Particularities and Clinical Applicability of Saccharin Transit Time Test

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Abstract

Introduction The importance of mucociliary clearance (MCC) for the respiratory system homeostasis is clear. Therefore, evaluating this defense mechanism is fundamental in scientific research and in the clinical practice of pulmonology and of associated areas. However, MCC evaluation has not been so usual due to the complexity of methods that use radiolabeled particles. Nevertheless, as an interesting alternative, there is the saccharin transit time (STT) test. This method is reproducible, simple to perform, noninvasive, does not demand high costs, and has been widely used in studies of nasal MCC. Although the STT test is widely used, there is still lack of a detailed description of its realization.

Objective The present literature review aims to provide basic information related to the STT test and to present the findings of the previous studies that used this method, discussing variations in its execution, possible influences on the obtained results and limitations of the method, as well as to relate our experience with the use of STT in researches.

Data Synthesis There are several factors that can alter the results obtained from STT tests, which would raise difficulties with proper interpretation and with the discussion of the results among different studies.

Conclusions Saccharin transit time is a widely used method for the evaluation of nasal MCC, and therefore, the standardization related to the previous and concurrent to test orientations, and also its execution, become essential to improve its accuracy, and allow comparisons among different studies.

Keywords
► mucociliary clearance
► airway management
► mucus

Introduction

Mucociliary clearance (MCC) is an important respiratory system defense mechanism, since the human airway surfaces are constantly exposed to various particles and microorganisms present in the ambient air.1–4 Its effectiveness depends on the quantity and on the quality of the mucus, on the structure, the synchrony and frequency of ciliary beating, and on the interaction between these components.5–7

Mucus is a barrier that entraps inhaled microorganisms in its mobile layer, and the cilia are the propellants, which act through coordinated beating. The interaction of these components is responsible for the removal of microorganisms from the upper and lower airways toward the oropharynx, where they are swallowed or expectorated, which avoids them from entering into direct contact with epithelial cells or reaching the alveoli.8–12

Since MCC is fundamental in lung defense, several methods have been described to evaluate it: some analyze separately the mechanical condition of the cilia (video microscopy, photometric method)3,13 or of the mucus (contact angle measurements, displacement of mucus by simulated cough
and frog palate, and others evaluate the interaction between the mucus and the cilia (clearance of inhaled radiolabeled particles, saccharin transit time [STT] test). However, the feasibility of this methodology is limited due to equipment and cost requirements, besides presenting some risks inherent to the exposure to radiation. The STT test was compared with the radioactively tagged particles method in the study of Puchelle et al. The authors found a good correlation between the methods for absolute results obtained in one measurement day and for changes between two measurement days. The STT is a useful method for scientific research, widely used in nasal MCC studies, as it is a reproducible, simple to perform, and noninvasive technique, besides being low-cost, making it an interesting alternative to other methods that require relatively complex, invasive, and expensive equipment, and demand greater technical aptitude from the examiners.

Given the importance of MCC in lung defense, its evaluation is necessary as a contribution to the clinical and functional screening of the individual. Thus, as the STT test is a practical and effective evaluation method, the present literature review aims to provide basic information related to the STT test and to present the findings of previous studies that used this method, discussing variations in its execution, possible influences on the obtained results, and limitations of the method, besides relating our experience with the use of STT tests in research.

Review of a Particular Subject

The Method

The STT test was first described in 1974 by Andersen et al. It consisted of the insertion of a sodium saccharin particle on the upper surface of the inferior nasal turbinate of the subject. Next, the subjects were asked to swallow once every minute and to notify the examiner when they noticed a sweet taste. The distance from the start of the mucociliary membrane to the far wall of the pharynx was measured with a probe, and from this measurement the mean velocity was determined.

This method was modified by Rutland et al. who, prior to the evaluation, kept the subjects for at least an hour in an environmental temperature between 21 and 24°C, with relative humidity between 30 and 50%, and requested that the subjects blow their nose gently to remove any excess secretion. The saccharin particle was 0.5 mm in diameter and was placed in the inferior turbinate of one nasal cavity at least 7 mm behind the anterior end of the turbinate to avoid the area of mucosa where the cilia beat in an anterior direction. Another difference in this study lies in the fact that the subjects were not instructed to swallow regularly and that the distance between the particle placement and the nasopharynx was not measured. Therefore, only the time was obtained, but not the velocity of clearance.

Since then, the STT technique has been used in several studies involving MCC, either to characterize different populations or to evaluate the effect of interventions such as the use of anesthetics, analgesics, barbiturates, tranquilizers, and antidepressants; not smoking for at least 12 hours; and not performing vigorous physical activities during the 12 hours preceding the test.

Table 1 Methodological variations in saccharin transit time test in the literature

| Variations in STT execution | Seated, with the neck extended, or maintained in the horizontal plane |
|-----------------------------|------------------------------------------------------------------|
| Positioning of the volunteer | Supine position        | 28,35,36 flexed, or maintained in the horizontal plane  |
| Nostril choice              | Non-obstructed nostril  | 21,39                                                   |
| Instrument for the placement of saccharin | Plastic straw | 28                                                        |
|                             | Cotton               | 40–42                                                    |
|                             | Surgical pincers     | 11,32,43                                                 |
| Location of saccharin placement | Inferior nasal turbinate | 11,30,32                                                 |
|                             | 1 cm behind the inferior nasal turbinate | 5,20,24,29,40  |
|                             | Below the middle nasal turbinate | 12                           |
|                             | 2 cm inside the nostril | 2,28,34,39                                               |
| Utilized amount of saccharin | 1 particle of 0.5 mm, 1 mm, or 1.5 mm in diameter | 5 mg, 2.46, 25 mg, 22 or 250 micrograms (µg)            |
| Guidance during the test    | Not to cough, sneeze, blow, or scratch the nose | 2,43,47–50                                                   |
|                             | Breathe normally or through the mouth | 2,39                                                   |
|                             | Swallow normally | 12, 21, 22, every 30 seconds, 40, 52, 53, every 60 seconds, or regularly |

Abbreviations: STT, saccharine transit time.
This guidance is given due to the fact that MCC changes in different conditions, such as age, level of physical activity in daily life, smoking, and use of drugs and other substances, such as caffeine and alcohol. Therefore, it is essential to consider these aspects and control them, when possible, before evaluating this lung defense mechanism.

The normality values for STT have been published for the Spanish population. Plaza Valía et al\textsuperscript{21} found a median of 16 minutes, and 50\% of their results ranged from 12 to 20 minutes (interquartile interval). While these values can shed light on what can be expected as a result of this test, they might not be representative of other populations, with different ethnicities and living in different environmental conditions. To the best of our knowledge, there are no studies presenting reference values for other populations.

**Factors that Influence MCC**

**Age**
The respiratory system undergoes changes with advancing age, such as loss of lung elasticity, decrease in diaphragm strength, lung function decline, and an increase in the susceptibility to infections.\textsuperscript{22} Studies indicate that age also interferes with MCC.\textsuperscript{11,22} A correlation analysis has shown that MCC becomes progressively slower with advancing age, beginning at the early twenties,\textsuperscript{21,55} probably due to an increasing incidence of defects in the structure of the cilia.\textsuperscript{11}

**Septal Deviations**
Kamani et al\textsuperscript{56} have shown that young adults with septal deviations presented impaired MCC in both nostrils when compared with matched controls. When looking only at the study group, the concave (opposite side) presented even more impaired MCC than the convex side of the deviation. Therefore, this anatomical alteration might be considered an exclusion criterion for cross-sectional studies comparing different cohorts. In the case of longitudinal/interventional studies, it should be considered, a priori, whether this alteration could implicate possible bias in the findings.

**Smoking**
Smoking is an accelerator of lung function decline.\textsuperscript{57} Besides interfering in the respiratory tract, it causes inflammation and mutagenic effects, which can result in the development of malignant neoplasias.\textsuperscript{38–60} Stanley et al\textsuperscript{29} evaluated the MCC of 29 smokers and of 27 nonsmokers and observed higher values of STT in the first group (20.8 ± 9.3 minutes) compared with the second (11.1 ± 3.8 minutes). More recently, Proença et al\textsuperscript{23} also observed a higher STT in smokers after 8 hours of abstinence (16 ± 6 minutes) compared with nonsmokers (10 ± 4 minutes). However, immediately after smoking, smokers presented a similar STT to nonsmokers (11 ± 6 minutes). Most likely, this represents an immediate defense response. Cigarette smoke leads to an increase in the ciliary beat frequency, probably as a consequence of the stimulation of sensory receptors from the epithelium or by the action of inflammatory mediators. Therefore, in addition to the chronic condition of smoking, the influence exerted by acute exposure to cigarette smoke should also be considered before evaluating MCC.

**Physical Activity in Daily Life**
Exercise is, in general, classified as a stressful stimulus,\textsuperscript{61} which can generate acute responses and chronic adaptations.\textsuperscript{62} The first is associated with increased levels of adrenergic mediators,\textsuperscript{63} and these stimulate ciliary beat frequency and, therefore, the MCC.\textsuperscript{64} Proença et al\textsuperscript{28} evaluated the interference of physical activity in daily life in MCC and found that both nonsmokers and even light smokers with a high level of physical activity in daily life presented faster STTs than individuals with a less active or inactive lifestyle.

**Ingested Substances**
Some ingested substances also influence the functioning of MCC. It is known that a brief exposure to alcohol can quickly stimulate the cilia, through the production of nitric oxide and the activation of the kinase dependent protein, whereas prolonged exposure blocks the β-agonist stimulation of kinase protein activity and ciliary beating.\textsuperscript{6,65}

Caffeine consumption is related to autonomic modulation alteration resulting in an increased respiratory rate and bronchodilatation.\textsuperscript{66,67} It is known that MCC is also, at least in part, influenced by the autonomic system.\textsuperscript{54} It has been shown in humans that anticholinergic agents slow clearance,\textsuperscript{58} while cholinergic stimulation\textsuperscript{69} and sympathomimetic agents speed clearance through changes in the ciliary beat frequency.\textsuperscript{68,70}

**Drugs**
Some drugs are employed for the purpose of changing MCC. Begrow et al\textsuperscript{71} observed that the use of standard Myrtol improved MCC in rats. Boek et al\textsuperscript{72} found that MCC improved under the action of salbutamol, while it reduced under sodium chloride, and xylometazoline caused no significant change. Bercin et al\textsuperscript{52} found that the topical nasal medications xylometazoline hydrochloride, fluticasone propionate, and seawater, which are often used without medical prescription, may worsen the MCC of individuals with nasal air flow lower than 500 ml and concluded that these drugs should be used carefully and selectively in patients with nasal complaints.

Other medications, which are not employed to act on MCC, can also cause alterations as a side effect. Houtmeyers et al\textsuperscript{73} conducted a review on the effects of routine clinical use of medications on MCC and concluded that anticholinergics (tertiary ammonium compounds), aspirin, anesthetics, and benzodiazepines (tranquilizers and anxiolytics) depress the MCC, probably by decreasing the ciliary beat frequency and mucus secretion. On the other hand, cholinergic agents, methylxanthines (theophylline, aminophylline, and bamifyline), sodium cromoglycate (anti asthmatic), antibiotics (those orally administered for chronic rhinosinusitis, such as penicillin, cephalosporin and sulfonamide), surfactant, hypertonic saline solution, and water aerosol improve the MCC, apparently by increasing the ciliary beat frequency and mucus secretion, and stimulating fluid secretion in the airway surface.
Circadian Cycle
The circadian cycle refers to rhythmic biological phenomena that occur in all forms of life and are influenced by the solar cycle (dark/light cycle) and by the environment. In humans, it is related to internal regulators of the central nervous system and interferes with the organization and sequencing of metabolic and physiological events, such as body temperature, blood hormone levels, urinary volume, cognitive and motor performance, sleep-wake cycle, and the breathing control system. The upper and lower airways undergo normal cyclic changes; the size of the tracheobronchial tree decreases at night and increases during the day, and the venous erectile tissue of the nasal mucosa demonstrates normal cycles of congestion and constriction that cause alternations in the air flow from one nostril to the other over a period of several hours.

Environmental Conditions
Temperature, relative humidity, and altitude also interfere with MCC, as the nose, besides filtering the inhaled air, also participates in heating and humidification processes, ceding heat and water from its mucosa.

Experimental and clinical studies have shown decreased MCC under environmental temperature changes due to increased mucus secretion by the nasal epithelium in order to facilitate heat exchange, and altered ciliary beat frequency, which is slower at lower temperatures.

Prolonged exposure to low humidity also results in greater dehydration of the nasal mucosa, which causes a change in the rheological properties of the mucus and impairs ciliary movements.

At high altitudes, both conditions, low humidity and temperature, are added together, submitting the respiratory system to a more hostile condition, in which MCC is also impaired.

Studies of the Last Decade
Table 2 presents the studies published over the past 10 years in journals indexed in the PubMed and BIREME databases, written in English and Portuguese, found through the keywords mucociliary clearance and saccharin.

Experience Report
Considering the aspects that interfere in MCC mentioned in the literature, along with the experience acquired after years of use of STT in developed researches, our research group has standardized STT execution as follows:

Previous orientations: Request the patients to abstain from alcoholic substances, foods and beverages containing caffeine, cigarettes, and drugs for at least 12 hours prior to the evaluation and ask them not to perform strenuous physical activity the day before, as these are associated with increased levels of adrenergic mediators that stimulate the ciliary beat frequency, and thus the clearance. If it is necessary to temporarily cease using any medication to perform the STT, the doctor should be consulted.

Evaluation scheduling: Ensure the subjects present clinic stability. If they are apparently healthy, consider a week free from fever, cough, and/or increased mucous production, since these are common symptoms of respiratory tract infections and it is known that this impairs MCC. For patients with lung disease, consider 30 days free from exacerbation.

It is essential that the same period of the day is chosen for the evaluations. It is preferable to schedule them in the morning, since the previous night, in most cases, the subjects sleep, and in these sleeping hours they do not make use of the substances previously described, making it easier to complete the required 12 hours of abstinence. In addition, in the first hours of the morning, subjects are normally exposed to environmental pollution for less time until the time of evaluation.

Preparation of the evaluation environment: The environment should be quiet, free from people flow and previously prepared to a maintained temperature of 25°C and to a relative humidity between 50 and 60%, since variations in these parameters interfere in the MCC.

Required materials: For the preparation of the environment, an air conditioner unit and a humidifier are needed to ensure the required temperature and relative humidity.

For the placement of sodium saccharin, a plastic straw, trimmed to facilitate the deposition of particles inside the nostril, should be used.
Table 2 Studies published in the last decade that employed the saccharin transit time test to evaluate mucociliary clearance

| Reference values                        | Plaza Valli et al51; 2008 Arch Bronconeumol: 1.372 | Sample | Obtained results |
|-----------------------------------------|--------------------------------------------------|--------|------------------|
|                                          | 249 healthy nonsmokers.                           |        | The STT mean was 17.17 ± 8.43 minutes, and the median was 16 (12–20) minutes. There was no difference between the STTs of men and women, but they were positively correlated with age. |

| Special physical conditions             | Deniz et al86; 2014 Am J Rhinol Allergy: 2.302  |
|-----------------------------------------|--------------------------------------------------|
|                                          | 122 patients with mild, moderate and severe obstructive sleep apnea syndrome (OSAS), and 49 healthy subjects as control group |
|                                          | Mild and moderate OSAS had STT similar to that of the control group. Severe OSAS had a slower STT. In all groups, smokers had a slower STT than nonsmokers. |

| Special physical conditions             | Baby et al87; 2014 Lung India                     |
|-----------------------------------------|--------------------------------------------------|
|                                          | 30 adult smokers and 30 adult nonsmokers. Volunteers were healthy and aged between 21 and 40 years old. |
|                                          | STT was prolonged in smokers in comparison to nonsmokers. STT was also increased in subjects smokers for a longer time. |

| Special physical conditions             | Janic et al88; 2013 Oral Surg Oral Med Oral Pathol Oral Radiol: 1.457  |
|-----------------------------------------|--------------------------------------------------|
|                                          | 144 patients who sustained zygomatico-maxillary-orbitalis fracture |
|                                          | STT was impaired on the affected side compared with the control side. However, it did not vary regardless of age, gender, degree of injury, method of treatment, time since fracture, and duration of surgery. |

| Special physical conditions             | Xavier et al89; 2013 Respiration: 2.615           |
|-----------------------------------------|--------------------------------------------------|
|                                          | 24 adult nonsmokers and 75 smokers, divided into mild (n = 15), moderate (n = 34), and heavy (n = 27) smokers. |
|                                          | Heavy and moderate smokers had a greater STT than mild and nonsmokers. STT correlated with the concentration of exCO and cigarettes/day. |

| Special physical conditions             | Altuntas et al50; 2013 J Craniofac Surg: 0.686    |
|-----------------------------------------|--------------------------------------------------|
|                                          | 20 children infected with Crimean Congo hemorrhagic fever and 20 healthy children. |
|                                          | There was no difference between the STTs of infected and healthy children. |

| Special physical conditions             | Proença et al23; 2011 Rev Port Pneumol: 0.562     |
|-----------------------------------------|--------------------------------------------------|
|                                          | 19 active smokers and 19 nonsmokers (control). |
|                                          | Immediately after smoking, the STT of the smokers was similar to that of the control group. After 8 hours of smoking abstinence, the STT of the smokers was slower than that of the control group. |

| Special physical conditions             | Naiboglu et al25; 2010 J Laryngol Otol: 0.681     |
|-----------------------------------------|--------------------------------------------------|
|                                          | 18 adult patients with unilateral or bilateral epiphora and 20 healthy adults. |
|                                          | The STT of the patients was higher than that of healthy individuals. The STT was also higher in the affected nostril compared with the contralateral. |

| Special physical conditions             | Kirtsreesakul et al89; 2009 Laryngoscope: 1.979 |
|-----------------------------------------|--------------------------------------------------|
|                                          | 73 patients with mild intermittent allergic rhinitis (MIAR), moderate-severe intermittent allergic rhinitis (MSIAR), mild persistent allergic rhinitis (MPAR), or moderate-severe persistent allergic rhinitis (MSPAR). |
|                                          | MSPAR had the worst STT, followed by the MSIAR, MPAR, and MIAR groups. The STT correlated with the symptoms. |

| Special physical conditions             | Delehaye et al77; 2009 Auris, Nasus, Larynx: 0.948 |
|-----------------------------------------|--------------------------------------------------|
|                                          | 50 gastroesophageal reflux patients. |
|                                          | 74% of the patients, who had only typical gastroesophageal symptoms, had a higher STT than the other individuals, who also reported extraesophageal symptoms. |

| Special physical conditions             | Yoruk et al83; 2008 Rhinology: 1.72              |
|-----------------------------------------|--------------------------------------------------|
|                                          | 83 young men with silicosis and 84 apparently healthy individuals (control). |
|                                          | The STT of the patients was higher than that of the control subjects. |

| Special physical conditions             | Boatsman et al88; 2006 Otolaryngol Head Neck Surg: 1.625 |
|-----------------------------------------|--------------------------------------------------|
|                                          | 83 young men with silicosis and 84 apparently healthy individuals (control). |
|                                          | The STT of the patients was higher than that of the control subjects. |

| Special physical conditions             | Kamani et al102; 2006 Laryngoscope: 1.979        |
|-----------------------------------------|--------------------------------------------------|
|                                          | 20 patients with nasal septal deviation and 30 patients without septal deviation (control). |
|                                          | In patients with septal deviation, the STT was higher in the opposite nostril to the deviation, and both nostrils of these patients resulted in a higher STT than that of the control group. |

| Special physical conditions             | Nakagawa et al85; 2005 Chest: 5.85               |
|-----------------------------------------|--------------------------------------------------|
|                                          | 16 ICU patients who did not receive mechanical ventilation and had no nasogastric or enteral intubation, and 16 healthy individuals (control). |
|                                          | The STT improved in the recovery period after discharge from the ICU compared with at the time of admission. In healthy subjects, the STT was not changed. |

| Special physical conditions             | Rosen et al83; 2005 Laryngoscope: 1.979         |
|-----------------------------------------|--------------------------------------------------|
|                                          | 25 patients with HIV infection and 29 healthy controls. The patients received either placebo or guaifenesin for 3 weeks. |
|                                          | The STT of the patients was higher than that of the control group. There was no difference between the STT of patients receiving guaifenesin and of those receiving placebo. |

(Continued)
| Category | Author; publication year; journal and its impact factor | Sample | Obtained results |
|----------|-----------------------------------------------------|--------|-----------------|
| Effects of environmental pollution | Priscilla et al\(^a\)\(^b\); 2011 | 30 adult women who used biomass fuel and 30 adult women who used clean fuel (control). | STT was higher in women who used biomass fuel than in the control group. |
| Effects of environmental pollution | Ferreira Ceccato et al\(^a\)\(^b\); 2011 | 45 young sugarcane cutters, of whom 33 were nonsmokers and 12 were light smokers. | The STT was similar between smokers and nonsmokers and decreased at the end of the first day of harvest in both groups. |
| Effects of drug interventions | Oysu et al\(^a\); 2014 | 42 geriatric patients with nasal symptoms received either 2 weeks of isotonic sodium chloride solution (ISCS) followed by 2 weeks of N. sativa oil (NG oil), or the same treatment in the inverse order. | There was no change in mucociliary clearance during any of the treatment periods. |
| Effects of drug interventions | Gelardi et al\(^a\); 2013 | 56 patients with nasal polyposis received intranasal sodium hyaluronate 9 mg twice daily or saline solution for 30 days after endoscopic sinus surgery | Patients receiving sodium hyaluronate had faster STTs at 1 month compared with controls. |
| Effects of drug interventions | Riechelmann et al\(^a\)\(^b\); 2003 | 32 healthy volunteers exposed to 0 (control), 500, 1,000, and 5,000 μg/m3 of calcium carbonate powder for 3 hours. | There was a dose-dependent acceleration in the STT after exposure to dust concentrations and a slowing in the control situation. |
| Effects of drug interventions | Bencova et al\(^a\)\(^b\); 2012 | 43 healthy young men made use of inhaled hypertonic saline solution. | The STT decreased 30 minutes after inhalation of the solution. There was no correlation between STT and nasal nitric oxide. |
| Effects of drug interventions | Bilgi et al\(^a\)\(^b\); 2011 | 50 adult patients were divided into two groups; one received low flow inhalational anesthesia, and the other, high flow. | The STT in the immediate postoperative period in both groups was higher than before the intervention. The increase in STT of the high flow group was higher than in the low flow group. |
| Effects of drug interventions | Isaacs et al\(^a\); 2011 | 27 healthy adults who received nasal irrigation with 50 ml of 1% baby shampoo. | The STT was higher 15 minutes after the administration of the solution when compared with preadministration. |
| Effects of drug interventions | Cingi et al\(^a\)\(^b\); 2010 | 100 adult patients with allergic rhinitis, who used sea water and saline solution spray. | The STT decreased by 12% with the use of sea water and by 4% with saline solution. |
| Effects of drug interventions | Gorpelougou et al\(^a\)\(^b\); 2010 | 40 young patients with acne vulgaris received oral isotretinoin for at least 3 months. | The STT improved in both groups after 12 weeks of surgery, but there was a greater magnitude in the group using dexamethasone. |
| Effects of drug interventions | Foonanant et al\(^a\)\(^b\); 2008 | 110 patients with rhinosinusitis undergoing endoscopic sinus surgery, half of which received dexamethasone in sea water spray, and the other half, saline solution spray. | There was no difference in STTs before and after the use of each type of anesthesia, or among the three anesthetics. |
| Effects of drug interventions | Kesimci et al\(^a\)\(^b\); 2008 | 60 patients undergoing neck or ear surgery, of which 20 received the anesthetic sevoflurane, 20 isoflurane, and 20 desflurane. | There was no difference in STTs before and after the use of each type of anesthesia, or among the three anesthetics. |
| Effects of drug interventions | Unsal et al\(^a\)\(^b\); 2008 | 54 patients with persistent allergic rhinitis who underwent chemosurgery with trichloroacetic acid. | The STT decreased 1 month and 1 year after surgery, when compared with presurgery. |
| Effects of drug interventions | Zhang et al\(^a\)\(^b\); 2008 | 29 healthy subjects received application of oxymetazoline spray. | The STT of the evaluated subjects increased after 30 minutes of the application of 2 sprays of oxymetazoline. |
| Effects of drug interventions | Kim et al\(^a\)\(^b\); 2006 | 20 patients with chronic sinusitis underwent endoscopic sinus surgery, and an antibiotic was administered in one nostril, and in the other, saline solution. | The STT decreased in all evaluations (1, 3, and 6 months) compared with the time immediately after surgery, with no difference between the nostrils. |
### Table 2 (Continued)

| Category | Author; publication year; journal and its impact factor | Sample | Obtained results |
|----------|---------------------------------------------------------|--------|------------------|
| Effects of surgical interventions | Yazici et al106; 2014 Int J Pediatr Otorhinolaryngol: 1.350 | 33 children with adenoid hypertrophy (AH) and 31 with AH and otitis media with effusion (AHOME) undergoing surgical procedure | The STT improved in all patients after surgery. Patients with AHOME had slower pre- and postoperative STTs. Exposure to cigarette smoke and adenoid size had a negative correlation with STT. |
| | Ozkul et al105; 2014 J Craniomac Surg: 1.252 | 23 patients with symptomatic nasoseptal perforations, treated using the mucosal regeneration technique | STT improved at 3 and 6 postoperative months in comparison with the preoperative evaluation |
| | Parida et al106; 2013 Indian J Otolaryngol Head Neck Surg: 0.054 | 45 patients with symptomatic inferior turbinate hypertrophy undergoing diode laser turbinate reduction | There was prolongation of STT after the intervention. However, it returned to preoperative values after 6 months. |
| Effects of surgical interventions | Alobid et al102; 2013 Neurosurgery: 2.532 | 36 patients with pituitary adenoma who underwent the transnasal trans-sphenoidal endoscopic approach, and 14 patients with other benign tumors undergoing the expanded endonasal approach | Both groups showed a higher STT after surgery compared with baseline. In addition, patients submitted to the expanded endonasal approach showed a slower STT than the other group. |
| | Arnaoutakis et al24; 2011 Int J Pediatr Otorhinolaryngol: 1.350 | 10 children with adenoid hypertrophy, chronic adenoiditis, and/or chronic rhinosinusitis undergoing adenoidectomy | After 1 month of surgery, STT decreased compared with at the preoperative time. |
| | Miwa et al107; 2011 Ear Nose Throat J: 0.66 | 25 patients with chronic sinusitis, 10 of whom underwent maxillary sinus counteropening via extranasal approaches; 8 underwent enlargement of the maxillary sinus natural by intranasal endoscopic surgery; 4 received an indwelling maxillary sinus tube, and 3 received a Yami catheter | STT was similar between groups prior to the intervention. The STT decreased in all patients who underwent deobstruction and enlargement. In the group receiving the indwelling tube, the STT increased, and there was a decrease in STT in the catheter group. |
| | Yigit et al108; 2011 Ear Nose Throat J: 0.66 | 50 adult patients undergoing endoscopic dacryocystorhinostomy | Prior to surgery, the STT of both nostrils were similar. One and 3 months after surgery, the operated nostril showed a higher STT when compared with the contralateral nostril. |
| | Okuyuku et al84; 2009 Otolaryngol Head Neck Surg: 1.625 | 22 patients who underwent unilateral endoscopic dacryocystorhinostomy and 22 who underwent an external approach | The procedures resulted in STT increase in the nostril subjected to intervention compared with the contralateral, and there was no difference between the protocols. |
| Effects of surgical interventions | Chen et al109; 2008 Laryngoscope: 1.979 | 160 patients with allergic rhinitis, of whom 80 underwent submucosal resection of the inferior turbinate, and 80 who underwent assisted inferior turbinoplasty. The control group comprised 10 individuals without respiratory complaints. | Prior to the interventions, the rhinitis groups had worse STTs than the control group. One year after the surgery, there was a decrease in STT, which was maintained for up to 3 years in both groups. |
| | Hu et al110; 2008 J Otolaryngol Head Neck Surg: 1.625 | 21 patients with nasopharyngeal carcinoma undergoing endoscopic surgery and 5 control subjects | Control subjects showed lower STTs than the pre- and postoperative values in the case group. However, 1 year after the surgery, there was improvement in the STTs of the patients. |
| | Sakthikumar et al111; 2008 Indian J Otolaryngol Head Neck Surg: 0.054 | 20 patients with chronic sinusitis underwent functional endoscopic sinus surgery. | There was a decrease in STT 6 weeks after the surgery, when compared with the presurgery evaluation. |
| | Chen et al112; 2007 Int J Pediatr Otorhinolaryngol: 1.350 | 120 children with chronic nasal obstruction. 60 underwent submucosal resection (SR), and 60 underwent microdebrider-assisted | Before surgery, the STT of the children with nasal obstruction was higher than that of the control group. |

(Continued)
Table 2 (Continued)

| Category                                      | Author; publication year; journal and its impact factor | Sample                                                                 | Obtained results                                                                 |
|-----------------------------------------------|--------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Effects of surgical interventions             | Deniz et al\textsuperscript{13}; 2006 Otolaryngol Head Neck Surg: 1.625 | 39 patients underwent total laryngectomy, divided by time since the operation (more or less than 2 years) and also with associated conditions such as diabetes mellitus and smoking. The control group consisted of 36 healthy individuals. | The STT of individuals who had < 2 years since the surgery was lower than that of the control group. However, patients with > 2 years since the laryngectomy had higher STTs. Diabetic subjects, as well as smokers, presented higher STTs than healthy subjects, both in the surgery and control groups. |
|                                              | Huang et al\textsuperscript{14}; 2006 Int J Pediatr Otorhinolaryngol: 1.350 | 25 children with edematous and polyoid sinusitis undergoing endoscopic surgery, and 5 controls without sinusitis, undergoing adenoidectomy. | There was improvement in the STT after surgery in children with both types of sinusitis, and the group of edematous sinusitis became similar to the control group. |
|                                              | Unal et al\textsuperscript{15}; 2004 Clin Otolaryngol Allied Sci: 1.869 | 17 patients undergoing dacryocystorhinostomy. | Three months after the surgery, the operated nostril showed a worse STT compared with the side that had no obstruction. |
| Other interventions                           | Bhardwaj et al\textsuperscript{16}; 2013 AYU            | 40 patients with rhinosinusitis practiced alternate nostril breathing exercise for 40 days, 30 minutes daily, for 2 months | There was a reduction in the STT at the end of the intervention period. |
|                                              | Develioglu et al\textsuperscript{17}; 2013 Eur Arch Otorhinolaryngol: 1.458 | 40 adults underwent Ramadan (fasting on average 15 hours per day for 29 days), and 26 adults underwent Nineveh (60 uninterrupted hours of fasting). | Individuals who underwent Nineveh had slower STTs at the end of fasting than after 4 weeks of normal diet. There was no difference in the STT of the Ramadan group, or between groups. |
| Other interventions                           | Oozawa et al\textsuperscript{18}; 2012 Auris Nasus Larynx: 0.948 | 14 healthy men were exposed to low relative humidity (RH) for 4 hours with hydration with water, carbohydrate-electrolyte beverage (CE), and without prehydration (control). | The STT increased less in the CE group after 2 hours compared with the RH exposure group. Control and hydrated with water groups were not different. After 4 hours of low RH, the 3 groups presented similar increases in STT. |
|                                              | Parida et al\textsuperscript{19}; 2011 Indian J Med Sci: 1.67 | 50 patients with allergic rhinitis and permanent nasal obstruction undergoing tissue volume reduction by radiofrequency. | The STT did not change significantly between preintervention and 1, 3, and 6 months postintervention, except 1 week after the intervention. |
|                                              | Ramos et al\textsuperscript{20}; 2011 Respirology: 2.781 | 33 smokers enrolled in a smoking cessation program, and 33 nonsmokers (control). | Before quitting smoking, smokers showed higher STTs than controls. After 15 days of smoking abstinence, the STT decreased to normal levels and remained at these levels after 30, 60, 90, 120, and 180 days of abstinence. |
|                                              | Gupta et al\textsuperscript{21}; 2006 Indian J Otolaryngol Head Neck Surg: 0.054 | 50 patients with head and neck cancer treated with radiotherapy, and 20 healthy subjects who received no irradiation. | Before starting the radiation therapy, the STTs of the patients were similar to those of the control subjects. However, 6 months after the end of the treatment, the STT of the case group was impaired. |
|                                              | de Oliveira et al\textsuperscript{22}; 2006 Respir Med: 2.585 | 11 healthy subjects underwent 20 minutes of CPAP, and 5 controls, evaluated after 20 minutes of rest. | The STT decreased immediately after the use of CPAP and did not change in the control group. |
|                                              | Kamel et al\textsuperscript{23}; 2004 Acta Otolaryngol: 1.106 | 32 patients with nasopharyngeal carcinoma undergoing radiotherapy. | There was an increase in STT after radiotherapy. |

Abbreviations: µg/m³, micrograms per cubic meter; CPAP, continuous positive airway pressure; ex CO, exhaled carbon monoxide; HIV, human immunodeficiency virus; ICU, intensive care unit; min, minutes; STT, saccharin transit time.
The amount of introduced saccharin is standardized as 2.5 micrograms, which corresponds to ~5 particles of the substance.

Execution of the STT test: Subjects are in a sitting position, with the head supported in a slight extension (~10° neck extension) (Fig. 1B).

The placement of saccharin is performed under visual control, 2 cm into the inferior turbinates of the right nostril of the subjects. The right nostril is chosen as a way of standardizing and facilitating the reproduction of the method.

Subjects are asked to maintain their natural breathing and swallowing and not to get up, talk, cough, sneeze, or manipulate their nose. If this happens, the test is cancelled and rescheduled for another day. These guidelines are to prevent the change in airflow or mechanical touches from modifying the movement of the particles and interfering with the test results.

The expected flavor and nature of the substance should not be disclosed to prevent false positives.

Limitations of the Method

Despite subjects being instructed on how to breathe and swallow, these aspects are not objectively controlled by the evaluators and can vary among volunteers.

The test does not present visible results for evaluators, who take the report of the subjects as true. One way to avoid a false positive is not revealing the real flavor of the substance to be perceived by the subject, so the result is more reliable.

Even though saccharin presents a strong taste, its perception is subjective and may vary among subjects, and it is possible that some of them present altered taste, which would interfere in the results, not due to MCC conditions, but to individual taste perception.

The placement of saccharin, although not invasive, requires great attention and some manual skill training from the evaluator, since anatomical differences may hinder the insertion of the particle and even interfere with the exact location of deposition.

Cleaning the nostrils before the evaluation may be helpful to avoid possible additional mechanical barriers to the passage of the particle. However, the act of blowing the nose of the subject can interfere with the MCC due to the change in airflow.

Discussion

The STT test is an effective and widely used method in scientific research related to nasal MCC, which is essential in maintaining the health of the respiratory system. However, despite its simple implementation, some care is necessary to guarantee reliable results. In addition, a standardization of the application protocol is recommended so that future comparisons between different studies employing STT become possible in a reliable way.

The factors that can interfere with the results obtained by the STT test are worth highlighting: age, temperature, circadian cycle, presence of infections, use of drugs, of caffeine-based or of alcoholic substances, presence and intensity of smoking as well time of abstinence, physical exercise performance, and level of physical activity in daily life.

Final Comments

It is concluded that STT test is a widely used method for evaluation of nasal MCC, and, therefore, a standardization related to prior and concurrent test guidelines to professionals as well as to their execution is essential to improve the accuracy of the test, and to allow comparisons among different studies that employ it.

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