"VALIDATION OF ACOUSTIC RHINOMETRY IN OBJECTIVE ASSESSMENT OF NASAL AIRWAY:

STANDARDIZATION OF MEASUREMENTS AND APPLICABILITY"

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A Thesis Submitted as partial fulfillment of the requirements for the degree of

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Department of Otolaryngology, Faculty of Medicine

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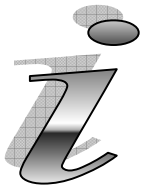
To my parents

Dr. Md. Rakibur Raza

&

Mrs. Rasheda Raza

i. ACKNOWLEDGEMENTS



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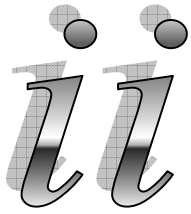
ii. LIST OF PUBLICATIONS



A. PUBLICATIONS IN JOURNALS

Paper I: *(submitted for publication)*

"Is Nasal Cavity Geometry Associated With Body Mass Index, Height And Weight?" **Raza MT**, Wang DY,

Paper II: *(***published***)*

Wang DY, **Raza MT**, Goh YT, Lee BW, Chan YH. Acoustic rhinometry in nasal allergen challenge study: which dimensional measures are meaningful? Clin Exp Allergy 2004;34:1093-1098

Paper III: *(paper under preparation)*

"Combination Therapy With Nasal Steroid And Oral Antihistamine Versus Monotherapy In Treatment Of Persistent Allergic Rhinitis" Chao SS, Wang DY, Chan YH, **Raza MT**, Pang YT

Paper IV: (**published**)

"Wang DY, **Raza MT**, Gordon BR. Control of nasal obstruction in perennial allergic rhinitis. Curr Opin Allergy Clin Immunol. 2004 Jun;4(3):165-170."

Paper V: *(Medicinal Chemistry Reviews-Online)*

"Biological Characteristic Of Histamine And Its Role In Allergic Rhintis" **Raza MT**, Wang DY,

Paper VI: *(submitted for publication)*

"Association Of Rhinitis With Atopy, Asthma, Diabetes And Cardiovascular Diseases." Wang DY, **Raza MT**, Heng CK, Chan YH.

B. CONFERENCES:

Oral presentations

Oral I: *Presenting author*

The 5th Combined Scientific Meeting incorporating The 4th GSS-FOM Scientific Meeting, 12-14 May 2004, Clinical Research Centre, National University Singapore, Singapore.

"Acoustic Rhinometry In Nasal Allergen Challenge Study: Which Dimensional Measures Are Meaningful?" Wang DY, **Raza MT**, Goh YT, Lee BW, Chan YH.

Oral II:

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Poster presentations

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Poster II: *Presenting author*

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"Correlation Of Body Mass Index, Height And Weight With Nasal Cavity Geometry In Adult Singaporeans" **Raza MT**, Wang DY

Poster III: *Presenting author*

5th International Symposium on Experimental Rhinology and Immunology of the Nose, November 17-19, 2003. Ghent-Belgium.

"Acoustic Rhinometry In Nasal Allergen Challenge Study: Which Dimensional Measures Are Meaningful?" Wang DY, **Raza MT**, Goh YT, Lee BW, Chan YH.

Poster IV: *Presenting author*

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"Association Between Rhinitis, Asthma And Some Other Major Illness" Wang DY, **Raza MT**, Heng CK, Chan YH.

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2004 AAAAI Annual Meeting: Visions to the Future - March 19-23, 2004, San Francisco, CA

"Association Between Rhinitis, Asthma And Some Other Major Illness" Wang DY, **Raza MT**, Heng CK, Chan YH.

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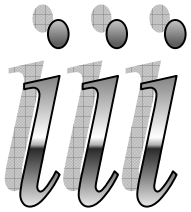
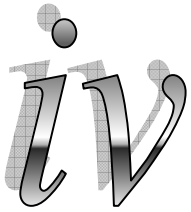


iv. SUMMARY



The nose is the natural and preferred respiratory passageway. Nasal obstruction is a common symptom and the etiology of nasal obstruction may be anatomical, physiological or pathological. Nasal mucosal inflammation is the most common pathologic cause and besides viral colds, allergic rhinitis is the most frequent cause of nasal obstruction.

Sensation of nasal obstruction may be subjective only. Perceptions often differ making it difficult to quantify by subjective complaints or clinical examinations alone. Therefore concurrent subjective assessment and objective measurement is advantageous. Subjective assessment can be made using a visual analogue scale or a point symptom score. There is still a need for a universally accepted objective procedure. Often one or more methods are used to complement each other.

Acoustic rhinometry (AR) defines objectively nasal cavity patency by acoustic reflections. It measures cross-sectional areas (CSAs) and internal nasal cavity volume (NV). However, methodological aspects of measurements may vary recordings and therefore a standardized procedure should be formulated in clinical and research applications of AR. The main objective of the present thesis is to validate the reliability of AR in the assessment of the nasal airway and to establish reference

values for nasal patency that can serve as a basis for further studies. This thesis consists of following experimental aspects: (1) Determination of standardized values and factors effecting normal nasal cavity dimensions in healthy individuals; (2) Validation of the use and reliability of AR, and its physical limitations in some pathological conditions in nasal cavity and paranasal sinuses; (3) Implications of AR in clinical and research works; and (4) Reviewing the recent advancements of procedural techniques, standardization and validation of AR.

Several topographical measurements for AR have been introduced, such as minimal CSA (MCA), CSA-3.3, 4.0 and 6.4 cm from the nostril and NV from 1 to 5 cm from the nostril. However there is no unvarying expert agreement on the significance of each measurement. In our study MCA appeared to be most sensitive and CSA 6.4 to be least reliable. We have proposed an MCA value of 0.74 ± 0.03 cm^2 for standardization in our local population. It has also been demonstrated that AR measurements are not affected by height, weight or body mass index (BMI).

Validation of different AR measurements with subjective methods had not been adequately evaluated before. We demonstrated an inverse relationship between point symptom score and objective measurements of AR. The strongest relationship was between nasal symptom score and MCA, followed by CSA 3.3, CSA 4.0 and CSA 6.4. With symptom scores of zero and one, there was a wider range of MCA but it is more specific with pathological conditions causing severe nasal obstruction (score 2 and 3).

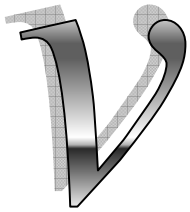
Using nasal cavity models, two studies concluded that measurements beyond a significant constriction may be unreliable. In a nasal allergen challenge study, we

demonstrated when the MCA reached an area <0.2 cm^2, measurements of CSA 3.3 and CSA 4.0 were reduced by 60 – 70%.

AR was utilized to measure changes in nasal patency following the administration of drugs. Nasal patency is one of the parameters that was used to compare the efficacy of three strategies (intra nasal corticosteroids, oral antihistamines or a combination of both) in the treatment of perennial allergic rhinitis (PAR). All three strategies had comparable efficacy and thus treatment should be based on patients' preference, compliance, comfort and cost.

In conclusion, standardization of AR measurements in the "normal nose" as compared to different types of structural and mucosal variations is important. Sources of error and physical limitations of AR measurements and procedural technique should be considered when using AR in clinic and research.

v. LIST OF ABBREVIATIONS



AD =area-distance

AR =acoustic rhinometry

ARhm =anterior rhinomanometry

BMI =body mass index

Bt =*blomia tropicalis*

CSA =cross-sectional area

CT scan =computer aided tomography scan

CV =coefficient of variation

DNS =deviated nasal septum

EPR =early-phase reaction

FDM =fluid displacement method

FP =fluticasone propionate

HIT =hypertrophied inferior turbinate

INC =intranasal corticosteroids

LPR =late-phase reaction

MCA =minimal cross-sectional area

MRI =magnetic resonance imaging

NAC =nasal allergen challenge

NV =internal nasal cavity volume

nPIF =nasal peak inspiratory flow

nPEF =nasal peak expiratory flow

OSA =obstructive sleep apnea

PAR =perennial allergic rhinitis

PBS =phosphate-buffered saline

QOL =quality of life

Rhm =rhinomanometry

RQLQ =rhinoconjunctivitis quality of life questionnaire

SAR =seasonal allergic rhinitis

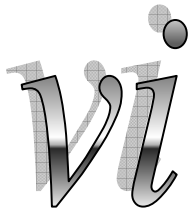
SD =standard deviation

TAA =triamcinolone acetonate

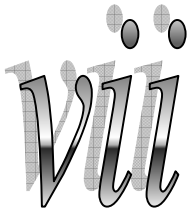
VAS =visual analogue scale

WHO =world health organization

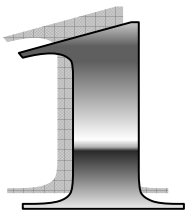
vi. LIST OF TABLES



vii. LIST OF FIGURES



1. INTRODUCTION



The nose is the natural and preferred respiratory passageway for all ages. However it's not simply an expressway of the respiratory tract. It aids us in breathing the breath able, eating the edible and smelling the smell able. It has also been linked with reproductive physiology and extravagant aesthetic morphology. No wonder nowadays the nose is not merely the singular curiosity of Otorhinolaryngologists, but also of Pediatricians, Allergists, Speech Pathologists, Orthodontists and of course Plastic Surgeons

The importance of an unobstructed nasal airway for a healthy existence has been emphasized since antiquity. Yet till today nasal obstruction remains a common symptom causing much distress. Nasal obstruction is characterized by insufficient airflow through the nose, which can be a subjective sensation, or the result of objective pathology **[1]**. Often, the doctor's assessment of a perfectly patent nasal airway might differ with the patient's complaint of an obstructed nose. Hence, subjective assessment along with objective measurement of the nasal airway will aid diagnosis, treatment, research and medico-legal documentation **[2]**.

Acoustic rhinometry (AR) defines objectively nasal cavity dimensions by acoustic reflections. AR is a static test and independent of airflow **[3]**. It measures cross-sectional areas (CSAs) and internal nasal cavity volumes (NVs). Several

topographical measurements of the area- or volume- distance have been introduced, such as MCA, CSA-3.3, 4.0 and 6.4 cm from the nostril and NV from 1 to 5 cm from the nostril. Although each measurement is suggested to represent a distal dimension of the nasal cavity, there is no uniform agreement among experts on the value and significance of each measurement in respect to the nasal cavity dimensions. Standardization of measurements, sources of error and physical limitations and validation of the procedure with other subjective and objective methods have not been adequately evaluated **[4]**.

Adults with high relative body mass have an increased demand for oxygen and thus may have to breathe with higher frequency or larger volumes during each inspiration **[5]**. In addition, an increased relative BMI is related to increased oral and nasal pressures, as well as an increased nasal airflow rate. Since there are higher airflow rates in subjects with high BMI, there might also be a correlation between BMI and nasal airway size and resistance to inspiratory airflow. AR is a useful method in measuring nasal airway size. Such measurements of individuals without any known nasal pathology will also be important in standardization of reference values for AR measurements.

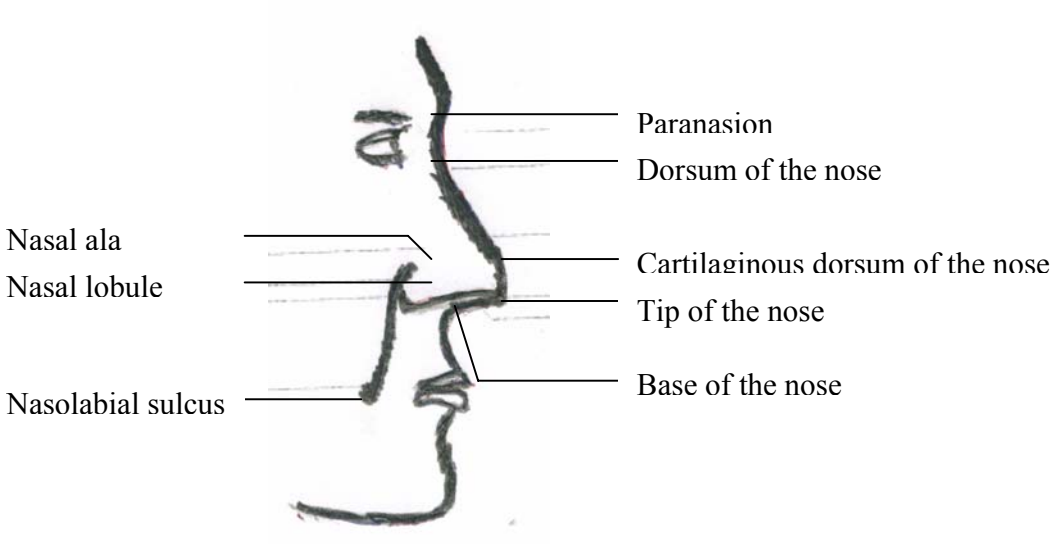
Allergic rhinitis may be effectively treated with intranasal corticosteroids and anti histamines, singly or as combination therapy. A short term intermittent therapy could be more acceptable for patients with perennial allergic rhinitis (PAR). As nasal obstruction is one of the major symptoms of PAR, an effective treatment should be able to improve nasal patency. AR may be used to measure objectively changes in nasal patency following administration of therapeutic measures.

2. BACKGROUND OF THESIS

2.1. THE NOSE

The nose has an osseo-cartilaginous framework. **Figure 1** illustrates the external features of the nose. The nasal cavity is divided into two parts by the osseo-cartilaginous nasal septum. The lateral wall of each cavity has turbinates or conchae projecting into the cavity and conforming it into a slit-like shape. The external bony opening of the nasal cavity is called the piriform aperture. The nasal vestibule is

Figure 1: Features of the external nose **[6]**



by Raza MT

located immediately posterior to this opening. The vestibule funnels air towards the nasal valve **[7].** The nasal valve is the narrowest part of the nasal cavity **[8].** The olfactory epithelium is located in the superior position of the cavity **[9].**

Nasal cycle is the cyclic fluctuation in the congestion of the nasal mucosa, which results in rhythmic and bilateral reciprocal alternation of nasal airway patency. However a classical nasal cycle is not a universal phenomenon **[10].**

2.1.1 The Nasal Micro-Vasculature

The nasal vessels **[Table 1]** play a central role in the pathophysiology of nasal obstruction. The nasal mucosal microvasculature is different from that of other parts of the respiratory tract **[Table 2]**. The capacitance vessels or blood sinuses

Table 1: Division of nasal vessels based on histological pattern, function and nerve supply **[11].**

Type	Vessel
Resistance vessels	Arteries Arterioles
Exchange vessels	Subepithelial capillaries Periglandular capillaries
Shunt vessels	Arteriovenous anastomoses
Capacitance vessels	Venous sinusoids Venules Veins

expand the mucosa during congestion. There are three potential muscular mechanisms that could be responsible; (i) Thick layer of smooth muscle in sinus walls. Contraction and relaxation of this muscle may cause change in blood capacity. (ii) Contraction of the muscle in "throttle veins" at the exit from the sinuses which may distend the sinuses or (iii) Enlargement of the caliber of the arteriovenous anastomoses at the entry to the sinuses. Since the nose is enclosed in bone, the expansion must encroach on the airway lumen causing a blocked nose **[11].**

Table 2: Difference between the microvasculature of the nasal mucosa with that of other parts of respiratory tract **[11]**

	Nose	**other parts of the respiratory tract**
Capacitance vessels	Highly developed	Absent or far less frequent
Arteriovenous anastomoses	Numerous	Absent
Nasal cycle	Present	Not demonstrated

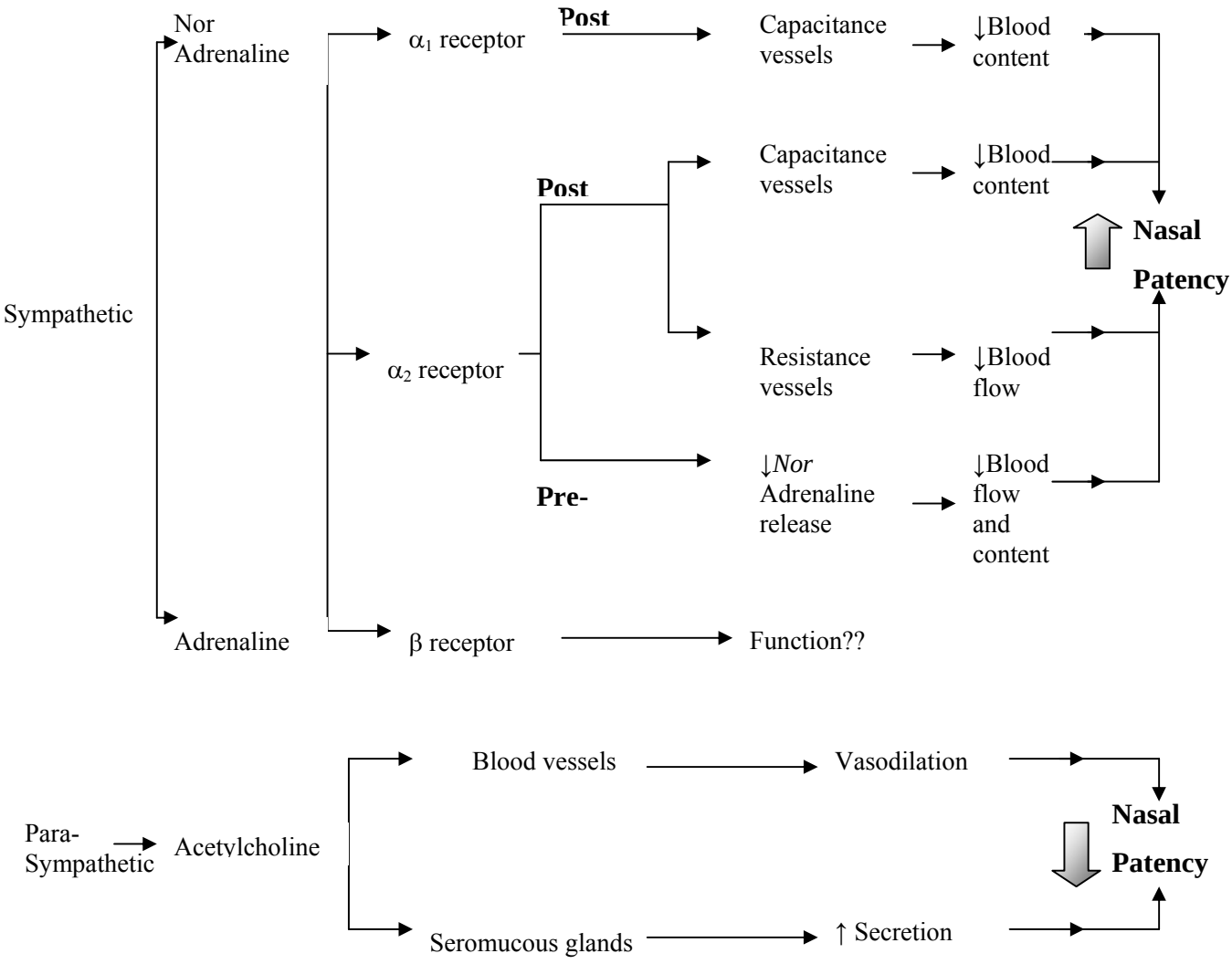
The nose, as an organ initiating reflexes affects itself and rest of the body **[12]**. Nasal blood vessels, glandular tissue and ciliary system may directly or indirectly influence nasal patency **[8]**. Nasal mucosal nerve supply probably provides the effective control of the nasal vasculature and the regulation of nasal patency and secretion. Its innervation includes parasympathetic, sympathetic, sensory/afferent, and somatic motor nerves, which combine in a variety of morphologic pathways **[Figure 2] [12]** Sympathetic arterial vasoconstriction reduces mucosal blood flow, sinusoidal filling, and mucosal thickness, and so restores nasal patency **[13]**. The actions of sensory nerves and parasympathetic reflexes play crucial roles in nasal pathology **[14]**. Neuropeptides also play an important role in the innervation of blood vessels and glands **[15]**. Nasal secretory tissue includes epithelial cells, submucosal glands, and relatively large anterior or lateral serous glands **[8]**.

2.1.2 The Normal Nose

It is difficult to determine a standardized dimension for "*the normal nose*". The anatomy of the nose varies with development, race, age and gender. Effects of BMI, height and weight are also a matter of study. Physiological events like nasal cycle and posture also affects normal nasal cavity dimensions. These factors must be taken into account in studies on environmental, clinical and pharmacological conditions.

Nasal airway measurements in adults should be evaluated in relation to gender, whereas in children nasal values of boys and girls are comparable. In a healthy adult population the normal values of airflow rate and oral and nasal pressures, nasal CSAs would be expected to be slightly higher in men than in women **[5, 16]**.

Figure 2: Role of sympathetic and parasympathetic innervation on nasal congestion.



Race is known to be one of the main important factors affecting nasal structure. A significant difference has been noted in Anglo-Saxon, Chinese and Negro noses **[17].** Negroes seem to have a larger bony aperture and thus hypertrophied inferior turbinate (HIT) on anterior rhinoscopy may be a normal state. Thus Orientals might have an increased amount of vascular tissue than Caucasians or Negroes **[18].** However no significant difference was demonstrated in between Chinese, Malay and Indian races **[19]** as well as in between Anglo-Saxon and Indian noses.

The pediatric nasal cavity differs from adults in both size and proportion. The nose achieves adult proportions only at age 12. In children there is a specific anatomical structure in each age. Due to these differences the pediatric nasal cavity may be grouped into four different age groups; newborns, 1-4, 4-8 and 8-12 year olds **[20, 21]**

Changing postures contributes significantly to the source of variation of nasal cavity patency. Nasal cavity dimensions decrease with change of posture from standing to supine and to lateral recumbent positions. It decreased when changing from sitting to supine postures but increased, when changing from sitting to standing postures. The mean volumes of the two sides of the nasal cavities are more significantly different in the sitting position but not in the supine posture, indicating that in the supine position the volume of the nasal cavities are more equal **[22, 23]**.

2.1.3 Pathology of the Nose

The anatomy of the nasal cavity is complicated. Septal deformities are often found in various locations. The impact on nasal patency by minor anteriorly deviated nasal septum (DNS) seems to be more important than posteriorly located major deformities.

The anterior part of the nose including the pyriform opening contains the narrowest segment of the nose **[24].** A long standing pronounced DNS might give rise to HIT due to compensatory changes. HIT may also be caused by concha bullosa or polypoidal mucosal transformation, and long-standing allergic or vasomotor rhinitis. Often it is due to a combination of several factors **[25]**.

Adenoidal hypertrophy is the commonest cause of nasal obstruction in the pediatric population. It may cause marked morbidity as regards to respiratrory physiology, facial growth and middle ear function**.**

Norback et al. **[26]** demonstrated that indoor air pollutants in schools might affect nasal patency. A decreased nasal patency at increased concentration of respiratory dust suggests a congestive effect of airborne particle pollutants. Their results suggested that different types of microorganisms might have different effects on nasal mucosa. Presence of *Aspergillus spp* and molds in the air decreased nasal patency. On the other hand a greater nasal patency at higher concentrations of bacteria was demonstrated.

Almost without exception all patients with nasal polyps suffer from nasal blockage. This is constant although it will vary with the size and position of the polyps **[27].**

Any space-occupying lesion from the nasal vestibule to the glottis can predispose to obstructive sleep apnea (OSA). Despite this most adult patients with OSA have no evident predisposing abnormality **[28]**. Nasal obstruction as a predisposing factor for OSA is still debatable **[29-33].** Nasal polyps, DNS and rhinitis are causes of nasal obstruction that might predispose to OSA. It is therefore important during diagnosis

of OSA to examine the nose for assessment of nasal airway and reveal any cause of nasal obstruction **[28].** Although surgical correction of nasal obstruction does not improve OSA consistently, nasal obstruction correction is suggested to be included in the overall treatment plan for OSA **[29, 34, 35]**.

The most common pathological cause of nasal obstruction is nasal mucosal inflammation. If viral colds are excluded, allergic rhinitis has become the commonest cause of nasal obstruction **[36].** Allergic rhinitis affects approximately 10-20% of the world population **[37-40].** Nasal obstruction is the most common symptom of PAR, and, although rhinorrhea is more common in seasonal allergic rhinitis (SAR), obstruction is still significant in many patients **[41]**. In a Singapore community health survey, nasal obstruction was the most prevalent identified nasal symptom (15.8%), compared to sneezing (11.7%), rhinorrhea (10.6%) and nasal itch (10.2%) **[42]**. In patients with PAR, continuous allergen exposure causes a persistent mucosal inflammation and thus persistent nasal obstruction. Control of nasal obstruction in PAR is thus important, and since it must be treated all year around; treatment choices, costs, and compliance all become important public health issues **[1]**.

2.2 NASAL PATENCY

2.2.1 Definition

Patency is "*the state of being freely open or exposed.*" Thus nasal patency can be defined as "*an objective measurement of how open the nose is"*. If the word patency is used in a correct way, nasal patency measurements should comprise CSAs and NVs. The practical useful methods for measurement include AR, computer aided

tomography (CT) scan and magnetic resonance imaging (MRI). However, recording nasal airflow with or without simultaneous pressure recordings is often included among methods (Rhinomanometry and nasal peak flow) for measuring nasal patency **[36, 43]**.

2.2.2 Factors Affecting Nasal Patency

Inflammation of the nasal mucosa, whatever the cause, is the most common pathologic cause of nasal obstruction. Etiology of nasal obstruction may be anatomical (DNS), physiological (nasal cycle, posture) or pathological (nasal polyp, foreign body). Nasal obstruction may be unilateral or bilateral, continuous or intermittent (at night, after exercise). If viral colds are excluded, allergic rhinitis has become the most common cause of nasal obstruction **[1, 36].** Body temperature, posture and exercise also influence nasal patency **[8]**

Decreased nasal patency is not always accompanied by increased nasal airway resistance, decreased nasal peak flow or reduced cavity dimensions **[36]**. Often the sensation of impaired nasal patency may be subjective only (atrophic rhinitis) and perception may vary from person to person. Sensation of nasal patency may also be related to nasal passage temperature. The nasal vestibule contains a dense distribution of cold receptors supplied by trigeminal nerve. Stimulation of the cold receptors misinterpret the sensory information to the brain leading to the subjective sensation of increased nasal patency in the absence of objective increase in nasal patency **[44, 45]**. L-menthol stimulates the cold receptors **[46]**. The cooler the nasal lining or the greater the drop in temperature on inspiration, the clearer the nose will feel **[47, 48]**.

No thermoreceptors were demonstrated in the nasal cavum (the major part of the nasal cavities that is lined by respiratory mucosa) **[49]**.

2.3 ASSESSMENT OF NASAL OBSTRUCTION

The importance of a patent nasal airway for healthy existence has been emphasized since antiquity. Yet till today nasal obstruction remains a common symptom causing much distress and is one of the most common symptoms encountered in primary care and specialist clinics. It is difficult to quantify by subjective complaints or clinical examinations alone, hence concurrent subjective assessment and objective measurement of the nasal airway is critical for clinic and research **[1, 2]**.

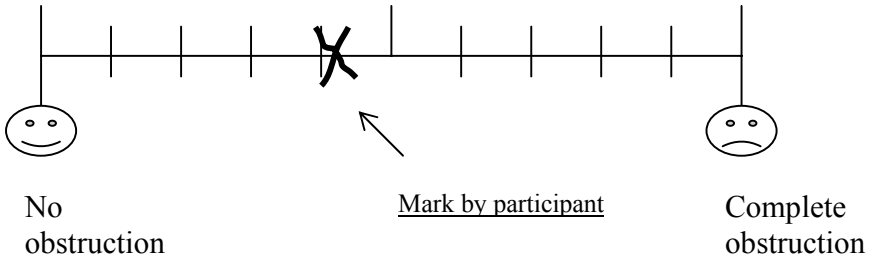
2.3.1 Subjective Assessment of Nasal Obstruction

Subjective assessment of nasal obstruction can be made using a visual analogue scale (VAS) or a point symptom score.

Visual analogue scale

The core question of the VAS is "*How do you feel on a scale from 0 to 100 (or 10*)?" **[50]**. The scale is a self-reporting device that measures the magnitude of internal state, (in this case nasal obstruction). Conventionally, the VAS is a line that is either vertically or horizontally oriented with anchors placed at both poles from 0 (no obstruction) to 10 **[51, 52]** or 100 **[53]** (severe or complete obstruction). Participants place a mark somewhere along the line that best indicates the magnitude of nasal obstruction according to their perception **[Figure 3]**. They are often asked to mark their discomfort for each nostril separately **[53]** or for combined sensation **[51]**.

Figure 3: Visual Analogue Scale



Subjective point symptom score

In a point symptom score **[2, 54]** the degree of nasal obstruction is categorized in well-defined points **[Table 3]**. The participant chooses the point, which associates best with the severity of nasal obstruction according to their perception.

Limitation of subjective assessment of nasal obstruction

It is difficult to estimate the extent and severity of nasal obstruction subjectively. Nasal obstruction is often a complaint of atrophic rhinitis, a disorder with wide nasal cavities **[36]**. Damage to trigeminal sensory nerve endings can cause a sensation of nasal stuffiness and similarly inhalation of menthol can cause a subjective improvement in nasal sensation of airflow without any change in nasal resistance **[55]**. What one patient considers nasal obstruction may bother another patient very little **[36]**. Children appear to have difficulty in self-assessment of symptoms and are often poor judges of the presence or severity of nasal obstruction **[56]**. Children with

Table 3: Subjective point symptom score

Point	Symptom score	Interpretation
0	None:	No obstruction evident
1	Mild:	Symptom clearly present but minimal awareness
2	Moderate:	Definite awareness of symptom which is bothersome but tolerable
3	Severe:	Symptom is hard to tolerate and interferes with activities of daily life/sleeping

chronically blocked nose often consider nasal obstruction "a normal condition" **[57].**

2.3.2 Objective Measurement of Nasal Patency

Although a number of procedures have been described for objective assessment of nasal obstruction, there is still a lack of a common consensus on a universally accepted method. One or more methods are often used to complement each other.

Methods of objective measurement:

1. Clinical examination:

Clinical examination of the nose can be performed with anterior and posterior rhinoscopy and nasal endoscopy. No significant correlation has been demonstrated

between anterior rhinoscopy, subjective assessment or other tests. Video recording during flexible endoscopy is a minor invasive procedure **[58].** After careful explanation and choice of suitable premedication (local anesthetic), endoscopy might be well tolerated in all instances if performed by a skilled endoscopist.

2. Radiological examination:

X-ray examination has been used in relation with evaluation of the paranasal sinuses which is increasingly being replaced by CT scan. CT scan and MRI are non invasive methods that can be used to depict the anatomy of the nasal cavities. CT scan is useful in visualizing bony defects, but not well suited for soft tissue imaging**.** MRI however is useful in imaging mucosal structures that are important factors in nasal patency and volume **[58]**. Use of CT scan and MRI remain to be limited due to expense. Repeated CT scan of head imply the risk for irradiation cataract, especially in infants and children **[59].**

3. Rhinohygrometry:

Rhinohygrometry, the misting of a cold shiny metal surface by warm airflow, is a simple inexpensive test. Modification of this traditional method has given the test a quantitative element in the assessment of nasal patency**.** However the semi-quantitative nature of rhinohygrometry renders it flawed for serious studies **[60].**

4. Rhinostereometry:

It is an optical direct non-invasive method for measuring nasal mucosal swelling with a high degree of accuracy. A surgical microscope is placed on a micrometer table. The apparatus is fixed to the subject with perfect alignment. The eye-piece has a

horizontal millimeter scale. The nasal cavity is viewed through the eyepiece. Since the microscope has a small depth of focus, changes in the position of the mucosal surface are registered in the plane of focus along the mm scale. The accuracy of the method is 0.2 mm **[61]**. The position of the head must be fixed to ensure accuracy during repeated measurements. This method gives only limited information of isolated structures and not of the larger part of the nasal airway. There are doubts about this method since only a few investigators have applied it and seldom has it been compared with other methods. Hallen and Graf **[62]** having compared the measurements of nasal mucosal swelling between AR and rhinostereometry, had concluded that although both the two methods were sensitive for studying nasal mucosal swelling there was a poor correlation between the two methods ($p<0.001$, $r=0.25$).

5. Fluid displacement method:

The nasal cavity is filled with fluid vertically from the nostril by means of a pump delivering constant flow. The pressure at the inlet is a measure for the height of the fluid, i.e., the distance into the nasal cavity. The speed of the rising surface is proportional to a change in pressure divided by the change in time. When the CSA of the cavity increases, the speed of the rising surface slows down, and vice versa. The fluid displacement method (FDM) is considerably accurate for measurements in small laboratory animals, but it can only be used post-mortem **[63, 64].**

6. Nasal casting:

Impression material is injected into the nasal cavity to produce casts. Casts are weighed to determine exact volume and sliced into segments of equal thickness for determination of CSA **[65]**.

7. Manometric rhinometry:

The principle is to turn the nasal cavity into a closed system and then extract a given volume of air from it. Any change in the volume of air within such a closed cavity results in a pressure change (Boyle's Law of Gases). This pressure change can be measured and the original volume of the nose, sinuses and nasopharynx can be calculated from it. This method lacks the spatial resolution of CT scanning but can be used where CT examination would be inappropriate, uneconomic, impractical or unethical. Unlike AR or Rhm (rhinomanometry), the results are not determined principally by the point at which airflow rate is limited **[66].**

8. Rhinomanometry:

Rhm is a useful clinical method. Standardization of Rhm is established and accepted **[67].** Nasal resistance of airflow is calculated from measurements of nasal airflow and transnasal pressure. Three types of Rhm can be used: (1) Active anterior Rhm (ARhm), (2) Active posterior Rhm and (3) Passive ARhm. Active ARhm is the most common and accurate method for clinical use **[68]**. The successful use of Rhm requires an experienced operator and significant subject co-operation in order to obtain reproducible and valid measurements. Rhm is time consuming and expensive for field application in occupational or community population studies of environmental exposures **[69]** and it cannot be performed in the presence of a septal

perforation or complete nasal blockage **[68].** At high levels of nasal blockage, airflow in the nose is turbulent and leads to inconsistent readings which reduce the reproducibility of Rhm recordings quite considerably **[70].**

9. Rhinoresistometry:

Analogous to Rhm, rhinoresistometry measures pressure difference and flow during respiration. Special software calculates additional parameters, such as: (1) flow resistance depending on flow; (2) degree of turbulence depending on flow; (3) hydraulic diameter as a parameter of width and (4) drag coefficient, describing the wall condition causing turbulence. The combination of rhinoresistometry and AR allows a better insight into structure and function of the nose. Both methods complement one another in their diagnostic outcome **[71].**

10. Nasal Peak Inspiratory and Expiratory Flow Meter:

Nasal peak inspiratory flow (nPIF) has been found to be useful for objectively comparing nasal patency between different treatment groups in clinical settings. For nPIF measurement, a modified nasal continuous positive airway pressure mask is attached to a portable spirometer. Forced maximal inspiration measurements are taken. Subjects are encouraged to inhale as hard and fast as they could through the nasal mask **[72]**. Most patients need several days to practice before they become competent. nPIF is as good as Rhm at assessing objective nasal patency. However Rhm is more sensitive in detecting the changes in nasal patency produced by exercise than a nPIF measurement **[73]**. Some authors suggest that nasal Peak expiratory flow (nPEF) is susceptible to technical errors. Submaximal expiration, air leakage from the

mouth mask and non linear nPEF apparatus can make results somewhat unreliable **[74]**.

11. Acoustic Rhinometry:

AR measures nasal cavity dimensions with incident and reflected sound waves. This method is described later in detail **[Figure 4]**.

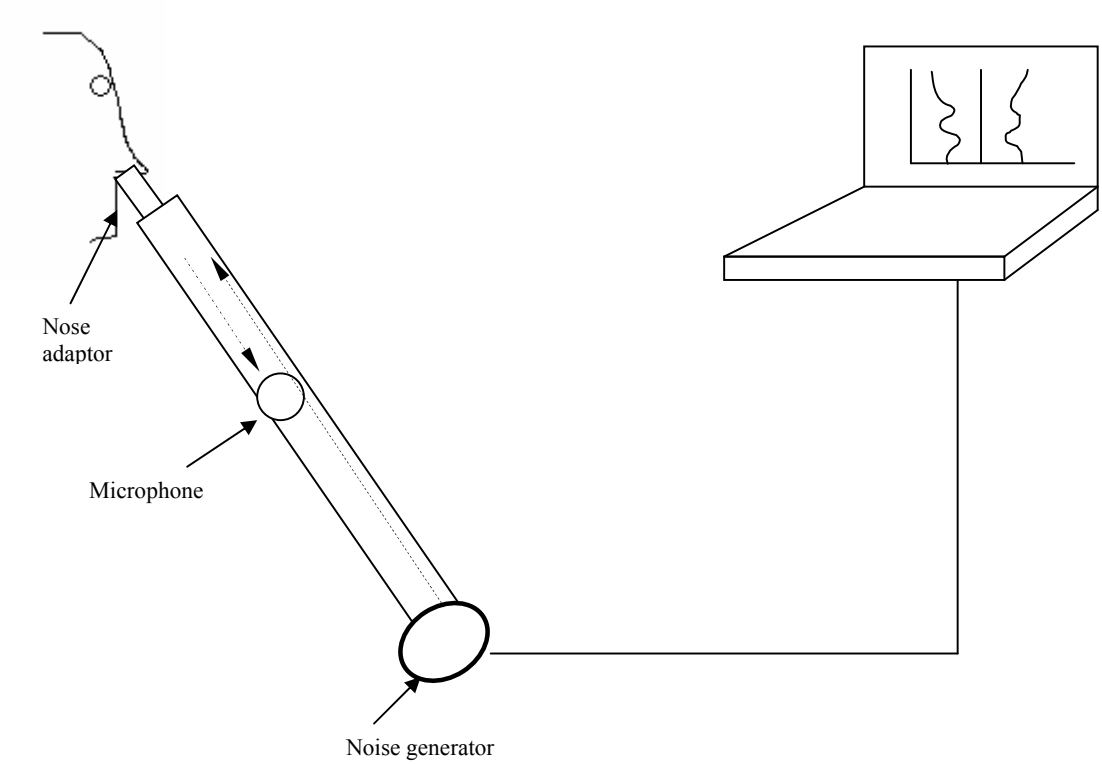
2.4 ACOUSTIC RHINOMETRY

2.4.1 Basic Principle

An acoustic impulse is fired down a semi-infinite cylindrical tube (AR tube) into the object under investigation (nasal cavity). The tube has a microphone in its midsection and is connected to the nostril by a contoured nosepiece. Initially spark plug was used to generate a spark but currently continuous wide band noise is used to generate the acoustic signal by a digital signal processor. The sound is propagated through the tube and nosepiece into the nostril and undergoes partial reflection and partial transmission at each change in CSA along the nasal cavity, creating a reflection sequence. This sequence returns from the nasal cavity and travels back up the AR tube without further reflection. Its passage is recorded by the microphone. The reflection sequence is termed the *input impulse response*.

Suitable algorithms enable both the reconstruction of the nasal cavity profile and the evaluation of its input impedance from the input impulse response **[Figure 6] [76, 77]**.

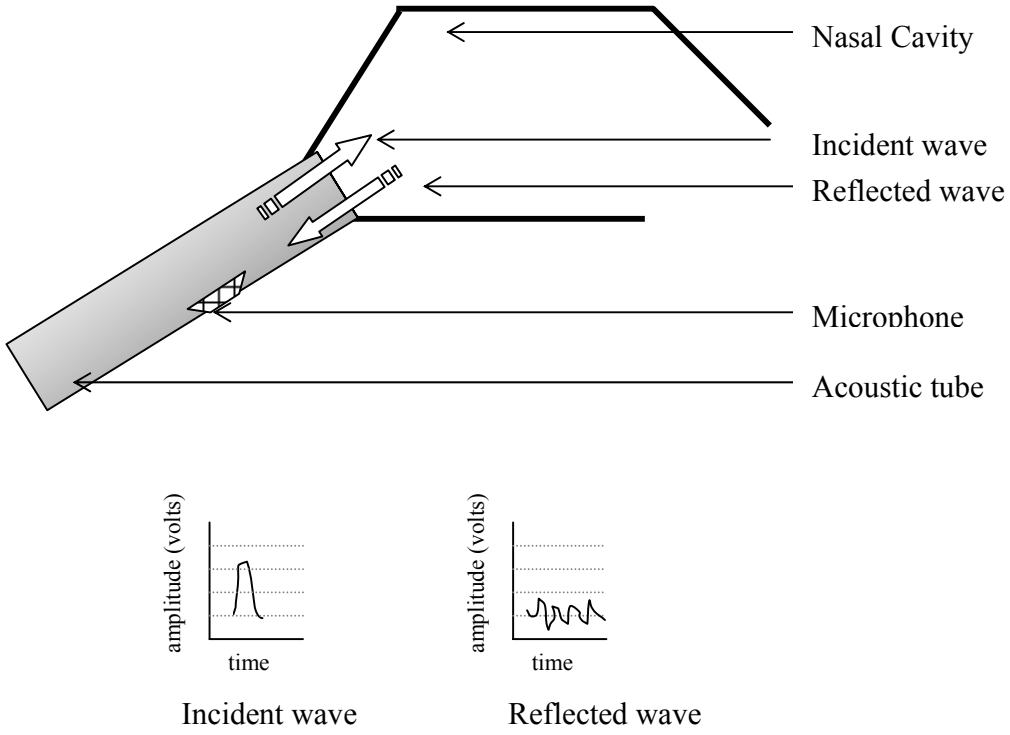
Figure 4: Acoustic rhinometry **[75]**



The waves are recorded by a microphone, and digitally analyzed at the rate of 20 times per second. The mean of 5 measurements is displayed as one curve, which is updated 4 times per second, ensuring dependable results. Objective measurements are recorded by measuring the CSA. This data is plotted as an 'area-distance function' which shows the CSA of the airway on the "*y*-axis" against distance on the "*x*-axis". Regions of narrowing are seen as dips in the curve and widening as peaks.

However these CSAs are not the real CSAs of the nasal cavity, but are hydraulic cross-sections (i.e. an imaginary circular cross-section with a surface equal to the slit

Figure 5: Diagram of basic principles of acoustic reflectometry in acoustic rhinometry **[76]**



like nasal cross-section that was measured at a certain distance from the distal part of the nozzle). Integration of the areas under the curve produces NV estimates **[3, 77].** Information is saved and can be retrieved for future reference. A printout provides the clinicians with numeric and visual displays of the sites and magnitude of nasal airway lumen dimensions defined by combined structural and mucosal components. The mucosal components are usually investigated further by determination of the extent of vascular congestion from measurements made before and after application of topical decongestant.

2.4.2 Measurements

Several topographical measurements of the AR area- or volume-distance have been introduced. The following measurements are usually taken on both sides of the nasal cavity as described in previous studies **[4, 10, 19, 78-82].**

- **MCA:** Minimum CSA between 1 cm and 5 cm from the nostril. Mean value (right and left) is calculated (mMCA).
- **d:** Distance (cm) to MCA from nostril is recorded.
- **CSA-3.3:** CSA at the distance of 3.3 cm from the nostril. It represents the anterior end of the inferior turbinate. Mean value (right and left) is calculated (mCSA-3.3).
- **CSA-4.0:** CSA at the distance of 4.0 cm from the nostril. It represents the mid-portion of the inferior turbinate that has the most abundant erectile tissue component. Mean value (right and left) is calculated (mCSA-4.0).
- **CSA-6.4:** CSA at the distance of 6.4 cm from the nostril. It represents the posterior nasal cavity. Mean value (right and left) is calculated (mCSA-6.4).
- **NV:** NV from 1-5 cm from the nostril is often recorded. Total NV (tNV) is calculated as the sum of the right and left NV. Occasionally NV 5-10 cm from the nostril is recorded.

2.4.3 Standardized Testing Procedure:

Methodological aspects of measurements may vary recordings. That is why it is important to formulate a standardized procedure of taking measurement. A uniform procedure is usually followed at the Department of Otolaryngology, National University Hospital, Singapore. The procedure is described here.

All AR measurement are performed using the RhinoScan module (Rhinometrics A/s. Lynge, Denmark). The module consists of basic system hardware (version SRE 2100), RhinoScan software, probes and nosepieces **[Figure 4]**.

All participants are first given adequate information of the procedure and advised to remove glasses (if any) or any nasal ornaments to avoid external pressure on the nose. They are acclimatized for 20 minutes prior to the test. The participants sit upright in an armchair, with the head properly supported and are advised to breathe through the mouth and hold their breath momentarily while the measurements are recorded.

Room temperature (24-26^{0}C) and relative air humidity (45-55%) are kept constant by means of central air-conditioning, and background noise is kept to a minimum (less than 60dB). Recalibration is done if necessary.

Each measurement is taken by an operator who has undergone training and developed skills under supervision. The operator is also aware of the physical limitations and factors influencing the reliability of AR.

Size of nosepiece is chosen accordingly as the opening must be equal or larger than the opening of the nostril **[83]**. The same type of nosepiece is used in follow-up

measurements. Separate nosepieces are selected for each participant and different types of nosepieces are used for each nostril. The left nosepiece is marked "S" and the right is marked "D".

The probe is handheld by operators while taking measurements on all subjects. The nosepiece is attached to the probe and is gently pushed up to (not into) the nostril without distortion, while ensuring a good leak free nostril-nosepiece interface. Even small leaks can cause significant dissipation of the acoustic probing signal and hence an overestimation of nasal CSA **[84]**.

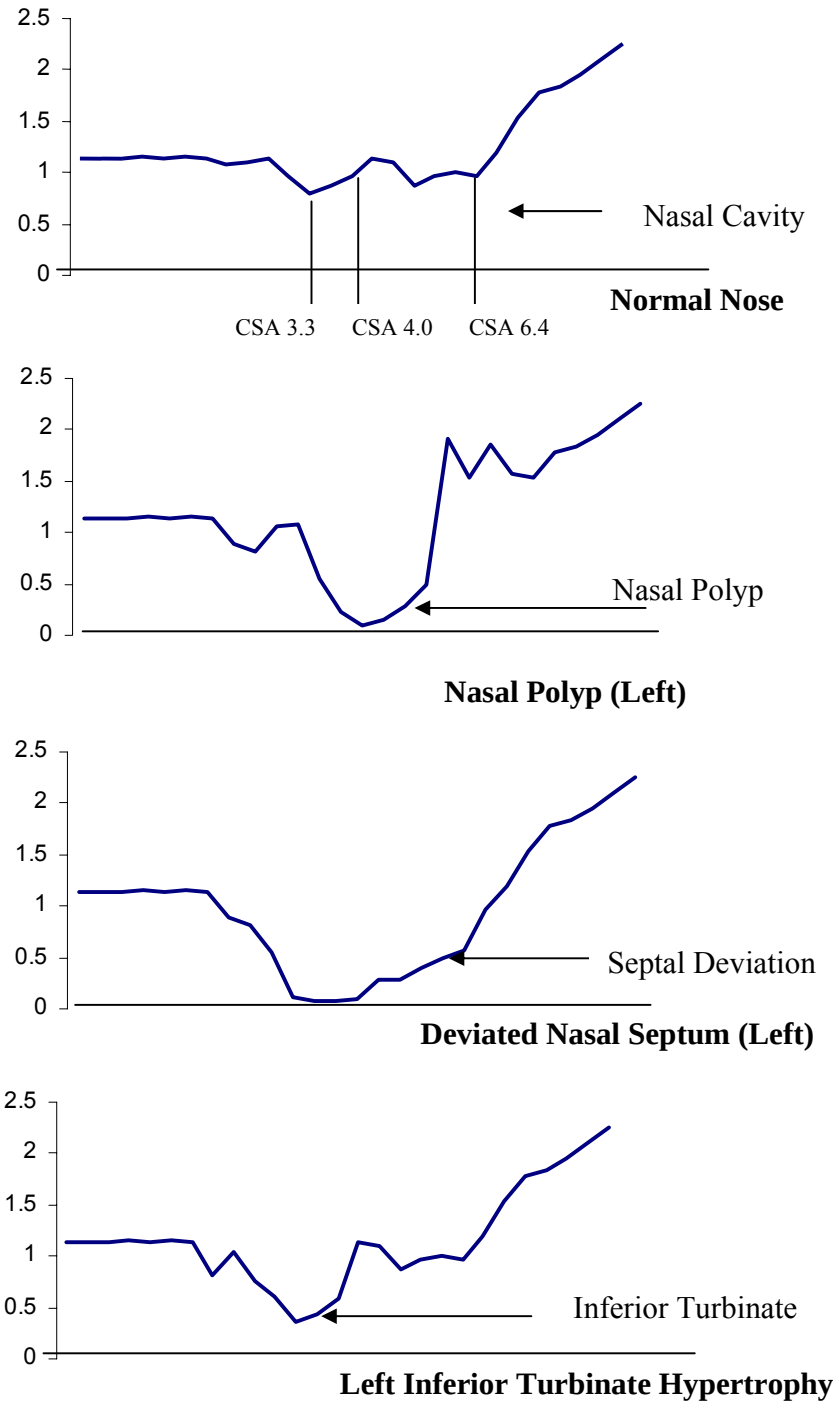
As soon as the nosepiece has been successfully fitted, the graph of the function of CSA to distance appears on the screen. Three consecutive measurements (graphs) are taken and the average is then calculated. The graph is saved for future reference. Diagrammatic representations of AR graphs in different conditions of the nose are illustrated in **Figure 6**.

2.4.4 Advantages and Disadvantages of Acoustic Rhinometry

Advantages

AR is a user-friendly procedure. It is a rapid, non-invasive and easy to perform test and requires minimal co-operation from the patient and causes little or no discomfort **[4, 81, 85, 86].** High reproducibility of AR makes it valuable for inter-individual comparisons [**4, 16. 81, 86].** During measurement the patient is in apnea. As a result respiratory or other involuntary movements can be avoided or minimized **[87]**. Its performance is not affected by pressure and flow **[85]**. AR can be performed when

Figure 6: Acoustic rhinometry graph (Left Nose)



there is complete unilateral nasal blockage. ARhm cannot be performed in the presence of complete unilateral nasal blockage **[87]**.

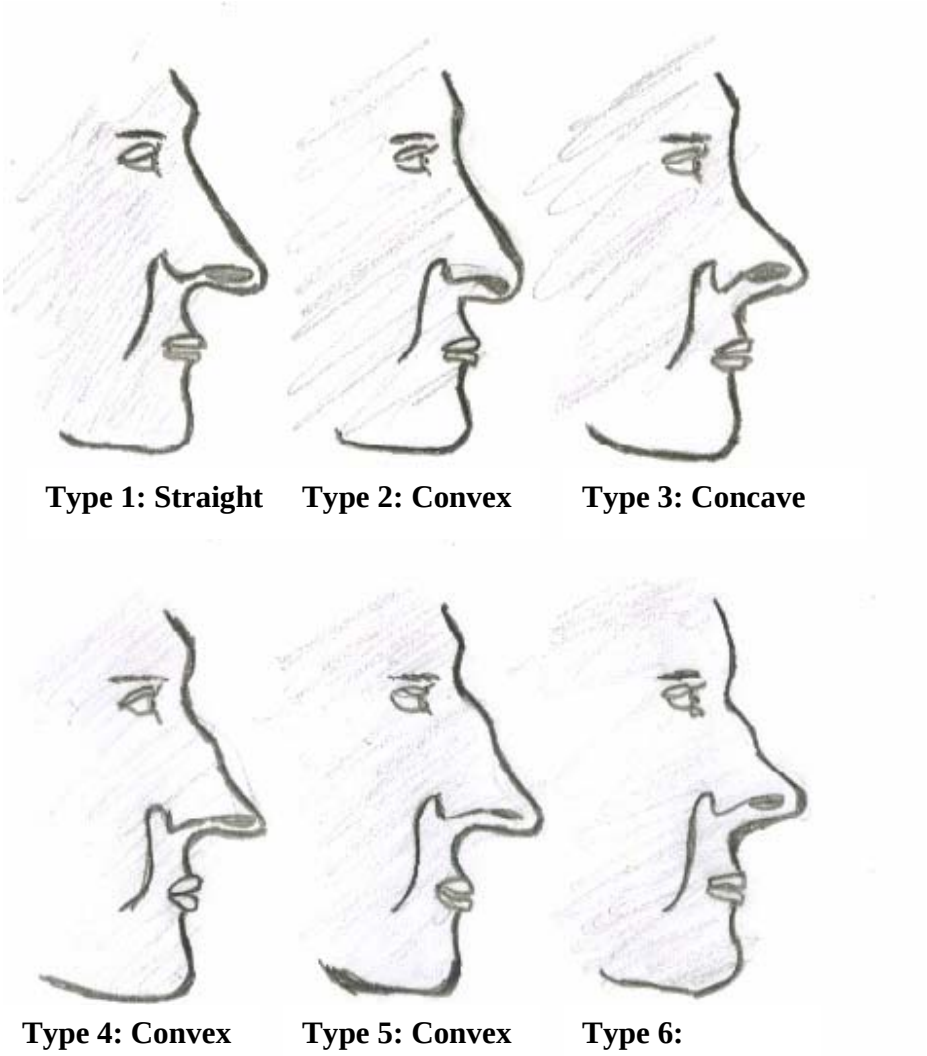
Disadvantages

There is still need for a standardized technique of measurements as well as values for different nasal cavity dimensions. In this article we have proposed a standardized procedure for AR measurement. AR measurements can be recorded within seconds. But if standardized procedures are followed then it may be time consuming. Patients are required to acclimatize for 20-30minutes before taking measurements **[87]**.

Nosepiece or nasal adapters can always induce nasal vestibule deformation. To conform to the different shapes and sizes of noses and nostrils, different nosepieces may be required **[Figure 7][Figure 8].** AR is very sensitive to leakage. Vaseline or viscid water-soluble gel is often needed to seal off the nozzle ostium-externum interface. There are no particular characteristics in the recording generated by AR to alert the operator that a leak has occurred **[87, 88]**.

There are some physical limitations or errors associated with the algorithms used in AR, which are (a) sinus ostium size, sinus volume, or CSA in the distal parts (approximately 5-10 cm into the nasal cavity) of the nasal cavity **[4, 89]**. (b) a significant constriction in the nasal valve area will affect the CSA and NV measurements beyond this point **[4, 90, 91]** and (c) distortion of the vestibule with the nasal tip adapter and anatomical variations of the columella, which changes the 0 reference points **[92]**. In addition to this, certain factors can affect the reliability of AR measurements **[84] [Table 4].**

Figure 7: Different types of nasal profile **[6]**

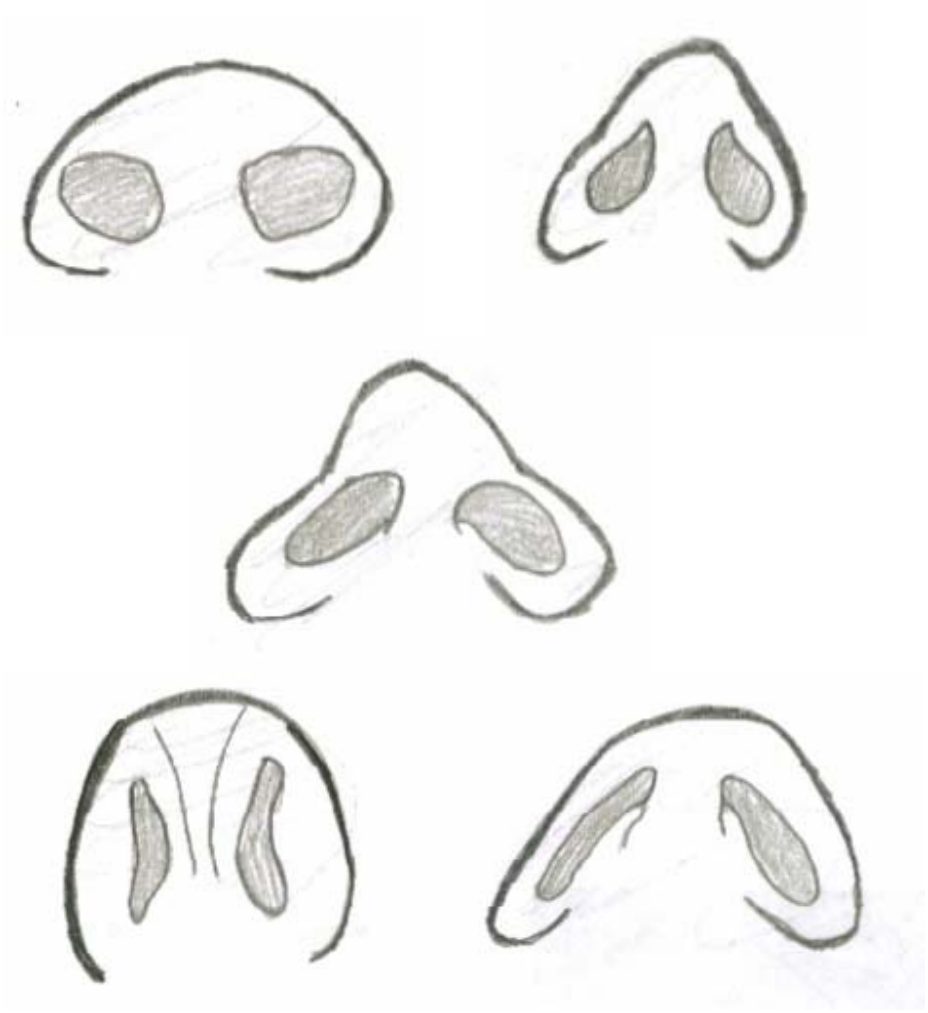


Type 1: Straight **Type 2: Convex** **Type 3: Concave**

Type 4: Convex above and straight below **Type 5: Convex and undulating** **Type 6: Concave and undulating**

by Raza MT

Figure 8: Different shapes of nostrils **[6]**



by Raza MT

Table 4: Factors affecting the reliability of acoustic rhinometry measurement **[84]**

Factors	
Operator	Improper connection at the nostril
	Non-reproducible positioning
	Misalignment of the probe in nasal axis
	Training and skill of the operator
Subject	Variation of posture
	Improperly controlled breathing
	Sinus cavity
	Degree of accuracy from top of the septum
	Occluded or partly occluded nasal cavity
Instrumentation	Calibration
	Evaluation of performance of instruments
Environment	Temperature
	Humidity
	Ambient external noise

2.4.5 Validation of Use

Documented measurements of human airways using acoustic reflection technique was done more than 20 years before it was first used for the nasal cavity. Interestingly due to certain technical aspects, the use of acoustic reflection technique in lower airway measurement has decreased in contrast to the increased use for nasal cavity measurements. Easy accessibility, less risk of cross modes, increased clinical application, less sound leakage and lowered computer costs may have favored the use in the nasal cavity **[58]**.

The different topographical measurements of the AR area- or volume-distance is suggested to represent a distal dimension of the nasal cavity. However as mentioned, there is no uniform agreement on the value and significance of each measurement in respect to nasal cavity dimension. MCA is the most frequently used AR determinant. In some subjects the MCA is located at the nasal valve while in others, especially in cases of turbinate hypertrophy, it is the anterior part of the inferior turbinate **[58]**. Under normal conditions, the MCA represents a narrow lumen of the functional valve, which is anterior (approximate 0.91 cm) to the anterior end of the inferior turbinate (at the distance of CSA 3.3 cm).

Standardization of measurements, sources of error and physical limitations of AR measurements have not been adequately evaluated. Possible errors and physical limitations of AR measurement due to the natural structure of nasal cavity and sinuses, and constriction in the nasal valve area have been observed in laboratory nose models, but not in the human nose. The effects of paranasal sinuses and low-

frequency acoustic resonances in the posterior part of the nasal cavity are not accounted for in the current AR algorithms **[89-91]**. Areas between 5 and 10 cm may be influenced by the sinuses and especially the ostia connecting them with the nasal cavity **[83]**. The measurement of both CSA and NV beyond a constriction area of less than 0.2 cm^2 or 0.28 cm^2 will cause significant systemic errors **[90, 91]**. Phipatanakul et al. used the MCA and NV measured at 0 to 5 cm and 5 to 10 cm from the nostril during the acute airway response to cat allergen exposure **[93]**. The authors concluded that although AR does provide an objective measure of nasal response to allergen exposure, it has significant limitations due to the lack of correlation with symptoms, the inability to measure a dose response, and the changes noted even among the control subjects. However, this unexpected result could be due to the uncorrected volume measurements since the MCA reported was very low (<0.1 cm^2) after cat allergen exposure.

Acoustic rhinometry and subjective assessment

Acoustic rhinometry and visual analogue scale

Objective measurements of nasal patency do not always correlate with a patient's subjective sensation of nasal obstruction and often some people are not able to evaluate their nasal patency in a correct way **[94].** Chan et al. **[51]** demonstrated no significant correlation between AR measurements (MCA and NV) with VAS despite a significant improvement of nasal obstruction in both VAS and AR measurements after treatment with Fluticasone propionate (FP). Roithmann et al. **[95]** could not demonstrate any significant correlation between combined (right and left) sensation of nasal patency (VAS) and total (right and left) MCA. However a significant

correlation was found between ipsilateral sensation of nasal patency (VAS) and ipsilateral AR measurements (MCA). The lack of association between total MCA with VAS may be because unilateral sensation enables subjects to better assess nasal airway patency. In the evaluation of nasal patency of patients with SDs **[96],** AR and Rhm were both very sensitive in revealing deviations in the anterior nasal cavity (Cottle area I-II) and that correlations were found more frequently between VAS and Rhm than between VAS and MCA, especially for severe deviations in area I and all deviations in area IV (deviations between 2.5 and 4.5cm). Other studies by Kim et al. **[97],** Tomkinson and Eccles **[98]** and Reber et al. **[99]** were also unable to demonstrate any correlation between VAS recordings and AR measurements.

The poor correlation between VAS and AR measurements could be due to the fact that VAS is actually a continuous *ordinal* data, whereas AR measurements are *numerical* data. As a result, small changes in the AR measurements may result in large shifts in the VAS. Additionally, the sensation of a nasal obstruction may not only be dependent on MCA and NV. It could be related to airflow patterns, the state of the mucociliary blanket and several other factors which can be affected by the underlying mucosal inflammation of rhinitis patients **[51]**.

Acoustic rhinometry and subjective point symptom score

Naito et al. **[47]** carried out a study to compare the sensation of nasal obstruction with measurements by Rhm and AR in Japanese adult patients with nasal complaints. The sensation of nasal obstruction on bilateral breathing was divided into five ranks or a 5-point subjective point symptom score. AR measurements were carried out by CSA

and NV.NV (0-4cm and 0-7cm) obtained from AR measurements correlated well with perception of nasal obstruction. In another study Mamikoglu et al. **[100]** demonstrated that nasal mucosal decongestion could be graded into five grades as mild, moderate, severe or markedly severe for objective evaluation of nasal congestion by AR.

Acoustic rhinometry and other objective methods

Corey et al. **[101]** evaluated the accuracy of AR with MRI in measuring CSA and NV within the first 6 cm from the nostril in the pre- and post- decongested nose. The correlations of CSA and volume measurements between the AR and MRI were high in the post-decongested and low in the pre-decongested nose. This may be due to nasal cycle or other unknown factors. The authors concluded that AR measurements (CSAs and NV) provide accurate information when compared with the MRI of the decongested nasal airway. However while comparing AD relationships of nasal cavities from five decapitated dogs and cats, Straszek et al. **[63]** concluded that MRI cannot be recommended as a gold standard for validation of AR. The reason might be because the estimated CSA from the MRI were very much dependent on subjective choices in the image processing and MRI also lacks the ability to define airspaces in communication with the nasal cavity. It might also be due to the complexity of the dog and cat nasal cavity.

AR and Rhm can provide accurate and reliable assessments of nasal patency to clinicians and researchers. However the two methods measure different aspects of nasal patency. AR measures nasal geometry calculating nasal CSA from hydraulic formula and Rhm measures nasal airflow and pressure. A significant, negative

nonlinear relationship between MCA (measured by AR) and nasal resistance to airflow (measured by Rhm) was demonstrated **[76, 102]**. The techniques can be complementary. AR may measure changes not measured by Rhm and vice versa. The resistance of a CSA may differ considerably depending on the shape despite a constant area **[58].** However AR measurements are direct quantification, independent of airflow and thus suitable for severely congested individuals. Severely blocked nose makes airflow turbulent and leads to inconsistent readings, which reduces the reproducibility of Rhm readings quite considerably. Additionally AR measurements are more sensitive to changes in obstruction giving AR an advantage over Rhm in nasal allergen challenge (NAC) studies. On the other hand AR assessment of CSA is localized to a specific site, whereas Rhm measurements assess all components of the nasal airway **[70, 102, 103]**.

Straszek and Pederson **[64]** explored the potential of AR in pharmacological research of nasal passageway in guinea pigs and rats. They compared AR findings with FDM. For guinea pigs AR only measured 70% of the volume by FDM for the first 2 cm of the nasal cavity. For rats AR only measured 83% (66-100%) of volume by FDM. The findings suggested that absolute nasal cavity dimensions are underestimated by AR in guinea pigs and rats. However this does not rule out that relative changes may not be correctly measured. The authors suggested that FDM might be possibly the most accurate alternative to AR for measurements of the nasal cavity geometry in small laboratory animals although it can only be used postmortem. In another study Straszek et al. **[63]** compared AR measurements with MRI and FDM measurements

in decapitated dogs and cats and demonstrated that AR underestimated CSA determined by FDM especially in the deeper parts of the nasal cavity.

2.4.6 Application

A PubMed search (www.pubmed.com) on August 10, 2004 was carried out with typing "Acoustic Rhinometry". The search yielded 402 results. The publication list was displayed after sorting out for "publication date", with the latest at the beginning of the list. The publication at the end of the list was by Lindholdt in 1989 **[104]**. There was a total of 33 (8.2%) publications during the last one year [from August 2003 to current]. This suggests a sustained interest in the application of AR after it was first mentioned 15 years back.

AR is being widely used in research and has been used to assess the relationship between nasal conditioning and nasal patency and geometry, changes in the nasal mucosa due to sex hormones**,** nasal physiology in professional athletes**,** effects of smoking on nasal patency and indoor air pollutants on nasal congestion **[105-111]**.

Huang et al. **[10]** investigated objectively and quantitatively nasal cycle using a combined measurement of Rhm, AR and VAS at short intervals of 10 min, as well as the response of nasal cycle fluctuation to nasal decongestant on 10 adult volunteers. A spontaneous change in nasal geometry and resistance, but not always a reciprocal pattern, was observed in every consecutive measurement (10 minutes interval). A significant negative correlation between both nasal passages was identified in five subjects by Rhm and only in two subjects by AR. These cyclic changes were, however, not detectable after the application of nasal decongestant. The period of

nasal cycle is estimated at 210 minutes (range from 140-263 minutes). The amplitude of daily fluctuation in MCA and NV was demonstrated to be generally less than 50% and for nasal resistance less than 100%, except higher values in allergic rhinitis subjects. In addition, even in as short as 10 minutes, the variation could be up to 14-18% for MCA, 12-13% for NV, 47-81% for resistance during inspiration and 62-63% for resistance during expiration. The authors concluded that a spontaneous fluctuation in nasal patency could be documented by either Rhm or AR every 10 minutes with irregular pattern, frequency and amplitude in both healthy and allergic rhinitis subjects. A detectable nasal cycle is not a universal phenomenon as it is frequently believed.

In another study Huang et al. **[19]** investigated the normal range of AR parameters in healthy volunteers from three racial groups in Singapore; Chinese, Malay and Indians. They also attempted to evaluate the role of these measurements in the documentation of structural abnormalities in the nose. AR measured MCA in the anterior 1 - 5 cm from nostril and NV between 0 to 5 cm from the nostril. The study demonstrated no significant difference in the normal range of AR measurements among the three races. AR was also able to determine the structural abnormality of the internal nasal cavity caused by DNS and HIT.

AR is gradually being used in numerous clinical studies and has been used to assess adenoidal tissue and the nasopharyngeal airway in children **[112, 113],** evaluating and comparing medical and surgical treatment of nasal polyps **[114-117]**, efficacy of septal and turbinate surgery **[71, 118-120],** adenoidectomy or adenotonsillectomy **[121, 122]** and nasal septal surgery in neonates **[123]**.

Chan et al. **[51]** evaluated, compared and correlated the effect of FP on the symptom of nasal obstruction by AR and VAS. A significant improvement in the VAS post-treatment compared to pre-treatment was noted. There was also a significant increase in NV and MCA after intranasal FP. Subjective improvements in symptoms did not correlate well with objective measurements as the correlation between VAS and AR was poor. The study proved AR to be a useful instrument in monitoring the effectiveness of medical therapy for perennial rhinitis.

Ozturk et al. **[124]** assessed the efficacy of triamcinolone acetonide aqueous nasal spray on nasal congestion by AR. Recorded AR measurements were NV (0 to 6 cm from the nostril), MCA, CSA 2.1 cm and CSA 4.02 cm. For statistical purposes and to control the effect of the nasal cycle, the sum of right and left nasal cavity values were used for analysis. All AR parameters measured in all patients improved significantly beginning from the second week of the treatment and remained so until the end of the treatment in all patients. There was also substantial symptomatic recovery in nasal obstruction according to patients' daily diary assessments. However there was no correlation between patients' own subjective assessment of nasal obstruction and objective AR assessment.

The reason behind the discrepancies between subjective assessment of nasal obstruction and objective AR measurements may be various, such as variation in subjects relative perception and tolerance of nasal obstruction, overestimation of the severity of nasal obstruction and comparatively increased sensitivity of AR in measuring nasal patency **[124]**.

3. AIM OF THESIS

The main objectives of the present thesis are….

"*…to validate the reliability of AR in the assessment of the nasal airway and to establish reference values for nasal patency that can serve as a basis for further studies*."

The specific aims of the individual studies were:

- To determine standardized values and factors effecting normal nasal cavity dimensions in healthy individuals. *(paper I and conference poster I & II).*

  Paper I: To investigate the relationship between nasal cavity geometry as measured by AR and body height, body weight and BMI in healthy adults and to determine standardized values for AR measurement.

- To validate the use and reliability of AR and identify the limitations of AR. *(paper II and conference oral presentation I and poster III).*

  Paper II: To investigate the quantitative value and possible errors of various AR area-distance (AD) measurements and to assess the relationship between the patient's subjective sensation and objective AR measurements in various nasal conditions.

- Use of AR in clinical and research work *(paper III and conference oral presentation II).*

Paper III: To determine if combination therapy with intranasal corticosteroid and oral antihistamine is superior to monotherapy in patients with moderate-severe PAR for symptom relief during treatment and prevention of relapse after cessation of therapy using subjective symptom score and AR.

4. SYNOPSIS OF THESIS

4.1 Acoustic rhinometry measurements

All AR measurements were done using the RhinoScan module (Rhinometrics A/S, Lynge, Denmark; version SRE 2100). Measurements were performed according to the standardized testing procedure described previously. Significance of the recorded measurements has already been mentioned.

4.2 Statistical analysis

All statistical analyses were performed using SPSS (SPSS Inc. Chicago, Illinois) statistical package (version 10.0) for windows. The statistical methods used will be described in individual studies

4.3 Paper 1: Relationship of body mass index, height and weight with nasal cavity dimensions and standardization of acoustic rhinometric values.

4.3.1 Objective

The nose varies with many anatomical and physiological factors. BMI, height and weight could also be a variable. BMI is calculated as a ratio between weight and height. It is a reliable indicator of body mass and fat **[125].** Adults with high relative BMI have an increased demand for oxygen and thus may have to breathe with higher frequency or more larger volumes during each inspiration **[5]**. In addition, an increased relative BMI is related to increased oral and nasal pressures, as well as an increased nasal airflow rate. Since the higher airflow rates were clearly evidenced in subjects with high BMI, there might also be a correlation between BMI and nasal airway size and resistance to inspiratory airflow. There are only a few studies investigating the relationship between BMI (including height and weight) and nasal cavity geometry, airflow rate and resistance **[5, 74, 126]**. Two previous studies carried out in Sweden and Finland demonstrated weak or no correlation between BMI and nasal cavity geometry in adults **[16, 74]**. Such a study has not been reported in the Asian population, which is important in standardization of reference values for AR measurements.

The objective of this study is to investigate the relationship between nasal cavity geometry as measured by AR and height, weight and BMI in healthy adults and to determine standardized values for AR measurement.

4.3.2 Material and methodology

A group of 73 volunteers were selected (44 males and 29 females). Subjects included were those without any nasal symptoms and no history of taking any medication for at least 1 month before entering the study. Individuals were excluded if there was a history of rhinitis/sinusitis or nasal structure malformations. BMI was calculated [BMI=Weight in kilograms/(Height in meters)^2]. AR measurements were performed in the standardized procedure as previously described.

4.3.3 Statistical analysis

All data were expressed as mean and median with minimum and maximum values. Pearson and Spearman correlations were used to investigate the association between BMI, height and weight and AR measurements. Correlations between the different AR measurements were also tested. A *p*- value of less than 0.05 was considered statistically significant.

4.3.4 Results

All study subjects completed this study. Age range of the study population was 18 to 64 years old with a mean (± standard error) of 34.9 ± 1.4 years. Characteristics of study subjects and BMI distribution is given in **Table 5** and **Table 6** respectively. There was no one in the obese class III category (BMI over 40 kg/m^2)**.** Values of different AR measurements are given in **Table 7**. There is a significant correlation ($p<0.001$) among all AR measurements. Measurements of BMI, height, weight showed no statistically significant correlation with any AR measurements. Scatter

plots showing distribution of height, weight and BMI in relation to MCA in the study population have been demonstrated in **Figure 9**, **Figure 10** and **Figure 11** respectively.

4.3.5 Discussion

The standardization for AR measurements in the "normal nose" as compared to different types of structural and mucosal abnormalities is important. A strict selection criteria was abided to select study subjects with healthy noses and a standardized procedure was followed to perform AR measurements**.** MCA is the most frequently used AR determinant. The mMCA was (0.74 ± 0.03 cm^2). This value correlated well with values of a previous study (0.75 ± 0.02 cm^2) that was performed in healthy adult Singaporean Chinese, Malays and Indians **[19]** in the same center**.** The same study also had demonstrated that there was no significant difference of AR measurements in these three races. Thus the AR measurements obtained could be used as a standardized normal value for the population of Singapore.

According to our study nasal cavity size did not change with increasing BMI. Whether this lack of correlation has any role on illnesses associated with increased BMI could be a matter of interest. The mean BMI of the study population was 23.1 kg/m^2 (median of 22.7 kg/m^2), which is close to an adult ideal BMI as recommended by WHO (World Health Organization**) [127].** The age, weight, height and BMI distribution corresponded well with a cross-sectional population study carried out on 4723 adult Singaporeans **[128].** It indicates that the study population

Table 5: Characteristics of study subjects in paper 1

	Mean ± SD	Median	Minimum	Maximum
Female				
Age (yr)	36.6 ±10.9	37	18	59
Weight (kg)	57.9 ± 11.8	55.0	38.0	88.0
Height (m)	1.57 ± 6.4	1.56	1.44	1.67
BMI* (kg/m^2)	23.9 ± 4.9	22.7	15.6	37.6
Male				
Age (yr)	33.5 ± 11.7	30	22	64
Weight (kg)	66.9 ± 9.3	65.5	38.0	86.0
Height (m)	1.71 ± 7.3	1.72	1.50	1.88
BMI* (kg/m^2)	22.7 ± 3.3	22.7	13.2	30.5

*BMI, Body mass index

Table 6: Body mass index distribution of the population in paper 1

BMI* (kg/m^2)	**WHO** classification**	**Study (n)**
< 18.5	Underweight	4
18.5-24.99	Normal range	50
≥ 25.00	Overweight	19
25.0-29.9	Preobese	15
30.0-34.99	Obese class I	3
35.0-39.9	Obese class II	1
≥ 40.0	Obese Class III	0

* BMI, Body mass index
** WHO, World Health Organization **[127]**

Table 7: Acoustic rhinometric measurements in paper 1

	Right ± SE	**Left ± SE**	**Mean ± SE**	**Total ± SE**
CSA-3.3 (cm^2)	1.24 ± 0.07	1.30 ± 0.06	na	na
CSA-4.0 (cm^2)	1.76 ± 0.12	1.68 ± 0.08	na	na
MCA (cm^2)	0.74 ± 0.04	0.74 ± 0.03	0.74 ± 0.03	na
V (cm^3)	5.69 ± 0.20	5.60 ± 0.17	na	11.3 ± 0.3

CSA, Cross sectional area
MCA, Minimum cross sectional area
V, Volume of nasal cavity 1 to 5cm from the nostril.
NA, not applicable

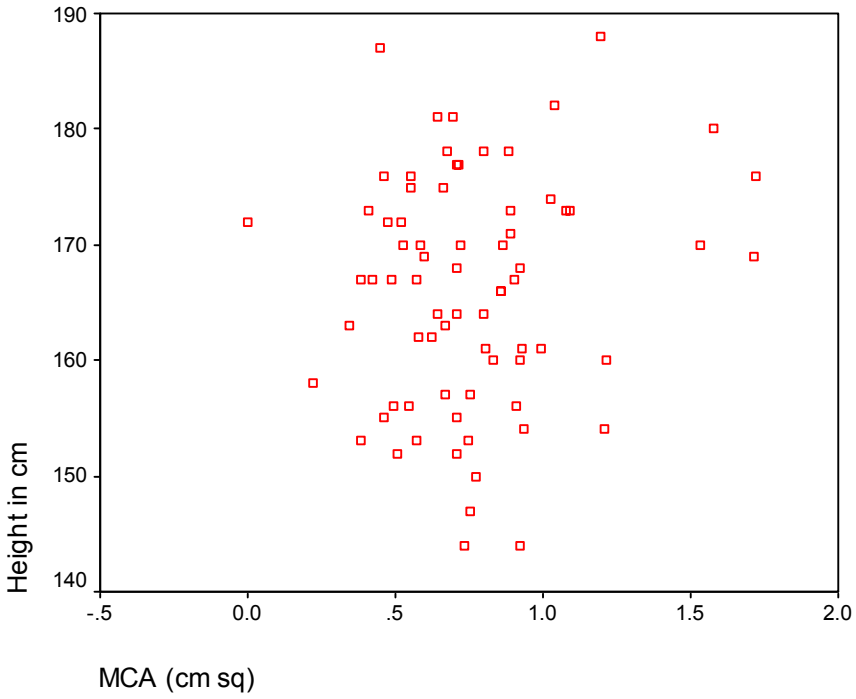


Figure 9: Distribution of minimal cross sectional area values in relation to height (cm) of study population in paper 1

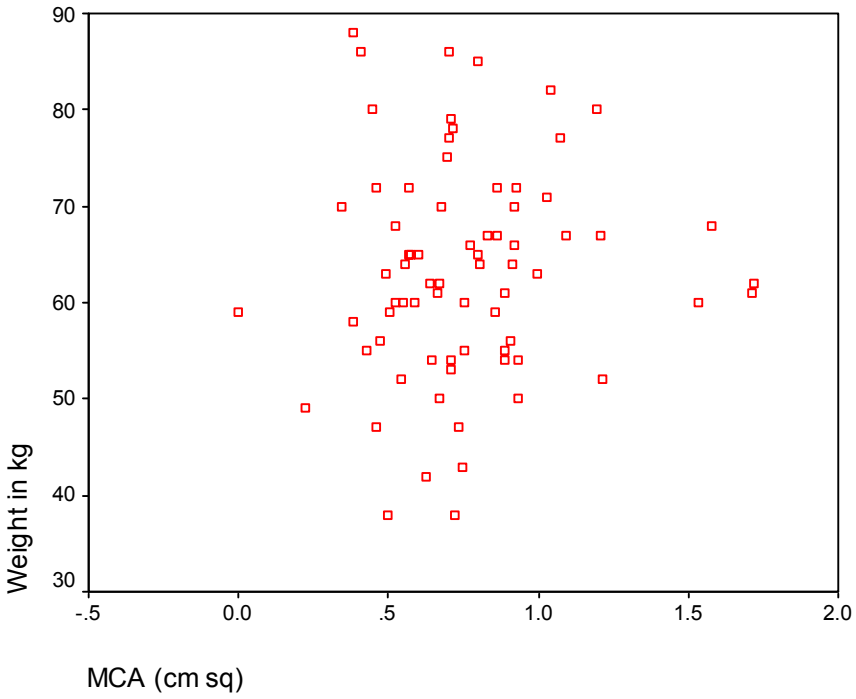


Figure 10: Distribution of minimal cross sectional area values in relation to weight (kg) of study population in paper 1.

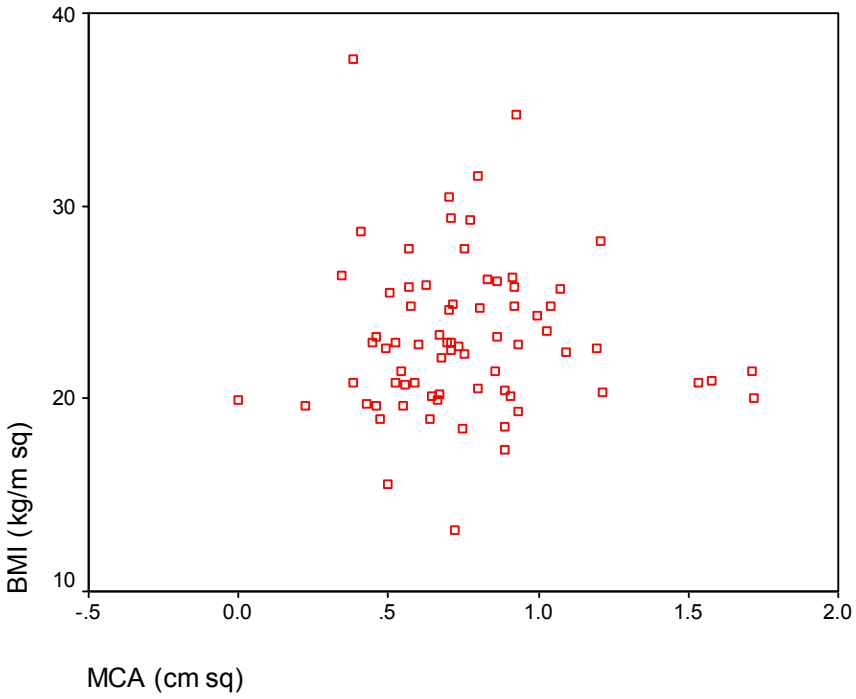


Figure 11: Distribution of minimal cross sectional area values in relation to Body mass index (kg/m^2) of study population in paper 1

was representative of the Singaporean population. However we did not have any patients in our study with morbid obesity (Obesity class III, BMI > 40 kg/m^2) **[127]**. Further studies to illustrate the effect of a very high BMI on nasal cavity geometry and respiratory physiology are needed.

Nasal decongestants can change the normal mucosal turgidity, thereby invalidating the measurements as indicators of normal anatomical and physiological status in healthy noses **[74].** The high mucosal blood volume and increased vascular tissue lining in the bony turbinates has effect on nasal cavity physiology, like nasal wall compliance **[129]**. Nasal wall compliance increases progressively from the nasal valve to the anterior and medial part of the inferior turbinate and to the middle meatus region (although the turbinates are located within a non distensible bony cavity). After decongestant, compliance decreases and became similar in these three regions. Acclimatization period reduces mucosal variability during measurement All subjects were acclimatized for 20 minutes prior to the test **[58].** There is still a lack of a standardized method of use of decongestants in clinical and research purposes. Efficacy of decongestants differs on route of administration, type of preparation, time duration after administration and method of application. In the non-decongested nose a significant difference in mMCA has been demonstrated between three racial groups (Oriental, Caucasians and Negroes). After application of a decongestant, Orientals and Caucasians become a homogenous population with the value for Negroes remaining significantly higher. This would suggest that much of the difference in MCA seen between Orientals and Caucasian was due to an increased amount of vascular tissue in Orientals. The fact that this remained significantly higher in

Negroes after decongestion would suggest that they have a larger bony aperture. Thus the findings of apparent HIT on anterior rhinoscopy in Negroes may be the normal state **[18]**. Therefore, we did not use decongestants as did two similar studies carried on the European population **[16, 74].**

4.4 Paper 2: Clinical value of acoustic rhinometry measurements, and the relationship between subjective sensation and objective acoustic rhinometry measurements

4.4.1 Objective

All possible sources of errors and physical limitations have to be considered when using AR as an investigational tool in study of nasal physiology and pathophysiology in various clinical and experimental settings. Standardization of measurements, sources of error and physical limitations of AR measurements have not been adequately evaluated**.** In addition, erectile tissue in the nose, especially the inferior turbinates, fluctuates greatly in size depending on physiological changes (e.g., nasal cycle, body temperature, posture and exercise) and response to inflammation **[10]**. All these factors have to be taken into account when using AR as an investigational tool in different studies.

The main objective of this paper is to investigate the quantitative value and possible errors of various AD measurements of AR and to assess the relationship between the patient's subjective sensation and objective AR measurements in various nasal conditions.

4.4.2 Material and Method

Fifteen adult patients (8 males and 7 females) between 21 and 44 years of age (mean age of 28.4 years) with ongoing PAR were recruited. The patients had no acute nasal symptoms and had not taken any medication during the previous two weeks (at least

30 days for any nasal or systemic corticosteriods). Their sensitization to *Bt* (*blomia tropicalis*) was confirmed by a positive skin prick reaction. Crude extract of *Bt* was prepared from cultured mites, as described previously **[130]**.

Nasal obstruction was recorded using a 4 point symptom score **[Table 3]**. AR measurements were performed in the standardized procedure as previously described.

Nasal allergen challenge

The NAC was carried out in a double-blind manner using nasal spray, 1 puff (0.04 ml of allergen solution) per nostril. The study subject was asked to be in complete apnea during spraying. This precaution would prevent the provocation extract from entering the lower airway. The NAC was started by using phosphate-buffered saline (PBS) (diluent of allergen extract) and then subsequently increasing concentrations of *Bt* extracts; 0.6 μg/ml (low), 6 μg/ml (medium) and 60 μg/ml (high) at intervals of 15 min. Subjective and objective symptoms were collected as a baseline, 15 minutes after each nasal challenge and at 30 min, 1, 3, 5 and 7 hours after the last challenge in order to study the early-phase reaction (EPR) and late-phase reaction (LPR). After a washout period of at least 2 weeks, 6 of the patients underwent an identical challenging procedure with only PBS as a control.

4.4.3 Statistical analysis

A repeated measurement analysis was performed to assess the time-trend of the responses and mean differences between the mite-challenge subjects and controls taking into account the group & time interactions. Coefficient of variation (CV) was

used to compare the variability of the AD measurements at each CSA area over time. Spearman's correlation was applied to investigate the relationship between AD measurements of AR and subjective symptom scores.

4.4.4 Results

All study subjects completed the study.

Subjective nasal symptoms

Figure 12 shows the mean nasal (±SD) symptom scores before and after NAC with control solution (PBS) and *Bt*. There was a dose-response increase in nasal obstruction score after *Bt* challenges with a maximal blockage (mean score of 2.33±0.25) at 30 min after challenge. There was a significant difference (p=0.025) between the two groups with the study-subjects experiencing a significant change over time (p=0.011) but not the controls (time & group interactions, p=0.002).

AR area-distance measurements

Figure 13 shows the mean (±SD) of MCA, distance to MCA, CSA 3.3, CSA 4.0 and CSA 6.4 measurements at different time points after nasal challenge with *Bt* and control solution. For mMCA, mCSA 3.3 and mCSA 4.0, reduction of CSAs after nasal challenges with *Bt* are confirmed by statistically significant differences as compared to control challenge, as well as time trend and time group interactions. Maximal reduction of mMCA (0.26 cm^2) is associated with the maximal increase of mean distance to MCA (2.86 cm) at 30 min after NAC.

CV at different CSAs is shown in **Table 8**. The variation at mCSA 6.4 is more varied as compared to the other AD measurements as shown by the larger mean CV with a twice as large standard error and wider range (minimal and maximal values).

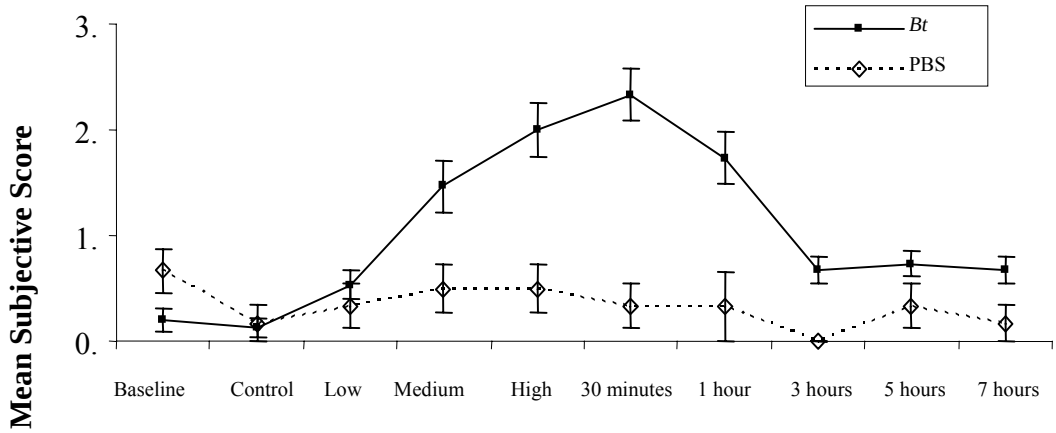
Relationship between nasal symptom scores and AR area-distances

There is an inverse relationship between symptoms score and MCA ($r=-0.568$, $p<0.001$) **[Figure 14].** Although there are significant correlations between nasal obstruction scores and all 4 area-distance measurements, it appears that the strongest relationship is found between nasal symptom score and mMCA ($r = 0.75$), and followed by mCSA 3.3 ($r = 0.54$), mCSA 4.0 ($r = 0.53$) and mCSA 6.4 ($r = 0.20$). In the correlation between MCA and the other 3 AD measurements, once again the CSA 6.4 measurement differs largely from other AD measurements in terms of their relationship with nasal obstruction score and MCA.

Influence of constriction of MCA (<0.2 cm^2) on area-distances beyond MCA

Results showed that when the MCA reached an area <0.2 cm^2, measurements of CSA 3.3 and CSA 4.0 were reduced by 60 – 70%.

Figure 12: Mean subjective symptom score of nasal obstruction before and after *Blomia tropicalis* (*Bt*) and control (PBS) challenge in paper 2 **[2]**



Differences between case and control: $p = 0.025$
Time trend: $p = 0.011$
Time & group interaction: $p = 0.002$.

Figure 13: Mean values (±SD) of MCA, CSA 3.3, CSA4.0 and CSA 6.4 after nasal challenge with house dust mite *Blomia tropicalis (Bt)* and control solution (PBS) in paper 2 **[2].**

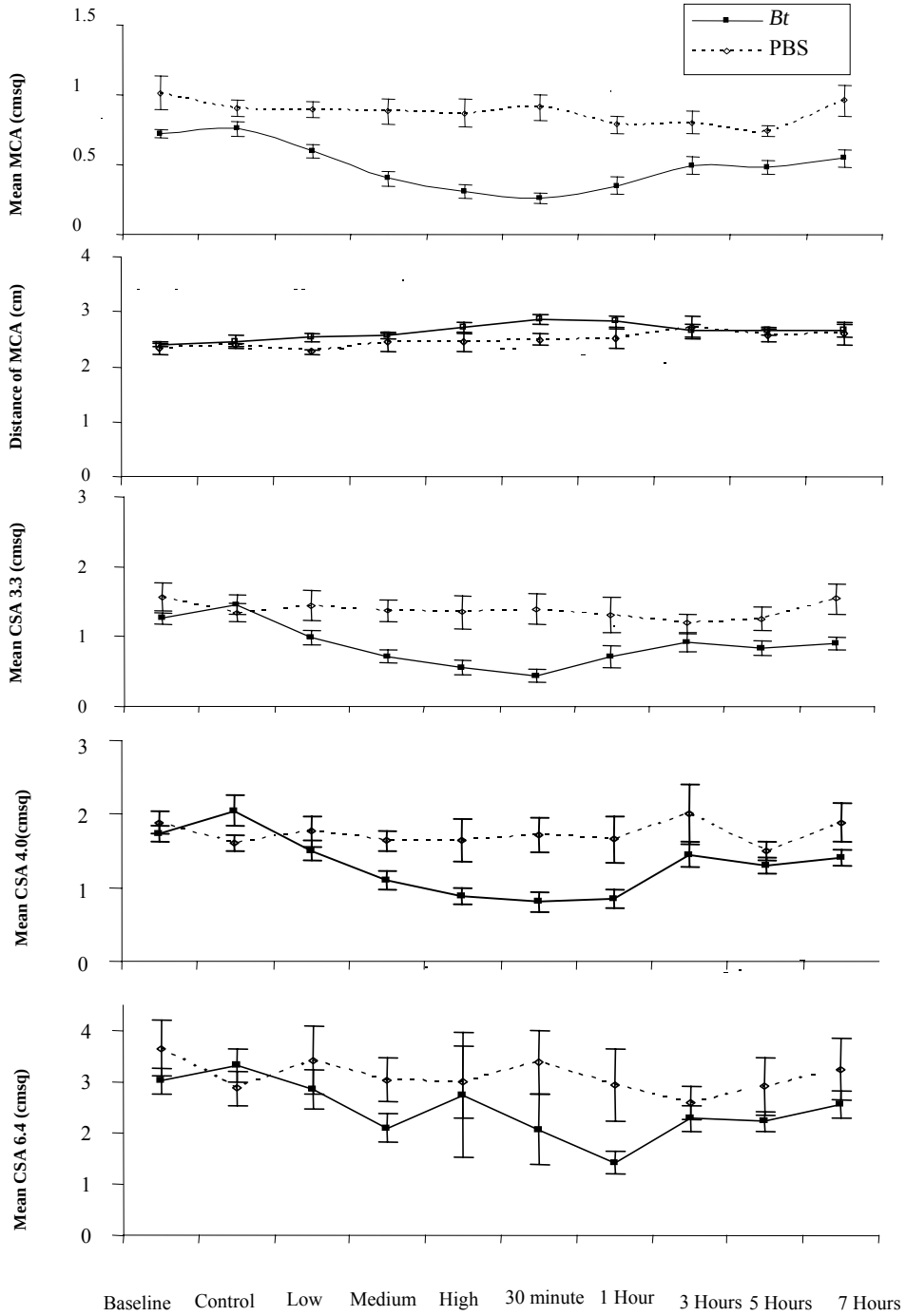
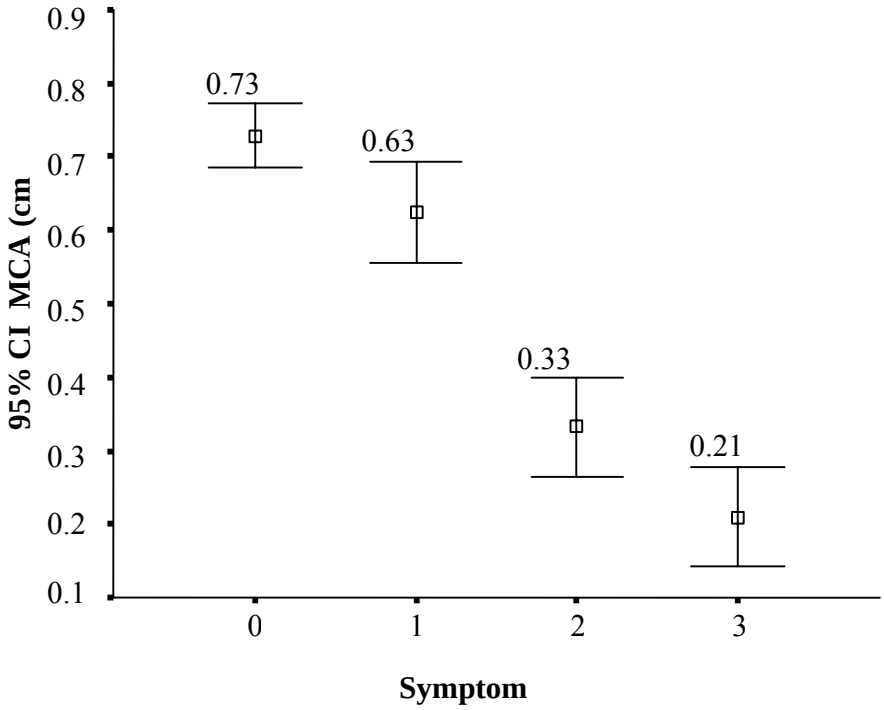


Table 8: Coefficient of variation at different cross sectional areas (cm^2) in study 2. Calculations were based on a total of 420 measurements; nasal challenges with *Blomia tropicalis* (n=15) and control solution (n=6) at 10 different time of measurements, right and left sides **[2]**.

Area in Distance (cm)	Coefficient of variation				
	Mean	**Standard error**	**Minimum**	**Maximum**	**Median**
MCA*	0.47	0.06	0.23	0.76	0.45
CSA 3.3	0.52	0.06	0.28	0.82	0.47
CSA 4.0	0.42	0.05	0.24	0.64	0.39
CSA 6.4	0.61	0.11	0.35	1.45	0.46

p = 0.533 (kruskal wallis test).
*: Minimum cross-sectional area.

Figure 14: Correlation between MCA and symptom score in paper 2. Spearman's correlation: r= -0.568 ($p < 0.001$). Values shown on the graph are mean (±SD) of MCA **[2].**



4.4.5 Discussion

AR area-distance measurements

Beside MCA the other common AR measurements are CSA at a distance of 3.3, 4.0 and 6.4 cm from the nostril. However MCA appears to be the most sensitive measurement. In study 2 we demonstrated that CSA 6.4 was found to be least reliable. It was reported that the effects of paranasal sinuses and low-frequency acoustic resonances in the posterior part of the nasal cavity are not accounted for in the current AR algorithms **[89].** Areas between 5 and 10 cm may be influenced by the sinuses and especially the ostia connecting them with the nasal cavity **[83].**

In some subjects the MCA is located at the nasal valve while in others, especially in cases of turbinate hypertrophy, it is the anterior part of the inferior turbinate **[68]**. Under normal conditions, the MCA represents a narrow lumen of the functional valve, which is anterior (approximate 0.91 cm) to the anterior end of the inferior turbinate (at the distance of CSA 3.3 cm). During allergic reactions, it moves more posteriorly to the anterior end of the inferior turbinate due to the dilative reaction of the capacitance vessels of the erectile tissue. In paper 2 the mMCA moved posteriorly from a baseline distance of 2.39 ± 0.16 cm to a distance of 2.86 ± 0.31 cm, thirty minutes after NAC.

Measurements beyond a significant constriction

It has been demonstrated with models that CSA and volume beyond a constriction area of less than 0.2 cm^2 or 0.28 cm^2 will cause significant systemic errors **[90, 91]**. In

normal adults the CSA of the nasal valve is 0.2-0.6 cm^2. As the constriction narrows (<0.2 cm^2) the measurements beyond this point are often underestimated **[91].**

MCA (left and right separately) was divided into two groups; <0.2 cm^2 and ≥0.2 cm^2 as measured during the time course of NAC, and then compared with the corresponding AD measurements (CSA 3.3, CSA 4.0 and CSA 6.4) beyond the MCA. Results showed that when the MCA reached an area <0.2 cm^2, measurements of CSA 3.3 and CSA 4.0 were reduced by 60 – 70%. This is particularly important when using AR in a nasal challenge study, which may cause severe nasal obstruction during the EPR.

Subjective measurements

There is an inverse relationship between subjective symptoms score and MCA (r=-0.568, p<0.001). With subjective symptom scores of zero and one, there was a wider range of MCA which corresponded well with a wide variation of normal nasal cavity dimensions. Interestingly, MCA range is more specific with pathological conditions causing severe nasal obstruction (score 2 and 3).

Although there are significant correlations between nasal obstruction scores and all 4 area-distance measurements, it appears that the strongest relationship is found between nasal symptom score and mMCA (r = 0.75), and followed by mCSA 3.3 (r = 0.54), mCSA 4.0 (r = 0.53) and mCSA 6.4 (r = 0.20). The correlations between MCA and the other 3 area-distance measurements are shown in **[Table 9]**. CSA 6.4 measurement differed largely from other AD measurements in terms of their relationship with nasal obstruction score.

Table 9: Interrelationships of acoustic rhinometry area-distance measurements, and their relationship with the subjective nasal obstruction scores in paper 2 **[2]**

Area in Distance (cm)	**Coefficient Correlation**	
	MCA	**Nasal Obstruction Scores**
MCA*	-	0.75 ($p<0.001$)
CSA 3.3**	0.807 ($p<0.001$)	0.54 ($p<0.001$)
CSA 4.0	0.631 ($p<0.001$)	0.53 ($p<0.001$)
CSA 6.4	0.359 ($p<0.001$)	0.20 ($p<0.001$)

*__MCA__ : Minimum cross-sectional area.
__CSA:__ Cross-sectional area

4.5 Paper 3: Comparison between combination therapy (intranasal corticosteroid and oral antihistamine) and monotherapy in perennial allergic rhinitis patients

4.5.1 Objective

The clinical application of AR has gradually increased. Numerous studies have been carried out with the aid of AR to evaluate and compare the efficacy of different medical and surgical modalities of treatment.

Allergic rhinitis may significantly impair the quality of life (QOL), limit daily activities and affect the performance and productivity of those affected. Nasal obstruction is the most common symptom of PAR **[41]**. To be effective in treating allergic rhinitis, any modality of treatment should be able to reduce nasal obstruction. AR can be used to measure objectively the efficacy of reducing nasal obstruction.

Both intranasal corticosteroids (INC) and antihistamines have been shown to be effective for allergic rhinitis. In patients with persistent disease, it is often difficult to ensure compliance for longer periods despite the continued presence of symptoms. Hence short term intermittent therapy could be more acceptable and practical. Such a therapeutic strategy has not been explored previously and the efficacy of INC and antihistamines, whether used singly or in combination in such a strategy has not been widely studied.

The objective of this study is to determine if combination therapy with INC and oral antihistamine is superior to monotherapy in patients with moderate-severe PAR for symptom relief during treatment and prevention of relapse after cessation of therapy.

4.5.2 Material and Methodology

Forty-two patients with moderate-severe PAR were randomized into 3 treatment groups to receive intranasal triamcinolone acetonate (TAA), fexofenadine or a combination of both for 4 weeks. Patients were assessed during the initial randomization visit and at the end of the 4-week treatment period. Treatment was terminated after 4 weeks unless special requests were made for continuation. Outcome measures recorded and analysed at initial and follow-up assessments included both subjective and objective parameters.

A 4- point scale was used to assess nasal symptoms (obstruction, itch, sneezing and rhinorrhoea) separately. The individual scores were added to get the total symptom score. Efficacy measures were changes from baseline in nasal symptom scores (both individual and total scores), disease severity, Rhinoconjunctivities QOL questionnaire scores (RQLQ), AR measurements (mCSA 3.3cm and tNV 1 to 4cm from nostril) and patient-rated overall treatment efficacy at the end of therapy. AR measurement were recorded using the standardized testing procedure as previously described.

4.5.3 Statistical analysis

Postulating that a unit decrease from baseline in week 4 for each symptom score within treatment groups is of clinical significance, with a standard deviation of 1 for

the difference between week 4 and baseline, 14 subjects in each group were required to obtain a statistical significance basing on a 2-sided test of 5% and power 80%.

Data were expressed as values and percentages or as mean ± standard deviation where applicable. Analysis was performed using the Chi-square test (with Fisher's correction if necessary) for categorical variables with odds ratios presented where applicable. One-way analysis of variance (ANOVA) for continuous variables were performed when normality and homogeneity of variance assumptions were satisfied otherwise the Kruskal-Wallis test was applied. A p value of <0.05 was considered statistically significant.

4.5.4 Results

At week 4, the mean individual and total nasal symptom scores in all the 3 treatment groups were reduced and the improvement was significant compared to baseline. The combination group achieved better improvement than the monotherapy groups though inter group difference was not statistically significant.

Like nasal symptom score there was no significant difference between the groups in the mean change from baseline of the mCSA and tNV **[Table 10]**. However objective AR measurements at week 4, showed significant improvement in mCSA and tNV from baseline only in combination and TAA groups indicating improved nasal patency. No improvement was demonstrated in the fexofenadine group. Likewise patients in combination and TAA groups were more likely to rate their therapy as effective. (OR=8. 95% CI 1.8 - 35.7)

Compared to monotherapy, patients on combination therapy reported a significant improvement in quality of life (decrease in overall RQLQ score 2.14±1.34 vs 1.13±0.78 and 1.15±1.02 for combination vs nasal corticosteriod and antihistamine respectively) and reduction in disease severity (71.4% vs 50% and 21.4% respectively improved to mild PAR) during the treatment period. A high relapse rate (>70%) was observed in all groups after cessation of therapy.

4.5.5 Discussion

One-month combination therapy was not superior to monotherapy over the same duration for symptom relief or AR measurements f nasal patency. However combination therapy was associated with significant improvement in the patients' QOL and in reducing the disease severity compared to monotherapy. The disease control at the end of the treatment period was suboptimal and the relapse rate one month after cessation of therapy was high in all three groups.

Table 10: Mean acoustic rhinometry measurements: at baseline, week 4 and change from baseline at week 4 in study 3.

	TAA	Fexofenadine	Combination
mCSA			
Baseline	0.84±0.40	0.88±0.30	0.82±0.25
Week 4	1.03±0.37	0.87±0.40	1.09±0.35
Change from baseline	0.19±0.31*	-0.03±0.47	0.28±0.27*
tNV			
Baseline	4.92±0.92	4.71±1.14	4.47±0.89
Week 4	5.62±1.28	5.27±1.13	5.60±1.15
Change from baseline	0.70±0.92#	0.50±1.60	1.30±1.00#

Comparison within group between baseline and week 4,
* $p<0.05$
# $p<0.01$

5. CONCLUSION

"Acoustic rhinometry is a user-friendly procedure suitable for clinic and research. It is a rapid, non-invasive and easy to perform test that requires minimal co-operation from the patient causing little or no discomfort and is highly reproducible."

1. Acoustic rhinometry is a useful and objective investigational tool in the evaluation of nasal physiology and pathophysiology.
2. Several topographical acoustic rhinometry measurements of the area- or volume- distance have been introduced. We have demonstrated minimal cross-sectional area (MCA) to be the most sensitive parameter that correlates well with the sensation of nasal obstruction. Meanwhile cross sectional area measurements at 6.4 cm from the nostrils were found to be least reliable.
3. Possible errors and physical limitations of acoustic rhinometry measurements have been observed in laboratory nose models. We have demonstrated in humans that distal measurements beyond a significant constriction (MCA $\leq$ 0.2 cm^2) can be underestimated and should be ignored.

4. Methodological aspects of measurements can influence acoustic measurements. A standardized procedure of recording measurement has been described in detail in the thesis.

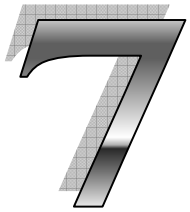
5. Acoustic rhinometry can be used successfully in clinic and research. We have defined the value for the normal nasal cavity dimensions for healthy Singaporean adults (mMCA was 0.74 ± 0.03 cm^2). By acoustic rhiometry measurements we also concluded that nasal cavity geometry is not affected by body mass index, body height and weight.

6. Acoustic rhinometry measurements of nasal airway patency helped to evaluate different treamtent therapies for allergic rhinitis.

6. FUTURE RESEARCH

- There were no subjects in our study (paper 1) with morbid obesity (Obesity class III, BMI > 40 kg/m^2). Further studies to illustrate the effect of a very high BMI on nasal cavity geometry and respiratory physiology are needed.
- A reference AR values for normal nasal cavity dimensions in children of our population (Singaporean) is also required which will help to understand pathogenesis of certain disease processes, as for example OSA and otitis media.
- The relationship between subjective sensation and objective acoustic rhinometry measurements has been seen in a NAC study (paper 2). Such relationship should be investigated in non-challenge patients.
- Standardized testing procedure is required to be compared with other procedures followed in other institutions for possible errors.

7. ADDITIONAL RESEARCH



7.1. Control of nasal obstruction in perennial allergic rhinitis.

Nasal obstruction, the cardinal symptom of PAR, is one of the most common symptoms encountered in primary care and in specialist clinics. It is difficult to quantify by clinical examination, and, hence, objective assessment of the nasal airway is critical to rhinologic research. Nasal obstruction in PAR must be treated the year round, and therefore treatment choices, costs, and compliance all become important public health issues.

Many inflammatory and neurogenic mediators released during allergic reactions are able to cause plasma exudation and vasodilatation, with resultant edema and swelling of the nasal mucosa. Recently, technological advancements have made it possible to qualitatively and quantitatively study the nasal airway, providing greater insights into the understanding of physiological fluctuation and pathophysiological manifestations of nasal patency. From recent international guidelines, the management of allergic rhinitis includes combining treatments of the upper and lower airways, by using patient education, allergen avoidance, pharmacological treatment, and specific immunotherapy. Surgery may be needed as an adjunctive intervention. Multiple methods have been introduced to treat turbinate hypertrophy. However, preservation of adequate nasal mucosal function is important, together with long-term results.

It is important that consensus recommendations for the management of allergic rhinitis be designed and implemented by all levels of medical specialists in order to improve treatment outcomes.

7.2. Biological Characteristic Of Histamine And Its Role In Allergic Rhintis

Histamine is a major mediator and antihistamines are among the most commonly used pharmacologic treatment of allergic disorders. Histamine stimulation of the nasal mucosa produces the classical symptoms of allergic rhinitis**.** Histamine exerts its actions through interaction with four recognized human histamine-receptor subtypes (H1-4). The role of histamine in nasal symptomatology is confirmed by the reproduction of nasal symptoms after nasal provocation with histamine and that these symptoms can be inhibited by the application of histamine receptor antagonists Effects on the human nose may be mediated via both H1R and H2R and the role of H3R has not been fully clarified. H1R stimulation reproduces any of the classical symptoms of rhinitis and therefore can be well controlled by H1-antihistamines, with the greatest effect on the neurally mediated responses. The vast majority of H1R on nasal mucosal blood vessels are localized on endothelial cells and stimulation of the HIR induces vascular permeability in the nasal mucosa. The role of H2R in capillary permeability is uncertain. The dilatation of nasal capacitance vessels responsible for the increase in nasal airway resistance is mediated via both H1R and H2R, but the effect of the H2R predominates. Vasodilation mediated by H1R is rapid in onset but short lived and that by H2R is slower in onset but more sustained. Therefore a combination of H1R and H2R antagonists are more effective than H1R blockers alone in reducing nasal congestion.

7.3. Association of Rhinitis with Atopy, Asthma, Hypertension and Some major illness

The aim of this study was to investigate the relationship between rhinitis, PAR, asthma and major illness (e.g., hypertension, coronary arterial disease, diabetics) in Singapore. A significant association between rhinitis and atopy, asthma, high density lipoprotein-cholesterol and age was found. In patients with PAR, significant associations were found between PAR and asthma, age, coronary arterial disease, diabetes(negative) and BMI (negative). Asthma was only associated with rhinitis and BMI, but not with atopy. There was no association between rhinitis/PAR and hypertension.

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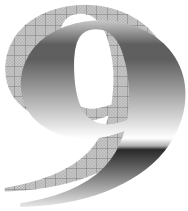
9. APPENDIX



(published papers, paper in press, slides of oral presentation and copy of poster presented in conference)

9.1 Paper 2: Clinical value of acoustic rhinometry measurements, and the relationship between subjective sensation and objective acoustic rhinometry measurements

(***published***)

Wang DY, **Raza MT**, Goh YT, Lee BW, Chan YH. Acoustic rhinometry in nasal allergen challenge study: which dimensional measures are meaningful? Clin Exp Allergy 2004;34:1093-1098

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Acoustic rhinometry in nasal allergen challenge study: which dimensional measures are meaningful?

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Summary

Background Acoustic rhinometry (AR) is commonly used as a quantitative assessment of nasal response to nasal allergen challenge (NAC). However, sources of error and physical limitations of various AR area–distance measurements have not been adequately evaluated.

Objective To investigate the clinical value of AR measurements, and the relationship between subjective sensation and objective AR measurements in the NAC study.

Methods Nasal challenge using increasing concentrations of crude *Blomia tropicalis* (*Bt*) extracts (0.6, 6, and 60 μg/mL) was performed in 15 adult patients (eight males and seven females) with ongoing persistent allergic rhinitis. Subjective symptom scores of nasal obstruction were recorded together with the objective AR measurements of the minimum cross-sectional area (MCA), distance to MCA and cross-sectional area (CSA) at 3.3, 4.0 and 6.4 cm from the nostril, during the 7 h after the last challenge.

Results The dose–response increase in nasal obstruction score was significantly ($P < 0.001$ for all) associated with decreases in mean MCA ($r = 0.75$), mean CSA3.3 ($r = 0.54$), mean CSA4.0 ($r = 0.53$) and mean CSA6.4 ($r = 0.20$). The mean MCA (± SD) for each subjective symptom score 0, 1, 2 and 3 was found to be 0.73 (± 0.22) cm^2, 0.63 (± 0.29) cm^2, 0.33 (± 0.17) cm^2 and 0.21 (± 0.14) cm^2, respectively. When the MCA (left and right separately) reached an area $< 0.2\,cm^2$, measurements of CSA3.3 and CSA4.0 were significantly reduced by 60–70%.

Conclusion This study demonstrates that AR is a useful and objective investigational tool, which correlates well with the sensation of nasal obstruction. MCA, CSA3.3 and CSA4.0 are more reliable measurements than CSA6.4 due to physical limitations. It is important to note that when the MCA is smaller than $0.2\,cm^2$, a common condition in the early-phase reaction, area–distance measurements beyond this point can be misinterpreted and should be considered with caution.

Keywords acoustic rhinometry, *Blomia tropicalis*, cross-sectional area, nasal allergen challenge, nasal obstruction, persistent allergic rhinitis

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Introduction

Nasal allergen challenge (NAC) is a valid and reliable tool for studying the pathophysiological mechanisms involved in allergic inflammation [1]. Nasal obstruction is one of the cardinal symptoms of allergic rhinitis. Therefore, subjective and objective measurements of nasal obstruction are essential in the assessment of quantitative nasal responses to allergens.

Acoustic rhinometry (AR) measures cross-sectional areas (CSAs) and the volume of the internal nasal cavity, which helps to define objectively the structural pathologies of the nasal passage [2]. In the literature, AR has been commonly used in nasal challenge studies with allergens or mediators (i.e., histamine) [3–9]. Several topographical measurements of the AR area– or volume–distance have been introduced, such as minimal cross-sectional area (MCA), distance to MCA, CSA at 3.3, 4.0 and 6.4 cm from the nostril. Although each measurement is suggested to represent a distal dimension of the nasal cavity, there is no uniform agreement among experts on the value and significance of each measurement in respect to nasal cavity dimension. In addition, possible errors and physical limitations of AR measurement due to the natural structure of nasal cavity and sinuses, and constriction in the nasal valve area have been observed in laboratory nose models, but not in the human nose [10–12].

In this study NAC using house dust mite *Blomia tropicalis* (*Bt*) was performed in patients with persistent allergic rhinitis (PAR). AR was performed, and the subjective sensation of nasal obstruction was recorded, during the early- and late-phase reactions after NAC. The aim of this study was to investigate the quantitative value and possible errors of various AR distance–area measurements in patients who experienced subjective symptoms varying from no obstruction to a maximal nasal obstruction caused by NAC. We assessed the

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relationship between the patient's subjective sensation and objective AR measurements in various nasal conditions.

Methodology

Study patients

Fifteen adult patients (eight males and seven females) between 21 and 44 years of age (mean age of 28.4 years) with ongoing PAR were recruited. Their sensitization to *Bt* was confirmed by a positive skin prick reaction. The patients had no acute nasal symptoms and had not taken any medication during the previous 2 weeks (at least 30 days for any nasal or systemic corticosteriods). A written informed consent was obtained from each subject. Approval to conduct this study was granted by the National Medical Research Council of Singapore and the Institutional Review Board of the Medical Faculty of The National University of Singapore.

Crude extract of Bt

Crude extract of *Bt* was prepared from cultured mites, as described previously [13]. In brief, the mites were harvested when the culture was approximately 4 weeks old. The mite culture was separated through a series of 500 and 125 μm sieves, by using a mechanical sieve shaker. Mites with sizes greater than 120 μm were transferred to a modified Tullgren, which was built up of five layers of gauze on a funnel that was attached to a 15 mL Falcon tube. A 60 W bulb was applied at a distance of 15 cm from the culture medium for 4 h. Most of the mites in the medium crawled through the gauze and down into the tube. Mites that remained in the funnel were then swept into the tube using a tiny soft brush after the gauze was removed. One gram of frozen or lyophilized mites was homogenized using a pestle and mortar in the presence of liquid nitrogen. Twenty-five millilitres of phosphate-buffered saline (PBS), 2 mM phenylmethyl–sulphonyl fluoride (PMSF) and 1 mM EDTA was used for protein extraction at 4 °C overnight. After centrifugation at 15 000*g* for 15 min, the supernatant of the extract was dialyzed overnight at 4 °C against PBS.

Nasal allergen challenge

The NAC was carried out in a double-blind manner using nasal spray, one puff (0.04 mL of allergen solution) per nostril [14, 15]. The study subject was asked to be in complete apnea during spraying. This precaution would prevent the provocation extract from entering the lower airway. The NAC was started by using PBS (diluent of allergen extract) and then subsequently increasing concentrations of *Bt* extracts; 0.6 μg/mL (low), 6 μg/mL (medium) and 60 μg/mL (high) at intervals of 15 min. Subjective and objective symptoms were collected as a baseline, 15 min after each nasal challenge and at 30 min, 1, 3, 5 and 7 h after the last challenge in order to study the early- and late-phase reactions. After a washout period of at least 2 weeks, six of the patients underwent an identical challenging procedure with only PBS as a control.

Subjective symptoms of nasal obstruction

Nasal obstruction was recorded using a symptom severity scale: 0 = none: no obstruction evident; 1 = mild: symptom clearly present but minimal awareness; 2 = moderate: definite awareness of symptom which is bothersome but tolerable; 3 = severe: symptom is hard to tolerate and interferes with activities of daily life/sleeping.

Measurement of AR

A SRE 2100 acoustic rhinometer (Rhinometrics A/S, Lynge, Denmark) was used to measure the nasal geometry. It was performed according to the standard procedure as described in our previous reports [16, 17]. Briefly, the subjects sat upright in an armchair, with the head properly supported, and breathed quietly through the mouth. An appropriately sized adapter was selected according to the shape of the subject's nostril. Every test consisted of three consecutive measurements of each side of the nasal cavity. The following CSA measurements were recorded:

- MCA: the minimal CSA at 1–5 cm from the nostril.
- Distance (cm) to MCA from the nostril.
- CSA at 3.3, 4.0 and 6.4 cm from the nostril, representing the anterior end of the inferior turbinate, the mid-portion of the inferior turbinate that has the most abundant erectile tissue component, and the posterior nasal cavity [2, 18, 19].

Mean values of the above measurements (right and left); MCA (mMCA), distance to MCA and CSA (mCSA3.3, mCSA4.0, mCSA6.4) were calculated.

Statistical analysis

A repeated measurement analysis was performed to assess the time trend of the responses and mean differences between the mite-challenge subjects and controls taking into account the group × time interactions. Coefficient of variation (CV) was used to compare the variability of the area–distance measurements at each CSA over time.

Spearman's correlation was applied to investigate the relationship between variables of AR area–distance measurements and subjective symptom scores.

Results

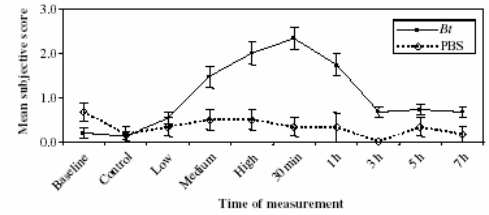
All study subjects completed the study.

Subjective nasal symptoms

Figure 1 shows the mean nasal (± SD) symptom scores before and after NAC with control solution (PBS) and *Bt*. There was a dose–response increase in nasal obstruction score after *Bt* challenges with a maximal blockage (mean score of 2.33 ± 0.25) at 30 min after challenge. There was a significant difference ($P = 0.025$) between the two groups with the study subjects experiencing a significant change over time ($P = 0.011$) but not the controls (time × group interactions, $P = 0.002$).

AR area–distance measurements

Figure 2 shows the mean (± SD) of MCA, distance to MCA, CSA3.3, CSA4.0 and CSA6.4 measurements at different timepoints after nasal challenge with *Bt* and control solution. For mMCA, mCSA3.3 and mCSA4.0, reduction of CSAs after



Differences between case and control: $P = 0.025$
Time trend: $P = 0.011$
Time & group interaction: $P = 0.002$.

Fig. 1. Mean subjective symptom score of nasal obstruction before and after *Blomia tropicalis* (*Bt*, $n = 15$) and control (phosphate-buffered saline (PBS), $n = 6$) challenge.

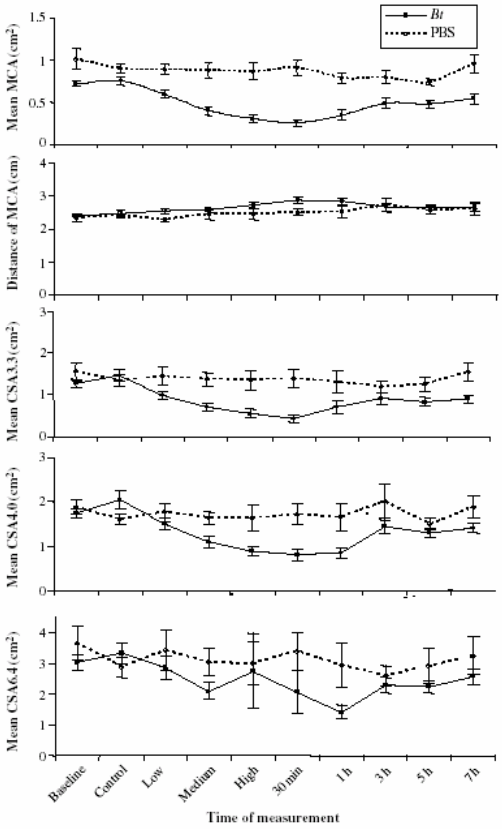


Fig. 2. Mean values (± SD) of minimum cross-sectional area (MCA), cross-sectional area (CSA)3.3, CSA4.0 and CSA6.4 after nasal challenge with house dust mite *Blomia tropicalis* (*Bt*, $n = 15$) and control solution (phosphate-buffered saline (PBS), $n = 6$).

nasal challenges with *Bt* are confirmed by statistically significant differences as compared with control challenge, as well as time trend and time × group interactions (Table 1). Maximal reduction of mean MCA (0.26 cm^2) is associated with the maximal increase of mean distance to MCA (2.86 cm) at 30 min after NAC.

CV at different CSAs is shown in Table 2. The variation at mCSA6.4 is more varied as compared with the other area measurements as shown by the larger mean CV with a twice as large standard error and wider range (minimal and maximal values).

Relationship between nasal symptom scores and AR area–distances

Spearman's correlation was performed to investigate the relationship between the subjective symptom score of nasal obstruction and objective measurements of AR; see Fig. 3. There is an inverse relationship between symptoms score and MCA ($r = -0.568$, $P < 0.001$). Although there are significant correlations between nasal obstruction scores and all four area–distance measurements, it appears that the strongest relationship is found between nasal symptom score and mMCA ($r = 0.75$), and followed by mCSA3.3 ($r = 0.54$), mCSA4.0 ($r = 0.53$) and mCSA6.4 ($r = 0.20$). The correlations between MCA and the other three area–distance measurements are shown in Table 3. Once again, the CSA6.4 measurement differs largely from other area measurements in terms of their relationship with nasal obstruction score and MCA.

Influence of constriction of MCA (< 0.2 cm^2) on area–distances beyond MCA

It was reported that in normal adults the CSA of the nasal valve is 0.2–0.6 cm^2. As the constriction narrows (<0.2 cm^2) the area and volume measurements beyond this point are often underestimated [12]. To test this hypothesis, we divided MCA (left and right separately) into two groups; <0.2 and ⩾0.2 cm^2 as measured during the time course of NAC (Table 4), and compared the corresponding area measurements (CSA3.3, CSA4.0 and CSA6.4) beyond the MCA. Results showed that when the MCA reached an area <0.2 cm^2, measurements of CSA3.3 and CSA4.0 were reduced by 60–70%.

Discussion

Nasal obstruction is one of the predominant symptoms of allergic rhinitis that can be registered subjectively and objectively [20]. It can be measured by sensation of nasal obstruction, nasal airflow and resistance induced by airflow, and CSA at various distances. AR is a static test of nasal luminal dimensions, which is independent of airflow [21]. Given the area–distance variation, different parameters can be determined; the common AR measurements are MCA, CSA at distances of 3.3, 4.0 and 6.4 cm from the nostril, which represent nasal valve, the anterior end of inferior turbinate, midportion of the inferior turbinate (or the anterior end of the middle turbinate) and the posterior nasal cavity, respectively [2–7, 18, 19, 22, 23]. However, standardization of measurements, sources of error and physical limitations of AR measurements have not been adequately evaluated.

The nasal valve region (the primary airway resistor) is considered to be a site of major pathophysiological concern [21]. However, the location and nature of the nasal valve is still not

Table 1. Statistical comparisons between nasal challenge with *Bt* ($n = 15$) and control solutions (PBS, $n = 6$) in different time of measurements

	Mean CSAs in distance									
	MCA (cm^2)		*D* (cm)		CSA3.3 (cm^2)		CSA4.0 (cm^2)		CSA6.4 (cm^2)	
	Bt	PBS	*Bt*	PBS	*Bt*	PBS	*Bt*	PBS	*Bt*	PBS
Time of measurements										
Baseline	0.72	1.01	2.39	2.33	1.26	1.57	1.74	1.88	3.02	3.65
Control	0.76	0.90	2.47	2.39	1.45	1.34	2.04	1.61	3.32	2.88
Low*	0.60	0.89	2.53	2.27	0.99	1.45	1.51	1.77	2.85	3.42
Medium*	0.40	0.88	2.58	2.44	0.72	1.37	1.10	1.64	2.10	3.04
High*	0.31	0.87	2.73	2.44	0.55	1.35	0.89	1.64	2.75	2.99
30 min	0.26	0.91	2.86	2.49	0.44	1.39	0.81	1.72	2.07	3.38
1 h	0.35	0.79	2.82	2.51	0.71	1.30	0.85	1.65	1.43	2.94
3 h	0.49	0.80	2.66	2.72	0.91	1.19	1.45	2.00	2.28	2.59
5 h	0.48	0.74	2.64	2.57	0.83	1.25	1.31	1.50	2.23	2.91
7 h	0.54	0.96	2.67	2.60	0.90	1.54	1.41	1.88	2.56	3.25
Statistical comparisons (*P*-value)										
Between groups	<0.001		0.184		0.008		0.038		0.281	
Time trend	<0.001		<0.001		<0.001		<0.001		0.45	
Time × group interaction	<0.001		0.306		<0.001		<0.001		0.757	

*Nasal challenge with increasing concentrations of *Bt*. *Bt*, *Blomia tropicalis*; PBS, phosphate-buffered saline; CSA, cross-sectional area; MCA, minimum cross-sectional area.

Table 2. Coefficient of variation at different CSAs (cm^2)

	Coefficient of variation				
Area in distance (cm)	Mean	Standard error	Minimum	Maximum	Median
MCA	0.47	0.06	0.23	0.76	0.45
CSA3.3	0.52	0.06	0.28	0.82	0.47
CSA4.0	0.42	0.05	0.24	0.64	0.39
CSA6.4	0.61	0.11	0.35	1.45	0.46

Calculations were based on a total of 420 measurements; nasal challenges with *Blomia tropicalis* ($n = 15$) and control solution ($n = 6$) at 10 different time of measurements, right and left sides. $P = 0.533$ (Kruskal–Wallis test). CSA, cross-sectional area; MCA, minimum cross-sectional area.

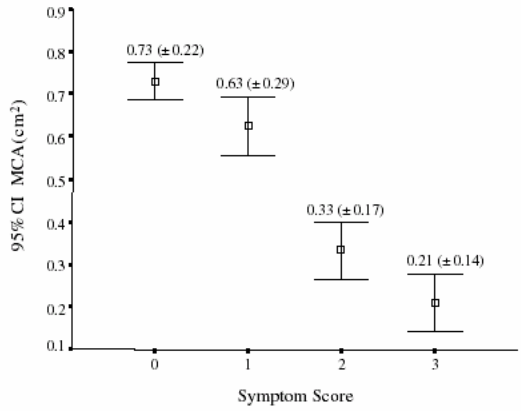


Fig. 3. Correlation between minimum cross-sectional area (MCA) and symptom score. Spearman's correlation: $r = -0.568$ ($P < 0.001$). Values shown on the graph are mean (± SD) of minimum cross-sectional area (MCA). Calculations were based on a total of 420 measurements; nasal challenges with *Blomia tropicalis* ($n = 15$) and control solution ($n = 6$) at 10 different times of measurements, right and left sides.

Table 3. Interrelationships of acoustic rhinometry area–distance measurements, and their relationship with the subjective nasal obstruction scores

	Coefficient correlation	
Area in distance (cm)	MCA	Nasal obstruction scores
MCA*	–	0.75 ($P < 0.001$)
CSA3.3	0.807 ($P < 0.001$)	0.54 ($P < 0.001$)
CSA4.0	0.631 ($P < 0.001$)	0.53 ($P < 0.001$)
CSA6.4	0.359 ($P < 0.001$)	0.20 ($P < 0.001$)

Calculations were based on a total of 420 measurements; nasal challenges with *Blomia tropicalis* ($n = 15$) and control solution ($n = 6$) at 10 different time of measurements, right and left sides. MCA, minimum cross-sectional area; CSA, cross-sectional area.

clear. The nasal cavity conforms to a slit-like shape due to three turbinates. This structure is physiologically important since it creates a turbulent inspiratory air stream and provides two-thirds of the total respiratory resistance. Some authors suggest that the nasal valve consists of the slit-like opening between the caudal end of the upper lateral cartilage and nasal septum, while others suggest it is composed of the caudal nasal septum, the caudal end of the upper lateral cartilage, the head of the inferior turbinate, and the remaining tissues surrounding the piriform aperture [22, 24]. It would appear that the nasal valve is a functional region rather than an area [21].

MCA is the most frequently used AR determinant. In some subjects the MCA is located at the nasal valve while in others, especially in cases of turbinate hypertrophy, it is the anterior part of the inferior turbinate [9]. Our data showed a mean (± SD) baseline MCA of $0.72 \pm 0.12 cm^2$ at a distance of 2.39 ± 0.16 cm that decreased rapidly to a minimum value of $0.26 \pm 0.14 cm^2$ at a distance of 2.86 ± 0.31 cm 30 min after NAC. Under normal conditions, the MCA represents a narrow lumen of the functional valve, which is anterior

Table 4. Frequency of MCA (right and left, $n = 30$) less than 0.2 cm^2 at different time of measurements and its influence on the measurements of CSA (3.3, 4.0 and 6.4 cm) beyond this point

	MCA <0.2 cm^2				MCA ≥ 0.2 cm^2			
		Distance–area (cm^2)				Distance–area (cm^2)		
	n	CSA3.3	CSA4.0	CSA6.4	*n*	CSA3.3	CSA4.0	CSA6.4
Baseline	0	–	–	–	30	–	–	–
Control	0	–	–	–	30	–	–	–
Low†	1	0.08	0.13	2.21	29	1.02	1.55	2.87
Middle†	6	0.25*	0.58*	2.05	24	0.83	1.23	2.11
High†	15	0.26**	0.6**	3.64*	15	0.85	1.18	1.86
30 min	13	0.19**	0.52**	2.34*	17	0.64	1.02	1.86
1 h	11	0.35**	0.37**	0.78**	19	0.92	1.13	1.80
3 h	4	0.25**	0.57*	1.02*	26	1.02	1.59	2.48
5 h	5	0.35*	0.76*	1.47	25	0.93	1.42	2.39
7 h	5	0.25**	0.67**	1.23*	25	1.03	1.56	2.82

*$P<0.05$, **$P<0.01$. †Nasal challenge with increasing concentrations of *Blomia tropicalis* (*Bt*).

(approximate 0.91 cm) to the anterior end of the inferior turbinate (at the distance of CSA3.3 cm). During allergic reactions, it moves more posteriorly to the anterior end of the inferior turbinate due to the dilative reaction of the capacitance vessels of the erectile tissue. There is an inverse relationship between symptoms score and MCA. With subjective symptom scores of zero and one, there was a wider range of MCA that corresponded well with a wide variation of normal nasal cavity dimensions. Interestingly, MCA range is more specific with pathological conditions causing severe nasal obstruction (scores 2 and 3) (Fig. 3).

There are some physical limitations or errors associated with the algorithms used in AR: (1) sinus ostium size, sinus volume or CSA in the distal parts (approximately 5–10 cm into the nasal cavity) of the nasal cavity [10]. (2) A significant constriction in the nasal valve area will affect the area and volume measurements beyond this point [11, 12]. (3) Distortion of the vestibule with the nasal tip adapter and anatomical variations of the columella, which changes the 0 reference points [22]. In addition, erectile tissue in the nose, especially the inferior turbinates, fluctuates greatly in size depending on physiological changes (e.g., nasal cycle, body temperature, posture and exercise) and response to inflammation. A spontaneous fluctuation in nasal patency can be documented every 10 min with irregular patterns, frequency and amplitude in healthy and allergic individuals [17]. All these factors have to be taken into account when using AR as an investigational tool in different studies.

Using nasal cavity models, two experimental studies have demonstrated that the measurement of both CSA and volume beyond a constriction area of less than 0.2 or 0.28 cm^2 will cause significant systemic errors [11, 12]. Following our data, a constriction of less than 0.2 cm^2 at the MCA caused a significant underestimation (60–70%) of the CSA measurements (Table 4). This is particularly important when using AR in a nasal challenge study, which may cause severe nasal obstruction during the early-phase reaction. In a previous report, Phipatanakul et al. [8] used the MCA and nasal cavity volumes measured at 0–5 and 5–10 cm from the nostril during the acute airway response to cat allergen exposure. The authors concluded that although AR does provide an objective measure of nasal response to allergen exposure, it has significant limitations due to the lack of correlation with symptoms, the inability to measure a dose response, and the changes noted even among the control subjects. However, this unexpected result could be due to the uncorrected volume measurements since the MCA reported was very low (<0.1 cm^2) after cat allergen exposure.

Among all the measures of CSA in this study, CSA6.4 was found to be least reliable, with a high CV compared with the other measurements and did not show a significant difference between *Bt* and control groups. It was reported that the effects of paranasal sinuses and low-frequency acoustic resonances in the posterior part of the nasal cavity are not accounted for in the current AR algorithms [10]. Areas between 5 and 10 cm may be influenced by the sinuses and especially the ostia connecting them with the nasal cavity [25]. It is important to note that all possible sources of errors and physical limitations have to be considered when using AR as an investigational tool in the study of nasal physiology and pathophysiology in various clinical and experimental settings.

In conclusion, AR has proved to be a useful and objective investigational tool in the evaluation of nasal physiology and pathophysiology. Among the AR area–distance measurement parameters, MCA appears to be the most sensitive and correlates well with the sensation of nasal obstruction. When MCA is smaller than 0.2 cm^2, a common condition especially in the early-phase reaction after NAC, other distal measurements beyond this point can be underestimated and should be ignored.

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9.2 Paper 6: Review of the pathology and management of nasal obstruction**.** (***published***)

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Control of nasal obstruction in perennial allergic rhinitis

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Purpose of review
Nasal obstruction, the cardinal symptom of persistent (perennial) allergic rhinitis, is one of the most common symptoms encountered in primary care and in specialist clinics. It is difficult to quantify by clinical examination, and, hence, objective assessment of the nasal airway is critical to rhinologic research. Nasal obstruction in persistent allergic rhinitis must be treated the year round, and therefore treatment choices, costs, and compliance all become important public health issues.
Recent findings
Many inflammatory and neurogenic mediators released during allergic reactions are able to cause plasma exudation and vasodilatation, with resultant edema and swelling of the nasal mucosa. Recently, technological advancements have made it possible to qualitatively and quantitatively study the nasal airway, providing greater insights into the understanding of physiological fluctuation and pathophysiological manifestations of nasal patency. From recent international guidelines, the management of allergic rhinitis includes combining treatments of the upper and lower airways, by using patient education, allergen avoidance, pharmacological treatment, and specific immunotherapy. Surgery may be needed as an adjunctive intervention. Multiple methods have been introduced to treat turbinate hypertrophy. However, preservation of adequate nasal mucosal function is important, together with long-term results.
Summary
It is important that consensus recommendations for the management of allergic rhinitis be designed and implemented by all levels of medical specialists in order to improve treatment outcomes.

Keywords
nasal obstruction, persistent (perennial) allergic rhinitis, acoustic rhinometry, international guidelines

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Abbreviations

CysLT	cysteinyl leukotriene
MCA	minimum cross-sectional area
HDM	house dust mite
IGC	intranasal glucocorticosteroid
PAR	persistent allergic rhinitis
SAR	seasonal allergic rhinitis
SIT	specific immunotherapy
VAS	visual analogue scale

1528-4050

Introduction

Nasal obstruction is characterized by insufficient airflow through the nose, which can be a subjective complaint, or the result of objective pathology. Inflammation of the nasal mucosa, whatever the cause, is the most common pathologic cause of nasal obstruction. If viral colds are excluded, allergic rhinitis has become the most common cause of nasal obstruction [1].

Recently, the Allergic Rhinitis and its Impact on Asthma (ARIA) consensus paper recommended replacing the terms seasonal allergic rhinitis (SAR) and perennial allergic rhinitis with intermittent allergic rhinitis and persistent allergic rhinitis (PAR) [2]. Nasal obstruction is the most common PAR symptom, and, although rhinorrhea is more common in SAR, obstruction is still significant in many patients [2]. In a Singapore community health survey, nasal obstruction was the most prevalent identified nasal symptom (15.8%), compared with sneezing (11.7%), rhinorrhea (10.6%) and nasal itch (10.2%) [3]. Control of nasal obstruction in PAR is thus important, and since it must be treated the year around, treatment choices, costs, and compliance all become important public health issues. This paper reviews the recent understanding of the pathogenic mechanisms, diagnosis, and advances in treatment of nasal obstruction, especially in PAR.

Pathophysiology of allergic rhinitis

The nasal cavity, with turbinates protruding from each lateral wall, is lined with pseudostratified columnar ciliated epithelium. It has important physiological functions of air-conditioning and filtering inspired air. Critical to this function is an extensive vascular bed, especially in the turbinates, that may lead to severe pathologic obstruction from acute or chronic inflammation. Many inflammatory and neurogenic mediators, such as histamine and arachidonic acid metabolites and sensory neuropeptides, released during allergic or irritant

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reactions [4], are able to cause plasma exudation and vasodilatation, with resultant edema and swelling of the nasal mucosa. Moreover, other mediators stimulate transendothelial leukocyte migration into the nasal mucosa, and activate these inflammatory cells to produce a slowly developing complex network of interactions between various mediators, cytokines, chemokines and cell adhesion molecules and their respective target cell types. In patients with PAR, continuous allergen exposure causes a persistent mucosal inflammation and thus persistent nasal obstruction.

Measurement of nasal obstruction

Nasal obstruction is difficult to quantify by clinical examination, and, hence, objective assessment of the nasal airway is critical to rhinologic research. Especially important is to characterize pathologic nasal obstruction and to distinguish it from the periodic nasal cycle, which is a normal variation in nasal patency. Our previous nasal allergen challenge study [5] demonstrated that positive nasal responses (100% increase in resistance) during the early-phase reaction (94%) and late-phase reaction (84%) are high enough (up to 300% increase) to be clearly different from the normal nasal cycle fluctuations (less than 100% increase) in healthy controls. Furthermore, our recent study showed that a classical nasal cycle with rhythmic and bilateral reciprocal alteration of the nasal airway patency is not a universal phenomenon. Spontaneous fluctuation in nasal patency every 10 min, with irregular pattern, frequency and amplitude was demonstrated [6••]. In subjects with PAR, the amplitudes of nasal patency fluctuation are even greater than in healthy controls.

Common methods used to objectively measure nasal patency and resistance include rhinomanometry and acoustic rhinometry. Rhinomanometry is a well-established technique that directly determines nasal airflow and airflow resistance [7]. Acoustic rhinometry is a newer technique that acoustically measures the nasal cross-sectional area and the internal nasal cavity volume [8], and thus assesses structural pathologies of the nasal passage. Both techniques are complementary, and both provide accurate outcome assessments of the nasal airway.

Evaluation of both subjective complaints and objective measurements of nasal obstruction are essential for research. Subjective assessment of nasal obstruction is commonly performed using a symptom severity score rating or a visual analogue scale (VAS). However, subjective complaints and objective measurements of nasal obstruction are not always concordant. For example, increased subjective nasal obstruction is not always accompanied by objective increased nasal airway resistance, decreased nasal peak flow, or reduced acoustic rhinometry values [1]. Suzina *et al.* [9•] showed this dissociation when they demonstrated that active anterior rhinomanometry is a sensitive test of obstruction, but is not specific for the detection of abnormalities in nasal airway resistance that create symptomatic nasal obstruction. Similarly, in our recent study [10•], the effect of 4-weeks treatment with fluticasone propionate on symptoms of nasal obstruction in patients with PAR was evaluated by using both a VAS and acoustic rhinometry measurements before and after the treatment. There was a significant improvement in the post-treatment VAS, as well as a significant increase in nasal cavity volume and minimum cross-sectional area (MCA). However, there was a poor overall correlation between the degree of subjective symptom improvement by VAS and that measured by acoustic rhinometry. This poor correlation between subjective and objective measurements could be due to the fact that the VAS records continuous ordinal data, whereas acoustic rhinometry measurements produce numerical data. Because human sensing is complex, and partially non-linear, it is possible that small changes in nasal shape, and in acoustic rhinometry measurements, may result in large shifts in the VAS.

On the other hand, in some studies, better correlation between subjective and objective obstruction measurements can be demonstrated. Our group performed a nasal allergen challenge study in PAR patients with house dust mite (HDM) allergy [11]. A four point subjective symptom score was compared with acoustic rhinometry results, and demonstrated a significant inverse relationship between symptom score severity and MCA ($r = -0.568$; $P < 0.001$). With subjective symptom scores of 0 (MCA 0.73 ± 0.22) and 1 (MCA 0.63 ± 0.29), there was a wider range of MCA values, corresponding to the normal variation of nasal cavity dimensions. The MCA range was less with more severe nasal obstruction (score 2, MCA 0.33 ± 0.17 and score 3, MCA 0.21 ± 0.14).

Control of nasal obstruction

Allergic rhinitis is an extremely common disease worldwide, affecting at least 10–25% of the population [2]. In Singapore, 71% of all rhinitis patients visited a primary care physician, and 20% had also seen an otolaryngologist because of their symptoms [3]. Therefore, in order to improve treatment outcomes, consensus recommendations for the management of allergic rhinitis should be designed for use by all levels of medical specialists. From recent international guidelines, the management of rhinitis includes combining treatments of the upper and lower airways, by using patient education, allergen avoidance, pharmacological treatment, and specific immunotherapy (SIT) [2]. Surgery may be needed as an adjunctive intervention.

Patient education

Patient education has been found to be critical to good asthma management, but few studies have shown the impact of education on rhinitis. Educational topics that are believed to be important are (1) what causes allergy symptoms, (2) which medications are useful for treating each symptom, (3) proper use of medications, (4) ways to reduce allergen exposure, and (5) explanation of the treatment plan.

Allergen avoidance

All rhinitis guidelines state that allergen avoidance should be an integral part of management strategy. Total allergen avoidance is very effective. However, because of wide variations in personal sensitivity and exposure levels, the magnitude of the reduction of allergen load needed to significantly decrease symptoms in any individual is unpredictable. It is widely believed that environmental controls with barriers and acaricides are helpful for treatment of HDM allergy in PAR patients. However, one well-designed study of the efficacy of mattress encasement showed no significant effect on clinical outcomes [12••].

Pharmacologic treatment

Pharmacologic agents can be very effective for treatment of allergic rhinitis, but no currently available drug has either long lasting or permanent effects. PAR patients will require treatment the year round, affecting both choice of treatment and cost of therapy. Since patients commonly expect quick symptomatic relief, convenience, low side effects, and low cost, educational programs will be essential to educate physicians about the evolving alternative treatment strategies.

Antihistamines

Classic and non-sedating antihistamines are effective for the relief of most nasal symptoms, including itching, sneezing and rhinorrhea, because they effectively block the histamine H_1-receptors that trigger plasma exudation and edema formation. However, H_1 antihistamines have only minor effects on nasal obstruction [13•,14•]. The dilatation of nasal capacitance vessels, and thus increases in nasal airway resistance, is mediated via both H_1 and H_2-receptors [15], but the effect of H_2-receptors predominates. Therefore, a combination of H_1 and H_2-receptor antagonists is more effective than H_1-blockers alone in reducing nasal congestion [16].

Intranasal glucocorticosteroids

Intranasal glucocorticosteroids (IGCs) are currently the most potent medication available for the treatment of allergic rhinitis. They were recommended as first-line antiinflammatory therapy for adults with moderate to severe SAR or PAR [2]. PAR patients especially benefit from IGCs, since obstruction is the main symptom. For example, Hughes *et al.* [17•] demonstrated that by using IGCs to decrease nasal obstruction in PAR, symptoms of daytime fatigue and somnolence could also be improved.

The rationale for using IGCs in the treatment of allergic rhinitis is that high drug concentrations can be achieved at receptor sites in the nasal mucosa, with a minimal risk of systemic adverse effects [2]. IGCs have a slower onset of action than H_1 antihistamines, with detectable effects at about 12 h, and maximum efficacy develops over days to weeks [2]. Because of this slow onset, and the need for regular treatment to maintain efficacy, in order to improve compliance when using IGCs it is very important to educate patients. Patient compliance is affected by many factors, including sensory attributes of the sprays [18,19•], and patient education. Even with thorough patient education, a substantial number (11%) of IGC patients still fail to take at least 50% of treatment doses, resulting in poor outcomes [20]. Finally, the expense of IGCs is an important concern for patients who need long-term medication [21].

Leukotriene antagonists

Leukotrienes are important mediators of allergic nasal obstruction. Drugs acting against leukotrienes are therefore potentially useful in the treatment of allergic rhinitis, as shown by the over 10 papers published in the past year regarding leukotriene antagonist treatment of SAR, and one for PAR [22•]. Currently, one leukotriene synthesis inhibitor and three leukotriene receptor antagonists are licensed. Two classes of leukotriene receptors, cysteinyl leukotriene (CysLT)1 and CysLT2, exist in human respiratory mucosa, but only the former is sensitive to leukotriene antagonists currently used to treat allergic rhinitis. Shirasaki *et al.* [23] studied turbinates from patients with nasal obstruction refractory to medical therapy. In-situ hybridization identified high levels of CysLT1 receptors in blood vessels and interstitial cells, but few receptors in airway epithelium and submucosal glands. Anti-CysLT1 receptor antibody was found to label eosinophils, mast cells, macrophages, neutrophils and vascular endothelial cells. In addition to blocking this broad stimulatory effect of leukotrienes on mediator-producing cells, leukotriene antagonists also exert their antiinflammatory effect on T helper type 1 and T helper type 2 cytokine polarization [22•,24•,25]. Leukotriene receptor antagonists have been found to be about equipotent with non-sedating antihistamines for overall rhinitis symptom relief, and superior for obstruction relief [26•]. In pilot studies, anti-leukotriene drugs appear to have significant activity against other nasal inflammatory disorders [27].

Decongestants

Decongestants, α-1 agonists, are very effective for treatment of nasal obstruction; their prolonged use,

however, risks rebound vasodilatation and rhinitis medicamentosa. Rebound effects can usually be avoided by using topical decongestants only for a short course (less than 7–10 days), while co-administering antiinflammatory drugs, such as oral or nasal glucocorticosteroids [2]. Oral decongestants have a less potent effect on obstruction than intranasal decongestants, but do not cause rebound [2]. Pseudoephedrine is currently the only available drug used in combination with oral antihistamines and showed a better reduction of global nasal symptoms as compared with the antihistamine alone. However, these combinations do cause more insomnia and nervousness (side effects due to pseudoephedrine). Moreover, children and elderly persons, who may be more susceptible to these effects, have not been sufficiently studied.

Chromones

Chromones, such as cromoglycate, are useful for preexposure use to prevent allergic rhinitis symptoms, and also relieve acute symptoms, but are not as potent as IGCs for nasal obstruction relief, and require frequent administration [28].

Surgery

In patients who suffer from PAR for many years, a severe drug-resistant hypertrophy and increase in glandular structures of the inferior turbinates may develop, which leads to constant nasal obstruction and watery nasal drip. Surgical reduction of the turbinates can reduce nasal obstruction and secretions [2]. However, unless nasal surgery is both properly indicated and performed with skill, outcomes may be poor. For example, Graif and Goldberg [29•] evaluated results by multiple surgeons of septoplasty, with or without turbinate reduction, to treat nasal obstruction in 53 PAR patients. One year after surgery, only 20 patients (38%) were definitely satisfied with their results. Surgical details were not presented, so the causes of these poor results cannot be determined.

Fradis *et al.* [30] treated 51 obstructed patients by submucosal radiofrequency diathermy, with good results in 76% after 2 months [30]. The argon plasma coagulator controlled nasal obstruction in all of 28 allergic rhinitis patients at 4 weeks after surgery [31•]. One patient relapsed at 6 months, and was successfully retreated by recoagulation. Supiyaphun *et al.* [32•] demonstrated, in 48 patients, that potassium-titanyl-phosphate laser turbinoplasty reduced nasal obstruction and other symptoms, in all patients, without significant complications. In another study, patients allergic to HDM only and those allergic to HDM and Japanese cedar pollen underwent laser turbinectomy during the pollen season [33•]. Four months after treatment, obstruction significantly decreased in both groups, but the improvement of sneezing and rhinorrhea was less pronounced in the pollen group. With any surgical approach, preservation of adequate nasal mucosal function is important, but rarely reported, especially in long-term follow-up. Passasli *et al.* [34••] analyzed the long-term efficacy of six surgical techniques (turbinectomy, laser cautery, electrocautery, cryotherapy, submucosal resection, and submucosal resection with lateral displacement) on 382 patients. After 6 years, only submucosal resection resulted in long-term normal nasal patency, mucociliary clearance, and physiologic local secretory immunoglobulin A production. The addition of turbinate lateral displacement improved the long-term results. Schmeltzer *et al.* reported up to 9 years follow-up after partial turbinectomy, and found over 93% long-term obstruction improvement, with no atrophy, and no long-term sequelae [35].

Allergen specific immunotherapy

There is good evidence from decades of multiple double blind studies that subcutaneous inhalant allergen immunotherapy is clinically effective to treat both SAR and PAR [36]. SIT may be able to alter the natural course of allergy, and prevent asthma [2,37]. SIT can significantly reduce the severity of allergic disease, including nasal obstruction, and decrease the need for anti-allergic drugs. SIT can be given as sublingual drops. A recent Cochrane review showed this to be effective, in adults, for reducing rhinitis symptoms and medication use [38••].

Nasal obstruction: special aspects

During the last decade, international guidelines and consensus statements have been developed to enhance the effectiveness and quality of management for allergic rhinitis patients. Though the underlying mechanisms and clinical manifestation of nasal obstruction are similar, special considerations in treatment are recommended in the following groups of patients.

Children

Nasal obstruction due to PAR is common in young children, and its treatment requires special thought. Children may not be cooperative for allergy testing, medication use, or SIT. Furthermore, parental cooperation is crucial for any treatment success. Immunotherapy is feasible by using sublingual drops. Nasal sprays can be used, if accepted by the patient. Nasal saline or cromoglycate is often helpful in milder cases. For more severe obstruction, topical decongestants are very useful, for short periods, to open the nose adequately to allow use of IGCs. Although IGCs are approved for children 2 years of age and older, there is persisting parental concern of possible side effects. However, a number of double-blind, randomized long-term studies of children have shown, with almost all currently used IGCs, no effect on either endogenous cortisol production or growth [2,39,40•,41•]. Oral medications can be hard to

use, due to poor taste or lack of a pediatric formulation. H_1 antihistamines are available, but have little effect on obstruction. Lai *et al.* [42] compared the long-term effects of ketotifen, oxatomide, and cetirizine for the treatment of PAR in children, and found that cetirizine was the most effective drug. The leukotriene receptor antagonist, montelukast, is available in granules for children aged 1 year and above.

Pregnancy

Allergic rhinitis is often a problem during pregnancy, because nasal obstruction is aggravated by pregnancy in up to a third of patients [43•]. Caution must be taken when administering medication to a pregnant woman, as most medications cross the placenta [2]. However, significant allergies, especially with coexistent asthma, must be adequately treated [44•]. The safest drugs are cromoglycate, IGCs, and, after the first trimester, H_1 antihistamines. SIT can be continued through pregnancy, but should not be initiated, due to anaphylaxis risk.

Sports

For patients who are professional athletes, it is important to observe anti-doping rules set by regulatory authorities, including the International Olympic Committee [2]. It is a serious matter for an athlete to be accused of banned drug use [2], so all prescriptions, especially for decongestants and other stimulants, should be cleared by the relevant authority well prior to any planned competitions.

Conclusion

Nasal obstruction is a common symptom of allergic rhinitis, especially in PAR. Obstruction is created by nasal mucosal inflammation, which is the result of a complex network of interactions between various mediators, cytokines, chemokines, and cell adhesion molecules, reacting to continuous allergen exposure. Techniques for quantitative dynamic and static measurement of nasal obstruction are available. These measurements are helpful to objectively define the structural pathologies of the nasal passages. Long-term obstruction control in PAR is important, since patients must be treated the year round. Any success at environmental control of allergens is worthwhile, since it reduces the need for other therapies. There is currently a good choice of medications for symptom relief and reduction of obstruction that can be effectively used in most PAR patients. Recent guidelines recommend antiinflammatory IGC treatment as more effective than symptomatic treatment alone, but cost and compliance may not always allow this option to be used. In some patients, immunotherapy, surgery, or both will be necessary. In young children and in pregnancy, treatment of nasal obstruction is more difficult, due to limitations of available medications.

In order to achieve good treatment compliance and optimal outcomes, educational programs about the most effective treatment strategies must be designed for both physicians and for their patients. Finally, there is clearly a need for further research on effective PAR therapies and methods for their application to the at risk population.

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9.3. Oral 1: Acoustic rhinometry in nasal allergen challenge study:

which dimensional measures are meaningful?

(***presenting author)***

Wang DY, **Raza MT**, Goh YT, Lee BW, Chan YH.

The 5th Combined Scientific Meeting incorporating The 4th GSS-FOM Scientific Meeting, 12-14 May 2004, Clinical Research Centre, National University Singapore, Singapore.

Acoustic rhinometry in nasal allergen challenge study: which dimensional measures are meaningful?

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Based on the study:

Acoustic rhinometry in nasal allergen challenge study: which dimensional measures are meaningful?

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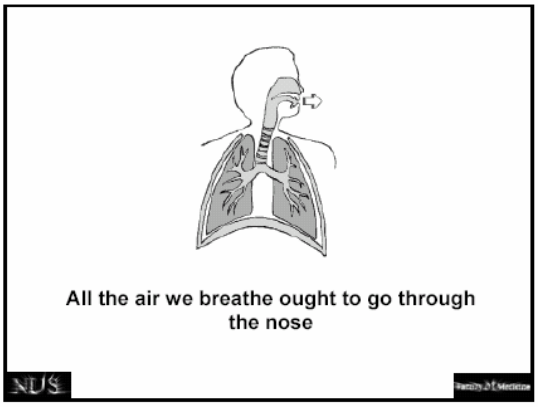
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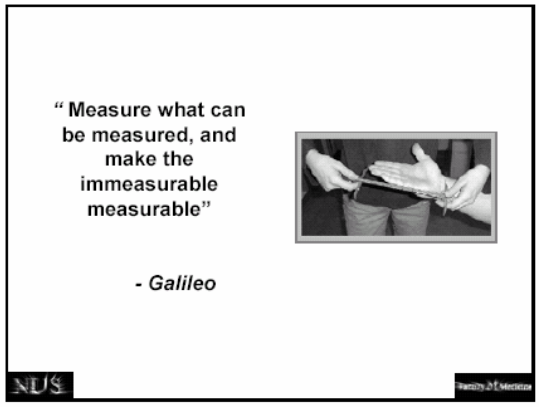
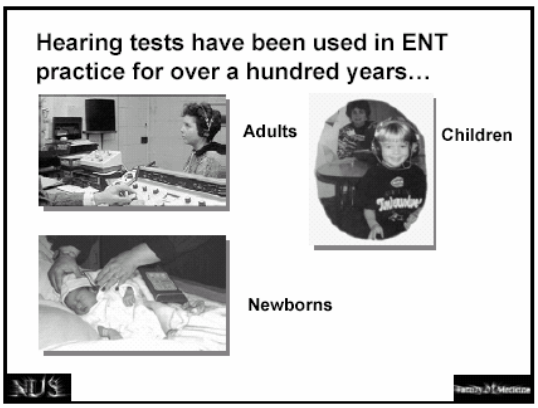
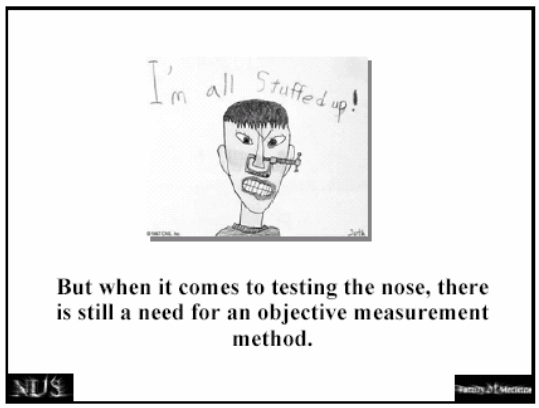
NUS


" Measure what can be measured, and make the immeasurable measurable"
- Galileo
NUS


Hearing tests have been used in ENT practice for over a hundred years…
Adults
Children
Newborns
NUS


I'm all Stuffed up!
But when it comes to testing the nose, there is still a need for an objective measurement method.
NUS

Nasal obstruction is a common symptom.

Therefore, measurement of nasal obstruction is desirable

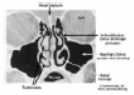
Assessment of nasal obstruction

- Subjective

Visual analogue scale
Subjective symptom score scale

- Objective

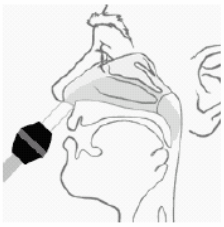
Acoustic rhinometry
Rhinomanometry
Rhinostereometry
Nasal peak flow
CT Scan
Magnetic resonance Imaging



CT scan

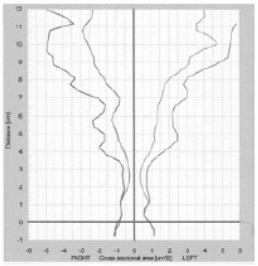
Anterior Active Rhinomanometry

Acoustic rhinometry



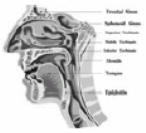
Incident and reflected waves are recorded by microphone

Acoustic rhinometry



Before and after a decongestant

What do we measure?



1. **Cross-sectional area**

   Mean CSA for the first 5cm and at 3 specific points in the nose (3.3, 4.0 and 6.4cm)

2. **Nasal volume**

   Calculated from CSA

NUS

What do we measure?

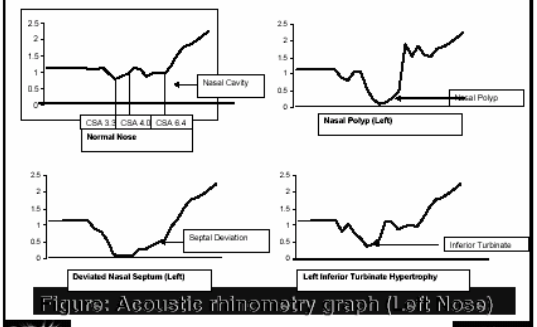


Figure: Acoustic rhinometry graph (Left Nose)

NUS

Nasal allergen challenge

Nasal obstruction is one of the cardinal symptoms of allergic rhinitis.

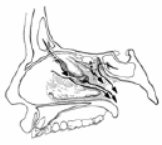
Events occurring during allergic reactions are easier to analyse with nasal allergen studies.

blomia tropicalis
(House dust mite)

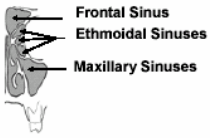
NUS

Limitations of acoustic rhinometry

Measurements beyond 5cm are unreliable because of the sinus ostia and volumes.



Sinus ostium size

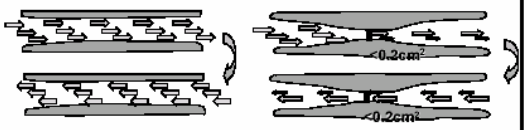


Sinus volume

Cross sectional area at 6.4 cm was most unreliable

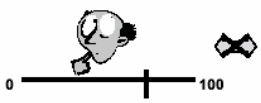
NUS

Limitations of acoustic rhinometry

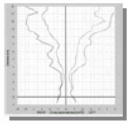


Acoustic measurements beyond a significant constriction (<0.2cm²) were consistently inaccurate

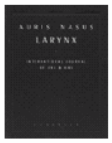
Subjective and objective assessment



Visual analogue scale



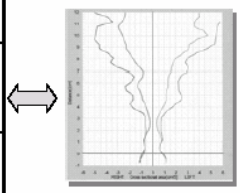
Acoustic rhinometry



Chan KO, Huang ZL, Wang DY. Acoustic rhinometric assessment of nasal obstruction after treatment with fluticasone propionate in patients with perennial rhinitis. Auris Nasus Larynx. 2003 Dec;30(4):379-83.

Subjective and objective assessment

Score	Degree	Interpretation
0	None	*No obstruction evident*
1	Mild	*Symptom clearly present but minimal awareness*
2	Moderate	*Definite awareness of symptom which is bothersome but tolerable*
3	Severe	*Symptom is hard to tolerate and interferes with activities of daily life/sleeping*



Acoustic rhinometry

Symptom severity scale

Subjective and objective assessment

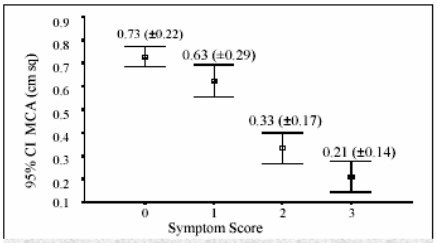


Fig: Correlation between MCA and symptom score. Spearman's correlation: r= -0.568 (p < 0.001). Values shown on graph are mean (±SD) of MCA.

Conclusion

Significant inverse relationship between four point subjective symptom score and AR measurements.

MCA appears to be most reliable.

CSA 6.4 was found to be least reliable

Measurements distal to a significant constriction (<0.2 cm^2) are unreliable and should be ignored.

Acknowledgement

Dr Wang De-Yun

Professor Alan G. Kerr

Thank you

9.4 **Poster 1:** "Correlation Of Body Mass Index, Height And Weight With Nasal Cavity Geometry In Adult Singaporeans" ***(presenting author)***

Raza MT, Wang DY

4th Combined Scientific Meeting, Incorporating Second Singapore Microarray Meeting. 15-18 January 2003, Clinical Research Centre, National University of Singapore

CORRELATION OF BODY MASS INDEX, HEIGHT AND WEIGHT WITH NASAL CAVITY GEOMETRY IN ADULT SINGAPOREANS

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Department of Otolaryngology, Faculty of Medicine, National University of Singapore

Background

A patent nasal passage is important. Nasal airflow rate and oral and nasal pressure increase with increasing BMI. This study aims to determine if with increased BMI, the nasal cavity geometry increases in healthy Singaporean Chinese, Malays and Indians

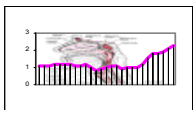
Acoustic Rhinometry (AR)

Sends sound waves into nose. Incident and reflected waves are recorded by microphone. In seconds the cross sectional areas and volumes is measured and a two dimensional graphic display of nasal cavity is provided.

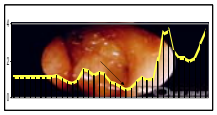
Minimally invasive, rapid, convenient and accurate

Are You Obese?

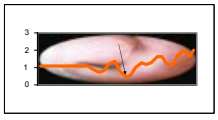
	Body Mass Index
Underweight	<18.5 kg/m^2
Normal weight	18.5-24.9 kg/m^2
Overweight	25-29.9 kg/m^2
Obesity	30 kg/m^2 or greater



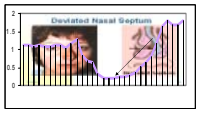
Normal Nose (Rt)
Rhinological Examination
General Anatomy: Normal
Septum: Normal
Turbinate (Inferior): Normal



Nasal Polyp (Lt)
Rhinological Examination
General Anatomy:Abnormal
Septum: Normal
Polyp: Yes and Massive



Inferior Turbinate Hypertrophy (Lt)
Rhinological Examination
General Anatomy: Normal
Turbinate (Inferior): Hypertrophy



Deviated Nasal Septum (Lt)
Rhinological Examination
General Anatomy: Normal
Septum: Deviation To Left Side

Measured Indices of the nasal Cavity

CSA-3.3	Cross Sectional Area at the distance of 3.3 cm from nostril
CSA-4.0	Cross Sectional Area at the distance of 4.0 cm from nostril
MCA	Minimum Cross Sectional Area
NV-5	Nasal Volume of the first 5 cm from the nostril

Research Questions

In the Adult Singaporean population is there a relationship between Nasal Cavity Geometry and…….

BMI?
Height?
Weight?

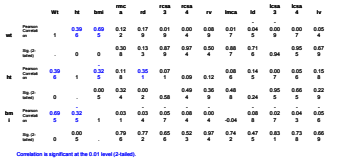
Method

In a national rhinitis survey study, 268 adult volunteers were called to attend a rhinologic examination in the ENT Clinic of NUH. Individuals were then excluded with the existence of any type of rhinitis/sinusitis and nasal structure malformations

Height and weight measured
BMI calculated
MCA , CSA-3.3, CSA-4 & NV-5 computed

Results

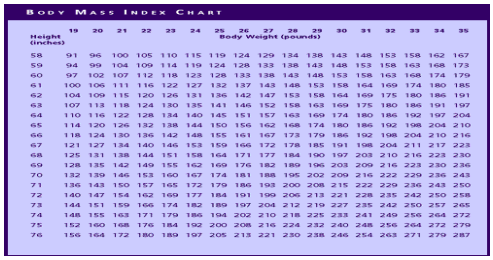
Although there is correlation of height and right distance of MCA no significant correlation was noted on left side. This requires further study



BODY MASS INDEX

Metric Formula
BMI =Weight in kilograms ÷ [Height in meters]^2 or
BMI = [Weight in kilograms ÷ Height in cm ÷ Height in cm] x 10,000

English Formula
BMI = [Weight in pounds ÷ Height in inches ÷ Height in inches] x 703



BODY MASS INDEX CHART

Height (inches)	Body Weight (pounds)																
	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
58	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167
59	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173
60	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179
61	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185
62	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191
63	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	191	197
64	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204
65	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210
66	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216
67	121	127	134	140	146	153	159	166	172	178	185	191	198	204	211	217	223
68	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230
69	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236
70	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243
71	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250
72	140	147	154	162	169	177	184	191	199	206	213	221	228	235	242	250	258
73	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265
74	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272
75	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279
76	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287

Conclusions

BMI and Nasal Cavity Geometry relationship — No
Height and Nasal Cavity Geometry relationship — No
Weight and Nasal Cavity Geometry — No

9.5 Poster 2: Acoustic rhinometry in nasal allergen challenge study which dimensional measures are meaningful? (***presenting author)***

Wang DY, **Raza MT**, Goh YT, Lee BW, Chan YH.Height And Weight?

5th International Symposium on Experimental Rhinology and Immunology of the Nose, November 17-19, 2003. Ghent-Belgium.

Acoustic rhinometry in nasal allergen challenge study: which dimensional measures are meaningful?

[1]WANG De Yun, [1]RAZA Md Tanveer, [2]GOH Yam Thiam, [2]LEE Bee Wah, [3]CHAN Yiong Huak.
Departments of Otolaryngology[1] and Paediatrics[2], Faculty of Medicine, The National University of Singapore. [3]Clinical Trial & Epidemiology Research Unit, Singapore

BACKGROUND

Acoustic rhinometry (AR) is commonly used in quantitative assessment of nasal response to nasal allergen challenge (NAC). Sources of error and physical limitations of various AR area-distance measurements are not fully understood

OBJECTIVE

- Clinical value of AR measurements and
- Relationship between objective AR measurements & subjective sensation of nasal obstruction in NAC study.

METHODS

Study patients

- 15 Adults (8 Males & 7 Females) with ongoing Perennial Allergic Rhinitis (PAR).
- Age: 21 to 44 years (mean 28.4 years).
- Sensitization to *Blomia tropicalis (Bt)* (confirmed by positive skin prick reaction).
- No acute nasal symptoms & history of taking medication during the last 2 weeks (at least 30days for any nasal and/or systemic corticosteriods)

NAC

- Nasal spray, 1 puff (0.04 ml of allergen solution)/nostril (Complete apnea prevents entry into lower airway)
- NAC started by using PBS (diluent of allergen extract)
- Then subsequently increasing concentrations of *Bt* extracts; 0.6 µg/ml (low), 6 µg/ml (medium) and 60 µg/ml (high) at intervals of 15 min.
- Symptom score collected as a baseline,15 min after each challenge and 30 min, 1 , 3 , 5 & 7 hours after last challenge to study the early-and late-phase reactions.
- After washout period (≤ 2 weeks) identical NAC with control (PBS) [6 patients].

Nasal Obstruction

Subjective: Symptom score

- 0=None (No evidence)
- 1=Mild (Clearly present but minimal awareness)
- 2=Moderate(Definite awareness, bothersome but tolerable)
- 3=Severe (Hard to tolerate, causing interference with activities of daily life/sleeping)

Objective: AR

- Standard procedure as described in previous reports [1]
- Measured Cross-sectional area (CSA) from the nostril:
  - •MCA: minimum CSA between 1 to 5 cm.
  - •Distance (cm) to MCA.
  - •CSA 3.3: 3.3 cm (anterior end of inferior turbinate) [2]
  - •CSA 4.0: 4.0 cm. (mid-portion of the inferior turbinate)
  - •CSA 6.4: 6.4 cm. (posterior nasal cavity)
- Mean (right and left) values were calculated.

Factors influencing the reliability of AR

1. Operator
2. Subject
3. Instrumentation
4. Environment

Physical limitations

1. CSA in the distal parts of the nasal cavity (approximately 5-10 cm into the nasal cavity)
   a. Sinus ostium size
   b. Sinus volume

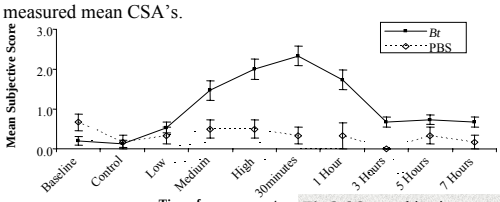
Fig 1: Effect of area-distance curves for pipe models [3].

Fig 2: Sinus Cavity

2. Measurements beyond a significant Constriction (CSA < 0.2cm²) [4]
3. Reference point changes.
   - Distortion of the vestibule with nasal tip adapter
   - Anatomical variations of columella

RESULTS

- Dose-response increase in nasal obstruction score was significantly ($p<0.001$ for all) associated with decreases in mean MCA and the three measured mean CSA's.



Differences between case and control: $p = 0.025$
Time trend: $p = 0.011$
Time & group interaction: $p = 0.002$.

Fig 3. Mean subjective symptom score of nasal obstruction before and after *Blomia tropicalis* (*Bt*) and control (PBS) challenge.

- When MCA (left and right separately) reached an area <0.2 cm², measurements of CSA 3.3, 4.0 and 6.4 were significantly reduced.

Table 1: Frequency of MCA (sides, n=30) < 0.2 cm² at different measurement times and its influence on the measurements of CSA 3.3, 4.0 & 6.4 cm beyond this point.

	MCA <0.2 cm² Distance-area (cm²)				MCA≥0.2 cm² Distance-area (cm²)			
	n	CSA3.3	CSA4.0	CSA6.4	n	CSA3.3	CSA4.0	CSA6.4
Baseline	0	-	-	-	30	-	-	-
Control	0	-	-	-	30	-	-	-
Low†	1	0.08	0.13	2.21	29	1.02	1.55	2.87
Middle†	6	0.25*	0.58*	2.05	24	0.83	1.23	2.11
High†	15	0.26**	0.6**	3.64*	15	0.85	1.18	1.86
30 min	13	0.19**	0.52**	2.34*	17	0.64	1.02	1.86
1 hr	11	0.35**	0.37**	0.78**	19	0.92	1.13	1.80
3 hrs	4	0.25**	0.57*	1.02*	26	1.02	1.59	2.48
5 hrs	5	0.35*	0.76*	1.47	25	0.93	1.42	2.39
7 hrs	5	0.25**	0.67**	1.23*	25	1.03	1.56	2.82

†: Nasal challenge with increasing concentrations
*: p<0.05
**p<0.01

- CSA6.4 measurement differs largely from other area measurements in terms of their relationship with nasal obstruction score and MCA.

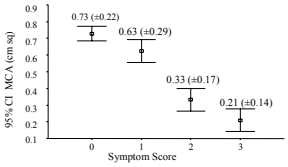


Fig 4: Correlation between MCA and symptom score. Spearman's correlation: r= -0.568 ($p < 0.001$). Values shown on graph are mean (±SD) of MCA.

Table 2: Interrelationships ($p < 0.001$) between AR measurements & subjective nasal obstruction scores

	Coefficient Correlation			
	MCA	CSA 3.3	CSA 4.0	CSA 6.4
Nasal Obstruction	0.75	0.54	0.53	0.2

Table 3: Interrelationships ($p < 0.001$) between different AR measurements

	Coefficient Correlation		
	CSA 3.3	CSA 4.0	CSA 6.4
MCA*	0.807	0.631	0.359

CONCLUSION

AR proved to be a useful and objective investigational tool in evaluating nasal physiology and pathophysiology. MCA appears to be the most sensitive and correlates well with the sensation of nasal obstruction. When MCA is smaller than 0.2 cm², other distal measurements beyond this point can be underestimated and should be ignored.

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1. Huang ZL, Wang DY Zhang PC, Dong F, Yeoh KH. Evaluation of nasal cavity by acoustic rhinometry in Chinese, Malay and Indian ethnic groups. Acta Otolaryngol 2001 Oct;121(7):844-8
2. Jang YJ, Lee JH, Jang JY. Acoustic rhinometric evaluation of the nasal response to exercise in patients with nasal septal deviation. Clin Otolaryngol 2000; 25: 423-7.
3. Cakmak O, Celik H, Cankurtaran M, Buyukltı F, Ozgirgin N, Ozluoglu LN. Effects of paranasal sinus ostia and volume on acoustic rhinometry measurements: a model study.J Appl Physiol 2003; 94: 1527-35.
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9.6 Poster 3: Association between rhinitis, asthma and some other major illness. (***presenting author***)

Wang DY, **Raza MT**, Heng CK, Chan YH.

The 5th Combined Scientific Meeting incorporating The 4th GSS-FOM Scientific Meeting, 12-14 May 2004, Clinical Research Centre, National University Singapore, Singapore.

Association between rhinitis,asthma and some major illness

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BACKGROUND

Rhinitis is as an inflammation of the lining of the nose, characterized by one or more of the following symptoms, nasal congestion, rhinorrhea, sneezing & itching (1). It is often associated with multiple co-morbidities like asthma, sinusitis, anosmia, otitis media, nasal polyps, lower airway infection & dental malocclusion, that might be due to different mechanisms such as a common genetic or epidemiological background, pathophysiological and functional interactions between rhinitis and surrounding organs.

A French study reported that rhinitis is strongly associated with systolic blood pressure (SBP) and hypertension in men (2).

A population-based German study did not demonstrate such association between rhinits and blood pressure (3).

OBJECTIVE

To investigate the relationship between rhinitis, persistent allergic rhinitis (PAR), asthma and other major illness (e.g., hypertension, coronary arterial disease, diabetes) in Singapore.

METHOD

Volunteers were recruited from two previous studies:

(1) A cohort of 214 adult subjects randomly selected to attend a national rhinitis survey study in the ENT out-patient clinic.

(2) 145 adult patients with PAR recruited for a clinical trial.

Definitions used in this study

Atopy.A positive serum specific IgE (equal or more than 0.35U/ml) to at least one of the inhalant allergens tested.

Rhinitis. The occurrence of two or more symptoms (nasal obstruction, rhinorrhea, sneezing and itchy nose) on most days during the past year (1). If patients coexisted with atopy, PAR is given.

Asthma. A history of paroxysmal attacks of breathlessness commonly associated with a tightness of the chest and wheezing (1), and asthma was previously diagnosed by a physician.

Hypertension. Presence of at least one of the following conditions: SBP of 140 mmHg or greater, diastolic blood pressure (DBP) of 90 mm Hg or greater or taking antihypertensive medication.

Major illness. Presence of major illness, i.e., diabetes mellitus (DM) and coronary artery disease (CAD) was recorded if subjects presented with particular symptoms and were previously diagnosed by a physician.

RESULTS

Table 1. Characteristics of the study population

	Descriptive data Number (%)
Sex	
Male	205 (57.1)
Female	154 (42.9)
Age	18 to 74 years
mean (±SD)	34.7±12.1
Medical history/diseases	
Atopy	233 (64.9)
Rhinitis	243 (67.7)
PAR*	183 (51)
Asthma	69 (19.2)
Hypertension	52 (14.5)
Diabetics	23 (6.4)
CAD**	17 (4.7)
Family history†	
Hypertension	108(30.1)
Diabetics	105(29.2)
CAD**	58(16.2
Smoking	
Smoker	19 (5.3)
Ex-smoker	52 (14.5)
Physical examination	
Height (cm)	165.1±9.1
Weight (kg)	63.9±13.5
BMI (kg/m^2)	23.4±4.2
SBP (mmHg)	120.8±13.2
DBP(mmHg)	78.9±9
Serological tests	
Total cholesterol (mM)	5.1±1.0
HDL-C***(mM)	1.3±0.4
LDL-C****(mM)	2.9±0.9
Triglyceride (mM)	1.7±1.2

*:Persistent allergic rhinitis
**: Coronary artery disease
***HDL-C: High Density Lipoprotein-Cholesterol
****LDL-C: Low Density Lipoprotein-Cholesterol
†: Only confined to 1st degree relatives

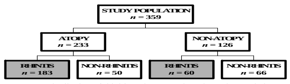

Figure 1: Distribution of rhinitis and atopy patients in study population

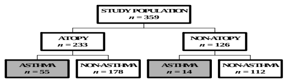

Figure 2: Distribution of asthma and atopy patients in study population

Table 1. Significant association of rhinitis, allergic rhinitis, asthma and hypertension with medical history, diagnosis and all measurements by multiple logistic regression analysis.

Name of disease measurements	*p* value	Odds ratio	95% CI*
Rhinitis			
Atopy	0.001	2.66	1.51 - 4.69
Asthma	0.001	4.35	1.77 - 10.69
HDL-C**	0.008	14.9	2.05 - 108.13
Age	0.003†	0.96	0.93 - 0.99
Persistent allergic rhinitis			
Asthma	<0.001	3.73	1.86 - 7.47
Age	[illegible]	[illegible]	[illegible]
Diabetes	[illegible]	[illegible]	[illegible] - 0.57
BMI****	[illegible]	[illegible]	[illegible]
Asthma			
Rhinitis	[illegible]	[illegible]	[illegible]
BMI	0.003	1.14	1.05 - 1.24

CI: Confidence Interval
*HDL-C: High Density Lipoprotein Cholesterol
**CAD: Coronary artery disease
***BMI: Body Mass Index
Negative association.

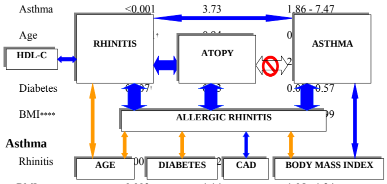

Figure 3: Association between rhinitis, asthma and some major illness. Positive correlation ; Negative Correlation

CONCLUSION

- There is a strong association between rhinitis/PAR and asthma.
- Atopy is a highly associated factor for rhinitis, but not for asthma.
- Positive correlation between PAR and CAD
- Negative correlation between PAR and DM
- No association between SBP and DBP with rhinitis.

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