated with STT (p=0.026) after linear regression. In fact, only subjects with history of chemotherapy had prolonged STT. The findings suggest that there are other factors to be aware of while evaluating mucociliary clearance, such as history of chemotherapy and autoimmune disease.

1 INTRODUCTION

Sputum retention is one of the most common problem in pulmonary rehabilitation. Sputum retention is a sign of inadequate mucociliary clearance. This problem can lead to pneumonia which could be life-threatening for the patient (Marini, 2016). This is why it is clinically important to recognize factors affecting mucociliary clearance.

Generally, there are two important factors affecting mucociliary clearance, mucus consistency and ciliary movement (Bonde, 2002). Increased mucus consistency is usually caused by lung or airway inflammation, but factors affecting ciliary movement are rather unexplored (Rubin, 2004). Smoking is a widely-known factor affecting ciliary movement (Baby, 2014), but other factors are still debatable. Malignancy and diabetes are also said to have deteriorating effect on mucociliary clearance, but data supporting it are scarce (Gupta, 2006; Gurung, 2017). On the contrary, aerobic exercise was found to have immediate effect in improving mucociliary clearance (Ramos, 2015).

Besides the modifiable factors mentioned above, there are other factors that might affect mucociliary clearance. Aging is one of the unmodifiable factors theoretically assumed to have negative effect on mucociliary clearance. Little is known regarding the mechanism of how aging affects mucociliary clearance. A study (Bailey, 2014) suggests that it might have something to do with protein kinase C epsilon (PKCε) of which activity in lung is increased with aging in mice, but it has not been explored in humans. The author speculated that increased PKCε activity can increase abnormal phosphorylation of axonemal proteins, especially outer dynein arm protein which has an important role in ciliary movement. Based on the assumption, geriatric patients have become a special concern in pulmonary rehabilitation because they are predicted to have slower mucociliary clearance. However, if we look at the clinical evidence, not a lot of studies have actually discussed this matter.

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Some studies found that mucociliary clearance is indeed slower in older patients, but with a cut-off of 40-45 years old (Ho, 2001; Paul 2013). This finding does not have significant relevance in our clinical settings because almost all patients are above 40 years old, both in outpatient and inpatient settings. Therefore, this study aims to evaluate the difference of nasal mucociliary clearance (NMC), measured by simple saccharin test, in middle-aged (40-59 years) and elderly (>60 years) patients which are the most common age groups in our clinical settings.

Nasal mucociliary clearance (NMC) is a mirror image of bronchial clearance. Ideally, NMC is measured by using radioisotope, so the physician will know both the time of NMC and the length of airway tract. However, the measurement is expensive and not feasible to be performed in daily clinical settings (Yadav, 2005). Therefore, in this study we used saccharin test as a simple test to measure NMC. Saccharin transit time (STT) was expected to be longer in elderly patients.

2 METHODS

This is a cross-sectional study held in August 2019 involving middle-aged (n=18) and elderly (n=12) patients in our outpatient clinic in Department of Medical Rehabilitation, Cipto Mangunkusumo National General Hospital, Indonesia. Consecutive sampling was performed to recruit subjects. The inclusion criteria were as follows: (1) patient aged 40-59 (middle-aged group) or ≥60 years old (elderly group), (2) no history of smoking, (3) no respiratory symptoms in the last 2 weeks (runny nose, cough, sore throat, dyspnea). Subjects were excluded if saccharin transit time (STT) exceeds 60 minutes because there is a possibility that the patient has impaired taste perception if this happens. Drop out criteria is when subjects could not follow our instruction or refuse to continue the study during the measurements. Wide criteria were .purposely used
and subjects with comorbidities were not excluded so that the subjects in this study reflect real patients in our clinical settings.

In this study, independent variable is age group and dependent variable is STT with history of diabetes and malignancy as confounding factors. We also measured forced vital capacity (FVC) and forced expiratory volume in one second (FEV1)/FVC ratio to see if there were any patients with obstructive or restrictive lung disease. After receiving explanation regarding the study and signing informed consent, subjects in this study were asked about some data including age, sex, history of diabetes, malignancy, and any other diseases. Medical records were also checked to match patient's information. Spirometry was then conducted according to the protocol of American Thoracic Society (ATS).

Lastly, the saccharin test was performed. Saccharin particle ($\pm$1 mm^3) was placed about 1 mm posterior to the anterior border of inferior turbinate. Subject was asked to flex his head about 10^o and breathe normally, but not allowed to sniff, sneeze, cough, eat, or drink during the test. Subject was then asked to swallow every 60 seconds. The time taken by the subject to perceive the sweet taste was noted as saccharin transit time (STT). All data were collected and linear regression test was performed to prove whether age group is an independent factor of NMC with history of diabetes and malignancy as possible confounding factors. The conduction of this study had been previously approved by the Ethical Committee of Faculty of Medicine, Universitas Indonesia.

3 RESULTS

Among our subjects, 83.3% (n=25) were female, 16.7% (n=5) had history of diabetes, and 13.3% (n=4) had history of malignancy. Mean age of middle-aged and elderly group were 53.44$\pm$4.85 and 69.92$\pm$7.37 years respectively. Besides FVC which was found lower in elderly patients (p=0.03), there is no significant difference in gender, history of diabetes, malignancy, and FEV1/FVC ratio between two groups (Table 1). Saccharin transit time (STT) was not found significantly different (11.9$\pm$5.8 vs 12.8$\pm$6.3 mins, p=0.696) between middle-aged and elderly patients using bivariate analysis.

Table 1: Baseline Characteristics of Patient

*Fissher test

**Unpaired t-test

Variable	Middle-aged (n=18)	Elderly (n=12)	p
Gender			0.364*
- Male	2	3	
- Female	16	9	
Diabetes			1.000*
- Yes	3	2	
- No	15	9	
Malignancy			0.268*
- Yes	4	0	
- No	14	11	
FVC (L)	1.99±0.53	1.56±0.41	0.03**
FEV1/FVC (%)	89.0±7.8	89.2±10.4	0.949**

Table 2: Linear Regression of Factors Affecting STT.

	β	*Standard Error*	95% CI	p-value
Model 1				
Constant	10.139	1.413	7.230-13.049	
Age group	1.123	2.061	-3.123-5.368	0.591
History of diabetes	1.889	2.524	-3.309-7.086	0.461
History of malignancy	6.653	2.910	0.660-12.646	0.031
Model 2				
Constant	10.623	1.084	8.395-12.851	
History of diabetes	1.954	2.486	-3.157-7.065	0.439
History of malignancy	6.154	2.724	0.555-11.752	0.032
Model 3				
Constant	10.936	1.001	8.882-12.989	
History of malignancy	6.329	2.695	0.779-11.860	0.026

The analysis was then continued using linear regression to find the association of age group, history of diabetes, and history of malignancy towards STT. At first, none of these factors had association with STT. The closest one was history of malignancy (p=0.069), but not statistically significant. However, it was noticed that a patient with Bechet's disease had an abnormally prolonged STT (26.13 minutes). When this patient was excluded and linear regression was reperformed, we found that history of malignancy had a significant association with STT (p=0.026). When we analyzed further the patients who had history of malignancy (n=4), only two of them had prolonged STT (>20 minutes). Further history taking revealed that these two patients had history of chemotherapy, as compared to the other two who only underwent surgery for their cancer.

4 DISCUSSION

The reason why it is important to know the pathophysiology of impaired mucociliary clearance is that the choice of therapy might differ. For example, hypertonic saline nebulization is given to dilute thick mucus, while salbutamol nebulization (mucokinetic) is used to improve ciliary beat frequency (Elkins, 2011). If mucociliary clearance is indeed slower in geriatric patients, mucokinetic agents might have a role in reducing sputum retention in elderly patients. However, if it is not the case, the management should be based on the condition of the patient rather than the age itself.

In this study we found that mucociliary clearance is not significantly different in elderly and middle-aged patients before and after linear regression test. Possible confounding factors such as respiratory symptoms, history of smoking, diabetes, and malignancy have been ruled out or included in multivariate analysis. This finding is different from previous studies (Ho, 2001; Paul 2013) which found significantly different STT in healthy patients below and above 40-45 years old.

A study (Ho, 2001) especially proved that aging has a significant correlation with mucociliary clearance ($r=0.64$, $p<0.001$). Similar result, but with weaker correlation was found in another study ($r=0.324$, $p<0.001$) (Valia, 2008). Based on this data we suspect that the effect of aging might be subtle so that significant difference will only be seen in two groups of patients with wide age gaps. This deduction is supported by a study (Oliveira-maul, 2013) ($n=252$) which found that age has a significant, but small effect in increasing the risk of having prolonged STT with the odds ratio of 1.02 (95% CI 1.003-1.033, $p=0.015$). It has to be noted though that this study used a cutoff of 12 mins to determine patients with prolonged STT, while other references used a cutoff of 20 mins (Deborah, 2014) and even 36 mins (Valia, 2008) for prolonged STT. This major difference could significantly alter the calculation of OR. Further study should be conducted to determine the normal value of STT in Indonesian patients.

The subjects in this study were recruited with wide criteria, only excluding patients with respiratory symptoms and smoking history. The purpose of this method was to recruit subjects whose characteristics were as close as possible as real patients in our clinical settings, as it is rare to find patients without comorbidities. Diabetes and malignancy were analyzed as confounding factors because few studies have found their relation to mucociliary clearance (Gupta, 2006; Gurung, 2017).

From the baseline characteristics, the subjects in this study had relatively normal lung function. Elderly patients were found to have lower FVC, but it is a normal finding since lung volume has been widely known to decrease along with age (Stanojevic, 2008). Other characteristics were not statistically different between groups. In this study we also found significantly different STT in patients who had history of chemotherapy. This finding is in accordance with the result of a study (Gupta, 2006) which found that STT in patients with chemoradiation is significantly longer than patients with radiotherapy alone (31.68 ± 1.32 vs 28.64 ± 1.88, $p=0.0047$). On the other hand, diabetes did not appear to have significant effect on STT. This finding is different from the result of a study (Gurung, 2017) which found that STT was longer in DM type 2 patients (16.51 ± 2.44 vs 9.96 ± 2.24 mins, $p<0.001$). However, this might be caused by the small number of patients with history of diabetes in our study, as it is not the main factor that would be evaluated.

One patient with Bechet's disease also had abnormally prolonged STT. A study (Ozbay, 2016) ($n=60$) found that NMC was significantly longer in subjects with Bechet's disease (13.4 ± 3.3 vs 9.0 ± 1.8 mins, $p<0.001$). Furthermore, this study also found a strongly positive correlation between NMC and the duration of Bechet's disease ($p<0.001$, $r=0.882$). This finding suggests that there might be other autoimmune diseases which could also impair mucociliary clearance.

Regarding the applicability of saccharin test itself, even though it is a very simple test feasible to be performed in daily clinical settings, we found that some patients complained of nose discomfort during the test. Some patients also firmly refused to be included in this study because they considered the test to be invasive, although it had already been explained thoroughly that the test is not harmful. The relatively long duration of the test also seemed to be a problem for the patient. Therefore, we suggest that unless sputum retention is the main problem and it is unclear whether the cause is impaired mucociliary clearance or other factors (e.g. inadequate cough), it is not recommended to perform saccharin test as a routine examination for mucociliary clearance. Physician should focus on history taking instead regarding possible factors affecting mucociliary clearance.

The limitations of this study are small sample size, no random sampling, and no blinding. The

subjects of this study were patients visiting our outpatient clinic for various reasons. If the patient agreed to be recruited in this study, they would have to spend more time after the consultation, therefore, it is somehow difficult to find subjects. The only confounding factors analyzed in this study were history of malignancy and diabetes, however, there might be other confounding factors that we still have not evaluated, such as structural abnormalities of the nose, which could not be thoroughly examined in this study due to limited resources. Nevertheless, we purposely did not set strict inclusion criteria so that the patients recruited in this study closely would reflect real patients in our clinical settings.

In conclusion, no significant STT difference was found between middle-aged and elderly patients in this study. Instead, history of chemotherapy and Bechet's disease were found to affect STT.

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