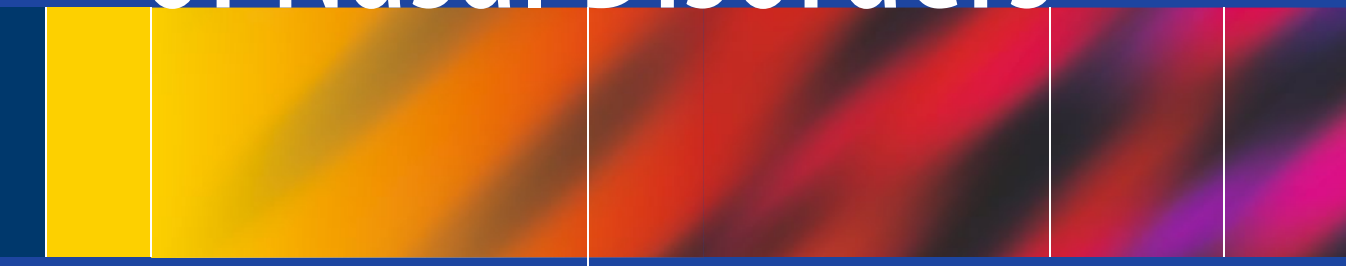
T. Metin Önerci
Editor

Nasal Physiology and Pathophysiology of Nasal Disorders



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To my loving wife, Semra, and my daughters, Özlem and Zeynep, for their support and accepting a part-time father.
To my teachers and colleagues who inspire me to learn and to my students who inspire me to teach.

T. Metin Önerci

Foreword

Interest in the function and malfunction of the nose has a long history, but this has accelerated in recent years with the application of new technology and methods of investigation. This book is therefore, very timely, covering all aspects of nasal physiology and pathophysiology. Consequently it has a wide appeal to basic scientists, clinical researchers, and physicians from many disciplines including otorhinolaryngology, allergy, immunology, and respiratory medicine.

Professor Onerci has gathered a distinguished group of authors, all contributors in their respective fields to comprehensively consider all aspects of this area which also have synergies with the lower respiratory tract and adjacent structures such as the eye, nasopharynx, and mouth.

All aspects of mucociliary function, olfaction, airway, and immune defense are covered in a number of detailed chapters from both a structural and functional perspective. Normal structure is considered macroscopically, microscopically, and ultrastructurally together with the consequences of disease and therapeutic intervention. Difficult clinical phenomena such as facial pain, the dry nose, and the effects of nutrition and age are all explored – providing insight and help in their management.

Everyone from medical students to experts will find this book fascinating and intellectually stimulating – I certainly did!

London, UK — Valerie J. Lund CBE

Preface

The human nose protruding as a pyramid from the midface is unique in the realm of mammals. In the earlier days, the nose was considered as an important structure in the middle of the face aesthetically and as a simple double tube for the passage of air to the lungs. It was also thought to have a relationship with the personality of a person. From the religious side, the nose was very important: "The life force within man came when God blew into his nostrils the soul of life and man became a living being" (Genesis 2:7). The nose is thus considered to be the organ through which the soul enters and leaves. Furthermore, the nose has also a special appreciation among the five senses: "In the Garden of Eden, Adam and Eva defiled four out of their five senses. They heard the serpent's alluring words, the fruit was a delight to the eyes, they touched it by taking from its fruit and they tasted it. But the sense of 'smell' remained untarnished. Accordingly, this sense denotes inner purity and deep attachment to God and the fulfilment of His Will" (Bnei Yissacher, Adar 1:10).

In the last century we learned that the nose is a highly complex organ with many functions and that it is the main internal organ that keeps functioning even to the last moment of our earthly existence. The nose, however, has not found the adequate appreciation as to its complex functions in the textbooks of physiology and rhinology.

The respiratory tract is considered to be a unified airway system, and any processes affecting the nose also affect the lower airways. The nose warms, humidifies, and filtrates more than 14,000 l of air per day. Through heat exchange, the nasal mucosa maintains the nasal cavity at a range of 31–37 °C. Vascular mucosa increases relative humidity to 95 % before air reaches the nasopharynx, requiring more than 680 g of water, which is approximately 20 % of daily water intake.

In addition to humidification, warming, and filtering out particles in inspired air, the nose also serves to provide first-line immunologic defense by bringing inspired air in contact with mucus-coated membranes. Physiologic nasal fluids, ciliary function, epithelial cells, and the secretory tissue (submucosal glands and anterior or lateral serous glands) are important in the defense system of the nose. The mucus secreted by the secretory tissue lines the mucosa and provides a physical barrier against invasion by pathogens and traps pathogens when they enter the nasal cavity. Trapping pathogens enables components of the mucus to attack and destroy the microbes. Antigen-binding proteins in the epithelium present allergens to antigen-presenting cells. These

cells introduce pathogens to the T-lymphocyte cells starting an immune response to destroy allergens presented to them. Epithelial cells also release factors such as cytokines which enhance inflammatory responses.

The nose is the source of many powerful reflexes, including for sneezing and sniffing, and reflexes affecting autonomic nervous function to the cardiovascular system, to the airways of the larynx, the lungs, and other organs. The nasopulmonary reflex suggests that pressure on one nasal sidewall causes ipsilateral pulmonary congestion.

The innervation of the nose includes parasympathetic, sympathetic, sensory/afferent, and motor nerves, which combine in a variety of pathways. Nasal secretion and the vasculature of the nose (capacitance vessels such as sinusoids and distensible venules, as well as arteriovenous anastomoses, arterioles, capillaries, and venules) are also under the influence of both parasympathetic and sympathetic nerves and can be affected by a wide range of neurotransmitters and mediators.

The nose serves as a contributing factor in the modification of the voice. Nasal aerodynamics play a role in modifying high-frequency sounds and consonants. They also contribute to the olfactory system. The active process of sniffing allows environmental particles to reach the olfactory system, which is located at the skull base.

Airway resistance is important for the expansion of lung tissue. The nasal passage provides airway resistance that helps to provide a level of pressure within the lungs which is vital for efficient lung function and blood oxygenation. Lack of resistance, and therefore poor oxygenation, will diminish the respiratory function, will lead to a feeling of tiredness and lethargy, and will disturb sleep. The lungs expand against a resistance until the pressure difference becomes sufficient to inhale enough air volume to the alveoli. With increasing lung volume and negative pressure, the expanding lung tissue keeps the airways open. The nose as a resistor prevents collapse of the alveoli. Only a harmonic balance between the lung and nasal resistance provides an optimal respiratory mechanism. Therefore, both resistances should not be judged separately. In adults, two-thirds of the total airway resistance is provided by the nose. In fact this can even be considered as one of the functions of the nose, in addition to olfaction and air-conditioning.

The interrelationship of nasal function with bodily functions necessitates a thorough understanding of the nasal physiology. The nose with its central localization has a paramount influence on neighboring structures such as the Eustachian tube and the nasolacrimal drainage system. In this volume, special attention has been given to the physiology of the growing nose, the behavior and development of nasal cartilages, and their reaction to trauma, infection, and surgery.

Such an organ deserves more attention not only for its physiology but also for the pathophysiology of the nasal diseases. Recent developments in the field of physiology of the nose and the pathophysiology of the nasal diseases opened new horizons in the diagnosis and the treatment of the nasal diseases. Therefore, it appears to be a good time to bring together in a comprehensive volume the latest information and knowledge on the physiology of such a pluripotent organ, the nose, and the pathophysiology of the nasal diseases.

Leading international experts were invited to author the book. Chapters are arranged with bulleted tips and pearls, as well as numerous illustrations to highlight the text. Almost all areas of nasal physiology have been covered. I hope this book will be used as a reliable and inspiring reference source by all physicians interested in rhinology and will serve to help them manage and treat their patients better.

Ankara, Turkey T. Metin Önerci

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Mucus, Goblet Cell, Submucosal Gland

1

Takeshi Shimizu

Keywords
Mucin • MUC gene • Mucus hypersecretion

Abbreviations

AP-1	Activated protein-1
AR	Allergic rhinitis
AZM	Azithromycin
CAM	Clarithromycin
CF	Cystic fibrosis
CREB	cAMP response element binding protein
CRS	Chronic rhinosinusitis
cysLTs	Cysteinyl leukotrienes
EGFR	Epidermal growth factor receptor
EM	Erythromycin
Foxa2	Forkhead box a2
IL	Interleukin
NF-κB	Nuclear factor κ-B
RA	Retinoic acid
STAT6	Signal transducer and activator of transcription 6
TGF	Transforming growth factor
TLR	Toll-like receptor
TNF	Tumor necrosis factor

Core Messages

Airway mucus is important for the host defense mechanism, acting as a physicochemical barrier to protect underlying epithelium from pathogens and particles. The major components of mucus are glycoproteins called mucins, which are secreted by epithelial goblet and submucosal gland cells. Mucins are large heterogeneous macromolecules containing hundreds of oligosaccharide chains attached to peptide backbones, which are encoded by several MUC genes. Hypersecretion of mucus is commonly observed in various sinonasal inflammatory conditions such as acute rhinitis, chronic rhinosinusitis, and allergic rhinitis. Mucus hypersecretion, leading to rhinorrhea, contributes significantly to the pathophysiology of these diseases by impairing mucociliary function, resulting in stagnation of pathological mucus that contains various inflammatory mediators and pathogenic microbes.

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1.1 Introduction

Airway mucus blankets all mucosal surfaces, providing a physicochemical barrier that protects underlying epithelium against bacteria, viruses, and inhaled particles and gases. Mucus maintains airway hydration and plays an important role in the innate immune system by trapping foreign and endogenous substances, facilitating clearance by mucociliary activity. Mucus also has antioxidant, antiprotease, and antimicrobial functions. Composed of water, ions, serum protein exudates, epithelial secretions, and glandular and goblet cell products, mucus contains various defensive components such as glycoproteins (mucins), antibodies, defensin, lysozyme, and lactoferrin.

The mucous blanket is subdivided into two layers: the outer mucous layer and the periciliary fluid layer. The outer mucous layer is a gel layer, produced mainly by secretions of epithelial goblet cells and submucosal glands. The periciliary fluid, or sol layer is produced by ion transport through the epithelium (Fig. 1.1). Ciliary beating takes place at 10–14 Hz in this periciliary layer, propelling the outer mucous layer toward the pharynx. Healthy mucociliary transport requires maintenance of a balance among volume and composition of mucus, adequate periciliary fluid, and ciliary beating (Terran et al. 2006). Mucus is essential for mucociliary transport. If mucus is replaced with saline, particles do not move even while cilia beat actively (Sadé et al. 1970).

Hypersecretion of mucus is an important characteristic of sinonasal inflammation that occurs in conditions such as acute rhinitis, chronic rhinosinusitis (CRS), and allergic rhinitis (AR). Hypertrophic, hyperplastic, and metaplastic changes in goblet cells of the surface epithelium and in submucosal gland cells are frequently observed in association with pronounced rhinorrhea. In pathological conditions, mucus hypersecretion and damaged epithelium impair mucociliary clearance, resulting in stagnant pathological mucus containing pathogenic microbes, various inflammatory mediators, and inflammatory cells, a situation that facilitates bacterial colonization and local inflammation, leading to infection and tissue damage.

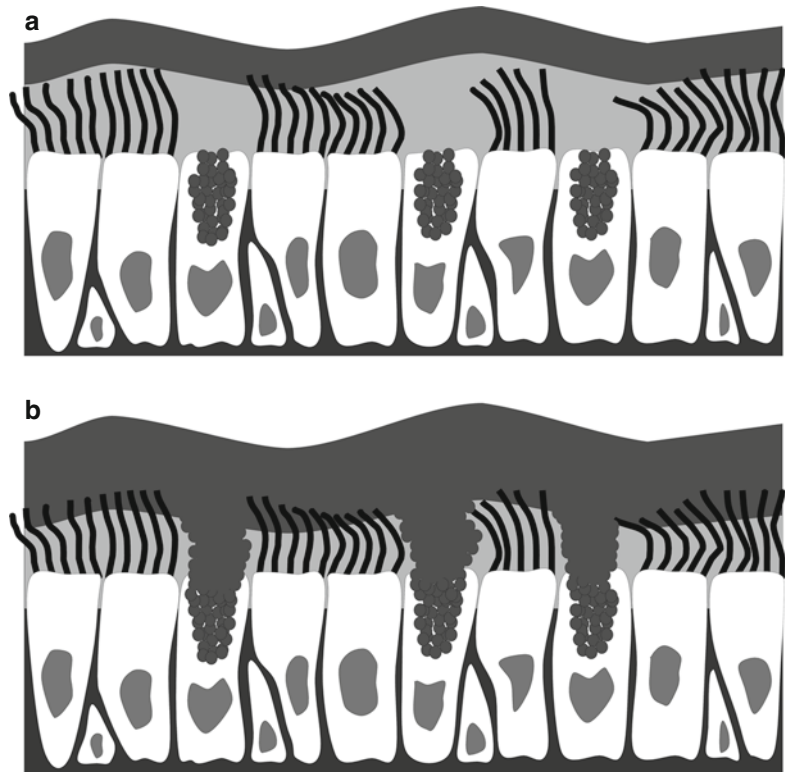

Fig. 1.1 Mucous blanket is subdivided into two layers: the outer mucous layer and the periciliary fluid layer. (**a**) Normal mucous blanket. (**b**) Pathological mucous blanket with hypersecretion of mucus. Mucus hypersecretion increases the viscoelasticity of the mucus, and mucus strands connect the outer mucous layer with the epithelial goblet cells, causing the disruption of periciliary fluid layer. These changes of mucus impair mucociliary interaction

The major components of mucus are glycoproteins called mucins, which are secreted by epithelial goblet cells and submucosal glands. Mucins are large heterogeneous macromolecules, containing oligosaccharide chains attached to peptide backbones, which are encoded by several MUC genes. Secreted mucins are stored in secretory granules and are released by regulated exocytosis.

This chapter will focus on mucus, goblet cells, and submucosal glands of the nasal mucosa and will summarize the mechanisms regulating mucus secretion and pathological mucus hypersecretion in sinonasal inflammation. Therapeutic strategies to inhibit mucus hypersecretion will be also discussed.

1.2 Mucus Composition

The nasal epithelium is covered by a mucous gel layer. Ciliary beating within the periciliary fluid layer propels the gel layer to the pharynx and is then swallowed together with entrapped particles and pathogens. Mucus is a heterogeneous mixture of water, glucose, various ionic solutes, antimicrobial proteins, cells, and cellular debris. Mucins are major glycoprotein components of mucus that contribute greatly to the viscoelastic and gel-forming properties of the mucous layer (Sheehan et al. 2004; Perez-Vilar 2007; Thornton et al. 2008).

Mucins are complex glycoproteins with oligosaccharide chains attached to peptide backbones, which are encoded by MUC genes. Mucins can be divided into two structurally and functionally distinct subfamilies: membrane-bound mucins and secreted mucins. Membrane-bound mucins have transmembrane and cytoplasmic domains that anchor the molecules to the apical cell membrane, where they participate in functions such as structural barrier formation, cellular adhesion, pathogen binding, and signal transduction (Williams et al. 2006; Curran and Cohn 2010). Extracellular subunits of membrane-bound mucins can be released from the plasma membrane into the mucus layer by proteolytic cleavage or by shearing forces. Some membrane-bound mucin genes are alternatively spliced to form transcripts that lack a transmembrane domain; these are present in airway secretion (Moniaux et al. 2000). Secreted mucins are stored in secretory granules located in the apical cytoplasm and are released by regulated exocytosis.

Secreted mucins have high molecular weights (more than 1,000 kDa) and are heavily glycosylated proteins (composed of 70–90 % carbohydrate moieties) with tandemly repeated amino acid sequences that are rich in serine and threonine. Different mucin genes contain various sizes and numbers of tandem repeat, and there are genetic polymorphisms within single mucin genes (Rose and Voynow 2006). Tandem repeats are sites of *O*-glycosylation, and hundreds of oligosaccharide chains are attached to a single core peptide (Fig. 1.2). Mucin glycosylation is determined by tissue-specific glycosyltransferase expression and by host and environmental factors that influence transferase expression. Mucin carbohydrate chains are highly heterogeneous, and this structural diversity may allow mucins to interact with many microorganisms

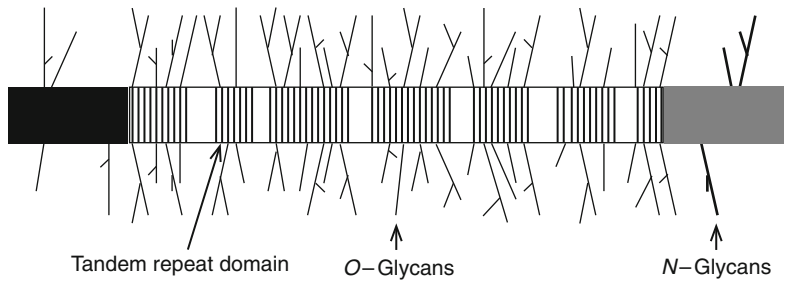

Fig. 1.2 A schematic model of a secreted mucin. Hundreds of *O*-glycans are attached to serine or threonine residues of tandem repeat domains in the MUC protein backbone. Secreted, gel-forming mucins contain cysteine-rich domains that permit oligomerization through the formation of disulfide bonds; they also aggregate through ionic and hydrophobic interactions with proteins and with other mucins

(Linden et al. 2008). These carbohydrate moieties are possible sites of attachment for pathogenic bacteria and viruses. Several recognition sites for respiratory pathogens have been identified; these promote their entrapment and removal by mucociliary clearance (Suzuki et al. 1986; Krivan et al. 1988; Roberts et al. 1989; Ramphal et al. 1991).

Secreted mucins contain cysteine-rich domains that permit oligomerization through the formation of disulfide bond; they also aggregate through ionic and hydrophobic interactions with proteins and with other mucins. These complex macromolecules provide the viscoelastic and space-occupying properties of the mucus gel layer (Evans and Koo 2009). Secreted mucins are negatively charged by sulfated and sialylated oligosaccharide chains. Mucins, the most plentiful high-molecular-weight polyanions of nasal mucosa, interact with and inhibit the effects of cationic inflammatory proteins such as leukocyte elastase and lysozyme (Van-Seuningen et al. 1992; Nadziejko and Finkelstein 1994). The negatively charged carbohydrates of mucins may protect against proteolysis caused by cationic inflammatory proteins and bacterial enzymes.

1.3 Mucin Genes

The mucin protein backbones are encoded by MUC genes. More than 20 human mucin genes have been identified throughout the respiratory, gastrointestinal, and reproductive tracts (Rose and Voynow 2006). In respiratory epithelium, mainly MUC1, MUC2, MUC4, MUC5AC, MUC5B, MUC7, and MUC8 are expressed, and similar expressions of mucin genes are observed in normal nasal mucosa (Martinez-Antón et al. 2006a; Ali and Pearson 2007) (Table 1.1). MUC2, MUC5AC, MUC5B, and MUC8 are secreted, gel-forming mucins that contain cysteine-rich domains for oligomerization and are responsible for the viscoelastic property of mucus. They are encoded by a cluster of highly related genes on chromosome 11 and by a similar gene on chromosome 12 (Evans and Koo 2009). MUC7 is a secreted, non-gel-forming mucin that exists as a monomer and so is not thought to contribute significantly to mucus viscoelasticity.

In the airways, MUC1 and MUC4 are the predominant membrane-bound mucins present on the apical membranes of epithelial cells. Membrane-bound mucins contain a highly glycosylated extracellular domain, a transmembrane domain, and a short cytoplasmic tail. Extracellular units can be released from cells under certain conditions and then potentially contribute to the mucus layer. Some MUC4 mucins secreted into airways are encoded by alternatively spliced transcripts that lack a transmembrane domain (Moniaux et al. 2000). The cytoplasmic tail domain participates in signal transduction and regulates a variety of biological functions (Singh and Hollingsworth 2006). In airway epithelial cells, MUC1 is a receptor for *Pseudomonas aeruginosa* flagellin (Lillehoj et al. 2002); MUC1 inhibits flagellin-activated Toll-like receptor (TLR)-5-mediated signaling and interleukin (IL)-8 release (Lu et al. 2006). Both MUC1 and MUC4 dimerize with and regulate the epidermal growth factor receptor (Song et al. 2001). Their roles in inflammation and cancer biology have been studied in detail (Hollingsworth and Swanson 2004; Kim and Lillehoj 2008; Hattrup

Table 1.1 Major mucin genes in human nasal mucosa

MUC gene	Mucin subfamily	Chromosome locus	Main tissue localization
MUC1	Membrane-bound	1q21–q24	Epithelial cells
MUC2	Secreted, gel-forming	11p15.5	Goblet cells
MUC4	Membrane-bound	3q29	Epithelial cells
MUC5AC	Secreted, gel-forming	11p15.5	Goblet cells
MUC5B	Secreted, gel-forming	11p15.5	Mucous cells of submucosal glands
MUC7	Secreted, non-gel-forming	4q13.3	Serous cells of submucosal glands
MUC8	Secreted, gel-forming	12q24.3	Goblet cells, mucous cells of submucosal glands

and Gendler 2008). However, their function in nasal mucosa remains to be elucidated.

Recent studies revealed the specific localization of mucins in nasal epithelial cells and submucosal glands. The membrane-bound mucins MUC1 and MUC4 are diffusely expressed at the apical surface of epithelial cells. The secreted, gel-forming mucin MUC5AC is mainly expressed in epithelial goblet cells, while MUC5B is the predominant mucin expressed in mucous cells of the submucosal glands. MUC2 is mainly expressed in epithelial goblet cells, but its expression is much lower than that of MUC5AC. MUC 8 is expressed in both epithelial goblet cells and mucous cells of the submucosal glands. The secreted, non-gel-forming mucin MUC7 is expressed in serous cells of the submucosal gland. Similar distributions of MUC genes seem to be found in nasal polyps (Ali et al. 2005; Martinez-Antón et al. 2006b). MUC2, MUC5AC, and MUC5B expressions are reported to be upregulated during airway inflammation in humans and in animals, and MUC5AC expression is the highest of the three (Zudhi Alimam et al. 2000; Voynow and Rubin 2009). Therefore, MUC5AC has been the most intensively studied MUC gene with regard to airway mucus secretion.

1.4 Goblet Cells and Submucosal Glands

Mucous cells in the surface epithelium (called goblet cells) and in submucosal glands are major sources of gel-forming mucins. Epithelial goblet cells contain numerous electron-lucent granules that fill most of the cytoplasm and fuse with the apical cell membrane before secretion (Fig. 1.3). The nucleus, numerous mitochondria, and the rough endoplasmic reticulum are restricted to a small volume in the basal aspect of the cells. Submucosal glands comprise a mixture of mucous cells and serous cells, and the mucous cells, the important source of gel-forming mucin, resemble epithelial goblet cells. These mucous cells can be detected histochemically by alcian blue and periodic acid Schiff's stains.

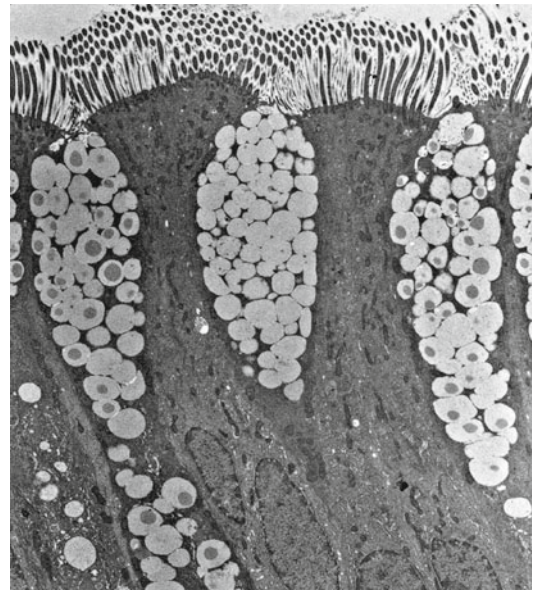

Fig. 1.3 Goblet cells of rat nasal epithelium induced by intranasal instillation of lipopolysaccharides. Numerous electron-lucent granules fill most of the cytoplasm and fuse with the apical cell membrane before secretion

Serous cells of submucosal glands contain discrete electron-dense granules containing secretory products including immunoglobulins, lysozyme, lactoferrin, and other antimicrobial enzymes, all of which are important for normal function of the airway innate immune system (Wine and Joo 2004). Thus, serous cells are an important source of antimicrobial peptides essential for host defense mechanisms, while mucous cells contribute to the viscoelastic property of airway mucus by producing gel-forming mucins. Human submucosal glands are innervated by parasympathetic and sensory efferent nerves, and the glands express muscarinic receptors. The parasympathetic (cholinergic) nervous system is the neural pathway most active in airway submucosal glands, and stimulation of cholinergic nerves or use of muscarinic receptor agonists induces marked mucus secretion (Fung and Rogers 1997; Wine 2007).

Mucus hypersecretion is a major characteristic of airway inflammation; it is associated with hypertrophy, hyperplasia, and metaplasia of epithelial goblet and submucosal gland cells.

An increased number of hypertrophic goblet cells are commonly observed in the nasal epithelium during experimental inflammation caused by inhalation of irritant gases or allergens or by viral or bacterial infection. In the human nose, the goblet cell density of the inferior turbinate ranges from 5,000 to 10,000 cells/mm^2, similar to that of maxillary sinus mucosa (Majima et al. 1997; Ali and Pearson 2007). However, changes of goblet cell numbers in patients with allergic rhinitis (AR) and chronic rhinosinusitis (CRS) are controversial.

Submucosal glands contribute to mucus hypersecretion in airway inflammation by secreting mucins, ions, and water; the submucosal gland cell density ranges from 1,000 to 2,000 cells/mm^2 in human inferior turbinate and maxillary sinus mucosa. In CRS patients, the number of submucosal gland cells increases to 2,000 to 4,000 cells/mm^2, and the area occupied by acini of the lamina propria also increases (Majima et al. 1997).

1.5 Regulation of Mucin Secretion

Mucin secretion is regulated by a multi-step process that includes synthesis and exocytosis. Mucin synthesis includes gene transcription in the nucleus, posttranscriptional modification and transport of mRNA, and translation in the endoplasmic reticulum. In the Golgi apparatus, oligosaccharides chains are then attached to the peptide backbone by glycosylation. The synthesized mucins are stored in secretory granules located in the apical cytoplasm until stimulated for subsequent release by exocytosis.

1.5.1 Mucin Production

Mucin gene expression is induced in response to a wide variety of inflammatory stimuli. MUC5AC is the predominant gel-forming mucin in the human airways and has been extensively studied for evaluation of mucin gene regulation and mucin glycoprotein secretion. A variety of epithelial stimuli (including bacterial products, viral infection, environmental pollutants and chemicals, proteases, inflammatory cytokines, and growth factors) upregulate mucin gene expressions during sinonasal inflammation (Fig. 1.4).

Many bacteria and bacterial products induce mucus hypersecretion in vivo and in vitro. Lipopolysaccharide/TLR-4, peptidoglycan/TLR-2 or TLR-6, and flagellin/TLR-5 signaling induce MUC5AC expression in airway epithelial cells through activation of transcription factors such as nuclear factor-κB (NF-κB), cAMP response element binding protein (CREB), and activated protein-1 (AP-1) (Thai et al. 2008, Voynow and Rubin 2009). Respiratory viral infections (including influenza virus and respiratory syncytial virus) induce mucin gene expression in mice (Barbier et al. 2012; Hashimoto et al. 2004), and rhinovirus stimulates MUC5AC expression in human airway epithelial cells (Hewson et al. 2010). Environmental pollutants and oxidants (such as cigarette smoke, acrolein, ozone, SO_2 and hydrogen peroxide) stimulate MUC5AC expression and mucin production (Shao et al. 2004; Deshmukh et al. 2008; Li and Meng 2007; Kim et al. 2008). Airway proteases (including neutrophil elastase, matrix metalloproteases, airway trypsin, and thrombin) stimulate MUC5AC expression and mucin secretion (Voynow et al. 1999; Shao and Nadel 2005; Deshmukh et al. 2005; Chokki et al. 2004; Shimizu et al. 2008).

The proinflammatory cytokines IL-1β and tumor necrosis factor (TNF)-α and the Th2 cytokines IL-4, IL-9, and IL-13 stimulate mucin production in vivo (Song et al. 2003; Cohn et al. 1999). Epithelial cell-derived cytokine IL-33 also induces mucin production in the mouse airway (Kouzaki et al. 2011). IL-13 is an important and essential mediator of mucin production in Th2-mediated airway inflammation through direct stimulation of epithelial cells (Whittaker et al. 2002). IL-13 activates signal transducer and activator of transcription 6 (STAT6), and then STAT6-dependent downregulation of the transcription factor forkhead box a2 (Foxa2) stimulates MUC5AC expression (Kuperman et al. 2002; Zhen et al. 2007). Foxa2 is a negative regulator of MUC5AC expression, and its deletion

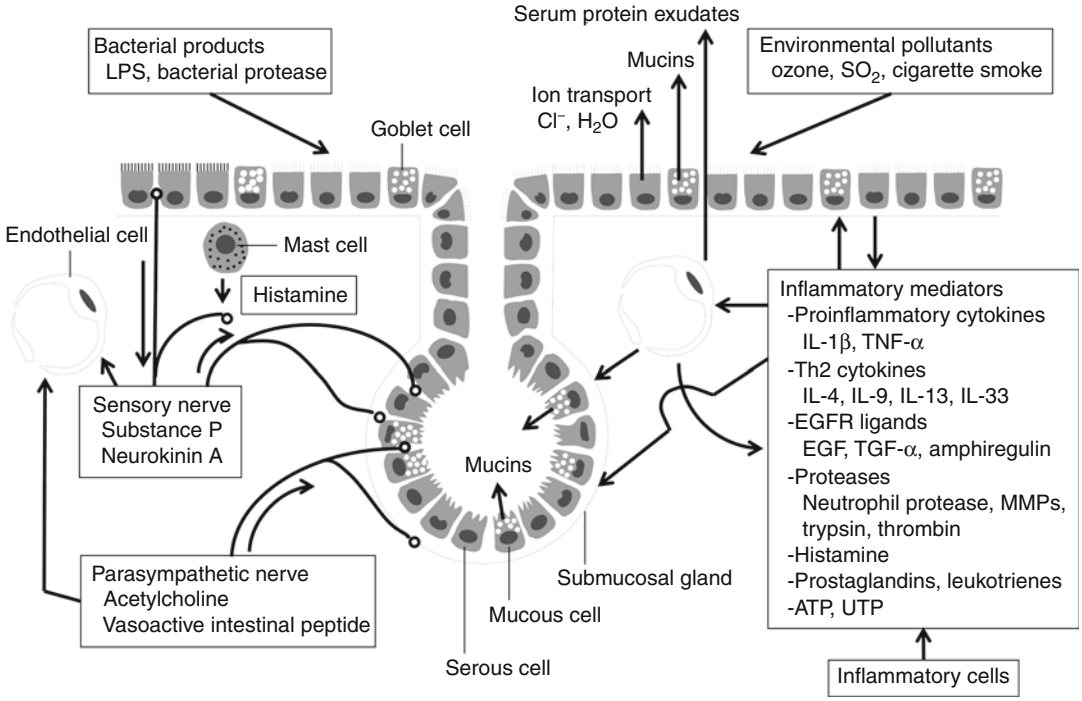

Fig. 1.4 A variety of environmental stimuli, inflammatory mediators, growth factors, and parasympathetic and sensory nerves are involved in mucus production and secretion in nasal mucosa

induces mucous metaplasia in the mouse lung (Wan et al. 2004).

Retinoic acid (RA) and its related analogs play an important role in cell growth and cell differentiation. In the airway epithelium, RA is essential for induction and maintenance of mucociliary differentiation (Yoon et al. 1997; Usui et al. 2000). Expression of the gel-forming mucins MUC2 and MUC5AC is RA dependent in cultured airway epithelial cells (Koo et al. 1999). Epidermal growth factor receptor (EGFR) signaling is also important for mucin production in a variety of animal models and in human airway epithelial cells. The EGFR ligands EGF, transforming growth factor (TGF)-α, and amphiregulin stimulate MUC5AC expression (Takeyama et al. 1999). Activation of EGFR is critical for in vivo and in vitro induction of mucin production in response to stimulation of airway epithelial cells by allergens, viruses, neutrophil elastase, and cigarette smoke (Takeyama et al. 2001; Burgel et al. 2001; Shim et al. 2001; Voynow and Rubin 2009; Evans and Koo 2009).

1.5.2 Mucin Exocytosis

Mucin exocytosis from epithelial goblet cells is stimulated by many inflammatory mediators including cholinergic agonists, neuropeptides, prostaglandins, leukotrienes, bacterial products, neutrophil elastase, inhaled pollutants, and nucleosides (Davis 1997). The nucleoside ATP is released in response to mechanical, irritant, and inflammatory stimulation of epithelial cells. Extracellular release of ATP activates P2Y2 purinergic receptors on the apical surface of airway epithelial cells, resulting in induction of calcium release and regulated exocytosis (Davis and Dickey 2008). Exocytosis is a complex process controlled by many regulatory molecules, including myristoylated alanine-rich C kinase substrate (MARCKS), which is essential for mucin release in vivo and in vitro (Li et al. 2001; Singer et al. 2004; Williams et al. 2006; Curran and Cohn 2010).

Mucus secretion from submucosal glands is regulated mainly by parasympathetic and sensory

nerves. Neurotransmitters and neuropeptides released by these nerves directly stimulate gland secretion (Fung and Rogers 1997). In airway inflammation, parasympathetic activity is stimulated by sensory nerves and histamine. Inflammatory mediators, such as prostaglandins, leukotrienes, and neutrophil elastase, also stimulate gland secretion.

1.5.3 Mucin Glycosylation

In addition to factors that regulate synthesis and release, mucin activity is also regulated by glycosylation (Linden et al. 2008). Th2 cytokines and TNF-α alter the glycosylation and sialylation of secreted mucins (Delmotte et al. 2002; Beum et al. 2005). The carbohydrate moieties of mucins are potential adhesion sites for bacteria and viruses (Lamblin et al. 1991). Inflammation-associated glycosylation of secreted mucin facilitates the interaction between mucus and microorganisms, leading to entrapment and removal by mucociliary clearance (Ramphal et al. 1989; Shimizu et al. 2001).

Increased modification of secreted mucin by sialylation and sulfation is commonly observed in airway inflammation (Carnoy et al. 1991; Shimizu et al. 1996; Schulz et al. 2007). Resulting carbohydrate moieties are negatively charged and have inhibitory effects against cationic inflammatory proteins and bacterial enzymes (Van-Seuningen et al. 1992; Nadziejko and Finkelstein 1994). Such alterations may be important mechanisms involved in host defense, as they lead to neutralization of these proteolytic enzymes and removal of pathogenic microbes. However, the precise biological function of mucin carbohydrate chains remains to be elucidated.

1.6 Pathophysiological Mucus Hypersecretion

Mucus hypersecretion is a common characteristic of the sinonasal inflammation seen in disorders like chronic rhinosinusitis (CRS) and allergic rhinitis (AR) and is the cause of rhinorrhea. A variety of inflammatory mediators and infiltrating cells are capable of stimulating mucus hypersecretion. Many inflammatory stimuli such as inhaled irritants, neutrophil products, lipopolysaccharide, viral and bacterial infections, and antigen challenge have been used to study mechanisms of mucus hypersecretion in animal models.

1.6.1 Chronic Rhinosinusitis (CRS)

CRS is a common nasal infectious disease with or without nasal polyps, characterized by the following symptoms: anterior and posterior nasal discharge, nasal obstruction, olfactory disturbance, headache, and facial pain. Hypersecretion of mucus in CRS patients may be induced by various inflammatory mediators such as the proinflammatory cytokines IL-1β and TNF-α, bacterial products, and neutrophil products. Mucin gene expression in nasal and sinus mucosa is similar to that in other respiratory epithelia. MUC 5AC, MUC5B, and MUC2 are major secreted, gel-forming mucins, and the production of these is upregulated in nasal mucosa and nasal polyps of CRS patients (Martinez-Antón et al. 2006b; Ali and Pearson 2007) (Fig. 1.5).

Excessive mucin production increases the viscoelasticity of the mucus, and mucus strands connect the mucous blanket with epithelial goblet cells (Rogers 2004) (Figs. 1.1 and 1.5). These changes of the mucus and the damaged epithelium impair mucociliary interaction. Obstruction of the nasal passages caused by inflamed mucosa or nasal polyps and mucociliary dysfunction lead to "mucostasis," an accumulation of stagnant, pathological mucus that contains various inflammatory mediators, inflammatory cells, and pathogenic microbes. Mucostasis triggers mediators, normally host protective, but which in this setting become host invasive, further exacerbating mucus hypersecretion, tissue damage, mucociliary dysfunction, and bacterial infection (Fig. 1.6). Successful treatment of CRS patients involves stopping the self-mediated inflammation caused by stagnant mucus. Nasal blowing, suction and irrigation, antral lavage, and

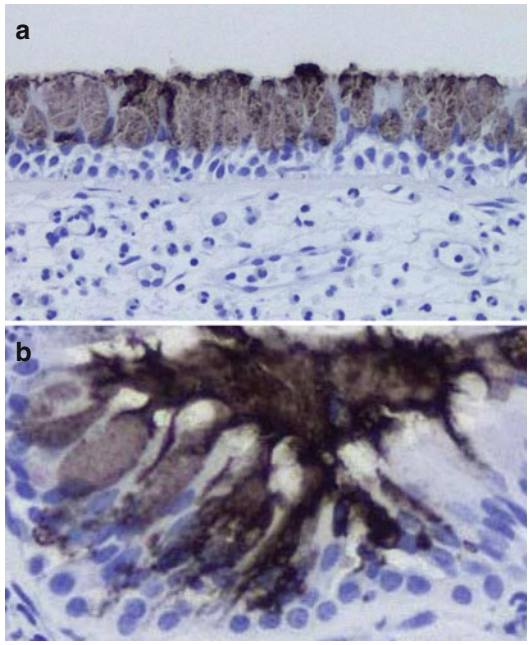

Fig. 1.5 Immunohistochemical staining of MUC5AC in nasal polyp of patient with chronic rhinosinusitis. Mucous granules of epithelial goblet cells (**a**) and the mucus layer of epithelial surface (**b**) are strongly stained. Mucus strands connect the mucous blanket with the epithelial goblet cells (**b**)

endoscopic sinus surgery are useful treatments to remove stagnant mucus and restore mucociliary clearance.

1.6.2 Allergic Rhinitis (AR)

AR is caused by IgE-mediated Th2 immune responses and is characterized by the following symptoms: sneezing, nasal obstruction, itching, and rhinorrhea. Histamine is a key mediator for allergic rhinitis, and histamine-induced cholinergic nerve stimulation is important for antigen-induced mucus hypersecretion. MUC5AC is a main secreted mucin, and it is found to be upregulated in AR patients (Voynow et al. 1998; Ali 2009).

Ovalbumin (OVA)-sensitized animals are commonly used to study the pathophysiologic changes of allergic inflammation. When hypertrophic and metaplastic changes in epithelial goblet cells are induced in a rat model of nasal allergy, intraepithelial mucus production is significantly inhibited by a Th2 cytokine inhibitor and by a cysteinyl leukotrienes (cysLTs) antagonist, indicating that Th2 cytokines and cysLTs (LTs C_4, D_4, and E_4) are important for mucus synthesis in AR (Shimizu et al. 2000; Shimizu et al. 2009). Mucus secretion (goblet cell exocytosis) can be evaluated by measuring the transient decrease of intraepithelial mucus. Histamine stimulates early-phase (1 hour after challenge) secretion through H1 receptor on cholinergic nerve terminals, and infiltrating inflammatory cells (eosinophils and/or neutrophils) play a role in late-phase (6 hours) secretion. CysLTs are important for both early-phase secretion and late-phase secretion (Shimizu et al. 2003b).

1.7 Therapeutic Strategies to Inhibit Mucus Hypersecretion

Mucus and mucociliary clearance serve important functions in the host defense system by removing irritants, allergens, pathogens, and dead cells from the airway. However, hypersecretion of mucus impairs mucociliary function and thus becomes part of the pathogenic process, causing symptoms such as nasal obstruction and anterior and posterior nasal discharge. Inhibition of mucus hypersecretion restores mucociliary clearance and improves symptoms. Selection of an appropriate therapeutic strategy is important because mechanisms of mucus synthesis and secretion differ among the diseases, stimuli, and types of inflammation.

1.7.1 Surgical Managements

Hypersecretion of mucus and obstruction of nasal passages impair mucociliary clearance, resulting in stagnation of mucus that contains host-invasive mediators and pathogenic microbes. Stagnation of mucus causes a vicious cycle of self-mediated inflammation in the pathogenesis of CRS (Fig. 1.6). For treatment of CRS patients, surgical removal of the stagnant mucus is very important. Nasal blowing and irrigations are useful for

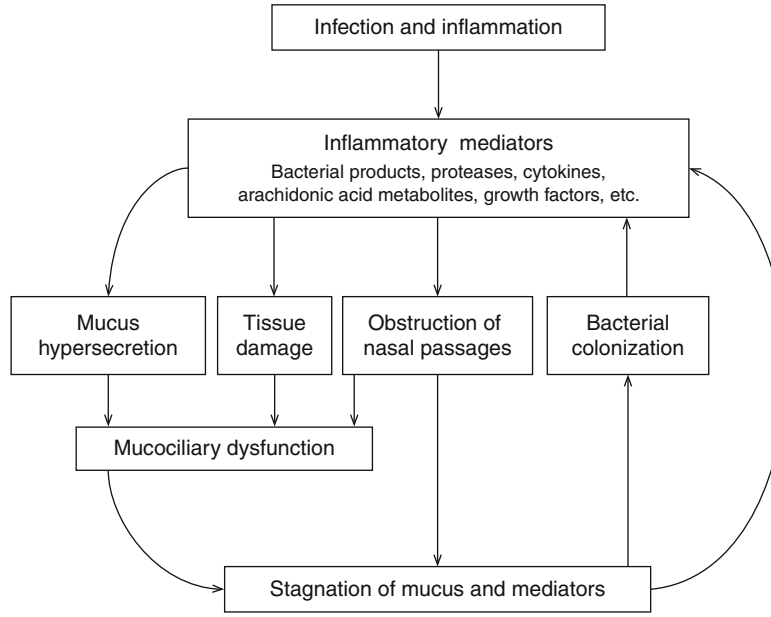

Fig. 1.6 A vicious cycle of self-mediated inflammation caused by the stagnant mucus in the pathogenesis of chronic rhinosinusitis. Mucus hypersecretion and damaged epithelium impair mucociliary function, resulting in "mucostasis," an accumulation of stagnant, pathological mucus that contains various inflammatory mediators and pathogenic microbes. These mediators and microbes exacerbate the local inflammation and further bacterial colonization. For treatment of patients with chronic rhinosinusitis, surgical removal the stagnant mucus is very important to stop the self-mediated inflammation

improving the symptoms (Suh and Kennedy 2011). Antral puncture and lavage decrease mucus viscoelasticity and improve mucociliary activity (Sakakura et al. 1985). Endoscopic sinus surgery to remove the obstructed mucosa and polyps is very effective for restoring mucociliary clearance (Min et al. 1995; Ikeda et al. 1997).

1.7.2 Mucolytic and Mucokinetic Agents

The formation of disulfide bonds to oligomerize gel-forming mucins contributes to the viscoelastic property of mucus. Increased viscoelasticity impairs mucociliary function. Mucolytic agents such as *L*-cysteine and *N*-acetylcysteine have free sulfhydryl groups that dissolve disulfide bonds and therefore decrease the viscoelasticity of nasal discharge and sputum (Majima et al. 1990; Yuta and Baraniuk 1997). Mucokinetic agents such as carbocysteine cannot break mucin disulfide bonds, but they improve mucociliary function and suppress goblet cell hyperplasia. These mucolytic and mucokinetic agents are reported to be effective as treatments for CRS patients (Wawrose et al. 1992; Mainz et al. 2011; Majima et al. 2012).

The release of large amounts of DNA from dead neutrophils contributes to increased mucus viscoelasticity. By decreasing the amount of DNA in sputum, inhaled DNase has become an important treatment for patients with cystic fibrosis (CF) (Fuchs et al. 1994). Inhaled hypertonic saline is also used to improve mucociliary clearance in CF patients (Donaldson et al. 2006); this stimulates water secretion into the airway by creating a temporary osmotic gradient. Hypertonic saline nasal irrigations are reported to be effective as treatment for CRS patients (Rabago et al. 2005).

1.7.3 Macrolide Antibiotics

The 14-member macrolides clarithromycin (CAM), erythromycin (EM), and roxithromycin and the 15-member macrolide azithromycin (AZM) are widely used to treat airway inflammation. Low-dose, long-term macrolide therapy has been reported to be very effective for patients with chronic airway diseases such as diffuse panbronchiolitis, chronic bronchitis, chronic obstructive pulmonary disease, CF, and CRS (Shirai et al. 1995; Kudoh et al. 1998; Jaffe

et al. 1998; Wallwork et al. 2006; Albert et al. 2011). The effects of these agents depend on anti-inflammatory and immunomodulatory rather than antibacterial actions.

CAM, EM, and AZM inhibit mucus hypersecretion and metaplastic and hypertrophic changes of nasal epithelial goblet cells *in vivo* and *in vitro* (Shimizu et al. 2003a; Shimizu and Shimizu 2012). They inhibit inflammatory responses of neutrophils, lymphocytes, macrophages, and epithelial cells and suppress gene expression and production of inflammatory cytokines and chemokines (Cervin and Wallwork 2007). In CRS patients, macrolide therapy reduces anterior and posterior nasal discharge and is effective for treating neutrophilic and lymphocytic inflammation. However, macrolide therapy is not effective for patients with eosinophilic inflammation, characterized by serum and tissue eosinophilia, high serum IgE, multiple polyposis, severe CT findings, and bronchial asthma (Suzuki et al. 2000; Wallwork et al. 2006; Haruna et al. 2009; Videler et al. 2011).

1.7.4 Anti-inflammatory Agents

Systemic and topical steroids are very effective for reducing mucus hypersecretion in patients with CRS and AR (Weiner et al. 1998; Rudmik et al. 2012). Glucocorticoids are potent anti-inflammatory agents that inhibit functions of a variety of inflammatory cells. Mucus hypersecretion is suppressed mainly by reductions in the release of secretagogue mediators such as histamine, leukotrienes, neutrophil elastase, and Th2 cytokines.

Anti-inflammatory agents such as antihistamines, cysLTs antagonist, Th2 cytokines inhibitor, and anticholinergic agents are clinically useful for reducing nasal AR symptoms, including anterior and posterior discharge (Greiner and Meltzer 2006; Suh and Kennedy 2011). All have been confirmed in animal model of allergic inflammation as inhibitors of nasal or tracheal mucus hypersecretion.

Conclusions

Mucin secretion is regulated by a multi-step process that includes synthesis and exocytosis. A wide variety of inflammatory stimuli upregulate mucin gene expression and induce mucus overproduction. During the past decades, there have been significant advances in our understanding of the biological roles of mucus and of mechanisms which regulate mucus hypersecretion, including (1) the structural biology of mucins and mucus, (2) regulation of mucin gene expression, (3) mechanisms of mucin synthesis and exocytosis, (4) epithelial cell differentiation and goblet cell metaplasia, and (5) development of animal models for studying mucus hypersecretion in sinonasal inflammation. Further understanding will provide the best possible therapeutic strategies for the treatment of various causes of mucus hypersecretion in sinonasal inflammation.

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Cilia, Ciliary Movement, and Mucociliary Transport

2

Mark Jorissen and Martine Jaspers

Keywords
Cilia • Dynein • PCD • SCD • Mucociliary transport • Ciliary beating

Core Messages

- Cilia are extensions of the apical membranes and are characterized by a 9+2 axonemal structure.
- Ciliary beating depends on the ATP-ase activity in the dynein arms and is characterized by a specific beating pattern.
- Structural and functional ciliary abnormalities can be the results of external factors (secondary ciliary dyskinesia) or inherited (primary ciliary dyskinesia).
- An active, coordinated ciliary beating is essential for mucociliary transport. Mucociliary transport is the final result of the functional and ultrastructural organization of the cilia at different levels.

2.1 Cilia

2.1.1 General Description

Cilia are tiny hairlike cell organelles, found on the surface of most cell types in the vertebrate body (Ferkol and Leigh 2012). There are two types of cilia: motile cilia and non-motile or primary cilia. Primary cilia or non-motile sensory cilia transmit signals to the interior of the cell. A second type of cilia, the motile cilia, is important for the movement of extracellular fluids. Motile cilia are found in the apical surface (ciliated epithelium) of the upper and lower respiratory tract, the oviducts of the female reproductive system, and ependymal cells lining the ventricles of the brain. These epithelial cells contain hundreds of motile cilia that beat together in a concerted manner to propel substances over the epithelial surface. Failure of these cilia to perform their normal function results in respiratory disease, sterility, or hydrocephalus.

Cilia, which line both the upper and lower airways, are covered by a thin layer of mucus and beat in a coordinated fashion propelling particles trapped in the mucus layer to the pharynx. Cilial defects may be either primary or secondary.

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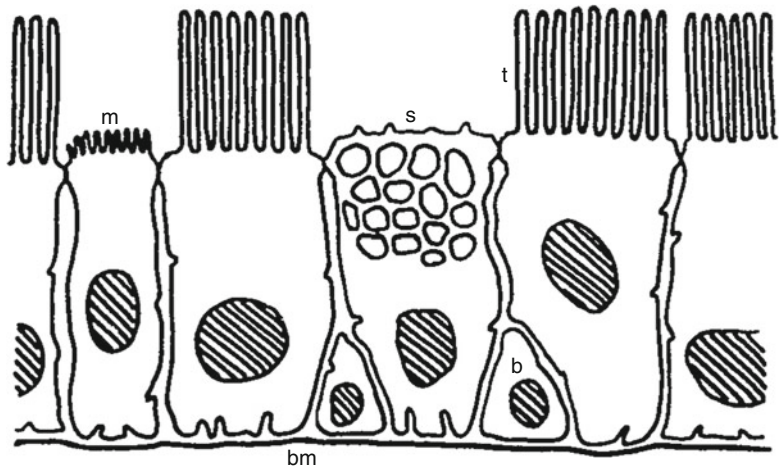

Fig. 2.1 *m* microvillar cell, *s* secretory cell, *t* ciliated cell, *b* basal cell, *bm* basal membrane

2.1.1.1 Ciliated Cells

The respiratory epithelium consists mainly of four cell types: ciliated columnar cells, non-ciliated columnar cells or brush cells with microvilli (m), goblet cells secreting mucin (s), and basal cells (b). The different cells types of the respiratory epithelium are illustrated in Fig. 2.1.

A ciliated cell has a diameter of 5 µm at its apex and carries 100–200 cilia at a density of 6–8/µm^2, interspersed with ±400 short microvilli (Rhodin 1966). The length of a cilium in the nose is 5 µm, in the larger airways 6–7 µm, and 5 µm in the smaller bronchiole (Jafek 1983). The diameter of the shaft or axoneme measures approximately 0.25 µm at the base and 0.13 µm in the distal segment.

2.1.1.2 Cilia

Cilia are motile hair-like extensions of the epithelial cells, surrounded by the ciliary membrane, a specialized extension of the cell membrane. The length of a cilium varies from 5 to 10 µm and the width between 0.1 and 0.3 µm. Each ciliated epithelial cell has 100–200 motile cilia.

2.1.2 Ciliary Structure

> The basic structure of cilia is "9 + 2 microtubuli." The intermicrotubular connections determine the function.

The ultrastructure of a cilium consists of nine outer doublets of microtubules surrounding a central pair of microtubules. This characteristic 9 + 2 organization of microtubules is called an axoneme, as viewed in cross section with the electron microscope (Fig. 2.2). The two central microtubules are surrounded by a central sheath with spokes directed toward the peripheral microtubular doublets. The outer doublets are connected by nexin links and with the central pair by radial spokes. Each outer doublet microtubule is composed of two subfibers, A and B, of which the A tubule is a complete microtubule with 13 protofilaments, while the B tubule is incomplete and contains only 10 protofilaments. Subfiber A bears inner and outer dynein arms with ATPase activity. The dynein arms are complex structures consisting of several heavy, intermediate, and light chains. The dynein heavy chains contain ATPase domains that act as molecular motors and slide the peripheral microtubular pairs relative to each other. Nexin links limit the relative motion of neighboring doublets and radial spokes control from the central pair. The basal body is a specialized centriole found at the base of the cilium that anchors the cilium in a specific orientation and is thought to be responsible for their formation. Ciliogenesis begins with the generation of basal bodies in the cytoplasm that then traffic to the apical surface, dock with and anchor to the plasma membrane, and elongate a ciliary axoneme. Basal bodies consist of nine microtubular triplets but do not have central microtubules, as seen by cross-sectional views with electron microscopy.

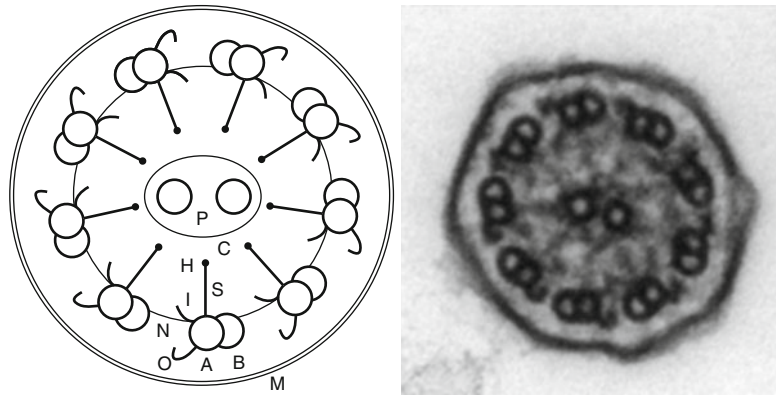

Fig. 2.2 Schematic drawing and photo of normal axonemal structure in transverse section. *A* microtubules A, *B* microtubules B, *C* central sheath, *H* spoke head, *I* inner dynein arm, *M* ciliary membrane, *N* nexin link, *O* outer dynein arm, *P* central pair of microtubules, *S* spoke

The basal body of a cilium is located just under the apical membrane and it is anchored in the cytoplasm by three types of accessory structures: (1) alar sheets, (2) a laterally directed basal foot, and (3) downward-directed ciliary rootlets at the base (see Fig. 2.3, left; Afzelius 1985). The basal foot indicates the direction of the effective stroke and is the most reliable reference for measuring ciliary (dis)orientation (Satir and Christensen 2007). Figure 2.3 shows a drawing of a longitudinal section of a ciliary axoneme and cross sections such as those can been seen at the indicated levels of the cilia. The image of Fig. 2.2 is a cross section of the main central part of a ciliary axonema.

Ciliary activity is generated by the sliding movements of the microtubules. During a beat the dynein arms undergo an attachment, retraction, and release with the adjacent doublet, which result in a sliding motion of the microtubule relative to each other. The energy needed for this is delivered by ATP hydrolysis by the ATPase domains of the dynein arms. The basal body anchors the microtubules, and the nexin links, the radial spoke, and probably the cell membrane restrict the degree of sliding between microtubules, thereby converting this sliding into bending (Merkus et al. 1998; Ferkol and Leigh 2012).

2.1.3 Structural Components: Dynein

Most of our knowledge about outer and inner dynein arm composition originates from studies in Chlamydomonas. Chlamydomonas outer dynein arm is composed of three heavy chains (α, β, γ), two intermediate chains, nine light chains, three docking complex proteins, and at least two associated proteins. The heavy chains are the sites for ATP hydrolysis required for ciliary motility (Pazour et al. 2006). The dynein heavy chains are composed of a head domain that produces a sliding force through an ATP-driven temporary interaction with an adjacent doublet B tubule and a tail domain that is stably fixed to the outer doublet A tubule (Fig. 2.4).

2.1.4 Structural Abnormalities

Up to 5 % abnormalities is normal.

In healthy persons more than 95 % of the cilia are ultrastructurally completely normal. Only in a minority of transverse section of cilia abnormalities are found. The percentage of abnormalities may increase as a result of inflammation, infection, and exposure to toxic agents. This is called secondary ciliary dyskinesia (SCD) to distinguish from the inherited abnormalities: primary ciliary dyskinesia (PCD).

Dynein deficiency remains most frequent ultrastructural abnormality in PCD. In up to 1/3 no ultrastructural abnormality is found.

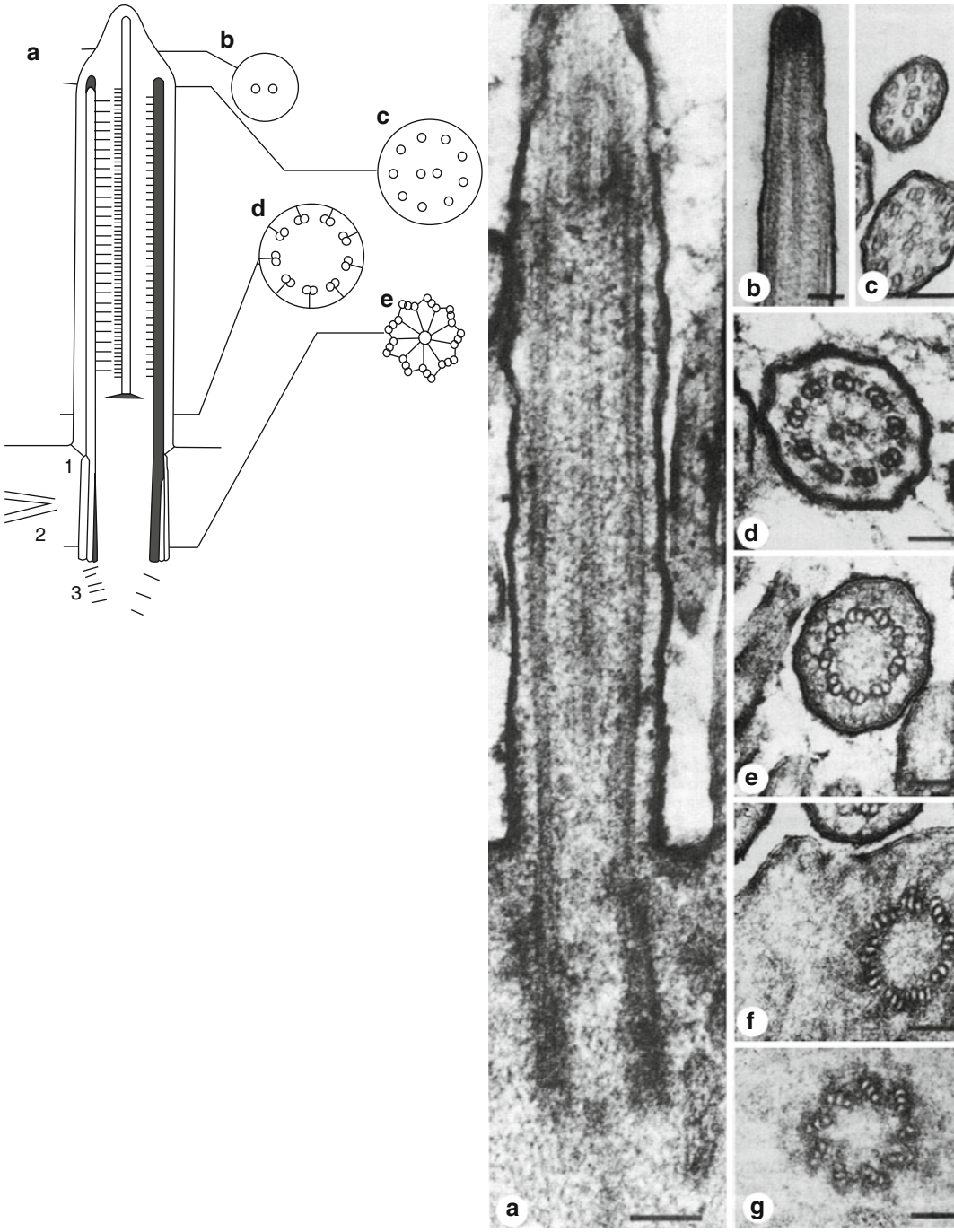

Fig. 2.3 (**a**) Drawing (*left*) and Transmission Electron Microscopy (TEM) photo (*right*) of a longitudinal section of a ciliary axonema; (**b**) longitudinal section of the tip and (**c**) until (**g**) cross sections such as those can been seen at the indicated levels; the image of Fig. 2.2 is a cross section of the main central part of the axonema. *1* fibers, *2* basal foot, *3* rootlets

Primary (genetic) defects in the structure and function of sensory and motile cilia result in multiple ciliopathies. The most prominent genetic abnormality involving motile cilia (and the respiratory tract) is primary ciliary dyskinesia (PCD). PCD reflects abnormalities in the

structure and function of motile cilia. The most common ultrastructural defects related to PCD are total or partial absence of dynein arms and absence or dislocation of central tubules. Besides, a significant number of PCD patients have cilia with normal ultrastructure but abnormal ciliary mobility (CBF and coordination). Based on the structural abnormalities found in PCD, patients can be classified in different subgroups (see also Figs. 2.5 and 2.6):

- Outer dynein arms deficiency (ODD)
- Partial outer dynein arms deficiency (part ODD)
- Outer + inner dynein arms deficiency (ODD + IDD)
- Eccentric central pair + inner dynein deficiency
- Central pair of microtubules absent
- PCD with normal ultrastructure
- Ciliary aplasia (no cilia and no basal bodies)

In the majority of patients, these abnormalities can be differentiated from the acquired abnormalities: secondary ciliary dyskinesia (SCD). However, there may be considerable overlap and in PCD patients frequently SCD abnormalities are found, because of the inflammation and infections. The most frequent ultrastructural abnormalities in SCD are the compound cilia, peripheral microtubular abnormalities, blebs of the axonemal membrane, excess cytoplasm, absence of the axonemal membrane, and ciliary disorientation of the central pair microtubules (see Fig. 2.7).

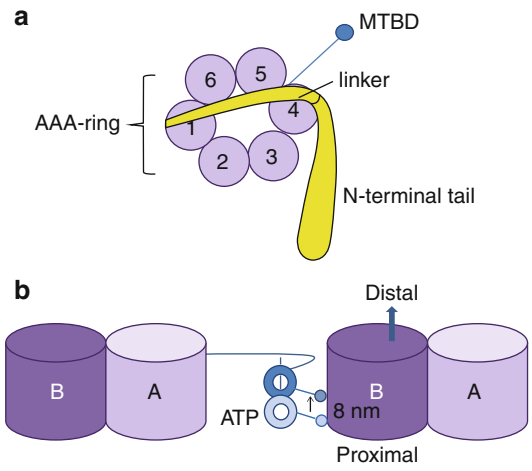

Fig. 2.4 The dynein motor unit or heavy chain consists of six tandemly linked AAA ATPase domains, which form a ring (Roberts et al. 2009), with the linker emanating from AAA1 and the coiled-coil stalk with the microtubule (MT)-binding domain located between AAA4 and AAA5 (**a**). Following ATP hydrolysis, the AAA rings of the dynein motor units were observed to move 8 nm toward the distal end of the axoneme (King 2010). As the motor is connected temporary to the adjacent B tubule via the MT-binding domain, located at the tip of the coiled-coil stalk, this would result in the B tubule being dragged distally (**b**)

2.1.5 Genetic Heterogeneity of PCD

The genetic heterogeneity of PCD is predicted by the complexity of the ciliary structure and the different structural component affected. Cilia consist of more than 250 proteins and thus many genes

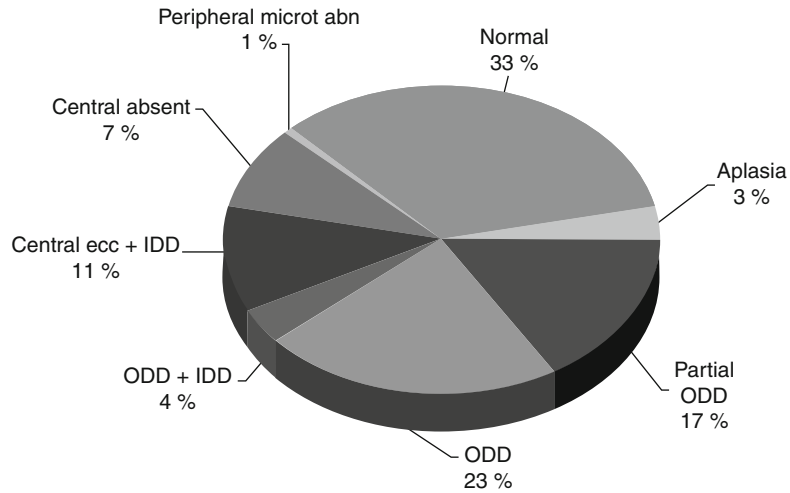

Fig. 2.5 Distribution of different ultrastructural subgroups in PCD base on a series of 202 patients in the UZ Leuven database

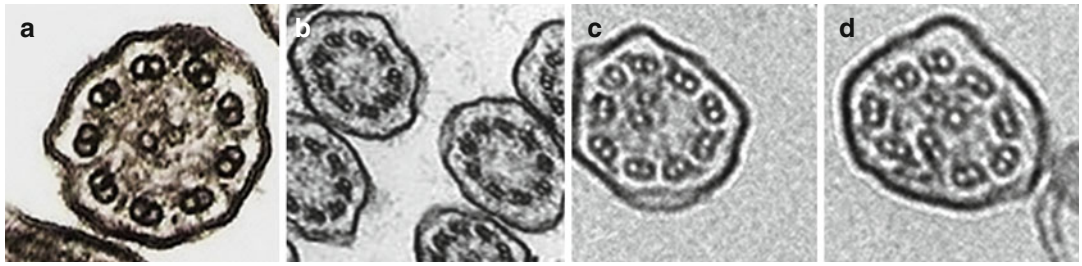

Fig. 2.6 Ultrastructural abnormalities in PCD: (**a**) dynein deficiency, (**b**) absent central pair, (**c**) eccentric central pair, and (**d**) eccentric central pair + transposition

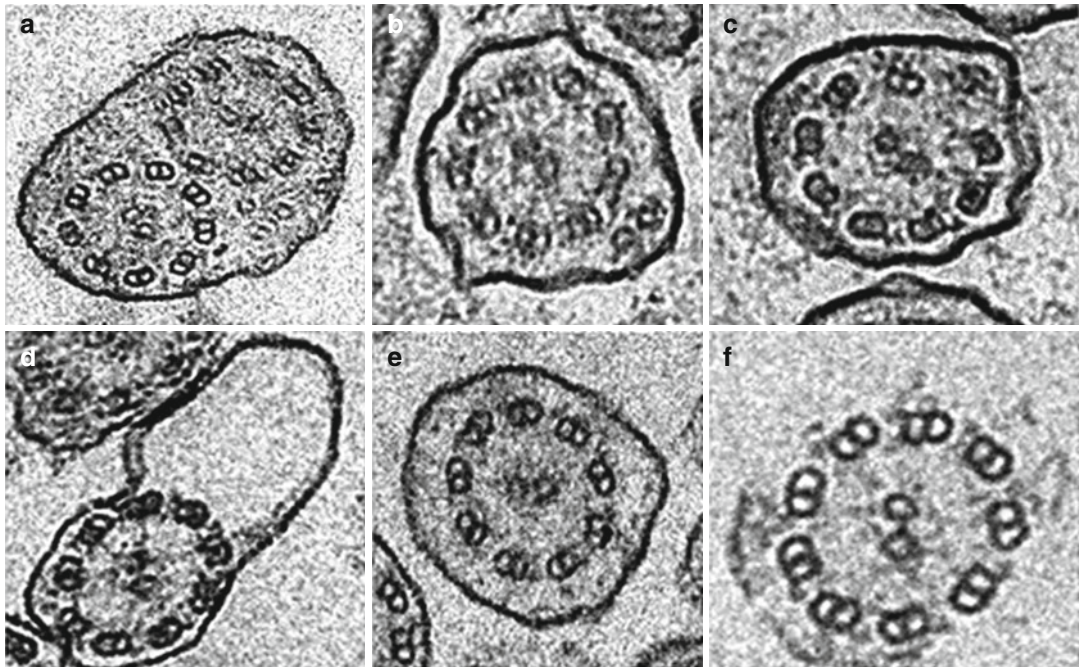

Fig. 2.7 Ultrastructural abnormalities in SCD: (**a**) compound cilia, (**b**) and (**c**) peripheral microtubular abnormalities, (**d**) blebs of the axonemal membrane, (**e**) excess cytoplasm, and (**f**) absence of the axonemal membrane: naked cilium

are involved in ciliary structure and function. Currently mutations in 12 different genes coding for axonemal proteins has been described, which explain about 50 % of PCD. Mutations in one of the 12 genes known to be associated with PCD (DNAH5, DNAI1, DNAI2, DNAH11, TXNDC3, C14orf104 (KTU), RSPH4A, RSPH9, LRRC50, CCDC39, CCDC40, and DNAL1) (Zariwala et al. 2011; Mazor et al. 2011) underlie specific ciliary ultrastructural defects identified by transmission electron microscopy. For instance, DNAH5, DNAI1, and DNAI2 cause outer dynein arm (ODA) defects (Hornef et al. 2006; Zariwala et al. 2006; Loges et al. 2008), while mutations in radial head spoke proteins (RSPH9, RSPH4A) and the coiled-coil domain containing proteins (CCDC39, CCDC40) are linked to central pair defects (Castleman et al. 2009; Becker-Heck et al. 2011). DNAH11 is the only gene identified so far linked to PCD patients with normal ultrastructure (Knowles et al. 2012).

Half of PCD families with ODA defects harbored DNAH5 mutations. DNAH5 encodes a heavy chain of the ODA. The prevalence of

DNAI1 mutations is 10–13 % in PCD patients with defined ODA defect but only 2–4 % in the whole cohort of PCD patients. All these genes combined explain approximately 50 % of PCD cases, therefore more genes need to be identified (Barbato et al. 2009; Zariwala et al. 2011).

2.2 Ciliary Movement

2.2.1 Ciliary Beat Cycle

The ciliary beat cycle consists of an effective and a recovery stroke.

Respiratory cilia have a rhythmical beating pattern and beat in a synchronous wave form. Every beat cycle consists of two active components: an effective stroke, during which the fully extended cilium moves in a plane perpendicular to the cell surface, and a recovery stroke, during which the bended cilium moves more parallel to the cell surface sideward and backward to its starting position; see Fig. 2.8. The duration of a recovery stroke is two to three times that of an effective stroke. After the effective stroke there is a short resting phase before the cilium starts its recovery stroke. The direction of the stroke depends on the orientation of the central microtubules (Merkus et al. 1998)

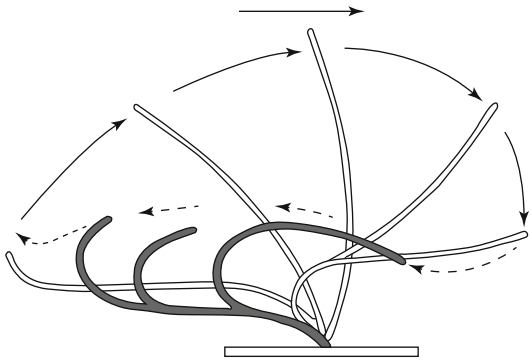

Fig. 2.8 Ciliary beat. The cilium performs an effective stroke (white cilium, *thin arrow*) and stays thereafter for some time in a resting position. The recovery stroke (black cilium, *dotted arrow*) is the start of a new cycle and takes place in a third dimension (From Satir 1974)

As mentioned above, the bending of the cilia is produced by sliding of the outer microtubule doublets against one another comparable with the actin-myosin system in muscles. The energy needed for the ciliary beat is produced by hydrolysis of ATP by the ATPase domains of the dynein arms. The velocity of the sliding movements and the frequency of the ciliary beat are correlated with the number of dynein arms and the concentration of ATP (Mallik et al. 2004; Sakakibara and Kamiya 1989).

A ciliated cell has approximately 200 cilia that beat in a coordinated way, and cilia on adjoining ciliated cells (unit of ciliated cells) are beating simultaneously. Ciliary beating is coordinated by calcium signaling between epithelial cells through gap junctions. Besides the regulatory effect of calcium on the ciliary beat, calcium is also involved in synchronizing the beat among cilia of one single cell as well as between cilia on different cells (Sanderson et al. 1988; Schmid and Salathe 2011). Ciliary beat frequency increases from the more peripheral parts of the respiratory tract to the more central parts. In larger airways like nose, trachea, and main bronchi, the frequency is 13–27 Hz; in smaller airways like middle ear, small bronchi, and bronchiole, the frequency is 7–12 Hz. The beat frequency increases with temperature and decreases with reduction in relative humidity of air.

Regulation of cilia that play a role in mucociliary clearance is complex, and any disturbance can lead to disease.

2.2.2 Factors Influencing Ciliary Activity

Several factors influencing the ciliary beat frequency have been described, including temperature, pH, and osmolarity (Ingels et al. 1991). A constant medium temperature is essential for accurate measurements, since CBF is temperature dependent. Ingels et al. (1991) demonstrated a linear relationship between CBF and temperature in the range from 22.5 to 40 °C. Changes in pH and osmolarity do not influence CBF when kept within a certain range. A pH change from 7.5 to 6.5 did not affect CBF, below a pH of 6.5

CBF decrease. Concerning osmolarity, a gradient of 150–225 mM (0.9–1.35 %) NaCl did not affect CBF substantially. In hypotonic (0.45 %) and hypertonic (1.5 %) saline solutions, CBF decreases about 50 % compared to the initial frequency (Van de Donk et al. 1980), while at 3 % saline cilia are complete immotile.

Beta-adrenergic influences on the respiratory mucosa are well known to cause enhancement of ciliary activity and mucociliary clearance (Wood et al. 1975; Sackner et al. 1976). However, considering that isoproterenol stimulates secretory function in airways (Melville et al. 1976), the question remained whether this increase in ciliary activity was due to a direct and specific action on the ciliated cells. Verdugo et al. (1980) demonstrated that isoproterenol directly stimulates the activity of ciliated cells of the respiratory epithelium and that this effect was β-adrenergic specific since the observed stimulation could be blocked by propranolol. Toxins derived from bacterial infections reduce ciliary activity of human nasal epithelial cells (Yun et al. 1999; Kim et al. 2000), and reduced ciliary activity can aggravate inflammation. Mallants et al. (2008) found that after a toxin-induced decrease, both bacitracin and clindamycin resulted in a complete recovery of CBF, suggesting that topical antibiotic treatment of nasal infections could result in a dual positive effect, namely, treatment of bacterial infection and recovery of the ciliary activity.

2.2.3 Abnormal Beating Patterns in the Context of PCD

Recent studies have confirmed that ciliary beat pattern is associated with specific ultrastructural defects in PCD (Chilvers et al. 2003). New high-resolution digital high-speed video (DHSV) imaging has allowed the precise beat pattern of cilia to be viewed in three different planes in slow motion or frame by frame. Using this technique, three patterns were identified and correlated with ultrastructural defects.

In the first pattern, the cilia are virtually immotile in large areas. Ciliary movement, when present, is restricted to slow, low-amplitude, stiff flickering motion. This is associated with either an isolated outer dynein arm defect or a combined inner and outer dynein arm defect.

In the second pattern, the cilia have a very abnormal stiff forward power stroke with a markedly reduced amplitude. This pattern is associated with an inner dynein arm defect or a radial spoke defect.

In the third pattern, the cilia beat in a large circular gyrating motion about the base of the cilium. This pattern is associated with transposition defects.

2.3 Mucociliary Transport

2.3.1 Structural and Functional Organization

Ciliary organization comprises four levels.

Mucociliary transport is the final result of the functional and ultrastructural organization of the cilia at different levels: single cilium, interciliary coordination, metachronal wave form, and mucociliary pathways (Jorissen 1998).

- First Level: Single Cilium
  A single cilium has a specific and well characterized ultrastructure: a 9+2 microtubular organization or axoneme. Morphological investigation at this level is mostly done with transmission electron microscopy (TEM). Ciliary beat frequency (CBF) is the most frequently used parameter of single ciliary function. Other parameters are the beating pattern, the amplitude, and the beat to beat variation (signal consistency Ingels et al. (1991); intracellular variability Jorissen et al. (1992)).
- Second Level: Ciliary Orientation and Coordination
  Cilia have to beat in a coordinated way to produce mucociliary transport, within one ciliated cell and between different cells. Ciliary activity is coordinated when all cilia beat in phase and in the same direction. This intra- and intercellular ultrastructural coordination can be studied using scanning electron microscopy (SEM) and transmission electron microscopy (TEM):

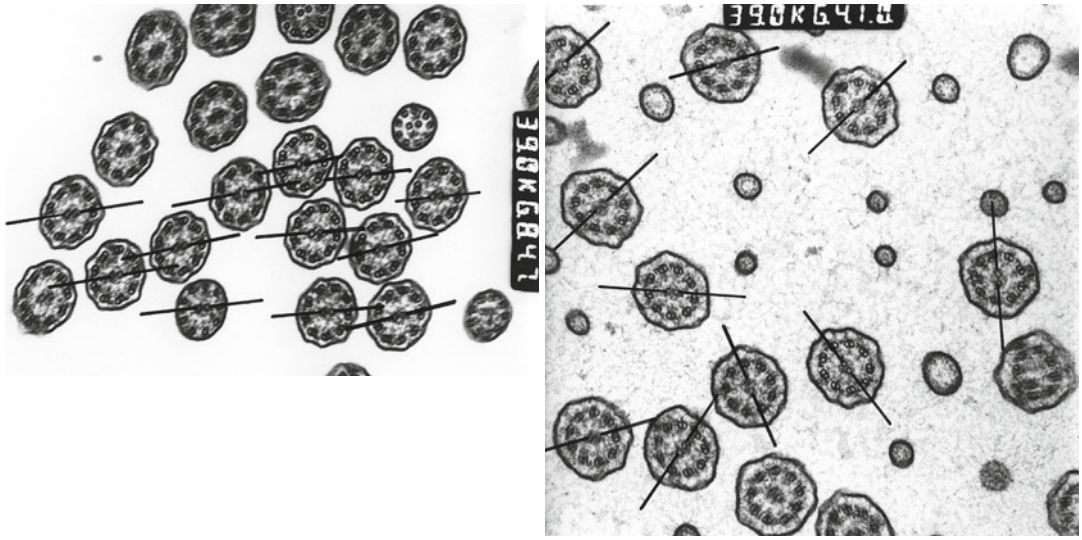

Fig. 2.9 Normal orientation with perfect alignment of all cilia (*left*) and random disorientation of the central pair in the context of PCD (*right*)

ciliary (dis)orientation. Ciliary orientation can be measured in TEM images of transverse sections in which the two central microtubules could be seen. A line is drawn through the central microtubular pair of each transverse sectioned cilium. The angle between this line and a reference line is measured for all cilia seen on one photograph; see Fig. 2.9. The standard deviation of all these measured angles is the ciliary disorientation. A normal value is 15°; >20° may be considered disorientation; >35° corresponds to random orientation (Jorissen and Willems 2004; Rautiainen et al. 1986, 1990; Rayner et al. 1996).

- Third and Fourth Levels: Metachronal Wave Form and Mucociliary Transport Pathways
  Finally, the coordination results in the metachronal wave form which can easily be seen in scanning electron microscopy and which is linked to the small phase difference between neighboring cilia within one cell but also intercellularly to a whole surface area. The metachronal wave form and the CBF are regulated by different intraciliary, intracellular, and intercellular mechanisms (Wong et al. 1993).

  At a macroscopical level this is organized in various streams that can only be measured overall as mucociliary transport. Mucociliary transport is the process by which ciliary activity causes transport of a thin film of mucus from the upper and lower respiratory tracts toward the digestive tract. Effective and coordinated ciliary beating is of the utmost importance for mucociliary transport.

2.3.2 Mucociliary Transport

Healthy airway surfaces are lined by ciliated epithelial cells and covered with an airway surface liquid, which is composed of two layers: the periciliary layer and the mucus layer. The low viscosity periciliary layer approximates the height of cilia and provides an optimal environment for ciliary beating (Knowles and Boucher 2002). The protective mucus layer on top of it is the secretory product of the goblet cells and the submucosal glands. It is a nonhomogeneous, adhesive, viscoelastic gel composed of water, carbohydrates, proteins, and lipids. This mucus layer traps foreign particles like dust, allergens, toxic substances, bacteria, and viruses from the air. Mucus is transported from the respiratory tracts into the pharynx by mucociliary clearance, where it is either swallowed or expelled via coughing. Mucociliary clearance in the airways is driven by the coordinated beating of ciliated cells in the airway epithelium. The permanent clearance of the

mucus toward the pharynx is the most important defense mechanism in the upper and lower respiratory tracts. The velocity of mucus clearance is 10–24 mm/min in the trachea, in the nose 4.5–7 mm/min, and in the bronchioli 0.5–2 mm/min. There is great variability between individuals, but for each individual the clearance rates are fairly constant. Airway diseases may influence mucociliary clearance by changes in the amount and in the viscoelastic properties of the mucus and the periciliary fluid and by changes in the number, the structure, and the activity of the cilia. These changes can be secondary and reversible or primary and nonreversible.

The mucociliary transport pathways are genetically defined and rather specific for each location. The different paranasal sinuses have specific pathways as well as the ostiomeatal complex and the nasal cavity.

Conclusion

Cilia are extensions of the apical membranes. The cilium itself is characterized by a 9+2 axonemal structure. An active, coordinated ciliary beating is essential for mucociliary transport. Ciliary beating depends on the ATPase activity in the dynein arms and is characterized by a specific beating pattern. In healthy persons 95 % of the cilia are ultrastructurally completely normal. Ciliary abnormalities can be the results of external factors (secondary ciliary dyskinesia) or inherited (primary ciliary dyskinesia). Ciliary function and structure are organized at different levels from the individual cilia, over interciliary and intercellular interaction, to the macroscopic level of the ciliated tapestry and mucociliary transport.

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Functional Defense Mechanisms of the Nasal Respiratory Epithelium

3

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Keywords
Sinonasal epithelium • Mucociliary clearance • Innate immunity • Adaptive immunity • Immune barrier • Toll-like receptors • Rhinosinusitis

Core Messages

- Sinonasal epithelium provides both a physical and immunologic barrier to infection.
- Intracellular junctions, mucus composition, and mucociliary clearance compose the mechanical barrier to pathogen invasion.
- Innate and adaptive immune responses form the immunologic barrier.
- Innate immunity provides a first-line defense to pathogens that circumvent the physical mucosal barrier by recognizing conserved pathogen-associated markers and activating a nonspecific inflammatory response.
- Adaptive immunity confers memory to particular pathogens, providing faster response to repeated infections.
- Sufficient stimulation of the innate immune system results in activation of and directs the type of subsequent adaptive immune response.
- Fungus and staphylococcal superantigens appear to be disease modifiers in chronic rhinosinusitis rather than the direct cause.
- Dysregulation in the adaptive immune response is the key factor in the pathogenesis of chronic rhinosinusitis.
- Understanding of host-specific sinonasal immune defenses will influence future therapies for CRS.

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3.1 Overview

The sinonasal epithelium is an important biological point of interface with the external environment, clearing foreign material without significant collateral tissue inflammation. Multiple components

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carry out this task, and while they are typically considered separately, they are functionally integrated. The first component is mucus produced by nasal glands and the epithelial goblet cells which traps particulate matter to be swept into the nasopharynx via mucociliary flow. The mucus also contains tonic levels of host defense molecules with antimicrobial properties, limiting microbial survival and proliferation. The next anatomic barrier is the epithelial layer with cells bound together via junctional complexes. Breaching these mechanical barriers brings exogenous agents in contact with receptors that activate the innate response. Secretion of host defense molecules is augmented, and chemokines and cytokines are secreted. The latter initiates inflammation and fosters the accumulation and activation of innate effector cells. If the stimulus is sufficiently strong, dendritic cells are activated to initiate the adaptive response consisting of T and B lymphocytes. The nature of this adaptive response is shaped, in large measure, by input from the epithelial cells. Hence the epithelium plays a pivotal role in maintaining homeostasis as well as initiating and likely regulating the immune response across the nasal interface. The various components of this system will be reviewed, and potential areas of dysfunction will be discussed as these may play a role in the development of CRS.

3.2 Anatomic Barrier

3.2.1 Epithelium Structure

The anterior nasal epithelium consists of stratified squamous epithelium with structural and barrier functions similar to skin. In addition to typical sebaceous and sweat glands, the nasal vestibule contains vibrissa - thick specialized hairs that assist in trapping particles - and many fine hairs for filtering smaller particles (Yee et al. 2010). At the internal nasal valves, the sinonasal epithelium transitions to pseudostratified ciliated columnar epithelium; this respiratory-type epithelium is found throughout the remainder of the sinonasal tract (Wagenmann and Naclerio 1992).

Sinonasal epithelium is respiratory epithelium with goblet, ciliated, and basal cells bound tightly to each other and the basement membrane.

Sinonasal epithelium consists primarily of ciliated cells, with variable concentrations of mucus-producing goblet cells and glands, and relatively few basal cells. The ciliated cells comprise approximately 70 % of the sinonasal epithelium and are responsible for mucous clearance from the sinonasal cavities. Each ciliated cell has hundreds of motile cilia at the apex that beat in unison as well as small, immotile microvilli that increase surface area and prevent drying (Busse and Holgate 2000). Each ciliated cell extends from the basement membrane to the surface of the mucosa with the cilia extending into the overlying mucous layer. Goblet cells comprise approximately 20 % of epithelial cells, but their density is irregularly distributed throughout the sinonasal epithelium. Goblet cells have a narrow area of basement membrane attachment and are packed with mucin-containing secretory granules. Their apices extend to the mucosal surface, are also covered with microvilli, and contain a large apical pore for secretion of mucin (Hilding 1967). Basal cells comprise less than 5 % of respiratory epithelium. They do not have an epithelial surface component and thus are exposed to fewer inhaled particulates and pathogens. Basal cells contain large numbers of hemidesmosomes that attach them firmly to the basement membrane and may function as respiratory cell progenitors (Evans et al. 1986).

3.2.2 Cilia and Mucus

The sinonasal respiratory epithelium is specialized to effectively trap and remove foreign material from the nasal cavity before it can cause inflammation or infection. When inspired particulates are removed, a reduction in irritation, allergic response, and pathogen invasion is achieved. The rheologic and immunologic

properties of nasal mucous composition combine with ciliary function to produce the phenomenon of mucociliary clearance that maintains a healthy sinus tract.

Respiratory mucus is responsible for trapping and neutralizing inspired environmental particulates. Nasal secretions from the goblet cells and submucous glands are augmented by fluid from the lacrimal glands and transudate from the underlying capillary bed to produce 600–1,800 mL of mucous per day. The composition of mucus is designed to trap and bind to particulates and allow for transport by cilia (Sleigh et al. 1988). Nasal mucous exists as a bilayer fluid overlying the epithelium comprised of an outer gel layer and pericellular sol layer. The gel layer is composed primarily of hydrated mucin, a thick mesh of glycoproteins produced by the respiratory goblet cells along with secretions from submucosal mucus glands. As the mucin is secreted, it hydrates and coalesces into mucin rafts overlying the watery pericellular sol layer. The viscous nature of the gel layer allows it to trap inspired pathogens and particulates larger than 0.5 μm (Antunes et al. 2009).

In addition, mucous also contribute to the respiratory host defense system directly. Mucins are known to recognize and bind to microorganism surface adhesins promoting the microorganism-mucin bond and promoting clearance. Mucin is known to bind to Mycoplasma pneumoniae, Streptococcus pneumoniae, Pseudomonas aeruginosa, influenza virus, and Escherichia coli (Adkinson and Middleton 2003). Mucins may bind and thus concentrate secreted innate immune defense molecules such as lactoferrin and lysozyme, which recognize and kill bacterial pathogens (Lamblin et al. 1992).

Mucus contains a variety of innate defense molecules to bind and neutralize pathogens.

Ciliated cells in human respiratory mucosa each contain 50–200 motile cilia extending from the apical surface. In humans, these respiratory cilia are approximately 6 um in length and are anchored by centriole-like basal bodies (Sleigh et al. 1988). Each cilium consists of an axoneme covered by an extension of the cell membrane. The axoneme is comprised of the "9 + 2" microtubular pattern that is preserved in ciliated cells throughout the body. The nine outer microtubule doublets are each connected radially to the two central microtubules and circumferentially to each other by dynein arms. It is these dynein arms that slide along the microtubules, generating force that is translated into microtubule movement (Satir and Sleigh 1990).

Ciliary motility generates a forward power stroke with the cilium fully extended, delivering force through the tip into the overlying gel phase of the mucous layer. This is followed by a recovery stroke with the cilium tip bent to sweep through the thin pericellular sol layer as it returns to its starting position (Antunes et al. 2009). Recovery is followed by a quiescent phase. Coordinated beating of the respiratory cilia creates a metachronous wave that propels the mucin rafts of the gel phase in the direction of the power stroke (Gheber and Priel 1989). The combination of mucus composition and ciliary beating creates the phenomenon of mucociliary transport, which is critical in maintenance of healthy sinonasal mucosa.

3.2.3 Mucociliary Clearance

The remarkable phenomenon known as mucociliary clearance (MCC) combines the biphasic properties of nasal mucus with coordination of the ciliated cellular beating to effectively clear the mucus blanket with trapped particulates from the nasal cavity. Nasal MCC function responds to environmental factors and is under continual dynamic modulation. Ciliary beat frequency increases as a reaction to stressors including increased breathing, cold air, exercise, or inflammation to accelerate mucus clearance (Braiman and Priel 2008). The mucus blanket is swept out of the sinus cavities in predefined patterns via natural ostia then into the posterior nasopharynx where it is swallowed and neutralized in the stomach.

Messerklinger classically described the defined mucus clearance patterns of the paranasal sinuses in 1966 (Messerklinger 1966). In the maxillary sinuses, mucus is swept upwards against gravity along the walls and roof towards the superomedially based maxillary ostium, into the ethmoid infundibulum, and then into the middle meatus. The anterior ethmoid cells each drain through inferiorly based individual ostia into the middle meatus. The posterior ethmoids drain into the superior meatus and then sphenoethmoid recess. The sphenoid sinus sweeps mucus anteriorly towards its natural ostium and also drains into the sphenoethmoid recess. The frontal sinus has the most complex clearance pattern. Mucus is cleared from the medial portion of the sinus in a retrograde fashion superiorly along the posterior wall away from the natural ostium, laterally along the roof to the anterior wall, and then carried inferiorly and medially towards the ostium (Donald et al. 1995).

Ciliated cells beat in a coordinated metachronous wave that rapidly clears the overlying mucus blanket.

The basis of modern endoscopic sinus surgery is to maintain functional MCC patterns. Surgical goals include relief of obstruction while utilizing mucosal-sparing techniques and preserving natural drainage pathways. Failure to incorporate natural ostia when opening a sinus can lead to recirculation particularly in the maxillary sinuses (Gutman and Houser 2003). Preservation of normal mucosa promotes restoration of natural mucociliary flow patterns. This is particularly true at the narrow nasofrontal duct where disruption of normal mucosa can lead to circumferential scarring with narrowing of the frontal duct, obstruction, and mucostasis.

3.2.3.1 Diseases Affecting Mucociliary Clearance

The sinonasal epithelium utilizes a mechanical barrier, effective mucociliary clearance, and optimal healing to maintain mucosal health. However, disease processes affecting ciliary function, rheologic properties of mucus, or obstruction of natural ostia results in altered MCC effectiveness and resultant infection (Cohen 2006). These include genetic conditions, allergy, asthma, and acute and chronic rhinosinusitis.

Mucociliary clearance efficiency declines with changes in mucus rheology, ciliary impairment, or narrowed sinus ostia.

Primary ciliary dyskinesia (PCD) is a disorder of the ciliary dynein arms resulting in systemically immotile cilia. These patients may have infertility and are unable to effectively transport mucus out of the sinorespiratory tract. The resultant mucus stasis results in chronic rhinosinusitis, bronchiectasis, and recurrent respiratory infections (Noone et al. 2004). Cystic fibrosis (CF) is an autosomal-recessive disorder of the CFTR gene resulting in abnormal electrolyte transport. Clinically, there is abnormal function of the goblet cells and highly viscous mucus. CF patients have defective MCC clearance due to inability of the cilia to adequately transport the thick mucus rafts and are subject to bronchiectasis and severe sinopulmonary infections (Wine 1999). Nasal polyps are found in approximately 40 % of CF patients and show a neutrophilic rather than eosinophilic pattern (Hadfield et al. 2000). However, these patients still display a wide spectrum in severity of their sinus disease despite having identical CFTR gene mutations (Cimmino et al. 2003).

Nasal irritants, allergy, and acute infection result in inflammation and mucosal edema that negatively affect mucociliary clearance. Acute upper respiratory infection has been shown to alter mucus composition, reduce ciliary motility, and create mucosal edema (Houtmeyers et al. 1999). When MCC function fails to clear sinuses in key areas such as the osteomeatal complex or eustachian tube orifice, associated sinusitis results.

Allergic challenge has been shown to increase transudate levels in nasal mucus. As a result, the depth of the periciliary layer increases, and the cilia tips cannot reach the overlying gel phase

to effectively propel the mucin rafts (Baumgarten et al. 1985). Swelling of the nasal mucosa in allergic rhinitis is also thought to obstruct sinus ostia leading to poor ventilation and mucostasis (Stammberger 1991). While the role of allergy in causal development of chronic rhinosinusitis is unclear, failure to address the allergic component clearly lowers success of surgical intervention in CRS (Lane et al. 2001).

Failure to address nasal allergies or smoke exposure leads to worse outcomes in treatment of CRS.

Exposure to cigarette smoke has been shown to significantly alter ciliary beat frequency and secretions resulting in reduced mucociliary clearance (Cohen et al. 2009). Long-term exposure has been proposed to cause epithelial and submucosal gland hyperplasia, squamous metaplasia, and increase epithelial permeability (Karaman and Tek 2009; Dye and Adler 1994) and to foster the formation of bacterial biofilms (Goldstein-Daruech et al. 2011). In addition, cigarette smoking and second-hand smoke have been shown to be independently associated with CRS (Tomassen et al. 2011; Garcia-Rodriguez et al. 1999). As such, exposure to cigarette smoke should obviously be avoided in patients with recurrent or chronic sinus disease.

In addition to relatively rare genetic disorders such as PCD and CF, multiple investigations have also demonstrated significant impairment of sinonasal mucociliary clearance in idiopathic CRS. Inflammatory changes seen in chronic rhinosinusitis with and without nasal polyposis can cause secondary ciliary dyskinesia. Possible pathophysiologic explanations include reduced ciliary beating, changing depth or viscosity of respiratory mucus, or alterations in epithelial integrity. CRS patients exhibit blunted ciliary beat frequency responses to adrenergic and cholinergic stimulation in explanted nasal epithelial cultures (Chen et al. 2006). Additional studies showed that when removed from the chronic inflammatory environment, cilia resume normal basal and stimulated beat frequency though recovery takes time. This suggests that a chronic inflammatory nasal environment reversibly suppresses normal ciliary function (Chen et al. 2007; Al-Rawi et al. 1998).

3.2.4 Epithelial Integrity

Sinonasal cells contain several types of intercellular junctions that serve both communication and attachment functions. Maintenance of epithelial integrity is important for cellular communication and prevention of pathogen invasion or foreign protein exposure to the underlying tissues. Sloughing of epithelial cells leaves a denuded basement membrane and evokes an inflammatory response.

Gap junctions primarily allow cell-cell transfer of ions and signaling molecules; they do not contribute significantly to adhesion (Yeh et al. 2003). Respiratory cells are held together on their lateral surfaces with adherens junctions and desmosomes, both of which contain cadherin proteins. Hemidesmosomes, which contain integrin proteins, attach cells tightly to the basement membrane and prevent cellular sloughing. The most important junctions, tight junctions, are critical in epithelial barrier integrity against invasion. Tight junctions attach adjacent epithelial cells in a narrow band just beneath their apical surface (Vermeer et al. 2003). The resultant epithelial surface is a watertight barrier to chemicals and particulates including proteins and pathogens at the surface.

Below the basement membrane lies the lamina propria, a network of blood vessels and loose fibrous stroma that contains immune cells responsible for pathogen detection and initial inflammatory response. Here reside the lymphocytes, plasma cells, macrophages, and dendritic cells which monitor the health of the epithelium. Pathogens that overcome the protective barriers of mucus and epithelium activate the innate and adaptive immune systems. Breakdown of the intracellular connections of the epithelium plays an important role in permitting stimulation of an immune response.

3.2.4.1 Diseases Affecting Epithelial Integrity

Invasion of pathogens into the underlying stroma requires disruption of the epithelium and penetration through the basement membrane. Viral pathogens, the initial cause of many upper respiratory tract infections, have developed mechanisms for epithelial disruption that target tight and adherens junctions, allowing for subsequent invasion into the underlying tissues (Takaon et al. 2005; Yeo and Jang 2010). Respiratory viruses disrupt the upper airway epithelial barrier, resulting in inflammation and predisposing for additional exposure to foreign material and potential tissue invasion (Pedersen et al. 1983). Nasal epithelial explant studies show viruses loosen epithelial tight junction bonds and penetrate the basement membrane within 24 h (Glorieux et al. 2011). Rhinoviruses, a major cause of the common cold, bind to intercellular adhesion molecule-1 (ICAM-1) on nasal epithelial cells, allowing RNA entry into the cell (Rossman 1994).

Fungi, bacteria, and allergens all carry significant intrinsic protease and virulence activity with the capacity of weakening tight junctions permitting access into the underlying tissues (Tieu et al. 2009; Zulianello et al. 2006). Intrinsic alterations in tight junction barrier function may be responsible for the increase epithelial permeability seen in allergic responses (Jeffery and Haahtela 2006). Penetration of antigenic proteins through the epithelium has been proposed as a major factor in asthma and atopy (Xiao et al. 2011).

> Respiratory viruses disrupt epithelial tight junctions and increase susceptibility to infection and inflammation.

Chronic inflammatory disorders may weaken the epithelial barrier function and predispose to infection. CRSwNP shows disruption of normal intercellular junctions including decreased levels of the desmosome cadherin proteins DSG2 and DSG3 (Zuckerman et al. 2008) and tight junction proteins claudin and occludin (Liu et al. 2009). Disruption of intercellular tight junction connections is seen in nasal polyposis (Rogers et al. 2011). Decreased production of protease inhibitors such as LEKT1, encoded by the gene SPINK5, has been found in CRSwNP (Tieu et al. 2009). This molecule acts as a proteinase inhibitor and regulates the processing of epithelial tight junctions critical to maintaining a barrier to infection. In addition, altered intercellular ion transport is seen in CRS and may interfere with coordination of ciliated cells leading to ineffective mucociliary clearance (Dejima et al. 2006).

3.3 Immunologic Barrier Function of the Sinonasal Epithelium

In addition to forming a physical barrier and providing clearance of pathogens from the nasal cavity, sinonasal epithelial cells (SNECs) contribute to the innate and adaptive immune responses. When the various mucosal barrier functions are circumvented by irritant or pathogenic particulates, the mucosal immune system must distinguish between normal commensal organisms and invading pathogens. In addition, the immune system must determine how to mount an appropriate level or intensity of response. The first of these responses, the innate immune system, consists of receptors, defense molecules, and cells that respond to microbial organisms in a relatively nonspecific manner. This innate response is an inborn, germ line-coded defense to generalized pathogen invasion and does not typically exhibit memory. Should the innate immune system be sufficiently challenged, it activates the adaptive arm of the immune system, with a delayed but highly specific T and B cell response capable of memory against specific pathogens. Emerging evidence also indicates that a diminished innate response coupled with a compensatory overactivation of adaptive immunity may play a role in the pathogenesis of the chronic mucosal inflammation seen in CRS.

> Pathogen recognition by the innate immune system results in a cascade of cytokines and chemokines that determine the type and strength of the inflammatory response.

3.3.1 Receptor Molecules

Innate immune responses in the sinonasal epithelium are initiated by membrane-bound and cytoplasmic pattern-recognition receptors (PRRs) that recognize highly conserved pathogen-associated molecular patterns (PAMPs) found in various bacteria, mycobacteria, viruses, and parasites as well as necrotic debris from cellular damage (Janeway and Medzhitov 2002). PRRs are also expressed on various types of antigen-presenting cells including dendritic cells, macrophages, and B cells. In addition SNECs express genes associated with antigen-presenting function (Lane et al. 2004). Once the innate immune response is activated, SNECs may also serve as antigen-presenting cells, increasing local tissue inflammatory response. Overall, stimulation of PRRs facilitates both the innate and the adaptive response.

Recognition of PAMPs by PRRs results in secretion of the endogenous antimicrobial factors that directly aid in pathogen clearance. PRR activation also stimulates SNECs and antigen-presenting cells (APCs) to release inflammatory cytokines and chemokines that attract other innate cellular defenses such as phagocytes. Other receptors detect cellular injury through damage-associated molecular patterns DAMPs (Claeys et al. 2003; Bianchi and Manfredi 2009). If the combination of cellular damage and PRR activation is sufficiently strong, the resultant innate immune response triggers cytokine patterns that initiate, and determine the nature of, the subsequent adaptive immune response (Meylan et al. 2006). See Fig. 3.1.

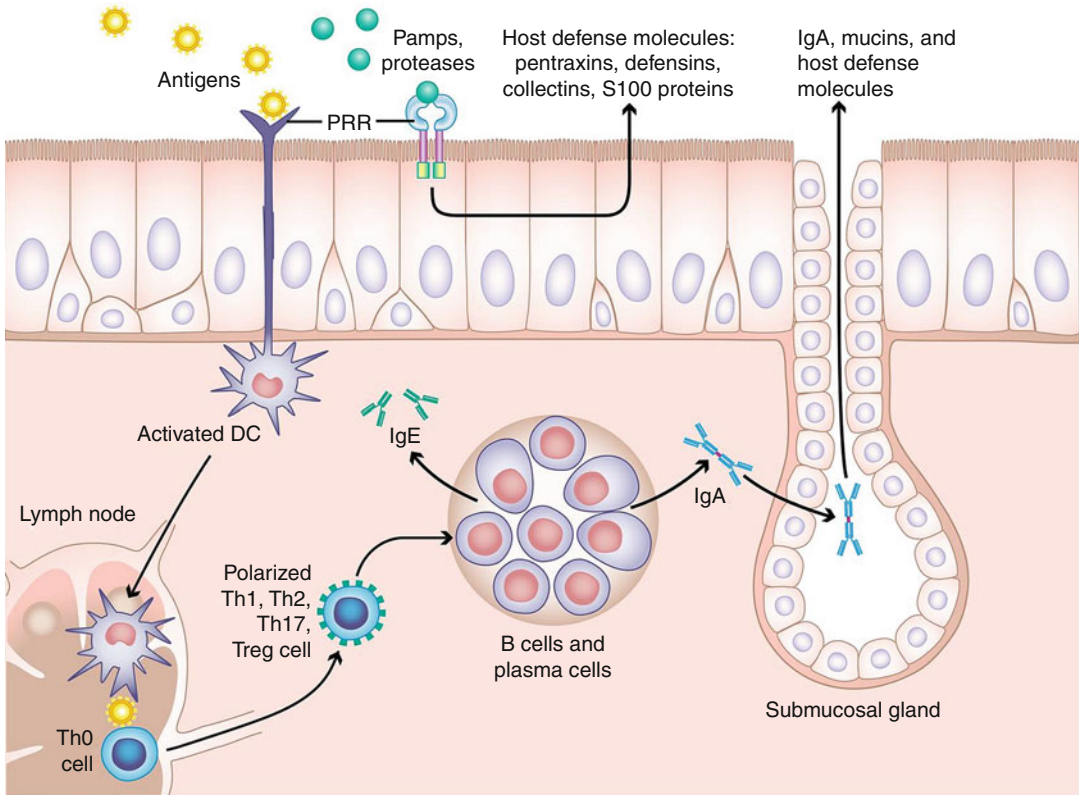

Fig. 3.1 Innate immunity at the epithelial surface involves PAMP activation of epithelial PRRs leading to release of host defense molecules. Exogenous proteases may activate PAR receptors or degrade tight junctional proteins. Secreted IgA, mucins, antiproteases, and host defense molecules are released into the nasal mucus to form a second line of innate defense. Sufficient PRR stimulation activates dendritic cells causing migration to local lymph nodes to present antigen fragments to naïve Th0 lymphocytes. The type and strength of antigen stimulation drive the adaptive immunity through polarized Th1, Th2, Th17, or Treg responses. B cells are stimulated to undergo proliferation, class switch recombination, and differentiation leading to production of IgE, IgA, and other immunoglobulins as well as stimulation of the cells of the adaptive immune system. *See text for details*

PRRs can be separated into three main classes: endocytic, secreted, and signaling. Endocytic PRRs are found on the surface of phagocytes, which recognize pathogenic PAMPs, engulf the pathogens, and present the antigens to lymphocytes of the acquired immune system. One example is the mannose receptor found on macrophages (Fraser et al. 1998).

Secreted PRRs are used as opsonins that trigger the complement cascade or signal phagocytosis. The most abundant of the secreted antimicrobial peptides in the nasal mucosa include lactoferrin, mannose-binding lectin, secretory leukocyte proteinase inhibitor, and lysozyme (Cole et al. 2002). These are released into the mucus by nasal epithelial cells in response to activation of PRRs and confer protection by inhibiting epithelial invasion or directly lysing the microorganism (Ooi et al. 2010).

Signaling PRRs trigger production of antimicrobial peptides and cytokines by epithelial cells in response to PAMPs (Medzhitov and Janeway 2000). Signaling PRRs found in nasal epithelium include the toll-like receptor (TLR) family, the nucleotide binding and oligomerization domain (NOD)-like receptor family (NLRs), and the retinoic acid-inducible-like receptors (RLRs).

Important pathogen recognition receptors (PRRs) include the TLR, NOD, and PAR families.

TLRs are transmembrane receptors expressed on various cell types including SNECs that recognize extracellular or intracellular PAMPs such as bacterial lipopolysaccharide (LPS) (Iwasaki and Medzhitov 2004). TRL2, TRL3, TRL4, TRL9, and possibly others are expressed in sinonasal epithelium and contribute to the host defense. TLR2 responds to gram-positive bacterial as well as fungal PAMPs, TLR 3 recognizes viral replication products, TLR4 recognizes bacterial endotoxin, and unmethylated CpG areas on pathogenic DNA activate TLR9 (Yeh et al. 2003). TLR activation triggers intercellular signaling through proteins MyD88 and TRIF, which affects gene expression through transcription factors NF-κβ, AP-1, and IRF3 (Vroling et al. 2008).

The NOD-like receptor family includes NOD-1 and -2, which have been shown to recognize bacterial cell walls including staphylococci (Fournier and Philpott 2005). NOD levels were increased in CRSwNP and levels decreased after nasal steroid use (Mansson et al. 2011). RLRs are intracellular receptors important for recognizing RNA derived from RNA and DNA viruses, though their role in sinonasal epithelial response is still being investigated (Schroder and Bowie 2007).

The protease-activated receptors (PARs) are a distinct set of receptors found on sinonasal epithelial cells that are activated by endogenous and exogenous proteases including those from bacteria, fungi, and allergens. Once activated, PARs evoke the NF-κβ signaling pathway, the results in chemokine and cytokine production, and phagocytic recruitment and potentially influence the subsequent acquired immune response based on the cytokine milieu (Hershenson 2007). PAR-2 activation by *Staphylococcus aureus* proteases results in increased levels of cytokine IL-8 (Rudack et al. 2007). Fungal proteases may drive the eosinophilic as well as neutrophilic response via PARs (Shin et al. 2006). SNECs secrete antiproteases such as LEKT1 coded by the *Spink 5* gene, which likely acts to protect PARs from both exogenous and endogenous protease stimulation. Reduced levels of LEKT1 have been associated with CRSwNP, suggesting that excessive PAR activation may play a role in polyp pathogenesis (Briot et al. 2009).

3.3.2 Host Defense Molecules

Sinonasal epithelial cells secrete a multitude of antimicrobial molecules into the surrounding mucus. Enzymes break down pathogen cell walls and include lysozyme, chitinases, and peroxidases. Foreign material is marked for phagocytosis by opsonins such as complement and pentraxin-3. Permeabilizing proteins include defensins and cathelicidins. Defensins are inducible and provide broad antimicrobial activity and

inhibit invasion of bacteria and viruses (Van Wetering et al. 2005). Cathelicidins are a family of secreted peptides that are active after extracellular cleavage. In humans, cathelicidin LL-37 directly disrupts bacterial membranes (Turner et al. 1998). They are chemotactic for effector cells of both the innate and adaptive immune system including neutrophils, monocytes, mast cells, and T cells and may modulate their activity (De et al. 2000). Collectins include surfactant proteins (SP-A, SP-D) and mannose-binding lectin; these proteins, long studied in lower respiratory mucosa, are also found in sinonasal secretions. They are important in reducing nasal bacterial colonization, inflammation, and infection (Crouch et al. 2000). Decreased surfactant levels are found in patients with cystic fibrosis, poorly controlled COPD, allergic fungal sinusitis, and CRS (Postle et al. 1999; Sims et al. 2008; Ooi et al. 2007). Binding proteins include mucin, discussed previously, and lactoferrin, which attaches to foreign material and facilitates its removal by MCC. PLUNC, another secreted antimicrobial, has important anti-biofilm properties. Diminished secretion of many but not all of these host defense molecules has been proposed as a common mechanism broadly underlying the etiology and pathogenesis of CRS (Tieu et al. 2009; Kern et al. 2008). See Fig. 3.2. The cause for this selective reduction is unclear but may be (1) a primary defect in the innate response or (2) a downstream secondary effect of the TH2 cytokines milieu associated with CRS (Ramanathan et al. 2008). Mechanistic studies to evaluate this have not been completed, but IL-22 and the STAT 3 pathway appear to broadly govern innate nasal

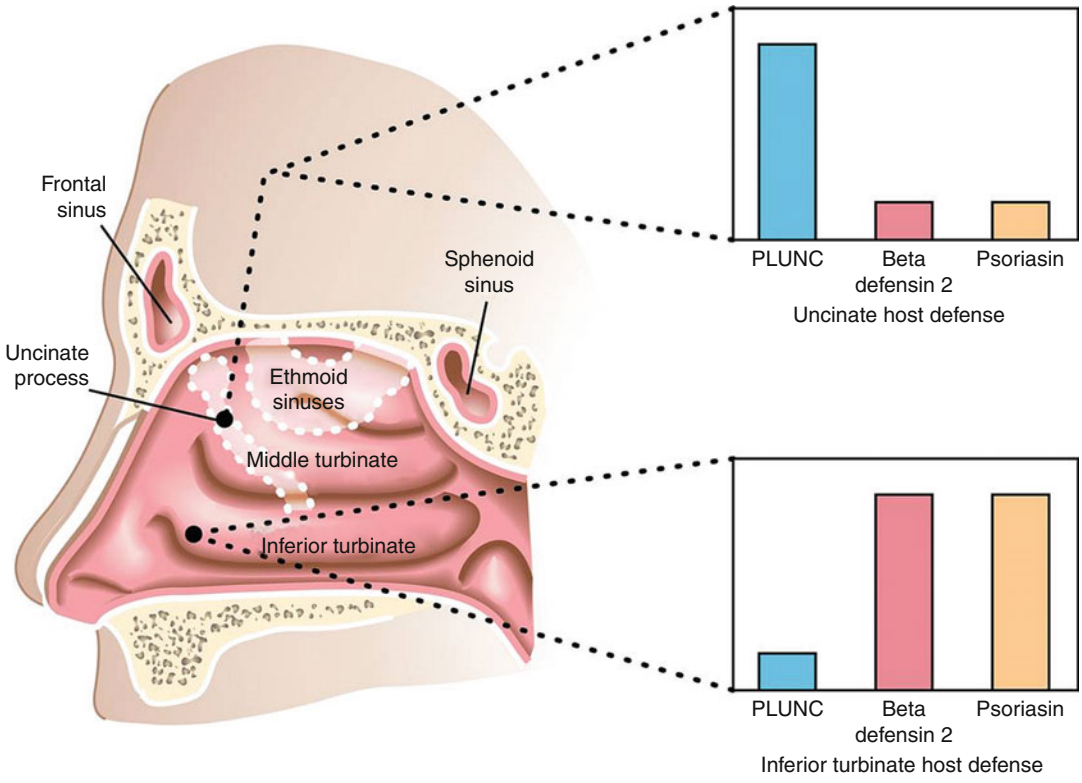

Fig. 3.2 Inferior turbinate and uncinate process tissue from of healthy patients were compared for levels of the mucosal innate defense molecules PLUNC, lactoferrin, pentraxin, S100A7, and hBD2. While levels of pentraxin remained the same between the two sites, polarization was noted with the remaining molecules. In nasal uncinate tissue, low levels of PLUNC and lactoferrin but high levels of S100A7 and hBD2 were found. In inferior turbinate tissue, the converse was true, suggesting that host defense molecules show regional specialization in human nasal airways

mucosal host defense and mechanical barrier integrity (Wolk et al. 2006; Pickert et al. 2009; Aujla et al. 2008). Diminished STAT 3 activity in the sinonasal epithelium has been identified in CRS supporting a primary innate defect (Peters et al. 2010).

A decrease in innate host defense molecules contributes to the pathogenesis of CRS.

3.3.3 Epithelial Chemokines and Cytokines

In response to PRR and PAR stimulation, sinonasal epithelial cells produce a variety of cytokines, which are small proteins that regulate inflammation and mediate associated pain, swelling, and vascular dilatation (Bachert et al. 1998). A partial list include IL-1, TNF, IFN, GM-CSF, eotaxins, RANTES, IP-10, IL-6, IL-8, MDC, SCF, TARC, MCP-4, BAFF, osteopontin, IL-25, IL-33, and TSLP (Kowalski et al. 2005; Nishi et al. 2009; Lu et al. 2009). These cytokines have a diverse array of functions including triggering inflammatory responses, activating and recruiting innate effector cells, and facilitating and shaping the adaptive response. To the last point, IL-1, IL-6, and IL-8 have all been identified as particularly important in modulating the transition between the two arms of the immune response (Lu et al. 2009). Newly identified epithelial-derived cytokines, including TSLP, IL-25, IL-33, and BAFF, help shape the local adaptive responses more directly. They foster B cell proliferation with immunoglobulin production and shaping the T helper profile via dendritic cell polarization (Kato and Schleimer 2007; Hammad and Lambrecht 2008). Defective regulation of these processes has been proposed as playing a role in the pathogenesis of CRSwNP. It has been noted that corticosteroids, a mainstay for treating inflammation and CRS, act in part via the downregulation of epithelial cytokine secretion but spare or even augment the epithelial secretion of host defense molecules (Schleimer 2004; Bobic et al. 2010). In this fashion, corticosteroids effectively upregulate the innate immune response and downregulate the adaptive response.

Epithelial-derived molecules directly contribute to the innate immune defense and shape associate B cell and T cell responses.

3.3.4 Epithelial Co-stimulatory Molecules and Inflammatory Enzymes

SNECs express co-stimulatory molecules, particularly homologues of the B7 family of cell-surface ligands (Kurosawa et al. 2003). Expression results in downregulation of T cell-acquired response and is induced by TNF-α and IFN-γ (Kim et al. 2005). Increased B7 family expression is induced by viral infection and CRS (Heinecke et al. 2008). Reactive oxygen species (ROS) are important in many of the processes discussed: mucin production, epithelial healing, response to toxins, and innate immunity (Avila and Schleimer 2008). They can be beneficial, generating hypothiocyanite and peroxide which aid in microbial killing. In addition, they may be induced by toxins, requiring neutralization by antioxidants in airway epithelial cells. ROS can also interact with reactive nitrogen species (RNS) to create tissue damage in disease (Pedersen et al. 1983). Of particular interest is nitric oxide (NO), an intracellular messenger that mediates inflammation and antimicrobial effects and regulates apoptosis. In particular, NO is produced in high concentrations in the paranasal sinuses and may limit bacterial colonization (Lundberg et al. 1995).

3.3.5 Cells of the Innate Immune System

Important cells of the innate immune response that respond to cytokines secreted by the sinonasal epithelium include dendritic cells, macrophages, neutrophils, eosinophils, natural killer (NK) cells, innate lymphocytes (ILC), basophils,

and mast cells. Macrophages and neutrophils are primary phagocytes which recognize and bind to pathogens that have been opsonized, or marked as foreign, by antibodies, complement, or collectins (Ooi et al. 2010). They then engulf the opsonized pathogens and neutralize them by a variety of methods including nitric oxide and radical oxygen species. In addition, macrophages assist in tissue homeostasis, removal of particulates, and tissue repair and influence the adaptive immune response. Two pathways of macrophage differentiation and activation exist: the M1, or classical, pathway and the M2, or alternative, pathway. The M1 pathway is driven by Th1 cytokines and fosters macrophages directed against intracellular pathogens. The M2 pathway is driven by Th2 cytokines and fosters macrophages specialized against helminthes, with additional roles in tissue repair and antibody formation (Martinez et al. 2009). High levels of M1 macrophages are seen in sinus mucosa and polyps of CF patients, while high levels of M2 macrophages are seen in CRSwNP tissues (Krysko et al. 2011; Claeys et al. 2005). Neutrophils are among the first cells to respond to infection and are important in early phagocytosis of extracellular microbes. Mucosal recruitment is triggered by PRR stimulation creating chemokines, particularly IL-8, which is also secreted in response to PAR-2 stimulation (Marseglia et al. 2007). Neutrophils kill using free radicals and many of the same antimicrobial peptides that are secreted in the nasal mucus. Their overactivation may contribute to pathogenesis of CRS, inflammation related to tobacco smoking, and CF-associated polyposis (Polzehl et al. 2006; Goldstein-Daruech et al. 2011).

High numbers of eosinophils are seen in mucosal surfaces in allergy and asthma. Eosinophils are granulocytes that respond to mucosal inflammation by degranulating and releasing stored cytokines. They are prominent in fungal and parasitic responses and release major basic protein, eosinophil-derived neurotoxin, and neutrophil elastase (Lee et al. 2010). Eosinophilia is also an important component of CRS where it contributes to mucosal damage and chronic inflammation (Harlin et al. 1988). Multiple studies have shown that tissue eosinophilia is correlated with severity of CRS and comorbid asthma (Bhattacharyya et al. 2001; Szucs et al. 2002). The highest levels of tissue eosinophils are seen in CRSwNP, particularly from Western populations (Jankowski et al. 1989). Eosinophil recruitment and activation is in large measure via epithelial cytokines and chemokines, including eotaxins, RANTES, and MCP (Mullol et al. 2006; Meyer et al. 2005; Jahnsen et al. 1999; Yao et al. 2009). The regulation of this secretion is in part through PRR stimulation but also via Th2 cytokines IL-4 and IL-13 (Matsukura et al. 1999; Kuperman and Schleimer 2008). The cellular sources of these Th2 cytokines are unclear, but presumably include Th2 helper T lymphocytes and innate lymphocytes (ILC). Other factors that may foster eosinophil activation and recruitment include staphylococcal superantigens, IL-25, IL-33, TSLP, SCF, and eicosanoids (Foreman et al. 2011; Van Zele et al. 2009; Buysschaert et al. 2010; Perez-Novo et al. 2006).

Upregulation of eosinophils is seen in allergy, asthma, and CRSwNP.

Mast cells are resident cells in the sinonasal mucosa that function in innate immunity and tissue repair but also play key roles in the pathogenesis of allergic rhinitis and possibly nasal polyposis. Stem Cell Factor (SCF), secreted by SNECs, is likely important in mast cell recruitment (Kowalski et al. 2005). Mast cell activation results in the secretion of preformed granules including histamine, prostaglandins, serotonin, and serine proteases. In addition, de novo synthesis and secretion of various cytokines, chemokines contain and eicosanoids also takes place. They can be induced to phagocytose pathogens as well, though this is not their primary function. Physiological activation occurs typically through stimulation of PRRs. In nasal disease states such as allergic rhinitis, mast cells are activated strongly via surface IgE bound to antigen (Stone et al. 2010). In CRSwNP, both IgE-dependent and IgE-independent pathways for mast cell

activation likely contribute to pathogenesis (Balzar et al. 2007; Pawankar et al. 2007). Specifically, mast cells may be able to induce and maintain eosinophilic inflammation leading to polyposis as well as influence the subsequent adaptive immune response.

Dendritic cells (DCs) are key cells in both the innate and adaptive responses via antigen capture, antigen presentation to immature T cells, and the secretion of soluble mediators. DCs phagocytose and thereby sample commensal organisms and pathogens at the sinonasal epithelial surface. Cytokine cross talk between SNECs and DCs helps determine DC polarization (Hammad and Lambrecht 2008). Polarized DCs then migrate to local lymph nodes and present a fragment of the engulfed pathogen, via major histocompatibility complex (MHC) type II on the cell surface, to immature T cells. DC cytokines strongly influence the subsequent T cell profile, secondarily polarizing the helper response (Perez-Novo et al. 2010). Overall, DCs act as a bridge from the innate to the adaptive immune response. SNECs acting through cytokines that influence DCs play a significant upstream role in shaping the subsequent adaptive response, which will be discussed below. Defects in this cross talk pathway may foster the development of CRSwNP.

3.3.6 Adaptive Immunity

The adaptive immune response is mediated by T and B cells and includes immunoglobulin and T effector processes that augment the faster, but less specific innate response. Sinonasal epithelial responses play a key upstream role in the adaptive response including the recruitment of cells of the T and B lineage. In addition, as mentioned above, the type, duration, and intensity of PRR activation by PAMP stimulus in SNECs, DCs, and other cell types are believed to shape the resultant T lymphocyte profile and to ensue antibody and cell-mediated response at the mucosal surface (Hammad and Lambrecht 2011).

B lymphocytes secrete immunoglobulins, or antibodies, to specific antigens, playing an important role in the memory of the adaptive immune response. Immunoglobulins help bind and trap commensal organisms and pathogens, aiding mechanical clearance and facilitating active killing via multiple mechanisms. In the nasal mucosa, B cells respond to antigen presentation by proliferating and undergoing differentiation into mature plasma cells that produce immunoglobulin. In normal mucosal defense, the primary antibody class is secreted IgA from extrafollicular B cells. This response works to limit bacterial colonization with a minimum of inflammation, is T cell independent, and helps maintain mucosal homeostasis. SNECs and other cell types secrete cytokines and chemokines that foster this baseline B cell activity with the capacity for upregulation in response to an immune challenge.

Staphylococcal superantigens and fungal elements act as disease modifiers in CRS.

During frank mucosal infection, secretory IgA is joined by IgG, resulting in the development of a robust inflammatory response. This response exhibits high affinity for the invading pathogens, is T cell dependent, and utilizes immunoglobulins generated by both tissue plasma cells and follicular B cells. Other immunoglobulins play a role in mucosal inflammation including IgM, IgE, and IgD (Cerutti et al. 2011). IgM is an early-response antibody that precedes the development of long-term IgG. IgE is important in allergic response, mast cell activation and survival, and homeostasis as well as defense against pathogens, especially parasitic infections. IgD, though little understood, may influence antigen binding and basophil activation against respiratory bacteria (Chen and Cerutti 2010).

In chronic inflammatory conditions such as CRS, immunoglobulin profiles are skewed from the normal, apparently in response to bacterial and fungal antigens. CRSwNP appears to show a particularly dysregulated B cell response. Higher levels of IgA, IgE, and IgG are seen in nasal polyp tissues compared to controls and to CRSsNP, and this may have pathophysiological significance. IgE facilitates mast cell degranulation and IgA is a potent activator for eosinophil degranulation (Pleass et al. 2007). The combined

presence of these antibodies with mast cells and eosinophils within nasal polyps may facilitate degranulation and tissue damage. It should be noted that these immunoglobulin levels do not reflect the systemic profile, indicating a localized mucosal response (Pant et al. 2009). Not surprisingly, higher levels of immunoglobulin-producing B cells and plasma cells are also found in nasal polyps, and the process of polyp growth may be orchestrated by abnormal local B cell proliferation and recruitment (Chen et al. 2009). Evidence suggests that this process may be driven by the epithelial cytokine BAFF, a TNF family member that influences B cell proliferation and class switching (Kato et al. 2008). BAFF is found at higher levels in nasal polyps and correlates with the number of B cells within the tissue. In mouse models, excessive BAFF has been associated with the development of autoimmunity. This process has also been documented in recalcitrant CRSwNP with the presence of high levels of local autoantibodies in the polyp tissue (Smurthwaite et al. 2001).

Abnormal B cell proliferation creates inflammation and tissue damage that may lead to polyposis.

Staphylococcal superantigenic toxins (SAGs) have been proposed as disease modifiers of nasal polyposis through the generation of a polyclonal IgE response including IgE directed against the SAGs themselves. The presence of IgE to these toxins within polyp tissue has been correlated with overall increases in polyclonal IgE, eosinophils, asthma, and severity of CRSwNP (Smurthwaite and Durham 2002; Gevaert et al. 2005). It is unclear whether this superantigen-driven process works through BAFF or another, superimposed, pathway.

3.3.7 T Cells and Cytokine Response

Homeostasis across the nasal mucosa is typically maintained via the mechanical barrier, innate immune responses, and tonic IgA secretion. When the mucosal barrier is breached, a protective response is initiated with SNECs, DCs, and other innate immune cells helping to guide the adaptive response and match it to the inciting stimulus. Minor damage is likely handled by activation augmentation of innate responses from SNECs and migrating innate effector cells. A more substantial breach will activate the adaptive response; IL-6 has been proposed as a key cytokines mediating the transition, suppressing innate responses and triggering production of chemokines that promote the adaptive response (Kato et al. 2008). At homeostasis, DCs still regularly phagocytize foreign material, but when activated and exposed to sufficient PAMP activation, such as would occur in a mucosal breach, they cease phagocytosis and acquire additional chemokine receptors. Chemokines, stimulated into production during the innate immune response, cause the DCs to migrate to nearby lymph nodes and to secrete the cytokine IL-1 (Bachert et al. 2010). Antigen from the phagocytosed pathogens is presented to naïve CD4+ T helper (Th) cells in the lymph tissue. These lymphocytes will differentiate into a specific T cell lineage, determining the type of adaptive immune response. This process is further activated by IL-1. The types, duration, and intensity of the PRR activation by PAMP stimulus are believed to influence the resultant cytokine production and shape the resultant T lymphocyte profile (Delves and Roitt 2000). As mentioned above, cytokines from SNECs and other innate cell types play a critical upstream role in this process matching the response to the pathogen.

Signaling cross talk between innate immune cells drives T cell differentiation.

Mature T cells migrate back to the sinonasal mucosa to mediate the adaptive response upon subsequent antigen challenge. T helper lymphocyte responses are divided based on cytokine profiles generated in response to the presented antigen stimulus. Classically, Th1 or Th2 responses were thought to be the primary adaptive sinonasal inflammatory pathways. The Th1 pathway shows high levels of IL-12 and IFN-γ

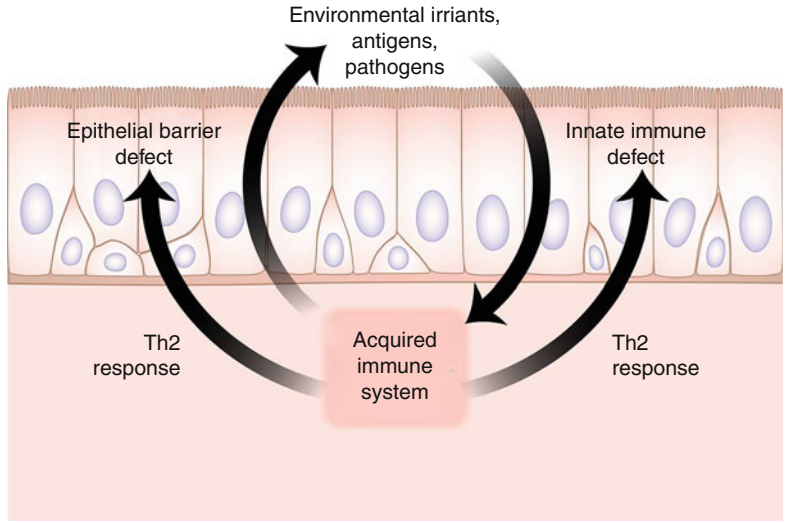

Fig. 3.3 Environmental agents stimulate the immune system inciting an innate response. If strong enough, an adaptive response is recruited as well. Typical protective responses include Th1 and Th17. If Th2 or Treg responses are generated, the innate response may be suppressed

and has a macrophage-rich cellular infiltrate. Th1 responses facilitate defense against intracellular pathogens, particularly viruses and intracellular bacteria including mycobacteria. They appear to be blunted in chronic obstructive pulmonary disease (COPD), psoriasis, Crohn's disease, and CRSsNP (Jones 2005). The Th2 pathway results in high levels of cytokines IL-4, IL-5, and IL-13 and has a more eosinophilic cellular response. Th2 responses are important in parasitic infections and are also seen in frequently allergic and asthmatic responses (Ramanathan et al. 2008). They are reduced in asthma, atopic dermatitis, ulcerative colitis, and CRSwNP (Schleimer et al. 2009). More recent data indicates that additional Th profiles are important in mucosal immunity. Th17 responses aid in defense against extracellular bacteria and fungi, particularly *Staphylococcus aureus* (Miller and Cho 2011). This response is fostered primarily by IL-17A as well as cytokines IL-6, TGF-β1, and IL-23 and has a neutrophilic cellular response (Tato and O'Shea 2006). Tregs are regulatory lymphocytes that foster immune tolerance with the goal of limiting excessive responses from other Th lineages; Treg differentiation is facilitated by TGF-β (Schleimer et al. 2009).

3.3.8 T Cell Response Modulation

Differentiation of CD4+ T cells into a specific lineage is determined in part by innate immune response, co-stimulatory signals, and the cytokine profile (Fokkens et al. 2012). Signaling cross talk between local DCs, SNECs, and resident innate immune cells, including eosinophils, mast cells, NK cells, and macrophages, generates the cytokines that drive the T cell differentiation (Zhu et al. 2010; Miller and Weinmann 2009). In addition, recent studies have suggested that circulating innate lymphoid cells (ILCs) migrate to the local site of immune stimulus and also play a role. These cells are presumably responding to chemokine homing signals emanating from resident cells and are termed "innate" because they recognize foreign substances via PRRs rather than immunoglobulin or T cell receptors. Capable of responding rapidly, ILCs bridge innate and adaptive immunity and may play the pivotal role in orchestration of the adaptive response as Th1, Th2, and Th17 ILC subsets have been described (Spits and Di Santo 2011). In terms of pathology, exceptionally high levels of Th2 ILCs have been observed in polyp homogenates from Western CRSwNP patients (Allakhverdi et al. 2009; Mjoesberg et al. 2011). See Fig. 3.3.

Innate lymphoid cells play a key role in orchestrating Th1, Th2, and Th17 responses.

3.3.9 NKT Cells, NK Cells, Cytotoxic T Cells, and Memory T Cells

In addition to the Th subsets discussed above, other T cell subsets play a role in mucosal immunity. Naïve CD8+ T cells differentiate and proliferate following exposure to antigen presented by DCs. Cytotoxic T cells are generated whose primary function is to eliminate intracellular microbes mainly by killing infected cells. These infected cells display microbial antigens on their surface, which the T cells recognize via their T cell receptors (TCR). Although not technically T cells, NK cells have a function similar to cytotoxic T cells but lack TCRs, recognizing foreign proteins by PRRs on their surface. NKT cells have characteristics of both T cells and NK cells with TCRs but with limited variability. Memory T cells are generated along with the effector T subsets and are numerically the predominant subset in nasal polyps (Sanchez-Segura et al. 1998). These cells are present in the mucosa and respond to subsequent antigen challenge.

Conclusion

The sinonasal mucosal defenses are a highly sophisticated interplay involving the local structural cells, resident innate response cells, and circulating innate and adaptive immune cells. In approximately 10 % of the Western population, this system fails in that foreign agents, while still cleared, trigger collateral inflammation of the mucosa of varying types and intensities. The associated clinical syndrome is broadly termed "CRS." Recent research in the field of CRS has been geared towards a better understanding of the specific pathway defects in the host. These specific genetic and epigenetic defects in the local immunologic pathways should eventually be associated with the various CRS phenotypes. Ultimately, greater understanding of sinonasal immune defenses will lead to more effective therapies for CRS in the future.

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Local Nasal Inflammation: T Cells and B Cells

4

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Keywords

Allergic rhinitis • Chronic rhinosinusitis • Nasal polyps • B cells • T cells • IgE • IL-5

Abbreviations

AID	Activation-induced cytidine deaminase
BCGF	B-cell growth factor
Bcl6	B-cell CLL lymphoma-6
BCR	B-cell receptor
Blimp1	B-lymphocyte-induced maturation protein 1
BSF-1	B-cell stimulatory factor-1 = IL-4
c-Maf	Musculoaponeurotic fibrosarcoma oncogene homolog
C-region	Constant carboxy-terminal region
CCR-7	C-C chemokine receptor type 7
CD	Cluster of differentiation
CDR	Complementary-determining region
CSF	Colony-stimulating factors
CSIF	Cytokine synthesis inhibitory factor
CXCL-13	C-X-C chemokine ligand
CXCR-5	C-X-C chemokine receptor type 5
DC	Dendritic cells
Fab	The antigen-binding site
FOXP3	Forkhead box protein P3
GATA-3	GATA-binding protein 3
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HMW-BCGF	High molecular weight B-cell growth factor
ICOS	Inducible co-stimulator
IFN	Interferons
IFNγ	Interferon-γ
Ig	Immunoglobulins
Ih2	Innate helper type 2 cells
IL	Interleukin
IRF-4	Interferon regulatory factor 4
iTreg cells	The inducible Treg cells
LPS	Lipopolysaccharide
M1	Classically activated macrophages

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MAF	Macrophage-activating factor
MHC	Major histocompatibility complex molecule
MPP type 2	Multipotent progenitor cells
NAP	Neutrophil-activating protein
NARES	Nonallergic rhinitis with eosinophilia syndrome
NHC	Natural helper cells
NK	Natural killer cells
NLR	NOD-like receptors
nTreg cells	The naturally occurring Treg cells
PAMP	Pathogen-associated molecular patterns
PpL	Protein L of streptococcus magnus
RAG proteins	Recombination-activating gene proteins
RORγt	RAR-related orphan receptor gamma
SA	Staphylococcus aureus
SAE	Staphylococcus aureus enterotoxins
SCF	Stem Cell Factor
SED	Staphylococcal enterotoxin D
SHM	Somatic hypermutation
SpA	Protein A of *Staphylococcus aureus*
TBX 21	T-box protein 21
TCR	T-cell receptor
Tfh cells	T follicular helper cells
TGFβ	Tissue growth factor β
Th	T helper cells
TLR	Toll-like receptors
TNF	Tumor necrosis factors
TNFβ	Tumor necrosis factor-β
Treg	T regulatory cells
TSLP	Thymic stromal lymphopoietin
V-region	Variable amino-terminal region
VDJ gene segment	Variable diversity, or joining gene segment
Vβ	Variable β-chain

Core Messages

- The local immune system is well developed in the nose and the paranasal sinuses and is of major importance in controlling incoming infections.
- If local inflammation persists, it can result in diseases such as allergic and non-allergic rhinitis and chronic rhinosinusitis with and without nasal polyposis.
- To have clear insight in the pathogenesis of these diseases, understanding of inflammatory cells, mediators and pathways in different populations is essential.
- Phenotyping and endotyping based on local inflammation are important in tailoring the right treatment for the right patient.

4.1 Physiology

4.1.1 Principles of Innate and Adaptive Immune System

4.1.1.1 Innate

The innate immunity is the first line of defense against pathogens, but can be overcome by many pathogens. This system does not provide memory.

4.1.1.1.1 Cellular

The first component of the innate immune system is the barrier made up by epithelia. This can prevent the pathogens from establishing local infection. When the pathogen succeeds to breach the barrier, there are cells and molecules available to destroy it. Cellular components of the innate system include dendritic cells (DC), natural killer cells (NK), macrophages, and granulocytes.

The recognition of a pathogen can be achieved by pattern recognition receptors, for example, including Toll-like receptors (TLR) and NOD-like receptors (NLR). These receptors recognize the pathogen-associated molecular patterns

(PAMP) on pathogens. The cytokines produced by the above-mentioned cells regulate the antigen-driven differentiation of the adaptive immune system (Spolski and Leonard 2008; Fazilleau et al. 2009).

4.1.1.1.2 Humoral

The humoral, or soluble, mediators of the innate system include antimicrobial peptides (e.g., defensins), mannose-binding lectin, surfactant proteins, lysozyme, lactoferrin, acute-phase reactants (e.g., C-reactive protein), and the complement system (Quinn and Cole 2007).

The complement system is one of the major mechanisms for converting pathogen recognition into an effective host defense. It is a system of plasma proteins that can be activated by a pathogen or by a pathogen-bound antibody. There are three pathways of complement activation: the classical pathway, the mannose-binding lectin pathway, and the alternative pathway (Thurman and Renner 2011). When the innate immunity is inadequate, it can still set the scene for the adaptive immunity.

4.1.1.2 Adaptive

The adaptive immune system specifically recognizes pathogens specifically and prevents reinfection, thanks to the memory.

4.1.1.2.1 Cellular

The adaptive immune system is based on clonal selection of lymphocytes bearing antigen-specific receptors (Fazilleau et al. 2009). When a T cell encounters a specific antigen in the secondary lymphoid tissue, it proliferates and its progeny differentiates into effector cells with a subset that differentiates into memory cells. If the receptor is specific for a self-antigen, the T cell is eliminated.

T cells and B cells cooperate, the T helper (Th) cells enhancing the antibody production by B cells. The cytokines produced by the innate system and activated T cells drive the expansion, effector function, and ultimately downregulation of the adaptive immune response (Spolski and Leonard 2008).

4.1.1.2.2 Humoral

The key cells in the humoral response are B cells and plasma cells. The goal of these cells is to produce immunoglobulins (Ig).

To ensure the specificity of the adaptive immune system, these receptors need to be highly diverse. In B cells there are three mechanisms to create this diversity. First there is "somatic recombination," where the separate gene segments encoding the V-regions are brought together. This arrangement process is directed by the RAG proteins (recombination-activating gene proteins). Then different light- and heavy-chain variable amino-terminal (V)-regions are associated, so forming the antigen-binding site (Fab). The Fab determines specificity, but how can the different effector response to the same antigen at different times or under different circumstances be explained? This leads us to the phenomenon "isotype switching." The isotype determines the immunological function and is defined by the heavy-chain constant carboxy-terminal (C)-regions. The same V-region can be expressed with different C-regions. When a B cell is stimulated with an antigen, "somatic hypermutation (SHM)" occurs. SHM is a point mutation of the V-region, what modifies the coding sequences for this region. AID (activation-induced cytidine deaminase), an exclusively B-cell-specific protein, is involved in the initiation of SHM (King et al. 2008).

4.1.1.3 Signaling Through Immune System Receptors

4.1.1.3.1 Antigen Receptor Structure

Lymphocyte antigen receptors are composed of two light chains and two heavy chains that are bound together by many non-covalent interactions. They are molecules with a highly variable V-region and a constant C-region. The C-region is responsible for the biological effector functions, while the V-region interacts with a specific antigen. The variable regions are an assemblage of two or three gene segments: the variable (V), diversity (D), and joining (J) gene segment.

The B- and T-cell receptors are structurally similar, but there are some important differences.

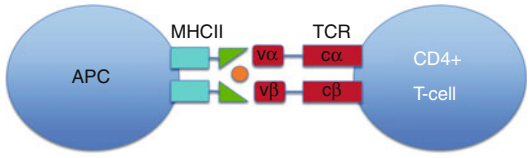

Fig. 4.1 Conventional antigens: T cells recognize the AG bound to MHC-II molecule. The antigen (*orange*) is presented by the APC in the peptide-binding groove (*green*) and is then recognized by the TCR (*red*)

Although, the B-cell receptor (BCR) can be membrane bound or can be a secreted antibody, the T-cell receptor (TCR) is always a cell-surface receptor (Fig. 4.1). Membrane-bound B-cell receptors can be IgM or IgD and are more expressed on mature B cells than on pre-B cells. The secreted BCR include IgM, IgE, IgD, IgG, and IgA. Another difference is that B cells can recognize the antigen in its native state, where the T cells only recognize a composite ligand of an antigen bound to a major histocompatibility complex molecule (MHC). An MHC is a membrane-bound glycoprotein with a peptide-binding groove. MHC-I molecules are expressed on the surface of all nucleated cells, while MHC-II cells are found only on antigen-presenting cells (APC).

At last, TCR genes are assembled by somatic recombination just like the BCR genes, but here in T cells this results in a greater diversity than in B cells. The reason is that the T cells have more J gene segments and there is a greater variation of the junctions between gene segments during the rearrangement

4.1.1.3.2 Signaling Pathways

Activation of an antigen receptor by an antigen, provided that there is a co-stimulatory signal through CD28, leads to phosphorylation of tyrosine residues by the receptor-associated protein tyrosine kinase. This activates signaling pathways, including through phospholipase C-γ and the small G-proteins. The G-proteins activate a MAP kinase cascade, which leads to phosphorylation and activation of transcription factors. The pathways converge to the nucleus and alter the patterns of gene transcription. This leads to clonal expansion and differentiation of cells.

Signaling through the co-stimulatory molecule CD28 also contributes to activating naïve T cells. Activating signals can be modified according to the environment (cytokines and other co-stimulatory molecules) and the developmental stage of the target cell. This allows modulation of the adaptive immune response (Spolski and Leonard 2008).

4.1.1.3.3 Other Signaling Pathways

T and B lymphocytes have receptors for many other extracellular signals that also regulate the development, activation, and longevity of the lymphocytes. Modulation of immune functions and inflammatory functions of the cell is regulated by the tissue microenvironments. For example, when activated lymphocytes bind the Fas ligand, they are programmed to die when the infection has been elucidated. Though members of the intracellular Bcl-2 family can inhibit this apoptosis.

Many cytokines signal through the Jak/STAT pathway. The cytokines interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21 have a common receptor, namely, the γc receptor (=orphan receptor). This receptor has the highest expression on B cells, but also on CD 4+ T cells, CD 8+ T cells, NK DC, and macrophages. They use the Jak/STAT pathway, PI3 kinase pathway, and MAP kinase pathway (Spolski and Leonard 2008).

4.1.2 The Components of the Immune System

A pluripotent hematopoietic stem cell gives rise to different lymphoid and myeloid lineages that participate in the innate and adaptive immune responses.

4.1.2.1 Myeloid Lineage

Granulocytes are further divided in neutrophils, basophils, and eosinophils. They circulate in the blood, and at time of infection or inflammation, they are recruited and act as effector cells.

Eosinophils are elevated in allergy and parasitic infections. The eosinophilopoietins IL-3, IL-5, and GM-CSF support their survival and there is an autocrine secretion. Therefore eosinophils

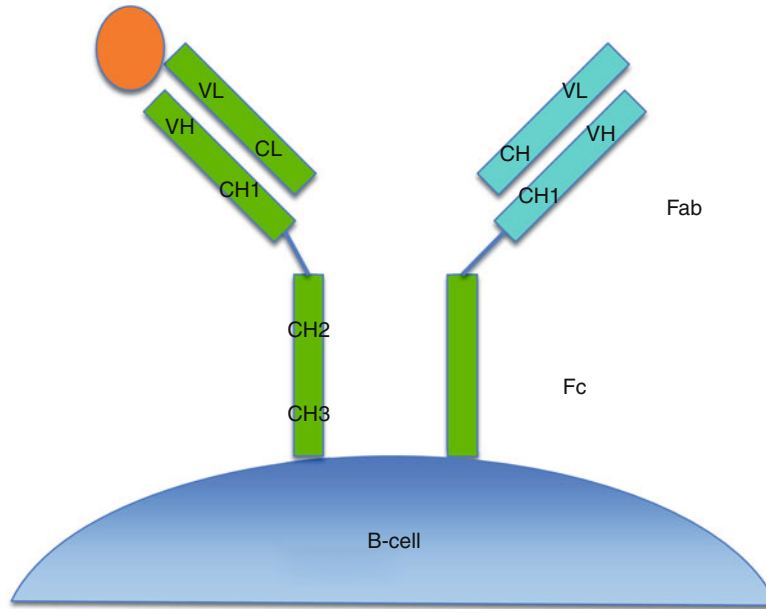

Fig. 4.2 Antigen binding by the BCR. Conventional antigens (*orange*) are recognized by the variable regions of the H and L variable chains of the BCR (*green*)

can proliferate and survive without help of other cytokine-producing cells. Hence controlling the growth of eosinophils is very important, what is attributed to tissue growth factor β (TGFβ). This endogenous downregulator also inhibits T cells and monocytes (Alam et al. 1994).

Basophils are important in allergic disease as they have the receptors on their surface that bind IgE, just like the mast cells. Neutrophils are essential in the defense against bacterial infections.

Macrophages, which originate from monocytes, and mast cells complete their differentiation at the tissue where they act as effector cells and initiate inflammation. Mast cells also have a role in defense against parasite infection and in allergic disease.

4.1.2.2 Lymphoid Lineage

4.1.2.2.1 Lymphocytes

The lymphocytes are important in the innate and adaptive immune system. There are two major types that mature in the primary lymphoid organs: B lymphocytes (which originate from the bone marrow) and T lymphocytes (that arise from the thymus). When mature, they bear antigen-specific receptors and they recirculate from the blood through the secondary lymphoid organs and again to the blood through the lymphatic vessels. Adaptive immune responses are initiated in the secondary lymphatic tissues: T cells encounter antigens, differentiate into antigen-specific cells and proliferate, while B cells proliferate, with T-cell help, into antibody-secreting cells.

NK are a third type of lymphocytes NK cells are a third type of lymphocytes. They are a part of the innate immune system. They recognize changes in the MHC-I and are activated by interferons.

4.1.2.2.2 B Lymphocytes

B lymphocytes govern the humoral adaptive immune response. Their function consists of producing antibodies, performing a role as APC, and developing into memory B cells. They are produced in the bone marrow, where they reach the IgM-positive immature state. They become transitional B cells in secondary lymphoid tissue. Once a B cell encounters an antigen (Fig. 4.2) and a signal from a T helper cell, it can differentiate into a plasma B cell or into memory B cell. So in most cases, the B cells necessitate help from a T helper cell, but in response to some pathogens, they can produce immunoglobulins without T-cell help. Critical processes such as somatic recombination and clonal selection are also termed "germinal center reaction." Germinal

centers are structures within follicles in secondary lymphoid tissue where antibody-forming cells are generated (King et al. 2008).

4.1.2.2.3 T Lymphocytes

T cells and their cytokines coordinate the cell-mediated immune response. They ensure the balance between the humoral and cell-mediated pathways while providing a negative feedback control to maintain self-tolerance. Activation of T cells by an antigen occurs via TCR and the co-stimulatory molecule CD28, what leads to production of IL-4 and IL-10 for a better T-cell/B-cell interaction (King et al. 2008).

In the T-cell areas, the first contact between T and B cells occurs. This contact necessitates CD28, CD40-CD40L interactions (central to the delivery of T-cell help to B cells), and OX40-OX40L interactions (necessary for accumulation of TFH cells in follicular regions) (Fazilleau et al. 2009). OX40L is upregulated by thymic stromal lymphopoietin (TSLP) (Oliphant et al. 2011). Then the B cell migrates extra-follicular to become a plasma cell or intrafollicular to form GC, where somatic mutation and affinity maturation occurs. The second T-cell/B-cell interaction is within the germinal center.

The TCR on most cells is the αβ-receptor, the second type of TCR is composed of γ- and δ-chains. It is thought that the latter type is not MHC restricted.

T lymphocytes can be CD3+CD4+ or CD3+CD8+. These molecules are used for immunophenotyping and are cell-surface molecules on white blood cells. They function as a receptor or ligand altering the behavior of a cell or act as an adhesion molecule.

4.1.2.2.3.1 CD8+ T Cells

CD8+ T cells are also called cytotoxic T cells. They are induced when a cell is infected by a pathogen. CD8+ T cells recognize MHC-I molecules found on the surface of infected cells. Their role is to eliminate these cells.

4.1.2.2.3.2 CD4+ T Cells

CD4+ T cells are called T helper (Th) cells. CD4+ cells recognize MHC-II molecules, which are found on the surface of antigen-presenting cells (B cells, macrophages, and dendritic cells) (Fig. 4.1) and display peptides coming from endosomes. Under adequate co-stimulation, this results in clonal selection, proliferation, and differentiation of CD4+ T cells with subsequently activation of other effector cells, such as macrophages and B cells. The B cells differentiate to plasma cells or germinal center cells under the control of Th cells. The germinal center B cells can then further develop to the memory B-cell compartment (Fazilleau et al. 2009). ICOS (inducible co-stimulator) is present on activated CD4+ cells and enhances T-cell responses when activated by ICOS ligand (ICOSL) (on APC).

When stimulated with an antigen, CD4+ T cells differentiate into different subsets in follicular regions (Fazilleau et al. 2009; Spolski and Leonard 2010), with different cytokine pattern and distinct cellular function in vivo (Fazilleau et al. 2009). The most important ones are T helper 1 (Th1), T helper 2 (Th2), T helper 17 (Th17), regulatory T (Treg), and T follicular helper (TFH) cells.

Th1 Cells

These cells activate cellular immunity mostly against intracellular pathogens during the type 1 response (Spolski and Leonard 2008; Fazilleau et al. 2009). Bacterial or viral products ligate TLRs on APC. This drives the production of IL-12 by dendritic cells, which is a Th1 differentiation factor (Barlow and McKenzie 2011). Tbet (T-box protein 21 = TBX 21) is the Th1 transcription factor. This leads to the production of typical Th1 cytokines: IL-2, interferon-γ (IFNγ), and tumor necrosis factor-β (TNFβ). Th1 inflammation is dominated by neutrophils (Zhang et al. 2008).

Th2 Cells

During the type 2 response, Th2 cells are important for the production of key cytokines IL-4, IL-5, IL-9, and IL-13. These are essential for antibody class switching to IgE and IgG1, recruitment of inflammatory cells (eosinophils, basophils, and mast cells), and goblet cell hyperplasia with subsequent mucus production. This response is important to fight parasitic infections, but this also promotes allergic disease and asthma. The Th2 subset transcription factors are GATA-3

(GATA-binding protein 3) and c-Maf (King et al. 2008). Mast cells and eosinophils can also express GATA-3. In contrast to Th1 and Th17 inflammatory responses, Th2-skewed inflammation is dominated by eosinophils.

Th1/Th2 Plasticity

The Th1/Th2 paradigm postulates that Th1 and Th2 are alternate, nonoverlapping cell fates (Fazilleau et al. 2009). It is suggested that the quality of the T-cell receptor signal determines the response. Low antigen dose and altered peptides are associated with Th2 differentiation, rather than Th1 response (Oliphant et al. 2011). When the equilibrium is in favor of Th2, too much IgE is produced, which is the hallmark of allergic disease. Both Th1 and Th2 cells support B-cell responses, enter follicular regions, and induce class switch. IFNγ and IL-4 result in switch to IgG1, IgG2a, and IgE. TGFβ can cause class switch to IgA. Both Th1 and Th2 cells can produce IL-2, IL-10, IL-13, IL-3, and GM-CSF.

4.1.2.2.3.3 Th17 Cells

Th17 is seen as an immediate response to extracellular bacteria and fungi (Fazilleau et al. 2009). RORγt (RAR-related orphan receptor gamma) is the transcription factor of Th17 cells, whose expression can be controlled by interferon regulatory factor 4 (IRF-4) and IRF-4-binding protein (Fazilleau et al. 2009). IL-17 and IL-21 are important Th17 cytokines.

Dysregulation of the Th17 subset and its cytokines can cause chronic inflammatory disease and autoimmune pathology.

4.1.2.2.3.4 T Follicular Helper Cells: Tfh Cells

The Tfh cells are involved in the germinal center (GC) formation and function (Fazilleau et al. 2009). Appropriate antibody specificity is created in the GC by immunoglobulin class switching and somatic mutation. This means Tfh cells are critical for a strong adaptive humoral response by regulating the development of antigen-specific B-cell immunity (Fazilleau et al. 2009; Spolski and Leonard 2010). At least 6 different subtypes of Tfh cells (King et al. 2008) can be distinguished according to the Th-cell differentiation and the programming of follicular locations (King et al. 2008; Fazilleau et al. 2009).

The differentiation of Tfh cells requires the transcription factor Bcl6 (B-cell CLL lymphoma-6) (Adamovic et al. 2008). Bcl6 is the regulator of GC lineage commitment, is a suppressor of plasma cell differentiation, and downregulates GATA-3 and IL-4 (King et al. 2008). Blimp1 (B-lymphocyte-induced maturation protein 1) is highly expressed in CD4+ T cells but not in Tfh cells. Blimp1 induction leads to differentiation of plasma cells from naïve or memory B cells (Spolski and Leonard 2008) and also has a role in T-cell regulation.

Bcl6 and Blimp1 are mutual inhibitory cross-regulators that determinate the terminal B-cell differentiation. They regulate the expression of each other and correlate with the plasma cell and memory cell phenotype (Spolski and Leonard 2008).

It is worth mentioning Roquin, a molecule which prevents activation and differentiation of self-reactive Tfh cells (King et al. 2008). It acts by limiting the expression of ICOS on T cells (Yu et al. 2007).

4.1.2.2.3.5 Regulatory T Cells: Treg Cells

These are suppressive cells and not effector cells such as the previously described cells. Other cells that can have an immunosuppressive function are the NK and CD8+ T cells (Mills and McGuirk 2004).

Two populations of Treg have been described: the naturally occurring Treg cells (nTreg cells) and the inducible Treg cells (iTreg cells). It is thought that nTreg cells develop in the thymus and can inhibit via cell-cell contact (Umetsu and DeKruyff 2006). The iTreg cells on the other hand seem to differentiate from naïve T cells after antigen presentation by a dendritic cell. The iTreg cells can suppress the immune system by secreting TGFβ1 and IL-10 (Mills and McGuirk 2004).

FOXP3 (forkhead box protein P3) is the transcription factor of the regulatory T cells. It is a marker of both nTreg cells (natural Treg cells) and iTreg cells (induced Treg cells).

Treg cells are important in controlling Th2 immune response. Lacking Treg cells is an important contributor in the development of allergy and asthma (Umetsu and DeKruyff 2006).

4.1.2.2.4 Innate Non-B/Non-T Cells

Four types of innate cells have been recently discovered in mice: nuocytes (Neill et al. 2010), innate helper type 2 (Ih2) cells (Price et al. 2010), natural helper cells (NHC) (Koyasu and Moro 2011), and multipotent progenitor cells (MPP type 2) (Saenz et al. 2010). Immunophenotyping can help to distinguish them. This group of innate cells seems to be important for the initiation of type 2 inflammation. They do not express markers that would identify them as B or T cells, but they can respond to many of the same signals (e.g., to the cytokines IL-2 and IL-7 and chemokines CXCL-12, CXCL-16, CCL25) (Barlow and McKenzie 2011). Ih2 and NHCs have more in common with the lymphoid than with the myeloid cells (Neill and McKenzie 2011). Nuocytes on the other hand are more similar to the myeloid lineage (Koyasu and Moro 2011).

Nuocytes are identified as lineage-negative ICOS+CD45+IL33RvarIL17BRvarIL13+ cells. These cells are termed nuocytes after "Nu," the thirteenth letter of the Greek alphabet, because they are IL-13-producing cells (Neill et al. 2010). The cytokine receptors IL-25R and IL-33R are important for their function. The ICOS molecule expressed by the nuocytes appears to be important in the induction of a type 2 response (Barlow and McKenzie 2011) and of MHC-II (Neill et al. 2010).

4.1.3 Cytokines

4.1.3.1 Definition

Cytokines are secreted proteins with growth, differentiation, and activation functions. They can act in an autocrine, paracrine, or endocrine mode. Several cytokine families are defined, including interferons (IFN) (Table 4.1), interleukins (IL) (Table 4.2), colony-stimulating factors (CSF) (Table 4.3), growth and differentiation factors (Table 4.4), tumor necrosis factors (TNF) (Table 4.5), and chemokines/histamine-releasing factors.

Importantly, the cytokines can be proinflammatory or anti-inflammatory (Kaplan 1997). Proinflammatory actions include chemotaxis of inflammatory cells, activation of B cells and T cells, the release of histamine by basophils, and the induction of the arachidonic acid metabolism. Anti-inflammatory cytokines are produced by suppressive cells and are essential to limit the inflammatory response.

The chemokine subfamily guides migration of cells. They are subdivided in the CXC and the CC subfamily (Kaplan 1997).

4.1.3.2 Cytokines and the Appropriate Immune Response

The activation of an appropriate immune program to a specific antigen is orchestrated by secretion of specific cytokines. Subclasses of CD4+ T cells can be selected based on their cytokine repertoire.

4.1.3.2.1 Th1 Cytokines

When bacterial or viral components activate the immune system by ligation of the TLR, type 1 immunity is promoted. The Th1 cell differentiation is well documented and initiated by IL-12, which is released by dendritic cells. This cytokine seems to be the link between the innate system and the adaptive immune response.

Th1 cells secrete type 1 cytokines: IL-2, IFNγ, and TNFβ (also known as lymphotoxin). Here IL-2 is critical for the initiation and cessation of the development of T cells and B cells (Sivakumar et al. 2004). The cytokines IFNγ and TNFβ also cause B-cell activation and they both display antiviral activity. They stimulate MHC-I and MHC-II expression and they promote chemotaxis and activation of phagocytes. TNFβ increases IL-6 and IL-8 production, which activate monocytes. IFNγ regulates IgE synthesis by inhibiting IL-4-mediated IgE secretion. Stimulation of macrophages by IFNγ, as well as by lipopolysaccharide (LPS), results in classically activated macrophages (M1). M1 release NO for killing intracellular pathogens. Importantly, macrophages are not terminally differentiated (Fairweather and Cihakova 2009).

Other Th1 cytokines include TNFα, macrophage-activating factor (MAF), IL-12, and IL-18. The cytokines IFNγ and IL-12 can act in an autocrine way and can be inhibited by IL-10.

4.1.3.2.2 Th2 Cytokines

The response on allergens or on parasites is Th2 dominated. It is suggested that TSLP, IL-25, and IL-33 are type 2-inducing cytokines (Fort et al. 2001; Schmitz et al. 2005). A source of these cytokines is the epithelium (Hammad and Lambrecht 2008; Saenz et al. 2008). The target cells seem to be novel innate populations, namely, nuocytes, Ih2 cells, and NHC and MPP (type 2) cells. These cells are all a source of IL-5 and IL-13, which are known type 2 cytokines (Zhou et al. 2005).

Key Th2 cytokines are IL-4, IL-5, IL-9, and IL-13. IL-4 is essential for IgE production and synergizes with IL-2, IL-5, and IL-6. On the other hand IL-4 downregulates IL-1, IL-6, TNFα, and FcγR. So the IgE class switch is enhanced by IL-4, IL-13, IL-2, IL-5, and IL-6 but inhibited by IFNγ and TNFβ. The Th2 cytokines IL-13 and to a lesser extent IL-4 would promote the alternatively activated anti-inflammatory M2 phenotype of macrophages (Kang et al. 2008; Fairweather and Cihakova 2009). IL-4 enhances Th2 cell generation and proliferation (GATA-3 upregulation), but not IL-13. So it acts autocrine on IL-4-producing T cells, which is inhibited by IL-12. Co-stimulatory proteins on B cells (CD40 and MHC II) are upregulated by IL-4, just like MHC-I/-II and low-affinity IgE receptors on macrophages. IL-13 inhibits Th1 cytokines, like IL-12.

Eosinophils are important cells in the TH2 response as they eliminate parasites and can cause an allergic reaction. IL-5 is the most important eosinophilopoietin, next to IL-3 and GM-CSF. These cytokines potentiate B-cell growth, differentiation, and isotype switch. Eotaxin is a member of the CC subfamily and promotes the migration to the tissues by means of adhesion receptors and chemokines (Zhang et al. 2008). Mast cells are also essential in the Th2 inflammation. After cross-linking IgE, they degranulate and histamine is released. Cytokines that contribute to mast cell proliferation are IL-3, IL-9, IL-10, and SCF (Stem Cell Factor).

Summarized, IL-25, IL-33, and TSLP, next to the IL-4-/GATA-3-dependent mechanism, are important to the Th2 differentiation (Oliphant et al. 2011).

4.1.3.2.3 Tfh Cells and Their Cytokines

The main cytokine secreted by Tfh cells is IL-21. IL-21 is important for the GC formation and for the generation of Tfh cells, as it is a potent inducer of BCL-6 and Blimp1. IL-21 acts via the specific IL-21R and the nonspecific γc receptor and is thus a member of the IL-2 family (Sivakumar et al. 2004). IL-21 mostly stimulates the immunity, but can also inhibit it by inducing apoptosis (Spolski and Leonard 2008).

Tfh cells have a high expression of ICOS that quantitatively contributes to the IL-21 production (King et al. 2008) and GC formation (Spolski and Leonard 2010).

The chemokine receptors on Tfh cells can explain their localization. Naïve Tfh cells that reside extra-follicular express CCR-7 (C-C chemokine receptor type 7). With maturation CCR-7 decreases and CXCR-5 (C-X-C chemokine receptor type 5) is upregulated (Fazilleau et al. 2009). CXCR-5 plays an essential role in the B-cell migration and is required for the development of B-cell follicles in secondary lymphoid tissue. It is transiently upregulated on Tfh cells subsequent to interaction with the combination of peptide-MHC-II. CXCR-5 helps to attract the cell to the developing GC. They migrate to the edge of a follicle, where they meet antigen-primed B cells. Thereafter the T cells migrate throughout the entire follicle. CXCR-5 is preserved while B cells and T cells are interacting, and this maintenance is supplied by the microenvironment. On the other hand, ICOS and IL-21 need antigen challenge for expression (King et al. 2008). CXCL-13 (C-X-C chemokine ligand 13) is also a major attribute of the Tfh cells. It must serve to attract CXCR-5+ B cells (Fazilleau et al. 2009).

4.1.3.2.4 Th17 Cells and Their Cytokines

Th17 cells are important for the extracellular bacterial clearance, in particular at sites where the human body interacts with the external environment. The differentiation and function of the Th17 cells are influenced by IL-6, IL-21, and TGFβ (King et al. 2008). The TH17 cells secrete among others IL-17 and IL-21. There are similarities between Th17 cells and Tfh cells, such as the expression of ICOS,

autocrine stimulation by ICOS and IL-21, and provision of B-cell help (King et al. 2008). But there are important differences as well (Spolski and Leonard 2010): Th17 cells do not express CXCR-5 and Tfh cells do not secrete Th17 cytokines other than IL-21 (King et al. 2008).

4.1.3.2.5 Treg Cells and Their Cytokines

The iTreg cells act by secreting the anti-inflammatory cytokines TGFβ1 and IL-10 (Mills and McGuirk 2004). The differentiation of Treg cells is influenced by IL-10, TGFβ, and IL-4 (Mills and McGuirk 2004; Van Bruaene et al. 2008). It is suggested that IL-4 could bind to the FOXP3 promoter and in this way prevent FOXP3 expression. This could explain the decrease of Treg cells in asthma and allergy (Zhang et al. 2008).

Treg cells and Th17 cells are mutually exclusive. They are both induced by TGFβ, but if IL-6 is present, the balance shifts in favor of Th17 and less Treg cells are developed (Spolski and Leonard 2008). Furthermore, RORCγt can bind FOXP3 and antagonize it (Fazilleau et al. 2009). When FOXP3 is absent, there are no Treg cells or the Treg cells are dysfunctional (Bennett et al. 2001) (Table 4.6).

4.1.3.2.6 Innate Non-B/Non-T Cells and Their Cytokines

It is still unclear what the specific function of these cells is, but they certainly respond to IL-25, IL-33, and TSLP and are a source of IL-13 and IL-5. They may not be the predominant source of IL-4 (Neill and McKenzie 2011). The genes of IL-4 and IL-13 are closely linked. The fact that these cells mainly secrete IL-13 can explain the distinct regulation of these two cytokines, and it also explains the dominant role of IL-13 in directing allergic response (Barlow et al. 2012). Ih2, NHC, and nuocytes share the expression of IL-25R and IL-33R.

4.2 Pathology

4.2.1 Allergic Rhinitis

The basis of every allergic disease is a sustained overproduction of IgE in response to common antigens (KleinJan et al. 2000). The history of the patient, a positive skin prick testing, and a measurement of serum-specific IgE antibodies are essential to prove the diagnosis. Total IgE has low predictive value, whereas antigen-specific IgE is more relevant and related to allergic disease. Allergic rhinitis can be subdivided in an intermittent and a persistent form. The severity can be classified as mild or moderate/severe.

This entity is per definition an IgE-mediated allergic response involving a Th2 inflammatory pathway. T cells are important in the IgE-mediated immune response, as they are the only cells recognizing antigen after processing by the APC. Furthermore the cells release cytokines (IL-4, IL-13, CD40L mediators) that induce selective somatic recombination of the immunoglobulin heavy chain regions in B cells. Ultimately this leads to the maturation of B cells in plasma cells (Rondon et al. 2010).

The inflammation in allergic rhinitis includes both an immediate IgE-mediated mast cell response as well as a late response, which is characterized by recruitment of eosinophils, basophils, and Th2 cells. The latter express among other cytokines IL-4 and IL-13, which are switch factors for IgE synthesis, and IL-5, an eosinophilopoietin.

Aeroallergens that are deposed in the mucus layer are ingested by APC, and thereafter the processed antigen is presented to the T cells. The Th cells subsequently release appropriate cytokines, including IL-4 and IL-13. Interaction with of B cells leads to isotype switching and the production of antigen-specific IgE. IgE in allergic rhinitis is monoclonal and induced by allergens. IgE interacts with the FcεR. The high-affinity FcεRI is expressed as a tetramer on basophils and mast cells, which are the best-known IgE effector cells. Other cells express this receptor as a trimer, namely, DCs, Langerhans cells, eosinophils, and monocytes (Maurer and Stingl 1995; Maurer et al. 1996; Novak et al. 2004; Hammad et al. 2010). The low-affinity FcεRII (=CD23) is expressed on a broad range of cells, including activated B cells, macrophages, eosinophils, T cells, NKT cells, follicular DC, and structural cells (Gould and Sutton 2008). Cross-linking of allergen-specific IgE with FcεRI on mast cells results in the degranulation and immediate-response rhinitis (Powe et al. 2010; Pawankar et al. 2011).

In the mucosa of patients with allergic rhinitis, an infiltration of Th2 cells, basophils, and eosinophils and resident cells including Langerhans cells and mast cells is found. Mast cells are effector cells in the immediate-response rhinitis, but they are also immunoregulatory cells of the late-phase allergic reaction and the ongoing allergic inflammation as well (Pawankar et al. 1997; Pawankar et al. 2011).

Eosinophils are important cells in chronic allergic disease (Silberstein 1995). Factors contributing to the eosinophilic inflammation are IL-5 and eotaxin. IL-5 reduces apoptosis and results in production and activation of eosinophils. Eotaxin promotes the migration to the tissues by means of adhesion receptors and chemokines (Zhang et al. 2008). The cytokine GM-CSF plays a role in the accumulation of eosinophils. It is secreted by epithelial cells, but mainly by the eosinophils themselves (Jankowski 1996). Even considering eosinophils produce less cytokines than T cells, the cytokine synthesis and storage and potential autocrine and paracrine usage may have particular pathophysiological relevance (Jankowski 1996).

4.2.2 Noninfectious, Nonallergic Rhinitis

Noninfectious, nonallergic rhinitis describes the patients who are nonatopic on blood test or on skin prick test but meet the clinical criteria indicative for persistent allergic rhinitis (ARIA guidelines). The term "idiopathic rhinitis" is often used to describe this disease of unknown etiology. Idiopathic rhinitis can be subdivided in nonallergic rhinitis (NAR) and a subgroup with eosinophilic syndrome (nonallergic rhinitis with eosinophilia syndrome = NARES) (Rondon et al. 2010). The latter is the most frequent, with the nasal mucosal inflammatory infiltrate similar to that of allergic rhinitis, namely, local nasal IgE production and positive response to nasal allergen provocation test (Rondon et al. 2007). Local nasal IgE production without systemic release explains the negative skin tests and negative serum-specific IgE. The locally produced IgE can cause sensitization of the mast cells to common aeroallergens (Rondon et al. 2010). So Th2-mediated inflammation is possible in the mucosa of subjects with nonallergic rhinitis, despite absence of atopic responses (Powe et al. 2010). The phenomenon of localized mucosal response independent of systemic atopic responses is called "entopy."

4.2.3 Inflammation in Chronic Rhinosinusitis Without Nasal Polyposis (CRSsNP)

Chronic rhinosinusitis without nasal polyposis (CRSsNP) is characterized by a Th1-polarized inflammation, which is dominated by neutrophils. This means that CRSsNP is characterized by high amounts of IFNγ, IFNα, and TGFβ (Bachert et al. 2006; Van Zele et al. 2006; Bachert et al. 2007; Van Bruaene et al. 2008). This type of inflammation results in fibrotic tissue remodeling, characterized by a higher collagen deposition in CRSsNP together with the presence of thick collagen fibers when compared to healthy controls. In contrast with CRSwNP, CRSsNP shows no deficit in Treg cell numbers or migration capacity and displays a much less severe inflammatory mucosal reaction.

Recently in both CRSsNP and CRSwNP, a novel mechanism of mast cell degranulation was identified: degranulation by free light chains (FLCs) (Redegeld and Nijkamp 2003). FLCs are highly present in nasal mucosa and nasal polyp tissue of CRSsNP and CRSwNP patients, respectively, emphasizing the local production (Groot Kormelink et al. 2012). The exact functional role of the increased local FLC expression needs to be further investigated.

4.2.4 Inflammation in Nasal Polyposis (CRSwNP)

The inflammatory pattern of chronic rhinosinusitis with nasal polyps is variable but mostly featured by a Th2-polarized inflammation. A local eosinophilic inflammation and high local levels of IgE are typically present. Furthermore, this Th2-skewed inflammation seems to be associated

with S. aureus carriership and an IgE response to S. aureus enterotoxins.

Interestingly not all nasal polyps are eosinophilic; neutrophilic inflammation (Th1/Th17 polarized) is observed in the cystic fibrosis population (Van Zele et al. 2006) and also in the Asian population (Zhang et al. 2008).

4.2.4.1 Th2-Skewed Inflammation

Th2 inflammation results in infiltration of eosinophils, Th2 lymphocytes, basophils, and mast cells. There is T-cell activation (suggested by an elevated Tbet, GATA-3, IL-2Rα) and a downregulation of Treg cells (concluded from the downregulation of FOXP3 and TGFβ1) (Van Bruaene et al. 2008; Zhang et al. 2008).

It remains unclear how the Th2 inflammation is initiated in nasal polyposis and how they can develop in both a Th1 and a Th2 inflammatory environment. The deficient Treg function contributes to the Th2-skewed inflammation (Van Bruaene et al. 2008). But does the new innate lymphoid population have a role in the initiation of the Th2 inflammation in CRSwNP? The possible role of IL-33 and TSLP in initiating the Th2-polarized inflammation is mentioned earlier (Fort et al. 2001; Schmitz et al. 2005). An increased IL-33 in epithelial cells in CRSwNP tissue is reported (Reh et al. 2010), and TSLP has a known role in the pathogenesis of asthma and atopy (Zhou et al. 2005; Headley et al. 2009).

The same inflammatory cells are found in CRSwNP and in allergic asthma as they are both characterized by Th2 inflammation and deficient Treg cells. The link between these two entities has clinical importance, as patients suffering from both CRSwNP and asthma are difficult to treat.

4.2.4.2 Eosinophilia and IL-5

Considering eosinophilia in nasal polyposis, this disease was thought to have an allergic etiology. However now it is clear that the eosinophils are present in allergic and nonallergic persons with nasal polyposis (Jankowski 1996; Ediger et al. 2005) and account for more than 70 % of the polyp patients in Western countries (Gevaert et al. 2005; Bachert et al. 2006). As mentioned earlier, IL-5 and eotaxin are essential in eosinophilic inflammation. IL-5 is the predominant cytokine in nasal polyposis, and the concentrations are highest in patients with nonallergic asthma and aspirin intolerance (Bachert et al. 2010). Furthermore it is shown that eotaxin-1 (CCL11), eotaxin-2 (CCL24), and eotaxin-3 (CCL26) are elevated in CRSwNP (Van Zele et al. 2006; Plager et al. 2010).

TGFβ is a fibrogenic growth factor that stimulates extracellular matrix ECM formation and chemotaxis of fibroblasts but inhibits the synthesis of IL-5. As consequence, TGFβ is low in CRSwNP (Bachert et al. 2006), what also explains the different remodeling process. In CRSwNP edema is found, where in CRSsNP fibrosis occurs. The eosinophilic inflammation has effect on extracellular matrix, with nasal polyposis as a possible consequence (Jankowski 1996). Summarized, markers of CRSwNP in the Western population are those of eosinophilic inflammation, namely, IL-5, ECP, eotaxin, and IgE (Van Zele et al. 2006). Several studies with anti-IL-5 intravenous injections were successful in patients with CRSwNP (Gevaert et al. 2011).

4.2.4.3 Immunoglobulin E

There are two types of IgE expression: the polyclonal type and the allergic type. The first does not or only partly relate to the serum IgE; the latter does (Gevaert et al. 2005). IgE in allergic rhinitis is monoclonal and induced by allergens, where in nasal polyposis it is polyclonal and induced by superantigens (see below). In the polyp tissue of 50 % of the CRSwNP patients, hyperimmunoglobulinemia E specific to staphylococcus aureus enterotoxin is found, which correlates with a high asthma prevalence (Gevaert et al. 2005). The polyclonal IgE in nasal polyps is produced locally, as it is dissociated in serum and polyp tissue. Organization of secondary lymphoid tissue in nasal polyps is demonstrated. The consequence of the high IgE concentration is the constant triggering of the IgE mast cell Fcε cascade and the subsequent chronic inflammation and growth of the polyp (Gevaert et al. 2005).

In conclusion it is stated that the polyclonal IgE in polyp tissue is probably produced locally

and is functional as it continuously activates the mast cells. Consequently polyclonal IgE contributes to chronic inflammation in CRSwNP (Zhang et al. 2011).

Subsequently to these findings, it can be assumed that anti-IgE (omalizumab) could be a treatment option for patients with nasal polyps. A recent study has proven clinical efficacy in patients with nasal polyposis and comorbid asthma (Gevaert et al. 2012).

4.2.4.4 Staphylococcus aureus (SA)

The nose is frequently colonized with staphylococcus aureus. The colonization rate in APA syndrome is highest with 87 %, followed by CRSwNP with 60 %, 33 % in controls, and 27 % in CRSsNP. The results of IgE against staphylococcus aureus enterotoxins (SAE) are similar: 80 % in APA syndrome, 28 % in CRSwNP, 15 % in controls, and 6 % in CRSsNP (Bachert et al. 2007). These enterotoxins have superantigen potential. Superantigens are bacterial or viral toxins that modulate the immune system. They are called superantigens because of their ability to result in a lymphocyte response of increased magnitude. Superantigens are capable to interact in a nonconventional manner with a high proportion of T or B cells through conserved sites in the variable regions of their antigen receptors (TCR/BCR) (Figs. 4.3 and 4.4). While bacteria classically stimulate the innate immune system and Th1 and Th17 in the adaptive response, it is recognized that bacterial products, such as superantigens (White et al. 1989), can induce Th2-mediated inflammation (Kotzin et al. 1993; Patou et al. 2008). The enterotoxins lead to more severe symptomatology and to comorbidity, such as persisting asthma (Bachert et al. 2006). The shift toward the Th2 pattern contributes to the colonization of Staphylococcus aureus and causes an environment where the SA can exert their full activity. The cytokine environment in tissue is an important determinant of the impact that SAE have on T-effector cells and Treg cells. Furthermore the macrophages are alternatively activated and phagocytosis of *staphylococcus aureus* is deficient (Krysko et al. 2011). An important question that remains to be answered is: Is the colonization with *staphylococcus* the cause of NP or is it a disease-modulating factor?

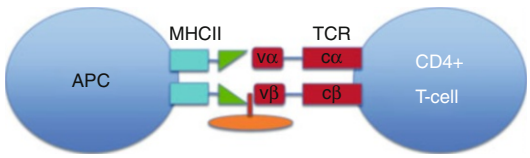

Fig. 4.3 T-cell superantigens: **Vβ** site of the TCR. The superantigen (*orange*) binds the MHC (*green*) outside the binding groove and binds the variable **β**-chain of the TCR (*red*)

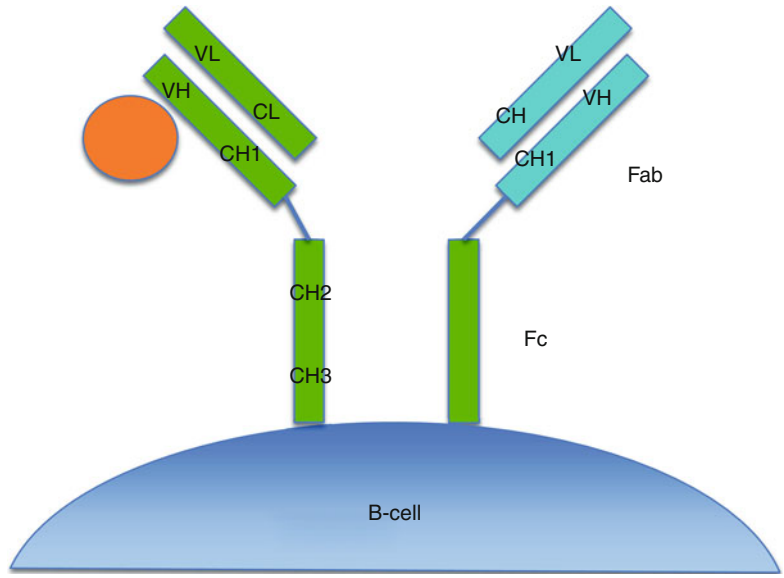

Fig. 4.4 B-cell superantigens. B-cell superantigens (*orange*) bind to the VH3 region of the BCR Fab (*green*)

Conclusion

The importance of local inflammation has long been underestimated. Diseases were divided in atopic or nonatopic based on their skin prick tests or serum IgE. Today we advocate disease phenotyping based on the local markers of inflammation. Especially as a wide series of new monoclonal antibody treatments are now ready for clinical use, the understanding of the pathogenesis is crucial to select the optimal treatment choice. The phenotyping of CRSwNP patients based on their local inflammation, i.e., the presence of IgE specific for SA, total IgE, and IL-5, can determine patients eligible for anti-IgE (omalizumab) or anti-IL-5 (mepolizumab) treatment.

Appendix

Table 4.1 Interferons

Interferon	Cellular source	Function
IFNα	B cells NK cells Monocytes/macrophages	Antiviral activity Upregulation MHC-I Antitumor activity Immune cytotoxicity
IFNβ	Fibroblasts Epithelial cells Macrophages	Antiviral activity
IFNγ	CD8+ T cells Th1 cells NK cells B cells Macrophages	Antiviral activity Upregulation MHC-I and MHC-II Effect on monocytes, NK cells, neutrophils: phagocytosis Granulocyte: adherence to epithelial cells Antigen-specific B-cell proliferation and differentiation Inhibition of IL-4-mediated IgE secretion (antiallergic activity) Regulation of IgE synthesis

Table 4.2 Interleukins

Interleukin	Source	Target cell and function
IL-1	Macrophage, monocyte B cell DC	T helper cell: co-stimulation B cell: maturation and proliferation NK cell: activation Granulocyte: adherence to epithelial cells Eicosanoids upregulation Induces TNF, IL-6, GM-CSF, IL-1 Antiviral activity (shares biological activities with TNF, but TNF has no direct effect on lymphocytes) Other: inflammation, acute-phase reaction, fever, etc.
IL-2 (TCGF)	Th1 cells	IL-2 is critical for the initiation and cessation of leukocyte development Activated T cells: growth and differentiation (IL-2 is the most potent and predominant T-cell growth factor TCGF) Activated B cells: proliferation and Ig secretion Natural killer cells Macrophages

Table 4.2 (continued)

Interleukin	Source	Target cell and function
IL-3 (multi-CSF)	Activated Th cells	Hematopoietic stem cells: differentiation and proliferation of myeloid progenitor cells
	Mast cells	Mast cells: growth and histamine release
	NK cells	
	Epithelium	
	Eosinophils	
IL-4 (BSF-1) (BCGF-1)	Th2 cells	Activated B cells: proliferation, differentiation into the Th2 subset, upregulation of co-stimulatory proteins (CD40 and MHC II), class switching (production of IgG1 and IgE, important in allergic disease; IL-4 is essential for IgE production and synergizes with IL-2, IL-5, IL-6)
	Macrophages	T cells: proliferation and differentiation
	Mast cells	IL-4 leads to GATA-3 upregulation and to the expression of IL-5 and IL-13
	B cells	Eosinophilia
		Macrophages: suppression of IL-1 production, MHC-I/-II upregulation, low-affinity IgE upregulation
		Mast cell hyperplasia
		Goblet cell hyperplasia
		NK cells: activation
		Downregulation of IL-1, IL-6, TNFα, FcγR
IL-5 (BCGF-2) (=T-cell-replacing factor)	Th2 cells	B cells: differentiation, IgA production
	Mast cells	Eosinophils (IL-5 = eosinophil differentiation factor): production, recruitment to nasal mucosa, activation, prolongs survival
	Eosinophils	IL-5 is the most important eosinophilopoietin (other: IL-3 and GM-CSF)
		ECP secretion
		CD8+ T cells: differentiation
IL-6 (=IFNβ2)	Th2 cells	Activated B cells: differentiation into plasma cells
	B cells	Plasma cells: antibody secretion
	Macrophages, monocytes	T cells: survival Th17 (augments IL-17, blocks FOXP3, promotes RORCγt, promotes IL-23R)(5)
	Endothelium	Neutrophil: priming
	Fibroblast (induced by IL-1, IL-2, TNF, and IFN and inhibited by IL-4 and IL-13)	Antiviral activity, upregulation of MHC-I
		Hematopoietic stem cells: induces the entry in cell cycle
IL-7 (LP-1)	Bone marrow stromal cells and thymus cells	Pro-B cell: differentiation and proliferation
		Pro-T cell: differentiation and proliferation
		NK cells
		Nuocytes: proliferation and expression of IL-5 and IL-13
IL-8 = CXCL-8 (chemokine) = NAP-1	Macrophage	Neutrophil: neutrophil chemotaxis, degranulation
	Lymphocyte	Basophil
	Endothelium	Lymphocyte: T-cell chemotaxis
	Epithelium (induced by IL-1, TNF, viruses)	Inhibition of IL-4-mediated IgE production, antiallergic
IL-9 (p40-MEA)	Th2 cells	T cell, B cell: potentiate IgG, IgM, and IgE and stimulate mast cell proliferation (MEA activity)
		Synergize with IL-3: RBC and megakaryocyte development
		Mast cell hyperplasia
		Goblet cell hyperplasia

(continued)

Table 4.2 (continued)

Interleukin	Source	Target cell and function
IL-10 (CSIF)	Th2 cells	Th1: inhibits Th1 cytokine production (TNFβ, IFNγ, IL-2)
	Tfh cells	Th2: stimulation (but inhibition of IL-4 and IL-5 production) inhibition of IL-4-induced IgE production
	CD8+ cells	Mast cell
	Macrophages	Eosinophil: inhibition of survival
	Mast cells	Macrophage: inhibits cytokine production (IL-1β, IL-6, IL-8, IL-12, TNFα)
	Monocyte (major source)	Monocyte: inhibition MHC-II expression
	Natural killer cells	B cell: proliferation, plasma cell differentiation
		NKC: inhibition cytokine production (TNFα, IFNγ)
		Summary: inhibition of cellular immunity and allergic inflammation, while stimulating humoral and cytotoxic immune response
IL-11	Bone marrow stroma	Bone marrow stroma
		Hematopoietic progenitor cell: IL-11 synergizes with IL-3 and IL-4
		Megakaryocytes: IL-11 synergizes with IL-3 and IL-6
IL-12	DC	Activated T cell: differentiation into cytotoxic cell with augmentation of TNFα, IFNγ, and IL-2 and suppression of IL-10. Shifts the inflammation toward Th1
	B cell	Inhibition of IL-4 (less IgE production, antiallergic)
	T cell (Th1)	NK cell: augmentation of TNFα, IFNγ
	Macrophage, monocyte	Indirect inhibition of IgE secretion
IL-13 (p600)	Activated Th2	Th2 cells: inhibition Th1, less IL-8, IL-10, IL-12
	Mast cells	B cells: stimulation of growth and differentiation (IgE isotype switch)
	NK cells	Eosinophilia
	Non-B/non-T cells (nuocytes)	Goblet cell hyperplasia
		Macrophages: inhibition macrophage inflammatory cytokines (IL-1, IL-6)
		IL-13 and IL-4 both induce IgE production (if IFNγ is absent) and downregulate IL-6
		Similar activity as IL-4, except IL-13 does not enhance Th2 generation or proliferation
IL-14 (HMW-BCGF)	T cells	Activated B cells: controls proliferation of B cells and inhibits Ig secretion
IL-15	Mononuclear phagocytes	T cells, activated B cells, NKC: proliferation
		Activity similar to IL-2
IL-16 (LCF)	Lymphocytes	CD4+ cells: chemotaxis
	CD8+ cells	
	Epithelial cells	
	Eosinophils	
IL-17	Th17	Epithelium, endothelium: augmentation inflammatory cytokines.
		Neutrophil recruitment and function
IL-18	Macrophages	Th1 cells: induce production of IFN
		NKC: activation

Table 4.2 (continued)

Interleukin	Source	Target cell and function
IL-21	Activated Th cells Tfh cells Th17 cells NK cells NKT cells	Macrophages: IL-21 induces CXCL-8 Dendritic cells: Inhibition of maturation Inhibition of function CD8+ cells: Co-stimulation of activation and proliferation of CD8+ cells, induction of cytotoxic cytokines, generation of memory CD8 + T cells CD8 + differentiation (inhibits downregulation of CD28 and CD62L, downregulates CD44; when combined with IL-15 there is an accumulation of CD44 and IFNγ) NK cells Differentiation and maturation of NK cells Low doses of IL-21 can help proliferation of committed NKC (when IL-2/IL-15 doses are suboptimal, it helps proliferation) Augment NKC cytotoxicity T helper cells Generation and migration of Tfh cells and Th2 cells Autocrine for Tfh cells (modulates CXCR-5, CCR) Autocrine for Th17 generation and differentiation (upregulation of IL-21 and induction of IL-23R what leads to upregulation of RORCγt) B cells: Augment CD40 driven B-cell proliferation, differentiation and isotype switching, Differentiation of B cells to plasma cells IL-21 cooperates with IL-4 in the regulation of Immunoglobulins: IL-21 + IL-4 + anti-CD40: augment IgE IL-21 + IL-4 + PHA: decrease IgE IL-21 can also antagonizes IL-4: Prevents proliferation of B cells cultured with IgM combined with IL-4 Can inhibit IL-4-mediated isotype switch (particularly IgE secretion) Mostly stimulates the immunity, but can inhibit it: Antagonize IL-4 function depending on nature of co-stimulatory proteins as well as the developmental stage of the target B cell Inhibit delayed-type hypersensitivity in mice Prevents IFNγ expression Stimulates IL-10 expression (CD4+/CD8+/NKC) Can be proapoptotic for B cells (if stimulated by TLR signals, polyclonal B cells with nonspecific Ig) and for natural killer cells. It can inhibit proliferation and stimulation of B cells, memory CD8+ cells, and NKC It can downregulate MHC-II on immature dendritic cells Summarized, it controls the strength and duration of the adaptive immune response

(continued)

Table 4.2 (continued)

Interleukin	Source	Target cell and function
IL-25	Th-2 cells	Member of Th17 family, but unlike the rest of this family, IL-25 is associated with a Th2-like inflammation and disease: eosinophilia, IgE, IL-5, and IL-13
	Mast cells	Th2 cells: stimulation and production of IL-4
	Eosinophils	Innate cells: stimulation and production of IL-5 and IL-13
	Basophils	NKT cells
	Macrophage	
	Epithelial cells	
IL-33	Th1, Th2, Th17	Induction of Th2 cytokines
	Eosinophil	Similar activity to IL-25: eosinophilia, IgE secretion, stimulation of innate lymphoid cells, and production of Th2 cytokines
	Mast cells	Active IL-33 is constitutively expressed in the nucleus of human epithelial and endothelial cells and acts as an alarmin. It is released following injury or tissue damage (apoptosis inactivates IL-33; necrosis releases IL-33 and causes type 2 inflammation); IL-33 then amplifies almost every type of inflammation, including Th1, Th2, and Th17
	Basophils	Dendritic cell: maturation and increase of potency
	Fibroblast	Non-B/non-T cell: IL-5 and IL-13 expression
	Epithelial cell	Basophil: IL-4 and IL-13 expression and histamine release
	Endothelial cell	IL-33 integrates both innate and adaptive immunity via basophils, mast cells, eosinophils, innate lymphoid cells, NKC and NKT cells, nuocytes, Th2 lymphocytes, and a CD34 precursor cell population
	IL-33 receptor = T1/ST2	High levels of IL-33 induce M1-macrophages, where low levels induce the M2 subset
		An infection can lead to Th2 response through IL-33 alarmin, which can also be the mechanism in allergy

Table 4.3 Colony-stimulating factor

CSF	Source	Function
EPO	Kidney, liver	Producing mature erythrocytes
GCSF	Monocyte/macrophage	Neutrophils: increased production, maturation, differentiation
	Fibroblast	
	Endothelial cells	
GM-CSF	Monocytes	
	Fibroblast	
	T cells	
	Endothelial cells	
M-CSF	Monocytes	Stimulates activity of neutrophils, eosinophils, monocytes, macrophages
	Fibroblast	
	Endothelial cells	
SCF	Stromal cells	Hematopoiesis
	Fibroblasts	Tissue mast cell generation and phenotype maintenance

Table 4.4 Growth and differentiation factors

	Source	Function
Oncostatin M	T cell Monocyte/macrophage	
TGFα	Monocyte/macrophage Keratinocytes Brain cells	Fibroblasts: stimulation Epithelial cells: stimulation
TGFβ	T cell, Th3 Neutrophil Eosinophil Monocyte Macrophage Platelets, fibroblasts Endothelial cell Epithelial cell	Induction of FOXP3 Inhibition of IL-4-mediated IgE secretion (antiallergic activity) Inhibition of T cells and B cells, inhibits Ig secretion Stimulates fibrosis, ECM formation
PDGF	Platelets, macrophages Endothelial cells Smooth muscle cells	Smooth muscle cell and Endothelial cell: proliferation
Leukemia inhibitory factor	Platelets Monocyte/macrophage Endothelial cells Smooth muscle cells	
Hepatocyte growth factor	Platelets, fibroblasts Monocyte/macrophage Endothelial cells Smooth muscle cells	
Epidermal growth factor	Macrophages	

Table 4.5 Tumor necrosis factor

TNF	Source	Function
TNFα (= cachectin)	Monocytes/macrophages	Cytotoxic activity Proinflammatory: chemotaxis of granulocytes B-cell activation Monocyte activation (IL-6 and IL-8 production) Neutrophils: activation (adherence, chemotaxis, degranulation) Antiviral activity Stimulation of MHC-I and MHC-II expression
TNFβ (= lymphotoxin)	T cells (IL-1, IL-3, GM-CSF, and IFNγ may induce TNF transcription)	See TNFα

Table 4.6 Transcription factors

T-cell subpopulation	Transcription factor
Th1	Tbet
Th2	GATA-3
Th17	RORCγt
Treg	FOXP3

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Mast Cells

5

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Keywords
Mast cells • Tryptase • Chymase • IL-13 • Glucocorticoid • FcεRI

Abbreviations

CPA3	Carboxypeptidase A3
cys-LT	Cysteinyl leukotriene
FcεRI	High-affinity receptor for IgE
GC	Glucocorticoid
GM-CSF	Granulocyte-macrophage colony-stimulating factor
IL	Interleukin
MCs	Mast cells
MC_T	T-type mast cells
MC_{TC}	TC-type mast cells
MIP	Macrophage inflammatory protein
NFAT	Nuclear factor-activated T
NF-κB	Nuclear factor-κB
PAF	Platelet-activating factor
PGD_2	Prostaglandin D_2
SCF	Stem cell factor
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor
TSLP	Thymic stromal lymphopoietin

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Core Message
Mast cells trigger not only the immediate-type allergic reactions in an IgE-mediated manner but also the late-phase allergic response and chronic allergic inflammation.

5.1 Introduction

Mast cells (MCs) serve as essential effector cells for acute IgE-mediated allergic reactions by releasing histamine and other vasoactive mediators, as seen in allergic rhinitis, for example. MCs are also recognized as important source of a variety of cytokines and chemokines. Thus, MCs trigger not only the immediate-type allergic reactions in an IgE-mediated manner but also the late-phase allergic response and chronic allergic inflammation, thereby regulating the function of other immune cells. MCs are present throughout connective tissues and mucosal surfaces, particularly at the interface with the external environment such as the skin and respiratory tract (Hawrylowicz et al. 2006). The nasal mucosa is the first barrier of the entire respiratory tract that encounters various pathogens or allergens. In this review, I will summarize the roles of MCs in allergic airway diseases by focusing on the role of human MCs in the airways.

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5.2 Origin and Distribution of MCs

MCs originate from hematopoietic progenitors. Kitamura et al. discovered two different mice strains genetically lacking MCs: *Sl/Sl*^{d} mice lacking SCF, which was turned out to be the mast cell growth factor, and *W/W*^{v} mice lacking KIT, which is the receptor for SCF. By using these "natural" MC deficient mice, it was established that immature MC progenitors can migrate from bone marrow into the tissue through blood circulation, unlike immature granulocytes which are kept in bone marrow. Then, these cells undergo maturation in the tissues under specific factors like stem cell factor (SCF) present within the microenvironment (Kitamura et al. 1977, 1978; Kitamura and Go 1979).

Phenotypically distinct subsets of MCs are present in rodents, based on their distinct staining characteristics, T-cell dependency, and functions, namely, connective tissue MCs and mucosal MCs (Befus et al. 1982; Pearce et al. 1982). Regarding T-cell dependency, it is well established that mucosal MCs can grow in the presence of interleukin (IL-)3 (Ihle et al. 1983). However, human MCs do not grow when hematopoietic cells are cultured with IL-3 (Saito et al. 1988). Although human IL-3 has a significant sequence homology with murine IL-3, the degree of homology between human and murine IL-3 was almost similar (approximately 26–28 % at amino acid sequence) to that between human IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF). Also, receptor structure for IL-3 is distinct between human and mouse. While human has a common β-subunit of the receptors for GM-CSF, IL-3, and IL-5, the mouse has two distinct β-subunits; one is specific for the IL-3 receptor and exists only on MCs, and the other is equivalent to the human common β-subunit (Miyajima 1992).

Regarding human MC phenotypes, two types of MCs have been recognized based on the neutral proteases they express. TC-type MCs (MC_{TC}) contain tryptase together with chymase, and other neutral proteases, whereas T-type mast cells (MC_T) contain tryptase but lack the other neutral proteases present in MC_{TC} (Irani et al. 1986). Also, MC_{TC} preferentially dwell in the connective tissue such as skin, while MC_T are often found in mucosa such as airway epithelium. In allergic rhinitis and asthma, MCs are known to accumulate within the epithelial compartment of the target organ. In fact, there is a selective increase of MC_T in the epithelial compartment of the nasal mucosa of the patients with allergic rhinitis (Enerback et al. 1986; Pawankar and Ra 1996).

Asthma can be divided into two subgroups ("Th2 high" and "Th2 low" asthma) based on epithelial cell gene signatures for the activity of Th2 cytokines such as IL-13 (Dougherty et al. 2010). The patients with Th2 high asthma have more infiltration of MCs into the airway epithelium. These subgroups can be diagnosed based on the level of serum periostin, which production is specifically induced by IL-13, and that the patients with Th2 high asthma subtype are more sensitive to anti-IL-13 therapy (Corren et al. 2011). These intraepithelial MCs express both tryptases and carboxypeptidase A3 (CPA3) but not chymase (Dougherty et al. 2010). According to classical definition (Irani et al. 1986), MC_T were not supposed to express CPA3. However, according to the recent data (Nakajima et al. 2004; Kashiwakura et al. 2004), all types of MCs and basophils seem to express CPA3. Therefore, we can consider these epithelial MCs at least as a sort of MC_T. MCs exposed to conditioned media from IL-13-activated epithelial cells showed downregulation of chymase but no change in tryptase or CPA3 expression (Dougherty et al. 2010). This may relate to the reason why MC_T are preferentially found in the mucosa and are deficient in primary immunodeficiency patients (Hawrylowicz et al. 2006).

As shown in Table 5.1, MC_{TC} can respond to various non-immunological stimuli such as C5a or substance P, while MC_T do not (Hawrylowicz et al. 2006). Kajiwara et al. recently reported that MC_T, but not MC_{TC}, express functional receptor for platelet-activating factor (PAF). It was found by searching preferentially expressed genes in lung MCs (MC_T) compared to skin MCs (MC_{TC}). Interestingly, these MC phenotypes, i.e., expression of chymase and receptors for these

Table 5.1 Characteristics of two phenotypes of human mast cells

Phenotype	MC_{TC}	MC_T
Proteases	Tryptase (+++) Chymase (+) Carboxypeptidase A3 (++) Cathepsin G (+)	Tryptase (++) Chymase (–) Carboxypeptidase A3 (+?)
Distribution	Skin (++) Intestinal submucosa (+) Intestinal mucosa (–) Alveolar wall (++) Bronchial subepithelium (+) Dispersed lung mast cells (–) Tonsils (++) Nasal mucosa (–)	Skin (–) Intestinal submucosa (++) Intestinal mucosa (++) Alveolar wall (–) Bronchial subepithelium (+) Dispersed lung mast cells (++) Tonsils (++) Nasal mucosa (++)
Relation to pathology	Increased in fibrotic diseases Unchanged in allergic and parasitic diseases Unchanged in chronic immunodeficiency diseases	Increased around the site of T cell aviation Increased in allergic and parasitic diseases Decreased in chronic immunodeficiency diseases
Response to non-immunological stimuli	Substance P (+) C5a (+) PAF (–)[a]	Substance P (–) C5a (–) PAF (+)[a]

Adapted from reference Hawrylowicz et al. (2006)

[a]Kajiwara et al. (2010)

non-immunological stimuli, are retained over weeks even when these MCs are cultured in the standard MC culture condition (supplemented with SCF and IL-6) (Kashiwakura et al. 2004; Kajiwara et al. 2010). This is contrasting to the results showing that MCs lose chymase by the factor(s) produced in the IL-13-activated epithelial cells (Dougherty et al. 2010). It would be interesting to know whether MCs, which have lost chymase by the IL-13-activated epithelial cell-derived factor(s), respond to substance P or PAF.

5.3 Role of MCs in Acute Allergic Reactions

MCs express more than 10^5 high-affinity IgE receptor (FcεRI) per cell. When MCs that have been sensitized with some specific IgE antibody are challenged with the specific allergen, they are activated by cross-linking of FcεRI molecules. Thus, activated MCs evoke immediate-type reaction by releasing their granules in which histamine, neutral proteases, and heparin had been stored. Then, lipid mediators such as cysteinyl leukotriene (cys-LT) or prostaglandin D_2 (PGD_2) are synthesized on their membranes and are released into microenvironment within several minutes.

Released histamine and lipid mediators cause acute allergic symptoms such as nasal discharge, bronchospasms, and urticaria. Histamine plays an essential role in acute skin allergic reactions, whereas cys-LT plays a pivotal role in bronchoconstriction. MCs almost exclusively express PGD_2 synthase compared to all other cell types. Although the role of PGD_2 in immediate-type reaction is unclear, it serves as chemoattractant for eosinophils, basophils, and Th2 cells.

Human MCs also exclusively express tryptase, one of the neutral proteases, among all human cell types. Tryptase constitutes 10 % of the MC by protein weight (Hawrylowicz et al. 2006). Proteoglycan (human MCs use "eosinophil" major basic protein instead of proteoglycan molecules) serves as a core protein in the crystalloid structure of the MC granules by binding to heparin and neutral proteases (Nakajima et al. 2002). The MC tryptase acts as trypsin-like

enzyme and thereby causes tissue remodeling such as abnormal proliferation of airway smooth muscles (Brightling et al. 2002).

5.4 Role of MCs in Allergic Inflammation

MCs secrete a variety of cytokines and chemokines several hours after allergen-induced degranulation via transcription of these genes. The representative cytokines/chemokines which are produced by activated human MCs are Th2 cytokines such as IL-5, IL-13, and GM-CSF and CC chemokines such as CCL1/I-309, CCL2/monocyte chemoattractant protein-1, CCL3/macrophage inflammatory protein (MIP-)1α, and CCL4/MIP-1β. Activated human MCs also secrete a substantial amount of CXCL8/IL-8 (Nakajima et al. 2002; Bischoff 2007). MCs can store and release some of cytokines such as tumor necrosis factor (TNF)-α during degranulation process. Regarding IL-4 production, it seems reproducible using mouse MCs. However, only a few groups succeeded to immunohistochemically demonstrate the presence of IL-4 on human MCs (Bradding et al. 1992; Pawankar et al. 1997). In any case, at least in human, basophils are more potent producers of IL-4. Instead, IL-4 potently activates human MC function and maturation. Human MCs can produce a substantial amount of another Th2 cytokine, IL-13, in response to IgE-mediated stimuli, and the IL-13 production is markedly enhanced by preincubation with IL-4 (Bischoff 2007). However, these cytokines and chemokines are not unique to MCs and are produced by other cell types. During antigen stimulation, more Th2 cytokines would be produced by proliferating T cells. We should consider the relative role of MCs in the allergic or innate-type inflammation by understanding cytokines/chemokines produced by other immune cell types and epithelial-mesenchymal tissues. For example, epithelial-mesenchymal tissue-derived thymic stromal lymphopoietin (TSLP) and IL-33 are now recognized as most important cytokines for both innate-type and allergic inflammation occurred in allergic diseases such as asthma. These two cytokines and CC chemokines such as CCL17 and CCL23 are produced in response to external stimuli and Th2 cytokines such as IL-13 and stimulate the chemotaxis and development of Th2 cells and the function of MCs. Other than Th2 cytokines and CC chemokines, tryptase, cys-LT, and TNF-α also stimulate epithelial-mesenchymal tissue (Hawrylowicz et al. 2006; Oboki et al. 2010; Takai 2012; Ito et al. 2012) (Fig. 5.1).

Although human MCs do not normally produce cytokines in response to other cytokines such as IL-4 without FcεRI cross-linking, it should be noted that IL-33, which are released during necrosis of epithelial-mesenchymal tissue, alone stimulate MCs to release a variety of cytokines such as IL-13 (Iikura et al. 2007). Regarding other innate immune responses, mouse MCs are proven to play an essential role in protection against microbial infection via Toll-like receptor (TLR)s (Supajatura et al. 2002; Nakajima et al. 1997; Krämer et al. 2008). Human MCs can express functional TLR4 after preincubation with IFN-γ. These MCs can produce more TNF-a, CCL5, CXCL10, and CXCL11 compared to IgE dependently activated MCs (Okumura et al. 2003).

Topical use of glucocorticoid (GC) is the first line therapy for allergic diseases such as asthma and allergic rhinitis. Although GC do not block the degranulation of MCs, these drugs downregulate the gene expression of FcεRI in MCs and thereby downregulate IgE-mediated activation of MCs. More notably, glucocorticoid can inhibit gene expression of a variety of cytokines in MCs. Even in short time incubation, GC blocks the nuclear factor-κB (NF-κB)-dependent gene expression of cytokines, such as IL-13, CXCL8/IL-8, and GM-CSF. On the other hand, GC does not inhibit nuclear factor-activated T (NFAT)-dependent gene expression of cytokines, such as CCL1, CCL3, and CCL4.

Interestingly, an immunosuppressive agent, FK-506 inhibits NFAT-dependent-, but not NF-κB-dependent-, gene expression (Kato et al. 2009). If these drugs are added simultaneously into the reaction buffer for MC activation, the expression of cytokines is almost completely

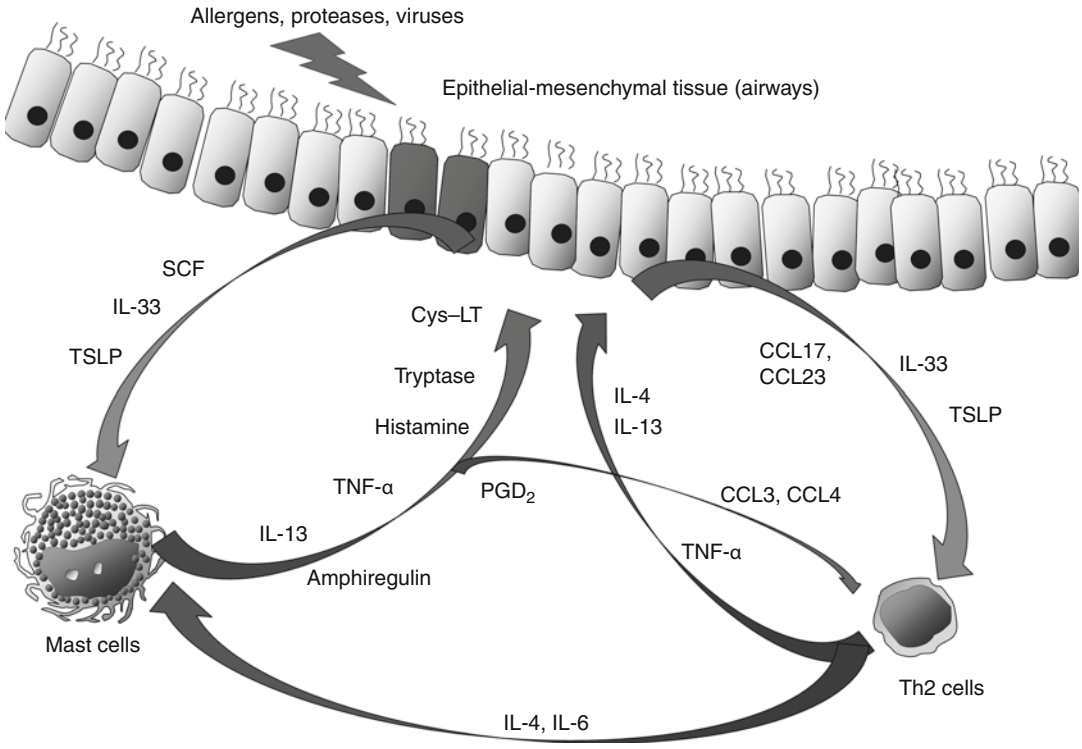

Fig. 5.1 Mutual stimulatory effect of mast cells, Th2 cells and epithelial-mesenchymal tissue on chronic allergic inflammation. These cell types are stimulating each other by releasing cytokines and mediators to form allergic inflammation in the airway. Among such cytokines, IL-13, IL-4 and IL-33 play a key role

blocked (http://www.ncbi.nlm.nih.gov/geo/, dataset number = GSE15174, submitted by Atsushi Kato). Among cytokine or growth factor genes, only IgE-mediated amphiregulin gene upregulation was not blocked by preincubation with GC and FK-506. Amphiregulin acts on airway epithelial cells to produce mucin and is upregulated in asthmatic airways (Okumura et al. 2005). It also relates to lung-tissue homeostasis, i.e., repair of the lung epithelia injured by viruses (Monticelli et al. 2011).

Conclusion

MCs trigger not only the immediate-type allergic reaction in an IgE-mediated manner but also the late-phase allergic response and chronic allergic inflammation, thereby regulating the function of other immune cells. While histamine, tryptase, and PGD_2 released in the immediate-type reaction are unique to MCs (or basophils), most cytokines and chemokines are produced by other cell types as well as MCs. It is necessary to determine the relative role of MCs in the allergic or innate-type inflammation by understanding cytokines/chemokines produced by other immune cell types and epithelial-mesenchymal tissues. The expression of these cytokines is almost completely blocked when GC and FK506 are added simultaneously into the reaction buffer for MC activation. It would be difficult to overwhelm this effect even if we could develop a new anti-MC drug.

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Macrophage

6

Hideyuki Kawauchi

Keywords
Macrophage • Dendritic cell • Scavenger • Antigen presentation • Immunological tolerance • Regulatory T cell • Chemokine • Toll-like receptor (TLR)

Core Message

- There are various immunocompetent cells including the so-called macrophages in human nasal mucosa. Those cells are essential for a defense system against various invading pathogens such as bacteria and virus.
- Those cells are also key players in the pathogenesis of rhinosinusitis and allergic rhinitis at the epithelial linings of nasal cavity and paranasal sinuses.
- Among them, macrophages are well known to have immunologically an important role as a scavenger cell and antigen-presenting cells (APCs), in order to mount innate and acquired immunity in the upper and lower respiratory tract.

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6.1 Part I. General Concept of Macrophage

6.1.1 Origin and Classification of Macrophages

Macrophage lineage cells are produced from pluripotent progenitor cells in the bone marrow (Stanley 2009). These cells require combined stimulus from colony-stimulating factor-1 (CSF-1) and factors including interleukin-1 (IL-1), IL-3, GM-CSF, and interferon-gamma so far, to differentiate to mature functional macrophages distributed to peripheral tissues through the blood vessel and lymphatic circulation. The definition and nomenclature of tissue-resident macrophage or recruiting inflammatory macrophage is taken into account with evidence that the monocyte subpopulations may possess different propensities to give rise to particular resident populations, particularly in mucosal surface such as the respiratory and digestive tract. It is clearly demonstrated that blood monocytes are heterogeneous in terms of their expression of key molecules, chemokine receptors, and cell adhesion molecules (Geissmann et al. 2010). But it is yet to

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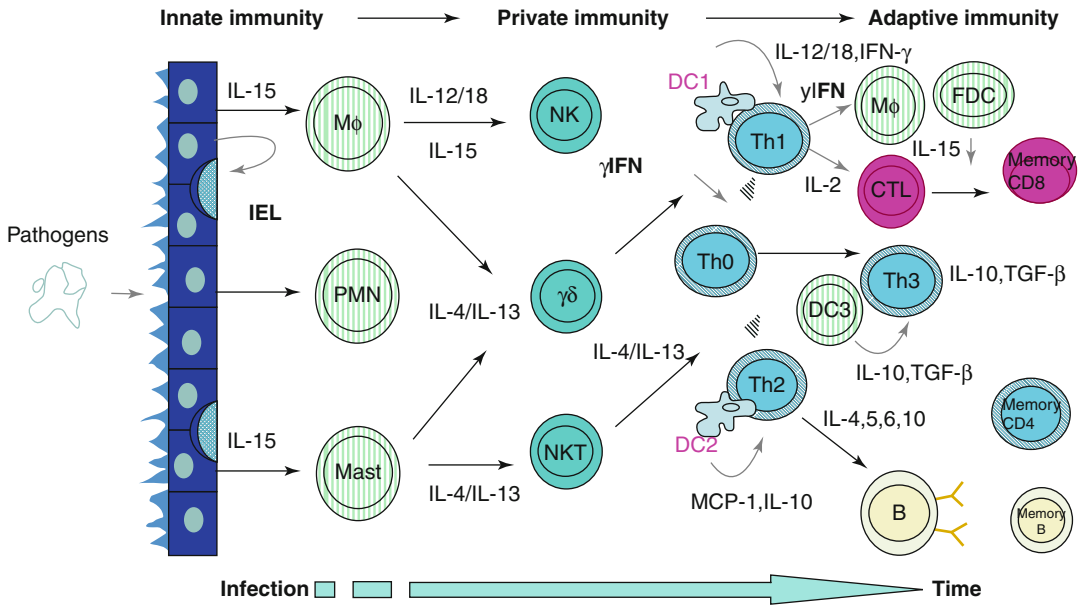


Fig. 6.1 The mechanisms of host defense system from innate to adaptive immunity. *PMN* polymorphonuclear cells, *CTL* cytotoxic lymphocytes, *Mo* macrophages, *DC* dendritic cells

remained to categorize the monocyte subsets how to further divide in terms of their effector functions with distinct stimuli and locations.

6.1.2 Heterogeneity and Markers

Tissue macrophages have many characteristics, including extensive lysosomes and stellate morphology and location, and they are heterogeneous in terms of function and surface marker expression, although we already know their phagocytic and antigen-presenting cell (APC) function. For example, CD11c in humans is a marker for the mononuclear phagocyte system and was later shown to be an active complement receptor 4 (CR4) that is induced during macrophage maturation, although CD11c is clearly not linked to APC function. More importantly, various cell surface molecules in response to Toll-like receptor (TLR) signaling are functionally of particular interest because they determine the ability of macrophage lineage cells to interact with pathogens, and with other cell types, to generate an appropriate innate and acquired immune responses (Fig. 6.1). But, there are no markers that are expressed specifically and ubiquitously on all macrophage lineage cells except CSF-1 receptor. Co-stimulatory molecules (CD80, CD86, CD40) are considered to be essential for antigen uptake and antigen presentation from macrophages to T and B cells. And chemokine receptors and integrin family on macrophages may determine the recruitment and locations in tissues. However, with many reasons, surface marker expression cannot be taken as the sole indication of lineage, function, or destiny among macrophages (Taylor et al. 2005).

6.1.3 Recruitment of Macrophages into Peripheral Mucosal Inflammatory Sites

Macrophages are recruited into peripheral mucosal inflammatory sites with a wide range of different stimuli. If microbial infection takes place, neutrophil infiltration precedes and releases toxic agents designed to kill extracellular pathogens, and then macrophages come and evacuate degradated pathogens and apoptotic neutrophils. The tissue-entering process of these cells is called as chemotaxis. Chemokines are essential for the recruitment of inflammatory cells into the peripheral mucosal inflammatory sites (Sallusto and Baggiolini 2008). Chemokines are subdivided,

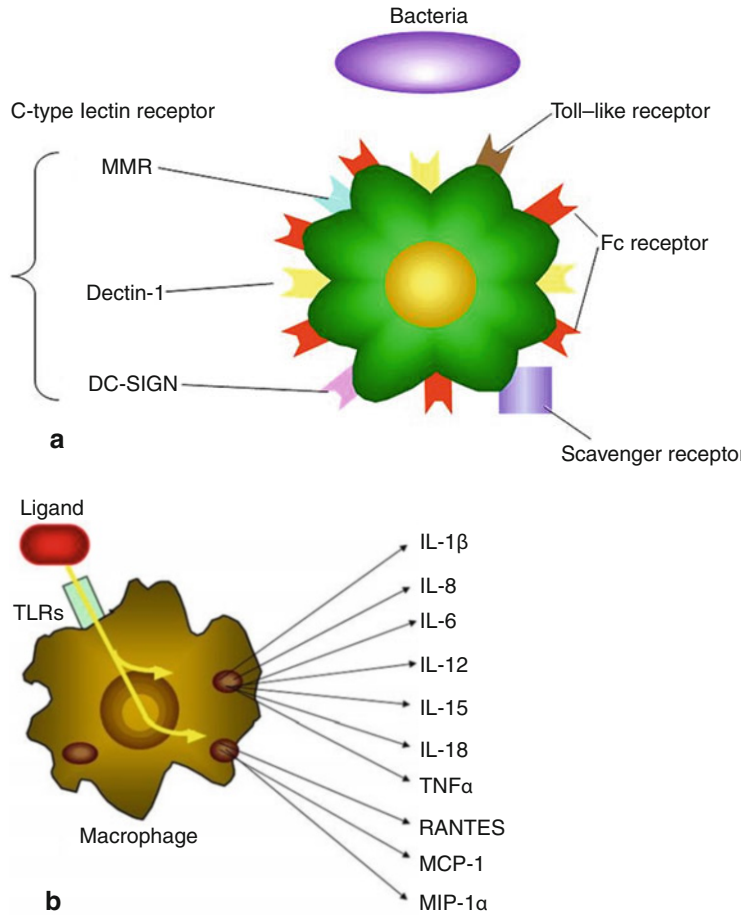


Fig. 6.2 (**a**) Pattern recognition receptors on macrophages. (**b**) Cytokines and chemokines produced by macrophage via Toll-like receptors

based on the core cysteine motifs that form disulfide bonds to fold the molecule. CC chemokines have two adjacent cysteines, while in CXC chemokines, there is an intervening amino acid. Chemokine receptors are classified in accordance, CCR, CXCR, and CX3CR families. Expression of specific chemokine receptors on different populations of macrophages and dendritic cells provides different kinds of effector mechanism for their differential recruitment in response to different signals and, consequently, might modify inflammatory reaction in mucosal sites such as respiratory or digestive tract.

6.1.4 Phagocytosis

Phagocytosis is a front-line defense against pathogen attack, so almost by definition, a pathogen is an infectious agent that avoids being killed by phagocytosis. Phagocytosis is a process that requires a mechanism for self-nonself discrimination (Aderem and Underhill 1999). Macrophages possess numerous receptors that allow the direct recognition of particles based upon novel sugars, lipids, protein sequences, and concentrations of charge that are unique to pathogens (so-called pathogen-associated molecular patterns) (Fig. 6.2a, b). Particles may also be recognized indirectly if they are coated with opsonins such as specific antibodies or complement components.

6.1.5 Antigen Presentation by Macrophages and Dendritic Cells

It is generally accepted that antigens derived from extracellular sources must be taken up, processed by macrophages (phagocytic antigen-presenting cells) and dendritic cells (nonphagocytic or

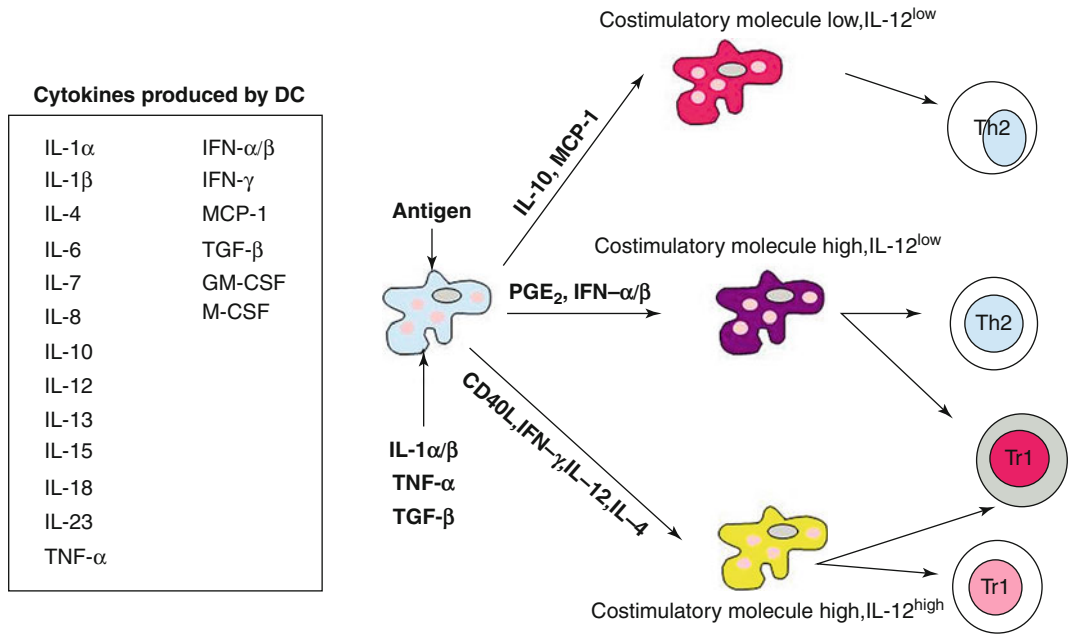


Fig. 6.3 Schematic function of dendritic cells

much less-phagocytic antigen-presenting cells), and afterwards presented to T lymphocytes (Fig. 6.3). The process of uptake, processing, and presentation is now well understood (Jutras and Desjardins 2005; Hume 2008). However, recognition of the antigen major histocompatibility complex (MHC)-II complex by the T cell receptor is not sufficient to trigger T cell activation. Moreover, T cell activation needs second costimulatory signals from the APC in the form of specific cytokines and coreceptors.

6.1.6 Macrophage Activation

Activated macrophages are strongly positive for class II-MHC molecules and adapted to kill microorganisms and tumor cells and present antigen to T lymphocytes. The classical macrophage activating factor, produced by stimulated Th1 lymphocytes and NK cells, is interferon-gamma (Schroder et al. 2004). Classical macrophage activation, involving a synergistic interaction between interferon-gamma and a pathogen molecule such as lipopolysaccharide (LPS), is just one of the numerous interactions that occur between distinct stimuli. We know that LPS acts on macrophages to initiate a cascade of inflammatory processes that are essential for innate immunity in upper respiratory tract such as middle and inner ear as well (Kawauchi et al. 1998; Kawai and Akira 2010). T cell products are, of course, only part of the story of macrophage activation. Macrophages respond directly to pathogen-associated molecular patterns (PAMPs). They recognize them through the plasma membrane and cytoplasmic receptors such as the Toll-like receptors and intracellular receptors of the NOD-like receptor (NLR) family (Chen et al. 2009).

6.1.7 Role of Macrophages in Induction of Immune Tolerance

Immunological tolerance is described as no ability of acquired immunity to respond to specific antigens. Central tolerance induction occurs in the thymus for T cells and the bone marrow for B cells. The main mechanism for central tolerance in T cells is the induction of T cell death. Dendritic cells (DCs) are found in abundance in the thymus, where newly produced T cells are educated to become functional $CD4^+$ T or $CD8^+$

T cells and undergo selection to eliminate clones against self. Low-affinity reactive T cells are positively selected and allowed to survive and reach the periphery. The mechanism of peripheral tolerance is a little different from central one but includes T cell death, anergy, and active suppression by regulatory T cells (Tregs). In this mechanism, DCs could contribute by inducing apoptosis in T cells and by producing IL-10 that induces Tregs (Lipscomb and Masten 2002).

6.2 Part II. Distribution of Macrophages in Murine and Human Nasal Mucosa

There are so many reports as regards the actual distribution of macrophages and dendritic cells in murine and human nasal mucosa, by employing immunohistochemistry with various specific antibodies to those cells. Ichimiya and Kawauchi reported in their article that in nasal mucosa of conventional (CV) mice, Mac-1 positive macrophages, mast cells, and all cell types of lymphocyte subsets were present (Ichimiya et al. 1991). But, in the nasal mucosa of specific-pathogen-free mice, all cell types were fewer in number than those of CV mice. And they concluded that macrophages and lymphocytes are mobilized to nasal mucosa, responding to continuous antigenic stimuli, and play an important role in the local defense mechanism of the upper respiratory tract. The analysis of macrophages in human nasal mucosa is abundant, and all published articles demonstrated the significant contribution of macrophages to provoke immune responses and control inflammation in nasal mucosa. Albegger investigated to find out macrophages and lymphocytes in cluster formation of human nasal polyps, employing a light and electron microscopy (Albegger 1977). And his data indicated that cell clusters were consisted mainly of macrophages and lymphoid cells. In their study, within the clusters, the cells showed intimate physical contacts being performed by microvilli with varying length, suggesting cell-to-cell interaction. These cell clusters may remind us of morphologically those found in vitro and in vivo in the course of immune responses. Jahnsen et al. in their histological study of human nasal mucosa demonstrated the dense network of human leukocyte antigen-DR$^+$ cells with dendritic morphology not only in the epithelium but also in the lamina propria (Jahnsen et al. 2004). In addition, they also reported that, in both compartments, these cells could be divided into two main populations based on their phenotypic characteristics: the majority expressed a macrophage-like phenotype (CD11b$^+$CD14$^+$CD64$^+$CD68$^+$RFD7$^+$), whereas the smaller population was predominantly constituted by CD1c$^+$CD11c$^+$ immature DCs. Krysko and Bachert aimed to determine macrophage phenotypes in nasal mucosa of chronic rhinosinusitis with nasal polyp (CRSwNP) and chronic rhinosinusitis without polyp (CRSsNP) and to examine phagocytosis of *Staphylococcus aureus* (*S. aureus*) in these pathologies (Krysko et al. 2011). They reported that more M2 macrophages were present in CRSwNP than in CRSsNP. This also was positively correlated with increased levels of IL-5, ECP, and locally produced IgE and decreased levels of IL-6, IL-1β, and IFN-γ. In their study, phagocytosis of *S. aureus* by human tissue-derived macrophages was reduced in CRSwNP as compared to macrophages from the control inferior turbinates. Furthermore, they concluded that decreased phagocytosis of *S. aureus* and an M2 activation phenotype in CRSwNP could potentially contribute to the persistence of chronic inflammation in CRSwNP.

6.3 Part III. Modification of Macrophages and Dendritic Cells and Its Clinical Impact on Inflammatory Disorders Such as Allergic Rhinitis

In this part, I would like to introduce a couple of our experimental data in mice as regards how macrophages or dendritic cells are modifying the sinonasal inflammation such as allergic rhinitis and rhinosinusitis. Mature DCs are established as unrivaled APCs in the initiation of immune responses, whereas steady-state DCs are demonstrated to induce peripheral T cell tolerance and consequently attenuate autoimmune-mediated inflammation in animal experiments (Yogev et al. 2012; Mizuno et al. 2012).

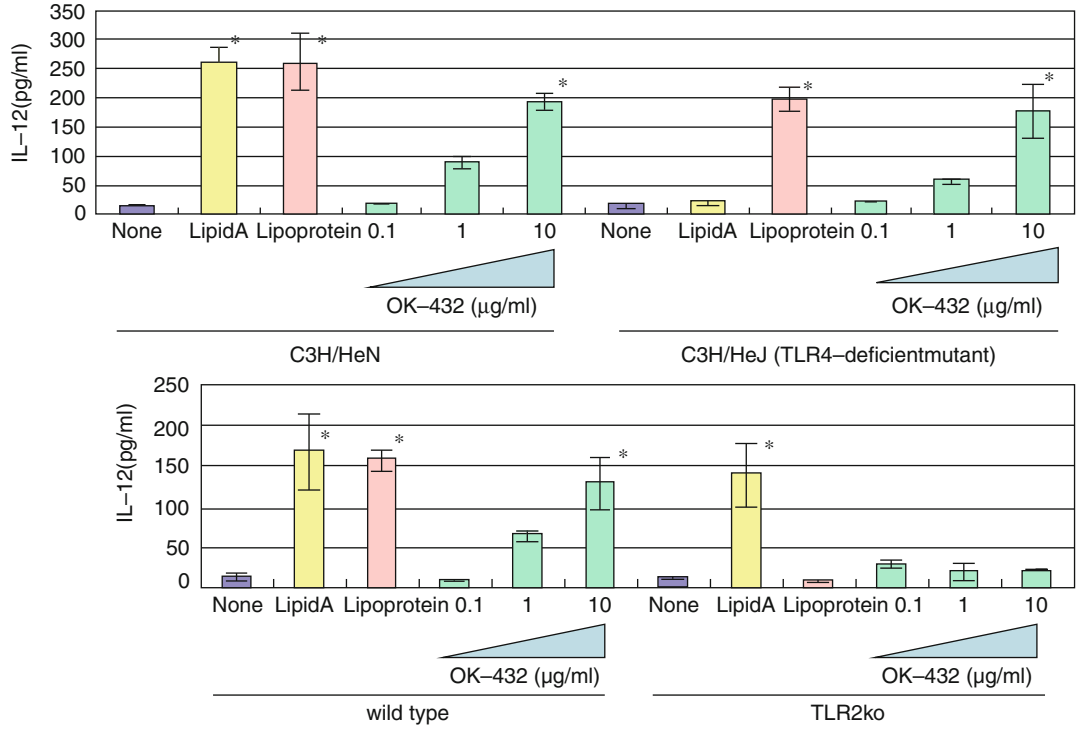


Fig. 6.4 IL-12 production from macrophages with OK-432 stimulation in C3H/HeN, C3H/HeJ, and TLR2 knockout mice

In our series of animal experiments, macrophage activation with OK-432 and its effect on allergic rhinitis (Kawauchi et al. 2009) and regulatory role of lymphoid chemokines CCL19 and CCL21 in the control of allergic rhinitis (Takamura et al. 2007; Kawauchi et al. 2011) are introduced as examples, in order to explain how macrophages or DCs modify the sinonasal inflammation such as allergic rhinitis and rhinosinusitis.

6.3.1 Endogenous IL-12 Induction from Macrophages by OK-432 and Its Effect on the Murine Allergic Rhinitis Model

OK-432, preparation of a low-virulence strain (Su) of *Streptococcus pyogenes* (Group A) killed by a penicillin and lyophilized, is a stiff inducer of Th1 cytokines and brings out anticancer effect in cancer-bearing mice. OK-432 has been reported to consist of many bacterial components, such as peptidoglycan and M-protein. Recently, Toll-like receptor (TLR) family proteins are reported to play a role of recognition of bacterial components and induce interleukin-12 (IL-12) from macrophages. So, we have examined the role of TLR2 for the recognition of OK-432 by macrophages and the effects of OK-432 on allergic rhinitis model. As results, interestingly, IL-12 production by macrophages derived from TLR2 *knockout* mice was markedly reduced in comparison with that of macrophages derived from wild type of mice (Fig. 6.4). Besides, no regulatory effect of OK-432 was observed on allergic rhinitis model in TLR2 *knockout* mice, although nasal symptom of wild type of mice was attenuated upon nasal antigen challenge after systemic sensitization with OK-432 pretreatment (Figs. 6.5 and 6.6). These findings strongly suggest that OK-432 pretreatment provokes macrophage activation to induce IL-12 via TLR2 signaling pathway and consequently suppress Th2-mediated allergic inflammation in nasal mucosa (Fig. 6.7).

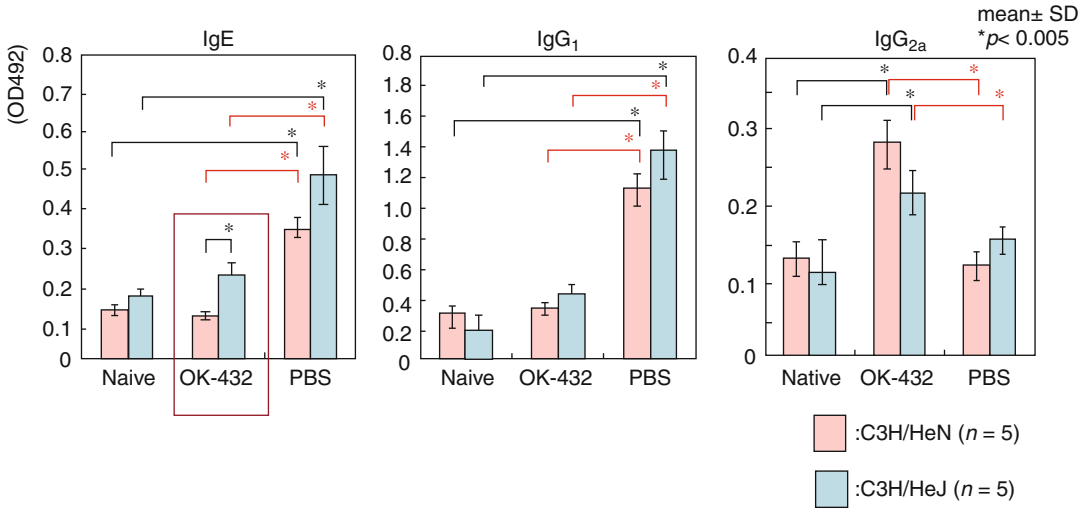


Fig. 6.5 Antigen-specific Th1 and Th2 antibody in serum of C3H/HeN and C3H/HeJ mice after systemic sensitization with OVA and CFA

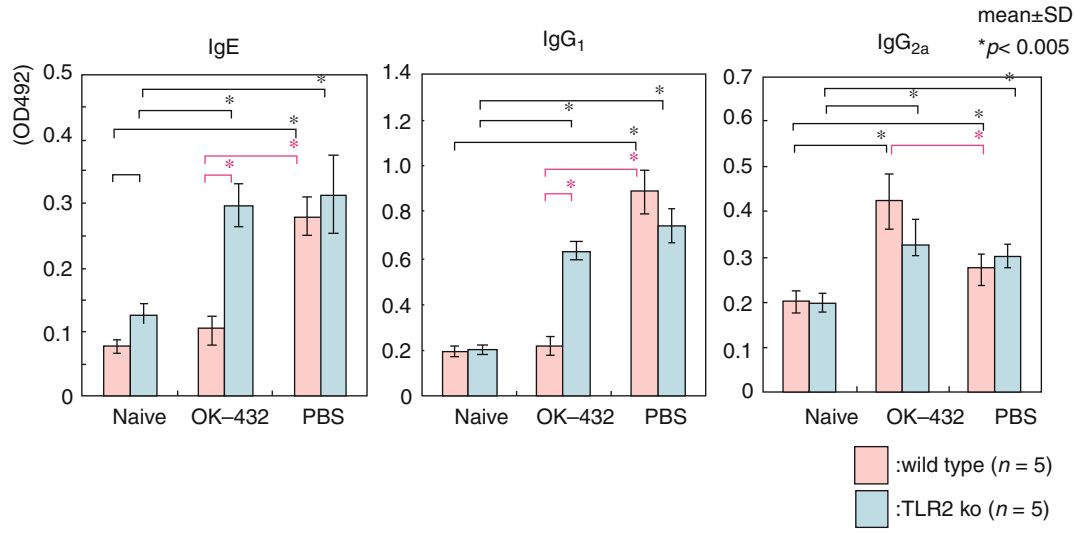


Fig. 6.6 Antigen-specific Th1 and Th2 antibody titers in sera of TLR2 knockout and wild-type mice

6.3.2 Regulatory Role of Lymphoid Chemokines CCL19 and CCL21 in the Control of Allergic Rhinitis

The lymphoid chemokines CCL19 and CCL21 are known to be crucial both for lymphoid cell trafficking and for the structural organization of lymphoid tissues such as nasopharynx-associated lymphoid tissue (NALT). However, their role in allergic responses remains unclear, and so our current study aims to shed light on the role of CCL19/CCL21 in the development of allergic rhinitis. After nasal challenge with OVA, OVA-sensitized *plt* (paucity of lymph node T cells) mice, which are deficient in CCL19/CCL21, showed more severe allergic symptoms than did identically treated wild-type mice (Nakano and Gunn 2001) (Fig. 6.8). OVA-specific IgE production, eosinophil infiltration, and Th2 responses were enhanced in the upper airway of *plt* mice. Moreover, in *plt* mice, the number of $CD4^+CD25^+$ regulatory T cells declined in the

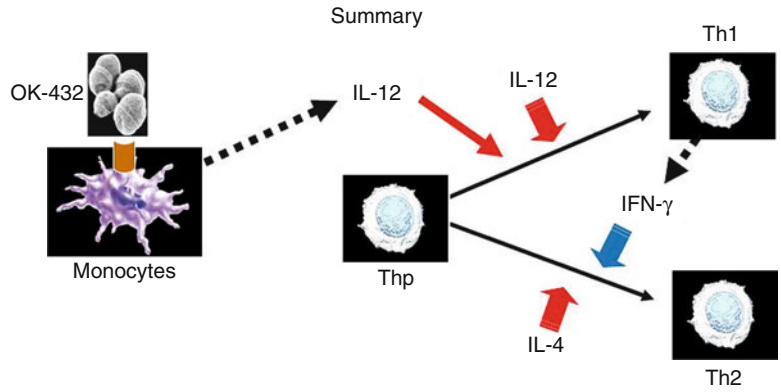


Fig. 6.7 Summary of the effect of OK-432, which is a potent Th1 inducive biological response modifiers, on the murine allergic rhinitis model. (1) OK-432 seems to induce IL-12 production from macrophages via TLR2 and activate Th1 response and consequently downregulate antigen-specific Th2 response. (2) Prophylactic treatment with like as OK-432 (Th1 inducer) may be anticipated to regulate the induction phase of type-I allergic response

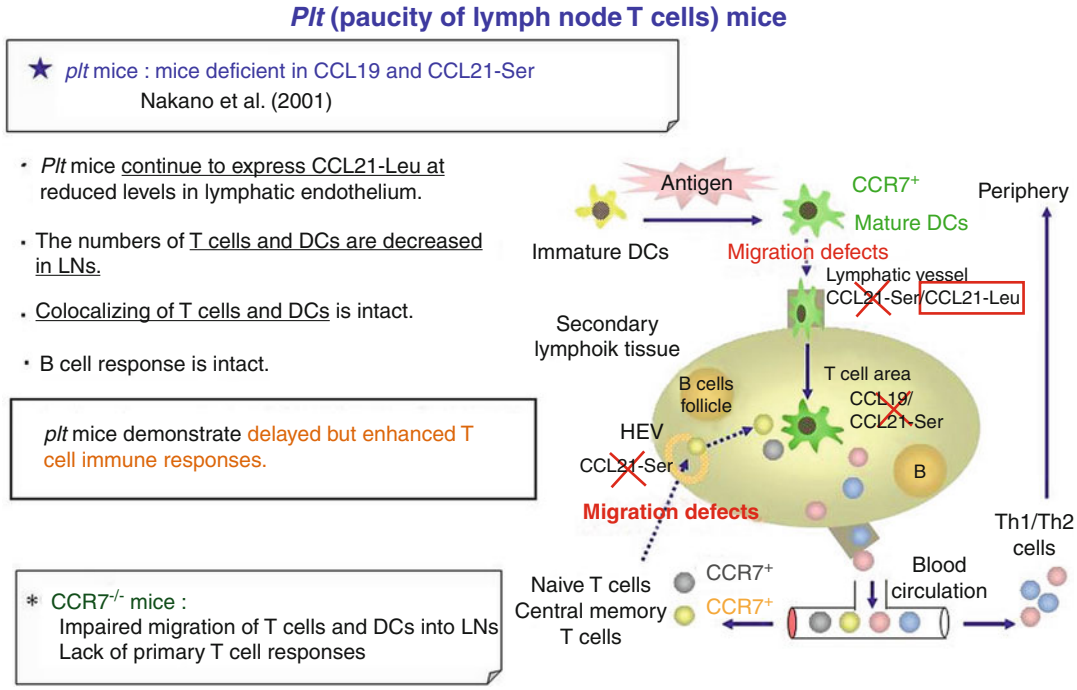


Fig. 6.8 Features of *plt* (paucity of lymph node T cells) mice

secondary lymphoid tissues, whereas the number of Th2-inducer-type $CD8^{+}CD11b^{+}$ myeloid dendritic cells (m-DCs) increased in cervical lymph nodes and NALT. Nasal administration of the plasmid-encoding DNA of CCL19 resulted in the reduction of m-DCs in the secondary lymphoid tissues and the suppression of allergic responses in *plt* mice. These results suggest that CCL19

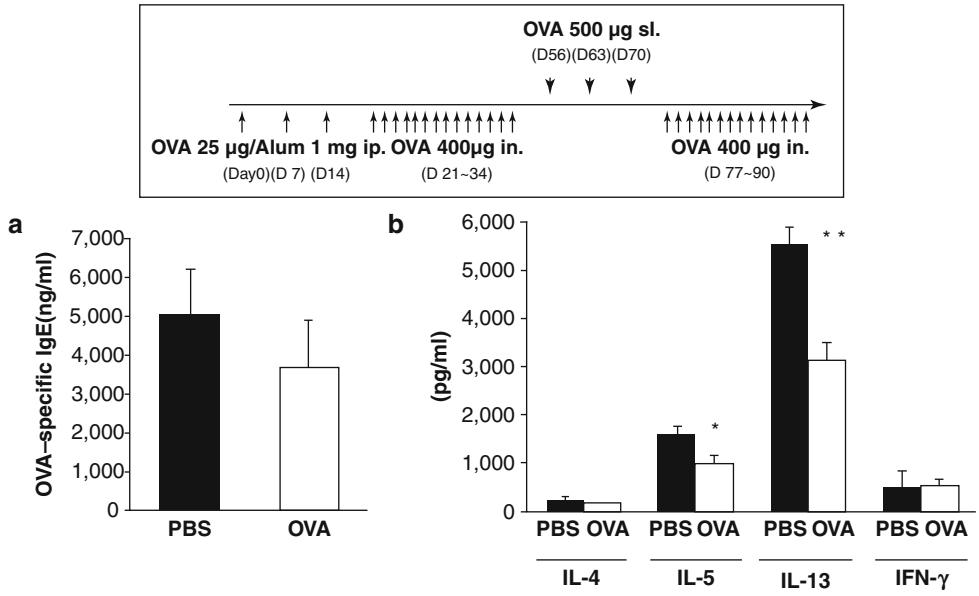


Fig. 6.9 Antigen-specific serum IgE production and Th1/Th2 profile in spleen of mice which received therapeutic sublingual OVA treatment after induction of allergic rhinitis. Mice were sublingually administered with either PBS or OVA after intraperitoneal sensitization and nasal challenges with OVA. Thereafter, the mice received consecutive nasal challenges with OVA again and examined for their allergic responses. (**a**) OVA-specific IgE levels in serum were assayed by sandwich ELISA. (**b**) Culture supernatants of $CD4^+$T cells of spleen obtained from sublingually treated mice with allergic rhinitis were assessed for Th1 and Th2 cytokine production levels by ELISA. These data are representative of two independent experiments containing three to five mice in each group. Significance was evaluated by an unpaired *t* test. $*p < 0.05$, $**p < 0.01$

and CCL21 act as regulatory chemokines for the control of airway allergic disease and so may offer a new strategy for the control of allergic disease. In a different study to focus on dendritic cells of regional lymph node, we constructed an effective murine model of sublingual immunotherapy (SLIT) in allergic rhinitis, in which mice were sublingually administered with ovalbumin (OVA) followed by an intraperitoneal sensitization and nasal challenge of OVA (Kawauchi et al. 2011). Sublingually treated mice showed significantly decreased allergic responses as well as suppressed Th2 immune responses (Fig. 6.9). Sublingual administration of OVA did not alter the frequency of $CD4^+CD25^+$ regulatory T cells (Tregs), but led to upregulation of Foxp3- and IL-10-specific mRNAs in the Tregs of cervical lymph nodes (CLN), which strongly suppressed Th2 cytokine production from $CD4^+CD25^-$ effector T cells in vitro. Furthermore, sublingual administration of plasmids encoding the lymphoid chemokines CCL19 and CCL21-Ser DNA together with OVA suppressed allergic responses (Fig. 6.10) (Yamada et al. 2012). These results suggest that IL-10 expressing $CD4^+CD25^+Foxp3^+$ Tregs in CLN are involved in the suppression of allergic responses and that CCL19/CCL21 may contribute to it in mice received SLIT (Figs. 6.11a–c).

To summarize our recent data, the important regulatory role of macrophage or dendritic cells and their interaction with T cells in nasal mucosa and its regional lymphoid organ are extensively demonstrated in accordance with human studies on these cells. However, further extensive basic and clinical research is required for pursuing the ideal treatment strategy.

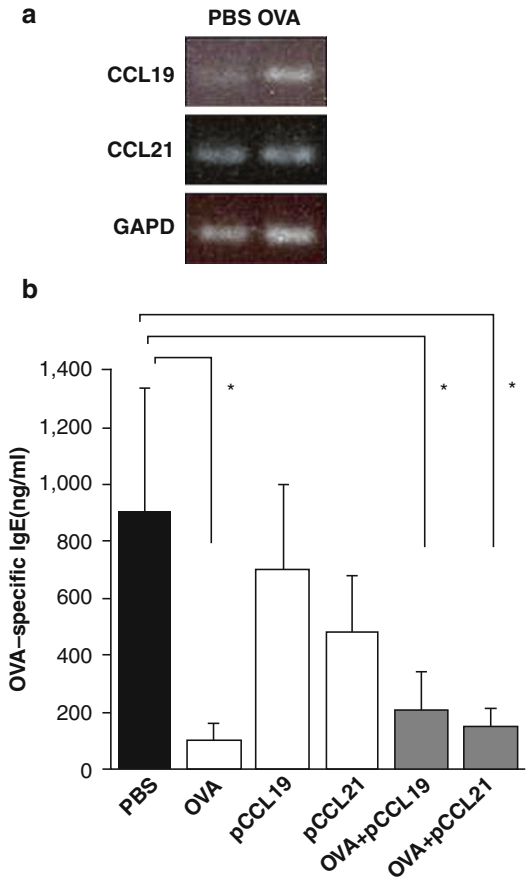
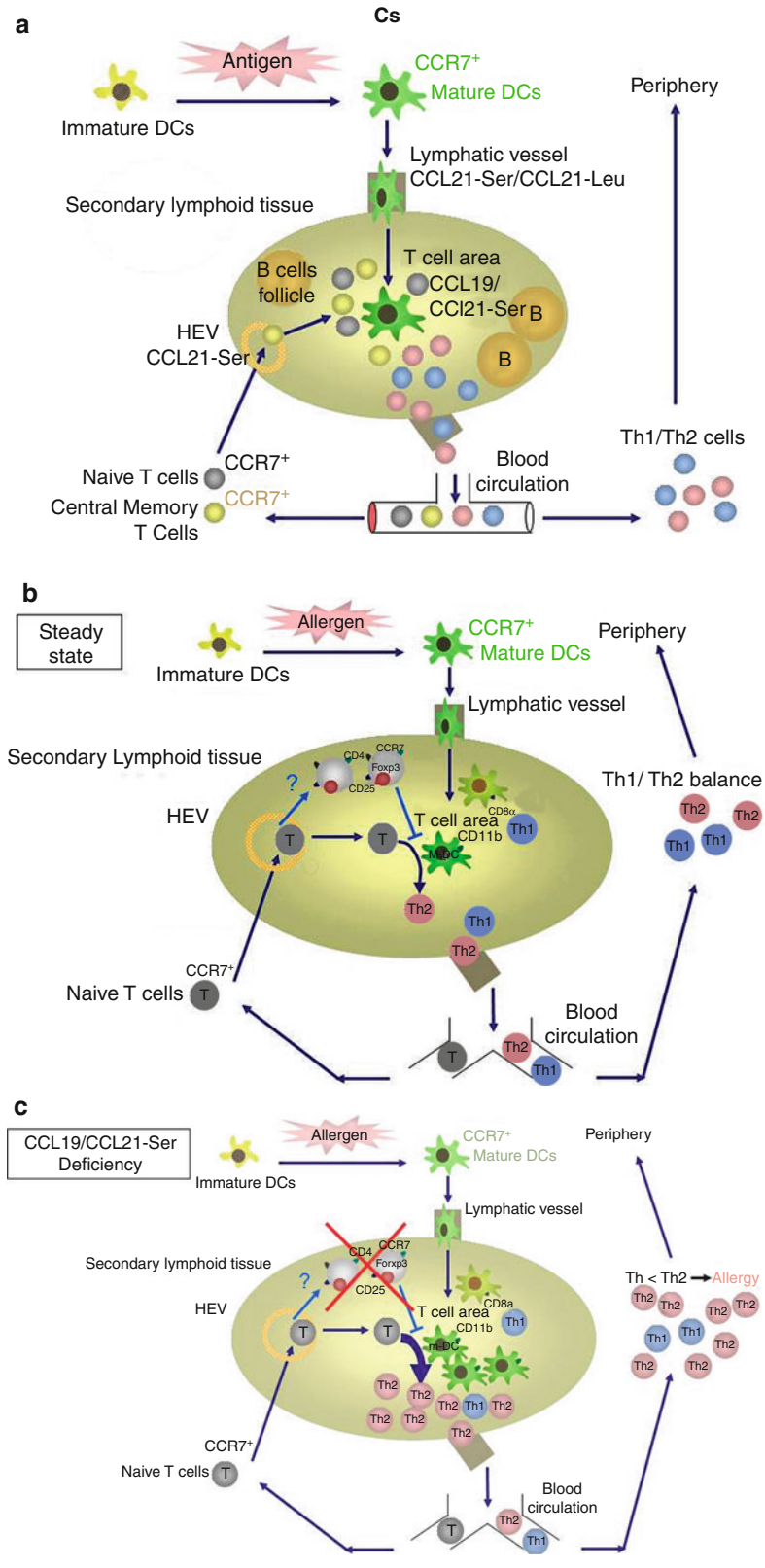


Fig. 6.10 Chemokine expression in CLN of sublingually treated mice and the effect of sublingual administration of pCCL19/pCCL21 with antigen on Th2-mediated allergic responses. (**a**) Semiquantitative RT-PCR was performed to assess mRNA expression pattern of chemokines, CCL19 and CCL21 in whole cells isolated from CLN of mice sublingually treated with either PBS or OVA. (**b**) Mice were sublingually administered with either PBS, OVA alone, 100 mg of pCCL19 together with OVA, and 100 mg of pCCL21 with OVA for total three times before systemic sensitization and nasal challenge. OVA-specific IgE levels in serum were assayed by sandwich ELISA

Fig. 6.11 (**a**) Chemokine receptor CCR7 and its ligands CCL19 and CCL21 are involved in the chemotaxis of T cells and DCs. (**b**) In steady state, naturally occurring Tregs have inhibitory effects to the interaction of naïve T cells and m-DCs for the suppression of excessive Th2 differentiation to inhaled allergen. (**c**) The deficiency of CCL19/CCL21 somehow inhibits the accumulation of Tregs, which work as suppressor of Th2 environment induced by m-DCs in the secondary lymphoid tissues, resulted in the establishment of Th2-dominant allergic disease


a
Cs
Antigen
CCR7+
Mature DCs
Periphery
Immature DCs
Lymphatic vessel
CCL21-Ser/CCL21-Leu
Secondary lymphoid tissue
T cell area
CCL19/
CCl21-Ser
B cells
follicle
B
B
HEV
CCL21-Ser
Th1/Th2 cells
Naive T cells
CCR7+
Blood
circulation
Central Memory
T Cells
CCR7+
b
Steady
state
Allergen
CCR7+
Mature DCs
Periphery
Immature DCs
Lymphatic vessel
Secondary Lymphoid tissue
CD4
CCR7
Foxp3
CD25
Th1/ Th2 balance
HEV
T cell area
CD8α
CD11b
Th1
m-DC
Th2
Th1
Th2
CCR7+
Naive T cells
Blood
circulation
c
CCL19/CCL21-Ser
Deficiency
Allergen
CCR7+
Mature DCs
Periphery
Immature DCs
Lymphatic vessel
Secondary lymphoid tissue
CD4
CCR7
Foxp3
CD25
Th < Th2
Allergy
HEV
T cell area
CD8a
CD11b
Th1
m-DC
Th2
CCR7+
Naive T cells
Blood
circulation

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The Neutrophil and Chronic Rhinosinusitis

7

Martin Y. Desrosiers and Shaun J. Kilty

Keywords
Chronic rhinosinusitis • CRS • Neutrophils • Neutrophilic inflammation • Neutrophil extravasation traps • Inflammation • Pathophysiology of CRS • Upper airway • Sinus physiology • Sinus

Core Messages

- Chronic rhinosinusitis (CRS) is a complex heterogeneous inflammatory disease that has traditionally been characterized as primarily "eosinophilic" in nature but in which contributions from other cell types may lead to different sub-phenotypes of disease.
- Neutrophils are key inflammatory cells in the immune response, and while their role is less well understood in CRS, it may nevertheless be significant
- A better understanding of neutrophilic inflammation in CRS could lead to the development of new therapeutic strategies for CRS.

Descriptions of chronic rhinosinusitis (CRS) are frequently characterized by references to the eosinophilia present in CRS and in allergic diseases. However, the focus in assessment of inflammation in chronic rhinosinusitis is increasingly shifting away from Th2-dominated mechanisms to a consideration of the contributions by Th1 and Th17 mechanisms as well. This has led to an increased focus of interest in assessment of lymphocyte subpopulations and of cytokines associated with these inflammatory pathways.

Throughout this, the neutrophil, a somewhat ubiquitous inflammatory cell associated with both Th1 and Th17 patterns of inflammation, has been somewhat ignored. In this chapter,

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we review the structure and function of the neutrophil and review evidence for its potential implication in chronic rhinosinusitis.

7.1 Histologic Description

Neutrophils are the most abundant leukocyte in humans representing up to 60% of the circulating white blood cells. It is a member of the family of granulocytes, which also includes basophils and eosinophils. Neutrophils are considered an essential component of the innate immune system by virtue of their multiple actions in bacterial killing and sequestration. Neutrophils cause microbial death by three means: phagocytosis, by generating neutrophil extracellular traps (NETs), and through the release of soluble antimicrobials from their primary and specific granules (Brinkmann and Zychlinsky 2012).

Neutrophils derived their name from their differential response in staining from other granulocytes with hematoxylin and eosin or wright's Giemsa staining. Eosinophils intensely capture eosin, giving them their characteristic appearance under the microscope. The abundant azurophilic granules of the basophils give them a bluish hue. The neutrophil is instead characterized by the neutral aspect of its cytoplasmic staining and its multiply segmented nucleus (Fig. 7.1).

Neutrophils have a diameter of 12–15 μm. In circulating blood, neutrophils are in a quiescent, or resting state, and have a vaguely circular form. However, when activated, the shape changes, with the cell becoming more amoeba-like, with pseudopods extending in search of antigens.

The granules present in neutrophils contain a number of substances with either bactericidal or proteolytic actions. Primary (azurophilic) granules typically contain the bactericidal enzymes defensins and cationic proteins. They also contain proteolytic enzymes, cathepsin G, lysozyme, and myeloperoxidase. The specific (secondary) granules contain lysozyme, lactoferrin, as well as compounds involved in the formation of toxic oxygen species (Hager et al. 2010).

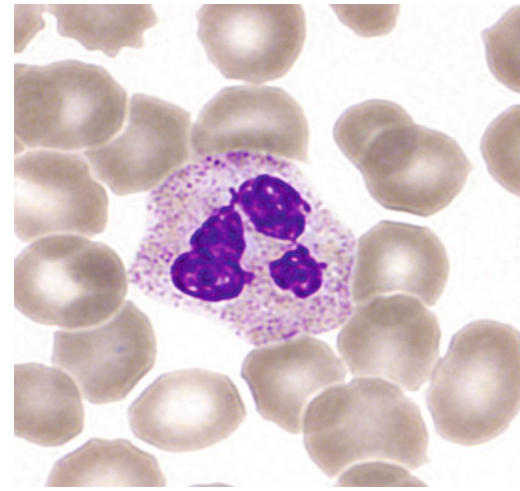

Fig. 7.1 Neutrophil on blood smear, Wright's Giemsa stain. Original magnification 100×oil immersion. Note the characteristic multi-segmented nucleus and mostly lilac-staining specific (secondary) granules and a few azurophilic primary granules. Surrounding cells are mature erythrocytes (Credit: Ruth F. Padmore MD, FRCPC, PhD, Ottawa, Canada)

7.2 Hematologic Progenitors

As granulocytes, neutrophils share their origins with basophils and eosinophils. These are derived from progenitor cells in the bone marrow and then differentiate through myelocytes into promyelocytes and then into the final differentiated cell.

Neutrophils have a relatively short half-life, up to 6 days. This is believed both to prevent the spread of pathogens that may parasitize within neutrophils to facilitate survival and dispersion and also to limit local tissue damage caused by the intense antibacterial activity of the neutrophil in a tissue.

7.3 Physiology and Function

Neutrophils are principally responsible for bacterial killing, which they enact through a variety of mechanisms. Prior to serving this role, neutrophils are primarily present in the circulation in an inactivated form. They then migrate into target tissues to exert their effects following activation by a variety of proinflammatory signals.

The transit from bloodstream to tissue begins with a process called diapedesis. This leukocyte extravasation process occurs when the activated neutrophil approaches the periphery of the blood vessel and then becomes attached to and migrates through the blood vessel wall in a process called diapedesis. This involves an interaction with receptors called intracellular adhesion molecules (ICAMs) and various selectins and integrins.

Arrived at the site of infection, the neutrophil exerts its antibacterial action through the following mechanisms:

1. Phagocytosis and killing of pathogens
2. Neutrophil extracellular trap (NET)
3. Protease digestion through the release of granule contents

The activated neutrophil can phagocytose bacteria by engulfing them and killing them within the cell through the generation of toxic substances. This process called the "oxidative burst" creates a high concentration of reactive oxygen species (ROS) through a process involving NADPH oxidase activation and the creation of superoxide dismutase (SOD). Through several steps, this leads to the production of hypochlorous acid (HClO), which may be bactericidal in itself and/or lead to the activation of the necessary proteases (van den Berg and Kuijpers 2011).

More recently, a role for extracellular trapping and killing of bacteria by neutrophils has been described by the formation of "extracellular NETs." In this mechanism, neutrophils secrete a mesh composed of DNA and various proteins outside the neutrophil, which serves to trap and destroy bacteria (Fig. 7.2). This may also limit the propagation of infection as well. NETs which form intravascularly are responsible for many of the clinical manifestations of sepsis.

The neutrophil also plays a role in limiting potentially negative effects of inflammation through the secretion of various serine proteases. The most well known of these is alpha-1-antitrypsin, which serves to limit the extent of damage caused by neutrophil elastase released from granules in tissue. Individuals with low levels of alpha-1-antitrypsin may have inordinate responses to trauma. In smokers, this may lead to the development of emphysema.

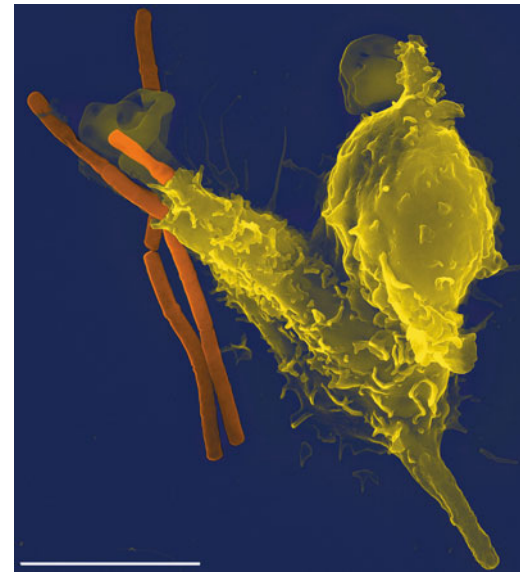

Fig. 7.2 Neutrophil extravasation trap (NET). In this scanning electron microscope image, an Anthrax bacteria (*orange*) is being engulfed by a single neutrophil (*yellow*), by generation of a NET (By Volker Brinkmann [CC-BY-2.5 (http://creativecommons.org/licenses/by/2.5)], via Wikimedia Commons)

7.4 Implication in Disease

Low levels of circulating neutrophils, or neutropenia, may occur from genetic causes or from infectious or toxic causes, one of which the most familiar is chemotherapy. Individuals with neutropenia are particularly susceptible to infection by bacterial pathogens.

The neutrophil may also be involved primarily in inflammatory diseases. Familial Mediterranean fever is a relapsing disorder where individuals present with bouts of acute inflammation characterized by hyperthermia, arthralgia, and peritonitis. Due to a dysfunction in the MEFV gene, individuals have a reduced amount or structural malformations of a protein called pyrin which makes up part of the cytoskeleton of leukocytes. Pyrin abnormalities lead to defective inflammation regulation and, subsequently, to inappropriate or prolonged inflammatory activity (Savic et al. 2012). It is a disorder not directly linked to neutrophil level, but rather to function, as described for alpha-1-antitrypsin deficiency above.

7.5 Implications in Respiratory Disease

While interest in the role of granulocytes in the development of chronic respiratory disease has principally focused upon the role of the eosinophil in the pathogenesis of asthma, evidence is increasing to support a role of the neutrophil in the development of both asthma and chronic obstructive pulmonary disease.

Assessment of a large cohort of individuals with hard-to-treat asthma has identified phenotypes characterized by neutrophilic inflammation in expectorated sputum. This has led to a consideration of neutrophilia in the pathogenesis of steroid resistance in asthma (Gibson et al. 2001; Moore et al. 2010).

The neutrophil has also been implicated in chronic obstructive pulmonary disease. Apart from alpha-1-antitrypsin deficiency, as mentioned above, neutrophil elastase has been shown to be increased in individuals with COPD (Foreman et al. 2012). This is even more pronounced in individuals with COPD and also presenting symptoms of bronchitis. Experimental evidence implicating the neutrophil in COPD exists (Moore et al. 2010). It has also been demonstrated that the administration of aerosolized neutrophil elastase in mice leads to rapid damage to the surface epithelium with loss of ciliated respiratory, mucosa, and a resultant mucosal hyperplasia (Voynow et al. 2004).

7.6 Implication in CRS

As for lower respiratory tract disease, interest in the inflammation in CRS has focused mainly on Th2-mediated inflammation due to the postulated importance of the eosinophil, and therapeutic strategies have focused mainly on the Th2 axis. However, an increasing body of work is emerging to suggest that the neutrophil may play a role in the development of CRS in a subpopulation of patients with this disorder.

The first attention to neutrophils in CRS was derived by reports of predominant neutrophilia in nasal polyps from Asian subjects and in patients with cystic fibrosis (Wen et al. 2012; Rowe-Jones et al. 1997). However, later reports have demonstrated pronounced heterogeneity in these groups, with both high-neutrophil and low-neutrophil subgroups being present. Interestingly, a focus on differences between Asian and Caucasian neutrophils in polyps has identified the existence of two groups, one roughly characterized by high IL-5 levels and second by a predominantly Th1/Th17 activation pattern (Ba et al. 2011).

Work in our laboratory with cultured sinus epithelial cells harvested from CRS patients and controls without CRS has identified a molecular signature with high spontaneous inflammation present in only a subgroup of CRS cells. Interestingly, simultaneously obtained biopsy specimens from patients where cultures were obtained show similar levels of tissue eosinophilia in both populations. However, neutrophilic infiltrate is present in only the group with the high-inflammation molecular expression signature.

7.7 Therapeutic Implications

Implications for the importance of this finding are characterized by recent studies outlining poor prognosis and lesser response to steroid therapy in individuals with "neutrophilic" CRS. In a study from Brazil, Valera et al. (2010) report that high NFkB activation, a characteristic feature of Th1 axis activity, results in a poorer response to steroids and a rapid recurrence of disease.

The impact on response to therapy has also potential importance, as a Chinese group recently identified a lesser response to oral steroids in individuals with neutrophilia on biopsy of their nasal polyps. In a similar direction, Al-Mot et al. (2011) identified a predominant neutrophilia in the sinus pathology of post-ESS patients who demonstrated a poor response to topical steroid irrigations, whereas patients whose polyps had a low neutrophil level had a favorable response to topical steroid therapy.

7.8 Summary

Taken together, these findings suggest that the neutrophil may play an important role in the subgroup of patients with a "neutrophil" predominant

phenotype of CRS. New methods for recognizing the presence of this disease will be important, as this "neutrophil" phenotype is independent of currently used clinical phenotypic markers, the presence or absence of nasal polyposis. This may require novel diagnostic approaches to tailor therapy to individual disease status.

Lastly, recognition of the potential importance of this subgroup may require a different therapeutic approach than has been employed to date for "routine" CRS, possibly requiring the use of alternative, nonsteroid-based anti-inflammatory treatments for the management of disease in these individuals.

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The Role of Eosinophils in Rhinologic Diseases

8

Jens Ponikau, Hirohito Kita, and David A. Sherris

Keywords
Eosinophil • Innate and Acquired Immunity • Chronic Rhinosinusits • Sinusitis • Major Basic Protein (MBP)

Core Messages

- In rhinology, eosinophils are important effector cells in allergic rhinitis (AR) and chronic rhinosinusitis (CRS).
- Eosinophils show different activation and degranulation pattern in AR versus CRS.
- In CRS, eosinophils do not degranulate in the tissue but in the mucus.
- Eosinophils release toxic and damage inflicting major basic protein in CRS, but not AR.

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8.1 Introduction

The eosinophil granulocyte, although likely first observed by Wharton Jones in 1846 in unstained preparations of peripheral blood, was so named by Paul Ehrlich in 1879 because of the intense staining of its granules with the acidic dye eosin (Gleich and Adolphson 1986). Since that time, the eosinophil has been the subject of extensive investigation. Its occurrence in such disparate conditions as parasitic infections, presumably for the benefit of the human host, and hypersensitivity diseases, perhaps to the detriment of the patient, although paradoxical, has become better understood as a consequence of newer information. Eosinophils are resident and nonpathologic in various organs such as gastrointestinal tract and mammary glands, and they may play roles in tissue and immune homeostasis of these organs.

However, eosinophils are strikingly absent in the nose and paranasal sinuses in healthy individuals, which is in contrast to their presence in three distinct rhinologic diseases:

1. Chronic rhinosinusitis (CRS)
2. Allergic rhinitis (AR)
3. Upper respiratory viral infection (common cold)

In addition, nonallergic rhinitis with eosinophilia (NARES) has been described as a syndrome. However, it is poorly defined only as lack of

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detectable IgE combined with evidence of eosinophils present in the nasal cavity. Coupled with the understanding that CRS is not limited to the sinuses but usually also involves the nasal cavity (and consequently the terminology change from chronic sinusitis to chronic rhinosinusitis) and the similarity of symptoms, no evidence exists to distinguish NARES from a mild or early stages of CRS, and for the purpose of this chapter is treated as such.

In the above immune responses, eosinophils are recruited into the sites of inflammation where they produce an array of cytokines and lipid mediators and release toxic granule proteins. These molecules may regulate immune response, cause tissue damage, and facilitate tissue repair. Eosinophils can also present antigens to naïve and memory T cells and initiate/amplify antigen-specific immune responses. This review summarizes the biological and immunological properties of eosinophils and discusses the roles of eosinophils applied in the field of rhinology.

8.2 Eosinophils at Baseline Condition

8.2.1 Eosinophils Are Resident in Several Tissues at Baseline Condition

The life cycle of the eosinophil is divided into bone marrow, blood, and tissue phases. Eosinophils are produced in bone marrow from pluripotential stem cells. The stem cells differentiate into a progenitor, which is capable of giving rise to mixed colonies of basophils and eosinophils, pure basophil colonies, or pure eosinophil colonies. Among various hematopoietic factors, those important for eosinophil proliferation and differentiation are interleukin (IL)-3, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-5. IL-3 and GM-CSF are relatively nonspecific and stimulate proliferation of neutrophils, basophils, and eosinophils. In contrast, IL-5 potently and specifically stimulates eosinophil production (Sanderson 1992).

Although the eosinophil is a formed element of the peripheral circulation, it is primarily a tissue-dwelling cell. In healthy individuals, most eosinophils are found in the gut (but not in the esophagus), mammary gland, uterus, thymus, and bone marrow; the gastrointestinal eosinophil is the predominant population of eosinophils (Mishra et al. 1999). At baseline condition, eosinophils are present in the gastrointestinal tract independent of adaptive immunity and enteric flora, and the eosinophil levels are regulated by the constitutive expression of eotaxin-1 and eosinophil chemokine receptor, CCR3 (Humbles et al. 2002; Pope et al. 2005). Eosinophils also home into the thymus, mammary gland, and uterus, as controlled by eotaxin-1 (Gouon-Evans et al. 2000).

As mentioned above, the eosinophil is absent in the nose and paranasal sinuses and only present in disease stages, suggesting a crucial role as an effector cell in the above diseases.

8.3 Immunoregulatory Roles of Eosinophils

Previously, eosinophils have been considered an end-stage effector cell. However, accumulating evidence suggests that eosinophils can perform various immune regulatory functions likely through presentation of antigens and production and release a range of cytokines and other immunomodulatory molecules.

8.3.1 Eosinophils Present Antigens

Eosinophils possess the ability to internalize, process, and present antigenic peptides within the context of surface-expressed receptors. It also has the capacity to provide costimulatory signals to T cells through surface expression of molecules such as CD80, CD86, and CD40 and ability to physically interact with CD4+ T cells (Spencer and Weller 2010). Similarly, following airway allergen challenge of mice, eosinophils traffic to and accumulate within draining lymph node, where they upregulate MHC II, CD86, and CD54 (Duez et al. 2004). Murine eosinophils process and present antigen to T cell clones and hybridomas (Del Pozo et al. 1992) and to

antigen-primed and naïve CD4+ T cells in vitro (Padigel et al. 2006). In humans, although circulating eosinophils from healthy donors are generally devoid of surface MHC II expression, they are induced to express MHC II (Lucey et al. 1989) and costimulatory molecules (Celestin et al. 2001; Ohkawara et al. 1996) with appropriate cytokine stimulation and after transmigration through endothelial cell monolayer (Yamamoto et al. 2000).

8.3.2 Production of Cytokines and Other Immunomodulatory Molecules by Eosinophils

Eosinophils are a source of a number of regulatory or proinflammatory cytokines and chemokines (Hogan et al. 2008; Moqbel and Lacy 2000). For example, eosinophils produce cytokines, which are able to act on eosinophils themselves, the so-called "autocrine" cytokines, including IL-3 and GM-CSF (Kita et al. 1991; Moqbel et al. 1991). Eosinophils from CRS patients with nasal polyps also express TGF-β1, suggesting that TGF-β1 synthesis by eosinophils may contribute to the structural abnormalities of nasal polyps, such as stromal fibrosis and basement thickening (Ohno et al. 1992). Indeed, eosinophil-derived TGF-β enhances proliferation and collagen synthesis of lung and dermal fibroblasts (Levi-Schaffer et al. 1999). TGF-α produced by cytokine-activated eosinophils increases mucin production by airway epithelial cells (Burgel et al. 2001). Thus, a number of evidence exists to demonstrate the ability of eosinophils to influence the tissue cells, leading to remodeling of tissues and changes in their physiological properties (e.g., hyperreactivity to exogenous stimuli).

By producing cytokines and chemokines, eosinophils may modulate the functions of other immune cells. Human eosinophils can produce IL-4 (Moqbel et al. 1995; Nakajima et al. 1996), and IL-4 protein has been localized to eosinophils in airway (Nonaka et al. 1995) and skin (Moqbel et al. 1995) tissue specimens from patients with IgE-mediated allergic diseases. Furthermore, when stimulated with eotaxin (CCL11) or RANTES (CCL5), human eosinophils rapidly release stored IL-4 by vesicular transport to the local milieu (Bandeira-Melo et al. 2001). Thus, eosinophils can provide a strikingly wide variety of cytokines and chemokines, suggesting that eosinophils are potentially involved in diverse biological responses, from tissue remodeling to activation of resident and infiltrating immune cells.

In addition to producing these cytokines, eosinophils secrete mediators with the potential to promote Th2-type immune responses. Another immunomodulatory factor generated by human eosinophils is one of their granule proteins, namely, eosinophil-derived neurotoxin (EDN) (see below for more details). EDN is an RNase A superfamily member, and in addition to its antiviral properties, EDN is a chemoattractant (Yang et al. 2003) and activator (Yang et al. 2004) of dendritic cells (DCs). As a consequence, EDN enhances Th2 responses through a TLR2-dependent mechanism (Yang et al. 2008).

8.3.3 Immunoregulatory Functions of Eosinophils In Vivo

The immunomodulatory functions of eosinophils in vivo are demonstrated in murine models of allergen sensitization and challenge with ovalbumin (OVA) and helminth infection. Eosinophils recruitment into the sites of Th2-type inflammation was considered previously a result of activation of adaptive immune response that produces IL-5 and eotaxins (Rothenberg and Hogan 2006). However, in vivo studies with helminth infection models revealed that an early wave of eosinophil influx into inflammation sites precedes that of lymphocytes (Sabin et al. 1996; Voehringer et al. 2004, 2006 and that it occurs even in mice deficient in adaptive immunity (Shinkai et al. 2002; Sabin and Pearce 1995). Notably, in IL-5/eotaxin double-knockout mice, in which eosinophil numbers in both blood and tissues are severely decreased, IL-13 production of Th2 cells in response to OVA challenge is attenuated. This defect in Th2 cells was restored by eosinophil reconstitution (Mattes et al. 2002), suggesting

regulation of adaptive Th2-type immune response by eosinophils.

The roles of eosinophils in asthmatic airway inflammation were subsequently addressed directly by using eosinophil-deficient animals. Both Lee et al. (2004) (Phil mice) and Yu et al. (2002) developed mice depleted of eosinophils through different genetic alteration. When sensitized and challenged with OVA, Th2-type airway inflammation and asthma-like pathology (e.g., airway hyperreactivity, airway remodeling, and mucus production) were attenuated in both mouse models, and these responses were restored by reconstitution of eosinophils alone (Walsh et al. 2008) or a combination of eosinophils and antigen-specific T cells (Jacobsen et al. 2008). Likewise, airway production of Th2 cytokines and asthma-like pathology were diminished exposed intranasally to the product of fungus *Aspergillus fumigatus* (Fulkerson et al. 2006). This demonstrates that eosinophils are necessary to induce the pathophysiological changes associated with bronchial asthma.

8.4 Effector Functions of Eosinophils

As summarized in the reviews (Gleich and Adolphson 1986; Rothenberg and Hogan 2006; Hogan et al. 2008), eosinophils contain numerous highly basic and cytotoxic granule proteins that are released upon activation. They also produce an arsenal of enzymes and lipid mediators, which are implicated in effector functions of eosinophils.

8.4.1 Granule Proteins

Human eosinophil granules contain major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), and EDN. Those proteins are located in the characteristic secondary granules of the eosinophils (Fig. 8.1a). MBP is stored in a crystalline stage, forming the characteristic rectangle core of the granule, whereas the other proteins are stored in the surrounding matrix of the granule (Fig. 8.1b). Its name is derived from the fact that MBP is the most basic protein in the humans with a pH of 11.3, and it makes up over 50 % of the entire granular protein load of the eosinophil. Human MBP binds to and directly damages and destroys the surfaces of parasites (Gleich and Adolphson 1986) and is also directly toxic to tumor cells and other mammalian cells by disrupting the integrity of lipid bilayers (Abu-Ghazaleh et al. 1992).

Human ECP is a basic neurotoxic protein, with antiviral and antiparasitic properties, and human EDN is a powerful neurotoxin that can severely damage myelinated neurons in experimental animals (Gleich and Adolphson 1986). EDN as well as ECP have antiviral activities and decrease the infectivity in RSV suspensions (Rosenberg and Domachowske 2001; Domachowske et al. 1998b). When purified eosinophils, EDN, or ECP was added to RSV viral suspensions, the viral titer is reduced, dependent on the ribonuclease activities of EDN and ECP (Domachowske et al. 1998a, b). Interestingly, ribonuclease A lacked this antiviral activity, suggesting that ribonuclease activity is necessary but not sufficient for the antiviral effects of EDN and ECP. Furthermore, in guinea pigs infected with parainfluenza, pretreatment with anti-IL-5 and reduction of eosinophils strikingly increased the viral content in the airways (Adamko et al. 1999), suggesting a potential role for eosinophils in viral immunity and explaining the influx of eosinophils in upper viral infections and the subsequent clinical relevant exacerbation of CRS and asthma during common colds.

EPO is a member of a mammalian peroxidase family. EPO is a central participant in generating reactive oxidants and radical species by activated eosinophils (Mitra et al. 2000). Eosinophil activation in vivo shows oxidative damage of proteins through bromination of tyrosine residues (Wu et al. 2000). Furthermore, eosinophils are a major source of nitric oxide-derived oxidants in specimens from patients with severe asthma (MacPherson et al. 2001).

Considerable evidence exists to link these eosinophil granule proteins and human diseases.

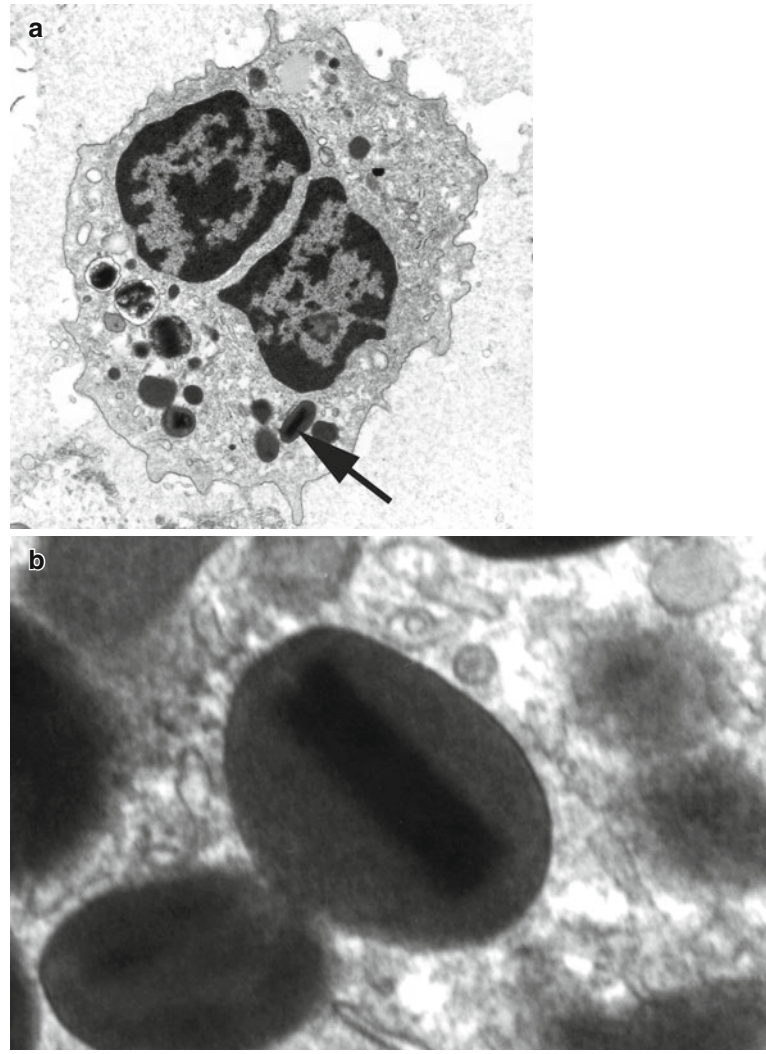

Fig. 8.1 (**a**) Electron microscopy of tissue eosinophil in CRS. Note the *black arrow* pointing to a characteristic secondary granule (transmission electron microscopy, original magnification ×7,000). (**b**) Electron microscopy of an eosinophil secondary granule with its characteristic, rectangle core, which is entirely made up out of MBP (transmission electron microscopy, original magnification ×55,000)

For example, the concentrations of MBP in the bronchial alveolar lavage (BAL) fluids from patients with asthma and from monkeys are correlated with the severity of bronchial hyperreactivity (Gleich et al. 2000, 1993). MBP has been localized to damaged sites of bronchial epithelium in patients with asthma and chronic rhinosinusitis (Gleich 2000; Ponikau et al. 2005). Instillation of human MBP and human EPO provokes bronchoconstriction, and MBP increases airway responsiveness to inhaled methacholine (Gleich et al. 2000). Interestingly, polyglutamic acid antagonizes MBP's ability to increase respiratory resistance and bronchial hyperreactivity in cynomolgus monkeys (Gundel et al. 1991), suggesting that the cationic nature of MBP contributes to the damage and physiological changes. In vitro, MBP acts as an antagonist for M2 muscarinic receptors. Many eosinophils localized close to nerves with extracellular MBP adhering to the nerves (Costello et al. 1997). Finally, neutralization of endogenously secreted MBP, either with a polyanionic peptide or with antibodies to MBP, can prevent antigen-induced bronchial hyperreactivity in guinea pigs (Costello et al. 1999). Marked deposition of free EDN is also observed in affected tissues from patients with eosinophilic esophagitis (EoE) (Kephart et al. 2010) (see Fig. 8.1). Deposition of EDN is reduced in certain patients

with EoE who are treated with anti-IL-5 antibody (Straumann et al. 2010).

Several proinflammatory enzymes have been associated with the eosinophil (Gleich and Adolphson 1986). Arylsulfatase B is located predominantly in the small granules of the eosinophil. β-glucuronidase activity in eosinophils is about twice that in neutrophils, and exposure of eosinophils to opsonized zymosan particles releases up to 24 % of the total cellular β-glucuronidase.

8.4.2 Activation of Human Eosinophils Takes Multiple Stages

In early 1980s, increased number of unusual human eosinophils with a specific gravity <1.085 g/ml (Rothenberg et al. 1988) was reported in peripheral blood of patients with eosinophilic disorders, such as hypereosinophilic syndrome (Winqvist et al. 1982) and asthma (Fukuda et al. 1985). These eosinophils, called "hypodense eosinophils," were highly reactive to stimuli and showed increased survival, adhesion, leukotriene synthesis, superoxide production, and antibody-dependent cytotoxicity as compared to "normodense eosinophils" (Lopez et al. 1986, 1988). Thus, eosinophils in human blood are not a homogenous population but represent various magnitudes of activation. It was found later that eosinophil exposure to activating cytokines, such as IL-3, IL-5, and GM-CSF, leads to development of the hypodense eosinophil.

IL-3, IL-5, and GM-CSF, besides being growth and maturation factors for eosinophils, stimulate several functions of mature human eosinophils. Among human peripheral blood leukocytes, eosinophils are the only cells having detectable levels of IL-5 receptors in agreement with the specific action of IL-5 on human eosinophils (Ingley and Young 1991; Migita et al. 1991). Other Th2 cytokines, such as IL-4 and IL-13, also activate eosinophils. IL-4 upregulates the binding of eosinophils to IgA (Bracke et al. 1997). IL-4 or IL-13 acts synergistically with TNF-α or IL-5 for increased expression of CD69.

8.4.3 Eosinophil Activation in Innate Immunity

Fully activated human eosinophils appear to defend against large, nonphagocytosable organisms, most notably the multicellular helminthic parasites and fungi. Some of the mechanisms used by eosinophils in host defense against these organisms may also produce detrimental effects on the host. Several lines of evidence have indicated that bacterial and/or viral infections may exacerbate allergic inflammation. Direct activation of eosinophils by microbe-derived molecules may explain the mechanism.

Importantly, eosinophils are activated by a natural cysteine protease from mite allergens, *Der f 1*, and release their granule proteins (Miike and Kita 2003). Eosinophils also recognize the aspartate protease activity and cysteine protease activity that are produced by fungus *Alternaria alternata* (Matsuwaki et al. 2009) and cockroaches (Wada et al. 2010), respectively, and they release granule proteins and cytokines. Thus, human eosinophils are equipped with machineries that recognize and respond to proteases, such as those found in microbes and at allergic response sites, resulting in active release of proinflammatory mediators.

An association between fungal exposure and asthma has been widely recognized (Bush and Prochnau 2004). Moreover, exposure to *Alternaria* is a risk factor for respiratory arrest in patients with asthma (O'Hollaren et al. 1991). These airborne fungi and their products may contribute to the development and exacerbation of allergic airway diseases. For example, fungal products, e.g., proteases, induce immunological and inflammatory reactions, resulting in a Th2-like cytokine response and the destruction of mucosal barrier functions (Kheradmand et al. 2002). Extracts of *Alternaria* potently induces eosinophil degranulation (Inoue et al. 2005). *Alternaria* also strongly induces other activation events in eosinophils, including increases in intracellular calcium concentration, cell surface expression of CD63 and CD11b, and production of IL-8. Interestingly, *Alternaria* does induce neutrophil activation, suggesting specificity for

fungal species and cell type. In addition, when human eosinophils are exposed to live *Alternaria alternata* fungus, eosinophils release their cytotoxic granule proteins into the extracellular milieu and onto the surface of fungal organisms and kill the fungus in a contact-dependent manner (Yoon et al. 2008). Eosinophils do not express common fungus receptors, such as dectin-1, but use their versatile β2 integrin molecule, CD11b (see below for more details), to recognize and to adhere to a major cell wall component, β-glucan.

The role of IgE in mediating eosinophil activation is controversial. Eosinophils isolated from patients with eosinophilia degranulated in response to anti-IgE antibody or IgE-coated parasites (Kita et al. 2003; Moqbel et al. 1990). Eosinophils can potentially express three types of IgE receptors, the low-affinity IgE receptor, lectin-type IgE-binding molecule (Truong et al. 1993), and high-affinity IgE receptor. It has been claimed that the high-affinity IgE receptor, FcεRI, is present on eosinophils from patients with eosinophilia and that various functions of eosinophils, including degranulation and parasite cytotoxicity, are mediated through this receptor (Gounni et al. 1994). On the other hand, the number of high-affinity receptors expressed on the surfaces of eosinophils from patients with allergic diseases or airway eosinophilia was minimal or undetectable (Seminario et al. 1999), and the ligation of IgE FcεRI receptor did not result in detectable eosinophil degranulation (Kita et al. 1999).

8.5 Differences in the Eosinophilic Inflammation Between Allergic Rhinitis and Chronic Rhinosinusitis

The events and the pathophysiology of allergic rhinitis have been well understood. The inhalation of an allergen where an individual has produced corresponding, circulating IgE antibodies will cause (within 10 min) a cross-link of the IgE FcεRI receptors situated on the mast cells. This will result in an immediate degranulation and histamine release from the mast cells, resulting in histamine-mediated symptoms of sneezing, clear anterior rhinorrhea, and nasal obstruction. About 2–8 h after antigen challenge, eosinophils enter the nasal tissue as part of the so-called late-phase allergic reaction (together with further mast cells, B and T lymphocytes), leading to further nasal obstruction.

In contrast to allergic rhinitis, the early-phase immediate reaction is missing in CRS, explaining the lack of allergic rhinitis specific, histamine-related symptoms (sneezing, anterior clear rhinorrhea). Another clinical distinction between CRS and AR is that CRS can occur with or without nasal polyps, while AR never leads to nasal polyposis. While some investigators follow the notion that due to different severities in the cytokine pattern, CRS with and without nasal polyps should be viewed as two different entities, while others see it as a different spectrum of disease, with inflammatory mucosal thickening on one side of the spectrum, to gross nasal polyps on the other side. The severity of the inflammation can be easily overlooked if patients are given systemic steroids or other anti-inflammatory medication before harvesting the tissue for examination. This distinctive eosinophilic inflammation is also very heterogeneous (i.e., without eosinophilic infiltration in one area of a nasal mucosal tissue specimen, but with intense eosinophilic infiltration in another area of the same specimen) (Hamilos et al. 1998). Thus, reports in which only single biopsies are examined and in which it was unclear whether patients had received steroids before the biopsies were taken need to be interpreted carefully regarding the intensity of the eosinophilic infiltrate.

The eosinophilic inflammation in CRS occurs independently of an IgE-mediated inflammation, as evident by the fact that more than 50 % of CRS patients have no detectable IgE-mediated allergies. This in return suggests nonallergic mechanism driving recruitment, migration activation, and degranulation. Indeed, very different mechanisms have been identified.

Central to the migration of eosinophils from the vasculature into the tissue is the expression of vascular cell adhesion molecule-1 (VCAM-1), which has been identified in the vascular

endothelium in CRS patients (Rains and Mineck 2003). This expression occurred independent of any IgE-mediated allergy and explains the presence of eosinophils in allergic as well as nonallergic patients with CRS (Rains and Mineck 2003). VCAM-1 is known to specifically bind to the VLA-4 (very late-appearing antigen-4) on eosinophils, thus causing selective adhesion and migration of eosinophils from the vasculature to the sinus and nasal tissue (Rains and Mineck 2003). VCAM-1 expression is induced via either IL-4 or IL-13, which shares the same receptor on the endothelial cells. IL-4 is present and IL-13 is absent in allergic rhinitis, which is in contrast to nonallergic CRS, where only IL-13 is present in the tissue, but IL-4 is absent. In patients with CRS and allergies, both IL-4 and IL-13 are present. This cytokine pattern indicates that eosinophils are recruited via two distinct cytokines, IL-4 in AR and IL-13 in CRS; however, both diseases can coexist as CRS with allergies (comorbidity), with both Il-4 and Il-13 present.

Significantly elevated levels of IL-5, the key cytokine that mediates eosinophil differentiation, survival, and activation, are present in tissue specimens of CRS patients and AR patients, and not in those of healthy controls (Ricchetti et al. 2002; Salo et al. 2005; Sanchez-Segura et al. 1998, 2000; Shin et al. 2004; Simon et al. 1997). A majority of the IL-5 staining cells are lymphocytes (68 %), followed by eosinophils (18 %) and mast cells (14 %) (Taylor et al. 2002). The exact combination of source cells for IL-5 in AR is not known. While many different allergens can lead to the release of IL-5 in AR via the IgE-mediated pathway in AR, a trigger for the nonallergic production of IL-5 in CRS was unknown.

Recently, Shin et al. (2004) demonstrated that certain molds induced the elevated production of IL-5 in isolated peripheral blood mononuclear cells (PBMCs), which contained lymphocytes and other cells that can serve as antigen-presenting cells from 16 out of 18 CRS patients stimulated with Alternaria antigens. More importantly, PBMCs from none of the 15 healthy controls did produce elevated IL-5 levels (Shin et al. 2004). PBMCs from allergic and nonallergic CRS patients produced similar amounts of IL-5, indicating that this reaction is independent from an IgE-mediated allergic reaction (Shin et al. 2004). In addition, PBMCs from CRS patients stimulated with either Cladosporium (6/18) or Aspergillus (4/18) antigens also show increased production of IL-5; no response is seen with Penicillium antigen (Shin et al. 2004).

But not only IL-5 was produced by the CRS patients' immune cells in response to Alternaria. The mold also induced the release of large amounts of IL-13 in all the CRS patients studied, the cytokine triggering the recruitment of eosinophils from the vasculature into the tissue in CRS. Again, not of the healthy controls were producing any detectable IL-13.

Furthermore, production of interferon-γ (IFN-γ), a Th1 cytokine which facilitates destruction of parasites by eosinophils, was 5.5 times higher in PBMCs from CRS patients stimulated with Alternaria antigen compared with production by healthy control PBMCs (Shin et al. 2004). When nasal secretions from nine healthy controls and nine CRS patients were examined, there were no differences in their levels of total Alternaria proteins (Shin et al. 2004), indicating that both groups had similar levels of Alternaria in their nasal mucus. This study was important since it was the first to demonstrate a nonallergic pathway in CRS leading to the production of the crucial cytokines for the eosinophilic inflammation. In addition, it also showed a specific trigger for the cytokine production, a common mold being present in nose of every person tested.

Recently it was shown that CRS patients exhibit severely damaged epithelium and thickened basal membrane, features of airway remodeling seen as also seen in asthma, which is in contrast to their absence in AR (Fig. 8.2a, b). It has been demonstrated that eosinophilic MBP is capable to produce those changes, and indeed MBP has been localized with the epithelial damages found in CRS (Gosepath et al. 2004; Hamilos et al. 1995). Interestingly, toxic MBP levels have measured in CRS, but free MBP could not be measured in AR mucus, explaining the damage in CRS, and its absence in AR. This suggest that MBP is released in the mucus in CRS, but not in AR.

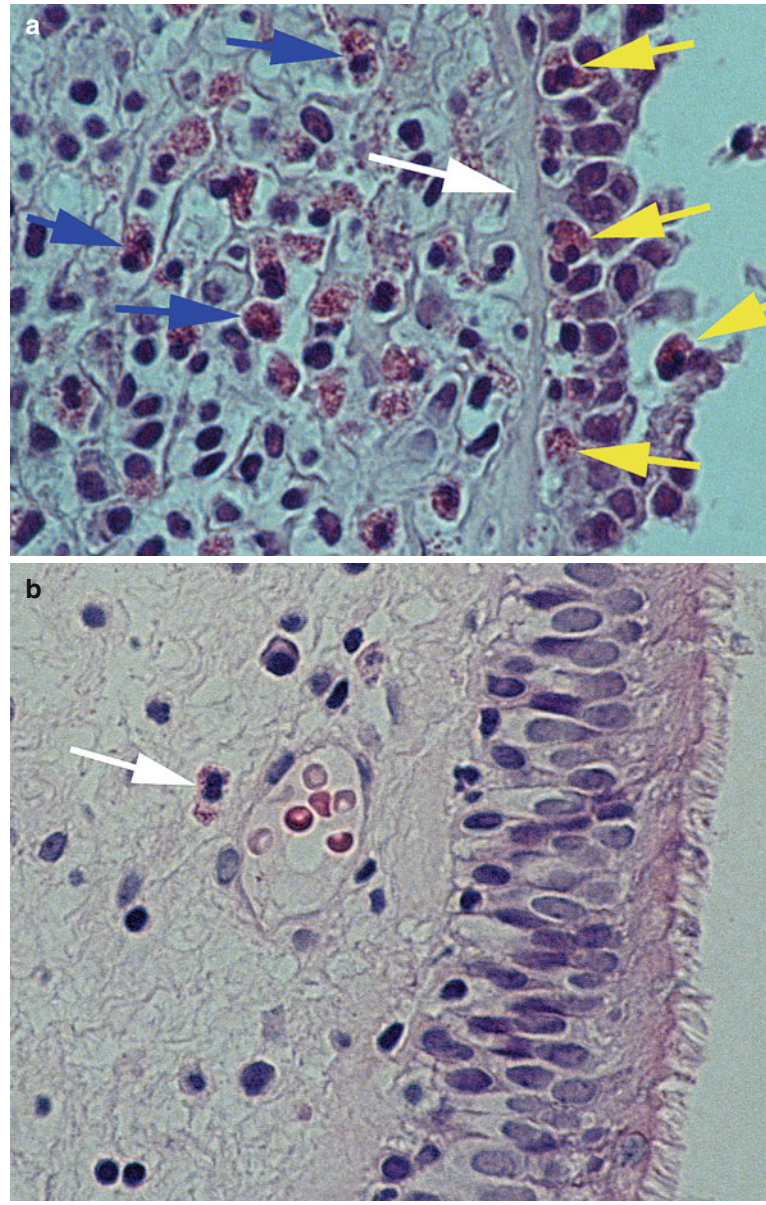

Fig. 8.2 (**a**) Tissue from CRS patient shows intact tissue eosinophils (*blue arrows*) and eosinophils traveling through the severely damaged epithelium (*yellow arrows*). Note the missing upper layers of epithelial cells and missing cilia, suggesting that the damage is inflicted from the luminal side. The *white arrow* highlights the thickened basal membrane (original magnification ×1,000, HE). (**b**)Tissue from AR patient reveals intact epithelium including cilia and scattered eosinophils (*white arrow*). Note also the absence of basal membrane thickening (original magnification ×400, hematoxylin and eosin)

Two prospectively designed histologic studies of tissue and mucus obtained during CRS surgery used extra caution to preserve the mucus. While eosinophils were intact in the tissue and in the epithelium, eosinophilic-rich mucus with clusters of aggregated eosinophils was found in 96 % (97/101) and 94 % (35/37) of consecutive CRS patients (Inoue et al. 2005; Kita et al. 2003). Another study demonstrated that eosinophils released their toxic MBP in the mucus within these clusters, and not in the tissue (Hamilos et al. 1996). Estimated concentrations of MBP within the clusters, based on digital analysis of the intensity of the MBP staining, were as high as 2 mM and exceeded those capable of mediating epithelial damage. Overall, the clusters of eosinophils and intense eosinophil degranulation in the mucus suggest that eosinophils merely travel through the CRS tissue to the mucus (Fig. 8.3a, b).

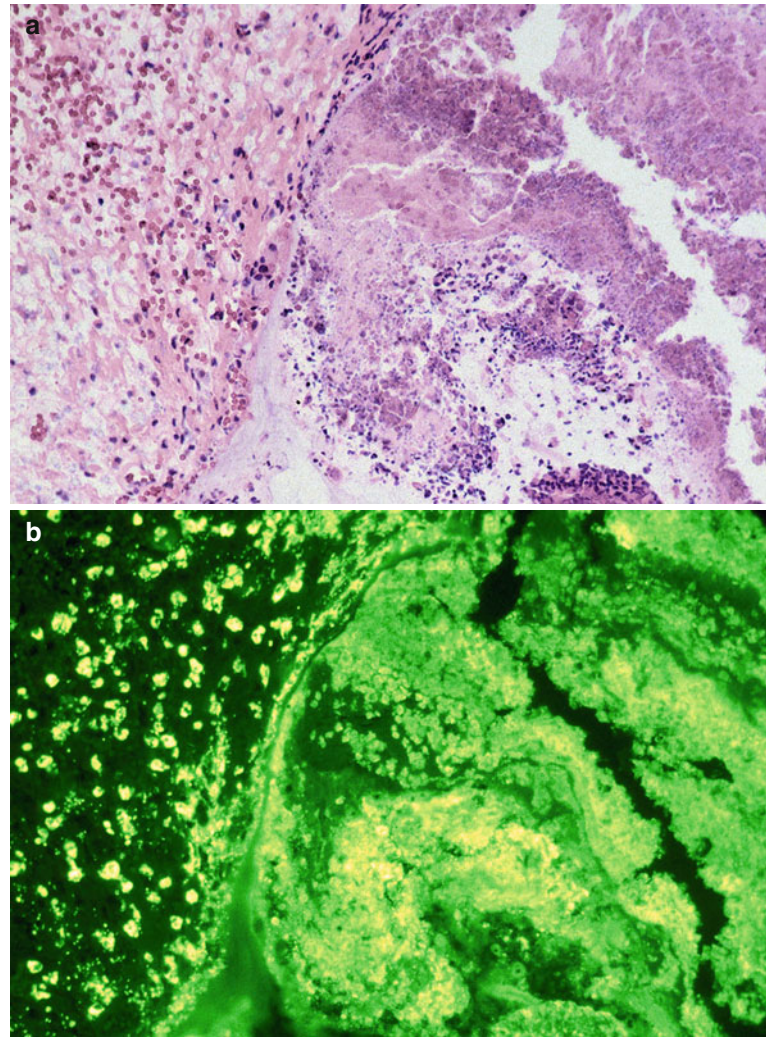

Fig. 8.3 (**a**) CRS tissue and attached eosinophilic mucin shows massive eosinophilic migration of eosinophils from the tissue (*left side of the image*) into the mucus (*right side of the image*). The mucus contains large sheets (clusters) of eosinophils and eosinophilic debris (original magnification ×400, HE). (**b**) Serial section of 2a with immunofluorescent staining with an antibody against MBP reveals intact eosinophils in the tissue (*left side of the image*) and free eosinophil granules. In contrast, once the eosinophils have reached the mucus, MBP is diffusely release in toxic concentrations. Note that MBP staining reaches brightness in the mucus exceeding the one inside the intact tissue eosinophils, indicating continues deposition of free MBP into the same eosinophilic clusters in the mucus (original magnification ×400, anti-MBP)

These in vivo observations explain the patterns of damage in CRS, where only the outer layers of tissue are damaged (Fig. 8.2a, b), suggesting that the damage to the epithelium is inflicted from the outside (luminal side). This epithelial damage may predispose CRS patients to be susceptible for the secondary bacterial infections, leading to acute exacerbations, which are observed clinically and absent in AR. Because bacteria typically elicit a neutrophilic inflammation, these acute exacerbations of CRS are presumed to be of bacterial origin. However, the underlying eosinophilic inflammation that predominates in CRS is unlikely to be caused by bacterial infection, suggesting a nonbacterial etiologic mechanism for CRS.

In a recent study, eosinophils from healthy people that were incubated with Alternaria and Penicillium antigens released significant amounts of eosinophil-derived neurotoxin (EDN), a marker of eosinophil degranulation (Weschta et al. 2004). When eosinophils from patients with asthma or allergies were used, they even released about 70 % more EDN compared to the healthy controls. The fraction from Alternaria alternata, which induced the degranulation, had a molecular weight of ≈60 kDa, was highly heat labile, and worked protease dependant through a G protein-coupled receptor, identified as β2 integrin of the CD11b receptor (Weschta et al. 2004). Other fungal antigens, including Aspergillus, Cladosporium, and Candida, did not induce

eosinophil degranulation, nor did neutrophils respond to Alternaria extracts, suggesting the presence of a fungal species and cell-type-specific novel innate immune response to certain fungi in human. Thus, both innate and acquired immune responses to environmental fungi such as Alternaria (independent of IgE antibodies to Alternaria) may increase production of the cytokines and provide cellular activation signals necessary for the robust eosinophilic inflammation in CRS patients.

8.6 Summary and Future Directions

Eosinophils fulfill distinctive and different function in CRS versus AR, although frequently overlapping clinically. Those differences presumably result in two different pathophysiological mechanisms, mainly distinguishable through the clustering of eosinophils and the subsequent release of the eosinophil-specific toxic major basic protein (MBP) into the mucus in CRS. In contrast, in allergic rhinitis, the eosinophils appear to follow more a process of a controlled cell death, without the release of toxic major basic protein (MBP) and without the subsequent epithelial damage. This difference in the degranulation patterns explains the different clinical and pathophysiological presentation between CRS and AR. Understanding the details of those mechanisms and the eosinophil's function is needed to further improve the care of patients suffering from these two eosinophilic, inflammatory diseases in rhinology.

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Nasal NO and Its Role in the Physiology of the Nose and Diagnosis

9

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Keywords
Nitric oxide • Nasal homeostasis • Pathophysiology

Core Messages

- NO is a gas primarily produced within the paranasal sinus cavities, playing a role in airway homeostasis.
- Nasal NO levels may be normal, increased, or decreased in upper airway diseases.
- Nasal NO represents a screening test for primary ciliary dyskinesia.

9.1 Introduction

Since the last decade, growing attention has been paid to nitric oxide (NO) as a noninvasive marker of inflammation of the airways. Exhaled NO (eNO) measurement has become a routine diagnostic tool in monitoring lower airway inflammation, since it had been shown to be a noninvasive parameter of monitoring lower airway inflammation (Alving et al. 1993). However, most of the NO is being produced in the sinonasal cavities, without clear insight into its precise role in upper airway homeostasis. Nasal NO (nNO) may be involved in the innate antibacterial effects of the airway mucosa, regulation of ciliary beat frequency, and/or local regulation of blood flow. In addition, nNO is believed to contribute to lower airway homeostasis. The measurement of nNO is nowadays a good screening test for primary ciliary dyskinesia and, therefore, has diagnostic value.

9.2 Nitric Oxide (NO)

Nitric oxide (NO) is a colorless and odorless gas that is present in air exhaled through the mouth or nose. NO is produced from arginine and oxygen by nitric oxide synthase (NOS) (Scadding and Scadding 2009). Constitutively expressed neuronal and endothelial forms exist as well as an induced form, iNOS, which appears to be upregulated within the respiratory tract in response to pro-inflammatory signals. NO came to prominence for its role in vasodilatation and subsequently as a neurotransmitter

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and inflammatory mediator. The role of NO in the airways is complex (Scadding 2007), possibly including antibacterial effects, pro-inflammatory effects, and regulation of blood flow and ciliary beat frequency. Exhaled NO (eNO) levels are raised in eosinophilic asthma, and measurement of this has become a standardized, but not yet widespread, tool in diagnosis and management of asthma. It can potentially provide a rapid, low-cost, objective measure of lower airway inflammation.

Far greater levels of NO are produced in the upper than in the lower respiratory tract, with major contributions from the sinuses and to a lesser extent from the nasal mucosa.

9.3 Nasal NO

Measurement of nNO represents a useful tool for research purposes as well as for screening for PCD (Scadding et al. 2011). Nasal nitric oxide may be normal, raised, or lowered in disease states. However, its measurement may be a useful tool in the diagnosis and management of patients with chronic rhinosinusitis, nasal polyps, and CF, as well as in the diagnosis of PCD (Scadding et al. 2011). Levels of nNO may follow the clinical changes after medical as well as surgical treatment in patients with CRS with/without nasal polyps (Scadding et al. 2011).

Measuring both bronchial and nasal nitric oxide may assist the combined management of upper and lower airways, but is not routinely performed in clinical practice so far.

High levels of NO are produced constitutively in normal individuals within the paranasal sinuses by calcium-independent nitric oxide synthase, with levels measured at 20–25 ppb. Additionally, nitric oxide is also formed in the nasal mucosa by inducible NOS (iNOS) in response to inflammation. NO and its metabolites are toxic to micro-organisms and likely form part of the innate defense mechanism of the respiratory tract. NO may also stimulate cilia beat frequency within the epithelium and regulate nasal vascular tone.

9.4 Technique for Measuring nNO

As for exhaled NO (eNO), nNO can also be measured by chemiluminescence, using noninvasive techniques, providing immediate results. A number of different techniques have been used to ensure sampling from the upper airways only including breath holding and breathing against resistance.

In contrast to measuring eNO, high baseline levels in nNO make background environmental NO levels less of a problem. Conversely, there is a high degree of interindividual variability amongst healthy controls. Moreover, there is also a significant degree of intraindividual variation over time, meaning that changes of 20–25 % or less may be accounted for by normal variation rather than change in disease status or response to medication (Ragab et al. 2006). Additionally, the lack of universal standardization of testing procedures means that levels recorded by different study groups vary considerably even amongst equivalent patient populations. The factors affecting eNO levels such as recent exercise or time of day may similarly affect nNO measurements. Local factors such as nasal volume and patency may also be important.

9.5 Value of nNO Measurement in Clinical Practice

Despite the above limitations, nNO has a number of potentially useful clinical applications. With regard to diagnosis, nNO is useful as a screening tool for patients with possible PCD; levels less than 100 ppb, particularly if these persist following decongestion, should stimulate investigation of mucociliary structure and function. The test is objective and may be easier to perform than a saccharine clearance test in younger children. Similarly, nNO may provide a useful tool in diagnosis of CF in the context of upper respiratory tract symptoms; levels significantly lower than in controls have been reported in some studies, but not others. nNO has a potential role in the diagnosis and assessment of CRS, especially when

associated with NP. Interestingly, despite the increased expression of iNOS in polyp epithelium, low nNO levels have been found in two large studies. Moreover, nNO inversely correlated with endoscopic NP size, CT scores, and clinical severity of disease. Conversely, in a study involving chronic rhinosinusitis patients with and without polyps, no correlation between nNO and CT scores was found, although patients were again found to have lower baseline nNO than controls.

Low nNO levels in chronic rhinosinusitis are thought to reflect obstruction at the sinus ostium and impairment of gas transfer out from the sinuses. This is supported by the finding of raised nNO following medical and surgical treatment of rhinosinusitis with or without polyps (Ragab et al. 2006).

A number of recent studies have focused on the possible use of humming to improve the sensitivity of nNO measurements. Weitzberg and Lundberg found that humming induced a large increase in nNO (Weitzberg and Lundberg 2002) and that these increases were not detected in patients with nasal polyps and sinus ostium obstruction. Furthermore, they suggested that the absence of a normal response to humming during nNO measurement could be used to identify allergic rhinitis with sinus ostium obstruction. Whether this adds significant value to standard testing has yet to be fully appreciated.

9.6 Diagnosis of Primary Ciliary Dyskinesia (PCD)

In children with rhinosinusitis presenting with longstanding and persistent anterior rhinorrhea, one may be interested in the evaluation of the function of the mucociliary clearance system for the exclusion of PCD. Normal mucociliary transport is essential for the maintenance of healthy sinuses. In case of infection with secondary ciliary dysfunction and/or congenital dysfunction of the cilia like in PCD, the mucociliary transport is inadequately or not taken place. In PCD, lack of mucociliary transport may lead to chronic rhinosinusitis and bronchiectasis. In chronic inflammation, mucostasis, hypoxia, microbial products, toxic inflammatory mediators may induce secondary ciliary changes like in secondary ciliary dyskinesia (SCD), with inadequate mucociliary transport. The mucociliary transport (MCT) mechanism ensures the clearance of entrapped particles in the mucus lining the nasal mucosa towards the hypopharynx. Several nonabsorbable substances have been used for the evaluation of MCT in patients, like saccharin or dyes like methylene blue. As the MCT can only be measured in cooperative patients with patent nasal cavities and in the absence of severe mucosal disease, this test has limited diagnostic value due to its low sensitivity and specificity.

No ideal test is available for the diagnosis of PCD. In case of suspicion of PCD in a patient with rhinosinusitis since birth, familial history of PCD, and associated features of Kartagener syndrome, i.e., situs inversus and infertility, one should consider diagnostic tests of ciliary function by evaluation of CBF, electron microscopic evaluation of the dynein arms of the cilia, and/or evaluation of the cilia after ciliogenesis in vitro. As these techniques are not available in routine ENT practice, one may rely on measuring nasal NO levels as low NO levels have been associated with PCD and therefore represent a good screening tool for PCD.

9.7 Concluding Remarks

Nasal NO measurement represents a useful diagnostic tool in PCD. However, variable baseline levels of nNO and interindividual variability make nNO measurement of little value in the diagnosis and management of uncomplicated rhinitis.

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Olfaction

10

Caroline Huart, Philippe Eloy, and Philippe Rombaux

Core Messages

- The gene family that encodes olfactory receptors corresponds to the largest family of genes in the mammalian genome.
- The olfactory bulb contains major structures that can be considered to be the first olfactory structure: the glomeruli. The glomeruli are the only relay between the periphery and the cortex.
- The olfactory system presents unique properties as compared to other sensory systems. They are (1) the predominance of ipsilaterality of the olfactory projections, (2) the conduction of odor-evoked signals without an obligatory thalamic relay and (3) the intimate overlap with limbic regions of the brain, involved in the determination of our personal and social behavior.
- Normal olfactory function varies as a function of age and sex.
- Smell disorders have severe consequences; including impaired quality of life, daily life problems, altered food choices, and consumption patterns than can negatively impact health and even depression.
- The evaluation of patients suffering from olfactory disorders requires a precise clinical work-up procedure.
- There are several causes of olfactory dysfunction and it is essential to investigate about the etiology of olfactory dysfunction. The most frequent are chronic rhinosinusitis, post-infectious olfactory loss and post-traumatic olfactory loss.
- Management of patients should include information about consequences for daily life and coping strategy, focusing on instructional information about fire alarms, domestic gas, hygiene, etc.

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10.1 Introduction

Olfaction is one of the most ancient senses. Nevertheless, the field of olfaction has received far less attention as compared to other sensory modalities. This is mostly due to the technical challenge of working with odorous stimuli and the difficulties of measuring brain activity induced by a chemosensory stimulus.

Although a majority of people consider it as one of the less important senses, this sense plays a major role in our interaction with the environment. Not only olfactory system acts for the detection of potential danger in the environment, such as smoke or gas, but also it influences our nutrition, social behavior, well-being, and memory processes.

This chapter proposes a global view of human olfaction. First we will extend on physiology of olfaction, paying a particular interest to olfactory pathways. Then, we will study pathological situations associated with olfactory dysfunction. More particularly, we will see into detail postinfectious olfactory loss, posttraumatic olfactory loss, and sinonasal-related olfactory disorder.

The aim of this chapter is to provide to clinicians an update in the field of olfaction in order to improve the counseling and treatment of patients with olfactory disorders. Also, based on the physiology and pathology of olfaction, we aim to highlight the importance of olfaction in our daily life and, hence, the importance of a global care of the patients.

10.2 Physiology

10.2.1 Embryology

The olfactory placode is induced at the end of the 4th week of pregnancy when the local ectoderm makes direct contact with the prosencephalic vesicle. Some cells of the olfactory placode will differentiate into primary neurosensory cells, further constituting the olfactory neuroepithelium. At the end of the 5th week, these cells will develop axons, reaching the neurons from the anterior wall of the prosencephalon, which becomes the telencephalon. This will induce the development of the olfactory bulb which begins to differentiate from the telencephalon. At the 7th week, the olfactory bulb individualizes at the tip of each hemisphere. It will then lengthen and come to lie on the cribriform plate of the ethmoid bone at the 12th week of pregnancy. Secondary neurosensory cells will differentiate inside the olfactory bulb and their dendrites synapse with axons of the primary neurosensory cells. Axons of secondary neurosensory cells will group to form the olfactory tract and synapse with cortical olfactory areas of the entorhinal paleocortex and archicortex (Drews 1995; Larsen 2003).

10.2.2 Olfactory Pathways

The olfactory system detects odorant molecules dissolved in air and trapped in the airflow passing through the nasal cavity. Nasal turbinates will guide the airflow to the olfactory cleft, allowing the odorant molecules to reach the olfactory neuroepithelium.

10.2.2.1 The Olfactory Neuroepithelium

The olfactory neuroepithelium is located in the upper part of the nasal vaults. It covers the cribriform plate of the ethmoid bone, medially to the middle turbinate, and can extend to the superior turbinate, the superior part of the septum, and the middle turbinate (Leopold et al. 2000). In adult humans, its surface area is 2.5 cm^2 per nasal fossa. The location of the olfactory epithelium is dependent on individual factors and is thought to change with age, resulting from a conversion of olfactory neuroepithelium to respiratory epithelium or due to loss of olfactory neurons with age or from damages (smoke, toxics, chemicals, chronic infection).

The olfactory neuroepithelium is a pseudostratified columnar epithelium covering a lamina propria. It is composed of (1) olfactory receptor neurons (ORNs); (2) supporting cells; (3) basal cells, some of which serve as ORN stem cells for the regeneration of new olfactory sensory neurons throughout life; and (4) the duct of the Bowman's glands (which are located in the lamina propria) (Fig. 10.1).

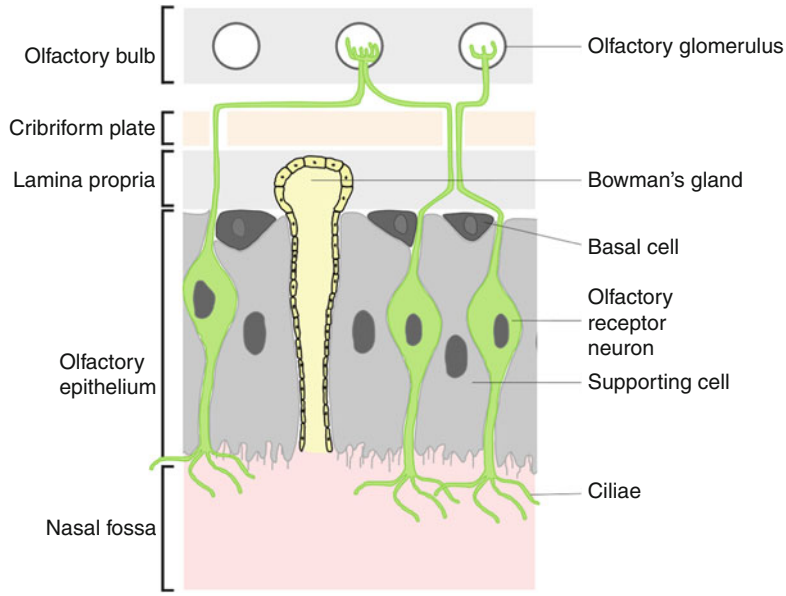

Fig. 10.1 Schematic representation of olfactory neuroepithelium. The olfactory neuroepithelium is composed by olfactory receptor neurons, supporting cells, and basal cells. The dendritic extension of olfactory receptor neurons carries on its surface several cilia, where the olfactory receptors are located. The axons run through the cribriform plate of the ethmoid bone and reach the olfactory bulb where they synapse with mitral cells in spherical structures named glomerulus

The ORNs are bipolar cells, with their dendritic extensions directed toward the olfactory cleft and carrying on its surface several cilia that project into the mucus. Odorants are carried through the mucus layer by olfactory binding proteins and bind to olfactory receptors located on the ORNs. In 1991, Axel and Buck (Buck and Axel 1991) discovered a family of approximately 1,000 genes that encode for an equivalent number of olfactory receptors, corresponding to the largest family of genes in the mammalian genome (Zhang and Firestein 2002), highlighting their important role in physiology. In the majority of mammals, most of these genes are functional, but in primate the number of functional genes decreases and is to about 350 in humans (Crasto et al. 2002). Axel and Buck found that each ORN possesses only one type of odorant receptor and each receptor is specialized for a small number of odors. Hence, a given odorant will bind a typical pattern of olfactory receptors. The binding results in the activation of G proteins. The activation of G proteins stimulates the formation of cyclic AMP. Increased levels of cAMP open cyclic nucleotide-gated channels. This causes the opening of the channels and Ca++ influx. This influx activates chloride channels, opening them up and, causing Cl- to leave, finally depolarizing the ORN and generating the action potential.

ORN axons converge into the olfactory nerves, passing through the cribriform plate of the ethmoid bone and projecting directly to the ipsilateral olfactory bulb where they synapse into spherical structures known as the glomerulus.

10.2.2.2 The First Olfactory Structure: The Olfactory Bulb

The olfactory bulb is ovoid in shape and located in the anterior cranial fossa, above the cribriform plate of the ethmoid bone, under the frontal lobe. It contains a major structure that can be considered to be the first olfactory structure: the glomerulus. The glomerulus is the only relay between the periphery and the cortex. Each glomerulus collects ORN axons from the same type of odorant receptor (Fig. 10.2). ORN axons and dendrites of mitral cells synapse in the glomerulus.

The olfactory bulb has a multilayered cellular architecture. It encompasses 6 different layers: (1) the external layer is composed of ORN axons, (2) the glomerular layer is composed by glomeruli wherein axons of ORN synapse with dendrites of mitral cells, (3) the external plexiform layer consists of dendrites of mitral and tufted cells, (4) the mitral and tufted cell layer contains cell bodies of

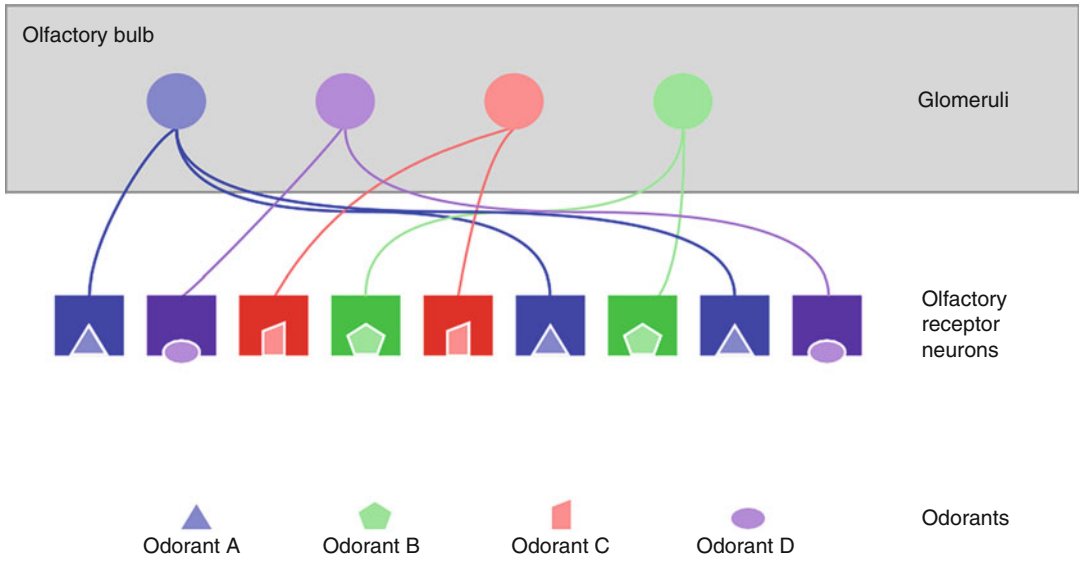

Fig. 10.2 Basic schematic representation of odor coding at the level of neuroepithelium and glomeruli. Odorant molecules bind with specific olfactory receptor neurons. Each olfactory receptor neuron possesses only one type of odorant receptor. Olfactory receptor neurons carrying the same type of receptor send their axon to the same glomerulus at the level of the olfactory bulb

mitral and tufted cells (second-order olfactory neuron), (5) the internal plexiform layer, and (6) the granule cell layer contains rows of mitral and tufted axons and granule cells which are interneurons.

Axons of the mitral cells and tufted cells coalesce to form the olfactory tract, located at the base of the forebrain.

Centripetal information is secondary to neuronal activation, with glutamate as the principal neurotransmitter.

10.2.2.3 The Second Olfactory Structures: The Primary Olfactory Cortex

As compared to all other senses, olfaction is particular in that second-order olfactory neurons send information directly to primary olfactory cortex. In humans, the olfactory bulb is connected to the primary olfactory cortex by the fibers of the lateral olfactory tract (LOT). The LOT conveys olfactory information to a wide number of brain areas within the frontal lobe and the dorsomedial surface of the temporal lobe, often referred to as the primary olfactory cortex.

The primary olfactory cortex comprises the piriform cortex, which covers the uncus, the entorhinal cortex, the anterior olfactory nucleus, the periamygdaloid cortex, the olfactory tubercle, and nucleus. These projections are mainly ipsilateral but there are also contralateral connections via the anterior commissure (Cleland and Linster 1995; Royet and Plailly 2004; Lascano et al. 2010). Some of the structures of the primary olfactory cortex then project to the tertiary highest cognitive centers of the brain. The major projection of the piriform cortex is the thalamus, but it will also project to the insular cortex, the orbitofrontal cortex (neocortex), and the hypothalamus. The entorhinal cortex supplies afferent input to the hippocampus, while the olfactory tubercle connects to the thalamus. The amygdala is the major source of afferents to the hypothalamus (Fig. 10.3). Interestingly, there are many interactions between the secondary olfactory structures: between the anterior olfactory nucleus and the piriform cortex, the piriform cortex and the olfactory tubercle, and the piriform cortex and the entorhinal cortex.

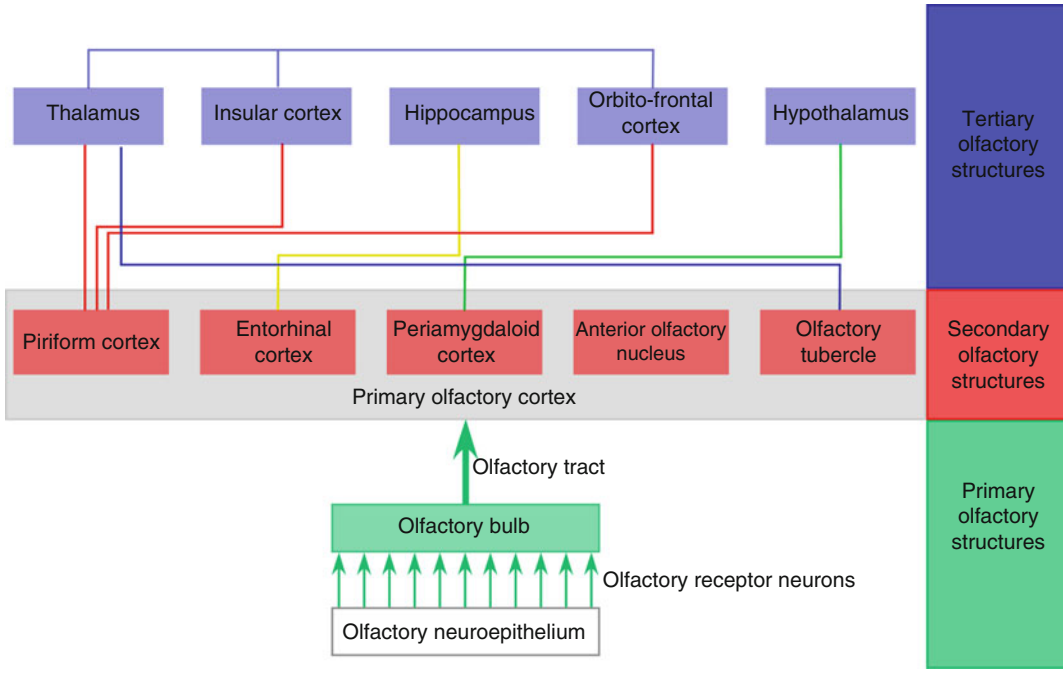

Fig. 10.3 Schematic diagram of major olfactory pathways

10.2.2.4 The Tertiary Olfactory Structures

The tertiary olfactory structures are the thalamus, the hypothalamus, the amygdala, the hippocampus, the orbitofrontal cortex, and the insular cortex.

The thalamus receives information from the piriform cortex and the olfactory tubercle. The hypothalamus, the orbitofrontal cortex, and the insular cortex also receive afferent input from the piriform cortex, while hippocampus is connected to entorhinal cortex. We should also note that there are also some interactions between these tertiary olfactory structures. In this way, the thalamus connects to the orbitofrontal cortex and the insular cortex. Therefore, the orbitofrontal cortex and the insular cortex receive direct input from the piriform cortex and indirect input via the thalamus.

10.2.2.5 Centrifugal Information

Most secondary and tertiary structures have numerous centrifugal fibers leading to the olfactory bulb, with GABA and acetylcholine as principal neurotransmitter. The supposed aim of this centrifugal information is to allow the brain to control the incoming flow of olfactory signals.

10.2.2.6 Properties of Olfactory Pathways

The olfactory pathways are distributed to different brain structures that are involved in the determination of our personal and social behavior. For example, the connections with the:

1. Hippocampus and limbic system are thought to influence our memory system.
2. Amygdala system could act on emotional, motivational, and craving circuits.
3. Hypothalamus, that mediates feeding regulation, could influence our feeding behavior.
4. Orbitofrontal cortex mediates our conscious perception of odors and could influence our preferences (Shepherd 2006).

Hence, odor perception may affect our behavior and plays a major role in our interaction with the environment.

The olfactory system presents unique properties as compared to other sensory systems. They are (1) the predominance of ipsilaterality of the

olfactory projections, (2) the conduction of odor-evoked signals without an obligatory thalamic relay, and (3) the intimate overlap with limbic regions of the brain (Gottfried 2006):

1. Odor processing remains principally ipsilateral (Cleland and Linster 1995; Royet and Plailly 2004; Lascano et al. 2010) all the way from the nasal periphery to the primary olfactory cortex. This feature is different for other sensory modalities such as the visual or auditory systems which, early in the processing pathways, supply sensory information in both hemispheres. This may help the cortex to better discriminate and to make bilateral odor comparisons and perhaps to provide differential access to odor memories.
2. The absence of an obligatory thalamic relay is also in contrast with other sensory modalities in which an incoming signal undergoes thalamic modulation prior to being delivered to the sensory-specific cortex (Gottfried 2006). The absence of thalamic sensory integration in the olfactory pathways would seem to have an evolutionary explanation (Gottfried 2006).
3. The connections between the olfactory system and the limbic system appear to be involved in the emotional and memory background to odorant stimuli, our social behavior, and the formation of novel stimulus-reinforced associations (Gottfried 2006).

10.2.3 Orthonasal and Retronasal Olfaction

Paul Rozin noted that smell is unique in having a "dual nature" – meaning that it can sense signals originating outside (orthonasal) or inside (retronasal) the body (Rozin 1982).

Orthonasal olfaction refers to odorants originating outside and sniffed in through the nares to reach the olfactory neuroepithelium. This route is used to smell odors from the environment, such as perfumes, food aromas, smoke, predator smell, social odors, or pheromones. Orthonasal olfaction is processed by olfactory pathways and is influenced by the visual pathway.

Retronasal olfaction refers to odorants originating from the back of the mouth and reaching the olfactory neuroepithelium via the nasopharynx. This retronasal stimulation occurs during food ingestion. It is activated only when breathing out through the nose, between mastication, or swallowing (Taylor et al. 2000; Shepherd 2006). The retronasal olfaction, also termed as "flavor," account for an important part of food identification. This explains why a majority of patients suffering from smell disorder also complain of "taste" disorder, although their sense of taste is intact. On contrast to orthonasal olfaction, flavor perception is not only processed by olfactory pathways but is also influenced by almost all sensory modalities, which are taste, touch, sound, and proprioception (for a review, see Shepherd 2006). Indeed, the orbitofrontal cortex receives connections from other sensory neocortical areas (taste, hearing, touch, and vision) (Ongur et al. 2003) (Fig. 10.4). Since it is receiving multisensory input and integrating these different sensory informations, the orbitofrontal cortex is an important area to influence our food preferences and choices.

10.2.4 Olfactory and Trigeminal Interactions

The nasal fossa has double innervations from olfactory and trigeminal afferents. Although odorants are defined as volatile compounds having the ability to activate the olfactory system, the vast majority of odorants will actually activate both the olfactory and trigeminal system. Sensations resulting from the activation of the olfactory system are those of odors, while sensations induced by the stimulation of the trigeminal nerve are somatosensory (tactile, thermic, pain, humidity).

Olfactory and trigeminal systems closely interact with each other, and the stimulation of these two systems leads to important overlap in their activation pattern in the brain (Zald and Pardo 2000; Hummel et al. 2005; Boyle et al. 2007; Iannilli et al. 2007; Bensafi et al. 2008). The interaction between both systems is

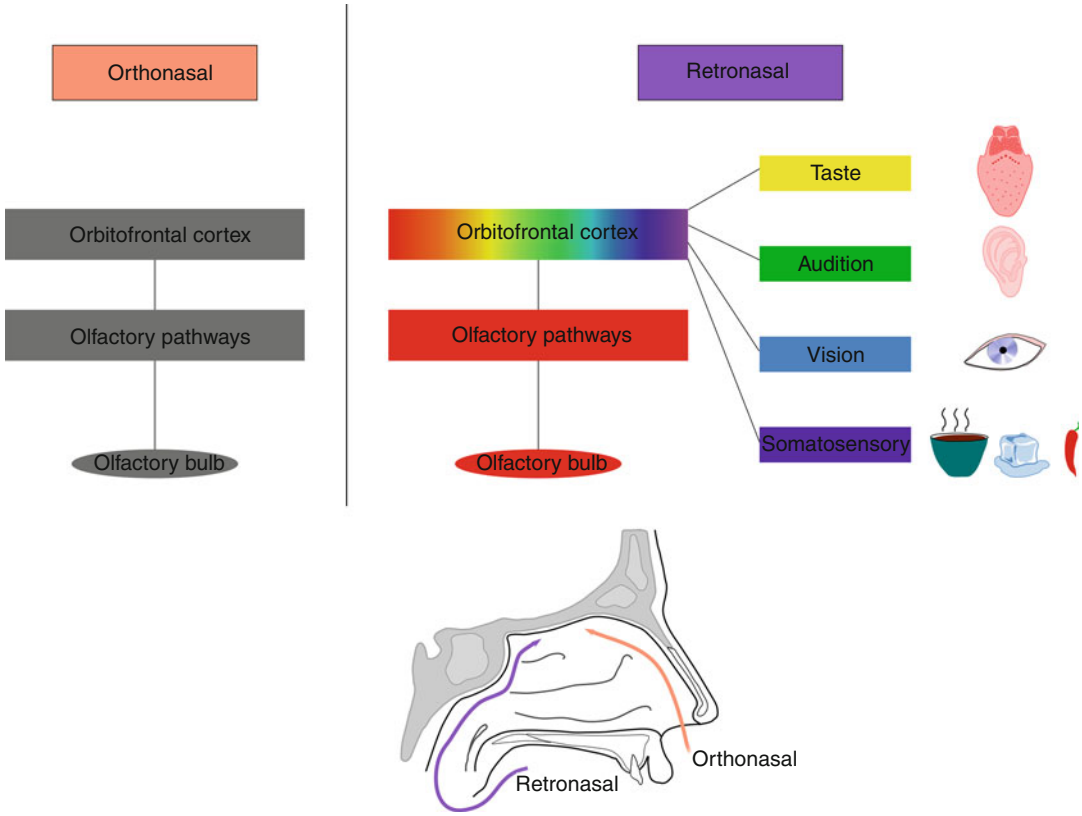

Fig. 10.4 Schematic representation of the central processing of orthonasal and retronasal olfaction. Orthonasal olfaction is processed by the olfactory pathways. On contrast, retronasal olfaction is not only processed by olfactory pathways but is also influenced by other sensory modalities, which are taste, sound, vision and proprioception. These multisensory informations are integrated in the orbitofrontal cortex

complex and takes place both at a peripheral and central level (for a review, see Hummel and Livermore 2002; Brand 2006). This interaction is difficult to predict, but it has a powerful influence on odor perception both at different concentration of a single stimulus and between mixtures of chemosensory stimuli. According to the literature, the pattern of interaction seems to depend on stimulus quality, intensity, and relative intensity of olfactory and trigeminal components of the mixture (for a review, see Hummel and Livermore 2002). Some reports have investigated the olfactory modulation of trigeminally mediated sensations in patients with olfactory loss, demonstrating that a close interaction and many compensatory mechanisms exist (Frasnelli et al. 2007).

10.2.5 Variability in Normal Olfactory Function

Such as other senses the olfactory function decreases over time, and it has been described in numerous previous studies that there is a strong decrease in olfactory function above the age of 55 years (Murphy et al. 2002; Hummel et al. 2007). Several mechanisms have been proposed to explain this age-related olfactory dysfunction. At a peripheral level, changes in mucociliary movement, mucus composition, submucosal blood flow, and epithelial thickness might disturb the transport of the odorant to the receptor (Rawson 2006). At the level of the neuroepithelium, it is assumed that the regeneration of olfactory receptor neurons decreases over age (Naessen

1971; Conley et al. 2003). At a central level, brain damages due to chronic ischemia or systemic disturbance might also be proposed as a potential cause of age-related olfactory disorder.

Hummel et al. reported that there is a differential change of olfactory functions with aging. Indeed, olfactory thresholds decrease more strongly with age as compared to odor discrimination and odor identification (Hummel et al. 2002a, 2007). Since threshold measurements best reflect the function of the peripheral olfactory system than other olfactory tests (Jones-Gotman and Zatorre 1988; Hornung et al. 1998; Moberg et al. 1999), this finding might indicate that age-related change of olfactory function is at least in part due to damage of the olfactory epithelium (Hummel et al. 2007). Nevertheless, we should also keep in mind that age-related decrease of olfactory function might also be a consequence of side effects of drugs, onset of neurodegenerative diseases, etc.

A sex-related difference in olfactory function has also been widely reported (Doty et al. 1985; Brand and Millot 2001; Lundstrom et al. 2005; Lundstrom and Hummel 2006; Hummel et al. 2007), with women outperforming men. Several causes have been proposed to explain this phenomenon, such as hormonal effects and congenital factors. However, the origin of this sex-related difference is still unclear.

Finally, some healthy people might present a specific anosmia. That is a physiological condition where a person of otherwise normal olfactory acuity is unable to detect a specific odorant. Specific anosmias have been described for series of odors (Amoore 1991). It is admitted that specific anosmia has a genetic basis, and the occurrence of specific anosmia indicates that specific receptors are necessary for perceiving specific odors (Amoore et al. 1968; Wysocki and Beauchamp 1984; Gross-Isseroff et al. 1992; Lancet et al. 1993; Menashe et al. 2003). One of the most frequent and well-known specific anosmia is androstenone anosmia. The prevalence of this specific anosmia is still a matter of debate. It is usually admitted that about 30 % of the population is unable to detect the odor of the androstenone. But there is a high variability in the prevalence reported in the literature, ranging from 1.8 to 75 % (for a review, see Bremner et al. 2003). This might be at least in part explained by the various stimulation methods, criterion for non-detection, and concentrations that were used in the different studies (Bremner et al. 2003).

10.3 Pathology

Although olfaction is often described as one of the less important sense, smell disorders have severe consequences, including impaired quality of life, daily life problems (cooking, detection of potentially dangerous odors) (Temmel et al. 2002), altered food choices and consumption patterns that can negatively impact health (decreased body weight, overuse of salt inducing blood hypertension, overuse of sugar inducing diabetes mellitus, impaired immunity etc.), and even depression (Deems et al. 1991).

The incidence of olfactory dysfunction among the population is still a matter of debate. Authors report an incidence of 1–3 % of dysfunction among population (Hoffman et al. 1998; Murphy et al. 2002). Nevertheless a study by Landis et al. reported higher values of olfactory dysfunction among population without sinonasal complaints, with a rate of 4.7 % of anosmia and 16 % of hyposmia. The frequency of parosmia and phantosmia were reported with a rate of 2.1 and 0.8 %, respectively (Landis et al. 2004).

The evaluation of patients suffering from olfactory disorders requires a precise clinical workup procedure in order to (1) determine the etiology of the olfactory dysfunction, (2) assess olfactory function, and, hence, (3) provide an optional treatment, a prognosis, and appropriate counseling to patients. Assessment of olfactory function is reviewed in Chapter 33.

10.3.1 Classification of Olfactory Disorders

10.3.1.1 Quantitative Olfactory Disorders

Quantitative olfactory disorders are hyposmia, hyperosmia, and anosmia (Table 10.1). Hyposmia

Table 10.1 Classification of smell disorders

Quantitative smell disorders	Qualitative smell disorders
Hyposmia	Parosmia
Anosmia	Phantosmia
Functional anosmia	Olfactory agnosia
Specific anosmia	
Hyperosmia	

refers to a decreased ability to smell. This is a common condition. Indeed, Landis et al. reported that up to 16 % of the general population is hyposmic (Landis et al. 2004).

Hyperosmia is a rare condition and refers to enhanced ability to smell. It can happen after exposure to toxic vapors (Henkin 1990) or during migraine (Blau and Solomon 1985).

Anosmia refers to the lack of ability to smell. It is assumed that about 5 % of the general population exhibit functional anosmia (Landis et al. 2004). Functional anosmia refers to a significantly reduced ability to smell although some smell sensations can be present.

10.3.1.2 Qualitative Olfactory Disorders

Qualitative olfactory disorders are parosmia, phantosmia, and olfactory agnosia. Parosmia is a sensation that a given odor is different than the typical odor for this substance. Parosmia is typically associated with reduced olfactory sensitivity and is particularly frequent in patients suffering from postinfectious olfactory loss (up to 50 %) (Reden et al. 2007). It is also associated with posttraumatic olfactory loss or sinonasal-related olfactory disorder. Studies found a prevalence of parosmia in 19 % (Nordin et al. 1996), 20 % (Landis et al. 2010), and 28 % (Reden et al. 2007) of patients presenting to "smell and taste" clinics, while the prevalence of parosmia in the general population is reported to be 2.1 % (Landis et al. 2004) to 4 % (Nordin et al. 2007). It is typically unpleasant. Euosmia is a rare form of parosmia with a pleasant parosmia to selected odorants (Landis et al. 2006). The pathophysiology of parosmia is not clear. There are two hypotheses: the central and the peripheral hypotheses. In periphery, loss of olfactory receptor neurons changes the integrity of the olfactory image, resulting in an incomplete and meaningless picture of the odorant. Centrally, it has been proposed that the integration and interpretation of odors are altered (Leopold 2002).

Phantosmia is the perception of an odor when none is present. It may be reed to a wide range of pathologies (postinfectious olfactory loss, posttraumatic olfactory loss, rhinosinusitis, neurologic, etc.).

Finally, olfactory agnosia is defined as the inability to recognize odor sensation.

10.3.2 Etiology of Olfactory Disorders

There are several causes of olfactory dysfunction. The most frequent are chronic rhinosinusitis, postinfectious olfactory loss, and posttraumatic olfactory loss. These three etiologies account for up to two-third of the patients with olfactory disorder (Murphy et al. 2003; Rombaux et al. 2009b); therefore, we will largely extend on these three pathologies. However, several pathologies might also affect olfactory function, such as neurological disease, metabolic diseases, toxics, and tumoral disease of the sinonasal cavities or brain (Table 10.2). It is therefore essential to investigate about the etiology of olfactory dysfunction. An algorithm for the management of olfactory dysfunction is proposed in Fig. 10.5.

10.3.3 Chronic Rhinosinusitis

In the literature, chronic rhinosinusitis (CRS) is described as the most common cause of olfactory dysfunction, accounting for 14–30 % of cases (Mott and Leopold 1991; Seiden and Duncan 2001; Raviv and Kern 2004; Holbrook and Leopold 2006). Inversely, olfactory impairment is a common symptom affecting 61–83 % of patients with CRS (Orlandi and Terrell 2002; Bhattacharyya 2003; Litvack et al. 2008; Soler et al. 2008). Nevertheless up to one-quarter of

Table 10.2 This table summarizes the different etiologies of olfactory disorders

Rhinologic disease
Chronic rhinosinusitis (with or without nasal polyps)
Allergic rhinitis (Apter et al. 1992; Cowart et al. 1993; Guilemany et al. 2009)
Atrophic rhinitis (Huart et al. 2012)
Postsurgical (Landis et al. 2005; Huart et al. 2012)
Olfactory cleft syndrome
Postinfectious olfactory loss
Posttraumatic olfactory loss
Congenital anosmia
Neurological disorder
Alzheimer's disease
Idiopathic Parkinson's disease
Tumor
Intranasal
Esthesioneuroblastoma
Adenocarcinoma
Intracranial
Gliomas
Olfactory meningiomas
Toxic (Amoore 1986; Schwartz et al. 1989; Upadhyay and Holbrook 2004)
Metals (cadmium, manganese, mercury, aluminum)
Gases (formaldehyde, methyl bromide, styrene, chlorine)
Solvents (toluene, butyl acetate, benzene)
Hairdressing chemicals
Intranasal zinc
Drug induced (for review, see Schiffman 1991; Nores et al. 2000)
Chemotherapy drugs
Analgesic (antipyrine)
Local anesthetics (cocaine HCl, procaine HCl, tetracaine HCl, lidocaine)
General anesthetics
Antimicrobial (amoxicillin, aminoglycosides, macrolides, doxycycline, pyrazinamide)
Antirheumatics (mercury/gold salts, D-penicillamine)
Antithyroids (propylthiouracil, thiouracil)
Cardiovascular, hypertensives (angiotensin conversion enzyme inhibitors, nifedipine, amlodipine)
Gastric medication (cimetidine)
Intranasal saline solutions (with acetylcholine, menthol, zinc sulfate)
Opiates
Sympathicomimetics
Metabolic/endocrine (for a review, see Schiffman 1997)
Adrenocortical insufficiency
Cushing's syndrome
Hypothyroidism
Pseudohypoparathyroidism
Hepatic (Temmel et al. 2005) or renal failure (Frasnelli et al. 2002)
Psychiatric (Turetsky et al. 2009)
Idiopathic

Pathologies that are underlined are deeply commented in the text

patients with CRS are unaware of their decreased olfactory abilities, probably because the olfactory dysfunction in CRS develops slowly, and in consequence only a few patients note this disorder (Nordin et al. 1995).

Psychophysical test results show that patients with CRS have quantitative disorders, between hyposmia and anosmia (Mott and Leopold 1991; Seiden and Duncan 2001; Raviv and Kern 2004; Holbrook and Leopold 2006; Welge-Luessen 2009), and may report fluctuating symptoms (Apter et al. 1999). Also it is widely known that patients with CRS with polyps have a higher incidence of smell symptoms and anosmia than patients with CRS without polyps (Hellings and Rombaux 2009). Some studies have described that the severity of quantitative disorders is related to the importance of the sinonasal disease (Litvack et al. 2008; Litvack et al. 2009a). Indeed, the mean endoscopy score and the mean CT score are significantly higher (more abnormal) in patients with hyposmia and anosmia than in patients with normosmia (Litvack et al. 2009a). Also, the opacification of the olfactory cleft on the CT scan seems to have a negative correlation with the olfactory function (Chang et al. 2009).

Patients with CRS not only report quantitative olfactory dysfunction but also qualitative dysfunction such as parosmia and phantosmia. However, these symptoms seem less frequent when related to sinonasal disease than to other etiologies (i.e., postinfectious, posttraumatic), and Reden et al. (2007) reported incidence of parosmia and phantosmia in patients with CRS of 28 and 7 %, respectively.

Traditionally, olfactory dysfunction in CRS is explained by a conductive olfactory loss, caused by swollen or hypertrophic nasal mucosa or nasal

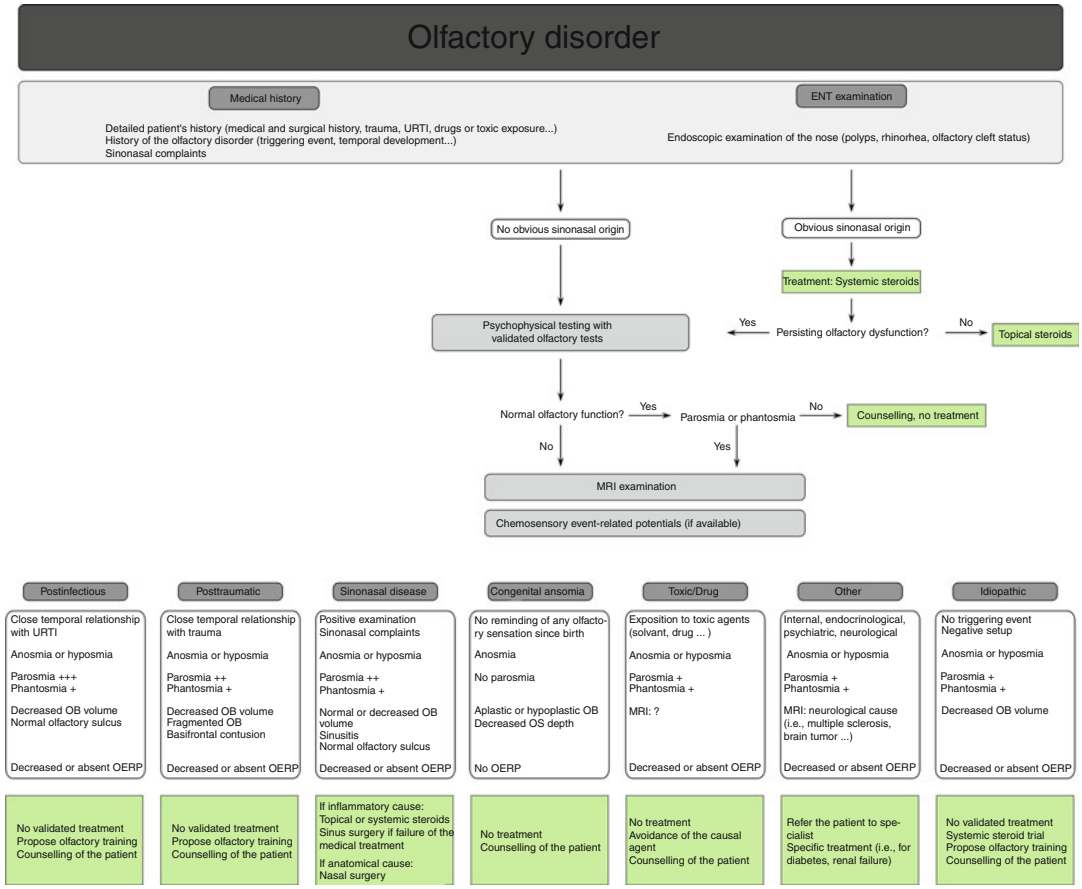

Fig. 10.5 Algorithm for the management of olfactory disorders. *URTI* upper respiratory tract infection, *OB* olfactory bulb, *OS* olfactory sulcus, *OERP* olfactory event-related potentials

polyps, inducing an impaired access of odorants to the olfactory cleft. But clinical studies have failed to prove this hypothesis, as there is only little correlation between nasal resistance and the degree of olfactory dysfunction (Doty and Frye 1989). In addition, results of surgical therapy, although improving the nasal patency, are sometimes uncertain when considering the olfactory dysfunction.

Nowadays, it is generally agreed that the olfactory disturbance is due to an inflammatory process in the olfactory cleft (Konstantinidis et al. 2007) rather than a pure obstruction. Indeed, biopsies of the olfactory neuroepithelium in patients suffering from CRS revealed inflammatory and apoptotic pathological changes in the nasal mucosa, including the olfactory receptor neurons and olfactory supporting cells (Naessen 1971; Hellings and Rombaux 2009), and the degree of inflammation in the neuroepithelium was proved to be related to the severity of olfactory dysfunction (Kern 2000). This could be explained by the fact that inflammatory cells release inflammatory mediators, which are known to trigger hypersecretion in respiratory and Bowman's glands (Getchell and Mellert 1991; Downey et al. 1996; Hellings and Rombaux 2009). Hypersecretion of Bowman's gland is thought to alter the ion concentrations of olfactory mucus, affecting the olfactory transduction process (Joshi et al. 1987; Kern et al. 1997). Finally, it has been demonstrated that cytokines and mediators, particularly those released by eosinophils, may be toxic to olfactory receptor neurons (Nakashima et al. 1985; Apter et al. 1992).

Patients with nasal polyps show a higher incidence of olfactory disturbances and a higher incidence of anosmia than patients with CRS without polyps. This more severe symptomatology may be explained by the conductive olfactory loss induced by polyps but also by degenerative changes associated with recurrent infections, scarring, chronic nasal medication, exotoxins, and enhanced secretion of cytokines from *Staphylococcus aureus* infection and neurotoxic cytokines released by a huge eosinophilic population (Joshi et al. 1987; Vento et al. 2001; Litvack et al. 2008; Wang et al. 2010; Bernstein et al. 2011).

Medical imaging is useful in the assessment of patients suffering from sinonasal-related olfactory dysfunction. Using CT scan, Litvack et al. (2009a) have shown that the severity of quantitative olfactory disorder is associated with the importance of the sinonasal disease and that mean CT score is significantly higher in patients with hyposmia and anosmia than in normosmic patient. It was also demonstrated that the opacification of the olfactory cleft has a negative correlation with the olfactory function in patients with CRS and that it is significantly correlated with the postoperative olfactory results: patients with mild opacification having better postoperative results than patients with moderate and severe anterior olfactory cleft opacification (Kim et al. 2011). MRI is also interesting. Indeed, Rombaux et al. (2008) demonstrated that the olfactory bulb volume is correlated with the sinonasal disease score, and patients having a sinonasal disease score $\geq$12 significantly have larger olfactory bulb volume than patients with higher score. Smaller olfactory bulb volume is thus associated with a higher degree of sinonasal pathology. On contrast the olfactory function of the patients assessed with psychophysical testing was only slightly decreased or was even normal, emphasizing the idea that the olfactory bulb volume changes are more sensitive to subtle changes in the olfactory system than results of psychophysical testing.

Medical and/or surgical treatment must be proposed to patients suffering from sinonasal-related olfactory disorders since (1) they are effective in this pathology and (2) it has been demonstrated that patients reporting an improvement of their olfactory abilities have a better quality of life than patients reporting no improvement (Miwa et al. 2001). Only a few clinical studies have been conducted dealing with the improvement of olfactory function as a primary outcome in sinonasal disease treatment. Clinical trials of medical treatment for smell disorders associated with CRS have evaluated the efficacy of nasal and oral corticosteroid treatment. We found a recent study evaluating the efficacy of antihistamines (levocetirizine) on the smell loss in patients with persistent allergic rhinitis (Guilemany et al. 2012), but we found no studies about other drugs that are currently used in the treatment of CRS (antileukotrienes).

Corticosteroids with their potent anti-inflammatory effects are admitted to be the standard treatment for olfactory disorders induced by CRS. Their action mechanism on olfactory function might be explained by an inhibition of the release of proinflammatory mediators (i.e., cytokines, adhesion molecules, mast cells, basophiles, eosinophils) and a reduction in mucosa swelling (Mygind et al. 2001; Demoly 2008). Following EPOS 2012 recommendations, nasal steroids are recommended as the first-line treatment for CRS with or without nasal polyps (Fokkens et al. 2012). Studies have evaluated the efficacy of different topical corticosteroids such as betamethasone, flunisolide, mometasone furoate, fluticasone propionate, budesonide, and beclomethasone. Studies show that these drugs appear to be highly effective for most of the symptoms associated with CRS, including smell disorder, with a rapid onset of action and a cumulative effect after several days of use. In addition, they have the advantage of being a local therapy with limited side effects. Nevertheless the improvement in olfaction is frequently transient and incomplete (Lildholdt et al. 1995; Golding-Wood et al. 1996; Mott et al. 1997; Blomqvist et al. 2003; Stuck et al. 2003; Hellings and Rombaux 2009). Oral steroids are recommended in the treatment of CRS with nasal polyps as a second-line treatment (Fokkens et al. 2012). Several studies have investigated their efficacy in patients with CRS with or without polyps. They have

shown that these potent anti-inflammatory drugs increase the olfactory function and they appear to be more effective than nasal steroids (Heilmann et al. 2004; Vaidyanathan et al. 2011). Moreover, an initial oral steroid therapy followed by topical steroid therapy seems to be more effective than topical steroid therapy alone (Vaidyanathan et al. 2011). Nevertheless oral steroids have important side effects if they are frequently administrated or if their administration is prolonged. Bonfils et al. (2006) evaluated the risk of oral steroid treatment in patients with CRS with nasal polyps and showed that almost 50 % of patients who received more than three short courses of oral steroid treatment had an asymptomatic adrenal insufficiency. Oral corticosteroids should thus be prescribed only if necessary and should be avoided if possible.

Functional endoscopic sinus surgery (FESS) is widely accepted as a treatment for chronic rhinosinusitis with or without nasal polyps after failure of the medical therapy. The only randomized study to attempt comparison between steroid therapy and polypectomy showed significant improvement of subjective and objective olfactory function in both groups, remaining for 1 year. However, these results should be tempered by the fact that the smell evaluation methodology was not described (Lildholdt 1989).

Several studies have investigated the effect of FESS on olfactory function (for a review, see Bonfils et al. 2009). Nevertheless the literature shows that there are major variations in the selection of patients for the surgery, and some studies have poor validity because of poorly defined patient groups, lack of clear inclusion or exclusion criteria, poor description of the surgical procedure, and poor description of the olfactory evaluation tool. In this literature, olfactory function was assessed either by subjective patient self-reported olfactory function or by semi-objective olfactory testing (i.e., UPSIT). Considering patient self-reported olfactory function, authors agree that FESS lead to a significant improvement of olfactory dysfunction (Levine 1990; Lund and MacKay 1994; Klossek et al. 1997; Jakobsen and Svendstrup 2000) (for a review, see Bonfils et al. 2009). Only few studies have investigated the effect of FESS on olfactory function by using semi-objective olfactory testing. They have also shown that FESS has a significant positive effect on olfactory function (Lund and Scadding 1994; Min et al. 1995; Downey et al. 1996; Klimek et al. 1997; Delank and Stoll 1998) (for a review, see Bonfils et al. 2009). Some authors have investigated the correlation between the severity of CRS and surgical outcomes on olfaction. It was reported that the improvement after FESS is significantly better in patients with severe olfactory dysfunction, whereas it is not in patients with mild olfactory dysfunction (Litvack et al. 2009b; Soler et al. 2010). The degree of nasal obstruction, the extent of the rhinosinusitis disease (evaluate by symptom score or CT scan), and the coexistence of nasal polyps or allergic rhinitis do not predict the possibility of olfactory improvement after FESS (Bhattacharyya 2006; Wright and Agrawal 2007; Jiang et al. 2009).

Finally, Gudziol et al. (2009) explored the influence of the treatment of CRS on the olfactory function. They measured olfactory bulb volume, using MRI, and olfactory function of patients suffering from CRS before treatment and 3 months after. They showed that the olfactory bulb volume significantly increases after treatment and that the increase of olfactory bulb volume correlated significantly with an increase in odor thresholds.

10.3.4 Postinfectious Olfactory Loss

Postinfectious olfactory loss is defined as a sudden loss of olfactory function following an upper respiratory tract infection (URTI) and was described for the first time more than 20 years ago (Henkin et al. 1975). The upper respiratory infection subsides over time and leaves the patient with an olfactory dysfunction that persists over a long period. There is a close connection in time between the URTI and the onset of the olfactory disorder (Seiden 2004). The exact pathogenic agent is rarely determined but is assumed to be viral, and so this disease is known as “post-viral” or “postinfectious” olfactory loss.

The exact incidence of olfactory dysfunction following URTI is not known as many patients with URTI do not report their symptoms, so the exact incidence of common cold in the population is unknown. However, postinfectious olfactory loss is diagnosed in approximately one-quarter of the patients in groups presenting to specialized centers such as smell and taste clinics (Cain et al. 1988; Deems et al. 1991; Sugiura et al. 1998; Bonfils et al. 1999).

Patients with postinfectious olfactory loss are usually women, and the disease typically occurs between the fourth and the sixth decades of life (Sugiura et al. 1998; Seiden 2004; Rombaux et al. 2009a). Onset of the URTI is often sudden and awareness of the olfactory dysfunction is present when major symptoms secondary to the infection subside. Many patients also have endoscopic or radiological evidence of rhinosinusitis. It is therefore mandatory to treat this condition and observe the impact of this treatment on the sensorineural disorder. Patients usually complain of moderate to severe olfactory loss, but the degree of olfactory loss is usually less severe than in patients with head trauma (Duncan and Seiden 1995). Parosmia and phantosmia are also present and range to 10–50 % (Henkin et al. 1975; Leopold et al. 1991; Reden et al. 2007). Seasonal variation in the incidence of postinfectious olfactory loss has been demonstrated with the highest incidences being in March and May (Konstantinidis et al. 2006). This is probably due to the seasonal variation of viral particles such as parainfluenza virus type 3 (Sugiura et al. 1998; Suzuki et al. 2007; Wang et al. 2007).

Diagnosis should be based on (1) history of an olfactory disorder following a URTI and a close temporal relationship between the two, (2) patency of the olfactory cleft at the endoscopic examination, and (3) absence of any other causes such as toxic exposure (medication taken to treat the URTI and possibly causing an olfactory disorder themselves), an inflammatory process in the nasal fossa (diagnosed with an endoscopic evaluation), or neurological problems such as neurodegenerative diseases.

The exact mechanism leading to postinfectious olfactory loss is not yet fully understood. Viral particles may damage the olfactory receptor neuron and provoke immune response that also leads to damages in the olfactory neuroepithelium and damages the central olfactory pathways. Viruses are also capable of penetrating the brain via the fovea ethmoidalis. Many viruses may cause olfactory impairment, examples being the influenza virus, parainfluenza virus, respiratory syncytial virus, Coxsackie virus, adenovirus, poliovirus, enterovirus, and herpes virus. The exact determination of the viral agent is not useful in the clinic and viral serology is not mandatory. Experimental intranasal infection with influenza virus A leads to increased apoptosis and increased fibrosis in the olfactory neuroepithelium (Mori et al. 2002, 2004). This mechanism is thought of as a protective one that limits the access of viral particles to the brain. Histopathological findings relating to the olfactory neuroepithelium of patients with postinfectious olfactory loss have revealed that severely affected patients have reduced numbers of ciliated olfactory receptor cells (Doty 2008). Moreover, dendrites of the olfactory receptor neurons usually fail to reach the epithelial surface and therefore have no contact with odorant particles. Attempting to correlate the importance of the olfactory neuroepithelial damage with the extent of the olfactory dysfunction as well with the chances of recovery generated conflicting results (Yamagishi et al. 1994; Doty 2008). Overall, postinfectious olfactory loss is probably secondary to a viral attack both at a peripheral level (olfactory neuroepithelium) and at a central level (olfactory bulb), and these two sites interact both in the pathological condition and in the recovery phase.

MRI findings show that olfactory bulb is reduced in patients with postinfectious olfactory loss, and there is a strong correlation between olfactory bulb volume and the olfactory dysfunction, with the lowest olfactory bulb volume being in patients with severe olfactory dysfunction and parosmia (Mueller et al. 2005; Rombaux et al. 2006).

At present there is no medical therapy that has been proven effective. Many drugs have been tried in nonrandomized and uncontrolled trials: topical or systemic corticosteroids (Heilmann

et al. 2004), zinc sulfate (Henkin et al. 1976; Aiba et al. 1998), quinoxaline derivative (Quint et al. 2002), alpha lipoic acid (Hummel et al. 2002b), and pentoxifylline (Gudziol and Hummel 2009). Although early promising results with some molecules have been demonstrated, these medications helped patients to achieve partial or full recovery in unpredictable ways (Hummel 2000). Olfactory training has also been provided with some interesting results: 28 % of the patients achieved olfactory improvement (Hummel et al. 2009). Olfactory training was given for 12 weeks based on four different odors (phenylethyl alcohol, eucalyptus, lemon, cloves) and was required at least 10 min twice a day by this protocol. For patients with qualitative disorders such as phantosmia or parosmia, some authors advocate the surgical removal of the neuroepithelium, possibly damaging quantitative capacity but resolving the qualitative problem (Leopold et al. 2002). This option has been adopted in very few cases. Although such treatment is based on empirical grounds, patients with second or multiple episodes of olfactory dysfunction during an URTI should receive corticoid treatment if the olfactory loss persists after the URTI symptoms in order to reduce the risk of viral injury and permanent olfactory dysfunction.

The spontaneous recovery of olfactory performance is found, due to the plasticity of our olfactory system, in about one-third of the postinfectious olfactory loss patients (Hummel 2000). Olfactory function may decline (rare) or not change, show some improvement or a major improvement, and improve into the absolute normal range or into the range adjusted for age (London et al. 2008). Several prognosis factors have been described in the literature. Prognosis seems to be more favorable when the psychophysical testings reveal incomplete olfactory loss (i.e., hyposmia vs. anosmia) (Reden et al. 2006; London et al. 2008; Hummel and Lotsch 2010). Age and sex also seem to be important in the assessment of the prognosis since women and younger patients tend to recover more frequently than men and older patients (Reden et al. 2006). Another possible prognostic factor is the duration of the disease although results are more controversial for this factor (London et al. 2008; Hummel and Lotsch 2010). Electrophysiological measures are also predictive of recovery since it was demonstrated that the presence of olfactory event-related potentials at the time of diagnosis is linked to a better outcome in patients with postinfectious olfactory loss (Rombaux et al. 2010a). With regard to the meaning of qualitative olfactory disorders, reports have been mixed in relation to the likelihood of recovery (Reden et al. 2007; Hummel and Lotsch 2010). Finally, since postinfectious olfactory loss has a major impact on the daily life and there is no proven medical therapy, counseling patients and giving them the best prognosis for recovery seems to be of primary importance.

10.3.5 Posttraumatic Olfactory Loss

Posttraumatic olfactory loss was first described in the medical literature in 1864 by Hughlings Jackson, who described the case of a patient suffering from definitive anosmia after being knocked off his horse. Head trauma is, according to Nordin's literature review published in 2008, the third most common cause of olfactory disorder (Nordin and Bramerson 2008). The incidence of olfactory disorder following head injury is difficult to estimate because (1) patients admitted to emergency often fail to receive an assessment of their sense of smell due to the potentially life-threatening nature of head trauma and the frequent occurrence of other injuries requiring immediate medical attention; (2) the time and the resources for such an examination are lacking in emergencies; (3) patients are not able to recognize their loss of olfactory function, more especially when there is an associated neurological deficit; (4) there is no medical follow-up if the olfactory disorder has no subjective impact for the patient; and (5) there is a lack of reports about spontaneously resolving olfactory disorder. For these reasons, the reported incidence is probably underestimated and variable depending on recruitment: in patients seen at a head injury clinic, incidence is estimated at between 2 and 12 % (Reiter et al. 2004; Swann et al. 2006) and at between 8 and 20 % in smell and taste centers

(Deems et al. 1991; Nordin et al. 1996; Mori et al. 1998; Seiden and Duncan 2001; Bramerson et al. 2007; Reden et al. 2007).

The patients at most risk of posttraumatic olfactory loss are young male adults. This is thought to be related to increased severity of trauma in this population. In both sexes generally, patients aged over 70 are most at risk (Harris et al. 2006; Swann et al. 2006). The most common type of trauma is a fall in 61 % of patients, followed by car accidents in 20 % and assault in 13 % (Swann et al. 2006). Several risk factors for the development of posttraumatic olfactory loss have been described. They are (1) the severity of the injury with more severe trauma being at higher risk of olfactory dysfunction (Renzi et al. 2002; Eftekhari et al. 2006; Swann et al. 2006), (2) the impact location and direction with a higher prevalence of posttraumatic olfactory loss when the front or the back of the head is stuck rather than the side (Cross et al. 2006; Swann et al. 2006), and (3) the age of the patient, with a higher risk in the elderly patients (Harris et al. 2006). In addition, it is important to note that in a traumatic context, olfaction might also be affected by the treatment of the injury, possibly complicating the etiological diagnosis (i.e., neurosurgical procedures, facial fracture reductions, usage of drugs such as opioids, and antimicrobial agents).

Typically, patients experience a sudden onset of olfactory symptoms (Deems et al. 1991). This onset has been reported as having a more severe impact on quality of life (Hummel and Nordin 2005) compared with progressive olfactory disorders, which may go unrecognized (Landis et al. 2003). Head trauma produces, on average, a greater degree of olfactory decrement as compared with other etiologies of olfactory dysfunction (Deems et al. 1991; Harris et al. 2006). Posttraumatic olfactory disorder patients have anosmia ranging from 48 to 78 % and hyposmia ranging from 5 to 27.4 % (Leopold 2002; Reiter et al. 2004; Cross et al. 2006; Swann et al. 2006). Qualitative disorders are found fairly commonly in patients with head trauma. Parosmia is reported in 14–35 % of cases (Seiden and Duncan 2001; Bramerson et al. 2007; Reden et al. 2007) and phantosmia in 10–41 % of the patients (Nordin et al. 1996; Bramerson et al. 2007; Reden et al. 2007). The prevalence of parosmia tends to decrease over time.

Three possibly coexistent lesions are likely to cause posttraumatic olfactory loss (Reiter et al. 2004). First, injuries to the sinonasal tract with obstruction of the passage to the olfactory cleft can lead to an obstructive posttraumatic olfactory loss. Second, shearing of the olfactory nerves at the cribriform plate might induce an olfactory loss. A wound, a tearing, or a shearing of the axons as they emerge from the cribriform plate to enter the bulb above it may occur after (1) a translational shift of the encephala secondary to posteroanterior coup and contrecoup forces in the case of occipital impact or (2) fractures is the naso-orbito-ethmoid region involving the cribriform plate. Third, contusions and brain hemorrhage involving olfactory bulbs and/or the olfactory cortex might also produce an olfactory disorder.

No medical treatment has yet been proven to be effective, but olfactory training seems to be efficient also in case of posttraumatic olfactory loss (Hummel et al. 2009).

The prognosis seems to be reserved: some improvement may be expected in about one-third of the patients, although complete recovery is only achieved in 10–15 % (Deems et al. 1991; Reden et al. 2006, 2007; London et al. 2008). Recovery is most likely to occur within the first 6 months to 1 year after the initial insult (London et al. 2008). However, late recovery has been described, occurring until 9 years after the trauma (Sumner 1964; Zusho 1982; Mueller and Hummel 2009).

10.3.6 Congenital Anosmia

Congenital anosmia is defined as the absence of olfactory sensation since birth or early childhood. This condition can be divided in (1) syndromic anosmias (e.g., Kallmann's syndrome (Kallmann et al. 1944) and Klinefelter's syndrome (Hazard et al. 1986; Pawlowitzki et al. 1987), congenital insensitivity to pain (Goldberg et al. 2007; Weiss et al. 2011), and ciliary dysfunction (Kulaga et al.

2004; McEwen et al. 2007) or (2) anosmias without evidence of other defects (isolated anosmia since birth or early childhood), which seems to be more frequent than syndromic anosmia (Jafek et al. 1990; Leopold et al. 1992; Yousem et al. 1996; Assouline et al. 1998). Although 5 % of the general population is anosmic (Landis et al. 2004), congenital anosmia remains a rare cause of olfactory disorder, and isolated congenital anosmia account for about 1 % of anosmias.

Diagnosis of congenital anosmia is based on anamnesis (patients have no recollection of ever being able to smell), psychophysical and electrophysiological assessment of olfactory function and imagery. Magnetic resonance imaging is the imaging modality of choice for the assessment of olfactory apparatus in cases of suspected congenital anosmia. Indeed, we know from the literature that in isolated anosmia and in Kallmann's syndrome, the olfactory bulb and olfactory tract can be aplastic or hypoplastic (Klingmuller et al. 1987; Truwit et al. 1993; Abolmaali et al. 2002). The depth of the olfactory sulcus is also a useful indicator of congenital anosmia since we know that the depth of the olfactory sulcus at the level of the "plane of the posterior tangent through the eyeballs" reflects the presence of olfactory bulbs and tracts (Abolmaali et al. 2002) and clearly indicates isolated anosmia if it is smaller than 8 mm (Huart et al. 2011).

When diagnosing a congenital anosmia, it should be discussed to realize a genetic and endocrinological evaluation. Also, since this disease cannot be treated, it is mandatory to give the patient or its parents the best information about this disease and to give counseling about everyday life (i.e., gas and smoke alarms, particular attention when cooking, and hygiene).

10.3.7 Neurological Disorders

It is well known that some neurodegenerative diseases, such as idiopathic Parkinson's disease and Alzheimer's disease, are associated with early olfactory dysfunction (Mesholam et al. 1998). Because of the high prevalence of these neurodegenerative diseases in elderly subjects, the early diagnosis of these diseases constitutes a major public health issue for our aging societies. At present, the early differential diagnosis between idiopathic Parkinson's disease and parkinsonism associated, for example, to multiple system atrophy, Lewy body disease, or corticobasal degeneration remains difficult, such as the differential diagnosis of mild cognitive impairment that may be the early expression of Alzheimer's disease, but also other forms of neurodegenerative diseases, and late-life depression. Many studies have suggested that the evaluation of the olfactory function can contribute significantly to the early diagnosis of these pathologies.

In idiopathic Parkinson's disease (IPD), olfactory dysfunction was first described by Ansari and Johnson in 1975 (Ansari and Johnson 1975). Olfactory disorders are often considered as an early and reliable sign of idiopathic Parkinson's disease (IPD), since they are present in more than 90 % of all IPD patients (Hawkes et al. 1999; Herting et al. 2008). In accordance with the staging of Braak (Braak et al. 2003), it has been hypothesized that the early development of olfactory dysfunction is due to the early involvement of olfactory regions in the course of the disease. Several recent studies have shown that people suffering from idiopathic hyposmia or anosmia have an increased risk of developing IPD (Haehner et al. 2007; Ponsen et al. 2009) and that chemosensory event-related potentials are delayed or absent in IPD patients (Welge-Lussen et al. 2009). While IPD is associated with marked olfactory dysfunction leading to anosmia, other causes of parkinsonism are not associated with strong olfactory dysfunction. For example, olfactory disorders would be moderate in multiple system atrophy and absent in Parkin's disease and in vascular parkinsonism (Katzenschlager and Lees 2004).

Olfactory disorders can also constitute one of the first signs of Alzheimer's disease (AD) (Djordjevic et al. 2008). The time course of histopathological changes in AD also indicate that olfactory dysfunction should precede cognitive dysfunction. Indeed, it has been shown that the formation of neurofibrillary tangles occurs first in the entorhinal cortex, while cognitive symptoms

appear only once neuropathological changes have spread to the hippocampus and temporal neocortex (Djordjevic et al. 2008). Olfactory discrimination of AD patients is significantly lower than olfactory discrimination of patients suffering from mild cognitive impairment, which itself is lower than that of age-matched control subjects (Westervelt et al. 2008). In addition, a recent clinical study has shown that the olfactory bulb and olfactory tract volume is decreased in AD patients and that this atrophy is already present at an early stage of the disease (Thomann et al. 2009). Since early diagnosis of AD remains problematic, assessment of olfactory function should be useful for the early differential diagnosis of AD. This should be further investigated.

10.3.8 Olfactory Cleft Disease

Olfactory cleft disease is defined as an olfactory dysfunction due to a pathological process limited to the olfactory cleft that can be visualized on clinical or radiological examination. Only few authors have report this entity (Biacabe et al. 2004; Liu and Ni 2006; Trotier et al. 2007). Biacabe et al. showed that olfactory disability was the major symptom of olfactory cleft disease, and they identified three possible pathological processes inducing olfactory cleft disease – malformative, inflammatory, and inflammatory associated with anatomical deformities of olfactory cleft boundaries – and, hence, suggested that computed tomography scanning is useful for the diagnosis of this disease. Finally they showed that medical therapy was effective in lowering olfactory thresholds in 25 % of the cases. Nevertheless, until now, indications of functional endoscopic surgery remain to be defined after failure of medical therapy.

10.3.9 Miscellaneous

Several other pathologies that might affect the olfactory function, such as tumors, toxics, drugs, and endocrine disorder, have been described. They are reported in Table 10.2.

10.3.10 Idiopathic Olfactory Loss

For a large number of patients, no obvious etiology to the olfactory disorder can be found. These people are thus considered as suffering from idiopathic olfactory loss. The reported prevalence of idiopathic olfactory loss in the literature range from about 20 % (Deems et al. 1991; Reden et al. 2007) to one-third (Bramerson et al. 2007) of patients suffering from olfactory disorder. These patients not only complain of quantitative olfactory disorder but may also complain of qualitative olfactory dysfunction (Reden et al. 2007; Rombaux et al. 2010b).

Previous work has indicated that idiopathic olfactory loss may be related to sinonasal disease. In fact in a study of 55 patients, almost one-third of patients with idiopathic olfactory loss responded to systemic treatment with corticosteroids (Heilmann et al. 2004), possibly indicating the presence of inflammation-related dysfunction. Hence, systemic steroid trial should be proposed to patients suffering from idiopathic olfactory loss. Olfactory training seems to be effective and should thus be proposed to patients suffering from idiopathic olfactory loss (Hummel et al. 2009).

Finally, it is important to keep in mind that some patients with idiopathic olfactory loss may develop idiopathic Parkinson's disease or Alzheimer's disease (Koss et al. 1988). Haehner et al. (2007) observed that over the course of 4 years, 2 out of 30 patients suffering from idiopathic olfactory loss developed clinically manifest idiopathic Parkinson's disease.

10.3.11 Olfaction and Quality of Life

We must note that olfactory dysfunction severely impairs the quality of life of patients, including detection of hazardous events, eating habits and cooking, nutritional intake, and interpersonal relations (Temmel et al. 2002). Furthermore, it has been demonstrated that patients suffering from olfactory disorders have a higher prevalence of mild to severe depression as compared

to the general population (Deems et al. 1991). Using questionnaire of olfactory disorder and psychometric tests, some authors reported that patients suffering from quantitative olfactory impairment significantly complain more than patients with normosmia and this was even more important if they had associated parosmia (Frasnelli and Hummel 2005; Neuland et al. 2011). Indeed, parosmia leads to higher rate of mild depression than quantitative olfactory disorders. Finally, since patients reporting an improvement of their olfactory abilities have a better quality of life than patients reporting no improvement (Miwa et al. 2001), it is essential to investigate about the etiology of olfactory dysfunction in instance to provide an optimal treatment to the patients.

Several studies have also highlighted the link between age-related olfactory loss and nutritional disorders in older people. As reported earlier, there is a physiological decrease of olfactory function with advancing age. This age-related olfactory disorder impacts negatively the food intake of older people. Indeed, not only older people might have a reduced interest in food and, hence, reduced food intake but also they tend to have less varied diet and consequently might develop deficiencies. This is problematic since inadequate diet and malnutrition are associated with a decline in functional status, impaired muscle function, decreased bone mass, immune dysfunction, anemia, reduced cognitive function, poor wound healing, and delay in recovering (Ahmed and Haboubi 2010). This may constitute a major public health issue in our aging population.

10.3.12 Counseling of the Patient

Consequences for daily life and coping strategy should be integrated in clinical management of patients, focusing on instructional information about fire alarms, domestic gas, hygiene, etc.

Nutritional recommendations should also be proposed to the patients in order to avoid altered food choices and consumption patterns than can negatively impact health (decreased body weight, overuse of salt inducing blood hypertension, overuse of sugar inducing diabetes mellitus, impaired immunity, etc.).

Finally, as reported earlier, olfactory training seems to be effective and should thus be recommended to patients (Hummel et al. 2009).

Conclusion

Describing the olfactory pathways, we have shown that olfactory system has connections with brain areas associated with memory processes, feeding circuits, and emotional, motivational, and craving circuits. Hence, it is easy to understand that, although often neglected, the olfactory system plays a preponderant role in our everyday life and strongly influence consciously or nonconsciously on emotions, social behavior, nutrition, memory, etc. Therefore, we can easily understand that olfactory disorders severely impact our quality of life and that patients suffering from olfactory disorders need a particular support. Indeed, physicians taking care of patients suffering from olfactory disorders must pay a particular attention to the quality of life of patients and to the potential negative impact of olfactory dysfunction on the patient's health (nutrition, detection of danger, depression, etc.).

Since medical and surgical treatments are still missing today, it is mandatory to know the pathologies associated with olfactory disorder and to be able to assess the olfactory function of patients in order to provide them complete information about the nature of their olfactory disorder and their prognosis, as well as advices about occupations, safety at home, and how to make food more palatable and safe to eat.

Nowadays, about 20 % of the population is hyposmic. But this number could increase in the future years due to our aging population. This might constitute a major public health issue in the future years considering the close relationship between olfactory dysfunction and nutritional disorders in elderly people. Further researches are thus mandatory in order to propose new treatments to recover or to compensate for the olfactory loss.

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Physiology and Pathophysiology of Sneezing and Itching: Mechanisms of the Symptoms

11

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Keywords
Sneeze reflex • Sneezing • Itching • Physiology • Pathophysiology

Core Messages

- Despite its being such a commonplace phenomenon suffered the world over, little is known about the sneeze reflex action, which sometimes becomes a sign associated to a series of different medical conditions.
- The sneezing reflex may be divided in two phases. The first is a nasal or sensitive phase, following stimulation of the nasal mucosa by chemical or physical irritants. The efferent or respiratory phase consists of eye closing, deep inspiration, and then a forced expiration with initial closing of the glottis and increasing intrapulmonary pressure. The sudden dilatation of the glottis gives rise to an explosive exit of air through the mouth and nose, washing out mucosal debris and irritants.
- Clinical studies using positron emission tomography indicate that there is no isolated itching center in the brain but that there are different cortical centers which are involved in the processing of the itch.
- The factors that play role in the etiology of sneeze reflex are rhinitis, photic sneeze reflex, physical stimulants of the trigeminal nerve, central nervous system pathologies, psychogenic sneezing, snatiation reflex, and sexual ideation.

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Sneeze is a coordinated protective respiratory reflex which occurs due to stimulation of the upper respiratory tract, particularly the nasal cavity (Songu and Cingi 2009). Apparently, activation of the central and peripheral nervous system plays a major role in the pathophysiology of this process. Sensory nerves of the afferent trigeminal system including myelinated Aδ-fibers and thin, nonmyelinated C-fibers of the nasal mucosa transmit signals generating sensations, including itching and motor reflexes, such as sneezing. These nerves can be stimulated by various reasons. Sneeze reflex frequently accompanies rhinitis of allergic or nonallergic origin. Sneeze can also arise due to bright light or sun (ACHOO syndrome), physical stimulants of the trigeminal nerve, psychogenic or central nervous system pathologies, and even due to a full stomach (snatiation reflex) or a sexual ideation. In this chapter, we aimed to review the physiology, pathophysiology, etiology, diagnosis, treatment, and complications of sneezing and itching.

11.1 Historical Perspective

Sneezing has always been a remarkable sign and a noteworthy occurrence throughout the history. In Asia and Europe, the sneezing superstition extends through a wide range of race, age, and country. Homer tells in his epic literary work, Odysseia, that Penelope rejoiced greatly when her son Telemachus sneezed when she expressed a wish. In another part in Odysseia, the Athenian General Xenophon gave a dramatic speech exhorting his fellow soldiers to follow him to liberty or to death against the Persians. He spoke for an hour motivating his army and assuring them a safe return to Athens until a soldier underscored his conclusion with a sneeze. Thinking that this sneeze was a heavenly favorable sign from the gods, the whole army sprang to an attack. Xenophon's death after destruction of his army by the Persians can be considered as the first complication of sneezing in history. Hippocrates has mentioned that sneezing is dangerous only prior to or following a pulmonary disease. Otherwise, it is beneficial, even in patients with fatal illnesses. Celsus of Rome has suggested that sneezing is an evidence of convalescence from illness. Aristotle has proposed that sneezing is a holy sign since it arises from lungs which are the principle and most divine parts of the body (Aristotle 330BC; Disraeli 1864; Prioreschi 1998). The Greeks and the Romans took sneezing as a sign of wellness and expressed their good wishes to the person who sneezed using the phrase "live long" or "May Jupiter bless you." In pagan culture, a person who sneezed was believed to get rid of the devil in his body and was congratulated passionately in every medium. It was also believed that sneezing made a person's body open to invasion by the Satan and evil spirits or even caused part of one's soul being "thrown out of the body." The remnant of this pagan tradition still exists today in the expression "live a long life" or "God bless you." After the pandemics of the plague in Europe, the view of sneezing changed and it began to be assumed as a sign of a great danger. In the fourteenth century, during the great pandemic of plague, the so-called *black death*, Pope Gregory VII declared the sentence "May God bless you" as a short prayer to be said following every sneeze to protect against the plague (Ovesen 2003). However, the plague eliminated one third of the European population since the Pope, or the powers that be, failed to think of taking measures in order to protect the public against the disease-causing rats or the fleas, which were the real vectors. This short prayer used in the past by the Christian population as a protection against disease is now a common everyday expression which has been passed on to the modern Christian society as an inheritance (Knowlson 1910).

In the Talmud, which consists of religious texts including the Jewish law and history, it is considered to be a favorable omen if someone sneezes while praying. It is a sign that just as God looks favorably toward him on earth so too will he look favorably toward him in heaven. According to a common belief that still exists in the Republic of China and Japan, if a person sneezes without a reason, this means that somebody else is talking about him. It is believed that good things are told about him if he sneezes once

and bad things if twice. In Naples the person who sneezes thinks that he is remembered by another person. In the Indian folkloric culture, sneezing before starting a work is believed to bring bad luck; therefore, the work is started after a glass of water is drunk to avoid bad luck (Knowlson 1910).

11.2 Physiology and Pathophysiology

The largest part of the nasal cavity and the paranasal sinuses are covered by a multilayered ciliated epithelium in the respiratory region. Olfactory cells, sustentacular cells, and submucosal adenoids are located in the roof of the nose including areas of the medial and upper nasal concha and upper septum in the olfactory region (Klimek et al. 1997). The nasal mucosa is covered by a bilayered secretion film which is produced by submucosal adenoidal and goblet cells. This secretion film includes a low viscous sol film in which cilia move and an apical, highly viscous gel film. This specific assembly serves the physiological cleaning of respiratory air through the mucociliary apparatus. Cholinergic input causes an increased secretion of the submucosal cells. However, goblet cell stimulation has also been shown by substance P (SP) releasing sensory nerves in a rat model (Kovacs et al. 2005). The cavernous tissue of the nasal concha consists of venous sinusoids and regulates the respiratory resistance. Filling of these sinusoids is regulated by sympathetic stimulation as adrenergic fibers are distributed around arteries, arterioles, and veins of the human nasal mucosa (Klimek et al. 1997).

The sneezing reflex may be divided in two phases. The first is a nasal or sensitive phase, following stimulation of the nasal mucosa by chemical or physical irritants. Many distal branches of trigeminal nerve terminate in the facial skin transmitting tactile, pain, and temperature sensations while some branches distribute in the nasal mucosal epithelium (Nishino 2000). These branches are myelinated sensory fibers of small diameter which terminate with receptor endings. Some of these receptors are triggered by chemical stimuli while others are sensitive to tactile and mechanical stimuli (Nishino 2000). Afferent neural stimuli are transmitted to the trigeminal ganglion via anterior ethmoidal, posterior nasal, infraorbital, and ophthalmic branches of trigeminal nerve (Wallois et al. 1991). The trigeminal nerve is important for the nociceptive sensory supply of the nasal mucosa in addition to the face, oral mucosa, cornea, and conjunctiva. Itching and sneezing are generated by the activation of trigeminal afferent nerve terminals in the nasal mucosa (Widdicombe 1990). These nociceptive nerve fibers consist mainly of two types of fibers: the thin Aδ-fibers that mediate acute perceptions with a quick adaption and activation only during the actual irritation and the nonmyelinated C-fibers which adapt slowly and communicate dull burning, difficult to locate perceptions, which outlast acute pain (Torebjork and Hallin 1973). In allergic rhinitis, immunologically triggered inflammation results in the recruitment and activation of both types of fibers that result clinically in itching and sneezing (Ader et al. 1995).

Clinical studies using positron emission tomography indicate that there is no isolated itching center in the brain but that there are different cortical centers which are involved in the processing of the itch (Pfaar et al. 2009; Hsieh et al. 1994). Activation of the anterior gyrus cinguli, the supplementary motor cortex, and the inferior parietal lobe partly explains the connection between itching and the related reflex of scratching (Schmelz et al. 1997; Suranyi 2001). Using functional MRI, the activation of corresponding cortical units following painful trigeminal stimulation has been shown (Hummel et al. 2005). In this regard, neuropeptides produced in the cell body of C-fiber neurons can also be transported in granule structures within the cytoplasm to nerve terminals in the central nervous system. This leads to "central sensitization," a phenomenon associated with activation of nociceptive C-fibers (Sarin et al. 2006).

Upon reaching a threshold, the second phase—the efferent or respiratory phase—begins once a critical number of inspiratory and

expiratory neurons have been recruited (Batsel and Lines 1975). This consists of eye closing, deep inspiration, and then a forced expiration with initial closing of the glottis and increasing intrapulmonary pressure. The sudden dilatation of the glottis gives rise to an explosive exit of air through the mouth and nose, washing out mucosal debris and irritants.

The number of particles expelled during a forceful sneeze, of which the sizes range from 0.5–5 μm, is estimated to be 40,000. The estimations concerning the speed of a sneeze range between 150 and 1,045 km/h (nearly 85 % of the sound velocity) (Nishino 2000).

11.3 Etiology

The factors that play role in the etiology of sneeze reflex are listed in Table 11.1.

Table 11.1 Etiology of the sneeze reflex

(A) Rhinitis
(B) Photic sneeze reflex (ACHOO syndrome)
(C) Physical stimulations of the trigeminal nerve
(D) Central nervous system pathologies
(E) Psychogenic (intractable) sneezing
(F) Snatiation* reflex
(G) Sexual ideation or orgasm

11.3.1 Rhinitis

It is the inflammation of the nasal mucosa causing nasal stuffiness, rhinorrhea, nasal pruritus, and sneezing (Bousquet et al. 2001).

11.3.1.1 Allergic Rhinitis

Allergic rhinitis is the inflammation of the mucosa lining the nasal cavity in the form of IgE-dependant type I hypersensitivity reaction (Bousquet et al. 2001). Allergic rhinitis is a common disorder, which represents a considerable burden both on individual patients and on society (Ozdoganoglu and Songu 2012; Cingi et al. 2010b). Itching and sneezing represent two of the main bothersome symptoms, apart from nasal obstruction and rhinorrhea in allergic rhinitis (Ozdoganoglu et al. 2012). In allergy-related nasal inflammation, it can be demonstrated that especially the neurotransmitter SP is released by C-fibers (Ader et al. 1995; Kim and Baraniuk 2007). SP is significantly increased in the nasal lavage of patients with allergic rhinitis, in contrast to healthy subjects, which is interpreted as a sustained stimulation of the sensory system (Klimek and Schäfer 1996). Exogenically administered SP results in a dose-dependent occurrence of nasal symptoms in asymptomatic patients with allergic rhinitis and controls, without elevation of inflammatory mediators. In addition to SP, other neuropeptides, including calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP), are increased in nasal lavage fluids after nasal provocation in allergic rhinitis (Mosimann et al. 1993). An important feature of allergic rhinitis is hyperresponsiveness influenced by products of the allergic reaction including eicosanoids; cytokines such as IL-6, Il-1β, and TNF-α; and, most importantly, neurotrophins including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). NGF targets nociceptor fibers, leading to upregulated activity, increased SP content, and dendrite sprouting (Levi-Montalcini 1987). The allergen-induced increased BDNF expression in the nasal mucosa significantly correlated with the maximal increase of total nasal symptom score in allergic rhinitis (Raap et al. 2008) (Fig. 11.1).

11.3.1.2 Infectious Rhinitis

In more than 50 % of cases, rhinovirus is the responsible agent for common cold (nasopharyngitis) which is the most common clinical form of viral infections. Inhalation, close contact with the infected person, contact with the objects contaminated with the virus such as door handles, school desks, household goods or phones, are all ways of contracting the virus. The most common prodromal manifestations include high fever, nasal irritation, and sneezing. Nasal symptoms are also present in influenza (flu) caused by influenza virus; however, they are likely to be overshadowed by malaise, fatigue, myalgia, and high fever. Bacteria may infiltrate the tissue and cause

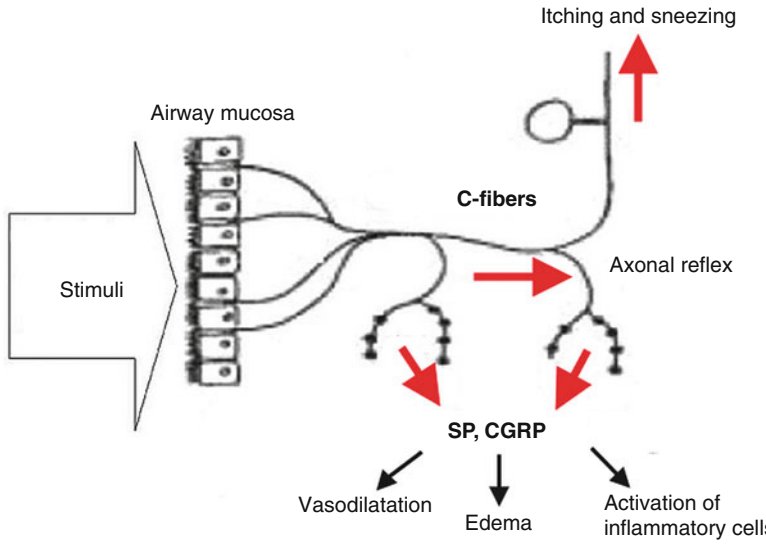

Fig. 11.1 Schematic presentation of the processes involved in "neurogenic inflammation" leading to itching and sneezing. Activation of afferent trigeminal C-fibers by several stimuli including allergen contact may result in an efferent liberation of substance P (*SP*) and calcitonin gene-related peptide (*CGRP*) via axonal reflex. This further leads to vasodilatation, edema, and recruitment/migration of inflammatory cells

infections during the course of viral rhinitis due to impairment of mucosal integrity and ciliary function. Clinical picture of rhinitis may occur during the course of specific bacterial diseases such as diphtheria, rhinoscleroma, lepra, tuberculosis, syphilis, and glanders. Opportunistic fungal infections which develop in AIDS, chemotherapy, prolonged intensive care unit stay, and disorders of neutrophil number and function such as neutropenia and diabetes may cause rhinitis.

11.3.1.3 Nonallergic Noninfectious Rhinitis

Every sneezing paroxysm does not mean an allergic rhinitis or common cold. There are also many rhinitis clinical pictures of unknown etiology that may cause sneezing and are classified as "nonallergic noninfectious rhinitis." The commonly observed clinical pictures in this group are NARES and vasomotor rhinitis and are usually confused with allergic rhinitis.

NARES (Nonallergic Rhinitis with Eosinophilia Syndrome)

It is a nasal hyperreactivity syndrome, manifested by sneezing paroxysms and watery discharge followed by nasal stuffiness and hyposmia in which the increased eosinophil count exceeds 20 % of total leukocyte number in the absence of an IgE-dependant allergy (Dykewicz et al. 1998). The suspected etiology is the infiltration of circulating eosinophils into the site of inflammation because of the increased level of substance P as a result of alterations within the nasal mucosa due to irritation, senility, or other factors.

Idiopathic (Vasomotor/Nonallergic and Non-eosinophilic) Rhinitis

It is a short course hyperreactive nasal mucosal disease of sudden onset manifested by nasal stuffiness, watery nasal discharge or postnasal drip, and sneezing. Eosinophilia is not found in nasal secretions and allergy tests are negative. The most important clinical feature that differentiates vasomotor rhinitis from NARES is the sudden onset of the symptoms which relieve immediately following disappearance of triggering factors. Environmental factors including cold and dry air, high amount of moisture, dyes, chlorine water, perfume, tangs, cigarette smoke, exhaust gas, and other inhaled irritants may initiate the symptoms of vasomotor rhinitis. A typical

example is a sudden onset of nasal stuffiness and short-lasting though forceful sneezing paroxysm in the morning time after being exposed to cold and dry air. Individual factors such as fatigue, stress, and sexual activity may develop the clinical picture as well (Fairbanks and Kaliner 1998).

11.3.1.4 Others Causes of Rhinitis

Many other clinical pictures classified as nonallergic and noninfectious rhinitis are also common causes of sneezing. *Occupational rhinitis* is the most commonly observed one among these clinical pictures and is triggered by dense cigarette smoke, cold air, air fresheners, formaldehyde, and other chemical irritants in the workplace (Stevens 1991; Dykewicz et al. 1998). *Hormonal rhinitis* may occur in cases of physiologically increased levels of estrogen such as puberty, menstrual cycle, and pregnancy or in case of receiving exogenous estrogen while on oral contraceptives (King and Mabry 1993; Dykewicz et al. 1998). Inhibiting acetylcholinesterase activity, estrogen leads to edema formation in the nasal mucosa while progesterone causes congestion through vasodilatation in capacitance vessels and sneezing occurs (Incaudo 2004). As a result of sympathetic hypoactivity in hypothyroidism, parasympathetic activity relatively increases leading to vasodilatation in the nasal mucosa and an increase in secretions. Drug-induced rhinitis may be manifested in two clinical patterns. In *medicamentous rhinitis* many drugs affect nasal mucosa through different mechanisms of action and cause sneezing. It is usually observed in treatments with antihypertensive drugs (reserpine, guanethidine, phentolamine, methyldopa, hydralazine, and prazosin), beta blockers (propranolol, nadolol), aspirin, and other NSAIDs (Cingi et al. 2011). *Rebound rhinitis,* on the other hand, develops as a result of prolonged usage of vasoconstrictor drops or sprays (King and Mabry 1993; Dykewicz et al. 1998; Fairbanks and Kaliner 1998). In *geriatric rhinitis*, atrophy in submucosal glands due to senility and severe irritation in sensitive nerve endings result in nasal stuffiness and sticky and thick mucus which may cause sneezing. *Atrophic rhinitis* is a rare pathological condition in etiology of which bacterial infections, deficiency of vitamin A or D, and iron or estrogen deficiencies are suspected. In contrast to clinical conditions concerned, many different factors may develop irritant-induced rhinitis and cause sneezing (Fairbanks and Kaliner 1998). Some of these include dust, smoke, perfume, powder, sharp odor, ammonia, inhalation of corrosive gases or chemicals, mechanical obstruction of the nasal cavity, chymic irritation due to cauterization or silver nitrate application, capsaicin, application of airflow into superior nasal meatus by a catheter, and repetitive nasal electrical stimulation (Imamura and Kambara 1992; Kitajiri et al. 1993; Kira et al. 1997). Capsaicin, the active ingredient obtained from hot chili peppers, stimulates the nasal small unmyelinated C-fiber afferent nerves to release various tachykinins. These nerves, with their somata in the trigeminal ganglion, transmit the information to the central nervous system through the trigeminal dorsal horn in the medulla and lead to sneezing and a sense of pain (Geppetti et al. 1988). Although various peptides and tachykinins may be involved, it appears that the capsaicin-induced release of substance P is the most potent trigger of the sneezing response (Kitajiri et al. 1993; Imamura and Kambara 1992). Capsaicin also precipitates sneezing through a local axon reflex (Canning 2002).

11.3.2 Photic Sneeze Reflex

It seems that *some* people really do sneeze when they look at the sun or actually at any bright light (there is nothing special about the sun). Photic sneeze reflex is also called ACHOO (*a*utosomal dominant *c*ompelling *h*elio-*o*phthalmic *o*utburst) syndrome (Collie et al. 1978). This reflex was first described in the medical literature by Sedan in 1954 (Sedan 1954). It was shown to have an autosomal dominant inheritance pattern and is assumed to affect 17–35 % of the world population (Morris 1987). Photic sneeze reflex has been reported to be present in 23 % of medical students (Everett 1964). According to a Swedish study, 24 % of blood donors experienced sneezing on visual exposure to strong light (Beckman and Nordenson 1983).

We do not know exactly why this happens, but it might reflect a "crossing" of pathways in the brain, between pupillary light reflex arc and sneezing reflex arc. The reflex can be triggered only after the first exposure to light, never on repetitive stimulation, and many reports cite a refractory period before the reflex can be elicited suggesting that a polysynaptic pathway is involved. The first theory concerning the pathways mentioned belongs to Eckhardt et al. who suggested that stimulation of the optic nerve triggers the trigeminal nerve (Eckhardt et al. 1943). The afferent impulses of pupillary light reflex are transmitted via the optic nerve while the efferent impulses are transmitted via the oculomotor nerve. According to this theory, an indirect impulse is transmitted to the ophthalmic division of the trigeminal nerve. This impulse generates the nasal stimulation that causes sneezing by affecting the maxillary division of the trigeminal nerve as well. The second theory of crossing pathways belongs to Watson. Light falling on the retina stimulates afferent fibers to the pretectal nuclei, which then send interneurons to the Edinger-Westphal nuclei. The parasympathetic fibers from the Edinger-Westphal nuclei and the trigeminal afferent fibers from the cornea both pass through the ciliary ganglion, where they may participate in transmission (Watson 1875). Parasympathetic generalization may also contribute to photic sneeze. Stimuli which excite primarily one branch of the parasympathetic nervous system tend to activate other branches. Thus, the parasympathetic branches of the oculomotor nerve which are activated to generate pupillary constriction against the bright light cause secretion and congestion in the nasal mucosa by triggering the parasympathetic activation by the pterygopalatine ganglion. This process triggers sneezing (Brubaker 1919).

What is the benefit of photic sneeze reflex? Photic sneezing reflex exists in animals for which the smell sensation is vital to survive and can be used to clean the nasal cavity. Animals such as cats and dogs sneeze largely through their nose while the adults sneeze through their mouth. The reflex arc may also be useful to a limited extent in human beings when it is considered that the nasal respiration is dominant in the neonatal period. Babies have no other way to get rid of the annoying little tickle caused by normal mucus. Young children sometimes have more disgusting ways of dealing with that sensation, but babies just sneeze often with the help of photic sneeze reflex.

In conclusion, photic sneeze reflex, which can lead the drivers to have accidents following a sudden exposure to sunlight at the end of a long tunnel, or can cause a plane crash by inactivating the masks of jet pilots, can be considered to be an annoying "holdover" of evolution (Benbow 1991; Breitenbach et al. 1993).

11.3.3 Physical Stimulants of the Trigeminal Nerve

Physical or mechanical stimulants in the innervation zone of the trigeminal nerve may trigger sneezing reflex. Some of these stimulants include pulling hair, tearing off eyebrows, or orbital injections administered frequently during ocular surgery under local anesthesia (Wallois et al. 1997; Sekizawa et al. 1998).

11.3.4 Central Nervous System Pathologies

The lateral medullary syndrome (LMS), or Wallenberg's syndrome, often results from occlusion or dissection of the vertebral artery. Vertebral artery dissection has been blamed on many different life events, such as sneezing (Schievink 2001). Paroxysmal sneezing at the onset of LMS is usually interpreted as a cause, since a violent sneeze could potentially result in a vertebral artery dissection causing LMS. Due to inactivation of sneezing center in LMS, sneezing cannot occur although the sensation of sneezing is present (Martin et al. 1991; Hersch 2000; Bernat and Suranyi 2000). Localization of the human sneeze center was described in a patient with right LMS, initially presenting with violent sneezes and followed by brief loss of the sneeze reflex with eventual recovery (Seijo-Martinez et al. 2006).

Sneezing may commonly accompany temporal lobe and grand mal epilepsy. It may be observed during the aura prior to an epileptic seizure or it may develop as an autonomic reflexive response during the seizure as well (Penfield and Kristiansen 1951; Penfield and Jasper 1954). Beverwyck commented upon the analogy of the epileptic seizure with hiccups and sneezing and noted that the physiological and anatomical basis for such a hypothesis remained to be unexplained (Temkin 1945). In the mid-nineteenth century, Jackson used the term epilepsy "as the name for occasional, sudden, excessive, rapid and local discharges of grey matter" (Jackson 1958). Jackson further commented upon the healthy and yet random discharge and concluded that "a sneeze is a sort of healthy epilepsy."

11.3.5 Psychogenic (Intractable) Sneezing

Intractable sneezing, first described by Shilkrel in 1949, is a rare pathological condition that has been detected in more than 50 cases in literature up to present (Shilkrel 1949; Bhatia et al. 2004; Sulemanji et al. 2011). Kanner referred to a 13-year-old girl who had incessant sneezing for over 2 months and whose progress was followed by a daily newspaper communique (Kanner 1957). A diagnosis of hysteria was made and subsequent psychotherapy eliminated the sneezing. Yater referred to similar explosive repetitious episodes and considered them to be a sort of imitation of the true act of sneezing (Yater and Barton 1942).

Psychogenic intractable sneezing occurs mainly in adolescent girls for which a cause may not be found. Organic lesions or causes should always be carefully excluded (Sulemanji et al. 2011). Patients are usually refractory to various medications and have an otherwise unremarkable extensive workup (Bergman 1984; Lin et al. 2003). Inspiratory phase is quite short and the amount of nasal mucosal secretion expelled very low. Eyes may remain open during sneezing. It usually develops due to psychogenic factors and is refractory to medical treatment (Gopalan and Browning 2002). Approximately 25 % of the reported cases resolve without any form of treatment, except counseling of the patient and family (Sulemanji et al. 2011). Psychogenic sneezing responds well to psychological measures such as psychotherapy, biofeedback, relaxation exercises, supportive psychotherapy (i.e., explanation of nature of illness, suggestion to overcome symptoms), and behavior therapy (reward when there is symptom reduction, aversion therapy, hypnosis, and relaxation). The role of anxiolytic drugs lies in reducing underlying anxiety and making the patient more amenable to psychotherapy (Guner et al. 2010).

Medically unexplained physical symptoms usually carry diagnostic difficulties for the physicians (Sulemanji et al. 2011). The most important factors that increase these diagnostic difficulties are the possibility of an underlying physical illness and the uncertainty encountered as to how far the investigations for physical causes should go. It was determined that in some somatization patients, organic pathologies were revealed during follow-up. Paradoxically, it is known that repetitive and advanced investigations for any organic etiology in conversion disorder may increase the anxiety and doubts in the family and thus prolong the duration of the illness. In conclusion, one must not assume that every case of paroxysmal sneezing is of psychogenic origin. Due to the nature of such a disorder, these patients should undergo medical evaluations before a psychogenic cause is even considered.

11.3.6 Snatiation* Reflex

An uncontrollable sneezing attack developing as a result of stretching of the stomach following an excessive nutrition is first described by Teebi et al. as a reflex with autosomal dominant inheritance pattern (Teebi and Al-Saleh 1989). The mechanism of development is unknown. Snatiation* is a combination of the words "sneeze" and "satiation." Snatiation also stands for "*S*neezing *N*oncontrollably *A*t a *T*une of *I*ndulgence of the *A*ppetite-a *T*rait *I*nherited and *O*rdained to be *N*amed" (Hall 1990). This abbreviation was supposed to facilitate the future cases

to be evaluated in the same class. Recently, two patients have been reported, who state that several members of their family sneeze on a full stomach (Bhutta and Maxwell 2009). This report doubles the number of families with snatiation reflex in the medical literature.

11.3.7 Sexual Ideation or Orgasm

An association between sexual excitement and sneezing was first described in the nineteenth century (Watson 1875; Mackenzie 1884) followed by a young German otolaryngologist who developed a theory of "nasal reflex neurosis" due to the finding of erectile tissue in both nasal mucous membranes and genital areas (Young 2002; Jones 1974). The first report of this phenomenon in the literature describes a 69-year-old man who complains of severe sneezing immediately following orgasm, with no associated psychiatric morbidity (Anonymous 1972). Stromberg in 1975 and Korpas in 1979 described male orgasm as a precipitant for the sneeze reflex (Stromberg 1975; Korpas and Tomori 1979). Recently, Bhutta described a middle-aged man with uncontrollable fits of sneezing with sexual thought. The patient had no other rhinological symptoms and psychiatric morbidity (Bhutta and Maxwell 2008). Bhutta et al. performed a search of Internet "chat rooms" and found 17 people of both sexes reporting sneezing immediately upon sexual ideation and three people after orgasm. Although Internet reports do not give an accurate incidence, their findings do suggest that it is much more common than recognized.

11.4 Diagnosis, Differential Diagnosis, and Management of Rhinitis

The evaluation of a patient with sneezing should be individualized according to the duration and severity of the symptom. Laboratory tests are not necessary in the majority of patients, since the diagnosis is usually obvious from the history and physical examination.

It should be remembered that the history of the patient is the most important and determining stage for the diagnosis (Kramer 2006). The patient should be asked what his/her main complaint is; the duration and frequency of the symptoms like nasal discharge, stuffiness, and pruritus if present; whether the nasal discharge or stuffiness is present on one side or both, perennial or seasonal; whether he/she has allergic complaints, past trauma, past nasal surgery history, known diseases, and drugs used; and also how these symptoms effect the quality of life. In female patients it is also important to ask whether she is pregnant or on oral contraceptives (Incaudo 2004). One of the most common signs of allergic rhinitis in children is a horizontal creasing over the nasal tip. This physical examination sign develops as a result of habitual rubbing, which is also called *allergic salute,* after a duration of at least 2 years, a repeated action in order to relieve pruritus and improve respiration. This habit may turn into facial grimacing in adulthood for social reasons. *Allergic shiner*, on the other hand, is permanent pigmentation on the skin of lower eyelid which present as dark circles at the beginning stage. It develops due to subcutaneous hemosiderin through a capillary leak during periorbital venous stasis as a result of nasal mucosal congestion. *Dennie-Morgan folds* are short semilunar lines or folds found below the inferior eyelid. These lines develop due to venous blood retention cause by continuous spasm of Müller's muscle under the inferior eyelid. *Silky long eyelashes* are another outstanding concomitant sign of allergy. Clinical examination including anterior rhinoscopy and nasal endoscopy provides large information about pathologies related to septum and lateral nasal wall. Allergy is prediagnosed with medical history and physical examination. If the patient has a medical history and complaints that are compatible with allergy, in vivo (prick test, SET, scratch test) and/or in vitro (serum-specific IgE) allergy tests should be performed (Settipane and Klein 1985). The skin prick test is the most common epidermal test. A positive allergen skin test that is compatible with the medical history and findings of physical examination should be assumed to be significant

(Skoner 2001). RAST (radioallergosorbent test) and ELISA (enzyme-linked immunosorbent assay) tests measure the amount of allergen-specific IgE antibodies. Since there is no risk of systemic reactions during the application of these tests, they can safely be performed on pregnant women, on patients with a past history of systemic reaction, during measuring the sensitivity to antigens with a high risk of systemic reaction, on patients with skin diseases, on people who use drugs that may affect the prick skin test results, and in medicolegal cases where objective data are needed and also on children. The changes that develop due to gradually increasing doses of the allergen are followed by nasal provocation test. This test is performed when objective data are needed for occupational rhinitis, and it is rather used for scientific studies. Nasal cytology is not a diagnostic method performed for routine clinical practice and considered as an evaluation that does not provide a sufficient support alone (Scadding 2001). The use of acoustic rhinometry and rhinomanometry, which are the most common objective nasal airway tests, is confined because they have high costs and is time demanding in terms of application and interpretation (Galen 1997). Mucociliary function may be evaluated for differential diagnosis in patients with rhinitis (Shaari et al. 2006). Radiological examination is not necessary in a patient prediagnosed with rhinitis as long as an additional pathology is not suspected.

The treatment of persistent or recurring sneezing should be directed at the cause whenever possible. The best treatment in patients with allergic rhinitis is to avoid the allergen (Cingi et al. 2010c). Medical treatment or when needed, even immunotherapy when needed, is used in patients who do not benefit from avoidance or environmental control (Gunhan et al. 2011; Cingi et al. 2010a; Bousquet et al. 2009, 2010). Some patients may benefit from adjunctive surgical treatment. The management of common cold and influenza is symptomatic. Decongestants, antipyretics, bed rest, and increased fluid intake are recommended. Systemic antibiotics are preferred in patients who develop bacterial infections secondary to a viral infection while agent-specific antibiotic treatment is applied in those who develop rhinitis secondary to specific bacteria. It is vital to diagnose the patient and initiate the treatment immediately, particularly in fulminant fungal infections. The initial stage in the treatment of the patients with NARES is avoiding the irritant environmental conditions. Medical treatment is considered in case the initial stage fails to succeed. The success of steroids in early phases decreases in long-term administrations due to decreased steroid receptors on eosinophils. Oral and topical decongestants may be used adjunctive to steroid therapy. Capsaicin, a substance isolated from chili pepper extract, has an initial stimulating effect on C receptors which turns into an inhibiting effect following repetitive applications. Antihistamines are of no use and treatment of vasomotor rhinitis is palliative. Oral and topical decongestants can be applied. Topical corticosteroids are not always beneficial. Ipratropium bromide, which prevents the secretions from serous and seromucous glands inhibiting the cholinergic system, may be effective. Antihistamines are of no use. In the treatment of gestational rhinitis, medication should definitely be avoided for the first 10 weeks, and the treatment should definitely be applied with obstetric advice in the following periods. Isotonic saline sprays may be useful for pregnant women due to their humidifying and mucosal cleaning effects. The first line medical treatment for allergic rhinitis in pregnant women is cromolyn sodium, a mast cell stabilizer. Beclomethasone and triamcinolone are the topical steroids of choice for those who do not benefit from cromolyn sodium. The safest antihistamine during pregnancy is chlorpheniramine and the safest oral decongestant is pseudoephedrine. In the management of rebound rhinitis, the inducing drug should be discontinued and oral or parenteral corticosteroids should be administered in order to relieve the patient's complaints, and the treatment should be supported with topical nasal corticosteroids. Surgery may be necessary if irreversible changes have developed in the inferior conchae. The purpose of the treatment in geriatric rhinitis should

Table 11.2 Differential diagnosis of rhinitis in terms of history and laboratory tests

Feature	Allergic rhinitis	Infectious rhinitis	NARES	Vasomotor rhinitis
Onset of symptoms	Seasonal/perennial	Seasonal	Perennial	Perennial
Symptoms	*Sneezing* Nasal stuffiness Nasal pruritus Nasal discharge Postnasal drip	*Sneezing* Nasal stuffiness Nasal discharge Fever Myalgia	*Sneezing* Nasal stuffiness Nasal discharge	*Sneezing* Nasal stuffiness Nasal discharge Postnasal drip
Triggering allergen	Yes	No	No	No
Triggering irritant	Yes	No	Yes	Yes
Allergy tests	Positive	Negative	Negative	Negative
Nasal cytology	Eosinophilia	Neutrophilia	Eosinophilia	Rare Eosinophilia

be to provide sufficient intracellular moisture. For this purpose, it is appropriate to humidify the nasal mucosa with solutions including a combination of isotonic solution and glycerine and to add guaifenesin to treatment which stimulates the submucosal glands. Isotonic solutions can be combined with glycerine for the initial management of atrophic rhinitis. Other solutions can be antibiotherapy, estrogen support, vitamins A and D administration, iron support, or corticosteroid administration. It has also been recommended to practice surgical closure of one or both nostrils for a period of 1 year, or surgical procedures to narrow the nasal cavity have been recommended. Avoiding irritant substances should be the initial approach for the management of occupational or irritant-induced rhinitis (Table 11.2).

11.5 Complications of Sneeze Reflex

Since the symptoms of majority of upper respiratory tract infections include cough and sneezing, numerous particles disperse into the air during the course of these diseases. The most important complication of sneezing that affects public health is spread of droplet infections, tuberculosis in particular. The incidence of tuberculosis, which was taken under control through the improvement of efficient treatments in the second half of the twentieth century, began to increase again due to certain factors including the outburst of HIV infection, the decrease in the importance given to disease control, and poverty (CDC 1994; Adler and Rose 1996).

Gwaltmey et al. have determined that the intranasal pressure increases up to 176 mmHg during sneezing with the mouth and the nostrils closed (Gwaltney et al. 2000). Complications pertaining to this high pressure have been reported in literature. These complications include acute aortic dissection, cerebral venous thrombosis, loss of hearing due to fracture footplate, abortus, orbital emphysema, pneumocephalus, acute wide-angle glaucoma, pneumatocele of the lacrimal sac, intimal tear of the arteriovenous fistula, retinal hemorrhage, and costal fracture reported in a patient with osteoporosis (Rochels et al. 1989; Sharir et al. 1992; Whitehead 1999; Gonzalez 2005; Baydin et al. 2005; Fonseca et al. 2007; Birkent et al. 2008; Gupta et al. 2010).

Conclusion

Sneezing is a phenomenon that is common to all humans and is widespread in the animal kingdom as well. It may play an important role in maintaining health in ways that we don't currently understand. Sneezing, which can not consciously be controlled, is a protective reflex for the body during which facial, pectoral, and abdominal muscles function concordantly maintaining the respiration. It is rarely a sign of serious illness or impending disaster as feared by previous generations. On the other hand, it can be remarkably annoying. A thorough knowledge of this reflex can be a valuable aid in the diagnosis of other concomitant diseases.

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The Dry Nose

12

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Keywords
Dry nose • Rhinitis sicca anterior • Rhinitis atrophicans • Empty nose syndrome

Core Messages

- An unequivocal definition of dry nose (DN) is not available. Symptoms range from the purely subjective sensation of a rather dry nose to visible crusting of the (inner) nose (nasal mucosa), and a wide range of combinations are met with. Relevant diseases are termed rhinitis sicca anterior, primary and secondary rhinitis atrophicans, rhinitis atrophicans with foetor (*ozaena*) and empty nose syndrome. The diagnosis is based mainly on the patient's history, inspection of the nose, endoscopy of the nasal cavity, sinuses and nasopharynx, with CT, allergy testing and microbiological swabs being performed where indicated.
- Treatment consists in the elimination of predisposing factors, moistening, removal of crusts, avoidance of injurious factors, care of the mucosa, treatment of infections and, where applicable, correction of an overlarge air space.

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12.1 Symptoms

One of the chief functions of the nose is to warm and moisten the inspired air, while another is to recover the water in the expired air (Keck and Lindemann 2010).

The nature of the in- and outflow of the air within the nasal cavity is of decisive importance for this air-conditioning feature. In this context, optimal distribution of the inspired air over the

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nasal turbinates ensuring intimate contact of the air with the surface-moist mucosal membrane is essential.

The expression dry nose (DN) has not been unambiguously defined. In the main it is based on relevant anamnestic patient information. ENT specialists often employ the term rhinitis sicca, although here, too, a clear definition is lacking. Symptoms range from the purely subjective sensation of a somewhat dry nose to visible crusting of the nose, and a wide range of combinations are possible:

- Sensation of dryness in the nose
- Itching and mild burning sensation
- Nasal obstruction
- Crusting, scabs and "bogies", possibly associated with an (unpleasant) smell
- Epistaxis
- Diminished sense of smell

12.2 Etiology

Possible causes of dry nose include a variety of diseases, external and internal factors and environmental conditions:

- Local mechanical irritation.
- Climatic or environmental factors.
  - Dry room or environmental air (relative humidity <50 %)
  - Heated room or hot environment
  - Long-distance flights
- Workplace conditions.
  - Dry air and clean-room condition (Su et al. 2009)
  - Cold and heat
  - Dusty conditions (e.g. grinding/polishing of plaster, granite, chalk, cement, wood arsenic, nickel carbonyl, tobacco smoke)
- Drugs (cocaine).
- Side effects of medications (see Table 12.1).
- Supportive nasal administration of oxygen (Miyamoto and Nishimura 2008).
- Symptoms of other diseases (granulomatous, infectious, rheumatic and immunological disorders).
  - Wegener's granulomatosis, sarcoidosis, tuberculosis, syphilis and leprosy (Fig. 12.1)
- Wound healing phase after endonasal sinus surgery and surgery on the nose.
- Anatomical changes to the outer and inner nose, with modification of normal airflow.

Table 12.1 Medications with the side effect dry nose

Substance group	Generic name	Indications
Retinoids (1–10 %)	Isotretinoin	Severe forms of acne
	Tretinoin	Promyelocyte leukaemia
Doxepin (tricyclic antidepressant)		Depressive conditions, anxiety syndrome, mild withdrawal symptoms in alcoholics and drug-dependent persons, agitation, sleep disorders
Methyldopa (1‰–1 %)		Hypertension (of pregnancy)
Sympathomimetics (local)	Dipivefrine (eye)	Glaucoma
	Naphazoline	Diverse forms of rhinitis, only short-term use recommended
	Oxymetazoline	
	Phenylephrine	
	Tetryzoline	
	Tramazoline	
	Xylometazoline	
Antihistaminics, first generation	Clemastine	Urticaria, allergic rhinitis
	Dimenhydrinate	Vertigo, nausea, vomiting
	Dimethindene	Itching, itching dermatoses, allergies
	Diphenhydramine	Difficulty getting to sleep, difficulty staying asleep
	Promethazine	Agitation in underlying psychiatric illnesses, possibly vomiting, nausea and sleep disorders
	Terfenadine	Allergic rhinoconjunctivitis, allergic skin disorders

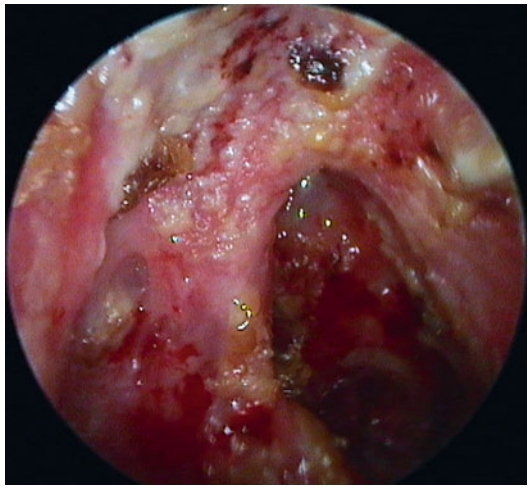

Fig. 12.1 Dry nose in a patient with Wegener's disease

- Allergic rhinitis, in particular house dust mites and moulds.
- Permanent sequelae of surgery on the nose and paranasal sinuses.
- Sequelae of head and neck radiotherapy.
- Patients with obstructive sleep apnoea (OSA) or continuous positive airway pressure (CPAP) treatment in sleep apnoea patients (Brander et al. 1999). Moistening led to a reduction in symptoms (Worsnop et al. 2009).
- Old age.

Dry nose may be the first symptom of an incipient cold with a runny nose; in such a case, however, it is of only limited duration.

Although an increased susceptibility for infections has frequently been postulated and is pathophysiologically plausible, it has never been confirmed as the sole cause. The mechanical and functional integrity of the mucous membrane is considered a major natural defence mechanism against infection. Depending on the degree to which it dries out, mucociliary transport and even the epithelial barrier may be impaired.

Epidemiological data on the prevalence of dry nose are not available. However, in particular when questioned, many people confess to be sufferers and admit to the use of numerous therapeutic measures, mostly ointments and sprays or nasal douches.

In old age, anatomical changes and an involution atrophy of the mucosa result in an increase in such complaints as impairment of nasal breathing and dry nose, and the following phenomena may occur:

- Hanging nasal tip and shortening of the columella (Zankl et al. 2002)
- Reduced mucociliary clearance (Ho et al. 2001; Sakakura et al. 1983; Armengot et al. 1993; Sunwoo et al. 2006)
- Reduction in the number of goblet cells and elastic fibres in the nasal mucosa (Sahin-Yilmaz and Corey 2006)
- Reduced sensitivity of the nasal mucosa (Wrobel et al. 2006)
- Enlargement of the nasal cavity resulting from involution atrophy of the nasal mucosa (Kalmovich et al. 2005; Lindemann et al. 2005a)
- Decrease in the body's water content (Slavin 2009)

Altered airflow due to changes in geometry leads to changes in the conditioning situation (Lindemann et al. 2005a, b), with the result that in over 60-year-olds, the air-conditioning capacity becomes impaired: both intranasal air temperature and humidity decrease (Lindemann et al. 2008).

A familial, i.e. genetic, impairment of nasal air-conditioning has been reported by Sahin-Yilmaz et al. (2007), who investigated 47 pairs of twins (Sahin-Yilmaz and Corey 2006).

12.2.1 Clinical Entities

In common with the symptom itself, a number of individual diseases associated with the symptom dry nose and crusting are not only unclearly defined but also overlap. In the literature, the following descriptions are to be found:

- Rhinitis sicca anterior (Fig. 12.2)
- Primary rhinitis atrophicans/primary atrophic rhinitis (= PAR) – rhinitis atrophicans with foetor (*ozaena*) (Fig. 12.3)
- Secondary rhinitis atrophicans/secondary or diffuse atrophic rhinitis (= SAR)

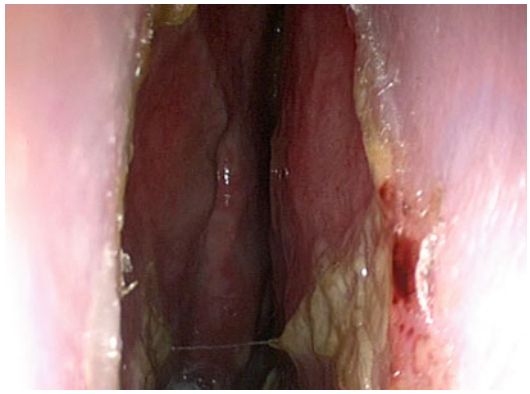

Fig. 12.2 Rhinitis sicca anterior with dry skin in the nasal vestibule and thin yellowish crusts

12.2.1.1 Rhinitis Sicca Anterior

The term rhinitis sicca anterior defines a chronic inflammation in the region of the anterior part of the nose usually affecting the anterior and caudal septum and/or the corresponding lateral nasal vestibule. Due to irritation (mechanical, finger picking; toxic; persistent secretion; respiration; (air)flow characteristics; dry, hot and dusty environment), drying, superficial erosion and/or ulceration with (thin) crust formation occur.

Patients experience a sensation of dryness, itching and increased crust formation. The crusts are thin and dry and do not extend into the posterior part of the nasal cavity, as is the case with atrophic rhinitis. Usually there is no foetid smell – only an occasional patient experiences mild foetor caused by bacterial colonisation of the small crusts. Manipulations may give rise to a vicious circle of increased crusting and persistent complaints. In the individual case, continued irritation and manipulation may result in perforation of the nasal septum.

Treatment consists in the application of a protective film to the skin of the nasal vestibule, to allow the chronic inflammation disrupting its integrity to self-heal while avoiding mechanical irritation (Fig. 12.1). This is usually achieved by the application of ointments. Nasal sprays containing dexpanthenol have also been used with success (Kehrl and Sonnemann 1998).

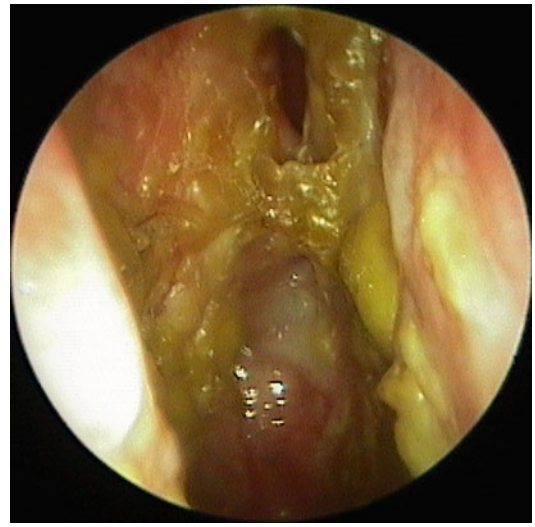

Fig. 12.3 Dry nose with persistent excessive crusting in a female patient with primary atrophic rhinitis

12.2.1.2 Primary Atrophic Rhinitis (PAR)

Primary atrophic rhinitis is a gradually progressive chronic degenerative condition of the nasal mucosa of unknown etiology. Progressive atrophy of all the constituents of the mucosa (epithelium, glands and vessels together with osteoclasis) mainly affects the turbinates. The respiratory epithelium undergoes stepwise metaplastic changes. Histologically, atrophy of the serous and mucous glands, loss of the cilia and goblet cells, chronic infiltration of the lamina propria with granulations and scar formation are seen. Some publications also report diminished vascular density together with peri- and endarteritis. The histological changes explain the disturbance to mucociliary transport. Thick secretion that is not transported away promotes the formation of bacterially contaminated crusts that may then be a source of recurrent bacterial Infection. If rhinitis atrophicans is complicated by foetid crust formation, rhinitis atrophicans with foetor (stinking nose, ozaena) results. Microbiological investigation usually detects *Klebsiella ozaenae* (100 % of the 45 patients of Moore and Kern (2001)) but also *Staphylococcus aureus*, *Proteus mirabilis*, *E. coli* and other bacteria (*Bordetella bronchiseptica* and *Pasteurella multocida*).

Endoscopic examination reveals a markedly large and wide nasal cavity and visibly dry mucosa. The turbinates are clearly diminished in size. With ozaena, yellowish-green crusts are found on the mucosa. Apart from crusting, the patient usually also suffers from hypo- or anosmia. Foetor may give rise to social problems.

The cause of PAR is unknown, but both genetic and infectious causes are under discussion. The condition is more commonly seen in association with low socio-economic status, a poor diet and iron deficiency. A much less frequent use of antibiotics in countries with a higher incidence of the condition may have a role to play. The fact that women are more frequently affected suggests a possible endocrinal factor. Over the past years and decades the prevalence of PAR has declined.

12.2.1.3 Secondary Atrophic Rhinitis (SAR)

Secondary atrophic rhinitis develops in the soil of an underlying disease or may result from previous therapeutic measures. Therefore, it is a collective term for several conditions with a different etiology but a similar clinical feature with the subjective feeling of a dry nose, crusting, gegebenenfalls nasal obstruction, foul smelling and epistaxis as outlined above. In contrast to PAR, there is no osteoclastic activity, so the term diffuse atrophic rhinitis may be more suitable. Pathogenetic factors leading to SAR are:

- Prior radical endonasal surgery. Persistent chronic rhinosinusitis in addition may increase the probability of the development of SAR (Ly et al. 2009).
- Prior radiotherapy of the head and neck.
- Sjögren's syndrome.
- Extremely rarely: prior trauma.

In the largest collection of cases to date 197 patients with sRA the following causes were identified (Moore and Kern 2001):

- Complete removal of the lower and middle nasal turbinates (24 %)
- Partial removal of the lower and/or middle nasal turbinates (56 %)
- Endonasal sinus surgery without turbinectomy (10 %)
- Partial maxillectomy to remove a tumour (6 %)
- Nasal trauma requiring surgical reconstruction (1 %)
- Granulomatous disease (1 %)

Empty nose syndrome (ENS) is defined as a form of iatrogenic SAR, occurring after radical endonasal surgery in particular resection of the nasal turbinates (lower and/or middle), usually in connection with an operation on the nasal sinuses (Chhabra and Houser 2009; Payne 2009; Scheithauer 2010). It is characterised by the symptoms nasal and pharyngeal dryness, paradoxical impairment of nasal respiration, dyspnoea and hyposmia, in some cases associated with depression (Houser 2007).

The disturbed sense of smell is the result of the changed airflow. The dryness of the pharyngeal mucosae is due to the fact that, in contrast to the normal situation, drier intranasal air (no moisture since turbinate mucosa is lacking) results in disrupted airflow in the region of the choanae and also impinges on the posterior wall of the nasopharynx at increased velocity (Scheithauer 2010). According to Houser, pain too is a typical symptom caused by the action of cold air on the mucosa covering the sphenopalatine ganglion (Houser 2007).

Resection of the lower and middle turbinates reduces the effectiveness of the climatisation function of the nose by 23 % (Naftali et al. 2005; Passàli et al. 1999). The paradoxical impairment of nasal respiration is explained by the unphysiological airflow, the reduced nasal airway resistance, the lack of areas of functional mucosa together with the simultaneous enlargement of the nasal cavity and the curtailed contact between air and mucosa (Scheithauer 2010). Enlargement of the nasal cross section reduces the airway resistance and thus the pressure gradient at the air/mucosa surface. In turn, this causes malfunction of the nasopulmonary reflexes, which may lead to a worsening of pulmonary function. In contrast, optimal nasal airway resistance is important for the dilatation of the peripheral bronchioles and for improved alveolar gas exchange.

The risk to develop SAR after resection of the turbinates depends on the extent of resection, individual factors of the patient itself and other external factors which are not clearly defined up to now. Some authors did not find any sign of SAR after total resection of the inferior turbinates (Cook et al. 1995; Eliashar 2001; Ophir 1990; Talmon et al. 2000); others report SAR in 2–22 % (Passàli et al. 1999; Courtiss and Goldwyn 1990; Elwany and Harrison 1990; Martinez et al. 1983; Oburra 1995; Odetoyinbo 1987).

12.3 Diagnosis

Extensive history taking is always followed by inspection of the outer and inner nose (Table 12.2). This should, for example, identify any anatomical deformations that might cause dry nose by changing the flow of air through the nose. For the purpose of detecting minor lesions in the nasal vestibule in patients with rhinitis sicca anterior, the use of a microscope may prove useful. Endonasal inspection should look for septal deviation or perforation and note the size and shape of the turbinates, the presence and nature of crusts, the humidity of the mucosa, polyps or tumours, postnasal secretion and the nasopharyngeal status.

A CT of the nasal sinuses is indicated when signs of chronic rhinosinusitis are found or to obtain adjunctive evidence of PAR. Typical signs of PAR in the CT include:

- Thickened mucosa in the paranasal sinuses.
- The osteomeatal complex can no longer be defined due to the destruction of the normal anatomy.
- Hypoplasia of the maxillary sinus.
- Enlargement of the nasal cavity with destruction of the lateral nasal wall.
- Bony destruction of the inferior and middle turbinates.

Testing for allergy is important, for example, in order to diagnose a house mite allergy, which may be associated with the symptom dry nose. When endoscopic examination reveals purulent streaks or crusting, swabs should be taken for a microbiological examination.

Table 12.2 Diagnostic workup of dry nose

Medical history
Inspection of the external and inner nose
Endoscopy of the nasal cavity and nasopharynx, where indicated, also of (operated) paranasal sinuses
Where indicated, CT of the paranasal sinuses
Allergy testing
Microbiological swab

The diagnosis is based on the case history, endoscopic findings and, where necessary, adjunctive diagnostic measures.

12.4 Treatment

Treatment of dry nose comprises:

- Elimination or amelioration of triggering or promoting factors
- Moisturisation (Table 12.3)
- Sufficient daily drinking amount
- Cleansing (when crusts are present) and care of the mucosa
- Treatment of obvious infections
- Where applicable, the elimination of an overlarge endonasal air space

The individual may have only limited control over environmental factors. The importance of the latter is obvious when dry nose is no longer experienced during a holiday but reappears when this is over.

By far the most common complaint is a subjective dry nose with no endoscopic findings with the possible exception of a somewhat dry mucosa in the anterior nose. This is the case in almost all those patients exposed to unfavourable climatic or workplace conditions and also the large group of patients with obstructive sleep apnoea syndrome undergoing CPAP treatment. Also affected are patients operated on the nose, before the climatisation function has normalised.

Apart from the strict avoidance of local manipulation, these patients require humidification and care of the dry areas. For this purpose the market offers wide range of ointments, oils, sprays and nasal irrigation (Table 12.4).

Table 12.3 Substances for moistening the nose and mucosal care

Nasal douches with saline solution
NaCl solution
Special saline solution
Isotonic–hypertonic, with and without buffering (alkaline)
Nasal ointments
Dexpanthenol
Salt-containing nasal ointments
Diverse other formulations
Nasal oils
Sesame oil
Vitamin A oil
Salt water sprays
Hyaluronic acid nasal spray
Dexpanthenol nasal spray

Table 12.4 Basic rules for the treatment of dry nose

Elimination of promoting factors
Environmental and workplace situation
Dietary, iron and vitamin deficiency (?)
Moistening
Local (nasal irrigation, inhalation, nasal spray)
Environment (elevated air humidity)
Systemic: sufficient liquid intake
Removal of crusts (nasal irrigation, instrumental removal by ENT clinician)
Avoidance of injurious factors
Local (nose picking, cotton carrier, decongestant nose drops, ointments containing potentially injurious substances – imidazoline derivates, cortisone applied to the skin of the nasal vestibule, …)
Systemic drugs (see Table 12.1)
Care of the mucosa
Oils
Ointments
Occlusion
Treatment of infections
Allergic rhinitis
Ozaena
Chronic rhinosinusitis
Correction of an overlarge air space
Occlusion
Augmentation

The nose should be humidified, viscous mucus flushed and liquefied; all inflammation-inducing and inflammation-promoting substances should be cleared out. A protective film should be applied to prevent drying. Transepithelial water loss can be countered by the nasal application of saline solutions or other substances (Miwa et al. 2006).

12.4.1 Nasal Irrigation, Nasal Saline Spray and Inhalation

Nasal irrigations are recommended for a large number of diseases of the nose and nasal sinuses (Brown and Graham 2004). Precisely how nasal irrigation works is not clear. It is postulated that the improvement in mucosal function is due to:

- Direct physical cleansing by flushing out thick mucus, crust, debris, allergens, environmental toxins, etc. (Michel 2006; Schmidt n.d.)
- Removal of inflammation mediators
- Improvement of mucociliary clearance by improving the ciliary beat frequency (Boek et al. 1999; Talbot et al. 1997)
- In a recent review article published in 2009 (Rabago and Zgierska 2009), nasal irrigation is recommended:
- As adjunctive treatment for chronic rhinosinusitis (Grade A evidence: consistent study results of good quality)
- As adjunctive treatment for allergic rhinitis and viral ARS and follow-up treatment after nasal sinus surgery (Grade B evidence: inconsistent results or limited quality)
- For rhinitis of pregnancy, acute bacterial RS, also sarcoidosis or Wegener's disease (Grade C evidence: consensus recommendations, usual practice, expert opinion, results of case series)

The above shows that on the one hand nasal irrigation is a common recommendation, while on the other the indication dry nose is not explicitly included in the recommendation, since informative studies that can be integrated into the evidence-based recommendations are very rare.

Nevertheless, nasal irrigations are an important therapeutic option in patients with dry nose. In the case of recurrent crust formation, it is virtually indispensable as an adjunctive aid to instrumental clearing by the ENT physician.

The most commonly employed nasal sprays are salt solutions. In addition to household salt – iodised or non-iodised – pharmaceutical grade

salts as well as special nasal spray salts and brines are used (Michel 2006; Schmidt n.d.). These solutions may be isotonic, hypotonic, hypertonic, unbuffered or buffered. Mildly hypertonic saline solutions (up to approximately 3 %), with or without buffering, are all suitable for nasal irrigation. However, it is currently not clear which saline solution is best for what indication.

For isotonic saline solutions (isotonic unbuffered, buffered Emser saline solution), numerous investigations have shown that daily application over the long term produces positive results (prevention and treatment of upper airway infection/rhinosinusitis, aftercare following surgery on nasal sinuses) with no relevant side effects.

In principle, saline sprays serve the same purpose as nasal irrigation. Although no systematic comparison has been reported, the remark by Schmidt that diffuse moistening of the nasal mucosa can be achieved only with irrigation, since the spray is merely a punctiform application, is accurate and the potential therapeutic effect must therefore be considered smaller. For the present, the extent to which the admixture of other substances results in a real benefit in the treatment of dry nose remains uncertain.

Inhalation with saline solutions with the aim of moistening the mucosa is also recommended and applied. In view of the resulting diffuse moistening of the mucosa, this can be considered positive in the case of dry nose. Unfortunately, no meaningful studies are available.

12.4.2 Nasal Ointments

Despite the fact that many patients often use nasal ointments, no meaningful studies on their use in dry nose are available.

A moistening effect is achieved with intranasal use: the application of a nasal ointment reduces nasal water loss – as also does the application of glycerol 10 % (Miwa et al. 2006).

Elberg reported on the effect of Emser salt applied in the form of Nisita® Nasal Ointment in 1,500 cases including pre- and post-operative applications in patients undergoing operations on the nose and nasal sinuses (Elberg 1977). Neither pain nor infections were observed with regular application, despite the fact that no antibiotic was given. Follow-up care was reportedly considerably facilitated and abbreviated.

The quality level must, however, as in company-sponsored application studies – which are not considered here – be Grade V evidence.

In comparison with dexpanthenol nasal ointment, dexpanthenol nasal spray proved just as effective, or even tendentially superior, in terms of its effect on mucociliary transport (saccharine test) reported by Verse et al. in a prospective, randomised, open, crossover study (Verse et al. 2004). Its advantage vis-à-vis the ointment is presumably the fact that it reaches the upper parts of the nasal cavity.

Topical dexpanthenol is said to reduce transepidermal water loss, to activate in vivo and in vitro fibroblast proliferation and to accelerate the re-epithelialisation process (Ebner et al. 2002).

12.4.3 Nasal Oils

Oils in a not-too-high concentration bring about an improvement in the nasal ciliary beat frequency (CBF). In contrast to Miglyol 840 and thyme oil, sesame oil, soy oil, peanut oil, lavender oil, eucalyptus oil and menthol increased the CBF, the effect being higher at a concentration of the oils of 0.2 % than at 2 % (Neher et al. 2008). According to Riechelmann et al. a mixture of menthol, eucalyptus oil and pine needle oil in concentrations up to 5 % had no major negative effect on CBF but did at concentrations of between 7.5 and 10 g/m^3 (Riechelmann et al. 1997). With conventional inhalation, concentrations of max. 1 % are to be expected.

In a randomised crossover study involving 79 patients with dry nasal mucosa, Johnsen et al. 2001 showed that in comparison with a sodium chloride solution, treatment with sesame oil resulted in a superior moistening effect (Johnsen et al. 2001). Dryness and subjectively impaired nasal respiration were improved significantly better by sesame oil in comparison with saline irrigation. Björk-Eriksson et al. also reported a significant effect of sesame oil (3 × 3 puffs of 25

µl spray daily for 30 days) on the symptoms impaired nasal respiration, dryness (burning sensation, itching, irritation) and crust formation in 20 patients with dry nose and 15 patients post-radiation treatment (Björk-Eriksson et al. 2000). A total of five patients reported side effects (one each with unpleasant odour, itching and disturbed nasal respiration and runny nose in two).

12.4.4 Others

Home remedies and self-treatments recommended in the Internet are mostly concerned with achieving moisturising, the application of oils and the prevention of drying, but the efficacy of the respective measures remains unclear. Homeopathy always recommends an individual constitutional approach to treatment.

In the elderly patient with dry nose, Slavin recommends moistening the nasal mucosa and looking out for medicament side effects (in particular avoidance of first-generation antihistaminics and decongestive nose drops) (Slavin 2009).

A rough topographical endoscopically orientated classification may be useful for the differential treatment of the dry nose symptom:

- In the case of problems localised in the anterior nose (rhinitis sicca anterior in the widest sense) with a visible lesion and possibly crusting, the first indication is the local application of ointment. Relevant comparative studies are not available. Potentially injurious substances (decongestant medications, cortisone, allergising substances) should be avoided.
- Vague complaints of dry nose in the absence of visible changes to the nasal mucosa would appear the most likely indication for moisturising measures (nasal irrigation, inhalation, moisturising sprays). The question as to whether admixed medicaments can diminish the water loss on expiration needs further investigation.
- Dry nose with visible intranasal crust formation is the domain of nasal irrigation, which is better able to remove crusts than inhalation or sprays.

12.4.5 Treatment of Atrophic Rhinitis

Basic treatment consists of the above outlined measures for dry nose. In the case of atrophic rhinitis moistening measures must be accompanied by removal of any crusts and scabs. For this purpose, not only the commonly employed instrumental removal by the ENT specialist but also nasal irrigation is used. As suitable solutions, the literature mentions not only the classical irrigation solutions (buffered and unbuffered solutions of common salt or special salts) but also solutions of 25 % glucose in glycerine and antibiotics (Bahadur and Take 2008). Tap water and other hypotonic solutions are to be rejected.

Bacterial superinfections are treated with specific antibiotics. For ozaena antibiotic treatment is reported to achieve long-lasting results, e.g. rifampicin 600 mg daily for 12 weeks (Bahadur and Take 2008) and ciprofloxacin 2×500–750 mg for 8 weeks (Nielsen et al. 1995).

Operative measures aim to reduce the size of, or temporarily occlude, the nasal cavity. Although occlusion can resolve the problem of crusting and the considerable social stigma of foetor, it also impairs nasal breathing and the sense of smell. For the diminishment of nasal cavity size using submucosal implantation of tissue, foreign material should not be used despite that some authors describe promising result (Goldenberg et al. 2000; Rice 2000). Goldenberg et al. 2000 implanted Plastipore, a high-density polyethylene sponge with micropores, and reported excellent results in six patients and good results with only minor crusting in two patients and one extrusion after 18 months (Goldenberg et al. 2000). Rice used hydroxyapatite for augmentation in one case and reported good results (Rice 2000). According to Houser more suitable materials are the patient's own cartilage (e.g. rib cartilage) or acellular dermis (AlloDerm®) (Houser 2007). He treated eight patients with the implantation of AlloDerm®, which resulted in a significant improvement in symptom scores (SNOT 20) after at least 3 months. For treatment planning the cotton test is suggested: moistened cotton is applied to the area to be augmented for 20–30 min. If the test is positive, the patient can be offered

the augmentation. Friedman et al. (2002) and Moore and Kern (2001) reported some success with acellular dermis, too, in 5 of 10 and 7 of patients, respectively.

12.5 Prophylaxis

Since the uncritical resection of the nasal turbinates represents a significant and frequent factor in the genesis of dry nose, secondary RA and ENS, the following points must be strongly emphasised:

- The main objective of nasal turbinate surgery must be the preservation of functional mucosa while creating an adequately large volume capable of ensuring climatisation and the cleansing of the respired air and also preserving physiological airway resistance (Scheithauer 2010).
- Without adequate justification the middle turbinate should not be resected. Reduction of the lower nasal turbinate should first be given careful consideration, simultaneous removal of both the lower and middle turbinates should not be done for a non-tumourous condition (Rice et al. 2003).

Conclusions

Despite that there is no clear definition of dry nose, many patients complain of this symptom. A carefully taken patient's history and thorough rhinologic examination by an experienced and vigilant clinician are the key elements to optimal outcomes. The turbinates should be handled very cautiously in sinonasal surgery.

Pearls

- There is no clear definition of what a dry nose is.
- Symptoms range from the purely subjective sensation of a rather dry nose to visible crusting of the (inner) nose (nasal mucosa).
- Relevant diseases are rhinitis sicca anterior, primary and secondary rhinitis atrophicans, rhinitis atrophicans with foetor (*ozaena*) and empty nose syndrome.
- Drugs and environmental factors can induce a dry nose.
- The diagnosis is based mainly on the patient's history, inspection of the nose and endoscopy of the nasal cavity, sinuses and nasopharynx.
- Treatment consists in the elimination of predisposing factors, moistening, removal of crusts, avoidance of injurious factors, care of the mucosa, treatment of infections and, where applicable, correction of an overlarge air space.
- Normal turbinates should be preserved in sinonasal surgery.

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Physiology of the Aging Nose and Geriatric Rhinitis

13

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Keywords

Geriatrics • Nasal physiology • Rhinitis • Presbyosmia • Nasal conditioning capacity • Airflow • Treatment

Core Messages

1. Demographic trends worldwide make the knowledge of age-related changes in nasal physiology crucial for otolaryngologists.
2. Physiological changes of the nose with age include structural changes of the superstructure, alterations of the structure of the respiratory epithelium, decreased function of this epithelium manifested by decreased ciliary function, blunted vascular responses, decreased intranasal sensitivity and olfaction, reduced immune defense, and decreased ability to humidify air.
3. Such changes lead to major complaints of rhinitis in older patients and contribute to a range of nasal diseases.
4. Geriatric rhinitis is complex to categorize but can be divided by cause into allergic and nonallergic groups.
5. Allergic causes can receive standard therapies and symptoms tend to be milder in older patients.
6. Nonallergic causes are more difficult to treat and require careful attention to the precise triggers and symptoms; therapies are targeted to symptom.
7. Nonspecific treatments such as humidification, mucolytics, and saline irrigations are generally safe and effective.
8. Surgical and medical treatments for geriatric rhinitis are safe and effective, but special considerations of geriatric issues such as polypharmacy, alterations in hepatic and renal function, and side-effect profiles must be made.

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13.1 Importance of Aging in Rhinology

Societies are facing a massive demographic shift in the next 30 years, with a rapid aging of the world population. Data from the United Nations shows that in both developed and underdeveloped nations, the percentage of the population over 60 will rise significantly. Indeed, the proportion of older persons was 8 % in 1950, 10 % in 2000, and is projected to reach 21 % in 2050 (http://www.un.org/esa/population/publications/worldageing19502050/). According to the 2010 United States Census, 13 % of the American population is greater than 65 years of age, a 15.1 % increase over the prior 10-year period (Werner 2011). Similar trends are apparent for Western Europe and even countries with younger age distributions such as China. Hence, we need to accelerate our understanding of the effects of aging and both normal physiology and disease. Given the dramatic aging population in both developing and developed nations, physicians must understand and address the special needs of this expanding group of patients. All organ systems are affected by aging in a myriad of ways, making this a population with significant medical need and significant challenge for clinicians.

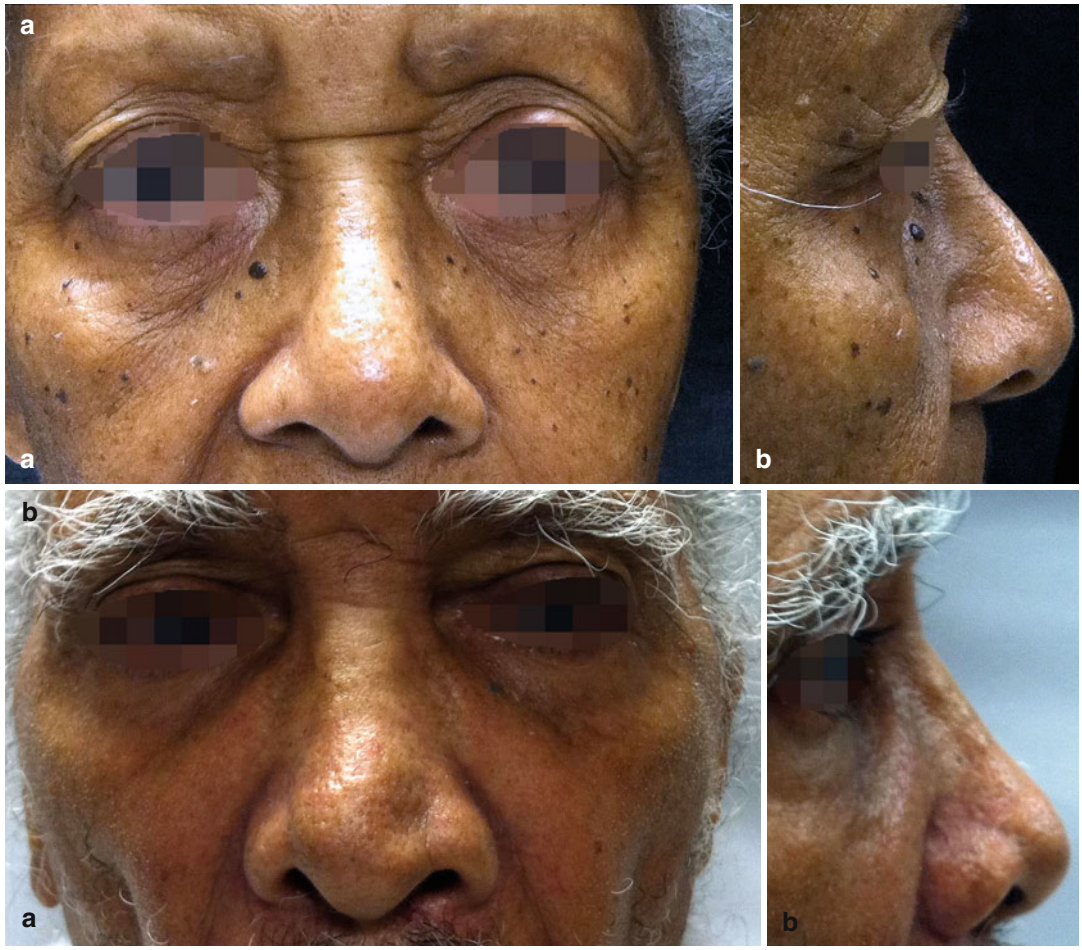
The study of geriatric medicine has advanced in the past four decades with the development of fellowship training programs in medicine dating back to the 1970s. Programs such as the Department of Veterans Affairs Geriatric Research, Education, and Clinical Centers (GRECC) were organized to increase translational research in geriatric medicine and promote the advancement of clinical care for older people (Supiano et al. 2012). The creation of the National Institute on Aging (NIA) in 1974 and efforts of private organizations (e.g., the American Federation for Aging Research [AFAR]) have resulted in increase efforts to understand aging and disease and treat or mitigate its effects. We must parallel these efforts in Otolaryngology-Head and Neck surgery in general (and Rhinology in particular) if we are to meet the needs of our older patients. However, our field still needs more research in and clinical focus on otolaryngologic manifestations of aging and its effects on disease. An effort has been made to form groups, such as the American Society of Geriatric Otolaryngology (ASGO), and programs for surgical specialists such as the Dennis W. Jahnigen Career Development Program of the American Geriatrics Society to encourage research and education about caring for older adults (American Society of Geriatric Otolaryngology 2007). More attention in Rhinology is needed.

When caring for this older population, one key principle of geriatrics is that attention should be paid not only to prolongation of life but equally importantly to improving quality of life. This chapter will address how anatomy and function of the nose change with age, important diseases of the nose in older subjects, and treatment methods allowing us to provide the best rhinologic care for older adults.

13.2 Anatomical Changes of the Aging Nose

13.2.1 Anatomy

Aging affects all portions of the face including the nose, starting with its cover, the skin (Figs. 13.1 and 13.2a, b) (Kahn and Shaw 2010). Thinning of the epidermis and decreased collagen production cause the skin to lose its elasticity. Other skin changes, including the development of rosacea and rhinophyma, are more common in the elderly. Anatomical changes in older adults that affect the structure and function of the nose include thinned nasal skin, weakened nasal cartilages, weakened fibrous attachments between upper and lower lateral cartilages, and ptosis of the nasal tip (Cochran et al. 2007). Edelstein and others have found that the anatomy of the nose undergoes several changes with age, including a decrease in the nasolabial angle, a decrease in the height to length ratio of the nose, weakening/separation of the upper and lower nasal cartilages, decreased glycosaminoglycans causing increased porosity of nasal cartilage, retraction of the nasal columella, resorption of bone resulting in maxillary hypoplasia, atrophy of collagen



Figs. 13.1 and 13.2 (**a**, **b**) Two examples of the geriatric nose, profile and frontal views. Note the skin changes and external structural effects of aging

fibers, and attenuated and fragmented fibroelastic attachments (Rohrich et al. 2004; Patterson 1980; Hirschberg et al. 1995; Edelstein 1996). These changes make the nose appear longer, deprojected, and underrotated (Quatela and Pearson 2009). Some studies have revealed increased cross-sectional area at the internal nasal valve in older adults. For example, although it is difficult to objectively assess patency at the internal nasal valve, Kalmovich et al. attempted to measure endonasal geometry changes in the geriatric population. Using acoustic rhinometry, they found that there was a statistically significant gradual increase of endonasal volumes and minimal cross-sectional areas with age, except in the oldest group of men over 80 years of age (Kalmovich et al. 2005). Similarly, Kim et al. demonstrated an increased cross-sectional area at the internal nasal valve associated with age, but no difference in nasal resistance before and after decongestion in any age group greater than 20 years old, supporting their hypothesis that the increased area is related to changes in the non-erectile structures of the nose. In general, however, the sum result is a restriction in nasal airflow, particularly at the nasal valve region, an important site of nasal resistance. In summary, the structural changes seen in the aging nose may result in nasal obstruction and abnormal airflow.

Anatomic changes of the nose are, in part, related to changes of the cartilaginous structures as well as weakening of soft tissue attachments.

The biochemical composition and mechanical properties of cartilage change with age, resulting in a tendency to collapse. For example, there is a decrease in the glycosaminoglycan content of nasal septal cartilage with increasing age, resulting in stiffening with decreased fluid flow through the tissue. Additionally, there appears to be a slight increase in hydroxyproline content with increasing age. These changes are similar to those seen in articular cartilage during the aging process. Although the physical stresses on articular cartilage are much different than that of septal cartilage, the similarity of their biochemical changes may represent systemic effects on cartilage with age (Rotter et al. 2002).

There are two practical considerations of these data for clinical practice. First, anatomic changes are likely to affect airflow through the nose in older patients, resulting in restrictions that may cause dryness, irritation, and obstruction. These problems may exacerbate existing conditions and contribute in a large way to patient symptoms. Secondly, older adults may seek septorhinoplasty to alleviate such functional problems and also for cosmetic desires. Careful consideration must be given to these patients as they may have underlying significant medical comorbidities, such as hypertension, coronary artery disease, or diabetes, placing them at higher risk for elective surgery. Cochran et al. noted that many older patients at the time of rhinoplasty had ossified septal cartilage, making it more frequently necessary for auricular or costal cartilage to be harvested (Cochran et al. 2007), potentially lengthening operative time. It would be prudent to have medical and anesthesia clearance prior to proceeding with elective surgery in any older patient and several guidelines exist to make this determination (Stefan et al. 2011; Palmer 2009). Nevertheless, nasal surgery in older subjects can be safe and effective when approached carefully (Ban et al. 2010). As with all rhinologic patients, psychological motivation for the procedure needs to be assessed. Geriatric patients frequently have to deal with significant life issues, including death of loved ones, lack of social support, financial challenges, and struggles with quality of life. One must assess whether older patients have taken ample time to consider any cosmetic surgery prior to proceeding. Most importantly, assessment of the functional consequences of rhinoplastic procedures on this patient subset is critical to maintain airflow.

13.3 Physiological Changes with Age

New research is helping to elucidate some of the subtle changes in the physiology of the nose over time that may lead to symptoms and/or disease in older adults. Although we are far from fully understanding comprehensively how the nose changes over time, further study of the known physiological changes will help us to provide better medical and surgical treatment regimens for these patients.

13.3.1 Alterations in Nasal Function

A common result of aging is nasal dryness, a frequent complaint in older patients. This condition may present with crusting, irritation, epistaxis, or obstruction. Although this is not well studied, etiologies include mucosal and glandular atrophy, vascular changes which reduce nasal humidification, and medication use (e.g., antihypertensives, which affect vascular regulation in the nose, or first-generation antihistamines, which inhibit cholinergic responses in the nose). Structural changes in the nose may also contribute by causing turbulent airflow which dries the mucosa. The mucosa itself is altered. Schrödter performed biopsies of the middle turbinate in 40 subjects of varying ages and found significant atrophy of the epithelium in the older subjects (Fig. 13.3) (Schrödter et al. 2003). This analysis found thin epithelium and also increased thickness of the basement membrane. Also, the percentage of normal ciliated respiratory epithelium declined in the older subjects. Similar studies using electron microscopy corroborate this finding (Toppozada 1988). Increased expression of caspase 3, an apoptotic marker, indicates that part of the defect may be in the ability of the epithelium to renew

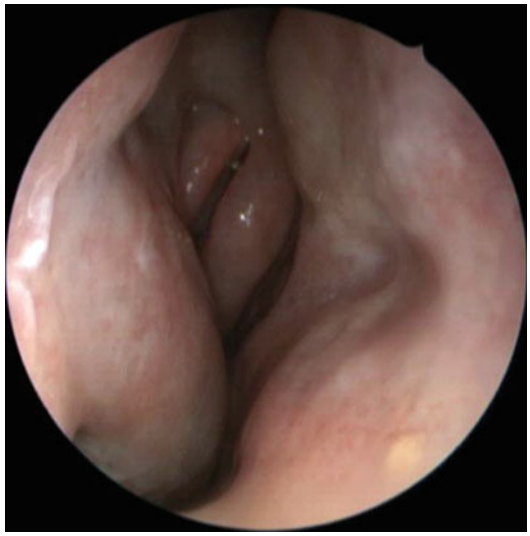


Fig. 13.3 Endoscopic view of geriatric patient with atrophy of endonasal mucosa

itself, and there are other functional aspects of the epithelium (toxin neutralization) that may be affected (Getchell et al. 1993). This matches what we see clinically, a thinner, atrophic epithelium in older subjects when examined with nasal endoscopy.

Another major alteration affecting this symptom is in one of the main functions of the nose: the ability to warm and humidify air (Naclerio et al. 2007). The two major mechanisms leading to the alteration in nasal conditioning capacity (NCC) are changes in the nasal mucosal temperature (NMT) and the volume of the nasal cavity. During inspiration of air, water evaporates from the nasal mucosa to condition inspired air, leading to heat loss and, consequently, a decrease in NMT (Cole 1954). Lindemann found that using *in vivo* air temperature and humidity measurements at the nasal valve and the region just anterior to the head of the middle turbinate, both temperature and humidity values were significantly lower in older subjects (mean age 70 years old) compared to younger subjects (median age 27 years old) (Lindemann et al. 2008). Additionally, nasal volumes appeared to be larger in the older age group. Increased turbulence of airflow may be one result causing the sensation of nasal obstruction despite larger space (paradoxical nasal blockage). Endonasal geometries are indeed enlarged in older subjects (Kalmovich et al. 2005). This suggests that NCC in older subjects is compromised. Thus, lower ability to warm and humidify air may be present in older subjects, potentially affecting lower airway function. This may also contribute to the increased dryness in this population.

We may take some analogy from changes in the oral mucosa. As with the nose, the lubrication of the oral cavity changes with age. Although there should not be a decrease in saliva production with age, unless altered by medications or systemic conditions, there are changes in the consistency of the saliva, including a decrease in mucin concentration and decreased secretion of protective IgA antibodies (Ritchie 2002). This may lead to increased caries, periodontal disease, and poorer nutritional status.

A second area of altered nasal physiology with age is in mucociliary clearance. Kim noted decreased ciliary beat frequency in vitro nasal epithelial cells taken from patients older than 60 years of age (Kim et al. 2007). Ho et al. also found decreased nasal mucociliary clearance by the crude saccharin clearance test and the more sensitive measure of ciliary beat frequency by a photometric test (Ho et al. 2001). However, there is likely significant interindividual variability in this phenomenon since Sakakura et al. showed that 70 % of patients older than age 60 retained saccharin transport times comparable to their younger counterparts (Sakakura et al. 1983). Diabetes and hypertension, both increased in prevalence in older subjects, are also associated with decreased ciliary function (de Oliveira-Maul et al. 2012). In summary, if the cilia are not moving as rapidly, this can lead to symptoms of mucus buildup, rhinitis, inflammation, or infection, from persistence of organisms and molecules trapped in the mucus layer (Fig. 13.4). Hence, both the structural components and the function of the epithelial lining of the nose in older patients demonstrate significant changes with age that may affect airflow, mucus quality and production, and mucociliary clearance.

A third way nasal function is altered with age is regulation of vascular responses in the nose.

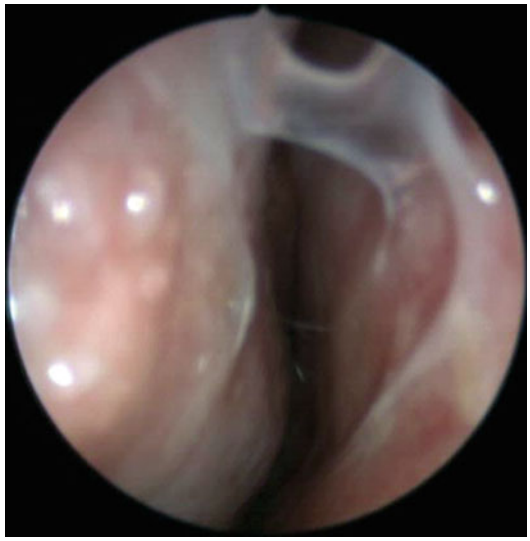


Fig. 13.4 Endoscopic view of geriatric patient with thickened nasal mucus, a common complaint in this patient population

Nervous control of vascular tone in the nose is important in the regulation of the critical functions of the nose, to warm and humidify air, and also may affect diseases involving vasodilation such as allergic and nonallergic rhinitis. Tillmann found that vascular regulatory responses are reduced with age (Tillmann et al. 2009). Fifty-two subjects were acclimated to the laboratory environment for 5 min and baseline measures of perfusion by optical rhinometry were performed. The subjects were then moved to supine position for 30 min, which should alter blood flow. Older subjects had more rapidly increased perfusion, but did not return to baseline in contrast to younger subjects. This study suggests that autonomic control of nasal blood flow is altered in older subjects, potentially affecting humidification (as described above) and the other functions of the nose discussed above. Using liquid crystal thermography exhalation monitoring to measure nasal cycle, Doty found decreased regulation of the nasal cycle in older adults (Mirza et al. 1997). Overall, the proportion of subjects exhibiting the alternating rhythmicity associated with the classic nasal cycle decreased with age. No association was present between nasal cycle parameters and scores on the mini-mental state examination (MMSE). The results suggest that the classic nasal cycle may be a marker for age-related central nervous system changes. These phenomena may also be important in nonallergic rhinitis.

13.3.2 Olfaction and Nasal Sensitivity

Olfaction, mediated by the olfactory nerve, and sensitivity of the nose, controlled by the somatosensory system and mediated by the trigeminal nerve, both decrease with age. In 1994, the National Health Survey determined that 3.2 million people, or 1.65 % of adults in the United States, had chronic chemosensory problems involving smell and/or taste; 40 % of these adults were aged 65 years and older, with an exponential increase seen with increasing age (Hoffman et al. 1998). Adults over 65 years of age have approximately half the intensity of smell and irritant sensation as subjects between the ages of 18 and 25 (Stevens et al. 1982). In another study, the sensitivity of the nose was assessed by providing tactile stimulation with monofilaments of progressively larger sizes. Adults 50–65 years of age required significantly less stimulation to detect sensation of the monofilament as compared to adults aged 66 and above (Salzano et al. 2010).

In order to understand how the olfactory system is altered with age, we first need a better understanding of the normal olfactory system. The olfactory mucosa is distributed along the upper portion of the nasal septum, below the cribriform plate, and along the medial aspect of the superior turbinate, as well as along the roof of the middle turbinate (Paik et al. 1992). On histologic examination, there is a patchy distribution of olfactory epithelium, which becomes increasingly sparse with aging because olfactory epithelium becomes replaced with respiratory epithelium over time. Robinson et al. demonstrated in a murine model that there is an increase in apoptotic gene expression of olfactory neuron receptors with increasing age, likely resulting in increased cell death (Robinson et al. 2002). Over time, even small toxin exposures, including heavy metals, such as manganese, cigarette

smoke, or volatile chemicals, may cause harm to the olfactory epithelium (Lafreniere and Mann 2009). In mice it has also been seen that there is decreased regeneration of the neuroepithelium of the olfactory bulb with increasing age (Suzukawa et al. 2011). Because olfactory stem cells regenerate with time, any alteration of this turnover may also contribute to age-related olfactory loss, either from insult or from inherent aging. All of these may contribute to a decrease in function of the olfactory system as one ages.

Age-related olfactory loss (presbyosmia) is an important public health problem worldwide (Hoffman et al. 1998; Wysocki and Gilbert 1989; Brämerson et al. 2004; Landis et al. 2004). In the USA, olfactory complaints from the approximately 14 million individuals over age 55 who are affected lead to over 200,000 physician visits annually (NIDCD 2010; NAMCS 1979). This sensory impairment of aging affects critical functions such as nutrition (Mattes and Cowart 1994; Mattes et al. 1990; Miwa et al. 2001), sensation of pleasure (Wolfe et al. 2008), detection of environmental hazards (Santos et al. 2004), mood, cognition, behavior (Herz and Schooler 2002; Schiffman et al. 1995a, b), sexuality (Bhutta 2007; Jacob et al. 2002), and general well-being (Neuland et al. 2011), and therefore, it poses a profound burden on older adults. Indeed, up to one-third of older subjects report dissatisfaction with their ability to smell (Wysocki and Pelchat 1993), and ~50 % are unable to detect the standard warning odor in natural gas (Cain and Stevens 1989). Importantly, decline in olfaction has been linked to several neurodegenerative conditions, mentioned above (Hawkes 2006; Handley et al. 2006; Kovacs 2004; Schubert et al. 2008; Wilson et al. 2006, 2007a, b, 2009). If this link involves shared genetic or environmental risk factors, then understanding the pathogenesis of presbyosmia may have broad implications for a wide array of problems, especially regarding other sensory impairments of aging (Li and Lindenberger 2002). Thus, olfactory sensory loss is related to factors that are critical to the physical well-being, social function, and quality of life of older adults. Because olfaction declines over time, the clinical impact will increase as our population ages.

Acquired chemosensory complaints are also important in Otolaryngology. In addition to traumatic injury or post-viral olfactory loss, cancer chemotherapy can affect olfaction. For example, patients undergoing palliative chemotherapy treatment for cancer frequently had complaints of dysgeusia and sensitivity to odors while undergoing treatment. Those patients with severe complaints were found to have lower calorie intake, increased weight loss, and lower quality of life scores, than in patients with less severe complaints (Hutton et al. 2007). Because the olfactory epithelium regenerates, one cause of this could be a decrease in stem cells with age in the olfactory mucosa, either inherently or after stimulation of regeneration by injury. Indeed, telomere shortening has been observed in the regenerative response to chemical injury of the olfactory epithelium in a mouse model, providing evidence that telomere shortening impairs the regenerative capacity of this tissue (Watabe-Rudolph et al. 2011). So, aging may lessen the ability of the olfactory mucosa to survive respiratory insult by toxins.

There are many systemic causes of chemosensory dysfunction. Olfactory deficits are seen in neurologic disorders, such as Alzheimer's disease, Huntington's disease, Parkinson's disease, and Korsakoff's psychosis, all of which generally affect the elderly. It is important to counsel patients with hyposmia or anosmia, as they may be unaware of noxious materials in their surroundings. They should obtain natural gas detectors if they have natural gas stoves, oven, or heat at home as they may not be able to detect a fuel leak. Additionally, they should be aware of dates on food products, label leftovers, and dispose of foods reaching their expiration dates to avoid food spoilage. Lastly, smoke detectors should be checked regularly for function and efforts must be maintained to promote nutrition.

13.3.3 Immunosenescence

Immunosenescence is the term used to describe the decreased function of the immune system with age. Both the adaptive and innate immune systems

are impaired (Wang et al. 2010; Shaw et al. 2011). Decreased immune response is believed to contribute to increased infections, autoimmune disease, and cancers in the elderly population.

There are several effects of immunosenescence in the nose. IgA is an immunoglobulin that is secreted along the respiratory and gastrointestinal tracts, where it helps to neutralize a variety of pathogens. Alford demonstrated that IgA levels can be measured in nasal secretions and comprise approximately 38 % of nasal wash proteins in normal patients. He also showed that IgA levels in nasal secretions decrease significantly with age (Alford 1968). In a murine model, it has been shown that mucosal immunity wanes prior to systemic immunity in studies where vaccination to cholera toxin was performed by mucosal and subcutaneous methods, respectively, in different ages of mice (Koga et al. 2000).

IgE levels also decrease with age. Mediaty and Neuber studied 559 individuals with atopic dermatitis, allergic rhinitis or asthma, and insect allergy. In all patients, except those with atopic dermatitis or those with high total serum IgE >300 kU/l, total and specific serum IgE levels were significantly decreased in patients aged greater than 60 compared to their younger counterparts. They hypothesized that there may be more robust mechanisms in atopic dermatitis or conditions resulting in high serum IgE that lead these patients to have a more persistent response. Additionally, the type of atopic disease and the age of disease onset may impact IgE levels (Mediaty and Neuber 2005).

Immunosenescence is poorly studied as it affects the upper airway. However, we can extrapolate findings from the lower airway (Busse and Mathur 2010). In that location, there are several immune alterations that might facilitate persistence of asthma, a related airway disease to rhinitis. These include changes in airway neutrophil, eosinophil, and mast cell numbers and function as well as altered antigen presentation, decreased specific antibody responses, and altered cytokine profiles. The sum of these changes might affect susceptibility to upper respiratory tract infections.

In summary, this is a complex area in which there is little data on the nose specifically, but age-related changes in immune function are likely to impact nasal physiology and disease in older patients.

13.4 Geriatric Rhinitis

13.4.1 Overview

Rhinitis is a pervasive complaint in physicians' offices. It is estimated that 20–40 % of subjects living in Western countries are affected by rhinitis. Rhinitis may be allergic or nonallergic in nature, with approximately 50 % of rhinitis patients belonging to each group (Fokkens 2002). These forms of rhinitis affect older subjects as well, though because allergy wanes with age, nonallergic rhinitis tends to predominate. There are many potential causes of rhinitis in the geriatric population. Edelstein noted that six nasal complaints were more prominent in older adults: nasal drainage, postnasal drip, sneezing, coughing, olfactory loss, and gustatory rhinitis (Edelstein 1996). Regarding quality of life in an Italian study, geriatric patients with rhinitis underwent clinical evaluation and responded to the Rhinasthma questionnaire (Ventura et al. 2012). All patients also underwent skin prick testing, measurement of total IgE level, and nasal cytologic analysis. In the older patients the epithelial to goblet cell ratio was decreased. The quality of life in older people was more impaired than in young adults. These authors concluded that quality of life is more heavily impaired compared with young adults. However, one study showed that nasal-specific quality of life measures show no deterioration in older subjects and do not therefore correlate with changes in nasal function (Lindemann et al. 2010). Further investigation of this topic is warranted to elucidate this paradox.

13.4.2 Allergic Rhinitis

Allergy is defined as an immediate type IgE-mediated response to an allergen exposure, where IgE is bound to mast cells and its attachment to

an allergen results in degranulation of the mast cell with histamine release. The diagnosis of allergy can be confirmed by skin, in vitro, or provocation testing. The Allergic Rhinitis and its Impact on Asthma (ARIA) consensus categorizes allergic rhinitis as either intermittent allergic rhinitis (IAR) or persistent allergic rhinitis (PAR). IAR denotes that symptoms are present less than 4 days per week or less than 4 consecutive weeks per year. PAR indicates that symptoms are present greater than 4 days per week and more than 4 consecutive weeks. These can be further categorized as mild or moderate/severe based on impact of quality of life (Bousquet et al. 2008).

Although allergy is well studied, the majority of studies performed to date involve either the pediatric population or young adults. In older adults, the incidence of allergic rhinitis actually decreases with age along with atopy as detected by skin prick tests. Karabulut et al. noted that only 50 % of older adults have positive skin prick tests as compared to 70 % of younger adults when matched for allergic symptoms including nasal, eye, pulmonary, and dermatologic symptoms (Karabulut et al. 2011). Subjects from French cohort aged 65 years and over ($n=352$) found that respiratory allergy is present in older people and that there is an association between smoking and IgE level independent of allergic reactivity to common allergens in the elderly, highlighting the importance of environmental factors in rhinitis (Raherison et al. 2004). A recent longitudinal study analyzed allergic sensitivity 15 years after primary testing. Skin prick test (SPT) and evaluation of serum total and specific IgE and nasal eosinophils were conducted in 108 subjects from Palermo, Sicily, in Italy. In general, rhinitis symptoms tended to be milder at follow-up. All parameters examined decreased with time. However, the changes in rhinitis symptoms appear to be related to changes in the nasal eosinophils, independently of SPT and specific IgE (Di Lorenzo et al. 2013). Thus, in general allergic disease and markers decline with age.

One practical consideration for these patients is that because elderly patients frequently have atrophic or photodamaged integument, skin testing for allergy may actually be less reliable than in younger adults. There is evidence that there are decreased numbers of mast cells in atrophic skin, thereby making the possibility of a false-negative result higher. In older subjects, an area of skin that is protected from the sun can be considered for skin testing, a histamine control used so that the most dramatic obtainable response can be visualized, and consideration given to in vitro testing if no reliable area of skin is present (King and Lockey 2003). Both skin and *in vitro* testing must always correlate with patient history for accurate diagnosis. Allergic disease in the older patient population has been reviewed recently (Cardona et al. 2011).

13.4.3 Nonallergic Rhinitis

There are many causes of rhinitis which are not allergic in nature, but can be equally bothersome to patients and have a marked impact on quality of life. The data regarding this phenomenon are less developed, as compared to those for allergic rhinitis. Studies of patients presenting to allergists have demonstrated that 23–52 % of patients with rhinitis have the nonallergic form (Schroer and Pien 2012). Patients can also be sensitized to allergens at any time, thereby changing the categorization of their rhinitis. No good diagnostic techniques are available to distinguish between the subtypes of nonallergic rhinitis, but a diagnosis is based on history and symptoms and negative allergy testing. Additionally, there is no set classification system for nonallergic rhinitis. Further confusing the matter is allergic and nonallergic rhinitis can coexist ("mixed rhinitis"). Interestingly, it has been observed that 70 % of patients with nonallergic rhinitis present during adulthood (age > 20), whereas 70 % of patients with allergic rhinitis initially present during childhood (age < 20). There is also a greater propensity for females to be affected, compared to males (Togias 1990). Recent study of nonallergic rhinitis suggests that local IgE production may be involved. The only approved treatment for nonallergic rhinitis currently is intranasal antihistamines which are effective in some cases. Nonallergic rhinitis, therefore, is a major disorder

of older adults. Due to its complex nature, however, our understanding of its pathophysiology in general and specifically in older adults is limited, resulting in limited ability to treat this problem effectively. A trial and error method of different nasal medications is usually pursued.

13.4.4 Vasomotor Rhinitis

Vasomotor rhinitis is one form of nonallergic rhinitis and is often viewed as an idiopathic diagnosis that is considered when a patient has no evidence of allergy, infection, eosinophilia, hormonal changes, or drug exposure (Lal and Corey 2004). Symptoms include nasal congestion, nasal drainage or postnasal drip, and perennial symptoms; however, pruritus is rare (Shah and McGrath 2012). There is also typically no cytological evidence of nasal mucosal inflammation (Settipane and Charnock 2007). Vasomotor rhinitis is a poorly understood condition but believed that the primary cause is autonomic nervous system dysfunction with either a diminished sympathetic drive or an elevated parasympathetic drive causing increased nasal congestion and resistance.

13.4.5 Drug-Induced Rhinitis

Many medications can have the adverse effect of causing rhinitis. This can especially affect the geriatric population, as they are often on numerous medications to control other comorbidities. It is important to consider polypharmacy as a cause of the patient's symptoms and see if removing medications, rather than adding more of them, may help. Aspirin, or other nonsteroidal anti-inflammatory drugs (NSAIDs), which are commonly taken by older adults, may cause acute inflammation in the nose in susceptible patients via the inhibition of COX-1. The breakdown of arachidonic acid to the lipoxygenase pathway is favored causing decreased prostaglandin E_2 and an increase in cysteinyl leukotrienes, which include LTC_4 which is thought to be a lead contributor to aspirin-exacerbated asthma (Varghese et al. 2010). Many other medications can cause rhinitis in older patients. There are also neurogenic-type medications, such as alpha- or beta-adrenergic antagonists, which work by decreasing sympathetic tone. This causes primarily congestion but also rhinorrhea. Medications such as clonidine and methyldopa fall within this category of medication. Phosphodiesterase-5 inhibitors, which is used for erectile dysfunction, may reportedly impact the erectile tissues of the nose and have been associated with nasal stuffiness and epistaxis (Hicklin et al. 2002). Certain antihypertensives, psychotropic agents, and hormonal treatments, including estrogen therapy, can also cause rhinitis. Their mechanisms of action have not been fully elucidated. Lastly, rhinitis medicamentosa can affect adults who overuse nasal decongestants, causing rebound nasal congestion.

When medication use is thought to be the cause of rhinitis, a pharmacist or geriatrician may be useful in giving recommendations about changing the medication. Polypharmacy is frequently an issue in the geriatric population, and these patients need close monitoring for drug interactions, as well as adverse side effects.

13.4.6 Atrophic Rhinitis

Atrophy related to structural changes of the nasal structure and intranasal function can cause atrophic rhinitis which frequently affects the elderly with a mean age of occurrence of 52–56 years (Settipane 2011). Symptoms include dryness and crusting of the nasal mucosa, with possible underlying bony resorption (Liston and Siegel 1981). Anatomic and physiological changes may cause atrophic rhinitis, including structural changes of the mucosal glands, vasculature, and connective tissue of the nose as well as cholinergic hyperactivity. Patients with atrophic rhinitis complain of drying of the nose, nasal congestion, and rhinitis and sometimes fetor is noted. Thick nasal secretions increase worsening postnasal drip symptoms and lead to frequent clearing of the throat. Treatment of this condition is difficult as it is impossible to reverse or mitigate the

physiological changes. Intranasal steroids, expectorant drugs, and nasal saline sprays are recommended though their efficacy in this group is understudied (Wallace et al. 2008). Aggressive use of nasal humidification, emollients, and saline irrigation is helpful.

13.4.7 Gustatory Rhinitis

Patients with gustatory rhinitis have profuse watery or mucoid rhinorrhea while eating, with hot and spicy foods often being the trigger. This condition may present in all age groups but has been reported to worsen with age. The pathophysiology is not well understood, and there are many theories as to its cause. One theory is that odors may activate receptors on the mucosa directly, resulting in secretions from goblet cells and submucosal glands. This, however, would not explain why some patients have symptoms while eating foods that are neither hot nor spicy. Another theory is that patients have stimulation of the sensory portion of the trigeminal nerve which causes a reflex parasympathetic response with activation of postganglionic, cholinergic, muscarinic, and parasympathetic fibers. This results in activation of the submucosal glands, causing rhinorrhea (Georgalas and Jovancevic 2012). This condition is a common complaint among rhinologic patients and causes great social discomfort as patients are inhibited from sharing meals with friends. It can be treated easily with intranasal anticholinergics.

13.4.8 Hormonal Rhinitis

Pregnancy induces congestion and rhinorrhea, although the mechanism of rhinitis of pregnancy is not clearly understood (Ellegard 2006). Through studies of the influence of ovarian hormones on rhinitis, it has been seen that rhinitis may be associated with hormonal peaks, such as those during ovulation or pregnancy, despite the fact that the absolute amount of estrogens present at these times are very different. The number of beta estrogen receptor positive cells in tissues has been correlated with rhinitic symptoms (Philpott et al. 2008b). One would think that in postmenopausal women, who deal with overall decreased levels of estrogens, unless undergoing treatment with exogenous hormones, it would have a large influence on nasal symptoms, but the influence of these hormonal changes have not been elucidated. Some studies demonstrate that when hormones are given exogenously at a steady rate, such as with oral contraceptive pills or hormone replacement therapy, there is no subsequent rhinitis (Philpott et al. 2008a). Interestingly, the nose is being sought at a route of administration of hormonal replacement therapy. This treatment is still under investigation.

13.4.9 Chronic Rhinosinusitis

Inflammatory causes of rhinitis must be considered in the geriatric population. Chronic rhinosinusitis is the sixth most common chronic condition in people older than 65 (Colclasure et al. 2004). Seventeen percent of patients aged 65–74 years old may suffer from chronic rhinosinusitis. As some elderly may be relatively immunocompromised because of diabetes mellitus or other underlying illnesses or treatments for medical conditions, some lower-virulence organisms must be considered while treating these patients (Zacharisen 2000). Standard treatments for this condition are useful in older patients as well.

13.5 Treatment of the Geriatric Patient with Rhinitis

13.5.1 Overview

It is useful to review Slavin's key suggestions for approaching the older patient with rhinitis (Slavin 2009). First, this condition is neglected and impacts quality of life. One must consider anatomic changes related to aging before treating. Geriatric issues such as polypharmacy, cognitive dysfunction, changes in body composition, impairment of liver and renal function, and the cost of medications in the face of limited

resources are key medical and social issues in this group. One must categorize the etiology of the problem and its related symptoms and treat specific ones. Moisture in general is key to improved nasal symptoms in this age group. Specifics of medications will be reviewed below, but important note should be made of potentially dangerous side effects in this age group. In general, however, several medications are helpful for this problem.

13.5.2 Medical Therapies

In the United States, 58 % of adults over age 65 take five to nine medications and 18 % take ten or more. In Germany, patients over age 65 take 66 % of all prescribed medications, despite representing only 22 % of the total population (Hofer-Dückelmann 2012). Polypharmacy has truly become a major issue and careful attention needs to be paid to avoiding drug interactions and adverse side effects from medications. Although rhinitis can be a bothersome condition, its treatment is intended primarily to improve quality of life, and thus, its medical treatment should not interfere with other more pressing medical conditions.

13.5.3 Avoidance

In patients with allergic rhinitis, avoidance measures would make intuitive sense; however, to date no study has been able to prove that avoidance measures are effective. Despite potentially reducing the number of allergens present, environmental modifications have not been proven to have any impact on rhinitic symptoms (Bousquet et al. 2008). As many of these interventions have no negative sequelae other than cost or logistics, patients may still want to consider them. In patients with known dog or cat allergies, it would make sense to avoid having those animals as pets, but the evidence is weak regarding this impact, as they are likely to encounter cat and dog dander in public situations. If patients already have pets, to which they are allergic, they may want to avoid keeping those pets in the bedroom or frequently used living spaces. Patients with dust mite allergies may find it helpful to decrease the amount of dust in the home by having hardwood floors instead of carpeting, washing sheets in hot water between 55 and 60 °C, keeping a HEPA air filter, and vacuuming and cleaning regularly. Cost should be taken into consideration as many elderly patients are on a fixed budget and some of these measures may be expensive, without any evidence of benefit in randomized clinical trials. No single measure of avoidance is likely to be of benefit, but patients may find multiple measures to be helpful (Tran et al. 2011).

13.5.4 Increasing Nasal Moisture

One of the most important treatments for atrophic rhinitis or rhinitis secondary to age-related, structural changes of the nose is to maintain and improve moisture. Although there is not much evidence regarding the efficacy of nasal saline irrigation, it is a cheap, safe, and frequently recommended treatment regimen for patients with rhinitis from many different causes. Such solutions may also increase mucociliary clearance. Isotonic saline preparations seem to be the most beneficial with the least side effects (Thorton et al. 2011). They can be used four to six times daily. Home humidifiers may also provide benefit.

Guaifenesin is a mucolytic agent that has been available in the United States for over 50 years. Although its mechanism of action is not entirely understood, it functions as an expectorant, which helps to increase the volume of mucous production, as well as decrease the viscosity of mucous (Storms and Farrar 2009). It can be used in dosages of up to 2,400 mg/day (Little 2005). Many clinicians have found this treatment to be helpful in older patients and side effects are minimal.

13.5.5 Emollients

Emollients (petroleum jelly is perhaps the most common) have been found to decrease crusting and dryness of the nose. In a Swedish study, there

was a significant decrease in nasal dryness, followed by nasal stuffiness and crusting, during cold weather months in patients receiving pure sesame oil intranasally versus isotonic sodium chloride solution. Emollients such as mineral oil should be avoided because if aspirated, may cause lipoid pneumonitis (Johnsen et al. 2001). Hence, care in using these treatments should be taken.

13.5.6 Oral and Intranasal Antihistamines

Second-generation antihistamines, such as loratadine, fexofenadine, and cetirizine, are very effective in treating rhinitis, sneezing, and nasal and ocular pruritus associated with allergic rhinitis. These agents are less likely to cause sedation when compared to first-generation agents, as they are less lipid soluble, and do not readily cross the blood–brain barrier. First-generation antihistamines have been associated with work-related injuries, decreased mentation, and driving accidents (Kay and Quig 2001), problems that might be exacerbated in older subjects. Diphenhydramine is a well-known first-generation antihistamine, which possesses some anticholinergic properties. The elderly are particularly susceptible to these medications and delirium may result even with dosages as small as 5–50 mg (Ochs et al. 2012); therefore, its use should be avoided in the elderly if possible.

Intranasal antihistamines, such as azelastine, azelastine hydrochloride, and olopatadine, are well-tolerated treatments for allergic and nonallergic rhinitis and have a low side-effect profile (Chaaban and Corey 2012). Patients may also complain of bitter taste. Intranasal application of azelastine demonstrates six to eight times lower systemic absorption than oral preparations. There are some reports of sedation when compared to placebo, although this is decreased as compared to other oral second-generation antihistamines. Intranasal antihistamines are safe treatment alternatives to oral second-generation antihistamines and provide relief against both the early- and late-phase allergic responses and nonallergic responses (McNeely and Wiseman 1998).

13.5.7 Intranasal Anticholinergics

The only approved topical anticholinergic is ipratropium bromide (0.03 %) nasal spray (Tran et al. 2011). It not only helps to decrease watery rhinorrhea but has also been found to increase the nose's ability to warm and humidify air (Assanasen et al. 2000). Ipratropium bromide functions by antagonizing acetylcholine transport in parasympathetic efferent nerves, thereby decreasing secretion from submucosal glands (Sapci et al. 2008). In a study by Malmberg et al., ipratropium bromide has been proven to decrease nasal secretions and be preferred over placebo by the elderly population (Malmberg et al. 1983). The side-effect profile is low and includes nasal dryness, bleeding, headache, dry mouth/throat, blurred vision, and urinary hesitancy (Meltzer 1992).

13.5.8 Corticosteroids

Intranasal corticosteroids are generally first-line treatment for allergic rhinitis. They function by decreasing the inflammatory response of the nose with a complex mechanism including inhibiting responses of lymphocytes, eosinophils, mast cells, basophils, neutrophils, monocytes, and macrophages (Meltzer 2011).

There are numerous formulations available by prescription, including mometasone furoate (Nasonex®), fluticasone furoate (Veramyst®), ciclesonide (Omnaris®), fluticasone propionate (Flonase®), budesonide (Rhinocort®), triamcinolone (Nasacort®), and beclomethasone (Beconase®). Flonase® is FDA approved for the treatment of nonallergic rhinitis, and Rhinocort® has also been found to be of benefit in reducing obstruction, nasal drainage, and sneezing in nonallergic rhinitis (Meltzer 2011).

Despite concerns about potential systemic effects of steroids and how it relates to the elderly, there does not appear to be any increased risk of cataract formation or decreased bone mineral density in adults with the current dosages of intranasal corticosteroids and their low bioavailability (Benninger et al. 2003; Allen 2000). Care

should be taken regarding the one common side effect of these medications, epistaxis, which can be more common in the older patient.

Oral corticosteroids are used at times in patients with nasal polyposis or acute/chronic rhinosinusitis to decrease congestion; however, these medications come with systemic risks. Systemic steroids have effects on the hypothalamic-pituitary axis, cataract formation, metabolism, and osteoporosis, and long-term use can increase intraocular pressures (Sastre and Mosges 2012).

13.5.9 Decongestants

Decongestants are available in topical or oral preparations. Topical preparations, such as Neo-Synephrine or oxymetazoline, should only be used for short periods of time as they may lead to rhinitis medicamentosa in some patients. They function by stimulating the endogenous release of norepinephrine which acts on alpha-receptors to cause vasoconstriction in the nose (Doshi 2009). Oral decongestants, such as pseudoephedrine, also work by stimulating alpha-receptors. As they work systemically, they may have undesired effects, especially in the elderly, including urinary retention or elevation in blood pressure. Pseudoephedrine has been known to potentiate arrhythmias, hypertension, myocardial infarction, and stress cardiomyopathy (Zlotnick and Helisch 2012). Additionally, its use should be avoided in patients with insomnia, prostatic hypertrophy, or glaucoma (Shah and McGrath 2012). Because of its many potential side effects, it would be prudent to avoid its use in older patients.

Conclusions

As medicine and technology allow for longer life expectancies, the importance of caring for older patients will increase across the globe. Understanding the physiology of the aging nose will aid in better diagnosis and treatment of rhinologic conditions in the geriatric population. Careful attention should be paid to the presence of comorbidities and issues surrounding polypharmacy. As clinicians, we should strive to improve our skills for taking care of age-related conditions.

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Nutrition and the Upper Respiratory Tract

14

James Bartley

Keywords
Zinc • Omega-3 • Vitamin A • Vitamin D • Probiotics • Milk • Immunity • Allergy • Infection • Upper respiratory

Core Messages

- Nutrient deficiencies are common among children and the elderly.
- Probiotics may have a role in the prevention of upper respiratory infections
- Zinc taken daily reduces the incidence of the common cold and reduces both the duration and severity of symptoms once one has developed a cold.
- Vitamin D deficiency is common in the developed world.
- Increasing evidence indicates that vitamin D supplementation has a potential role in the prevention of upper respiratory disease; however, optimal vitamin D levels and dosage regimens remain to be determined.

14.1 Introduction

While many basic scientific studies indicate that nutritional deficiencies can lead to illness and disease, in clinical practice diagnosing and treating potential deficiencies can be difficult. Nutrient deficiencies vary between developing and developed countries. In developing countries multiple nutritional deficiencies may be present, whereas in developed countries obesity and vitamin D deficiency are important nutritional issues (Taylor and Camargo 2011). Nutrient deficiencies are common in children (Black et al. 2008) and in the elderly particularly those in long-term residential care (Cowan et al. 2004). Increasing evidence indicates that zinc and vitamin D supplementation may have a potential role in the prevention of upper respiratory disease (Bartley 2010; Singh and Das 2011; Taylor and Camargo 2011).

14.2 Probiotics

Probiotics are live organisms that, when consumed in adequate quantities, provide health benefits to the host (Reid et al. 2003). Probiotics may have a role in the treatment of both upper

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respiratory infection and allergic rhinitis. Animal studies indicate that probiotics could be beneficial in the treatment of upper respiratory infection (Yasui et al. 2004; Racedo et al. 2006). Probiotics appear useful in reducing acute upper respiratory infection frequency and reducing antibiotic use, but they do not reduce the infective episode length (Hao et al. 2011).

In vitro, certain human upper respiratory flora strains, mainly streptococcal species, appear able to prevent pathogenic colonization and infection of the upper respiratory tract (Fujimori et al. 1996; Brook and Gober 1999; Bernstein et al. 2006). *Corynebacterium* spp., a common bacterium of healthy nasal flora, has prevented *Staphylococcus aureus* colonization of nasal cavities in 71 % of volunteers (Uehara et al. 2000). In vivo Esp-secreting *Staphylococcus epidermidis* eliminates *Staphylococcus aureus* from the anterior nose (Iwase et al. 2010). The possibility also exists that the local application of "healthy bacteria" could prevent upper respiratory disease.

> The possibility exists that the local application of "healthy bacteria" could prevent upper respiratory disease, but this has yet to be translated into clinical practice.

When compared to allergic children, *Bifidobacteria* and *Lactobacilli* are found more commonly in the intestinal flora of healthy children (Kalliomaki et al. 2001; Özdemir 2010). Probiotic bacteria in the intestinal microbiota appear to protect against atopy. When probiotics have been given, clinical improvement in allergic rhinitis symptoms has been reported (Peng and Hsu 2005; Giovannini et al. 2007; Ivory et al. 2008; Kawase et al. 2009; Kopp and Salfeld 2009). However, the selection of which probiotic strain/strains, supplement timing, as well as the dosage and method of administration continues to be debated (Kopp and Salfeld 2009; Özdemir 2010).

14.3 Iron

Bacteria need iron for the respiration, DNA synthesis, and free radical-scavenging mechanisms (Doherty 2007). In nasal mucus, the iron-binding proteins transferrin and lactoferrin maintain low iron levels, which protects against microbial infection (Johnson and Wessling-Resnick 2012). In the host, iron deficiency impairs cell proliferation and immune function (Gera and Sachdev 2002). However, iron deficiency is not associated with an increased risk of acute lower respiratory tract infection (Gera and Sachdev 2002), which indicates that it is probably not an upper respiratory infection risk factor. Low iron levels can be associated with other micronutrient deficiencies, particularly zinc deficiency (Bhandari et al. 2007; Grant et al. 2011).

14.4 Vitamin A

Vitamin A is required for epithelial integrity, the production of red blood cells, as well as humoral and cellular immunity. Vitamin A deficiency increases the susceptibility to a number of illnesses including diarrhea (Fischer Walker and Black 2007), measles (Hussey and Klein 1990), and lower respiratory infections (Mayo-Wilson et al. 2011), but not susceptibility to upper respiratory infections (Brown and Roberts 2004). Cod liver oil, as well as children's multivitamin/mineral supplement with selenium and other trace metals, reduces pediatric visits for upper respiratory illness during the winter and early spring by 36–58 % (Linday 2010). Cod liver oil contains vitamin A, but it also contains vitamin D and omega-3 fatty acids, which makes it difficult to totally attribute these results to vitamin A.

14.5 Omega 3

Omega 3 and omega 6 oils are essential fatty acids oils that are eicosanoid precursors, which play important roles in the inflammatory response (Thien et al. 2002; Bath-Hextall et al. 2005). High levels of omega-3 fatty acids in the diet are associated with a decreased risk of allergic rhinitis (Hibbeln et al. 2007). Regular fish consumption before the age of 12 months is also associated with a reduced risk of allergic sensitization to inhalant allergens during the first 4 years of life (Nafstad et al. 2003; Kull et al. 2006). However, omega-3 fatty acid supplementation alone does

not improve allergic rhinitis symptoms (Thien et al. 1993). In those patients with Samter's triad (salicylate intolerance, asthma, and nasal polyps), high-dose omega-3 supplementation can be useful clinically (Healy et al. 2008).

High-dose supplementation with omega 3 may be useful in patients with Samter's triad (salicylate intolerance, asthma, and nasal polyps).

14.6 Zinc

Zinc is important in innate immunity. Zinc is involved in T and B lymphocyte function, as well as Th1 cytokine production. The macrophage, in particular, is adversely affected by zinc deficiency (Shankar and Prasad 1998; Haase and Rink 2009). The role of zinc supplementation in the prevention of lower respiratory infection (Brooks et al. 2005; Aggarwal et al. 2007) does not appear to have been translated into the possible prevention of upper respiratory bacterial infection. Zinc taken daily reduces the incidence of the common cold in young children (Singh and Das 2011). Zinc also reduces both the duration and severity of symptoms once one has developed a cold (Singh and Das 2011), although the interpretation of this meta-analysis has been debated (Science et al. 2012). In clinical practice, the assessment of zinc deficiency can be difficult (Gibson et al. 2008).

14.7 Milk

Excessive milk consumption has a long association with increased respiratory tract mucus production and asthma (Bartley and McGlashan 2010). Such an association cannot be explained using a conventional allergic paradigm. In the human colon, ß-casomorphin-7 (ß-CM-7), an exorphin derived from the breakdown of A1 milk, stimulates mucus production from gut MUC5AC glands (Zoghbi et al. 2006). In the presence of inflammation similar mucus overproduction from respiratory tract MUC5AC glands characterizes many respiratory tract diseases (Kirkham et al. 2002; Ding and Zheng 2007). ß-CM-7 from the blood stream could stimulate the production and secretion of mucus production from these respiratory glands. One would have to have a slightly leaky gut and coexisting respiratory inflammation.

A number of studies suggest that the exclusion of milk products from the diet may improve asthma symptoms. In the 1950s, Rowe and Rowe suggested that a variety of foods could contribute to asthma and found symptoms often improved in asthma patients on an exclusion diet (Rowe and Rowe 1956). In an unblinded study, when milk was excluded from the diet, the symptoms of cough and nasal congestion improved particularly at night. Recording bias was used to explain the effect (Pinnock et al. 1989). More recently, in a single-blind prospective study, 22 children with asthma (13 in the experimental and 9 in the control group) received an egg- and milk-free diet for 8 weeks. The children of the experimental group exhibited distinctly decreased IgG antibody concentrations toward ovalbumin and beta lactoglobulin. In 5 children in the experimental group, the peak expiratory flow rate was increased markedly when compared to children in the control group (Yusoff et al. 2004). These studies support the clinical observation that in some situations a cow's milk exclusion diet benefits some patients.

Vitamin D has an important role in innate immunity through the production of the two antimicrobial peptides: cathelicidin and defensin ß2.

14.8 Vitamin D

Vitamin D (25(OH)D) deficiency is common around the world (Holick 2007). Vitamin D is made largely by sun exposure (Holick 2007). Vitamin D appears to have important roles in both innate and adaptive immunity (Bartley 2010). Vitamin D has an important role in innate immunity through the production of the two antimicrobial peptides (AMPs): cathelicidin and defensin ß2. AMPs are synthesized and released largely by epithelial cells and neutrophils. AMPs

kill bacteria by inserting themselves into the bacterial cell membrane bilayers to form pores by "barrel-stave," "carpet," or "toroidal-pore" mechanisms. Recent evidence also suggests that AMPs inhibit cell-wall synthesis, nucleic-acid synthesis, protein synthesis, enzymatic activity as well as disrupt mitochondrial membranes (Brogden 2005).

In American adults, serum 25(OH)D levels >75 nmol/L were associated with a reduced incidence of upper respiratory tract infection (Ginde et al. 2009). Rickets is associated with an increased risk of acute respiratory tract infection, particularly pneumonia (Mariam and Sterky 1973; El-Radhi et al. 1982; Banajeh et al. 1997; Muhe et al. 1997; Najada et al. 2004; Banajeh 2009). Pinto and colleagues found low 25(OH)D levels in urban African American, but not white subjects, with chronic rhinosinusitis (Pinto et al. 2008).

Historically, supplementation with cod liver oil (containing vitamin D) was shown to reduce upper respiratory tract infection frequency. The beneficial effect was attributed to vitamin A (Holmes et al. 1932, 1936). In one interventional cohort study where 60,000 IU of vitamin D was given weekly for 6 weeks to children with recurrent respiratory tract infection the incidence of recurrent respiratory tract infection in the children receiving supplementation reduced to that of the control group (Rehman 1994). In some studies where 25(OH)D was given for skeletal health, a reduction in infection risk has also been noted (Aloia and Li-Ng 2007; Avenell et al. 2007).

In recent years a number of randomized controlled trials (Table 14.1) looking at the role of vitamin D supplementation in the prevention of upper respiratory tract infection have been published (Li-Ng et al. 2009; Laaksi et al. 2010; Urashima et al. 2010; Camargo et al. 2012). Li-Ng and colleagues randomized 162 adults to receive 2,000 IU vitamin D_3 daily or matching placebo for 12 weeks. No difference in the duration or severity of URI symptoms was found (Li-Ng et al. 2009). The authors attributed this to a number of reasons. Firstly, the subjects started vitamin D supplementation during winter, rather than at the beginning. Since the half-life of 25(OH)D is at least 2–3 weeks, it is generally accepted that it takes 2–3 months for blood 25(OH)D levels to plateau with vitamin D supplementation if a loading dose is not given (Bacon et al. 2008). This meant that the subjects were reaching optimum 25(OH)D levels at the end of winter and the end of the trial. Secondly, the vitamin D dosage may have been inadequate and thirdly, the baseline 25(OH)D levels were higher than in previous studies meaning that vitamin D supplementation may have been less effective.

Urashima and colleagues gave 334 Japanese school children vitamin D_3 1,200 IU daily or placebo (Urashima et al. 2010). There was a 50 % reduction in children who were diagnosed with influenza A (primary outcome). However, if one combines the number of cases of influenza A and influenza B, there was no reduction in total influenza infections between the vitamin D treated and the control group. Laaksi and colleagues supplemented 164 young Finnish men with only 400 IU/day of vitamin D_3. Absence from duty due to respiratory tract infection and number of days absent was lower in the treated group. The proportion of subjects without any days absent was slightly higher in the vitamin D supplementation group (Laaksi et al. 2010). Martineau and colleagues used high-dose vitamin D_3 in the treatment of pulmonary TB (Martineau et al. 2011). The number of people who had upper respiratory tract infection symptoms was recorded. One of seventy-one patients receiving at least one dose of vitamin D_3 as compared to 6 of 70 receiving at least one dose of placebo reported symptoms. This secondary outcome was of borderline statistical significance ($p = 0.06$). In a recent RCT of 247 Mongolian children with vitamin D deficiency in winter, vitamin D supplementation halved the risk of upper respiratory infections (Camargo et al. 2012).

In the randomized controlled trial (RCT) where Japanese children were given 1,200 IU daily or placebo, children with a previous diagnosis of asthma, there was also a significant reduction in number of asthma attacks (Urashima et al. 2010); only 2 asthmatic children taking vitamin D and 12 taking placebo had "asthma

Table 14.1 Randomized controlled trials (RCTs) on the effect of vitamin D supplementation on respiratory infection

Study authors and n	Type of study, vitamin D dosage, and duration of intervention	Results	Comment
Aloia and Li-Ng (2007), $n=204$	3-year RCT using 2,000 IU/day of vitamin D_3 in African American women	Number of flu or cold episodes in the treated group were 1/3 of the placebo group (8 vs 26, respectively)	Significant reduction of reported flu; small sample
Avenell et al. (2007), $n=1,700$	RCT using 800 IU D_3/day for 24–62 months	No difference in infection or antibiotic usage in previous week	Small dose
Li-Ng et al. (2009), $n=162$	RCT using 2,000 IU vitamin D_3/day for 12 weeks	No significant difference in incidence of flu or cold symptoms	With this dose regimen, it may take more than 3 months to achieve adequate vitamin D levels
Urashima et al. (2010), $n=334$	RCT using 1,200 IU vitamin D_3/day in school children for 4 months	RR of 0.58 compared with control group ($p=0.04$). Asthma attacks significantly reduced in treatment group ($p=0.006$)	Significant reduction of influenza A but not influenza B
Laaksi et al. (2010), $n=164$	RCT using 400 IU vitamin D_3/day for 6 months	No statistically significant difference in days off ($p=0.06$); supplemented group reported as healthier	Low vitamin D supplement and supplemented group almost showed a significant result
Martineau et al. (2011), $n=126$	RCT – 100,000 IU vitamin D_3 at baseline, 12, 28, and 42 days	No significant difference in time to sputum culture conversion ($p=0.14$). Reduction in upper respiratory infection ($p=0.06$)	Sputum culture conversion hastened in *tt* genotype of the *Taql* VDR polymorphism ($p=0.02$)
Majak et al. (2011), $n=48$	RCT of a single dose of 500 IU D_3/day	A significant reduction in acute infective asthma exacerbations due to an upper respiratory infection ($p=0.029$)	Children with a decreased 25(OH)D level eight times more likely to have an asthma exacerbation
Camargo et al. (2012), $n=247$	RCT of 300 IU D_3/day in vitamin D-deficient Mongolian children	Incidence of upper respiratory tract infections halved	

attacks." Recently, Majak and colleagues reported in an RCT on the role of vitamin D supplementation (vitamin D_3 500 IU daily) vs placebo for 6 months in Polish children with newly diagnosed asthma (Majak et al. 2011); the investigators observed a significant reduction in asthma exacerbations due to acute upper respiratory tract infections ($p=0.029$).

Vitamin D deficiency has been linked to an increased incidence of atopy including allergic rhinitis (Ehlayel et al. 2011). However, Hyppönen and colleagues have reported that regular vitamin D supplementation (≥2,000 IU/day) of Finnish infants increases the risk of developing allergic rhinitis and asthma at the age of 31 (Hyppönen et al. 2004). In a separate study in the UK, they also linked deficient (<25 nmol/L) and excessively high (>135 nmol/L) serum 25(OH)D levels with elevated serum IgE levels (Hyppönen et al. 2009). The relationships of vitamin D with allergy appear complex, but a possible "U" shape relationship exists with both low and high 25(OH)D levels predisposing to atopy (Bartley 2010).

A number of RCTs are currently underway worldwide investigating the role of vitamin D supplementation in upper respiratory infection

and allergic disease (Bartley 2010). While preliminary data appears promising, optimal 25(OH)D levels and vitamin D treatment regimens for the prevention and/or management of respiratory infections remain to be determined.

Conclusions

Increasing evidence indicates that probiotics, zinc, and vitamin D supplementation could be important clinically. The diagnosis of zinc deficiency in clinical practice can be difficult (Gibson et al. 2008). A number of trials investigating the role of vitamin D supplementation in the prevention of upper respiratory disease are currently underway. Increasing evidence indicates that in vitamin D-deficient patients, vitamin D supplementation can be beneficial in the prevention of upper respiratory tract infection particularly in asthmatic children.

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Nose as a Route for Drug Delivery

15

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Keywords

Nasal route • Nasal drug delivery • Intranasal administration • Nasal therapeutic agents • Intranasal delivery • Small-molecule drugs • Topical drugs • Systemic drugs • Central nervous system-acting drugs • Biomolecular drugs

Core Messages

IN administration of topical drugs (decongestants, antihistamines, corticosteroids or antimicrobials) has been widely used for symptomatic relief and prevention/treatment of nasal dysfunctions, such as nasal congestion and acute or chronic rhinosinusitis.

IN administration is now recognised as a therapeutically viable way for delivery of systemic drugs as alternative to the parenteral and oral routes.

Over the last years, new pharmaceutical formulations and novel delivery strategies have been developed offering promising opportunities to expand the delivery of small-molecule drugs and biomacromolecular drugs by the nasal route.

Nasal drug delivery is particularly interesting for compounds such as polar small drugs, and therapeutic peptides and proteins.

IN drug delivery is a patient-friendly administration route avoiding the pain associated with parenteral administration

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and that enables to circumvent poor stability in gastrointestinal fluids, poor intestinal absorption and/or hepatic first-pass metabolism related with oral route.

A wide variety of IN drugs exhibit plasma concentrations and systemic bioavailability frequently higher than those obtained for oral administration. Sometimes they are even comparable to those obtained after IV administration.

The potential of the nasal route for administration of drugs into systemic circulation has been remarkably evidenced for a wide variety of drugs and it is particularly interesting when a rapid onset of action is a key requirement.

IN administration is currently emerging as a promising way for direct delivery of drugs to the brain, which may be extremely useful for treatment of neurological conditions such as epilepsy, Alzheimer's disease and Parkinson's disease.

IN delivery of some CNS-acting drugs has afforded higher concentrations in the brain than those reached after IV administration, probably due to readily access to the brain, avoiding the blood–brain barrier.

Non-invasive mucosal routes, with less importance for drug delivery in the past, have now assumed a greater interest for delivery of peptide-, protein- and nucleic acid-based drugs or vaccines, particularly the nasal route.

In the pharmaceutical formulation of peptide-, protein- and other biomacromolecular-based drugs intended for IN delivery, the use of suitable vehicles, enzyme inhibitors and/or penetration enhancers is of paramount importance.

The use of suitable vehicles, enzyme inhibitors and/or penetration enhancers is of paramount importance during the development of IN pharmaceutical formulations of peptide-, protein- and other biomacromolecular drugs.

The successful IN administration of some polypeptide drugs (desmopressin, calcitonin, buserelin, nafarelin and oxytocin) has promoted an extensive evaluation of the nasal route for delivery of many other protein and peptide drugs currently used as injectables.

The immunisation through the nasal route is an interesting opportunity that has been increasingly explored over the last years. The recent developments lead us to believe that the availability of new vaccines for IN delivery will be greatly expanded in the near future.

15.1 Introduction

Nasal drug delivery is now well recognised as a useful alternative to oral and parenteral routes. Undoubtedly, the intranasal (IN) administration of medicinal products for the symptomatic relief and prevention or treatment of topical nasal conditions has been widely used for a long period of time. However, recently, the nasal mucosa has seriously emerged as a therapeutically viable route for the systemic drug delivery. Among the primary target drugs for IN administration are those compounds with poor stability in gastrointestinal fluids, poor intestinal absorption and/or extensive hepatic first-pass elimination, such as polar small drugs, peptides and proteins. The nasal drug delivery seems to be also an encouraging way to circumvent the blood–brain barrier (BBB) enabling direct nose-to-brain delivery of central nervous system (CNS)-active agents.

Over the last years, several comprehensive reviews have been published discussing in some detail particular aspects of drug delivery through the nasal route. Therefore, this chapter is built based on this information and focuses on recent developments in the area, discussing the major factors affecting nasal drug delivery and highlighting nasal therapeutic agents currently available on the market and also some candidates for IN administration.

15.2 Intranasal Delivery of Topical Drugs

IN route has been widely used for a long time as an attractive option for local (or topical) drug delivery. Typical examples of locally acting intranasally administered drugs are decongestants, antihistamines, corticosteroids and antimicrobials. They are mainly indicated in the treatment of nasal congestion, rhinitis and sinusitis (rhinosinusitis), inflammation and infection. Topical therapies enable direct drug delivery to the target organ (biophase) and the use of lower effective doses which minimises the potential for systemic adverse effects that may occur with oral and parenteral therapy. The choice between topical and systemic therapy depends on spectrum disease and on the efficacy to safety ratio of each therapy (Bitter et al. 2011; Costantino et al. 2007; Salib and Howarth 2003).

15.2.1 Decongestants

Topical nasal decongestants are widely prescribed for the symptomatic relief of nasal congestion in common cold, allergic and nonallergic/vasomotor rhinitis, acute and chronic rhinosinusitis (CRS) and nasal polyposis (Meltzer et al. 2010).

The most common nasal topical decongestants are phenylephrine, pseudoephedrine, oxymetazoline and xylometazoline. The first two are sympathomimetic amines while the others are imidazoline derivatives. Their pharmacologic effect results from direct or indirect activation of postsynaptic α-adrenergic receptors of the nasal mucosa vasculature; this produces vasoconstriction and subsequent decrease of mucosa swelling and nasal resistance to airflow which leads to decongestion (Corboz et al. 2008). Both groups are α-adrenoceptors agonists; however, sympathomimetic amines preferentially bind to α_1-adrenoceptors while imidazolines predominantly address α_2-adrenoceptors. Moreover, imidazoline derivatives also cause a reduction in the nasal mucosal blood flow due to their activity on the resistance vessels (α_2-adrenoceptors) which contributes to nasal decongestion (Caenen et al. 2005; Hochban et al. 1999). The effect of topical decongestants has already been studied in the past by several authors using different methods (Bende and Löth 1986; Maranta and Simmen 1996). The most common problem associated with overuse of topical decongestants is rebound nasal congestion, reduction in efficacy (tachyphylaxis) and nonspecific nasal hyperreactivity. This clinical condition is defined as rhinitis medicamentosa and it limits the practical utility of topical decongestants to short-term therapies. The treatment options for rhinitis medicamentosa include the immediate suspension of nasal decongestant and some authors suggest the use of corticosteroids (Akpinar et al. 2012; Graf 1997; Vaidyanathan et al. 2010). This has recently been the motivation for a novel approach consisting in the simultaneous use of nasal decongestants and corticosteroids to overcome the limitation of the long-term use. Vaidyanathan et al. (2010) evaluated the effect of combining IN fluticasone propionate with oxymetazoline after 14 days of treatment with IN oxymetazoline alone. After 3 days of this combined administration (day 17), tachyphylaxis of response and rebound congestion, induced by the prolonged use of IN oxymetazoline, were reduced by IN fluticasone propionate concomitant administration. This finding along with other studies may open new perspectives for the prolonged use of topical decongestants in clinical practice (Akpinar et al. 2012; Vaidyanathan et al. 2010).

15.2.2 Antihistamines and Corticosteroids

IN antihistamines and corticosteroids are efficacious topical drugs used in the treatment of allergic rhinitis (AR). This pathology is defined as an inflammation of the nasal mucosa caused by a hyperactive immune system response to benign, non-infectious environmental aeroallergens (e.g. pollens, mites, animal danders) (Dykewicz and Hamilos 2010).

Antihistamines, the commonly known H_1 receptor antagonists, are particularly effective at reducing the symptoms of sneezing, nasal itching and rhinorrhoea in AR. Interestingly, as reviewed

by Howarth in 2000, in vitro investigations revealed that some antihistamines have also the potential to modify the inflammatory process, in addition to their H_1 histamine receptor blocking action. However, for these effects to be fully evident, in vivo antihistamine doses must be higher than those usually tolerated, leading to sedative adverse effects. Thus, the topical IN delivery of antihistamines appears as an advantageous strategy to directly target the organ with therapeutic drug concentrations, minimising the risk of systemic adverse effects (Howarth 2000; Meltzer et al. 2010; Salib and Howarth 2003).

Topical nasal antihistamines represent the latest therapeutic option added to the armamentarium of AR management. IN antihistamines include levocabastine, azelastine and olopatadine and their efficacy is equal or superior to that of second-generation oral antihistamines. These topical agents have a rapid onset of action, which makes them an appropriate "as required" therapy for episodic AR symptoms relief (Dykewicz and Hamilos 2010; Kaliner et al. 2009; Sur and Scandale 2010).

Although levocabastine is a second-generation antihistamine, it causes some sedation when administered orally. For this reason and because of its remarkable potency, levocabastine was subsequently developed for IN delivery. Topical levocabastine has an onset of action of 10–15 min and is effective for up to 12 h (Salib and Howarth 2003).

Topical azelastine is another second-generation antihistamine that has been developed to overcome the sedation effects of oral administration. This drug offers an onset of action of 15 min and has a systemic bioavailability of 40 % following IN administration. The estimated systemic exposure of topical azelastine is six to eightfold lower than that observed for the oral drug. IN azelastine exhibits superior efficacy compared to IN levocabastine. In a double-blind parallel group study, levocabastine and azelastine nasal sprays provided a good symptomatic treatment of seasonal AR; however, azelastine was statistically more effective and safer than levocabastine (Falser et al. 2001).

Olopatadine is the most recent topical nasal antihistamine introduced in the market. Firstly, it was approved as an ophthalmic solution, but in 2008, olopatadine appeared as a nasal spray indicated for the treatment of seasonal AR. Clinical trials of olopatadine nasal spray have shown an onset of action within 30 min and a significant efficacy in relieving nasal allergy symptoms, including nasal congestion (Kaliner et al. 2009; Roland et al. 2010).

The AR and its impact on asthma guidelines recommend the use of IN antihistamine in mild persistent disease or in occasional symptoms for intermittent disease. In the case of IN corticosteroids, they should be regarded as first-line therapy for moderate to severe persistent disease (Salib and Howarth 2003).

IN corticosteroids are recognised as "the gold standard" of therapeutic choice in AR. Compared with oral or local antihistamines, IN corticosteroids are more effective in what concerns the relief of nasal congestion symptom. There are a wide variety of IN corticosteroid molecules; they include beclomethasone, budesonide, triamcinolone acetonide, flunisolide, fluticasone propionate, mometasone furoate, ciclesonide and fluticasone furoate (Salib and Howarth 2003; Sastre and Mosges 2012). This pharmacological class acts very early in the inflammatory pathway, modifying the ability of pro-inflammatory transcription factors to up-regulate gene expression (Howarth 2000). This mechanism of action implies a time delay between administration and clinical activity. Hence, IN corticosteroids have a slower onset of action (several hours) than IN antihistamines with maximum efficacy developing over a period of days and weeks. In most cases, a once-daily regimen is sufficient and compatible with patient compliance; in severe cases and during exacerbation, twice-daily administration is indicated (Salib and Howarth 2003).

Since oral and some high-dose inhaled corticosteroids have systemic adverse effects, IN administration of corticosteroids emerges as a promising alternative route to enhance the safety profile of these agents. Nevertheless, one should be aware of the possibility of these topical agents reaching the systemic circulation in sufficient concentration to produce adverse effects

(Salib and Howarth 2003; Sastre and Mosges 2012). The newer IN corticosteroid agents (e.g. fluticasone propionate, mometasone furoate, ciclesonide, fluticasone furoate) have pharmacokinetic properties that minimise their systemic bioavailability compared to older IN corticosteroids (e.g. beclomethasone, flunisolide, triamcinolone acetonide, budesonide) and oral agents (e.g. methylprednisolone). The systemic bioavailability of the newer IN corticosteroids drugs is negligible (<1 %) which contributes for minimal risk of systemic adverse effects (Sastre and Mosges 2012). Drug lipophilicity plays an important role in pharmacokinetic profile and pharmacodynamic action of IN corticosteroids. Increased lipophilicity is associated with greater deposition and slower release from the nasal respiratory tissue, greater binding affinity for corticosteroid receptor and consequently less free drug is available for systemic absorption, which results in fewer systemic adverse effects. Fluticasone furoate is a novel-enhanced affinity corticosteroid recently approved by the Food and Drug Administration (FDA) in 2007; experimental studies have shown that it has the most potent and fastest anti-inflammatory activity (Giavina-Bianchi et al. 2008). The clinical efficacy of IN corticosteroids does not depend only on the relative affinity for corticosteroid receptor but also on the drug retention in the nasal mucosa. This may be primarily attributed to lipophilicity as in the case of fluticasone propionate; however, for budesonide, an additional contribution is provided by its ability to reversibly form fatty acid esters in the mucosa that may hold and release the regenerated budesonide locally. This reversible nasal metabolism adds to lipophilicity to originate the higher retention of budesonide when compared to fluticasone propionate (Petersen et al. 2001).

15.2.3 Antimicrobials

Since the early 1990s, topical antimicrobial treatment of CRS has attracted increasing attention. Although the exact aetiology and pathophysiology of CRS are still unknown, bacteria and fungi appear to be implicated in the development of this disease. Furthermore, bacterial and fungal biofilms, which are microcolonies embedded in an extracellular polysaccharide matrix with greater antimicrobial resistance than planktonic bacteria, have been associated with chronic infections. The aims of CRS treatment are reduction of nasal and paranasal mucosal inflammation, control of infection and re-establishment of mucociliary clearance (MCC) (Dykewicz and Hamilos 2010; Foreman et al. 2012; Suh and Kennedy 2011). The mainstay of CRS treatment is topical corticosteroids and oral antibiotics; the efficacy of topical antibiotics is still under investigation. These have the theoretical advantage of achieving higher concentrations of antibiotics at the target site which has been shown to be effective against bacteria in biofilm form. Moreover, topical usage is less liable to produce systemic adverse effects (Lim et al. 2008).

A systematic review of IN antimicrobials in the management of CRS was presented by Lim et al. (2008). Antimicrobials investigated included topical tobramycin, mupirocin, *N*-chlorotaurine, fosfomycin, ceftazidime, cefmenoxime and amphotericin. The purpose of this study was to identify evidence for the benefit of topical antimicrobials in several CRS subgroups, classified according to method of delivery, culture-directed or empiric therapy, presence or absence of previous surgery, stable or acute exacerbations of CRS and type of antimicrobial (antibiotics and antifungals). The authors concluded that a low level of evidence points to the efficacy of topical antibiotics in both stable and acute exacerbations of CRS and no definite conclusion could be made regarding the use of antifungals (Adappa et al. 2012; Lim et al. 2008). In what concerns the mode of delivery, there was evidence for the use of nasal irrigation or nebulisation rather than delivery by nasal spray. Nebulisers and nasal irrigations have advantages over the nasal sprays for the successful delivery of topical drugs. In fact, nasal sprays achieve a smaller deposition surface area than that covered by nebulisation and their drug distribution effect depends on MCC which is impaired in CRS. Although non-aerosol based, nasal irrigations may be beneficial; their efficacy may arise from removal of inflammatory cells

and excess mucus with consequent improvement of sinus drainage, rather than from direct action on sinus pathology (Adappa et al. 2012; Lim et al. 2008). Lim et al. (2008) also reported that culture-directed bacterial studies present a higher level of evidence than empiric treatment. The American Academy of Otolaryngology – Head and Neck Surgery recommends irrigation or nebulisation with ceftazidime, aminoglycoside (e.g. tobramycin) and quinolones (e.g. ciprofloxacin, levofloxacin) when cultures present pseudomonas and the use of amphotericin B irrigation in cases of proven fungal infections. The highest level of evidence was found for studies with post-surgical patients. Topical antibiotics may play a unique role in CRS patients with post-surgery infections with *Streptococcus aureus* and pseudomonas. In summary, topical antibiotics should not be first-line management but may be successfully used in refractory patients to the recommended topical corticosteroids and oral antibiotics. However, a full evaluation of this emergent modality of CRS treatment requires more investigation (Adappa et al. 2012; Lim et al. 2008).

15.3 Intranasal Delivery of Systemic Drugs

As the market for the IN delivery of topical drugs matures, the potential of IN route for administration of drugs acting systemically has been investigated at a remarkably fast rate. Indeed, the IN administration is today regarded as a potential alternative route for systemic delivery of drugs that are conventionally administered by intravenous (IV) route or that undergo extensive first-pass metabolism after oral administration (Bitter et al. 2011; Illum 2012). Nevertheless, the nasal route is less suitable for chronic drugs that must be frequently administered daily, and drugs that require sustained blood levels should not be considered for nasal delivery unless they are included in sustained-release type dosage forms for nasal administration (Atluri et al. 2005). This is mainly due to the anatomic and physiological characteristics of the nose, transport mechanisms involved throughout nasal systemic absorption and physicochemical properties of the drugs.

Due to its anatomical localisation, high vascularisation and permeability, the respiratory mucosa around the turbinates is recognised as the main site for systemic entry of drugs. Generally, lipophilic drugs easily diffuse through nasal mucosa by the *transcellular* route (Illum 2002), while the polar drugs are mostly transported through small connections between epithelial adjacent cells, called tight junctions (Arora et al. 2002). However, only polar compounds with molecular weight lower than 1,000 Da can cross this semipermeable membrane as the normal diameter of tight junctions is 3.9–8.4 Å (Alsarra et al. 2010).

15.3.1 Intranasal Systemic Delivery of Small Molecules

The awareness that drugs may reach widespread circulation in few minutes after nasal administration expanded remarkably the number of systemically acting drugs marketed as nasal formulations (Table 15.1). Furthermore, the number of investigations regarding the feasibility of IN route for delivering many other small compounds to the systemic circulation is also continuously emerging (Table 15.1).

Underlying this wide interest on exploiting nasal cavity for systemic delivery is the rapid and direct systemic absorption of compounds, the circumvention of gastrointestinal and hepatic first-pass metabolism and, consequently, the achievement of higher drug plasma levels and higher bioavailability through nasal route than oral administration. IN drug administration may enable the reduction of the dose administered, a quick onset of pharmacological activity and fewer side effects.

Among the several alternative formulations currently developed and under development, solution-based formulations are the most frequent because they are the easiest to administer and they have the greatest chance for systemic drug delivery across the nasal mucosa. Moreover, systems incorporating mucoadhesive excipients and/or enzyme inhibitors and/or

Table 15.1 IN small systemic drugs on the market or under development

Drug (or drug candidate)/ trade name	Indications	Status	References
Acyclovir	Antiviral drug	Under development	Alsarra et al. (2008, 2010) and Pires et al. (2009)
Atropine sulfate	Treatment of peptide ulcer disease	Under development	Behl et al. (1998)
Apomorphine	Medication for erection	Under development	Costantino et al. (2007)
Buprenorphine hydrochloride	Analgesic drug	Under development	Behl et al. (1998)
Butorphanol/Stadol NS®	Migraine	Market	Grassin-Delyle et al. (2012)
Carvedilol	Cardiovascular drug	Under development	Patil et al. (2010, 2012) and Pires et al. (2009)
Estradiol/Aerodiol®	Hormone replacement therapy	Market	Bitter et al. (2011) and Grassin-Delyle et al. (2012)
Fentanyl/Instanyl®, PecFent®	Breakthrough pain	Market	Bitter et al. (2011), Christrup et al. (2008) and Grassin-Delyle et al. (2012)
Haloperidol	Antipsychotic	Under development	Grassin-Delyle et al. (2012)
Ketamine	Analgesic drug	Under development	Bitter et al. (2011)
Meclizine hydrochloride	Management of nausea, vomiting and dizziness	Under development	Behl et al. (1998)
Metoclopramide hydrochloride	Antiemetic drug	Under development	Behl et al. (1998), Bitter et al. (2011) and Costantino et al. (2007)
Morphine	Analgesic drug	Under development	Grassin-Delyle et al. (2012), Pires et al. (2009) and Stoker et al. (2008)
Naloxone/Narcan®	Treatment of opioid overdose	Market	Costantino et al. (2007)
Nicotine/Nicotrol NS®	Smoking cessation	Market	Grassin-Delyle et al. (2012)
Nifedipine	Management of vasospastic angina	Under development	Behl et al. (1998), Costantino et al. (2007) and Kubota et al. (2001)
Nitroglycerin	Prevention of angina pectoris due to coronary artery disease	Under development	Behl et al. (1998) and Kubota et al. (2001)
Ondansetron	Prevent nausea and vomiting	Under development	Costantino et al. (2007) and Hussain et al. (2000)
Pentazocine	Analgesic drug	Under development	Illum (2002)
Propranolol hydrochloride	Management of hypertension and angina pectoris	Under development	Alsarra et al. (2010), Behl et al. (1998) and Costantino et al. (2007)
Ranitidine hydrochloride	Treatment of duodenal ulcers	Under development	Behl et al. (1998)
Scopolamine	Motion sickness	Under development	Costantino et al. (2007)
Scopolamine hydrobromide	Prevention of nausea and vomiting induced	Under development	Behl et al. (1998)
Sufentanil	Analgesic drug	Under development	Behl et al. (1998)
Sumatriptan/Imitrex®	Migraine	Market	Grassin-Delyle et al. (2012)
Zanamivir	Antiviral drug	Under development	Cass et al. (1999) and Grassin-Delyle et al. (2012)
Zolmitriptan/Zomig®	Migraine	Market	Costantino et al. (2007)

nasal permeation enhancers have been developed in order to improve the therapeutic efficacy once they enhance drug nasal residence time, prolong duration of action and increase the absorption extent of drugs (Grassin-Delyle et al. 2012; Jiang et al. 2010; Pires et al. 2009).

15.3.1.1 Analgesic Drugs

Opioids are considered the cornerstone of an analgesic regimen and are indicated for the treatment of breakthrough pain and acute, moderate to severe and chronic pain. Ideally, they must exhibit a rapid onset time and a prolonged duration of action that coincides with the episode's time course. Although oral and parenteral solutions are generally used for treatment of the breakthrough pain, the onset effect is not achieved before 30–45 min and the maximal effect within 1 h (Tveita et al. 2008). IN administration of opioids arises hence as a hope to easily and quickly achieve pain relief and improvement of the life quality of patients.

Indeed, a wide variety of opioid drugs have been under investigation, including morphine, fentanyl and buprenorphine. Although recognised as the standard opioid for cancer pain relief, morphine has a significant intestinal and hepatic first-pass metabolism that limits its bioavailability, which is around 20–32 % (Fitzgibbon et al. 2003). Similarly, the bioavailability of morphine solutions administered intranasally rounds only 10–22 % in humans and sheep (Illum et al. 2002) probably due to its low lipophilicity. In order to increase the nasal residence time, the bioavailability and the elimination half-life time of morphine after its IN administration, a wide variety of formulations have been currently under development, including formulations containing chitosan as microspheres or in solution (formulations based on starch microspheres coupled with lysophosphatidylcholine) (Illum et al. 2002) and solutions added of oleic acid as absorption promoter (Fitzgibbon et al. 2003). One of the most relevant clinical studies consisted in assessing the pharmacokinetic profile and tolerability of Rylomine™ composed by morphine mesylate and chitosan in 13 subjects (Stoker et al. 2008). Based on the area under the concentration-time curve (AUC) values, bioavailability of IN morphine was considerably higher when compared to the other administration routes.

In opposition to morphine, fentanyl and butorphanol can be effectively and quickly absorbed at nasal cavity without using absorption promoters due to their relative high lipophilicity and low molecular weight. Particularly, IN fentanyl is currently marketed (Table 15.1) as two distinct forms: the aqueous solution Instanyl® and the pectin-based mucoadhesive formulation PecFent®. In a pharmacokinetic study in 19 cancer patients with breakthrough pain, nasal spray fentanyl was quickly absorbed through the nasal mucosa, attaining peak plasma concentrations within 12–15 min when administered at 50, 100 and 200 μg (Kaasa et al. 2010). One of the most important in vivo studies within this framework consisted in a balanced, randomised, double-blind, two-way crossover study in which patients received the same fentanyl dose by IN and IV administration (Christrup et al. 2008). The time to onset of action of around 10 min and the onset and duration of analgesia were not significantly different between single doses of IN and IV fentanyl in these adults. Recent researches have also shown an improvement of the bioavailability of fentanyl when administered as IN mucoadhesive formulations (Fisher et al. 2010; Kaasa et al. 2010).

Sumatriptan and zolmitriptan are analgesic drugs particularly used for migraine and cluster headaches. They are currently available as nasal formulations that provide onset times significantly quicker than those obtained after oral dosing (Dodick et al. 2005; Gawel et al. 2005) (Table 15.1). This success is due to the high lipophilicity of sumatriptan and zolmitriptan that facilitate their systemic absorption through nasal respiratory mucosa (Uemura et al. 2005) but also due to their direct access to CNS as it is referred in Sect. 15.4.1.5.

15.3.1.2 Cardiovascular Drugs

For a long time, nasal administration has been investigated as an attractive route for administration of cardiovascular drugs such as propranolol, nifedipine, nitroglycerin and carvedilol (Costantino et al. 2007).

The IN dosing of propranolol provides a pharmacokinetic profile that is very similar to that of IV administration, specifically when regarding the onset time and bioavailability (Ahn et al. 1995).

Bioadhesive sodium alginate microspheres of metoprolol tartrate for IN systemic delivery were also investigated as an alternative therapy for the treatment of hypertension and angina pectoris (Rajinikanth et al. 2003). Promising results were found in rabbits and rats, with maximum plasma drug concentrations (C_{max}) clearly higher after IN administration than those after oral administration.

Nifedipine is a calcium channel blocking agent frequently used for the treatment of angina pectoris and hypertension. Kubota et al. (2001) performed a crossover clinical study in order to investigate the optimal administration method of nifedipine for rapid management of hypertension. It is interesting to highlight that although the value of C_{max} was clearly lower after IN administration of nifedipine than that obtained for oral administration, the mean serum concentration of nifedipine 5 min after IN administration was higher (and remained higher until after 15 min). These results sustain that IN administration of nifedipine guarantees the fastest increase of drug plasma concentrations and the most significant effect on blood pressure reduction.

More recently, IN administration of carvedilol, a non-selective β-adrenergic antagonist also used in the treatment of hypertension and stable angina pectoris (Packer et al. 2002), has been under investigation due to its significant hepatic first-pass metabolism and low absolute bioavailability (25 %). Recent investigations reported that when administered by IN route to rabbits, sodium alginate microspheres and mucoadhesive chitosan microspheres containing carvedilol, the mean residence and half-life times of the drug were at least twice of those observed after IV administration. Furthermore, the high absolute bioavailability and the low t_{max} achieved for carvedilol sustain that both pharmaceutical formulations are promissory to prolong the therapeutic effect of carvedilol (Patil et al. 2010, 2012).

15.3.1.3 Antiviral Drugs

The antiviral acyclovir is currently available as several dosage forms that present limitations. Firstly, the intestinal absorption of acyclovir is slow, variable and incomplete, with an absolute bioavailability of approximately 15–20 % which requires a frequent oral dose regimen. On the other hand, its low solubility in water and lipids hamper the administration of acyclovir by intramuscular route (Shao et al. 1994). Even when intravenously administered, acyclovir is mainly excreted unchanged through urine by glomerular filtration and tubular secretion, demanding a high dose to be administered in order to attain therapeutic drug concentrations.

Hence, the IN administration of acyclovir emerged recently as an innovative strategy that could maintain the drug for a longer time in systemic circulation within effective and non-toxic concentration ranges (Alsarra et al. 2008). Since acyclovir is also practically impermeable through the nasal mucosa, neutral mucoadhesive liposomes were formulated in order to enhance the nasal penetration and systemic absorption. In a study performed in rabbits, the absolute bioavailability of nasal liposomes with acyclovir was 60.7 % while that of free acyclovir was only around 5 %. This discrepancy was also observed for AUC values, clearly demonstrating that liposomes pass directly into systemic circulation, resulting in a considerable systemic concentration of acyclovir (Alsarra et al. 2008).

Similarly, zanamivir is another antiviral drug which, although presenting higher bioavailability when administered by IN route than orally (Cass et al. 1999), is poorly absorbed at nasal level especially due to its high hydrophilicity. Thus, similar investigations to those executed for acyclovir are expected to be soon performed for zanamivir.

15.3.1.4 Antiemetic and Motion Sickness Drugs

The nasal delivery of drugs for the treatment of nausea and motion sickness is steadily appearing as a desirable alternative to parenteral and oral medications especially because a rapid onset of action is required in acute situations.

Moreover, the gastric dysmotility associated to the pathological situation is probable to affect the intestinal drug absorption and the drug fraction that is absorbed after oral administration.

For instance, when orally administered, metoclopramide bioavailability is highly variable (32–98 %) and it has a short half-life (3–4 h) that demands an oral administration three to four times daily. The IN administration of metoclopramide is identified as a good alternative (Mahajan and Gattani 2010). There are, however, limitations related to the low permeability across the nasal mucosa and the rapid MCC of metoclopramide, and in order to overcome these features, new nasal formulations have been developed and are under investigation. They consist on aqueous solutions added of absorption enhancers to increase nasal permeability (Zaki et al. 2006) or on gel and mucoadhesive formulations to prolong the residence time at the nasal absorption local and facilitate the drug uptake (Mahajan and Gattani 2010; Tas et al. 2009). Zaki et al. (2006) demonstrated that when nasal spray solution was administered to humans, the C_{max} of metoclopramide was significantly higher than that observed after oral administration while values of t_{max} and half-life time were significantly lower (Zaki et al. 2006). However, no statistical differences were observed for the mean residence times of metoclopramide, and therefore, the same research group developed and administered gel and mucoadhesive formulations composed by gellan gum (0.4 %, w/v) and Carbopol (0.15 %, w/v) to rabbits. The superior absolute bioavailability of the nasal gel compared to the oral solution clearly indicated higher absorption of metoclopramide when administered intranasally. Favourable results were also found for gel dosage forms based on mucoadhesive polymer sodium carboxymethylcellulose for IN administration of metoclopramide to sheep (Tas et al. 2009).

Ondansetron has also been under investigation to be administered by IN route, although it is currently available in IV solutions and oral dosage forms. The low oral bioavailability of ondansetron in humans (60 %) and its administration at least 30 min prior to chemotherapy sessions (Gungor et al. 2010) propelled Hussain and collaborators (2000) to investigate for the first time the feasibility of ondansetron IN administration to rats. The plasma concentration-time profiles for IN administration were comparable to that of IV administration and the rapid absorption through the nasal mucosa allowed ondansetron to reach systemic circulation almost instantaneously. Equivalent results were also reported by Gungor et al. (2010). Nevertheless, several ondansetron formulations have been developed and demonstrated to enhance drug delivery, reduce the onset time and prolong drug effect duration in relation to the oral administration (Cho et al. 2008; Gungor et al. 2010)

Scopolamine, an antimuscarinic agent indicated for motion sickness, is another example of a drug in this area that is suitable for IN dosing as depicted by human pharmacokinetic studies developed by Ahmed et al. 2000.

15.3.1.5 Erectile Dysfunction Drugs

Sildenafil citrate is considered a standard treatment for erectile dysfunction. It is rapidly absorbed after oral administration but only with an absolute bioavailability of 40 %, an onset of action time within 15.5 min and effect duration of approximately 40 min (Deveci et al. 2004). Recently, Elshafeey et al. (2009) attempted to take advantage of nasal administration to improve these limitations and developed a new microemulsion of sildenafil citrate composed of oleic acid/Labrasol/Transcutol/water. The research group achieved drug concentrations that were nearly twofold higher than those obtained for oral tablets. A higher bioavailability and faster onset systemic levels were also observed for IN formulation probably due to the fact that liver metabolism was bypassed.

15.4 Intranasal Delivery of CNS-Acting Drugs

The brain is a delicate organ that plays a set of vital functions to maintain convenient body homeostasis; therefore, its integrity is ensured by specific physiological barriers and mechanisms of defence which efficiently protect and isolate

the CNS from harmful endogenous substances and external insults (e.g. xenobiotics and virus).

The BBB represents one of the strictest structural and functional barriers in segregating the brain from the systemic circulation. It is characterised by the presence of non-fenestrated capillary endothelial cells with intercellular tight junctions, a very high transendothelial electric resistance (Misra et al. 2003; Vyas et al. 2005a) and a high metabolic activity associated to the expression of numerous carrier-mediated efflux transporters (Anderson 1996; Rautio et al. 2008) that regulate the influx and efflux of a variety of compounds. Unfortunately, the CNS delivery of proficuous therapeutic agents is also frequently prevented. In the last decades, several different approaches have been attempted in order to circumvent the BBB and to deliver drugs efficiently to the brain for therapeutic or diagnostic applications (Illum 2000). For example, recent developments have generated much interest in the possibility of exploiting the IN administration as a non-invasive alternative route for delivery of drugs to the CNS. In fact, assuming the olfactory region as a unique direct connection between the nose and the brain, the IN administration has emerged as a promising approach for the delivery of therapeutic agents to the CNS bypassing the BBB (Hanson and Frey 2008; Illum 2004; Vyas et al. 2005a).

In many CNS disorders, a rapid and/or specific targeting of drugs to the brain would be beneficial. Therefore, valuable efforts have been conducted to improve brain delivery of various therapeutic agents via the IN route, in order to provide higher drug bioavailability at the biophase and consequently better therapeutic efficacy.

15.4.1 Nose-to-Brain Drug Delivery

IN drug administration provides a promising method to deliver therapeutics from the nasal cavity directly to the CNS, bypassing the BBB. Indeed, IN delivery represents an attractive alternative to oral and parenteral routes since, in addition to being non-invasive, it also allows the avoidance of gastrointestinal destruction and hepatic first-pass metabolism. Direct transport of drugs to the brain may lead to reducing systemic exposure and peripheral side effects, which allows the decrease of the dose and frequency of dosing as well as minimises toxicity and improves therapeutic efficacy by achieving desired drug concentrations at the biophase (Kumar et al. 2008; Seju et al. 2011). In addition, the rapid onset delivery of drugs to the CNS and the higher brain uptake congregate the essential conditions for the application of the IN route in the management of emergency situations (Florence et al. 2011; Li et al. 2002; Vyas et al. 2006a; Wolfe and Bernstone 2004).

The possible transport pathways by which a drug can be delivered to the CNS after IN administration are schematically depicted in Fig. 15.1. In general, therapeutic agents can travel from the nasal cavity to the brain via the olfactory route by two possible mechanisms: the olfactory epithelial pathway and the olfactory neural pathway (Merkus and Van den Berg 2007). Similar to drug absorption through nasal respiratory mucosa, in the olfactory epithelial pathway, drugs can be absorbed across the olfactory epithelium either by transcellular or paracellular transport.

In the olfactory neural pathway, drugs can be transferred via axonal internalisation with subsequent transport along the olfactory sensory nerves directly to the brain. Nevertheless, it is believed that such transport is slow, taking hours or even days for drugs to reach the brain parenchymal tissue (Dhuria et al. 2010; Thorne and Frey 2001). As an alternative, it was suggested that drugs after traversing the olfactory epithelium could make their way by paracellularly entering into the perineuronal channels that surround the olfactory nerves, requiring only few minutes (<30 min) to travel along the olfactory axon up to the cerebral spinal fluid (CSF) (Dhuria et al. 2010). Recently, trigeminal nerve pathway has also been advocated as another and additional valid route for the transport of molecules directly from the nasal cavity to the brain (Dhuria et al. 2010; Ross et al. 2004; Thorne et al. 2004).

The hypothetic mechanisms of direct delivery of drugs from nasal passages to the CNS were

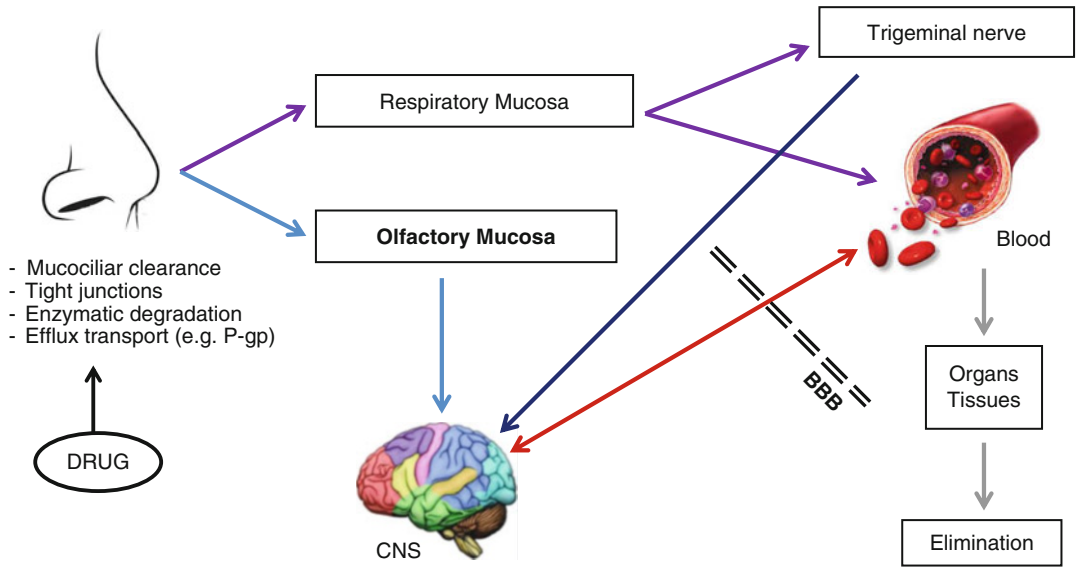

Fig. 15.1 Schematic representation of the possible pathways involved in the transport of drugs from nose to brain

described; notwithstanding, the contributions underlying each one are not yet clearly elucidated. Generally, the rapid appearance of a drug in the brain and CSF indicates preferential involvement of extracellular transport pathways rather than the olfactory neural route. However, the possibility of occurring later axonal drug internalisation cannot be entirely ruled out. Nasally applied drugs could reach the CNS by means of one or a combination of various transport pathways (Fig. 15.1).

15.4.1.1 Alzheimer's Disease Drugs

Several oral acetylcholinesterase inhibitors including rivastigmine, donepezil, galantamine and tacrine have been used for the treatment of Alzheimer's disease symptoms. Notwithstanding, oral administration of such molecules has often been associated with low bioavailability, extensive first-pass metabolism, short elimination half-life, hepatotoxicity and severe gastrointestinal side effects (Costantino et al. 2008).

The potential of the IN delivery route for targeting acetylcholinesterase inhibitors to the brain seems to provide valuable benefits and has been investigated in animal models. The uptake of NXX-066 (a physostigmine analogue) in the CSF after nasal and IV administration to rats was investigated in order to assess whether a direct nose-to-brain pathway is involved (Dahlin and Björk 2001). Study results demonstrated that only low concentrations of NXX-066 were detected in the CSF following both routes of administration. However, nasal administration resulted in extremely rapid and complete absorption of NXX-066 into the systemic circulation exhibiting an absolute bioavailability near to 100 %. The high values of nasal bioavailability suggest that this route could be a suitable alternative to oral and parenteral administrations.

The concentrations of tacrine in blood and brain after IN and IV administration to mice were also evaluated by Jogani et al. (2007). Pharmacokinetic data revealed that drug concentrations in brain tissue were found to be significantly higher for IN administration and the delivery of nasal tacrine to the brain showed to be much quicker than given via the IV route. These findings demonstrated that after IN delivery, a preferential nose-to-brain transport is implied in the selective distribution of tacrine to the brain.

15.4.1.2 Parkinson's Disease Drugs

Until now, there is no cure for Parkinson's disease but its symptoms can be attenuated by the replacement of the dopamine basal levels at the brain. However, dopamine is unable to cross

the BBB in appreciable amounts making its administration via oral and parenteral routes not feasible. Therefore, levodopa (L-dopa) is currently the gold standard treatment in Parkinson's disease, since it easily penetrates the BBB and is rapidly converted to dopamine within the brain. Unfortunately, the clinical response to oral L-dopa is commonly variable and unreliable, due to its erratic absorption and first-pass metabolism (Kao et al. 2000). Additionally, about 95 % of the drug undergoes decarboxylation to dopamine in the peripheral tissues (Dahlin et al. 2000), compromising the amount of unchanged drug available to reach the brain and enhancing the occurrence of adverse effects. In this context, the transfer of dopamine along the olfactory pathway to the CNS following nasal administration has been assessed in rodents (Dahlin et al. 2000, 2001). The experimental results showed that there was an effective transport of dopamine from the nasal cavity into the CNS, since concentration levels after nasal administration were, in comparison to IV injection, 2.3 and 6.8 times higher in the CSF and olfactory bulb, respectively (Dahlin et al. 2000). Nevertheless, the fraction of the nasally administered drug that reached the brain tissue was only 0.12 % of the total dose, suggesting that higher doses of dopamine may be required to guarantee therapeutic efficacy (Dahlin et al. 2000).

The potential of direct nose-to-brain transport of L-dopa was also investigated in rats. Although the AUC values of nasal L-dopa were more than two times higher in plasma and brain comparatively to oral administration, a large fraction of drug was systemically absorbed via the nasal route, and therefore, the fraction of drug transported by the direct nose-to-brain pathway was minimal (Kim et al. 2009). More promising results were achieved by Kao et al. (2000) using the prodrug approach. Following IN administration of the butyl ester prodrug of L-dopa, CNS bioavailability of L-dopa was improved comparing to an equivalent dose given intravenously.

15.4.1.3 Anticonvulsant and Antiepileptic Drugs

Oral administration of anticonvulsant drugs has generally been associated with high systemic distribution into nontargeted tissues, peripheral adverse effects and limited brain uptake. Moreover, patient's physical condition immediately after a convulsive episode is incompatible with the oral ingestion of a tablet dosage form. Apart from its advantages on the clinical emergencies in acute seizure situations, nasally administered anticonvulsant drugs may represent a valuable approach for the long-term treatment of epilepsy by providing the decrease of the dose, frequency of dosing and related side effects thus improving therapeutic efficacy and tolerability.

IV benzodiazepines, such as diazepam, lorazepam, midazolam and clonazepam, have been used as the first-line therapy for the termination of seizure activity in *status epilepticus*. However, benzodiazepines IV dosing may unleash hypotension, cardiac dysrhythmia and respiratory failure (Li et al. 2000). Aiming to minimise the disadvantages and potentiate the therapeutic index of such drugs, several studies were carried out on the subject of IN delivery. A comparative study between IV injection and three nasal formulations of clobazam (solution, microemulsion and mucoadhesive microemulsion) was performed in mice in order to assess and characterise its pharmacokinetic profile and pharmacodynamic performance (Florence et al. 2011). The pharmacokinetic results revealed that the systemic blood distribution of the drug was significantly lower with IN-administered formulations comparatively to IV injection, thus ensuring drug targeting at the site of action and minimising the possibility of systemic side effects. Furthermore, higher brain AUC and C_{max} for microemulsion formulations reflect an enhanced CNS uptake, indicating that a preferential nose-to-brain transport may be involved, revealing consistency with similar previous studies with clonazepam (Vyas et al. 2006a). By virtue of their lipophilic nature and lower interfacial tension, microemulsions heighten the drug permeability across the nasal mucosa. On the other hand, the incorporation of a mucoadhesive agent (Carbopol) improves drug uptake by opening tight junctions, increasing paracellular transport of the molecules.

To investigate brain targeting via nasal administration, the antiepileptic drug carbamazepine (CBZ) was chosen as a model. Taking into account that CBZ is absorbed slowly and

erratically after oral administration, displays a bioavailability of less than 50 % and usually attains peak plasma concentration 4–8 h after oral ingestion (Barakat et al. 2006), a direct delivery of this drug to the brain circumventing the BBB would be highly beneficial. In this context, a CBZ gel formulation composed by hypromellose and Carbopol 974P (3:1) was nasally administered to rats, aiming to compare CBZ concentrations in blood and brain tissue samples with other conventional routes, such as oral and IV administration (Barakat et al. 2006). Experimental data revealed that IN CBZ concentrations were greater in brain than in plasma, also achieving remarkably higher levels in CNS compared to oral or IV administration. A direct transport pathway from nose to brain was demonstrated since peak brain concentration after nasal administration was attained in only 5 min and CBZ absorption from the nasal cavity into the brain was rapid and complete.

15.4.1.4 Analgesic Drugs

Nasal administration of morphine is currently under development in order to overcome its extensive hepatic first-pass effect, affording a more rapid drug absorption and faster onset of action. Indeed, systemic absorption of morphine after nasal administration undoubtedly contributes to achieve these goals as already stated in Sect. 15.3.1.1. However, taking into account that morphine is a small hydrophilic molecule with limited BBB permeability, direct transport of the drug along the olfactory pathway from nose to the brain would be advantageous for pain relief. For these reasons, some investigations have been carried out in order to evaluate the direct access of morphine to the brain. Following IN administration of morphine to rodents, Westin and collaborators (2005) found that the drug was rapidly transferred via the olfactory epithelium to the CNS, reaching the highest concentration in the olfactory bulb after 15 and 60 min in rats and mice, respectively. Upon these facts, the same research group intended to quantify the olfactory transfer of morphine to the brain by comparing drug levels in brain and plasma after both IN and IV administration (Westin et al. 2006). The results showed that after nasal and IV administration of the same dose (1 mg/kg body weight), equal morphine concentrations were obtained in the brain at 5 and 15 min. However, brain to plasma AUC ratio from 0 to 5 min was substantially higher for nasal delivery compared to IV infusion, proving an early distribution of morphine to the CNS via the nasal route.

15.4.1.5 Migraine and Cluster Headaches Drugs

Sumatriptan and zolmitriptan are the drugs most commonly used in the effective treatment of migraine and cluster headaches (Jain et al. 2010). Although these drugs present potent analgesic activity on acute migraine pain relief, current oral therapies are commonly associated with a slow onset of action and significant hepatic first-pass metabolism which results in low absolute plasma bioavailability (Jain et al. 2010; Vyas et al. 2005b). Furthermore, the majority of migraine patients experience several gastrointestinal disturbances during the attacks making the intake of oral tablets often inappropriate (Yates et al. 2005).

Although systemic absorption of IN sumatriptan and zolmitriptan is undeniable, their eventual transport from the nasal cavity directly to the brain may also have an important contribution for the treatment of migraine and cluster headaches. Therefore, the assessment of nose-to-brain delivery of IN mucoadhesive microemulsions of both sumatriptan and zolmitriptan has been investigated in rats (Vyas et al. 2005b, 2006b). The mucoadhesive microemulsions showed better results than microemulsions or drug solutions given nasally. Superior pharmacokinetic results were even attained for the developed sumatriptan microemulsions compared to an already marketed nasal product (Vyas et al. 2006b). Comparatively to IV administration, higher C_{max} and AUC values were found in the brain at all sampling time points for nasally administered formulations, suggesting that preferential nose-to-brain transport may be attributed to both drugs. These findings were also sustained by Jain et al. (2010) who demonstrated that zolmitriptan is predominantly transported to the brain via the olfactory and trigeminal pathways.

15.4.1.6 Antipsychotic and Antidepressant Drugs

Atypical antipsychotic drugs are currently the first choice for the treatment of schizophrenia, and they are available in the market predominantly under oral dosage forms. Oral formulations are, however, related to low plasma drug bioavailability which frequently demands the increase of dose and frequency of dosing. As a consequence, the occurrence of adverse effects is also often potentiated. In this context, the development of IN delivery systems of several antipsychotic agents like risperidone and olanzapine has been attempted considering the potential of this route for direct brain targeting (Kumar et al. 2008; Seju et al. 2011). Promising results were obtained for the IN delivery experiments of a mucoadhesive nanoemulsion of risperidone- and olanzapine-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles using animal models. Higher drug concentrations were observed in the brain for the developed formulations compared to the plain solution of the drug given either nasally or intravenously. Pharmacokinetic data of olanzapine-loaded PLGA nanoparticles even showed an additional therapeutic gain by providing sustained drug delivery to the brain (Seju et al. 2011). In fact, the nanoparticle strategy offers an improvement in nose-to-brain delivery since, in addition to protecting the encapsulated drug from biological or chemical degradation and efflux P-glycoprotein (P-gp) transport, it also enables the increase of the drug residence time within the nasal cavity. As a result, the opportunity to provide sustained delivery of olanzapine is increased, allowing the enhancement of brain drug concentrations.

An IN delivery system of milnacipran was also investigated for the treatment of depression (Uchida et al. 2011). A pharmacokinetic assessment of plasma and CSF milnacipran concentrations following nasal drug delivery to rats revealed that, in comparison to intraduodenal administration, higher C_{max} and lower t_{max} were observed for both matrices. These pharmacokinetic data were in agreement with the results obtained for the pharmacodynamic evaluations in which the antidepressant effect after IN administration of milnacipran was higher and quicker than after oral dosing. The impact of the co-administration of IN milnacipran with 0.5 % chitosan was also addressed in this study. The incorporation of this polysaccharide into the nasal formulation led to an even greater antidepressant effect since it provided a long residence time of milnacipran within the nasal cavity, thus resulting in the increase of the systemic absorption as well as direct transport of the drug to the CNS.

15.4.1.7 Antiviral Drugs

The efficacy of antiviral therapy in the treatment of neuroinfections is often limited due to reduced drug uptake into the CNS as a consequence of its poor permeation across the BBB (Colombo et al. 2011). Indeed, most of the antiviral agents are highly hydrophilic compounds and therefore cannot passively diffuse through the BBB easily. Moreover, it is estimated that a huge part of them are also substrates of the P-gp efflux pump (Hanson and Frey 2007) which has a markedly role on CNS protection by hindering the access of a wide variety of substances to the brain.

Several studies have recently investigated the pharmacokinetics and brain distribution profiles of some antiviral agents after nasal and IV administration to animal models. A preferential transfer of zidovudine, a reverse transcriptase inhibitor, into the CSF and brain tissues following IN administration to rabbits was successfully demonstrated, providing a promising therapeutic option for the treatment of CNS dysfunctions caused by human immunodeficiency virus (HIV) (Ved and Kim 2011). By using a thermo-reversible gelling system comprising Poloxamer 407 as a mucoadhesive polymer and *n-tridecyl-β-D-maltoside* as a permeation enhancer, the authors guaranteed a larger increase of zidovudine brain bioavailability relatively to solutions given both nasally and intravenously. The existence of a direct nose-to-brain pathway to transport zidovudine from the nasal cavity to the CNS was also strongly proven. According to Ved and Kim (2011), approximately 99 % of zidovudine content was directly transferred to the brain via the olfactory route.

15.5 Intranasal Delivery of Biomacromolecular Drugs

IN administration represents a promising choice for delivery of a variety of high molecular weight therapeutic agents such as peptide-, protein- or nucleic acid-based drugs (Csaba et al. 2009; Singh et al. 2012). Because of the higher susceptibility of biological therapies to enzymatic degradation and due to their low permeability across the epithelium via transcellular and paracellular pathways, the absorption of these biomacromolecular drugs from mucosal sites is poor. Therefore, to increase their bioavailability, they are mostly administered by parenteral routes. Over the last years, new pharmaceutical formulations and novel delivery strategies have been developed offering promising opportunities to expand the IN delivery of biomacromolecules (Ozsoy et al. 2009; Singh et al. 2012).

As the nasal mucosa is one of the most permeable and highly vascularised tissues, also avoiding gastrointestinal and hepatic first-pass metabolism, the extent of absorption of biomacromolecules may be potentiated by IN administration comparatively to that achieved through oral route. Accordingly, the nasal route has gained a great interest as an alternative and non-invasive way for systemic and/or direct brain delivery of various classes of biological therapeutic agents (Ozsoy et al. 2009; Veronesi et al. 2011).

The recent advances in the field of biotechnology have promoted the emergence of a range of biodrugs. Besides therapeutic peptides and proteins, a broad variety of other biodrugs are coming into clinical practice or moving to a greater extent into clinical research, namely, vaccines, cell or gene therapies, cytokines, tissue growth factors and monoclonal antibodies (Csaba et al. 2009; Ozsoy et al. 2009; Singh et al. 2012). Hence, it is expected that the number of biomacromolecular drugs commercially available for administration via nasal route will progressively increase.

15.5.1 Peptides and Proteins

Peptides and proteins represent interesting targets for IN administration (Table 15.2). Nevertheless, as peptides and proteins are charged, hydrophilic and usually high molecular weight molecules, they are obviously poorly permeable across lipid biomembranes. Therefore, in the development of suitable protein- and peptide-based formulations intended for IN delivery, some chemical and pharmaceutical strategies need to be employed to overcome the physicochemical instability, enzymatic barrier of the nasal mucosa and low permeability, aiming to increase their bioavailability. Hence, in the formulation process of these medicinal products, the use of appropriate vehicles, enzyme inhibitors and/or penetration enhancers is of paramount importance (Bahadur and Pathak 2012; Mistry et al. 2009).

As previously referred, although the nasal mucosa poses a permeation barrier to high molecular weight therapeutics, the tight junctions between adjacent epithelial cells also limit the movement of molecules through the intercellular spaces, forming a barrier against paracellular drug delivery. However, the IN bioavailability of some macromolecules was considerably improved by using nasal permeation enhancers, which may affect the barrier function of the tight junctions (Costantino et al. 2007).

In spite of the advances progressively reached in the formulation of biological medicinal products, major hurdles remain to overcome the combined barriers of drug permeability, drug stability, pharmacokinetics and pharmacodynamics of peptide- and protein-based drugs (Gupta and Sharma 2009). Therefore, despite the hundreds of biological medicinal products already developed, these problems may explain why just a handful of non-injection biomacromolecular drugs have reached the market, mainly as IN formulations.

The success achieved with the IN administration of polypeptide drugs, such as desmopressin, calcitonin, buserelin, nafarelin and oxytocin, has promoted an extensive investigation of the viability of this route of administration for delivery of other protein and peptide drug candidates. Among them, human insulin represents perhaps the biomolecule most extensively assessed for systemic delivery by IN route (Benedict et al. 2011; Hallschmid et al. 2012; Jogani et al. 2008). In addition, many other

Table 15.2 Examples of nasal peptide-/protein-based drugs on the market or under development

Drug (or drug candidate)/ trade name	Indications	Status	References
Salmon calcitonin/ Miacalcin®, Fortical®	Osteoporosis	Market	FDAa (2012) and Singh et al. (2012)
Desmopressin/Minirin®, DDAVP®, Stimate®	Enuresis, diabetes insipidus, haemophilia A, von Willebrand's disease (type I)	Market	FDAa (2012) and Singh et al. (2012)
Buserelin/Suprefact®, Profact Nasal®	Prostate cancer, Endometriosis	Market	Mathias and Hussain (2010) and Singh et al. (2012)
Nafarelin/Synarel®	Endometriosis, precocious puberty	Market	Mathias and Hussain (2010) and Singh et al. (2012)
Oxytocin/Syntocinon®	Lactation stimulation	Market	Singh et al. (2012)
Insulin	Type I diabetes, obesity	Under development	Jogani et al. (2008)
Exenatide	Type II diabetes	Under development	Jogani et al. (2008)
PYY 336	Obesity	Under development	Jogani et al. (2008)
Bremelanotide	Sexual dysfunction	Under development	Jogani et al. (2008)
Leuprolide	Endometriosis, prostate cancer	Under development	Jogani et al. (2008)
Teriparatide (PHT_{1-34})	Osteoporosis	Under development	Devogelaer et al. (2010)
Human growth hormone	Growth failure	Under development	Steyn et al. (2010)
Leptin	Obesity	Under development	Schulz et al. (2012)
Erythropoietin	Neuroprotective (stroke, cerebral hypoxia)	Under development	Parra and Rodriguez (2012)
Glucagon	Severe hypoglycaemia	Under development	Teshima et al. (2002)
Glucagon-like peptide-1	Type II diabetes	Under development	Youn et al. (2008)
Octreotide	Acromegaly	Under development	Lerner et al. (2004)
Hirudin-2	Anticoagulation	Under development	Zhang et al. (2005)
Heparin (enoxaparin)	Anticoagulation	Under development	Yang et al. (2006)
Interferon alpha-2b	Viral infections	Under development	Gao et al. (2010)
Interferon beta	Multiple sclerosis	Under development	Thorne et al. (2008)

protein and peptide drugs currently used as injectables have also been evaluated for nasal delivery (Table 15.2). Moreover, due to the increasing evidences on the possibility of direct nose-to-brain delivery of large-sized drugs, the research work targeting the IN delivery of neuropeptides has been largely potentiated in the last years (Lochhead and Thorne 2012; Veronesi et al. 2011).

The peptide- and protein-based drugs currently available in the market as IN formulations will be discussed below.

15.5.1.1 Salmon Calcitonin

Calcitonin is a polypeptide hormone of 32 amino acids (molecular weight of 3.4 kDa) and it has a physiological role in the regulation of calcium homeostasis. Calcitonin is produced in humans and other mammalian species, and also in birds and fish (du Plessis et al. 2010; Ozsoy et al. 2009).

Salmon calcitonin is more potent than natural human calcitonin at inhibiting osteoclast function. Therefore, salmon calcitonin is favoured comparatively to the human calcitonin, and the former is the only form of this peptide commercially available (Lee et al. 2011). Although calcitonin is available as several formulations, the IN formulations are the most widely used (Chesnut et al. 2008). The salmon calcitonin nasal spray has shown to be effective but, like other peptides, presents a low IN bioavailability (3 %) comparatively to those achieved by intramuscular or subcutaneous injections (Ozsoy et al. 2009). As a result, new pharmaceutical formulations have been progressively

investigated to enhance the absorption of salmon calcitonin from nasal mucosa (Chen et al. 2009; du Plessis et al. 2010).

15.5.1.2 Desmopressin

Antidiuretic hormone (also called arginine-vasopressin) is produced in the hypothalamus and secreted by the neurohypophysis in conditions of increased plasma osmolality, decreased arterial pressure and cardiac volume reduction (Babey et al. 2011; Treschan and Peters 2006). A lack of arginine-vasopressin is the most common cause of diabetes insipidus (Babey et al. 2011). A dysfunction in the secretion of arginine-vasopressin may also induce the appearance of other clinical conditions (e.g. nocturnal enuresis) (Nevéus 2011). Thus, replacement therapy with the analogue desmopressin is justified in cases of insufficiency of arginine-vasopressin (Chanson and Salenave 2011).

Desmopressin (1-deamino-8-D-arginine-vasopressin; molecular weight of 1,069 Da) is a vasopressin analogue but retains the hormone's antidiuretic effects and also exerts haemostatic effects. Therefore, despite its clinical use in diabetes insipidus and complex enuresis states, desmopressin is also useful for treating or preventing bleeding episodes (Ozgönenel et al. 2007; Ozsoy et al. 2009). Desmopressin has been used in clinical practice for more than 30 years and it is commercially available as IN solution, injectable solution, tablets and more recently also as oral lyophilisate (Van de Walle et al. 2007, 2010).

Usually, therapeutic peptides are highly potent and specific in their functions, but difficulties in their administration require parallel development of viable delivery systems to enhance their bioavailability. Indeed, the systemic absorption of desmopressin is very low from available formulations. Therefore, efforts have been made to develop improved pharmaceutical formulations (Fransén et al. 2009).

15.5.1.3 Gonadotropin-Releasing Hormone (GnRH) Analogues: Buserelin and Nafarelin

The GnRH neuronal system is the final common pathway for central regulation of fertility. GnRH is a single neuroendocrine decapeptide produced in the hypothalamus (Balasubramanian et al. 2010; Moenter 2010).

Over the times, an intensive research of potent GnRH agonist analogues with acceptable pharmacokinetics has been carried out. In fact, by specific amino acid substitutions in the structure of the natural GnRH, several GnRH agonists were developed and are now clinically available, such as histrelin acetate (Shore et al. 2012), goserelin acetate (Berglund et al. 2012), leuprolide acetate (Tunn 2011), buserelin acetate (Safdarian et al. 2007) and nafarelin acetate (Takeuchi et al. 2001). However, like other peptide-based drugs, the majority of these GnRH agonists are only marketed in parenteral formulations. Fortunately, buserelin acetate and nafarelin acetate are both commercially available as a spray formulation suitable for IN delivery (Franco et al. 2001; Tuvemo et al. 2002). Nevertheless, the absolute IN bioavailability of buserelin (6 %) and nafarelin (2.8 %) is very low (Costantino et al. 2007). Hence, it remains as a remarkable challenge in the development of new formulations of buserelin and nafarelin affording a greater drug bioavailability after IN delivery.

15.5.1.4 Oxytocin

Oxytocin, a neurohypophyseal nonapeptide hormone, is well known not only for its prominent role in parturition and lactation but also as a drug of choice for prevention of the postpartum haemorrhage (Anderson and Etches 2007; Lee et al. 2009; Wei et al. 2010). Oxytocin is a drug frequently used in the management of labour or for preventing postpartum haemorrhage, particularly through parenteral administration (Arnott et al. 2000; Bellad et al. 2012; Zhang et al. 2011). On the other hand, as a nasal spray formulation, oxytocin has been used to assist breast-feeding and milk expression (Fewtrell et al. 2006). Indeed, for a long time, those evidences exist about the effectiveness and safety of oxytocin IN spray as a means of enhancing lactation (Ruis et al. 1981).

More recently, many research works have focused on possible functions of oxytocin in the brain. As a result, oxytocin appears to be involved in learning, anxiety, feeding, sexual and maternal

behaviour, aggression and pain perception, among others (Lee et al. 2009). Accordingly, the therapeutic spectrum for IN oxytocin delivery may be largely extended in the next years.

15.5.2 Vaccines

The majority of disease-causing viruses and bacteria reach the body through mucosal surfaces, including through the nasal mucosa (Chadwick et al. 2010). Immunisation by the nasal route is an interesting opportunity that has been increasingly explored. The nasal mucosa possesses many advantages for vaccine delivery; it is readily accessible (non-invasive needle-free option) and has a large surface area with a leaky and highly vascularised epithelium. In addition, and perhaps the most important aspect in this context, the nasal cavity is rich in nasal-associated lymphoid tissue (NALT) which is equivalent to that found in gut. The NALT is crucial to uptake the particulate carriers and is also an inductive and effective site of the immune system. NALT contains all the immunocompetent cells in the body that mediate the induction of mucosal immune responses to inhaled antigens. Moreover, IN vaccination becomes even more attractive because it is effective at inducing antigen-specific immune responses in both mucosal and systemic compartments (Kang et al. 2009; Zaman et al. 2010).

Despite the several well-recognised advantages of nasal vaccines, important limitations also exist. One of the most important limitations of nasal immunisation is the rapid clearance of the vaccine formulation from nasal mucosal surface owing to the MCC. Therefore, the use of mucoadhesive adjuvants to increase the residence time of vaccines in the nasal passages may be useful to improve their efficacy. Another limitation is the proteolytic activity of the nasal mucosal enzymatic barrier which, consequently, restricts the nasally delivered vaccines (Kang et al. 2009).

Actually, vaccines are based on protein antigens, or DNA (usually called *DNA vaccines*), and they are poorly permeable, unstable and susceptible to enzymatic degradation and, therefore, need to be protected. The advances in nanotechnology have brought the development of a great spectrum of nasal nanosystem carriers that provide protection against biological degradation and may facilitate the passage of the antigen across nasal barriers, leading to an efficient antigen presentation to the immune system. Some interesting reviews have been published focusing on the application of particulate systems as adjuvants and carriers for nasal vaccine delivery (Csaba et al. 2009; Köping-Höggård et al. 2005; Sharma et al. 2009). More recently, considerable advances have been made toward the development and testing of novel adjuvants and delivery vehicles to use in nasal vaccines, particularly *Lactococcus lactis* (Medina et al. 2010), adenoviral vectors encoding pathogen antigens (Tutykhina et al. 2011), live attenuated *Bordetella pertussis* BPZE1 strain (Li et al. 2011) and several strains of *Lactobacillus* (Wells 2011).

Despite the large number of vaccines commercially available for prevention of numerous infectious diseases, the majority is formulated for parenteral administration. Actually, in spite of the intensive research presently ongoing for developing nasal vaccines, it seems there is only currently authorised by FDA and/or European Medicines Agency (EMA) vaccines against influenza for IN administration in humans (FluMist®, FluMist® Quadrivalent and Fluenz®) (Chadwick et al. 2010; EMA 2012; FDAb 2012). Nevertheless, many other vaccines for IN delivery are under investigation, for instance, against measles (Simon et al. 2011), HIV infection (Hinkula et al. 2008), hepatitis B (Tiwari et al. 2011), *Mycobacterium tuberculosis* (Lorenzi et al. 2010), *Bacillus anthracis* (Wang et al. 2012), H5N1 influenza (Wu et al. 2012), *Streptococcus pneumoniae* (Xu et al. 2011), norovirus infections (Velasquez et al. 2011) and shigellosis (Tribble et al. 2010).

Although traditional vaccines have comprised subunit proteins, live attenuated viruses or killed bacteria, much attention has recently focused on non-replicating DNA or RNA vaccine delivery systems (Goodsell et al. 2008). Hence, as a result of the huge development achieved during the last years in the field of genetic engineering, and perhaps motivated by the successful clinical

introduction of the first gene-therapy medicinal product (Gendicine®) (Wilson 2005), the investigation of DNA- and RNA-based vaccines has significantly enhanced, targeting even the IN delivery of the therapeutic genes or oligonucleotides encoding antigens for specific pathogens.

Therefore, the most recent developments on IN delivery of vaccines lead us to believe that the nasal route is a viable option for effective immunisation and the clinical introduction of new nasal vaccines is expected in the next years.

Conclusions

Nowadays, the most part of IN medicinal products available in clinical practice are targeted toward local (or topical) relief or prevention of nasal symptoms usually associated to acute or chronic diseases affecting the upper respiratory tract, such as common cold, rhinitis and sinusitis. Over the last few years, some small-molecule drugs also reached the market for acute or chronic pain management, smoking cessation and hormone replacement therapy, but many others are currently under clinical or preclinical development. In addition to small-molecule drugs, the nasal route has also attracted the interest of scientific community for the delivery of therapeutic macromolecules such as proteins, peptides and nucleic acids; these biomolecules are highly susceptible to enzymatic or acidic degradation and, therefore, they are typically administered by parenteral routes; thus, in these cases, the IN delivery represents a viable alternative to oral route and enables to overcome the problems associated to parenteral drug delivery.

Hence, taking into account all the intrinsic advantages of the nasal route, and considering that it has become one of the most explored ways for non-invasive drug delivery, in the future, it will be certainly possible to routinely use a broad spectrum of nasal products for the pharmacological management of multiple clinical conditions.

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Physiology of Lacrimal Drainage

16

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Keywords
Lacrimal pump system • Krehbiel's effect • Bernoulli principle • Microciliation • Siphon effect • Capillarity

Core Messages

- There are many factors contributing to lacrimal elimination, but the most important mechanism is canalicular and sac pump mechanism.
- Canalicular pump is probably more important than the sac pump because following DCR, tears are still drained through the canaliculi to the nose.
- The pressure gradient between the canaliculi and the sac cannot be produced if the canaliculus is slit open. Therefore, the lacrimal canaliculi should be preserved and should not be damaged.
- Tear elimination is equivalent through the upper and lower canalicular systems. Therefore, attention should be given not to damage both the upper and lower canaliculus.

The lacrimal drainage system works to remove those tears secreted into the palpebral aperture to cover the cornea at a rate of 1.2 μl/min with a total 24-h secretory volume of approximately 10 ml (Hurwitz 1996). The tear film travels across the surface of the globe and eyelids, enters the puncta/ampulla, passes through the canaliculi, and enters the lacrimal sac/nasolacrimal duct/nasal passages. With blinking (orbicularis muscle contraction), the closure of palpebral aperture starts from lateral and proceeds to medial. This action propels the tears medially toward the lacrimal lake (Hurwitz 1996).

Factors contributing to lacrimal elimination may include:

- Evaporation of tears from the ocular surface
- Capillary attraction of the tears
- Reservoir drainage into the lacrimal sac (so-called Krehbiel flow)
- Siphon effect
- Microciliation and absorption of tears by the lacrimal sac mucosa

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- Bernoulli's principle and Venturi tube effect
- Physical forces such as gravity
- Canalicular and sac pump mechanism

16.1 Factors in Tear Flow

16.1.1 Evaporation

Much of the tears is lost by direct evaporation from the ocular surface. Low humidity and wind increase this loss. According to Schirmer almost half of the secreted tears were lost by evaporation (Hurwitz 1996).

16.1.2 Capillarity

Capillarity or capillary action is the ability of a liquid to flow in a narrow tube without assistance of gravity. This effect can be seen in the drawing of liquids in a thin tube or in porous materials such as paper. Capillary action can be noticed for the drainage of tears from the eye. The small canaliculi may act like a capillary tube. The canaliculi may draw tears through the punctum and transfer tears through the canaliculi. The fact that trauma to the canaliculi and loss of capillarity does not cause loss of function indicates that capillarity is not the only factor in drawing tears through the punctum (Hurwitz 1996).

16.1.3 Krehbiel Flow

Krehbiel flow is the flow of the tears from the punctum through the canaliculus due to changes of pressure within the lacrimal sac owing to the effect of the orbicularis tonus on both canaliculi and tear sac when the lids are open (Hurwitz 1996; Ahl and Hill 1982).

16.1.4 Siphon Effect

The word siphon refers specifically to a tube in an inverted U shape which causes a liquid to flow uphill, above the surface of the reservoir, without pumps, powered by the fall of the liquid as it flows down the tube under the pull of gravity, and is discharged at a level lower than the surface of the reservoir. It is important that while the siphon must touch the liquid in the (upper) reservoir (the surface of the liquid must be above the intake opening), it need not touch the liquid in the lower reservoir and indeed there need not be a lower reservoir – liquid can discharge into midair.

16.1.5 Microciliation and Reabsorption

The internal wall of the lacrimal canaliculi is lined by a stratified epithelium. Epithelial cells are faced by microvilli. The facing of epithelial cells by microvilli gives hints of reabsorption of lacrimal fluid inside the lacrimal ducts (Paulsen et al. 1998). Due to this reabsorption in the nasolacrimal sac and duct, the amount of tears leaving the nasolacrimal duct orifice in the nose is less than the amount of tears entering the puncta.

16.1.6 Bernoulli's Principle and Venturi Tube Effect

The relationship between the velocity and pressure exerted by a moving liquid is described by the Bernoulli's principle: as the velocity of a fluid increases, the pressure exerted by that fluid decreases. The Venturi effect is similar to Bernoulli's principle. The velocity of the fluid increases as the cross-sectional area decreases, with the static pressure correspondingly decreasing. According to the laws governing fluid dynamics, a fluid's velocity must increase as it passes through a constriction to satisfy the principle of continuity, while its pressure must decrease to satisfy the principle of conservation of mechanical energy. An equation for the drop in pressure due to the Venturi effect may be derived from a combination of Bernoulli's principle and the continuity equation.

The canaliculi narrow close to the common canaliculus, and the common canaliculus is a larger structure. Bernoulli principle and Venturi tube effect may play a role in the flow through the canaliculi. According to Venturi tube effect, narrowing of the canaliculi from lateral to medial increases the speed of flow from lateral to medial

and according to Bernoulli's principle movement over a low pressure area creates a suctional effect. Bernoulli's principle may also play a role in the lacrimal system at the nasal cavity sucking tears from the valve of Hasner area into the nose in addition to the ampulla and just distal to the common internal punctum (Sisler 1982).

16.2 Tear Flow and Elimination

16.2.1 Flow from the Lacrimal Lake Through the Puncta

The tears enter the puncta with three mechanisms (Hurwitz 1996):

1. A negative pressure would develop inside the punctum to suck the tears.
2. The small canaliculi may act as capillary tubes and would suction the tears through the small capillary tubes. However, capillarity is not the only factor in drainage because a slit canaliculus where capillarity has been destroyed usually functions well for other reasons.
3. Krehbiel's effect (Reservoir drainage into the lacrimal sac) Krehbiel suggested that even in the resting phase of the blink cycle, tears pass from the punctum through into the canaliculus. This may be due to changes of pressure within the lacrimal sac owing to the effect of the orbicularis tonus on both canaliculi and tear sac when the lids are open. However, if a DCR is performed, this effect may not be seen and therefore it is probably not the intracanalicular suction that is causing this effect, but sac suction (Hurwitz 1996; Ahl and Hill 1982).

16.2.2 What Canalicular System Is More Important for Tear Elimination: Upper or Lower?

Although it is believed that upper canalicular system is unimportant, experimental and clinical studies show that tear elimination is equivalent through the upper and lower canalicular systems (White et al. 1989; Daubert et al. 1990; Linberg and Moore 1988; Meyer et al. 1990). Surgeons should thus give equal consideration to a patient with lacerations of either the upper or lower canaliculus. Studies by White et al. (1989) and Daubert et al. (1990) have demonstrated equal tear flow between the upper and lower canalicular systems using radioactive dacryoscintigraphy flow studies. Meyer et al. (1990) studied fluorescein dye disappearance in 20 subjects and found that 90 % of patients showed minimal or no impairment with monocanalicular (either upper or lower) obstruction.

16.2.3 Flow Through the Canaliculi into the Sac

Although multiple mechanisms may contribute to lacrimal outflow, present evidence suggests that the most important factor is the active palpebral-canalicular pump. It has long been noted that the blinking mechanism readily drains tears even with the head held in an inverted position. When the palpebral blink mechanism is impaired, however, epiphora is common, such as in patients with facial paralysis.

16.2.4 Lacrimal Pump

There are two most popular lacrimal pump theories: one suggested by Jones (1973) and the other by Doane (1981). More recently, Becker (1992) proposed a tricompartmental model of the lacrimal pump, which in many ways is similar to the Doane model. The lacrimal pump models agree that eyelid closure results in a squeezing of the canaliculi with the nasal movement of tears into the lacrimal sac. The models diverge, however, in the analysis of the changes in the lacrimal sac pressure with eyelid closure and opening.

The first "lacrimal pump" theory is based on classic anatomic studies by Jones (1973), describing tendinous and muscular insertions exerting their action on and around the lacrimal sac. The Jones theory for this lacrimal pump involves three components:

1. The deep heads of the pretarsal orbicularis muscle (Horner's muscle)
2. The deep head of the preseptal muscle (Jones' muscle)
3. The lacrimal diaphragm (fascia around the sac)

The tensor tarsi (Horner's) muscle originates on the posterior lacrimal crest and divides to surround the canaliculi. It then becomes continuous with the pretarsal portions of the orbicularis muscle. Since some fibers of this muscle run in a parallel and sometimes spiral manner, the contraction of the muscle can draw the papillae of the puncta in a medial direction. This narrows the ampullae and shortens the canaliculi (Jones 1957). The Horner's muscle around the canaliculi pumps tears from the punctum through to the sac (Ahl and Hill 1982).

An additional strand of orbicularis muscle from the preseptal area inserting into the lacrimal fascia and posterior lacrimal crest (the deep head of the preseptal orbicularis muscle) was described by Jones and this muscle is named as Jones' muscle. According to Jones the muscular pull of this preseptal orbicularis muscle (Jones' muscle) on the lacrimal sac draws the lateral wall of the nasolacrimal sac laterally and creates a negative pressure within the sac (Jones 1956).

With blinking, contraction of the deep preseptal orbicularis fibers (Jones' muscle) draws the lateral wall of the nasolacrimal sac laterally, creating a negative pressure within the sac and allowing the inspiration of tears into the sac. The tears are forced along the canalicular system by contraction of the deep head of the pretarsal muscle (Horner's muscle). When the orbicularis relaxes and the eyelid opens, the sac collapses, forcing tears down the nasolacrimal duct. At the same time, the canaliculi open, siphoning tears into their lumen. Closing the eyelids again pushes and propels the accumulated tears into the lacrimal sac (Jordan et al. 2012).

Doane suggested a different mechanism of tear propulsion through the system. He noted that the puncta came together during the early phases of eyelid closure and occlusion of the puncta occurred as a first step in the tear pump. He postulated that contraction of the pretarsal orbicularis oculi muscle exerts lateral traction on the lacrimal sac wall, compresses the ampulla, and shortens the canaliculi, causing a pressure increase in the canaliculi propelling tear fluid within the canaliculi toward the lacrimal sac (i.e., positive pressure is created during a blink in both the canaliculi and the nasolacrimal sac as a result of muscle contraction occurring in the pretarsal and preseptal orbicularis fibers) (Jordan et al. 2012; Doane 1981). Doane further theorized that as the tension increases on the lacrimal fascia to open the fundus of the sac, the inferior portion closes more tightly, preventing aspiration of air from the nose. As the eyelids open, the puncta initially remain closed by the opposing lid until the end of the opening movement and a partial vacuum forms within the membranous lacrimal conduit. As the eyelid-opening phase of the blink continues, the two lacrimal puncta open and expose the adjacent lacrimal lake to this partial vacuum. Tears rapidly flow into the canaliculi during the 1– 3-s interval immediately after the blink. Once again, the canaliculi fill with fluid so that the pumping action of the next blink can continue the lacrimal elimination cycle. With relaxation of the deep head of the preseptal orbicularis muscle, elastic recoil of the lacrimal fascia collapses the lacrimal sac, expelling any fluid within the sac down into the now patent nasolacrimal duct. Thus the collapsing lacrimal drainage conduit was believed to push the tears through the system into the nose without the suction phase postulated by Jones (Doane 1981). To date, most evidence supports the Doane model (Burkat et al. 2006).

Becker observed that the superolateral wall of the lacrimal sac, which is attached to the deep head of the preseptal orbicularis, moved laterally with lid closure and medially with lid opening. The inferior half of the lateral wall of the lacrimal sac moved medially with lid closure and laterally with lid opening. Becker suggested a tricompartment model of the lacrimal pump that incorporates these findings. With lid closure, the orbicularis muscle contracts, compressing the canaliculi and pulling the superior half of the lateral wall of the lacrimal sac laterally. This creates a lower pressure in the superior sac, allowing tears to be propelled from the canaliculi into the sac. At the same time, the inferior half of the lateral sac wall moves medially, creating a positive pressure in the inferior sac and nasolacrimal duct, thus forcing tears down the duct into the nose. With lid opening, the orbicularis muscle relaxes,

allowing the canaliculi to open and the superior half of the lateral sac wall to move medially. The resulting negative intracanalicular pressure allows tears to flow from the lacrimal lake into the canaliculi, and the higher pressure in the superior sac closes the valve of Rosenmüller and forces tears from the superior to inferior sac and proximal nasolacrimal duct. At the same time, the inferior half of the lateral sac wall moves laterally, resulting in a negative pressure in the inferior sac and nasolacrimal duct (Becker 1992). These observations are in agreement with Doane's model, with the overall lacrimal sac pressure increasing with eyelid closure and reducing with eyelid opening.

These proposed lacrimal sac pumping mechanisms are based on anatomic studies and likely do not have a large role in normal lacrimal elimination, because the system functions quite well with the lacrimal sac completely open, as is the case after dacryocystorhinostomy (DCR). This shows that the canalicular pump is more important than the sac pump (Hurwitz 1996).

16.2.5 Flow from the Sac to the Nose

The flow of tears from the sac down through the duct has been postulated to be a siphoning effect and a gravitational effect. The fact that tears will flow through the lacrimal system even when one is standing on his head, means that it does not only depend on the gravitational effect but some other active mechanisms as well. The filling of the sac and the increasing pressure in the sac force the tears down through the duct. Each blink expels the fluid through the canaliculi to the sac and the sac expels the fluid to the duct (Hurwitz 1996).

16.3 Other Factors on Tear Flow

16.3.1 Effect of Respiration

It was postulated that respiration also plays a role in drainage of tears from the duct into the nose and that Bernoulli's principle has some effect on this function. However since the duct narrows as it approaches to the Hasner valve, Bernoulli's effect is minimal. On the other hand after DCR operation common canaliculus opens directly into the nose, and respiration and Bernouilli's principle plays a much more important role in these operated cases (Nik et al. 1984).

16.3.2 Valves

The function of the valves is to prevent or decrease the retrograde flow of tears and/or air currents. The most important valve is Hasner valve which is located at the lower end of the nasolacrimal duct. Hasner valve prevents air currents from within the nose being drawn up into the lacrimal duct (Hurwitz 1996).

Rosenmüller valve is located at the common internal punctum and prevents backflow from the sac into the canaliculi. This valve is not a real valve but it functions like a valve because of the anatomic angulation of the canaliculi and common canaliculus. This valve is especially important after DCR operation to prevent backflow of the tears from the nose into the canaliculi (Corin et al. 1990).

Although other valves at the punctum, the ampulla, and at the junction of the nasolacrimal sac and duct have been described in the literature, these are mainly mucosal folds and do not have much function.

16.3.3 Clinical Principles Derived from the Physiologic Information

The palpebral-canalicular pump mechanism in lacrimal elimination is the major mechanism. The canalicular pump is probably more important than the sac pump because following DCR tears are still drained through the canaliculi to the nose. In facial nerve paralysis, tears will not drain into the nose because orbicularis muscle is not functioning and cannot operate the canalicular pump although there is a patent opening. Therefore, the lacrimal canaliculi should be preserved and should not be damaged. Repeated instrumentation

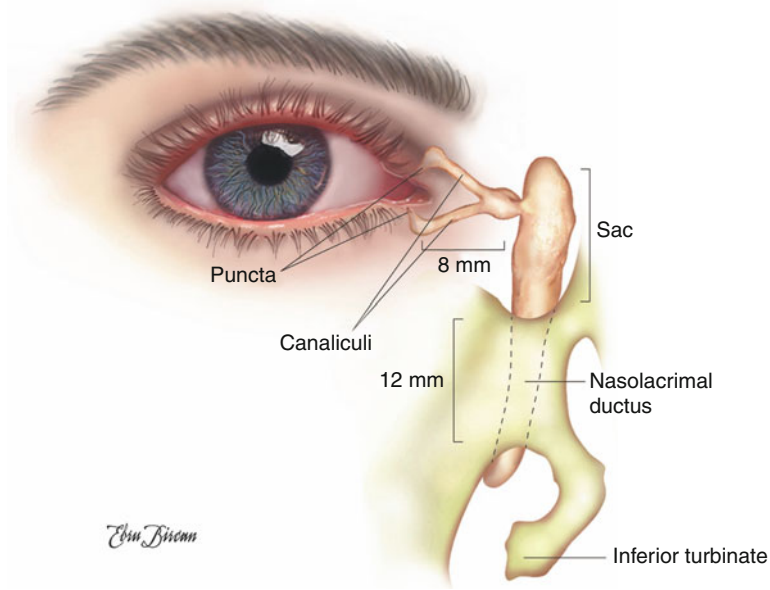

Fig. 16.1 Normal anatomy of the nasolacrimal system (Courtesy of TESAV)

of the lacrimal system or nasolacrimal duct probings may injure the canaliculi and thus permanently impair lacrimal elimination. It is very difficult to restore scarred fibrosed canaliculi. On the other hand, the pressure gradient between the canaliculi and the sac cannot be produced if the canaliculus is slit open. This information should caution clinicians against performing overly aggressive procedures on the lacrimal outflow system (Myron and Clinton 2006).

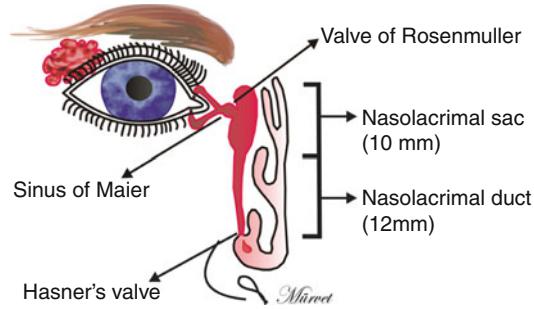

Fig. 16.2 Schematic representation of the nasolacrimal system (Courtesy of TESAV)

Conclusions

There are many factors which are important in lacrimal drainage system. The palpebral-canalicular pump mechanism in lacrimal elimination is the major mechanism. The canalicular pump is probably more important than the sac pump because following DCR tears are still drained through the canaliculi to the nose. Damage to the canaliculi should be avoided since the damage of the canaliculi impairs the lacrimal elimination. After DCR operation the physiology changes and some physiologic mechanisms may play a more important role. Tear elimination is equivalent through the upper and lower canalicular systems. Therefore, attention should be given not

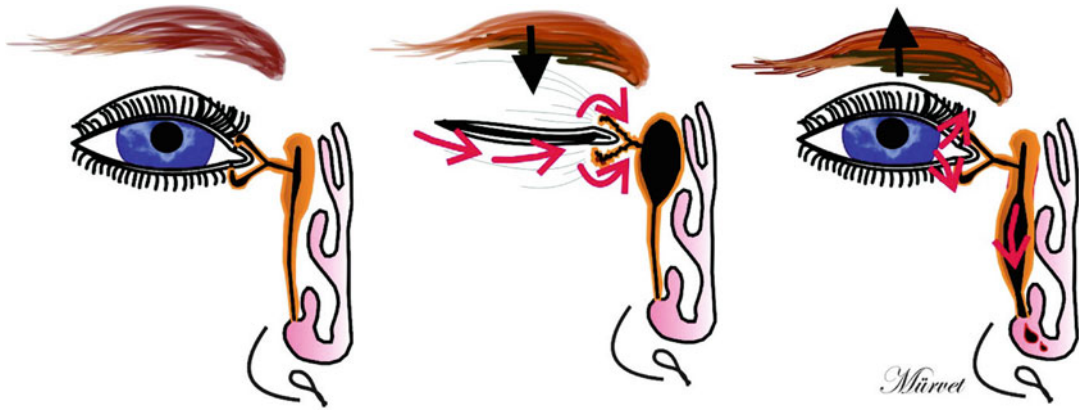

Fig. 16.3 The palpebral-canalicular pump mechanism in lacrimal elimination (Courtesy of TESAV)

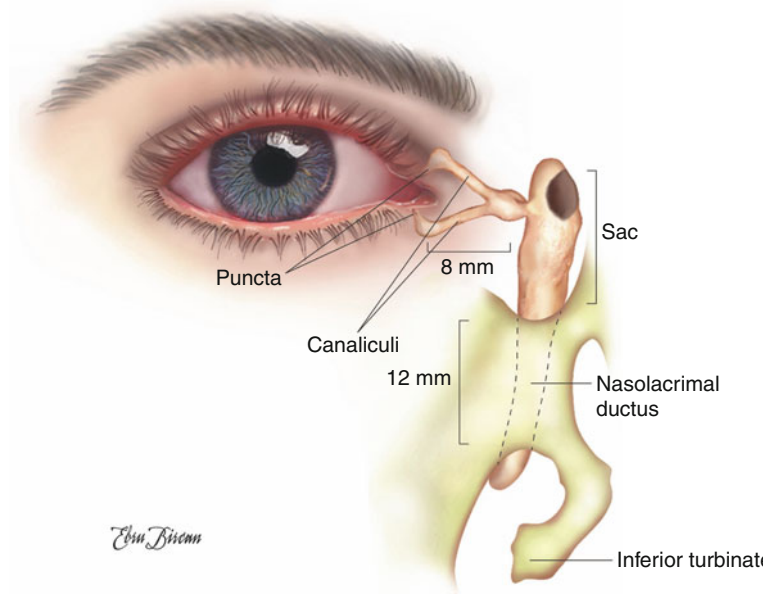

Fig. 16.4 Sump syndrome. If the rhinostomy opening is made too high during DCR operation, the drainage system will not function properly (Courtesy of TESAV)

to damage both the upper and lower canaliculus (Figs. 16.1, 16.2, 16.3, 16.4).

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Intranasal Trigeminal Perception

17

Philippe Rombaux, Caroline Huart, Basile Landis, and Thomas Hummel

Keywords

Chemosensory function • Trigeminal • Olfaction • Reflexes • Somatosensory function

Core Messages

- Intranasal trigeminal system mediates the sensation of temperature, pressure, perception of nasal airflow during breathing, nociception and participates to the chemosensory perception of odorant stimuli.
- Chemosensory perception is not only mediated by free nerve endings in the nasal mucosa but also by some trigeminal fibers in close contact with solitary chemosensory cells.
- Besides the sensory nerves, the parasympathetic and the orthosympathetic systems play an important role in the normal physiology of the nose
- Testing the intranasal trigeminal function, both psychophysically and electrophysiologically, is possible and may be used in the assessment of a patient with a chemosensory dysfunction.
- Healthy subjects need to have intact trigeminal and olfactory systems to have a full complete picture of the chemosensory stimulus.
- Olfactory and trigeminal systems interact both at a central and peripheral level.

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- In patients with olfactory loss, a compensatory mechanism probably exists between the olfactory and the trigeminal systems.

17.1 Introduction

The nasal mucosa through the intranasal trigeminal nerve is a full sensory organ, functionally organized and responsible for both the nasal patency perception and the chemosensory perception and also responsible to a certain degree for nasal inflammation. The primary function of the intranasal trigeminal system is to protect the upper and lower airways for potential life-threatening substances acting as a sentinel to shorten or stop inspiration reflexively.

Besides this protective somatosensory function, the intranasal trigeminal system also helps to the global chemosensory perception with the olfactory system. Indeed, most of the odorants stimulate the neural olfactory and intranasal trigeminal systems (Doty 1995).

Finally, the intranasal trigeminal system is also capable of inducing a neurogenic inflammation mainly through an axon reflex located in the subepithelial level of the nasal mucosa.

The olfactory (cranial nerve I) and the trigeminal (cranial nerve V) systems interact at different levels and this interaction is essential for the odor sensation (Cain and Murphy 1980). The olfactory system is more dedicated in identification task for hedonicity and alimentary behavioral, recognition and memory, behavioral and social comportments than the trigeminal system probably more oriented to protective function and reflexes.

17.2 The Nerves of the Nose

Sensory nerve endings from branches of the trigeminal nerve are located in the epithelia of the nose and sinuses, the eyelids and the cornea, the oral cavity and the skin. Fibers from the intranasal trigeminal nerve mediate the tactile sensation of temperature, pressure and perception of nasal airflow during breathing and participate to the chemosensory perception of odorant stimuli. Trigeminal receptors are located throughout the epithelia of the nasal mucosa and contribute to global perception of odorous stimuli reaching the nasal fossa and the upper airway.

The nasal cavity is innervated by two branches of the trigeminal nerves, i.e., the ophthalmic and the maxillary branches. The ethmoid nerve innervating the anterior nasal mucosa and the external surface of the nasal fossa is part of the ophthalmic division while the nasopalatine nerve which innervates the posterior part of the nasal cavity is part of the maxillary division. The trigeminal nerve has chemosensory and mechanosensory fibers. Mechanosensory fibers are large fast-conducting Aβ-fibers. Thin and fast-conducting myelinated Aδ-fibers and thin and slow-conducting unmyelinated C-fibers are responsible for thermoreception (cold and warm stimuli) and for nociceptive perception (pain, painful mechanical, noxious chemical stimuli). The sensations mediated by the trigeminal nerve are usually described as burning, stinging, itching, tickling, cooling and warming feeling. Trigeminal free nerve endings have receptors which may be activated through several factors such as changes in pressure, temperature, irritants, and humidity. Substance P, calcitonin gene-related peptide (CGRP), and other neuropeptides are found in the trigeminal nerve fibers (Finger et al. 1990). Some trigeminal fibers are in close contact with solitary chemosensory cells located in the nasal epithelium and more responsible for chemosensory perception because they are responsive to both bitter tastants and chemical irritants (Fig. 17.1).

At the receptor level, one of the first described nociceptors was the ion channel receptor family and characterization of one of these receptors was obtained with nicotinic acetylcholine receptor. Transient receptor potentials (TRP) channels are well expressed on sensory nerves and may influence cell function by mediating the flux of cations across the plasma membrane into the cytoplasm generating action potentials. Ion channels in the TRP family can be opened by many

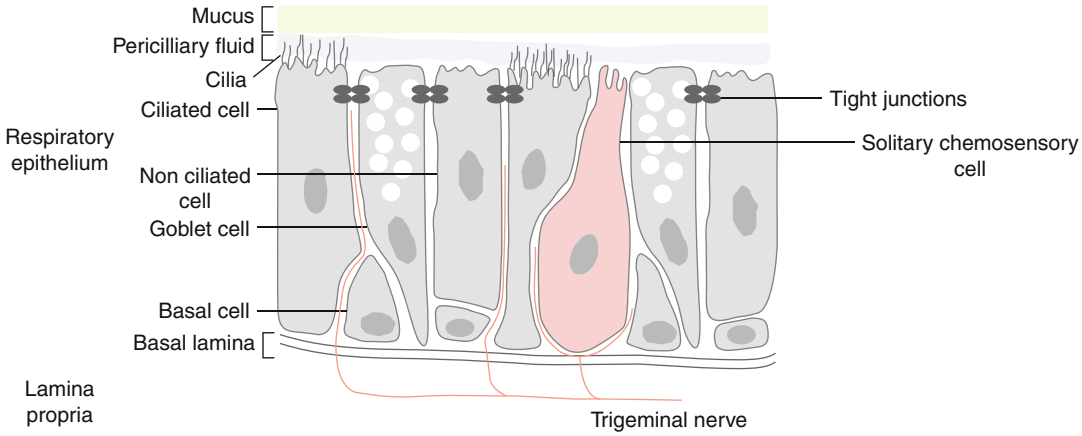

Fig. 17.1 Trigeminal fibers in close contact with solitary chemosensory cells and trigeminal nerve free endings located in the nasal epithelium and responsible for chemosensory and somatosensory perceptions

kind of stimuli, i.e., chemical or physical. The TRP family can be subdivided into six subfamilies and many of them are found at the free nerve ending of the trigeminal nerve such as the vanilloid receptor (TRPV1), the purinergic receptor (P2X), the acid sensitive ion channels (ASIC/DRASIC), the channel responsive to menthol (TRPM8) (cooling), the channel responsive to changes in heat and eugenol (TRPV3) (warming), and the channel responsive to isothiocyanate (TRPA1), the major compound of mustard oil (Bessac and Jordt 2008).

Like for the skin sensory perception, the unmyelinated C-fibers (slow conduction) are responsible for burning sensations and the myelinated Aδ-fibers (fast conduction) are responsible for stinging sensations.

The cell bodies of the trigeminal fibers are located in the Gasserian ganglion. Nerve fibers from the cell bodies thereafter participate to the sensory afferent system and project to the trigeminal sensory nucleus that extends from the rostral spinal cord to the midbrain. Interestingly, some individual cells in the ganglion send axons to the olfactory bulb indicating that some interaction exists at this level. Neurons then project to the amygdala and to the ventral posterior medial nuclei of the thalamus. Most of the ascending fibers cross towards the contralateral side with some fibers ascending ipsilaterally (different for the olfactory pathways (Brand 1999)). The nerve projections terminate in the primary somatosensory cortex (SI) and also in the secondary somatosensory cortex (SII) with a right hemispheric predominance (Hari et al. 1997; Rombaux et al. 2008a, b). Trigeminal activation also leads to insular cortex activation and to ventral orbitofrontal cortex mainly to the right side explaining at the central level the interactions with others chemosensory systems like taste and olfaction (Anton and Peppel 1991).

Besides the sensory nerves, the parasympathetic and the orthosympathetic systems play an important role in the normal physiology of the nose (Kaliner 1992). Parasympathetic nerves have acetylcholine as major neurotransmitter and acts on muscarinic receptors to induce increased glandular secretions and vasodilatation. Vasointestinal peptide (VIP) is another neurotransmitter of the parasympathetic system. The sympathetic system with noradrenaline and neuropeptide Y (NPY) as neurotransmitters acts on adrenergic receptors and induces vasoconstriction and increases nasal airway patency (Baraniuk et al. 1991; Baraniuk 1992).

Pathophysiological mechanisms and nasal symptoms are explained by the interdigitation of these neurologic systems, i.e., the trigeminal sensitive afferent (+ efferent axon reflex), the efferent parasympathetic, and the efferent orthosympathetic systems (autonomic systems) (Fig. 17.2).

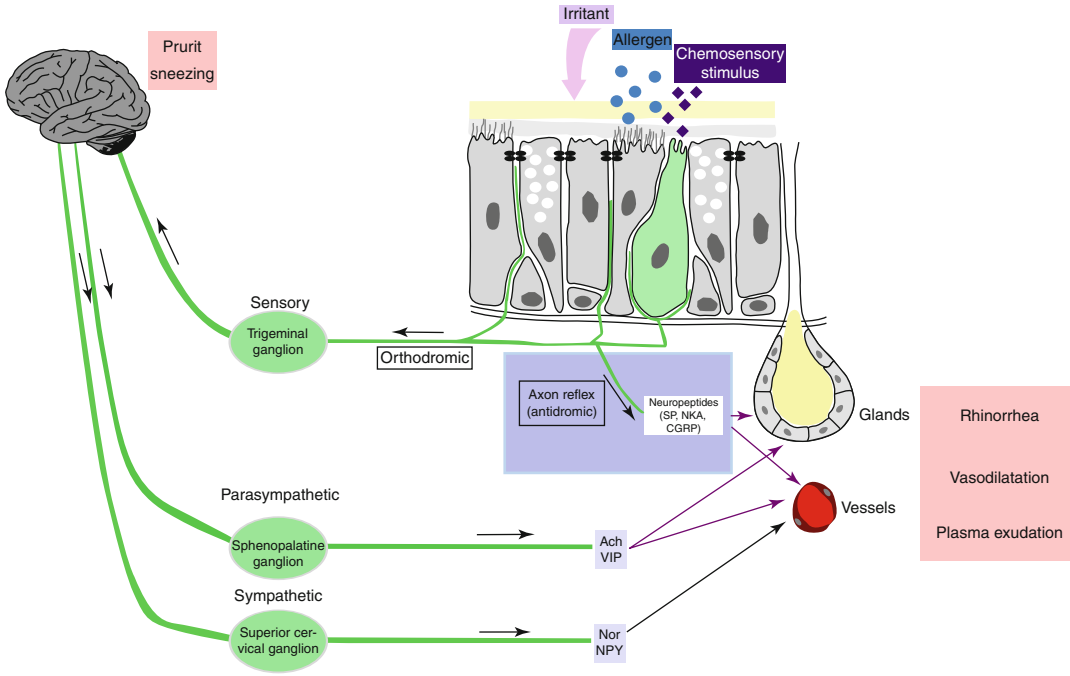

Fig. 17.2 Interdigitation of the neurologic systems found in the nasal mucosa, i.e., the trigeminal sensitive afferent (+ efferent axon reflex), the efferent parasympathetic, and the efferent orthosympathetic systems (autonomic systems)

17.3 Consequences of Activation of Trigeminal Receptor and Nasal Reflexes

The activation of the trigeminal system leads to the perception of potentially noxious stimuli, to a global chemosensory perception of odorant stimuli and to some nasal reflexes.The nasal fossa may be divided into two parts, the anterior one most dedicated to the chemosensory perception and the posterior one most devoted to mechanosensory functions. This has been demonstrated by Frasnelli et al. where it was clearly stated that anterior nasal mucosa is more sensible to chemosensory stimuli than mechanical stimuli, while the posterior nasal mucosa is equally sensible to both chemosensory and mechanical stimuli (Frasnelli et al. 2004). However, thresholds to detect chemosensory stimuli such as CO_2 is lower when the stimulus is given in retronasally compared to orthonasally (Melzner et al. 2011).

Therefore, nasal mucosa should not be seen as a homogenous tissue as it exhibits a varying degree of sensitivity to trigeminal stimuli depending on the stimulus quality and location in the nasal fossa (Scheibe et al. 2006).

Activation of trigeminal fibers leads to protective reflexes such as increasing secretions (saliva, tears, nasal mucus), decreasing breathing, sweating initiation, and closure of the nasal passage by augmentation of the turbinate volume.

Trigeminal nerve stimulation also induces many reflexes inducing different responses.The nasal cycle is probably the best known neurologic mechanism leading to a fluctuating congestion-decongestion of the nasal fossa secondary to a changing tone in the vasculature controlled by the autonomic system.

The naso-nasal reflex is supposed to be mediated by the parasympathetic system and explains many exacerbations of rhinorrhea and watery discharge (Baraniuki and Kim 2007).

The naso-ocular reflex is bilateral and mostly contralateral, secondary to chemosensory or tactile or physical stimuli. It induces watery eyes, lacrimation, and redness of the conjunctiva.

The "foot-cooling" reflex is secondary to a cold stimulation at the extremities of the inferior limb inducing in the nose a reduced blood flow and subsequently a nasal decongestion. This is also very similar to the reflexes observed in the nose when cooling of the face induces the same effect. Facial cooling through trigeminal receptors may even induce lower airway symptoms (Koskela and Tukiainen 1995).

The naso-cardiovascular reflex is secondary to trigeminal activation in the nose and is responsible for bradycardia and hypotension, may be present during nose surgery, and is of primary importance for the anesthesiologist.

The naso-respiratory reflex or naso-bronchial reflex is present when cold dry air is presented to the subject's nose inducing increased lower airway resistance.

Cold dry air stimulus may also be used to induce both long-lasting painful sensations (Lötsch et al. 1998) and secretory response in the nose (Fontanari et al. 1996). This mechanism is thought to be secondary to activation of capsaicin-sensitive fibers; alternatively, the change in the osmotic milieu of the respiratory epithelium may trigger activation of the nociceptive system. This may play a role in the pathophysiology of nasal hypereactivity and in the non-allergic noninfectious group of rhinitis (Bernstein 1991) and would lead to the development of capsaicin-based treatment for the patients suffering from these diseases (Lacroix et al. 1991; Marabini et al. 1991; Stjarne et al. 1991; Blom et al. 1998; Taylor-Clark et al. 2005a, b). Capsaicin delivered intranasally has proven its effect in the treatment of the nasal hyperreactivity found in idiopathic rhinitis patients (Van Rijswijk et al. 2003).

These responses may be present after single presentation of the stimulus or when repeated application of the stimuli is delivered. C-fibers and Aδ-fibers respond differently to repeated chemical stimulus. If stimuli are repeated, the burning painful sensation driven by C-fibers is increased, and this is the contrary for Aδ-fibers giving the stinging sensation. This is secondary to central nervous summation more than increase in the firing of the nerve fibers at the periphery.

17.4 Neurogenic Inflammation

The activation of sensory nerves and the release of neuropeptides from neuroendocrine cells found in the respiratory mucosa with a subsequent neurogenic inflammation may explain at least partially some diseases of the upper and lower airways (Lacroix and Landis 2008).

Stimulation of sensory trigeminal fibers may lead to the release of different neuropeptides such as substance P, neurokinin A (NKA), neuropeptide K (NPK), and calcitonin gene-related peptide (CGRP). These neuropeptides are increased in the upper and lower airways of these patients with airway inflammation in a similar way than the inflammatory components usually described as eosinophils or some proinflammatory cytokines (Shusterman et al. 2003).

There is a strong evidence that neuroendocrine cells, sensory neurons, and proinflammatory immune cells interact and promote inflammation and airway hyperreactivity. Neurotrophins such as nerve growth factor (NGF) or neurotrophins-3–4 are also linked to the development of a neurogenic inflammation.

In animals, dendrites of intranasal trigeminal nerve endings can be stimulated in an antidromic way. This antidromic stimulation is called the "axon reflex" and leads to the release of inflammatory neuropeptides form the varicosities of the nerve, producing vasodilation, increased vascular permeability and glandular activation. This phenomenon has been clinically proven in humans where specific activation of the intranasal trigeminal nerve ending produces nasal obstruction, congestion, watery discharge, and sneezing. This axon reflex probably plays a major role in the development of nasal hyperreactivity, non-allergic noninfectious rhinitis known as idiopathic rhinitis, and even allergic rhinitis via the substance P which exacerbates the eosinophilic recruitment after allergen challenge (for review, see Sarin et al. 2006).

17.5 Psychophysical Testing of the Intranasal Trigeminal Function

Testing of trigeminal function with psychophysics is based on threshold measurement, rating of suprathreshold stimuli, discrimination tasks, and lateralization tasks (Hummel 2000; Frasnelli and Hummel 2005).

Trigeminal function assessed with psychophysical testing revealed that sensitivity decreases with age (Wysocki and Cowart 2003).

Psychophysical evidence exists for qualitative specificity of the human intranasal trigeminal system. The nasal trigeminal system is less sensitive than the olfactory system for the majority of odorant stimuli. Recognition threshold of trigeminal stimulus such as CO_2 was measured between 32 and 47 % v/v for stimuli of 200 ms duration at an airflow of 8 l/min at body temperature. The threshold for detection can be lowered if stimulation duration is increased (Melzner et al. 2011).

Considering *pain ratings*, increase in perceived or painful sensitivity occurs more rapidly for trigeminal stimulus than for olfactory stimuli (Cain et al. 1998).

The trigeminal and the olfactory systems also have a different contribution on the presentation of *mixed compounds*. In normosmic subjects, trigeminal stimuli are perceived as more intense when they are accompanied by an olfactory stimulus while the olfactory stimulus seems to have no effect when a mixed compound is presented. The trigeminal stimulus may induce an additive or even a hyperadditive effect on the perception after a mixed stimulus presentation (Cornetto-Muniz and Hernandez 1990).

Qualitative discrimination task with trigeminal irritants demonstrate that human are capable to discriminate among different trigeminal stimuli even in the absence of any olfactory stimuli given concomitantly (Laska et al. 1997), even if this ability seems to decrease with age (Laska 2001). In contrast to odor stimulation, trigeminal stimuli can produce increase in pain intensity when repeated stimuli are given with a short interval demonstrating a sensitization effect while on the contrary a desensitization effect exists when repeated stimuli are delivered with long interstimulus interval (Hummel et al. 1994; Brand and Jacquot 2002). Temporal integration of trigeminal informations is thus different than olfactory temporal integration. Psychophysical studies with capsaicin have demonstrated a sensitization effect meaning that the subjective pain rating was increased after the second stimulation if the interstimulus interval was less than 1 min. On the contrary with a second stimulation delivered after 4 min, a desensitization effect was observed. This leads to the idea that repetitive delivery to the nasal mucosa was perhaps a treatment for patients with hyperalgia in the nasal fossa or for patients with non-allergic noninfectious rhinitis (Brand and Jacquot 2002). However, this mechanism is linked to the type of the stimulus and sensitization and desensitization in the nasal cavity do not follow the same processes in relation to the molecules studied (Jacquot et al. 2005).

Lateralization task revealed that trigeminal stimuli are perceived without error when the subjects blindfolded is asked to determine the side of stimulation and that this ability is lost for olfactory stimuli or when the odor has a mixed property between trigeminal and pure olfactory valence (Kobal and Hummel 1990). In others words, pure olfactory stimuli cannot be localized to the nasal cavity while on the contrary pure trigeminal stimuli can be localized. The results are lower in patients with an olfactory dysfunction independent of the cause of the olfactory problem (Hummel et al. 2003).

Subjective ratings of nasal patency are also influenced by the trigeminal system. For example, stimulation of the nasal fossa with menthol is accompanied by an increase of perceived nasal patency (Eccles et al. 1989) while on the contrary anesthesia of the nasal mucosa leads to a perception of decreased nasal patency even in both cases objective nasal patency did not change.

Many studies have been conducted on anosmic subject and trigeminal thresholds were found to be higher in anosmic subjects than in control (Cornetto-Muniz and Cain 1998). Age-related decline of intranasal sensitivity was also reported with psychophysical but also electrophysiological evidence (Frasnelli and Hummel 2003).

17.6 Electrophysiology and Functional Imaging

Electrophysiological recordings from the intranasal trigeminal system may be obtained at the peripheral level, i.e., the negative mucosal potential (NMP) and at the central level by recording cortical responses after delivery of an intranasal trigeminal stimulus, i.e., the trigeminal event-related potential (Trigeminal ERP).

The NMP is recorded from the nasal mucosa and is thought to represent the summated receptor potentials of chemical nociceptors in a very similar way to the electro-olfactogram which represents the global activity of olfactory receptor neurons located in the olfactory neuroepithelium (Thürauf et al. 1991).

Human NMP may be obtained after CO_2 intranasal stimulation and the amplitude of the NMP is well correlated with the subjective pain rating (Kobal 1985; Hummel et al. 1996a, b). NMP may also be recorded by stimulating polymodal nociceptors such as TRPA1, TRPV1 and 2. Responses to the NMP are different according to the stimulus used, i.e., CO_2, menthol or ethanol (Meusel et al. 2010) and decrease in response to repetitive stimulation (Hummel et al. 1996a, b).

Trigeminal ERP may be obtained after repetitive stimulation with relatively selective trigeminal stimuli such as CO_2 with an interstimulus interval of 20–40 s and a concentration of 30–60 % v/v of CO_2 delivered by an olfactometer (Hummel 2000; Rombaux et al. 2008a, b) or with nicotine (Hummel et al. 1992). Without producing mechanical sensations (flow embedded in a constant 8 L/Min) and the thermoreceptor (temperature maintained constant at 36–37°), the recorded ERP may be viewed as a pure chemosensory component without interfering with mechanoreceptor.

When comparing the electrophysiological responses to subjective rating of the stimulus, the intensity increases more rapidly for trigeminal stimuli than for olfactory stimuli when the concentration of the stimuli increases (Lötsch et al. 1997).

Trigeminal ERP can also be meaningful in patients with an olfactory dysfunction. Patients with an olfactory dysfunction usually do not have any olfactory event-related potentials but trigeminal event-related potentials are usually present even if some subtle changes in latency and amplitude may be present (Rombaux et al. 2006, 2008a, b).

Electrophysiological studies both at the peripheral level (NMP) and at the cortical level (TERP) helped to understand the effects of gender, age, disease, i.e., loss of olfactory function, and drugs (Lundström et al. 2005).

PET-based investigation of cerebral activation following intranasal trigeminal stimulation revealed that olfactory and trigeminal informations have common pathways and that CO_2 activated the base of the posterior central gyrus (primary and secondary somatosensory cortex) and the piriform cortex, more in the right hemisphere (Hummel et al. 2009). This was confirmed by fMRI studies where anterior caudate nucleus, insula, cerebellum, and orbitofrontal cortex were also involved in the processing (Boyle et al. 2007; Iannilli et al. 2007b).

17.7 Olfactory and Trigeminal Interaction

Healthy subjects need to have an intact trigeminal and olfactory system to have a full chemosensory perception of the environment (Bouvet et al. 1987). Inhaled chemical compounds have the propensity to stimulate both systems even if relatively selective olfactory and trigeminal stimuli exist. Irritants are thought to stimulate free trigeminal nerve endings in the nasal epithelium but presumably below the level of the tight junction which renders them more sensitive to lipid soluble stimuli than to water soluble stimuli. Indeed, lipid soluble stimuli are more prone to pass across the mucus layer and the tight junction.

Trigeminal nerve fibers are also in close contact with the solitary chemoreceptor cells and respond to chemical stimuli that are water soluble (Finger et al. 2003). These cells are found in the respiratory and digestive tracts and have many of the characteristics of the taste cells because they have taste receptors mainly T2R bitter receptor,

Table 17.1 Major differences between olfactory and trigeminal sensory patterns

	Olfactory	Trigeminal
Cranial nerve	I	V
Nerve ending	In the olfactory neuroepithelium Olfactory receptor neuron	In the nasal mucosa Free nerve ending or in contact with solitary chemoreceptor cell
Hemispheric lateralization	Not major Mainly ipsilateral	Right Mainly contralateral
Major stimuli in research	Phenyl Ethyl Alcohol, H2S, Amyl Acetate	CO_2, capsaicin, allyl isothiocyanate
Lateralization task	Not possible	Possible
Effect of concentration increase on the subjective rating of the stimulus	Poor	Important
Effect of mixed stimulus on subjective rating	Poor	Important
Threshold	Usually low High sensitive	Usually high Low sensitive

TRPV1 and TRPM5 channels receptor (Lin et al. 2008). The chemosensory stimuli may thus activate the trigeminal nerve fibers surrounding the chemoreceptor cells directly if the stimulus is water soluble and above the level of the tight junction. In contrast, lipid soluble stimuli may activate the trigeminal free nerve ending below the level of the tight junction by diffusing across the junctional membrane.There is strong evidence that a cross modal plasticity exists between the two systems and that a mutual interaction exists both in normal and pathological conditions (Hummel and Livermore 2002).

Much information may be obtained from patients having lost one of the two systems. For example, anosmic patients may be good candidates to deeply study the trigeminal system. Patients with a complete loss of trigeminal function are more difficult to find even if post surgically treated patients (radical surgery for the inferior and middle turbinate's or empty nose syndrome, or patients who had undergone a Gasser ganglion removal) may have some interest to study olfactory abilities without any trigeminal interactions.

Interactions between the two systems exist at the peripheral level (trigeminal nerve with contact at the olfactory neuroepithelium, effect of substance P on the olfactory responses, alteration of receptor activity through modification of nasal permeability or mucus quality), at the olfactory bulb level and more centrally in cortical areas such as the piriform cortex, thalamus, insula, and orbitofrontal cortex. Indeed, some trigeminal collaterals are found in the olfactory bulb explaining the interdigitation of the olfactory and trigeminal systems (Schaefer et al. 2002).

When studies are conducted to determine the relative contribution on the perception of trigeminal, olfactory, and mixed stimuli, we can conclude at a relative dominance of the trigeminal system over olfactory sensation and also a dominance of mixed stimuli over either system alone (Livermore et al. 1992).

In healthy subjects both systems contribute to the complete picture of the chemosensory stimulus. At the periphery, both olfactory and trigeminal sensory informations attempt to mutually decrease the other sensory response as there is no need for the peripheral system to catch all the informations available from the outside world and entering the nasal fossa. At the central level, both the olfactory and trigeminal informations are converging; the resulting percept may a mutual amplification or inhibition of the various sensations depending, among other things, on stimulus quality, intensity, and salience (Cain and Murphy 1980) (Table 17.1).

Patients with an olfactory dysfunction have lower trigeminal sensitivity compared to controls (Hummel et al. 2003; Iannilli et al. 2007a, b) and loss of olfactory function leads to a decrease trigeminal sensitivity (Hummel et al. 1996a, b). Some studies have investigated the olfactory

modulation of trigeminally mediated sensations in patients with olfactory loss. These reports have shown that in anosmia, there are mixed sensory adaptation/compensation in the interaction between olfactory and trigeminal systems, where, in acquired anosmia, there is an increased trigeminal activation on mucosal level and a decreased responsiveness at a central level (Frasnelli et al. 2007). In congenital anosmia however, similar responsiveness to trigeminal stimuli was found when compared with healthy subjects (Frasnelli et al. 2007). Following these findings, Frasnelli et al. (2007) proposed a model of mixed sensory adaptation/compensation in the interaction between olfactory and trigeminal system. In this model, the primary trigeminal activation is (1) reduced on a mucosal level due to constant activation of intrabulbar trigeminal collaterals, inducing downregulation in the periphery of the trigeminal system, and (2) amplification on a central level in healthy subjects, due to functional integration of olfactory and trigeminal processes. They also hypothesized that in patients suffering from acquired anosmia, missing inhibition via the trigeminal collaterals in the olfactory bulb would lead to a compensatory up regulation in the periphery of the trigeminal nerve in the case of olfactory loss, hence inducing increased peripheral responsiveness. On central levels, however, missing olfactory augmentation of the trigeminal input would not be sufficiently compensated by the increased peripheral trigeminal input, thus leading to decreased amplitude of trigeminal event-related potentials (Frasnelli et al. 2007). Finally, recovering would lead to a compensatory mechanism and to an adjustment (Fig. 17.3).

Chemosensory reduction of trigeminal sensitivity in subjects with olfactory dysfunction

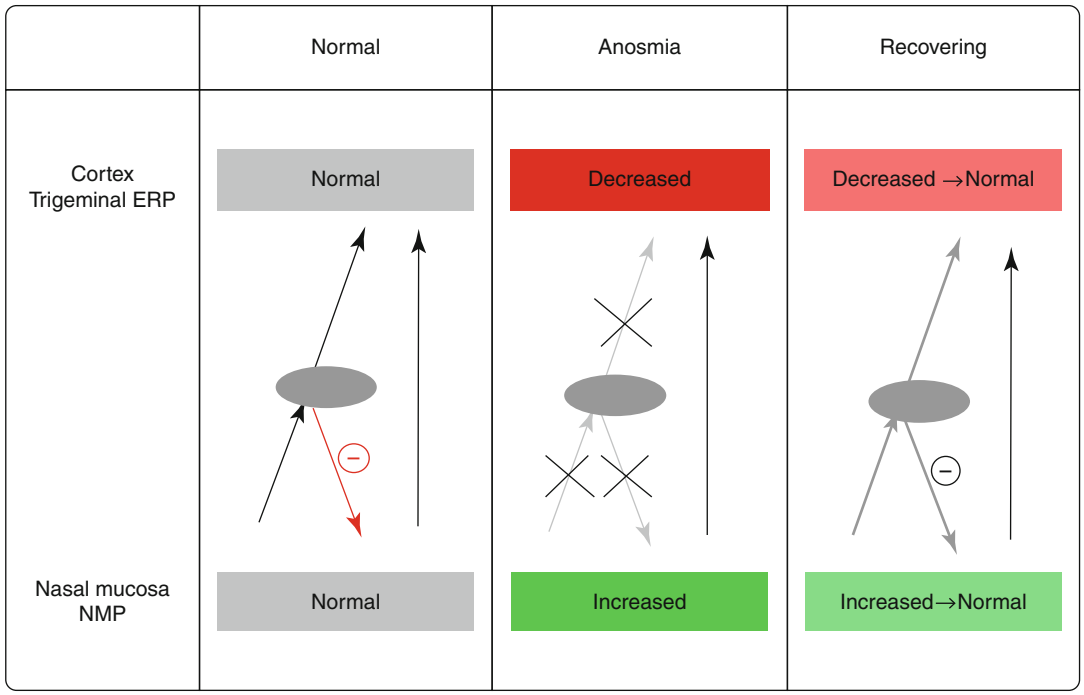

Fig. 17.3 Proposed model for olfactory and trigeminal interaction in normal condition, acquired olfactory dysfunction, and in the recovery phase. *Grey arrows* for olfactory pathways, *black arrows* for trigeminal pathways. In normal condition, constant activation of intrabulbar trigeminal collaterals inducing a downregulation in the periphery of the trigeminal system and amplification on a central level due to functional integration of olfactory and trigeminal processes. In patients suffering from acquired olfactory dysfunction, missing inhibition via the trigeminal collaterals in the olfactory bulb leading to an increased peripheral responsiveness and to a decreased amplitude of central trigeminal event-related potentials. Finally, recovering would lead to a compensatory mechanism and to an adjustment (Adapted from: Frasnelli et al. 2006)

seems to be specific of the chemosensory pattern as somatosensory information does not seem to be decreased (Frasnelli et al. 2006).

Finally patients with absence of trigeminal receptor, those without any remaining nasal mucosa after radical surgery also have a decreased olfactory function and this should be viewed as a plaidoyer against radical surgery if the surgeon wants to maintain intact chemosensory function in the nose (Husner et al. 2006; Huart et al. 2012).

Conclusion

The intranasal trigeminal system is not fully understood and its participation to the global chemosensory perception and to the somatosensory perception, i.e., the nasal patency merits further investigation. The olfactory-trigeminal interaction may be studied through the nature of the stimulus and the subsequent effect, the temporal integration of the stimulus (sensitization vs desensitization), the status of the subject (age, gender, anosmia), or the effects of some drugs (local anesthesia, antagonist receptor activity). Moreover, psychophysical testing of the intranasal trigeminal has not yet been established in clinical routine. It should be pointed out that the intranasal trigeminal system may deeply influence the overall chemosensory perception and that interfering with it would lead to a decreased chemosensory function and to a decrease of olfactory abilities. In the same vein of thoughts, interfering with this system is particularly devastating for the patient in regard to the nasal patency and to the perception of nasal airflow mediated by the somatosensory fibers. Finally, this system plays also an important role in neurogenic inflammation and in the pathogenesis of variants of non-allergic noninfectious rhinitis.

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Sinus Pain

18

James Bartley

Keywords

Migraine • Tension headache • Temporomandibular joint disease • Sinus pain • Medication overuse headache • Central sensitisation • Glial activation

Abbreviations

CNS	Central nervous system
CRS	Chronic rhinosinusitis
MOH	Medication overuse headache
TMJ	Temporomandibular joint
TLR	Toll-like receptor

Core Messages

- The functional state of the central nervous system as well as the site and intensity of peripheral noxious stimuli is important in pain perception.
- The glia, their receptors and their secreted signalling factors have a major influence on neural function.
- Migraine, tension headache and temporomandibular joint pain are manifestations of central sensitisation.
- While many patients with "sinus headache" may fulfil the criteria for tension headache, this does not exclude sinus infection contributing to central sensitisation.
- Sinus infection does not cause pain by itself; it simply influences sensory thresholds.
- Around the head and neck other pathologies apart from sinus infection can also be related to facial pain.

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18.1 Introduction

Patients with facial pain that has been attributed to potential nasal or sinus pathology present frequently to otolaryngologists. As well as considering the nose and sinuses as a potential cause, neurological, dental, rheumatological and musculoskeletal conditions need inclusion in a differential diagnosis. An otolaryngologist, who wishes to understand, diagnose and treat patients presenting with "sinus pain", has to move away from a simplistic "cause and effect" pain model to a central sensitisation model. Central sensitisation introduces the concept that the central nervous system (CNS) is continually modifying the degree, duration and spatial extent of pain in a way that reflects the functional state of the CNS, rather than the site or intensity of peripheral noxious stimuli (Woolf 2011). As well as a sensory pain component, many facial pain patients have associated anxiety and depression issues, which may also need to be addressed (Jacobson and Folstein 2003).

> The central nervous system is continually modifying the degree, duration and spatial extent of pain in a way that reflects the functional state of the central nervous system, rather than the site or intensity of peripheral noxious stimuli.

18.2 Pain Pathophysiology

In 1965, Melzack and Wall's "spinal gate control theory" replaced specificity theory (Melzack and Wall 1965). Specificity theory taught that the pain experience is proportional to the peripheral injury and the pathology. The view that nasal and sinus pathologies are directly responsible for chronic pain reflects this legacy. In 1983, a further paradigm shift occurred when Clifford Woolf showed that many of the pain hypersensitivity features that accompanied peripheral tissue injury or inflammation resulted from sensory signalling augmentation in the central nervous system (CNS) – a concept termed "central sensitisation" (Woolf 1983). Central sensitisation introduces the concept that the CNS modifies the degree, duration and spatial extent of pain in a way that reflects the functional states of the CNS, rather than the site or intensity of peripheral noxious stimuli (Woolf 2011). Central sensitisation is characterised by increased (often exquisite) sensitivity to light touch, muscle tenderness, referred pain as well as local reddening and oedema. A large body of experimental evidence and clinical research indicates that migraine, tension headache and temporomandibular joint pain are manifestations of central sensitisation (Woolf 2011).

> The glia, their receptors and their secreted signalling factors have been shown to have a major influence on neural function.

Most pain thinking and central sensitisation research has focused on synaptic plasticity triggered within the CNS by nociceptive inputs (Woolf 2011). More recently, the significance of the glia, gap junctions and membrane excitability have also been recognised (Fig. 18.1). In particular, the glia, their receptors and their secreted signalling factors have been shown to have a major influence on neural function (Guo et al. 2007; Scholz and Woolf 2007; Milligan and Watkins

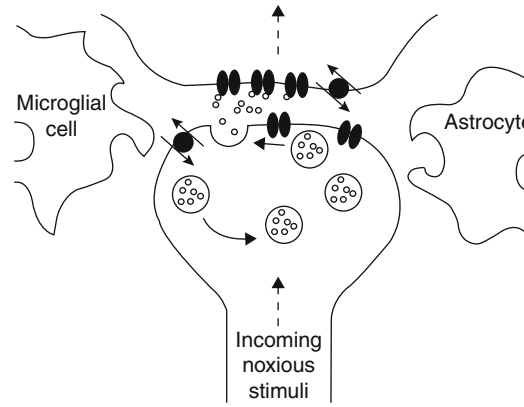

Fig. 18.1 The concept of a "tetrapartite" gliapse modulating synaptic strength based on the anatomical relationships between astrocytes, glia and neurons has superseded the previous synaptic model

2009). Activated glia produce and release a variety of neuroexcitatory substances. Toll-like receptors (TLRs), particularly TLR2 and TLR4, which respond to endogenous danger signals such as lipopolysaccharide that are associated with bacterial infection, have been implicated in glial cell activation (Scholz and Woolf 2007; Milligan and Watkins 2009; Liu et al. 2012).

18.3 Migraine/Chronic Tension Headache

Current migraine theory centres on sensory processing dysfunction of the brain stem or diencephalic nuclei. Neural events in the brain stem result in ensuing dilation of blood vessels, which in turn results in pain and further neural activation (Goadsby et al. 2002). Brain imaging studies using positron emission tomography show that the brain stem, particularly the periaqueductal grey matter (PAG), is activated at the beginning of a migraine attack (Weiller et al. 1995). The PAG is a major gateway to the limbic system and other sensory systems. The amount of light or sound coming into the body does not change during an attack; the brain's sensory response does. As well as during an attack, the sensory processing mechanisms in the brain stem and limbic system in migraine patients are often hypersensitive both before and after an attack, reflecting an ongoing central sensitisation (Welch 2003; Woolf 2011).

Many patients who present with symmetrical frontal or temporal headache have a tension-type headache. However, facial pain can also be lateralised to one side, usually to the left (Min and Lee 1997). Mid-segment pain, where patients present with normal sinus CT scans and pain over the maxillary sinuses, also has many features consistent with central sensitisation. It represents a version of tension-type headache affecting the mid-face (Jones 2004). Chronic tension headache is associated with pain and increased tenderness in the head, neck and shoulder muscles (Figs. 18.2 and 18.3). A common assumption has been the pain in the head and neck muscles causes the headache. However, the neck muscles can also be painful because of central sensitisation in the spinal cord or brain stem. People with chronic tension headache are often more sensitive not only around the head, neck and shoulder muscles, but also elsewhere such as in the low back and calves, indicating an overall central sensitisation (Fumal and Schoenen 2008; Woolf 2011).

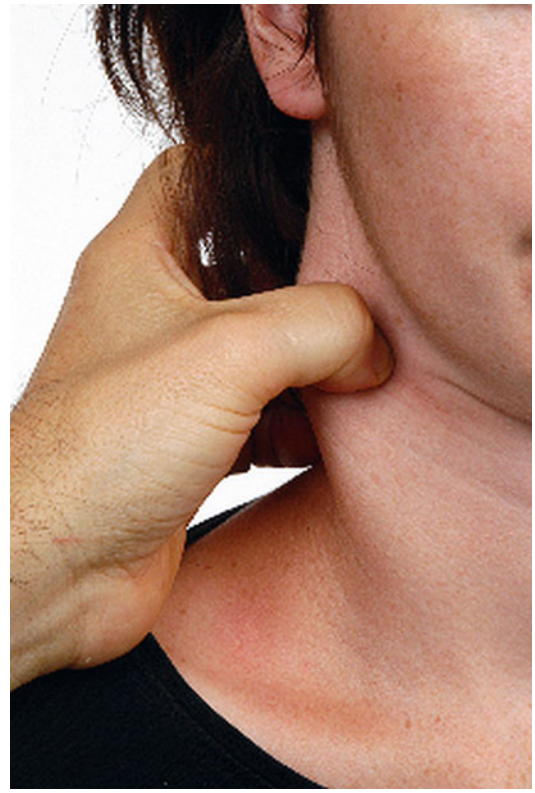

Fig. 18.2 To examine the sternocleidomastoid muscle for tenderness, the muscle needs to be examined up and down its length in a gentle pincer-like grip between thumb and forefinger

> The underlying pathophysiology behind migraine and tension headache is central sensitisation.

18.4 Medication Overuse Headache

In some people, the overuse of medication to treat their headache can make their headaches worse. It is important to take a medication history.

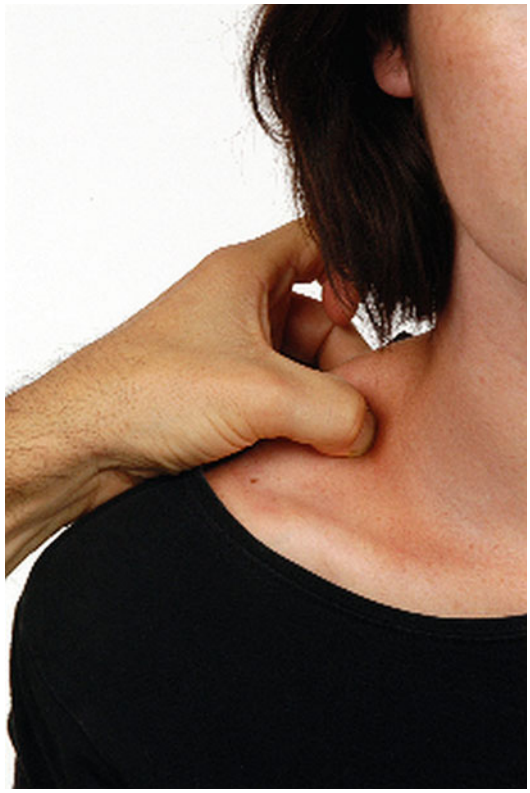

Fig. 18.3 A tender area in the superior midpoint of the shoulder in the upper trapezius muscle can be located if one palpates the superior aspect of the muscle between thumb and forefinger

If a person complains of daily headaches requiring regular pain medication (more than twice a week), the headache could be caused by the medications and, if so, will improve or disappear when the medications are discontinued. Medication overuse headache (MOH) can be a significant clinical challenge. The reality is almost every medication used to treat headache and migraine can cause MOH (Cupini et al. 2010). The general recommendation is patients come off these medications while under medical supervision.

18.5 Sinusitis

According to the diagnostic criteria of the 2004 International Headache Society, "chronic sinusitis is not validated as a cause of headache and facial pain unless relapsing into an acute stage" (Lipton et al. 2004). On the other hand, the American Academy of Otolaryngology – Head and Neck Surgery considers that facial pain or pressure is an important, although not exclusive, consideration in the diagnosis of CRS (chronic rhinosinusitis) (Levine et al. 2006; Meltzer et al. 2006). These views are the consensus opinion of experts in their respective fields. Many clinical studies show that the majority of patients presenting with "sinus headache" fulfil the diagnostic criteria for either migraine or tension headache (Silberstein 2004; Jones 2009).

> While many patients with "sinus headache" may fulfil the criteria for tension headache, this does not exclude sinus infection contributing to central sensitisation.

While the patients may fulfil the criteria for tension headache, this does not exclude sinus infection contributing to central sensitisation, which is the underlying pathophysiology of these conditions. A review of recent advances in our understanding of pain pathophysiology indicates that a chronic infective process such as sinusitis can induce a central sensitisation (Scholz and Woolf 2007; Milligan and Watkins 2009). TLRs, particularly TLR2 and TLR4, which have been implicated in glial cell activation (Fig. 18.1), recognise and respond to endogenous danger signals such as lipopolysaccharide that are released by damaged and dying cells associated with active bacterial infection (Milligan and Watkins 2009; Liu et al. 2012).

Clinical evidence of central sensitisation is seen in CRS patients. The well-known physical finding of tenderness to palpation or percussion over the affected sinuses that is experienced by patients with sinusitis may be indicative of either excessive peripheral or central sensitisation. Increased muscle tenderness in CRS (Figs. 18.2 and 18.3) has been measured (Naranch et al. 2002). The quality of clinical evidence supporting the role of sinus surgery in helping patients with facial pain is not of a high quality. However, the majority of prospective studies looking at the

results of endoscopic sinus surgery for facial pain/headache indicate that there is a group of CRS patients whose facial pain benefits from surgery (Tarabichi 2000; Moretz and Kountakis 2006; Phillips et al. 2007; Soler et al. 2008; Chester et al. 2009).

However, there are major limitations to these studies, and some of the improvement can be explained using other mechanisms. Some of these patients may have been suffering from medication overuse headache. The surgery, by itself, was an incentive to come off these medications. The natural history of these facial pain/headache conditions is also not known, and regression to the mean is also a potential mechanism. The breathing cycle is divided into inspiratory and expiratory phases. Nasal breathing slows the respiratory rate increasing the length of the expiratory phase (Ayoub et al. 1997). Increasing the expiratory phase of the respiratory cycle is known to increase the body's relaxation response (Cappo and Holmes 1984). Improving nasal breathing could thus facilitate relaxation techniques which are effective treatments for both migraine (Campbell et al. 2009) and tension headache (Carlson 2008).

Many patients with purulent secretions visible at nasal endoscopy have no headache or facial pain (Jones 2004). When many so-called "sinus pain" patients present acutely with symptoms, many have no evidence of infection (Jones 2004). There is also no correlation between the severity and location of the pain with the extent or location of mucosal disease (Tarabichi 2000; Levine et al. 2006). These observations can be explained using a central sensitisation model. Sinus infection does not cause pain by itself; it simply influences sensory thresholds. In many, but not all, patients, this is insufficient to cause pain. In other patients, the inflammation will be such that pain processing is influenced.

The otolaryngologist has to be aware that sinus infection is but one possible contributor to a lowering of the sensory thresholds; other pathologies can also be responsible for exactly the same symptoms. Patients diagnosed with fibromyalgia and tension headache, who also have nervous system sensory and pain regulation abnormalities, can report exactly the same sinus symptoms (Naranch et al. 2002). The key to successful nasal and sinus surgery in "sinus pain" patients lies not only in the surgery itself but in careful patient counselling and selection. One should not be operating if the CT scan shows no evidence of sinus disease. One should be careful about operating on CRS patients in the absence of significant infective symptoms or signs. Co-morbidities reflecting other potential pathologies such as anxiety, depression, fibromyalgia, irritable bowel symptoms and neck and low back pain should make the surgeon very wary of attributing "sinus pain" to sinus disease (Woolf 2011).

18.6 Contact Points and Nasal Obstruction

The theory that contact points within the nose could cause headache reflects specificity theory thinking. The prevalence of a contact point has not only been found to be the same in an asymptomatic population as in a symptomatic population. In symptomatic patients with unilateral pain when a contact point was present, it has been found on the side contralateral to the pain in 50 % of patients (Abu-Bakra and Jones 2001). The relationship between nasal obstruction and headache is controversial. Schonsted-Madsen et al. (1986) showed that relief of headache (pain localised to the forehead, glabella or above or around the eyes) was strongly related to relief of nasal obstruction (Schonsted-Madsen et al. 1986). A potential reason as to why improvement in the nasal airway might lead to improvement in tension headache has previously been described (Sect. 18.5).

Sinus infection does not cause pain by itself; it simply influences sensory thresholds.

The weight of evidence supports the view that chronic temporomandibular joint pain is not due to occlusal abnormalities.

18.7 Temporomandibular Joint Disorders

The weight of evidence supports the view that chronic temporomandibular joint (TMJ) pain is not due to occlusal abnormalities (Koh and Robinson 2004). Psychophysiological forces are important (Suvinen et al. 2005; Carlson 2008). The TMJ is lubricated by synovial fluid, which also nourishes the avascular cartilage and cartilaginous disc in the middle of the joint. Whenever the joint is compressed, the blood supply to the joint is reduced and the joint has difficulty manufacturing lubricating fluid. The friction within the joint increases, and the cartilaginous disc in the middle of the joint begins to stick (Nitzan 2001). In times of stress, people tend to breathe using their upper chest, which tends to lead to a forward head position and increased pressure on the joint or clench and grind their teeth. Increased pressure in the TMJ can lead to clicking and sticking of the cartilage disc. If the friction increases, the ligaments holding the disc in place stretch and the disc moves off the condylar head (Bartley 2011). In the absence of any major external trauma, before addressing any structural changes within the jaw joint, underlying psychosocial stresses, breathing re-education as well as musculoskeletal issues need to be addressed (Carlson 2008; Aggarwal et al. 2010).

18.8 Causes Removed from the Orofacial Area

A history of neck injury can often be overlooked. The nerve supply to the upper neck and head overlaps in the upper spinal cord. Using first principles, neck pain could be referred to the head. Alternatively, by sensitising the spinal cord to incoming pain messages, neck pain could lower the pain threshold to other sensory messages being received from the face and head. After a whiplash injury to the neck, areas well away from the original injury site – from the head to the feet – can be shown to be hypersensitive to normal sensory messages (Woolf 2011).

18.9 Psychological Well-Being

Anxiety and depression have significant associations with migraine, tension headache, CRS and TMJ disorders (Jacobson and Folstein 2003; Wasan et al. 2007). A systems review of the patient often reveals issues with poor short-term memory, palpitations, shortness of breath, irritable bowel symptoms, poor sleep quality, cold hands and feet as well as tingling of the hands in an ulnar nerve distribution. Anxious patients typically have difficulty going to sleep, whereas depressed patients tend to wake in the early morning. Depressive symptoms are important in deciding on treatment and in predicting treatment outcomes.

18.10 History Taking

Clinical diagnosis is largely dependent upon an accurate history. The initial differential diagnoses generated depend upon the clinician's experience, the patient's age and gender and the time course and site of the pain. An otolaryngologist has to integrate neurological, rheumatological, dental and musculoskeletal conditions in his/her differential diagnosis. Acute inflammatory causes are usually relatively obvious. Stress and cold wind typically make tension headache pain and TMJ pain worse, whereas heat makes it better. Many patients may have symptoms reflecting a sensitised nervous system, such as night sweats, unexplained itch, tinnitus, irritable bowel or bladder symptoms, heavy painful periods and altered sensation on combing their hair, as well as pain problems elsewhere in the body (Woolf 2011). These symptoms should make a clinician wary of attributing facial pain to CRS alone.

Neuralgias are characterised by sudden, intense, lancinating, burning or stabbing pain lasting only from few seconds to less than 2 min. This pain is often triggered by sensory or mechanical stimuli. Trigeminal neuralgia is typically seen in older females, unilateral and located in the second and/or third divisions of the trigeminal nerve. Rarely, pontine tumours or multiple sclerosis needs to be considered as a secondary

cause. If a cough or sneezing makes the headache worse, a posterior fossa lesion may need to be considered.

18.11 Examination

After routine otolaryngological examination, palpation for muscle tenderness (Figs. 18.2 and 18.3), and excessive reddening afterwards, provides important physical information about the state of the central nervous system. Sometimes there are subtle differences in swelling and redness between the two sides of the face. The pectoralis minor muscle as it inserts into the coracoid process, sternocleidomastoid (Fig. 18.2), the midpoint of the upper trapezius muscle (Fig. 18.3), masseter, temporalis and the suboccipital muscles are usually tender when examined using appropriate palpation techniques (Simons et al. 1999). Jaw joint and associated muscle tenderness together with limited and jerky jaw movements and clicking of the jaw joint may be found on clinical examination. The teeth can be examined for excessive wear (evidence of bruxism) or percussion tenderness. Alterations in facial sensation are best detected by comparing moving light touch between the two sides of the face in the three divisions of the trigeminal nerve. An examination of areas away from the head and neck often provides useful, additional information. People who are highly stressed tend to take small irregular breaths, largely in their upper chest. The low back, extensor forearm muscles and calves are often tender to palpation in pain patients as well (Woolf 2011). Clinically patients with unilateral facial pain are often found to be tender all down that side of the body. The muscle tenderness reflects the underlying status of the nervous system.

18.12 Investigations

18.12.1 Radiology

Further urgent investigation and neurological evaluation are warranted for patients presenting with facial pain together other significant symptoms/signs (Table 18.1). Diagnostic imaging tests (e.g. plain x-rays, dental x-rays, MRI, axial CT scan) may help determine or exclude a cause of pain. The choice and timing of test varies according to clinical suspicions and the findings on physical examination.

Table 18.1 Urgent investigation and neurological evaluation are required for facial pain patients presenting with the following symptoms

Grossly disturbed facial sensation
Facial palsy
Hearing loss and disturbed balance
Dysphagia
Dysphonia
Dysarthria

18.12.2 Blood Investigations

Certain blood tests may be useful in evaluating patients presenting with facial pain (Gerwin 2005). Some females will have an iron deficiency. Vegetarians and the elderly can have undiagnosed vitamin B12 deficiencies. People who have dark or brown skin are often at significant risk of vitamin D deficiency while living in countries with temperate climates. Blood tests for thyroid function are occasionally useful in tension headache patients. In a person aged over 50 years with a rapidly developing headache, an erythrocyte sedimentation rate (ESR) test is mandatory.

18.13 Management

Depending on the clinical diagnosis, a wide range of treatment options are available.Many of these interventions are outside the conventional knowledge base of many otolaryngologists, but some knowledge is useful if an otolaryngologist wishes to provide comprehensive care and diagnosis. Psychological interventions such as cognitive behavioural therapy and relaxation work can be extremely useful for migraine, tension headache and TMJ disorders (Campbell et al. 2009; Aggarwal et al. 2010). Attention to diet, sleep patterns, posture

and exercise can be important. Simple analgesics and nonsteroidal anti-inflammatory drugs are recommended for treatment of episodic facial pain. It is crucial to avoid frequent and excessive use of analgesics to prevent the development of MOH. Drugs such as gabapentin or low-dose amitriptyline at night can be useful.

Psychological interventions such as cognitive behavioural therapy and relaxation work can be extremely useful for migraine, tension headache and temporomandibular joint disorders.

Conclusions

Patients presenting with facial pain continue to be a diagnostic dilemma. Migraine, tension headache and sinus pain share a common underling pathophysiology. Around the head and neck, other pathologies apart from sinus infection can also be related to facial pain. These factors cannot be neglected and also need to be considered as part of the diagnostic workup. Because facial pain may involve a range of medical/surgical subspecialties, a multidisciplinary approach is often needed.

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Computational Fluid Dynamics of the Nasal Cavity

19

Ralph Mösges

Core Messages

- Computational fluid dynamics (CFD) is a mature technology used widely in engineering to solve and analyze problems that involve fluid flows.
- Computational fluid dynamics has been used to demonstrate physiologic and pathologic conditions of nasal flow and to support preoperative planning and control of postsurgical outcomes.
- Using high-definition three-dimensional imaging CFD may offer a chance to study the effects of medication on the tissues lining the surface of the nasal cavity.
- CFD may help to design devices for optimal nasal delivery of medications such as nasal spray applicators.
- CFD may become a universal tool for research, pharmaceutical development, but also for advanced patient care in rhinology.

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The nose is not a tube, nor can it be regarded as two pipelines transporting air to the lung.

The nose has multiple functions, enabling the exchange of gas between the circulating blood and the environment, humidification, warming and cleaning of the air, and last but not least it supports the sense of smell as an alarm function but also to find the ideal mate.

The nasal cavity is optimized for all these tasks and only surgical hybris can lead to the assumption that one could easily ameliorate its structure. It is this "plummer's mentality" that has transformed human beings with slightly obstructed noses into "nasal wrecks" suffering from the empty nose syndrome.

For a long time, otorhinolaryngologists have tried to measure nasal flow under conditions of obstruction, in order to surgically remove what deemed to be the obstacle to normal nasal breathing. But even in cases where the pre-/post-comparison of nasal flow, measured under defined conditions demonstrated significant improvements, patients were sometimes unhappy with the outcome. Septoplasty and turbinectomy are typical interventions with a high rate of "non-responders" to therapy, at least on the long run. The difference between objective nasal patency and the subjective feeling of obstruction has been very well described in excellent reviews (Baraniuk 2011). One of the reasons for this discrepancy may be that we measure nasal flow in our tests at pressures that are by far higher (150 Pa or 200 Pa) than those produced in a

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normal breathing cycle under resting conditions. However, the test equipment we use these days (and have been using over the last 20 years) does not allow for reliable, reproducible measurements at pressures as low as those occurring in real life. Therefore, especially in cases of obstructed anatomy, other methods may be more adequate to calculate nasal flow and the exchange of warmth and humidity at the borderline, the superficial tissue which is the mucous membrane lining the wall of the nasal cavity.

Physics has developed a tool for this task. It is called computational fluid dynamics (CFD), a mature technology used widely in engineering to solve and analyze problems that involve fluid flows (Leong et al. 2010). The mathematical predictions of CFD can also be applied to the nasal airflow. For numerical simulation of the nasal airflow, patients have to undergo computed tomography (CT) or magnetic resonance imaging (MRI) scans of the head (Bailie et al. 2006).

Many of the first flow simulation studies focused on nasal airflow biophysics (Ishikawa et al. 2006; Tan et al. 2012; Wen et al. 2008). CFD has already been used for the flow analysis of pathological cases (Chen et al. 2009, 2010, 2011; Garcia et al. 2010; Guo et al. 2009; Lee et al. 2009, 2010; Liu et al. 2012; Sun et al. 2008; Zhu et al. 2012) and has been proposed as a tool to predict actual surgical outcomes using virtual nasal surgery models (Bockholt et al. 2000; Iwasaki et al. 2012; Ozlugedik et al. 2008; Wexler et al. 2005; Xiong et al. 2008). A new field of application, for which CFD has been successfully used, is the three-dimensional visualization of the distribution and the consecutive effects of intranasally applied medications such as nasal steroids or decongestive nasal sprays (Chen et al. 2012; Frank et al. 2013; Garlapati et al. 2009).

It is the objective of this review, on the one hand, to present a summary of current applications of CFD in rhinology (demonstration of physiologic and pathophysiologic flow distributions in the nose, preoperative planning, and postsurgical assessment of rhinosurgery outcomes); on the other hand, we want to demonstrate that CFD is a powerful tool for the three-dimensional presentation of drug action on the nasal mucous membranes.

19.1 Current Applications of Computational Fluid Dynamics

19.1.1 Demonstration of Physiologic and Pathologic Flow Distributions in the Nose

An adequate example for the three-dimensional visualization of physiologic flow in the nasal cavity is found in the paper published by Ishikawa and colleagues in 2006. They investigated the differences between nasal inspiration and expiration on the basis of computed tomography. They found that during inspiration nasal flow in the middle meatus was considerably more pronounced and turbulent than during expiration (Ishikawa et al. 2006). Tan and coworkers observed a similar flow pattern in their clinical trial. During inspiration, turbulence occurred primarily in the anterior part and in the floor of the nasal cavity. In contrast, no turbulence occurred during expiration. They measured the maximum nasal flow around the plane of the palatine velum during both inspiratory and expiratory phases (Tan et al. 2012). Wen and colleagues also investigated the physiologic flow in the nose. They were able to demonstrate that the high velocities in the constrictive nasal valve area region and the high flow appeared close to the septum walls (Wen et al. 2008).

Moreover, pathophysiologic aberrations in the nasal cavity like septal deviations (Chen et al. 2009; Garcia et al. 2010; Liu et al. 2012; Sun et al. 2008), turbinate hypertrophy (Chen et al. 2010; Guo et al. 2009; Lee et al. 2009), nasal bone fracture (Chen et al. 2011), septal perforation (Lee et al. 2010), deviation of the external nose (Zhu et al. 2012), and their consequences can be visualized by means of CFD technology.

Sun and colleagues compared, for example, patients with nasal septum deviations with others without anatomical irregularities. They came to the conclusion that flow simulation allows to visualize the differences in nasal flow origination from abnormal anatomy (Sun et al. 2008). The Chinese scientist Liu demonstrated the influence of different forms of septum deviation on nasal flow characteristics (Liu et al. 2012). His compatriot Guo

proved that unilateral infraturbinal hypertrophy also changed the normal anatomy and influenced the aerodynamics of the nasal cavity. According to his work, these changes have a substantial effect on the important functions of the nose like humidification, warming of the inhaled air, and the sense of smell (Guo et al. 2009).

Bailie and coworkers validated in a clinical trial in five patients that flow simulations based upon computed tomography can help to analyze the function of the lower and middle turbinate regarding warm up and cool down of inhaled air. Moreover, this flow model may explain that shear stress created by the flow around the turbinates in Kiesselbach's area may induce nasal bleeding (Bailie et al. 2009). This clinical trial supported findings published by Pless and colleagues in 2004. They came to the conclusion that both the lower and the middle turbinates are primarily responsible for heat recovery during expiration and that areas of the highest decrease in temperature are characterized by turbulent airflow (Pless et al. 2004). Sommer and his working group attributed utmost importance to the middle turbinate for climatization and humidification of inhaled air (Sommer et al. 2012).

Ishikawa and colleagues gave primary attention to olfaction in their publication. In their three-dimensional flow model, they were able to demonstrate that inspiratory airflow is widely distributed in the olfactory region than exhaled air. In contrast, sniffing flow had the widest distribution in the olfactory region, although no increase in nasal flow was noticed in the flow model. They drew the conclusion that recirculation flow strongly promotes olfactory function in the nose (Ishikawa et al. 2009).

19.1.2 Preoperative Planning and Postsurgical Outcome Assessment in Rhinosurgery

Another stronghold of CFD is the field of preoperative planning and postsurgical outcome assessment in rhinosurgery. As early as 2000, Bockholt and colleagues investigated the potential benefit of nasal flow simulations in the field of rhinosurgery. They came to the conclusion that by setting up a three-dimensional model of the nasal cavity based upon CT slices, planning of a surgical intervention may be optimized and the outcome may be improved for the patient (Bockholt et al. 2000). In their clinical trial, Xiong and colleagues assessed the use of CFD for preoperative planning and postsurgical outcome control. By visualization of nasal airflow before and after a virtual endoscopic intervention, they could simulate patients' outcome (Xiong et al. 2008).

Other research groups confirmed the applicability of CFD to visualize the postsurgical outcome of various rhinosurgical interventions such as rapid maxillary expansion (Iwasaki et al. 2012), surgery of a hypertrophic turbinate [19], septoplasty, and partial lateral turbinectomy (Ozlugedik et al. 2008).

Another application of CFD technology is the clinical picture of sleep apnea syndrome. Sung and Xu conducted flow simulations in 2006 that resulted in a better understanding of the pathophysiology of obstructive sleep apnea syndrome in adults as well as in children (Sung et al. 2006; Xu et al. 2006). Bimaxillary surgery with maxillomandibular advancement to widen the post-glossal space is one standardized procedure in the treatment of obstructive sleep apnea syndrome (Prinsell 2002). In a clinical trial in two patients with sleep apnea syndrome conducted by Yu and coworkers, nasal airflow before and after surgical intervention (maxillomandibular advancement) was calculated on the basis of computed tomography slices. CFD demonstrated a postoperative widening of the upper airways with balanced volume flows and pressure patterns. The postsurgical clinical picture of the patient (reduced inspirative energy and better ventilation) confirmed the prognostic value of CFD (Yu et al. 2009).

19.1.3 Recently Developed Applications of Computational Fluid Dynamics

A new application of CFD is the visualization of drug effects on the nasal mucosa in three-dimensional flow simulations. Garlapati and his

working group investigated in their clinical trial the effects of the application of nasal sprays on the mucosa. Based upon magnetic resonance imaging, they could demonstrate that intranasal application of medication is most effective when the patient actively inspires during the application. Surprisingly the posture of the head had no significant influence on the distribution of the inhaled aerosol (Garlapati et al. 2009). Frank and colleagues complemented this observation with the finding that the posture of the head only influences the distribution of the nasal sprays in the case of absent or minimal inspiratory airflow (Frank et al. 2013). Chen and colleagues also investigated the effects of nasal sprays using CFD technology. With the nasal flow model of their patient, they could show that the distribution of nasally applied drugs with a particle diameter of 10 µm was significantly improved after functional endoscopic sinus surgery (FESS), resulting in a moderate nasal flow (Chen et al. 2012). Frank and coworkers agree to this observation saying that surgical correction of nasal anatomic deformities (e.g., nasal septum deviation) could improve drug delivery on the nasal mucosa (Frank et al. 2013).

The application of CFD technology is not only limited to the visualization of drug effects in healthy (Garlapati et al. 2009) subjects or patients that underwent surgery (Chen et al. 2012; Frank et al. 2013). It can also be used to study changes of the mucous membranes in patients treated for symptoms of allergic rhinitis. In two clinical trials, we have studied the anti-obstructive effects of antiallergic medications on the swelling status in a patient suffering from seasonal allergic rhinitis. This example is used to describe the methodology applied in CFD.

19.2 Methodology

19.2.1 Imaging and Grid Generation

19.2.1.1 Using Computed Tomography

The computational grid is generated based on a surface definition by a computer tomographic scan of the human nasal cavity which results in about 300 cuts 1 mm apart or less, a resolution of 512×512 pixels or higher per cut, and 2 bytes per pixel for the density resolution.

To allow a better interface detection, blurring must be reduced by sharpening the image, by applying a 3×3×3 convolution matrix filter, which emphasizes the voxel differences depending on the 3×3×3 neighborhood around the center voxel. This supports the manual segmentation of the nasal cavity by an experienced ENT specialist, who examines each slice of the three-dimensional image and identifies the region of interest (ROI) with a digital pen tablet. The image is then further preprocessed. A seeded region growing algorithm (Adams and Bischof 1994) is used to identify the previously detected ROI by placing seed points inside the fluid volume of the nasal cavity and recursively descending in the neighborhood of them. The identification is based on a lower and an upper threshold depending on the assignment method of the ENT specialist. Based on this segmentation, the Marching Cubes algorithm (Lorensen and Cline 1987) is used to extract the surface of the nasal cavity yielding a three-dimensional triangle representation. This algorithm is based on intensity detection along voxel edges and defines vertices along these lines by a bilinear interpolation between the intensities at the corners of the voxels. A set of triangles is defined for such a vertex configuration, which is looked up in a configuration table, containing 256 possible combinations. In a post-processing step, the surface is smoothed using a windowed sinc function (Taubin et al. 1996), removing high-frequency noise in Fourier space by applying a transfer function. In a final step, the surface is split into multiple parts. The nostrils and the throat are separated from the rest of the nasal cavity and are smoothed with a Laplace filter until convergence. This filter performs a relaxation of the mesh and iteratively moves all vertices into one plane. This step allows the proper application of the boundary conditions in the flow simulation. Based on this model, an automatic Cartesian grid generator creates the computational mesh. A minimal bounding cube is initially placed around the surface. This cube is then continuously split

into eight smaller cubes until a user-defined level of refinement is reached. During the splitting process, cells outside the fluid domain are removed.

Using a marching cube algorithm for triangulation of the scanning data, an unstructured surface with 200,000 nodes and 420,000 triangles can be obtained. For an exact match of the experimental flow conditions, pipes for in- and outflow are added. Via the grid generation tool, a structured grid of 450,000 nodes in 34 blocks (Fig. 19.2) is generated which has a nested O-topology and additional blocks underneath the turbinates. To ensure a divergence-free solution, the blocks match at their interfaces.

19.2.1.2 Using MRI

T2-weighted MRI is used to visualize detailed internal structures and restricted body functions. It provides a three-dimensional image of the nasal cavity, the sinuses, and the pharynx and allows the assessment of the nasal mucosa membrane swelling. To perform a fluid mechanical analysis of the flow in the human nasal cavity, the surface of the region of interest, i.e., the volume of the nasal cavity, is extracted from MRI data and processed in multiple steps (Eitel et al. 2010). Since MRI measures the fluid characteristics of different tissues, the distinction between bone and air is generally difficult because they contain no or only a small amount of fluid and give a similar MRI signal, i.e., these areas appear black.

To extract a suitable model of the nasal cavity from MRI data, the first step is segmentation. This is performed manually by an experienced radiologist on a graphic tablet. During the next step, the segmented volume is converted into a triangular mesh surface by a Marching Cubes algorithm. The surface then is smoothed and used for generating a volumetric grid again. This can be done by dividing a large starting cube containing the entire surface into eight smaller ones with the same size each. The small cubes now lying outside of the surface are omitted, while the cubes inside are further divided. The procedure finishes with a so-called Cartesian lattice of approximately 4.1 million cells. For more complex calculations including analysis of humidification, the lattice may have 25 million cells or more.

To simulate nasal airflow, the Navier-Stokes equations, which describe the motion of fluid substances, must be solved for every cell. Therefore, several boundary conditions are required. The applied "no-slip" condition defines the velocity at the walls of the nasal cavity as zero. At the nostrils, a constant inflow is set, which causes a stationary flow field to develop after a sufficient number of simulated time steps. Therefore, the assumption of a quasi-steady flow is needed. The local velocity and pressure is obtained for every cell of the simulated lattice. Since the inflow is set as a fixed input for all four flow simulations, the total flow is identical. The computational fluid dynamics model used implements a Lattice-Boltzmann method. It was validated experimentally by an artificial nose model.

19.2.2 Method of Solution

To simulate the flow field, the three-dimensional Navier-Stokes equations are solved. An explicit five-step Runge-Kutta method of second-order accuracy is used for time integration. The following boundary conditions are imposed. A no-slip isothermal wall condition is assumed and the pressure gradient normal to the wall is set to zero. At the inflow section, a parabolic velocity profile is prescribed with the mean velocity determined from an assumed isentropic expansion from a stagnation state to the local static pressure that is computed from the interior pressure distribution using a vanishing pressure gradient in the streamwise direction. At the outflow plane, the static pressure level is prescribed and a nonreflecting boundary condition of Poinsot and Lele is applied (Wheeler and Corey 2008).

The simulation was carried out using a Lattice-Boltzmann method and was performed on grids containing about $20 \times 10^{*}6$ cells. As for the imposed boundary conditions, a no-slip wall condition proposed by Bouzidi et al. (2001) was used. A volume flux of 125 ml/s was prescribed at the inflow boundaries with a von Neumann condition for the velocity. The density was extrapolated in surface normal direction by applying a Dirichlet condition. The outflow boundary condition was

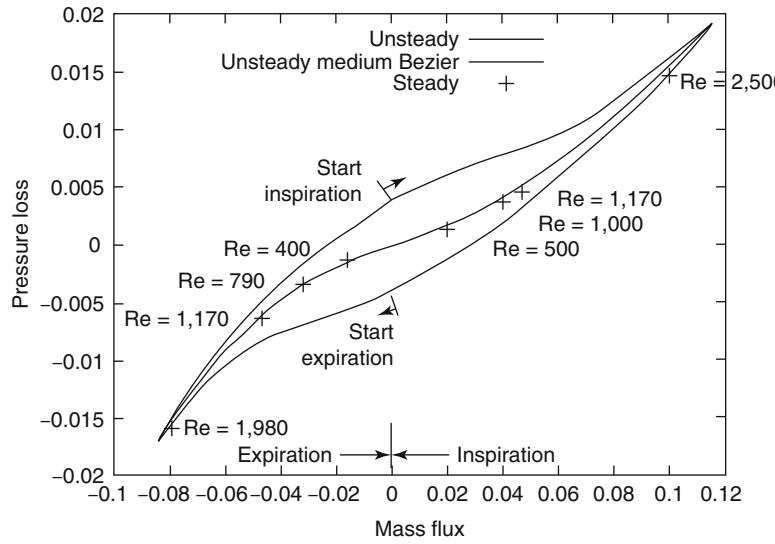

Fig. 19.1 Pressure loss over mass flux; Reynolds numbers indicating turbulent conditions

based on the formulation by Finck et al. (2007) and imposed a constant pressure and extrapolated the velocities. The Reynolds number based on the mean hydraulic diameter of the nostrils and a volume flux of 125 ml/s was calculated for all nasal cavity geometries to guarantee an equal volume flux in all cases (Fig. 19.1).

19.2.3 Virtual Reality-Based Visualization of Flow Simulation Results

Visualization is a fundamental ingredient for gaining insights into the simulation results.

In particular, visualization is indispensable to the understanding of complex, dynamic processes observed in computational fluid dynamics, whose scientific and technical analysis requires a multidimensional representation of flow in space and time. In comparison to 2-D or perspective representations, virtual reality-based visualization, i.e., stereoscopic and user-centered projection techniques, allow a much more intuitive comprehension of spatiotemporal correlations. In contrast to animation techniques, virtual reality is inherently interactive and thus allows an interactive exploration of simulation data.

In the context of the project, we are employing different visualization techniques tailored to the needs of the potential users. For the validation of the numerical simulation, we implemented standard visualization techniques like cut planes, isosurfaces, streamlines, and stream ribbons, all primarily based on the visualization toolkit. For the physicians, tailored visualization techniques are still to be determined and to be studied. The added dimensions in the visualization lead to the necessity of a user interface that enables the user to concentrate on the exploration and evaluation of the simulation data via dedicated navigation techniques, speech recognition, and advanced interaction methods for applying the visualization methods. The feedback of users shows that the multimodal user interface supports the visual validation process of the numerical simulation in such a way that the simulation results can be explored in an intuitive manner.

19.3 Application

19.3.1 Nasal Cavity 3D-Imaging-Based Modeling: An Assessment Tool for the Anti-obstructive Potency of Antiallergic Compounds

It was the objective of this study to visualize the anti-obstructive effect of intranasal steroid sprays (INS) in a patient with allergic rhinitis by

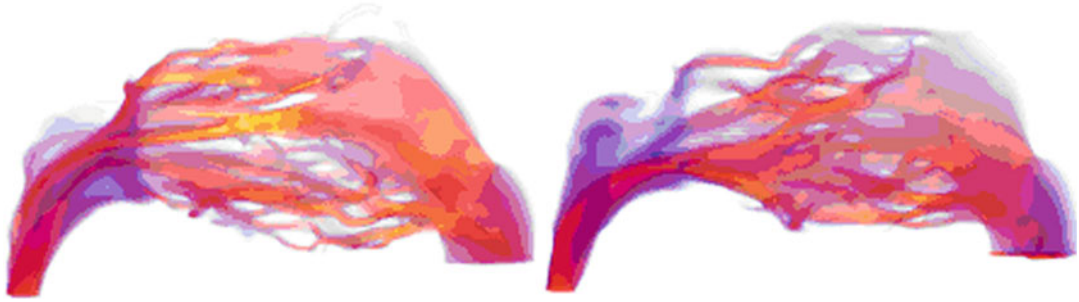

Fig. 19.2 Nasal airflow at baseline before (*left*) and after (*right*) allergen challenge

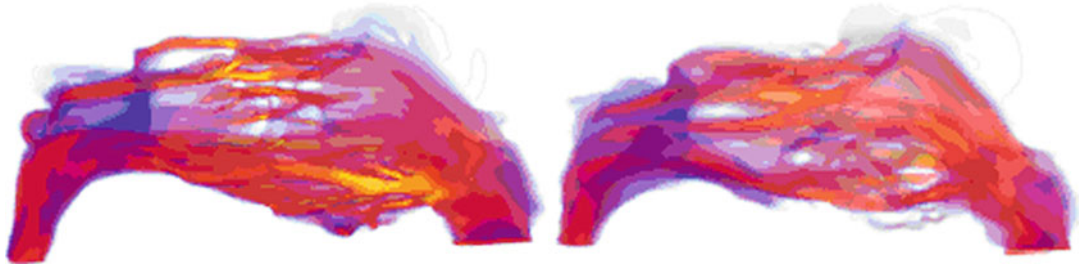

Fig. 19.3 Nasal airflow after 2 weeks of treatment with an intranasal steroid before (*left*) and after (*right*) allergen challenge

simulating the nasal airflow with computational fluid dynamics. The patient underwent magnetic resonance imaging (MRI). After nasal allergen challenge, all measurements were repeated 30 min later. During the following 2 weeks, the test subject applied the INS. Then again MRI was performed before and 30 min after allergen challenge.

Figure 19.2 compares the nasal flow before and after allergen challenge at baseline. Before allergen exposure, a pattern of widespread flow distribution over the entire nasal cavity can be noticed (left). After exposure to the allergen, flow to the more cranial parts of the nasal cavity becomes sparse (right).

Figure 19.3 shows the flow patterns in the nasal cavity calculated from the MRI-based model after 14 days of (prophylactic) treatment with an intranasal steroid. Again, the distribution of airflow at baseline is widespread over the entire nasal cavity. Velocity of airflow is somewhat reduced after allergen challenge, however, by far not as pronounced as before treatment. We therefore conclude that this demonstrates the anti-obstructive effect of the intranasal steroid.

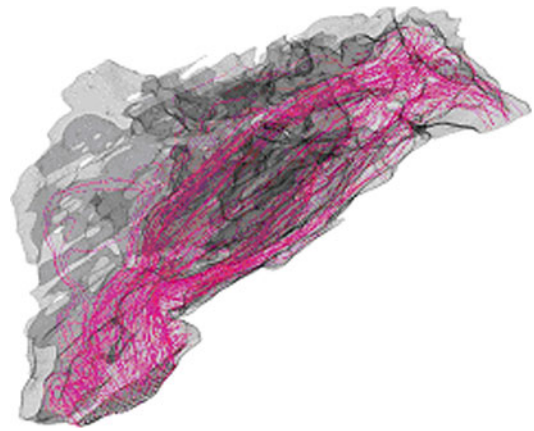

Fig. 19.4 Nasal airflow at baseline after allergen challenge

Similar improvements could be demonstrated for the treatment with an anti-obstructive antihistamine comparing the flow pattern at baseline (Fig. 19.4) with the flow pattern after 5 weeks of treatment (Fig. 19.5).

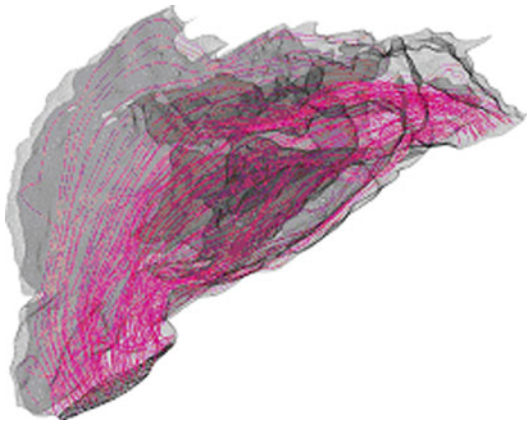

Fig. 19.5 Nasal airflow after 5 weeks of antihistamine treatment after allergen challenge

Conclusion

Leong and colleagues have pointed out the potential benefits of CFD technology applied to rhinology in their systematic review saying that "this technology has improved understanding of the complex nasal anatomy and the implications of disease and surgery on physiology" (Leong et al. 2010). We can only partially support this viewpoint. Nasal flow simulation primarily has served to demonstrate physiologic and pathological flow patterns in the nasal cavity. It has been used in individual cases for preoperative planning and for the assessment of outcomes in rhinosurgery. The origins of this method date back to the 1980s. Research has been ongoing in this field for more than 20 years without establishing the method in regular care. This is due to the fact that standards are still lacking and consensus on the interpretation of the findings and on reliable outcome parameters has not been reached. CFD technology can be a valuable but extremely complex and by consequence costly research tool for sophisticated problems like drug distribution in the nasal cavity or the visualization of drug effects on the nasal mucosa. There is however hope that these limitations will be overcome in future with further improvements in imaging and software technology.

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Physiology and Pathophysiology of Nasal Breathing

20

Gunter H. Mlynski

Keywords
Respiratory function • Nasal airflow • Nasal functional architecture • Nasal resistance • Flow behavior • Turbulence regulation • Nasal cycle • Rhinosurgery

Core Messages

- Normal respiratory function in the nose requires low physiological nasal airflow resistance and adequate contact between the air and a large mucosal surface in a narrow flow channel.
- Narrowing of the nasal airways and/or severe turbulence can cause a pathological rise in nasal resistance.
- Since resistance to flow rises exponentially with increasing stenosis, even slight narrowing in the area of the isthmus can lead to severe nasal obstruction. This fact is often overlooked.
- In terms of respiratory function, the nasal flow channel can be divided into an inflow area, a functional area, and an outflow area.
- In the inspiratory flow direction, the inflow area consists of the vestibulum, the isthmus, and the anterior cavum. After passing over the head of the inferior turbinate and the septum in the anterior cavum, the airstream is directed to the turbinate region and distributed over its entire cross-sectional surface and the degree of turbulence is regulated.
- In the functional area, the nasal turbinates not only represent a large surface, but through their adaptation in shape and size, they also create a uniform slit space between the septum and the lateral wall of the cavum, which promotes warming, humidification, and cleansing of the inspired air.
- The inspiratory outflow area consists of the nasopharyngeal meatus, the choanae, and the nasopharynx. Here the airflow becomes increasingly laminar and is redirected in the direction of the deeper air passages.
- A large thermal energy and humidity gradient is required between the mucosa

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and the airstream for effective warming and humidification of the air in the nose. These conditions are assured by the nasal cycle.
- The division of the nose into two sides by the septum makes it possible to alternate between working and resting phases to improve gradients of thermal energy and humidity.
- The nasal septum is rarely straight within the generally asymmetrical human skull. By means of a "physiological deviation" of the septum and adaptation of the configuration of the turbinates, a symmetrical slit space results on each side of the nose. Cyclical congestion of the turbinates makes it possible to have adequate working and resting phases.
- Adopting a more physiologically sophisticated perspective in functional rhinosurgery leads to the result that:
  - Physiological septal deviations would not be straightened.
  - Pathological septal deviations would not be fully straightened, but instead transformed into physiological deviations, thereby preserving the turbinates to the greatest possible extent.

20.1 Preliminary Remarks

The respiratory function of the nose is to warm, humidify, and clean the inspired air, since proper gas exchange in the lungs critically depends upon clean air at a temperature of 37° C with a relative humidity of 100 %. Every day the nose warms, moistens, and cleans 12,000–25,000 l of air (and during physical exertion, even more). This requires a complex anatomical architecture. For exchanging thermal energy, humidity, and decontamination, the flowing particles must make contact with a large mucosal surface. To meet this requirement, the surface area of the nasal mucosa is greatly expanded by the turbinates, thereby providing a mucosal surface of between 100 and 200 cm^2. The airstream has to be distributed over this entire contact surface. To enable the most efficient contact between the flowing air particles and the nasal mucosa (Mlynski et al. 2001), the following conditions must be met:

- *Nasal airway resistance* must be physiologically low, since in the presence of pathologically elevated nasal resistance, the nose partially or completely switches over to bypass mouth breathing (Leiter and Baker 1989; Fujimoto et al. 2009).
- The *correlation of the structure and respiratory function of the nose* is of particular significance:
  - The nasal airstream must be distributed over the entire mucosal surface in the nasal cavum.
  - Contact time between the air and the mucosa must be as long as possible.
  - For the necessary exchange of moisture and energy through convection and radiation, it is advantageous to have the narrowest possible flow channel (slit space), since this configuration facilitates these biophysical processes.

  These requirements are met by the structural architecture of the nose.
- *Formation and regulation of turbulence* in the nasal airflow are important preconditions for the proper respiratory function of the nose (Mlynski et al. 2001; Lang et al. 2003). Under conditions of laminar flow, only the particles in the airstream close to the wall will come in contact with the mucosa. This requires lateral movement, generated by portions of turbulent flow.
- The *nasal cycle* (see Chap. 21), with its alternating and often reciprocal congestion of the turbinates (Kayser 1895; Eccles 1996; Hanif et al. 2001; Lang et al. 2003), should be seen in relation to the respiratory function of the nose. The effectiveness of heat transfer through convection and radiation from the mucosa to the air and the transfer of moisture increases in proportion to the gradients between the mucosa and the air. With constant air perfusion, these temperature and humidity gradients would decrease over time. The nasal cycle, alternating periodic changes in the

congestion of the erectile tissues in the turbinates and the septum, creates working phases with large gradients and thus efficient respiratory function and resting phases, during which the decreased gradient is elevated once again. In this way, the nasal cycle is an extremely important foundation for proper respiratory function of the nose (Eccles 2000; Lang et al. 2003; Beule 2010).

In what follows, we will present these four prerequisites for the proper respiratory function of the nose in greater detail. It is important to recall that these requirements should not be viewed in isolation; instead, it is only when they operate in concert that a function as extraordinary and complex as that of the nose can be accomplished. Even the absence of a single prerequisite can significantly impair overall function. Given the background of the high incidence of unsatisfactory long-term physiological outcomes from septoplasty (Mlynski 2005), this implies that surgical improvement of nasal airway resistance must not occur at the expense of other prerequisites for proper respiratory function. The nose cannot be viewed simply as an airway. The respiratory function of the nose depends upon highly complex biophysical processes (Keck and Lindemann 2010), which can be significantly affected, often for the worse, by rhinosurgical interventions (Stoksted 1969; Dommerby et al. 1985; Haraldsson et al. 1987; Grymer and Rosborg 1987; Fjermedal et al. 1988; Illum 1997; Dinis and Haider 2002; Mlynski 2006; Wiesmiller et al. 2006; Kastl et al. 2009; Scheithauer 2010). Insights from nasal physiology and pathophysiology must be more broadly incorporated into rhinosurgical practice (Mlynski 2005).

20.2 Nasal Airway Resistance

Airway resistance is the resistance to flow that arises from friction-related energy loss by the streaming particles as they hit against each other and the wall of the nasal air channel. The loss of pressure in the flow channel ΔP is a measure of energy loss (Fig. 20.1). Energy loss increases with increasing flow velocity.

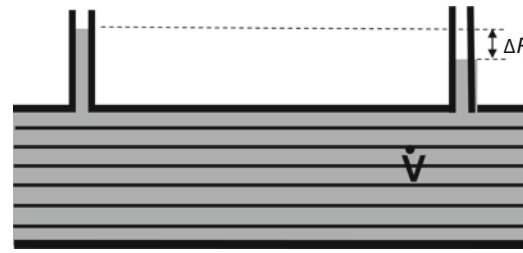

Fig. 20.1 Flow paths in a tube with laminar flow (ΔP = friction-related pressure loss, $\dot{V}$ = flow velocity)

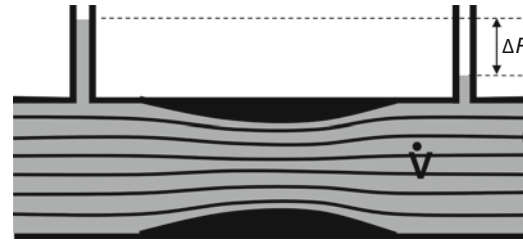

Fig. 20.2 Flow paths in a tube with a constriction with laminar flow (ΔP = friction-related pressure loss, $\dot{V}$ = flow velocity)

At points of narrowing in the flow channel, crowding of the flow paths results in increased energy loss and thus increased resistance to flow (Fig. 20.2).

The relation of resistance to the cross section of a narrowed area is not linear, but exponential. This means that narrowing in a wide channel (corresponding to the middle of the cavum) results in a smaller increase in resistance than narrowing in a tight channel (corresponding to the internal nasal valve) (Fig. 20.3).

This helps to explain why even minor constrictions located in the ostium internum (nasal valve) have such a pronounced effect on nasal airway resistance, whereas in the center of the nasal cavity, septal deviations have hardly any impact on airway resistance (Masing 1967; Hess et al. 1992; Dinis and Haider 2002). This means:

- That if there is concurrent narrowing in the internal nasal valve area and in the middle nasal cavum, it is almost always the valvular constriction that is critical for nasal obstruction.
- That in the presence of a deviation in the middle cavum, one must always search in addition for valvular constriction. These valvular

constrictions often turn out to be the actual cause of the elevated resistance (Dishoeck 1942; Cole et al. 1988; Bachmann 1989; Mlynski et al. 2001), but they can easily be overlooked; as a result, "physiological septal deviations" (Zuckerkandl 1882; Gogniashvili et al. 2011) are subjected to surgical correction in the cavum (see Sect. 20.3.2).

Turbulence also leads to increased airway resistance, since the flowing particles hit up against each other and against the wall through lateral movements, and this leads in the same way to energy loss (Fig. 20.4).

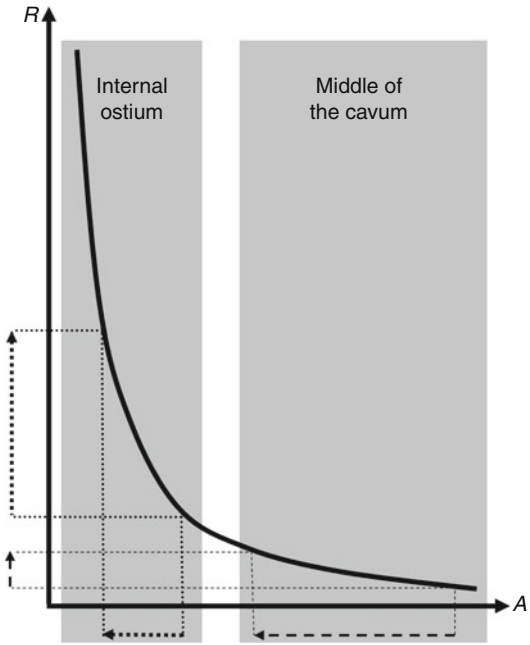

Fig. 20.3 Changes in nasal airway resistance (R) depending upon the cross-sectional area (A) in the area of the internal ostium and the middle of the nasal cavum

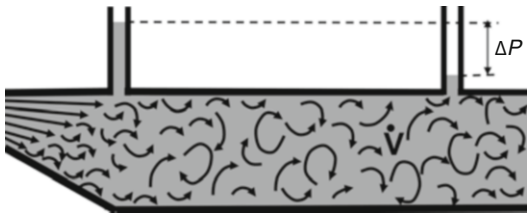

Fig. 20.4 Flow paths in a flow channel with turbulent flow (ΔP = friction-related pressure loss, $\dot{V}$ = flow velocity)

During turbulent flow, the increased resistance does not depend solely on the flow velocity but also on the friction coefficient λ. The friction coefficient, which is a dimensionless number, describes the aerodynamic characteristics of the internal surface of a structure through which air passes. This is comparable to the c_w–value, characterizing the external surface of a structure, where the air circulates around (e.g., for automobiles or airplanes).

20.3 Correlation of the Structure and Respiratory Function of the Nose

From a functional and fluid dynamic perspective, the nose is a very complicated structure. Researchers have been attempting to investigate the nasal flow channel for more than 100 years (Paulsen 1882; Kayser 1889; Rethi 1900; Burchardt 1905; Mink 1920; Takahashi 1922; Hellmann 1926; Dishoek 1936; Scheideler 1938; Tonndorf 1939; Masing 1967; Fischer 1969; Bachmann 1982a, b; Naito et al. 1989; Hess et al. 1992; Mlynski and Loew 1992a, b; Simmen et al. 1999; Mlynski 2000a, b; Mlynski et al. 2001; Gruetzenmacher et al. 2005, 2006).

For simplifying our understanding of its function, it is helpful to divide the nose into a few different sections. These sections can then be compared with mechanical form elements, whose impact on flow is known from fluid physics (Table 20.1).

Table 20.1 Fluid dynamic effects of structural form elements that may be compared to anatomical structures in the nose

Form element	Effect on flow dynamics
Bend	Altering the direction of flow
Nozzle	Decreasing turbulence, accelerating flow
Diffuser	Creating turbulence, decelerating flow
Concave opening	Divergence of flow paths
Slit space	Favors exchange of heat, humidity, and cleansing between the mucosa and the particle stream

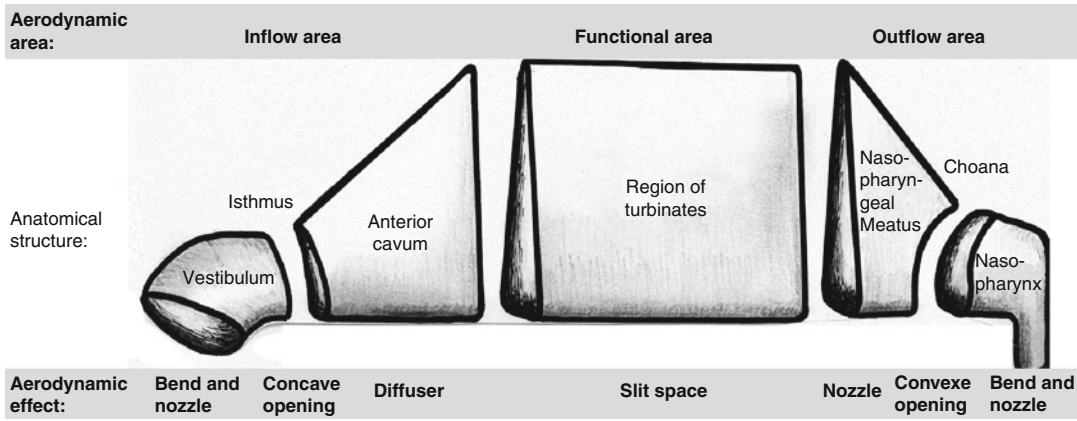

Fig. 20.5 Schematic representation of dividing the nose into regions and comparative form elements in the inspiratory flow direction

The schema presented in Fig. 20.5 goes back to Bachmann (1982a, b) and was then enhanced after we conducted extensive flow-experimental studies (Mlynski 2000a, b; Mlynski et al. 2001). The functional area is the principal location of the nasal turbinates. Here, the air is warmed, moistened, and cleansed. In the inspiratory direction, the inflow area is made up of the nasal vestibulum, the nasal isthmus, and the anterior cavum, with the head of the inferior turbinate and the erectile tissue of the septum. The nasopharyngeal meatus, the choanae, and the epipharynx constitute the outflow area.

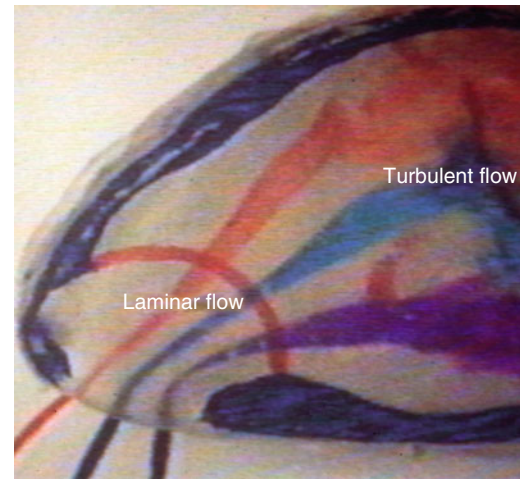

Fig. 20.6 Flow-experimental presentation of inspiratory flow in the inflow area The flow is directed towards the turbinate region (bend effect) and turbulent flow portions become laminar (nozzle effect). Laminar flow can be recognized from the sharp demarcation between the flowing medium and the colored particles provided for better visualization. With increasing turbulence, a diffuse coloration develops as a result of lateral movements of the flowing particles

20.3.1 Inflow Area

The *inflow area* consists of the nasal vestibulum, the nasal isthmus ("internal valve"), and the anterior cavum. The function of the inflow area is to configure the airstream so as to facilitate sufficient contact with the mucosa in the functional area. Figure 20.6 illustrates the course and character of flow in the inspiratory airflow direction in the inflow area of a nasal model (Mlynski et al. 2001).

20.3.1.1 Vestibulum Nasi

The *vestibulum nasi* is shaped like a short bent tube and thereby is equivalent to a *bend*. The curvature is created by the relative position of the external and internal nasal openings: the ostium externum (inflow opening of the bend) is more horizontal, and the ostium internum (outflow opening of the bend) is more vertical. The fluid dynamic effect of this bend redirects the inspiratory airstream from anterior and inferior towards the area of the turbinates (Fig. 20.6).

In this process, the relative position of the vestibulum to the cavum is of significance. In a drooping nose with a small nasolabial angle, the vestibulum is rotated with the alar cartilage pointed downwards. During inspiration, this leads to a very high flow course in the cavum (Fig. 20.7b). As a result, the mucosa in the inferior turbinate cannot contribute to the respiratory function. If the nasolabial angle is too large, the vestibulum and the alar cartilage are rotated upwards. As a consequence, the airstream runs very low through the cavum, and thus, the mucosa of the superior turbinate is no longer capable of contributing to respiratory function (Fig. 20.7c).

When the vestibulum is malpositioned, it is not possible to make use of the entire nasal flow channel, and this functional constriction, similar to an anatomical constriction, results in increased airway resistance.

In cases presenting with an abnormal nasolabial angle, the rhinosurgical challenge is to reconstruct the normal position of the alar cartilage. This means that the cephalic portions of the alar cartilage must be positioned on the caudal edge of the lateral cartilage. Therefore, correction of an inadequate or excessive nasolabial angle is necessary not only for aesthetic reasons but also from a functional point of view. Excessive elevation of the tip of the nose motivated by aesthetic considerations should be avoided.

Since the ostium externum is larger than the internal valve area, the vestibulum also has a nozzle effect in the inspiratory direction. In a nozzle, progressive constriction of cross-sectional area serves to reduce turbulent flow areas. As a consequence, the flow character of inspired air in the next and physiologically narrowest area of the nose, the nasal isthmus, is predominantly laminar (Fig. 20.6). This is of importance, since turbulent flow in this narrowing would result in very high levels of resistance to flow.

The nozzle effect of the nasal vestibulum must be preserved in rhinosurgical procedures. This means that one must not overexpand the isthmus in an effort to reduce resistance. The ostium internum must remain proportionately smaller than the ostium externum. Excessive expansion leads to a ballooning phenomenon that creates highly turbulent flow in the cavum as a result of the elimination of the nozzle effect in the vestibulum.

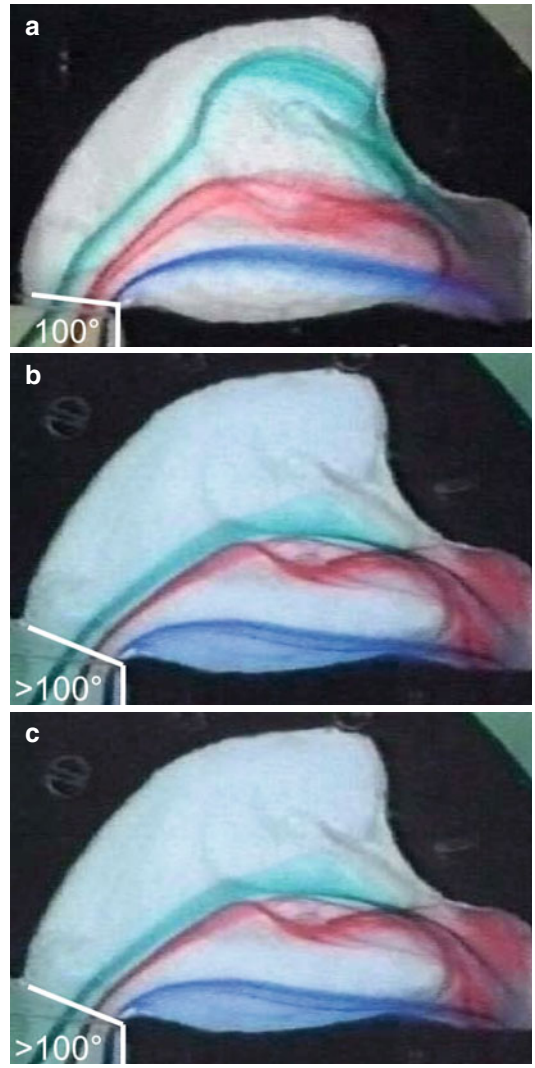

Fig. 20.7 Course of inspiratory flow in nasal models with various positions of the vestibulum to the cavum (**a**) Normal position: air is distributed over the entire region of turbinates (**b**) Vestibulum rotated downwards in the presence of a drooping nose with a pathologically diminished nasolabial angle: air flow runs only through the upper region of the nasal cavum (**c**) Vestibulum rotated upwards in the presence of a nose with a tip rotated excessively upwards: airflow runs only through the lower part of the nasal cavum

The function of the vestibulum as a nozzle also results in an acceleration of the local flow velocity, which may cause portions of the mobile

lateral vestibular wall to be sucked in, as a consequence of the Bernoulli effect. Typically, this suction phenomenon (also referred to as "nasal valve collapse") only begins to occur with forced breathing (flow >500 ml/s). When suction occurs in this situation, the effect is known as "physiological nasal valve collapse," which can be understood as protecting the mucosa against excessive nasal air perfusion. By contrast, "pathological nasal valve collapse" begins to arise at low flow velocities and in extreme cases even at rest. Thus, it leads to symptoms of nasal obstruction.

Most cases of pathological nasal valve collapse result from constrictions of the vestibulum and the ostium internum. This is because negative pressure in a flow channel depends upon the velocity of flow, which depends in turn upon the width of the channel: the narrower the channel, the greater the local flow velocity. The rhinosurgical implication in these cases is the physiological need to expand the area of constriction.

20.3.1.2 Isthmus Nasi

The *isthmus nasi* is the narrowest region along the nasal flow channel and thus the site with the highest resistance to airflow (Dishoeck 1942; Masing 1967; Fischer 1969). The effects of a constriction on flow and the relationship between cross-sectional area and resistance were presented in Sect. 20.2.

In the inspiratory flow direction, *concave curvature of the internal nasal ostium*, which serves as the aperture for air passing from the vestibulum to the cavum, can also affect the dynamics of flow. An aperture with a concave curvature has the same impact on flow paths as a concave lens does on light rays: it creates divergence of the flow paths, thereby making a contribution to distributing flow over the entire surface area of the turbinate region (Mlynski 2000b; Mlynski et al. 2001) (Figs. 20.6 and 20.8).

In view of these functional considerations, resections of the caudal edge of the lateral cartilage must be performed in such a way as to preserve the concave shape of the nasal ostium internum.

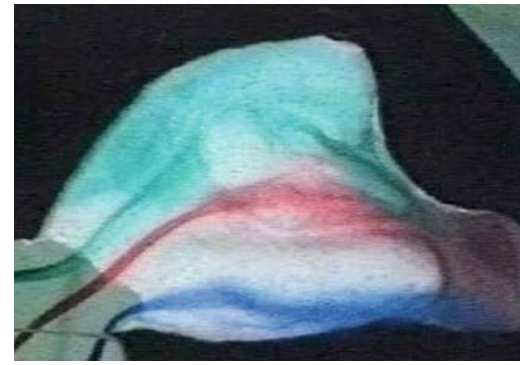

Fig. 20.8 Flow-experimental presentation of inspiratory airflow in a nose model without a vestibulum. The concave curved surface of the internal nasal orifice causes divergence of the flow paths in the cavum

20.3.1.3 Anterior Nasal Cavum

In the inspiratory direction, due to the expansion in cross-sectional area distal to the ostium internum, the *anterior nasal cavum* shows the fluid dynamic characteristics of a *diffuser*. This is the location of the principal structures for regulating turbulence, the head of the inferior turbinate, and the erectile tissues of the septum, the intumescentia septi. Depending on the expansion in cross-sectional area and the flow velocity, a diffuser generates portions of turbulent flow (Mlynski et al. 2001). The operating principle of the nasal diffuser in relation to respiratory function is presented in Sect. 20.4.

The second positive effect of the expansion in cross-sectional area in the anterior cavum is deceleration of flow. The slow velocity of airflow in the turbinate region results in a prolongation of contact time with the mucosa, thus favoring the exchange of heat and moisture.

20.3.2 Functional Area

The *functional area* in the nose is the turbinate area. In this region, the nasal cavity is constricted into a narrow space by the turbinates. As a result, the nasal cavity is actually not a cavity at all, but a slit space. This slit space is necessary for the proper respiratory function of the nose (see Sect. 20.3.2). Analysis of CT images through the

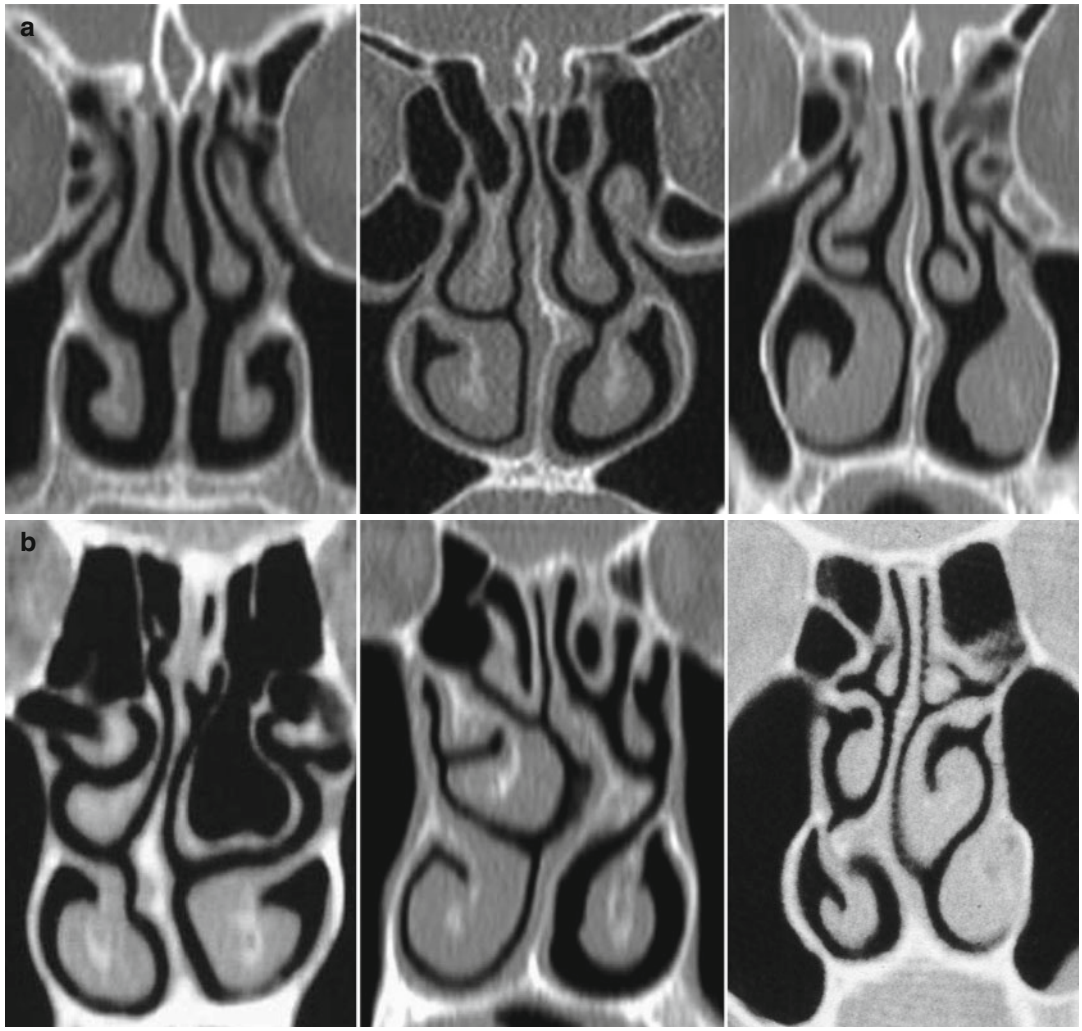

Fig. 20.9 Coronal CT images through the functional area of different noses. The turbinates adapt to the space provided by the lateral wall of the cavum and the septum in the case of slight asymmetry of the cavum and physiological septal deviation (**a**), and even in the case of marked asymmetry with pathological septal deformities (**b**), so that whenever possible, a continuous slit space is maintained

nose (Fig. 20.9 shows a few examples) reveals that the width of the slit remains quite constant across the entire cross section of the cavum, even though it is extremely rare for the septum to be straight. The lateral walls of the cavum are always asymmetrical. The septum divides the nose into two unequally wide but fully separate structural cavities. The turbinates adjust themselves in shape and size to the space determined by the lateral wall of the cavum and the septum, resulting in the creation of a continuous, uniform slit space.

Even the septum makes a contribution to the creation of a constant slit space through its shape and variable thickness (Fig. 20.10).

By the end of the nineteenth century, Zuckerkandl (1882) discovered using his large collection of skulls that in the ubiquitously asymmetrical human skull, the septum is not usually straight, but instead displays "physiological deviations." The common observation on the part of ENT specialists that not every septal deviation causes nasal obstruction

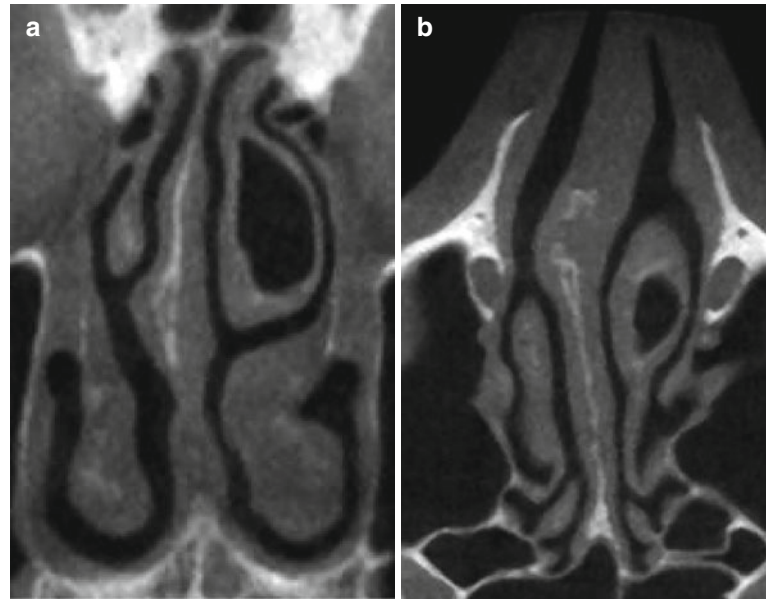

Fig. 20.10 (**a**) coronal and (**b**) axial CT images through the nose As a result of the interplay between the shape and size of the nasal turbinates and the width of the septum with its erectile tissues, the asymmetrical nasal cavity is narrowed down to form a possibly uniform slit space

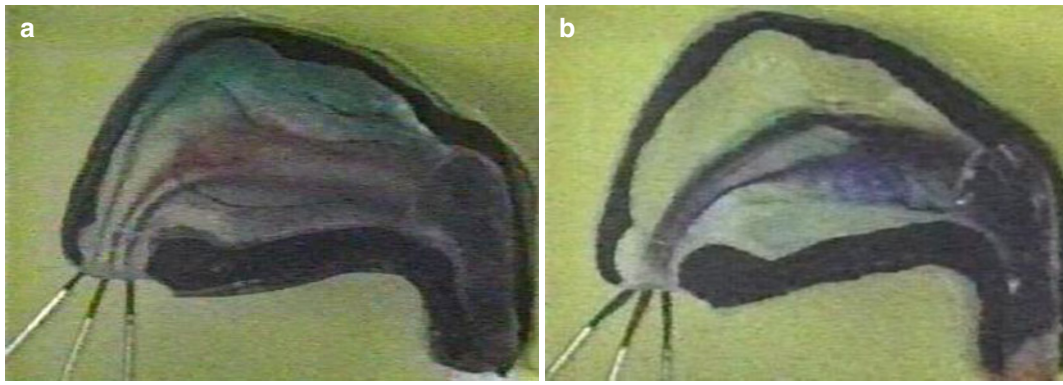

Fig. 20.11 Flow-experimental presentation of the inspiratory airflow in nose models (**a**) before and (**b**) after significant reduction in the size of the middle turbinate. Flow is distributed in (**a**) across the entire turbinate region, but in (**b**) it is limited almost exclusively to the wide space in the center of the nasal cavity. As a result, the inferior and superior turbinates are unable to contribute to respiratory function

(Altissimi et al. 1992; Hanif et al. 2003) attests to the validity of physiological deviation. In fact, the literature suggests up to 90 % incidence of septal deviation in a normal population (Sooknundun et al. 1986; Podoshin et al. 1991; Uygur et al. 2002; Gola et al. 2002; Gogniashvili et al. 2011).

We define physiological deviation of the septum as a bend in the nasal septum in the absence of significant narrowing of the slit space, that means without elevation of nasal airway resistance.

A uniform width of the slit space enables distribution of the airflow across the entire cross-sectional surface. Since airflow follows the path of least resistance, local enlargement, as seen after extensive surgical reduction of the size of the turbinates, leads to significant disruption in the course of the airflow. In this situation, the air flows almost exclusively through the enlarged space (Fig. 20.11), so that large areas of the mucosa can no longer contribute to respiratory function because they are inadequately aerated (Mlynski et al. 2001).

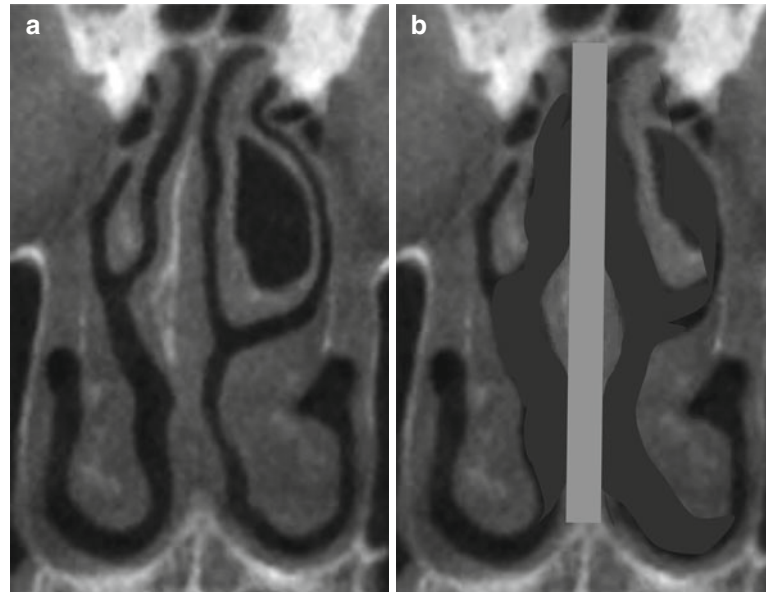

Fig. 20.12 (**a**) Coronal CT image through a nose with physiological septal deviation (**b**) Same CT image with imitated straightening of the septum and reduction of the turbinates on the opposite (concave) side of the deviation

These insights have two important implications for rhinosurgery:

- It is necessary to rigorously preserve the slit space at the most uniform possible width or, if necessary, to reconstruct the slit space in cases of atrophic rhinitis or "empty nose syndrome."
- In the case of the compensatory enlargement of the turbinates associated with septal deviation, the procedure should be very conservative and, if possible, not involve any resection. This procedure should be followed in most cases of deviation occurring after puberty, since they almost always involve compensatory swelling rather than true hyperplasia. The turbinates will regress in size following septal correction (Kim et al. 2008). In cases of septal deviation occurring before puberty, lateroposition of the os turbinale is frequently an adequate treatment.
- Physiological septal deviations need to be identified as such and should not be corrected. Figures 20.12 and 20.13 show that inadequate surgery in these cases would lead to unphysiological, excessively wide spaces inside the nose.

The goal of surgical procedures to relieve nasal obstruction resulting from septal deviation should not be a completely straight septum and small turbinates to create the widest possible nose as a flow channel. The frequent occurrence of sicca symptoms after functional rhinosurgery (Stoksted 1969; Dommerby et al. 1985; Haraldsson et al. 1987; Grymer and Rosborg 1987; Fjermedal et al. 1988; Illum 1997; Dinis 2002; Mlynski 2006) should provide the impetus for more careful attention to physiological aspects during surgical procedures. From this point of view, the maintenance or restingoration of the nasal slit space is critical.

20.3.3 Outflow Area

The *outflow area* of the nose configures the inspiratory airstream in such a way as is required for passage into the lower airways.

20.3.3.1 Nasopharyngeal Meatus

In the *nasopharyngeal meatus,* the cross-sectional surfaces become smaller in the inspiratory direction. From the perspective of fluid dynamics, this structure has the effect of a nozzle, which diminishes turbulent portions of flow. In the subsequent deeper inspiratory airways, the flow is laminar in nature.

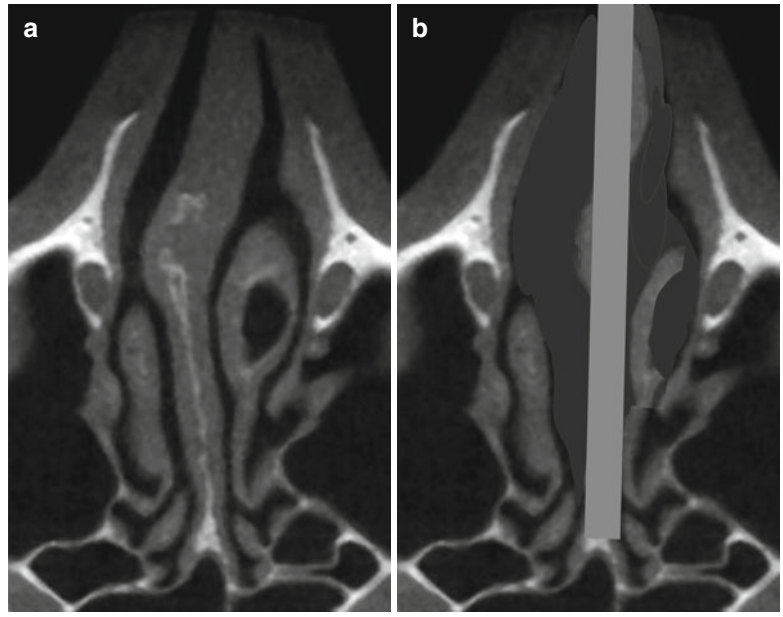

Fig. 20.13 (**a**) Axial CT image through the same nose as shown in Figure 20.12 with physiological septal deviation (**b**) Same CT image with imitated straightening of the septum and reduction of the turbinates on the opposite (concave) side of the deviation.

20.3.3.2 Choana

In the inspiratory direction, the *choana* is a convex-shaped opening between the cavum and the nasopharynx. This is where the flow paths converge. The airstream thus becomes narrower and adapts to the dimensions of the lower airways.

20.3.3.3 Nasopharynx

As a bend, the *nasopharynx* leads to a change of direction of about 90°. The air is redirected towards the lower airways.

20.4 The Formation and Regulation of Turbulence in the Nose

If the cross-sectional area of a flow channel expands, this generates sideways movement of the streaming particles and decreases laminar flow parallel to the walls of the channel. The greater the expansion in cross-sectional area, the greater the resulting degree of turbulence, that is, the ratio of sideways to forward movements of the streaming air particles. The cross-sectional expansion of a diffuser can be characterized in terms of its opening angle φ (Fig. 20.14).

The anterior cavum has the form and function of a diffuser (Mlynski 2000a, b; Mlynski et al. 2001). The ostium internum as the physiological narrowing marks the beginning of the nasal diffuser. The widest cross section in the nose is located in front of the head of the middle turbinate and thus marks the end of the nasal diffuser.

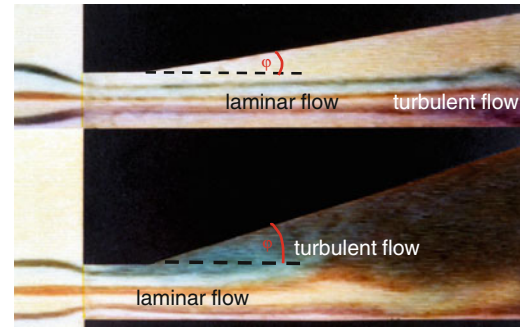

Fig. 20.14 Development of turbulence in a diffuser Turbulent portions of flow, which can be recognized by a diffuse coloration of the stream as a result of sideways movements, only begin to form at the end of a diffuser that has a small increase in cross-sectional area (*upper image*: small opening angle **φ**). With a greater increase in cross-sectional area (*lower image*: larger opening angle **φ**), turbulent portions of flow already begin to develop at the beginning of the diffuser

As presented in Fig. 20.15, the nasal diffuser is capable of regulating the extent of expansion in its cross-sectional area, and thus the degree of turbulence of the nasal airstream, by means of

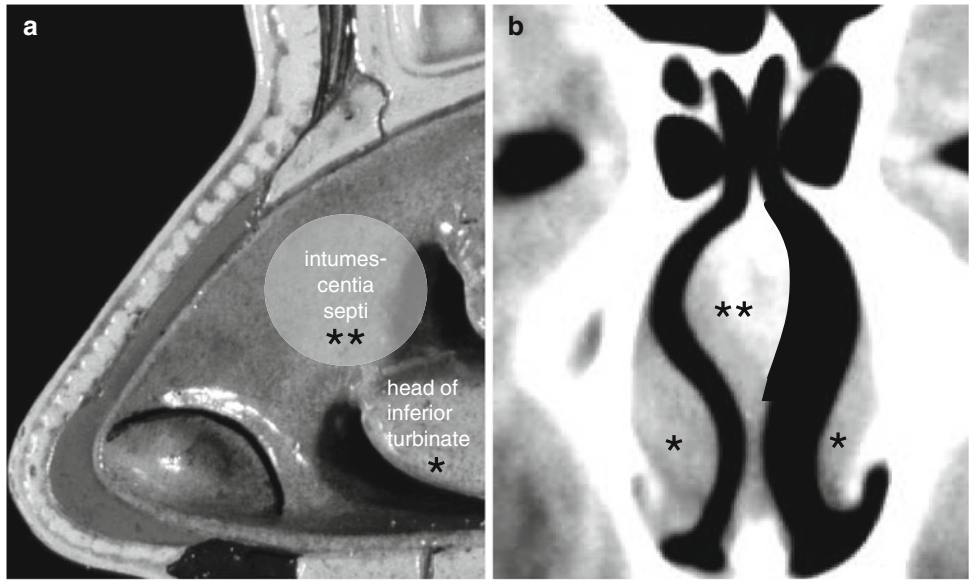

Fig. 20.15 Regulation of turbulence in the nasal diffuser by congestion and decongestion of the inferior turbinate (*) and the septal erectile tissues (**) (**a**) Anterior cavum with its structures for turbulence regulation: the head of the inferior turbinate and the intumescentia septi (**b**) Changes in the cross-sectional area and thus in the degree of turbulence by congestion (*right nose* in the CT image) and decongestion (*left nose* in the CT image)

varying degrees of congestion in the head of the inferior turbinate and the erectile tissues of the septum (intumescentia septi) (Mlynski et al. 2001; Lang et al. 2003).

Besides a large opening angle, a narrow inflow opening of a diffuser can also lead to greater turbulence.

Turbulence does not merely serve to improve contact of air with the nasal mucosa. Turbulent flow also leads to dehydration of the mucosa and increased resistance to flow (Fujimoto et al. 2009; Wiesmiller et al. 2006). Turbulence is responsible for a much smaller increase in resistance than is caused by areas of narrowing. In most cases, the sense of nasal "stuffiness" reported by patients does not arise from elevated resistance to airflow but instead is a subjective sensation resulting from turbulence and dryness in the nose.

20.5 The Nasal Cycle

The nasal cycle is presented in detail in the chapter "Nasal Cycle." At this point, only a brief presentation from the perspective of physiology and pathophysiology is included.

The nasal cycle is of vital necessity for warming and humidifying the inhaled air we breathe (Lang et al. 2003; Kim et al. 2006). The mucosa of the turbinates and portions of the septum are equipped with specific kinds of venous plexuses. By means of these erectile bodies, the autonomic nervous system initiates a cyclical and in normal cases reciprocal alternation in the state of congestion of the nasal mucosa on the two sides of the nose (Kayser 1889; Eccles 1996; Hanif et al. 2001; Lang et al. 2003). This change in mucosal congestion creates a reciprocal alternation in airflow resistance and turbulence behavior (Kayser 1895; Gilbert and Rosenwasser 1987; Eccles 1996; Hanif et al. 2001; Lang et al. 2003; Churchill et al. 2004; Kim et al. 2006; Chen et al. 2009, 2010; Beule 2010). The central neural regulation of this process appears to be located in the hypothalamus. During the working phase, airflow resistance is low. A high degree of turbulence favors mucosal contact by the streaming particles (Fig. 20.16a). In the resting phase, the nose is scarcely perfused with air because of the high level of airway resistance and airflow is predominantly laminar (Fig. 20.16b). In this way,

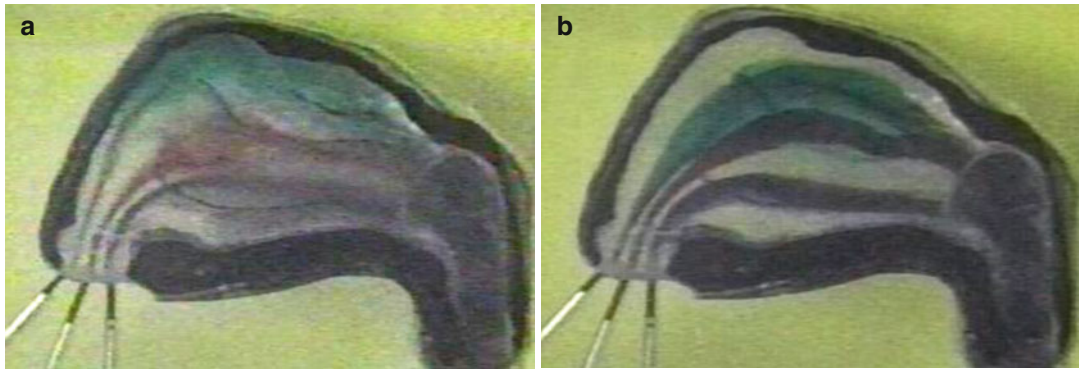

Fig. 20.16 As a consequence of turbulence regulation in the anterior cavum, the inspiratory airflow in the functional area of the nose is predominantly laminar during the resting phase (**a**) and predominantly turbulent during the working phase (**b**)

the mucosa can store up heat energy and humidity in preparation for the next working phase.

Various reports have suggested that incidence of the nasal cycle is between 20 and 80 % (Eccles 1996; Hanif et al. 2001; Mirza et al. 1997). The variability in these reports may well be explainable by different observation periods in different studies. Since the introduction of long-term rhinoflowmetry (Gruetzenmacher et al. 2005), we have learned that phases of the nasal cycle may last up to 14 h. An observational period shorter than 14 h is thus unsuited for drawing any inferences about the occurrence of the nasal cycle. Our own investigations suggest that with the exception of severely pathological noses, the nasal cycle occurs in all human beings (unpublished data).

Sufficient phases are important to supply the body with adequate amounts of oxygen. During the working phase, the airway resistance on the decongested side of the nose must be low enough to provide an adequate oxygen supply for the organism without bypass mouth breathing, even during moderate physical exertion (Lind 1984; Sawyer et al. 2007).

In a resting phase, it is equally important that it is possible to close off one side of the nose through congestion of the turbinates, so as to allow the mucosa to store thermal energy and moisture for the next working phase. When the slit space is excessively enlarged on one side of the nose as a result of surgery, that side can no longer be adequately narrowed through congestion of the turbinates and is compelled to remain in a continuous working phase. In noses that have been excessively widened by surgery, the absence of resting phases and the presence of pathological turbulence lead to dehydration of the mucosa.

The division of the nose into two sides by the nasal septum and the nasal cycle are connected. Without such a division, it would not be possible to alternate between working and resting phases and thus maintain high thermal and humidity gradients between the mucosa and the air. The division of the nose only works properly if the position of the septum and the size and shape of the turbinates with their erectile bodies create a wide enough slit space during the working phase and the narrowest possible slit space during the resting phase. This does not require a straight septum, but the septum needs to be centrally situated between the turbinates of the asymmetrical nasal cavities.

Conclusions

In recent years, our understanding of the relationship between efficient respiratory function and the very complex structure of the nose has grown substantially. What is less satisfying is the lack of transfer of this knowledge into rhinosurgical practice. This is a basic reason for the nonsatisfying long-term results after functional rhinosurgeries. Therefore, in the following, the physiological and pathophysiological principles will be summarized and conclusions will be drawn for rhinosurgical practices in relieving nasal obstruction. For reasons of

completeness, we will include some points that are self-evident:

- An increased respiratory resistance results in mouth-bypass breathing. This causes the partial or total elimination of the nasal respiratory function. A pathologically increased nasal resistance therefore needs to be reduced on to a physiological level.
- During surgical removal of a nasal obstruction, correction of the septum and the turbinates is of essential importance. Before doing septoplasty, it needs to be determined if the existing deviation is causing the nasal obstruction or if it is a physiological deviation. In this case, the actual reason causing the patients complaints (e.g., narrowing of isthmus) needs to be identified.
- Surgical approaching requires rethinking:
  - The goal of septum correction is not necessarily a straight septum, but rather a septum that fits well in the center between the lateral nasal walls.
  - The slit space in both nasal sides must be wide enough to provide adequate room for a sufficient air flow during the working phase of the nasal cycle and be closed to the greatest possible extent during resting phase.
  - In cases where there is compensatory enlargement of the turbinates, one has to abandon the purely reflexive idea that every septoplasty must be combined with reduction of the turbinates. With their cyclical changes in congestion, the turbinates are very important elements in the proper respiratory function of the nose. Therefore, they should be preserved to the greatest extent possible. Prior to undertaking any operative procedures, it is important to differentiate between swelling and hyperplasia by comparing the situation before and after decongestion and to modify the surgical treatment accordingly.
  - Resective procedures are rarely indicated for the treatment of swelling in the turbinates, which is often compensatory. As described in Sect. 20.3.2, the turbinates have the capacity to regress in their degree of congestion and to adapt their shape to fit the available space.
  - In rare cases of hyperplasia, a reluctant turbinoplasty is indicated, which often can be limited to the anterior area in the form of an "anterior turbinoplasty."
  - For septal deviations occurring before puberty, one often observes that the turbinate bone has grown far towards the medial side in the cavity of the deviation. In these cases, lateroposition of the inferior turbinate is indicated in order to create a symmetrical slit space.
- Reconstruction of the inflow area requires particular attention when treating deformities in the external nose. If necessary, it is essential that:
  - The position of the alar cartilages relative to the lateral cartilage be rotated so as to create a normal nasolabial angle and correct the vestibular bend effect.
  - The height of the septum in the cartilaginous area of nose be corrected in order to correct the configuration of the valve area and repair an excessively broad (saddle) nose or an excessively small valve angle (tension nose). This will also normalize the nozzle effect of the nasal vestibulum.
  - In treating deformities of the diffuser related to deviated noses, the pyramid must be symmetrically reconstructed. Broad noses must be narrowed, and narrow noses broadened.
  - In the anterior cavum, when reconstructing the diffuser, one must pay particular attention to create a centrally positioned septum. If possible, the head of the inferior turbinate should not be touched and only reduced if absolutely necessary and then by means of a reluctant anterior turbinoplasty.

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Function of the Turbinates: Nasal Cycle

21

Rainer K. Weber and Jochen A. Werner

Keywords
Nasal cycle • Inferior turbinate • Nasal airway resistance • Nasal physiology • Turbinate surgery

Core Messages

- Spontaneous changes in nasal airway resistance in the two separate nasal passages due to congestion and decongestion of nasal venous sinuses are called nasal cycle. One respiratory function of the nose is to sufficiently condition the respirated air which goes along with the nasal cycle.
- It is important to consider the nasal cycle and other physiologic changes in the congestion of the nasal mucosa when making a clinical assessment of a patient complaining of nasal obstruction. The indication for surgery should be based on clinical history, on examination by anterior rhinoscopy and nasal endoscopy, and by considering these physiologic variations in addition to measurements of nasal airway patency. Long-term rhinoflowmetry offers a new possibility for investigating nasal patency for up to 72 h.

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21.1 Definition of Nasal Cycle

The respiratory function of the nose is to sufficiently condition the respirated air which is maintained by supplying the mucosa with thermal energy and fluid for humidification. This is supplied by the blood circulation and in coherence with the nasal cycle (Grützenmacher et al. 2005). The erectile tissue enables the turbinates to cyclically congest and decongest. One side of

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the nose is in its working phase conditioning the air, with an unimpeded air passage and increased turbulence. At the same time, the contralateral side is in its resting phase, saving energy and moisture by high airway resistance and low turbulence (Lang et al. 2003).

The airflow through the nose is regulated by the activity of the erectile venous tissue of the nasal mucosa (Eccles 1982). The nasal epithelium has a very complex vascular nature with a submucosal plexus of venous sinuses lining the nasal mucosa. These venous sinuses from erectile tissue are well developed in the anterior part of the nasal septum and the inferior turbinate (Hanif et al. 2000). These submucosal cushions of the venous sinuses expand and shrink depending on the degree of congestion, hence altering the calibre of the nasal passages and influencing the nasal airflow.

An enlargement of this tissue leads to a reduction of the nasal lumen and increases the flow resistance. The cyclic congestion and decongestion of the nasal mucosa is called nasal cycle (Eccles 1982) and is observed in about 80 % of the people (Hasegawa and Kern 1977; Heetderks 1927; Lenz et al. 1995; Masing and Wolf 1969). As the nasal cycle had already been described by Kayser in 1895, the description was later performed by rhinoscopy (Heetderks 1927; Kayser 1895), rhinomanometry (Hasegawa and Kern 1977; Battle 1989; Drettner 1961, 1967; Schlegel and Gammert 1991; Stoksted 1952, 1953; Stoksted and Nielsen 1957), acoustic rhinometry (Lang et al. 2003), rhinoresistometry (Lang et al. 2003), radiologic tomographic imaging (Masing and Wolf 1969), computed tomography (Cole et al. 1983b), or magnetic resonance imaging (Cole et al. 1989; Kennedy et al. 1988; Webber and Jeffcoat 1987; Zinreich et al. 1988).

Rhinomanometry reveals an opposite swelling behaviour of both nasal sides, while the total resistance of the two nasal sides, the nasal passage, and the respiratory work remain relatively constant (Hasegawa and Kern 1977; Drettner 1967; Stoksted 1952, 1953; Cole 1982; Cole et al. 1979).

Magnetic resonance imaging could show that even the ethmoid mucosa is involved in the nasal cycle, however, only to a lower degree (Kennedy et al. 1988). Also the tubal function changes with the nasal passage resistance in a homolaterally concordant way (Koch and Pau 1982).

By means of radiologic tomographic procedures, Masing could show that in cases of nasal obstruction or non-existing nasal breathing, the classic nasal cycle can no longer be observed but paradox or irregular turbinate movements occur, which confirms the observations made by Stoksted (Stoksted 1952, 1953; Stoksted and Nielsen 1957) and Keuning (1968). In the anterior and posterior parts of the nose, the changes were comparable so that the hydraulic diameter of the whole nose seemed to be equally maintained. In cases of significant septal deviation, no nasal cycle could be found. In only two of six cases, a unilateral turbinate movement was observed on the obstructed side. The nasal cycle stopped with the beginning of acute rhinitis (Masing and Wolf 1969).

Rhinoresistometry and acoustic rhinometry could reveal the changes of the nasal turbulence occurring in the context of the nasal cycle (Lang et al. 2003). During the resting phase, a laminar airflow was observed. During the working phase (decongested side), turbulences were also found with low speed. The increasing turbulence was caused by an increased cross-section surface of the anterior nasal area. Hereby, the turbinates and the mucosa of the nasal septum decongested.

Long-term rhinoflowmetry is a complementary tool in addition to established rhinological diagnostics. The nasal flow can be investigated up to 72 h. Therefore, it appears to be an ideal tool to measure the cyclic alterations of the nasal cycle (Grützenmacher et al. 2005).

Keerl et al. were the first to realise visualisation by means of nasal endoscopy and dynamic description with time-lapse video. In analogy to the clinical and rhinomanometric observations that the total resistance of both nasal sides is almost constant (Hasegawa and Kern 1977; Cole 1982), the congestive procedures on one side occur nearly parallel to the decongestive procedures of the contralateral side (Fig. 21.1a–e). Most of the time, continuous swelling patterns are found with congestion of one side and decongestion of the contralateral side. These swelling changes are relatively rapid with 15 min in our analysis for a cyclic duration of 5 h.

With the endoscopic description in memomotion, the extent of the congesting process could be evaluated precisely. The processes of congestion and decongestion occur relatively rapidly so that the turbinates remain most of the time in a kind of plateau phase of submaximal to maximal congestion or decongestion. The size of the turbinates varies between very small and very large

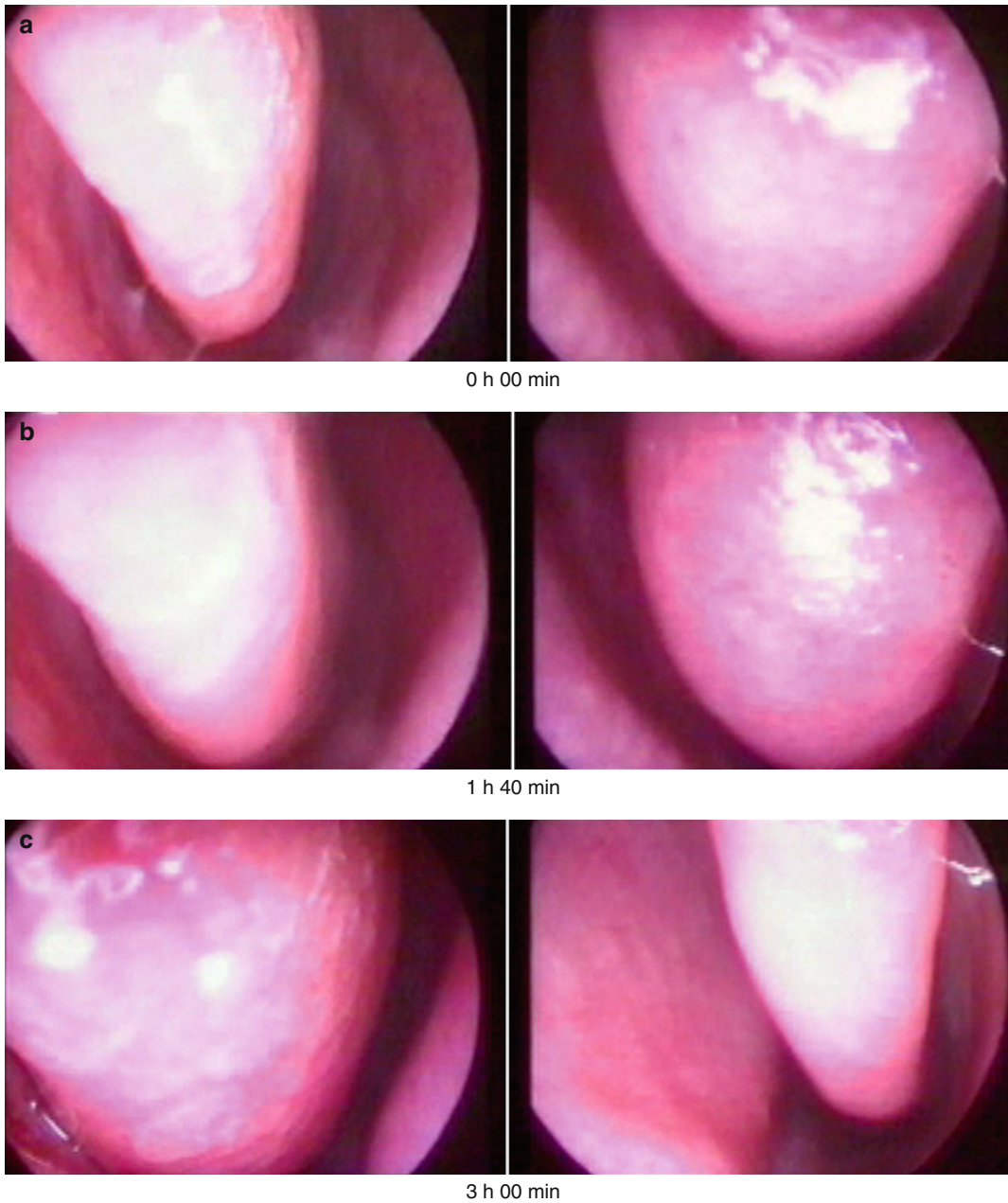

Fig. 21.1 (**a**–**e**) Swelling of inferior turbinate according to the nasal cycle in a healthy young man (parallel endoscopy using a 0° endoscope): (**a**) Decongested mucosa on the right and congested mucosa on the left side at the beginning (**b**) Change of swelling (**c**) Maximal congestion on the right and maximal decongested mucosa on the left side (**d**) Reciprocal change of swelling (**e**) Same situation at the end of the nasal cycle as at the beginning

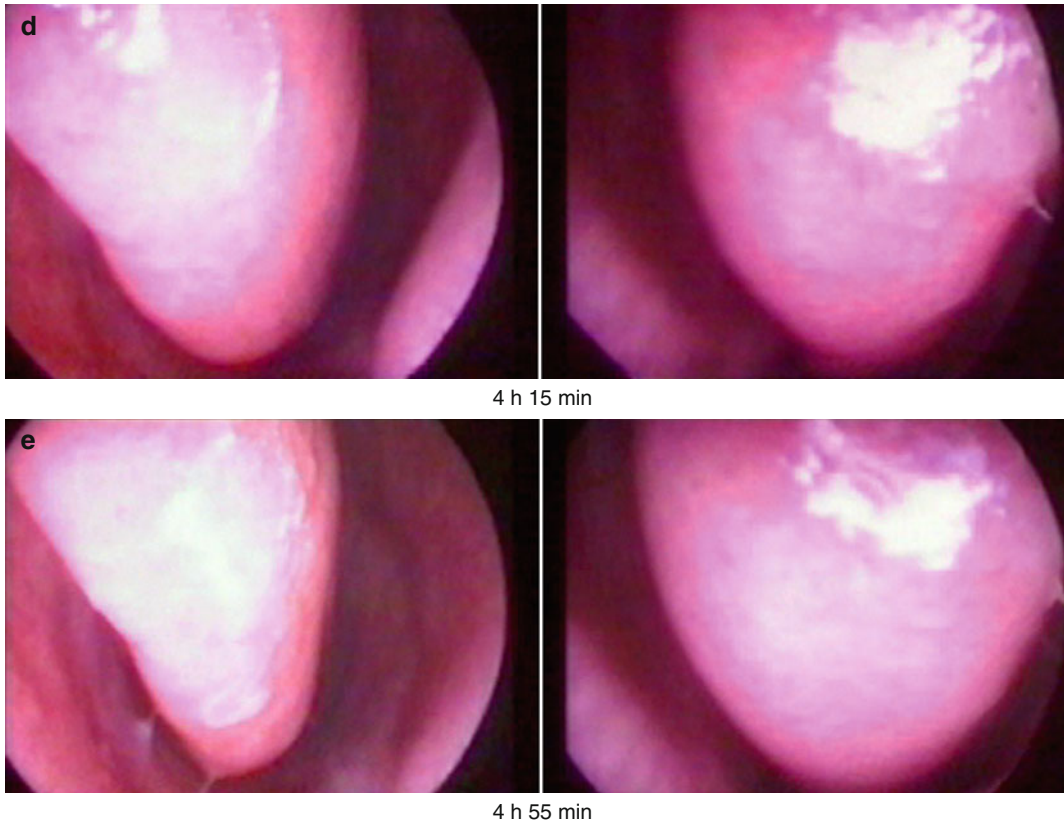

Fig. 21.1 (continued)

with complete obstruction of the nasal cavity in the visible area. During the course of the cycle, complete decongestion of both turbinates never occurred. For a short phase, a similar middle congestion status of both turbinates can be found.

The diagnosis of hyperplastic turbinates is often made in the clinical routine, but with the background of the mentioned results, it must be reconsidered. Hyperplasia means first the enlargement of tissue by cellular multiplication. During the nasal cycle, the healthy turbinate continuously changes from a low to a high degree of congestion. Internal and external factors additionally influence the extent of the swelling situation. As the physiology of a normal turbinate allows each size of minimal to maximal, there is no reference for the diagnosis of hyperplasia or hypertrophy or for definition of a standard normal size. Even if one side of the nose is completely obstructed because of the maximally congested inferior turbinate, the other free side allows a sufficient nasal air passage because it is decongested according to the physiologic nasal cycle. Only the bilateral massive swelling of the inferior turbinates seems to be unphysiologic (Keerl et al. 1995; Weber and Keerl 1996). It seems to be appropriate to use in the daily language exclusively the term of congested or enlarged turbinate and to use the term of hyperplasia only for enlarged turbinates with neoplastic changes of the surface (polypous, mulberry-like changes).

Besides the congesting and decongesting processes, regular changes of the secretory production could be observed endoscopically (Weber and Keerl 1996) as they had already been described by Melon (1968). The congesting turbinate seemed to become increasingly humid so that the maximally congested situation led to small droplets. This may be considered as the cause of

the parasympathic tonus prevailing on this side. During the decongesting phase, the mucosa dries more and more, partly with resulting small dry layers. In this context, the dehydrating effect of nasal breathing accompanies the sympathomimetic and reduced parasympathic tonus.

21.2 Types of Nasal Cycles

Three types of nasal cycles are described (Grützenmacher et al. 2005): the classical reciprocal type, the in-concert type (simultaneous reduction and increasing of the nasal passage on both sides), and the irregular type.

In addition, Kern describes three types of noncycle nose: there is no fluctuation of the nasal passage, the fluctuation is moderate only on one side, and the fluctuation does not change from one side to the other (Kern 1981).

The cyclic duration is very variable with an interval of about 1–6 h (Eccles 1982; Hasegawa and Kern 1977; Heetderks 1927; Keuning 1968; Keerl et al. 1995; Weber and Keerl 1996; Eccles 1978).

More recent quantitative studies using numerical parameters seem to show that true periodicity and reciprocity of nasal airflow exist only in 21–39 % of the population, reciprocity being the truly reciprocal changes in air flow between right and left passages and periodicity being the regularity of changes in airflow occurring with time in each nasal passage. Otherwise, these studies used measurement periods no longer than 8 h. So the time period of examination may be too short to discover the nasal cycle as was outlined by Grützenmacher.

Also in children, a nasal cycle can be revealed (Gallego et al. 2006; van Cauwenberge and Deleye 1984; van Cauwenberge 1980; van Cauwenberge et al. 1984). For children up to the age of 6, it amounts to a mean of 1 h and 20 min and is not influenced by physical activity. Even infections do not significantly influence the nasal cycle.

Even if the distribution of the nasal cycle types changes, a fluctuation of the nasal passage is found in laryngectomised patients (25 % classical type, 40 % irregular type, 35 % in-concert type) (Fisher et al. 1994).

According to Ingels et al. (1990), no correlation is found between the ciliary beating rate (CBR) of the nasal epithelia and the rhinomanometrically measured passage of the nasal cavity. The CBR of different cells in the same biopsies was clearly different.

In contrast to this, Doyle and van Cauwenberge (1987) could detect a higher mucociliary clearance rate with increased nasal passage by means of the saccharin test. Also Soane et al. (2001) found a significant acceleration of the mucociliary clearance on the free side in comparison to the obstructed nasal side with a factor of 2.5:1 using the radioisotope method.

21.3 Origin, Function, and Regulation of the Nasal Cycle

Finally, the origin and the function of the nasal cycle are unknown (Eccles 1982; Cole 1982; Maran and Lund 1990). According to Mlynski et al. (2000), the decongested side is in the working phase of the nose (Grützenmacher et al. 2005). The respirated air passes through the decongested nasal side; the air is conditioned, i.e. warmed up, moistured, and cleaned. The congested side is in its resting phase.

The regulation of the nasal cycle is probably performed by the central sympathomimetic tonus (Eccles 1978, 1982, 2000; Hanif et al. 2000). This tonus is controlled by two centres in the brain stem. They are connected with each other and dominate the tonus via the right and left cervical sympathomimetic nerval fibres finally asymmetrically and alternating over a period of several hours.

Changes of the nasal patency that are related to positional changes may be explained by two different mechanisms: an increased central venous pressure when changing from a standing to a lying position and a reflectory change of the nasal vasomotoric tonus when a lateral lying position is taken. The increase of the venous pressure causes an increased filling of the nasal venous sinusoids and an increase of the nasal resistance. The passive hydrostatic effect adds to each asymmetry in

the context of the nasal cycle. The side with the highest degree of congestion generally has the highest increase of swelling and is completely obstructed (Cole and Haight 1986). Lying down leads to a temporary disturbance of the nasal cycle with congestion of the mucosa and increased flow resistance. The amplitudes of the changes of the resistance in the nasal cycle are higher in supine and lateral position (Cole et al. 1979; Cole and Haight 1986, 1984; Haight and Cole 1984).

The reciprocal changes of the nasal patency when taking a lateral lying position are induced by the pressure in the area of the shoulder girdle, the lateral thorax, and the hip that are the most sensitive regions. During local anaesthesia in the area of the skin, surface of the axilla cannot suppress this reflectory reaction; this is possible by an intercostal neural blockade (Haight and Cole 1986). This leads to the effect that the upper side of the nose is mainly open for nasal passage. An explanation may be that this avoids closure of the inferior side of the nose when lying on the ground so that nasal breathing is still possible.

The diagnosis of nasal obstruction and the nasal patency has to bear in mind the physiologic nasal cycle as well as changes of the nasal respiratory resistance in dependence of the surrounding conditions (temperature, probably humidity, irritating substances) (Battle1989; Schlegel and Gammert 1991), the physical activity, body position (Rao and Potdar 1970; Hasegawa and Saito 1979; Rundcrantz 1969; Jackson 1970), or pharmacological influences (Baumann and Masing 1970).

Physical activity leads to a reduced nasal resistance (Eccles 2000; Cole et al. 1983a; Dallimore and Eccles 1977; Hasegawa and Kern 1978; Richerson and Seebohm 1968). According to some studies, the nasal resistance mostly increases with cold temperatures (Battle 1989; Salman et al. 1971; Takagi et al. 1969). Schlegel reports about a main decrease of the resistance with cold temperatures and an increase with warmth. The change of the humidity of 20 % to more than 90 % has no influence on the nasal patency (Salman et al. 1971).

The nasal cycle may influence the nasal allergy provocation test (Pirilä et al. 1997; Sipila et al. 1990; Gilbert and Rosenwasser 1987; Gungor et al. 1999). Gotlib et al. (2005) found that the determination of the bilateral reduction of the cross-section surface in the area of the inferior turbinates is more sensitive than the determination of the one of the more reactive side. However, the risk of a spontaneous unilateral total increase of the nasal resistance must be considered.

There is some evidence to suggest that the nasal cycle is associated with ultradian rhythms of the cerebral hemispheres which affects cognitive function of the brain (Shannahoff-Khalsa et al. 1991; Block et al. 1989). Alternating dominance of cerebral hemispheric activity can be demonstrated in humans by EEG, and relative changes in electro-cortical activity seem to have a direct correlation with the nasal cycle (Werntz et al. 1983). These studies found a greater EEG activity on the side contralateral to the decongested side of the nose; a significant improvement in spatial and verbal cognitive function performed by the contralateral (in females) and ipsilateral (in males) cerebral hemisphere occurred in unilateral forced nasal breathing (Shannahoff-Khalsa et al. 1991). This may explain why some patients with nasal obstruction find this more than just a simple annoyance. The nasal obstruction may have effects on the ability to work during daytime (Hanif et al. 2000).

Patients with upper respiratory tract infections become far more apparent with a significant increase in the amplitude of the changes than healthy people (Eccles et al. 1996).

Conclusion

The nasal cycle and other spontaneous variations in nasal airflow and the two separate nasal passages must be considered when making a clinical assessment for patients complaining of nasal obstruction. In addition to the clinical history, examination by anterior rhinoscopy and endoscopy of the nose, and classical measurements of the nasal airflow like rhinomanometry or acoustic rhinometry, the long-term rhinoflowmetry may be a helpful tool in assessing these patients.

Pearls

- Spontaneous changes in nasal airway resistance due to congestion and decongestion of nasal venous sinuses are called nasal cycle.
- Three types of nasal cycles are described with a duration of about 1–6 h.
- The regulation of the nasal cycle is probably performed by the central sympathomimetic tonus.
- Consider the nasal cycle and other physiologic changes in the congestion of the nasal mucosa when making a clinical assessment of a patient complaining of nasal obstruction.
- Long-term rhinoflowmetry offers a new possibility for investigating nasal patency for up to 72 h.

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The Nasal Valves

22

Oren Friedman

Keywords
Nasal obstruction • Nasal valve • Nasal valve collapse • Functional rhinoplasty

Core Messages

Nasal valve obstruction is a common complication following rhinoplasty:

- There is an internal nasal valve and an external nasal valve.
- Internal nasal valve is the area between the upper lateral cartilage, nasal septum, and inferior turbinate.
- External nasal valve is the area at the nasal vestibule, defined by the alar rim.
- Nasal valve collapse may occur at rest, as in the case of an inverted V deformity or tension nose deformity with associated middle third pinching.
- Nasal valve collapse may only occur as a result of the negative inspiratory forces associated with breathing air in through the nose which then collapses the nasal sidewalls.
- There are a number of medical devices which dilate the nose, or provide strength to the nose, and which provide nonsurgical relief of nasal airway obstruction associated with nasal valve collapse.
- There are a variety of surgical interventions that are available for the treatment of nasal valve obstruction, some of which are highlighted in this chapter.

22.1 Introduction

The primary function of the nose is to allow for proper airflow into the human body. We rely on the nose not only to permit adequate volumes of air to reach the lungs but also to humidify, warm, and filter the inspired air in order to optimize pulmonary gas exchange. The nose is also the organ of olfaction – when functional, it allows us to experience the joys of pleasurable scents and tastes and to beware potentially harmful environmental pathogens. Finally, being a central facial feature, the nose is a major determinant of facial

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aesthetics. When the nose is in harmony with the remainder of the face, attention is directed to the eyes, the focal point of human communication. A displeasing nose that is not harmonious with the remainder of the facial features distracts our attention from the eyes and draws it to the distracting and displeasing nasal shape.

Patients often seek rhinoplasty to alter the shape of their nose, in order to make it more harmonious with the face. Too often, surgeons focus exclusively on the patient's cosmetic complaints – the surgeon may correct the cosmetic deformity but neglect the functional problems; or worse, they may correct the cosmetic deformity and, in the process, unintentionally and unknowingly worsen nasal breathing. Nasal obstructive problems that occur following cosmetic rhinoplasty may not be sensed by the patient, nor recognized by the surgeon, for many years following the rhinoplasty – the surgeon may never learn that he or she has created a functional problem, and the destructive surgical technique is thus repeated. Often, primary and secondary nasal breathing dysfunction is the result of nasal valve compromise (Fischer and Gubisch 2006; Kern and Wang 1993; Constantian and Clardy 1996). It is therefore essential for nasal surgeons to understand the nasal valve – terminology and definitions, structural anatomy, anatomical changes which occur with rhinoplasty, and surgical techniques to improve nasal valve function and nasal airflow. This chapter will focus on the contribution of the nasal valve to nasal breathing.

22.2 Nasal Obstruction

Nasal airway obstruction is a complex issue which may result from a variety of etiologies including structural anatomical causes (surgically correctable problems such as septal deviations, turbinate hypertrophy, and nasal valve collapse) and physiological nonanatomical causes (not surgically correctable problems such as mucosal hyperreactivities, rhinitis, nasal polyps). Nasal septal deformities and turbinate hypertrophy have been widely recognized as primary contributors to nasal airway obstruction and are therefore the most common targets of surgical interventions. When applied appropriately, septoplasty and turbinate reduction often help to improve the subjective sense of nasal airflow. However, some patients may experience no improvement, while others may actually sense a worsening of their nasal obstruction despite a straightened septum and shrunken turbinates. In these cases, increased airway resistance may be associated with nasal valve collapse, including a narrowed valve angle or a weakened nasal sidewall which collapses under the dynamic forces of nasal inspiration. In recent years, nasal valve disorders have been increasingly recognized as important contributors to nasal airway obstruction, and surgical treatment of the nasal valve has become an integral component of nasal obstruction management. Respecting the structural integrity of a functional nasal valve and correcting a functionally weak nasal valve help to insure improved patient quality of life outcomes following nasal surgery (Rhee et al. 2005; Younes et al. 2006; Most 2006).

22.3 Definitions of Nasal Valves

22.3.1 Overview

The nasal valves are the narrowest portion of the nasal airway, accounting for over half of the total nasal airway resistance. But what are the nasal valves, and where are they located? There are a total of four different "nasal valves," including an internal and an external nasal valve on either side of the nose. It is essential to distinguish between the internal and external nasal valves, as these represent distinct anatomical and physiological entities (Cole 2003; Bridger 1970; Constantian 1994).

22.3.1.1 What Is the Internal Nasal Valve?

The area defined as the "internal nasal valve" is the narrowest portion of the nasal airway, and it is therefore the primary regulator of nasal airflow. It is the area bound by the nasal septum medially, the caudal edge of the upper lateral cartilage laterally, the floor of the nose inferiorly, and the

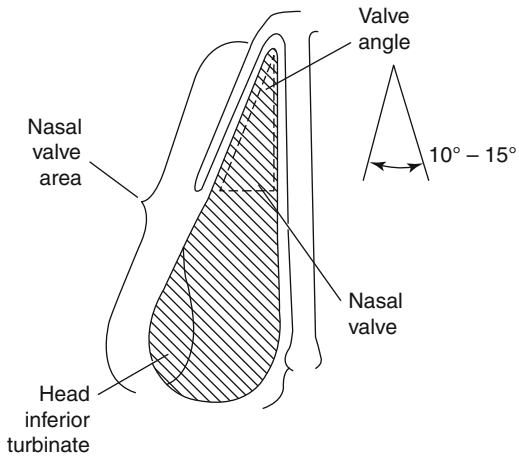

Fig. 22.1 Anatomy of the nasal valve

head of the inferior turbinate inferolaterally (Fig. 22.1). The normal angle between the upper lateral cartilage and nasal septum is 10–15°, and the cross-sectional area of this region is approximately 55–64 mm squared (Bridger 1970). A smaller cross-sectional area or a narrowed angle between the upper lateral cartilage and nasal septum may contribute to increased airway resistance and the sensation of nasal airway obstruction.

22.3.1.2 What Is the External Nasal Valve?

The "external nasal valve" is located in the nasal vestibule, and it is an area bound by the alar rim and columella, including the medial crus, nasal spine, and soft tissues covering the nasal sill and floor. As with the internal nasal valve, the external valve either may be narrowed at rest (i.e., vestibular stenosis) or may have a floppy and weak lateral component (i.e., alar rim) which narrows under the influence of negative pressure associated with nasal inspiration (Constantian 1994).

22.3.1.3 Influences on Nasal Valve Strength

The external skin covering, the internal mucosal covering, the intrinsic cartilage, and the subcutaneous muscles all contribute to the strength and stability of both the internal and external nasal valves ((Vaiman et al. 2004; Aksoy et al. 2010).

22.3.2 Internal Nasal Valve Collapse

22.3.2.1 Static Internal Valve Compromise

Internal nasal valve collapse may be categorized as static or dynamic (Apaydin 2011; Park 1998). Static internal nasal valve collapse is a narrowing of the middle third of the nose at rest – that is, the angle between the upper lateral cartilage and nasal septum is anatomically small and the resultant area of the valve is similarly reduced. Static collapse is often seen as a result of nasal trauma or previous rhinoplasty in which a weakening of nasal support structures leads to an overly narrowed angle between the upper lateral cartilage and nasal septum (i.e., this may result from simple surgical maneuvers such as skin elevation, mucosal elevation, separation of the upper lateral cartilages from the septum). Static internal valve collapse may also result from scarring of the medial segment of the upper lateral cartilage to the nasal septum following the separation of those structures along with their intervening mucosa. Elevation of the skin-soft tissue envelope, damage to the nasal dilator muscles, and weakening of the mucosal support of the middle third cartilages all contribute to a weakening of nasal valve support.

22.3.2.2 Identifying Static Internal Valve Compromise

Middle third narrowing at rest, that is, static internal nasal valve collapse, may be seen upon simple external inspection of the nose in which a pinched middle third may be visible. This often results in a discontinuity along the brow-tip aesthetic line as the middle third is pinched and narrowed, while the upper third, which is supported by bone, remains wide. Classically, the inverted V deformity has been linked to the separation of the upper lateral cartilages from the overlying nasal bones during rhinoplasty, but it is actually seen more commonly either in patients with internal nasal valve collapse who have never undergone previous rhinoplasty or in patients who have had a standard dorsal reduction rhinoplasty without disarticulation of the upper lateral

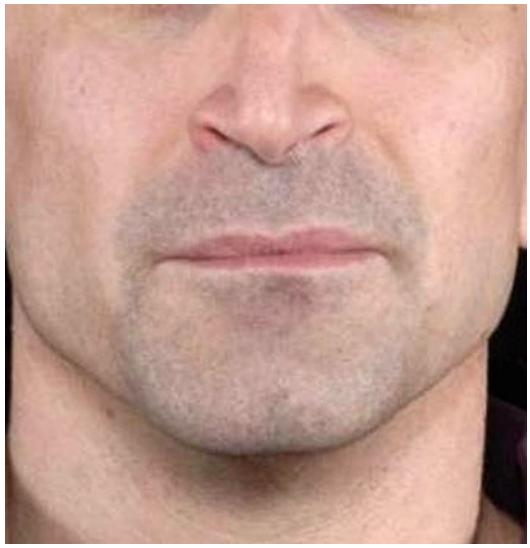

Fig. 22.2 Static internal nasal valve collapse visible in the middle third of the nose

cartilages from the nasal bones (Fig. 22.2). Static internal nasal valve collapse may appear clinically as scar tissue, strictures, or webbing in the valve angle (as might occur after separation of the upper lateral cartilage and mucosa from the septum without sparing the mucosal attachments between the two structures). Congenital or traumatic weakness or absence of the upper lateral cartilages or other deformities (thickening, twisting) of the upper lateral cartilages may result in static narrowing of the middle third of the nose. Additionally, in patients with an overprojected tension-type nasal deformity, overgrowth of the nasal septum causes the angle between the upper lateral cartilage and the nasal septum to be excessively narrowed. Such patients may also frequently be found to have thin and weak upper lateral cartilages, which tend to add a dynamic component to the internal nasal valve collapse.

22.3.2.3 Dynamic Internal Nasal Valve Compromise

Dynamic internal nasal valve collapse is an active narrowing of the upper lateral cartilage and middle third of the nose which occurs only with nasal inspiration through a valve which, at rest, appears of normal size (Fig. 22.3a–d). Dynamic nasal valve collapse, in which the middle nasal third appears normal at rest but narrowed upon gentle nasal inspiration, often results from an inherent weakness of the nasal sidewalls (Fig. 22.4). Thin, weak, detached, or absent upper lateral cartilages cannot provide the necessary strength along the nasal sidewall to withstand the negative pressures created by inspiratory nasal airflow – as a result, the sidewalls of the nose fall in as the negative pressure created by nasal inspiration draws them inward. Previous rhinoplasty in which the upper lateral cartilages have been weakened or detached from the nasal septum, congenitally or developmentally thin upper lateral cartilages, and absent upper lateral cartilages may all contribute to such structural weaknesses of the nasal sidewall. In such cases, the patient may not have obvious findings suggestive of nasal valve collapse upon inspection at rest, such as an inverted V deformity or a pinched middle third, but when asked to inspire gently through the nose, there is an active narrowing of the middle third which becomes obvious to the examining physician. In order to appreciate dynamic nasal valve collapse and its effects on nasal breathing, it is often helpful for the examining physician to apply gentle lateral traction on the cheek adjacent to the nose (i.e., Cottle maneuver) to assess for improvements in nasal breathing that might occur with stiffening of the lateral nasal wall by digital traction. Additionally, in order to pinpoint the precise location of the collapse, it is helpful to introduce a cotton tip applicator or ear curette into the suspected area of collapse and observe improvements in nasal obstructive symptoms when the precise site of obstruction is stiffened with the examiner's help. Application of external nasal dilation devices further helps identify internal nasal valve collapse.

22.3.3 External Nasal Valve Collapse

The external nasal valve is an area primarily supported by the lower lateral cartilages and their overlying skin and soft tissue covering and is defined anatomically by the region between the columella and the alar rim. The size, shape, and

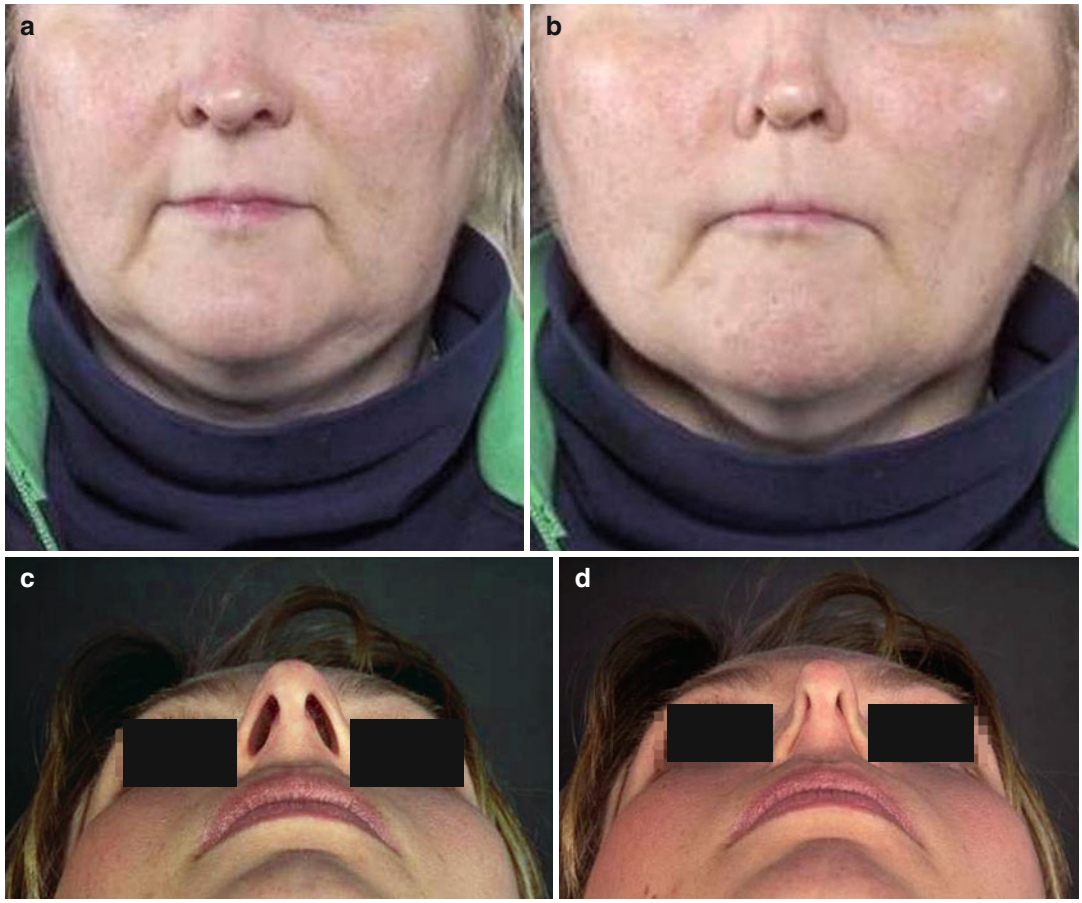

Fig. 22.3 (**a**, **b**) Dynamic internal nasal valve collapse. The nasal sidewalls collapse inward under the force of negative inspiratory pressure. (**c**, **d**) Dynamic external nasal valve collapse on gentle nasal inspiration

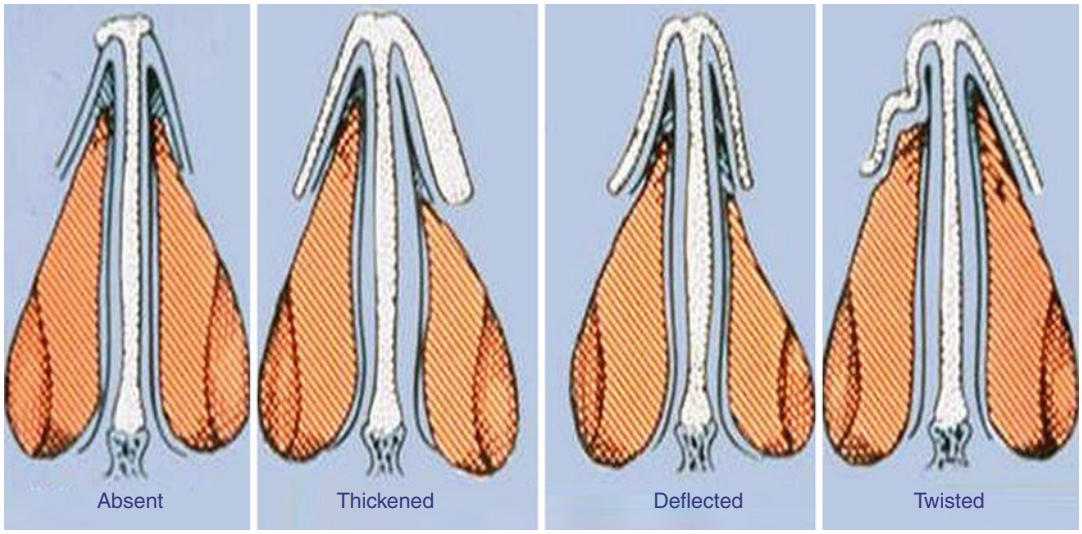

Fig. 22.4 Variability of inherent structure of upper lateral cartilage

strength of the lower lateral cartilages create the nasal vestibular aperture that defines the external nasal valve. Static narrowing of the external nasal valve (vestibular scarring and stenosis, alar rim collapse) may be seen with trauma, soft tissue triangle injury, reconstruction of nasal skin cancer defects, cleft lip repair, alar base narrowing procedures, significant caudal nasal septal deformities in Cottle area 1, or secondary to a variety of other causes. Functionally unfavorably shaped lower lateral cartilages may narrow the external nasal valve aperture and contribute to nasal obstruction simply due to the shape of the cartilages (concave lower lateral cartilages that impinge on the airway, lateral crural cephalic malposition with resultant concavity along alar rim, etc.). For example, in the case of tension-type nasal deformities in which the vestibular aperture at the level of the nasal rim is narrowed and pinched, we see the shape of the lower lateral cartilage affecting the size of the nasal vestibule – a tent-pole-like overprojection of the tip results in a narrow nasal vestibule secondary to "slit-like nostrils."

Dynamic external nasal valve collapse occurs when the valve appears normal at rest, but upon inspiration through the nose, there is collapse of the alar rims. Primary weakness of the lower lateral cartilage and malposition of the lower lateral cartilage (as with vertically oriented lower lateral cartilages) often lead to dynamic external valve collapse – in both situations, the lower lateral cartilage malposition and inadequate soft tissue support at the rim lead to an inability to support or withstand the negative inspiratory forces generated by nasal breathing. In examining a patient with external valve collapse, it is best to simply observe the nose during quiet breathing and watch the nasal vestibule for narrowing of the alar rim on gentle nasal inspiration. As with internal valve collapse, application of lateral traction with the examiner's hand, a cotton applicator or wax curette, or with an external nasal dilator will help to identify the precise area of weakness and may further help demonstrate to the patient what may be achieved with surgical correction of the external nasal valve weakness.

22.3.4 The Aging Nose

A common and increasingly more prevalent clinical scenario in which we find nasal obstruction associated with both internal and external nasal valve collapse is in the aging patient. The aging nose undergoes structural changes that result in various weaknesses that lead to nasal valve collapse and nasal obstruction. A significant loss of nasal support occurs with thinning of the nasal bones and skin, thinning and weakening of the upper lateral cartilages, laxity in the supportive attachments between the upper and lower lateral cartilages at the scroll region, weakening of the lower lateral cartilages, and laxity in the supportive fibrous attachments between the lower lateral cartilages and the nasal septum and maxilla. Additionally, just as in the rest of the body, the nasal muscles likely atrophy with age, which may add to the collapsibility of the nasal sidewall. The structural changes associated with aging contribute to the drooping of the nasal tip (tip ptosis), narrowing and weakening of the internal valve, and narrowing and weakening of the external nasal valve – all of which contribute to both functional breathing problems as well as to the aesthetic changes that are typical of the aging nose. As we face a global aging of the population, nasal surgeons around the world will likely see increasing numbers of patients for surgical correction of nasal breathing (Toriumi 1996; Guyuron 1997; Rohrich and Hollier 1999).

22.4 Treatment

Over the past 10–15 years, there has been an increased awareness of the nasal valve as a contributor to nasal airway obstruction, resulting in a flurry of scientific publications on the matter, innovations in therapeutic options, and increasing applications of a multitude of both surgical and nonsurgical treatments to correct the nasal valve contribution to nasal obstruction (Park 1998; Kern 1978; Gassner et al. 2006; Friedman et al. 2004; Paniello 1996; Akcam et al. 2004; Vaiman et al. 2005; Guyuron et al. 1998; Toriumi

et al. 1997; Sen and Iscen 2007; Mendelsohn and Golchin 2006; Ng et al. 1998; Sheen 1984; Clark and Cook 2002; Stucker et al. 2002; Stucker and Hoasjoe 1994; Menger 2006; Rohrich et al. 2002; Andre et al. 2006; Byrd et al. 2007). Evaluation of the patient begins with a thorough history, eliciting signs that may hint at nasal obstruction and nasal valve collapse. Does the patient mouth breathe, snore, awaken tired? Has the patient used breathing dilator devices in the past or had prior nasal surgery? The answers to these questions will help guide the patient and surgeon in deciding whether there is a nasal valve component to the nasal obstruction and whether nasal surgery might be of benefit.

Many of the surgical techniques that have been described for nasal valve repair have focused on secondary nasal surgery to improve nasal function following rhinoplasty (Sheen 1984; Clark and Cook 2002; Stucker et al. 2002; Stucker and Hoasjoe 1994). Armed with a better understanding of the nasal valve, recent refinements in surgical techniques, and an accompanying thorough preoperative evaluation, findings of internal and/or external nasal valve collapse may often be identified in previously unoperated individuals who complain of nasal obstruction. Such patients often have improvements in nasal breathing with the Cottle maneuver or with the application of external nasal dilator devices. Treating the patient with nasal breathing devices at home allows the patient to experience the quality of life improvements associated with correction of nasal valve obstruction. In this way, it helps to communicate to the patient what they might expect from surgical nasal valve intervention. Patients are then better able to make informed decisions about the desirability of surgical intervention for nasal valve obstruction. Additionally, the application of such breathing devices helps in defining the site of obstruction more precisely in order to optimize surgical outcomes (Gruber et al. 2011). Primary and secondary functional nasal surgery with correction of the dysfunctional nasal valve has been previously shown to significantly improve quality of life in patients complaining of nasal obstruction who have preoperative findings of nasal valve collapse (Rhee et al. 2005; Younes et al. 2006; Most 2006).

22.5 Surgical Techniques

A multitude of surgical techniques to address the dysfunctional nasal valve have been described in the past few decades (Apaydin 2011). No single technique stands out as the "gold standard," as being able to solve all of the causes and types of nasal valve collapse. Rather, there are many useful techniques which may be incorporated into the surgical plan depending upon the specific clinical needs of the patient. The overall goal of nasal valve surgery is to widen the existing nasal valve area and to strengthen the structural support elements that maintain a patent valve area at rest and which minimize dynamic collapse of the nose that results from the negative inspiratory forces of nasal breathing. This section highlights a number of techniques that have been found useful and are used routinely as part of a comprehensive surgical correction of nasal valve dysfunction. There are many others that may be found in the surgical literature.

Both endonasal and external approaches may be utilized for various nasal valve procedures depending on the needs of the patient and surgeon preferences. With proper patient selection, either general anesthesia or local anesthesia with sedation may be used for nearly all nasal valve surgery. In the absence of comorbidities, nasal valve surgery is generally performed on an outpatient basis. As with all nasal surgery, it is important to use as little anesthetic as necessary so as not to distort the nasal anatomy. It is also essential to allow adequate time for the anesthetic to take effect in order to minimize the bleeding and maximize visualization. As with all surgeries, the general principle is to minimize the aggressiveness of the surgical intervention in order to minimize the potential risks of the procedure, but at the same time to maximize the benefit to the patient by selecting the proper group of techniques for the proper situation.

22.5.1 Spreader Grafts

Static and dynamic internal nasal valve collapse may be treated with this technique. Spreader grafts are used to widen the narrowed valve angle, thereby enlarging the nasal valve area in both static and dynamic valve collapse. In cases of static collapse, the widening of the middle third of the nose also results in a smoothening of the brow-tip aesthetic line. Ideally, spreader grafts are made of septal cartilage, but in cases of previous surgery in which inadequate septal cartilage remains, conchal cartilage or rib cartilage may be utilized. Alternatively, in patients with a prominent dorsum who are undergoing dorsal reduction, the upper lateral cartilage excess may be folded on itself to lie between the septum and upper lateral cartilage to serve as an "auto-spreader graft" or a "spreader flap." Standard left hemitransfixion incision is made to access the septal cartilage. Mucoperichondrial flaps are elevated on one or both sides of the septum depending on the septal pathology. Septoplasty is performed in standard fashion, and septal cartilage is harvested for use as a spreader graft. The upper lateral cartilages are separated from the dorsal septum to create space for the spreader grafts (Fig. 22.5). The spreader grafts should be long enough to extend from under the nasal bones to the caudal edge of the upper lateral cartilage. They measure approximately 3–5 mm in height and are the thickness of the septal cartilage. Occasionally, wider grafts may be required in which case a layering of multiple pieces of septal cartilage may be stacked together to provide adequate thickness. Auto-spreader grafts or spreader flaps involve the turning of upper lateral cartilages to lie between the septum and lateral upper lateral cartilage in order to take advantage of the local tissue excess.

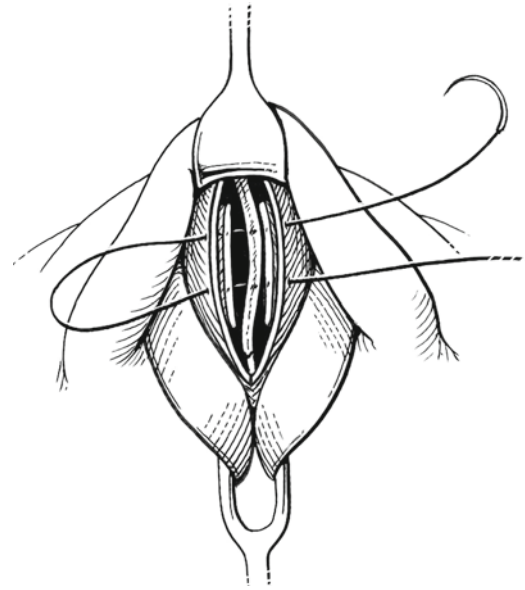

Fig. 22.5 Application of spreader grafts with horizontal mattress suture

22.5.2 Alar Batten Grafts

Alar batten grafts are versatile grafts that may be used for both internal and external nasal valve collapse depending on where they are positioned (Fig. 22.6). The region of collapse is identified. If collapse is noted in the external nasal valve, along the alar rim, the graft may be placed along the rim of the nose to provide greater strength and an outward curvature to the nasal rim. A marginal incision is made along the inferior margin of the lower lateral cartilage with a 15 blade, while a double-prong skin hook is utilized for countertraction. A sharp scissor is used to dissect a precise pocket along the nasal rim to the alar-facial groove. A cartilage graft measuring 3–10 mm in width by approximately 7–10 mm in length is harvested from either the septum or the conchal bowl and applied to the pocket. The graft should extend from the alar-facial groove either to the dome or to the area just lateral to the soft tissue triangle in order to avoid a sharp edge being seen through the skin of the soft tissue triangle. It may overlap the lateral crus superiorly. If less support is needed, a smaller graft may be used and has been referred to as an alar rim graft. The marginal incision is closed with simple interrupted 5-0 chromic suture.

If collapse is noted in the middle third of the nose, the alar batten graft is placed in the middle third of the nose. An intercartilaginous incision is

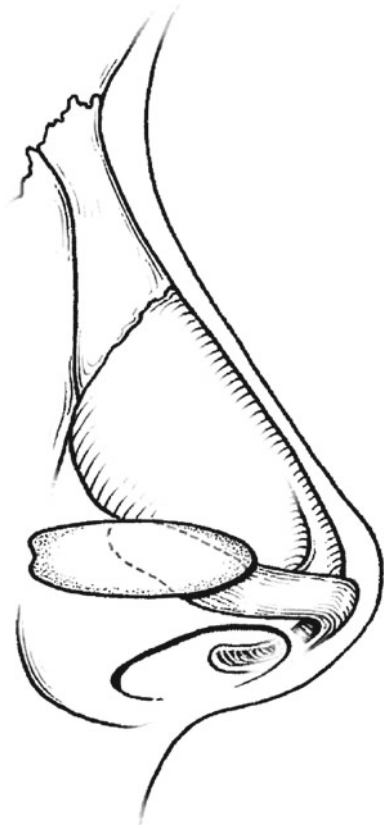

Fig. 22.6 Alar batten grafts may be placed at point of greatest nasal sidewall collapse to correct internal or external valve collapse

made with the 15 blade scalpel, and a precise pocket is created superficial to the upper lateral cartilage down to the pyriform aperture. The graft is applied to the pocket, directly on the upper lateral cartilage. As the skin thins, these grafts may become visible over time. An alternative technique involves the placement of the graft deep to the upper lateral cartilage, most often at the scroll region (the junction of the upper and lower lateral cartilage) which is commonly the region of greatest collapse. The grafts are then sutured to the overlying cartilage with two or three throws of 5-0 chromic or PDS suture to avoid movement of the graft. These underlay grafts (similar to lateral crural strut grafts) often hide better than the alar batten grafts. The intercartilaginous incision is then closed with interrupted 5-0 chromic suture.

22.5.3 Butterfly Graft

The "butterfly graft" is a highly effective procedure to correct nasal valve obstruction. It relies on the elastic nature of conchal cartilage to spring open the internal nasal valve.

Conchal cartilage is harvested through an anterior helical rim incision or postauricularly. A skin incision is made, followed by blunt and sharp dissection to free the conchal cartilage. A 1-cm-wide by 2-cm-long cartilage graft is harvested. Cautery to insure hemostasis of the ear harvest site is performed. Running 6-0 fast-absorbing gut suture was used to close the skin incision, and a compressive dressing was placed on the donor site to prevent hematoma formation. The ear dressing is removed on postoperative day one.

Intercartilaginous incision is made on both sides of the nose and connected to a complete transfixion incision. Skin-soft tissue elevation is achieved along the nasal dorsum in a standard sub-SMAS plane to the rhinion and a subperiosteal plane from the rhinion to the nasion in order to allow for proper skin redraping. If a significant or exaggerated supratip depression is present, the graft is simply placed in the supratip depression, and its ends are secured to the caudal-most aspect of the upper lateral cartilages with a single throw of 5-0 PDS suture on either side (Fig. 22.7). Once the graft is fixed in position, the skin is redraped and the dorsum is inspected and palpated for irregularities. If irregularities are noted, the dorsum is reduced further to create a smooth contour. Frequently, especially in patients with thin skin, crushed cartilage grafts are placed on the nasal dorsum, cephalic to the upper edge of the butterfly graft, to camouflage the edges of the graft and create a smooth dorsal contour. Mucosal incisions are closed with 5-0 chromic suture.

22.5.4 Nasal Valve Flaring Suture

Skin and soft tissue envelope is elevated off the osseocartilaginous understructure of the nose as previously described. Once the incisions are made and the tissues have been elevated,

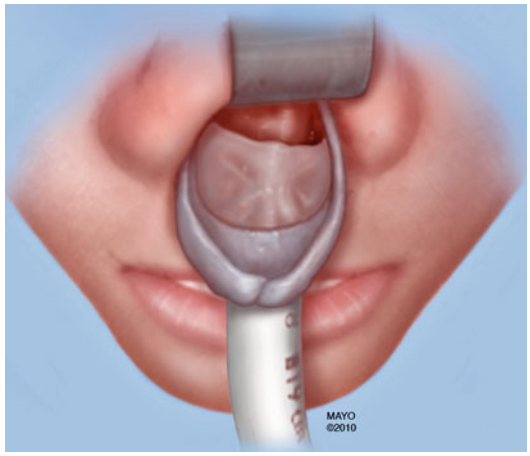

Fig. 22.7 Butterfly graft as seen through an external approach (By permission of Mayo Foundation for Medical Education and Research. All Rights Reserved)

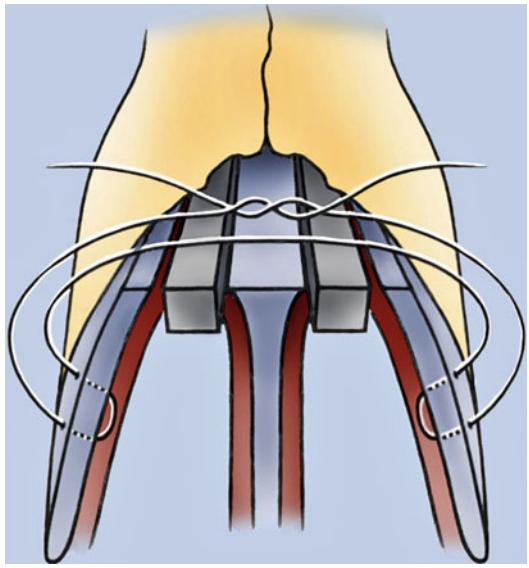

Fig. 22.8 Horizontal mattress flaring stitch to support upper lateral cartilage

a retractor is placed under the skin flap to expose the upper lateral cartilages. A horizontal mattress stitch (I prefer 5-0 PDS) is thrown from one upper lateral cartilage to the other and tied tightly over the nasal dorsum. As the suture is tied down, the upper lateral cartilages elevate outward, thereby widening the nasal valve angle and area (Fig. 22.8). Nasal valve flaring sutures may be used alone or in combination with various other techniques in order to maximize the widening of the valvular airway. Incisions are closed as previously described.

Conclusion

Current trends in nasal surgery demand that both nasal form and function be addressed. It is no longer acceptable to sacrifice the long-term function of the nose simply to obtain improvements in nasal appearance, and many believe it is similarly unacceptable to sacrifice nasal cosmetics simply to improve nasal function. In the ideal circumstance, form and function should go hand in hand if we are to maintain the best interest of the patient.

A wide variety of surgical approaches have been described to correct nasal valve compromise. Many of these techniques may result in improvements in both form and function and provide longstanding success in both primary and secondary nasal surgery. It is imperative for the modern nasal surgeon to be familiar with the underlying surgical anatomy of the nose, as well as with the types of nasal valve collapse, and the multitude of techniques available to correct the different deformities in order to obtain consistently successful surgical outcomes.

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Nose and Sleep Breathing Disorders

23

Anne-Lise Poirrier, Philippe Eloy, and Philippe Rombaux

Keywords

Sleep-disordered breathing • SDB • Snoring • OSA • Nasal obstruction • Physiopathology of nose obstruction and SDB • Treatment of nasal obstruction • Nasal collapse • Polysomnography

Core Messages

- The nose is the input channel for the airflow. Its rigid and erectile structures determine the outline and the output of the airflow in the upper airway. Nose obstruction, due to reversible or non-reversible factors, produces collapsing forces that are manifest downstream in the collapsible pharynx. Moreover, nose pathologies result in unstable oral breathing, decreased activation of nasal-ventilatory reflex and reduced lung nitric oxide. Long-term oral breathing impacts on the craniofacial growth. The management of nose pathologies could be medical, mechanical (nose dilators) or surgical. Nasal management should be integrated in a multimodal approach, considering the involvement of a multi-level obstruction, and truly reflecting the complexity of sleep disordered breathing.

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23.1 Introduction

Sleep-disordered breathing (SDB) is a clinical entity that is more and more recognised by physicians since the 1970s. It consists of a wide spectrum of sleep-related breathing abnormalities. Those related to increased upper airway resistance include snoring, upper airway resistance syndrome (UARS) and obstructive sleep apnoea-hypopnoea syndrome (OSAHS) (Young et al. 1993).

Snoring is associated with changes in the calibre of the upper airway which reduce flow and increase airway resistance and is a manifestation of increased turbulence in nasal flow (Phillipson 1993; Pirsig 2003). UARS is caused by sleep-related flow limitation and increase in upper airway resistance that precipitates arousals. UARS results in fragmented sleep and excessive daytime sleepiness. Obstructive sleep apnoea (OSA) syndrome is the complete or partial collapse of breathing despite ongoing respiratory effort. In patients with OSA, recurrent obstruction of the pharynx during sleep results in frequent episodes of airflow cessation, leading to significant hypoxemia, fragmentation of sleep and excessive daytime sleepiness. Obstructive sleep apnoea is a leading cause of neuropsychiatric conditions (e.g. sleepiness, depression, cognitive dysfunction), cerebro- and cardiovascular diseases (e.g. pulmonary and systemic hypertension, congestive heart failure, myocardial infarction, stroke), metabolic disorders, sexual dysfunction, loss in work productivity and increased risk of motor vehicle accidents. OSA represents a major public health problem (Phillipson 1993).

In the Wisconsin Sleep Cohort, a stratified random sample of Wisconsin state employees ages 30–60 years, the prevalence of OSA was 9 % in women and 24 % in men. The incidence increases with age and tobacco and alcohol use and is associated with metabolic and anatomical features (obesity, retrognathia, high anteroposterior cervical diameter, macroglossia, large tonsils, hypertrophic tongue base, large neck size, gastroesophageal reflux and nasal obstruction) (Young et al. 1993; Phillipson 1993).

In the past, snoring was considered mainly as a common ordinary disorder that only affected men and was regarded as a social annoyance particularly for the bed partner. Nowadays many clinicians are regarding SDB as a spectrum of diseases in which a patient can move from a snorer without apnoea to a snorer with apnoea. These disorders form actually a continuum. They share a common physiopathology: a multilevel airway obstruction (Primhak and Kingshott 2012).

As the nose plays a major role in the physiology of the respiratory tract, it is important to analyse the role of nasal disorders in the pathogenesis of SDB and the effects of rhinologic treatments on snoring and OSA. This topic has not yet received definitive conclusions because of contradicting reports in the literature. The number of patients with polysomnography-documented OSA and treated only by nasal surgery is far less important than the number of cases treated with other therapies within the last two decades. The reason is not quite clear, but one could be that the success rate of nasal management alone for SDB is low and the prediction of individual success is not possible (Pirsig 2003).

23.2 Nose Anatomy and Physiology

The nose is the input channel for the airflow and the "touchable" beginning of the airways. About 70 % of the resistance met by the inspired airflow during its passage through the upper and lower airways is located into the nose (Ferris et al. 1964). The nose may be roughly divided into outer and inner anatomy. The outer nose is supported by the nasal bones, the paired upper lateral and lower lateral cartilages and the nasal septum and is covered by the subcutaneous tissue and skin. The inner nose includes the nasal septum on the medial wall of the nasal cavity and the turbinates and the osteomeatal complex on the lateral wall. During inspiration, air is spinning into the nose through the nasal valve. It can be divided into external and internal nasal valves (Spielmann et al. 2009; Rhee et al. 2010).

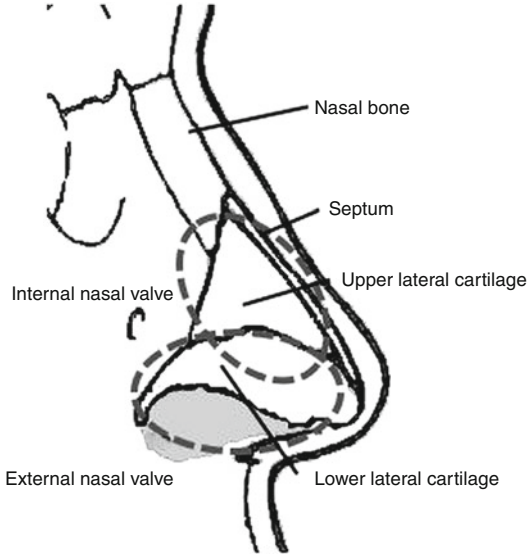

Fig. 23.1 Anatomy of the external nose

The external nasal valve comprises the alar cartilages, the nasal wing and the columella and has a shape of an inverted "funnel". Its role consists of orientating the airflow into the nasal cavities without generating any resistance (Courtiss and Goldwyn 1983). The internal nasal valve is formed by the junction of the upper lateral cartilages with the nasal septum, the septum, the head of the inferior turbinate and the piriform aperture (Fig. 23.1). The normal angle between the upper lateral cartilages and the septum is about 10–15° and represents the nasal region with the smallest cross-sectional area and the greatest resistance to nasal airflow, crucial to determine nasal resistance (R_N) (Rhee et al. 2010). The internal nasal valve plays a major role in the physiology of the nose and particularly in air conditioning. Its functioning depends on the shape of the cartilages, the tonus of the dilator muscles and the degree of congestion of the nasal mucosa. The airstream is first directed upward through the internal nasal valve, then bends about 90° posteriorly and flows via the nasopharynx to the lower airways.

The diameter of the valve influences directly the velocity of the airflow. On gentle inspiration, the nasal valve is usually patent. During deep inspiration (exercises or sniffing), the airflow could create a Bernoulli's effect, which accelerates the flow in this narrow cleft and decreases the pressure on each side of the nasal vestibule leading to the collapse of the nasal wing. Patients suffering from a valve collapse may experience nasal obstruction even during normal breathing.

The congestion of the nasal mucosa varies physiologically, spontaneously and alternatively from side to side with time. One side is blocked, while the other side is patent. This alternates every 3–7 h in adults, leading to a spontaneous cycle phenomenon called nasal cycle. Surprisingly, thanks to this alternation of resistance on each side, the total nasal resistance remains constant (Kennedy et al. 1988).

The paranasal sinus cavities play also a major role in the physiology of the nose. The sinonasal architecture is organised around the ethmoid bone. The perpendicular plate of the ethmoid articulates medially to the septal cartilage, while the outer wall of the ethmoid, including middle concha, articulates laterally with the vertical plate (ascending process of the frontal bone) of the maxilla. On the lateral nasal wall is the osteomeatal complex (OMC). The OMC comprises the middle turbinate, the uncinate process and the bulla ethmoidalis. In this particular anatomical area drain the secretions from the anterior paranasal cavities such as the anterior ethmoid cells, the frontal sinus and the maxillary sinus. Anatomical variations of the different structures of the OMC have been described in the literature such as concha bullosa, paradoxically bent middle turbinate and medially bent uncinate process. In the past ones believed that these anatomical variations were associated to chronic rhinosinusitis. Now most authors do not consider these variations to be responsible of the pathogenesis of chronic sinusitis by themselves.

23.3 Nose Pathologies

All pathologies causing nasal obstruction can cause or worsen SDB (Rappai et al. 2003). The reasons for nasal obstruction are complex and varied, but the causes can be simplified as nonreversible factors, such as anatomic deformities, and reversible factors, such as mucosal oedema and congestion (Table 23.1).

Table 23.1 Causes of nasal obstruction

Nonreversible	Internal/external valve collapse
	Septal deviation, hematoma, perforation
	Other malformation of the nasal framework
	Vestibular synechiae or scars
	Concha hypertrophy
	Nasal polyposis, antrochoanal polyp
	Foreign body, nasal packing
	Benign tumours: angiofibroma, inverted papilloma
	Malignant tumours: squamous cell carcinoma, adenocarcinoma, melanoma
	Meningocele
	Choanal atresia and other craniofacial anomalies
Reversible	Allergic/nonallergic rhinitis: NARES-NANIPER
	Acute or chronic rhinosinusitis with or without polyps
	Drug-induced or occupational rhinitis
	Atrophic rhinitis
	Pregnancy
	Wegener or other granulomatosis

23.3.1 Nonreversible Factors

Deformity of the nasal septum and/or the nasal pyramid can obviously be associated with uni- or bilateral persistent nasal obstruction. In case of nasal septum deviation, the patient can complain of a uni- or bilateral nasal obstruction depending on the shape, type and location of the deviation (Mladina et al. 2008). Anterior nasal septum deviation is more commonly responsible of nasal obstruction than posterior septal deviation (Grymer et al. 1997). The patient can also complain of a contralateral nasal obstruction, explained by a compensatory hypertrophy of the mucosa of the inferior turbinate. Nasal collapse is another cause of nasal obstruction that is underrated and underestimated by numerous ENT doctors. Nasal obstruction can be revealed during effort, sport or exercises or can be present in a normal and calm breathing. Patients with previous facial nerve palsy or post-traumatic or postsurgical adhesions developed at the level of the nasal vestibule or the columella can present a unilateral nasal collapse. The diagnosis is made by the Cottle manoeuvre or by an anterior and posterior active rhinomanometry and acoustic rhinometry.

23.3.2 Reversible Factors

Nasal obstruction can be caused by a rhinitis. Allergic rhinitis is a very common condition. Bauchau and Durham reported a high heterogeneity of allergic rhinitis incidence among the different European countries and a maximal incidence in Belgium with 29.5 % of the population (Bauchau and Durham 2004). According to ARIA guidelines, the rhinitis can be intermittent or persistent, mild, moderate or severe (Brozek et al. 2010). Indoor allergens can cause symptoms during sleep such as house dust mites, animal danders or fungi.

NARES (nonallergic rhinitis with eosinophils) is another type of rhinitis; the eosinophils are present in the nasal smears, and the patient dramatically improves when he uses a nasal topical steroids. There is no sensitisation to any aeroallergens. Loss of smell is a common symptom. This disease can be a precursor of a true nasal polyposis.

NANIPER (nonallergic noninfectious perennial rhinitis) was called in the past vasomotor rhinitis. The aetiology is unknown, the treatment often disappointing except for nasal obstruction.

Rhinitis medicamentosa is a typical cause of nasal obstruction in a patient who (mis)uses nasal topical decongestant. With time the patient consumes more and more nasal drops. Typically nasal obstruction increases during the night.

Acute and chronic rhinosinusitis with and without polyps are associated with nasal obstruction. Acute rhinosinusitis gives symptoms for a maximum of 6 weeks, whereas chronic rhinosinusitis is symptomatic for more than 12 weeks (Fokkens et al. 2012). Nasal polyposis affects 9 % of the general population. It can be restricted to the nose and sinuses or be associated with asthma and aspirin intolerance. Major symptoms in nasal polyposis are nasal obstruction and loss

of smell. There are different classifications used to categorise the polyps. In the Caucasian population, nasal polyposis is associated with a chronic inflammatory infiltrate rich in eosinophils. Oedema, epithelial shedding, pseudocyst formation and changes in the extracellular matrix are some histological characteristics of the common nasal polyposis.

23.4 Physiopathology of Nose Obstruction and SDB

23.4.1 Starling Resistor Model

Nasal obstruction produces collapsing forces that are manifest downstream in the collapsible pharynx (Georgalas 2011; McNicholas 2008). In the respiratory model based on a Starling resistor, the nose is a key determinant of upper airway resistance (Fig. 23.2) (Farre et al. 2008; Horner 2012). Nasal pressure (P_N) is zero (atmosphere reference value) in normal conditions. Nasal resistance (R_N) determines the maximum flow (V_{max}) in the downstream collapsible pharynx. In the pharynx, P_{crit} is the critical value of airway pressure leading to complete collapse and stop of airflow. P_{crit} depends on transmural pressure and external pressure applied by respiratory muscles. The maximum airflow is defined by $V_{max} = (P_N - P_{crit})/R_N$. This equation implies that increase in nasal resistance (R_N) leads to decrease in upper airway flow (V_{max}). Conversely, increase in nasal pressure (P_N) by continuous positive airway pressure (CPAP) device improves upper airway flow (V_{max}) (Gold and Schwartz 1996).

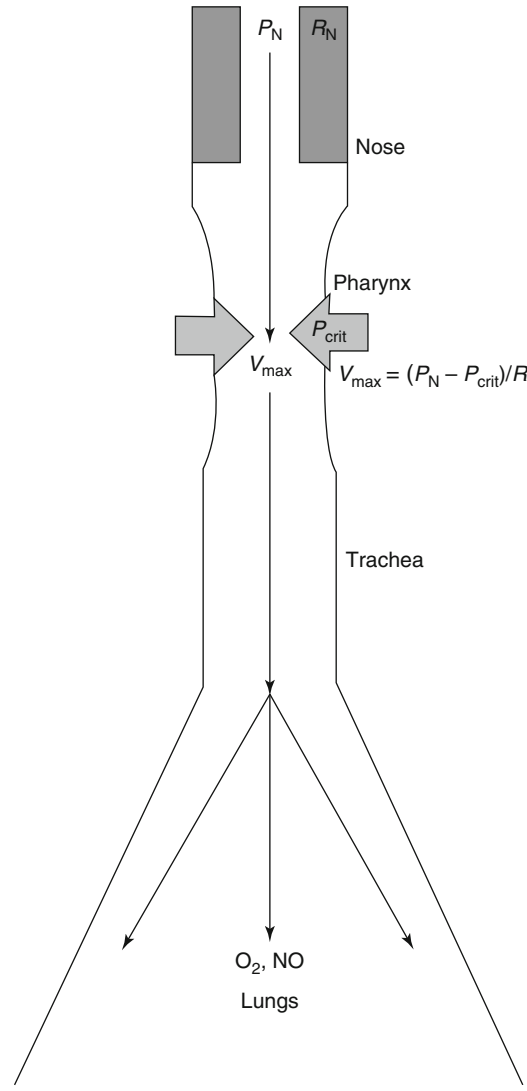

Fig. 23.2 Model of the lungs and upper airway compartments of breathing. The upper airway behaves like a Starling resistor in that obstruction at the inlet produces collapsing forces that are manifest downstream in the collapsible segment, the pharynx. Airflow ceases in the pharynx at a critical value of airway pressure (P_{crit}). Maximum flow (V_{max}) in the pharynx is determined by nasal pressure (P_N) and resistance (R_N) from the equation $V_{max} = (P_N - P_{crit})/R_N$ (Drawing adapted from Ferris et al. (1964))

23.4.2 Oral Breathing

Nasal obstruction may lead to mouth breathing and mouth opening, which, in turn, results in inferior movement of the mandible with associated decrease in pharyngeal diameter. The base of the tongue may also fall backwards reducing the posterior pharyngeal space.

Although the precise mechanisms are not fully understood, oral breathing could be an adaptive response once a particular threshold of nasal airflow resistance is exceeded. Combined recording of oral and nasal breathing during sleep indicates that normal subjects partition flow between nasal and oral routes, with the majority of airflow occurring through the nasal route (Fitzpatrick et al. 2003a).

The route of breathing has profound influence on upper airway resistance during sleep. Oral breathing results in an unstable airway and increases total airway resistance. Oscillation of the soft palate, posterior movement of the jaw angle and posterior retraction of the tongue during mouth opening compromise oral-breathing airflow (Georgalas 2011; Fitzpatrick et al. 2003b).

23.4.3 Nasal Receptors

A few studies suggest nasal airflow has a stimulant effect on ventilation, probably via nasal mechanoreceptors maintaining respiratory pacing. Application of local anaesthetics to the nasal mucosa increases the episodes of airway occlusion (McNicholas et al. 1993; White et al. 1985) and impairs the arousal response to airway occlusion (Berry et al. 1995). The parasympathetic nervous system may play a role in the control of breathing and in the hyperpneic responses associated with airflow obstruction. The parasympathetic nervous system component includes neural receptors in the airways as well as afferent and efferent pathways that travel in the vagus nerves (Ko et al. 2008).

23.4.4 Nitric Oxide

Another item playing a major role in snoring and OSA is the nitric oxide (NO). Airborne NO is largely produced in the epithelium of the paranasal sinuses and is involved in the regulation of pulmonary function (Lundberg 2008; Lundberg and Weitzberg 1999). During inspiration through the nose, high levels of NO follow the airstream to the lower airways and the lungs. Nasally derived NO increases arterial oxygen tension and reduces pulmonary vascular resistance. NO enhances therefore blood flow preferentially in well-ventilated areas of the lung, thus optimising ventilation/perfusion matching (Lundberg 1996; Blitzer et al. 1996). In obstructive sleep breathing disease, nasal NO fails partly to reach the lungs, resulting in ventilation/perfusion mismatch (Haight and Djupesland 2003). Lack of NO could also participate in incoordination of pharyngeal and thoracic muscles and in sleep fragmentation. Furthermore, long-term complications of OSA might be due to the repeated temporary dearth of NO in the tissues, secondary to a lack of oxygen (Haight and Djupesland 2003). After their passage to the alveoli in the inspired air, both oxygen and NO are removed by haemoglobin and are transmitted to the tissues. Repetitive hypoxia/reoxygenation adversely impacts endothelial function by promoting oxidative stress and inflammation and reducing NO availability. This vicious spiral mediates the cardiovascular manifestations of OSA (Atkeson and Jelic 2008).

23.5 Craniofacial Development

23.5.1 Morphogenic Perspective

Nose function not only has a direct role in upper and lower airway breathing in adults but also has a long-term impact on the development of the anterior skull base and the maxilla. The influence of nasal patency on the development of the anterior skull base and the maxillary bone has been previously demonstrated in mammals (Paludetti et al. 1995; Scarano et al. 1998). Experimental blockage of rat nostrils resulted after 2–4 months in anatomical changes of the superior maxilla, the skull base and the jaw (Paludetti et al. 1995; Scarano et al. 1998). Nasal obstruction in monkeys resulted in downward and backward rotation of the mandible and changes in dental occlusion (Yamada et al. 1997). Likewise, oral breathing may modify craniofacial growth in children (Peltomaki 2007). Predominant oral breathing during critical growth periods in children could be inscribed in the bones and lead to breathing disorders (Principato 1991). Cephalometric control studies have shown that mouth-breathing children have a higher tendency for clockwise rotation of the growing mandible (Harari et al. 2010). Because of mouth breathing, tongue position in the oral cavity is low, and the balance between forces from the cheeks and tongue is different compared with healthy children. This leads to a lower mandibular position and extended head pos-

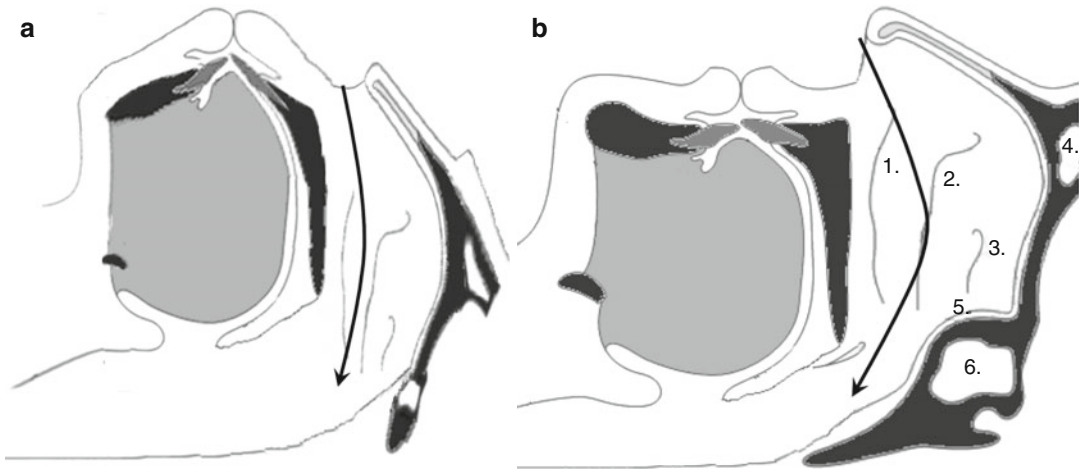

Fig. 23.3 (**a**) In chimpanzee, the upper airway is larger, which lowers the risk of collapse. The nasal airflow is horizontal (*arrow*). (**b**) In normal human, airflow is directed upward through the nasal valve. The outer nose creates a curvilinear airflow pattern (*arrow*). The latter adjusts the "angle of attack" of airflow hitting the palate, thus contributing to the pharyngeal opening. Anatomy of the internal nose: *1* Inferior turbinate, *2* Middle turbinate, *3* Superior turbinate, *4* Frontal sinus, *5* Spheno-ethmoidal recess, *6* Sphenoid sinus (Drawing adapted from McNicholas et al. (1993) and White et al. (1985))

ture. Malocclusion and skeletal discrepancy may be partially corrected after adenotonsillectomy (Peltomaki 2007). Similarities in cephalometric studies from OSA adults and mouth-breathing children suggest that the apnoeic pattern develops early in the clinical history of patients with OSA (Juliano et al. 2009). However, OSA in children differs that in adults. The involvement of nasal resistance is greater in children, with serious consequences for growth and development (Erler and Paditz 2004). In adults, cephalometric measurements of normal subjects and patients have shown a relationship between OSA and transverse dimensions of nasal cavities, limited laterally by the vertical plates of both maxillae. OSA patients have narrower nasal framework and maxillary bone proportions (Poirrier et al. 2012). Craniofacial features in the pathophysiology of OSA could explain ethnic differences in OSA prevalence and severity for a given level of obesity (Cakirer et al. 2001; Ip et al. 2001).

23.5.2 Phylogenic Perspective

Researchers have speculated that the outer nose may have an evolutionary benefit in human. In addition to an ornamental role for sexual selection, it may play a role in creating a curvilinear airflow pattern (Stupak 2010). During the course of human evolutionary development, the midface is shortened, and the upper airway is narrowed to form a collapsible and distensible tube. This evolution permits the production of spoken language but also results in a predisposition toward upper airway collapse during sleep (Davidson 2003; Davidson et al. 2005; Shprintzen 2003). The development of the human outer nose could be assumed as a compensatory development. The curvilinear airflow pattern provided by the nose adjusts the "angle of attack" of airflow hitting the palate, thus contributing to the pharyngeal opening (Stupak 2010). From this hypothesis, the external nose could provide an evolutionary benefit in the protection against OSA (Fig. 23.3).

23.6 Patient Evaluation

23.6.1 Clinical Examination

In case of snoring associated or not to obstructive apnoea, a thorough and complete examination of the nose is mandatory. The nasal pyramid must be

evaluated, particularly the dorsum, the lateral cartilages and the columella. A nasal valve collapse must be ruled out by the inspection of the external nose and the Cottle manoeuvre.

Then an anterior rhinoscopy evaluates the nasal septum, the shape and colour of the mucosa of the inferior turbinates and the presence of crust, blood, secretions or polyps (Mladina 1987). Mladina and colleagues defined seven types of septal deviation in a cohort of 2,589 adults. They identified three types with vertical crests, one type with a bilateral deformity, two types with horizontal deformities and another type with atypical deformities (Mladina et al. 2008). Each type may be associated to some degree of nasal obstruction.

Eventually nasal endoscopy must examine the middle meatus, the olfactory cleft and the posterior aspect of the nasal cavity. Nasal polyposis can sometimes be diagnosed with nasal endoscopy only.

23.6.2 Investigations and Functional Testing

Besides the history taking, the patient self-assessment and the anterior rhinoscopy, some investigations must be performed to evaluate the nasal obstruction.

Rhinomanometry and acoustic rhinometry allow for indirect evaluation of nasal anatomy and function (Cole 2000). When these are performed in a supine position, these investigations have more value in assessing nasal breathing of patients with sleep disorders (Virkkula et al. 2003b). Rhinomanometry uses an intranasal closed loop system to measure nasal airway resistance. Acoustic rhinometry uses acoustic reflections to provide information about cross-sectional area and nasal volumes within a given distance. Acoustic rhinometry gives an anatomic description of a nasal passage, whereas rhinomanometry gives a functional measure of the pressure/flow relationships during the respiratory cycle. Both techniques are proposed to assess the efficacy of different treatments and for assessment of the patient prior to nasal surgery. Rhinomanometry and acoustic rhinometry provide "snap-shot" measurements, which may not be representative of a more chronic condition, since nasal turbinate size and function are dynamic processes that may change considerably over a few hours. It is also important to point out that rhinomanometry and acoustic rhinometry tests do not correlate well with a patient's subjective perception of nasal obstruction. The patient's subjective perception of the degree of nasal obstruction has been shown to be a more sensitive predictor of positive outcome from medical/surgical management than objective anatomic or physiologic measurements alone. Nasal values measured by acoustic rhinometry and rhinomanometry are correlated inversely with polysomnographic values (apnoea-hypopnoea index, oxygen desaturation index) in nonobese patients (Virkkula et al. 2003a, b; Yahyavi et al. 2008). The association of nasal obstruction measured by posterior rhinomanometry and Mallampati score >3 is predictive of OSA (Liistro et al. 2003). Acoustic rhinometry is also important to measure the nasal valve area (Cakmak et al. 2003).

Nasal inspiratory peak flow gives a measure of bilateral nasal airflow at maximum effort, but does not reflect a physiological measure of nasal airflow. It is however a validated technique to assess the responsiveness of a clinical intervention (Wilson et al. 2003). It should be associated to lung function evaluation as it is influenced by lower airway as well as upper airway function (Nathan et al. 2005).

The levels of NO in the nose can easily be measured noninvasively. NO is altered in several airway disorders, including allergic rhinitis, ciliary dysfunction and sinusitis. The NO value measured is a sum of NO from the sinus via the ostia and the nasal mucosa. NO measurement is mainly valuable for sinonasal disease (Lundberg 2008). Its significance to sleep disorders is currently experimental (Haight and Djupesland 2003).

While they provide objective outcome, the measures of nasal function reflect only one aspect of the disease and may thus not encompass all the other aspects. In recent years, there has been a great expansion in the number and use of quality-of-life questionnaires and other patient-based outcomes in health care. Nasal Obstruction Symptom Evaluation (NOSE) score,

Sleep Outcomes Survey (SOS), Visual Analogue Scales (VAS), Sino-Nasal Outcome Test (SNOT) and other surveys have been applied to objectify outcomes in nose and sinus surgery (Lindsay 2012; Hopkins et al. 2009; Piccirillo et al. 2002). Though subjective, they correlate with objective measurements and integrate general health issues, sleep perception and emotional aspects. They include a cluster of interconnected symptoms associated to the nose function. Septorhinoplasty is remarkably effective in improving sleep-related items of the SNOT-22 questionnaire (Poirrier et al. 2013). Beyond the nasal airflow, questionnaires reflect the patient's perception, suffering and hope. They could help the physician to meet the patient expectations and to provide a reliable follow-up.

Nasal endoscopy and CT scan are two other tools to evaluate the anatomy of the nose and paranasal sinuses. These two examinations are routinely done in all rhinologic work-up.

As obstructive SDB is the consequence of multilevel airway obstruction, nasal evaluation should be integrated with a careful anatomical assessment involving in some cases sleep nasendoscopy, MRI or cephalometry. Lastly, polysomnography remains the gold standard to assess the quality of sleep and to calculate the sleep parameters, including apnoea index, hypopnoea index, apnoea-hypopnoea index, snoring time, amount of REM sleep and sleep latency. Breathing flow can be recorded overnight by means of a thermistor placed at the airway opening (nose and mouth). Inspiratory pressure is indirectly measured by means of chest and abdominal inductance plethysmography belts. Additional devices have been designed to measure nasal pressure (Grover and Pittman 2008) or to record mandible movement (Senny et al. 2012; Maury et al. 2013) during sleep.

23.7 Patient Management

23.7.1 Rationale

The rationale to treat nasal obstruction is to improve nasal patency, re-establishing physiological breathing and minimising oral breathing during sleep. The aim of the treatment is also to reduce nasal resistance and improve the negative intraluminal pressure which generates upper airway collapse. Nasal obstruction can be relieved medically or surgically.

23.7.2 Medical Treatment

Only reversible causes of nasal obstruction can be treated with medications. The commonest causes of inflammation of the mucosa of the upper respiratory tract are allergic rhinitis, acute and chronic rhinosinusitis and nasal polyposis.

23.7.2.1 General Treatment of Allergic Rhinitis

As allergic rhinitis (AR) is the best documented disease, we will focus the following paragraph on it. AR is a very common hereditary health problem. It affects 20–40 million US people, approximately 26 % of the United Kingdom population, 29.6 % of the Belgian population and approximately 10–25 % of the population worldwide (Storms 2008). It is characterised by inflammation of the upper airway mucous membranes mediated by binding of antigens to specific immunoglobulin E (IgE). The patients suffer from nasal symptoms (itching, sneezing, rhinorrhea and nasal congestion), ocular symptoms (red itchy eyes) and headache. AR has a negative impact on the patient's quality of life. The patient usually suffers from an impairment of the quality of sleep, daytime fatigue, impaired cognitive function and reduced work productivity and performance (Marshall et al. 2000; Wilken et al. 2002; Kessler et al. 2001). AR represents a heavy burden in terms of direct and indirect costs for the patient and the community. There are many drugs on the market to treat it. ARIA proposed some guidelines to use them in a more effective way (Bousquet et al. 2010). H1-antihistamines are certainly the best-known medications to treat AR in adults and children. There are actually two generations of H1-antihistamines: the older ones (the first generation) and the newer ones (the second generation).

First-generation H1-antihistamines are in many countries over-the-counter drugs. A GA(2)

LEN position paper recommends to forbid their use over the counter in particular in patients with SDB because they are all sedating and have poor receptor selectivity (Church et al. 2010). They penetrate the blood–brain barrier. Their proclivity to interfere with neurotransmission by histamine at central nervous system H1 receptors potentially leads to drowsiness, sedation, somnolence and fatigue resulting in impairment of cognitive function, memory and psychomotor performance. In addition, the central H1-antihistaminic effects are primarily responsible for the potentially life-threatening toxicity of first-generation H1-antihistamines overdose. They have been implicated in civil aviation, motor vehicle and boating accidents, deaths from accidental or intentional overdosing in infants and young children and suicide in teenagers and adults. Finally, they exacerbate daytime somnolence because they decrease the quality of sleep and reduce rapid eye movement (REM) sleep. Moreover, they have anticholinergic properties, which can cause dry mouth and make mouth breathing even more uncomfortable in the allergic individual with nasal obstruction (Ferguson 2004). The first generation of H1-antihistamines should therefore be avoided in SDB patients.

The second generation of H1-antihistamines is not associated with fatigue, sedation and dizziness even at high dose. They do not change the structure of the sleep because they have more affinity to the H1 receptor, do not pass the blood–brain barrier and do not have anticholinergic properties (Church et al. 2010). The H1-antihistamines are effective drugs: they improve significantly itching, sneezing and rhinorrhea, but they are not so effective on nasal congestion. The recommended indications to prescribe an H1-antihistamine are mild to moderate intermittent AR and mild persistent AR. Azelastine, a topical H1-antihistamine, significantly reduces rhinorrhea and improves subjective sleep, but evidence is lacking on its effects on daytime sleepiness and nasal congestion (Golden et al. 2000).

Topical intranasal glucocorticoids are considered the gold standard for the treatment of all forms of AR. For the most recent molecules, they have a low systemic bioavailability and a high affinity to the receptors. They have a long-lasting effect with minor adverse events. They are active on sneezing, rhinorrhea and nasal congestion. A meta-analysis published in 1998 confirmed the place of the intranasal steroids in the treatment of AR (Weiner et al. 1998). One position paper of the Joint Task Force for the American Academy of Allergy, Asthma and Immunology does not recommend their use over the counter because of the side effects observed in the past with the older generations of topical glucocorticoids (Passalacqua et al. 2000). The plasma concentrations of intranasal fluticasone and mometasone are low due to extensive metabolism and clearance by cytochrome P450 enzyme 3A4. Caution is recommended when co-administered with potent CYTP3A4 inhibitors, especially in HIV population. Current antiretroviral regimens often contain the HIV protease inhibitor ritonavir, and co-administration with topical fluticasone results in a dramatic increase in the latter bioavailability. This may result in iatrogenic Cushing's syndrome as alerted in increasing number of case reports (Mahlab-Guri et al. 2011; Kedem et al. 2010; Valin et al. 2009; Samaras et al. 2005). Ironically, in patients treated by ritonavir, older generations of topical glucocorticoids appear to be safer options (Foisy et al. 2008). Apart from these particular cases, second-generation topical glucocorticoids (fluticasone, mometasone) remain the first-line and safest treatment for main patients with allergic rhinitis. Intranasal corticosteroids have broad anti-inflammatory activities. They are the most potent long-term pharmacologic treatment of congestion associated with allergic rhinitis and show some congestion relief in rhinosinusitis and nasal polyposis (Table 23.2).

Topical decongestants reduce congestion associated with allergic rhinitis, but because of the risk of rhinitis medicamentosa, they should not be used for prolonged periods. Oral decongestants reduce nasal congestion but may have adverse effects on sleep, even insomnia, because of their stimulatory effects and their association with systemic side effects.

Oral leukotriene receptor antagonists can be of some help in the management of patients unresponsive to the conventional medications. They effectively reduce rhinorrhea, congestion and inflammatory mediators (Ferguson 2004).

Table 23.2 Effect of medical treatment on sleep-related breathing disorders

Reference	Study	Medication	*n*	Symptoms improvement	PSG improvement
Kerr et al. (1992)	Controlled, prospective	Xylometazoline + nasal dilator	10	Yes	No
Craig et al. (1998)	Controlled, prospective	Fluticasone	20	Yes	–
Hughes et al. (2003)	Controlled, prospective	Budesonide	22	Yes	–
Ratner et al. (2003)	Controlled, prospective	Fluticasone vs. montelukast	705	Yes	–
Craig et al. (2003)	Controlled, prospective	Fluticasone	32	Yes	No
Kiely et al. (2004)	Controlled, prospective	Fluticasone	24	Yes	Yes
Craig et al. (2005)	Controlled, prospective (pooled study)	Fluticasone/budesonide/ flunisolide	42	Yes	No
McLean et al. (2005)	Controlled, prospective	Xylometazoline + dilator strip	10	No	Yes
Gurevich et al. (2005)	Controlled, prospective	Budesonide	26	Yes	–

Anticholinergic ipratropium bromide is not considered effective in relieving nasal congestion; however, limited data suggest that sleep and quality of life may be minimally improved with this treatment (Rabasseda 2012).

23.7.2.2 Management of SDB in Rhinitis Patients

Patients with perennial allergic rhinitis often present with nasal congestion, poor sleep quality, daytime fatigue and loss of productivity. Pharmacologic therapy that reduces nasal congestion should improve these symptoms. In the literature there are a lot of publications related to the management of allergic rhinitis and the impact on sleep (Table 23.2). These studies often demonstrate positive effects of the medical treatment on the SDB. However, the majority of these papers are based on subjective assessment (disease-specific quality-of-life measures, quality-of-life questionnaires, general questionnaires, Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, etc.). Only a few studies have objectively assessed sleep (using polysomnography) in allergic rhinitis. In 20 patients with allergic rhinitis and symptoms of daytime sleepiness, flunisolide significantly improved sleep quality and congestion but not daytime sleepiness (Kakumanu et al. 2002). A similar study with fluticasone propionate showed improvement in subjective sleep parameters, but there was no significant change in objective sleep measurements recorded on polysomnography (Craig et al. 2003). On the other hand, Kiely et al. have demonstrated a slight decrease in the AHI in snorers with rhinitis treated with fluticasone propionate compared with placebo (Kiely et al. 2004). Nasal obstruction secondary to allergic inflammation has an impact on sleep quality, and topical corticoid therapy seems to have a positive effect on sleep quality (Rombaux et al. 2005). In one study, 25 patients with seasonal AR and 25 healthy volunteers underwent two consecutive nights of PSG before and during the pollen season (Stuck et al. 2004). There were statistically significant differences between the two groups in sleep parameters, including increases in the apnoea index, hypopnoea index, apnoea-hypopnoea index, snoring time, amount of REM sleep and sleep latency. Nevertheless, the changes were not considered clinically relevant, as values remained within normal limits. Further research involving objective measures is thus still necessary.

23.7.2.3 Treatment of Nasal Valve Collapse with Nasal Dilators

Nasal valve dysfunction is another underrated and underdiagnosed cause of nasal obstruction. The nasal valve obstruction can be static or dynamic. The diagnosis is made by clinical examination, Cottle manoeuvre, anterior and posterior active rhinomanometry and acoustic rhinometry. An easy way to treat a patient with a nasal valve collapse is to use a nasal dilator. Nasal dilators are an attractive method of decreasing nasal resistance in

Table 23.3 Effect of nasal dilators on sleep-related breathing disorders

Reference	Study	Nasal dilators	*n*	Symptoms improvement	PSG improvement
Hoijer et al. (1992)	Noncontrolled, prospective	Nozovent	10	Yes	Yes (36 %)
Hoffstein et al. (1993)	Noncontrolled, prospective	Nozovent	15	–	No
Liistro et al. (1998)	Noncontrolled, prospective	Breathe right	10	–	No
Todorova et al. (1998)	Noncontrolled, prospective	Breathe right	30	Yes	Not significant
Gosepath et al. (1999)	Noncontrolled, prospective	Breathe right	26	–	Yes (15 %)
Bahammam et al. (1999)	Controlled, prospective	Breathe right	18	–	No
Schonhofer et al. (2000)	Noncontrolled prospective	Nozovent	21	–	No
Pevernagie et al. (2000)	Noncontrolled, prospective	Breathe right	12	–	No
Djupesland et al. (2001)	Controlled prospective	Breathe right	18	–	Slight if MCA <0.6 cm^2

MCA mean cross-sectional area

the valve area with subsequently a probable positive impact on snoring and/or apnoea (Petruson 1990). Measurements of nasal resistance in awake subjects with a nasal dilator have shown a reduction in resistance, though not uniform, depending on the compliance of the nasal vestibule walls (Petruson 1994). The dimension of the nasal valve is increased by approximately 30 %. Most sleep studies have considered two devices commercially available as nasal dilators: Nozovent®, an internal device, and Breathe Right®, an external device. Other products are now commercially available like Nasanita®, Airplus®, Respir+®, Francis alar dilator®, Ognibene dilator® and Side Strip® (Ellegard 2006; Riechelmann et al. 2010). There is even a paper on how to bend your own nasal dilator from a plastic-coated paper clip (Cheng and Iriarte 1998). These devices have been studied in patients with polysomnographic measurements in nine studies (Table 23.3). The conclusions from these studies are that nasal dilators may reduce the subjective sensation of snoring. However, objective measurements of snoring and sleep parameters such as AHI reveal that nasal dilators are ineffective in the vast majority of the SDB patients. Nasal dilators may be more effective in patients with SDB with concomitant chronic rhinitis (Pevernagie et al. 2000). Djupesland et al. found that Breathe Right® was an effective treatment of snoring in a subgroup of patients with morning nasal obstruction and when acoustic rhinometry has revealed a minimal cross-sectional area <0.6 cm^2 (Djupesland et al. 2001). Based on this information, nasal dilators although ineffective for the vast majority of apnoeic patients may be recommended as a trial for non-apnoeic snorers. Nasal dilators have no side effects and are relatively inexpensive. They may improve CPAP tolerance and reduce the CPAP pressure level (Schonhofer et al. 2003).

23.7.3 Surgical Management

Surgery concerns nonreversible causes of nasal obstruction: nasal septum deviation, hypertrophy of the mucosa of the inferior turbinates, nasal collapse and nasal polyposis. Two procedures are frequently performed: septoplasty associated or not to turbinates reduction.

Septoplasty involves removing excess septal cartilage and reshaping the cartilage to bring it to the midline. The procedure is usually done under general anaesthesia. Turbinate reduction can be performed with different methods: laser, electrocautery or radiofrequency ablation. The procedure can be done under local or general anaesthesia. Surgery of the nasal valve is not yet extremely popular in SDB. Concerning the nasal polyposis, there is a wide variety of procedures ranging from endoscopic-guided polypectomy (Jankowski et al. 2006; Devars du Mayne et al. 2011).

Table 23.4 summarises the effect of surgical procedures on SDB. Most studies were uncontrolled case series (Li et al. 2011). The main surgical procedure was septoplasty, associated or not with turbinoplasty. Only 11 patients (among 420

Table 23.4 Effect of nasal surgery on sleep-related breathing disorders

Reference	Study	Procedure	*n*	Symptoms improvement	PSG improvement
Verse et al. (2002)	Controlled, prospective	Septoplasty, septorhinoplasty, FESS	26	Yes	No
Kim et al. (2004)	Noncontrolled, retrospective	Septo-turbinoplasty	21	Yes	Yes (19 %)
Virkkula et al. (2006)	Noncontrolled, prospective	Septo-turbinoplasty, septorhinoplasty	40	No	No
Koutsourelakis et al. (2008)	Controlled, prospective	Septoplasty	49	–	No
Li et al. (2008b)	Noncontrolled, prospective	Septo-turbinoplasty	51	Yes	No
Li et al. (2008a)	Noncontrolled, prospective	Septo-turbinoplasty	52	Yes	
Morinaga et al. (2009)	Noncontrolled, prospective	Septo-turbinoplasty, FESS	35	–	Yes (23 %)
Tosun et al. (2009)	Noncontrolled, prospective	FESS	27	Yes	No
Li et al. (2009)	Controlled, prospective	Septo-turbinoplasty	66	Yes	No
Choi et al. (2011)	Noncontrolled, prospective	Septo-turbinoplasty, FESS	22	Yes	No
Sufioglu et al. (2012)	Noncontrolled, prospective	Septoplasty, septorhinoplasty, FESS	31	Yes	No

pooled subjects) underwent septorhinoplasty (Verse et al. 2002; Virkkula et al. 2006; Sufioglu et al. 2012), and the management of the nasal valve was not specifically described. These studies confirmed that current nose surgery improves subjectively the snoring, the daytime sleepiness and the quality of life but failed to improve objective PSG data. Absence of pharyngeal obstruction could predict the success of nose surgery (Morinaga et al. 2009). Conversely, increased nasal resistance could predict the failure of CPAP therapy (Nakata et al. 2005). Most studies have not demonstrated that reducing nasal obstruction and resistance from various causes and using various techniques (e.g. septoplasty, turbinectomy, polypectomy, turbinoplasty) correlate with a significant reduction in objective OSA indicators, such as the apnoea-hypopnoea index (AHI) or nocturnal oxygen desaturation. Three studies suggested the efficacy of combined nasal and pharyngeal surgery on polysomnography parameters (Li et al. 2005; Stow et al. 2012) or snoring (Carroll et al. 2012). Friedman et al. have also suggested that sometimes postoperative polysomnographic data may be worse for mild OSA patients after nasal obstruction relief (Friedman et al. 2000). They explain this paradoxical effect of nasal surgery by the fact that nasal obstruction relief may allow the patients to sleep in deeper sleep stages. Therefore, apnoea and sleep fragmentation increase because patients sleep more comfortably.

Discrepancies in nose surgery outcome studies may be explained by the variety of surgical procedure, the heterogeneity of patients studied and the variety of outcome measurements (quality-of-life questionnaire, polysomnographic values, subjective snoring) (Kotecha 2011). The pathophysiology of the nose function in sleep-related breathing disorders could explain the relative failure of nose surgery. First, these disorders involve multilevel airway obstruction, including airway length, lateral wall thickness, tongue volume and skeletal structure (Mohsenin 2001). One single intervention is therefore unlikely to address the disease. In obese patients, these upper airway anatomic factors may be masked, and obesity is the main etiologic factor for priority handling. Second, usual nose surgery (septoplasty, turbinoplasty) does not attend to correct nose bony framework, which determines the transverse nasal airway dimension, and does not adjust the curvilinear airflow pattern, which is important for the nasopharynx opening. Some researchers speculate that nasal valve surgery combined with a mouth-closing oral appliance may be an ideal therapy for sleep apnoea in nonobese patients

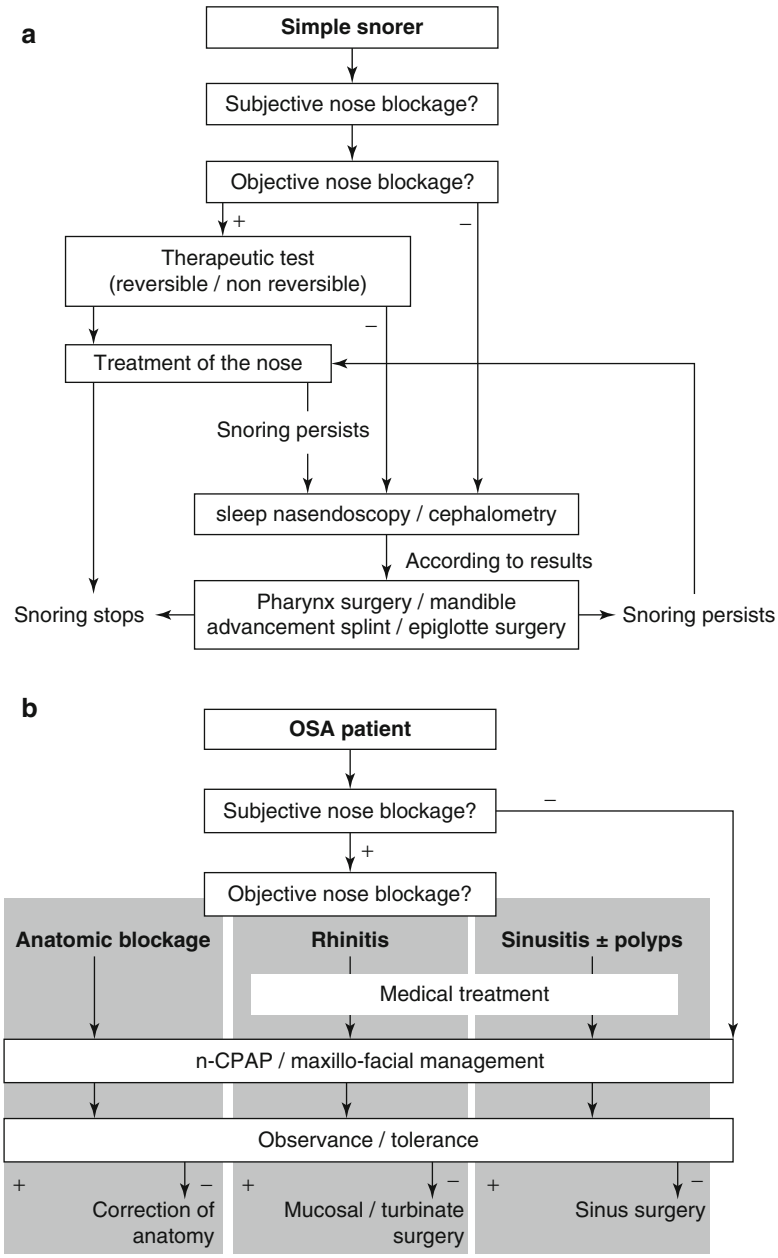

Fig. 23.4 Simplified management scheme for adults with simple snoring (**a**) and OSA (**b**)

(Stupak 2010). This intervention could address the curvilinear airflow pattern and promote nose breathing. Further studies are however necessary to design future surgical algorithms.

Another group of patients that may be considered for nasal surgery are those who have failed CPAP therapy (Kotecha 2011). CPAP therapy remains the first-line therapy of OSA but may cause rhinitis itself and compliance rates ranging from 65 to 80 %. Dry nose or mouth in the morning affects 65 % of the patients. Sneezing and nasal drip are present in more than 35 % of the patients and nasal congestion in 25 % (Pepin et al. 1995). Using a humidifier reduces only poorly the nose side effects (Pepin et al. 1995). A high nasal resistance is a significant risk factor for non-acceptance of CPAP (Sugiura et al. 2007). Careful evaluation of the nose is mandatory to identify the factors that may be correctable, in order to improve compliance. Septoplasty ± turbinoplasty has been shown to allow

for reduced pressure levels of CPAP and easier use of the apparatus (Friedman et al. 2000). Likewise, radiofrequency turbinate reduction increases CPAP adherence (Powell et al. 2001). Early identification and management of OSA patients with high nasal resistance can potentially improve CPAP treatment outcome. However, variable additional factors also impact CPAP compliance, such as individual perception of symptoms and improvement in sleepiness and daily function from initial use of CPAP. For these reasons, larger, well-designed studies are needed to confirm the durability of any beneficial effect on CPAP compliance from nasal surgical procedures for individuals with OSA (Zonato et al. 2006; Weaver and Grunstein 2008; Friedman and Wilson 2009).

To summarise, reducing nasal obstruction and resistance from various causes and using various techniques improve subjectively the snoring, the daytime sleepiness and the quality of life but fails to improve significantly objective data at the polysomnography, such as the apnoea-hypopnoea index (AHI) or nocturnal oxygen desaturation. When some positive effects have been reported, improvement of sleep apnoea occurs only in approximately 15–20 % of the patients. Results of nasal surgery in patients with sleep apnoea/hypopnoea are therefore barely predictable. Nevertheless, nasal procedures improve CPAP compliance in individuals with OSA and nasal obstruction requiring high CPAP settings. A simplified management scheme for adults with SDB is proposed in Fig. 23.4.

Conclusions

Increasing evidence shows that nasal resistance is a contributing risk factor for sleep-related breathing disorders. Nevertheless, nose management alone fails in many cases to address the objective parameters of SDB (Verse et al. 2002; Kohler et al. 2009, 2007). Compelling data are lacking concerning the exact role of obstructed nasal breathing in the pathogenesis of obstructive sleep disorders (Rappai et al. 2003; Chen and Kushida 2003). Under an evidence-based approach, nasal surgery in OSA patients with nasal obstruction effectively ameliorates clinical symptoms of snoring and daytime sleepiness and consequently improves quality of life. However, the efficacy of nasal treatment alone in treating OSA is limited. Nasal management should be integrated in a multimodal approach (diet/smoking cessation/CPAP/mandibular splint/multilevel surgery), truly reflecting the complexity of SDB.

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Pathophysiology of Obstructive Sleep Apnea

24

Kivanc Gunhan

Keywords
Obstructive sleep apnea • Physiology of sleep • Pathophysiology • Wakefulness • Upper airway patency • Pharyngeal collapsibility • Neuromuscular • Neuroventilatory

Core Messages

- Obstructive sleep apnea (OSA) is a common sleep disorder affecting 4 % of men and 2 % of women and is characterized by recurrent episodes of upper airway obstruction and is associated with reductions in ventilation, resulting in recurrent arousals and episodic oxyhemoglobin desaturations during sleep.
- Significant clinical consequences of the disorder cover a wide spectrum including daytime hypersomnolence, neurocognitive dysfunction, cardiovascular disease (hypertension, stroke, myocardial infarction, heart failure), metabolic dysfunction, respiratory failure, and cor pulmonale.
- The major risk factors for the disorder include obesity, male gender, hormones, age, anatomical factors, genetic factors, posture, and gravity.
- Wakefulness provides compensatory neuronal activation of dilator muscles in an anatomically compromised collapsible pharynx supporting ventilator control. Accordingly, when this activation is lost at sleep onset, the airway narrows and/or collapses.
- The mechanical determinants of airway patency are similar to those regulating caliber of any collapsible tube. There is a critical closing pressure (P_{crit}) of the passive airway, which is defined as the pressure inside the airway at which the airway collapses. With increasing P_{crit}, as the differential between Pupstream and P_{crit} decreases, inspiratory airflow limitation will eventually develop and complete airway occlusion occurs.
- Neuromuscular controls of upper airway dynamics during sleep influence the pharyngeal muscle tone and upper airway collapsibility. A variety of defective

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respiratory control mechanisms are found in OSA, including impaired chemical drive, defective inspiratory load responses, and abnormal upper airway protective reflexes.

- Tonic and phasic EMG activity of pharyngeal airway dilator muscles (genioglossus and tensor palatine) is progressively reduced from wakefulness to NREM to REM sleep. Changes in proprioceptive and chemoreceptor feedback play a significant role in the dynamics of upper airway caliber. Chemoreceptor influences also have substantial effects on upper airway muscle recruitment, and in the case of CO_2, upper airway motor neurons relative to phrenic motor neurons have a substantially higher threshold for inhibition (via hypocapnia) and activation (via hypercapnia).

24.1 Pathophysiology of Obstructive Sleep Apnea

> Hypnos was the god of Sleep. He resided in Erebos, the land of eternal darkness, beyond the gates of the rising sun living in the dark cave, in the Hades (Underworld), whose entrance was full of poppies and other hypnotic plants; and that through his cave the river of forgetfulness, Lethe, used to flow. From there he rose into the sky each night in the train of his mother Nyx (the goddess of Night).
>
> Hypnos was often paired with his twin brother Thanatos (the god of peaceful Death). He was married to the youngest of the Graces – Pasithea, a deity of hallucination or relaxation and Morpheus and Phobetor (the gods of Dreams) were their sons.
>
> Hesiod, Theogony (Greek epic, C7th B.C.) (Hesiod 1987)

In the early ages of humanity, sleep was defined as a world of unknown hand in hand with death, whose mystery was full of dreams where everything was forgotten. Compared to other widely studied human behaviors, sleep has been a rather misunderstood phenomenon over the course of human history. Physicians regarded sleep as nothing more than a monolithic loss of consciousness and believed that it was caused by a lack of blood flow to the brain. Many famous scientists and philosophers like Hippocrates, Aristotales, Plato, Galen, and Avicenna had commented over the physiologic and psychological aspects of sleep throughout history, but sleeping and dreaming has been one of the most underresearched areas of human behavior. Despite centuries of speculation and research, we still do not know what sleep really is or exactly what it is for. Allan Rechtschaffen suggested in 1978 that "If sleep does not serve an absolute vital function, then it is the biggest mistake the evolutionary process ever made" (Rechtschaffen 1978).

We have only really begun to study and to understand sleep apnea over the past 40 years. Observations of periodic breathing in sleep were first reported in the mid-1850s, and in the 1870s, physicians reported on several cases of obstructed apneas as "fruitless contractions of the inspiratory and expiratory muscles against glottic obstruction with accompanying cyanosis during sleep" (Rechtschaffen 1978). During the latter half of the nineteenth century, several cases of obese persons with extreme daytime sleepiness were described (Lavie 2003) and labeled the "Pick Wickian syndrome" after Charles Dickens Fat Boy Joe as described in the Pickwick Papers in 1837. By the mid-1960s, Gastaut et al. recognized obstructive sleep apnea in obese subjects as intermittent airway obstruction with frequent arousals, thereby providing the first comprehensive links between obesity, sleep-induced airway obstruction, sleep fragmentation, and daytime sleepiness (Gastaut et al. 1967). Following these key observations, research proceeded slowly with case reports of obstructive sleep apnea and the occasional use of chronic tracheostomy for treatment in the early 1970s (Guilleminault et al. 1973).

Not until recently have scientists attempted to understand how and why we sleep. Currently,

there are four major theories explaining why we sleep, which are adaptive or evolutionary, energy conservation, restorative, and brain plasticity theories. On the other hand, there have been over 100 diseases defined as sleep disorders.

Disturbance of sleep is one of the most detrimental components to our health. Sleep disorders are extremely common in the general population and can lead to significant morbidity. Sleep disturbances lasting at least several nights per month have been reported by 30 % of the population (Young et al. 1993). Sleep disorders may cause or exacerbate preexisting medical and psychiatric conditions and are associated with high rates of depression, anxiety, and impaired daytime functioning (Punjabi et al. 2002; Young et al. 1993). They may also lead to poor occupational performance, motor vehicle accidents, cardiovascular and endocrine disorders, or heightened pain perception (Nieto et al. 2000; Punjabi et al. 2002).

24.2 Obstructive Sleep Apnea

The International Classification of Sleep Disorders, second edition (ICSD-2), subdivides sleep disorders into eight major categories: insomnia, sleep-related breathing disorders, hypersomnias of central origin, circadian rhythm disorders, parasomnias, and sleep-related movement disorders (Adams et al. 2001). Sleep-related breathing disorder describes a group of disorders referring to momentary, often cyclical, cessations in breathing rhythm (apneas) or momentary or sustained reductions in the breath amplitude (hypopneas), sufficient to cause significant arterial hypoxemia and hypercapnia. These apneas and hypopneas are specific to the sleeping state and are accompanied by:

1. A compromised, often even completely closed, extrathoracic upper airway "obstructive" event
2. A marked reduction or cessation of brain stem respiratory motor output "central" event
3. A combination of central and obstructive events

These ventilatory inadequacies and their accompanying intermittent hypoxemia often lead to transient arousals from sleep and sleep state fragmentation throughout the night and cause overcompensatory responses of the autonomic nervous system. Obstructive sleep apnea, the most common such disorder, is characterized by the repetitive collapse or partial collapse of the pharyngeal airway during sleep and the need to arouse to resume ventilation. Sleep is thus disrupted, yielding waking somnolence and diminished neurocognitive performance. The recurrent sleep arousal in association with intermittent hypoxia and hypercapnia has been implicated in the occurrence of adverse cardiovascular outcomes and insulin resistance. Despite considerable progress, most patients remain undiagnosed, and the principal therapeutic approach, continuous positive airway pressure (CPAP), remains somewhat cumbersome and hence not associated with optimal compliance rates.

Obstructive sleep apnea is a highly prevalent disease, affecting 4 % of men and 2 % of women. The major risk factors for OSA include obesity, male gender, postmenopausal status, age, anatomical factors, posture and gravity, genetic factors, and hypothyroidism (Table 24.1).

In the presence of an anatomically compromised, collapsible airway, the sleep-induced loss of compensatory tonic input to the upper airway dilator muscle motor neurons leads to collapse of the pharyngeal airway. In turn, the ability of the sleeping subject to compensate for this airway obstruction will determine the degree of cycling of these events. Several of the classic neurotransmitters and a growing list of neuromodulators have now been identified that contribute to neurochemical regulation of pharyngeal motor neuron activity and airway patency.

Knowledge and understanding of the pathogenic basis, clinical presentation, and diagnosis of OSA are essential for the development of preventive, screening, and therapeutic strategies to reduce the public health burden of the disorder (Adams et al. 2001).

Table 24.1 Mechanisms involved in the genesis of OSA

Obesity	High body mass index. Central or visceral obesity is quite important. Predisposing factors: abdominal circumference >94 cm in men and >80 cm in women; neck circumference >40 cm
Gender	Prevalence is higher in men than in women. Women present greater genioglossus muscle tone, which can be considered a defense mechanism designed to maintain upper airway permeability
Hormones	Estrogen and progesterone promote the maintenance of upper airway permeability (by improving muscle tone) as well as increasing respiratory drive. The androgens induce greater fat deposition and relaxation of the pharyngeal dilator muscles. Menopause also increases the risk of OSA
Age	The activity of the upper airway musculature is decreased with aging
Anatomical factors	Micrognathia and hypoplasia of the mandible are associated with the posterior positioning of the base of the tongue and with upper airway narrowing. Thickening of the lateral pharyngeal walls also causes upper airway narrowing
Genetic factors	Some risk factors, such as craniofacial structure, distribution of body fat, neural control of the upper airways, and central respiratory command, can be inherited
Posture and gravity	The dorsal decubitus position promotes the posterior positioning of the tongue and soft palate, thereby reducing the area of the oropharynx
Other causes	Acromegaly, Down's syndrome, hypothyroidism, genetic syndromes, and deposition diseases (amyloidosis and mucopolysaccharidosis) can promote the narrowing of the upper airways, which are predisposing factors for OSA

24.3 Influences of Wakefulness on Ventilatory Control

Remarkably, sleep apnea patients experience little or no problems with their breathing or airway patency while awake. In fact, the great majority of people with sleep apnea possess ventilatory control systems that are capable of precise regulation of their alveolar ventilation and arterial blood gases with extremely small variations from the norm throughout the waking hours. In addition, these healthy control systems, while awake, possess sufficiently sensitive feedback and feed forward controls to ensure precise coordination of chest wall and upper airway "respiratory" muscle recruitment so as to provide maximum airway diameter, low airway resistance, and optimum lung volumes and respiratory muscle lengths, regardless of the ventilatory requirement.

To underscore the importance of the "waking stimuli" to breath and to upper airway patency and to ventilatory control, consider the following qualitative influences of sleep on the control of breathing. Electrical activity from medullary inspiratory neurons, EMG activity of diaphragm and abductor muscles of the upper airway in healthy humans and/or in cats, shows reductions in amplitude upon the transition from awake to NREM sleep, usually accompanied by a mild-to-moderate hypoventilation (2–8 mmHg $PaCO_2$) and two- to fivefold increases in upper airway resistance (Dempsey et al. 2002). Sleep induces consistently greater proportional reductions in the EMG activity in the upper airway versus chest wall pump muscles (Orem et al. 2002).

$PaCO_2$ can be lowered substantially (using mechanical ventilation) during wakefulness with little or no disruption of breathing pattern; however, in NREM sleep, very small transient reductions in $PaCO_2$ (even only to the waking level) result in significant apnea (Meza et al. 1998).

Sleep-disordered breathing leading to repeated bouts of ventilatory overshoots and undershoots and accompanying swings in arterial blood gases and intrathoracic pressure takes on many forms. Commonly, sleep-disordered breathing is divided into so-called "central" events, denoting an absence or marked reduction in central respiratory motor output to respiratory pump muscles, or "obstructive" events, which are comprised of respiratory efforts against a closed upper airway. However, as we discuss below, most cyclical sleep-disordered breathing events are driven by anomalies in both anatomical and neurochemical control of upper airway and/or chest wall respiratory musculature.

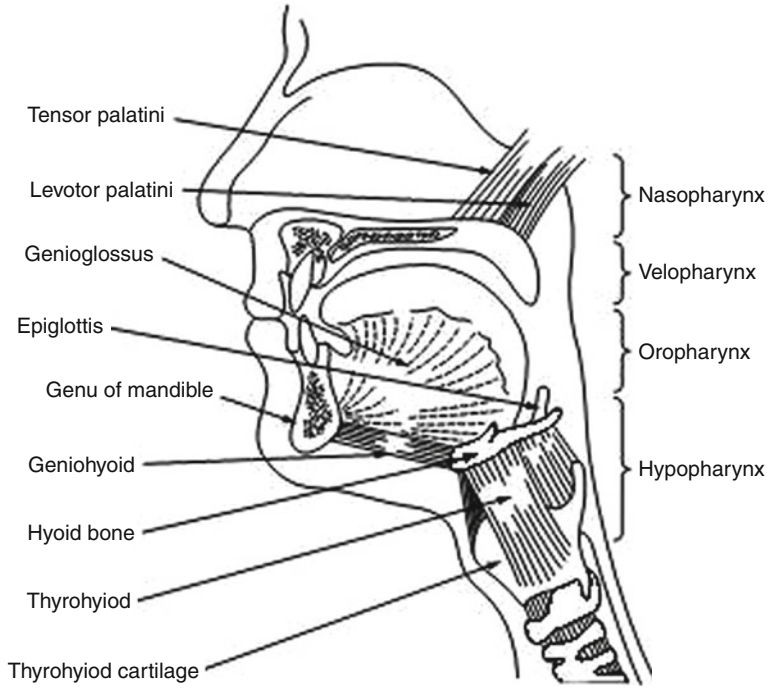

Fig. 24.1 Anatomy of the upper airway and the important muscles controlling the airway patency

In short, the process is initiated because the wakeful state provides compensatory neuronal activation of dilator muscles in an anatomically compromised collapsible pharynx; accordingly, when this activation is lost at sleep onset, the airway narrows and/or collapses. However, the tendency to result (or not to result) in repeated cyclical apneas is the end product of multiple compensatory processes that vary markedly among and within individuals. Concepts have continued to evolve as we learn more about the neurophysiological mechanisms governing control of respiratory rhythm and its coupling with upper airway control and states of consciousness and applying these principles to human patients during sleep.

We will discuss the pathophysiology of OSA in three steps. First, we detail the varied structural and functional determinants of an anatomical predisposition for airway closure, an absolutely essential component for OSA. The second essential component is sleep. This section emphasizes the effects of the sleeping state on mechanisms underlying both obstructive and central apnea and ventilatory instability. Finally, we attempt to integrate anatomical deficits with mechanisms underlying central neurochemical control of breathing stability and compensatory neuromuscular control of upper airway caliber, to explain the repetitive nature of OSA.

24.3.1 Anatomical Determinants of Upper Airway in OSA

The pharyngeal airway is a complex structure that serves several purposes including speech, swallowing, and respiration. The human pharynx is composed of more than 20 muscles and divided into four sections that include the nasopharynx (from the nasal turbinates to the start of the soft palate), velopharynx (from the start of the soft palate to the tip of the uvula), oropharynx (from the tip of the uvula to the tip of the epiglottis), and hypopharynx (from the tip of the epiglottis to the level of the vocal cords) (Fig. 24.1). The human pharynx can be considered as a collapsible tube that is uniquely susceptible to collapse due to the presence of a floating hyoid bone, a longer airway, and a less direct route for inspired air to travel when compared to other mammals. The presence of soft tissues and bony structures,

which increase extraluminal tissue pressures surrounding the upper airway, can predispose the pharynx to collapse. In contrast, the actions of pharyngeal dilator muscles maintain pharyngeal patency due to reflex pathways from the central nervous system and within the pharynx. The presence of these opposing forces suggests that increased pharyngeal collapsibility is due to alterations in anatomically imposed mechanical loads and/or in dynamic neuromuscular responses to upper airway obstruction during sleep.

24.3.1.1 Unique Anatomy of the Human Airway

The upper airway is a complex structure required to perform deglutition, vocalization, and respiration. In the human, this structure must also perform tightly controlled and complex motor behaviors required for speech. Upper airway obstruction in sleep is most prevalent in the human in part because the hyoid bone, a key anchoring site for pharyngeal dilator muscles, is not rigidly attached to skeletal structures (Friberg et al. 1997). In other mammals, the hyoid bone is attached to the styloid processes of the skull. Thus, the human pharynx has no rigid support except at its extreme upper and lower ends where it is anchored to bone (upper) and cartilage (larynx); therefore, pharyngeal cross-sectional area will vary with lumen pressure. Humans depend critically on the coordinated actions and interactions of over 20 skeletal muscles that dilate and stent open the oropharynx.

Beyond the hyoid arch, it is also pointed to the anatomical changes in the adult human upper airway during the evolutionary development of speech as a potential major contributor to OSA (Moser and Rajagopal 1987). Specifically, the gradual descent of the larynx to a position greatly inferior to the oropharynx separated the soft palate from the epiglottis in which the tongue encroaches significantly on the available space.

24.3.1.2 Sites of Airway Collapse

Studies using nasal pharyngoscopy, computer tomography and magnetic resonance imaging, or pharyngeal pressure monitoring have shown that one or more sites within the oral pharyngeal region are usually where closure occurs in most subjects with OSA, and this region is also smaller in OSA patients versus controls even during wakefulness (Schwab et al. 2005). Although the retropalatal region of the oropharynx is the most common site of collapse, airway narrowing is a dynamic process, varying markedly among and within subjects and often includes the retroglossal and hypopharyngeal areas (Tankersley et al. 1999).

24.3.1.3 Soft Tissue and Bony Structure Abnormalities

The recent use of quantitative imaging techniques has allowed advances that reveal important differences in both craniofacial and upper airway soft tissue structures in the OSA patient. The reduced size of cranial bony structures in the OSA patient includes a reduced mandibular body length, inferior positioned hyoid bone, and retroposition of the maxilla, all of which compromise the pharyngeal airspace (Bacon et al. 1990). Airway length, from the top of the hard palate to the base of the epiglottis, is also increased in OSA patients, perhaps reflecting the increased proportion of collapsible airway exposed to collapsing pressures (Malhotra et al. 2001). As expected, these craniofacial dimensions are primarily inherited, as the relatives of OSA patients demonstrated retroposed and short mandibles and inferiorly placed hyoid bones, longer soft palates, wider uvulas, and higher narrower hard palates than matched controls (Schwab et al. 1997).

Enlargement of soft tissue structures both within and surrounding the airway contributes significantly to pharyngeal airway narrowing in most cases of OSA. An enlarged soft palate and tongue would encroach on airway diameter in the anterior-posterior plane, while the thickened pharyngeal walls would encroach in the lateral plane. Volumetric time overlapped magnetic resonance imaging (MRI) or computer tomography (CT) images strongly implicate the thickness of the lateral pharyngeal walls as a major site of airway compromise, as the airway is narrowed primarily in the lateral dimension in the majority of OSA patients (Schwab et al. 1997). Furthermore,

treatment with CPAP, weight loss, or mandibular advancement all show increases in the lateral pharyngeal dimensions (Schwab et al. 1997). There are many potential causes of lateral wall thickening in OSA patients. First, as shown in both humans and rodent models, obesity is a major contributor to airway compression through increased area and volume of pharyngeal fat deposits (Brennick et al. 2009). This excess fat deposition has also been observed under the mandible and within the tongue, soft palate, or uvula. Obesity also gives rise to excess fat-free muscular tissue, thereby increasing the size of many upper airway structures and compressing the lateral airway walls. In children with OSA, tonsillar hypertrophy and adenoid hypertrophy form the major anatomical contributors to airway narrowing (Brennick et al. 2009).

24.3.1.4 Obesity and Lung Volume

Obesity also contributes indirectly to upper airway narrowing, especially in the hypotonic airway present during sleep, because lung volumes are markedly reduced by a combination of increased abdominal fat mass and the recumbent posture. In turn, the reduced lung volume reduces the "tug" on the trachea induced by the traction exerted via mediastinal structures by negative intrathoracic pressures and by the diaphragm descent, thereby further increasing the thickness of the lateral pharyngeal walls and narrowing the airway.

24.3.1.5 Airway Edema and Surface Tension

Surface tension of the liquid lining the mucosa affects collapsibility of the upper airway in the same way as it has been well documented in the lung's airways. A higher surface tension in the upper airway wall of OSA patients has been reported using a method that quantifies surface tension as the force required to separate two surfaces bridged by a droplet of the liquid under study. Furthermore, in limited studies, surfactant therapy in OSA patients was shown to significantly reduce airway collapsibility and improve apnea-hypopnea index (AHI) by 20–30 % (Gleadhill et al. 1991).

24.3.1.6 Obesity, Leptin, and Inflammation

Central, or visceral, obesity is associated with the greatest risk for OSA (Shinohara et al. 1997). This suggests that factors other than pure mechanical load may contribute to the pathogenesis of respiratory disturbances during sleep. The concept is now emerging that visceral fat depots, which represent a rich source of humoral mediators and inflammatory cytokines, can impact on neural pathways associated with respiratory control (Schwartz et al. 2008). Perhaps the most well-studied adipocyte-derived factor affecting respiratory control is leptin, which was initially determined to have a primary role of binding to receptors in the hypothalamus to reduce satiety and increase metabolism. Leptin can also act as a respiratory stimulant, and impairment of the leptin signaling pathway, as occurs in leptin-resistant or leptin-deficient states of obesity, causes respiratory depression in mice and is associated with obesity hypoventilation syndrome in humans. Even though obesity and OSA are associated with elevated circulating levels of leptin, if centers in the brain impacting on respiratory control act in a similar leptin-resistant manner to hypothalamic regions controlling appetite and metabolism, then impaired leptin signaling in the CNS may contribute to respiratory depression as predicted in murine studies.

In addition to respiratory control, animal studies show that leptin is also critical in lung development and affects the distribution of muscle fiber types in the diaphragm. However, as yet there is no direct evidence that impaired leptin signaling can impact on the control of respiratory muscles of the upper airway, although it may play a role in nocturnal hypoventilation, particularly in REM sleep where respiration is markedly depressed in leptin-deficient mice (Tankersley et al. 1999).

24.3.2 Mechanical Determinants of Upper Airway Patency

Mechanical determinants of airway caliber of the human pharynx in sleep are similar to those

regulating caliber of any collapsible tube (Schwab et al. 2005). Other well-known biological examples in respiratory physiology include intrathoracic airway collapse upon forced exhalation, collapse of pulmonary capillaries in the lung apex, and collapse of alae nase at high inspiratory flow rates. A Starling resistor model developed by Schwartz and colleagues consists of a collapsible tube with a sealed box interposed between two rigid segments (Gold and Schwartz 1996). The critical closing pressure (P_{crit}) of the passive airway is defined as the pressure inside the airway (P_{in}) at which the airway collapses. The pressure gradient during airflow through the system is defined by Pupstream and P_{crit} and remains independent of Pdownstream. Therefore, with increasing P_{crit}, as the differential between Pupstream and P_{crit} decreases, inspiratory airflow limitation will eventually develop, and when the P_{us} falls below P_{crit}, complete airway occlusion occurs (Fig. 24.2). Effective therapy for sleep apnea requires that the P_{us} to P_{crit} pressure differential be widened, and this can be accomplished by either:

1. An increase in P_{us} with appropriate amounts of CPAP applied at the airway opening, or
2. By decreasing P_{crit} via either reducing the collapsing pressures on the airway (e.g., weight loss or alteration of cranial-facial anatomy or increasing lung volume) or by augmenting "active" neuromuscular control of airway tone (Gold and Schwartz 1996)

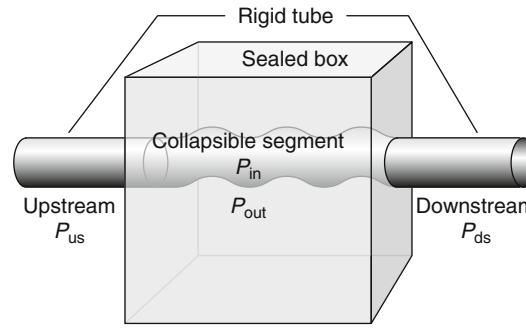

Fig. 24.2 Starling resistor model of obstructive sleep apnea. In the Starling resistor model, the collapsible segment of the tube is bound by an upstream and downstream segment with corresponding upstream pressure (P_{us}), downstream pressure (P_{ds}), and upstream resistance and downstream resistance. Airway occlusion occurs when the surrounding tissue pressure (P_{out}) (comprised of pharyngeal muscles and pharyngeal and submucosal fat, mucosal edema, etc.; see Sect. IIIC) becomes greater than the intraluminal pressure (P_{in}), resulting in a transmural pressure of zero. In this model of the upper airway, P_{us} is atmospheric at the airway opening, and P_{ds} is the tracheal pressure. The critical closing pressure of the collapsible airway (P_{crit}) is represented by P_{in}. When the P_{crit} is significantly lower than P_{us} and P_{ds}, flow through the tube occurs. When P_{ds} falls during inspiration below P_{crit}, inspiratory airflow limitation occurs and is independent of further decreases in P_{ds}. Under this condition, the pharynx is in a state of partial collapse, and maximal inspiratory airflow varies linearly as a function of the difference between P_{us} and P_{crit}. Finally, when P_{us} falls below P_{crit}, the upper airway is completely occluded

24.3.3 Neuromuscular Control of Upper Airway Dynamics in Sleep

Clearly the effects of airway anatomy on airway collapsing pressure in a hypotonic airway are a critical determinant of obstructive apnea. However, several lines of evidence also support neuromuscular factors as significant determinants of airway collapsibility in sleep. First, tonic and phasic EMG activities of pharyngeal airway dilator muscles (genioglossus and tensor palatine) are progressively reduced from wakefulness to NREM to REM sleep and further inhibited coincident with the "phasic" eye movement events in REM. This powerful effect of state has been adequately documented in tracheostomized animal models and recently has been demonstrated in OSA patients in whom the potentially confounding, compensatory responses to sleep-induced changes in upper airway resistance, negative pressure, $PaCO_2$, and respiratory motor output were controlled through the use of either CPAP or positive pressure controlled mechanical ventilation (Lu et al. 2006). These state effects on the neuromuscular control of the upper airway likely explain, along with reductions in lung volume, why P_{crit} is never positive in the waking state, even in OSA patients.

Second, neuromuscular factors also play a significant role in the dynamic breath-to-breath and intrabreath regulation of upper airway caliber,

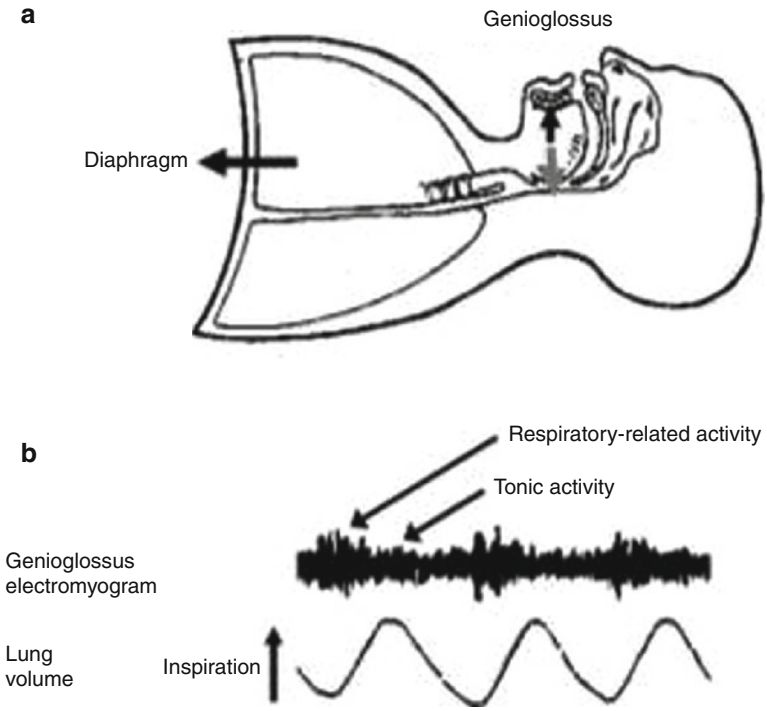

Fig. 24.3 (**a**) Contraction of the diaphragm and chest wall muscles leads to the generation of subatmospheric pressures in the thoracic cavity and airflow into the lungs. For effective lung ventilation, however, this airflow must pass through an open upper airspace. Activation of the pharyngeal muscles, such as the genioglossus muscle of the tongue, helps keep the upper airspace open for effective passage of air. Pharyngeal muscle activation acts to enlarge the airspace. Importantly, reduced pharyngeal muscle tone in sleep can reduce the size of the upper airspace and even promote complete airway obstruction. This tendency for airway collapse is exacerbated by increased weight of the tongue or neck (e.g., caused by obesity), an already anatomically narrow upper airway (e.g., caused by adenotonsillar hypertrophy), or the supine sleeping position. (**b**) The pharyngeal muscles exhibit respiratory-related activity superimposed upon a background of tonic activity. The background tonic muscle tone contributes to baseline airway size and stiffness. The increased pharyngeal muscle activity during inspiration enlarges and further stiffens the airspace to resist the subatmospheric collapsing pressures generated during inspiration

through changes in proprioceptive and chemoreceptor feedback. During inspiration, the passive pharynx narrows as intraluminal pressure is progressively reduced because of energy lost in overcoming frictional airway resistance and increases in flow velocity secondary to the Bernoulli effect operating in a reduced lumen size (Schwab et al. 2005). This collapsing effect of a reduced luminal pressure is opposed during inspiration by a reduction in dynamic compliance, i.e., collapsibility, of the airway achieved via reflex activation of pharyngeal dilator muscles. In turn, the reflex activation occurs in response to negative pressure airway mechanoreceptors located principally in the larynx and to a lesser extent in the superficial layers of the pharyngeal wall, with their afferent projections located in the superior laryngeal nerve, and also in glossopharyngeal and trigeminal nerves (Schneider et al. 2002). Large changes in negative pressure in the isolated upper airway trigger a dual protective reflex, which restores airway patency by both activating airway dilators (to reduce airway compliance) while inhibiting diaphragm EMG activity (which minimizes intraluminal negative pressure) (Fig. 24.3). Vagally mediated feedback influences on laryngeal, tongue, and hyoid muscle via pulmonary stretch receptors also protect against airway collapse as the rate of lung inflation is slowed in the face of

increased airway resistance, thereby reflexly activating upper airway motor neurons.

Finally, chemoreceptor influences also have substantial effects on upper airway muscle recruitment, and in the case of CO_2, upper airway motor neurons relative to phrenic motor neurons have been shown to have a substantially higher threshold for inhibition (via hypocapnia) and activation (via hypercapnia) (Weiner et al. 2002).

In summary, the evidence to date supports important roles for both anatomical and neural control of dilator muscles to the regulation of upper airway caliber in the sleeping human. The relative contributions of these factors will vary widely among and within individuals with, for example, patterns of fat deposition on the one hand and neurochemical sensitivity for dilator muscle recruitment on the other.

24.4 Measurements of Pharyngeal Collapsibility

Quantitative measurements of mechanical and neuromuscular contributions to pharyngeal collapsibility have been difficult to derive during sleep. One approach has been to model the upper airway as a collapsible tube (i.e., a Starling resistor) as mentioned above. The relationship of pressure and flow through collapsible tubes has been well defined in the pulmonary and systemic circulation, the intrathoracic airways, and more recently the upper airway. In the Starling resistor model (Fig. 24.2), the collapsible segment of the tube is bound by an upstream and downstream segment with corresponding upstream pressure (P_{us}), downstream pressure (P_{ds}), and upstream resistance and downstream resistance. Occlusion occurs when the surrounding pressure (P_{crit}) becomes greater than the intraluminal pressure, resulting in a transmural pressure of zero. In this model of the upper airway, P_{us} is atmospheric at the airway opening, and P_{ds} is the tracheal pressure. When the P_{crit} is significantly lower than the P_{us} and P_{ds} ($P_{us} > P_{ds} > P_{crit}$), flow through the tube follows the principles of an Ohmic resistor. When the P_{ds} falls during inspiration below P_{crit} ($P_{us} > P_{crit} > P_{ds}$), inspiratory airflow limitation occurs and is independent of further decreases in P_{ds}. Under this condition, the pharynx is in a state of partial collapse, and maximal inspiratory airflow varies linearly as a function of the difference between the P_{us} and P_{crit}. Finally, when the P_{us} falls below P_{crit} ($P_{crit} > P_{us} > P_{ds}$), the upper airway is occluded.

Operationally, P_{crit} in the human upper airway is determined by lowering the nasal pressure until inspiratory airflow ceases. Measurements of P_{crit} have been shown to define a spectrum of upper airway obstruction from normal breathing ($P_{crit} < -10$ cm cmH_2O), to snoring (P_{crit} range, −10 to −5 cmH_2O), to obstructive hypopneas (P_{crit} range, −5 to 0 cm cmH_2O), and, finally, obstructive apneas ($P_{crit} > 0$ cmH_2O) during sleep (Gleadhill et al. 1991). Patients with the upper airway resistance syndrome (UARS), an entity characterized by flow-limited breathing that results in arousals, have been shown to have P_{crit} levels that are between snoring and hypopneas (Gold et al. 2002). Depending on the methodology, measurements of P_{crit} reflect either the contributions of anatomically imposed mechanical loads on the upper airway or dynamic neuromuscular responses that maintain upper airway patency (Fig. 24.4).

24.5 Contribution of Anatomic Factors to OSA

OSA is known to be associated with alterations in upper airway anatomy. Structural changes including tonsillar hypertrophy, retrognathia, and variations in craniofacial structures have been linked to an increased risk of sleep apnea, presumably by increasing upper airway collapsibility (Lyberg et al. 1989; Moser and Rajagopal 1987; Watanabe et al. 2002). Ethnic differences in craniofacial features are one potential mechanistic explanation for observed differences in OSA prevalence and severity for a given level of obesity (Lyberg et al. 1989). During wakefulness, CT and MRI studies have demonstrated increased fatty tissue deposition and submucosal edema in the lateral walls of the pharynx, both of which narrow the pharyngeal lumen and may predispose to obstruction during sleep (Haponik et al. 1983).

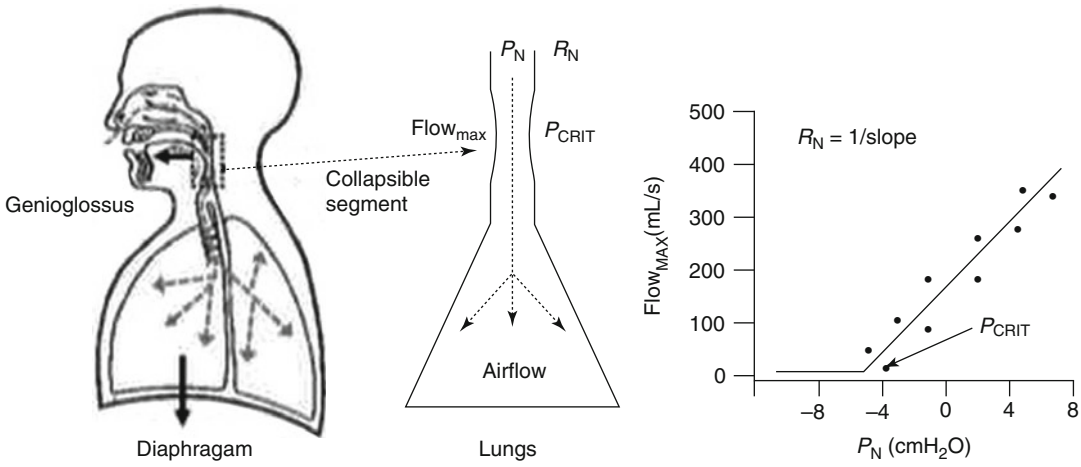

Fig. 24.4 Airflow into the lungs is generated by contraction of the primary respiratory muscles (e.g., diaphragm and intercostal muscles) and modulated by contraction of the secondary respiratory muscles (e.g., genioglossus muscle), which helps keep the upper airway open for effective airflow. The upper airway has been modeled as a collapsible tube where maximum airflow through the collapsible segment of the pharynx ($Flow_{MAX}$) is determined by upstream nasal pressure (P_N) and resistance (R_N). Airflow ceases in the collapsible pharyngeal segment of the upper airway at a particular value of critical pressure (P_{CRIT}). Maximum airflow through the upper airway is determined by $(P_N - P_{CRIT})/R_N$. This relationship is linear, and experimentally induced decreases in P_N decrease $Flow_{MAX}$ and ultimately elicit complete airway collapse

Based on the presence of upper airway anatomic alterations in OSA patients, it has been proposed that structural or mechanical alterations are a primary determinant of upper airway obstruction during sleep (Isono et al. 1997). Recent data suggest that structural alterations in the lateral pharyngeal walls and tongue aggregate on a familial basis, suggesting genetic susceptibility to OSA (Schwab et al. 2006). In addition, experimental data in the absence of neuromuscular activity demonstrate a reduction in maximal pharyngeal area and elevated P_{crit} in OSA subjects compared with normal subjects (Isono et al. 1995). Furthermore, obesity, jaw position, acromegaly, tonsillar hypertrophy, and a smaller bony enclosure surrounding the pharynx have been demonstrated to predispose toward pharyngeal collapsibility (Kato et al. 2000). These studies imply that upper airway structural differences distinguish OSA patients from normal subjects and may predispose to upper airway obstruction when protective neuromuscular mechanisms wane at sleep onset (Fogel et al. 2005).

Obesity, the major risk factor for OSA, has been linked with elevations in neck circumference and increased amounts of peripharyngeal fat, which could narrow and compress the upper airway (Davies and Stradling 1990). Furthermore, increased parapharyngeal fat has been correlated with increased sleep apnea severity (Shelton et al. 1993). The compressive effects of fatty tissue deposited around the pharynx may increase upper airway collapsibility and possibly offset the effects of dilator muscles that maintain airway patency. Obesity may also increase pharyngeal collapsibility through reductions in lung volumes, particularly decreases in functional residual capacity, which are accentuated with the onset of sleep. Reductions in function residual capacity may increase pharyngeal collapsibility through reductions in tracheal traction on the pharyngeal segment. Conversely, increases in lung volumes result in increased tracheal traction and stabilize the upper airway during inspiration (Series and Marc 1993). In OSA patients, increases in lung volumes have been shown to decrease continuous positive airway pressure (CPAP) requirements and OSA severity, suggesting corresponding improvements in pharyngeal collapsibility (Heinzer et al. 2005, 2006).

24.6 Contribution of Neuromuscular Factors to OSA

It should be noted, however, that anatomically imposed mechanical loads on the upper airway might not be sufficient to produce pharyngeal collapse during sleep. For example, women have been shown to have a smaller pharynx and oropharyngeal junction than men, despite having a lower prevalence of OSA (Mohsenin 2001). Furthermore, measurements of P_{crit} under conditions of low neuromuscular activity, which reflect upper airway mechanical loads, demonstrate significant overlap between OSA and normal subjects (Patil et al. 2007). Thus, nonstructural (i.e., neuromuscular) factors must also play a role in protecting the upper airway. In fact, changes in upper airway neuromuscular activity during sleep were originally described by Remmers et al., who demonstrated that genioglossal electromyogram (EMGGG) activity was reduced at apnea onset and increased with arousal when airway patency was restored (Remmers et al. 1978). Subsequently, it was recognized that upper airway obstruction could trigger a variety of neuromuscular responses that restore upper airway patency by recruiting muscles that dilate and elongate the airway. Various pharyngeal muscle groups are important in stabilizing the upper airway throughout the respiratory cycle (tonic activity, e.g., tensor palatini) and in dilating the airway during inspiration (phasic activity, e.g., genioglossus). Pharyngeal motor output is modulated by a number of factors that include wake versus sleep state-dependent mechanisms, local mechanoreceptor responses to negative pressure, and ventilatory control mechanisms.

In OSA patients during wakefulness, elevated genioglossal and tensor palatini muscle activity has been observed and is significantly lowered with the application of positive nasal pressure (Mezzanotte et al. 1996). In contrast, normal subjects had lower levels of genioglossal and tensor palatini muscle activity that were not further reduced when positive nasal pressure was applied. These observations suggested that increased upper airway dilator muscle activity compensates for a more anatomically narrow upper airway in the OSA patient. Thus, reductions in upper airway muscle activity with sleep onset through serotonergic, cholinergic, noradrenergic, and histaminergic pathways may lead to upper airway obstruction and have been hypothesized to be due to the loss of a "wakefulness stimulus" that may be greater in OSA patients than healthy control subjects (Mezzanotte et al. 1996).

Pressure-sensing mechanisms play a prominent role in modulating upper airway neuromuscular activity during wakefulness and sleep. A negative pressure reflex within the upper airway serves to stabilize the upper airway during inspiration. At least three lines of evidence suggest that the negative pressure reflex is primarily mediated by mechanoreceptors within the pharynx. First, there is a tight relationship between EMGGG and pharyngeal pressure independent of the central respiratory pattern generator within the brain stem (Akahoshi et al. 2001). Second, topical anesthesia to the pharyngeal mucosa attenuates the relationship between genioglossal muscle activity and pharyngeal pressure with an increased number of obstructive apneas and hypopneas during sleep in normal subjects and loud snorers and/or increased duration of apneic episodes (Berry et al. 1995). Third, marked decreases in EMGGG activity with corresponding increases in pharyngeal collapsibility have been observed in patients when breathing through a tracheostomy compared to nasal breathing, suggesting that negative pressure within the pharynx during inspiration stabilizes upper airway patency (Malhotra et al. 2000; Schneider et al. 2002).

It is possible that OSA results from trauma to the upper airway due to repetitive collapsing and opening of the upper airway over time, resulting in muscle and neuronal fiber injury. Upper airway sensory pathways may be impaired in OSA patients because temperature, two-point discrimination, and vibratory thresholds are disrupted in OSA patients compared to normal individuals (Guilleminault et al. 2002; Kimoff et al. 2001). Sensory receptor dysfunction could attenuate the response of upper airway dilator muscles to the

markedly negative airway pressures generated during periods of upper airway obstruction. Further evidence for sensorimotor dysfunction and an upper airway myopathy is provided by graded histopathologic and immunochemical alterations in the palatopharyngeus and muscularis uvulae in OSA patients, relative to asymptomatic snorers and normal subjects (Friberg et al. 1997; Lindman and Stal 2002). The extent to which such mechanisms are important in the pathogenesis of OSA, however, remains to be established.

24.7 Contribution of Neuroventilatory Factors to OSA

Ventilatory control mechanisms may also play a role in modulating pharyngeal collapsibility during sleep. Preactivation of the pharyngeal dilator muscles stabilizes the upper airway prior to the inflow of air and suggests CNS coordination between the upper airway and diaphragm. The CNS is influenced by central and peripheral chemoreceptors with conditions of hypercapnia and hypoxemia increasing central drive to the upper airway and decreasing pharyngeal collapsibility (Seelagy et al. 1994). Increased hypercapnic ventilatory responses, prolonged circulatory times, or low oxygen stores within the body can result in ventilatory instability that leads to the development of periodic breathing (Cherniack and Longobardo 2006). Sleep also unmasks a highly sensitive apneic threshold (the $PaCO_2$ level below which an apnea occurs) that remains within 1–2 mm Hg of the normal waking eupnic $PaCO_2$ level. Therefore, a brisk ventilatory response as seen during an arousal in the susceptible individual can result in hypocapnia that is near or at the sleeping apneic threshold and result in a hypopnea or apnea with the reinitiation of sleep (Dempsey et al. 2004). In fact, measurements of loop gain, a measure of ventilatory control instability, have been demonstrated to be high in patients with more severe OSA compared to patients with mild OSA (Eckert et al. 2007; White 2005). In contrast, during periods of ventilatory instability, individuals with low levels of mechanical loads on the upper airway appear to be resistant to the development of upper airway obstruction (Wellman et al. 2004).

Nevertheless, whether alteration of loop gain is important in the pathogenesis of upper airway obstruction or is a consequence of OSA has not been established. OSA can develop in normal subjects with the application of negative nasal pressure to the upper airway (lowering the P_{us} near or below the P_{crit} level seen in normal subjects), which reduces the transmural pressure across the upper airway to near or below zero and results in upper airway obstruction with recurrent obstructive hypopneas and/or apneas (King et al. 2000).

24.8 Interaction of Anatomic and Neuromuscular Factors on Pharyngeal Collapsibility

It is likely that a combination of upper airway mechanical loads and disturbances in neuromuscular mechanisms accounts for the pathogenesis of OSA. For example, in a group of OSA subjects, one third of the variability in OSA severity was ascribed to mechanical loads, suggesting that neuromuscular mechanisms accounted for the remaining two thirds (Younes 2003). Using techniques to partition the relative contribution of mechanical and neuromuscular factors toward pharyngeal collapsibility, it has been shown that OSA patients during sleep have both an increased mechanical load on the upper airway (passive P_{crit}) and impaired neuromuscular responses to upper airway obstruction (active P_{crit}). As demonstrated in Fig. 24.4, a P_{crit} of approximately −5 cmH_2O represents the disease threshold, above which obstructive hypopneas and apneas occur. In normal subjects, when mechanical loads on the upper airway lowered the P_{crit} below the disease threshold, OSA is not present. In contrast, subgroups of normal subjects elevate mechanical loads that raised the P_{crit} above the

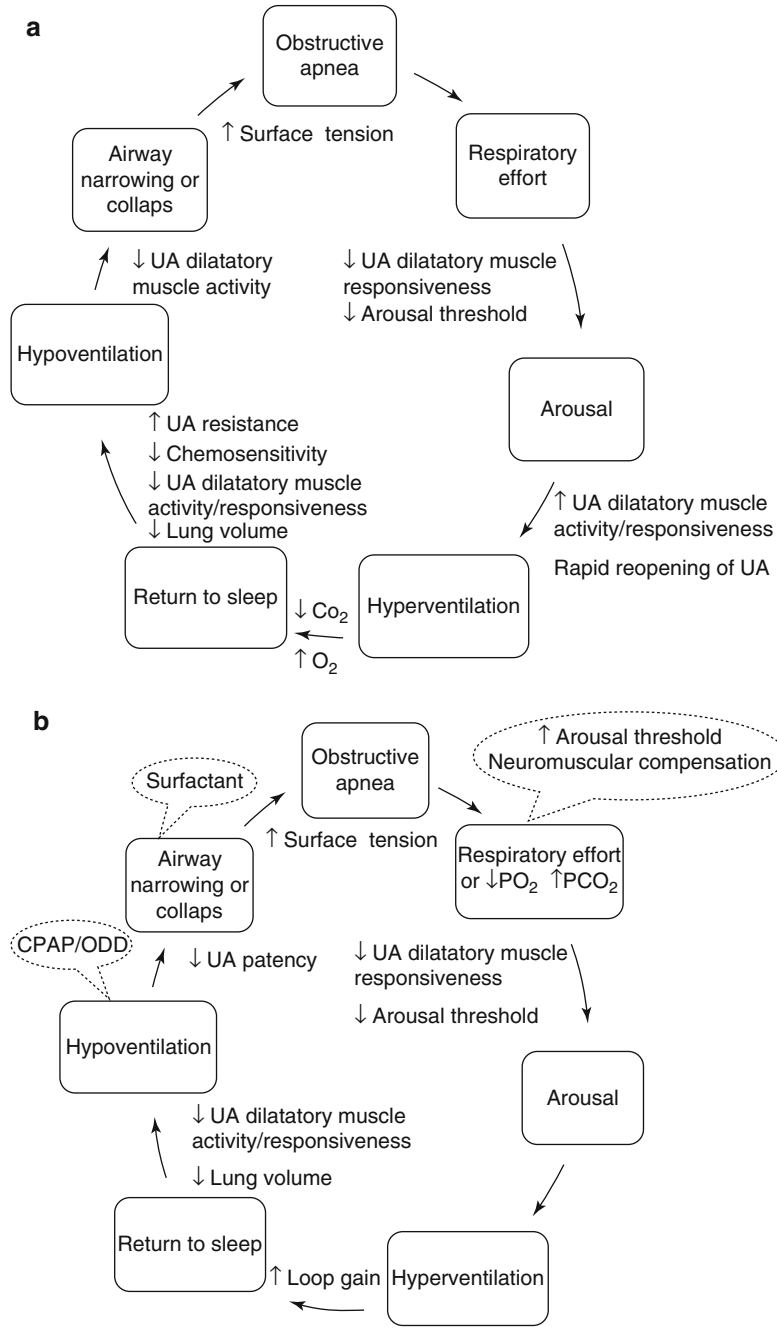

Fig. 24.5 (**a**) A scheme of the protective or beneficence (outside the circle) and unfavorable (inside the circle) physiologic process that is related to the pathophysiological sequences developing in OSA. (**b**) A stepwise scheme of the various pathophysiological events (inside the circle) predisposing or aggravating the clinical findings in the course of OSA. Some of these events are related to each other such as increasing loop gain may decrease the upper airway dilatatory muscle activity, hence increasing the respiratory response to arousal and prone to cyclic respiration. Dotted lines determine the potential management approach to the current event (*UA* upper airway, *CPAP* continuous positive airway pressure, *ODD* oral dental device)

disease threshold and placed them at risk of OSA but are protected through the recruitment of neuromuscular responses that lowered the P_{crit} below the disease threshold. The development of OSA requires a "two-hit" defect, with defects in both upper airway mechanical and neuromuscular responses.

The summary of the above-mentioned mechanisms is briefly shown in two schemes below (Fig. 24.5a, b).

Conclusion

Obstructive sleep apnea is a common sleep disorder that can present in a variety of ways. With a fundamental understanding of the pathophysiology of OSA, the physician can routinely integrate questions into their review of system that will assist in appropriate referral for polysomnography and diagnosis of the disorder. Knowledge of common patterns of OSA may help to identify patients and guide therapy.

The pharyngeal muscles are essential for effective lung ventilation because they help maintain an open upper airspace for the unhindered passage of air into the lungs. Sleep, especially rapid eye movement sleep, however, causes fundamental modifications of pharyngeal muscle tone and reflex responses that in normal individuals lead to airway narrowing and hypoventilation. In individuals with already anatomically narrow upper airways, these effects of sleep predispose them to inspiratory flow limitation (hypopneas), airway closure, and OSA. Obstructive sleep apnea is a common disorder, which is associated with serious clinical, social, and economic consequences.

The primary defect is probably an anatomically small or collapsible pharyngeal airway, in combination with a sleep-induced fall in upper airway muscle activity. Current understanding of the pathophysiological basis of the disorder suggests that a balance of anatomically imposed mechanical loads and compensatory neuromuscular responses is important in maintaining upper airway patency during sleep. OSA develops in the presence of both elevated mechanical loads on the upper airway and defects in compensatory neuromuscular responses.

A sleep history and physical examination are important in the identification of patients and appropriate referral for polysomnography. Understanding nuances in the spectrum of presenting complaints and polysomnography correlates is important for diagnostic and therapeutic approaches. Knowledge of common patterns of OSA may help to identify patients and guide therapy.

Although obesity is a major risk factor for OSA, roughly 30 % of patients with OSA are not obese, emphasizing the need for a high index of suspicion in clinical practice. Further, the prevalence of OSA is two to three times greater in men than in women and in older compared to middle-aged individuals. Menopause is a well-established risk factor for OSA in women. OSA can yield major neurocognitive manifestations including excessive daytime sleepiness/fatigue, impaired cognition, reduced quality of life, and an up to sevenfold increased risk of road traffic accidents. Treatment of OSA leads to improvements in many of these outcome measures. There is evolving evidence to support the role of OSA as an independent risk factor for adverse cardiovascular sequelae. Although some argue that OSA was simply a marker of an unfit patient group, rigorous recent studies have shown that OSA is causally linked to a number of important sequelae. OSA is now a well-established risk factor for hypertension (both incident and prevalent), stroke and probably myocardial infarction, congestive heart failure, and death. OSA has been causally linked to the development of hypertension based on large rigorous cross-sectional and longitudinal epidemiological studies, mechanistic animal studies, and most recently interventional trials. The underlying causes of OSA vary considerably between afflicted individuals. Important components likely include pharyngeal anatomy, pharyngeal dilator muscle responsiveness to respiratory challenges during sleep, the arousal threshold, and the instability of the negative feedback control system regulating ventilation (loop gain).

The pathophysiology of OSA is complex and incompletely understood. A narrowed upper airway is very common among OSA patients and is usual in adults due to nonspecific factors such as fat deposition in the neck or abnormal bony morphology of the upper airway. Functional impairment of the upper airway dilating muscles is particularly important in the development of OSA, and patients

have a reduction both in tonic and phasic contractions of these muscles during sleep when compared to normals. A variety of defective respiratory control mechanisms are found in OSA, including impaired chemical drive, defective inspiratory load responses, and abnormal upper airway protective reflexes. These defects may play an important role in the abnormal upper airway muscle responses found among patients with OSA. Local upper airway reflexes mediated by surface receptors sensitive to intrapharyngeal pressure changes appear to be important in this respect.

A better understanding of the integrated pathophysiology of OSA should help in the proper management of this important multifaceted disorder and the development of new therapeutic techniques.

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Physiology: Rhinomanometry

25

John Pallanch

Keywords
Rhinomanometry • Nasal obstruction • Airway resistance • Nasal airway obstruction • Nasal cavity • Nasal blockage • Nasal provocation tests

Core Messages

1. Rhinomanometry allows objective assessment of nasal resistance, the ratio of transnasal pressure over transnasal airflow measured during nasal respiration.
2. Many aspects of the study of nasal physiology have been studied with the aid of rhinomanometry.
3. Rhinomanometry assesses the overall effect of nasal airway dimension and shape on the passage of air through the nose.

25.1 Introduction

Rhinomanometry is the simultaneous measurement of airflow through the nose and pressure across the nose during breathing. Figure 25.1 shows plots of transnasal pressure and flow during respiration. As the patient inspires, the curves go downward showing a decrease in pressure and the corresponding movement of air in the direction of the lungs. As the patient changes to expiration, the curves move upward, corresponding to pressure increasing and causing the movement of air out of the nose. Dividing the maximum pressure reached during normal inspiration by the highest flow gives a nasal resistance value that correlates with the symptom of nasal obstruction in symptomatic patients. This objective test has been crucial in increasing understanding in many areas of nasal physiology. While the extent of its use varies in different parts of the world, it is still used in research and in clinical assessment of nasal function.

Resistance calculated at the maximum pressure and flow correlates with the symptom of nasal obstruction.

This chapter will provide a framework to put the role of rhinomanometry in context among the other tools used to objectively assess nasal function. The methods of rhinomanometry will be described. The research role that rhinomanometry has played in discoveries in nasal physiology will be covered including the nasal cycle, changes

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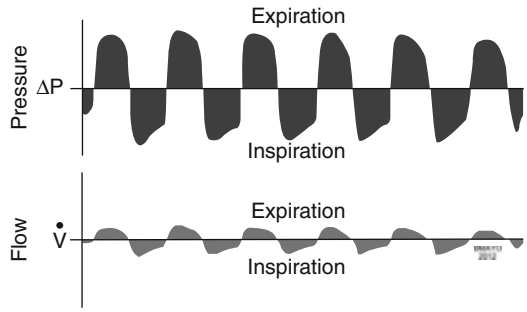


Fig. 25.1 Shows a plot of pressure and flow during respiration. As the patient inspires, the curves go downward showing a decrease in pressure and the corresponding movement of air in the direction of the lungs. As the patient changes to expiration, the curves move upward corresponding pressure increasing and the movement of air out of the nose

with growth, posture, and exercise; changes to the downside of the nose when a patient is lying down; and resistance in the normal nose and the nose with disturbed breathing function. The chapter ends with a summary of the clinical applications for which rhinomanometry has been used.

25.2 The Context of Rhinomanometry in Assessing Nasal Respiratory Function

25.2.1 What Are the Functions Associated with Nasal Respiration?

The movement of the diaphragm and lungs results in the movement of air through the nose. The passage of air through the nose is beneficial for the lungs because of the warming, humidification, and protective functions of the nose. The mucous layer in the nose can trap particulates, allowing the cilia to sweep them away (assessment of ciliary function covered by M. Jorissen in Chaps. 2 and 28). In addition, elements of the immune system are able to have contact with antigens, stimulating protective responses (covered by R. Kern in Chap. 3). Furthermore, air is delivered to the olfactory area providing the enhancement of taste and the protective function of detecting potentially harmful substances or organisms (assessment covered by P. Rombaux in Chaps. 10 and 30). The measurement of some of the important physiologic components of nasal respiration, warming, humidification, mucociliary clearance, and olfaction, is covered in other chapters in this book as noted above.

As air passes through the nose, comfortable nasal breathing corresponds with a dimension and shape of the nasal airway that in general optimizes the above functions. Rhinomanometry assesses the overall effect of nasal airway dimension and shape on the passage of air through the nose.

> Comfortable nasal breathing corresponds with a dimension and shape of the nasal airway that in general optimizes the multiple functions of the nose.

25.2.2 What Anatomic Elements Are Encountered During Nasal Respiration?

Measurement of the nasal airway assesses the nasal airstream which may be variably affected by the physical dimension of the components of the nasal airway including the vestibule, valve area, turbinates, and sinus openings. The presentation of these anatomic elements as air is *inspired* through the nose is different than the shape of the presenting surfaces as air is *expired*. This may reflect different functions of the two phases.

The first part of inspiration is the passage of air through the vestibule in a curve first superiorly and then toward the nasal valve area. The airstream then passes through a narrower area referred to as the internal valve. This corresponds to the area under the caudal end of the upper lateral cartilages and is clearly seen on casts or volume renderings of the nasal airway (Fig. 25.2). As the airstream leaves the valve area, it is dispersed in a wider distribution, thus providing contact with more surface area of the turbinates than if the airstream had passed unimpeded. The turbinates provide the working surface of the nose. By having protuberant curved surfaces,

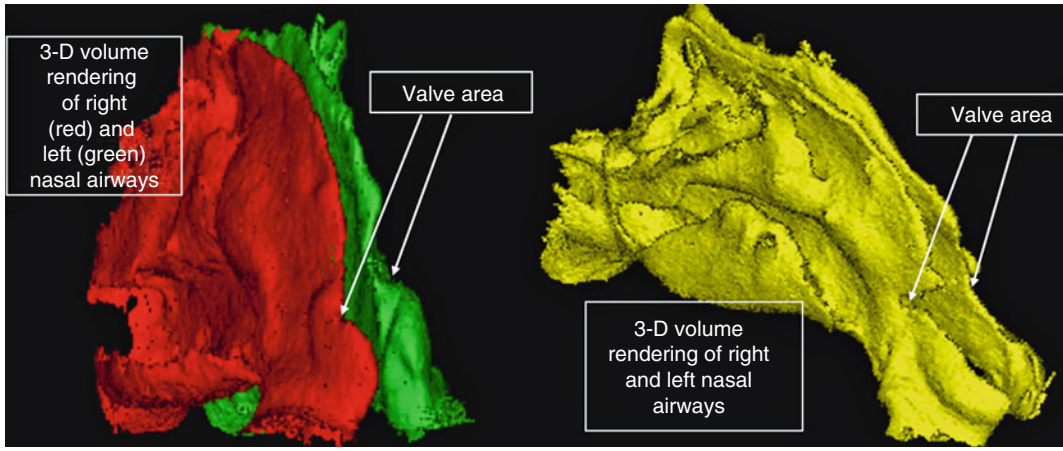


Fig. 25.2 Volume rendering of the nasal airway. Using 3D image analysis software and CT scans, the nasal airway is portrayed. This gives the same image early anatomists accomplished with wax castings. Note the narrow part of the airway at the valve area

they act as flanges in the airstream providing increased surface areas on which to contact the air for humidification, warming, and filtering. The air then passes on to the choana and turns again, this time in the direction of the larynx and tracheobronchial tree.

As the inspired airstream passes the uncinate, the natural os of the maxillary sinus is protected from exposure to the passing airstream. Openings from the frontal sinus, anterior ethmoid cells, and posterior ethmoid cells are similarly sheltered by presenting baffles though maxillary sinus accessory openings and postsurgical openings can present additional openings to the inspired air. Computational fluid dynamics (CFD) studies have suggested only minimal, if any, effect of single maxillary sinus openings on the respiratory airstream in a typical (unoperated) nose, whereas the presence of an accessory os can result in some airflow into the maxillary sinus (Hood et al. 2009; Zhu et al. 2012).

When considering any possible impact of the nasal passage during expiration, retention of heat is usually mentioned. This may be facilitated by having the air pass over the turbinates before encountering the restriction of the valve area. The baffles that sheltered the ostia in the inspiratory direction now may function to catch the expired air. Some associate this phenomenon with nitric oxide from the maxillary sinus serving a regulatory function in respiration (for measurement of nitric oxide, see Chap. 9 by P. Hellings). Computational fluid dynamics (CFD; see below) in 3D models showed an increase in maxillary sinus airflow rate with high expiratory flow rates simulating nose blowing (Zhu et al. 2012).

> As the airstream leaves the valve area, it is dispersed in a broader distribution, thus providing contact with more surface area of the turbinates than if the airstream had passed unimpeded.

25.2.3 Objective Measurement of Nasal Respiratory Function

Of the various anatomic elements present, measurements of the airstream are primarily influenced by the dimension of the valve and turbinates, by the relative thickness of the mucosal lining, and, at times, by the respiratory effort of the patient.

The objective methods of assessing the nasal respiratory passages include (a) measurement of the dimension of the airway, (b) measurement of the nasal airflow alone, and (c) rhinomanometry, the simultaneous measurement of the transnasal pressure and airflow.

25.2.3.1 Measurement of the Dimension of the Airway

The assessments of the dimensions of the nasal airway are not measurements of the airflow through the nose during respiration. Imaging with CT or MRI and then doing a 3D reconstruction of the airway will demonstrate the airway dimensions in different parts of the nose. This can be helpful especially when used in conjunction with computational fluid dynamics (CFD).

Acoustic rhinometry (see Chap. 26 by E. Hizal and O. Cakmak) also measures the airway dimension by calculations done on sound waves reflected back by intranasal structures. While this is not an assessment of the flow of air through the nose, it can be useful for measuring relative airway dimensions as well as changes with time, treatment, or various interventions (Lal et al. 2006).

Computational fluid dynamics (CFD) uses imaging, typically a CT scan done at one point in time, to generate a 3D model of the airway and then apply fluid dynamic modeling to that airway (Zhao and Dalton 2007). By using different transnasal pressures representing a respiratory cycle, the software can calculate the relative flow velocity in a number of anatomic sites in the nasal airway for various points in time during respiration. This capability offers exciting possibilities for the future study of the impact of various anatomic variations or pathology on the airstream. Those studying nasal physiology will be faced with the task of finding the meaning of the plethora of different flow vectors that result from CFD analysis of the nasal airway. To identify the meaningful parameters derived from the large amount of data is a tantalizing possibility for future study that will be facilitated by ever increasing computer processing speed and data handling (see Chap. 19 by R. Mösges).

25.2.3.2 Measurement of the Nasal Airflow Alone (Peak Flow Measurement)

Measuring only nasal airflow is popular especially with physicians who already use similar equipment to monitor their asthmatic patients by measuring peak lower airway flows. While this has the limitations of some dependence on patient effort, it has been relatively popular because of its simplicity and the ready availability of the equipment (Timperley et al. 2011). It has been demonstrated that physicians would like to have a simple tool for objective assessment of results in allergic rhinitis (Serrano et al. 2007). Since the rate of flow changes throughout the respiratory cycle, taking the measurement at some constant point can help decrease the variability of results and provide a standard for comparison. In this case, the "constant" point is the "peak" airflow reached with maximal effort. Peak nasal inspiratory flow can be measured by modifying the peak flow device for nasal inspiration. The measurements can be affected by valve collapse occurring at higher airflows that may not occur at normal physiologic flows (Barnes and Lipworth 2007). Nonetheless, this method has been popular, and normative values have been collected (Ottaviano et al. 2006; Papachristou et al. 2008; da Cunha Ibiapina et al. 2011; van Spronsen et al. 2012).

Both peak nasal inspiratory flow (PNIF) and peak nasal expiratory flow (PNEF) measurements have been used. There is some debate about the variability of results (Blomgren et al. 2003; Teixeira et al. 2011), but the tests have been shown to be useful, particularly for challenge testing in patients with allergic rhinitis (Wilson et al. 2003).

25.2.3.3 Rhinomanometry: The Simultaneous Measurement of the Transnasal Pressure and Airflow

Collecting simultaneous pressure and flow values allows the calculation of nasal resistance or conductance. Calculation of the ratio of pressure to flow could be done at any one of many simultaneous pressure-flow values along the continuously changing curve during respiration (Fig. 25.3). Using a specific airflow value at which to measure the pressure-flow values is an important element allowing consistent comparisons. Viewing the entire sigmoid pressure-flow curve also allows the observation of the position and amount of curvature that reflects the amount of flow the patient is generating for

the range of pressures occurring in the course of their nasal breathing. Rhinomanometry is used (except in rare studies) to assess the pressure and flow across the entire nasal airway, from nasal entrance to nasopharynx.

The use of CFD analyses done from CT images inspires thoughts of using microsensors to inobtrusively detect the pressure and flow changes during respiration for multiple sites in the nasal airway. Just as Lindemann (Lindemann et al. 2006) had actual measurements using tiny thermocouples to validate the corresponding CFD calculations they did for temperature at many sites in the nose, multiple localized pressure and flow measurements could verify the results of CFD analyses that yield multiple differing flow vectors at different anatomic sites in the nasal airway. Such validation of CFD, if combined with actual pressure measurements for a given patient, could move it out of the category of assessing airway dimensions to the category of yielding measured information about nasal airflow.

The plot of pressure and flow during inspiration and expiration yields a sigmoid curve that is closer to the *x*-axis (pressure axis) when nasal obstruction is greater.

25.2.4 Rhinomanometry for Measurement of Nasal Respiratory Function

As noted in the introduction, when rhinomanometry is performed, continuous measurement of transnasal pressure shows a rising and falling curve in the positive and then negative direction throughout each respiratory cycle (Fig. 25.1). As the changing pressure drives an accelerating and then decelerating flow of air, a plot of airflow shows a similar positive and negative excursion. Plotting pressure (*x*-axis) versus flow (*y*-axis) during inspiration and expiration yields a sigmoid curve that is closer to the *x*-axis when obstruction is greater (Figs. 25.3 and 25.4). Vogt

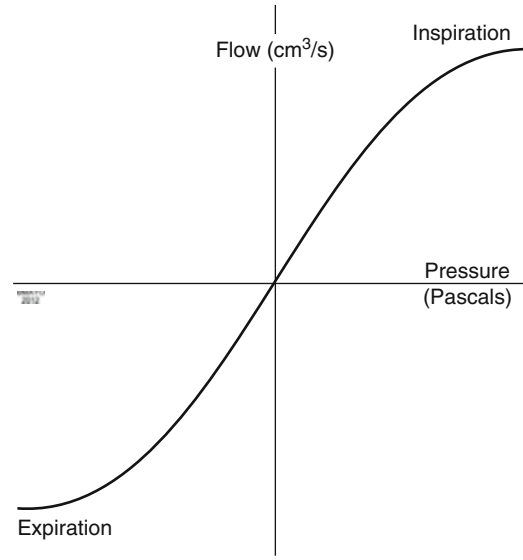


Fig. 25.3 The plot of pressure versus flow. Each point represents the simultaneous measurement of pressure and the corresponding flow value. Pressure values are on the *x*-axis and flow values on the *y*-axis. The sigmoid shape of the curve shows that in general there is a gradual increase in the pressure to flow ratio as one goes further out the curve toward the maximum values reached in normal respiration. Thus, for a given patient, the resistance value reported can vary depending on the point on the curve that is selected for calculating the result

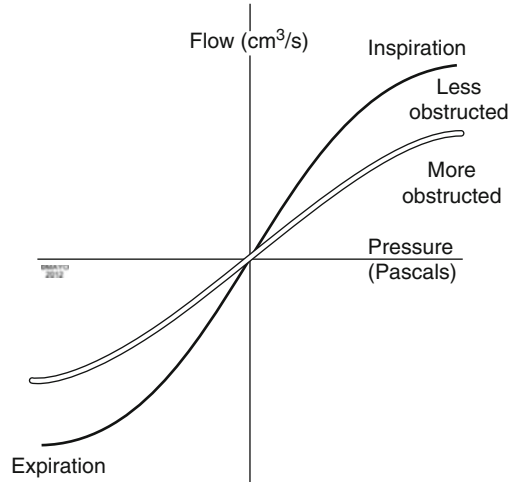


Fig. 25.4 The sigmoid pressure-flow curves for two different patients. The curve that is closer to the *x*-axis (pressure) represents the more obstructed nasal airway with higher resistance values

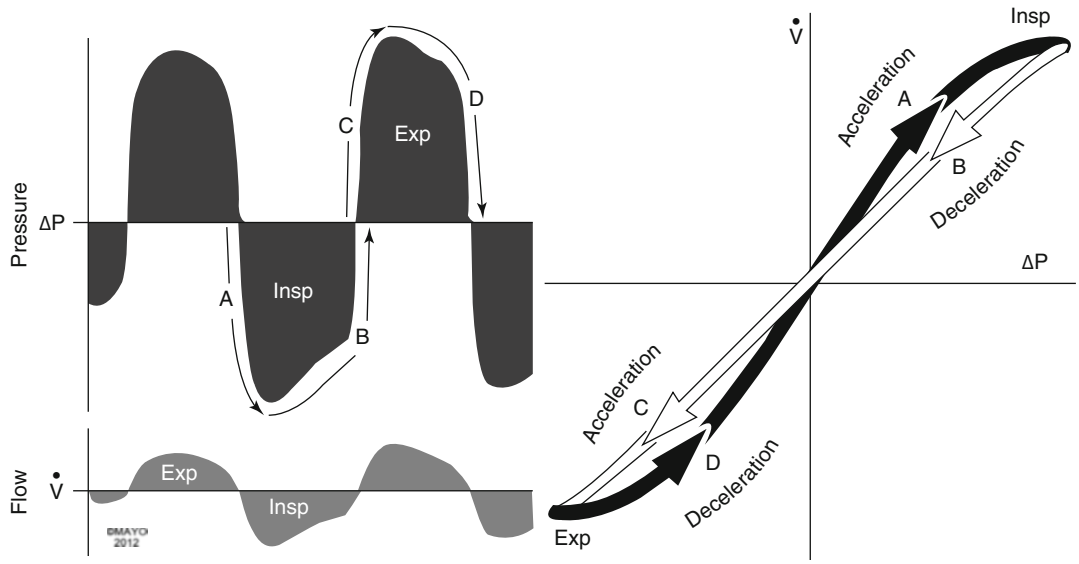


Fig. 25.5 The path of the pressure-flow curve away from the origin during inspiration (the accelerating limb, *A*) does not follow the same curve on the path back to the origin (decelerating phase, *B*). The same is true for the expiratory limb (*C*, *D*)

pointed out that the path of the pressure-flow curve away from the origin during inspiration (the accelerating limb) often does not follow the exact same curve on the path back to the origin (decelerating phase). The same is true for the expiratory limb (Fig. 25.5).

25.3 How Is the Measurement Done with Rhinomanometry?

25.3.1 Different Techniques: Most Common Method

The most commonly employed method of doing rhinomanometry is called anterior masked rhinomanometry. The different methods of rhinomanometry are distinguished by the location of the pressure detection and the apparatus for flow measurement. Table 25.1 lists the different types (methods) of rhinomanometry and the methods of pressure and flow detection that define them.

For measurement of the nasal airway of a patient with a nasal septal perforation, only the total airway is measured because the septal perforation would cause an error in unilateral pressure assessment. Anterior rhinomanometry thus is not used in patients with nasal septal perforations. Since the total airway is not measured when the anterior method is used, it is necessary to derive the total airway values by adding the right and left flow values for each corresponding pressure value along the pressure-flow curve (Fig. 25.6).

25.3.2 Transnasal Flow Measurement: Anterior or Posterior Method

Flow through the nasal airway is most commonly measured by attaching a flowmeter at the outlet of the mask which is sealed tightly on the patient's face. The usual flowmeter consists of pressure detection on either side of a resistive element. Originally nozzles were used to measure the flow through each nostril. When using a mask (or body plethysmograph), unilateral measurements can be done by occluding the opposite nostril with tape.

Since the total airway is not measured when the anterior method is used, it is necessary to derive the total airway values by adding the right and left flow values for each corresponding pressure value along the pressure-flow curve (Fig. 25.6).

Table 25.1 The different types of rhinomanometry. Anterior masked rhinomanometry is the type most commonly employed

Type of rhinomanometry	Flow detection	Pressure detection	Side(s) that can be directly measured
Anterior masked with full face mask	Device on outlet of full face mask	Catheter with sealed connection to non-measured nostril	Unilateral
Anterior masked with partial face mask	Device on outlet of partial face mask	Catheter with sealed connection to non-measured nostril	Unilateral
Anterior with nozzle	Device connected to nozzle held to nostril opening	Nozzle held to non-measured nostril	Unilateral
Posterior with full face mask	Device on outlet of full face mask	Catheter by nasopharynx – either transoral or transnasal	Total or unilateral
Posterior with partial face mask	Device on outlet of partial face mask	Catheter by nasopharynx – either transoral or transnasal	Total or unilateral
Body plethysmograph	Movement of chest inside body plethysmograph	Posterior catheter by nasopharynx – either transoral or transnasal or anterior catheter to non-measured nostril	Total or unilateral

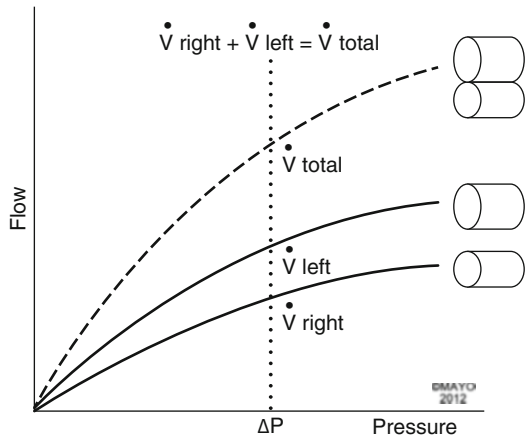


Fig. 25.6 For a given pressure value, the total flow is equal to the right-sided flow plus the left-sided flow, both measured at that pressure value. Flows are only additive if measured at the same pressure. This is analogous to two electrical currents being additive at the same voltages

25.3.3 Transnasal Pressure Measurement for Posterior Rhinomanometry

Measurement of transnasal pressure requires pressure detection in two sites, outside the nose and in the nasopharynx. Measurement of pressure outside the nose is easily done when the patient is wearing a mask by measuring the pressure inside the mask. Measurement in the nasopharynx can be done in several ways. As shown in Table 25.1, in anterior rhinomanometry, the nasopharyngeal pressure is detected using a tube sealed over the opposite nostril, turning the unmeasured nasal passage into an extension of the tube (Fig. 25.7). In posterior rhinomanometry, the nasopharyngeal pressure is measured by a catheter that is held in the back of the oropharynx with the lips sealed or by a tube passed to the nasopharynx along the floor of the nose (Fig. 25.8). The first of these methods can take extra time to learn for some patients.

It is also possible to measure a segment of transnasal pressure using a double catheter with the two openings on each side of the segment to be measured or by passing a catheter only partially along the floor of the nose. This methodology has only been employed in research but could potentially assess resistance at particular areas of the anatomic dimension of the airway, e.g., at a site suspected to be causing the symptom of nasal obstruction. This calculation uses the approximation of assuming a constant flow along the length of the nasal airway. Haight and Cole passed a catheter progressively further along the nasal airway while measuring the pressure at its tip and found that the greatest change in pressure and resistance occurred at the nasal valve (Haight and Cole 1983).

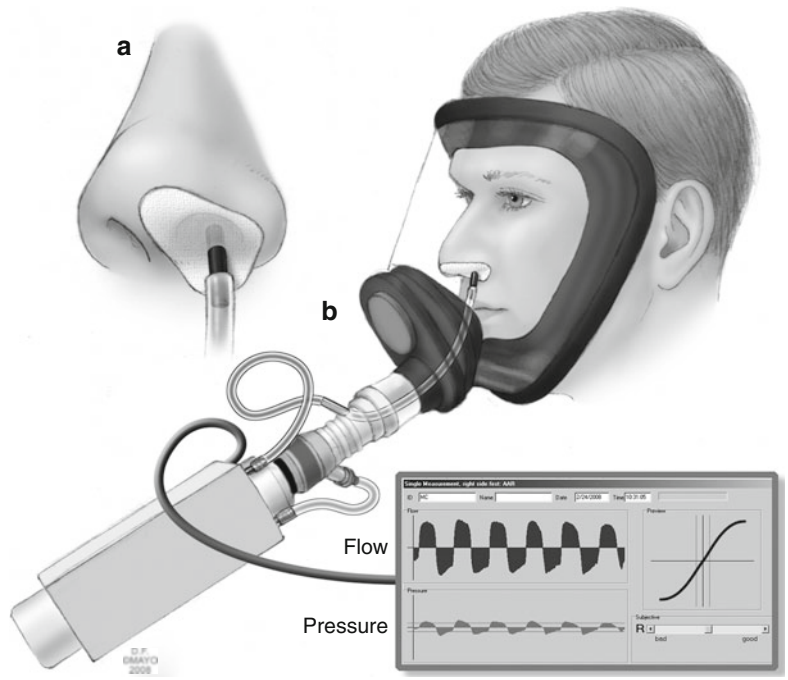


Fig. 25.7 Depiction of anterior masked rhinomanometry. A full face mask (**b**) is being used to avoid any distortion by the nasal alae. The pressure detection for the nasopharyngeal pressure is done with the tube that is sealed to the left nostril (**a**)

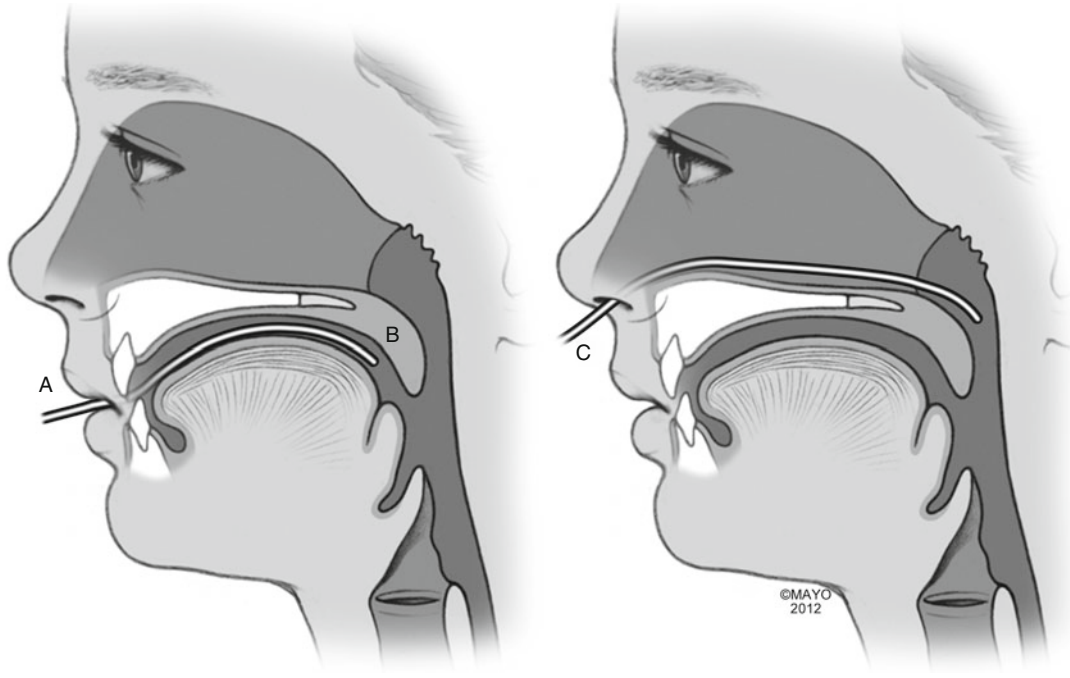


Fig. 25.8 Two methods of measuring the nasopharyngeal pressure in posterior rhinomanometry. The figure on the *left* shows the pressure detection tube being held in the oropharynx with the lips sealed (*A*) and the patient holding the soft palate open (*B*). The figure on the *right* shows the pressure catheter (*C*) passing along the floor of one of the nasal passages back to the nasopharynx. The small dimension of the tube is considered to have negligible effect on the airflow measurement on that side

25.3.4 Nasal Resistance or Conductance

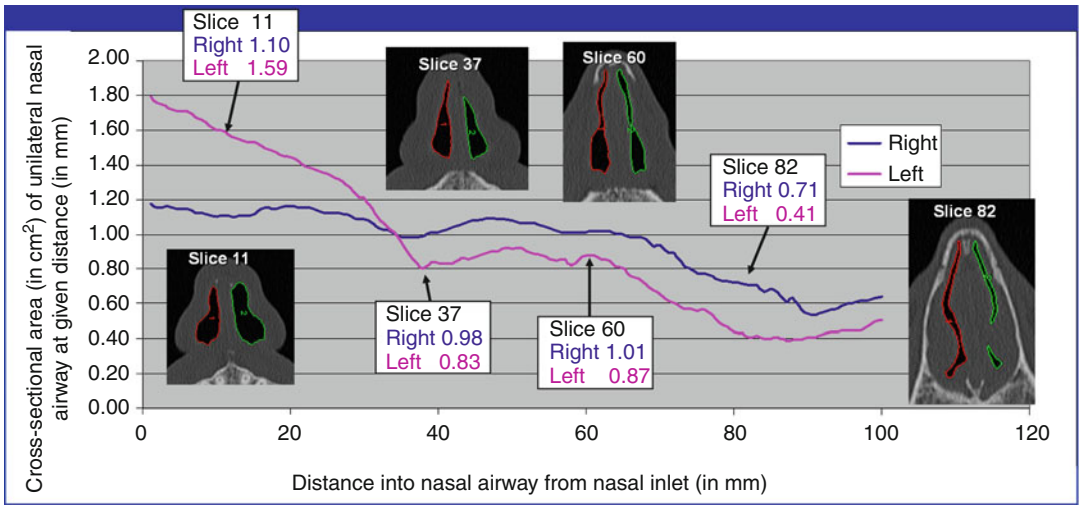
Resistance at a given point during the cycle of pressure and flow values can be obtained by dividing pressure by the corresponding flow at that point. Conductance is used by some and is the ratio of flow over pressure, the inverse of resistance. Typically resistance (or conductance) values are taken from inspiration, though some devices also report expiratory values.

Since rhinomanometry measures the simultaneous flow and pressure for the entire length of the nasal airway, it is generally thought that it primarily reflects the minimal effective cross-sectional airway. Figure 25.9 shows an example in which the cross-sectional area of an airway is smallest posteriorly rather than in the valve area. In this example, the right valve area has a smaller cross section than the left valve area, but the cross sections further posteriorly are smaller still with the left being the least. In this patient, the left side, which had the smallest overall cross section, is the same side that has the higher measured resistance and the same side where the patient felt the greatest obstruction.

25.4 Rhinomanometry Has Been Instrumental in Understanding Elements of Nasal Physiology

25.4.1 Measuring Changes That Occur in the Passage of Air Through the Nose with Growth and with Age

Children have smaller nasal passages and thus higher average nasal resistance. Nasal resistance has been shown to decrease as children grow to adulthood. Interestingly, Thulesius found nasal resistance to decrease as adults aged (Thulesius et al. 2009).



	Flow 150	Res150	Reff Ins	VR Rvert Ins	Sx side	Sxs subj
Right	526	0.29	0.33	0.37		50
Left	404	0.37	0.45	0.50	left worst	36

Fig. 25.9 The plot of the cross-sectional area of right (*blue*) and left (*pink*) nasal airway as one goes further back (along the *x*-axis in mm's) in the nasal airway. A 3D reconstruction was done from high-resolution CT scans, and successive cross-sectional areas were calculated perpendicular to the center vector of airflow through the nasal airway. Note that at the valve area (30 mm in) the right-sided cross-sectional area is smaller, but that (at 80–90 mm) the smallest overall cross-sectional area occurs posteriorly on the opposite (*left*) side of the nose

25.4.2 Measuring the Nasal Cycle

Unilateral nasal resistance measurements have been used to document the periodicity of the nasal cycle. One side of the nose is put at rest as the other is open and doing the work of humidifying, warming, and filtering the air. In some patients, it was found to be fairly regular, and in others, it was shown to be rather irregular (Hasegawa et al. 1979; Hasegawa and Kern 1990).

25.4.3 Discovering the Cause of Downside Obstruction When Lying on One's Side (or with Pressure Application in Yoga)

When asked why the downside of the nose becomes more obstructed when lying on one's side, many will say it is due to "gravity." Rhinomanometry was used to demonstrate that this is not the case. Haight (Haight and Cole 1986, 1989) mapped the pressure receptors on the side of the body that when activated cause relative congestion of the tissues on that side of the nose. This phenomenon is also known to Yoga practitioners who apply pressure with a hand placed in the axilla to enhance the breathing through the opposite nostril.

In the nasal cycle, one side of the nose is put at rest as the other is open and is doing the work of humidifying, warming, and filtering the air.

25.4.4 Quantitating Airway Change with Recumbency

Hasagawa has used rhinomanometry to demonstrate the significant increase in nasal resistance that can occur with recumbency (Hasegawa 1982). Just as our cardiovascular system has to make appreciable adjustments to maintain the same blood flow to our brain and extremities when we change to recumbency, the same regulatory parasympathetic/sympathetic pathways affect the relative congestion of the nasal tissues, particularly in certain individuals, resulting in increased nasal resistance and obstruction in the recumbent position.

25.4.5 Assessing Nasal Airway Change with Exercise and CO_2

Studies using rhinomanometry have shown the opening of the nose with exercise (Cole et al. 1983). Measurements of nasal resistance revealed the increase in nasal obstruction occurring as increased amounts of CO_2 is delivered in the inspired air (McCaffrey and Kern 1979b).

25.4.6 Finding the Normal Range and Abnormal Range of Nasal Resistance Values

If nasal resistance is measured in a standardized fashion for a large group of people, it is possible to show the distribution of "normal" resistance values for that population. This has been done for the sides of the nose as well as the total nose. By then comparing the nasal resistance of a patient against this distribution of normal values, one can determine if the patient has nasal resistance that is far outside the normal range (Pallanch et al. 1985).

25.4.7 Measuring Disturbance in Nasal Respiratory Function

By measuring a large group of patients who complained of the symptom of nasal obstruction, it was possible to describe the range of resistance values that are "abnormal" (McCaffrey and Kern 1979a). The significance of an abnormal unilateral resistance value must be considered in the light of the variation that occurs with the nasal cycle in the non-decongested nasal airway. Measuring the unilateral nasal airway after thorough decongestion can

eliminate a major portion of the contribution of the nasal cycle in many individuals, but it will also change the overall range of "normal" and "abnormal" values to lower resistance ranges (Pallanch et al. 1985). The total resistance of the nasal airway is relatively constant (Hasegawa 1982) through the course of the nasal cycle in the non-decongested nose. Some investigators have therefore suggested the use of total resistance as a value to measure the degree of nasal obstruction.

Pressure receptors on the downside of the body cause the downside nasal airway to have higher resistance.

25.4.7.1 When Is Disturbance in the Nasal Airstream Significant?

If an abnormal value of nasal resistance is measured, is this always of significance? By "significance" in patients, we usually mean that they are experiencing a symptom or condition that warrants treatment. Like an abnormal audiogram, it is the patient's choice as to whether any condition confirmed or found by a test is treated. Like any test, it is possible to have an abnormal result, but for a patient not to feel that they have sufficient symptoms to be treated.

25.4.7.2 Studying the Correlation of Elevated Resistance with the Symptom of Nasal Obstruction

There continues to be active debate about whether objective measurements of the nasal airway correlate with the symptom of nasal obstruction (Andre et al. 2009; Barnes et al. 2010; Eccles et al. 2010; Hopkins 2010; Hopkins et al. 2010; Williams et al. 2010; Nivatvongs et al. 2011) (see also G. Mylinski Chaps. 20 and 27). There has also been interesting work about the sensation of nasal obstruction being related to cold receptors that are stimulated by menthol-like compounds (Eccles et al. 1990). If there is more resistance to airflow, then is it the narrower airway causing less flow and thus less cold receptor stimulation that causes the sensation of obstruction?

Elevated values of nasal resistance have been shown to correlate with the symptom of nasal obstruction (McCaffrey and Kern 1979a; Pallanch 1995; Vogt et al. 2010). Several studies have looked at which parameter derived from the pressure-flow curve data obtained by rhinomanometry would best correlate with symptoms. Two studies (Pallanch 1995; Vogt and Zhang 2012) found the maximal resistance during normal respiration to be a parameter that correlated with symptoms better than other parameters. Phillip Cole (personal communication) explained this best, noting that the greatest time during the respiratory cycle (Fig. 25.1) was spent at the extremes of the pressure and flow curves; thus, it would follow that a parameter from this location would have the greatest correlation with patient's symptoms.

In general, recumbency increases nasal resistance.

The variability of the nasal cycle and "subjective" symptoms introduces some noise in demonstrating this correlation. It is most easily shown for larger values of unilateral obstruction and in patients who are experiencing symptoms (as opposed to studies on patients who had no symptoms of nasal obstruction). When studies have been done looking for a correlation with the sensation of obstruction in subjects who are not experiencing obstruction, there is more "noise" (variation) making the correlation less clear (Clarke et al. 1995). Most subjects with nasal obstruction are able to distinguish the side with the higher resistance and to give a grading of their obstruction that correlates with other patients who are experiencing obstruction of their nose (Pallanch 1995). This ability to perceive the side of highest resistance has been quantitated and found to be best when there is more than a slight difference in resistance between the sides of the nose at the time of the test (Thulesius et al. 2012).

25.4.7.3 Providing Objective Assessment When Crusting and Dysfunction of Nasal Lining Occur Due to Disturbance in the Airstream

When considering the symptoms of nasal obstruction, the question arises as to whether a patient can have a nasal airway that is too open and a corresponding measure of nasal resistance that is too low. While this is not a common scenario in the measurement of nasal resistance, patients with noses that appear widely patent, dry, and crusty can be shown to have lower resistance. This would suggest that a surgeon's goal of lowering resistance when treating the nasal airway needs to be tempered in this case by maintaining the normal physiologic range of nasal resistance for the unilateral and total nasal airways. This is consistent with the avoidance of disrupting nasal physiology by such procedures as the total removal of turbinate tissues.

Another interesting application of rhinomanometry that can be applied in this context is the measurement of nasal resistance in a patient who complains of symptoms suggesting the type of nasal dysfunction found in patients with the "empty nose syndrome" (see also Chap. 36 by E. Kern), but in whom the exam looks reasonable. Normal measured nasal resistance in this context would support looking for other explanations for the patients' symptoms.

25.4.8 Studying the Airflow in Conditions of Varying Temperature and Humidity

Rhinomanometry has shown that nasal resistance increases when a patient breathes colder than normal air (Cole et al. 1983).

By measuring nasal resistance, studies have looked for whether breathing air of different humidities resulted in any change in amount of nasal obstruction. Ivarsson and Malm found no significant difference in breathing air of different percent humidities (Ivarsson and Malm 1990).

Exercise resulting in a higher pulse rate decreases nasal resistance.

25.5 Clinical Applications of Rhinomanometry

25.5.1 When Things Do Not Add Up During Clinical Assessment

We have all been confronted with the cases in which a patient complains bitterly about nasal obstruction, but we are not able to see pathology that would account for the symptoms. Furthermore, some patients who have only minimal symptoms have what appears to be dramatic anatomic obstruction. It is in these cases that objective testing can be particularly helpful in being the "tiebreaker." In the first example, if airway testing demonstrates a significant nasal restriction, it agrees with the patient's complaints and makes us look further for the cause. If the airway testing shows a widely patent airway, it supports our exam observations and cautions that a procedure to increase the dimension of the airway to try to help this patient's feeling of obstruction would be ill advised.

This use of the test results relies on the knowledge that there is a correlation between measured airway restriction and the symptom of nasal obstruction for many patients, giving us an objective basis for comparison to use with the patient who seems to have contradictory findings. Further clinical examples have been described (McCaffrey 1997).

25.5.2 For Assessment of Surgical Candidate's Chances of Optimal Outcome

Studies have been done showing the value of rhinomanometric results in optimizing the selection of patients who will be helped by nasal airway surgery (Sipila 1992; Suonpaa 1993).

25.5.3 To Analyze Changes in Patients Who Do Not Have Symptomatic Improvement with Surgery

We all want to learn from our patients who continue to have symptoms despite our surgical intervention for their airway. Rhinomanometry, applied as noted in Sect. 25.5.1 above, can suggest whether it is the still unhappy patient's symptoms that are exceptional (patients with an unusually high resistance threshold for comfort) or whether there is still some measureable obstruction in the airway.

25.5.4 Challenge Testing

Some patients may have reactions to airborne antigens yet have negative skin testing. In these cases, a more direct method of identifying allergens and degree of allergic response can be done with challenge testing (Schumacher and Pain 1979; Bachmann 1987; Fireman 1988; Doyle et al. 1995; Wang and Clement 1995). Rhinomanometry is done first. Then the patient inhales the challenging antigen. Subsequent rhinomanometry can detect significant change in nasal obstruction caused by the antigen in an allergic patient.

25.6 Summary/Conclusion

The observation has been made that viewing the nasal airway will not by itself tell us about the *function* of the nasal airway. Measuring the transnasal pressure and flow using rhinomanometry has provided a greater understanding and insight into the physiologic function of the nasal airway.

Understanding normal physiology comes first. Next comes understanding what is different when patients have disturbance in function that causes symptoms. To fully learn what can be changed to yield improvement in function, we seek measurements of function that correlate with improvement. Rhinomanometry has played a significant role in the ongoing search for these answers so that we can optimize our ability to help our patients.

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Acoustic Rhinometry

26

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Keywords

Acoustic rhinometry • Nasal cavity • Nasal valve • Paranasal sinus • Inferior turbinate • Middle turbinate • Paranasal sinus ostia • Nasal cavity volume • Decongestion • Limitations

Abbreviations

AR	Acoustic rhinometry
CT	Computed tomography
MRI	Magnetic resonance imaging

Core Messages

- Acoustic rhinometry technique is principally based on the computation of cross-sectional area–distance curves from the analysis of the reflected sound waves by the anatomical structures in the nasal cavity.
- Acoustic rhinometry measurements of the healthy adult nasal cavity are reasonably accurate to the level of the paranasal sinus ostia. Beyond this point, acoustic rhinometry overestimates cross-sectional areas.
- The nasal valve is identified by a pronounced minimum (the first minimum after the nostril) on the acoustic rhinometry area–distance curve. However, the second, third and fourth local minima on the acoustic rhinometry area–distance curve do not correspond to any anatomic structure in the nasal passage. These three minima are caused by acoustic resonances in the portion of the nasal cavity beyond the nasal valve.
- Acoustic rhinometry fails to provide quantitative information about paranasal sinus volume, paranasal sinus ostium size, nasal cavity volume between the nostril and choana and the effects of decongestion on the volume of the nasal mucosa. The diagnostic value of this method is limited with the anterior part of the nasal cavity.
- Clinical studies that do not take the limitations of the technique into account may easily lead to misinterpretations.

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26.1 Introduction

Acoustic rhinometry (AR) was introduced as an objective tool for the assessment of the nasal cavity geometry in 1989 by Hilberg (Hilberg et al. 1989). AR measurements require minimum patient cooperation and can be performed practically, quickly and easily. Due to its advantages, the technique is widely accepted in a short time. Clinical applications of acoustic rhinometry include determination of the localisation and degree of an intranasal anatomic pathology that affects nasal patency, evaluation of the results of a nasal surgery such as septoplasty and turbinate surgery, assessment of the effects of medications on the nose that are used systemically or topically and comparison of different therapeutic methods. Furthermore, AR gives idea about the reversible component of the nasal obstruction as the measurements before and after decongestion of the nose can be compared. In other terms, AR is potentially useful in the assessment of the nasal cavity geometry, nasal patency and results of various medical and surgical therapies. However, complex anatomy of the nasal cavity, operator mistakes and factors inherent to the AR algorithms and physics may influence the measurement of the area–distance function in the nose and lead to systematic errors. In this chapter, we will try to give some essential information on AR and attempt to cover important aspects of the technique, especially from the clinical point of view.

26.2 History

There have been numerous efforts to understand the nature and functions of the nose throughout the centuries. First records in written history describing the nasal cavity can be found in the Papyrus Ebers of ancient Egypt, because of its functional importance in mummification process. Since then, different methods for the examination of nose have been used. Evolution of the scientific method has given rise to attempts to meet the need for more quantitative evaluation methods. In line with this, a simple nasal patency test was introduced by Zwaardemaker and modified by Glatzel, in which the size of the vapour condensation on a cold metal plate or mirror caused by the expired air through one side of the nose was compared to the other (Foxen et al. 1971). Evaluation of the sound during forced expiration (introduced by Bruck) or humming (introduced by Spiess) was proposed to give a diagnostic idea about the occluded side of the nose (Hilberg 2002). The twentieth century witnessed brilliant developments which facilitated the use of more quantifiable and objective nasal evaluation tools such as rhinomanometry and acoustic rhinometry.

Acoustic waves can be used to determine the location of objects in different media, i.e. gases (air), liquids (water) or solids (Earth's crust). Indeed, some animals such as bats, whales or dolphins are using sound for object detection for millions of years. Use of sound for object detection in water was first documented by Leonardo da Vinci, who proposed inserting a tube into water and place an ear to the tube in order to detect vessels (Leighton 1998). Evolution of the scientific method within decades and development of physical and mathematical techniques have led to the development of acoustics as a science, and physical properties of the sound have started to be illuminated. Accumulation of scientific data in turn gave rise to innovative thoughts, and technological applications of the knowledge on acoustics have started to emerge. One of those applications was SONAR (sound navigation and ranging) systems which have been used for detecting submarines in World War I. Acoustic waves have also been used for object detection in solids, i.e. seismic surveys that aimed to investigate underground structures in the Earth's crust. Through the use of electronics and development of modern computer systems, sound measurement and analysis reached new levels of complexity and accuracy. Acoustic reflections have been used to assess the geometry of upper airways, including pharynx, glottis, trachea and lungs, after the 1970s. Acoustic rhinometry was then first introduced by Hilberg et al. in 1989 (Hilberg et al. 1989).

26.3 Theoretical Background and Criticism

The basic idea behind the acoustic rhinometry method is similar with other methods of acoustic object location and consists of impacting an incident acoustic wave into a medium to generate a reflected

acoustic wave. The size and the location of an object through the route of acoustic waves can be determined by calculation of the amplitude of reflected waves and the time difference between the incident and reflected waves, respectively. However, some phenomena related with the inherent nature of acoustic waves and acoustic properties of the medium in which the wave propagates interfere with the measurements and make calculations complicated. Acoustic waves are longitudinal waves that oscillate along the same direction as they move. During their route, they exhibit some characteristic patterns like reflection and diffraction. Reflection can be defined as the change in direction of the wave at an interface between two different media. Diffraction is, in general, bending of the waves around small obstacles and scattering of waves past small ostia. Similar effects occur when sound waves travel through a medium with varying acoustic impedance. As the waves propagate within a medium (gas, liquid or solid), they are reflected by structures or dissimilar media on their route. But some of the waves penetrate through those structures or media and continue to propagate. The waves that remain on their route will be reflected again by other structures or dissimilar media. Additional reflections, thus, will be added to the acoustic image, and analysis and comparison of the waves that are sent into and reflected back from a heterogenous or irregular medium will become almost impossible. A solution to this problem, i.e. analysis of the acoustic image with multiple backward reflections, was offered by Ware and Aki in 1969 (Ware and Aki 1969). By the Ware-Aki algorithm, it was then possible to analyse the sound waves that were reflected by different layers through the route of the wave. Ware-Aki algorithm, which is used in acoustic rhinometry technique, however, has some assumptions regarding the ideal properties of airway. This algorithm assumes that the sound waves are plane waves, and it does not account for losses (airway wall nonrigidity, viscous losses) or nonplanar wave propagation effects (Celik et al. 2004; Cankurtaran et al. 2003; Cakmak et al. 2003a). In order to understand the reasons of some artefacts and errors on acoustic rhinometry area–distance curves, these assumptions will be explained briefly.

The first reconstruction algorithm used in acoustic reflectometry was developed under the ideal conditions of no losses in the propagating wave and that all frequencies were covered by the acoustic pulse. The assumption of planar wave propagation is fundamental to passage area measurements made with AR. Waves are assumed to propagate along the axis of the airway in one dimension. If the frequency of the sound waves is high and therefore the wavelengths are too short, sound waves do not move along a plane and start to be reflected between the walls of the nasal cavity. This, in turn, causes additional delays in the reflected waves, complicates the relation between incident and reflected waves and eventually affects cross-sectional area and distance computations. In other words, planar wave assumption determines and limits the spatial resolution and the frequency bandwidth of the method and imposes limitations on the transverse sizes of an airway model (Celik et al. 2004; Cankurtaran et al. 2003; Cakmak et al. 2003a).

Spatial resolution is defined as the smallest axial distance that separates two cross-sectional areas that can still be resolved by AR. In rigid-walled airways, the spatial resolution is approximately equal to one-sixth of the shortest wavelength of the incident sound pulse. The frequency bandwidth of the incident sound pulse is important in determining the spatial resolution of the technique and hence has a major influence on the accuracy of AR measurements. The limited frequency bandwidth of the AR technique may increase the rise distance and thereby produce a smoother incline in the area–distance curve (Celik et al. 2004; Cakmak et al. 2005b).

The Ware-Aki algorithm is valid under the condition that the acoustic impedance of the one-dimensional acoustic pathway is continuous. If there is a finite sudden jump in the acoustic impedance, the transformations and the potential functions used in the mathematical formulation of this algorithm are not well defined. In other words, the Ware-Aki algorithm is not suitable for calculating the area–distance function at locations where there are abrupt changes in the acoustic impedance (Celik et al. 2004; Cankurtaran et al. 2003; Cakmak et al. 2003a, 2005b).

It has been argued that any form of energy loss or sound wave attenuation would reduce the amplitude of the reflected wave, which, in turn, would lead to area underestimation. Viscous

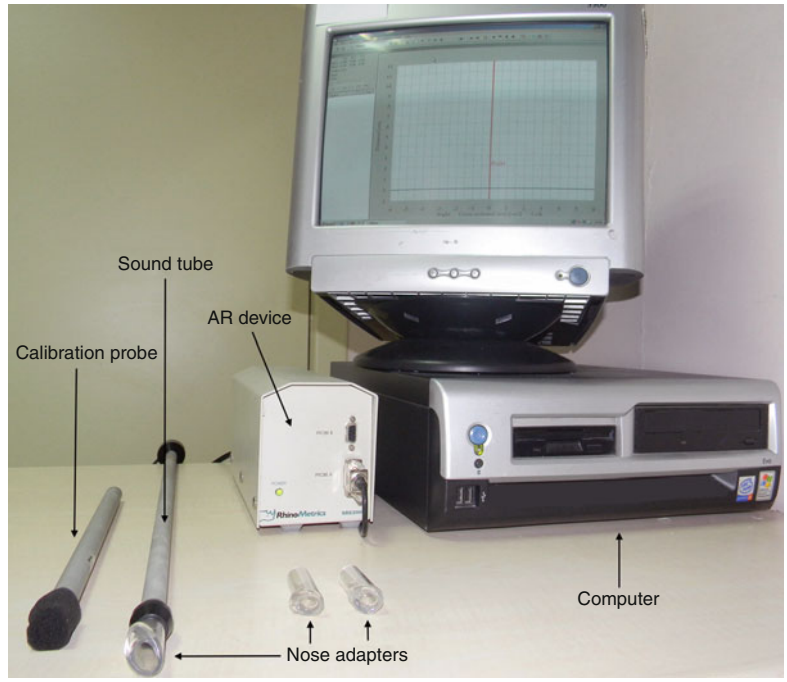

Fig. 26.1 Acoustic rhinometry equipment (Rhinoscan SRE 2000, Interacoustics A/S, Assens, DK)

forces, transmission losses and internal losses that take place as the sound wave is transmitted through the constriction in an airway model have all been attributed to area underestimations that occur with AR. However, the main reason of area underestimations distal to an anterior constriction seems to be a "barrier effect", i.e. "barrier" created by the anterior constriction that reflects most of the incident sound power. In models with constrictions (inserts) of small passage area, the high-frequency components of the acoustic pulse generated by AR equipment do not reach the portion of the model beyond the constriction, because these waves are reflected back from the barrier created by the constriction (Celik et al. 2004; Cankurtaran et al. 2003; Cakmak et al. 2003a, b, 2005a). The effect of a constriction on AR measurements will also be covered in nasal valve section below.

26.4 Acoustic Rhinometry Equipment

Acoustic rhinometry is based on the principle of computation of cross-sectional area–distance curves from the analysis of the reflected sound waves by the anatomical structures in the nasal cavity. In other terms, analysis of the sound waves that are sent into and reflected back from the nasal cavity gives the cross-sectional area at a given distance.

A picture and a schematic representation of acoustic rhinometry unit can be seen in Figs. 26.1 and 26.2, respectively. Acoustic waves that are produced by a loudspeaker pass through a sound tube and a nose adapter, which is a detachable pipe that establishes a connection between the AR device and the nose. The sound waves that cross the nose adapter then reach the nose. As the sound waves propagate in the nasal cavity, they are reflected by the anatomical structures. A microphone that is placed within the sound tube detects the waves that are reflected back and transforms these into electrical signals. These signals are then amplified by an amplifier and converted into numeric data by an analogue–digital converter. Numerical data is then analysed by a computer. Frequency bandwidth of the sound waves that are sent into the nasal cavity may contain all audible frequencies between 20 and 20,000 Hz. However, low-pass filters exclude the frequencies over 10,000 Hz since interferences

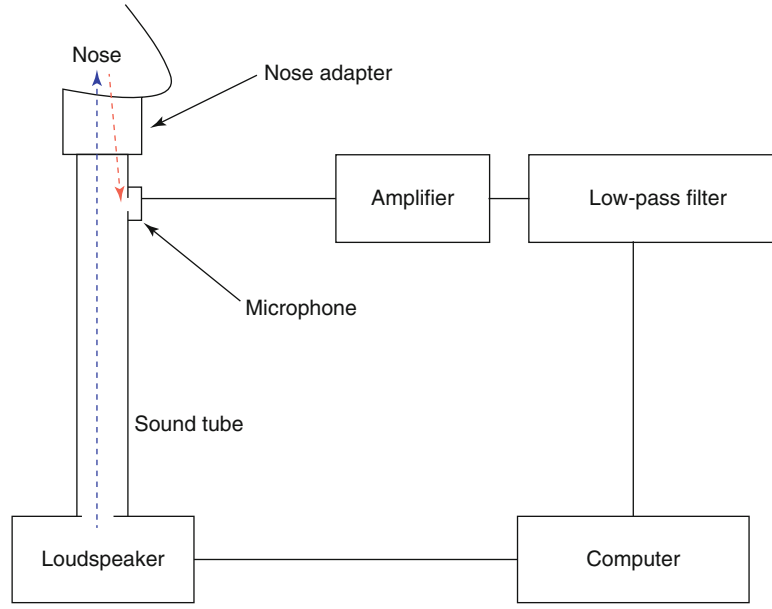

Fig. 26.2 Schematic representation of an acoustic rhinometry circuit

and diffractions increase as the wavelength of the sound waves travelling in nasal cavity decrease (Hilberg 2002; Celik et al. 2004; Cankurtaran et al. 2003; Cakmak et al. 2003a).

The changes in cross-sectional area of the airway affect acoustic impedance. Since the nasal cavity is not a straight pipe and has an irregular and complex anatomy, acoustic waves show different reflection patterns at differing cross-sectional areas on their route. Although the mathematical background of the analysis is very complex and will be detailed to some extent later in this chapter, computerised calculations basically give two parameters for a given cross-section: Comparison of the amplitudes of the sent and reflected sound waves gives cross-sectional areas, while the time difference between the sent and reflected sound waves gives the distance of a given cross-sectional area to the reference point. These data are then combined and an area–distance curve is obtained. The areas here define the cross-sectional areas that are vertical to the acoustic pathway, i.e. the way that acoustic waves follow in the nasal cavity. Cross-sectional area of a given section is plotted on vertical, while distance of that section to the reference point is plotted on horizontal axis of the graph. In order to evaluate the nasal valve region better, vertical axis can be plotted in logarithmic scale.

26.5 Test Technique

Classic acoustic rhinometry utilises single impulse and one microphone (transducer) setup. However, there are other methods that use two microphones (Louis et al. 1994) or devices that use continuous acoustic stimulation (Djupesland and Lyholm 1997). Although the theory is identical to that of the single-impulse method and the test technique is similar, a continuous wide-band noise model allows for almost real-time adjustment of the equipment since a visual output is generated more than 20 times per second (Straszek 2008).

By means of the modern computer software, the use of acoustic rhinometry is relatively simple. Since external noise, temperature and humidity have potential effects on measurements, testing room should have standard environmental conditions. Test should be applied by experienced staffs that are aware of the recommendations for reliable testing (Fisher et al. 1995). Both sides should be tested separately. Single measurement takes about a few seconds, and whole testing process ends in a couple of minutes. After the device is switched on and computer program is opened, calibration is simply done by following the on-screen instructions that are provided by the manufacturer. Calibration should be done every time the device is

Fig. 26.3 Various types of nose adapters are designed to achieve a better fit to shape of the right or left nostril

Fig. 26.4 During the measurements, nose probe should be placed accordingly to prevent acoustic leak. Distortion of the nose should be avoided

opened. The patient should have a sitting position and position should not be changed during the tests. Swallowing and breathing should be avoided during the measurements. Any kind of secretions can narrow the airway and affect the measurements. Hence, nasal cavity should be cleaned off from secretions before the test (Cakmak et al. 2001). Several types of nose adapters with different rim shapes are available (Fig. 26.3). A nose adapter that would best fit to the shape of the patient's nostril should be chosen and attached to the probe. To avoid acoustic leak, a medical sealant gel should be applied circumferentially to the edge of the nose adapter, providing an air secure contact between the nose adapter and the nostril (Hamilton et al. 1997). Nose probe should be placed accordingly to prevent acoustic leak, but distortion of the nose or changes in position of the nose probe should be strictly avoided (Fig. 26.4).

Measurements should be repeated for at least three times to obtain the most correct results. By this way, erroneous measurements due to acoustic leakage or distortion of the vestibule owing to incorrect positioning of the probe can be detected and eliminated.

The operator should be aware of the above-mentioned testing principles and instructions. Besides the operator errors, complex anatomy of the nasal cavity, physical limitations of the AR and factors inherent to the AR algorithms may influence the measurements and lead to systematic errors. Nasal cavity has a complex geometry consisting of cartilaginous and bony framework covered with erectile tissue and mucosa including a narrow segment of nasal valve at the anterior part and sinus ostia more posteriorly. Narrow segments at anterior parts negatively affect the measurements of more posterior parts, and this leads to a potential problem since the narrowest part of the nasal cavity, the nasal valve, is on anterior part of the cavity. Similarly, ostia of the paranasal sinuses affect AR measurements, and cross-sectional areas behind the paranasal sinus ostia are overestimated. In order to understand the results of AR measurements, we will try to take a closer look to the cross-sectional area–distance curve.

26.6 Cross-Sectional Area–Distance Curve

In order to interpret AR results correctly, it is essential to know how some anatomical structures in nasal cavity appear on AR area–distance

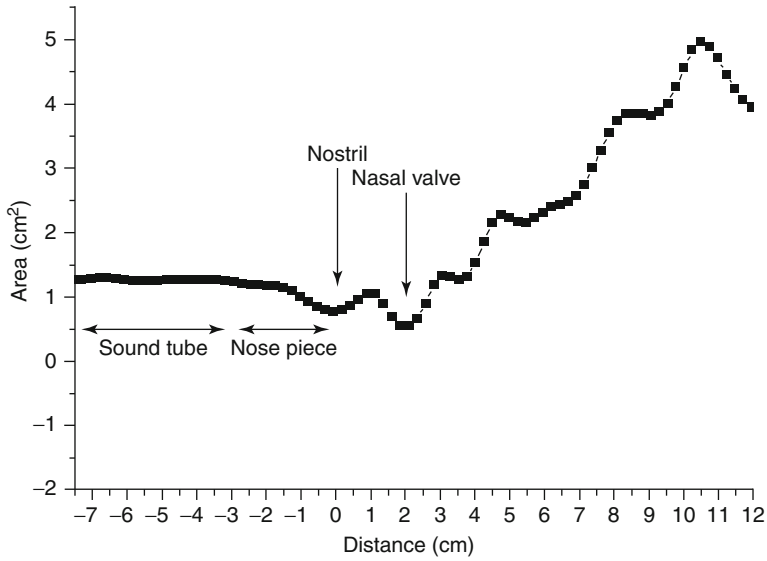

Fig. 26.5 A typical AR cross-sectional area–distance curve. Start point of the nasal cavity (nostril) is accepted as "0 cm". Horizontal axis gives the distance of a given cross-sectional area that is perpendicular to the acoustic axis to the nostril. The cross-sectional area of that section is plotted on vertical axis

curves and how these structures' localisations and size affect the area–distance curve.

In a typical AR area–distance curve, there is a minimum on the junction between the nose adapter and the nostril (Fig. 26.5). This minimum is generally not considered as a "minimum" and hence not termed as the "1st minimum", since it occurs at "0 cm" which is the start point of the nose. First minimum after the nostril represents the nasal valve region (Fig. 26.5).

There is no clear consensus on interpretation of AR results, even in healthy humans. Inspection of the literature reveals that up to four local minima have been commonly observed on the AR area–distance curves, and different terms have been used to define these minima. The terms "1st constriction, I-notch, CSA1, MCA, start of isthmus region, start of valve region or ostium internum" have been used for the first minimum, which was attributed to the nasal valve; "2nd constriction, C-notch, CSA2, inferior concha or piriform aperture" have been used for the second minimum, which was attributed to the head of the inferior turbinate; and "CSA3" have been used for the third minimum, which was usually attributed to the middle turbinate (Hilberg 2002; Cakmak et al. 2003b). However, recent experimental studies with nasal cavity models and clinical studies revealed that the second and third minima on cross-sectional area–distance curves do not represent an anatomical point, and hence, most of these terms might be used inappropriately (Celik et al. 2004; Cankurtaran et al. 2003, 2007; Cakmak et al. 2001, 2003a, 2003b 2005a, 2005b; Tarhan et al. 2005).

In healthy humans, cross-sectional areas measured by different imaging modalities, such as CT and MRI, were compared with AR cross-sectional area measurements, and the techniques were found to give comparable results especially on the anterior part of the nasal cavity (Cakmak et al. 2003b, 2005b; Terheyden et al. 2000; Hilberg et al. 1993; Min and Jang 1995; Gilain et al. 1997; Corey et al. 1997; Dastidar et al. 1999). Regarding the validation of AR curve with imaging modalities, a methodological issue has to be concerned. Areas calculated on AR measurements are the cross-sectional areas that are perpendicular to the sound wave propagation axis (acoustic axis). In some of the validation studies, images of the nose were taken perpendicular to the base of the nose, not to the acoustic axis, and the reference point to be used in distance measurements was either chosen as the anterior nasal spine (Hilberg et al. 1993; Gilain et al. 1997) or tip of the nose (Dastidar et al. 1999) or even not clearly defined (Corey et al. 1997). Studies that do not care to the sloped anatomy of the nasal cavity or use different reference points may lead into significant errors when interpreting the AR curve.

In a study on healthy humans, the actual cross-sectional areas of the nasal cavity together with the actual locations of the nasal valve, the head of the inferior turbinate, the head of the middle turbinate, the openings of the ostia of the maxillary and frontal sinuses and the choanae were calculated from computed tomography sections perpendicular to the curved acoustic axis of the nasal passage (Cankurtaran et al. 2007). The findings were then compared with the corresponding cross-sectional areas measured by AR. Comparison of the CT- and AR-derived area–distance curves both before and after decongestion revealed that the nasal valve is identified by a pronounced minimum (the first minimum after the nostril) on the CT- and AR-derived area–distance curves. However, neither the head of the inferior turbinate nor the head of the middle turbinate could be distinctly identified on the CT area–distance curves of healthy humans. The same held true for the AR measurements in both cadaver cast models and healthy humans (Cakmak et al. 2005b; Cankurtaran et al. 2007). The second and third minima on the AR area–distance curves did not correspond to the actual locations of the head of the inferior turbinate and the head of the middle turbinate determined from CT, neither before nor after decongestion (Cakmak et al. 2005b; Cankurtaran et al. 2007).

In a study that used cast model of the nasal cavity of a cadaver, Cakmak et al. demonstrated that AR was able to detect changes in cross-sectional area larger than approximately 0.19 cm^2 and 0.38 cm^2 at the head of the inferior turbinate and the head of the middle turbinate, respectively (Cankurtaran et al. 2007). This finding suggests that AR cannot resolve any change in the cross-sectional area of the nasal passage at each of these specific anatomic sites that is smaller than the corresponding limit. In addition, the ability of AR in measuring abrupt changes in cross-sectional area is poor, because of the limited spatial resolution and the long rise distance of the technique (Celik et al. 2004; Cakmak et al. 2005b).

In summary, with the exception of the first minimum after the nostril, which represents the nasal valve, the subsequent minima on the AR area–distance curves for both non-decongested and decongested nasal cavities do not correspond to any anatomic structure in the healthy human nose (Figs. 26.6a, b and 26.7a, b). These minima are formed because of the acoustic resonances in nasal cavity behind the nasal valve region. Effects of some important anatomical landmarks on AR cross-sectional area–distance curves are summarised below.

26.7 Nasal Valve

The nasal valve area is widely accepted as the most important part of the nasal passage with respect to its essential role in respiratory physiology. Boundaries of this triangular region are formed by the caudal septum (medial wall), caudal edge of the upper lateral cartilages and head of the inferior turbinate (lateral wall) and floor of the nose (inferior wall). Nasal valve is the narrowest part of the nasal passage and functions as an essential regulator of nasal airflow. The accuracy of AR measurements in the anterior part of the nose, which contains the nasal valve, is substantial in terms of the value of this method in rhinology. Individual anatomical variations of the anterior narrow segment might significantly limit the role of AR as a diagnostic tool for the entire nasal cavity.

As mentioned above, the nasal valve is identified by a pronounced minimum (the first minimum after the nostril) on the AR area–distance curve. Experimental studies on pipe models and nasal cavity models have shown that AR gives an accurate measure of the distance from the nose adapter to the narrow segment that simulates nasal valve, and AR measurements of the anterior nasal passage are reasonably accurate if the nasal valve area is within normal adult ranges (Cankurtaran et al. 2003; Cakmak et al. 2005a). Clinical studies that compare the cross-sectional areas derived by AR and by imaging modalities such as computed tomography and magnetic resonance imaging also showed that AR is a valuable method for measuring nasal valve area (Cakmak et al. 2003b; Cankurtaran et al. 2007; Terheyden et al. 2000; Hilberg et al. 1993; Min and Jang 1995; Gilain et al. 1997;

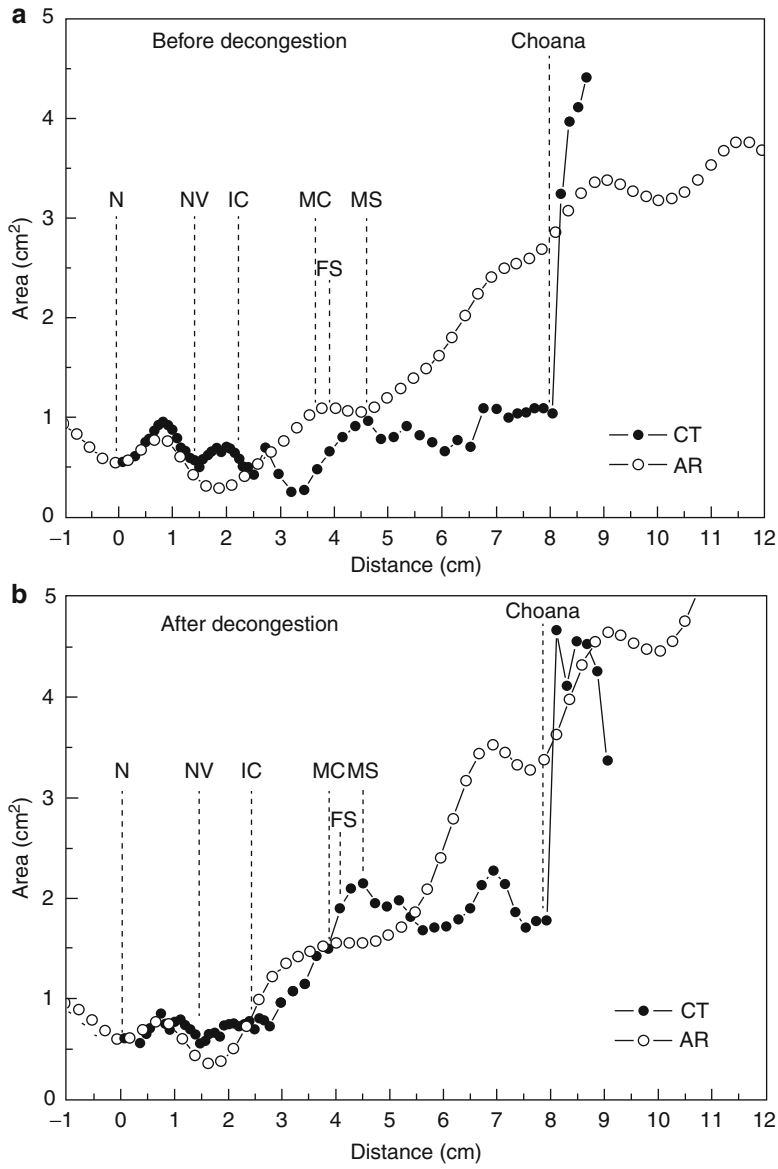

Fig. 26.6 The cross-sectional area–distance curves of a healthy human's nasal cavity as determined by computed tomography and acoustic rhinometry, before (**a**) and after (**b**) decongestion. Actual locations of the anatomical structures are determined on computed tomography sections and depicted on the graphs with vertical dashed lines. The ability of acoustic rhinometry to detect the anatomical structures in nasal cavity can be seen. Acoustic rhinometry fails to quantify the volume change after decongestion (*CT* cross-sectional area–distance curve as determined by computed tomography, *AR* cross-sectional area–distance curve as determined by acoustic rhinometry, *N* nostril, *NV* nasal valve, *IC* head of the inferior concha [turbinate], *MC* head of the middle concha [turbinate], *FS* frontal sinus ostium, *MS* maxillary sinus ostium)

Corey et al. 1997). These studies noted significant correlations between the cross-sectional areas obtained by imaging modalities and AR, with particularly high agreement in the anterior part of the nasal cavity and nasal valve. For the area of the nasal valve, agreement between the AR and imaging techniques was apparent when imaging was obtained perpendicular to the acoustic axis that follows the curve of the nasal passage through the centre of the curved airway (Cakmak et al. 2003b).

One of the best-recognised problems with acoustic pulse-response analysis is its inability to precisely measure the cross-sectional areas beyond narrow apertures. Concomitantly, the accuracy of AR measurements of the nasal cavity depends greatly on nasal passage anatomy, especially that of the narrowest section. In model studies, the cross-sectional area and the length of the narrow segment have been shown to be the factors that most significantly influence the accuracy of AR (Celik et al. 2004). When the cross-sectional

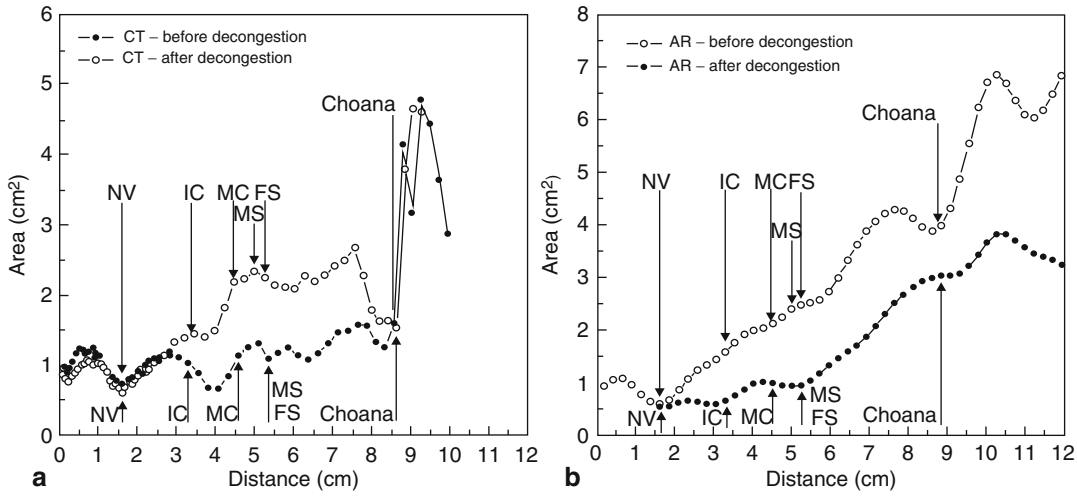

Fig. 26.7 The cross-sectional area–distance curves of a nasal cavity before and after decongestion, as determined by computed tomography (**a**) and acoustic rhinometry (**b**). Actual locations of the anatomical structures before and after decongestion are determined on computed tomography sections and depicted on the graphs with arrows. Acoustic rhinometry fails to detect the localisations of the anatomical structures except for the nostril and nasal valve (*CT* cross-sectional area–distance curve as determined by computed tomography, *AR* cross-sectional area–distance curve as determined by acoustic rhinometry, *N* nostril, *NV* nasal valve, *IC* head of the inferior concha [turbinate], *MC* head of the middle concha [turbinate], *FS* frontal sinus ostium, *MS* maxillary sinus ostium)

area and the length of the narrowest part of the passage were relatively small and short, the probability of measurement error was higher. It is well established that the area of a region beyond a severe constriction may not be measured accurately by AR, and a narrowing in the anterior part of the nasal cavity causes errors in AR-derived areas posterior to the site of constriction (Hilberg et al. 1989; Cankurtaran et al. 2003; Cakmak et al. 2001; Hilberg and Pedersen 2000; Hilberg et al. 1998). The results obtained for living human subjects suggest that when the nasal valve passage area is within the normal adult range, AR is a valuable method for measuring the cross-sectional areas of the nasal cavity anterior to the paranasal sinus ostia (Cankurtaran et al. 2007; Tarhan et al. 2005). In other terms, accuracy of AR measurements is closely related with the narrowest section of the nasal passage, the nasal valve, and the passage area of the nasal valve is the most important limiting factor when quantifying the geometry of the anterior nasal cavity with AR. The effects of nasal valve passage area on accuracy of AR measurements were examined by Cankurtaran et al. using simple pipe models with a constriction (Cankurtaran et al. 2003). These authors demonstrated that the constriction reflects most of the incident sound power. In models with constrictions of small passage area, the high-frequency components of the acoustic pulse generated by AR equipment do not reach the portion of the model beyond the constriction, because these waves are reflected back from the barrier created by the constriction. This finding is of vital importance for AR because the transmitted sound waves probe, and hence provide information about, the cross-sectional area posterior to the constriction. Accordingly, an examiner should expect relatively higher degrees of error when measuring the cross-sectional area of a nasal cavity model beyond a constriction of small passage area. Since AR measures the intensity of reflected sound waves and compares this with the intensity of incident waves, AR-measured cross-sectional areas beyond the constriction (a nasal valve that is smaller than normal adult size) are underestimated, and the corresponding area–distance curve shows pronounced oscillations (Celik et al. 2004; Cakmak et al. 2005a).

The anatomy of the human nose is complex, and the spectrum of individual differences is

broad. For patients with pathologies that narrow the nasal valve, such as septal deviations, polyps, tumours, webs, strictures or alar cartilage insufficiencies, the value of AR for measuring the entire nasal cavity is limited. All users of this technique must be aware of the effects of nasal valve to prevent misinterpretation of AR findings during clinical assessment.

Together with the nasal valve, the second important anatomical structure that affects the AR measurements is paranasal sinuses.

26.8 Paranasal Sinuses

To interpret the AR measurements correctly, it is essential to know how paranasal sinuses affect AR area–distance curves and to what extent the AR measurements give idea on paranasal sinus and their ostia. At this point, the effect of nasal valve on AR measurements should be noticed once more. Model studies revealed that as the area of the nasal valve decrease (<0.283 cm^2), the areas of both the nasal valve and regions posterior to the nasal valve are underestimated and oscillations appear (Celik et al. 2004; Cankurtaran et al. 2003; Cakmak et al. 2003a, 2005a). Clinical studies on healthy humans supported the results of the experimental studies and showed that AR gives reliable results between the nostrils and sinus ostia if the nasal valve area is in normal range (Cankurtaran et al. 2007; Tarhan et al. 2005). Even if the nasal valve area is within normal range, the areas posterior to the sinus ostia are overestimated, and the degree of error increases for the areas that are located more posteriorly.

Clinical and experimental studies revealed that AR measurements behind 5–6 cm, where sinus ostia are located, can include significant mistakes and AR measurements cannot give accurate information about the paranasal sinuses and sinus ostia (Celik et al. 2004; Cakmak et al. 2003a, 2005a; Tarhan et al. 2005). The effects of paranasal sinus volume and their ostia on AR measurements have been assessed with model studies, in detail (Cakmak et al. 2003a, 2005a). The pipe models that have been used for that purpose were consisting of a main pipe with a side branch as Helmholtz resonator. The neck diameter (simulating sinus ostium) and the cavity volume (simulating the paranasal sinus) were variable. The results of those studies showed that small ostia had little impact on AR measurements, regardless of sinus volume (Cakmak et al. 2003a, 2005a). However, AR overestimated cross-sectional areas posterior to the simulated sinus ostium when the ostium was large. Overestimation was more pronounced as the diameter of the sinus ostium and volume of the sinus increased. This result suggests that for patients who have a large sinus ostium and large paranasal sinus volume (i.e. after functional endoscopic sinus surgery), the precision of AR measurements beyond the sinus ostium is lower. Paranasal sinus volume can influence the area–distance curve beyond the ostium, but this effect is significant only when the sinus is connected to the nasal cavity by a relatively large opening (Cakmak et al. 2005a).

Since AR cannot measure the cross-sectional areas on posterior nasal cavity correctly, it also cannot give accurate data on nasal cavity volume. The results of a clinical study revealed that AR overestimates nasal cavity volume by 21 % before decongestion and 24 % after decongestion, when compared with volume measured by CT (Cankurtaran et al. 2007). The nasal cavity volume difference with decongestion was 30 % more in AR measurements, when compared with CT measurements (Cankurtaran et al. 2007). In other words, AR overestimates the effect of decongestion on nasal cavity erectile tissue mass.

In order to understand the reasons of the area overestimation behind the sinus ostia, it is essential to review the physical properties of the AR technique once more. The reason for area overestimations is not the acoustic energy loss to the sinuses through the ostia, but it is the interaction between the nasal cavity and paranasal sinuses (Tarhan). The physical principle of AR is based on the reflections of the sound waves that propagate in a pipe (Hilberg et al. 1989, 1998; Hilberg and Pedersen 2000; Hoffstein and Fredberg 1991). As the cross-sectional areas change within the pipe, sound waves are partially reflected, and the changes in acoustic impedance at each point constitute a reflection series. Reflection series of the pipe is

termed as the "input impulse response of the pipe", and cross-sectional areas are calculated as a function of the distance (Hilberg et al. 1989; Fredberg et al. 1980; Jackson et al. 1977). Experimental data that include input impulse response is transformed into cross-sectional area–distance curve by the Ware-Aki algorithm (Ware and Aki 1969). Sound waves that pass through the nasal valve are exposed to multiple reflections at localisations with acoustic impedance changes such as sinus ostia. Oscillations that are formed by the resonator characteristics of paranasal sinuses are also superimposed with the waves that are reflected from the posterior parts of the nasal cavity. The Ware-Aki algorithm misinterprets superimposed waves and this leads to area overestimations. Previous experimental studies showed that complex acoustic resonances of the paranasal sinuses and nasal cavity and thus the acoustic resonance effects of sinuses and posterior nasal cavity are not accounted in Ware-Aki algorithm, which is still used in AR calculations (Cakmak et al. 2003a). The results from healthy humans also showed that the reason of area overestimations behind the paranasal sinus ostia was not sound loss through the sinus ostia to the sinuses, in both non-decongested and decongested cavities (Tarhan et al. 2005).

In summary, AR does not give reliable data on the dimensions of the paranasal sinus ostia, volumes of the sinuses, nasal cavity volumes between nostril and choana and the effect of the decongestion on nasal mucosa. AR overestimates the cross-sectional areas behind the sinus ostia. The diagnostic value of this method is restricted with the anterior part of the nasal cavity. Thus, the volume measurements in any instance should be done for the area between 0 and 5–6 cm.

26.9 Applications of Acoustic Rhinometry

A simple search on the Medline/PubMed database with the words "acoustic rhinometry" between 1989 and 2012 reveals more than 790 studies. Together with the need for an objective tool to evaluate nasal patency, some attractive factors such as relative ease of use and low application costs seem to keep this technique as a popular tool for research. Theoretically, acoustic rhinometry can be used to assess the geometry of nasal airway and the effect of anatomical, physiological or pathological conditions that interfere with nasal patency.

AR has been used to assess the effects of environmental factors (effect of temperature (Yamagiwa et al. 1990; Lundqvist et al. 1993), posture (Lal et al. 2006; O'Flynn 1993), nasal cyclus (Fisher et al. 1993), and inhaled pollutants, gases or particles (Hilberg 2002)), pharmacological agents (decongestants (Fouke and Jackson 1992; Hochban et al. 1999), antibiotics (Samolinski et al. 1998), steroids (Rimmer et al. 2012; Wandalsen et al. 2010), nasal irrigations (Friedman et al. 2006), anti-allergic drugs (Yamagiwa 1997; Li et al. 2009; Kim and Jang 2010), systemic drugs (Aydin et al. 2008), nasal challenge testing (Mygind and Dahl 1996)) and surgical therapies on nasal airway. It also has been used in evaluation of allergic and non-allergic rhinitis, snoring and sleep apnea (Antila et al. 1997). AR can be a useful tool for evaluation of the symptom of nasal obstruction and for documenting the pretreatment and posttreatment outcomes of surgical or medical therapies, for both medical and medicolegal purposes (Holmstrom 2010; Moore and Eccles 2011; Andre et al. 2009; Batra et al. 2009).

Acoustic rhinometry has been shown to be reproducible in animal studies, both in vivo and postmortem (Straszek 2008; Straszek and Pedersen 2004). However, physical and technical improvements for more accurate and applicable results and modification and optimisation of the equipment for measurement of small dimensions (Kaise et al. 1999) are necessary to use this technique in animal studies.

Acoustic rhinometry has also been used for measurements in children (Mostafa 1997; Riechelmann et al. 1993, 1999). Due to the uncomplicated and non-invasive nature of the technique, it may prove to be a useful tool in examination of the airways in children. However, the dimensions of the nasal cavity and thus the nasal valve in this population are usually much smaller than those of the adults. Accordingly, limitations of the technique and the validity of measurements should always be kept in mind (Buenting et al. 1994a, b).

Conclusion

In conclusion, AR is potentially helpful in defining the geometry of nasal cavity, measurement of nasal patency and assessment of the results of nasal medical and surgical interventions. However, AR measurements can include significant mistakes due to the operator's technique and nasal passage anatomy. AR measures the cross-sectional areas in anterior part of the nose with high accuracy and overestimates the cross-sectional areas behind the paranasal sinus ostia. In other terms, diagnostic value of the technique is limited with the anterior part of the nasal cavity. Nasal valve can be identified as a minimum on AR area–distance curves (first minimum after the nostril). The second, third and fourth minima on AR area–distance curves cannot be associated with an anatomical structure in nasal cavity. These minima are formed because of the acoustic resonances in nasal cavity behind the nasal valve region. The cross-sectional areas behind the paranasal sinus ostia are overestimated with AR. This is not because of the sound loss to the sinuses through the sinus ostia, but because of the interactions between the nasal cavity and paranasal sinuses. Acoustic rhinometry cannot give quantitative data about the volumes of the paranasal sinuses and dimensions of the sinus ostia, neither before nor after decongestion. Acoustic rhinometry significantly overestimates the effect of decongestion on nasal mucosa. Clinical studies that do not take the potential errors of AR into account can easily be misinterpreted. Physical limitations should be taken into account to develop better AR equipment and related computer software.

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New Measurement Methods in the Diagnostic of Nasal Obstruction

27

Gunter H. Mlynski

Keywords

Rhinomanometry • Rhinoresistometry • Acoustic rhinometry • Long-term rhinoflowmetry • Extent of nasal obstruction • Objectification of obstruction causes • Nasal diffuser • Preoperative management • Postoperative quality control

Core Messages

- Accurate preoperative analysis of the extent and cause of nasal breathing complaints in combination with a stronger physiological perspective in surgical therapy is needed if we are to make progress beyond unsatisfactory long-term outcomes with inadequate improvement in nasal airway obstruction and frequent postoperative sicca symptoms.
- New measurement methods need to be developed to objectify nasal obstruction, since rhinomanometry is only capable of adequately differentiating the degree of obstruction, but not its causes.
- Rhinoresistometry, a refinement of rhinomanometry, makes it possible to objectively determine not only the degree of obstruction but also swelling, skeletal stenosis, inspiratory collapse of the nasal valves, and pathological turbulence as possible causes of nasal obstruction.
- By combining rhinoresistometry with acoustic rhinometry, it is possible to accurately localize skeletal stenoses and determine the causes of pathological turbulence.
- Rhinoresistometry and acoustic rhinometry only enable the objective measurement of conditions in the nose at the time of measurement. Long-term rhinoflowmetry has been developed to overcome this limitation.
- Long-term rhinoflowmetry yields information about the nasal cycle in specific conditions and provides an objective measurement of reactive congestion over a 24-h period under the usual conditions of the patient's everyday life.
- New techniques for the diagnostic evaluation of nasal obstruction make it possible to set better surgical indications

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prior to functional nasal surgical interventions and to better plan the surgery.
- Rhinoresistometry, acoustic rhinometry, and long-term rhinoresistometry now offer the practitioner tools that allow essential postoperative quality control in functional nasal surgery.

27.1 Preliminary Remarks

Despite a number of significant advances in recent decades in the area of procedures for the diagnostic evaluation of nasal obstruction, there has been a striking failure until now to implement routine objective preoperative diagnostic testing prior to functional and aesthetic nasal surgery or postoperative quality control.

Rhinomanometry (RMM) is currently being used throughout the world for the objective measurement of nasal obstruction (Clement and Gordts 2005). This procedure measures nasal airflow at a given pressure. This method enables objectification of the extent of nasal obstruction. RMM does not permit differentiation between the four principal causes of obstruction, mucosal swelling, skeletal narrowing, inspiratory collapse of the nasal valves, and/or pathological increases in turbulence, which often have quite different effects on elevated nasal airway resistance.

However, evaluation of nasal air patency is not sufficient by itself and in some cases may even be misleading. Thus, nasal airway resistance can be decreased by resecting the nasal turbinates, thereby improving airflow. The results of RMM testing might simulate functional improvement (Mlynski and Beule 2008), even though, in fact, nasal respiratory function has been largely destroyed after resection of the nasal turbinates (Stoksted 1969; Dommerby et al 1985; Haraldsson et al. 1987; Grymer and Rosborg 1987; Fjermedal et al. 1988; Illum 1997; Dinis and Haide 2002; Mlynski et al 2001; Mlynski 2006; Gruetzenmacher et al 2006; Scheithauer 2010).

RMM only provides an evaluation of nasal airflow at one point. However, nasal resistance varies depending upon the velocity of flow due to changing turbulence behavior and also often varies dynamically because of collapse of the nasal valves from suction as a result of the Bernoulli effect (see Sect. 23.2).

For these reasons, we must consider RMM as being of limited value for the diagnostic evaluation of nasal obstruction (Mlynski and Beule 2008). Until now, this has had the effect of leaving many surgeons skeptical about the overall value of functional testing in the field of functional rhinosurgery. As a consequence, RMM has been further refined into rhinoresistometry (RRM) (Mlynski and Löw 1993).

Recently, acoustic rhinometry (ARM) has established itself as an additional procedure for rhinological diagnostic testing (see Chap. 27). It enables measurement of the cross-sectional area of the nasal flow channel in relation to the distance from the external nasal ostium (Clement and Gordts 2005). With ARM it is possible to objectify the extent and localization of areas of nasal constrictions (Clement and Gordts 2005; Corey 2006). Since airway resistance does not depend solely on the magnitude of the cross-sectional area of a flow channel but also on its shape, ARM cannot be used by itself to estimate the extent of nasal obstruction. ARM also permits conclusions about the possible causes of pathological turbulence in the nose (see Sect. 27.2.2).

RMM, RRM, and ARM only permit an assessment of nasal obstruction at the time of measurement. Therefore, long-term rhinoflowmetry (LRM) was developed (Gruetzenmacher et al. 2005b; Ohki et al. 2005). Using this method, nasal airflow can be measured separately on each site of the nose over a 24-h period. The LRM technique permits side-specific measurement of nasal airflow and thus documentation of the nasal cycle. It yields information on the functionality and adaptive capacity of the nose during periods of increased oxygen demand resulting from physical activity under the typical conditions of a patient's everyday life.

This book devotes a separate chapter to RMM and to ARM. In this chapter, RRM and LRM will be described in Sect. 27.2. In addition, we will show how ARM can be used to make inferences about the causes of pathological nasal turbulence.

In Sect. 27.3, we will demonstrate how the combination of RRM and ARM (and in specific cases, including LRM) can make it possible not only to objectify the extent of nasal obstruction but also to differentiate among its possible causes. This diagnostic paradigm will be illustrated by means of clinical examples.

The subjective sensation of nasal obstruction is contingent not solely on airway resistance but also on a number of additional factors, and it cannot be completely measured even with the latest methods (Gogniashvili et al. 2011). Especially because of the known discrepancy between objective measurements of functional impairment and subjective sensation (Naito et al. 1988; Jones et al. 1989; McCaffrey et al. 1989; Kim et al. 1998; Andre et al. 2009), the objectification of the physical parameters contributing to functional impairment is important for effective planning of treatment.

There is a need for an accurate preoperative analysis of the extent and cause of nasal breathing difficulties in combination with a stronger physiological perspective in surgical therapy if we are to make progress beyond unsatisfactory long-term outcomes (Stoksted 1969; Shermann 1977; Tuschen 1977; Dommerby 1985; Grymer 1987; Haraldson 1987; Fjermedal 1988; Gordon 1989; Jessen 1989; Samad 1992; Bohlin 1994; Illum 1997; Truilhe 2000; Dinis and Haide 2002). The latency between surgery and the emergence of sicca symptoms, which often is measured in several years, reflects the compensatory capacity of the healthy mucosa (Bhandarkar and Smith 2010). It makes it more difficult to recognize the causal relationship with surgery, something that will only be possible in the context of prospective cohort studies that look at long-term outcomes (Chen et al. 2008; Liu et al. 2009).

27.2 New Techniques for the Diagnostic Evaluation of Nasal Obstruction

In the following section, we will describe new techniques for objectifying nasal obstruction and its causes.

27.2.1 Rhinoresistometry (RRM)

Motivated by the inadequacy of information obtained through rhinomanometric testing and the capabilities afforded by modern computer technology, RMM was further refined into RRM (Mlynski and Löw 1993; Mlynski and Beule 2008). Based upon the laws of fluid dynamics, this method uses values measured by rhinomanometry for the pressure difference between the external nasal orifice and the choanal area together with airflow velocity to compute diagnostically relevant parameters. The equipment and the measurement procedure used in RRM completely correspond to this used in active anterior RMM. However, for the rhinomanometric equipment, the guidelines established by the "International Committee on Objective Assessment of the Upper Airways" (Clement and Gordts 2005) need to be followed. In addition, to determine the extent of nasal obstruction, RRM permits the differentiation between the possible causes of a nasal obstruction: narrowing caused by swelling, by skeletal narrowing, and/or by inspiratory collapse of the nasal valves and/or a pathological turbulence behavior.

The results of RRM are presented by means of graphs and numerical values. The graphs allow the reader to make a "diagnosis at a glance," and the numerical values are used for precise analysis. The curves and numerical values are presented in red for the right side of the nose and blue for the left side. Measurements taken before mucosal decongestion are shown in a light color. Measurements taken after decongestion are shown in a dark color.

27.2.1.1 Graphical Presentation

Figure 27.1 shows the graphics used in rhinoresistometry.

Upper Graph: Inspiratory and Expiratory Nasal Airway Resistance in Relation to Flow Velocity

Flow-dependent increase in resistance is presented in the upper graph (Fig. 27.1). It is apparent that in both inspiration and expiration, nasal airway resistance rises with increasing flow velocity.

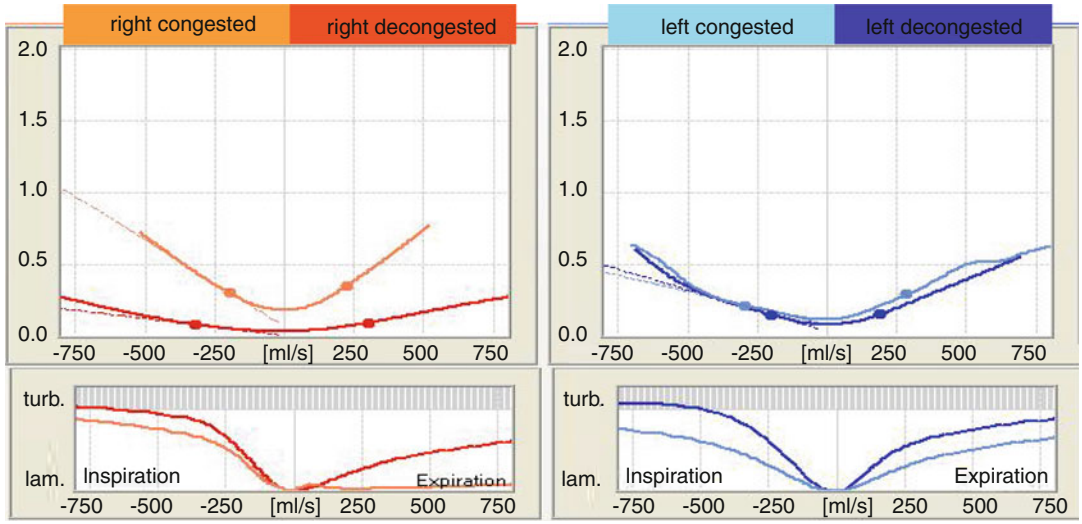


Fig. 27.1 Graphic representation of the findings from RRM. Right side of the nose, *red*; left, *blue*. *Light-colored curves*: before decongestion of the mucosa. *Dark-colored curves*: after decongestion of the mucosa. *Upper graph*: nasal airway resistance. *Lower graph*: turbulence flow behavior of the nasal airstream. *x*-axis: left of the midline: inspiratory flow in ml/s. right of the midline: expiratory flow in ml/s. *y*-axis: *upper graph*: resistance in sPa/ml. *lower graph*: turbulent flow behavior: *lam.* laminar, *turb.* turbulent

We know from physiology that during moderate physical activity, maximal breath flow (both sides of the nose combined) of approx. 500 ml/s is required to maintain adequate oxygen supply. During heavy physical activity, the oxygen need is met through supplemental bypass breathing through the mouth. As a result, flow velocities rarely exceed 500 ml/s in the nose. For this reason, we describe the range between 0 ml/s and 500 ml/s as the *zone of "physiologically required nasal airflow*."

However, experience tells us that when patients put on the breathing mask for the test, they breathe more deeply. The patient achieves flow velocities of up to 800 ml/s. This is the reason we see very long inspiratory and expiratory curves in rhinomanometric testing. In RRM the inspiratory and expiratory portions of the curves are marked with points where the flow through the right and left side of the nose totals 500 ml/s. This makes it possible to see at a glance how much each side of the nose is contributing to total flow during moderate physical activity and what levels of nasal flow resistance are reached on each side of the nose during "physiologically required airflow."

The graph enables us to evaluate nasal airway resistance for each side of the nose "at a glance": the higher the path of the curve, the greater the nasal obstruction. In Fig. 27.1, the right side of the nose is obstructed prior to decongestion.

In addition, by examining the distance between the curves before and after decongestion, we can differentiate between the portions of nasal airway resistance due to congestion and due to skeletal narrowing. In Fig. 27.1, a decongestant effect can be seen on the right side. At the measurement before decongestion, there was mucosal congestion on the right side of the nose (e.g., during a resting phase in the nasal cycle). After decongestion, resistance is low on both sides of the nose. Thus, there is no obstruction related to skeletal narrowing on either side of the nose.

Figure 27.2 shows rhinoresistometric resistance curves in a nose with mucosal congestions and skeletal obstruction on the right.

After decongestion, nasal resistance improves (the mucosal component), but the resistance still remains elevated (the skeletal component).

Besides detecting obstruction at a glance, it is also possible to establish the diagnosis of

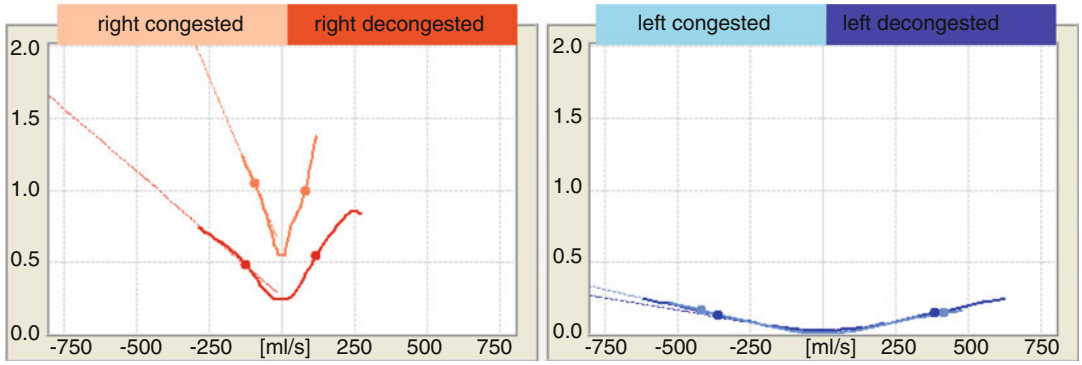


Fig. 27.2 Rhinoresistometry resistance curves from the right side of a nose obstructed by mucosal congestion and skeletal constriction with normal findings on the *left*

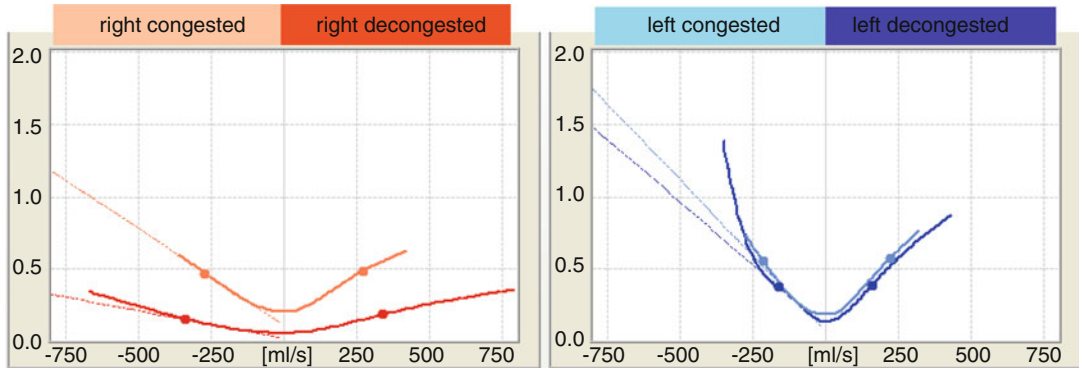


Fig. 27.3 Resistance curves measured by rhinoresistometry (*continuous lines*) and resistance curves calculated with a stable lateral vestibular wall (*dotted lines* on the inspiratory side of the curve). Right before decongestion: no NVC. Right after decongestion and left before decongestion: physiological NVC. Left after decongestion: pathological NVC

inspiratory nasal valve collapse (NVC) by looking at the graph. In the graphical presentation of nasal airway resistance, the inspiratory arm includes a calculated curve as an interrupted line, which indicates the flow-dependent increase in airway resistance in the presence of a stable vestibular wall (without collapse resulting from suction and the Bernoulli effect). Deviations of the measured (continuous line) curve from the (interrupted) straight line indicate abnormalities in the width of the flow channel, such as those resulting from NVC (Fig. 27.3).

The measured and calculated curves will be congruent if the nasal valves are not sucked in during inspiration as a result of the Bernoulli effect (Fig. 27.1, right prior to decongestion; Fig. 27.2, all curves; Fig. 27.3, right prior to decongestion). The greater the extent of NVC, the more sharply the measured curve will deviate from the calculated curve (Gruetzenmacher et al. 2005a). Slight deviation at high flow velocities (>500 ml/s) indicates *physiological* collapse of the nasal valves (Fig. 27.1, right prior to decongestion and left before and after decongestion; Fig. 27.3, right after and left prior to decongestion). One can identify *pathological* collapse of the nasal valves on the basis of a large deviation of the measurement from the calculated curves (Fig. 27.3, left after decongestion).

The graphical representation allows us to estimate the proportion of the increase in nasal airway resistance caused by collapse of the nasal valves. It also makes it possible to establish an initial assessment of how much improvement in nasal airway resistance might be expectable as a result of surgical stiffening of the lateral vestibular wall.

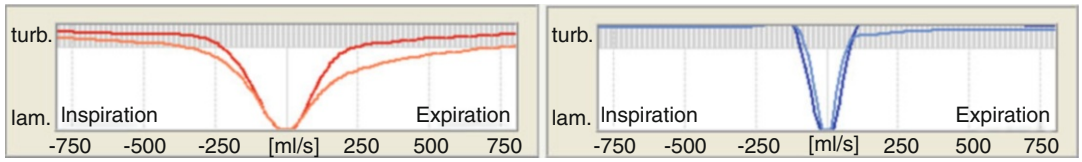


Fig. 27.4 Turbulence curves from rhinoresistometry. *x*-axis: left of the *y*-axis: inspiratory flow in ml/s. right of the *y*-axis: expiratory flow in ml/s. *y*-axis: degree of turbulence. The *x*-axis corresponds to pure laminar flow (*lam.*), and the upper blue-gray bars correspond to marked turbulence (*turb.*). Right nose (*red*): typical of physiological transition from laminar to turbulent flow behavior. Left nose (*blue*): typical of pathological turbulent flow behavior

Lower Graph: Inspiratory and Expiratory Turbulence Behavior in Relation to Airflow Velocity

In the RRM, the lower graph (Fig. 27.1) displays the turbulence behavior of nasal airflow in relation to airflow velocity. The level on the x-axis corresponds to pure laminar flow, and the upper blue-gray bars correspond to marked turbulence.

At very low flow velocities, flow is laminar in any flow channel (Mlynski and Loew 1992) and thus in the nose as well. In inspiration and expiration, as the velocity of flow increases, laminar flow portions transition into turbulent flow portions. This "transitional zone" is important for the respiratory function of the nose. It creates the optimal situation for conditioning the air. It provides for adequate mucosal contact by the streaming air without leading to drying out or cooling of the mucosa. At very high airflow velocities, nasal airflow becomes purely turbulent (Mlynski and Loew 1992; Churchill et al. 2004; Sawyer et al. 2007; Chen et al. 2009, 2010; Leong et al. 2010). Pure turbulence hardly ever occurs in a normal nose. When high airflow velocities are required to provide adequate oxygen supplies during heavy physical activity, oral bypass breathing is unconsciously switched on so that the nasal airstream decreases (see above: zone of "physiologically required nasal airflow").

Nasal airflow should become more turbulent when the mucosa is in a decongested state (corresponding to the working phase of the nasal cycle) as a condition for sufficient mucosal contact than in the congested state (corresponding to a resting phase in the nasal cycle). In the resting phase (decongested mucosa), the flow character should not become purely turbulent up to an airflow velocity of 250 ml/s (Fig. 27.1, bilaterally; Fig. 27.4, right side of the nose).

In pathological turbulence behavior, there is a rapid transition to pure turbulence so that pure turbulence will already develop in the nose at a flow rate <250 ml/s (Fig. 27.4, left side of the nose).

Excessive turbulence in the nose can be the cause of elevated airway resistance, and it can also cause a sense of stuffiness and sicca symptoms at low levels of airway resistance.

27.2.1.2 Numerical Values

Besides using the graphical representations to establish a "diagnosis at a glance," the numerical values make it possible to precisely estimate the extent and the causes of obstruction. Different individuals with the same degree of nasal obstruction may have quite varied levels of symptoms depending on their age, gender, body mass index, level of physical fitness, and associated illnesses. Therefore, the reference values presented here should not be applied rigidly. They are simply benchmarks for the purpose of orientation. The values were determined through studies on both rhinologically healthy patients and patients with nasal obstruction (Marschall 1997; Enßen 2005; Fiebig 2007; Gogniashvili et al. 2011).

Nasal air resistance (R) is numerically reported at a flow velocity of 250 ml/s before and after decongestion. As presented in Sect. 27.2.1.1, the maximum flow velocity still within the zone of physiologically required flow is around 500 ml/s. If we assume that with moderate physical activity, both sides of the nose will enter the working phase of the nasal cycle (which is known as the "in-concert" cycle), at this level of activity, each side of the nose should have a flow rate of about 250 ml/s. No mouth-bypass breathing should occur with moderate physical activity (Olson and Strohl 1987). This is the reason that for a total flow rate = 500 ml/s, there must be no nasal obstruction present. Thus, for the practical

evaluation of nasal obstruction, the resistance measured at 250 ml/s is an important value (Gehring et al 2000; Sawyer et al. 2007).

The extent of nasal obstruction can be estimated according to the reference values in Table 27.1.

Hydraulic diameter (d_h) is a measure of the width of the nasal cavum. The nasal cavity is a space with irregular cross sections. Therefore, its width cannot be defined simply by its diameter as with a round tube. In technological science, the usual practice when dealing with an irregular cross section is to use the "hydraulic diameter." This is the diameter of a tube of the same length with a round cross section that has the same resistance to flow as the irregularly shaped flow channel. The figures shown in Table 27.2 can be used as reference values for estimating the width of the interior of the nose.

Hydraulic diameter is shown before and after decongestion. Using these values, one can identify a mucosal swelling and a skeletal narrowing as the cause of nasal obstruction. The increase in magnitude of the hydraulic diameter by decongestion is an index of mucosal swelling. If the hydraulic diameter remains low after decongestion, this is evidence of skeletal stenosis. A very large hydraulic diameter indicates a nose that is too wide.

Numerical values for NVC are calculated before and after decongestion. To objectify the extent of NVC, a calculation is made of the percentage increase in resistance (ΔR) caused by suction at a flow velocity of 500 ml/s (Fig. 27.5, left). If this flow velocity cannot be achieved, the calculation is performed at maximum inspiration (Fig. 27.5, right).

Table 27.1 Standard values for nasal resistance at 250 ml/s for evaluating nasal obstruction

Resistance at 250 ml/s	Extent of obstruction on one side of the nose
<0.17 sPa/ml	No obstruction
0.17–0.35 sPa/ml	Slight obstruction
0.36–0.70 sPa/ml	Moderate obstruction
>0.70 sPa/ml	Severe obstruction

Table 27.2 Standard values for hydraulic diameter for determining the width of the nasal flow channel

Hydraulic diameter	Width of the nose
<5.5 mm	Too narrow
5.5–6.5 mm	Normal width
>6.5 mm	Too wide

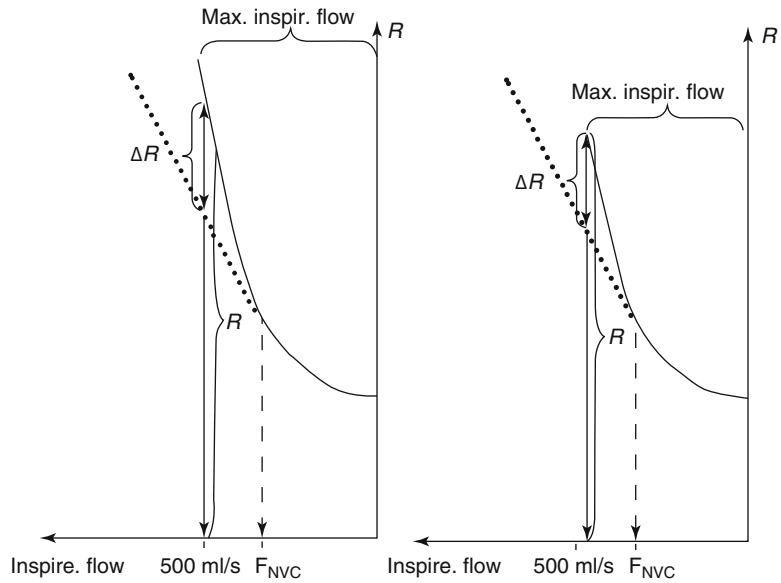


Fig. 27.5 Schematic representation of the inspiratory arm of an RRM curve during NVC for calculating the increase in resistance **Δ***R* caused by sucking in the lateral wall of the nasal vestibulum. *Left*: calculation with maximum inspiratory flow >500 ml/s. *Right*: calculation with maximum inspiratory flow <500 ml/s. ____ Measured RRM curve, …..... Calculated curve for a stable lateral vestibular wall, F_{NVC} Flow rate at which NVC begins, *R* Resistance at flow rate = 500 ml/s or at maximum inspiratory flow, **Δ***R* Percent increase in resistance as a result of NVC

Table 27.3 Standard values for the increase in resistance (ΔR) as a result of NVC for differentiating between physiological and pathological NVC

ΔR	NVC
<25 %	Physiological
>25 %	Pathological

Table 27.4 Standard values for the friction coefficient λ as an index for the tendency of the inner nasal walls to create turbulence

Friction coefficient λ	Turbulence
Up to 0.30	Normal tendency for turbulence
<0.30	Severe tendency for turbulence

The numerical value for the increase in resistance from NVC (ΔR) allows us to estimate the magnitude of the suction phenomena as well as to differentiate between physiological and pathological NVS, in accordance with Table 27.3.

In addition, the nasal airflow velocity at which suction/collapse begins (F_{NVC}) is quantified. The nasal valves should not be significantly collapsed/sucked in ($\Delta R < 25$ %) at airflow velocities up to the maximum physiologically required nasal airflow of 500 ml/s.

The *friction coefficient* λ is reported during inspiration and expiration, both before and after decongestion. This index characterizes the configuration of the inner nasal wall in relation to its degree of "streamlining," that is, its impact on the development of turbulent flow, which is important for the warming and humidifying function of the nose (Keck and Lindemann 2010). A low λ-value suggests an internal configuration that causes few turbulent regions of flow. High λ-values indicate greater turbulence formation.

Using the reference values in Table 27.4, the interior of the nose can be evaluated with respect to its tendency to trigger turbulence.

In the nose, the λ-value changes over the nasal cycle: it increases after decongestion in the working phase. This promotes the mucosal contact with the flowing air that is required for thermal and humidity exchange. In the resting phase, the friction coefficient becomes lower, and the airflow becomes more laminar (Lang et al. 2003).

Values over 0.030 indicate severe turbulence, which can cause elevated airway resistance, sicca symptoms, and/or a feeling of stuffiness.

Figure 27.6 presents rhinoresistometry graphs and numerical values from a patient with right mucosal congestion, right skeletal narrowing, and left pathological turbulence behavior.

Figure 27.7 shows RRM findings from a patient with "empty nose syndrome" (Beule 2010; Scheithauer 2010), with post-decongestion values on both sides that are characteristic of an excessively wide nose (hydraulic diameter after decongestion >6.5 mm) with marked turbulence ($\lambda > 0.03$), in the graph prior to and after decongestion, there is pure turbulence at a flow <250 ml/s.

27.2.2 Measuring the Nasal Diffuser Using Acoustic Rhinometry (ARM)

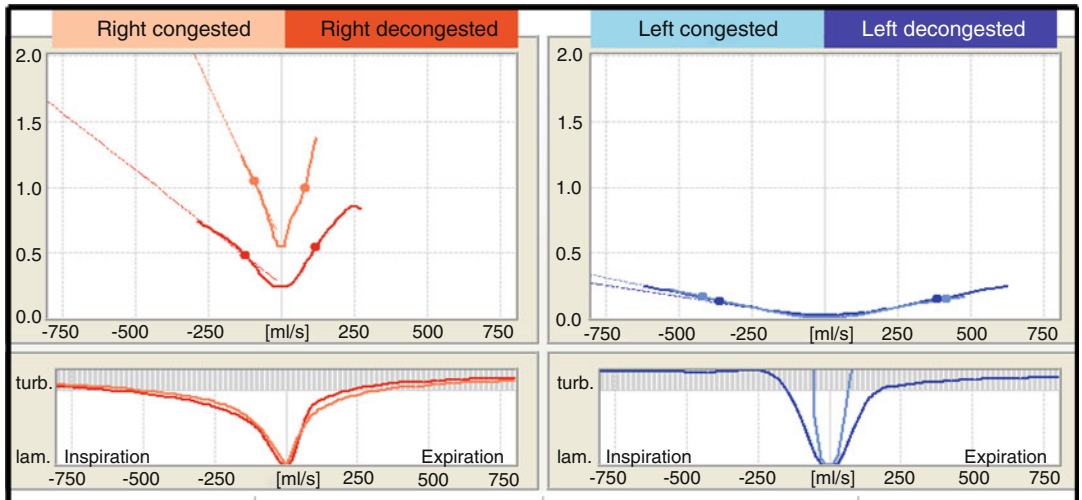
ARM is presented in detail in Chap. 26 Here, we will describe in addition how acoustic rhinometry can be used to obtain evidence about the causes of pathological turbulence in the nose (Fig. 27.8).

The occurrence of turbulence in a diffuser rises directly in proportion to increases in the cross-sectional area and to decreases in the size of the diffuser entry opening (see Sect. 23.4).

The entry opening in the nasal diffuser corresponds to the inner nasal valves and thus to MCA1 as calculated by acoustic rhinometry. It is only when there is a ballooning phenomenon present that the diffuser starts out already at the external nasal ostium.

Increases in cross-sectional area along the nasal diffuser are evaluated by measuring the diffuser opening angle φ. This indicator is used in fluid physics in order to characterize cross-sectional expansion in circular diffusers (Fig. 27.9).

In accordance with this principle, the opening angle φ is calculated for the nasal diffuser (anterior cavum) using the cross-sectional area measured by ARM (Fig. 27.10). The angle φ indicates



Before decongestion	Right	Left	
R (250 ml/s)	>0.2	0.09	sPa/ml
d_h	2.7	8.1	mm
λ	12	42	$\times 10^{-3}$
Flow at NVC			ml/s
ΔR			%

After decongestion	Right	Left	
R (250 ml/s)	0.69	0.09	sPa/ml
d_h	4.1	8.6	mm
λ	30	40	$\times 10^{-3}$
Flow at NVC			ml/s
ΔR			%

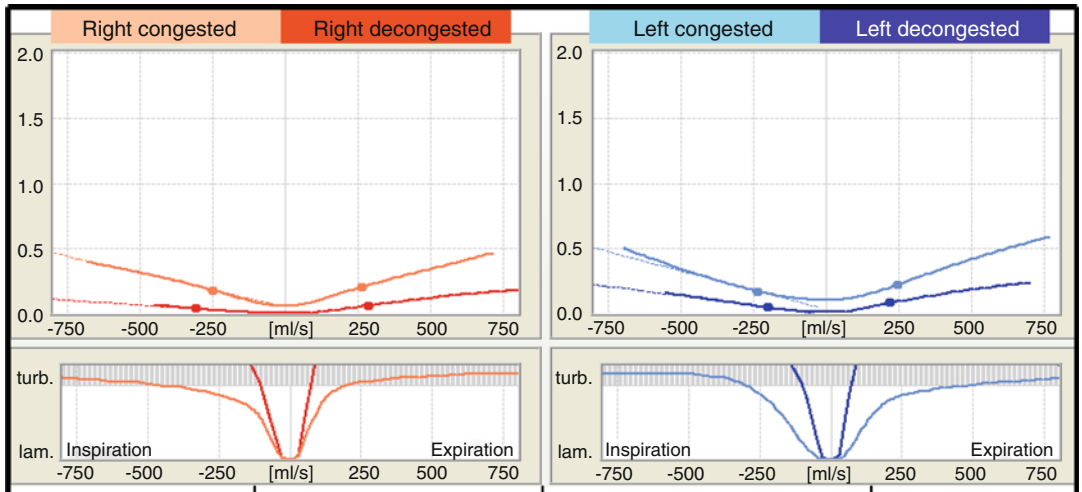
Fig. 27.6 Results of rhinoresistometry measurements in a patient with severe nasal obstruction as a result of mucosal congestion and skeletal stenosis as well as pathological turbulence on the left side from an excessively wide nose

the occurrence of turbulence in the nose in the inspiratory flow direction.

The diffuser angle in relation to triggering nasal turbulence can be assessed using the reference values in Table 27.5.

In the presence of a pathological friction coefficient $\lambda > 0.03$ as measured by RRM, the diffuser opening angle provides information about one possible cause of the high level of turbulence. Figure 27.10 shows the results of ARM with a large diffuser opening angle on the right, especially after decongestion.

It has to be considered that even if the opening angle in the nasal diffuser plays the principal part in the occurrence of turbulence, structures other than a narrow diffuser entry opening (e.g., a deformed nasal vestibule, bands, or spurs) may also increase the level of turbulence in the nose.



Before decongestion	Right	Left	
R (250 ml/s)	0.18	0.09	sPa/ml
d_h	5.7	8.1	mm
λ	34	42	$\times 10^{-3}$
Flow at NVC			ml/s
ΔR			%

After decongestion	Right	Left	
R (250 ml/s)	0.03	0.07	sPa/ml
d_h	8.2	7.6	mm
λ	64	63	$\times 10^{-3}$
Flow at NVC		144	ml/s
ΔR		5	%

Fig. 27.7 Results of rhinoresistometry measurements in a patient with "empty nose syndrome"

27.2.3 Long-Term Rhinoflowmetry (LRM)

LRM was developed because RMM, RRM, and ARM only allow for estimating nasal obstruction at a certain time point of the measurement (Lang et al. 2003). Some patients complain about symptoms that occur at other times of the day. LRM makes it possible to measure nasal flow separately for each side of the nose, along with heart rate to serve as an index for physical activity over a 24-h time period under the patient's everyday conditions of life. Nasal flow is measured using standard commercial nasal oxygen cannulas and the heart rate using standard EVG electrodes. Recording is performed by means of a battery-powered portable device (Fig. 27.11).

Figure 27.12 illustrates the graphical curves resulting from an LRM examination. The upper graph presents the maximal nasal flow values during inspiration separately for each side of the nose in relation to time. The lower graph shows the heart rate for estimating physical activity, respiratory rate, as well as nasal minute ventilation in relation to time.

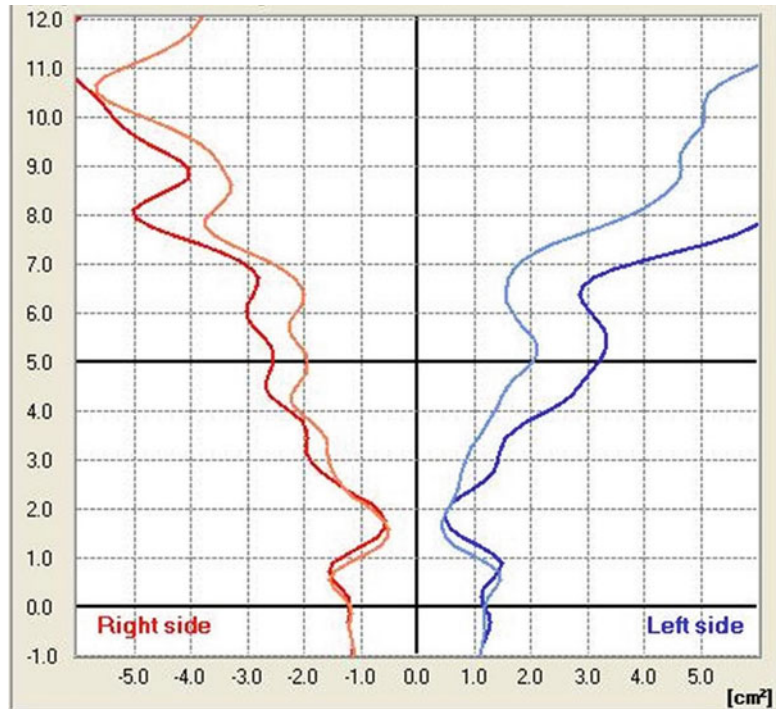


Fig. 27.8 Results of ARM. The nasal diffuser is marked in color on both sides (right, *red*; left, *blue*; before decongestion, *light*; after decongestion, *dark*)

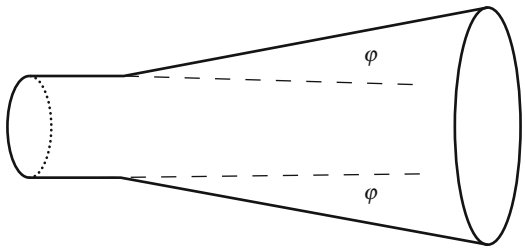


Fig. 27.9 Schematic representation of the diffuser opening angle **φ** in a circular diffuser

27.2.3.1 Upper Graph (Figs. 27.12 and 27.13)

The flow-time curves allow for the visual assessment of the nasal cycle at a glance. At physical rest or light physical activity, a "classical type" of nasal cycle should occur, with reciprocal alternation between the two sides of the nose in working and resting phases. With increasing physical activity, the simultaneous transition of both sides of the nose into the working phase (the "in-concert" cycle) may be seen as a physiological response to increased oxygen demand. In this situation, the nasal flow in both sides should reach between 250 ml/s and 500 ml/s, as shown in Fig. 27.12. These flow velocities could not be reached in the presence of increased nasal air resistance with the deployment of mouth-bypass breathing. An example is shown in Fig. 27.13.

27.2.3.2 Lower Graph (Figs. 27.12 and 27.13)

Heart Rate (Orange Curve)

Heart rate is used as an index of physical activity.

The values in Table 27.6 may thus be used for approximation.

Please note that these values may vary considerably between individuals.

Heart rate is an index of physical activity and thus provides evidence about oxygen demand. Therefore, in assessing the curves for flow, respiratory rate, and nasal minute volume, the heart rate is an important point of reference.

Respiratory Rate (Purple Curve)

The resting respiratory rate is 12–16 breaths per minute.

The respiratory rate curve provides an indication of the effectiveness of the patient's breathing technique. In conditions of increased oxygen

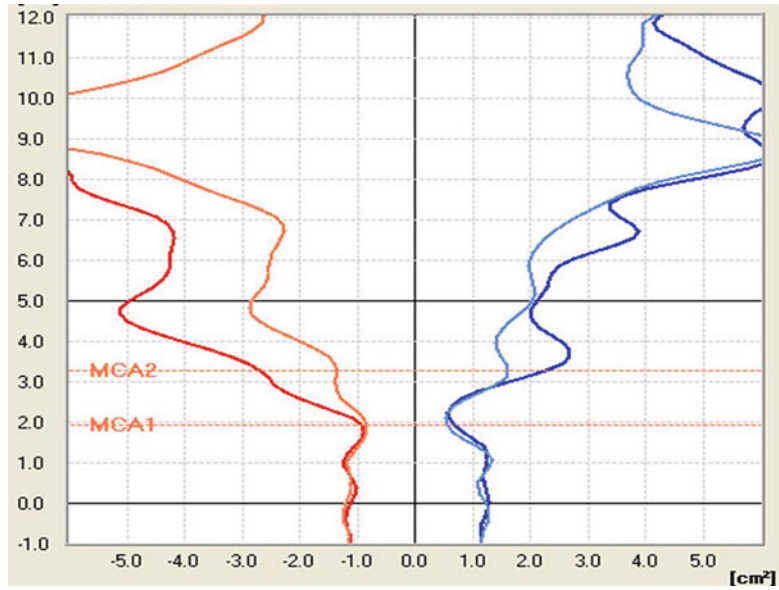


Fig. 27.10 Results of acoustic rhinometry measurements with a deformed diffuser on the right (marked in *red*). With the help of a regression scale (……..), the diffuser opening angle **φ** can be calculated

Table 27.5 Reference values for the diffuser opening angle **φ** in relation to triggering turbulence in the nose

Turbulence in the nose	Diffuser opening angle φ
Slight turbulence formation	<7°
Moderate turbulence formation	7°–9°
Severe turbulence formation	>9°

demand under stress, there are two breathing techniques available to increase minute ventilation:

- Increasing the respiratory rate with/without increasing tidal volume.
- Decreasing respiratory rate with increased tidal volume. Due to the lower percentage of dead-space ventilation, this technique is more effective.

Nasal Minute Volume (NMV) (Green Curve)

Nasal minute ventilation is the total volume of air that passes through both sides of the nose in one minute. In combination with the physical activity, one can use the reference values in Table 27.7.

If the measured values for the nasal minute ventilation fall below the indicated reference value (as in Fig. 27.13), one can conclude with great certainty that mouth-bypass breathing is taking place. This can be a sign of nasal obstruction (Leiter and Baker 1989). Table 27.8 can be used for an initial evaluation of the obstruction.

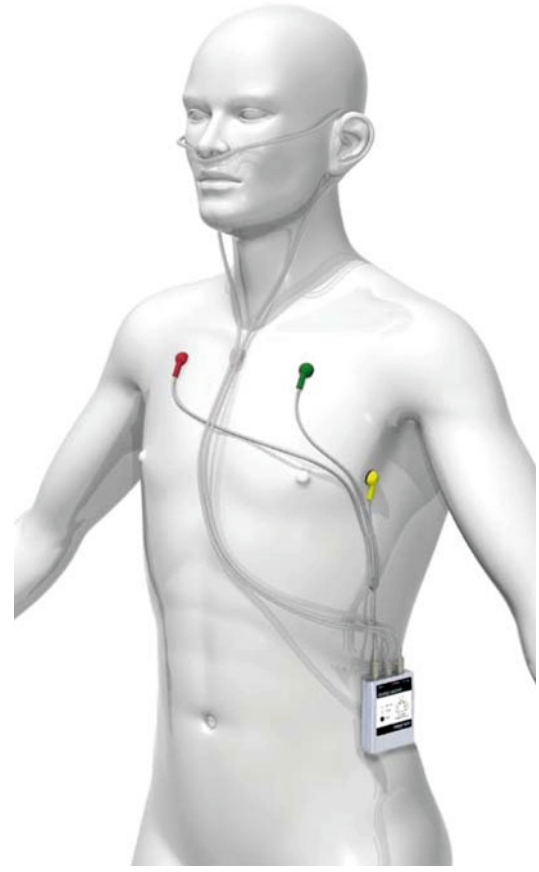


Fig. 27.11 Measurement system for long-term rhinoflowmetry

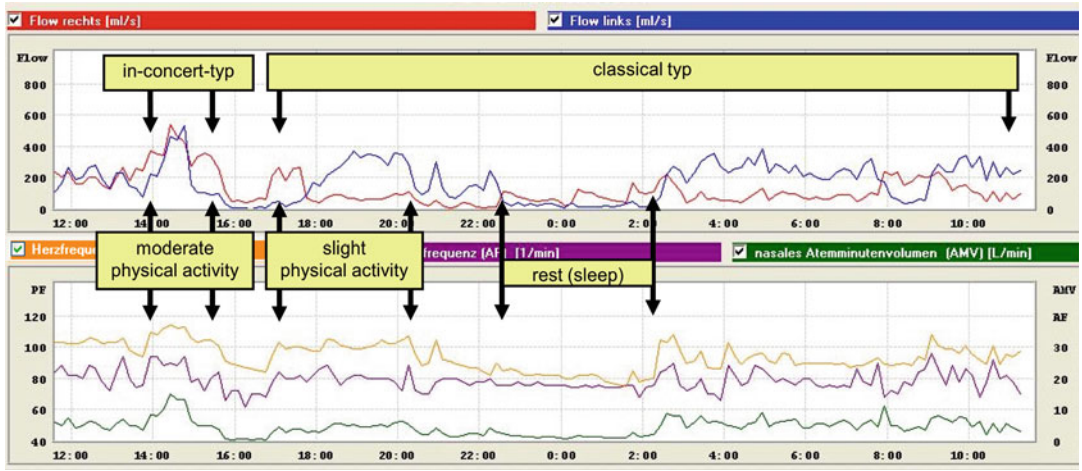


Fig. 27.12 Findings from LRM in a person with normal nasal breathing. To better grasp the relation between physical activity and mucosal congestion in the nose, in this figure the type of cycle and the amount of physical activity were marked. *x*-axis: time of day in hours. *y*-axis: *upper graph*, nasal respiratory velocity at maximal inspiration in ml/s (*red* right nose, *blue*, left nose). *Lower graph*: *orange*, heart rate (*HF*); *green*, nasal respiratory minute volume (*NMV*) in l/min; *purple*, respiratory rate (*AF*)

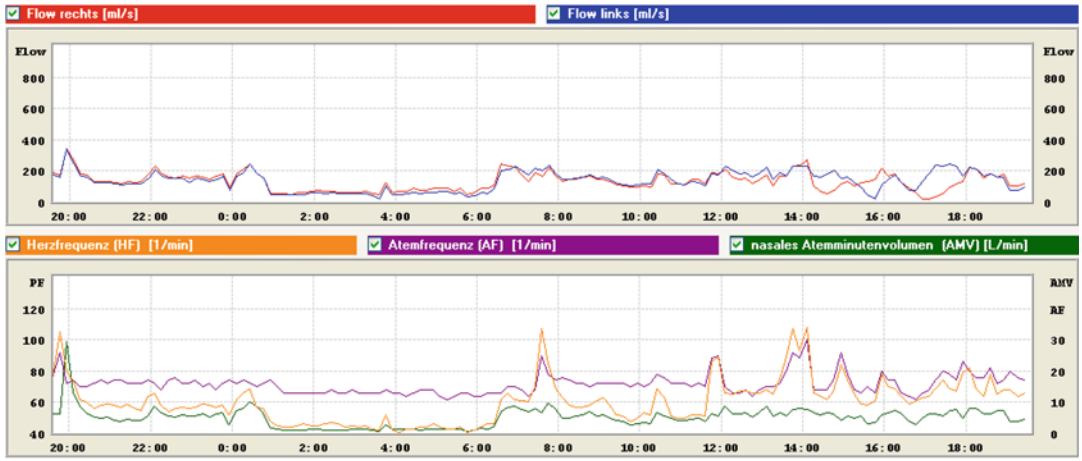


Fig. 27.13 Findings from LRM with bilateral nasal obstruction. The nasal respiratory minute volume (*green curve*) suggests mouth-bypass breathing during the day (values under 10 l/m, with the exception of the 8:00 PM value) and complete mouth breathing at night between 1:00 AM and 6:00 AM as a result of nasal obstruction

Table 27.6 Standard values for heart rate in relation to physical activity

Heart rate	Physical activity
<80/min	Physical rest
80–90/min	Slight physical activity
100–120/min	Moderate physical activity
>120/min	Severe physical activity

Table 27.7 Standard values for nasal respiratory minute volume as related to physical activity

Physical activity	Nasal respiratory minute volume
Physical rest	At least 5 l/min
Light physical activity	At least 10 l/min
Moderate physical activity	At least 20 l/min
Severe physical activity	At least 30 l/min

Table 27.8 Onset of mouth breathing during physical activity at different degrees of nasal obstruction

Onset of mouth-bypass breathing during	Extent of nasal obstruction
Physical rest	Severe obstruction
Slight physical activity	Moderate obstruction
Moderate physical activity	Slight obstruction
Severe physical activity	No obstruction

27.2.3.3 Indications for Long-Term Rhinoflowmetry

LRM is not required for every patient with nasal obstruction. It is indicated when the magnitude of nasal obstruction determined by RMM or RRM does not fully explain the patient's symptoms. Since nasal airway resistance accounts for about 60 % of total airway resistance, a deficiency in the respiratory musculature or the cardiovascular system or poor general physical condition may lead to symptoms that occur at even normal or slightly elevated levels of nasal airway resistance, which the patient compensates for through mouth-bypass breathing. In such cases the LRM shows low levels of baseline nasal minute ventilation that do not increase with increased physical activity.

In diagnosing sicca symptoms and in evaluating the "empty nose syndrome," LRM can likewise be a valuable diagnostic tool. The complete absence of resting phases suggests that the nose is too wide or that the congestive capacity of the nasal mucosa has been so greatly reduced that closure of the nose permitting a resting phase is no longer possible. In such cases, LRM often shows only minimal nasal minute ventilation, since these patients minimize nasal airflow unconsciously switching over to mouth-bypass breathing as a way to reduce chronic dryness in their nose by minimizing nasal airflow. In this way, they create resting phases for the nose by means of mouth-bypass breathing. Such LRM findings provide an indication for the treatment option of surgically reducing the nasal cavity width. If resting phases can still be observed in the nasal cycle, this would justify conservative therapy (see examples Sects. 27.3.2.6 and 27.3.2.7).

27.3 Diagnostic Procedures for Objectifying Nasal Obstruction and Its Causes

27.3.1 Combination of RRM, ARM, and LRM

Using RRM, ARM, and LRM, it is possible to obtain different but complementary information regarding nasal obstruction:

- RRM provides flow-dynamic information about the extent of obstruction (airway resistance), about the effects of a constriction (hydraulic diameter), and about the impact of the internal nasal structure on the occurrence of turbulence (friction coefficient λ). In addition, by measuring inspiratory NVC, the proportion of nasal airway resistance attributable to the Bernoulli effect can be estimated.
- ARM provides a geometric survey of the interior of the nose up to a depth of 5 cm from the outer nasal orifice (Mlynski et al. 2005) and thereby yields information about the structure of the inner nose with regard to stenoses and the occurrence of turbulence.
- LRM measures the nasal airstream over a 24-h period (separately for each side of the nose) along with the heart rate under the conditions of the patient's everyday life. This provides information about the nasal cycle as an important foundation for the circadian respiratory function of the nose, about the physiological changes in the swelling of the nasal mucosa to improve nasal airflow during periods of increased physical activity, and about pathological changes in congestion at all times day and night.

The complementarity of these three methods leads to the conclusion that combining them would be useful for improving the diagnostic evaluation of nasal obstruction. Every patient complaining of nasal obstruction should undergo RRM and ARM. A supplemental LRM should be performed:

- If the patient's symptoms occur at times of day or night other than the time of testing
- If the endonasal findings and the results of acoustic and rhinoresistometric testing cannot

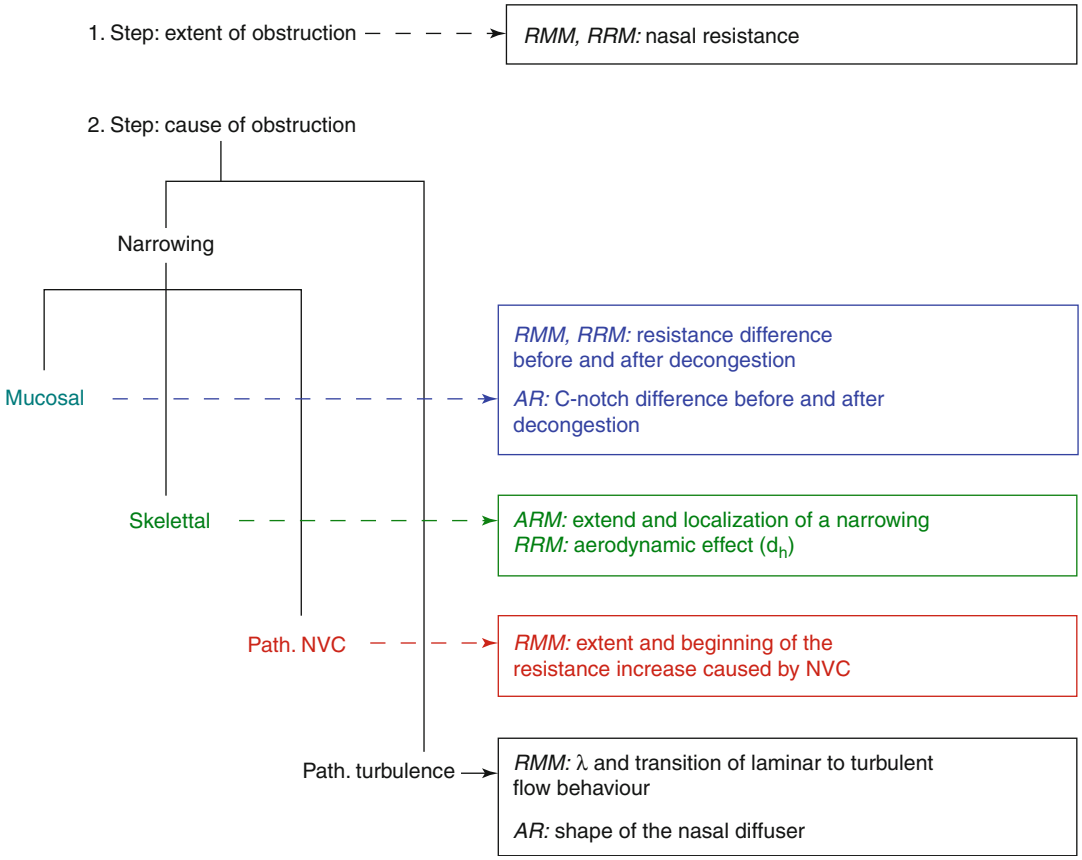


Fig. 27.14 Schematic representation: procedure for diagnosing the extent and the cause of nasal obstruction using RRM and ARM

fully explain the symptoms reported by the patient

- If insight into the nasal cycle is necessary, e.g., in the presence of unexplained fluctuating conditions of congestion, for sicca symptoms, and when mouth breathing predominates despite only minor nasal obstruction

The extent and the causes of nasal obstruction should be objectively determined according to the algorithm presented in Fig. 27.14.

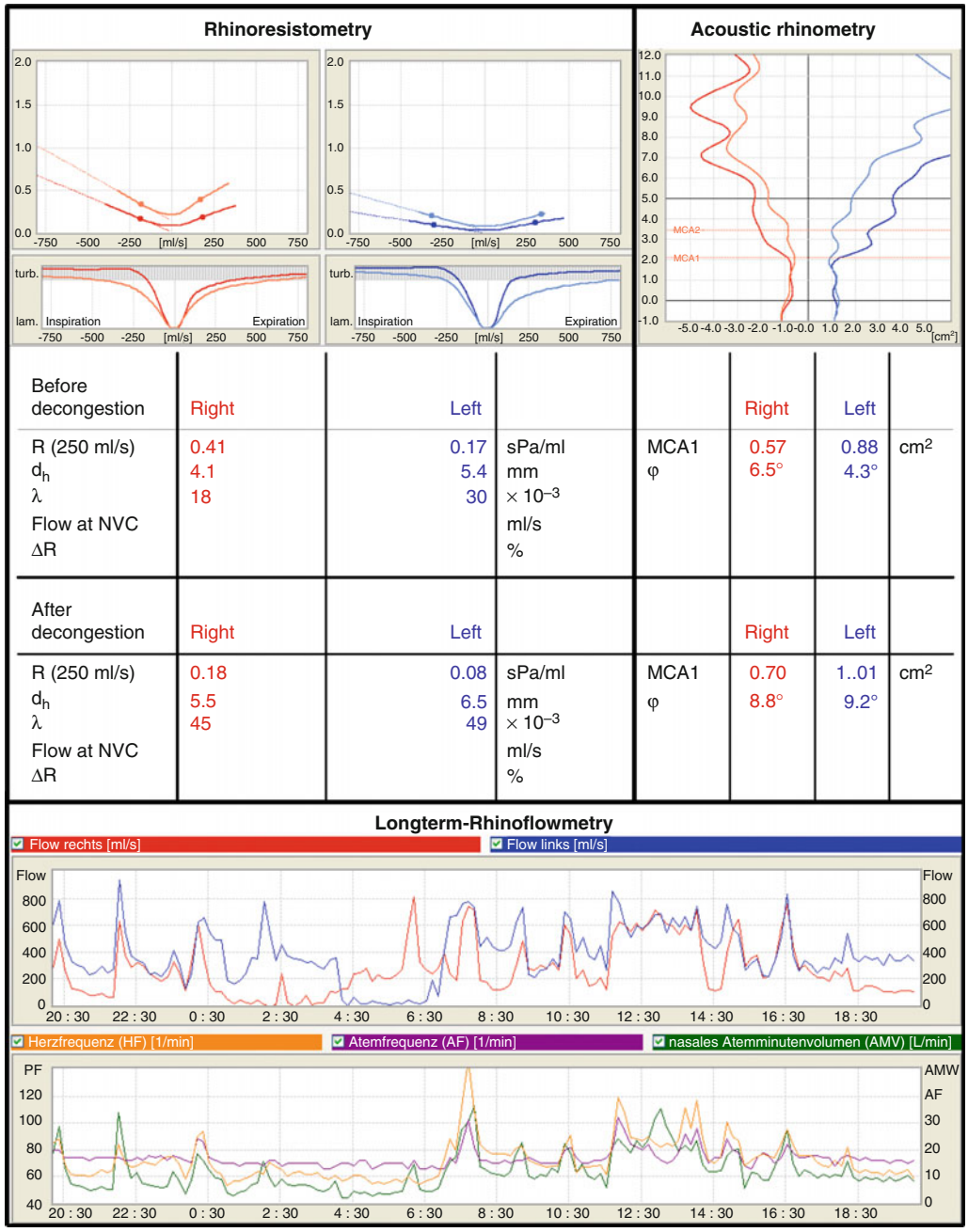
27.3.2 Examples

In the following section, we will use clinical examples to demonstrate how the combination of RRM and ARM allows to diagnose the extent and the cause of nasal obstruction. LRM will be additionally included in a few of the examples for didactic purposes, even though it would only be necessary for establishing the diagnosis in examples 6 and 7.

In describing the findings, we will employ the classification of regions in the nose recommended by Cottle (1961) (Table 27.9).

Table 27.9 Cottle's classification of the nasal regions 1–3

Cottle region	Anatomical area in the nose
Region 1	External nasal ostium (nostrils)
Region 2	Isthmus nasi (nasal isthmus)
Region 3	Region beneath the cartilage and bony pyramid, corresponding in terms of fluid dynamics to the nasal diffuser (see Chap. 23, Sect. 3.1.3)



Before decongestion	Right	Left			Right	Left	
R (250 ml/s)	0.41	0.17	sPa/ml	MCA1	0.57	0.88	cm^2
d_h	4.1	5.4	mm	φ	6.5°	4.3°	
λ	18	30	$\times 10^{-3}$				
Flow at NVC			ml/s				
ΔR			%				

After decongestion	Right	Left			Right	Left	
R (250 ml/s)	0.18	0.08	sPa/ml	MCA1	0.70	1..01	cm^2
d_h	5.5	6.5	mm	φ	8.8°	9.2°	
λ	45	49	$\times 10^{-3}$				
Flow at NVC			ml/s				
ΔR			%				

Fig. 27.15 RRM, ARM, and LRM findings in a patient without nasal obstruction

27.3.2.1 Example 1: No Nasal Obstruction

- *History*: No trauma recalled.
- *Complaints*: No impairment of nasal breathing and slight sicca symptoms.
- *Endonasal findings*: Septal deviation to the right in region 2 and 3.
- *Measurement findings* of this case are shown in Fig. 27.15.
- *Analysis of the findings*:
  Extent of obstruction
  RRM resistance: *Before decongestion*, moderate obstruction on the right and no obstruction on the left.

After decongestion, on the right, borderline to slight obstruction and, on the left, no obstruction. Thus, the septal deviation to the right nasal side in region 2 and 3 is a physiological deviation. The moderate obstruction on the right prior to decongestion relates to congestion.

Cause of the obstruction

RRM hydraulic diameter: *The decongestant effect* of 4.1–5.4 mm on the right and of 5.5–6.5 mm on the left suggests greater mucosal congestion on the right than on the left.

After decongestion, the hydraulic diameter on both sides is in the normal range: no skeletal narrowing.

RRM turbulence: *Before decongestion*, the friction coefficient λ is normal on both sides: no pathological turbulence.

After decongestion, $\lambda > 0.03$ on both sides: intense creation of turbulence with quick transition from laminar to turbulent flow.

RRM NVC: Measured and calculated curves are congruent (bilaterally): no NVC.

ARM: Normal course of the curves. φ-values after decongestion are very large, which explains the increased turbulence after decongestion. Other ARM results are in the normal range.

LRM: At night and with slight physical activity, there is a classical type of nasal cycle with complete resting phases. In the second half of the night, NMV <51 min: this suggests mouth-bypass breathing.

With slight to moderate physical activity (HR: around 100/min.), there is a classical type of nasal cycle, but without complete resting phases. To cover the oxygen demand, the resting side has to participate somewhat. During a brief increase in heart rate (caused by an increase in physical activity), the flow in both sides of the nose increases and thus the NMV follows appropriately.

During each period of severe physical activity, an in-concert cycle occurs, with increased flow on both sides of the nose and a corresponding increase in the NMV.

Overall, there is a physiological response of the mucosa to oxygen need at rest and during physical activity.

- *Assessment*:
  There is normal nasal breathing in the presence of a physiological deviation of the septum toward the right. Severe turbulence in the decongested mucosa may be the cause of the sicca symptoms reported by the patient.

27.3.2.2 Example 2: Deviated Septum (Case 1)

- *History*: No trauma recalled.
- *Complaints*: Impaired nasal breathing on the left for many years.
- *Endonasal findings*: Septal deviation toward the left in region 2 and 3.
- *Measurement findings* of this case are shown in Fig. 27.16.
- *Analysis of the findings*:
  Extent of obstruction

  RRM resistance: *Before decongestion,* moderate obstruction on both sides.

  After decongestion, no obstruction on the right nasal side and moderate obstruction persistent on the left. Thus, the septal deviation is pathological.

  Cause of the obstruction

  RRM hydraulic diameter: *The decongestant effect* of 4.2–6.7 mm on the right nasal side suggests severe mucosal congestion. On the left, hardly any decongestant effect is to recognize.

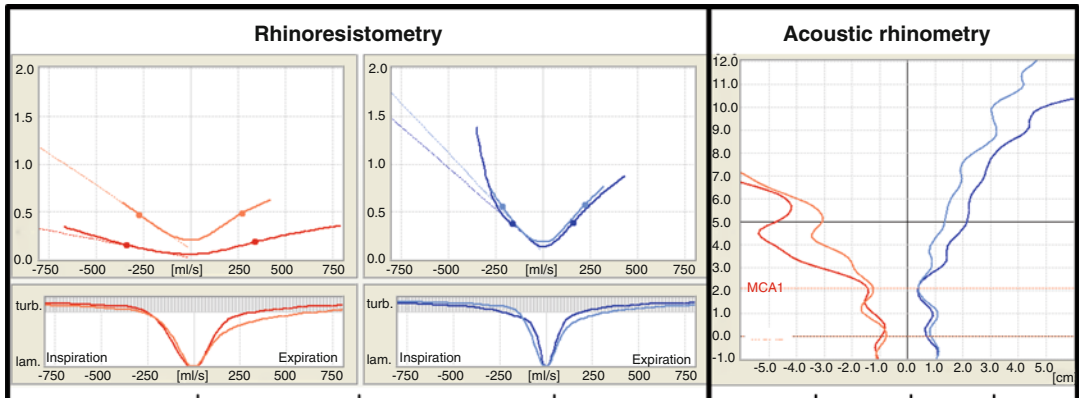
  After decongestion, the hydraulic diameter of 4.5 mm on the left suggests pathological septal deviation. At 6.7 mm the right nasal side is actually too wide.

  RRM turbulence: The λ-values of 0.029 on the right are in the borderline pathological range. On the left, λ is >0.03: increased triggering of turbulence.

  RRM NVC: On the right, physiological NVC after decongestion. On the left, there is considerable pathological NVC after decongestion with $\Delta R = 96$ %.

  ARM: The constriction on the left side localizes to the area of the isthmus.

  The cause of the marked turbulence in this case is not a large diffuser opening angle φ but rather the narrowed diffuser inflow opening. On the right side, after decongestion the angle is actually too large (9.1°).



Before decongestion	Right	Left			Right	Left	
R (250 ml/s)	0.44	0.66	sPa/ml	MCAI	1.22	0.40	cm^2
d_h	4.2	4.3	mm	φ	7.4°	4.3	
λ	29	46	$\times 10^{-3}$				
Flow at NVC			ml/s				
ΔR			%				

After decongestion	Right	Left			Right	Left	
R (250 ml/s)	0.11	0.58	sPa/ml	MCAI	1.42	0.37	cm^2
d_h	6.7	4.5	mm	φ	9.1	6.4	
λ	30	50	$\times 10^{-3}$				
Flow at NVC	280	213	ml/s				
ΔR	29	96	%				

Fig. 27.16 RRM and ARM findings in a patient with septal deviation, case 1

Clearly, the turbulence-triggering effect of the high increase in cross-sectional area of the diffuser is diminished by the wide diffuser opening.

- *Rhinosurgical planning*:
  Septoplasty
- *Justification*:
  Relocation of the septum toward the right in the isthmus area is possible since the right side is wide enough and the resistance is small enough. At the same time, the turbulence problem on the left will be diminished, since the narrow inflow opening of the diffuser will be expanded.

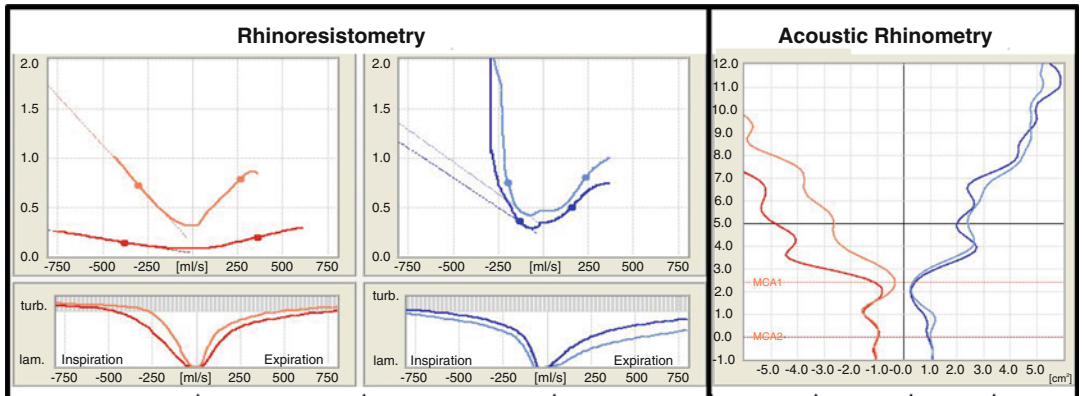
  In region 3 as well, relocation of the septum toward the right would have a beneficial effect, since λ and φ are already large on the right.

  For the same reasons, turbinate reduction on the right is contraindicated. On the left side as well, turbinate reduction would have an unfavorable effect on the nose, which is already too turbulent.

  The collapse of the nasal valve is caused by significant narrowing of the isthmus, which results in intense suction through the Bernoulli effect. The enlargement of this region by septoplasty would certainly be adequate to eliminate the suction. Therefore, stiffening of the lateral wall of the nasal vestibulum is unnecessary.

27.3.2.3 Example 3: Deviated Septum (Case 2)

- *History*: Trauma at age 21.
- *Complaints*: Impaired nasal breathing since time of trauma, left > right.
- *Endonasal findings*: Septal deviation toward the left in region 2 and 3.



Before decongestion	Right	Left			Right	Left	
R (250 ml/s)	0.62	1.83	sPa/ml	MCA1	0.33	0.40	cm^2
d_h	3.7	3.1	mm	φ	7.8°	4.3°	
λ	21	18	$\times 10^{-3}$				
Flow at NVC			ml/s				
ΔR			%				

After decongestion	Right	Left			Right	Left	
R (250 ml/s)	0.18	0.47	sPa/ml	MCA1	0.80	0.27	cm^2
d_h	5.4	3.3	mm	φ	8.6°	6.9°	
λ	21	11	$\times 10^{-3}$				
Flow at NVC		148	ml/s				
ΔR		259	%				

Fig. 27.17 RRM and ARM findings in a patient with septal deviation, case 2

- *Measurement findings* of this case are shown in Fig. 27.17.
- *Analysis of the findings*:
  Extent of obstruction
  RRM resistance: *Before decongestion,* moderate obstruction on the right and severe on the left.
  After decongestion, very slight obstruction on the right and moderate on the left. Consequently, the left septal deviation in region 2 and 3 constitutes pathological deviation.
  Cause of the obstruction
  RRM hydraulic diameter: *The decongestant effect* of 3.7–5.4 mm on the right suggests severe mucosal congestion on the right, which is causing moderate obstruction. On the left, there is hardly any objective evidence of a decongestant effect.
  After decongestion, the hydraulic diameter of 3.1 mm on the left suggests a significant skeletal stenosis. On the rights side, the hydraulic diameter does not completely normalize after decongestion. At 5.4 mm, it slightly exceeds the boundary value for stenosis.
  RRM turbulence: The λ-values are in the normal range bilaterally: normal transition from laminar to turbulent flow.
  RRM NVC: Pathological NVC is measured on the left side with $\Delta R > 200$ %.
  ARM: The constriction on the left side localizes to the MCA 1 area. It represents the cause of both the elevated resistance and the pathological NVC on the left.

On the right side, the moderate obstruction is caused by mucosal congestion, which extends as far as the isthmus region.

- *Rhinosurgical planning*:
  Septorhinoplasty with enlargement of the isthmus region bilaterally and anterior turbinoplasty on the right.
- *Justification*:
  Relocation of the septum toward the right is possible in the isthmus region, since the right side is wide enough after decongestion and the resistance on the right is low enough. However, the head of the inferior turbinate needs to be reduced by means of turbinoplasty.

  The NVC will be eliminated through enlargement of the isthmus, since the local flow velocity, and thus the Bernoulli effect, will be diminished as a result of increasing the cross-sectional area.

27.3.2.4 Example 4: Septal Deviation (Case 3)

- *History*: Trauma in childhood.
- *Complaints*: Nasal obstruction on the right.
- *Endonasal findings*: Septal deviation toward the right in region 2 and 3.
- *Measurement findings* of this case are shown in Fig. 27.18.
- *Analysis of the findings*:
  Extent of obstruction

  RRM resistance: *Before decongestion,* severe obstruction on the right and slight obstruction on the left.

  After decongestion, improvement, but persisting severe obstruction on the right. This represents a pathological septal deviation. On the left, the slight obstruction persists.

  Cause of the obstruction

  RRM hydraulic diameter: *The decongestant effect* of 2.9–3.9 mm on the right suggests major mucosal congestion, which contributes to severe obstruction. On the left, hardly any decongestant effect is seen.

  After decongestion, the hydraulic diameter of 3.9 mm on the right suggests significant skeletal stenosis. On the left side too, the hydraulic diameter of 4.9 mm after decongestion indicates the presence of a skeletal narrowing.

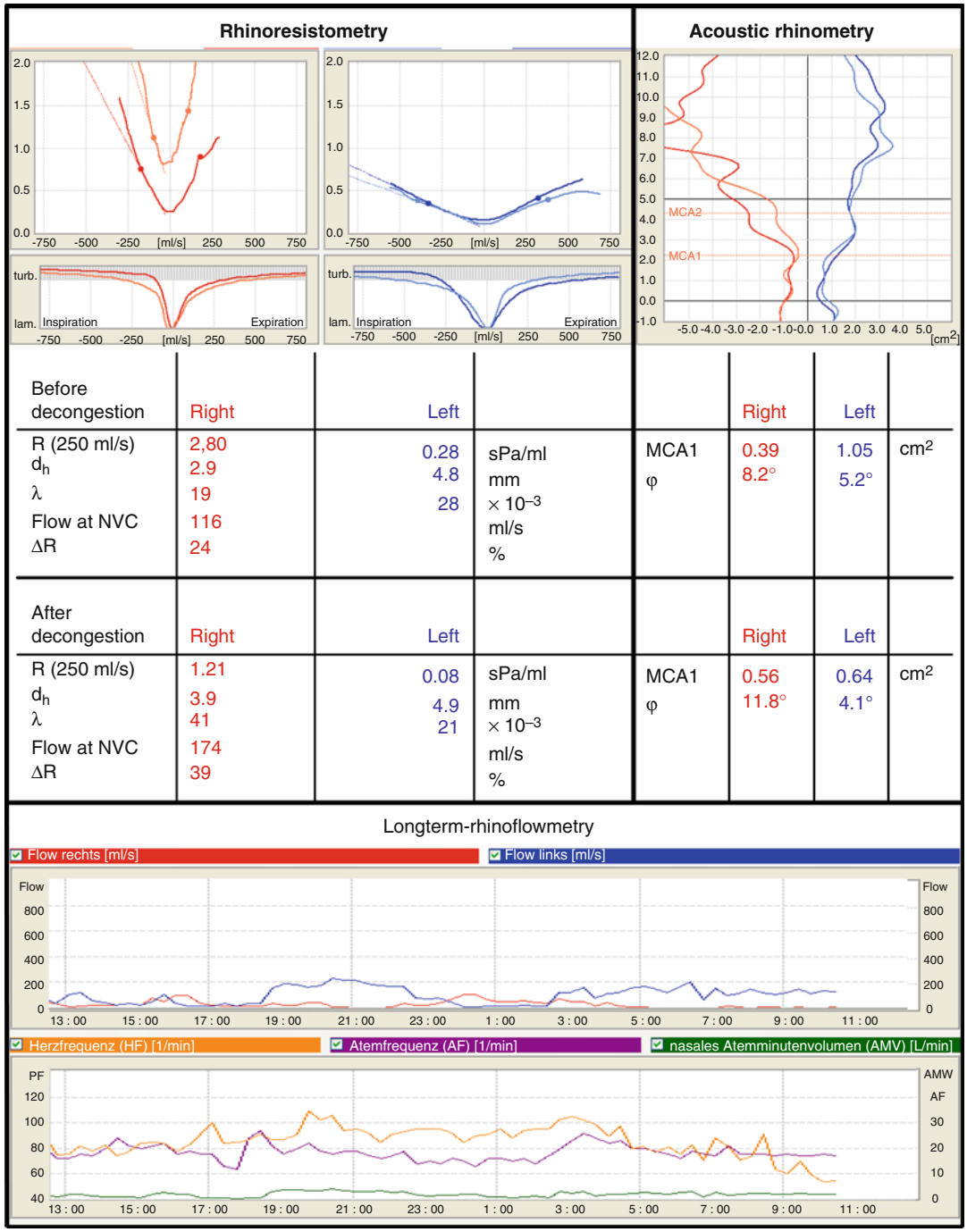
  RRM turbulence: The λ-value of 0.039 after decongestion is too high.

  RRM NVC: *Before decongestion,* there is a physiological NVC on the right, but *after decongestion*, it becomes pathological.

  ARM: The skeletal stenosis on the right side localizes to the MCA 1 area. It is the cause of both the elevated resistance and the pathological suction phenomenon.

  The skeletal narrowing on the left is located at the nasal entrance (septal subluxation).

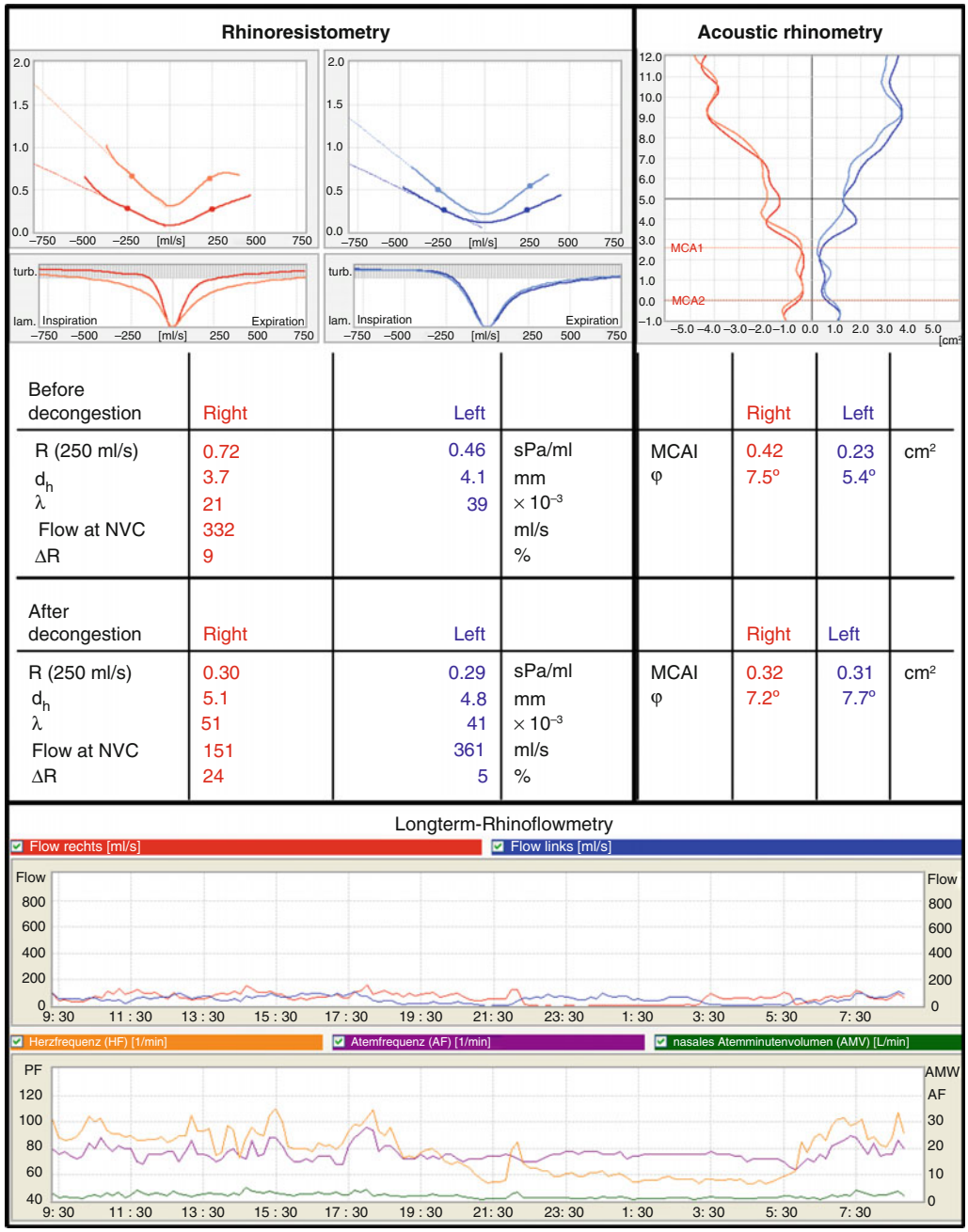
  LRM: The long-term rhinoflowmetry shows a unilateral cycle type. The right side is unable to take over any working phases as a result of the stenosis. Over the entire observation period, the low NMV suggests mouth-bypass breathing. The NMV also does not increase with physical activity.
- *Rhinosurgical planning*:
  Septoplasty
- *Justification*:
  The problem in this nose can be resolved through septoplasty, since the stenoses causing resistance in both sides are not localized at the same depth in the nose. Correcting the subluxation on the left will not narrow the right nostril and thus will not worsen resistance on the right. Correcting the deviation at the MCA1 level on the right should not cause worsening of resistance on the left, since the left side is very wide at this location. Expanding the isthmus region on the right will resolve both the suction phenomenon (narrowing of local flow velocity) and the turbulence problem (expansion of the diffuser entry and reduction of the diffuser orifice angle).



Before decongestion	Right	Left			Right	Left	
R (250 ml/s)	2,80	0.28	sPa/ml	MCA1	0.39	1.05	cm^2
d_h	2.9	4.8	mm	φ	8.2°	5.2°	
λ	19	28	$\times 10^{-3}$				
Flow at NVC	116		ml/s				
ΔR	24		%				

After decongestion	Right	Left			Right	Left	
R (250 ml/s)	1.21	0.08	sPa/ml	MCA1	0.56	0.64	cm^2
d_h	3.9	4.9	mm	φ	11.8°	4.1°	
λ	41	21	$\times 10^{-3}$				
Flow at NVC	174		ml/s				
ΔR	39		%				

Fig. 27.18 RRM, ARM, and LRM findings in a patient with septal deviation, case 3



Before decongestion	Right	Left			Right	Left	
R (250 ml/s)	0.72	0.46	sPa/ml	MCAI	0.42	0.23	cm^2
d_h	3.7	4.1	mm	φ	7.5°	5.4°	
λ	21	39	$\times 10^{-3}$				
Flow at NVC	332		ml/s				
ΔR	9		%				
After decongestion	**Right**	**Left**			**Right**	**Left**	
R (250 ml/s)	0.30	0.29	sPa/ml	MCAI	0.32	0.31	cm^2
d_h	5.1	4.8	mm	φ	7.2°	7.7°	
λ	51	41	$\times 10^{-3}$				
Flow at NVC	151	361	ml/s				
ΔR	24	5	%				

Fig. 27.19 RRM, ARM, and LRM findings in a patient with tension nose

27.3.2.5 Example 5: Tension Nose

- *History*: No trauma recalled.
- *Complaints*: Impaired nasal breathing bilaterally since childhood.
- *Endonasal findings*: Typical tension nose with slit-like nasal entrance and a positive U phenomenon. Slight vertical deviation of the septum toward the right in region 2.
- *Measurement findings* of this case are shown in Fig. 27.19.
- *Analysis of the findings*:
  Extent of obstruction
  RRM resistance: Before decongestion, severe obstruction on the right and moderate on the left.

After decongestion, slight obstruction bilaterally.

Cause of obstruction

RRM hydraulic diameter: Corresponding to a swelling, there is a decongestant effect bilaterally: on the right, from 3.7 to 5.1 mm and, on the left, from 4.0 to 4.8 mm. The low values after decongestion suggest bilateral skeletal stenosis.

RRM turbulence: The λ-values are too high on both sides after decongestion.

RRM NVC: The NVC on the right is physiological both before and after decongestion.

ARM: The skeletal constriction can be localized bilaterally to the entire nasal entrance.

LRM: The long-term rhinoflowmetry shows a classical type of cycle but with very low nasal airflow. The NMV <5 l/min corresponds to continuous mouth-bypass breathing.

- *Rhinosurgical planning*:
  Septorhinoplasty
- *Justification*:
  By tension release of the cartilaginous nose, the nasal vestibulum with the isthmus region will be widened.

  At the same time, the second cause of increased resistance, major bilateral turbulence, will be reduced, since the narrow inflow area of the diffuser will be expanded on both sides.

27.3.2.6 Example 6: Empty Nose Syndrome Without Residual Function of the Nasal Turbinates

- *History*: Status post septoplasty and repeated conchotomy on both sides.
- *Complaints*: The nose is continuously stuffy and dry with extensive formation of crusts.
- *Endonasal findings*: Septum in midline, very shrunken lower turbinates, and dry mucosa with crust formation bilaterally.
- *Measurement findings* of this case are shown in Fig. 27.20.
- *Analysis of the findings*:
  Extent of obstruction:

  RRM: No obstruction before or after decongestion, especially low values on the left.

  Cause of the symptoms:

  RRM hydraulic diameter: Large both before and after decongestion, the left wider than the right, and small decongestant effect.

  RRM turbulence: The λ-value is very high, both before and after decongestion. Especially after decongestion, transition to turbulent flow occurs at very low flow rates.

  RRM NVC: No NVC on either side.

  ARM: φ is bilaterally large, with high cross-sectional enlargement of the nasal diffuser as the cause of severe bilateral turbulence.

  LRM: No resting phases during the 14-h observational period.
- *Rhinosurgical planning*:
  Surgical reduction of the width of the nasal cavum, followed by conservative treatment.
- *Justification*: The LRM shows that the turbinates are no longer capable of swelling to close the nose for a resting phase. In the ARM and the RRM as well, no mucosal swelling can be detected.

27.3.2.7 Example 7: Empty Nose Syndrome with Residual Function of the Turbinates

- *History*: Status post septoplasty and bilateral conchotomy 2 years before.
- *Complaints*: Feeling of severe congestion and crust formation.
- *Endonasal findings*: Septum in midline, atrophic inferior turbinates, and mucosa bilaterally dry.
- M*easurement findings* of this case are shown in Fig. 27.21.
- *Analysis of the findings*:
  Extent of obstruction:

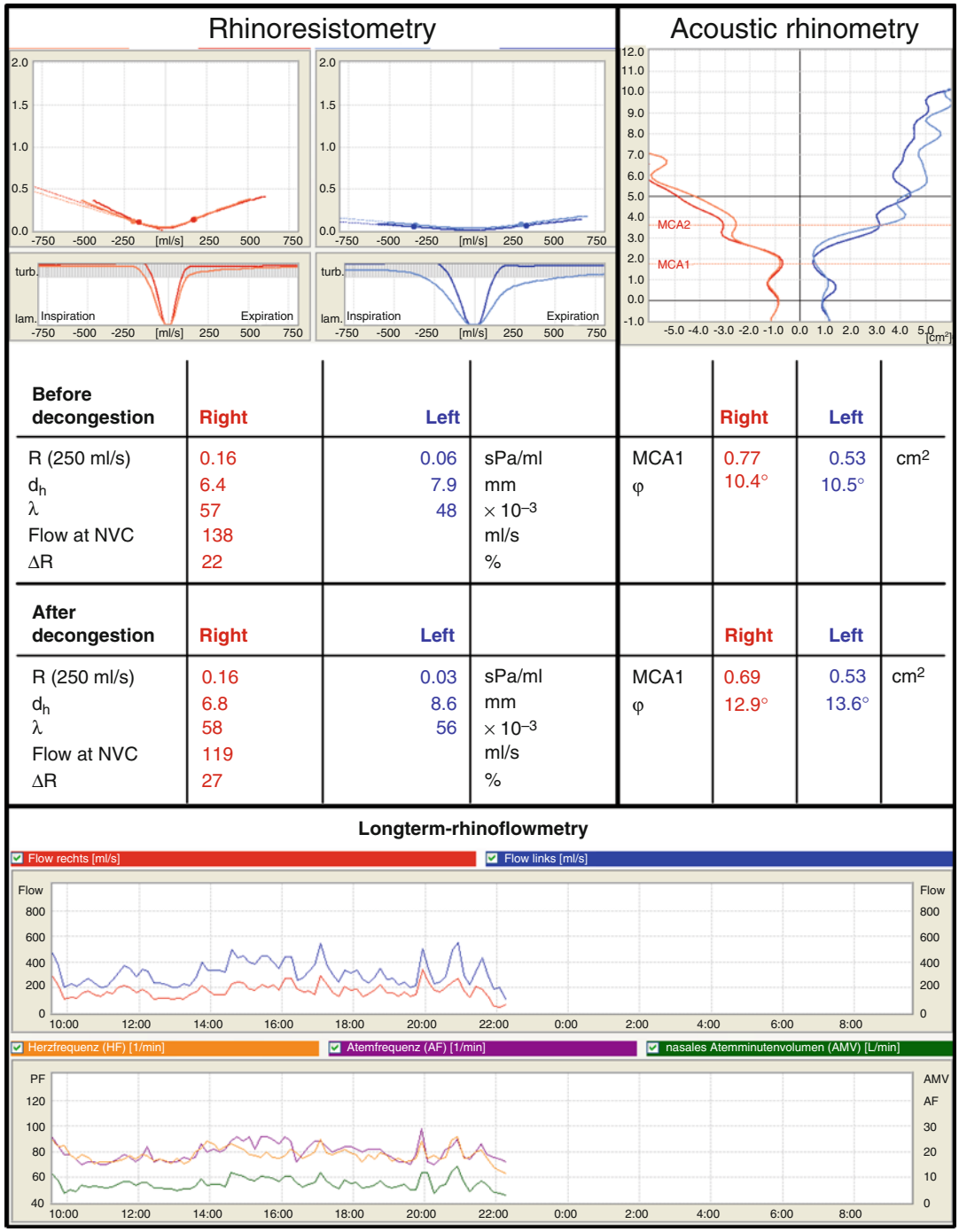
  RRM: *Before decongestion*, slight obstruction bilaterally. *After decongestion*, no obstruction.

  Cause of the symptoms:

  RRM hydraulic diameter: Significant decongestant effect: on the right, from 5.0 to 6.7 mm and, on the left, from 5.6 to 7.7 mm. *After decongestion*, corresponding to an extremely wide nose, the hydraulic diameter is too large on both sides.

  RRM turbulence: The friction coefficient λ is very large, before and after decongestion. Purely turbulent flow already occurs at very low flow rates.

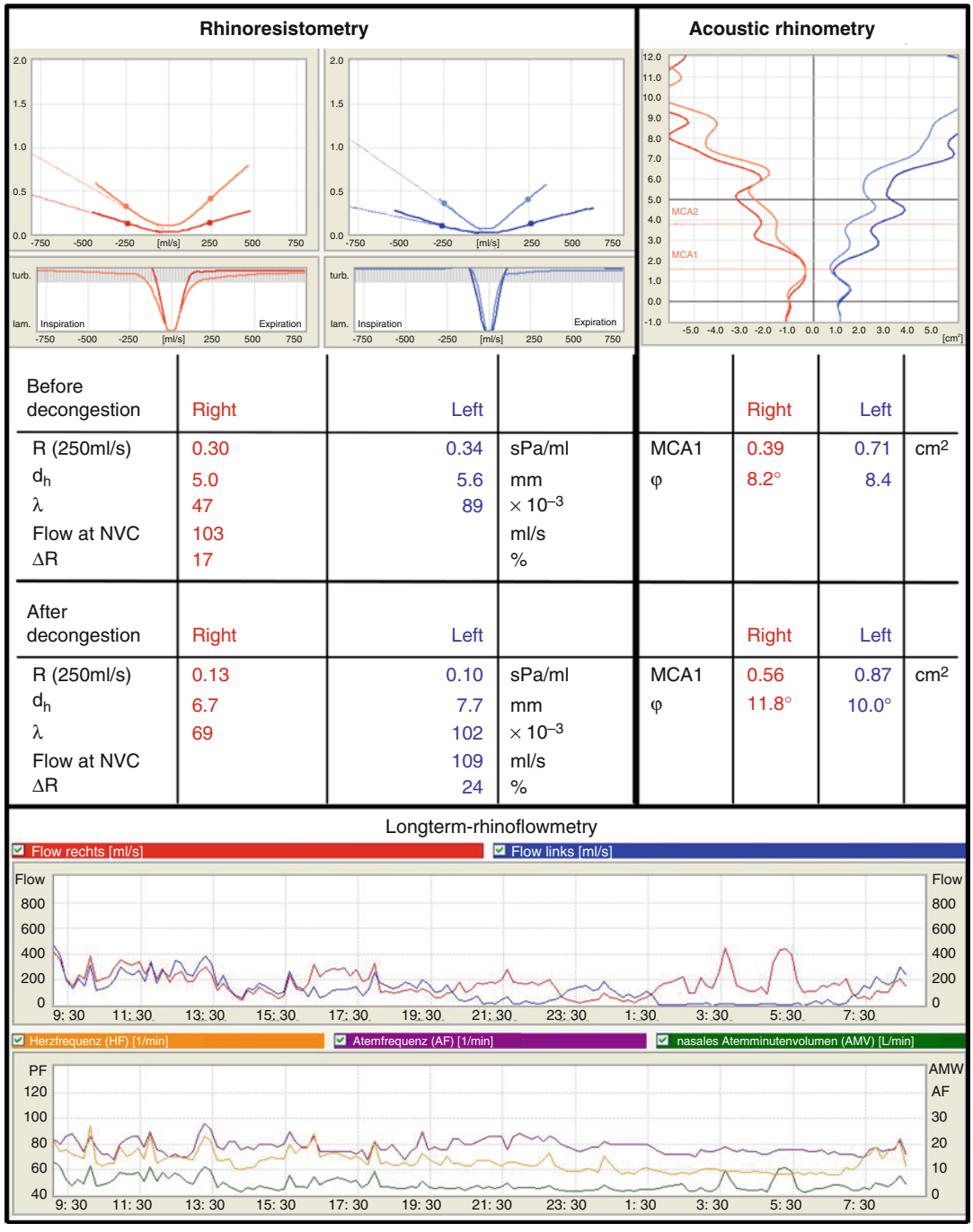
  RRM NVC: No pathological NVC on either side.



Before decongestion	Right	Left			Right	Left	
R (250 ml/s)	0.16	0.06	sPa/ml	MCA1	0.77	0.53	cm^2
d_h	6.4	7.9	mm	φ	10.4°	10.5°	
λ	57	48	$\times 10^{-3}$				
Flow at NVC	138		ml/s				
ΔR	22		%				

After decongestion	Right	Left			Right	Left	
R (250 ml/s)	0.16	0.03	sPa/ml	MCA1	0.69	0.53	cm^2
d_h	6.8	8.6	mm	φ	12.9°	13.6°	
λ	58	56	$\times 10^{-3}$				
Flow at NVC	119		ml/s				
ΔR	27		%				

Fig. 27.20 RRM, ARM, and LRM findings in a patient with empty nose syndrome without residual turbinate function



Before decongestion	Right	Left			Right	Left	
R (250ml/s)	0.30	0.34	sPa/ml	MCA1	0.39	0.71	cm^2
d_h	5.0	5.6	mm	φ	8.2°	8.4	
λ	47	89	$\times 10^{-3}$				
Flow at NVC	103		ml/s				
ΔR	17		%				

After decongestion	Right	Left			Right	Left	
R (250ml/s)	0.13	0.10	sPa/ml	MCA1	0.56	0.87	cm^2
d_h	6.7	7.7	mm	φ	11.8°	10.0°	
λ	69	102	$\times 10^{-3}$				
Flow at NVC		109	ml/s				
ΔR		24	%				

Fig. 27.21 RRM, ARM, and LRM findings in a patient with empty nose syndrome with residual turbinate function

ARM: Especially after decongestion, the φ-value is bilaterally large. Severe increase of cross-sectional area in the nasal diffuser as the cause of severe bilateral turbulence.

LRM: During the day, both sides are in the working phase until 4:00 PM, NMV is at 5 l/m, and there is no significant increase in flow during mild to moderate physical activity: suggestive of mouth-bypass breathing due to a feeling of congestion.

After 4:00 PM, classical nasal cycle with resting phases.

- *Rhinosurgical planning*:
  No surgical treatment.
- *Justification*:
  The resting phases observable on LRM indicate that there is still residual function of the turbinates. The RRM and ARM also permit quantification of mucosal congestion. Therefore, an attempt at conservative treatment is indicated using nasal irrigation. Only if symptoms persist should surgical treatment be considered (narrowing of the wide nasal cavity to a physiological slit space).

Conclusions

- The RMM does not allow a sufficient differentiation of nasal obstruction causes. It only provides the rhinosurgeon with insufficient information on a surgical approach. This leads to the fact that although RMM is worldwidely spread up to date, it has not yet been implemented in routine preoperative diagnostic. However, preoperative mismanagement may lead to an unsatisfying surgical result.
- RMM has been developed further to RRM. With this method, not only the extent of nasal obstruction can be objectified, it also allows a differentiation of the four possible causes of nasal obstruction:
  - Mucosal swelling
  - Skeletal stenosis
  - Inspiratory collapse of the nasal wing
  - Pathologically increased degree of turbulences
- With ARM the localization of the decisive narrowing of the obstruction and causes for pathological turbulences in the nose such as:
  - Strong increase of diameter in the nasal diffuser.
  - Narrow diffuser entrance May be diagnosed.
- LRM allows objectification of:
  - Changes in flow due to physiological swelling, separately in both sides of the nose, depending on physical stress
  - Pathological swelling under a patient's daily living conditions within the course of 24 h
- A combination of these methods allows a preoperative objectification of causes of a patient's complaints with nasal obstruction. With this, also the measurement-relevant precondition for a postoperative quality management as a fundament for an evidence-based therapy is given as it has become a matter of course in otology long since.

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Testing of Transport, Measurement of Ciliary Activity

28

Mark Jorissen and Martine Jaspers

Keywords
Mucociliary transport • Mucociliary clearance • Saccharin • Radioisotope transport • Nasal nitric oxide • Cell culture

Core Messages

- The mucociliary transport (MCT) can be studied by recording MCT as well as by measuring ciliary activity, but none of these tests are reliable for the diagnosis of inherited abnormalities.
- Most people with PCD have unusually low levels of nasal NO, but a low nNO measurement is notdiagnostic for PCD. Sequential monolayer-suspension cell culture with dedifferentiation and redifferentiation of the ciliated epithelium is the most reliable screening test for the diagnosis of PCD.

28.1 Introduction

Ciliary activity causes the transport of mucus in the airways, which is an essential defense mechanism of the respiratory tract. Inhaled particles, bacteria, and viruses are trapped in the mucus layer that covers the airways and are transported by the beat of the cilia to the nasopharynx, where they are either swallowed or coughed up. Inborn disorders of the mucociliary transport are due to ciliary dysfunction as in primary ciliary dyskinesia (PCD) or to increased viscosity of the respiratory secretions as in cystic fibrosis (CF). Also frequently mucociliary transport is impaired because of inflammation, infection, and exposure to ciliotoxic agents.

Mucociliary transport (MCT) can be studied by recording MCT in vivo, as well as by measuring ciliary activity in vitro. Methods based on nasal ciliary motility for the diagnosis of primary ciliary dyskinesia (PCD) are often hampered by the presence of acquired abnormalities (secondary ciliary dyskinesia (SCD)).

Mucociliary clearance can be evaluated by using the saccharine and/or the 99mTc-albumin colloid test as well as by measuring ciliary activity and is important in the diagnosis of primary ciliary dyskinesia.

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28.2 Testing of Transport

28.2.1 Testing of Transport In Vivo

The mucociliary transport rate can be measured in vivo either by using the saccharine test (Andersen et al. 1974; Andersen and Proctor 1983) or by using the radioisotope technique (De Boeck et al. 2005). If with one of these methods active mucociliary transport can be demonstrated, it is accepted that the diagnosis of PCD is excluded. An abnormal result can certainly not be considered as proof for the disease. It implicates only that further investigation is needed.

28.2.1.1 Saccharine Test

With the saccharine test, a particle of saccharine (most frequently dipped in a blue color, such as indigo blue powder) is placed on the inferior turbinate and the time elapsed before the patient taste the saccharine is measured. Patients are instructed to swallow at least once per minute. The appearance in the pharynx can be verified by the blue color in the pharynx. With this technique the mean normal mucociliary transport time (MTT) is about 10 min. MTT up to 30 min is still considered normal. If this takes more than 30 min, the test is considered abnormal. For this test cooperation of the individual is needed, since he/she has to report the sweet taste. Also sniffing, sneezing, and blowing the nose is prohibited since these may affect to position of the particles. This limits the use of the test in children. The saccharine has to be placed on the respiratory (ciliated) epithelium. Otherwise no transport will be found.

Most frequently a color (methylene blue, indigo blue, charcoal, etc.) is added to the test, as a visual control. Repeated examination will allow to verify the transport of the particle and to compare the appearance of the color in the pharynx with the perception of the sweet taste.

When combined with nasal endoscopy, the colored particles can be followed to evaluate the transport pattern. That technique can also be used to follow and study the pathways within the (maxillary) sinuses.

28.2.1.2 Nuclear Testing

> Up to now measuring the transport of radiolabeled albumin remains the most reliable method for measuring mucociliary transport.

When a minute amount of radiolabeled ^{99m}Tc-albumin colloid particles (De Boeck et al. 2005) is placed on the inferior turbinate or on the nasal septum, the migration can be followed with a gamma camera. Normally within 30 min the majority of the radioactivity must have disappeared from the nasal cavity. The percentage of radioactivity remaining in the nasal cavity can be calculated and in sagittal views the migration of the spot can be measured. It has been shown that the dosis radioactivity is that low that immotility does not create problems. In contrast to the saccharine test, this test is not influenced by sniffing. A normal test result is considered an exclusion criterion of PCD. If the particles moved insufficiently, further investigation is needed, because dysmotility could be due to upper airway infections or PCD. Moreover, in up to 25 % of individuals with SCD and also in controls, no migration of the tracer is found.

Marthin et al. (2007) studied an alternative method, the pulmonary radioaerosol mucociliary clearance technique, which has a higher specificity for PCD as secondary dysmotility is much less prevalent in the lower airways. The radioactive-labeled ^{99m}Tc-albumin transportation test is more reliable than the saccharine test but requires expensive equipment and can only be done in specialized centers.

28.2.2 Testing of Transport In Vitro

Bioptic or brushed material can be checked for the presence of cilia under phase contrast microscopy. Real movements such as displacements and rotations of cell clusters or cell sheets within the fluid and movement of particles within the fluid lining the cilia are criteria for the presence of coordinated ciliary activity. Absence of these elements in the

presence of ciliary activity is recorded as "uncoordinated ciliary activity." It should always be checked whether cilia are present.

28.3 Testing of Ciliary Activity

28.3.1 In Vivo

Laser light-scattering spectroscopy provides an improved, precise, and simple method to study ciliary activity. The light from a laser beam is directed at a ciliated surface, and due to the Doppler effect, the scattered light returning from the moving cilia has an altered frequency and phase induced by the movement of the reflecting surfaces of the cilia. The scattered light can be detected with a photomultiplier tube, and the spectral structure of its intensity fluctuations can be analyzed to provide quantitative information regarding the frequency and synchrony of the ciliary beat (Svartengren et al. 1989).

Other techniques are under development for measuring ciliary activity in vivo.

28.3.2 In Vitro

CBF is 8 Hz at room temperature and 12 Hz at 37 °C.

In vitro brushings from the nasal cavity or biopsy samples taken from the inferior border of the middle turbinate or from the inferior turbinate can be evaluated for coordinated ciliary beating and ciliary beat frequency (CBF). Using microscope photometry (Jorissen et al. 1992), CBF can be deduced from fast Fourier transform analysis of the light scattering. Normal CBF values depend on the temperature with normal values around 8 Hz at room temperature and 12 Hz at 37 °C.

The introduction of high-speed cameras (up to 500 Hz) created new possibilities (Sanderson and Dirksen 1985; Chilvers and O'Callaghan 2000): ciliary beat pattern analysis but also amplitude, degree, and speed of ciliary beat cycle. Also field analysis with measurement of ciliary coordination on a whole area of ciliated cells has become available (Dimova et al. 2005).

For clinical use only CBF is used, and one should realize that there is no good correlation between CBF and mucociliary transport velocity (Jorissen 1998).

28.4 Additional Testing

28.4.1 Nasal Nitric Oxide

Nasal nitric oxide (nNO) measurement is a good screening tool for PCD.

Nasal nitric oxide (nNO) was found to be 10-fold lower in PCD patients than in control patients, and it can be used as an easy screening test for the diagnosis of PCD. It is a noninvasive technique, but as it requires cooperation of the patient (breath-holding for stable plateau measurements), it is almost impossible to use it below 5 years of age. nNO measurement cannot be used neither for exclusion of PCD nor for proof of PCD since normal values can be observed in PCD and low values can be caused by other factors, e.g., obstruction (Lundberg et al. 1994; Bush et al. 1998; Karadag et al. 1999; Lefevere et al. 2000; Barbato et al. 2009).

28.4.2 Genetic Analysis

Making a diagnosis of primary ciliary dyskinesia (PCD) remains challenging. Molecular diagnosis involves time-consuming tissue culturing, cilia beating measurements, and/ or electron microscopy of microtubule structures.

Also at the genetic level, a diagnosis of PCD has been challenging. PCD is an autosomal recessive disease. Mutations in different genes can result in PCD, and from a genetic point the disease is very heterogeneous. So far, 12 genes (DNAH5, DNAI1, DNAI2, DNAH11, TXNDC3, C14orf104 (KTU), RSPH4A, RSPH9, LRRC50,

CCDC39, CCDC40, and DNAL1) have been found to cause PCD. However, they only explain disease in a fraction of the PCD patients (Zariwala et al. 2011). The ciliary axoneme is composed of over 250 proteins (Ostrowski et al. 2002), and a mutation in each of their genes possibly can result in PCD. Moreover, many of these genes turn out to be large, thereby hampering their genetic analysis. When sequencing mutation hot spot regions of the genes known to be involved in PCD by using the Sanger sequencing method, only in part of the cases, mutations were found. In the remainder of patients, the mutation could still be located outside the mutation hot spot regions of these genes or even other genes.

Since large genes are involved in PCD and since several genes are involved in PCD, sequencing patients for PCD mutations by using the Sanger sequencing method is too time-consuming and too expensive. Therefore, next-generation whole-exome sequencing is a powerful tool to identify genetic mutations in PCD and has considerable potential in clinical diagnosis (Berg et al. 2011).

In the future, better screening tests will probably become available or diagnosis via genetic screening might become possible. Next-generation sequencing is the rising star of diagnostics. Worldwide, further studies are being performed to identify candidate genes and to detect disease-causing mutations in these genes. Earlier diagnosis could help to prevent evolution into irreversible lung damage with bronchiectasis.

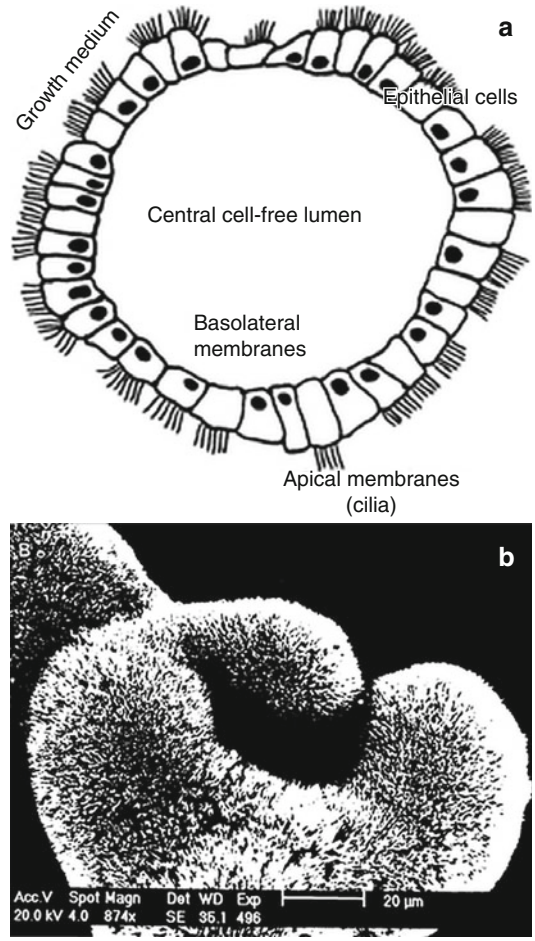

Fig. 28.1 (**a**) Schematic representation of a spheroid in suspension culture. (**b**) SEM picture of spheroid after 6 weeks in suspension

28.4.3 Cell Culture

> Evaluation of cilia after ciliogenesis in culture remains the most reliable diagnostic technique for PCD.

Epithelial cells from biopsies can be cultured in vitro. During the growth phase, epithelial cells will dedifferentiate and cilia will get lost completely. A sequential monolayer-suspension culture system can then be used to let epithelial cells redifferentiate (Jorissen et al. 1989) into ciliated cells (see Fig. 28.1).

These newly formed cilia do not express the acquired abnormalities, but the inherited abnormalities (PCD) are expressed in the culture system (Jorissen et al. 2000a). As the functional abnormalities are also clearly present, this culture can be used for the diagnosis of PCD (Jorissen et al. 2000b). PCD with normal ultrastructure would easily be missed with classical transmission electron microscopy on bioptic material (Jorissen 2000c). Ciliogenesis in vitro has also been achieved by placing the cells in an air-liquid interface culture system (Hirst et al. 2010).

Conclusion

The mucociliary transport rate can be measured in vivo using either the saccharine and/or color test or radioisotope transport testing as well as by measuring ciliary activity in vitro. Inborn disorders of the mucociliary transport as in primary ciliary dyskinesia (PCD) result in absence of mucociliary transport. Nasal nitric oxide (nNO) was found to be 10-fold lower in PCD patients. None of these tests is absolute reliable for the diagnosis of inherited abnormalities. Sequential monolayer-suspension cell culture with dedifferentiation and redifferentiation of the ciliated epithelium improves the reliability of PCD diagnosis.

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Nasal Defensive Proteins: Distribution and a Biological Function

29

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Keywords
Defensive protein • Mucin • Innate immunity • Epithelial cells • Glandular cells • Chemokines • Toll-like receptor (TLR)

Core Messages

- There are various defensive mechanisms in upper respiratory tract mucosal linings such as mechanical and functional barriers.
- The mechanical barrier of sinonasal mucosa consists of mucus, motile cilia, and respiratory epithelial cells linked by adhesion complexes that include tight junctions.
- The functional barrier in sinonasal mucosa is dynamic and more complex, being equipped with innate and acquired immune response among resident cells on the epithelia and immunocompetent cells in sinonasal submucosa.
- Various types of nasal defensive proteins in human nasal mucosa are responsible for exerting those defensive mechanisms. Those proteins are essential for a defense system against various invading pathogens such as bacteria and viruses and modulate allergic or infective chronic inflammations as well.
- Those proteins derived from epithelial cells or recruited inflammatory cells are also one of the important key players in the pathogenesis of rhinosinusitis and allergic rhinitis at the epithelial linings of nasal cavity and paranasal sinuses.
- Those defensive proteins could be classified from constitutional and functional aspects such as surfactants, mucins, antimicrobial peptides, and inflammatory cell-derived enzymes.
- Chemokines, cytokines, and various antibodies can be dealt with as defensive proteins, to provoke cellular interactions against microbial infections or pathogenesis of sinonasal persistent inflammations.

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29.1 General Concept of Nasal Defensive Proteins and Its Mechanism of Actions

29.1.1 Surfactants

Surfactant proteins are considered to play an important role in surfactant metabolism and host defense mechanisms in mucosal linings of respiratory tract. Surfactant proteins (SPs) are sialoglycoproteins and members of the collectin family. They are now distinguished as SP-A, SP-B, SP-C, and SP-D (Mason et al. 1998). They are hydrophilic proteins responsible for innate immunity (Mason et al. 1998; Wright 2003), as SP-A and SP-D bind various pathogens such as bacteria, viruses, and fungi at the initial phase of defense line of mucosal linings. On the other hand, SP-B and SP-C are hydrophobic proteins, contributing to surfactant function and packing and organizing of phospholipids (Weaver and Conkright 2001). SPs are now elucidated to be expressed in many mucosal sites such as gastric and intestinal mucosa (Bourbon and Chailley-Heu 2001), joints, peritoneum, nasal mucosa (Kim et al. 2007), maxillary sinus mucosa (Dutton et al. 1999), and middle ear mucosa as well (Dutton et al. 1999), employing various experimental methods with immunohistochemistry, western blotting, and reverse transcription-polymerase chain reaction (RT-PCR).

29.1.2 Mucins

29.1.2.1 Classification

Mucins are high molecular weight glycoproteins, constituting the major component of mucus secretions in various mucosal surfaces such as sinonasal cavity, middle ear, and Eustachian tube as well. There are secretory and membrane-associated forms of mucin, and they protect the epithelial surface and trap pathogenic bacteria and viruses for mucociliary clearance. Secretory mucins contribute to the viscid mucus of the respiratory, gastrointestinal, and reproductive tracts and typically form extremely large oligomers through linkage of their protein monomers by disulphide bonds. These proteins are secreted from the cell to form the mucous gel, which becomes an integral part of the mucociliary escalator. In contrast, the membrane-associated mucins have a hydrophobic membrane-spanning domain and have not been observed to form oligomer complexes. The histochemical profile of cellular glycoprotein in normal condition is quite different in regard with airway level, stage of maturation, and species. The majority of surface secretory cells contain a glycoprotein consisting of a protein backbone with sugar side chains, having terminal sialic acid, galactose residues, and a variable content of sulfate esters.

29.1.2.2 Mucin Genes

With the development of molecular biological techniques, the complementary deoxyribonucleic acid (cDNA) sequences of mucin genes can now be obtained and the amino acid sequences of the mucin peptide core deduced. Until now, 21 mucin genes (*MUC1–MUC21*) have been reported, but later on some of them were found as the same gene as already reported (Kerschner et al. 2009; Li et al. 2006). Among them, there are at least eight human mucin genes (*MUC1* to *MUC4*, *MUC5AC*, *MUC5B*, *MUC6*, and *MUC7*) and one mouse mucin gene (*MUC1*) confirmed to be present in respiratory tract mucosae.

29.1.2.3 Mucin Gene Expression and Upregulation in Animal Model

The specific mechanisms by which pathogens or mucosal irritants induce the mucin gene upregulation are unknown yet. It could be easily considered that they probably act either by increasing the transcription rate or decreasing the rate of degradation of mucin messenger ribonucleic acid (mRNA). Jany observed human *MUC2* gene expression in SO_2-exposed rats (Jany et al. 1991). They used rats exposed to 400 ppm SO_2 for 3 h·day-1, 5 days a week, for 1–3 weeks, and found increased numbers of goblet cells and visible mucinous secretions in the airway lumen. In addition, they employed the northern blot analysis using the total ribonucleic acid (RNA) extracted from the rat lung and hybridized it with

human *MUC2* cDNA (SMUC41) and demonstrated an upregulation of the *MUC2* gene in the SO_2-exposed rats.

29.1.2.4 Localization of Mucin Genes in Human Airways

A number of experimental approaches have been performed with regard to localization of mucin genes in human airways by in situ hybridization. As regard lung or bronchial mucosal linings, the localization of *MUC2* gene expression was reported by Audie et al. (Audie et al. 1993). In their study, bronchial mucosae were obtained from four patients, whose lungs had been surgically resected for cancer. A radiolabelled antisense oligonucleotide probe corresponding to the tandem repeat domain of *MUC2* was applied on the tissue specimens, and consequently it was localized to occasional goblet cells of the surface epithelium and to submucosal gland ducts, but not to their secretory acini. However, on the other hand, oligonucleotide probes to *MUC4*, *MUC5B*, and *MUC5AC* strongly labelled the gland acinar cells. These data indicate that several distinct mucin genes are expressed in the mucosa either by the same or distinct cells of the epithelium and glands. Li et al. (1997) demonstrated in nasal mucosa that *MUC2* mRNA transcripts are present in ciliated and basal cells of the surface epithelia, serous and mucous acini of submucosal glands, and occasionally mononuclear inflammatory cells. Voynow. et al. precisely compared expression levels of three mucin genes, *MUC*1, *MUC*2, and *MUC*5/5AC, in the respiratory tract of patients with cystic fibrosis, patients with allergic rhinitis, and normal individuals (Voynow et al. 1998). Mucin transcript levels in nasal epithelial cells free from inflammation were quantitated by an *MUC* mRNA slot-blot method. Their elegant study revealed that *MUC*5/5AC mRNA was expressed at five- to tenfold greater levels than *MUC*2 or *MUC*1 for all subjects and *MUC*2 mRNA levels were similar among all subject groups. To be generally considered, in situ hybridization demonstrated that MUC5AC-positive mucous cells are populated in upper respiratory epithelium whereas MUC5B-positive mucous cells are populated in mucous glands of upper respiratory epithelia. In contrast, middle ear epithelial cells are negative for MUC5AC mRNA transcripts, but spotty MUC5B mRNA transcripts are identified (Lin et al. 2001, 2003). This data remind us the transitional process of mucin member from the lower airway to the middle ear cavity. Preciado et al. found that MUC5B mucin is predominant in patients with chronic otitis media (Preciado et al. 2010a, b) and confirmed that transitional process. However, other mucins such as MUC2 may be involved in middle ear mucus of animal models (Lin et al. 1999), but their amount is limited or undetectable in human (Lin et al. 2001, 2003). Conclusively, the quantitative study of mucins and its comparison looks notoriously difficult and should be evaluated at the semiquantitative level, because of higher level of glycosylation representing a post-translational modification.

29.1.3 Antimicrobial Peptides

The body fluids and organized tissues naturally contain a variety of antimicrobial substances that kill or inhibit the growth of microorganism. The sources and activities of a variety of host antimicrobial substances are summarized in Table 29.1. Among them, a low molecular weight antimicrobial peptide, defensin, is introduced herein in relation to the various receptors contributing to innate immunity.

29.1.3.1 Defensin

Defensins are a family of evolutionarily related vertebrate antimicrobial peptides with a characteristic beta-sheet-rich fold and a framework of six disulphide-linked cysteines. Two main defensing subfamilies, α- and β-defensins, differ in the length of peptide segments between the six cysteines and the pairing of the cysteines that are connected by disulphide bonds. Defensins are abundant in cells and tissues that are involved in host defense mechanism of mucosal linings such as respiratory and intestinal mucosa. In many species, the highest concentrations of α-defensins are found in granules, the storage organelles of leukocytes (Ganz et al. 1985; Ganz 1987). β-defensins are mainly

Table 29.1 Antimicrobial substance of host origin present in body fluids and organized tissues

Substance	Common sources	Chemical composition	Activity
Lysozyme	Serum, saliva, tears	Protein	Bacterial cell lysis
Complement	Serum	Protein-carbohydrate lipoprotein complex	Cell death or lysis of bacteria; participates in inflammation
Basic proteins	Serum	Proteins or basic peptides	Disruption of bacterial plasma membrane
Lactoferrin and transferrin	Body secretions, serum epithelial cells	Glycoprotein	Inhibit microbial growth by binding (withholding) iron
Defensin	Epithelial cells, neutrophils	Oligopeptides	Cell death or lysis of bacteria
Peroxidase	Saliva, tissues, neutrophils	Protein	Act with peroxide to cause lethal oxidation of cells
Fibronectin	Serum, mucosal surfaces	Glycoprotein	Clearance of bacteria
Interferons	Virus-infected cells	Protein	Resistance to virus infections
Interleukins	Macrophages, lymphocytes	Protein	Cause fever; promote activation of immune system

produced by a variety of epithelial cells such as lung and middle ear (Bals et al. 1998; Moon et al. 2002), and 30 genes from DEFB1 to DEFB136 are currently identified as human β-defensin family. Human β-defensin 1 (DEFB1) is expressed constitutively, whereas β-defensin 2(DEFB4A) is induced by bacterial molecules (Moon et al. 2006; Wehkamp et al. 2004) as well as cytokines (Kao et al. 2004). Paneth cells are another site of high α-defensin concentration and contain defensin-rich secretory granules. Claeys et al. reported that there was no baseline detection of human β-defensin 2 in any sinus mucosal samples, and no upregulation was measured for human β-defensin 2 in paranasal sinus mucosa in patients with chronic sinusitis or nasal polyposis compared with control turbinate mucosa (Claeys et al. 2003). On the other hand, α- and β-defensins were detected in human nasal mucosa by Lee et al. (2002). They examined the expression of defensins in inferior turbinate mucosa of normal subjects and inferior turbinate mucosa and nasal polyps of patients with chronic sinusitis, employing reverse transcription-polymerase chain reaction (RT-PCR) and immunohistochemistry. According to their results, β-defensin 1 mRNA was expressed in all tissue samples. β-defensin 2 mRNA was detected in the turbinate mucosa and nasal polyps of patients with chronic sinusitis, but not in normal mucosa. Its expression level was significantly higher in nasal polyps than in turbinate mucosa. α-Defensin 5 and 6 mRNAs were not expressed in any tissues, but α-defensins 1, 2, and 3 were detected in all tissue samples obtained from patients with chronic sinusitis. These results suggest that β-defensin 1 may play a constitutive role in nasal defenses, whereas α-defensins 1, 2, and 3 and β-defensin 2 may be induced in response to local infection or inflammation.

The average concentration of defensins in these epithelial cells reaches the 10–100 μg/ml range (Harder et al. 1997), but the local concentrations might be higher because of uneven distribution.

Most defensins show antimicrobial activity against bacteria and fungi, especially when tested under low ionic strength conditions (Selsted et al. 1985; Lehrer et al. 1988) and with low concentrations of divalent cations, plasma proteins. It should be taken into consideration that under these optimal conditions, antimicrobial activity is observed at concentrations as low as 1–10 μg/ml (low micromole). Permeabilization of target membrane is the crucial step in defensin-mediated antimicrobial activity and cytotoxicity. It is also reported that defensins act as an immunomodulatory molecules, inducing IL-8 in epithelial cells and modulating complement activation (Van Wetering et al. 1997; Panyutich et al. 1994) and neutrophil apoptosis (Yang et al. 2002; Nagaoka et al. 2008).

29.1.3.2 Defensin Synthesis and Its Regulation

Defensin synthesis and release are regulated by various signals such as microbial signals, developmental signals, and cytokines. Human β-defensin 1 (DEFB1) is expressed constitutively with low level, whereas β-defensin 2(DEFB4A) is highly induced by bacterial molecules (Wehkamp et al. 2004; Kao et al. 2004) as well as cytokines (Claeys et al. 2003). Various signaling pathways are identified to orchestrate β-defensin 2 expression, such as toll/IL-1 receptor (TIR)-dependent NF-κB activation, TIR-dependent MAPK signaling, and NOD-2 dependent NF-κB activation. Wang et al. actually demonstrated that airway epithelia regulate expression of human β-defensin 2 through toll-like receptor 2 (Wang et al. 2003). Vora et al. also proved that human β-defensin 2 expression is regulated by toll-like receptor signaling in intestinal epithelial cells and that LPS and peptidoglycan stimulated β-defensin 2 promoter activation in a TLR4- and TLR2-dependent manner, respectively (Vora et al. 2004).

29.2 Brief Introduction of Toll-Like Receptors in Nasal Epithelial Cells and Signaling Pathway

29.2.1 Distribution of TLRs in Nasopharyngeal Mucosae and Involvement of IL-15 in Inflammation

We employed northern blot assay and RT-PCR to see the TLR distribution (Fig. 29.1) in upper respiratory mucosa and showed that human nasal epithelial cells constitutively expressed mRNA for TLR2, 3, and 6, but not for TLR4 and TLR9 (Fig. 29.2). Lipoprotein used as a pathogen-associated molecular pattern (PAMP) also induced IL-15 production of respiratory epithelial cells, which strictly depend on TLR2 (Fig. 29.3). In Fig. 29.3, in northern blot analysis, IL-15 mRNA was strongly expressed after lipoprotein stimulation. But in contrast, it was not found after lipid A stimulation as a ligand of TLR4. IL-15 concentration in the supernatants of CCL185 was also upregulated after lipoprotein stimulation in a

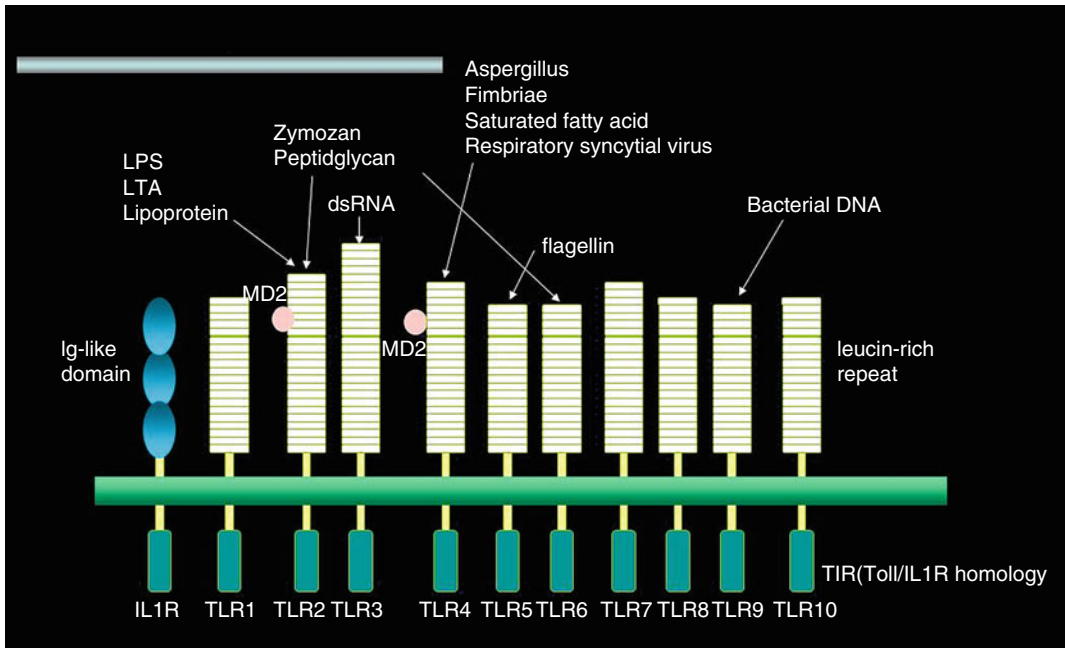

Fig. 29.1 Toll family proteins

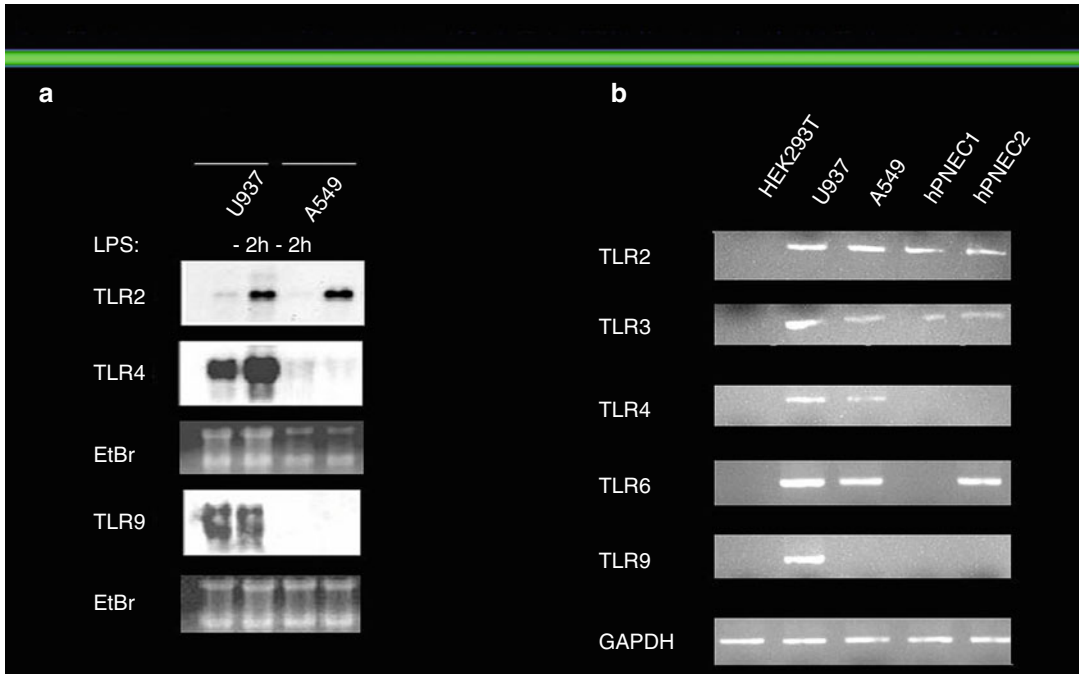

Fig. 29.2 Expression of TLRs on macrophages and nasal epithelial cells. (**a**) Northern blot assay. (**b**) RT-PCR

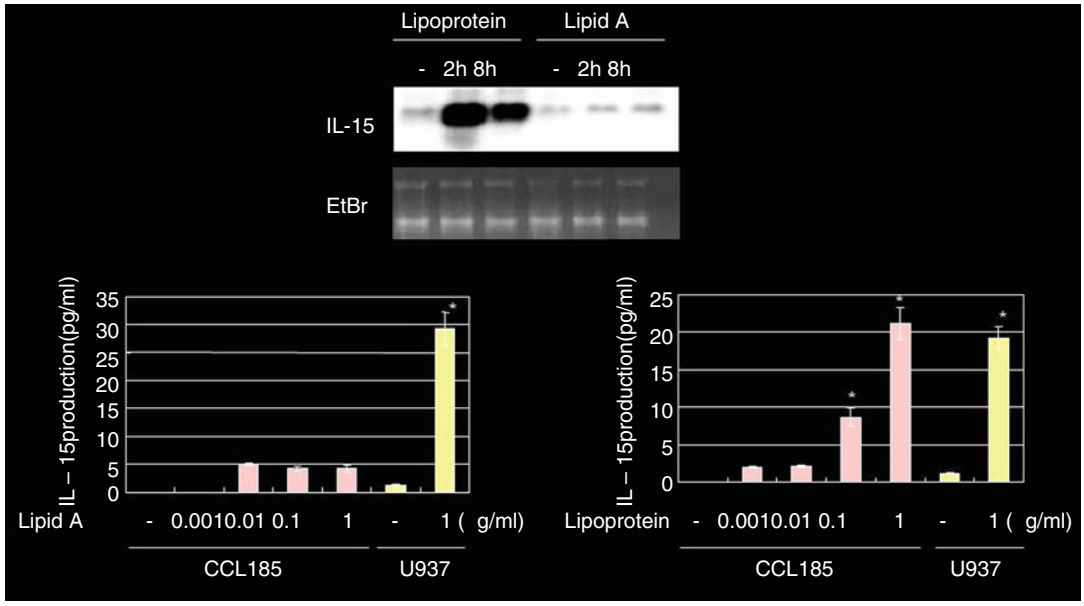

Fig. 29.3 Lipoprotein induces IL-15 from respiratory epithelial cells

dose-dependent manner. Figure 29.4 showed NF-kB activation of respiratory epithelial cells in response to lipoprotein. In western blot analysis, phosphorylation of IkB-alpha is detected in epithelial cells 15 and 30 min after lipoprotein stimulation. Luciferase assay and DNA-binding assay reveal that NFk-B activity actually correlated with the lipoprotein concentration.

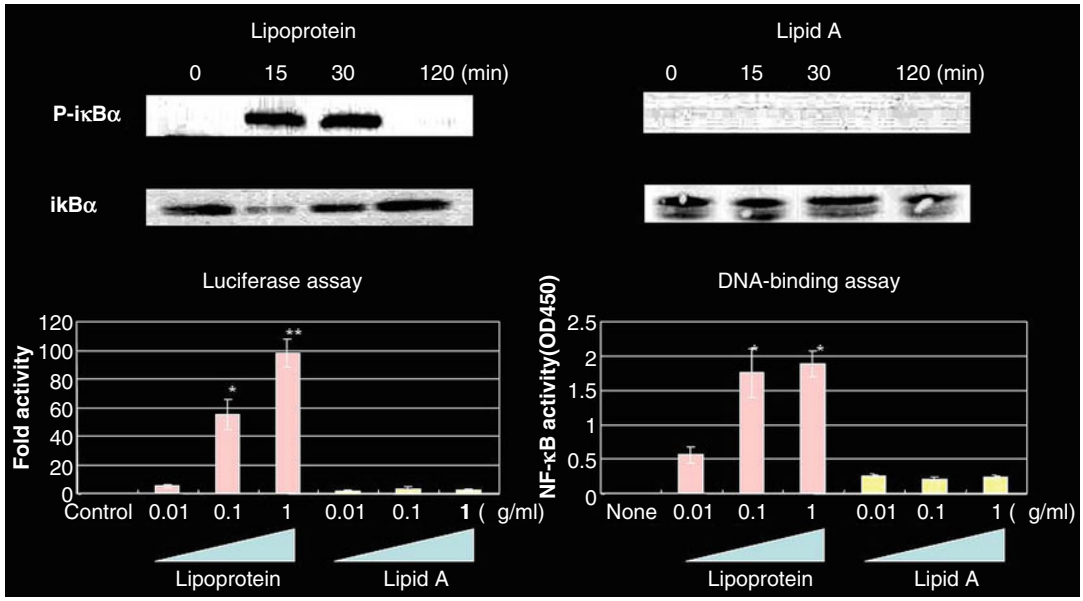

Fig. 29.4 NF-kB activation of respiratory epithelial cells in response to lipoprotein and lipid A

Conclusion

In this chapter, I have extensively introduced the significance of the so-called defensive proteins on the upper respiratory tract mucosal linings from various aspects. As you can see, there are so many complex factors involved in the defense line of our sinonasal mucosa in accordance with microbial invasion and pathogenesis of sinonasal disorders through intracellular signaling pathways. Further investigation of those mechanisms should be absolutely needed for elucidating pathologies of sinonasal disorders and seeking for promising therapeutic strategies.

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Assessment of Olfactory Function

30

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Keywords

Smell • Olfaction • Chemosensory event related potentials • Psychophysics • MRI • Olfactory bulb

Core Messages

- Precise clinical workup is mandatory in patients suffering from olfactory dysfunction, in order to (1) accurately assess their olfactory deficit and, hence, provide them appropriate counseling and prognosis, (2) assess recovery from or progression of the olfactory dysfunction, and (3) evaluate a therapeutic success.
- Self-assessment of olfactory function is not correlated to the results of olfactory testing.
- In psychophysical evaluation, it is important to evaluate both orthonasal and retronasal olfactory functions since these two pathways have different central processing.
- Psychophysical testings are semi-objective techniques and might be subject to patient's bias.
- Electrophysiological techniques are widely used to provide a relatively unbiased evaluation of olfactory system.
- MRI is the imaging modality of choice to evaluate the olfactory apparatus.

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30.1 Introduction

Evaluation of olfactory function in humans remained poorly explored for a long time. This was mostly due to the difficulty of producing selective and controlled olfactory stimuli (Moncrief 1962). Recently, the development of reliable techniques to investigate olfactory system has led to an increasing interest on the research on this field. Opposite to what has been assumed for many years, our chemosensory systems were shown to be an essential factor in terms of our behavior and well-being (for a review see Stevenson 2010).

In the last years, several authors have reported that olfactory disorders occur at a much higher frequency than previously assumed (Murphy et al. 2002; Bramerson et al. 2004; Landis et al. 2004; Landis and Hummel 2006), and it has been reported that 20 % of the population suffers from olfactory disorders (Landis and Hummel 2006). Hence, the field of research on olfaction is not only on interest for basic scientists but also for clinicians.

It is widely assumed that a precise clinical workup procedure is mandatory in order to assess the olfactory function of patients suffering from smell disorders. Indeed, it is essential to (1) accurately assess their olfactory deficit and, hence, provide them appropriate counseling and prognosis, (2) assess recovery from or progression of the olfactory dysfunction, and (3) evaluate a therapeutic success.

The direct way to monitor olfactory function is self-assessment. Nevertheless, self-assessment is biased by unspecific factors (i.e., nasal airway patency (Landis et al. 2003), mood (Savina et al. 2003)), and it seems to be uncorrelated to results from olfactory testings (Landis et al. 2003).

Several methods have been developed and validated to quantify the olfactory function.

Today, we dispose of reliable psychophysical testing, electrophysiological testing of chemosensory function, and high-performance imaging.

This chapter will focus on the techniques related to evaluation of olfactory function.

30.2 Psychophysical Evaluation

As mentioned in the chapter, "olfaction" odorants might reach the olfactory receptor neurons by two ways: orthonasally or retronasally. It has been demonstrated that these two pathways are different regarding to the perceptual (Hummel et al. 2006) and central nervous processing (Small et al. 2005). Clinically, intact orthonasal and altered retronasal olfaction (or vice versa) have been found in several conditions (Hummel et al. 2007a), although usually orthonasal and retronasal functions are well corrected. Hence, it is important to evaluate both orthonasal and retronasal olfactory function in patients complaining of olfactory disorders. Several tests have been proposed to assess psychophysically the olfactory function (for a review, see Scadding et al. 2011), based on odor identification, odor detection thresholds, odor discrimination, or a combination of two or more of these items. A non-exhaustive list of these tests is proposed in Table 30.1.

30.2.1 Orthonasal Olfactory Function

The evaluation of the orthonasal olfactory function is most often performed using psychophysical test such as Sniffin' Sticks test (Kobal et al. 1996; Hummel et al. 2007b) or the University of Pennsylvania Smell Identification Test (UPSIT) (Doty et al. 1984). The majority of odor tests are forced choice, meaning that the subject must provide a response even if no odor is perceived. The Sniffin' Sticks test (Fig. 30.1) consists of pen-like odor-dispensing devices that are presented in front of the nose of the patient. There exist two versions of the Sniffin' Sticks test: the screening test and the extended version. The screening test version is based on an odor identification test of 12 different odorants (Hummel et al. 2001). The extended version encompasses three different approaches, namely, tests for odor threshold (T), odor discrimination (D), and odor identification (I). The odor thresholds for n-butanol are assessed using a single-staircase, three-alternative forced-choice procedure. The odor discrimination is also assessed using a triple forced-choice procedure. Triplets of pens are presented to the subject, with two containing the same and one containing one different odorant.

Table 30.1 Non-exhaustive list of different tools to assess psychophysically olfactory function (for a review, see Scadding et al. (2011))

Identification tests	Thresholds tests	Identification and threshold tests	Identification, threshold, and discrimination tests
University of Pennsylvania Smell Identification Test (UPSIT) (Doty et al. 1984)	T&T olfactometer (Takagi 1987)	Connecticut Chemosensory Clinical Research Center Test (CCCRC) (Cain et al. 1983)	Sniffin' Sticks extended test (Hummel et al. 1997, 2007b)
Smell diskettes test (Briner and Simmen 1999)	Alcohol sniff test (AST) (Davidson and Murphy 1997)	Combined olfactory test (COT) (Robson et al. 1996)	Eloit and Trotier Olfactory Test (Trotier et al. 2007)
Odorant confusion matrix (Wright 1987)			Random test (Kobal et al. 2001)
Dutch odor identification test (GITU) (Hendriks 1988)			
YN-odor identification test (YN-OIT) (Corwin 1989)			
San Diego odor identification test (SDOIT) (Murphy et al. 2002)			
Cross-Cultural Smell Identification Test (CC-SIT) (Doty et al. 1995)			
Candy Smell Test (CST) (Renner et al. 2009)			
Culturally Adjusted University of Pennsylvania Smell Identification Test (CA-UPSIT) (Ahlskog et al. 1998)			
Scandinavian Odor-Identification Test (SOIT) (Nordin et al. 1998)			
Pocket Smell Test (Duff et al. 2002)			
Kremer et al. (1998)			
Sniffin' Sticks screening test (Hummel et al. 2001)			
Barcelona Smell Test (BAST-24) (Guilemany et al. 2009)			
Nez du vin Smell Test (McMahon and Scadding 1996)			
Retronasal test of olfactory function (Heilmann et al. 2002)			

Finally, odor identification is assessed for 16 common odors using a multiple-choice task identification of individual odors from a list of four descriptors. To judge olfactory function, results from the three subtests are summed up to provide a total TDI score with a maximum of 48 points (Kobal et al. 1996; Hummel et al. 2007b). The UPSIT uses 40 items. It encompasses four "scratch and sniff" booklets. Odorants are embedded in microcapsules placed on strips at the bottom of the page of booklets. The stimuli are released by scratching the strip with a pencil, and subjects have to choose one of the four proposed descriptors that best correspond to the respective odor (Doty et al. 1984; Tourbier and Doty 2007).

Fig. 30.1 Sniffin' Sticks test. The Sniffin' Sticks test consists of pen-like odor-dispensing devices that are presented in front of the nose of the patient. The extended version encompasses three different approaches, namely, tests for odor threshold (T), odor discrimination (D), and odor identification (I). To judge olfactory function, results from the 3 subtests, each quoted out of 16, are summed up to provide a total TDI score with a maximum of 48

Fig. 30.2 Retronasal testing. Psychophysical evaluation of olfactory function may be assessed retronasally by applying powderized substances in the middle of the tongue using squeezable plastic vials. Each substance is identified by means of a 4-verbal-item forced-choice procedure

30.2.2 Retronasal Olfactory Function

Retronasal olfaction is assessed following a standardized method using a row of 20 items. The substances presented to the subjects are grocery store condiments and food items available in powder (e.g., spices, instant soup). Powderized substances are applied using squeezable plastic vials (Fig. 30.2) in the middle of the tongue inside the oral cavity. Before application of the first stimulant and after each trial, subjects rinsed their oral cavity with tap water, in order to minimize the interindividual differences in salivation, which might interfere with the release of odorants. Each substance is identified by means of a 4-verbal-item forced-choice procedure (Heilmann et al. 2002).

These orthonasal and retronasal tests have the advantage of being easy to implement, having been validated in multicenter studies (Heilmann et al. 2002, 2007b), and of having high test-retest reliability (Doty et al. 1984; Heilmann et al. 2002; Haehner et al. 2009). There is a correlation between the orthonasal and retronasal score (Rombaux et al. 2009c) (Fig. 30.3). However, these tests have the disadvantage of being semi-objective and of being subjects to the patient's response bias. This may constitute a major issue when evaluating patients with olfactory disorder, particularly within a medicolegal context.

30.3 Electrophysiological Evaluation

Electrophysiological techniques are widely used to provide a relatively unbiased evaluation of sensory systems. Unlike other sensory modalities (auditory, visual, somatosensory), the use of electrophysiological recordings to assess the chemosensory system in humans was not possible for a long time. This was mostly due to the difficulty to produce selective and controlled olfactory stimulus (Moncrief 1962). Indeed, the major difficulties

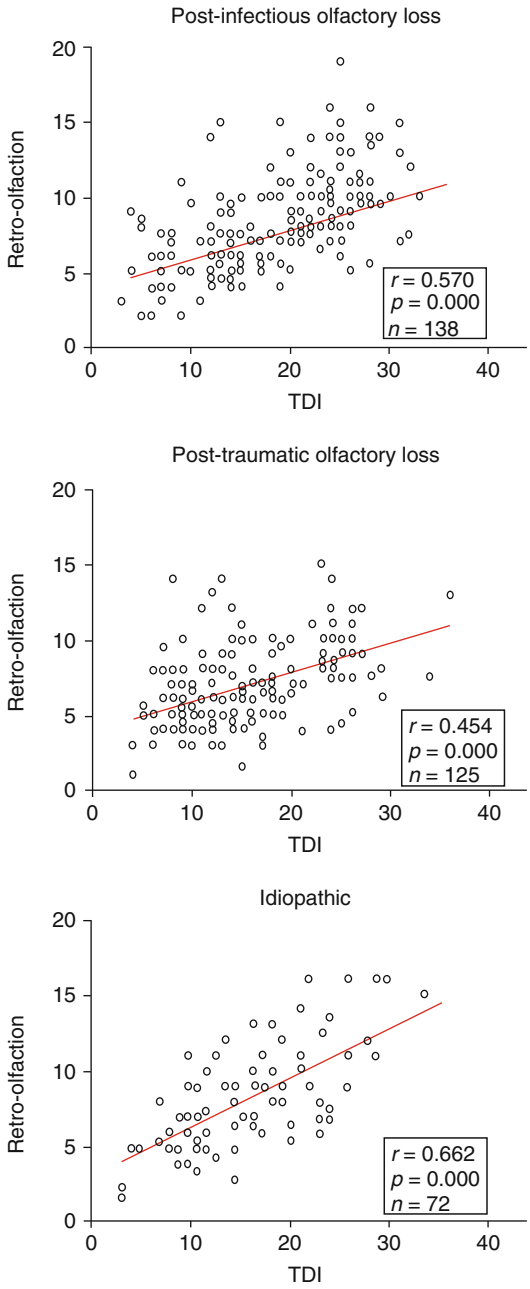

Fig. 30.3 Correlation between orthonasal and retronasal olfactory function. Figure illustrates the correlation between orthonasal and retronasal olfactory function in cohorts of patients suffering from postinfectious olfactory loss, posttraumatic olfactory loss, and idiopathic olfactory loss (unpublished data)

consist in delivering odorants on the mucosa without producing artifacts such as thermal, tactile, or nociceptive co-activation.

The development of stimulation devices allowing delivering selective stimuli opened new perspectives for exploring noninvasively how the human brain processes chemosensory information. This was interesting not only for basic scientists but also for clinicians, since we know that certain clinical situation, such as examining demented patients or children, or even medicolegal situation requires unbiased tests (Hummel et al. 2000, 2010a; Rombaux et al. 2009a, c).

30.3.1 Olfactometer

Early stimulation techniques relied on the delivery of brief, odorized air pulses. Inevitably, the sudden increase in airflow associated with the presentation of an air puff activates mechanosensitive trigeminal afferents and will produce brain responses, irrespective whether subjects would perceive the chemical stimulus or not.

In 1978, Kobal and Plattig (1978) introduced a device capable of delivering transient chemosensory stimuli to the olfactory neuroepithelium of the nasal mucosa. This air-dilution olfactometer delivers pulses of odorants embedded within a constant airflow at a constant temperature and humidity, thus avoiding concomitant mechanical or thermal stimulation of the nasal mucosa, making it possible to study brain responses related specifically to the activation of chemosensitive afferents (Fig. 30.4). Furthermore, using specific odorants, the device can be used to activate olfactory and trigeminal chemosensory receptors relatively selectively. For example, 2-phenylethanol is regarded as a relatively specific olfactory stimulant. It can be used to elicit olfactory event-related potentials (ERP). In contrast, gaseous CO_2 is regarded to be virtually odorless, but produces irritating sensations. It is used to elicit trigeminal chemosensory ERP (Kobal 1981; Hummel and Kobal 1999; Lotsch and Hummel 2006; Rombaux et al. 2006a, b, c, 2007). Several studies have shown that this technique can be used to explore the cortical processing of olfactory and trigeminal chemosensory input in humans, through the recording of olfactory and trigeminal ERP (Pause and Krauel 2000; Rombaux et al. 2006a, b, c; Laudien et al. 2008).

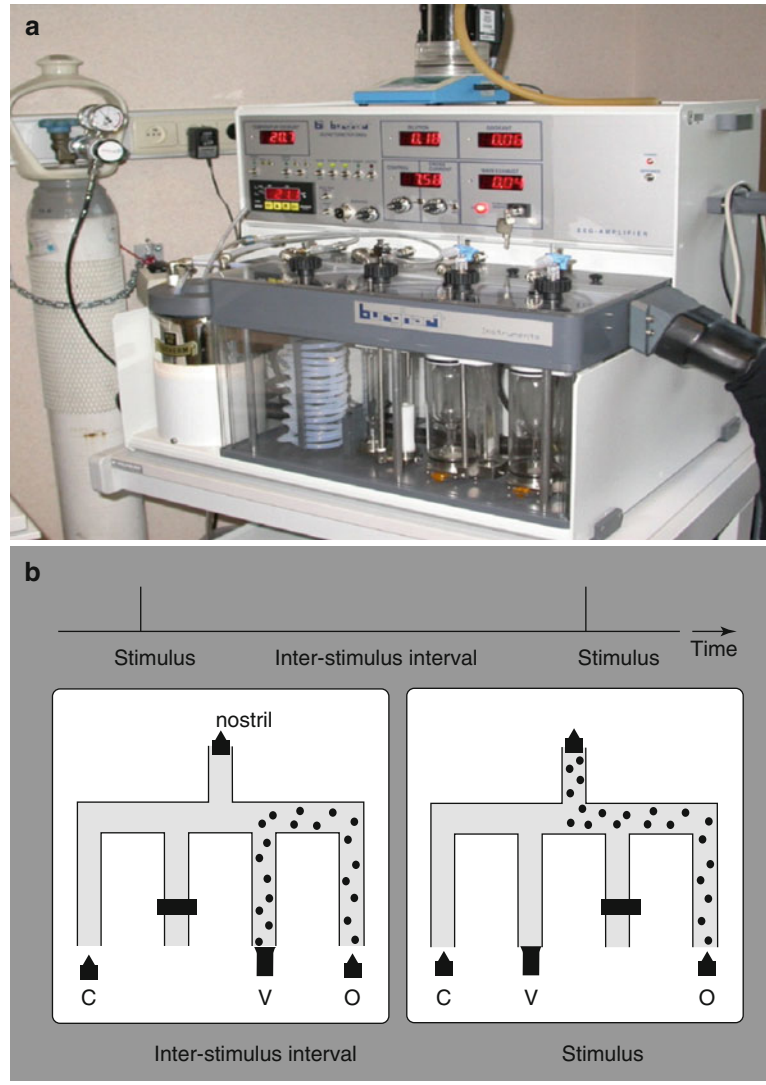

Fig. 30.4 Olfactometer. (**a**) Electrophysiological assessment of olfactory and trigeminal chemosensory function requires the use of an olfactometer that produces transient chemosensory stimuli to the olfactory neuroepithelium of the nasal mucosa. (**b**) The air-dilution olfactometer delivers pulses of odorants embedded within a constant airflow at a constant temperature and humidity, avoiding concomitant mechanical or thermal stimulation of the nasal mucosa (Olfactometer OM2S, Burghart Medical Technology, Wedel, Germany)

In addition, it has been shown that olfactory and trigeminal ERP exhibit a good test-retest reliability and were thus valuable for the clinical evaluation of patients (Hummel et al. 2000; Thesen and Murphy 2002; Welge-Lussen et al. 2003; Rombaux et al. 2009a, c).

30.3.2 EEG Data Analyses

30.3.2.1 Time-Domain Averaging

Until now, the electroencephalographic (EEG) responses to chemosensory stimulation have been identified mainly using across-trial averaging in the time domain. This procedure cancels out changes in the EEG signal that are not strictly time locked and phase locked to the stimulus onset and, thereby, enhances the signal-to-noise ratio of time-locked ERP (Hummel et al. 1998; Pause and Krauel 2000; Rombaux et al. 2006a, b, c; Boesveldt et al. 2007; Mouraux and Iannetti 2008). Using such an approach the EEG responses to chemosensory stimulation have been characterized as a negative wave peaking approximately 320–500 ms after stimulus onset (N1), followed by a late positive wave peaking approximately 450–800 ms after stimulus onset (termed as P2 and/or P3) (Kobal 1985; Hummel and Kobal 1992; Pause et al. 1996;

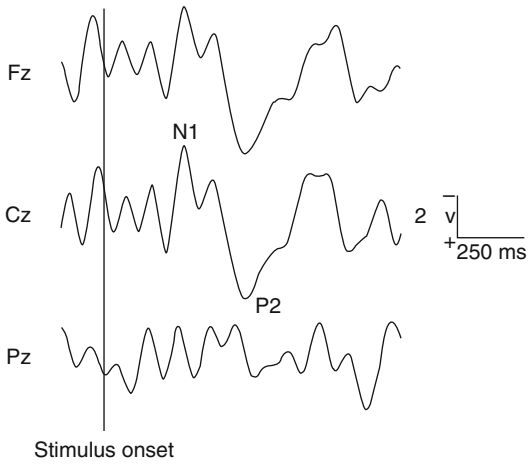

Fig. 30.5 Olfactory chemosensory ERPs (Fz, Cz, Pz vs. A1A2) in one healthy normosmic volunteer. 2-Phenylethanol (50 %v/v) was used to selectively activate olfactory afferents. 30 stimuli of each chemical were presented, lasting 200 ms (20-ms rise time), separated by a 60-s interstimulus interval. Olfactory stimulation elicited an olfactory event-related potential (OERP). Two distinct peaks can be identified, maximal at the scalp vertex: N1 and P2

Geisler and Murphy 2000; Rombaux et al. 2006a, b, c; Hummel et al. 2010a; Haehner et al. 2011) (Fig. 30.5). All of these responses exhibit largest amplitudes over the midline recording sites. While the centro-parietal maximum for the N1 amplitude is commonly observed for olfactory responses, a more central maximum is observed for trigeminal stimuli (Kobal 1985; Geisler and Murphy 2000; Livermore and Hummel 2004; Olofsson et al. 2006; Hummel et al. 2010a).

Unfortunately, chemosensory ERPs – in particular, olfactory ERPs – usually exhibit a low signal-to-noise ratio (Lotsch and Hummel 2006; Boesveldt et al. 2007; Rombaux et al. 2007). Hence, although the recording of chemosensory ERPs is considered as a technique having great potentials, its clinical usefulness remains limited, particularly in the context of clinical diagnosis.

Conventional time-domain averaging presents some drawbacks, which could contribute to the low signal-to-noise ratio of chemosensory ERPs. First, temporal jitter could affect the brain responses to chemosensory stimulation. This jitter would result from the variability in timing of the different steps separating the occurrence of the sensory event and the occurrence of a cortical response. If this jitter is significant, the elicited ERPs will be cancelled out by the time-domain averaging procedure, as the responses are no longer stationary across trials. Because of all steps implied in chemosensory transduction, it is reasonable to expect that the responses to chemosensory stimulation are subject to a significant amount of jitter and that this jitter leads to an important distortion of the averaged ERP waveform. Second, time-domain averaging is unable to reveal any transient event-related modulation of the power of ongoing EEG oscillations (i.e., event-related desynchronization and event-related synchronization), which are thought to reflect cortical activation or deactivation, as these oscillations are cancelled out by conventional time-domain averaging procedures.

Taken together, time-domain averaging is thus blind to a significant fraction of the elicited EEG response (ERPs subject to a significant amount of temporal jitter, ERD, and ERS). This could contribute to explain why CSERPs are sometimes difficult to identify even in healthy subjects.

30.3.2.2 Time-Frequency Analysis

Time-frequency analysis constitutes an alternative approach to reveal activity that is induced by a chemosensory stimulus, but not sufficiently stationary across trials to be revealed by classic averaging in time domain. In this way, it could increase the signal-to-noise ratio of chemosensory EEG responses. Different methods exist to perform a time-frequency decomposition of EEG epochs. These methods rely on techniques to estimate within each EEG epoch the amplitude of the signal as a function of time and frequency, regardless of the phase. The obtained time-varying expressions of oscillation amplitude are then averaged across trials, thereby disclosing both phase-locked and non-phase-locked modulations of signal amplitude, provided that these modulations are relatively well time locked to the onset of the event and consistent in frequency. Identified in the time-frequency domain, EEG responses to sensory stimulation can be characterized by their latency, their frequency, their magnitude (often expressed as percentage relative to baseline), and their scalp

distribution (Mouraux and Iannetti 2008). Several approaches have been proposed. At present, the continuous wavelet transform (CWT) is frequently used, as it is particularly well suited for the analysis of EEG signals. Indeed, by adapting the window width as a function of the estimated frequency, the CWT offers an optimal compromise for time-frequency resolution and is thus adequate for the evaluation of event-related modulations of the EEG spectrum within a wide range of frequencies (Mouraux and Iannetti 2008). The CWT can be performed in two ways. First, it can be applied at the level of each single EEG epochs (CWT-SINGLE). Second, it can be applied to the ERP waveforms obtained by averaging signals in the time domain (CWT-AVERAGE). The CWT-SINGLE transform enhances the signal-to-noise ratio of all time-locked EEG responses, regardless of whether they are phase locked to the onset of the stimulus, i.e., ERPs even when subject to a significant amount of temporal jitter, ERS, and ERD. In contrast, the CWT-AVERAGE average transform yields a time-frequency representation of the signals obtained using conventional time-domain averaging and will thus contain only EEG responses that are consistently phase locked to the stimulus. Therefore, EEG responses that are visible in both the CWT-SINGLE and CWT-AVERAGE can be considered as phase locked, whereas activities that are visible only in the CWT-SINGLE can be considered as non-phase locked (ERPs subject to jitter, ERS, and ERD) (Mouraux and Iannetti 2008). We have recently shown that the time-frequency approach markedly improved the signal-to-noise ratio of the EEG responses to chemosensory stimulation (in particular following olfactory stimulation), in comparison to conventional time-domain averaging. In addition, this approach allowed characterizing for the first time non-phase-locked components (ERS and ERD) that could not be identified using conventional time-domain averaging (Huart et al. 2012).

30.3.2.3 Event-Related Source Imaging

It is generally agreed that EEG has a high temporal resolution but a poor spatial resolution, whereas techniques based on hemodynamic measures (e.g., BOLD fMRI) have a poor temporal resolution but a high spatial resolution (Luck 2005). Although source analysis techniques are more appropriate to localize signals originating close to the scalp surface, several recent studies have suggested that EEG responses originating from deep brain structures can also be recorded and localized accurately (Kettenmann et al. 2001; Zumsteg et al. 2005). Source localization methods rely on mathematical models of the bioelectrical generators and the volume conductors within which they lie. The key limitation of these methods is that the inverse problem is highly undetermined and some assumptions have to be made when solving it. Hence, the validity of the obtained source configuration is strongly conditioned by the validity of these assumptions (e.g., assumptions concerning the number of sources or their approximate location). Source analysis of CSERP is probably particularly problematic, not only because of the relatively deep location of the hypothesized sources but also because multiple bilateral sources are thought to be simultaneously active, thus making it difficult to draw significant conclusions. Nevertheless, using high-resolution EEG, some researchers have attempted to localize the cortical structures generating the different components of CSERPs (Miyanari et al. 2006; Lascano et al. 2010). For example, in an attempt to provide information on the spatiotemporal sequence of information processing in the olfactory pathway, Lascano et al. (2010) performed source analysis of CSERPs, in which they suggested that olfactory input is processed first in the medial and lateral temporal cortex of the hemisphere ipsilateral to the stimulated nostril and only subsequently in the corresponding structures of the contralateral hemisphere. Until now, no clinical studies have been performed using such an analysis.

30.4 Imaging Evaluation

Advances in medical imaging allowed better morphological representation of chemosensory pathways and brain structures associated with chemosensory perception. Imaging modalities that are the frequently used in the clinical evaluation of

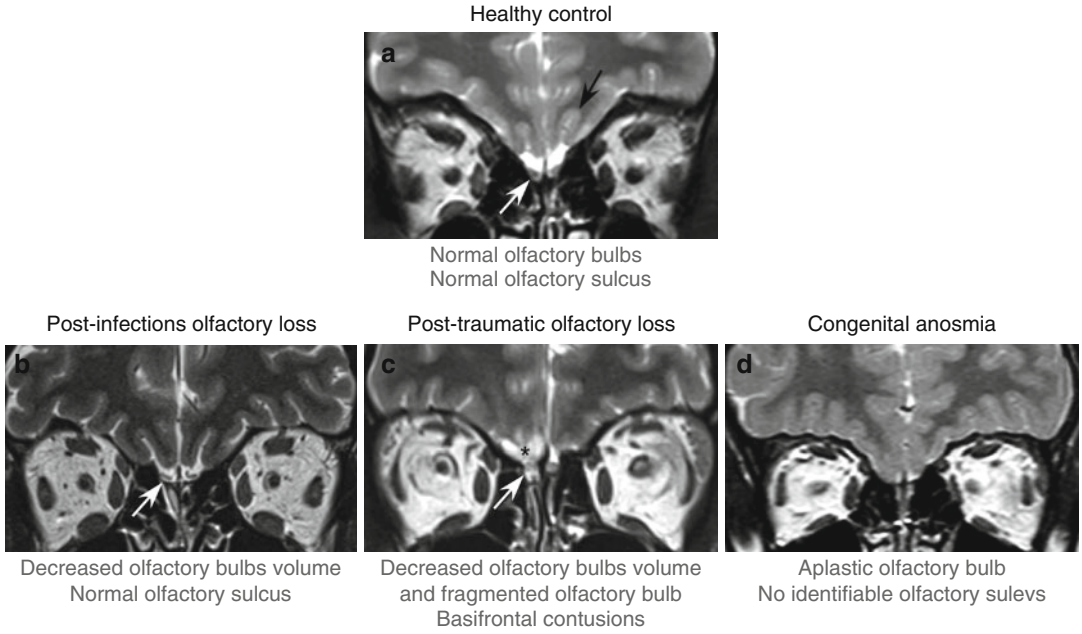

Fig. 30.6 MRI coronal T2-weighted 2-mm-thick views using fast spin-echo (FSE) sequence. Figure shows comparative pictures between control subject with normal olfactory function (**a**) and patients suffering from postinfectious olfactory loss (**b**), posttraumatic olfactory loss (**c**), and congenital anosmia (**d**). The control subject has normal olfactory bulbs (*white arrow*) and olfactory sulcus (*black arrows*). In contrast, the patient with postinfectious olfactory loss (**b**) has decreased olfactory bulb volume (*white arrow*), and the patient suffering from posttraumatic (**c**) olfactory loss exhibits fragmented olfactory bulb (*white arrow*) and basifrontal contusion, principally in the right gyrus rectus (*black asterisk*). Finally, the patient with congenital anosmia (**d**) has no identifiable olfactory bulbs and olfactory sulcus

patients include the computer tomography (CT) scan and magnetic resonance imaging (MRI). Recently, functional imaging became available.

30.4.1 Structural Imagery

MRI is the imaging modality of choice to evaluate the olfactory apparatus since it allows examining the olfactory bulb, olfactory tract, olfactory sulcus, and central olfactory projection areas (Fig. 30.6).

The olfactory bulb is often considered as the most important relay station in odor processing, and the olfactory bulb volume, assessed with MRI-based volumetric analyses, seems to be connected to the functional state of the olfactory system. Indeed, it was established that there was a good correlation between the olfactory bulb and the olfactory function not only in adults but also in children (Buschhuter et al. 2008; Hummel et al. 2011). Therefore, the assessment of the olfactory bulb volume is useful in the clinical evaluation of patients suffering from olfactory disorders. Several studies have shown that olfactory bulb volume was decreased in patients with postinfectious olfactory loss (Mueller et al. 2005; Rombaux et al. 2006a, b, c), posttraumatic olfactory loss (Yousem et al. 1996, 1999; Mueller et al. 2005; Rombaux et al. 2006a, b, c), idiopathic olfactory loss (Rombaux et al. 2010), congenital anosmia (Abolmaali et al. 2002), neurodegenerative disorder (Thomann et al. 2009), and psychiatric disease (Turetsky et al. 2000). Interestingly, a recent study conducted by Gudziol et al. (2009) showed that the olfactory bulb had a plasticity, since its volume can increase after treatment for chronic rhinosinusitis.

The olfactory sulcus is linked to the development of the olfactory system since it receives projections from the olfactory bulb and tract.

Hummel et al. showed that the depth of the olfactory sulcus in the plane of the posterior tangent through the eyeball (PPTE) was related to the overall olfactory function in healthy subjects (Hummel et al. 2003). It was also demonstrated that the depth of the OS in the PPTE was significantly smaller in patients with congenital anosmia (Abolmaali et al. 2002; Huart et al. 2011). The assessment of the OS in the PPTE is easy and quick to perform (Rombaux et al. 2009b) and should be considered as a standard in the evaluation of congenital anosmia (Huart et al. 2011). Nevertheless, it is still unknown if an acquired modification of sensory input may lead to morphological changes of OS. A recent study based on voxel-based morphometry has shown that in cases of acquired anosmia, there was a significant volume decrease in grey matter in primary as well as in secondary olfactory cortex (Bitter et al. 2011) (see below).

Central olfactory projection areas can also reveal abnormalities in pathologic situations. For example, in posttraumatic olfactory loss, contusions in basofrontal and temporal areas can be noted (Collet et al. 2009). In patients with multiple sclerosis, there seems to exist a correlation between smell loss and the lesions load in brain olfactory areas (Doty et al. 1998; Zorzon et al. 2000). In patients suffering from Alzheimer's disease, neurodegeneration in olfactory bulb and tract and mediotemporal lobe seem to be linked (Thomann et al. 2009). In addition, MRI can also reveal tumoral process in the brain, being responsible for the olfactory disorder (Choi et al. 2009; Mahdavi et al. 2009; Darie et al. 2010). Although MRI is the imaging modality of choice, CT scan can also be useful in the assessment of patients with olfactory dysfunction, mostly when associated with a rhinologic disease (i.e., chronic rhinosinusitis). CT is particularly useful for the diagnosis of olfactory cleft disease (Biacabe et al. 2004; Jankowski et al. 2007).

Recently, new automated whole-brain techniques have been developed, aiming to segment brain structures into grey and white matter and cerebrospinal fluid. These techniques, such as voxel-based morphometry and cortical thickness metric, allowed measuring the cortical thickness. In healthy subjects, it has been demonstrated that there is a link between the cortical thickness of some neuroanatomical structures (insula, medial orbitofrontal cortex, piriform cortex) and olfactory function, in that a thicker cortex is typically associated with better olfactory performance (Frasnelli et al. 2010). In hyposmic and anosmic patients, studies have also demonstrated a cortical atrophy in brain regions related to olfactory processing (Pardini et al. 2009; Wattendorf et al. 2009; Bitter et al. 2010, 2011). In addition, this cortical atrophy seems to correlate with the degree of olfactory dysfunction and the duration of the disease (Wattendorf et al. 2009; Bitter et al. 2010). However, the assessment of cortical thickness is usually not performed in the routine clinical evaluation of patients suffering of olfactory disorder.

To our knowledge, there are no studies investigating the neuroanatomical correlate of gustatory performances in humans.

30.4.2 Functional Imagery

The functional magnetic resonance imaging (fMRI) is a technique that measures the hemodynamic response in brain areas, related to the activity of a neuronal population. Numerous imaging studies using fMRI have provided considerable information regarding the processing of chemosensory information. Nevertheless, this technique is still mainly used in basic research and only few clinical conditions have been investigated.

Since the first fMRI study about olfactory system by Zatorre et al. (1992), numerous imaging studies have investigated the processing of olfactory information. Brain structures involved in olfactory processing include primary olfactory cortex (=piriform cortex) (Zatorre et al. 1992; Sobel et al. 2000; Gottfried et al. 2002; Cerf-Ducastel and Murphy 2003), orbitofrontal cortex (O'Doherty et al. 2000; Anderson et al. 2003; Gottfried and Dolan 2003; Gottfried et al. 2004), amygdala (Anderson et al. 2003; Gottfried et al. 2003; Herz et al. 2004), insular cortex (Royet et al. 2003; Wicker et al. 2003), cerebellum (Sobel et al. 1998), thalamus, and hypothalamus (Sobel et al. 1999; Zatorre et al. 2000).

Importantly, fMRI not only allows the structural identification of brain structures involved in olfactory processing but it also allows the identification of the functional role of certain brain areas. For example, the posterior piriform cortex seems to be involved in odor quality coding (Howard et al. 2009).

Among "pathologic populations" the most studied are patients with Alzheimer's and Parkinson's disease. It has been demonstrated that patients with Alzheimer's disease have a perceptual impairment of odor quality discrimination, which occurs in conjunction with a disruption of odor quality coding, for example, in the posterior piriform cortex (Li et al. 2010). It has also been demonstrated that patients with Alzheimer's disease show lower activation in the primary olfactory cortex than control subjects (Wang et al. 2010). In patients with Parkinson's disease, neuronal activities in the amygdale and hippocampus are reduced compared to controls (Westermann et al. 2008; Hummel et al. 2010b). In addition, activity of brain areas relevant for olfactory processing seems to be well correlated with the presence or absence of ERP. Indeed, patients having ERP have a higher activation than patients having no ERP (Welge-Lussen et al. 2009). Despite of these advances, as of today, fMRI is not performed in the basic clinical evaluation of individual patients suffering from olfactory disorder.

30.4.3 Diffusion Imagery

Diffusion tensor imaging (DTI) is an application of diffusion MRI technique. Diffusion MRI examines the local microstructural characteristics of water diffusion in tissues. DTI is based on the fact that the diffusion of water molecules in organic tissues is often anisotropic (Tanner 1979), and the diffusion coefficient of water may vary depending on the orientation along which the diffusion-weighted measurements are taken: water diffuses more rapidly in the direction aligned with the examined structure and more slowly in the perpendicular direction. In this way, this technique allows the tractography of nervous structures and can also, by evaluating the fractional anisotropy of brain regions, detect changes in white matter integrity. Although there are numerous studies reporting the use of tractography for the visualization of various cranial nerves (Hodaie et al. 2010; Chen et al. 2011; Kolbe et al. 2012; Smith et al. 2011), we found only one study about the diffusion tensor fiber tractography of the olfactory tract (Skorpil et al. 2011). Some authors have used the diffusion tensor parameters to study the relationship between olfactory impairment in Parkinson's disease and white matter abnormalities in central olfactory areas and showed that there was microstructural white matter reduction in central olfactory system of patients with early stage Parkinson's disease; these reductions seemed to be associated with the olfactory loss (Ibarretxe-Bilbao et al. 2010; Rolheiser et al. 2011; Zhang et al. 2011).

Since studies about this technique in the evaluation of olfaction are lacking, further investigations should be necessary to evaluate the usefulness of DTI techniques in the clinical, individual assessment of olfactory disorders.

30.5 Future Perspectives

Although progress has been made in the clinical evaluation of olfactory function, much is left unclear. This is particularly true in the matter of prognosis and differential diagnosis of patients suffering from olfactory disorders. Indeed, while for some patients the cause of the olfactory disorder is clear (e.g., posttraumatic olfactory loss, postinfectious loss), there is still a large population of patients for whom no clear etiology can be found. Also, we still miss a reliable tool to evaluate the prognosis of patients. We hope that future advances in electrophysiological techniques, such as time-frequency analysis, or in imaging techniques, such as fMRI or cortical thickness metric, will provide us with at least partial responses to these questions.

Conclusion

In the last years, the field of olfaction has known a considerable development. Nowadays, it is relatively easy to diagnose or confirm an olfactory dysfunction in clinical practice

owing to reliable and validated psychophysical and electrophysiological testing, and imaging techniques allowed to have a precise morphological representation of structures implicated in smell perception. In research, new electrophysiological (i.e., source analysis, time-frequency analysis) and new functional and morphological imaging techniques are being evaluated and seem very promising for the evaluation of patients suffering from smell or taste disorder; further studies are necessary to evaluate the usefulness of these techniques in clinical practice. Particular attention should be paid to assessment of differential diagnosis or evaluation of patient's prognosis, since these points remain unclear.

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Electron Microscopy and the Nose

31

Mürvet Hayran

Keywords
Nasal anatomy • Epithelium • Nasal ultrastructure • Transmission electron microscopy • TEM • Scanning electron microscopy • SEM • Vestibule • Respiratory region • Olfactory region

Core Messages

- Electron microscopy is a very important tool for evaluating the ultrastructural features of the nose and helping diagnose diseases related to nasal structures.
- Biopsies should be small (less than 2 mm) and fixed in seconds to prevent autolysis and to obtain optimum diffusion of the fixatives.
- Cilia are hairlike extensions of the apical plasma membrane containing microtubules. The basal body is a microtubule-organizing center located in the apical region of the ciliated cell. Existence of the characteristic "9+2" organization of the axonemes of the cilia and presence of the basal bodies are important for the normal function of the cilia.
- The goblet cell is common in the airway epithelium. The parasympathetic nervous system does not control release from goblet cells. Rather, these cells respond to physical and chemical irritants; however, mediators have not yet been clearly identified.
- Basal cells are stem cells from which other cell types arise. They lie on the basement membrane and do not reach the lumen.
- The olfactory segment is the region at the roof of the nasal cavity. In humans, the olfactory region is a small area formed by a modified pseudostratified epithelium. The olfactory epithelium is composed of olfactory receptor cells, supporting or sustentacular cells, basal cells, and brush cells. In contrast with the other regions of the nasal cavity, there are no goblet cells in this area.

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31.1 Electron Microscopy and the Nose

31.1.1 The Electron Microscope

The electron microscope is a type of microscope that uses an *electron beam* accelerated under high vacuum instead of light source to create an image of the specimen. In studying the microscopic anatomy of the nose, it is essential to understand the requirements and capabilities of the electron microscope and which tissues and cells should be clearly observed by electron microscopy.

The electron microscope uses an accelerated electron beam, emitted by a cathode and controlled by a series of electrostatic and electromagnetic lenses (Voutou and Stefanaki 2008; Ross and Pawlina 2011). Components of the electron microscope are (Fig. 31.1):

1. *Electron optical column*
2. *Electron gun* that consists of an electron source to produce electrons, such as a tungsten filament
3. *Magnetic lenses* to demagnify the beam
4. *Magnetic coils* to control and modify the beam
5. *Apertures* to define the beam and prevent electron spray
6. *Detectors* to collect, detect, and display the signal
7. *Digital imaging systems* that produce an image from the signal
8. *Vacuum systems* consisting of vacuum pumps and a vacuum chamber

There are two basic types of electron microscopy, *transmission electron microscopy* (TEM) and *scanning electron microscopy* (SEM).

TEM uses an electron beam that transmits through ultrathin (60–90 nm) sections that are glutaraldehyde-fixed and usually double-stained. TEM produces two-dimensional images on a *fluorescent screen*, photographic film, or CCD (charge-coupled device) camera. TEM can detect structures by the transmission of the electron beam and discriminate details of 0.2 nm. However, the quality of the obtained image mainly depends on the preparation of the biological sample (Ross and Pawlina 2011).

SEM obtains topographic, three-dimensional images with a resolution of about 2 nm. The lens system of SEM produces a small focused spot of electrons that are then scanned over the specimen surface by *deflection coil*. SEM is able to produce

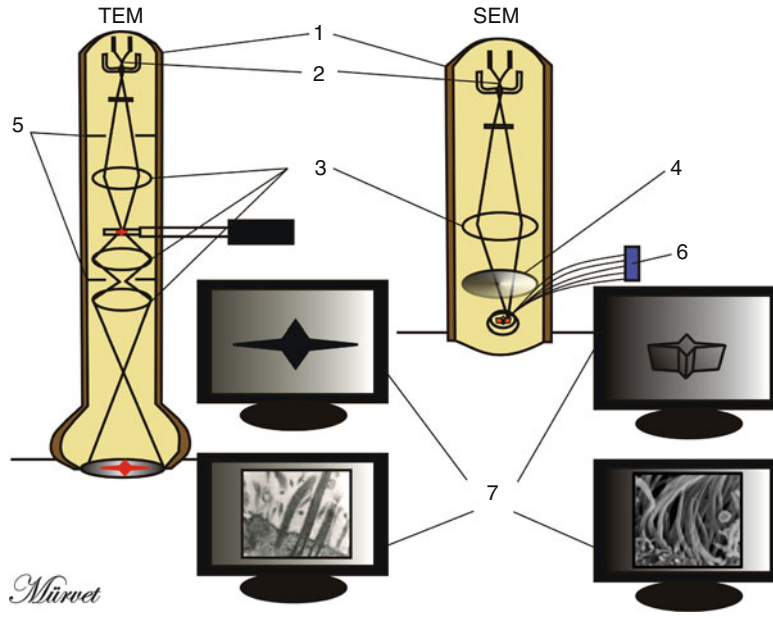

Fig. 31.1 Diagram of standard transmission electron microscopy (*TEM*) and scanning electron microscopy (*SEM*), showing major components: *1* electron optical column, *2* electron gun, *3* magnetic lenses, *4* magnetic coil, *5* apertures, *6* detector, and *7* digital imaging systems

an image by detecting secondary electrons and backscattered electrons generated from the specimen. A *secondary electron detector* in the SEM builds the image by mapping the signals of a finely focused electron beam that is scanned on the sample surface (Bozzola and Russell 1999; Potter and Love 1999; Ross and Pawlina 2011).

Both TEM and SEM can provide only black-and-white images. Although the original image is monochrome, micrographs can be colored digitally to emphasize details. In recent years, digital imaging systems provide incredible opportunities to obtain high-quality electron micrographs.

Biological materials usually require processing before being viewed by electron microscopy (Bozzola and Russell 1999; Ross and Pawlina 2011). The tissue preparation technique varies depending on the type of microscope and the type of specimen. Low-vacuum SEMs and the environmental scanning electron microscope (ESEM) overcome both these limitations (Slowko 2001).

The stages for tissue preparation for TEM are as follows:

(a) *Fixation*: can be achieved by perfusion and microinjection or immersion using various fixatives including aldehydes.
(b) *Post fixation*: performed in OsO_4.
(c) *Dehydration*: done with a graded series of alcohol.
(d) *Epoxy resin block preparation*: treat with propylene and embed in epoxy resin.
(e) *Semi-thin sectioning*: One- to two-micrometer-thick semi-thin sections obtained from the epoxy resin blocks should be stained with methylene blue or azure for light microscopy.
(f) *Ultrathin sectioning*: Ultramicrotome, an instrument for cutting extremely thin sections, is used for ultrathin sectioning of tissue. Ultrathin sections are obtained from selected areas and then double-stained with uranyl acetate/lead citrate.

During SEM sample preparation, after the fixation step, the specimens must be dried. Electron microscopists prefer to use *Critical Point Drying*. By removing carbon dioxide after the transition from the liquid to the gas phase at the critical point, the specimen can be dried without structural damage. Specimens must be mounted onto a holder that can be inserted into the scanning electron microscope. The last step prior to sample imaging is coating the samples. The objective of this coating is to increase its conductivity in the scanning electron microscope and to prevent the buildup of high-voltage charges on the specimen. Typically, specimens are coated with a thin layer of gold, gold palladium, or platinum (Bozzola and Russell 1999).

In addition to visual inspection, a grading system can be used to quantitatively evaluate the samples to compare different experimental conditions. The data can then be analyzed statistically to make further evaluations. This grading system was established based on similar principles of methods used for evaluating different tissue samples (Taşdemir et al. 1993; Kırkalı et al. 1995; Kaptanoğlu et al. 2000; Görgülü et al. 2001; Hazer et al. 2010).

It is important to pay close attention during the sample preparation to get small-sized (less than 2 mm) biopsy materials and to fix them in seconds to prevent autolysis and obtain optimum diffusion of the fixatives (Bozzola and Russell 1999).

31.1.2 Microscopic Anatomy of the Nose

The nose humidifies, filters, and warms the air we breathe as well as providing the sense of olfaction. The nose is considered to have two parts: *the external nose* and *the nasal cavity*.

The *external nose* consists of skin and a framework of compact bone and hyaline cartilage that forms a projection covered by skin. Electron microscopic observation of this part does not show any regional specifications. The skin consists of two main layers. The outer layer is the *epidermis*, which is composed of a keratinized and stratified squamous epithelium (Figs. 31.2 and 31.3) (see Sect. 31.1.2.1). The inner layer is the *dermis*, which is dense connective tissue including epithelial derivates of the skin such as hair follicles and sweat and sebaceous glands

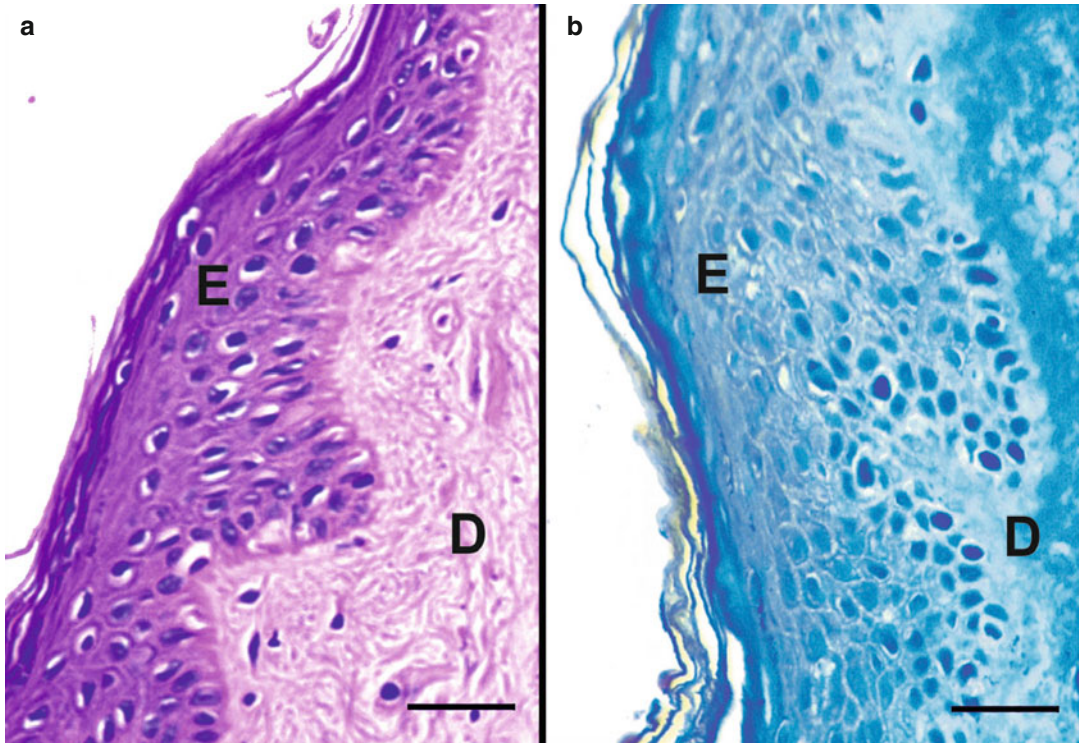

Fig. 31.2 The epidermis, which is composed of a keratinized stratified squamous epithelium (E), and the dermis (D) (scale bar: 25 μm). (**a**) Light micrograph of the epidermis of the external nose (paraffin block, stain: H&E). (**b**) Light micrograph of the epidermis of the external nose (Araldite block, stain: methylene blue). The specimens were obtained from a fresh frozen cadaver from a microscopic anatomy lab at Hacettepe University, Faculty of Medicine, Department of Anatomy. H&E hematoxylin and eosin

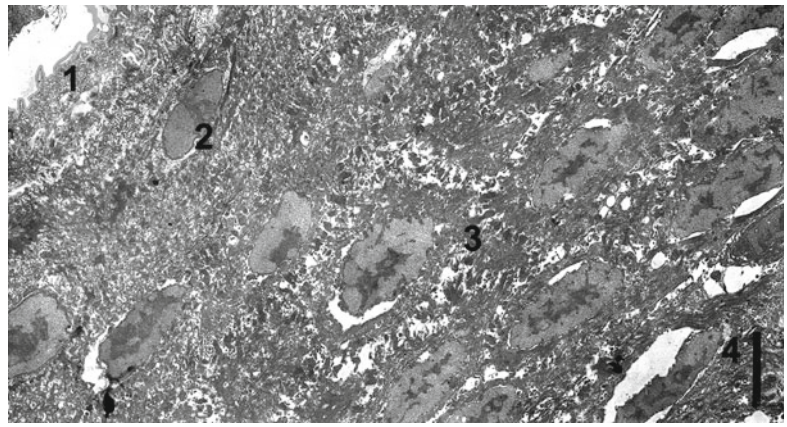

Fig. 31.3 Electron micrograph (TEM) keratinized stratified squamous epithelium of the epidermis of the external nose (scale bar: 5 μm) (Araldite block, stain: uranyl acetate/lead citrate). The specimen was obtained from a fresh frozen cadaver from a microscopic anatomy lab at Hacettepe University, Faculty of Medicine, Department of Anatomy. TEM transmission electron microscopy, *1* Stratum corneum, *2* stratum spinosum, *3* stratum granulosum and *4* stratum basale

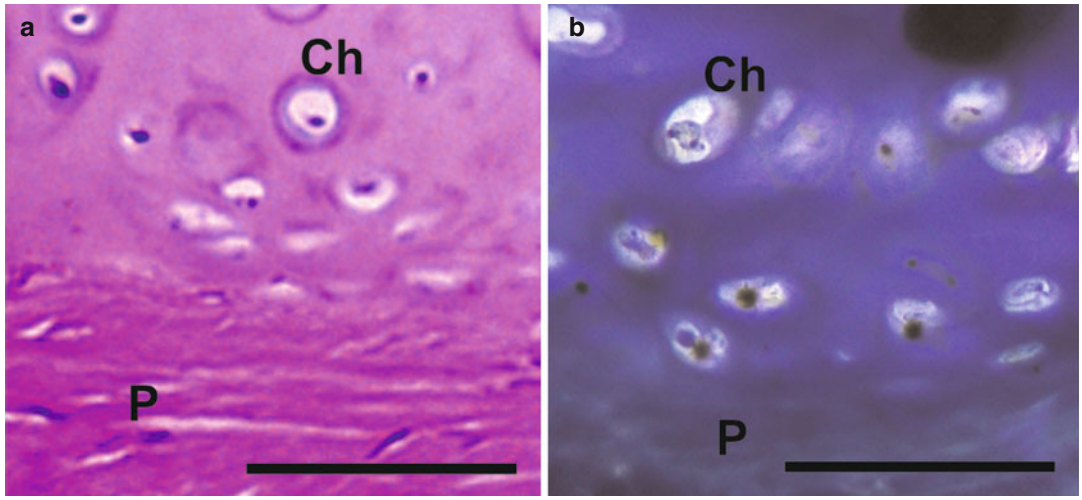

Fig. 31.4 The hyaline cartilage, rounded or ellipsoidal chondrocytes (Ch) and fibroblast-like cells of the perichondrium (P). (**a**) Light micrograph (paraffin block, stain: H&E) (scale bar: 100 μm). (**b**) Light micrograph (Araldite block, stain: methylene blue) (scale bar: 100 μm). H&E hematoxylin and eosin

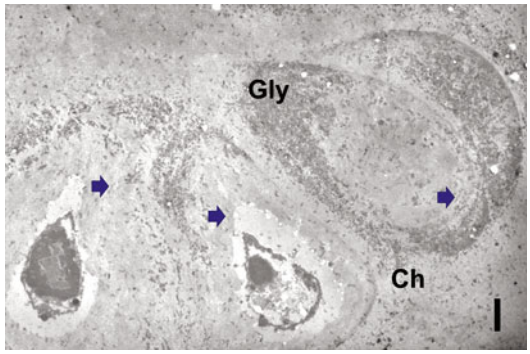

Fig. 31.5 Electron micrograph (TEM) of the hyaline cartilage, rounded or ellipsoidal chondrocytes (*Ch*) (scale bar: 2 μm) (Araldite block, stain: uranyl acetate/lead citrate). The specimen was obtained from a fresh frozen cadaver at a microscopic anatomy lab at Hacettepe University, Faculty of Medicine, Department of Anatomy. TEM transmission electron microscopy, *Arrows* cytoplasmic filaments, *Gly* coarse granules of glycogen

(Jones 2001). The supporting framework is composed of nasal bones, frontal process of the maxillae, and the nasal part of the frontal bone and septum, as well as major and minor alar cartilages. Bone is also a connective tissue characterized by a mineralized extracellular matrix containing mainly type I collagen along with other non-collagenous matrix proteins (Ross and Pawlina 2011). Bones of the external nose consist of layers of relatively thick compact bone with a layer of spongy bone covered by periosteum, which is a sheath of dense fibrous connective tissue containing *osteoprogenitor cells*.

The type of the cartilage that contributes to the framework of the nose is *hyaline cartilage* (Fig. 31.4). The matrix of the hyaline cartilage consists of collagen, predominantly type II fibrils and other cartilage-specific collagen molecules (Ross and Pawlina 2011). The chondrocytes are either rounded or ellipsoidal (Figs. 31.4 and 31.5). The plasma membrane is folded into a moderate number of microvilli. Numerous cytoplasmic filaments and coarse granules of glycogen are prominently present in the cytoplasm. The *Golgi complex* is also prominent and frequently contains dilated vesicles enclosing small dense particles. A small amount of rough endoplasmic reticulum is present, while unattached ribosomes are not numerous. There are a few lipid droplets in the cytoplasm. The nuclei are ovoid and usually contain a single large nucleolus (Fig. 31.5). Mitochondria are small and not very numerous. The matrix is composed mostly of collagen fibrils and matrix granules. Frequently, granules appear to be linked together by extremely fine intergranular fibrils, usually less than 50 Å thick, which connect the projections

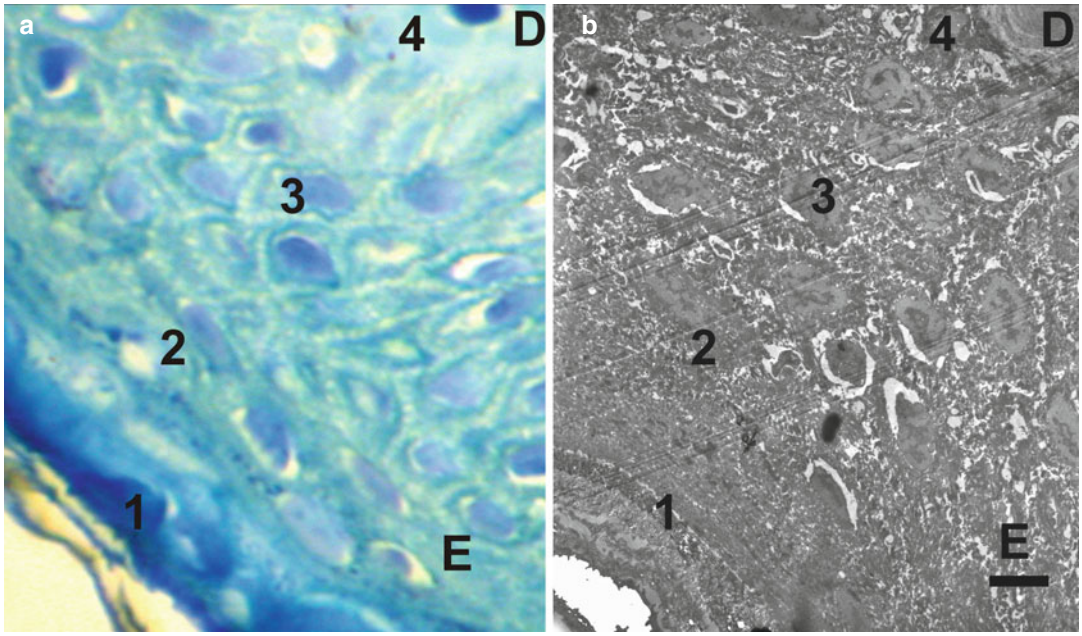

Fig. 31.6 (**a**) Light micrograph of the epidermis of the vestibule (scale bar: 5 μm) (Araldite block, stain: methylene blue). (**b**) Electron micrograph (TEM) of the epidermis of the vestibule (scale bar: 5 μm) (Araldite block, stain: uranyl acetate/lead citrate). Both specimens were obtained from fresh frozen cadavers at a microscopic anatomy lab at Hacettepe University, Faculty of Medicine, Department of Anatomy. TEM: transmission electron microscopy. *E* epidermis, *D* dermis, *1* stratum corneum, *2* stratum spinosum, *3* stratum granulosum and *4* stratum basale

of adjacent granules. Infrequently, clusters of membrane-bounded matrix vesicles are observed between collagen fibrils of the matrix (Anderson and Sajdera 1971)

The *perichondrium*, a firmly attached dense connective tissue composed of fibroblast-like cells, surrounds the hyaline cartilage (Fig. 31.4).

The *nasal cavity* is divided into paired chambers separated by a bony and cartilaginous septum. Each chamber is divided into three regions:
(a) Vestibule of the nasal cavity
(b) Respiratory region
(c) Olfactory region

31.1.2.1 Vestibule of the Nasal Cavity

The nasal cavity extends from the *nares* anteriorly to the choanae posteriorly. Just behind the nares, the nasal cavity widens and forms the vestibule (Stenberg 1997). It is lined with keratinized stratified squamous epithelium and the dermis (Fig. 31.6) that contains connective tissue elements, many hair follicles (hairs in this region are called *vibrissae*) (Figs. 31.7 and 31.8), and sebaceous glands and sweat glands (Figs. 31.9 and 31.10) (see Sect. 31.1.2).

Stratified squamous epithelium consists of several layers of cells. The flattened cells form its outer layer and the deepest cells are columnar. The epidermis is composed of four distinct layers. These are the stratum corneum, stratum spinosum, stratum granulosum, and stratum basale (stratum germinativum) (Fig. 31.6). The cells of the stratum corneum are anucleate corneal cells (squamous), called corneocytes or cornified cells. The corneocytes are flattened cells that lack nuclei and cytoplasmic organelles. The cells contain aggregated keratin filaments. The upper spinous layer and granular cell layer also contain smaller lamellate granules called lamellar, membrane-coating granules (MCGs or Odland bodies). These are numerous within the upper spinous layer. They play an important role in providing the barrier and intercellular cohesion functions of the stratum corneum. They release

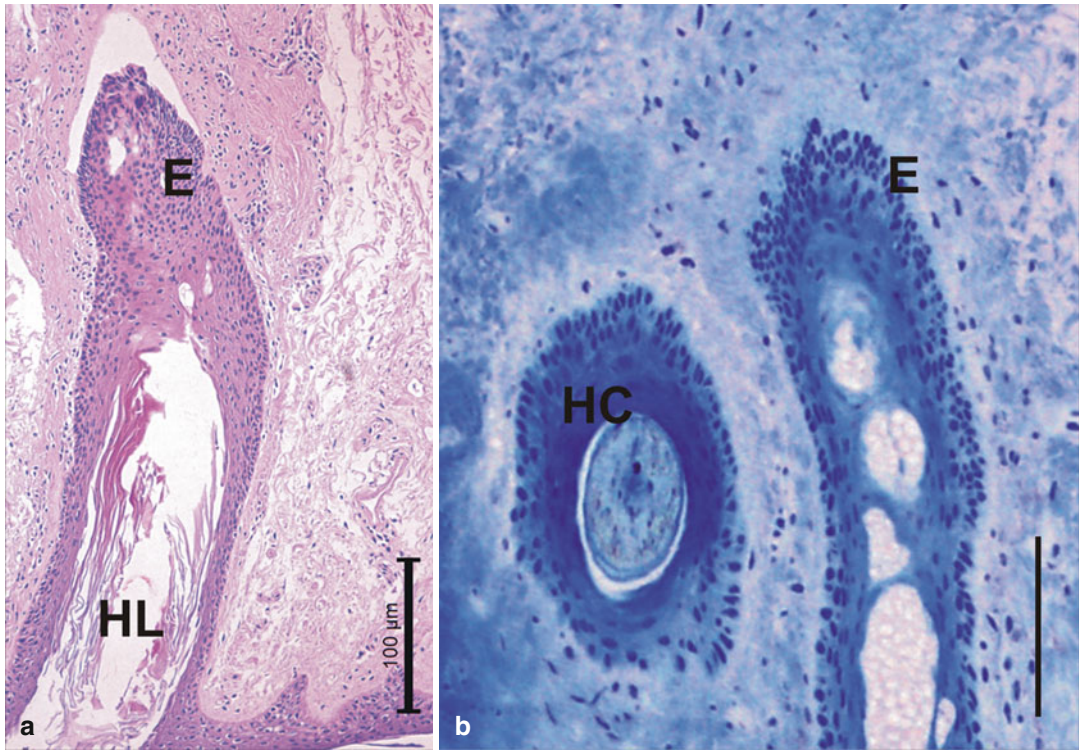

Fig. 31.7 Light micrograph from the dermis of the vestibule (scale bar: 100 µm). (**a**) Hair follicle and vibrissae, longitudinal section (paraffin block, stain: H&E). (**b**) Hair follicle and vibrissae, cross (*HC*) and longitudinal section (*HL*) (Araldite block, stain: methylene blue) (scale bar: 100 µm). The specimens were obtained from fresh frozen cadavers at a microscopic anatomy lab at Hacettepe University, Faculty of Medicine, Department of Anatomy. *H&E* hematoxylin and eosin, *E* epithelial cells

their lipid components into the intercellular space. The basal and spinous cells together are called *the Malpighian layer*, which includes cells such as melanocytes, *Langerhans cells,* and *Merkel cells*. When outer cells become damaged, cell division occurs within the basal layer. The cells move outwards to the stratum corneum, passing through the stratum spinosum. The characteristics of these cells then transdifferentiate to become the cells of the stratum corneum. There are biochemical and signaling interactions between the epithelial cells, including desmosomes, adherens junctions, gap junctions, and tight junctions (McGrath et al. 2010).

Posteriorly, where the vestibule ends, the stratified squamous epithelium becomes thinner and undergoes a transition to the pseudostratified epithelium that characterizes the respiratory region. At this site the sebaceous glands end (Ross et al. 1995). At the level of the limen nasi, the lining of the nasal cavity gradually changes from squamous epithelium to non-ciliated cuboidal or columnar epithelium. At the level of the *inferior turbinate*, the epithelium continues as *pseudostratified ciliated columnar epithelium* (Uraih and Maronpot 1990).

31.1.2.2 Respiratory Region of the Nasal Cavity

The mucosa of the respiratory region warms, moistens, and filters inspired air. The lamina propria of the respiratory region has a rich, vascular network that includes a complex set of capillary loops. The nasal mucosa microvasculature is composed of arterioles, venules, capillaries, and cavernous sinuses. Both arterioles and venules run parallel to the long axis of the nasal concha. The capillaries and cavernous sinuses are

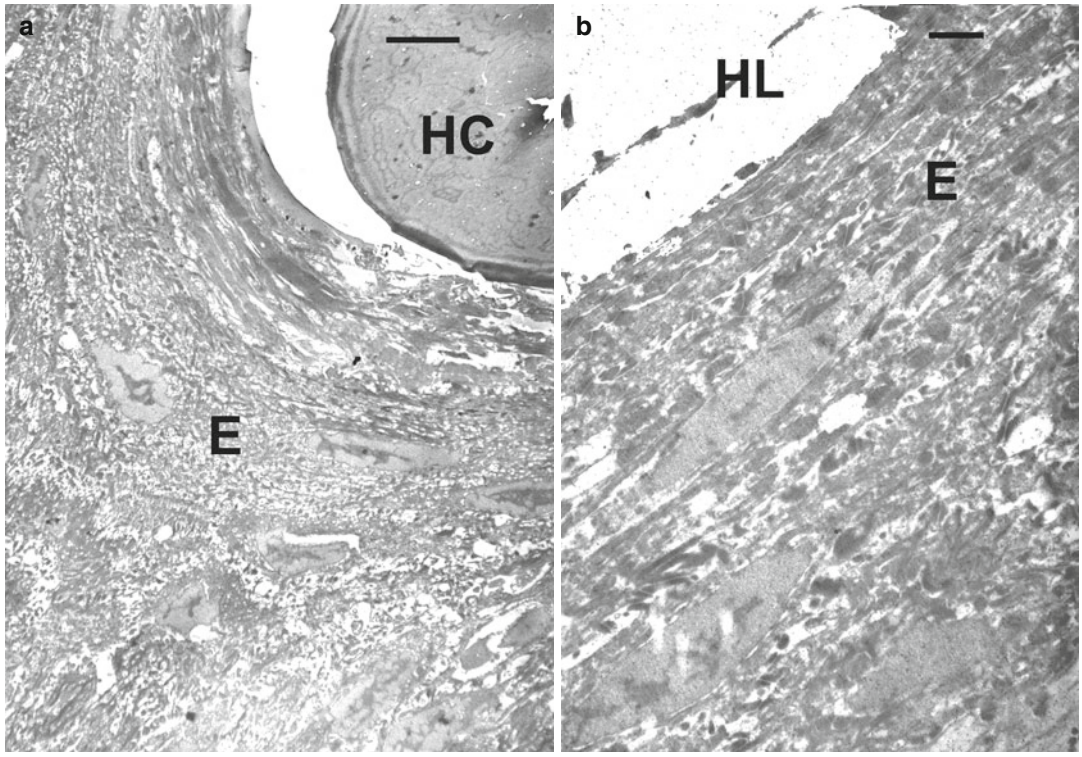

Fig. 31.8 Electron micrographs (TEM) from the dermis of the vestibule. (**a**) Cross and (**b**) longitudinal sections of the vibrissae (scale bar: 5 μm) (Araldite block, stain: uranyl acetate/lead citrate). The specimen was obtained from a fresh frozen cadaver at a microscopic anatomy lab at Hacettepe University, Faculty of Medicine, Department of Anatomy. *TEM* transmission electron microscopy *E* epithelial cells

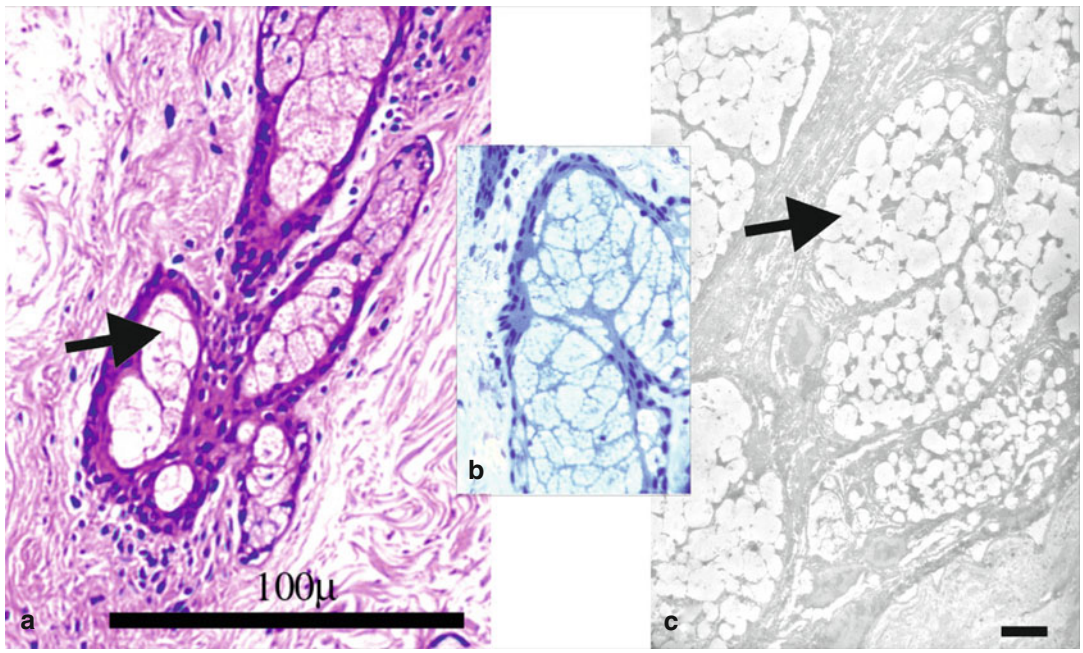

Fig. 31.9 The sebaceous glands (*arrows*) from the dermis of the vestibule (scale bar: 5 μm). (**a**) Light micrograph (paraffin block, stain: H&E). (**b**) Light micrograph (Araldite block, stain: methylene blue). (**c**) Electron micrographs (TEM) (Araldite block, stain: uranyl acetate/lead citrate). *H&E* hematoxylin and eosin, *TEM* transmission electron microscopy

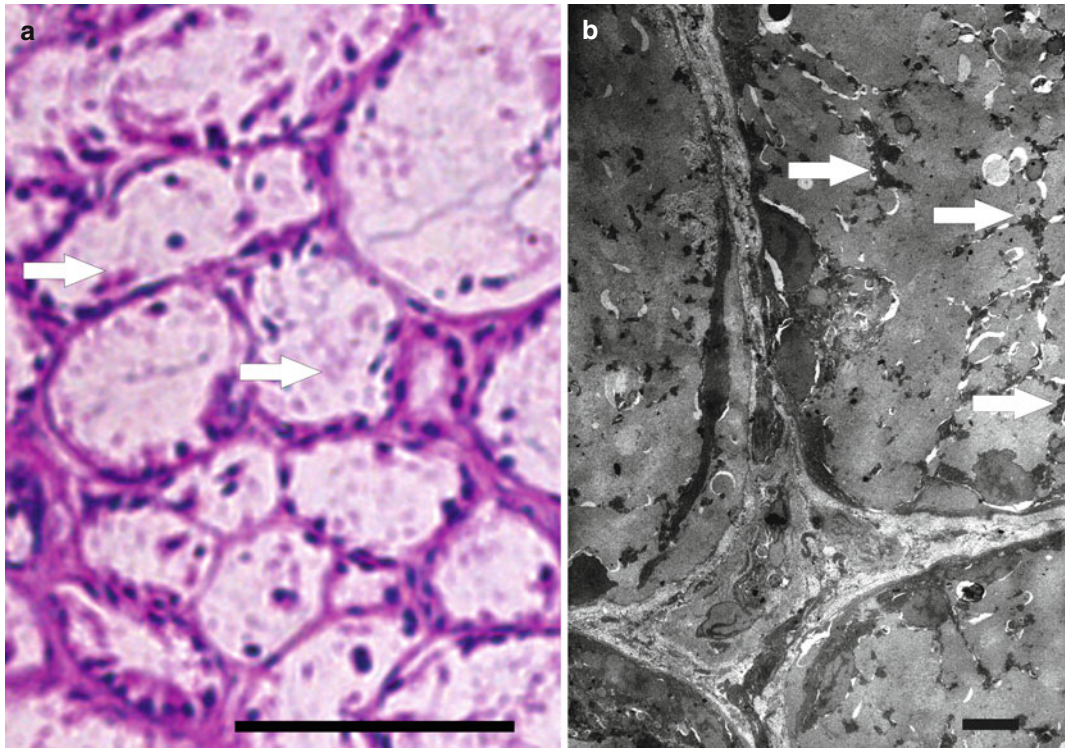

Fig. 31.10 The sweat glands and their myoepithelial cells (*arrows*) from the dermis of the vestibule. (**a**) Light micrograph (paraffin block, stain: H&E) (scale bar: 5 μm). (**b**) Electron micrographs (TEM) (Araldite block, stain: uranyl acetate/lead citrate) (scale bar: 100 μm). *H&E* hematoxylin and eosin, *TEM* transmission electron microscopy

particularly abundant and interconnect with numerous short anastomoses to form a rich dense network (Chen 1989). The arrangement of the vessels allows the inhaled air to be warmed by blood flow through the part of the capillaries closest to the surface. These capillaries provide a mechanical heat exchange system. Submucosal capillaries and venules have fenestrated endothelial linings and relatively porous basement membranes, facilitating the transit of fluid and white blood cells to the mucosal surface. The lamina propria then becomes distended with fluid, resulting in a marked swelling of the mucous membrane and a consequent obstruction of the air passage. This makes breathing difficult. The mucosa contains large venous-like spaces known as *swell bodies*, which may become congested during allergic reactions or infections. The morphological view of fenestrated endothelia might change in response to alterations in the physiological conditions. It is essential to define the different shapes and courses of the muscle cells responsible for constriction and dilatation of nasal swell bodies for proper clinical diagnoses (Grevers and Kastenbauer 1996).

The nasal vasculature is controlled by dense innervations. Myelinated nerve bundles and small axons are found in the arterial wall located in the adventitia. Veins also have nerve structures, but they are fewer and found in the muscle layer. Therefore, no axons are present in capillaries. The differences in the density of axons indicate that these vessels are controlled by neural structures and play an important role in the swelling of the nasal mucosa (Riederer et al. 1997).

Seromucous glands are one of the main components of human nasal mucosa. Their secretion contributes to the moistening function of the goblet cells in the respiratory epithelium. The terminal segments of the glands are surrounded by

contractile myoepithelial cells in a basketlike fashion. These cells, in particular, show a high number of mitochondria (Mir-Salim et al. 1998). This innervation pattern is important in understanding the control of different physiological glandular functions. Unmyelinated nerve fibers have typical neuronal components such as neurofilaments, neurotubules, and mitochondria in their cytoplasm (Knipping et al. 2000).

Inhaled agents contact the nasal mucosa and cause a local immune response. Because of the nature of these local immune responses, nasal mucosal antibody production is best achieved via direct stimulation of IgA-committed, nasal-associated lymphoid tissue-derived B cells (Heritage et al. 1997).

The respiratory region constitutes most of the volume of the nasal cavities. The medial wall of the respiratory region, the *nasal septum*, is smooth, but the lateral walls contain three shelf-like, bony projections called turbinates or conchae. The turbinates increase surface area to more efficiently warm inspired air. This air is also filtered by the mucus-covered walls of the nasal cavity. Particles trapped in this layer of mucus are transported to the pharynx by means of coordinated sweeping movements of cilia and are subsequently swallowed. Therefore, these motile cilia play a critical role in mucociliary clearance. This segment is lined by a ciliated, pseudostratified columnar epithelium. The pseudostratified respiratory epithelium actually consists of one layer of cells, but their nuclei frequently lie at different levels, and some cells do not reach the epithelial surface. Hence, the epithelium looks stratified even if all the cells rest on a basement membrane located between the epithelial cells and the loose lamina propria. Basal cells, situated close to the basement membrane, replace the ciliated cells or the goblet cells when needed (Lane 2004; Ross and Pawlina 2011). The lamina propria is attached to the *periosteum* of the adjacent bone. The submucosa contains blood vessels, venous plexus, glandular elements, sensory nerves, and immune system cells.

The ciliated, pseudostratified columnar epithelium of the respiratory region is composed of five cell types: ciliated columnar cells, non-ciliated columnar cells, goblet cells, basal cells, and brush cells (Fig. 31.11). All of these cells can be investigated under TEM (Fig. 31.12). However, because some of these cells do not reach the surface of the epithelium, only three types (ciliated, non-ciliated, and goblet cells) can be seen during SEM studies (Fig. 31.13).

The anterior one-third of the nasal cavity is non-ciliated. Cilia begin just behind the front edge of the inferior turbinate. The posterior part of the nasal cavity, as well as the paranasal sinuses, is densely covered by cilia (Mygind and Dahl 1998). However, the epithelium on the tips of the nasal turbinates is cuboidal and sparsely ciliated. Additionally, mild squamous metaplasia may be seen around these areas (Uraih and Maronpot 1990).

Ciliated columnar cells, the predominant cell type at the surface, rest on the basement membrane and project both *cilia* and *microvilli* from their apical surface into the nasal lumen (Lane 2004) (Fig. 31.14). Ciliated and *non-ciliated columnar cell*s interact with neighboring cells by tight junctions and by interdigitations of the cell membrane. The cytoplasm contains many mitochondria located apically (Fig. 31.15), indicating a highly active metabolism (Mygind and Dahl 1998).

Each ciliated cell contains approximately 1,000 motile cilia (Lane 2004). Cilia are hairlike extensions of the apical plasma membrane containing an *axoneme*, a microtubule-based internal structure. Ultrastructurally, cilia are anchored to basal bodies below the cell surface. The *basal body* is a centriole-derived microtubule-organizing center located in the apical region of the ciliated cell. The basal body consists of nine short *microtubule triplets* arranged in a ring. The basal bodies are associated with several accessory structures (alar sheets, basal feet, and striated rootlets) that anchor them in the cytoplasm. Axonemes are formed by microtubules arranged in a characteristic "9+2" pattern. Nine outer pairs of microtubules make a cartwheel pattern at the periphery of the axoneme, surrounding two single microtubules in the center (the inner microtubules) (Fig. 31.16). Each of the paired

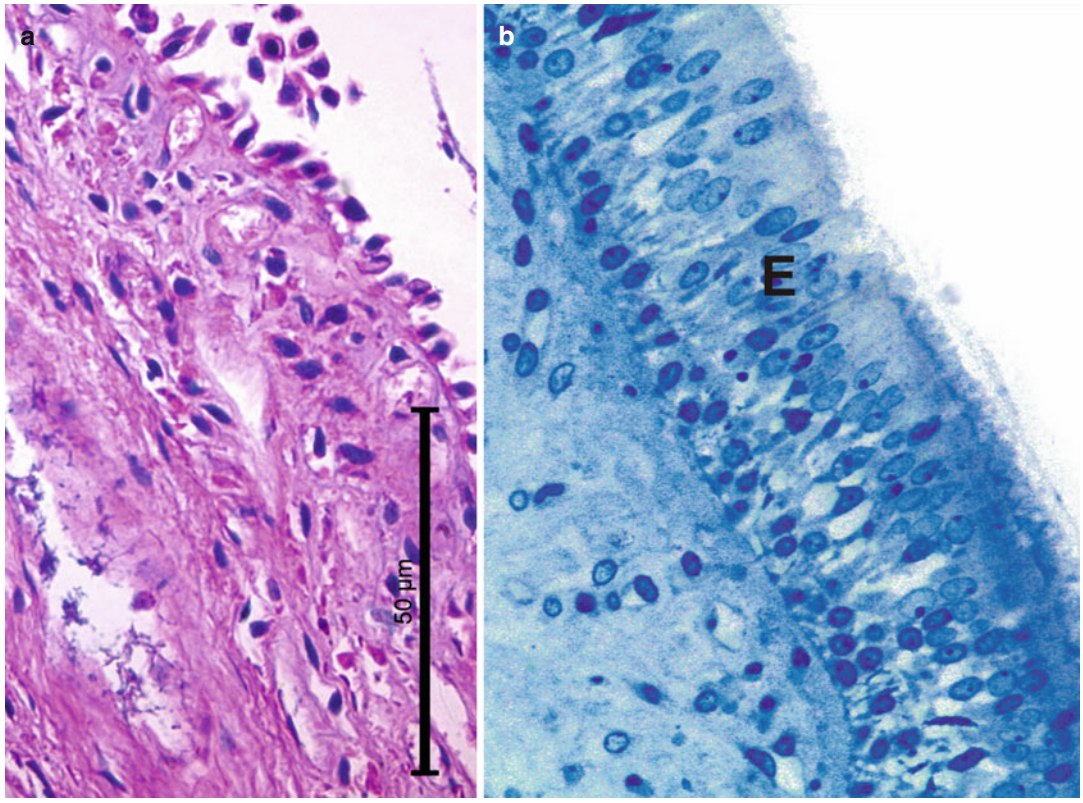

Fig. 31.11 The pseudostratified columnar epithelium (*E*) of the respiratory region. (**a**) Light micrograph of the epidermis of the external nose (paraffin block, stain: H&E) and (**b**) light micrograph of the epidermis of the external nose (Araldite block, stain: methylene blue) (scale bar: 50 µm). The specimens were obtained from fresh frozen cadavers at a microscopic anatomy lab located at Hacettepe University, Faculty of Medicine, Department of Anatomy. *H&E* hematoxylin and eosin

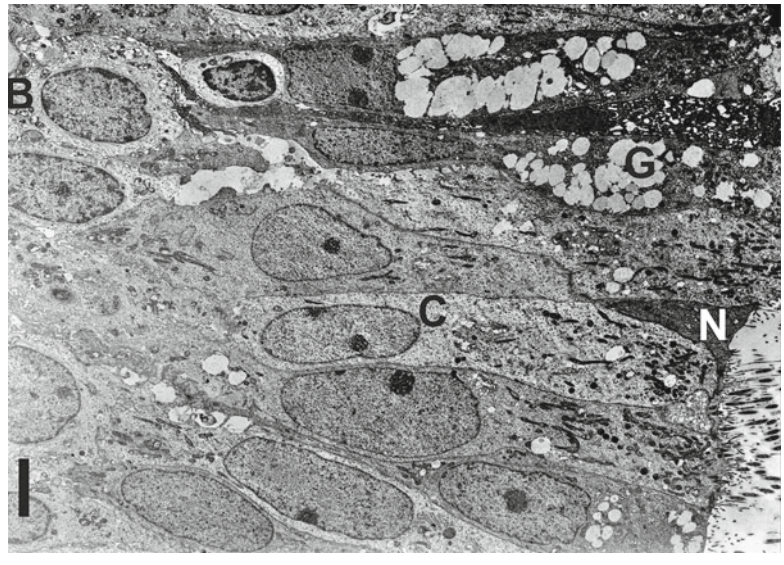

Fig. 31.12 Electron micrograph respiratory epithelium (TEM) (scale bar: 5 µm) (Araldite block, stain: uranyl acetate/lead citrate). The specimen was obtained from a fresh frozen cadaver at a microscopic anatomy lab at Hacettepe University, Faculty of Medicine, Department of Anatomy. TEM: transmission electron microscopy. *B* basal cell, *C* ciliated cell, *G* goblet cell, *N* non-ciliated cell

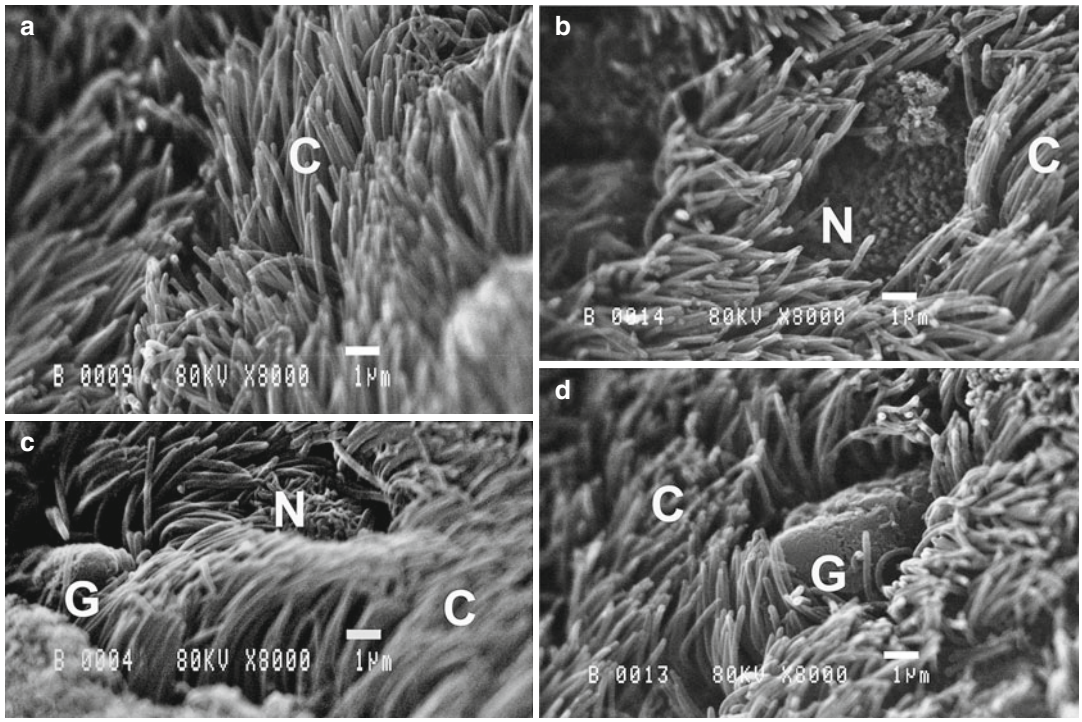

Fig. 31.13 (**a**–**d**) Different areas on the nasal mucosal surface. Electron micrograph of the respiratory epithelium (SEM) (scale bar: 1 µm). Surface invaginations of three types of the cells: ciliated (*C*), non-ciliated (*N*), and goblet (*G*) cells. *SEM* scanning electron microscopy

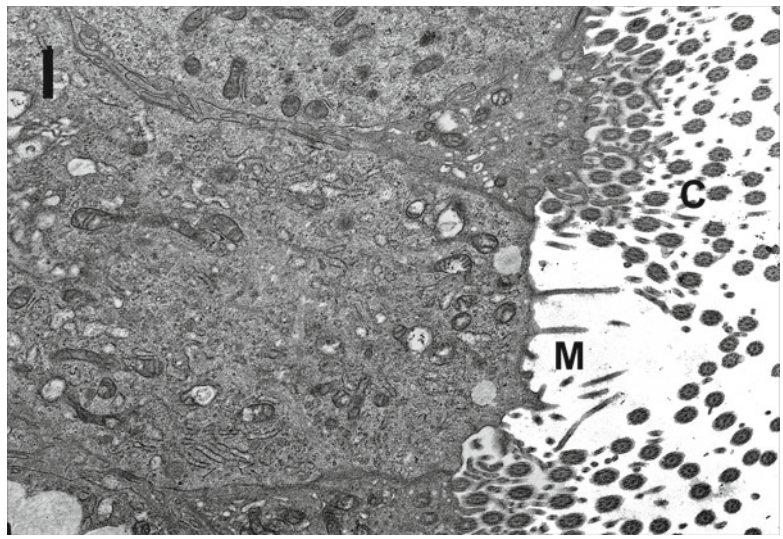

Fig. 31.14 Electron micrograph (TEM) of ciliated columnar cells, the predominant cell type on the surface, resting on the basement membrane and projecting both cilia (*C*) and microvilli (*M*) from their apical surface (scale bar: 1 µm) (Araldite block, stain: uranyl acetate/lead citrate). The specimen was obtained from a fresh frozen cadaver at a microscopic anatomy lab at Hacettepe University, Faculty of Medicine, Department of Anatomy. *TEM* transmission electron microscopy

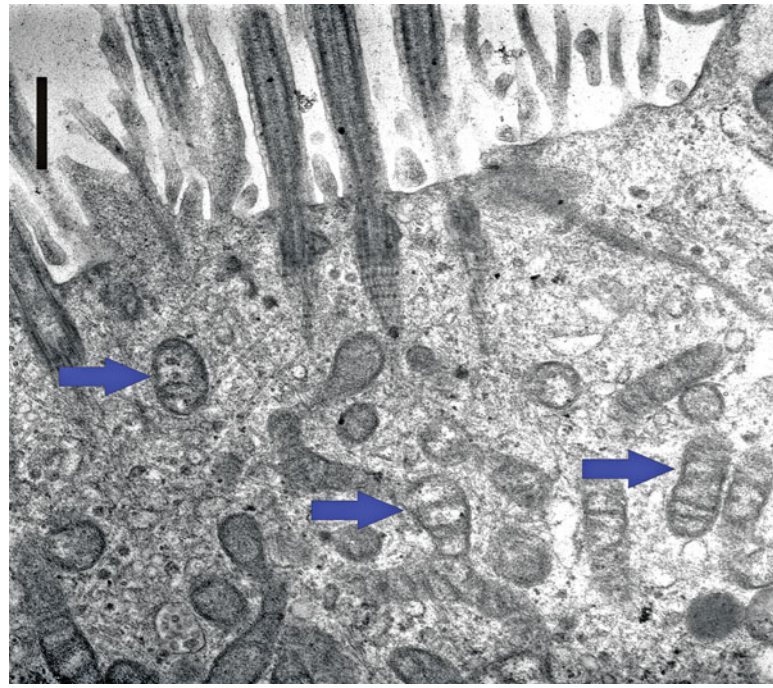

Fig. 31.15 Electron micrograph (TEM) of the apical cytoplasm of columnar cells with numerous mitochondria (*arrows*) (scale bar: 500 nm) (Araldite block, stain: uranyl acetate/lead citrate). The specimen was obtained from a fresh frozen cadaver at microscopic anatomy lab at Hacettepe University, Faculty of Medicine, Department of Anatomy. *TEM* transmission electron microscopy

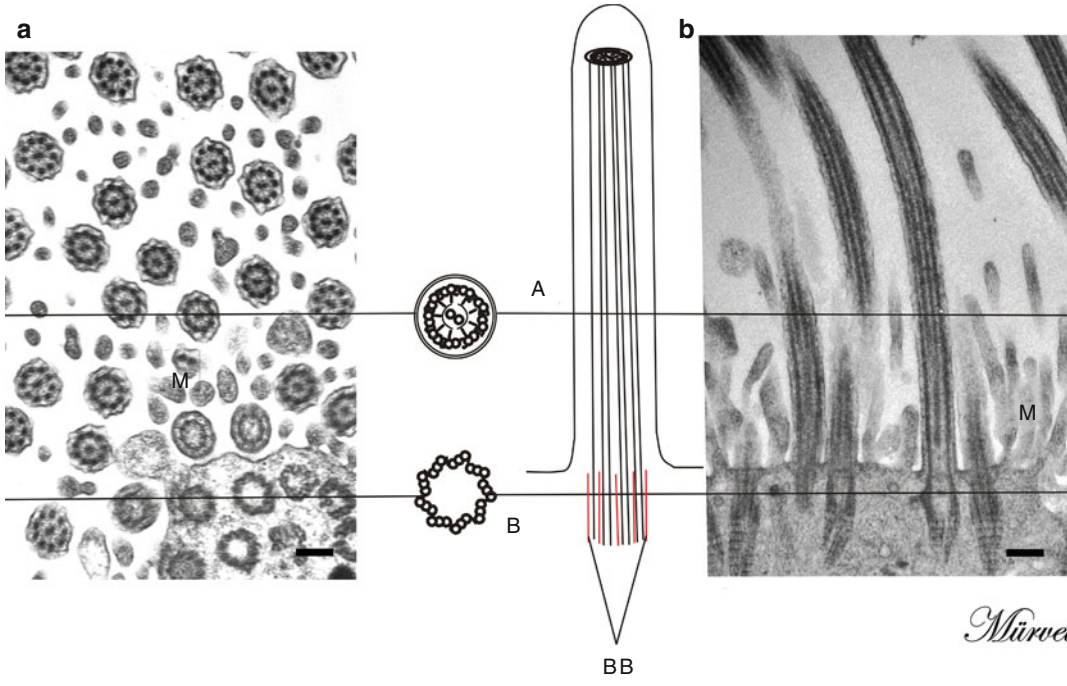

Fig. 31.16 Diagram showing the basic structure of cilia and electron micrographs of the cross (**a**) and longitudinal (**b**) sections of the cilia (scale bar: 200 nm). *Line A* and *line B* indicate cross-section levels of the cilia, indicating the cilia and the basal body, respectively. *M* microvilli

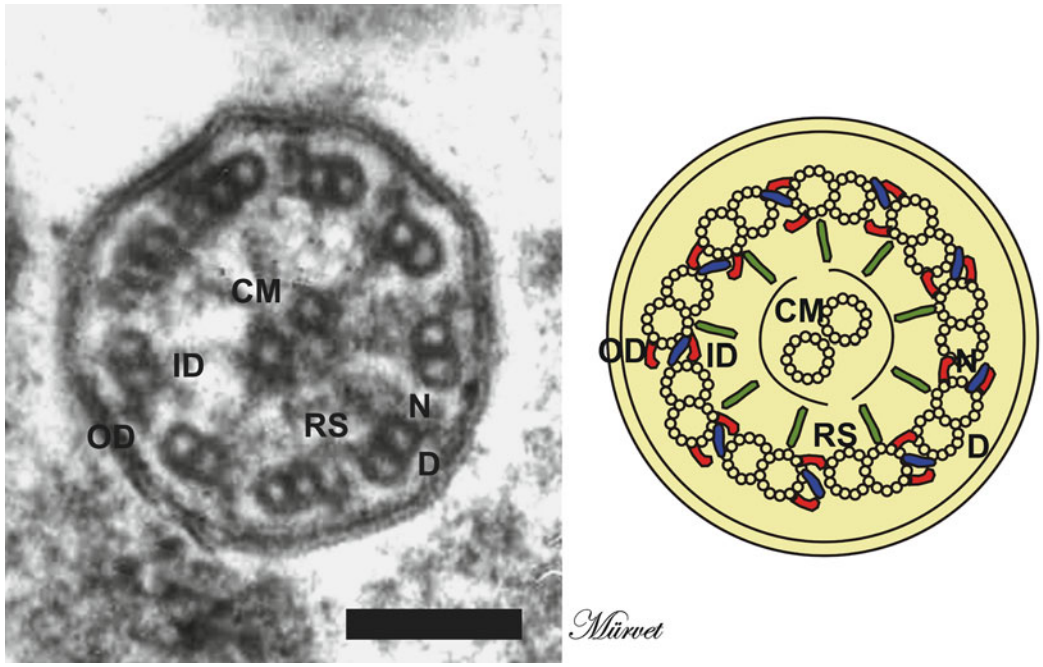

Fig. 31.17 Cross section of the cilia showing the organization of the axoneme (scale bar: 100 nm), microtubule pairs (doublet) (*D*), inner doublet (*ID*), outer dynein (*OD*) arms (comprising ciliary dynein), and an elastic substance called nexin (*N*). The two central microtubules (*CM*) are separate; however, they are partially enclosed by a central sheath projection. Radial spokes (*RS*) extend from each of the nine doublets toward the two central microtubules

microtubules of the ciliary axoneme is continuous with two of the triplet microtubules of the basal body. When examining a cross section at high resolution, each outer microtubule pair (*doublet*) can be seen to be regularly arranged *dynein arms* (*ciliary dynein*). Dynein is a microtubule-associated motor protein. Each microtubule pair is linked to adjacent pairs by an elastic substance called nexin. Although the two central microtubules are separate, they are partially enclosed by a central sheath projection. *Radial spokes* extend from each of the nine doublets toward the two central microtubules (Lane 2004; Ross and Pawlina 2011) (Fig. 31.17).

All columnar cells, ciliated and non-ciliated, are covered by *microvilli*, short and slender fingerlike cytoplasmic processes containing a core of actin filaments (Figs. 31.13 and 31.18). They are uniformly distributed over the entire apical surface and increase the surface area of the epithelial cells, thus promoting exchange processes across the epithelium (Ross and Pawlina 2011). The microvilli also prevent drying of the surface by retaining moisture that is essential for ciliary function (Mygind and Dahl 1998).

Another characteristic cell type of the airway epithelium is the goblet cell (Fig. 31.19). The moistening and protecting of the nasal mucosa by secretion is mainly provided by mucous and seromucous glands. However, goblet cells also contribute to nasal secretion. The release mechanisms from goblet cells are not controlled by parasympathetic nervous system. It is considered to be in response to physical and chemical irritants, but the mediators have not yet been clearly identified. The surface epithelial cells are joined by tight junctions, but ultrastructural studies have shown discontinuity of tight junctions around filled goblet cells (Mygind and Dahl 1998).

Basal cells are stem cells from which the other cell types arise. They lie on the basement membrane and do not reach the lumen (Fig. 31.12).

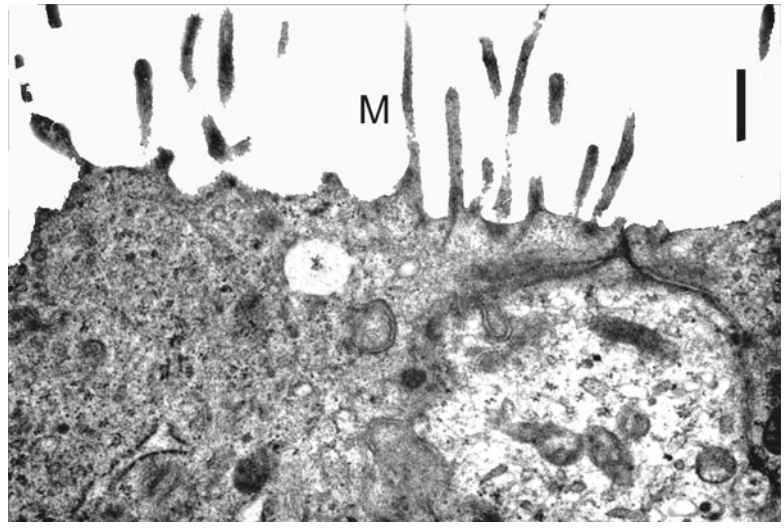

Fig. 31.18 Electron micrograph of a non-ciliated cell of the respiratory epithelium (TEM) (scale bar: 500 nm). *TEM* transmission electron microscopy, *M* microvillus

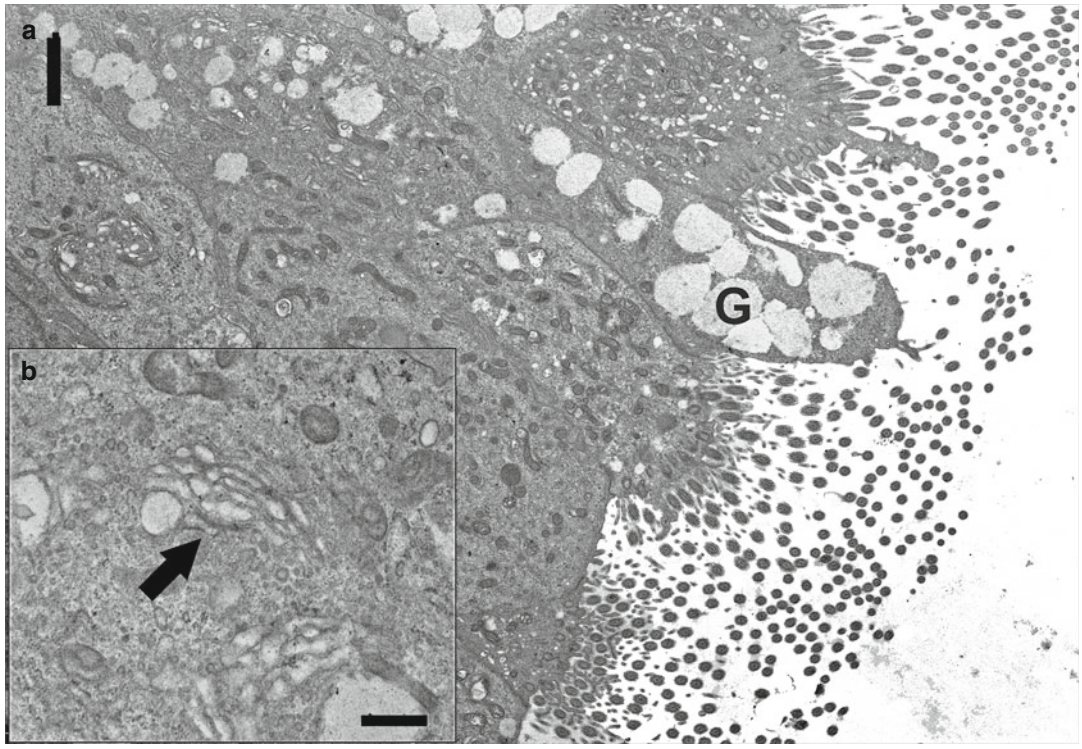

Fig. 31.19 (**a**) Electron micrograph of the respiratory epithelium (TEM) (scale bar: 2**µ**m). Characteristic secretory cell called a goblet cell (*G*) and (**b**) Golgi complex (*arrow*) (scale bar: 500 nm) (Araldite block, stain: uranyl acetate/lead citrate). The specimen was obtained from a fresh frozen cadaver at a microscopic anatomy lab at Hacettepe University, Faculty of Medicine, Department of Anatomy. *TEM* transmission electron microscopy

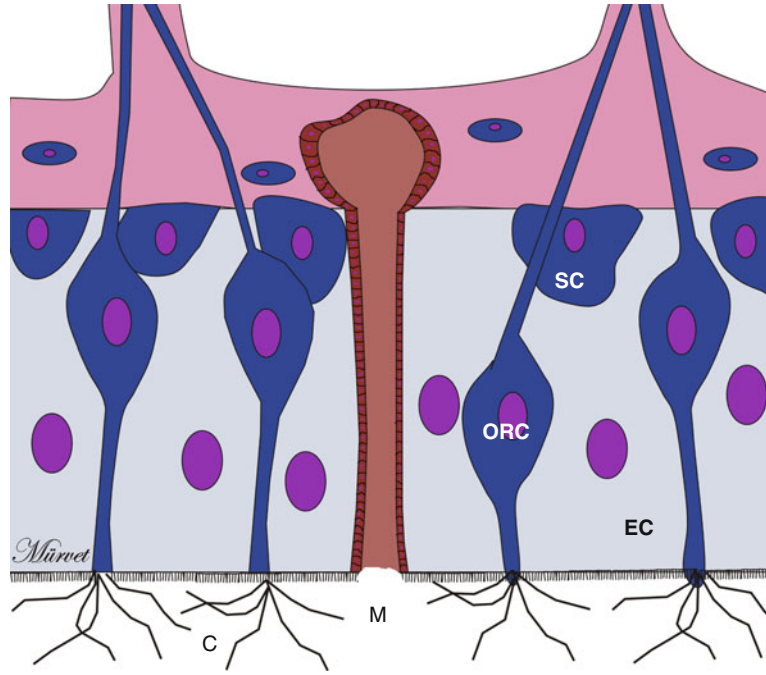

Fig. 31.20 Diagram of the olfactory epithelium. The olfactory receptor cells (*ORC*), which have specialized cilia (*C*), supporting cells (sustentacular cell) (*SC*), and epithelial columnar cells (brush cells) (*EC*) with large, blunt microvilli (*M*) on their apical surfaces

Small granule cells and cells that resemble basal cells contain secretory granules.

*Brush cell*s, a general name for those cells in the respiratory tract, bear short, blunt microvilli.

The *vomeronasal organ* of Jacobson (VNO) is the paired embryonic remnant that is situated under the lower anterior side of the nasal septum. It forms a tubular sac with a diameter of approximately 0.2–0.6 cm. Columnar epithelium with microvilli on their apical surface lines this tubular structure. In many vertebrates, the VNO is highly developed to establish intense olfactory sensibility (Sternberg 1997). Differences in the frequency of morphological patterns of the VNO between the sexes may be one of the factors leading to variations in pheromone perception between men and women (Meredith 2001; Baum 2012). Even with a large number of literature on the human VNO, there is little consensus of its persistence and functionality in humans. While their precise function is unknown, it is believed to be associated with pheromone recognition and food flavor perception (Bhatnagar and Smith 2001; Meredith 2001; Carvalho et al. 2008; Uraih and Maronpot 1990).

31.1.2.3 Olfactory Region of the Nasal Cavity

The olfactory region is located on the roof of the nasal cavity. Human olfaction is not as highly developed as it is in other animals. In humans, the olfactory region is formed by a modified pseudostratified epithelium occupying a small area. The olfactory epithelium is composed of *olfactory receptor cells*, *supporting* or *sustentacular cells*, basal cells, and brush cells. In contrast with the other regions of the nasal cavity, there are no goblet cells in this segment.

Olfactory receptor cells are bipolar neurons (Fig. 31.20) that are spindle-shaped neurosensory cells. At one end they have sensitive hairlike protrusions and nerve fibers at the other end. They have numerous microvilli and long slender cilia on their apical surface. Olfactory receptor cells have a single dendritic process-forming olfactory vesicle. The cilia have typical basal bodies and rise from the olfactory vesicle to the epithelial surface. The cilia are nonmotile or have limited motility. The basal pole of the olfactory receptor cell gives rise to unmyelinated axonal processes that leave the epithelial compartment. They are

grouped into bundles and pass through the cribriform plate of ethmoid bone to form the olfactory bulb of the brain. Mitochondria and smooth-surfaced endoplasmic reticula are abundant in their cytoplasm. They also possess lipofuscin granules, which causes the yellowish color of human mucosa. Adherens junctions are present between these cells and the olfactory cells, but gap and tight junctions are absent (Ross and Pawlina 2011).

Airborne chemicals diffuse across the mucous membrane and reach the cilia, leading to stimulation of the olfactory receptor neuron. Each olfactory receptor makes a specific kind of olfactory receptor protein. The receptors, when stimulated, activate signaling cascades that eventually generate action potentials.

The other cell type in this mucosa is the *supporting cell* (sustentacular cell). Their function is to provide both metabolic and physical support to the olfactory cells, similar to that of glial cells (Ross and Pawlina 2011; Mygind and Dahl 1998).

The olfactory epithelium also contains a limited number of brush cells. As previously noted, these cells are detected in the epithelium of the other regions responsible for air passage conduction. They are columnar cells that exhibit large, blunt microvilli at their apical surface, a feature from which their name is derived. The basal surface of the brush cell makes synaptic contact with nerve fibers that penetrate the basal lamina. The nerve fibers are the terminal branches of the trigeminal nerve (cranial nerve V) that functions in general sensation rather than olfaction. Brush cells appear to be involved in the transduction of general sensory stimulation of the mucosa (Mygind and Dahl 1998).

Basal cells are the progenitors of the other mature cell types. These are small rounded cells located close to the basal lamina. Their nuclei are frequently invaginated and lie at a level below those of the olfactory cell nuclei. The cytoplasm contains few organelles, a feature consistent with their role as a reserve or stem cell. They proliferate and differentiate into supporting cells.

The lamina propria of the olfactory mucosa is directly contiguous with the periosteum of the underlying bone. This connective tissue contains numerous blood and lymphatic vessels, unmyelinated olfactory nerves, myelinated nerves, and olfactory glands (*Bowman's glands*). The olfactory glands, a characteristic feature of the mucosa, are branched tubuloalveolar serous glands that secrete via ducts to the olfactory surface. Lipofuscin granules are prevalent in gland cells, and in combination with the lipofuscin granules in the supporting cells of the *olfactory epithelium*, they give the mucosa its natural yellow-brown color. In the lamina propria, short ducts composed of cuboidal cells lead away from the glands. As the ducts pass through the basal lamina into the olfactory epithelium, the ductal cells become squamous and are then difficult to discern under light microscopy (Mygind and Dahl 1998). The serous secretion of the olfactory glands serves as a trap and solvent for odoriferous substances. Constant flow from the glands rids the mucosa of remnants of detected odoriferous substances so that new scents can be continuously detected as they arise (Mygind and Dahl 1998).

31.1.3 Clinical Orientation of the Microscopic Anatomy of the Nose

Examination of samples with electron microscopy is particularly aimed to evaluate alterations and damages of the ultrastructural features of the nose. Many diseases related to nasal structures are the subject of the electron microscopic studies, including primary ciliary dyskinesia, allergic rhinopathy, and chronic inflammatory hyperplasia. Electron microscopy is also useful for the diagnosis in these cases. Ciliary impairment is the most common cause of obstructive nasal diseases. "Secretion" and "obstruction" are predominant clinical symptoms in rhinology affecting patients with disorders of the nose (Grevers and Kastenbauer 1996). The surface characteristics of the cells should be investigated under SEM in cases of ciliary dysfunction. TEM studies are useful for many of the other diagnoses. For many years, the cytological examination of nasal

secretions has been included among laboratory diagnostic tests and performed with various methodologies (blowing, washing, or scraping). However, the results obtained differ in terms of their reliability and information. Using electron microscopy, the study of nasal mucosa can be extended to the epithelial cytostructure with a detailed depiction of even the thinnest ultrastructural components (cytoplasm and organelles, cilia, and intercellular junctions) (Bozzo et al. 2005).

Conclusion

Electron microscopic investigation of the ultrastructural features of the nasal structures, especially nasal mucosal cells, provides important information for both clinical diagnosis and research. Nasal epithelial cells can be used as indicators when detailed investigation of the epithelium is needed, not only for nasal structures but also for the whole air pathway. Epithelial changes, inflammation, or other pathological conditions including mediator release and receptor expression can be observed. In addition to the biopsy materials, specimens can be established from minimally invasive nasal brushings (McDougal et al. 2008). Diagnosis for some undifferentiated neoplasms of nose and nasal sinuses should also be performed by electron microscopy. Ultrastructural histopathology of human olfactory dysfunction can also be used for classification and diagnosis of patients with olfactory disorders.

Both clinicians and researchers can take advantage of being aware of the benefits of electron microscopy and the ultrastructural features of the nose. This awareness offers new horizons for future research and more advanced diagnoses of patients.

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Genetic Background of the Rhinologic Diseases

32

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Keywords
Rhinologic diseases • Epigenetic • Allergic rhinitis • Cystic fibrosis • Vasomotor rhinitis • Nasal polyps

Core Messages

- It is expected that the prevalence of allergic rhinitis in the Western world will reach 50 % within the next 15 years.
- Exposure early in childhood to microbes and infections leads to modification of the immune system, a reduced risk of IgE sensitization and a decreased risk of AR throughout life.
- People who have persistent nonallergic rhinitis based on allergy skin test and serum-specific IgE test result might have a localized form of allergic rhinitis.
- Information on the genetics of allergic diseases is valuable not only for analyzing the molecular basis of allergic diseases but also for investigating new drugs.
- Environmental effects on various genetic variants as well as epigenetics determine the fate of chronic nasal diseases.
- CFTR genotype affects progression of airway obstruction in CF.
- The studies demonstrated a role of various modifier genes such as ADIPOR2, EDNRA, IFRD1, IL-8, MBL2, TCF7L2, MSRA, SERPINA1, and TGF-b1 in CF for pathologies of pulmonary function, liver disease, intestinal obstruction, diabetes, and infection.
- Alleles in the promoter (−509) and first exon (codon 10) of TGF-b1 are correlated with worse lung function.
- ΔF508 homozygosity was associated with clinical severity of paranasal sinus diseases and with the presence of polyps on endoscopy.

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32.1 Introduction

Rhinologic diseases are very commonly seen pathologies all over the world. They affect millions of people and cause huge social and economic burdens. In this chapter, the genetic origin of the main rhinologic diseases is discussed. These are allergic rhinitis, chronic sinusitis, vasomotor rhinitis, cystic fibrosis, and nasal polyps.

32.2 Architecture and Function of the Sinuses

The paranasal sinuses and turbinates are formed from the primordial ridge during fetal development. Each sinonasal structure develops from these ethmoturbinals separate from the inferior turbinate. Although there is a fairly consistent pattern to the formation of these structures, resulting in a series of oblique structures that attach to the ethmoid bulla, the extent and complexity of pneumatization can be variable. There is only the ethmoid sinus at birth, while the maxillary, frontal, and sphenoid sinuses are not fully formed and expand out from these primary structures into their relevant cranial bones during childhood and adolescence. Although the structure of the sinuses is well known, there are different opinions to explain the purpose and functions of the paranasal sinuses. Among these, lightening the weight burden of the cranium, adorning vocal resonance, or constituting a thermal insulation are the most common ideas. Also, a recent theory proposes that they form a "crumple zone" for the crucial structures of the head such as brain and eyes to diminish damaging forces resulting from sudden trauma (Kellman and Schmidt 2009).

It is shown that cranial sinuses produce nitric oxide. This molecule has many functions in the immune system such as killing microorganisms (bacteria, viruses, and fungi) and tumor cells. So the sinuses assist the innate immune defense of the airway. Proper functioning of the sinuses depends on sufficient drainage of their produced mucus and normal ventilation. In this regulation, mucociliary clearance is a highly coordinated effort that consists of millions of beating cilia to direct any mucus or particles toward the ostia of the sinus. This process is quite prone to obstruction during swelling or inflammation of the nasal mucosa. Therefore, it causes a decrease in ciliary beat frequency and results in poor drainage from the sinus ostia (Chen B et al. 2006). This situation leads to stagnation of sinus secretions and a decrease of oxygen level in the sinus, subsequently reducing mucociliary clearance and nitric oxide production.

32.3 Histopathologic Features of the Nasal and Sinus Mucosa

The nasal mucosa is composed of a ciliated pseudostratified columnar epithelium which includes ciliated and nonciliated columnar epithelial cells, goblet cells, and basal cells (National Institute 1979; Mygind and Jacobi 1997). These cell types lie on a basement membrane which includes types I, III, and IV collagen fibrils; but, generally some of these cells cannot reach the luminal surface and lead to the illusion of a stratified layer. Just beneath the basement membrane is a cell-free zone, which includes fibronectin and collagen types III and V and a submucosal layer consisting of glands, inflammatory and interstitial cells, extracellular matrix, nerves, and blood vessels. There are three types of glands within this layer: mucous, seromucous, and serous glands. These glands, throughout epithelial goblet cells, synthesize the mucus that overlies the epithelium and serve an antimicrobial function. Furthermore, they transport particulate matter, antigens, and bacteria by mucociliary clearance. Serous glands synthesize secretory IgA, which is essential in mucosal defense (White and Kaliner 1992). The submucosal gland area constitutes almost 25 % of the lamina propria, while this ratio is only 15 % in individuals without nasal allergies. Normally, lymphocytes, macrophages, and mast cells are the basic cells in the nasal mucosa, and nasal mast cells are usually found immediately beneath the basement membrane.

32.4 Allergic Rhinitis and Its Genetic Background

32.4.1 Introduction

Allergic rhinitis (AR) is a growing health and social problem worldwide and the most common type of chronic rhinitis. Lots of children become symptomatic and are diagnosed before 6 years of age. Recent data indicate that 10–30 % of adults and up to 40 % of children in developed countries suffer from this disease. The prevalence of AR has increased considerably after 1950 in Western populations. Moreover it is thought that within the next 15 years, the prevalence of allergic rhinitis in the Western world will reach 50 %. Almost 80 % of all patients with AR have symptoms before 20 years of age. In some patient, symptoms of AR can be detected before 2 years of age (Wright et al. 1994). Current data suggest that 44–87 % of patients with rhinitis might have mixed rhinitis, both of allergic and nonallergic types (Settipane and Charnock 2007).

Environmental and lifestyle factors are important in this prevalence increase. Because it is hard to consider changes in genetic composition of a population in a short time, one of the most powerful hypotheses to elucidate this prevalence increase is the hygiene hypothesis. It suggests that exposure early in childhood to microbes and infections leads to altered immune system, a reduced risk of IgE sensitization and a decreased risk of AR throughout life. AR is a debilitating disease on individual and social levels, and it has a major negative impact on morbidity, lost working days, high cost for medical treatment, and reduced school performance. Allergic rhinitis occurs when inhaled allergens interact with IgE antibodies on cells in the airway. AR can sometimes be a restricted disease without systemic response of IgE sensitization, like an increase in serum-specific IgE levels or a positive allergen skin test result. Patients with AR may initially present symptoms like nonallergic rhinitis. These patients may have nasal symptoms for longer than 2 years but negative skin test result and absence of serum-specific IgE response to allergic disease's nasal markers. On the other hand, some of patients with persistent nonallergic rhinitis may have increased eosinophil number, increased specific and total IgE levels, as well as increased T cell counts in their nasal lavage sample compared with healthy control subjects. These findings must alert us that people who have persistent nonallergic rhinitis based on allergy skin test and serum-specific IgE test result might have a localized form of allergic rhinitis (Saltoun and Avila 2008). In these cases examination of nasal mucosa and nasal challenge tests may help to identify these patients.

32.4.2 Allergic Rhinitis and Asthma

It must be emphasized that AR should be evaluated as a global systemic disease. Allergic inflammation does not necessarily limit itself to the nasal airway, but the attending physician must also be aware of the possible comorbidities of AR, including asthma, conjunctivitis, sinusitis, and otitis media (van Cauwenberge et al. 2006). Allergic asthma and rhinitis are comorbid conditions that are associated pathophysiologically and epidemiologically (Bousquet et al. 2008; Wallace et al. 2008). Epidemiological studies have shown that up to 80 % of patients with asthma demonstrate symptoms of rhinitis, while approximately 20–40 % of patients with AR have clinical asthma. Both are airway diseases in which IgE antibody sensitization to aeroallergens is a prominent feature. The link between asthma and rhinitis in particular has gained much interest. There is evidence that systemic trafficking of inflammatory cells from local inflammation in one portion of the respiratory tract can induce inflammatory changes in the other; segmental bronchial allergen challenge in patients with AR has been shown to result in both bronchial and nasal inflammatory responses (Wallace et al. 2008). There is growing evidence that rhinitis is a risk factor for the development of asthma, independent of atopy. Additionally, the airway mucosa of nose and bronchi has many similarities, and the clinical and pathophysiological changes in asthma and AR are often very comparable. Although

there are still some differences that should be highlighted, the strong relationship between rhinitis and asthma has introduced the concept of "the united airway disease."

32.4.3 Allergic Rhinitis and Genetics

On the basis of genetic studies, multiple groups have tried to identify a susceptibility gene for allergy using the candidate gene approach and/or genome-wide screening. Each of these two approaches suggested genetic heterogeneity of allergic diseases. Candidate genes identified so far are associated with various diseases in different ethnic groups and their function is being investigated. Based on the information accumulated thus far and the information on the human genome sequence, future advances in research on genetic factors for allergic diseases will likely lead to the establishment of more effective prophylaxis and therapy for these diseases.

There is now overwhelming support for a genetic component to allergic diseases. Information on the genetics of allergic diseases is valuable not only for analyzing the molecular basis of allergic diseases but also for investigating new drugs (Toda and Ono 2002).

Recent rapid improvements in the field of genetics have disclosed several pathways that are crucial for AR pathogenesis and perhaps more importantly have shown that AR behaves like typical complex diseases. That is, conditions in which various genetic variants that are individually mild may be capable of major phenotypic effects when acting in concert within a certain environmental context. Researches in genetics of AR have made much progress over the last decade and are expected to advance even further in the near future, as increasingly powerful analytical tools are being developed to unlock the complexities of genetic diseases. However, some formidable challenges still remain for AR geneticists: i.e., the identification of all the genes involved in the disease, the mechanisms underlying the phenotypic heterogeneity of AR, the difficulties in replicating associations between genotype and phenotype across populations, and last, but not least, understanding how environmental and developmental factors interact with genetic determinants to affect disease susceptibility (Vercelli 2008).

A significant association of IL-13 arg130-to-gln (R130Q) SNP (147683.0002) with serum total IgE levels in Chinese adult patients with allergic rhinitis was found (Wang et al. 2003). They determined that the patients with a gln/gln genotype showed much higher serum total IgE levels as compared with an arg/arg genotype.

In a Korean population composed of 295 patients with allergic rhinitis and 418 controls, Li et al. (2006) determined a significant association between allergic rhinitis and 3 SNPs of the FOXJ1 gene:-460C-T (rs880213), 1805G-T (rs1868823), and 3375G-C (rs3192453). Haplotype analysis disclosed that the main haplotype, CGG of the 3 SNPs, respectively, was significantly associated with allergic rhinitis ($P = 0.000018$). There was no association between the SNPs and serum IgE levels. Based on these data, it was suggested that dysregulation of FOXJ1 may influence T cell activity.

Haagerup et al. (2001) performed a genome-wide scan to identify susceptibility genes for allergic rhinitis in affected sib-pair families. From 100 Danish nuclear families selected for allergy, families having at least two full sibs with clinical allergic rhinitis and enhanced specific IgE against at least 1 of the 11 tested allergens were chosen. A total of 33 sib-pair families were qualified for the genome-wide scan that was undertaken using 446 microsatellite markers. The collected data were analyzed by nonparametric multipoint linkage analysis using the maximum likelihood score (MLS) approach. One major candidate region on chromosome 4q24-q27 (lod score of 2.83) was revealed. There is evidence of linkage between allergic rhinitis and the region spanning from the marker D4S1651 to D4S2394, which is approximately 13 cm and which potentially harbors a specific susceptibility gene. Another eight regions including 2q12-q33, 3q13, 4p15-q12, 5q13-q15, 6p24-p23, 12p13, 22q13, and Xp21 showed evidence of linkage detected by lod scores in the range of 1.04–1.63.

Among these eight regions, two regions were in line with previous findings associating chromosome 2q33 and 6p23 with asthma and asthma-associated phenotypes.

Fine mapping in three independent Danish samples was performed by Brasch-Andersen et al. (2006), consisting of a total of 236 sib-pair families with clinical allergy, including the 33 sib-pair families with allergic rhinitis originally studied by Haagerup et al. (2001). Analysis of 28 microsatellite markers on chromosome 3q displayed significant linkage to 3q13.31 for rhinitis (MLS = 5.55, identity by descent, or IBD = 63.9 %) and for atopy (MLS = 3.71, IBD = 61.7 %). An MLS of 5.1 (IBD = 67.3 %) was obtained when sib pairs with both rhinitis and atopy were analyzed.

32.4.4 Molecular Targets for AR Therapy

The worldwide efforts to discover susceptibility genes in allergic diseases are motivated by the conviction that the identification of disease genes may facilitate the design of new classes of anti-inflammatory compounds. Molecules concerned with the allergic reaction, such as cytokines, chemokines, their receptors, major histocompatibility complex molecules, and transcription factors, could provide a candidate drug target. Current medications for AR such as antihistamines and leukotriene receptor antagonists are aimed at symptom relief and block the production of proinflammatory cytokines to suppress allergic inflammation. However, SYK (*s*pleen tyrosine *k*inase) inhibitors can block the allergen-induced release of all mast cell mediators like eicosanoids and cytokines. Therefore, SYK kinase is a desirable therapeutic target for acute and chronic allergic inflammation. SYK kinase inhibitors are now entering clinical trials. A series of 2,4-diaminopyrimidine compounds were developed as SYK kinase inhibitors using cell-based structure–activity relationships with primary human mast cells. One of these compounds, referred to as R112, was suitable for intranasal delivery and was tested for safety and efficacy in allergic rhinitis patients. In a park environment, R112 showed remarkable relief of acute allergic rhinitis symptoms with rapid onset of action. These results indicate the clinical significance of inhibiting SYK kinase in allergic upper airway disorders (Masuda and Schmitz 2008). Figure 32.1 shows the SYK kinase pathway and its relation with FcεR.

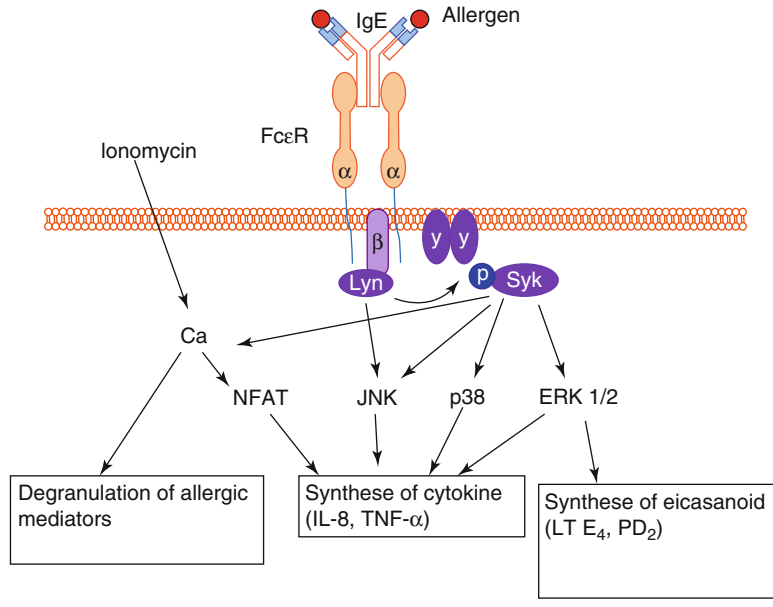

Fig. 32.1 Allergens bind FcεRI and trigger Syk-mediated signaling pathway resulting in mast cell degranulation, eicosanoid mediator synthesis, and cytokine production. Ionomycin, a calcium mobilization agent, can also induce degranulation of mast cells

Ramasamy et al. reported association of three loci for either AR or grass sensitization through evaluation of genome-wide meta-analysis of genetic variants. The HLA variant rs7775228, which cis-regulates HLA-DRB4, was strongly associated with grass sensitization and weakly with AR. Variants in a locus near chromosome 11 open reading frame 30 (C11orf30) and leucine-rich repeat containing 32 (LRRC32), which was previously associated with atopic dermatitis and eczema, were also strongly associated with both phenotypes (rs2155219). The third genome-wide significant variant was rs17513503, which is located near transmembrane protein 232 (TMEM232) and solute carrier family 25, member 46 (SLC25A46). They also observed strong associations of both AR and IgE sensitization to grass with a common (minor allele frequency, 47 %) polymorphism in the 11q13.5 locus (Ramasamy et al. 2011).

Lu et al. (2011) found that the CT/CC genotypes in IL-4 C-590T were associated with a significantly decreased risk of mite-sensitized PER (adjusted odds ratio (OR) = 0.64, 95 % confidence interval (CI) 0.45–0.92), compared to the TT genotype. Moreover, persistent allergic rhinitis (PER) patients with CT/CC genotypes had significantly lower serum levels of total IgE than those with TT genotype ($P = 0.001$). However, there was no significant association of the IL-13 and IL-4RA polymorphisms with mite-sensitized PER ($P = 0.05$).

Kruse et al. (2012) reported genome-wide significant linkage to a novel AR locus at 1p13 and suggestive linkage to two novel regions at 1q31-q32 and 20p12. The locus has previously been demonstrated to have suggestive linkage with asthma (Denham). Possible candidate genes are the glutathione S-transferase M1 (GSTM1) (Ober and Hoffjan 2006) and acidic mammalian chitinase (CHIA) genes located at 1p12-p13, earlier shown to be associated with asthma (Bierbaum et al. 2005). Chromosome 20p12 is also a novel finding in regard to AR. However, it has previously been found to have linkage with atopy as well as asthma (Denham et al. 2008).

Several studies have found an association of filaggrin (FLG), a filament-associated protein that binds to keratin fibers in epithelial cells with various allergic conditions and diseases including atopy as well as atopic dermatitis (AD), asthma, and AR (Rodriguez et al. 2008).

At 2q13-q14, the interleukin 1 gene cluster (IL-1A, IL-1B, and IL-1RN) previously associated with AR (Joki-Erkkila et al. 2003).

At 20p13, a disintegrin and metalloproteinase domain 33 (ADAM33) gene residing almost 3 Mb from the maximum linkage signal has previously been associated with AR. Toll-like receptors 7 and 8 (TLR7 and TLR8) located at Xp22 confer susceptibility to several allergic diseases and among these are AR (Kruse et al. 2012).

Yousri et al. (Hussein et al. 2012) showed that the genotype and allele frequencies of the TLR2 Arg753Gln and TLR4 Asp299Gly polymorphisms are not significantly different between asthmatic children or allergic rhinitis as compared to controls ($P > 0.05$ for each) or even when compared further with IgE level. However, it is shown that the mutant allele of TLR2 or TLR4 polymorphisms was significantly associated with the moderate to severe groups compared to the mild group in both atopic asthmatics and allergic rhinitis group ($P > 0.001$ for each). In conclusion, their study demonstrated a lack of association of TLR2 and TLR4 polymorphisms with asthma and allergic rhinitis but suggests significant association between these genetic variants and the disease severity.

32.4.5 Allergic Rhinitis and Epigenetics

The immune system is heavily affected by environmental changes. One of the good and current examples of this situation is the remarkable increase of all immune diseases with urbanization. Likewise, rising prevalence of immune diseases in infancy indicate that there may be an essential early period of sensitivity. During fetal life, essential arrangements occur such as structure, function, and response patterns of many systems. So, elucidating early events may offer important insights into the pathogenesis of the disease, as well as the pathways of environmental influence.

A variety of environmental exposures in pregnancy such as maternal diet (Prescott and Saffery 2011), pollutants like cigarette smoke (Noakes et al. 2003), and microbial exposure (Prescott et al. 2008) have been shown to alter immune function. Conspicuously, the same determinants were identified as potential immune modifiers in epidemiological studies of allergic disease.

The effects of diet are potentially complex. More studies are needed to examine the effects of related dietary nutrients such as vitamins B2, B6, and B12, methionine, and choline, which may be implicated in epigenetic effects through their effects on folate-mediated one-carbon metabolism.

Belinsky et al. also showed that exposure to the ultrafine particulate matter found in pollution may also change DNA methylation in maternal and fetal DNA and may be associated with altered inflammatory response pathways.

There is current exciting evidence that some pathogens can affect the epigenetic profile of the host cell, influencing or mimicking mechanisms that participate in DNA methylation and histone modification (Arbibe et al. 2007). The studies also showed that allergy protection by in utero microbial exposure in rural farming environments is correlated with enhanced neonatal Treg (regulatory–suppressor T cells; these cells downregulate the immune system, thus keeping tolerance to self-antigens) function, FOXP3 expression, and associated epigenetic effects (hypomethylation) of the FOXP3 gene (Schaub et al. 2009).

Several specific nutritional changes have been correlated with the rising allergic propensity, including a decrease in omega-3 polyunsaturated fatty acids (n-3PUFA), soluble fiber, antioxidants, and other vitamins (Devereux et al. 2007), based on epidemiological associations and immunological effects. Similarly, antioxidants have been shown to have effects on T cell regulation and induction of IL-12 production by antigen-presenting cells (Utsugi et al. 2003). So, this could induce development of Th1 and repress Th2 responses. Devereux et al. showed an immunomodulatory role for maternal dietary antioxidants during pregnancy; this, combined with evidence that oxidative stressors can trigger epigenetic changes and alter disease risk (see below), indirectly suggests a role for these pathways (Breton et al. 2009).

A recent study in mice also showed that exposure to diesel exhaust particles augments the production of IgE after allergen sensitization through the hypermethylation of IFNγ and hypomethylation of the IL-4 locus (Liu et al. 2008). In placental tissue, nicotine has also been shown to alter cytokine production via NFκB (Dowling et al. 2007).

The current and remarkable rise in allergic diseases and the very early onset of disease indicate that in utero events have a more essential effect on immune development and allergic susceptibility than genomic inheritance. Above all, as epigenetic modifications are commonly reversible, this may provide for the development of novel therapeutic compounds that may be efficacious in arresting or even reversing the allergy epidemic (Prescott and Saffery 2011).

A recent large gene expression microarray study of unstimulated CD4+ T cells found no differences between allergic and nonallergic individuals (Hansel et al. 2008).

The existence of monozygotic (MZ) twins who are discordant for intermittent allergic rhinitis (IAR) suggests disease mechanisms that are independent of genetics (Bell and Spector 2011). Sjogren et al. for the first time performed mRNA and microRNA expression microarray analyses of CD4+ T cells from MZ twins discordant for IAR. They analyzed the CD4+ T cells outside the pollen season, after in vitro allergen challenge and during the pollen season without in vitro allergen challenge. The allergen challenge in vitro resulted in significant differences in mRNA and protein levels between the allergic and healthy twins. The cytokines IL-4, IL-5, and IL-13 were increased in the supernatants from allergic twins. In their study, they performed microRNA expression arrays of all the twin pairs, but found no significant differences. Next, blood samples were taken during pollen season from four MZ twin pairs discordant for IAR (Sjogren). Consequently they identified disease-relevant mRNAs and proteins that differed between the

discordant MZ twins. No differences in microRNA expression were determined. Because the MZ twins are almost genetically identical, the observed altered expression of essential disease-associated genes and proteins may have epigenetic causes (Sjogren et al. 2012).

In conclusion, the role of genetic as well as epigenetic factors in the pathophysiology of nasal diseases, including allergic rhinitis, is becoming more evident. Environmental effects on genetic variants and epigenetics determine the fate of chronic nasal diseases. Clarification of such relationships and mechanisms will lead to novel molecular diagnostic and therapeutic approaches for these kinds of diseases.

32.5 Role of Genetics in Chronic Rhinosinusitis

32.5.1 Introduction

The first contact of the respiratory system with the external environment occurs in the nose, which is responsible for air filtering, humidification, and temperature regulation. Because of this close contact of the respiratory mucosa with a great variety of allergens and pathogens, upper respiratory illnesses are one of the most frequent diseases in humans. Chronic rhinosinusitis (CRS) is characterized by a chronic inflammatory condition of the sinonasal mucosa, but it is mostly defined by its clinical manifestation rather than inflammation pattern. CRS presents with chronic symptoms such as nasal congestion, anterior or posterior nasal drainage, hyposmia, and facial pain (Tomassen et al. 2011). It is highly prevalent. According to an analysis of the 2008 National Health Interview Survey data, almost 1 in 7 adults suffered from rhinosinusitis (Pleis et al. 2009). Additionally, it has a huge effect on quality of life and health-care expense in terms of antibiotic prescriptions filled, lost work days, and lost school days (Bhattacharyya 2009). The disease is characterized by chronic inflammation of the sinonasal mucosa, and because inflammation of the nasal and sinus mucosa often coincides, it is named "rhinosinusitis" in current literature. It is an attempt to stress the concept that patients present with symptoms attributable not only to the sinuses but also to nasal inflammation that might often, but not always, be present.

The term chronic refers to symptoms persisting for more than 12 weeks with no definitive resolution. Also, the most recent consensus definitions subclassify CRS into CRS without nasal polyposis (CRSsNP), CRS with nasal polyposis (CRSwNP), and allergic fungal rhinosinusitis (AFRS) (Hamilos 2011). A study showed that the inflammatory mediator profile in the nasal mucosa of patients with CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP) is similar. It further strengthens the idea that rhinitis and sinusitis can indeed be classified as one disorder entity and supports the use of the term rhinosinusitis. Although primary allergic or upper respiratory tract infectious inflammation in the nose can cause sinus ostia obstruction and subsequent sinusitis, it remains unproved from prospective studies whether and how often this occurs.

Historically, chronic sinusitis has been considered a single unimodal clinical disease. But in recent years chronic sinusitis has been recognized as comprising several diseases with different causes, with each one characterized by a definite histological pattern and gene and protein expression. Identification of specific disease subgroups and their etiologies is important for correct differential diagnosis and to apply appropriate therapeutic intervention.

32.5.2 Chronic Sinusitis (CS)

For diagnosis of CS, it is important to see symptoms of nasal irritation, anterior and posterior rhinorrhea, and nasal congestion with the accompanying presence of pressure or pain in a "sinus" distribution area that last for more than 12 weeks (Slavin et al. 2005). But validation with nasal endoscopy or computed tomography (CT) imaging is important because there can be significant overlapping of these symptoms that are very likely to be of migraine or midfacial pain syndrome origin (Perry et al. 2004).

Chronic sinusitis has been divided into two subgroups depending on presence or absence of NPs (Slavin et al. 2005). Some researchers determined a significant correlation between nasal polyposis and the presence of tissue eosinophilia. However, both the presence and degree of eosinophilia in NPs can be quite variable, and researchers did not observe eosinophilia in a large patient group with idiopathic nasal polyposis (Bachert et al. 2001). These results support the opinion that certain forms of CS such as allergic fungal sinusitis (AFS) (Schubert and Goetz 1998) and aspirin-exacerbated respiratory disease (AERD) (Mascia et al. 2005) may be more likely to produce NPs and present rich eosinophilic infiltrate into the sinus cavity. Polyposis can present as a complication in any form of CS. So it should not be used as the basis for diagnosis or decisions regarding treatment. Evaluation of the presence or absence of NPs can be especially important in clinical practice for identifying patients who are more or less likely to have eosinophilic disease and thereby also identifying patients who are more or less likely to respond to eosinophil-targeted medicines. However, it should be emphasized that, in practice, CS presents as a spectrum of disorders in which the level of eosinophilia and predilection for polyposis exist on a continuum. Although we will stress the different features of the pathology of eosinophilic and noneosinophilic forms of these diseases, in daily life patients can generally present with variable overlapping symptoms.

32.5.3 Remodeling Theories

When we look at the histological investigation of CRS, two different remodeling types are seen. One of them is CRSsNP, which is associated with fibrosis, basement membrane thickening, subepithelial edema, goblet cell hyperplasia, and mononuclear cell infiltration. The other is CRSwNP, which is associated with an edematous stroma with albumin deposition, pseudocyst formation, and subepithelial and perivascular inflammatory cell infiltration.

Table 32.1 ARIA classification of allergic rhinitis

ARIA classification for allergic rhinitis	
"*Intermittent*" *rhinitis*	"*Persistent*" *rhinitis*
Symptoms are present:	Symptoms are present:
≤4 days a week	≥4 days a week
or ≤4 consecutive weeks	and ≥4 consecutive weeks
"*Mild rhinitis*"	"*Moderate/severe*" *rhinitis*
None of following items are present:	≥1 of following items are present:
Sleep disturbance impairment of daily activities, leisure, and/or sport impairment of work or school work, troublesome symptoms	Sleep disturbance impairment of daily activities, leisure, and/or sport impairment of work or school work, troublesome symptoms

Adapted from Bousquet et al. (2001)

Remodeling is a dynamic balance between production and degradation of extracellular matrix (ECM) and is regulated by various factors among which TGF-b has a central role. The Treg cells are one of the most important factors in the remodeling process. TGF-b is also an essential factor in the remodeling process in the airways. It is responsible for attraction and induction of proliferation of fibroblasts, and it also causes upregulation of ECM synthesis. A recent study showed that TGF-b1 and 2 protein concentrations, TGF-b receptor I and III mRNA expression, and the numbers of activated pSmad 2-positive cells were significantly lower in patients with CRSwNP than control subjects. However, in patients with CRSsNP, TGF-b1 protein concentration, TGF-b receptor II and III mRNA expression, and the number of activated pSmad 2-positive cells were significantly higher than control subjects (Van Bruaene et al. 2009). Indeed, the upregulation of the TGF-b signaling pathway in patients with CRSsNP causes excessive collagen deposition associated with fibrosis, while its downregulation at the protein level in patients with CRSwNP causes edema formation and a lack of collagen production (Table 32.1).

Past investigations have focused on inflammatory differences, but recent information from studies comparing patients with CRSsNP and patients with CRSwNP showed that TGF-b proteins and their signaling might be suitable markers to distinguish between the different CRS subtypes.

32.5.4 Chronic Infectious Sinusitis

There is a significant loss of barrier and innate immune functions in all types of CS, making these patients highly prone to frequent and long-standing episodes of acute sinusitis. As a consequence, all forms of CS generally copresent with anaerobic bacteria, gram-negative organisms, *Staphylococcus aureus*, and other bacterial colonization in the sinuses. However, chronic infection (i.e., an episode of acute sinusitis persisting beyond 12 weeks despite antibacterial therapy) is less often the cause of CS, and, when present, the clinician should consider whether there is an underlying immune deficiency, HIV infection, immotile cilia syndrome, or cystic fibrosis. At the present time, investigation into the presence of allergic atopy or anatomic abnormalities is recommended for patients with CS because these factors might have a causative or modifying role on disease. The exact significance of these factors with relation to sinus inflammation is unknown, but their impairment might cause a decreased level of patient improvement (Rosenfeld et al. 2007; Table 32.2).

Table 32.2 Clinical manifestation of chronic sinusitis

1. Infectious	Idiopathic Associated with immune deficiency
2. Eosinophilic	AFS CHES AERD
3. Noneosinophilic	Idiopathic Induced by anatomic tendency Induced by Chronic rhinitis
4. Cystic fibrosis	

32.5.5 Noneosinophilic Sinusitis (NES)

Idiopathic noneosinophilic sinusitis (NES) is thought to result from chronic or recurrent blockage of the sinus ostia caused by anatomic predisposition like septal deviation viral rhinitis, allergic rhinitis, or other causes. As a consequence, these processes cause recurrent and prolonged bacterial infections, possibly in association with barotrauma of the sinus cavities and harm to the respiratory epithelium, ciliary destruction, prominent mucous gland, and goblet cell hyperplasia similar to bronchial epithelium in asthma disease, bacterial colonization, and biofilm formation (Payne et al. 2011). A mononuclear cell infiltrate with few neutrophils is observed in the inflammatory component of this form of sinusitis (19). If neutrophils are presented, it indicates recent infection, persistent infection, or CF. Prominent remodeling with dense deposition of collagen and other matrix proteins is characteristic for NES.

32.5.6 Molecular Basis of NES

Knowledge about the development of this disease is very limited, and as such, there are very few studies that have investigated whether there is a genetic component to NES. One study identified the plasminogen activator inhibitor 1 (PAI-1) gene as a possible candidate (de Alarcon et al. 2006). Subsequently, recent observations related to expression of PAI-1 and the thrombotic/fibrinolytic pathways further suggest a role for PAI-1 in CS (Shimizu et al. 2011). The 4G allele of PAI-1 is involved in the arrangement of fibrosis in asthmatic patients and especially in airway remodeling that leads to irreversible obstruction (Cho et al. 2001). In this study, overrepresentation of the 4G allele was observed in the NES group compared with the control group of subjects without sinus disease (0.53 vs. 0.45) (de Alarcon et al. 2006). In a recent study on subjects (excluding asthma, atopy, or aspirin intolerance and thus were more likely to have NES), it was found that patients with CS had an increased prevalence of a GG genotype at position 2,174 of the IL-6 promoter compared with a control group without sinus disease (odds ratio, 2.65) (Kosugi et al. 2009). There is an effect of IL-6 on the differentiation of naive CD4 T1 cells to TH17 lineage, so this result conforms with the finding of an increased TH17 signature in NE-NPs (Zhang et al. 2008).

IL-6 is also important for plasma cell differentiation, and this function also is consistent with the previously discussed role for humoral immunity in patients with NES.

32.5.7 Chronic Hyperplastic Eosinophilic Sinusitis (CHES)

CHES is an inflammatory disease. It is characterized by intensive eosinophil accumulation in sinuses and also rarely accompanied with NP tissue. NPs generally associate with CF, AFS, and AERD. The presence of nasal polyposis (especially in association with asthma) has been recognized as suspicion for CHES diagnosis. But if we want to clearly diagnose CHES, histochemical staining of tissue for eosinophils or thorough determination of eosinophil-derived mediators such as major basic protein or eosinophil cationic protein is needed. The sinus tissue in patients with CHES presents a pronounced increase in cells that cause differentiation, survival, and activation of eosinophils that synthesize chemokines (e.g., CCL5, CCL11, and CCL24), cytokines (e.g., IL-5 and GM-CSF), and proinflammatory lipid mediators (e.g., cysteinyl leukotrienes [CysLTs]) (Perez-Novo et al. 2005). In addition, eosinophils are recruited and subsequently provide the essential growth factors for their own activation, proliferation, and survival (Hamilos et al. 1998). Thus, in contrast to NES, CHES behaves as an everlasting syndrome. As a consequence, it frequently does not respond well to surgery alone (Lee et al. 2010). The exact cause of CHES is not well understood. Some patients with CHES show allergic sensitization as determined by skin prick test or IgE immunoassay results. Aeroallergens usually do not reach healthy sinus cavities. When this disease involves blockage of the sinus ostia, it is more difficult for aeroallergens to gain access to the sinus (Gwaltney et al. 2000). Although aeroallergens do not reach the sinuses, their contact with nasal passage exacerbates sinus inflammation in these patients. Furthermore such nasal challenges increase eosinophil influx into the sinuses (Baroody et al. 2008). Since there is no direct access to the sinuses, some studies suggest that local and/or systemic lymphatic recirculation of inflammatory cells (such as eosinophils, eosinophil precursors (Denburg and Keith 2008), dendritic cells, and TH lymphocytes) between the nasal epithelium, nasal/sinus lymphatics, bone marrow, and sinus tissue may cause this disorder. Some research suggests that allergic IgE sensitization toward commensal fungi and bacteria colonies within the sinuses might be another disease mechanism (Ponikau et al. 1999). CHES shares a lot of histological and immunologic features with asthma and frequently associates with asthma, suggesting that CHES and asthma might include a similar idiopathic immune process, as airways, respectively (Braunstahl et al. 2001).

32.5.8 Molecular Basis of CHES

The close relation between CHES and NP formation has been shown in more than 30 studies addressing a possible genetic linkage. Several genes from the inflammatory pathway were found to relate/correlate with CHES, thus indicating a role for dysregulation of cytokine production in the pathogenesis of CHES. A few studies have replicated the relation between IL-1a and CS, similar to the relation between IL-1a and NPs. They found a greater risk related with the G allele at position 14,858 in exon 5 of the gene (Endam et al. 2010). Several studies have also found that the 2308 G-to-A polymorphism in the TNF-a gene is associated with CS and NPs (Batikhan et al. 2010); however, other studies were unable to replicate these findings (Endam et al. 2010).

A study in patients with asthma reported that a C-to-T polymorphism at position 2,590 of the IL-4 promoter may be connected to increased risk of asthma (Park et al. 2006). Two cohort studies have also shown this polymorphism to be associated with the development of NPs (Park et al. 2006). IL-1ra, IL-1 receptor-like 1, IL-33, and matrix metalloproteinase 9 have been determined

as other relevant inflammatory genes. The MHC genetic region is very significant for the development of CHES. Various genes within this region have been especially associated with defects in antigen presentation as a cause for disease. A 2- to 5-fold increase in disease risk is associated with the HLA-DQA1* 0201 allele (Molnar-Gabor et al. 2000). Also, more than 12 other HLA alleles have been described in disease pathogenesis, but many of them have not been replicated in later studies.

32.5.9 Aspirin-Exacerbated Respiratory Disease (AERD)

AERD, also known as the Samter triad, is a condition characterized by NPs, asthma, and aspirin sensitivity (Samter and Beers 1968). Aspirin intolerance presents in 20 % of adult asthmatic patients. Incidence increases to 30 % if asthma is also associated with CS or nasal polyposis (Vally et al. 2002). The key features of this disorder are its association with severe and extensive pansinusitis and its propensity to develop de novo in adulthood. In patients who use aspirin regularly, if pansinusitis is present on CT scan examination, it may indicate aspirin sensitivity (Mascia et al. 2005). Nasal polyposis in AERD is aggressive with multiple polyps. Polypoid changes are characterized by rapid growth and frequent recurrence after surgery (Szczeklik and Sanak 2000). Despite the diffuse involvement of the sinuses with inflammatory tissue, the patient is asymptomatic, and compared with acute sinusitis or NES, patients seldom suffer from headaches or "sinus pressure." However, anosmia is one of the consistent complaints and perhaps causes the greatest morbidity.

32.5.10 Molecular Basis of AERD

Increased leukotriene synthesis is typical for AERD, so genes related to leukotriene synthesis or response have been the center of attraction for many researchers. LTC4S is the most important rate-limiting enzyme in leukotriene synthesis. Some studies have found an A-to-C base substitution at position 2,444 of the LTC4S promoter, which increases LTC4S expression (Sanak et al. 2000). Some researchers subsequently identified a relationship between this base change and AERD (Kawagishi et al. 2002), while others have not (Van Sambeek et al. 2000). Thus, the significance of this substitution is still unclear. 5-lipoxygenase is the first enzyme in the leukotriene synthesis pathway. There are multiple variants of the tandem repeat GGGCGG within the promoter of the 5-lipoxygenase gene and Sp1, (In et al. 1997). One study found an increased risk for the development of AERD related with this gene (odds ratio, 5.0) (Choi et al. 2004). Additionally, another study showed that this polymorphism gives rise to the severity of airway hyperresponsiveness in patients with AERD (Kim et al. 2005). There are also other proteins in the leukotriene pathway associated with AERD such as CysLT1 and CysLT2 receptors. Finally, a few studies have reported a relation between the histocompatibility locus and the development of AERD, but these studies have not yet been replicated.

32.5.11 Allergic Fungal Sinusitis (AFS)

Sometimes**,** mold living commensally in the sinuses can cause activation of innate immune pathways and synergistically evoke robust TH2 lymphocyte and eosinophilic inflammatory responses. Initially, AFS was only attributed to Aspergillus species, but it is now known that many fungi species can be associated with AFS, including Cladosporium, Alternaria, Penicillium, Curvularia, and Bipolaris (Robson et al. 1989). The key feature of AFS is specific IgE sensitization, which is demonstrated by skin prick tests or serum immunoassays and measurement of increased total serum IgE concentrations. AFS generally develops in young, immunocompetent, and atopic subjects (Schubert and Goetz 1998). AFS has some features that distinguish it from other forms of eosinophilic sinusitis, such as its often being unilateral and limited to one or a few

sinuses. Dense material fills and expands the sinuses and can typically be detected with CT scan (Mukherji et al. 1998). The mucous and inflammatory responses frequently occupy a space in the nasal cavity and lead to expansion into proximate tissue. This blocks the sinus ostia and subsequently causes bone absorption with resultant expansion into the orbits and cranium (Lydiatt et al. 1994).

32.5.12 Genetics of AFS

There is only one study that shows a genetic linkage with AFS. In a study of 74 subjects including 44 enrolled with AFS, a weakly significant association of disease was determined with the MHC class II allele HLA-DQB1*03 (Schubert et al. 2004), however, many subjects from the control group had at least one fungal species in the skin prick test.

32.6 Genetics of Cystic Fibrosis and Pathophysiology in Airways

32.6.1 Introduction

Cystic fibrosis (CF) is the most common lethal autosomal recessive genetic disorder, with a rate of approximately 1 in 2,500 live births among Caucasians. There are approximately 80,000 children and young adults with CF in the world. Genetic and nongenetic factors contributing to the disease and its variants have been widely investigated. Though the major gene responsible for the pathophysiology of CF is the cystic fibrosis transmembrane conductance regulator (CFTR) gene, recent research suggests that variations in other so-called modifier genes have an important influence on phenotypic differences in this disease. In recent years, multiple candidate modifier genes have been investigated**,** in particular, genes that are involved in the control of infection, immunity, and inflammation (Cutting 2005).

32.6.2 Rationale for Cystic Fibrosis

Subjects with CF typically present with disease in the lungs, sweat gland, pancreas, intestine (which is especially important during the newborn period), liver, and male reproductive tract (Welsh et al. 2001). CFTR controls chloride across the apical membranes of polarized epithelia (Anderson et al. 1991). Disruption in CFTR function inhibits the transport of sodium, chloride, and water across epithelial tissues, and so it causes insufficient hydration of mucous secretions in CF patients. Certain organs are eventually damaged from/by blockage in the luminal space and follows recurrent cycles of inflammation and fibrosis (Cutting 2007; Welsh et al. 2001). Many CF patients suffer from intestinal malabsorption and an abnormal nutritional status due to obstruction of the exocrine pancreas. The major cause of death in CF patient is complications arising from obstructive lung disease, a condition which occurs in approximately 90 % of patients (Cystic Fibrosis Foundation 2005).

32.6.3 Genetics and CF

Lung function measurements are notably different among CF patients with identical CFTR genotypes (e.g., F508del homozygotes) (Kerem et al. 1990). In fact, analysis of almost 40,000 patients in the CFTR2 database showed low correlation between CFTR mutations and FEV1. There are only a few mutations that cause a milder pancreatic phenotype (e.g., p. Arg455Glu) (De Braekeleer et al. 1997; Gan et al. 1995). In aggregate, these studies show that factors other than the CFTR genotype affect the progression of airway obstruction in CF.

Recurrence of complications in affected siblings at rates higher than in unrelated patients indicates a genetic effect, but care must be taken to account for the effect of similar environment for siblings. A more powerful approach is to compare monozygous (MZ) and dizygous (DZ) twin pairs for concordance for qualitative traits and correlation for quantitative traits. When MZ pairs show a stronger correlation than DZ pairs

for a clinical feature, it shows that genetic factors may be responsible (Falconer 1965).

A higher correlation between composite measures of lung function and body mass index (BMI) was observed in 29 MZ versus 12 DZ twin pairs. This was the first twin-based assessment of the contribution of gene modifiers to CF disease severity and suggested genetic control of this trait (Mekus et al. 2000). Analysis of lung function and weight for height as independent measures did not show significant differences between the MZ and DZ twin pairs. Another comparison of 38 MZ pairs with six same-sex DZ pairs and 61 same-sex sibling pairs under 3 years of age demonstrated heritability of lung function based on FEV1 measurements ranging from 0.54 to 1.0 (Vanscoy et al. 2007). Variance analysis of 231 pairs of affected siblings showed an insignificantly higher estimate of heritability for the FEV1 measures (0.68–1.0) (Vanscoy et al. 2007). In aggregate, these studies show that genetic modifiers have an essential role in determining FEV1, a key measure of lung function, which is correlated with survival.

Collaco et al. recruited 134 MZ twins and 272 DZ twins and siblings when living together and after moving apart to estimate the relative effect of genetic and environmental factors on FEV1 among CF patients. Differences in lung function between MZ twin pairs while living together in the same house supplied an estimate of the effect of unique environmental and stochastic contributions. Changing the home environment to independent living was used to assess the effect of shared environment. The effect of genetic factors was estimated by comparing the similarities in lung function measures in MZ and DZ twin pairs when living together and subsequently when living apart. These methods showed that genetic and nongenetic factors had approximately equal effects on lung function. Analysis of 58 MZ twins and 568 DZ twins and siblings showed similar estimates for the genetic and nongenetic contributions to lung function variance (Stanke et al. 2011).

32.6.4 Modifier Genes in CF

Two independent studies with more than 500 patients combined showed that more than nine genes can be involved in modifying some feature of the CF phenotype. Several recent studies provide detailed lists of all the CF-related/modifier genes that have been studied thus far (Knowles 2006; Stanke et al. 2011).

These studies demonstrated the role of various modifier genes such as ADIPOR2, EDNRA, IFRD1, IL-8, MBL2, TCF7L2, MSRA, SERPINA1, and TGF-b1 in CF for pathologies of pulmonary function, liver disease, intestinal obstruction, diabetes, and infection. Three studies in CF patients showed earlier age of infection with Pseudomonas aeruginosa (Pa) to be related with mannose-binding lectin (MBL) deficiency genotypes. Lung disease severity, which is measured by FEV1 and infection status, is correlated with and two of them are changed by the age of the patient and by CFTR genotype. In aggregate, MBL2 genotype was found to be related to infection status more than the other variables (McDougal et al. 2010). Hence, deficits in MBL causes/can cause a predisposition to early infection with *Pa*, which leads to more severe lung disease than that observed in patients of the same age and CFTR genotype but who do not have MBL deficiency.

The Genetic Modifier Study (GMS), one of the largest CF genetic modifier studies to date**,** analyzed 808 F508del homozygotes drawn from the extremes of lung function (highest 30 percentile and lowest 30 percentile) and reported that alleles in the promoter (−509) and first exon (codon 10) of TGF-b1 are correlated with worse lung function (Drumm et al. 2005). This finding was studied in 498 patients with different CFTR genotypes and was separately confirmed when a haplotype composed of the opposite alleles at −509 and codon 10 was correlated with improved lung function (Bremer et al. 2008). Six studies including over 2,500 CF patients determined a relationship between TGF-b1 and CF lung function, while one study including 118 patients did not (Brazova et al. 2006) and another involving 171 patients (Arkwright et al. 2000) found a relation between worse lung function and the opposite alleles than those reported by Drumm et al. (2005) and Bremer et al. (2008).

Three SNPs in the highest ranking gene, the interferon-related developmental regulator 1 gene (IFRD1), were identified in the whole

GMS sample and showed a relationship using transmission-based methods in the family-based CF Twin and Sibling Study (TSS) (Vanscoy et al. 2007). IFRD1 acts via transcriptional mechanisms to alter neutrophil function in response to bacterial infection, as demonstrated by cell- and mouse-based studies.

It was demonstrated that variants in the interleukin-8 (IL-8) gene correlated with lung function. This result supported the idea that modification of CF lung disease may be caused by altered neutrophil response to infection (Hillian et al. 2008). IL-8 is a mediator that has a role in neutrophil chemotaxis and is distinctly increased in the airway secretions of CF patients.

There are other mechanisms, which seemingly contribute to CF lung pathology as demonstrated by evidence that variants in the endothelin receptor type A (EDNRA) gene correlate with lung disease severity. Correlation between a variant in the 3' untranslated region of EDNRA was identified in 709 F508del homozygous patients in the GMS study and replicated in three independent samples of CF patients. Also**,** alleles of the EDNRA variant are associated with differences in RNA transcript level, which indicates a possible functional role. Given that variation of EDNRA has been implicated in vasoconstrictive diseases as a result of effects on smooth muscle function, it was hypothesized that this gene may modulate CF lung disease by changing smooth muscle tone in the airways and vascular system (Darrah et al. 2010).

32.6.5 Cystic Fibrosis and Nasal Findings

Clinical manifestations in the upper airways (UAW) occur in almost 100 % of CF patients, appearing as recurrent sinusitis, rhinitis, and/or nasal polyposis (Cepero et al. 1987; Ramsey and Richardson 1992). The frontal sinuses seldom develop in these patients, perhaps because of the early occurring/earlier occurring disorder of sinusitis which hinders pneumatization (Ledesma-Medina et al. 1980). Sinusitis onset and nasal polyposis commonly occur between 5 and 14 years of age, with adult onset being unusual.

Most patients with CF (over 90 %) (Umetsu et al. 1990; Weber et al. 1999) develop chronic and recurring rhinosinusitis with or without nasal polyps. Modified mucus composition and viscoelasticity cause decreased mucociliary clearance and blockage in paranasal sinus drainage ostia, thereby promoting local inflammation, hypoxia, and increased carbon dioxide partial pressure. Mucosal edema generally develops after impaired ciliary function and bacterial colonization, usually by Staphylococcus aureus and Pseudomonas aeruginosa (Batsakis and El-Naggar 1996; Cimmino et al. 2003).

Franco et al. reported a relation between sinonasal symptoms and cystic fibrosis. They found most common symptoms like cough (45 %), oral breathing (44 %), sleep disorders (42 %), and nasal obstruction (37 %) in CF patients. Twenty-eight patients (28 %) had purulent nasal discharge, and 41 % had medial bulging of the nasal lateral wall (Franco et al. 2009). It is reported that nasosinusal involvement may worsen pulmonary disorder (Daniel 2006). Hence, otorhinolaryngologists should investigate these patients in more detail for signs of pulmonary diseases. A recent study in Brazil (Sakano et al. 2007) demonstrated more attention to the nasosinusal findings of CF patients, because CF is genetically very heterogeneous, with many types of mutations and a wide diversity in clinical presentations (Gentile and Isaacson 1996).

ΔF508 homozygosity was found more frequently in the patients undergoing sinus surgery (58 %) compared with a control population (48 %) (Moss and King 1995). Lastly, a study reported that ΔF508 homozygosity was associated with clinical severity of paranasal sinus diseases and with the presence of polyps on endoscopy in 113 patients (Jorissen et al. 1999).

32.6.6 CF and Nasal Polyposis

Nasal polyposis in CF patients was first described almost 50 years ago (Lurie 1959), but there is little known about its pathophysiology (Hulka 2000). The prevalence of nasal polyposis varies by population (Sakano et al. 2007). The incidence of nasal polyps has been observed in 6 to

48 % of cases (Shwachman et al. 1962) by the time cystic fibrosis is diagnosed. Nearly 4 % of patients already have symptomatic nasal polyposis when their diagnosis of CF is established, and it is expected that nearly 14 % of patients will undergo surgical intervention for their nasal polyp disease (Cimmino et al. 2003).

Weber et al. showed that nasal polyps were estimated in 39.1 % of CF patients and, interestingly, all of them were older than 6 years of age, presenting with recurrent pneumonia in 82.6 %, pancreatic insufficiency in 87 %, and malnutrition in 74 %. No correlation was seen between nasal polyps and sweat chlorine concentration, genotype, clinical signs of severity, and nasal symptoms. Nasal polyps regressed in seven patients treated with topical steroids, while six patients showed complete resolution (Weber and Ferrari 2008).

Some researchers reported that patients with nasal polyposis had better pulmonary function, however a higher rate of Pseudomonas aeruginosa colonization, more hospitalizations, and more prevalence of allergy to Aspergillus fumigatus than the comparison group. They found no statistically different genotype distribution between the group with polyposis and the control group. But they also emphasized that the prevalence of the compound heterozygous genotype is higher within the nasal polyposis group than within controls (Cimmino et al. 2003).

32.7 Role of Genetics in Nasal Polyposis

32.7.1 Introduction

The nasal polyp is one of the final manifestations of chronic inflammation. Nasal polyposis is a chronic inflammatory disorder of the upper respiratory tract that 1 to 4 % of the human population suffers from (Pawankar 2003). The lamina propria of nasal polyps usually presents great numbers of eosinophils and lymphocytes. In chronic inflammation, inflammatory cells produce neuropeptides, cytokines, and growth factors. These molecules lead to an extensive network of cellular interactions. In addition, resident structural cells can synthesize many of these molecules. Fibroblasts, epithelial cells, and endothelial cells help to organize the inflammatory process in nasal polyps (Liu CM et al. 2002).

Recently, it has been shown that there are proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1b (IL-1b) in the epithelial and endothelial cells of nasal polyps. Also, cell adhesion molecules such as very late antigen-4 (VLA-4) have been found on the surface of eosinophils, while integrins such as vascular cell adhesion molecule-1 (VCAM-1) have been shown on the surface of the small venules of the nasal polyp. Lastly, the presence of chemokines such as regulated upon activation normal T cell expressed and secreted (RANTES), eotaxin, and IL-8 in the epithelium of the nasal polyps has been determined.

The nasal polyp tissue and the nasal mucosa have a sufficient collection of inflammatory molecules to combat efficiently against different agents such as allergens, bacteria, fungi, chemical particles, and viruses that come into the nose from the external environment. One of the most significant cells to offer an immune response may be the lymphocyte subpopulations. The percentages of TH_1 lymphocytes (which produce IL-2 and interferon-α [INF- α]) and TH_2 lymphocytes (which produce IL-4 and IL-5 cytokines) in the nasal pharyngeal tonsillar lymphocytes and peripheral blood lymphocytes have been determined in patients with nasal polyposis (Bernstein et al. 2001). These same researchers have described the lymphocyte subpopulations and cytokines in nasal polyps (Bernstein et al. 2004).

32.7.2 Mucosal Irritation and the Role of Staphylococcal Exotoxin

As the nasal polyp symbolizes a final point in chronic inflammation, it is difficult to describe the initial events that trigger the inflammatory process in the lateral wall of the nose. Some substances, such as allergens, bacteria, viruses, air pollutants, and fungal elements, enter the

submucosa of the lateral wall of the nose and damage the airway epithelium. These irritants lead to changes in some of the possible modifications of the respiratory epithelium that may take place after entrance of these particles. These changes include the following: first, the synthesis of inflammatory eicosanoids, which are potent cell activators and chemoattractants; second, proinflammatory cytokines such as TNF-α and IL-1, which have major effects on growth, differentiation, migration, and activation of inflammatory cells; and, third, specific cell adhesion molecules, which have an essential role in managing the inflammatory cell. Lastly, major histocompatibility class II antigens have a crucial role in antigen presentation to T cells (Salik et al. 1999) and are also responsible for consequent activation of T cells. Figure 32.2 shows the possible changes in respiratory epithelium after the entrance of bacteria, virus, allergens, and fungal elements.

Various cytokine subtypes are produced by stimulation of epithelial cells by these elements. Shortly after exposure, activation of specific inflammatory cells occurs. Hence, the early growth of nasal polyposis may be the effect of stimulation of the epithelium by allowing irritants to change or damage the surface epithelium metabolically or physically. A cascade of inflammatory alterations takes place after this surface epithelium is damaged (Fig. 32.2).

A superantigen concept for massive nasal polyposis has been postulated. S. aureus is the most common bacterial species found in the nasal mucus. It has been shown in different studies that these bacteria synthesize exotoxins and that the corresponding variable-β region of the T cell receptor is also upregulated in polyp lymphocytes (Bernstein et al. 2003). Based on these results, it is postulated that toxin-producing Staphylococci cause the preliminary damage to the lateral wall of the nose. These exotoxins can act as superantigens, which lead to proliferation of lymphocytes, which in turn synthesize cytokines that are associated with the massive proliferation of inflammatory cells that are observed in massive nasal polyposis.

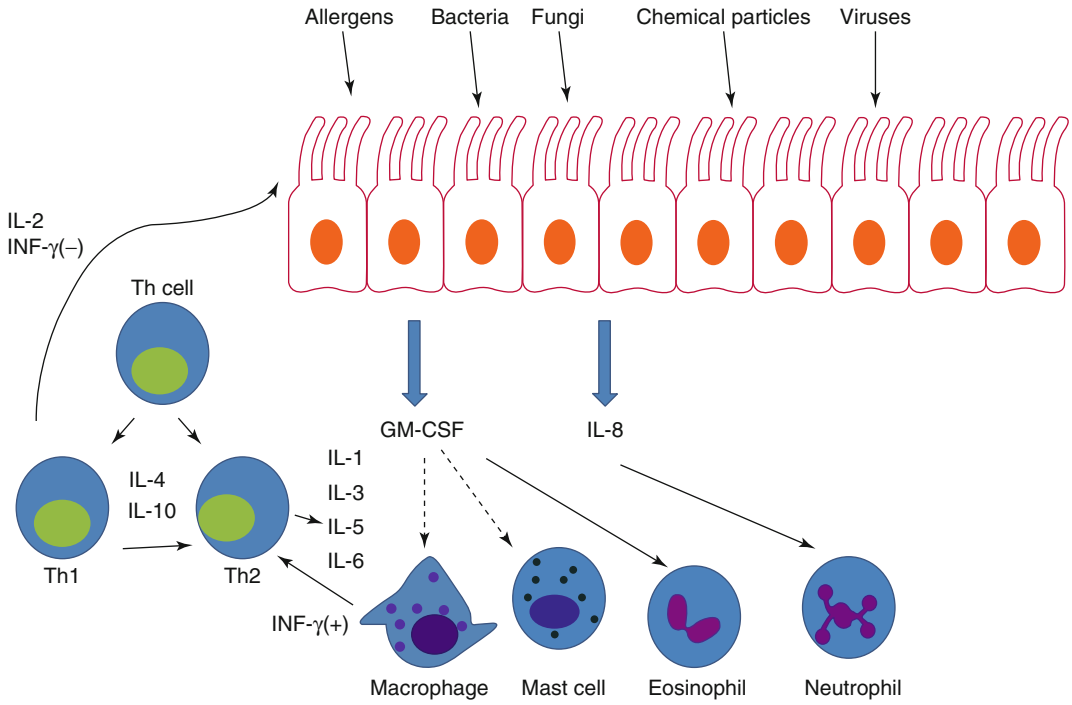

Fig. 32.2 Schematic presentation of epithelial damage in nasal polyp

32.7.3 Proinflammatory Cytokines Produced in Nasal Polyps

TNF-α and IL-1β cytokines play a role in the second process involved in the development of nasal polyposis after the initial mucosal irritation. The basic function of these two cytokines is the upregulation of endothelial adhesion molecules implicated in inflammatory reactions. TNF-α and IL-1β increase the production of endothelial adhesion molecules such as intracellular cell adhesion molecule-1 (ICAM-1) and VCAM-1. It has lately been shown by in vitro studies and animal experiments that certain adhesion molecules are important for adherence of eosinophils to endothelium and their subsequent extravasations.

Eotaxin and RANTES, which are cysteine/cysteine chemokines, attract and stimulate eosinophils in vitro and direct eosinophils into inflammatory lesions. There is strong evidence supporting the hypothesis that cytokines released from activated CD4 T cells mostly account for the restricted accumulation and activation of eosinophils in allergy-related disorders. It has been reported that these T cells produce some cytokines such as IL-4 and IL-13, which are also known as TH_2 cytokines. These cytokines play a role in favored extravasations of eosinophils through selective stimulation of VCAM-1 and IL-5. Also granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-3 are essential for eosinophil activation and survival (Sun et al. 1999). However, many studies propose that TH_1 cells are the main cells in nasal polyps and their release of INF-γ and IL-2 are highly present in nasal polyps. Thus, the recruitment of eosinophils may be linked to both TH_1 and TH_2 cytokines (Hamilos et al. 1995).

The specific localization of the eosinophil onto the vascular endothelial surface of the nasal polyp occurs due to the interaction of VLA-4 on eosinophils and VCAM-1 on venule endothelial cells. Eosinophil migration occurs within the nasal polyp venules after blood flow slowing down, and the subsequent transepithelial migration of these eosinophilic cells into the lamina propria of the nasal polyp occurs via influence of chemokines such as RANTES and eotaxin. One study suggests that the eosinophil is the main cell in the nasal polyp, where eosinophils constitute up to 80 % of the inflammatory cells (Bernstein et al. 1997).

Lymphocytes are enormously widespread cells accompanied by eosinophils found in the lamina propria of the nasal polyp. It is believed that protracted survival of these cells occurs via the autocrine upregulation of cytokines within the lamina propria of the nasal polyp. For instance, at least three cytokines (IL-3, GM-CSF, IL-5) are shown to decrease apoptosis of eosinophils (Bates et al. 2004). They have an impact on the long-term survival of eosinophils and their activation. Among these, IL-5 appears to have the most powerful effect in increasing the survival of eosinophils in the nasal polyp. Also, it was determined that the eosinophil itself can react by producing similar cytokines in an autocrine upregulation pattern. This vicious cycle of autocrine upregulation increases the recruitment of more eosinophils into the nasal polyp so that the chronic inflammatory state of eosinophils is extended.

32.7.4 Eosinophils and Electrophysiology of Respiratory Surface Epithelium

Airway mucus secretion is stimulated by eosinophilic cationic protein and inhibited by eosinophilic major basic protein (MBP) (Lundgren et al. 1991). Just over a decade ago, Jacoby and colleagues (1988) showed that MBP increased net chloride secretion. Also, MBP significantly facilitates sodium flux into the epithelial cell. Although there was a large change of chloride in and out of the cell, the net flux of chloride was not clearly determined. Finally, the short-circuit current seemed to be increased significantly with MBP compared with the control group.

One of the potential new strategies for the management of nasal polyps is based on the effect of amiloride and other sodium channel blocking agents (such as furosemide) on water

movement into and out of nasal mucosa. Amiloride notably reduced sodium absorption and the short-circuit current. Hence, amiloride or furosemide may be useful as topical agents that could reduce sodium absorption into the cell and thereby reduce cellular and subcellular edema. It is approved by the findings from the bioelectric studies suggesting that nasal polyp epithelial cells have a normal luminal chloride channel which was controlled by increased chloride permeability after isoproterenol administration. Amiloride caused a larger decrement in sodium absorption in nasal polyp cells than in cells from the inferior turbinate mucosa. Amiloride is a specific blocker of the apical sodium channel and reduces the basal voltage and basal short-circuit current. These results show that sodium absorption may be increased in nasal polyps.

The mediators such as MBP produced by inflammatory cells of nasal polyps may increase sodium absorption, which could cause water retention in the epithelium of the lamina propria of polyps. The efficacy of corticosteroid treatment for nasal polyps depends on the inhibition of the synthesis of multiple cytokines. Recently, decreased expression of the CFTR protein in remodeled human nasal epithelium from non-CF patients was demonstrated (Dupuit et al. 1995). In normal adult pseudostratified human nasal surface epithelium, the CFTR is localized to the apical domain of the ciliated cells, whereas in CF, the mutated DF 508 CFTR gene causes an abnormal cytoplasmic location of the CFTR protein. Airway epithelial damage, in CF or non-CF patients, may induce a remodeling of the surface epithelium characterized by a change in the morphologic structure from normal columnar pseudostratified to basal hyperplasia, mucus cell hyperplasia, or squamous metaplasia. These histological findings are found in human polyp epithelium in the non-CF patient. Thus, abnormally low expression of the CFTR protein not only may be caused by the CFTR gene mutation in CF but also may be associated with airway surface epithelial differentiation and remodeling as occurring in nasal polyps from non-CF patients.

Table 32.3 Inflammation changes in different CRS subtype

CRS with NP		CRS without NP	
TGF-β1 ↑	Edema	TGF-β1↑↑↑↑	Fibrosis
T_{reg} ↑	T_H2 + T_H2 –	T_{reg} ↑↑↑↑	T_H1

32.7.5 Medical Treatment of Chronic Rhinosinusitis with Massive Nasal Polyposis Based on the Molecular Biology of Inflammation

Patients with CRS and massive nasal polyposis typically have eosinophilic and lymphocytic infiltration in the lateral wall of the nose. In the phases of inflammation, there is a complex interaction between cytokine molecules. It gives rise to increased numbers and survival of eosinophils and lymphocytes in the nose. Hence, a rational approach to the medical treatment of this chronic inflammatory disorder can be properly achieved only after a complete understanding of the cytokine network (Table 32.3).

The major pathologic aspect of CRS with and without nasal polyposis is chronic inflammation. Hence, application of specific anti-inflammatory drugs such as corticosteroids, which are the most commonly utilized drugs in the treatment of CRS**,** particularly with nasal polyposis, is useful. Antileukotriene therapy has also been found useful in the management of nasal polyposis. This drug may be especially effective in the aspirin-sensitive patient who has CRS with nasal polyposis.

Erythromycin and clarithromycin have prominent effects against neutrophils and some inflammatory cytokines, and interest in the potential anti-inflammatory effects of macrolide antibiotics has increased in the last 50 years. However, there are many reports of increasing bacterial resistance to macrolides for many significant species that specifically cause upper respiratory tract infection.

Microorganisms can stick on various surfaces and shape a three-dimensional constitution known

as biofilm. After a biofilm has been formed on the mucosal surface, the bacteria harbored in the biofilm are less exposed to the immune response and less vulnerable to antibiotics. One study mentions that the use of furosemide and amiloride was found to be valuable in the postoperative treatment of CRS with nasal polyposis (Passali et al. 2003).

Anti-IgE therapy is a compelling new therapeutic molecule for the neutralization of IgE and the inhibition of IgE synthesis (Bez et al. 2004). Monoclonal anti-IgE therapy may be a logical approach in the treatment of chronic hyperplastic sinusitis when allergy is a major factor in a patient with IgE-mediated hypersensitivity.

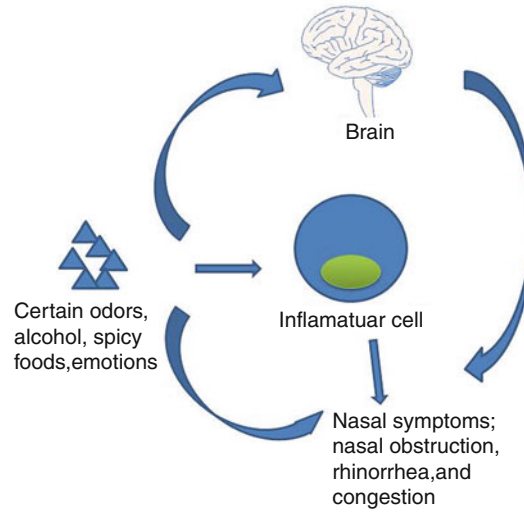

Fig. 32.3 Possible mechanism of VMR

32.8 Vasomotor Rhinitis and Its Genetic Background

32.8.1 Introduction

Rhinitis is an inflammation of the nasal area and generally characterized by rhinorrhea, nasal congestion, sneezing, and/or nasal itching (International Consensus Report 1994). It is classified into subtypes of allergic, nonallergic, occupational, hormonal (pregnancy and hypothyroidism), drug induced, and food ingestion induced (Dykewicz et al. 1998). Vasomotor rhinitis (VMR) is the most common type of chronic nonallergic rhinitis (NAR). Millions of people suffer from vasomotor rhinitis and it causes uncomfortable symptomatology. VMR is an idiopathic condition diagnosed after exclusion of infection, allergy, eosinophilia, hormonal changes (such as pregnancy), and exposure to drugs. Hence, sometimes scientists have described it as a "wastebasket diagnosis" (Corey 2003; Smith 2003).

Certain odors, alcohol, spicy foods, emotions, and environmental factors such as temperature, barometric pressure changes, and bright lights exacerbate these symptoms (Druce et al. 1998) (Fig. 32.3). Allergic and nonallergic rhinitis have notably overlapping symptoms, but the causes appear to be entirely different (Druce et al. 1998).

Skin testing or in vitro tests for allergen-specific IgE are usually used for allergic rhinitis (AR) or VMR diagnosis. Also, a patient may have both allergic and nonallergic components and this is named "mixed rhinitis." These patients must be recognized properly because positive testing to a specific allergen may cause the clinician to ignore the role and management of nonallergic factors.

32.8.2 Epidemiology

Approximately 19 million people suffer from NAR in the United States and a further 26 million experience mixed rhinitis.

32.8.3 Pathophysiology of VMR

Several hypotheses have been suggested for the pathophysiology of VMR.

32.8.3.1 Trauma

Surgical and nonsurgical trauma has been accounted to cause VMR as a long-term complication.

32.8.3.2 Autonomic Dysfunction

Patients with vasomotor rhinitis are clinically separated into two subgroups: "runners," who present "wet" rhinorrhea, and "dry" patients, who show nasal obstruction and airflow

resistance with minimal rhinorrhea. Many researchers have endeavored to explain the pathogenic mechanisms for these subgroups. An imbalance in the autonomic input to the nasal mucosa has been held responsible for VMR since the 1950s. Recent theories postulate that increased cholinergic glandular secretary activity is responsible for runners, while nociceptive neurons with increased sensitivity to generally innocent stimuli are responsible for dry patients. Recent studies by Jaradeh et al. and by Loehrl et al. (2002b) have suggested that VMR is due to a hypoactive sympathetic nervous system rather than a hyperactive parasympathetic system. There are some factors that trigger symptoms of VMR such as changes in temperature or humidity, smoke, alcohol, odors, perfumes, sexual arousal, and emotional factors (Corey 2003). A study (Braat et al. 1998) determined nasal hyperreactivity to cold air using anterior rhinomanometry. Numata et al. (1999) determined nasal hyperreactivity to histamine using acoustic rhinometry.

32.8.3.3 Cytokines and VMR

Chen et al. showed that there were no significant differences in levels of IL-10, IL-13, or IL-16 between vasomotor rhinitis and normal controls. But the level of IL-12 in vasomotor rhinitis was lower than that of normal controls. Further research is needed on the role of IL-12 in vasomotor rhinitis (Chen J et al. 2007).

32.8.3.4 Light and Electron Microscopic Findings

Giannessi et al. (2003b) recently studied microscopic and ultrastructural alterations in the nasal mucosa of VMR patients. VMR patients who underwent inferior turbinate reduction showed abnormal epithelium in 80–90 % of the nasal surface with light microscopy. They observed decreases in epithelial thickness and loss of ciliated and goblet cells in the nasal surface. Also, ultrastructural studies supported light microscopic findings. They detected ciliary loss, lack of tight junctions, loss of vibratile cilia, loss of goblet cells and ciliated cells, and marked expansion of the intercellular spaces.

32.8.3.5 Neuropeptides

Some scientists have investigated the neurogenic and molecular mechanisms of VMR. Tai and Baraniuk (Settipane and Lieberman 2001) suggest that sensory nerve endings and autonomic dysfunction have a role in VMR. Stimulation of nasal sensory nerves caused sensations of pain and stuffiness. Type C nociceptive nerves synthesize some neuropeptides such as substance P (SP) and calcitonin gene-related peptides, and it increased plasma extravasation and glandular secretion. Groneberg et al. (Groneberg) studied the neuropeptide content of mucosal parasympathetic, sympathetic, and sensory nerves of patients with toxic rhinitis caused by chronic cigarette smoke exposure. They measured concentrations of calcitonin gene-related peptides, SP, vasoactive intestinal peptide, and neuropeptide tyrosine (NPY) and determined significantly increased concentrations of vasoactive intestinal peptide and NPY in the nasal mucosa of toxic rhinitis compared with normal subjects. Also the level of SP expression was increased. SP is generally distributed in nerve fibers near submucosal glands and blood vessels, whereas NPY is found near submucosal blood vessels. SP have many functions in the body such as increasing plasma extravasation, glandular secretion vasodilatation, and mucociliary clearance. Vasoactive intestinal peptide (VIP) is a neurotransmitter that has a role in the inhibitory noncholinergic airway nervous system and it always dilates bronchus and vasculature. Increased levels of VIP may lead to hypersecretion. Groneberg et al. (2003) postulated that a separate subclass of nerves might be responsible for the pathophysiology of toxic rhinitis and that major changes in the content of mucosal nerves occur in toxic rhinitis.

Schierhorn et al. (2002) investigated ozone-induced releases of SP and neurokinin A, and ozone stimulation was found to increase SP and neurokinin A levels. Also, it was reported that the ozone-induced increase in neuropeptides in allergic patients was higher as compared with nonallergic patients. Ozone might increase sensory nerve activity in the upper airways and as a result increase neuropeptide release in the upper airways.

32.8.3.6 Nitric Oxide

The function of nitric oxide (NO) in the pathogenesis of VMR was studied by Giannessi et al. (2003a) and by Ruffoli et al. (2000). Three isoforms of NOS have been shown in the human nasal mucosa. Nicotinamide adenine dinucleotide phosphate (NADPH) is used by all isoforms of NOS as a cofactor. Hence, NADPH-diaphorase histochemistry is used to investigate NOS in tissues. The damaged epithelium with containing cells with marked reactivity to NADPH-diaphorase was found in nasal respiratory epithelium in VMR by Giannessi et al. (2003a). Basal cells in VMR presented strong NADPH-diaphorase activity, while NOS activity was negative in basal cells of normal subjects.

NO is known to have cytostatic and cytotoxic effects against microbes and cancer cells. Inducible NOS stimulation could synthesize a high degree of NO, and it could cause decreased viability of normal tissue and necrosis. High-level NOS expression in the nasal epithelium could lead to a constant high level of NO and result in constant epithelial damage. This has been postulated as one of the possible pathogeneses of VMR. Repression of mucociliary clearance, decreased number of tight junctions, and disruption in the basement membrane continuities might permit environmental agents to interact directly with the subepithelial structures. Consequently, symptomatic VMR is caused by increased responsiveness to the afferent trigeminal fibers, and recruitment of secretory and vascular reflexes could occur in the nasal respiratory mucosa.

Cervin et al. (1999) studied the functional effects of NPY receptors on blood flow and NO concentrations in the human nose by using dose-dependent effects of intranasal application of NPY. They showed that application of NPY leads to vasoconstriction and a decrease in NO levels. Braat et al. (2002) showed that pollution and meteorologic factors are linked with severity of symptoms in VMR patients. They determined that minimum daily temperature and the levels of ozone and NO had the highest association with the severity of symptoms.

32.8.3.7 Nasal Secretory Proteins

The protein analysis of nasal washes to differentiate VMR from other forms of rhinitis was studied by Iguchi et al. (2002) and Tosun et al. (2002). Iguchi et al. (2002) investigated control, VMR, and perennial AR subjects. The total protein and albumin level in AR was higher than the total protein and albumin level in NAR ($P<0.01$ for both). It is shown that the difference in total protein and albumin concentration between normal control subjects and NAR was also statistically significant ($P<0.05$ for both). The control subjects had the lowest total protein and albumin levels in their nasal lavage. They also found a protein with a molecular weight of 26 kDa. The identity of this protein has not been determined yet, but it is believed to derive from the nasal glands since its secretion can be provoked in normal volunteers with pilocarpine nasal spray. The average level of this protein was significantly higher in AR subjects compared with control subjects ($P<0.01$) and NAR subjects ($P<0.05$). The level of the 26-kDa protein in NAR was higher than in control subjects but it was not statistically significant. It is suggested that increased vascular permeability led to increased albumin concentration in nasal discharge. The level of the 26-kDa protein is therefore enhanced due to increased gland secretion. In the NAR group, vascular permeability may have been increased over control subjects, but gland secretion was minimal, and the 26-kDa protein level remained low. Hence, presence of the 26-kDa protein can be used to distinguish AR from NAR.

The gel electrophoretic assessments of proteins in nasal washings of patients with AR and VMR were studied (Tosun et al. 2002). The average total level of proteins, 66-kDa proteins and 26-kDa proteins, was determined to be higher in AR compared with those from VMR. The lowest rate of these proteins was seen in control group. The differences in the mean concentration of proteins in AR, VMR, and control group were statistically significant ($P<0.05$).

Aust et al. (1997) studied the gene expression of eight types of mucin in control and vasomotor inferior turbinates, and the only difference observed between normal and VMR turbinates was a minor decrease in mucin 1, transmembrane

(MUC 1) gene expression in the vasomotor group. They suggested whether this decrease could begin abnormal neurogenic signals that lead to an increase in nasal secretions in VMR.

32.8.3.8 Acid Reflux

It is suggested that there is a relation between laryngopharyngeal reflux and VMR based on autonomic dysfunction (Loehrl et al. 2002a). Patients with VMR and those with extraesophageal manifestations of gastroesophageal reflux show findings of autonomic dysfunction. Patients with both VMR and esophageal reflux show a considerably greater degree of autonomic dysfunction compared with patients with only VMR. Shaker et al. investigated the intrapharyngeal distribution of gastric acid refluxate (Shaker et al. 2003) in reflux laryngitis, VMR, and control subjects using dual pharyngeal and esophageal probes. The study determined that the number and extent of reflux events in the esophagus and lower pharynx are indistinguishable between patients and control subjects.

Conclusions

Rhinologic diseases are very common worldwide. It is known that these diseases have a significant genetic background. A lot of development in the field of genetics has achieved over the last decade, and it is expected to advance even further in the next, as increasingly powerful analytical tools are being developed to solve the complexities of genetic diseases. These progress in information about the genetics of allergic diseases and new tools help not only for illuminating the molecular basis of these diseases but also for developing new therapies. In the future, many rhinologic diseases with chronic progress will have a chance to be treated through new developments in the field of genetics.

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Vomeronasal Organ

33

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Keywords
Vomeronasal organ • Nasal physiology • Sense of smell

Core Messages

- Conflicts on the existence and function of vomeronasal organ in human nose still goes on.
- The blind-ending tube lined by pseudostratified epithelium, associated with submucosal glands seems highly likely to be the remnant of the vomeronasal organ.
- Local and systemic effects of Vomeropherin pregna-4,20-diene-3,6-dione supports the functionality of the human VNO and its repercussions in autonomic and psychophysiological functions. On the other hand some researchers suggest that the human VNO does have epithelia that may be able to serve as a chemical sensory organ but there seem to be no connections between the VNO and the central nervous system.

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The vomeronasal organ (VNO) is the peripheral sensory organ of the accessory olfactory system. It is a paired organ located at the base of the nasal septum or in the roof of the mouth in most amphibians, reptiles, and mammals (Meredith 2001).

The VNO constitutes an accessory olfactory organ that receives chemical stimuli, pheromones, which elicit behavioral, reproductive, or neuroendocrine responses among individuals of the same species (Witt and Hummel 2006). Frederik Ruysch discovered the vomeronasal cavities in humans in 1,703. He described a "canalibus nasalibus" on each side of the anterior

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part of the nasal septum of a young cadaver. Kölliker made a detailed study of the position of the vomeronasal cavities in the nasal septum of dead fetuses, children, and adults. The opening of the cavity is visible as a pit at the surface of the septum (Trotier et al. 2000).

Ludwig Lewin Jacobson described in great detail the vomeronasal organ in a number of mammalian species. However, he also noted the lack of development of the vomeronasal structure in humans (Trotier and Døving 1998).

33.1 VNO Anatomy

Researchers describe a blind-ending tube lined on all sides by a pseudostratified epithelium and with associated submucosal glands. It seems highly likely that this structure is the adult human remnant of the vomeronasal organ (Johnson et al. 1994). The vomeronasal cavities were located at the base of the most anterior part of the nasal septum which can be detected by computed tomography. Histological studies indicated that the vomeronasal cavities consisted of a pit generally connected to a duct extending in a posterior direction under the nasal mucosa. Many glands were present around the duct, which contained mucus (Trotier et al. 2000). There are some conflicts about the description and identification of VNO, VNO pit, and VNO cavity. In some studies, researchers described the variates of nasopalatine fossa (NPF) and the nasopalatine recess (NPR). There are some questions about the endoscopic view of the vomeronasal pit. NPF and the NPR are discrete, but variable, structures found to be located adjacent to the VNO region. The NPF is not a vomeronasal pit. A septal mucosal pit could hide the vomeronasal duct opening. The VNO is a submucosal structure located 2–8 mm superior to the NPR and cannot be positively identified either macroscopically or endoscopically (Bhatnagar et al. 2002). However, in another study, the vomeronasal cavities were claimed to be observed by endoscopy in some adults, but they lacked sensory neurons and nerve fibers (Trotier 2011). A study on the human VNO revealed the following major results: (1) a VNO is detectable in approximately two-thirds of the population and bilateral VNOs are present in approximately 40 % of investigated subjects, (2) its localization on the left and right nasal septum is almost symmetrical, and (3) detectability of the VNO is not related to age or gender (Knecht et al. 2001).

33.2 VNO Histology

The human VNO was found to be variable in form. The thickness of the epithelium was variable both medially and laterally and comprised tall cells with discontinuous cilia on their free surface (Kunwar et al. 2001). Human VNOs also varied in anteroposterior and superoinferior position relative to the anterior nasal spine and the nasal cavity floor (Smith et al. 2001).

The epithelium lining the human VNO is explained as unlike that of VNOs in other species and unlike that of olfactory or respiratory epithelium in humans. There are many elongated cells presenting a microvillar surface to the lumen of the organ but most are not similar to microvillar vomeronasal sensory organs (VSNs) of other species. They have not been shown to have axons leaving the epithelium nor to make synaptic contact with axons in the epithelium. Therefore, if these cells are chemosensitive, they have no obvious way of communication with the brain (Stensaas et al. 1991).

These unique elongated bipolar microvillar cells have been found to stain with several immunomarkers (Monti-Bloch, Jennings-White et al. 1998). The histology of the vomeronasal epithelium (VNE) appeared extremely heterogeneous. There were sections of stratified, respiratory, and typical pseudostratified vomeronasal epithelia consisting of slender bipolar cells. Mostly negative immunohistochemical results for OMP indicated that the human VNE does not function like the mature olfactory epithelium (Witt et al. 2002). These cells show physiological properties similar to chemosensory receptor cells of other mammalian species. And the presence of some bipolar cells positive for both protein gene product (PGP) 9.5 and soybean lectin pointed to

a neuron-like activity of a small subset of VNE cells. Immunohistochemical localization of three molecular markers, neuron-specific enolase (NSE) and PGP 9.5 for neurons and neuroendocrine cells, and olfactory marker protein for olfactory receptor neurons was investigated in the VNE of adult humans. NSE and PGP 9.5 immunoreactive cells were identified in the VNE (Takami et al. 1993).

The VNOs of humans and chimpanzees had some structural similarities to nonhomologous ciliated gland ducts seen in other primates. However, certain distinctions from the VNOs of other primates or nonhomologous epithelial structures characterize the human/chimpanzee VNO: (1) bilateral epithelial tubes; (2) a superiorly displaced position in the same plane as the paraseptal cartilages; (3) a homogeneous, pseudostratified columnar morphology with ciliated regions; and (4) mucous-producing structures in the epithelium itself (Smith et al. 2002).

33.3 Genes Related to VNO

TRPC2, a gene that is essential for VNO function in the mouse, is a pseudogene in humans (Rodriguez and Mombaerts 2002). TRPC2 is expressed only in the VNO, the loss of selective pressure on this gene can serve as a molecular marker for the time at which the VNO became vestigial (Liman and Innan 2003). Transcripts of the V1RL1 vomeronasal receptor are found in human olfactory mucosa, and this may reflect the fact that in humans (and some other mammals) the accessory olfactory system has been absorbed into the main olfactory system (Rodriguez et al. 2000). In 2006, it was shown that a second mouse receptor subclass is found in the olfactory epithelium. Called the trace amine-associated receptors (TAAR), some are activated by volatile amines found in mouse urine, including one putative mouse pheromone (Liberles and Buck 2006).

Orthologous receptors exist in humans providing evidence for a mechanism of human pheromone detection (Pearson 2006).

33.4 VNO Responses

There does appear to be some process located in or near the VNO pit that produces, selectively, an electrical response to small quantities of some chemicals. "Vomeropherin" has been suggested as a name for chemicals that elicit this response and as a general term for substances that stimulate the VNO in any species (Monti-Bloch and Grosser 1991). The first type of response is a local negative electrical potential, termed the "electrovomeronasogram" (EVG) recorded from the VNO pit region in awake human subjects. It is named by analogy with the electro-olfactogram (EOG) which can be recorded from the surface of the olfactory epithelium in response to odor stimulation (Pearson 2006). As a second type of response, it has also reported preliminary evidence that bipolar cells aspirated from the human VNO pit show electrical responses to some "vomeropherins." These are the EVG-eliciting steroids related to skin chemicals this group has proposed to be human pheromones (Monti-Bloch, Jennings-White et al. 1998).

33.5 VNO Function

Pheromone communication is known to exist in almost all social animals (Comfort 1971). Also, studies have shown that people can determine the sex of another person through their odor (Russell 1976). In addition to the traditional olfactory system, often termed the main olfactory system, in the vast majority of terrestrial animals an accessory olfactory system has also evolved specifically to detect pheromones as opposed to other environmental odorants (Meisami and Bhatnagar 1998).

Pheromones or vomeropherins have been found in human smegma and vaginal secretions and, more importantly, in human apocrine glands (Gower and Ruparelia 1993). There are many studies attempting to weigh the evidence for and against human VNO function, to separate this issue from the question of pheromone communication, and finally to provide a

working definition of "pheromone." VNO is found in humans, and it is thought to be nonfunctional, as the vomeronasal receptor and signal transduction genes are pseudogenes in man (Doty 2001). In addition to the existence of a functional vomeronasal-pituitary pathway in adult humans and effect on gonadotropin pulsatility, the vomeropherin also produces concurrent reflex autonomic effects after VNO stimulation (Berliner et al. 1996).

Vomeropherin pregna-4,20-diene-3,6-dione (PDD) produces a local dose-dependent effect in the male human VNO. This is followed by a mild parasympathomimetic effect characterized by a 10 % increase of vagal tone, together with decreased frequency of electrodermal activity events. Furthermore, PDD locally delivered to the male human VNO significantly decreases serum LH and testosterone. This evidence supports the functionality of the human VNO and its repercussions in autonomic and psychophysiological functions, as well as in neuroendocrine secretions (Monti-Bloch, Diaz-Sanchez et al. 1998). According to another study, occlusion or absence of the VNO did not affect either the perceptual measurements or the functional processing of the putative human pheromone androstadienone (Frasnelli et al. 2011).

As a result the human VNO does have epithelia that may be able to serve as a chemical sensory organ; however, the genes that encode the VNO receptors are nonfunctional pseudogenes in humans. Also, while there are sensory neurons in the human VNO, there seem to be no connections between the VNO and the central nervous system (Grammer et al. 2005).

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Physiology of the Nasal Cartilages and Their Importance to Rhinosurgery

34

Wolfgang Pirsig

Keywords

Nasal cartilages • Fetal nose • Physiological septal deviation • Septal abscess • Septal perforation • Septal histology • Cartilaginous fractures • Nasal valve surgery • Congenital septal deviation • Alar collapse • Septal reconstruction

Core Messages

- The complex framework of the human nasal cartilages, unique among mammals, is the mobile portal to the respiratory system providing conditions for the passage of airstreams and the generation of nasal resistance and turbulence.
- The septodorsal (septolateral) cartilage is the dominating structure for nasal and midfacial growth and decisive for the appearance and several functions of the nose. Together with the erectile lining of the nasal cavities, the cartilaginous framework enables air-conditioning and the acting of the nasal cycle.
- The anterior nose with the nasal valve as its crucial functional region is the narrowest part of the upper airways and provides two-thirds of the total airway resistance.
- Due to its protruding exposition, it is especially vulnerable to external injuries and may react as a protecting crumpled zone. This exposition also is the reason why most of the obstructing structures of the nasal airways are diagnosed in the anterior nose.
- Long-term observations have shown that the most effective outcome after functional and aesthetic rhinosurgery is achieved by focusing on restoring the physiological functions of the anterior nose, the site of the most resistive nasal segments.

The human nose, with its prominent bridge, its elongated tip and its downturned nostrils, is unique. Besides sniffing strange odours, it acts as a vital air-conditioning unit, warming, cleaning and moistening the air we breathe in before it reaches the delicate lungs. Assisting this – and

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also adding resonance to the voice – are the nasal sinuses, but the price we pay for possessing these valuable cavities is an all too common susceptibility to local infections.

This precise summing up of appearance and functions of the nose including its Achilles' heel tendon, the diseases, was published in 1985 by the zoologist Desmond Morris in his outstanding book 'Bodywatching' (Morris 1985).

In the following chapter, I'll focus on some functional aspects of the cartilaginous framework of the human nose with emphasis on its vulnerability and long-term results following surgical treatment. Why do we have a nose of such a protruding shape, which is divided by the septum into two parallel halves? Why is this mobile organ built up by a complex framework of hyaline cartilages and covered by muscles? Why do we need this nose at all, although we can survive by breathing through the mouth? I asked anatomists, physiologists, rhinosurgeons, biologists and also engineers for stream technology. The answers varied, several ended with a question mark, but in all of them the terms 'turbulence', 'resistance' and 'air-conditioning' were somehow mentioned.

34.1 Part I: Anatomical Considerations

34.1.1 Nomenclature

The lower two-thirds of the nose are built up by a framework of the following hyaline cartilages: septal cartilage (quadrangular cartilage in adulthood), a partition separating the two nasal cavities; soft tissue part of the septum is the septal turbinate (septal body or intumescentia septi or septal tuberculum); two triangular (upper lateral) cartilages as expansions of the septal cartilage forming together the T-bar-shaped framework also known as septodorsal or septolateral cartilage; two paraseptal (vomeronasal) cartilages, lying along the inferior margin of the caudal septal cartilage, attached to the vomer posteriorly and to the maxillary crest anteriorly; two alar (lower lateral or lobular) cartilages composed of a medial and lateral crus melted together at the dome on the tip; and some sesamoid (accessory) cartilages in the soft tissue area between triangular cartilage, lateral crus and piriform aperture, in the so-called hinge area.

In this chapter, the terms septum, septal, septodorsal, paraseptal, triangular, alar and sesamoid cartilages will be used.

34.1.2 Intrauterine Development

A two-tube system and a still unruffled entrance are recognisable in the fourth month of fetal development of the cartilaginous nose (Fig. 34.1). The cartilaginous framework consists of a T-bar-shaped bilateral vault fused in the midline to the septal cartilage. The complete sidewall of the cartilaginous nasal capsule is superiorly connected with the spheno-ethmoidal cartilage and dorsally with the septal cartilage which posteriorly merges into the cartilaginous anterior skull base with the crista galli. Both vaults are separated by the supraseptal groove. Caudally, the margin of the sidewall bends medially to join with the inferior turbinate. Thus, the palatine bone, the vomer and the paraseptal cartilage are visible.

In the sixth fetal month, ingrowth of connective tissue divides the cartilaginous nasal capsule into the individual septal cartilage, lateral cartilages and alar cartilages. Thus, the complex cartilaginous nasal portal is developed which later forms the cartilaginous framework of the mobile nose.

In the model of the fetal cartilaginous capsule aged 30–32 weeks (Fig. 34.2), we look on the two vaults of the lateral cartilages fused together with the septal cartilage in the supraseptal groove. The median portion bifida septi remains as the rest of the fusion of the vaults. Two semicircular-shaped cartilaginous bars have been almost completely separated from the caudal septal cartilage. They encompass the nasal vestibule medially, dorsally and laterally to form the definite alar cartilages. In the medial upper angle of the alar cartilage, an isolated piece of cartilage is visible on the right-hand side, while on the left-hand side, it is still a process in

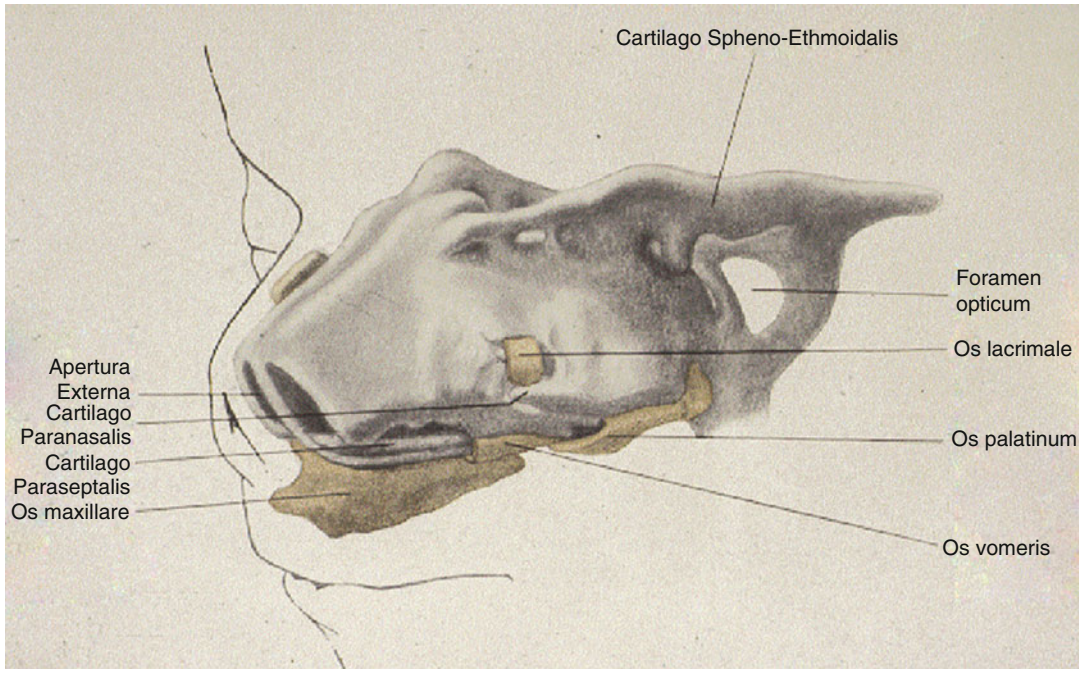

Fig. 34.1 Nasal skeleton of a fetus (8 cm) in oblique side view (Peter 1913)

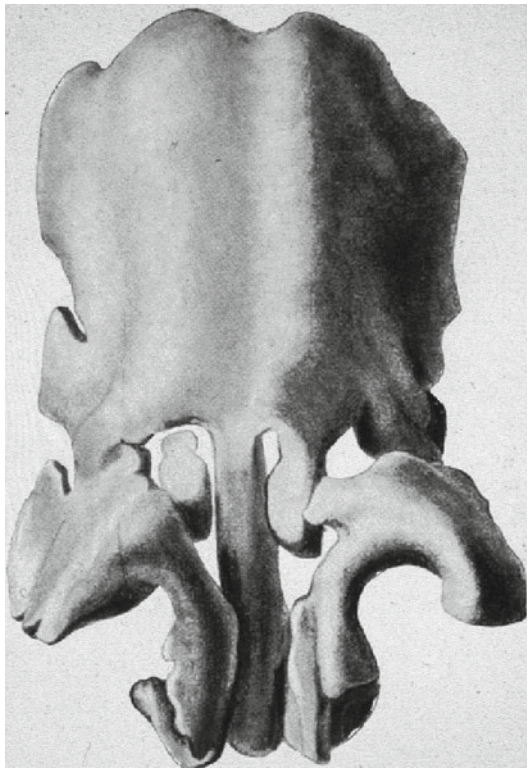

Fig. 34.2 Model of the cartilaginous nasal capsule of a fetus (27.5 cm, 30–32 weeks) (Peter 1913)

connection with the left sidewall. Later, these pieces become the sesamoid cartilages. The same happens to small processes of the lateral sidewall which are concealed by the semicircular cartilage in Fig. 34.2. The paraseptal cartilages are concealed by the caudal part of the semicircular cartilages. The triangular cartilages are not yet differentiated. In the newborn, they are still continuous with the cartilaginous anterior skull base. Their caudal margins are firmly connected to the alar cartilages and to the piriform aperture. In the newborn, the alar cartilages are developed as separate structures as in the adult and overlap with their cranial margins and the caudal margins of the triangular cartilages.

34.1.3 Postnatal Development

The septal cartilage of the newborn is progressively transformed from posteriorly, cranially and caudally into a unit of posterior bone and remaining anterior quadrangular cartilaginous plate as clearly depicted by Virchow in 1857 (Virchow 1857). This old knowledge has recently

been supported by Kim et al. (2010) who evaluated the anatomical correlations among components of the nasal septum using computed tomography. They found again that the area of the cartilaginous septum decreases with age, while the area of the perpendicular plate increases with age at the expense of the area of the septal cartilage. However, the area of the total nasal septum remains constant.

In the first decade of life, the triangular cartilages show regression from the cephalic to the caudal end under the nasal bones until being transformed in the approximately triangular shape of the adult nose. Only a small cartilaginous remnant of the triangular cartilage remains overlapped by the caudal margin of the nasal bone. Caudally, the triangular cartilages are overlapped by the cranial margins of the alar cartilages.

Very rarely the regression process of the triangular cartilage is retarded or even impeded. This may happen in case of a median nasal fistula or of a nasal dermoid cyst which can cranially end at the crista galli. Nasal bifidity is another congenital malformation with impeded regression of the triangular cartilages.

Potter et al. (2000) studied 35 adult, white cadaveric specimens and specially focused on the caudal attachment of the triangular cartilage to the septal cartilage, where usually a small cleft facilitates mobility between the caudal edge of the triangular cartilage and the septum, the so-called weak triangle of Converse. The attachment ranged from no cartilaginous connection (68 %) to complete fusion (32 %), i.e. a coincident location of the anterior septal angle and the caudal edge of the triangular cartilage.

In the adult, the relationship between the triangular cartilage and the lateral crus of the alar cartilage shows four variations (Dion et al. 1978). Most often Dion et al. found an overlap of the caudal margin of the triangular cartilage by the cranial margin of the lateral crus. Less frequently are the relationships ‘end to end’, ‘scroll’ and ‘opposed scroll’.

Each cartilage of the cartilaginous vault is encased in its own fibrous capsule, whose fibres decussate, form a fibrous band or aponeurosis and join the capsule of an adjacent cartilage. This aponeurosis, acting as a flexible membrane, allows freedom of movement between the neighbouring cartilages. According to Hinderer (1971), the most distinctive fibres are:

1. Those between the terminal ends of the triangular cartilage and septum that supply the mobility necessary for valve action between these two structures
2. Those between the caudal end of the septum and the medial crura of the columella which form the membranous septum
3. Those between the caudal margin of the triangular cartilages and the cranial border of the alar cartilages

A permanent continuity between the encasing fibrous capsule of the triangular cartilage and the periosteum of the nasal bone was found by Bruintjes et al. (1998), supporting the clinical observation of the firm connection between the nasal bones and the triangular cartilages.

Additional mobility of the interacting nasal cartilages is provided by the thin layer of seven muscles covering the external nasal pyramid. Besides their mimic function, some muscles act as dilators of the valve region or openers of the nostrils or provide stability for the lateral nasal wall (Bruintjes et al. 1996). Especially, the dilator naris accompanies each nasal inspiration, thus directly varying with ventilation, nasal resistance, hypoxia and hypercapnia. It stabilises the anterior nasal airway and precedes diaphragmatic contractions and ceases to act with mouth or tracheostomal breathing (Cole 1993).

The framework of nasal cartilages with their fibrous connections and covering muscle layer acts as shield and portal to the erectile lining of the nasal cavities. Eugene Kern from Rochester, USA, termed the nasal mucosa ‘the organ of the nose’ to sum up all its many functional tasks which are described in other chapters of this book. While the nasal vestibule is covered with squamous epithelium continuing some millimetres around the edge of the caudal margin of the triangular cartilages, the nasal mucosa with ciliated cylindrical epithelium starts in the

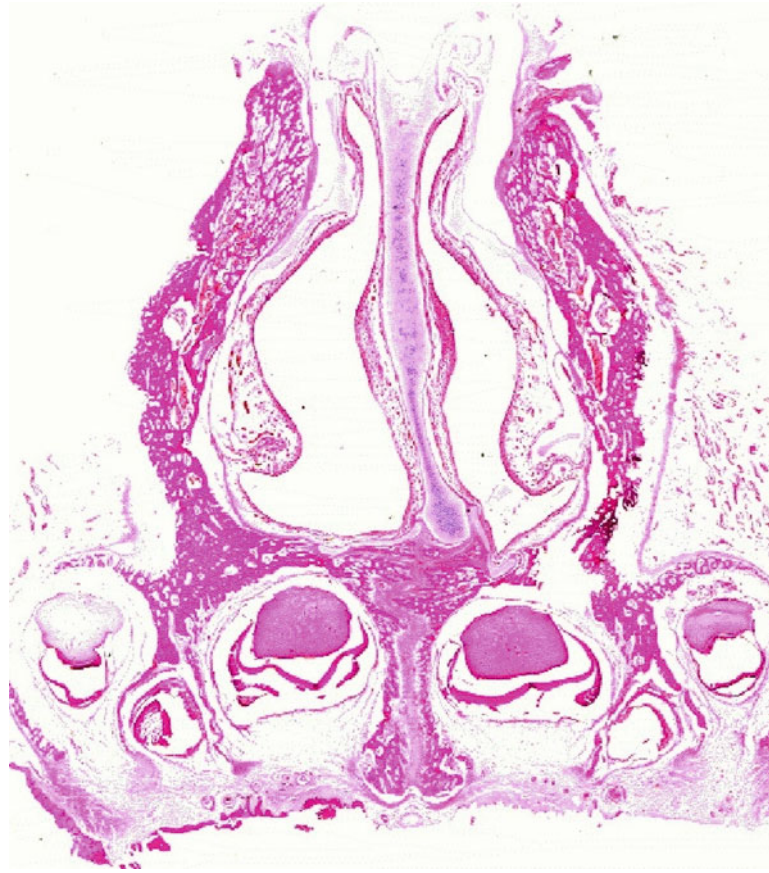

Fig. 34.3 Section through the posterior valve region of a newborn cadaver specimen. Note heads of the inferior turbinates, deviated anterior septal cartilage with septal body and asymmetric maxilla. Hematoxylin-eosin (gift of Lindsay Gray/Perth to author 1975)

posterior valve region (Bachmann and Legler 1972; Wustrow 1951). Figure 34.3 shows the histological section through the posterior valve region of a newborn. The heads of the inferior turbinates catch our eyes as elevations from the mucosal lining of the lateral walls. The slightly deviated cartilaginous septum with its mucosal lining presents its thickening in the middle covered by the thick pad of erectile mucosa, the septal body or intumescentia septi. The different thickness of the vertically cut septal cartilage is clearly visible: the thick cranial part merges caudally with a thin segment to end in the broad deviated cartilaginous foot embedded in the premaxillary bone. This pattern of different cartilaginous thickness remains persistent throughout lifetime as investigated by van Loosen et al. (2000).

34.2 Part II: Functional Aspects

In this book, nasal functions like breathing, resistance, turbulence and nasal cycle are treated in special chapters in detail. Thus, I can confine to a few comments on functions where nasal cartilages are essentially involved like in the nasal valve region or the vulnerable anterior septum.

The anterior septodorsal cartilage, the parasepta l and the alar cartilages with the sesamoid cartilages form the framework of the nasal lobule and thus the portal to the upper airways. Soft tissue connections between the cartilages of varying thickness and several small muscles acting on their outside enable mobility and/or stability of the lateral nasal walls. Thus, the entrance to the nose can be dilated and narrowed to modify the inspiratory and expiratory airstreams. The

entrance of the airflow is comparable with two flat, oval, hollowed structures, the nasal vestibules, which terminate in the aperture between the septum and the caudal end of the triangular cartilages, both parts of the nasal valve region. The vestibule is at an oblique angle to the cavum (Bachmann and Legler 1972). According to Cole's studies (Cole 1993, 2003) the nasal valve region consists of four anatomical airflow-resistive components: the aperture between septum and triangular cartilage, the bony entrance to the nasal cavum which is occupied by erectile tissues of both lateral (head of inferior turbinate) and septal nasal walls (including septal body) that modulate the cross-sectional area of the airway and airflow resistance. Two-thirds of the total nasal resistance during inspiration is provided by the nasal valve region. This has clearly been proved by Haight and Cole (1983) using pressure-sensing cannulas. As two-thirds of the total airway resistance to breathing is created in the nose – one-third is provided by the open mouth (Swift et al. 1988) – the nasal valve region is the main resistor of the total airway. The narrow nasal valve region with the smallest cross-sectional area of the nasal cavum accelerates the inspired air, creating turbulence. Valve constrictions disrupt the laminar characteristics of the inspired air as it enters the body of the cavum and thereby enhance exchanges with the nasal mucosa of heat, water and noxious materials. In the widened nasal cavum, airflow decreases its speed (Cole 2003).

In clinical praxis the physician has to face several patients complaining of breathing problems which are caused by a disturbed anatomy of the nasal valve region, especially patients with a tension nose or a saddle nose. A patient with a tension nose presents with a prominent, curved, small dorsum due to a too large and too high septum. Other characteristics are the increased projection of the tip, slitlike nostrils with an elongated columella and elongated thin nasal alae. The feet of the medial crura are cranially shifted, thus broadening the base of columella. The nasolabial angle is enlarged and often the upper incisivi are showing. The valve angle is less than 10° which results in bilateral alar collapse during inspiration.

In the cartilaginous saddle nose, the septum is too short mostly due to fractures or perforations. The caudal septodorsal cartilage is depressed which causes an enlargement of the valve angle to more than 20°. The nostrils with ballooning alae are elliptically distorted; the columella is shortened and often retracted. Although the nasal cavities look very wide, the main complaint of the patients is insufficient breathing due to too much turbulence of the airstreams.

The fact that the nasal septum divides the nose in two parallel halves is the condition for cyclic activities of the erectile nasal mucosa. Kayser in 1895 (Kayser 1895) first reported on the spontaneous, cyclical congestion and decongestion in the nasal cavities. The anatomic conditions for this mucosal behaviour are mainly provided by its capacitance vessels. The 'working phase' of one nasal cavity characterised by decongestion of the cavernous tissues alternates with the 'resting phase' characterised by congestion of the mucosa (Cole 2003; Hasegawa and Kern 1978; Lang et al. 2003). Changes of flow and resistance during the nasal cycle have been studied using rhinomanometry (Hasegawa and Kern 1978; Stoksted 1953). By means of acoustic rhinometry, Fisher et al. (1993) measured the changes of the cross-sectional areas in the nasal cavities due to congestion and decongestion.

Using the combination of endoscopic imaging, rhinomanometry and acoustic rhinometry, Lang et al. (2003) observed a periodic change in turbulence behaviour in addition to the known cyclical changes of flow resistance and nasal width. In the resting phase, mainly laminar flow was found. During the working phase, the onset of turbulence occurred already at low velocities. The increase of turbulence during the working phase was created by the increase in cross-sectional area in the anterior cavum due to decongestion of the mucosa of the head of the inferior turbinate and the septal body.

The nasal cartilages are insofar involved in the process of the nasal cycle as they provide the anatomical trigger zones for the transition from laminar to turbulent airflow, namely, the anterior nasal cavum between the nasal valve region and the head of the middle turbinate.

Bruintjes et al. (1998) studied the kinematics of the lateral nasal wall which is made up of three parts: (a) the osseous-cartilaginous chain of nasal bone, triangular cartilage and the lateral crus of the alar cartilage; (b) the hinge area with the sesamoid cartilages between the lateral piriform aperture and the lateral margin of the lateral crus; and (c) the ala, the part between piriform aperture and alar cartilage, not supported by cartilage. While part (a) is relatively stable and part (b) much more compliant, they found part (c) being the most compliant part of the lateral nasal wall. They also studied the muscles influencing the lateral nasal wall and its compliance. With this knowledge of the mechanical properties of the lateral nasal wall, they were able to analyse pathological clinical conditions, which may occur at the level of the nasal valve and at the level of the vestibule or nostril. Thus, they could explain, for instance, the physiological alterations caused by facial nerve palsy where muscle denervation may lead to alar collapse (May et al. 1977).

Loss of alar stability with nasal obstruction during inspiration is often caused by inadequate surgical procedures for the nasal lobule. Mostly the continuity of the osseous-cartilaginous chain, 'nasal bone-triangular cartilage-lateral crus of alar cartilage', is destroyed (Kasperbauer and Kern 1987). Detailed knowledge of these anatomical connections could help to reduce such adverse surgical sequelae.

The alar collapse associated with the drooping tip of elderly people may result from nasal muscle atrophy, a change in cartilage resilience and stretching of the intercartilaginous fibrous tissue with loss of cartilage overlap in the intercartilaginous junction (Krmpotic-Nemanic et al. 1971). The surgical procedure of the so-called rhinolift could reduce the breathing problems of the elderly people. Via intercartilaginous incisions in the limen nasi, the cephalic margins of the lateral alar crura are bilaterally partly resected. After elevating the dorsal skin of the nasal pyramid and excision of an oval piece of skin in the nasal root, both mobilised alar cartilages can be lifted and fixed, thus widening the angles of the nasal valves.

The elastic nasal cartilages are useful elements for protective functions. The 9-year-old boy in Fig. 34.12 is a good example to explain the function of the septal cartilages as a 'crumpled zone' in case of severe anteroposterior load. Between 1970 and 1972, I performed septorhinoplasty according to the techniques of Cottle, Goldman and Masing in 92 children with a mean age of 10.5 years (Pirsig and Knahl 1974). The indication was obstructed nasal breathing due to established posttraumatic nasal deformities. Intraoperatively, fractures and defects were visible in the anterior septodorsal cartilage with involvement of the nasal valves and sometimes of alar cartilages in 44/92 noses. These noses were damaged by loads from frontal and/or below. 23/92 noses showed fractures in the septodorsal cartilage like the previous group and in addition fractures of the nasal bones and perpendicular plate caused by mainly anteroposterior load. This means that 67/99 or 72 % of the children suffered nasal obstruction due to damaged nasal cartilages in the anterior nose.

The build-up of the septal cartilage in regions of different thickness (van Loosen et al. 2000) through the whole life is one component to react more elastically to front load. A second component of more compliance is the vaultlike construction of the septodorsal and alar cartilages with their joint-like fibrous interconnections (Bruintjes et al. 1998). Note the distortion of the caudal septodorsal cartilage of the boy in Fig. 34.12 (3): a 90° angle of the caudal septum with fractures in the caudal edge and depressed edges of the triangular cartilages. Van Velzen et al. (1997) published the prepared septal cartilage of a 4-year-old boy who died in a frontal accident. The fracture lines in the cartilaginous septum followed the thin regions of the cartilage as sites of minor resistance in reaction to load.

In idealised and patient-specific models, Lee et al. (2010) recently published the reactions of the human septal cartilage exposed to anteroposterior load. They found the maximum stress areas in the nasal septum in the vicinity of the bony-cartilaginous junction and the anterior nasal spine, which are consistent with clinical experience. The findings of their study also suggest that the septum does function as a 'crumpled zone', absorbing a significant amount of stress before it is transmitted to the skull.

The extreme variant of a damaged crumpled zone nose is the classic boxer's nose, the so-called rubber nose, mainly formed by the alar cartilages. The septodorsal cartilage is shrunken to a minimum; nasal bones and anterior nasal spine are pressed down to the level of the piriform aperture or resorbed.

34.3 Part III: Alterations of Nasal Cartilages

The functions of the nasal cartilages can best be recognised in children and adults with a disturbed cartilaginous framework. The growing nose is influenced by genetic and epigenetic influences such as oxygen supply, nutrition, hormones, medication, infections and injuries including nasal surgery as a controlled trauma, to name a few. In this part, examples are presented describing some long-term influences on the nasal cartilages citing literature and own case reports.

34.3.1 Lacking Septodorsal Cartilage

Already in utero, the septodorsal cartilage, being composed of the septal and both triangular cartilages, develops as the dominating structure for nasal and midfacial growth. This was shown in 1791 by Soemmerring (Soemmerring 1791) who published a newborn's skull with a lacking septodorsal cartilage and the skull of a healthy newborn for comparison (Fig. 34.4). In the deformed newborn, the nasal bones and the incisive parts of the maxilla are not developed. The size of the piriform aperture is reduced to one-third in width compared with the healthy newborn. Height and width of the maxilla are reduced, while the contours of the orbital cavities are distorted compared with the healthy newborn.

34.3.2 Lacking Alar Cartilages

The following case shows that congenitally lacking of both alar cartilages did not impede the growth of nose and midface apart from the complete lacking nasal lobule (Fig. 34.5). The 15-year-old boy came from a family with no genetic nasal disorders and an uneventful pregnancy of his mother. There was a complete absence of both alar cartilages. The pseudocolumella was formed by skin covering the caudal septal cartilage. The caudal margins of the triangular cartilages were covered by thick skin on the right and thin skin on the left side. All the other nasal structures were inconspicuous. The boy's breathing was normal (Pirsig 1989).

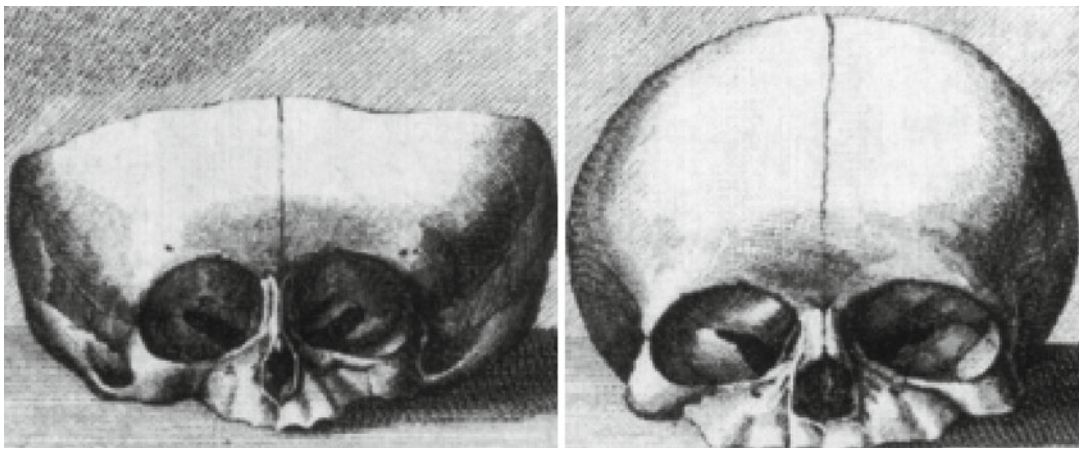

Fig. 34.4 Skulls of newborns with lacking septodorsal cartilage (*left*), with normal midface (*right*) (Soemmerring 1791)

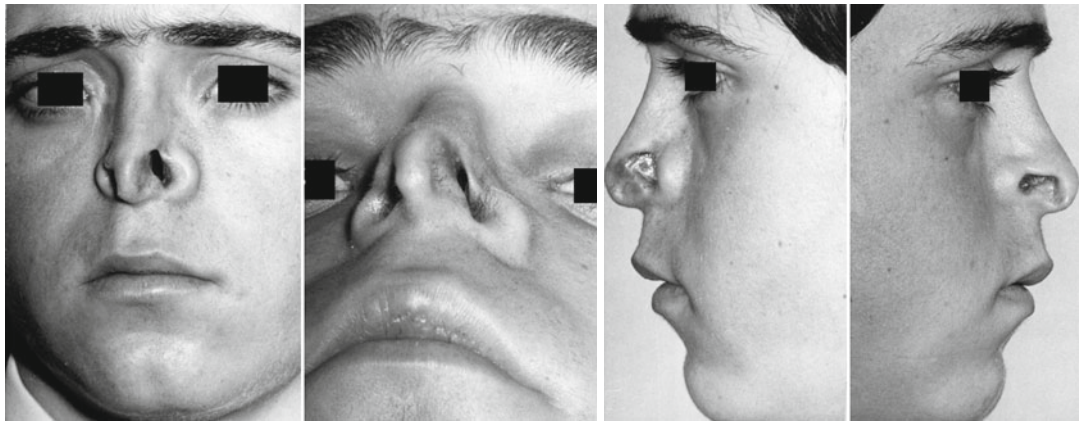

Fig. 34.5 Fifteen-year-old boy with congenital lack of both alar cartilages (Pirsig 1989)

34.3.3 Physiological Septal Deviation

The anatomical term 'physiological septal deviation' was introduced by Zuckerkandl (1882) who defined this type of septal deformation as a bended septum within the asymmetrical human skull. He published several examples on beautiful lithographs (Fig. 34.6). Comparable histologic sections of his own cases were published by Gray (1978) who kindly left me a few of them like in Fig. 34.3. In more recent publications (Gogniashvili et al. 2011; Mlynski 2005) on this topic, the incidence of the physiological septal deviation is reported between 30 and 75 % for children and between 13 and 96 % in adults, with strikingly less patients reporting to suffer from subjective symptoms (Hanif et al. 2003). From the physiological point of view, it is practical to characterise the physiological septal deviation by normal endonasal resistance (Gogniashvili et al. 2011). Many of these physiological septal deviations develop during the fetal life in connection with the asymmetrical maxillary growth. Often the non-pathological role of this deviation is not recognised and a septal operation is indicated, although it is useless or even worsens the nasal symptoms. A septal body may be mistaken as pathological septal deviation or the real cause of nasal obstruction such as a problem of the nasal valve or an inspiratory ala collapse is failed to be recognised.

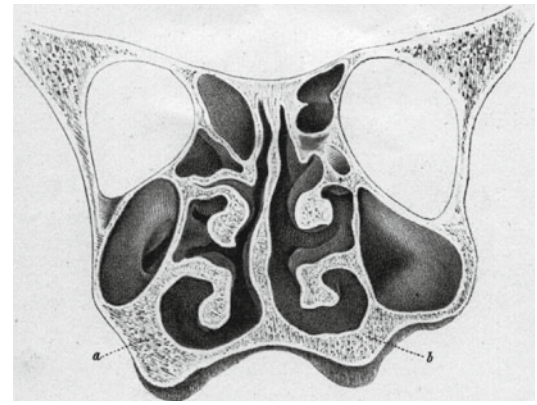

Fig. 34.6 Physiological septal deviation in an asymmetrical skull; The thicker spongiosa (**a**) compared to the thinner one (**b**) narrows the right maxillary sinus (Zuckerkandl 1882)

Until now, the diagnosis of the 'physiological septal deviation' has mainly been made by nasal endoscopy and the subjective history of the patient to be free of nasal breathing problems. In a prospective cohort study, Gogniashvilli et al. (2011) investigated 158 patients between 18 and 40 years using rhinoresistometry, acoustic rhinometry, endoscopy and visual analogue scales for subjective complaints. They defined the normal one-sided nasal resistance as less or equal to 0.35 sPalcm^3 at a flow velocity of 250 cm^3/s. Applying this benchmark, the unselected group of non-rhinological patients was differentiated into 144 subjects with physiological nasal resistance and 44 with pathological septal deviation.

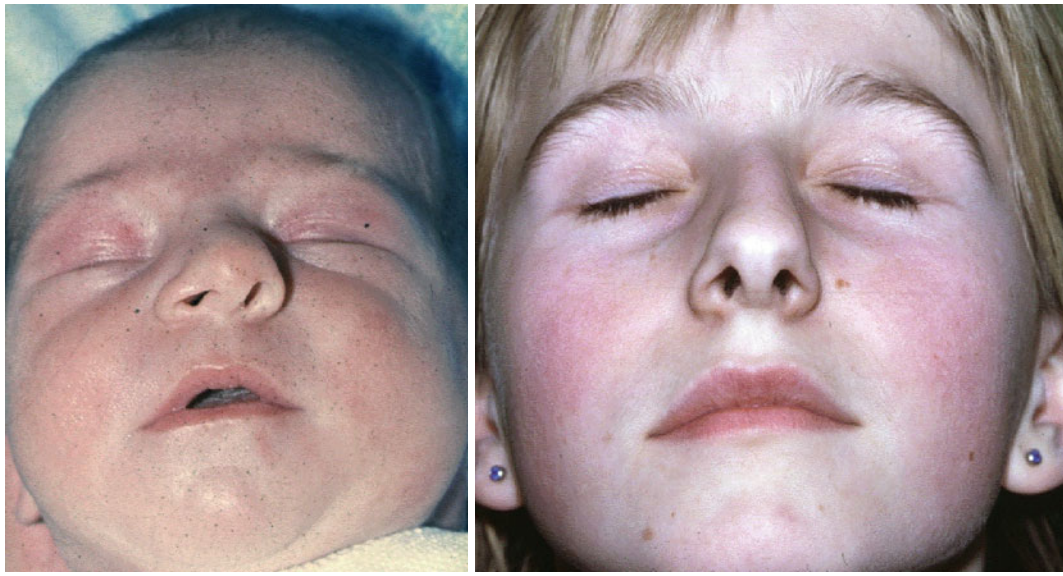

Fig. 34.7 Female newborn with a non-replaceable nasal deviation (*left*). 12 years later, the girl presents with an inverted C-shaped nasal deviation and nasal obstruction (*right*) (Pirsig 1992; unpublished)

This means an incidence of 72.2 % physiological septal deviation in an unselected cohort which fits well with the data mentioned above.

34.3.4 Congenital Nasal Deviations

The histological depiction of a slight septal deviation in a newborn without signs of an acute injury is documented in Lindsay Gray's Fig. 34.3. In neonates, two types of nasal deviation are observed: a septal dislocation that can easily be replaced in the midline and a nasal deviation that cannot be replaced by manipulation. The first type is considered as nasal trauma during delivery. The second type had been published by several authors since the end of the nineteenth century (Pentz et al. 1994) and more detailed by Cottle (1951) who generally concluded: 'For these, expectant waiting is recommended unless there is complete inability to breathe and eat. One sees remarkable improvement in the appearance and development of these noses without surgical intervention. During the first decade, however, some will require surgical aid'. To find out the incidence of these two types of nasal deviation, we investigated 3,425 children, born in 2 years between 1980 and 1981, in the Obstetric Department of the University of Ulm, Germany. A total of 110 (3.23 %) of these neonates, belonging to the Caucasian population, showed deviated nasal structures. 81 (2.37 %) of these dislocated septa could easily be replaced by a closed reposition. In 29 (0.86 % of 3,425) newborns, reposition of the deviated nasal structure was impossible, thus leaving the baby with a deviated septum and bony pyramid like the neonate in Fig. 34.7 (left) who presents nasal deviation to the left, oblique columella and asymmetrical nostrils.

Over a period of 11–12 years, 14 children out of 29 newborns with the non-replaceable nasal deviation were prospectively followed by the author and a second otorhinolaryngologist (Pentz et al. 1994). No child had a history of nasal trauma in the meantime. The results show that the newborns' noses, deviated intrauterinely due to some unknown reasons, did not spontaneously restore in each case. Nine children had a completely straight bony pyramid, symmetric nostrils and reported of subjectively normal breathing. Four children had proven nasal allergy and presented bilateral hypertrophy of the inferior turbinates. Eight of the nine septa showed slight deviations, spurs or crests. Eight of these nine children had malocclusion, two of them

having been treated orthodontically. We considered these eight children as having a 'physiological septal deviation' in an asymmetrical skull, as described by Zuckerkandl in 1882 (Zuckerkandl 1882). However, five girls of the 14 children showed a deviation of the nasal pyramid to the same side as found at birth, in one girl markedly (Fig. 34.7 – right), in a second girl only minor and in three cases slightly. In four of these five girls, a longitudinal deviation, corresponding to the deviation of the bony pyramid, was evaluated by nasal endoscopy and measured by acoustic rhinometry. One of the five girls complained of moderate obstructive breathing, which was caused by allergic rhinitis. All five girls showed a malocclusion, two of them being under orthodontic therapy.

34.3.5 Acromegaly

Acromegaly is an endocrine disease due to growth hormone excess originating from somatotrophic adenoma of the pituitary gland. Patients complain about the coarsening of the facial contours caused by a bony proliferation of the skull and mandible and by an excessive nasal growth. Our groups in Ulm and Zurich (Vetter et al. 1984) investigated the growth mechanism of the septal cartilage in six acromegalic patients. Small strips of septal cartilage were obtained during septoplasty from healthy adults or during transnasal hypophysectomy from acromegalic patients. Growth activity in five different areas of the septal cartilage was measured by in vitro incorporation of 35 S-labelled sulphate and 3 H-labelled thymidine. The growth activities in the posterior area, which is situated anterior to the septoethmoidal junction, were significantly enhanced compared to a control group of hormonally normal adults. Growth activities in the anterior caudal end and in the suprapremaxillary area were not different in both groups. This indicates that growth hormone excess in acromegaly enhances human septal growth by stimulating the growth activities in the posterior area.

In another study (Vetter et al. 1985), five different enzymatic pathways were analysed in these septal areas. Cathepsin D, an acid proteinase, was not influenced by the augmented growth hormone level in acromegaly, whereas cathepsin B, a neutral proteinase, showed its highest activity in the caudal prolongation and the posterior area and was significantly increased in all areas in acromegaly. Beta-hexosaminidase activity was highest in the central and posterior area and caudal prolongation of the septum. In acromegaly, a significant increase of its activity was found in the suprapremaxillary and posterior area. Acid phosphatase activity was highest in the caudal prolongation of the septum, but its activity was significantly increased in all tested areas in acromegaly. Alkaline phosphatase activity could only be found in the posterior area and the caudal prolongation in healthy adults. However, in acromegaly this enzyme could be detected in the central area and the posterior end of the suprapremaxillary area, suggesting an altered process of mineralisation. Thus, a distinct local pattern of enzymes related to intercellular substance metabolism and mineralisation can be demonstrated in the septal cartilage of healthy adults and acromegalic patients.

34.3.6 Damaged or Lacking Triangular Cartilage

What happens when parts of the septodorsal cartilage are damaged or removed? Verwoerd and Verwoerd-Verhoef (2010) found that the behaviour of hyaline cartilage of the human nose appeared to be comparable to that of other mammals, especially of rabbits. Their results can be supported by the following own observation. Because of histologically suspected sarcoma, the left nasal bone and triangular cartilage in a 6-year-old boy had to be resected in 1973 (Pirsig 1992). Fortunately, a curable circumscribed osteomyelitis was diagnosed. Following this boy 7 years later, we found a shortened left nostril with the bony pyramid deviating to the left and the nasal tip deviating to the nonoperated side. The left piriform aperture was positioned higher and the left nasal process of the maxilla was reduced. The left inferior turbinate was smaller than the right-sided one, the caudal end of the septal cartilage slightly deviated to the right

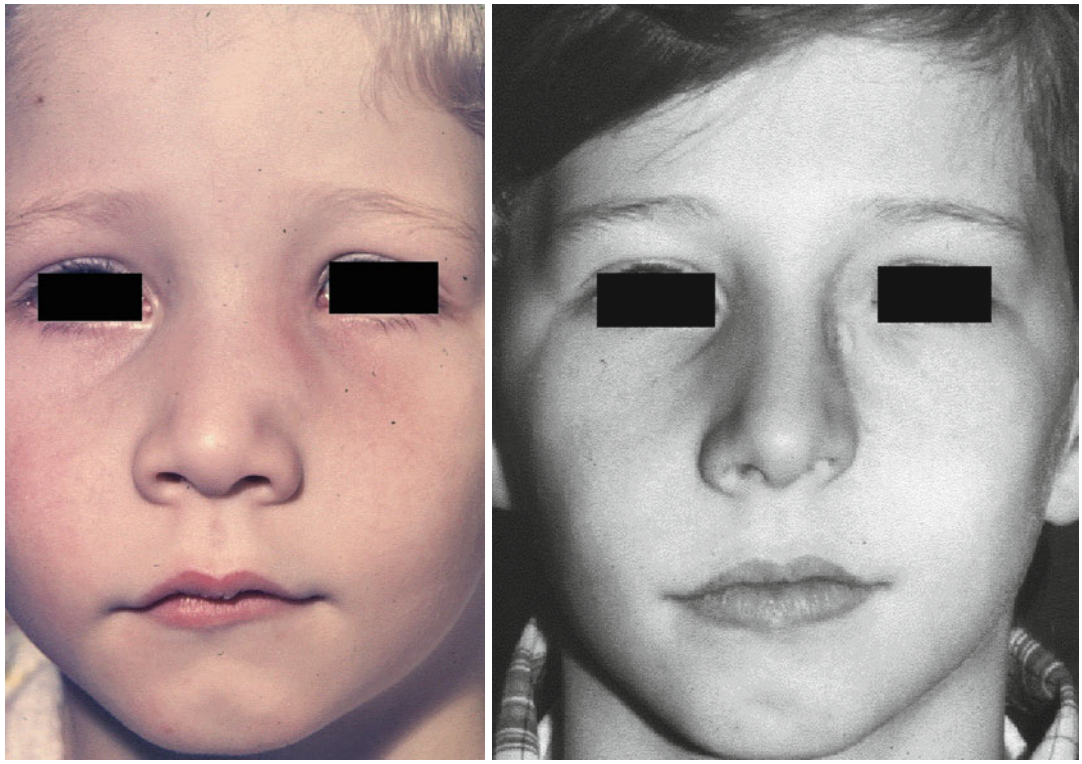

Fig. 34.8 6-year-old boy before resection of left triangular cartilage (*left*); midfacial growth inhibition at age of 13 years (*right*) (Pirsig 1992)

(Fig. 34.8). Thus, the resection of one triangular cartilage and the nasal bone in connection with an infection affected the growth of nasal and midfacial structures. These findings are similar to Poublon's results from the Rotterdam group after unilateral resection of the triangular cartilage in growing rabbits (Poublon 1987).

34.3.7 Some Histological Aspects of Traumatised Nasal Cartilage

As there is a detailed description of this topic by Verwoerd-Verhoef in this book about the sequelae of different kinds of injury to the nasal cartilage in man and especially in growing animals, I confine to three topics associated with the pathophysiology of the human nasal cartilages.

The first aspect are the effects of incomplete fractures which are the main reasons for the more or less obstructive bending of the septal cartilage. During nasal surgery these bends are often difficult to transform into a straight septal plate, a problem which Hunter Fry associated with the disturbed interlocked stresses within the hyaline nasal cartilage (Fry 1967). Ten Koppel et al. (2003) added new convincing data to this problem, more discussed below. Figure 34.9 shows the biopsy from a vertical strip of septal cartilage with an incomplete fracture. The 8-year-old boy had a nasal trauma some years ago and underwent a septoplasty alio loco because his anterior septum obstructed both anterior nasal cavities (Pirsig 1979). In Fig. 34.9, a scar of fibrous tissue is filling the cartilaginous defect, measuring approximately 30 % of the thickness of the intact cartilage. According to the finds of Fry (1967) and Ten Koppel et al. (2003), one should expect a bending of the cartilage to the other side. One possible explanation for the bending to the opposite direction may be that the power of the granulation tissue which first fills the incomplete

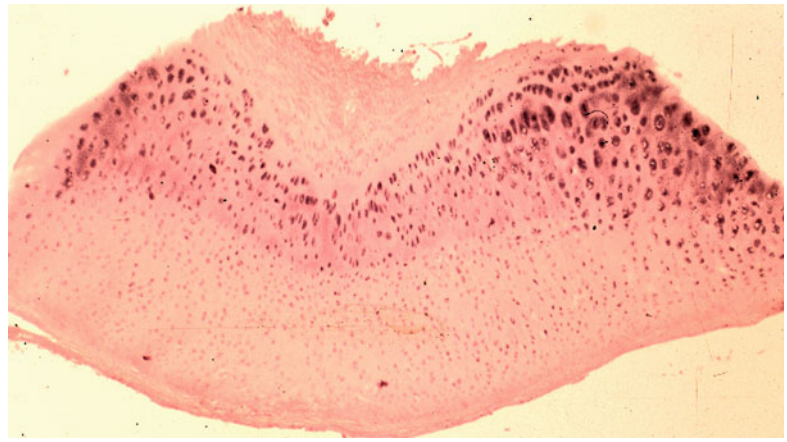

Fig. 34.9 Histological section of a biopsy of septal cartilage with a vertical incomplete fracture filled with scar tissue in an 8-year-old boy. Hematoxylin-eosin (Pirsig 1979)

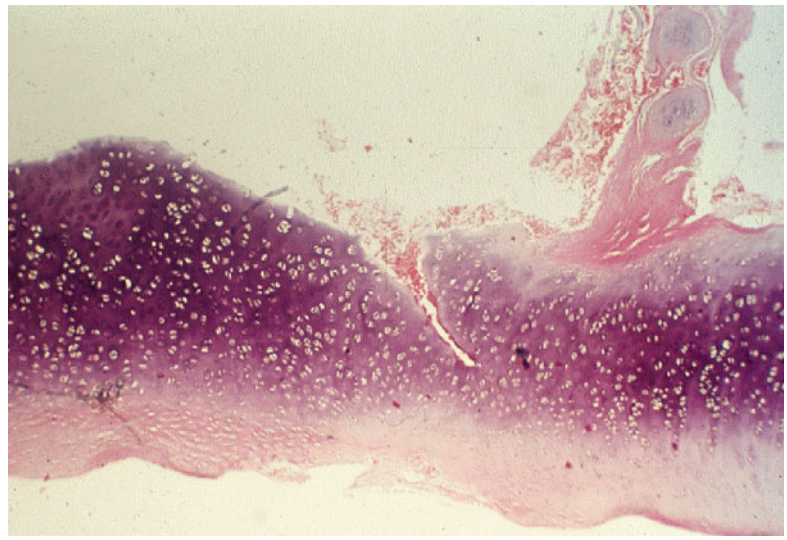

Fig. 34.10 Histological section of a biopsy of a traumatised septal cartilage at the age of 3 years, taken from the 12-year-old boy. In the upper right corner, two pieces of regenerated cartilage grown within the damaged perichondrium. Hematoxylin-eosin (Pirsig 1979)

fracture during healing is strong enough to achieve the bending to the unexpected direction. In the 1960s and 1970s when septoplasty was often performed only by unilateral elevation (tunnelling) of the mucoperichondrium from the septum, recurrences of septal bending were observed, although the septum looked straight at the end of the operation (Eitschberger et al. 1980). One reason was that small incomplete cartilaginous fractures on the side with the mucoperichondrium left attached could cause bending because the elevated mucoperichondrium had changed the balance of the interlocked stresses within the cartilage in an unpredictable manner. That's why many rhinosurgeons bilaterally elevate the mucoperichondrium to better recognise pathologies and incomplete scars of the septal cartilage.

The second aspect is the partial regeneration of pieces of septal cartilage within its traumatised inner perichondrium in children. The nasal perichondrium is built up by a thick outer layer and a thin inner layer. The inner layer usually remains connected with the hyaline cartilage when properly elevating the mucoperichondrium from the septal cartilage during surgery, because it contains fibres which end inside the cartilage. In case of its damage by surgical or nonsurgical trauma, the inner layer has the potential to create new cartilage (Duynstee et al. 2002; Pirsig and Lehmann 1975; Pirsig 1979). Figure 34.10 shows the histological section from a piece of destroyed anterior

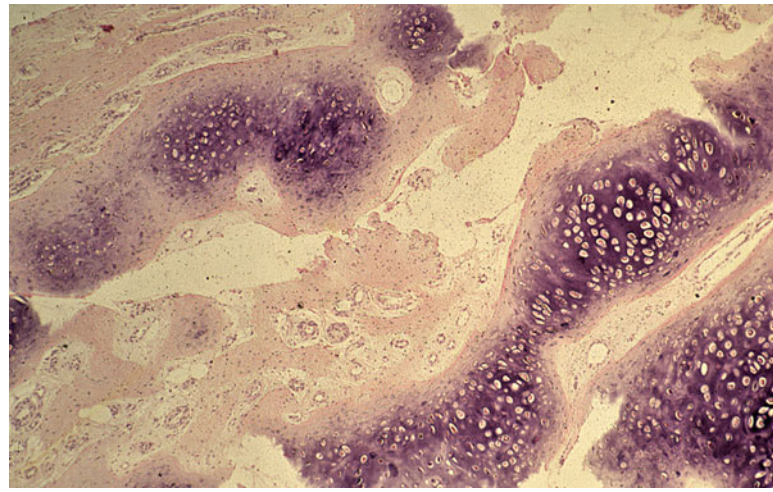

Fig. 34.11 Histological section of a biopsy from a cartilage-like layer attached to the fractured anterior septum of a 9-year-old boy. Islands of regenerated cartilage and vessels in the scared perichondrium. Hematoxylin-eosin (Pirsig and Lehmann 1975)

septal cartilage removed during septoplasty in a 12-year-old boy. In the right upper corner, two pieces of new cartilage are visibly grown within the torn perichondrium of the damaged septal cartilage after the untreated nasal injury at the age of 3 years (Pirsig 1979).

In Fig. 34.11, the histological section shows an accumulation of regenerated hyaline cartilaginous islands embedded in connective tissue with vessels. The biopsy was taken from the cartilage-like layer firmly attached to the remnant of the anterior septal cartilage of a 9-year-old boy during septoplasty. These islands had developed in the multiply torn perichondrium of the damaged anterior septum within 8 years of impeded nasal growth. The boy suffered a severe frontal nasal injury at the age of 1 year which caused a hypoplastic nose with obstruction of the anterior nose (Fig. 34.12). Unfortunately, such a layer of 'floppy cartilage' can only be used as 'filling tissue', but not for anterior septal reconstruction (Pirsig and Lehmann 1975).

The third histological example demonstrates how the lack of nasal cartilage leads to atrophy of nasal erectile lining. It is well known that submucous septal resection may induce atrophy of the septal mucoperichondrium and septal perforation, while interposing pieces of cartilage between the mucoperichondrial flaps can markedly reduce this tendency to atrophy (Schwab and Pirsig 1997). Nasal septa from cadavers with previous submucous septal resection were histologically investigated and compared with age-matched nonoperated septa (Bewarder and Pirsig 1978; Schwab and Pirsig 1997). In areas where the cartilaginous septum had been removed, most of the secretory epithelium was replaced by squamous cells. The submucous layer was markedly reduced in thickness (Fig. 34.13). The submucous vessels were reduced in number and size, and the submucosal glands were partly atrophic. The site of the former septal cartilage was filled with dense connective tissue containing only a few vessels. These finds demonstrate the importance of interposing autogenic cartilage plates between the elevated perichondrium flaps at the end of septoplasty to reduce the propensity for mucosal atrophy.

34.3.8 Transposition Technique

In cases of severe destruction of the anterior septal cartilage due to a frontal trauma, an established technique to reconstruct the caudal septum and the valve area is to remove the remnants of the anterior septum and to replace them by a boomerang-shaped cartilaginous or bony part from the posterior septum. In the late 1960s, I learnt this procedure from Helmut Masing in Erlangen, Germany, who termed it 'transposition technique'. After satisfying results in adults, we used this technique in an 11-year-old boy suffering from bilateral nasal obstruction after a frontal nasal injury

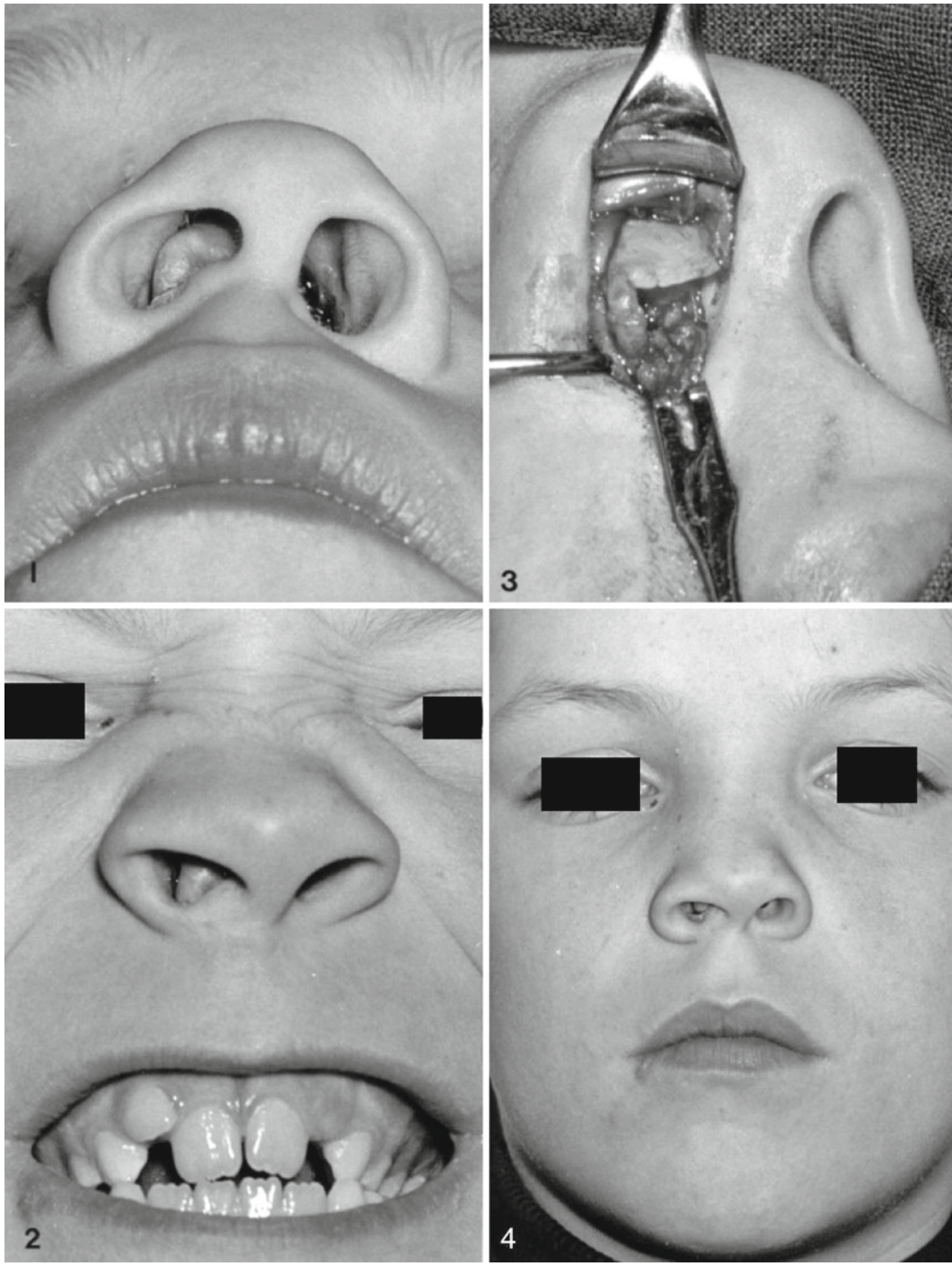

Fig. 34.12 Three pre- and one intraoperative photographs of the 9-year-old boy in Fig. 34.11. Figures of base (*1*), with damaged bite (*2*), intraoperative (*3*), and frontal view (*4*). (Pirsig, unpublished)

some years ago. Via the hemitransfixion incision an 'empty columella' was found with a few small cartilaginous remnants isolated from the scars between the mucoperichondrial flaps. From the posterior septum which was not yet ossified, a boomerang-shaped cartilage was harvested. This

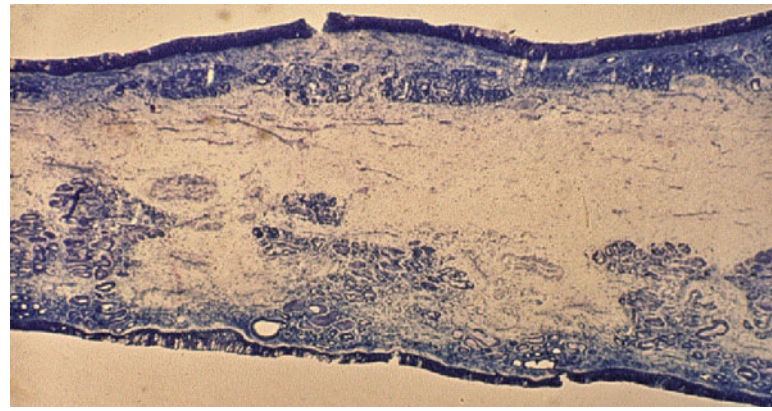

Fig. 34.13 Histological section through septal remnant after submucous septal resection 10 years ago in a 51-year-old man; Giemsa staining (Pirsig, unpublished)

transplant was anteriorly fixed between the hypoplastic anterior nasal spine and the supra-tip region under the nasal dorsum to restore the valve angles. The cartilaginous remnants from the anterior septal region were inserted into the posterior septal region. A follow-up after 11 years postoperatively including an X-ray film of the nose (Fig. 34.14 – right) revealed the ossification of the posterior autogenic transplant. This was one reason why the transplant did not grow within the 11 years postoperatively. As a consequence I prefer to use autogenic cartilage from the ear to reconstruct the destroyed anterior septum in children instead of harvesting cartilage from the posterior septum (see back-to-back technique). The nasal appearance after 16 postoperative years is shown in Fig. 34.14. The young man reported a normal breathing in all the years. The nose with a slightly depressed lobule showed a retracted columella and a slight maxillary retrusion as signs of growth inhibition.

34.3.9 Frontal Nasal Trauma

As mentioned above, the septodorsal cartilage is the dominating structure for nasal and midfacial growth. This also means if the septodorsal cartilage is markedly damaged by mechanical loads or diseases, this is mirrored in the whole nose and often in adjacent midfacial tissues. Thus, as to the long-term outcome of a septorhinoplasty, the crucial effect for the nasal reconstruction depended on the repair of the damaged septodorsal cartilage and not of the distorted nasal bony structures. A mostly satisfying repair is much easier to perform in the nose injured by a lateral load with lateral distortions of the nasal tissues than in the nose after an anteroposterior load with infraction and dislocation of the bony and cartilaginous nose. In Fig. 34.15, we see a girl with an untreated frontal nasal trauma at the age of 6 years (left). The nose shows a slight bony deviation to the right side, a minor C-shaped bending of the dorsum, and a small saddle. The harmony of the midfacial proportions is not yet disturbed. Her photograph at age 17 (Fig. 34.15 – middle) shows an underdeveloped nose, still a 'child's nose', with a marked bony deviation, the saddling more pronounced and the lobule hypoplastic. The maxilla is retruded. The midfacial harmony is severely disturbed. On the sketch (Fig. 34.15 – right), drawn during the open approach at age 17, the pathologies of the bony and cartilaginous nasal structures are clearly visible: distorted, asymmetric, infractured nasal bones, asymmetric piriform aperture, scars in the fractures of the bent triangular cartilages and the deformed and fractured caudal septal cartilage. A closed reposition at the time of the nasal trauma would probably have prevented the development of the crooked bony pyramid, but not the formation of the numerous scars due to the incomplete and complete fractures of 'the T- bar- shaped septodorsal cartilage', to use a term of Carel Verwoerd from Rotterdam, the Netherlands. This is an example of an acutely injured nose which cannot properly be treated by immediate surgery because the whole septodorsal framework is irreversibly disturbed by the anteroposterior load!

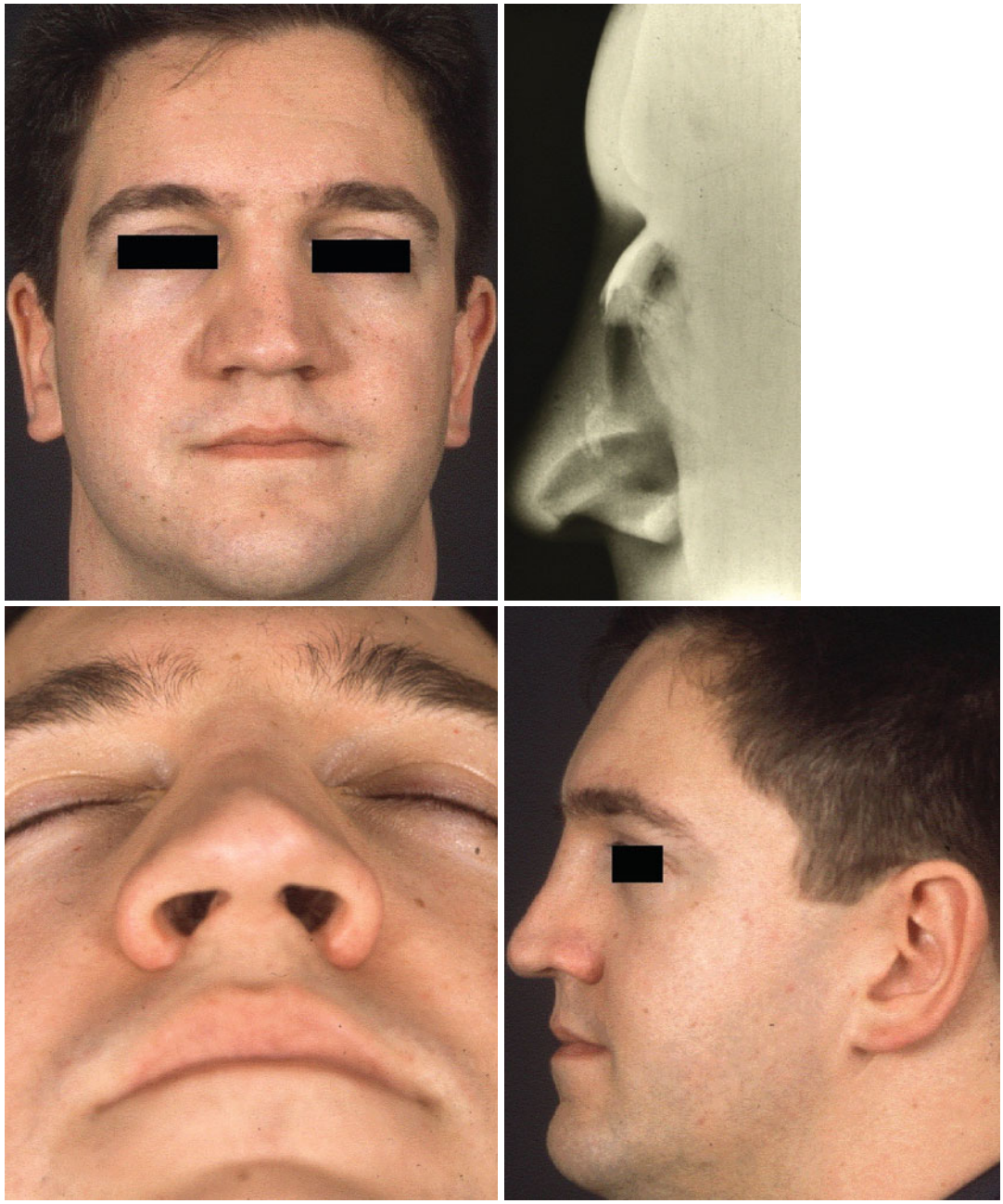

Fig. 34.14 Young man, 16 years after a septoplasty at the age of 11 using the transposition technique. Ossification of the transplant visible on X-ray film 11 years postoperatively (Pirsig, unpublished)

34.3.10 Lateral Nasal Trauma

In Fig. 34.16, we see the preoperative photographs of a girl of 11 years who had an untreated mainly lateral nasal trauma at the age of 6 years and complained of permanent mouth breathing and severely reduced olfaction. At school she was teased as 'butter witch'. A functional and aesthetic septorhinoplasty was performed including paramedian, lateral and transverse osteotomies and

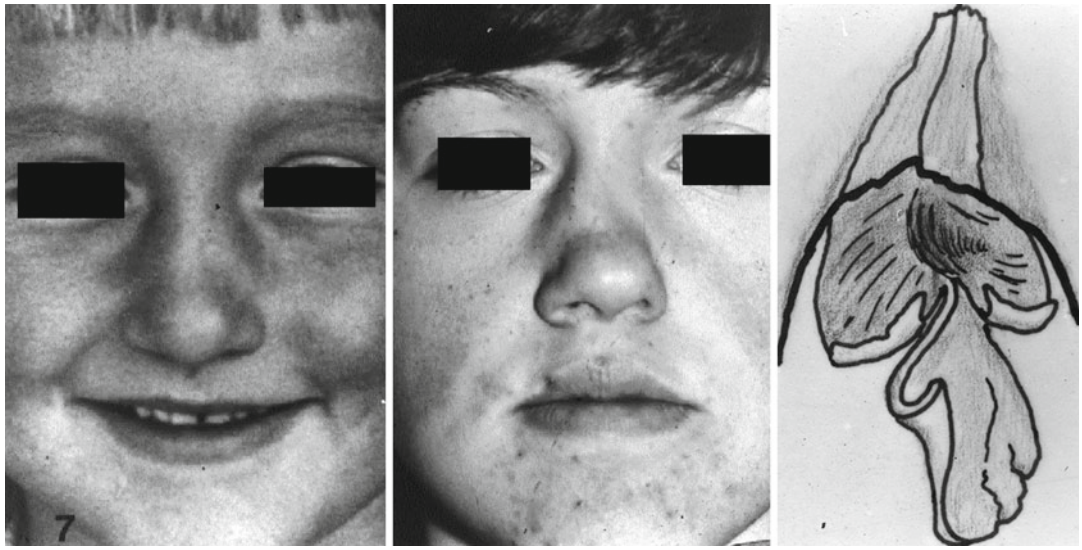

Fig. 34.15 Untreated nasal trauma in a 6-year-old girl (*left*), at 17 years (*middle*), and drawing with pathologic finds of the nasal bones and septodorsal cartilage (*right*) (Pirsig 1992)

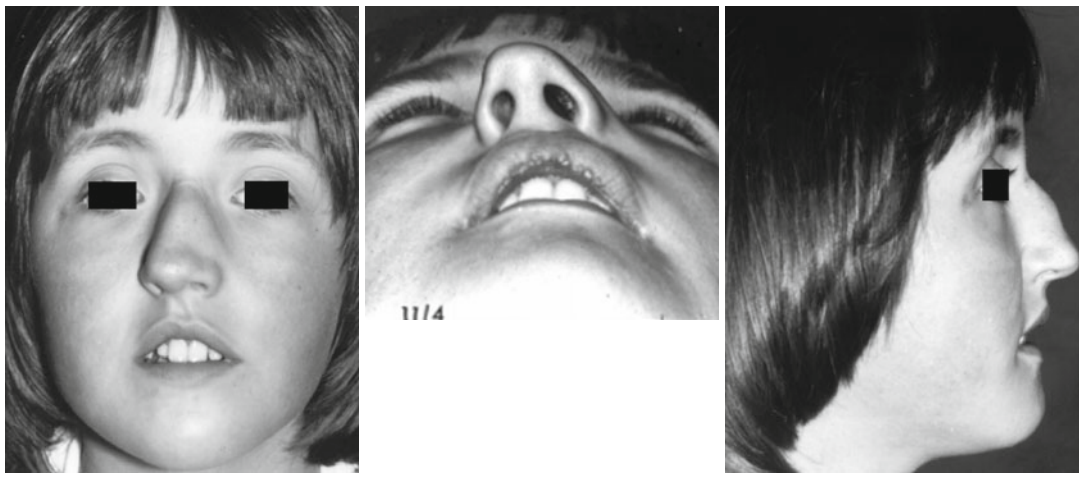

Fig. 34.16 Girl of 11/4 years preoperatively (Pirsig 1986)

removal of a cartilaginous-bony hump (Pirsig 1986). In Fig. 34.17 we look into the face of a self-confident young woman with an inconspicuous nasal appearance, 8 years after nasal surgery. Her sense of olfaction had markedly improved. If this girl at the time of her nasal injury had been treated by a closed nasal reposition, most of her emotional and physical suffering due to her nose problem would probably have been avoidable. This example demonstrates how the osteotomised nasal bones follow the position of the reconstructed septodorsal cartilaginous framework. It also underlines the experience that nasal osteotomies do not impede nasal growth in children. Further it shows that the outcome of repaired noses damaged by a lateral load is much better than the long-term results after reconstructing noses damaged by a frontal load as seen in Fig. 34.14.

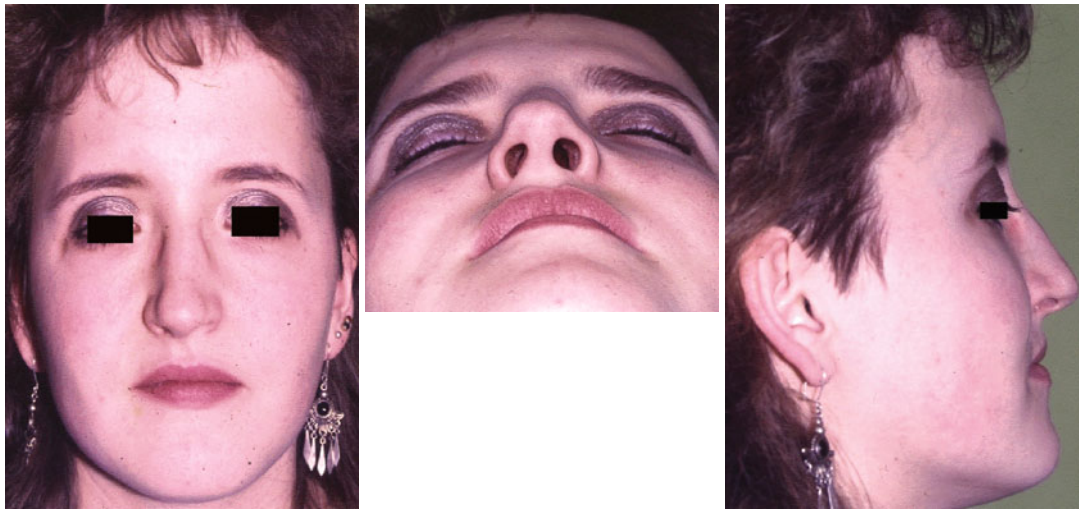

Fig. 34.17 Young woman as in Fig. 34.16, 8 years after functional and aesthetic septorhinoplasty (Pirsig, unpublished)

34.3.11 Scoring the Nasal Cartilages

Cartilage can be shaped by scoring, gridding or cross hedging to straighten a convexity or to sculpt it. In an ex vivo experiment on nasal septal cartilage of adult rabbits, Ten Koppel et al. (2003) demonstrated that there is a clear linear relationship between the depth of incision and the resulting degree of cartilage bending when incisions are made up to half of the cartilage thickness. If the incision surpasses the half of the cartilage, the resulting bending becomes unpredictable. In addition, their in vivo experiments showed 10 weeks after surgery that the scored cartilage of the healed septum maintained the imposed shape and its degree of bending in all animals towards the non-scored side. The authors conclude that with the results of this model, the effect of cartilage scoring can be better predicted during rhinosurgery. This may hold true for adult nasal cartilages.

On the other side we know from van Loosen et al. (2000) who investigated septa from birth to 62 years that the thickness of the septal cartilage is considerably variable in both the anteroposterior and cranial-caudal direction. This pattern of cartilaginous thickness remains persistent throughout lifetime, but cannot exactly be evaluated during surgery with the mucoperichondrium attached or elevated from the septal cartilage. The surgeon can only recognise the cartilaginous thickness at defined sites by cutting through the whole cartilage. If only one side of the cartilaginous surface is incised, one cannot find out where half of the septal cartilage is reached (see Fig. 34.9). Therefore, a vertical scoring of exactly the same depth over a length of 3 cm, for instance, will result with slight differences in bending due to the diverse thickness of the septal cartilage over this length in the valve region. This means the predictability of the amount of bending becomes questionable.

Another reason for the unpredictability of the scoring effect is connected with the incomplete wound healing of the septal cartilage (Pirsig 1979; Verwoerd et al. 1989; Verwoerd-Verhoef et al. 1998). After healing of an incompletely incised cartilaginous surface, a scar of connective tissue fills the cartilaginous gap, which influences the amount and direction of bending. Figure 34.18 shows the part of a distorted septal cartilage (3.7 cm long) removed during revision septoplasty at the age of 14 years (Pirsig 1992). The boy had been operated 6 years before alio loco because of traumatic septal deviation. The previous surgeon had unilaterally scored the septal

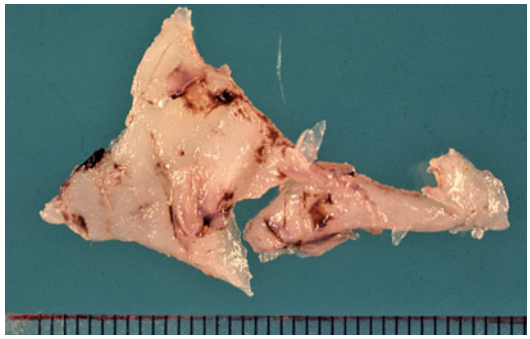

Fig. 34.18 Remnants of the anterior septal cartilage of a 14-year-old boy. The cartilage had been scored by 10 incisions 6 years ago, which resulted in partial resorption and unpredictable bending of the surface (Pirsig 1992)

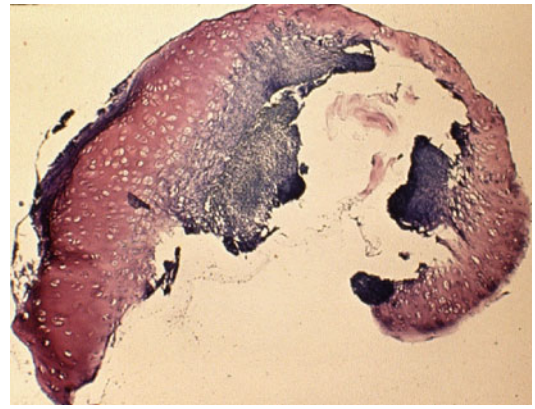

Fig. 34.19 Septal abscess 10 days ago. Histological section through a biopsy of the partially necrotizing septal cartilage; toluidine blue (Pirsig 1979)

surface by oblique, nearly parallel incomplete incisions which resulted in the markedly distorted piece of septal cartilage removed at revision septoplasty. One can recognise the remnants of the parallel scorings and their diverse mode of healing ranging from resorption with small cartilaginous defects to hardly visible scars of the cartilaginous surface. This irregular surface pattern is due to the different thickness of the septal cartilage and its incomplete wound healing following scoring. That's why I don't recommend scoring septal cartilage in children.

34.3.12 Nasal Septal Abscess

Among the acquired nasal injuries during childhood, the septal abscess can not only destroy the septal cartilage but also affect midfacial tissues. The growth inhibition is more pronounced the earlier the abscess happened, especially in the first decade. The majority of septal abscess is caused by acute nasal injury. Blood vessels are disrupted in the mucoperichondrium, which is not torn, because it is thicker and more elastic in children than in adults. The resulting hematoma is highly susceptible to infection. White blood cells invade the cartilage, create an acid pH and destroy it within some hours. This happens due to cathepsin D, a necrolytic and autolytic collagen-degrading enzyme with optimum in the acid pH. This enzyme is normally distributed all over the healthy septal cartilage. This finding helps to explain the rapidity of the cartilage destruction (Fig. 34.19) in many cases of septal abscess (Pirsig 1979).

Immediate action is required. After puncture for bacterial culture, the abscess is drained through a hemitransfixion incision. Pus and necrotic tissues are removed. The defect is immediately reconstructed by transplantation of autogenic ear cartilage to avoid dorsal saddling and columellar retraction. The incision is left partially open for drainage. Loose internal dressings are applied; antibiotics are administered systemically. It has been shown that each septal abscess will result in some nasal growth inhibition. However, the immediate transplantation of autogenic cartilage can mostly prevent the typical saddle nose formation (Huizing 1984; Pirsig 1984).

Figure 34.20 shows that the amount of growth inhibition caused by a septal abscess depends on the age of the affected child: the earlier the nasal injury, the more pronounced is the damage to the nose and midface (Pirsig 1984). The three adolescent girls came for nasal surgery, all at the age of 16 years. All had a history of a drained septal abscess. During surgery in all of them a subtotal loss of the septal cartilage was revealed. The nasal injury occurred at 3 years (left), 5 years (middle) and 7.5 years (right). The differences in nasal length, height, tip projection and maxillary retrusion are striking.

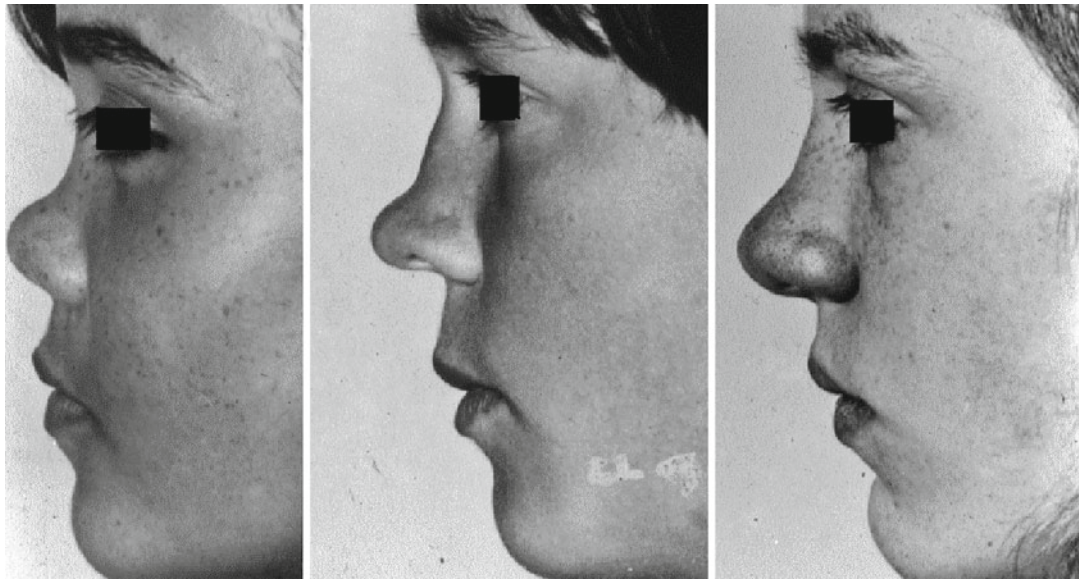

Fig. 34.20 Three female adolescents aged 16 years with drained septal abscess at age 3, 5 and 7.5 years, respectively (Pirsig 1984)

34.4 Part IV: Remarks on Nasal Reconstruction

34.4.1 Anterior Nose and Nasal Cavities

The nasal cartilages form a complex triangular framework for a mobile nasal lobule which acts as the portal to the upper airways. The eye-catching shape of this cartilaginous pyramid may provoke emotions ranging from delight at first sight of a beautiful person to frightful reactions setting eyes on destroyed nasal remains. The increase of the nose in size also mirrors the development of Homo sapiens sapiens into different populations during mankind's settling in the whole earth from Africa. Or, as Desmond Morris summed it up: 'the human nose grew taller and longer as mankind spread out and away from its hot moist Garden of Eden, keeping its air-conditioning function up to scratch' (Morris 1985).

The composition of this cartilaginous framework is so unique in each individual and may concern rhinosurgeons because they cannot predict the outcome of their surgical procedures. Essential functions for the whole airways are triggered and controlled in the anterior nose. On the other hand, the protruding position in the midface makes the nose more vulnerable against external damages. No wonder that the anterior nose is also the site of most nasal obstructions caused by cartilaginous and bony distortions as mentioned above. Although prospective studies on the incidence of rhinosurgical mistakes and complications are lacking, the adverse results are most often associated with the surgery of the nasal cartilages. Cartilages heal following their intrinsic laws and do not behave the way the surgeons want. In particular complications of septoplasty are due to wrong indications as a consequence of an incorrect or incomplete analysis and interpretation of the anatomical structures and the nasal functional tests (Schwab and Pirsig 1997).

Therefore, the clinical diagnostics should especially focus on the finds of the anterior nose, supported by endoscopy, rhinomanometry, acoustic rhinometry, rhinoresistometry and long-term study of the nasal cycle (Lang et al. 2003; Mlynski 2005). Cole and co-workers (Cole 1993; Cole et al. 1988), who contributed many basic data on the functions of the anterior nose, concluded from their studies as to nasal treatments

that it is seldom necessary to extend septal and/or turbinate surgery far beyond the piriform aperture in the treatment of nasal obstruction (Cole 2003). For many patients I can fully support this statement.

To restore the disturbed structures of the anterior nose, our surgical options are septorhinoplasty to form a straight anterior septum and correction of the nasal valve regions and enlarged erectile tissues, for instance, by turbinoplasty of the inferior turbinate. The septal turbinates should better be preserved. The reconstruction of the valve region is sometimes more effective for breathing than a septoplasty alone. If transplants or implants are used, they should be cartilage-like as to elasticity, thus avoiding the creation of an immobile and vulnerable anterior nose. This also means to prefer autogenic tissues. If autogenic bone is used, it should be a boomerang-shaped piece instead of a rigid L-shaped bone.

The aim to reconstruct the nose posteriorly to the valve regions is to create physiological slitlike nasal cavities providing a proper nasal resistance, turbulence and nasal cycle for breathing, air-conditioning and olfaction. This cannot be achieved by performing one schematic surgical procedure, but only by applying several technical options tailored for the individual pathological nasal finds. This means for the septum that it need not be reconstructed as a straight plate in the middle and posterior nose, but it should be placed approximately in the middle between the always asymmetrical lateral nasal walls. It is of utmost importance to create an adequate distance of the septum to the erectile tissues of the lateral walls which enables the achievement of the above mentioned functions (Mlynski 2005). This may also mean to leave a physiological septal deviation as it is grown or to transform a crooked septum into a physiological septal deviation. Figure 34.21 shows an example of this 'philosophy'. The crooked and airway obstructing septum to the left impacted by the medially deformed right-sided middle turbinate was surgically corrected and is still slightly deviated to the left. In addition, the right-sided inferior turbinate was submucously reduced. After 3 months the slitlike nasal cavities enabled normal breathing with a bilateral nasal cycle.

34.4.2 One Option to Treat a Nasal Valve Stenosis

Several procedures have been published to treat a nasal valve problem (Bloching 2007; Kern 1978). The following technique has successfully been used since 1975 by the author. The indication is a valve stenosis caused by a mostly congenitally too long caudal end of the triangular cartilage, often without a returning of the lower margin and a valve angle less than 10°.

A rhomboid piece of skin (marked red in Fig. 34.22) is excised from the cul-de-sac. After elevation of the nasal mucosa from the posterior aspect of the triangular cartilage, the cranial surface of the caudal end of the triangular cartilage (here depicted with a tiny returning) is freed from connective tissue and excised cranially from the remaining triangular cartilage (marked blue in Fig. 34.22). Closure of the incision using 5-0 sutures creates a slightly curved new part of the nasal valve region with an angle larger than 20° that acts as a bend which transforms inspiratory laminar airstreams in more turbulent ones. The efficiency of correcting a disturbed nasal valve region can be increased by adding the anterior turbinoplasty in case of an enlargement of the anterior inferior turbinate as shown by acoustic rhinometry (Lenders and Pirsig 1990). Especially in case of the physiological septal deviation, both methods may be sufficient to solve the functional breathing problem without touching the septum.

34.4.3 Back-to-Back Technique to Reconstruct the Anterior Septum

The severe destruction of the anterior nasal septum from trauma, including septal abscess and perforation, frequently produces saddling of the cartilaginous nasal dorsum with enlarged angles of the nasal valve. Functional and aesthetically acceptable long-term results of anterior septal and nasal valve reconstruction could be achieved in 26 patients after a mean follow-up of 36 months using a straight and balanced back-to-back

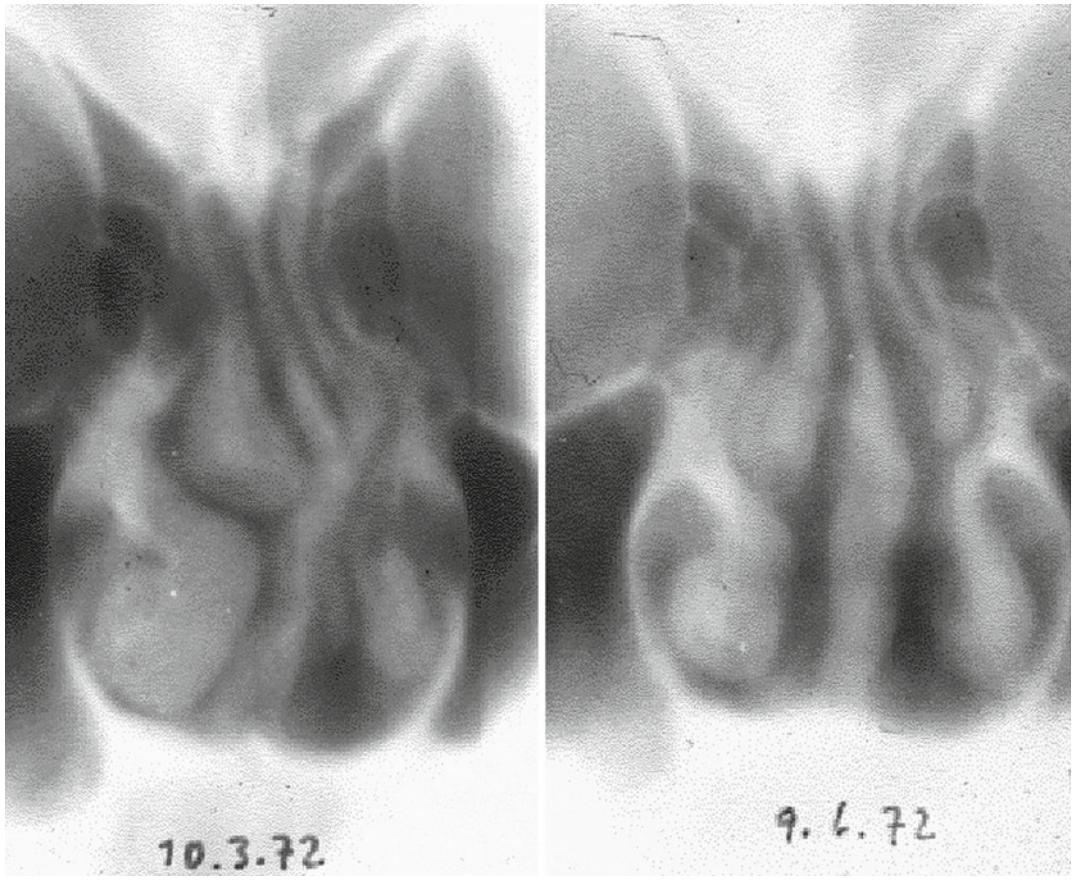

Fig. 34.21 X-ray images of a patient with septal deviation. *Left*: preoperatively. *Right*: 3 months after septoplasty and correction of the right-sided middle and inferior turbinates resulting in a physiological septal deviation and bilateral slitlike cavities (Pirsig 1972, unpublished)

autogenic ear cartilage introduced by the author in 1986 (Pirsig et al. 2004).

Ear cartilage grafts from the cymba-cavum concha complex were harvested through an anterolateral approach (Fig. 34.23). A special incision was used to divide the concave ear cartilage into two halves while preserving the posterior perichondrium. The graft was folded and fixed with guide sutures in its final position between the hypoplastic anterior nasal spine and the caudal end of the cranial septodorsal cartilage remnant. Thus, a viable, stable, balanced back-to-back graft of 2.5–3 cm length was created, long enough to reconstruct the anterior septum and the nasal valve and to correct part of the saddle nose deformity. The rest of the ear cartilage was used to fill the remaining cartilaginous saddle. At follow-up the back-to-back grafts showed no macroscopic signs of resorption. Graft position and shape had remained intact, and all noses were adequately projected and mobile. All patients but one felt satisfied with the functional and aesthetic result. The saddle completely disappeared in two-thirds of the patients. Nasal breathing considerably improved in 21 patients, remained the same in 4 patients and worsened in 1 patient.

Our long-term study also showed that even 42 % of the patients with a large septal perforation – which was not closed – reported of improved nasal breathing and marked reduction of previous nasal symptoms because the valve region had been reconstructed by the back-to-back transplant.

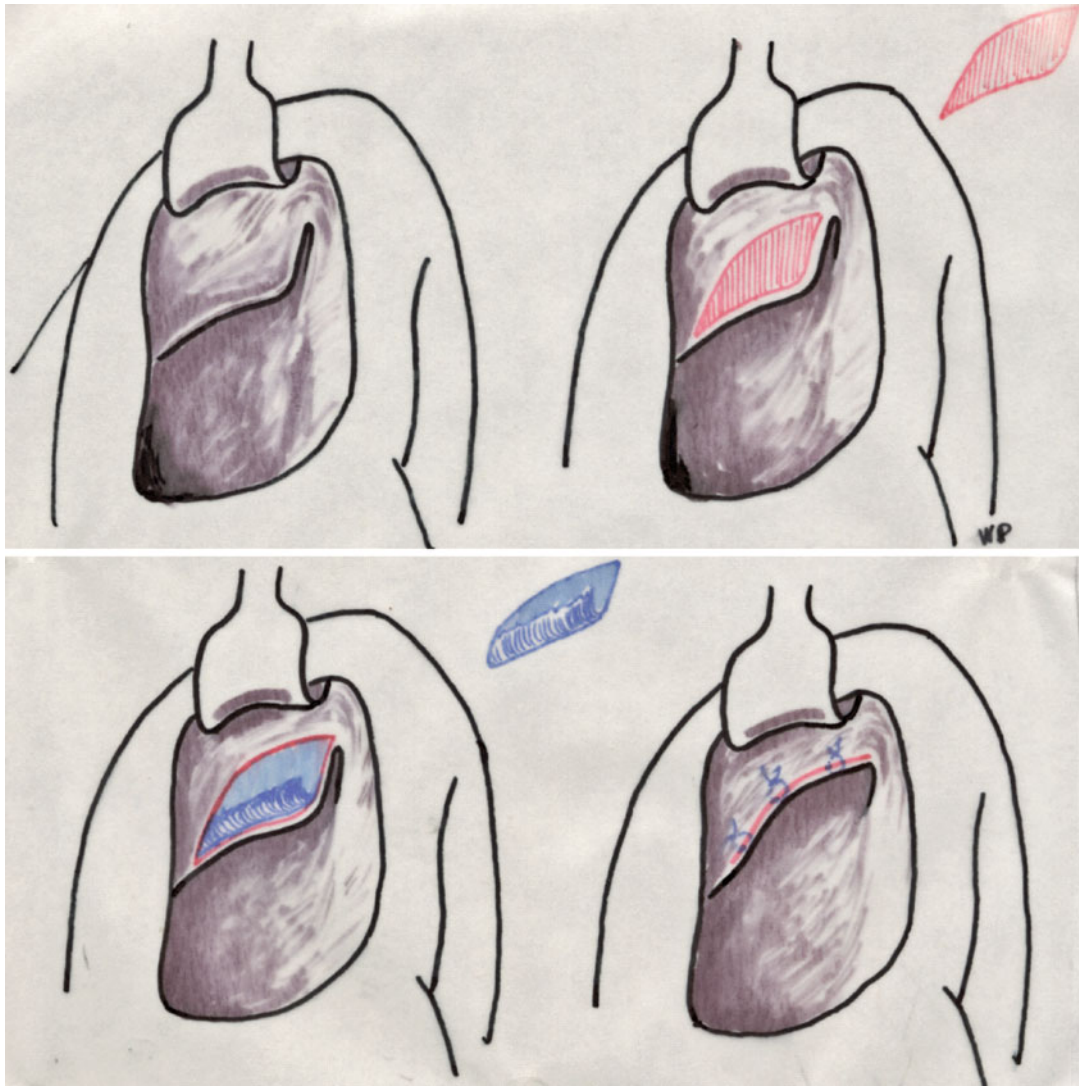

Fig. 34.22 Steps to enlarge the too small valve angle by shortening part of the caudal end of the triangular cartilage (Pirsig 1975, unpublished)

34.4.4 Closure of Septal Perforation in a Child

The worst sequela of the septal abscess is the septal perforation, especially during growth. We had to face this relatively rare sequela due to nose picking in early childhood in a Caucasian 7-year-old boy. He suffered nearly daily epistaxis, crusting and permanent mouth breathing. After insufficient conservative treatments, we decided to perform a pilot study in the 9-year-old boy to close the septal perforation of 1 cm in diameter in the area II and III according to Cottle (Fig. 34.24). Four bipedicled mucosal advancement flaps introduced by Fairbanks (1980) and Schultz-Coulon (1994) were used to reconstruct the mucosal lining. To fill the cartilaginous defect, a piece of autogenic mainly hyaline cartilage was taken that had been grown from a composite graft of demineralised bovine bone matrix (DBBM), enrolled in a pedicled perichondrial flap of the boy's right pinna. The Rotterdam group of Verwoerd and Verwoerd-Verhoef had shown the feasibility of this new type of composite graft applied in a two-step procedure for the reconstruction of defects in the cricoid ring (Bean et al. 1993) and anterior

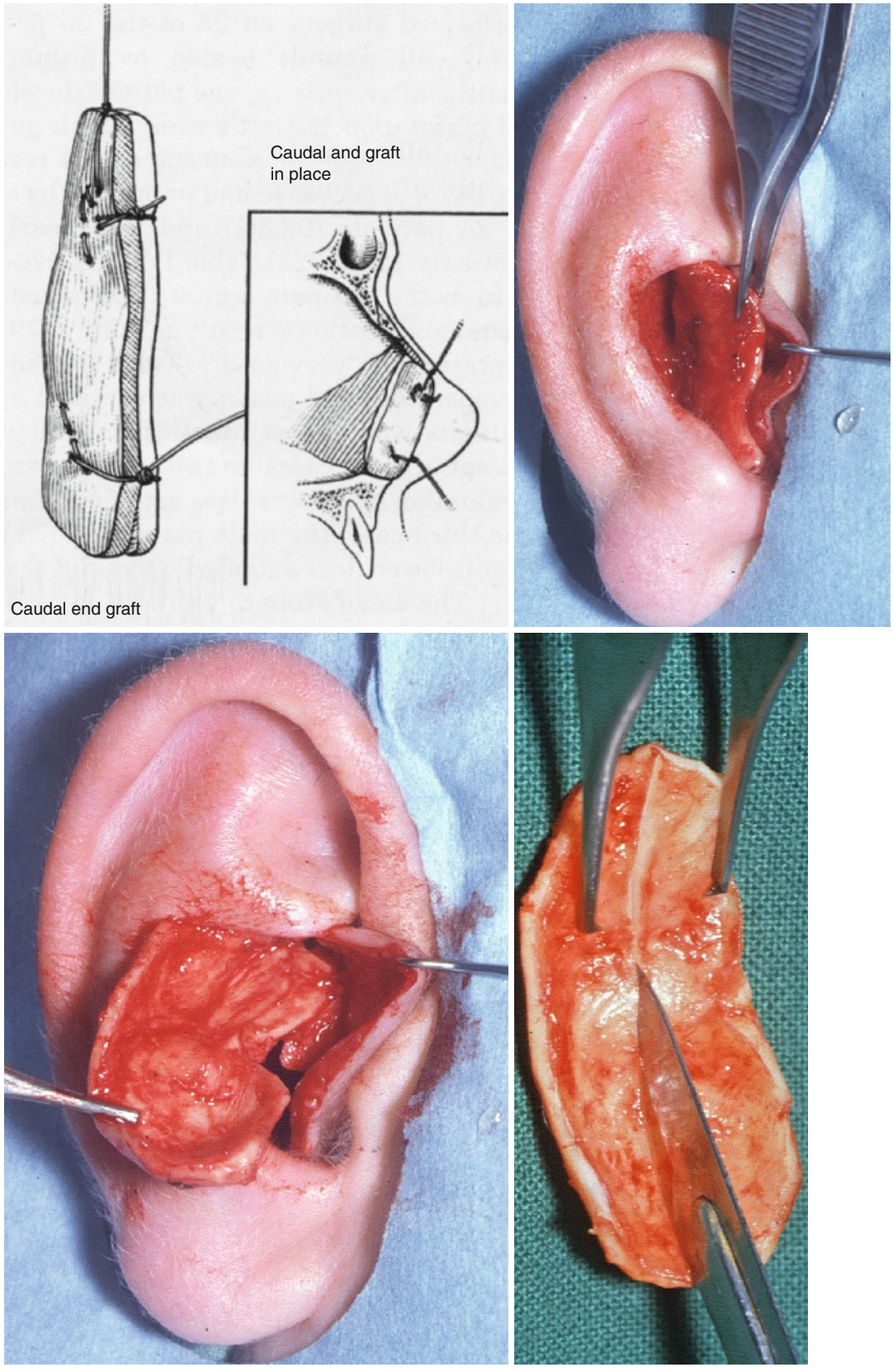

Fig. 34.23 Steps of back-to-back cartilage grafting (3 coloured figures, Pirsig, unpublished; drawing from Pirsig et al. 2004)

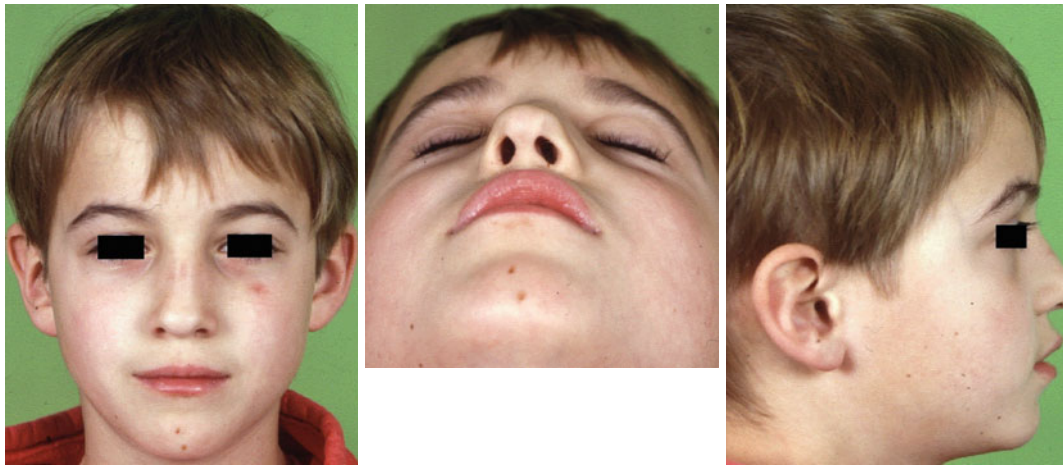

Fig. 34.24 Nine-year-old boy with septal perforation, preoperatively (Pirsig, unpublished)

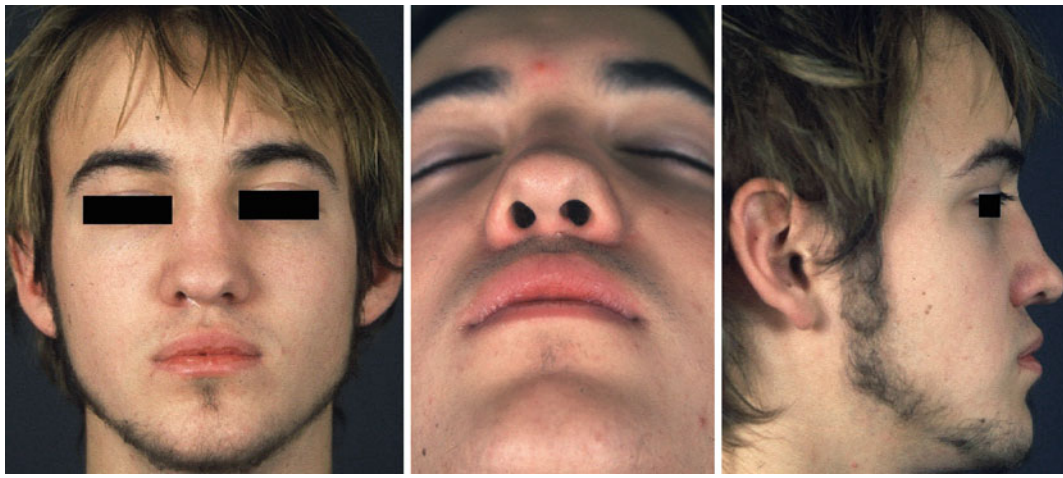

Fig. 34.25 Seventeen-year-old adolescent, 8 years after closure of septal perforation (Pirsig, unpublished)

laryngeal wall of growing rabbits (Bean et al. 1994). Furthermore, they could show that this neocartilage provided a valuable substitute for the lost parts of the cartilage and appeared capable of growth. The operation to close the septal perforation by implanting the transformed xenogenic DBBM in the septal defect of the boy of 9 years was successful. Details of the surgical procedure and histological findings were published 2 years later (Pirsig et al. 1995).

I could follow the adolescent over 8 postoperative years (Fig. 34.25). He had no breathing problems and epistaxis over all the years, but a dry nose which he treated with saline douches. The nasal length was adequate, but the lobule showed growth inhibition, a minimal cartilaginous sagging which was not visible preoperatively and a retracted columella. The septum was straight with ciliary activity on the sites of the former perforation. The maxillary retrusion was marked but already visible at the age of 9 years when signs of septal growth inhibition due to the perforation were already obvious. In a final step under local anaesthesia, I tried to improve the nasal appearance using pieces of ear cartilage. During this surgery I elevated the right

mucoperichondrium from the septal cartilage to get a look on the implant. There was a complete connection of the transformed cartilage with the original septal remnant. The surface of the implant was slightly tuberous and solid. Unfortunately, I could not evaluate whether the implant had grown.

Conclusions

Nasal cartilages function together in a complex anatomical framework connected by a web of connective tissues and partly covered by a layer of fine muscles. Their protruding position in the centre of the face may act as an eye-catcher, and their mobility may serve as a crumpled zone protecting the head against external frontal stress. The anterior nose with its two parallel tubes is the ideal portal to the respiratory system. In the valve regions, we find the narrowest cross-sectional areas of the nose, where two-thirds of the total respiratory resistance are generated. In these regions, the laminar airstreams are transformed into turbulent ones. Thus, together with the erectile lining of the nasal cavities, the anterior nose provides the tools for the air-conditioning of the respiratory system and for the acting of the nasal cycle.

No wonder that such a complex and exposed construction like the anterior nose is very vulnerable to all types of damaging influences and especially to mechanical injuries. The septodorsal cartilage is the dominating structure for nasal shape and midfacial growth. Particularly, its anterior part is most often involved in nasal injuries and its reconstruction mainly influences the surgical long-term outcome. Thus, rhinosurgeons should predominantly focus on the rehabilitation of this anterior nose with its complex cartilaginous framework and erectile lining. Diagnostic methods like endoscopy, acoustic rhinometry, rhinoresistometry and imaging allow a better insight into the structural and functional characteristics of the damaged soft- and hardware of the nose. A too mechanistic thinking for nasal reconstruction should be replaced by a concept of applying several technical options tailored for the individual pathological nasal finds and the requirements of nasal physiology. In this chapter, I presented some of my personal experience and how I got insight in the complexity of the nasal cartilages by long-term follow-up of the patients. One example is the acceptance of a physiological septal deviation which acts in harmony with the lateral walls instead of creating a straight anteroposterior septal plate just for optical beauty.

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Physiology and Pathophysiology of the Growing Nasal Skeleton

35

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Keywords

Nasal growth • Midfacial growth • Nasal disorders • Septum deformities • Cartilage wound healing • Septoplasty • Rhinoplasty • Tissue engineering

Core Messages

- The outcome of surgical interventions is largely dependent on the quality of wound healing of the tissues. However, in children, a second aspect of paramount importance is the impact on further growth.
- The knowledge of the anatomy of the nasal skeleton from birth to adolescence and current data concerning the 'normal' development of the midfacial profile are mandatory for physicians working in this field.
- Surgery of the nasal skeleton in children at different ages should restore form and function, optimise further growth and minimise the risks for abnormal development. As to restoring normal growth, clinical observations have currently not produced convincing evidence.
- Results of animal experiments have largely contributed to understanding developmental mechanisms of the nasal/midfacial skeleton, the way they are influenced by various surgical interventions, partial resections and fractures of the cartilaginous and bony nasal skeleton, and finally the possibilities to restore growth by surgery.
- Key issues seem to be (1) the dominant role of specific growth zones in the cartilaginous septum, the connection with the premaxilla (via the anterior nasal spine) and the connection of the upper lateral cartilages with the nasal bones and (2) the poor wound healing capacity

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of growing and maturing nasal cartilage and its deformation due to the release of interlocked stresses.
- The clinical long-term results as far as nasal growth is concerned after surgery at different ages, and studies on in vivo and ex vivo methods to enhance wound healing of growing hyaline (nasal) cartilage will improve clinical success rate.

35.1 Physiology of the Growing Nasal Skeleton

35.1.1 Introduction

Rhinosurgical procedures are common in the adult patient group, and techniques have been developed and improved based on the experience with large numbers of patients. Most common is the septoplasty which is performed to correct a symptomatic deviated septum of congenital, developmental or traumatic etiology. Performing such procedures in the paediatric age group is controversial because of concerns about retarding or otherwise altering nasal and midfacial growth patterns (Wong et al. 2010). Children as 'category' include patients from 0 years of age to adolescence. In this period, the nose is characterised by an increase of dimensions and an ongoing development of the supporting midfacial skeleton. Consequently, no 'standard' anatomy exists for children as for adults. The age-specific anatomy, the vulnerability of the immature skeleton and the morphogenetic processes providing a 'normal' adult nose should be respected when nasal surgery is considered for a child. The aim should be to restore the anatomy in the short term, whereas a 'normal' facial profile at the adult age has to be the – equally important – objective in the long run. However, which developmental processes should be restored and how?

Anecdotal clinical evidence in small series or single case reports suggests that nasal trauma, septal infection or even childhood septoplasty can cause severe morphological and functional disturbances of the nose later in life. The restriction of clinical observations is the temporariness without, in general, the possibility to follow up the developmental processes for a longer period or to analyse the effects of various well-defined injuries and treatment modalities in children of different age groups. Here comes in the value of research in experimental animals.

Experimental studies demonstrated the morphogenetic mechanisms which might be held responsible for a normal development of nose and upper jaw (the inferior wall of the nose!) and the developmental effects of lesions and surgical interventions of various parts of the nasal skeleton. Clinical evidence, facial morphogenesis in children and the interaction between wound healing, growth and surgical procedures, as studied in animal experiments, all contribute to current practice of nasal surgery in children.

The age-specific anatomy of the midface makes rhinosurgery in children different from adults.

Knowledge on the age-specific anatomy and developmental processes is essential for proper diagnosis and treatment of midfacial lesions in children. It became clear that the dimensional aspects of nasal growth, the evolution of the growth rate during childhood and the age at which the growth spurt ends, are related to gender (Meng et al. 1988). The growth rate of the facial skeleton (nose, upper and lower jaw) is higher compared to that of the brain skull. In the first years of life, the growth rate is also faster and only gradually decreasing to adulthood. The craniofacial ratio at birth is said to be 8:1 compared to 4:1 at 5 years of age and 2:1 in adulthood (Pirsig 2000). The human nasal septum is the dominating structure to determine the size and shape of the visible nose and, thus, influences the appearance of the face. Anatomy and dimensions of the nose are changing with increasing age. The baby face acquires an adult profile. The anatomical development of the nose with tissue maturation of the cartilaginous and bony parts, including their age-specific characteristics, are described below as they have to be considered important

and studied extensively before treatment or surgery is performed. Up to now, these morphogenetic processes in the septodorsal cartilage and in the sutures of the nasal pyramid and maxilla have been observed as more or less independent growth centres. The effects of frequently occurring injuries of the midfacial skeleton on further development of the face, however, point to a strong correlation between the various parts.

It appeared that the release of interlocked stresses and poor wound healing after fractures or loss of septum cartilage are key factors in maldevelopment of the midface and also form a serious risk factor in surgical reconstruction at a young age. These biological aspects of a surgical intervention have to be taken into account when the ultimate aim is to restore normal form and function of the nose and midface.

A review of the current clinical literature reporting results of nasal trauma and surgery in children demonstrates that definite conclusions are still hampered by various elements such as a lack of differentiation for the age of the patients at the moment of injury or surgery, a too short follow-up period after surgical treatment and an incomplete documentation of the surgical procedures applied (Verwoerd and Verwoerd-Verhoef, in press).

Studies in experimental animals like rabbits, guinea pigs and cats have contributed substantially to understanding the effects of trauma and surgery on the growing nasal and midfacial structures; these observations in larger series of pure-bred mammals could be defined by geometrical measurements and data statistically processed. Despite the differences between human and animal anatomy, the constituting elements of the facial skeleton show sufficient significant similarities to allow comparisons relevant for notion of pathophysiology of the human face and provide suggestions for treatment. In growing rabbits as well as in children, the nose and upper jaw grow faster and over a longer period than the brain skull.

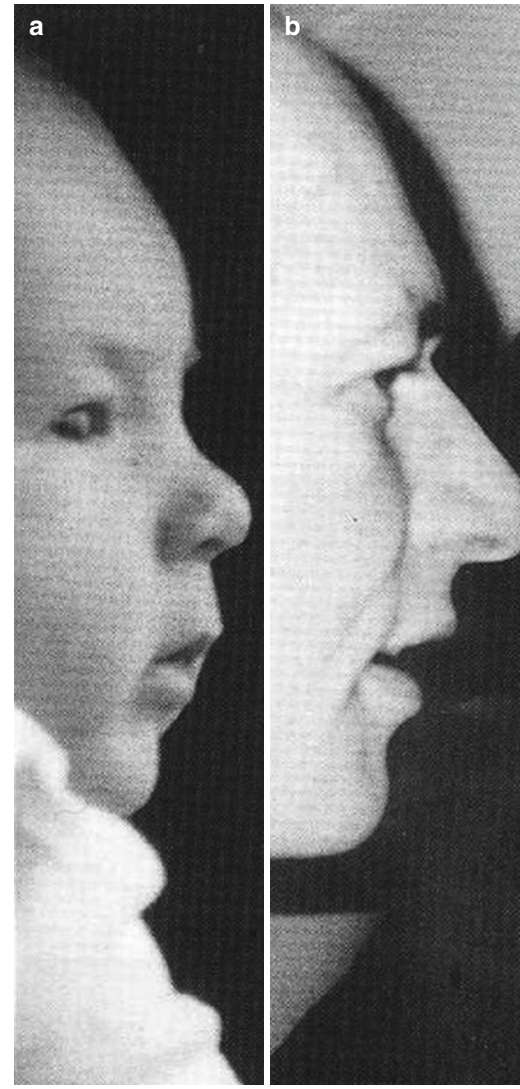


Fig. 35.1 The facial profile of a 3-month-old boy (**a**) and his father (**b**). Proportional differences between the facial and brain skull of father and son. The baby face shows smaller vertical dimensions, a less frontal projection of the nose and a larger nasolabial angle

35.1.2 The Facial Profile and Nasal Skeleton of the Newborn

In the newborn the dimensions of the splanchnocranium (maxilla, nasal pyramid and mandible) are small in proportion to the size of the neurocranium (brain skull)! The large dimensions of the latter are related to the rapid development of the brains during pregnancy which continues into the first years of life. The facial profile of the neonate (Fig. 35.1) shows smaller vertical dimensions of the midface, less frontal projection of the nasal dorsum and a larger nasolabial angle compared to the facial proportions in fully grown individuals (Verwoerd and Verwoerd-Verhoef 2010).

In the newborn, the cartilaginous and bony nasal skeleton demonstrates a few specific aspects. Septal cartilage and upper lateral cartilages on both sides form the three-dimensional septodorsal cartilage, a supporting structure for the nasal dorsum resembling a T-bar configuration (Poublon et al. 1990). The cartilaginous septum is based on the sphenoid (Fig. 35.2). The upper lateral cartilages extend under the nasal bones to merge with the cartilaginous anlage of the anterior cranial base. The nasal bones are fibrously connected in the sutures to the frontal and maxillary bones. At their ventral rim, the periost of the nasal bones is firmly connected to the perichondrium of the underlying upper lateral cartilages. The nasal bones are product of extra-cartilaginous ossification of cephalic mesenchyme. The first anlage of the vomer is also represented by islands of mesenchymal bone formation reaching from palatal bone to cartilaginous septum with extensions of ossifying mesenchyme along both sides of the septum cartilage. Enchondral ossification of the septum cartilage may be observed as early as the first months after birth near the anterior cranial base (Van Loosen et al. 1988). The cartilaginous septum shows a specific pattern of thinner and thicker zones; the thickness of the septum was found to vary between 0.4 and 3.5 mm. Two areas of thick cartilage are extending from the sphenoid in anterosuperior direction to the nasal dorsum (sphenodorsal zone) and the anterior nasal spine (sphenospinal zone), respectively (Fig. 35.2c). The thinnest part is found anteriorly between these two zones and the slightly thickened caudal rim.

In young children the cartilaginous nasal septum is based on the sphenoid, whereas the upper lateral cartilages extend under the nasal dorsum to merge with the cartilaginous cranial base. Dimensions and anatomical features change with increasing age.

In young rabbits a similar pattern of thicker and thinner areas has been demonstrated in the elongated septum (Tonneyck-Müller and van der Werf 1982, 1984). The thicker areas play a specific and important role in the postnatal development of nose and upper jaw as will be discussed in the paragraph on acquired malformations of the septum. Also in young rabbits, the septal and upper lateral cartilages form a T-bar based on the anterior skull base.

35.1.3 Midfacial Development from Neonate to Adolescent

In children the development of the cartilaginous nasal skeleton is a complex process including proliferation of chondroblasts, increase of intercellular matrix, tissue maturation and partial regression and enchondral ossification of the septodorsal cartilage. The dimensional growth of the septum cartilage shows its highest rate in the newborn and is slowing down gradually after the age of 2 years (van Loosen et al. 1996). From that time onwards, formation of new cartilage continues but is balanced by simultaneous loss of cartilage through enchondral ossification (Verwoerd and Verwoerd-Verhoef 2007). Mitotic activity of chondroblasts and expansion of the intercellular matrix might compensate for the loss of cartilage by ossification till the ratio between bony and cartilaginous parts has been changed to its definite state (Fig. 35.3). Consequently, the sagittal dimensions of the bony perpendicular plate are increasing relative to the cartilaginous part of the septum (Schultz-Coulon and Eckermeier 1976). The growing perpendicular plate will intervene between septal cartilage and sphenoid. The septum cartilage is later firmly connected to the thickened caudal rim of the perpendicular plate. The junction of cartilaginous septum and perpendicular plate – an important surgical landmark – will change from an intracranial position in young children to the extracranial location at the anterior margin of the nasal bones in adults. The basis of the septum cartilage shifts from the sphenoid to the anterior rim of the perpendicular plate (Fig. 35.4a).

The vomeral bone, which first anlage was present in the neonate will develop into a definite part of the osseous nasal skeleton (Verwoerd et al. 1989a). The vomer is enclosing the basal

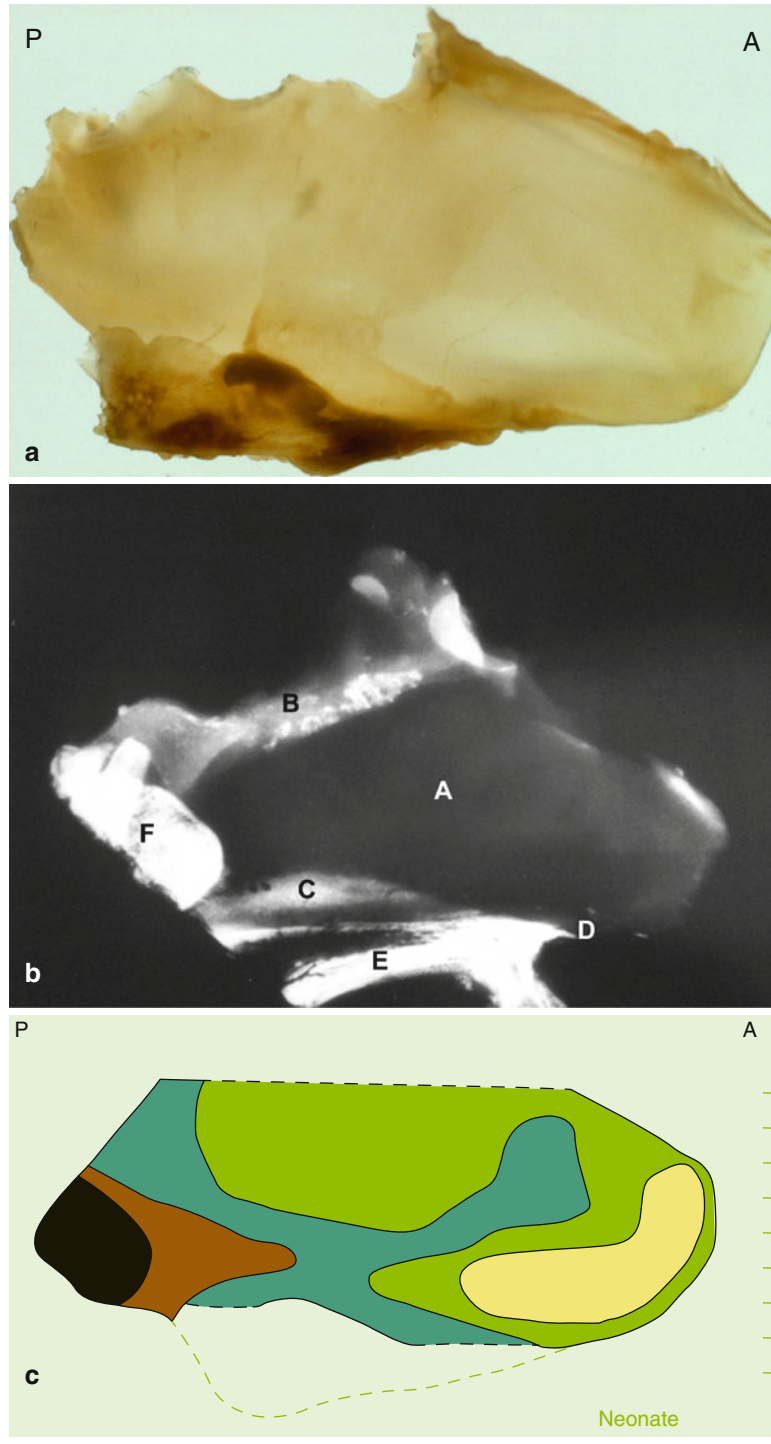


Fig. 35.2 Anatomical specimen of neonatal cartilaginous septum: (**a**) indentations at the border with the anterior cranial base concur with ossified parts lost during preparation; (A) anterior, (P) posterior. (**b**) Lateral radiograph of an anatomical specimen of a human neonate including the nasal skeleton, adjacent skull base and upper jaw. (*A*) Cartilaginous nasal septum, (*B*) lamina cribrosa, (*C*) vomeral wing, (*D*) anterior nasal spine, (*E*) palate, (*F*) sphenoid. (**c**) Schematic representation of the thinner and thicker zones in the human septum (superior part of the septum, adjacent to the anterior cranial base not included). The thinnest part (*yellow, 400–500μ*) is bordered by the columellar rim (*light green, 500–1,500μ*); sphenodorsal and sphenospinal zones of thicker cartilage (*blue-brown, 1,500–3,000μ*); sphenoid (*black*)

rim of the septum cartilage by two bony layers (vomeral wings) which converge inferiorly in the medial, unpaired bony plate separating the inferior part of the nasal cavities and extending in posterior direction to the choanal edge of the nasal septum. The moment at which the ossifying front of the perpendicular plate should reach the vomeral wings is not clearly defined

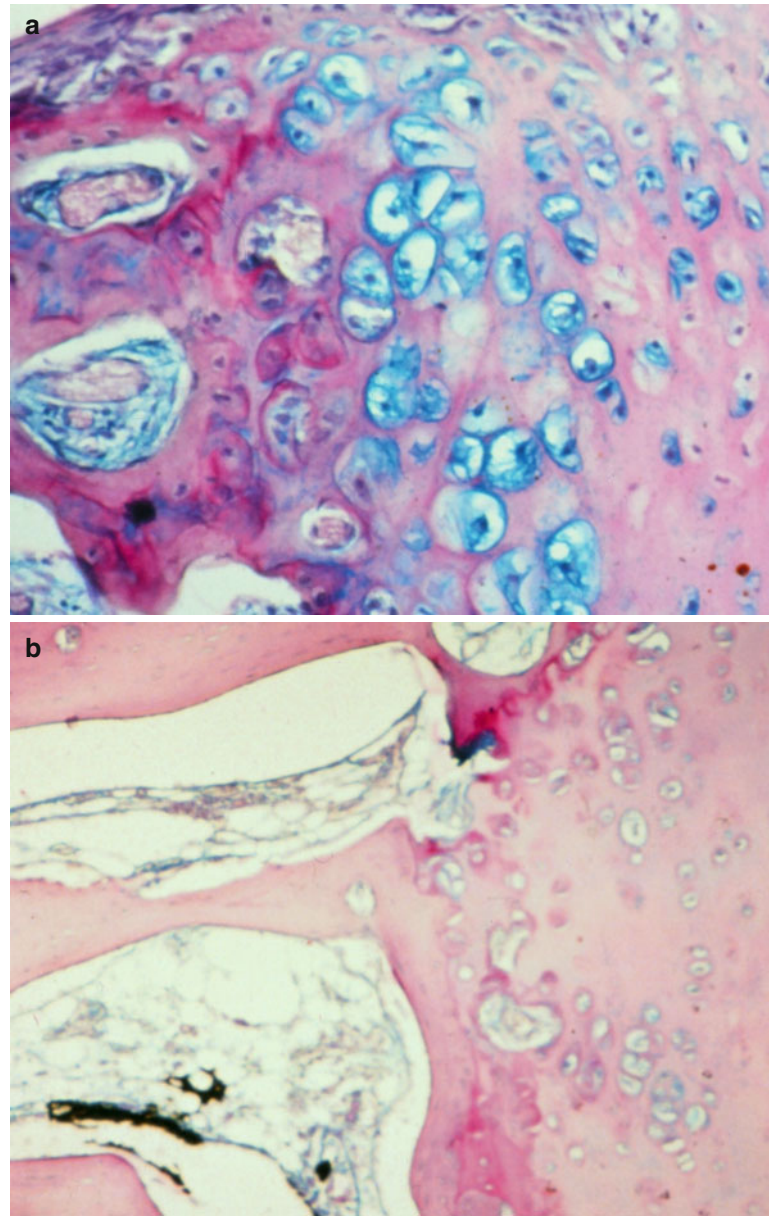


Fig. 35.3 The interface between septal cartilage (*right*) and bony perpendicular plate (*left*); (**a**) active enchondral ossification in a young child; (**b**) no signs of ossification in the adult stage

and may even surpass the age of 10 years, while an overlap between wings and plate has been found in adolescence. Cartilage may remain present in the bony canal formed by vomeral wings and perpendicular plate (vomeral tunnel) for a longer period and extend to the sphenoid, as sphenoid tail, but ultimately ossify in most individuals. Asymmetry of the vomeral wings (the ala on one side larger than on the other) may be observed when the sphenoid tail bulges out into one nasal cavity, sometimes in combination with a vomeral spine (Fig. 35.4b). Variations in the septovomeral junction are very common and a symmetrical development is exception rather than rule. In a study on human fetuses of 5 months old, it was observed by Takahashi that around 25 % demonstrated an abnormality of the septovomeral junction which could increase to almost 40 % at birth (Takahashi 1987). These deformities were ascribed to 'an imbalance of the "*overdeveloping*" septum (cartilage) and the pressure of the surrounding structures', the

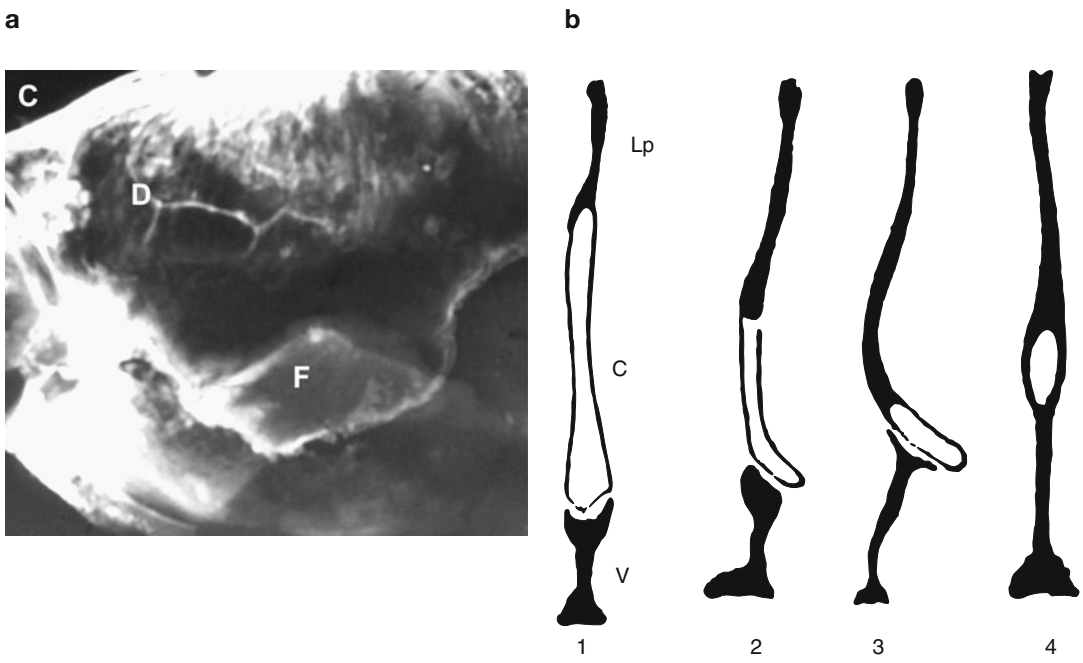


Fig. 35.4 Detail of a human nasal septum (17 years of age); (**a**) a lateral radiograph, with the overlap of vomeral wing and perpendicular plate; [*C*] anterior skull base, [*D*] lamina perpendicularis, [*F*] vomeral wing; (**b**) schematic representation (in frontal sections) of various modalities of the septoethmoidovomeral junction (after Takahashi 1987); [*1*] normal situation (*Lp* = lamina perpendicularis, *c* = cartilage, *v* = vomer), [*2*] asymmetrical development of vomer and cartilage, [*3*] asymmetrical development of vomer with formation of a vomeral spine, [*4*] sphenoid tail

last mentioned being the developing bony facial skeleton.

Progressive ossification of the septum cartilage results in an expanding perpendicular plate starting from the area of the anterior cranial base into ventrocaudal direction. The ventral rim of the perpendicular plate shifts gradually inferiorly and, therefore, is in children not a reliable point of orientation in relation to the anterior skull base. The junction between cartilagenous septum, perpendicular plate and vomer may demonstrate considerable variation but is thought to have been established between 10 and 14 years of age.

The length of the upper lateral part of the dorsoseptal cartilage will be reduced on both sides to finally around 5–8 mm. The progress of this reduction shows individual variation. While the dimensions of the nasal skeleton increase in size, the relation between cartilaginous and bony parts is going to be altered. This remodelling will result in a more anterior position of the cartilaginous part of the septum. It is an important issue which should be understood by the doctor at diagnosis and before treatment of the child might be started.

> Anatomical data do not give information pertinent to the developmental mechanisms of the facial skull. Animal experiments are necessary to analyse these morphogenetic mechanisms and the way they are affected by injury or surgery.

35.1.4 Postnatal Development of the Midfacial Skeleton in Mammals

The skulls of mammals demonstrate essentially similar components (Fig. 35.5). Various components however may show very different dimensions in different species. An example is the proportion between the skeletal components of the upper jaw. In the human skull, the premaxilla

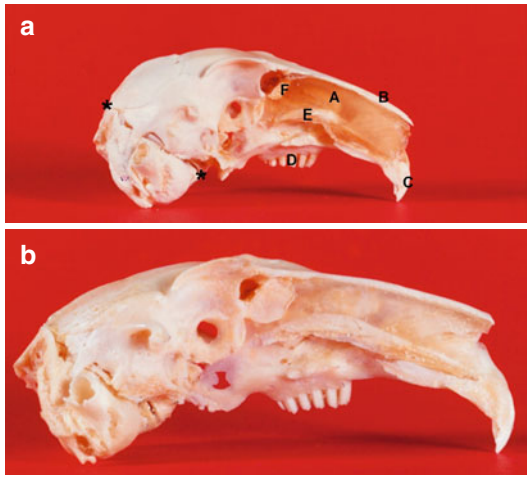


Fig. 35.5 Lateral aspect of the rabbit septum and skull (after removal of the right part of the nose and upper jaw) at the age of 4 (**a**) and 24 weeks (**b**) demonstrating the 'extra' growth of the nasal skeleton and upper jaw up to the adult stage, compared to the dimensional growth of the brain skull. *-* Line between lambdoid suture and spheno-occipital suture, (*A*) cartilaginous nasal septum, (*B*) nasal bone, (*C*) incisors, (*D*) molar complex, (*E*) vomeral wing, (*F*) perpendicular plate

is small compared with the maxilla, whereas in rodents, like the rabbit, the anteroposterior dimensions of the premaxilla exceed those of the maxilla. In children, the osteogenic activity of the premaxillo-maxillary suture is restricted to the first years of life contrary to rabbits in which sutural growth contributes to lengthening of the upper jaw and continues till sexual maturity.

Also in young rabbits the septodorsal cartilage extends under the nasal bones to the anterior cranial base, later followed by a reduction of the posterior part of the cartilage leaving only the most anterior part in situ. The cartilaginous septum remains in direct contact with the sphenoid. Only a small part will demonstrate ossification to form the perpendicular plate. Obvious differences compared to the human anatomy are demonstrated by the vomer. The vomer is a product of mesenchymal ossification along both sides of the cartilaginous septum and between the palatal bone and the inferior margin of the septum. The cartilaginous septum, anteriorly connected to the

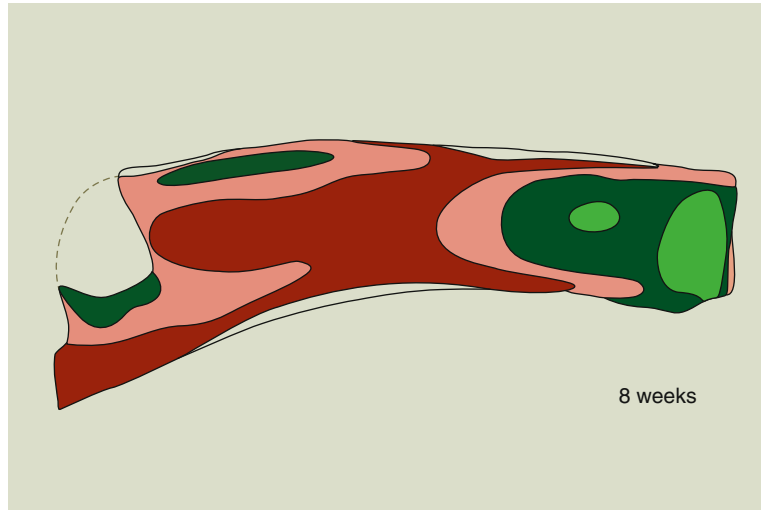


Fig. 35.6 Schematic presentation of regional differences in thickness of the cartilaginous nasal septum in an 8-week-old rabbit. The sphenospinal zone of thick cartilage extends from the sphenoid to the anterior nasal spine, whereas the sphenodorsal zone is extending under the nasal dorsum. In rabbits, the lower lateral cartilages have a common medial crus, which is connected by a thin cartilaginous membrane with the slightly thickened anterior rim of the 'real' cartilaginous septum; this thickened rim and the sphenodorsal and sphenospinal zones of thick cartilage enclose an area of thin cartilage; *l.green*: 50–250**µ**, *d.green:* 250–450**µ**, *l.red*: 450–650**µ**, *d.red*: 650–850**µ**

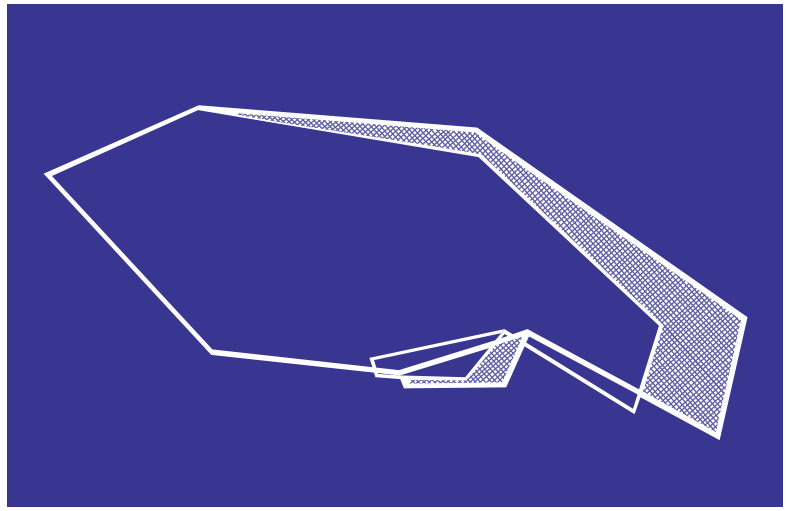


Fig. 35.7 Graphic representation of the 'extra' growth of the midfacial skeleton (with grid code) of the rabbit skulls between 4 and 24 weeks after birth; the line connecting lambdoid suture and the spheno-occipital suture (viz. Fig. 35.5a) has been made equal for both series; elongation of the upper jaw and the nose and forward shift of the molar complex result in the adult proportions between facial and brain skull

anterior nasal spine, shows thinner and thicker parts similar to those described for the human nasal septum (Fig. 35.6). A centro-anterior area of thin cartilage is surrounded by sphenodorsal and sphenospinal zones of thick cartilage and anteriorly bordered by a slightly thickened anterior rim. In growing rabbits, it was demonstrated that the 'extra' growth of nose and maxilla depends primarily on growth of the septodorsal cartilage (Fig. 35.7). The sphenodorsal zone of thicker cartilage is responsible for lengthening of the upper part of the T-bar, the upper lateral cartilages and indirectly of the overlying nasal bones. These upper laterals were found to stabilise the growing septum cartilage in a median position. Also in the rabbit the extension of the lateral cartilages under the nasal bones will be gradually reduced by ongoing regression (Fig. 35.8). Enlargement of the sphenospinal zone results in an increase in length and thus gradual shifting of the lower part of the septum and upper jaw. In the rabbit, the perpendicular plate will be limited to the most posterior part of the septum, whereas the majority of the septum remains cartilaginous. Also in the mouse, the cartilaginous septum increases in length much more rapidly than could be explained by caudal growth, implying that interstitial expansion is the more important contributor to septum development (Wealthall and Herring 2006).

Equally important as the septodorsal cartilage is for the growing midface are the sutures and their bone formation for the facial skeleton, the nose included.

35.1.5 Dimensional Growth of the Nose and Maturation

Postmortem anatomical studies suggested a phase of rapid growth directly after birth with a gradual deceleration after 5 years with the greatest velocity in the first 2 years (van Loosen et al. 1996, 1997). Conclusions drawn from a study in the Aegean Region of Turkey revealed that nasal height and nasal bridge length reached full maturation in females already at 12 years of age and in boys around 15 years (Akgüner et al. 1998). Nasal growth has further been studied by measuring cohorts of children and calculating 'standards' for various age groups, differentiating for boys and girls. Next to these horizontal studies, a few vertical studies have been published based on measurements in the same child at increasing

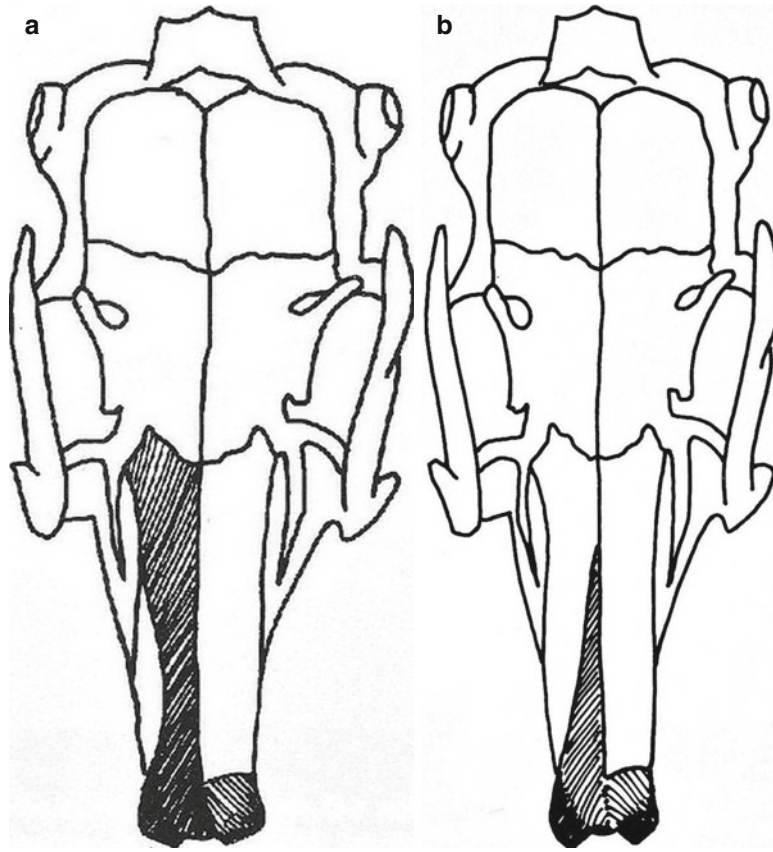


Fig. 35.8 Schematic representation of the regression of the upper lateral cartilage from (**a**) 4 to (**b**) 24 weeks; the left nasal bone is removed (Courtesy of Dr R.M.L. Poublon)

ages. Such a vertical study demonstrated in boys a period of accelerated growth, most frequently observed around the age of 13 years (Meng et al. 1988). In young girls, periods of accelerated growth were found to occur between the age of 6 and 8 years. Growth spurts have not been demonstrated in horizontal studies including large cohorts of children. In the last two decennia, most data on postnatal growth of the maxilla and the nose have been derived from lateral cephalographs in children of 7 years and older (Meng et al. 1988; Farkas et al. 1992; Zankl et al. 2002; Ochoa and Nanda 2004). In a recent review, the steepest descending slope of midfacial growth velocity is reported to take place at the average age of 13.4 years for adolescent girls and 14.7 years for boys (van der Heijden et al. 2008). It was suggested that 98 % of white, adolescent girls are 'nasally mature' at the age of 15.8 years and 98 % of the boys at the age of 16.9 years.

35.2 Pathophysiology of the Growing Nasal Skeleton

35.2.1 Congenital Anomalies

35.2.1.1 Midfacial Clefts and the Nasal Septum

Craniofacial growth is a dynamic process balancing form and function. This equilibrium is easily disturbed at various levels by passive or active change of one of the mechanisms involved, prenatally or postnatally. The impact of the interaction with the adhering muscles on the developing midfacial skeleton has been recognised in recent years (Stricker et al. 1990). A spectrum of midfacial malformations may be observed as part of a syndrome or as solitary deformity which may point to an interaction between growth of the nasal septum and the premaxilla-maxilla. One of the most well-known

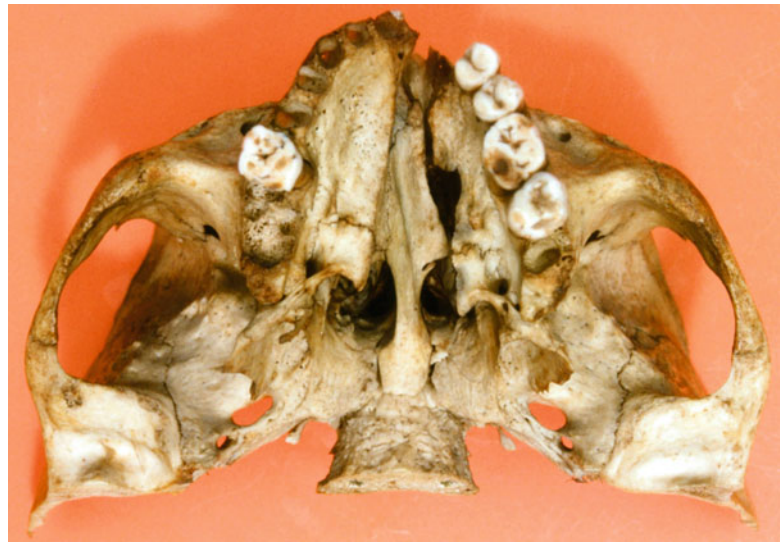


Fig. 35.9 Caudal view of a human skull with unilateral cleft of alveolus and palate (Dept. of Anatomy and Embryology, Amsterdam UMC). The maxillary segment on the cleft side demonstrates a medial collapse and a retroposition (asymmetrical position of the left and right tuber maxillae); deviation of vomer and premaxilla to the non-cleft side

congenital facial deformities is the cleft lip, alveolus and palate. In adult human skulls with facial clefts, which were known to be untreated, a specific pattern of growth disturbances could be observed (van Limborgh 1964; Atherton 1967). Unilateral clefts showed a deviation of the premaxilla to the non-cleft side, whereas the maxillary part on the cleft side had collapsed medially and fell behind compared to the non-cleft side (retrognathism). In addition, these skulls showed a specific malformation of the nasal septum with (a) a deviation of the perpendicular plate to the cleft side and (b) a disjunction between perpendicular plate and vomer (Fig. 35.9). The vomer, only connected to the palatal margin of the cleft, tends to a more horizontal position to meet the deviated perpendicular plate, suggesting a broadening of the nasal floor on the non-cleft side. From this study, it was concluded that these growth anomalies of the maxilla and nasal framework were part of a cleft syndrome, specific for each type of cleft (Verwoerd et al. 1989a, b). Collapse of the upper alveolar arch and maxillary retrognathism were also observed in adult members of a North-Borneo tribe who were born with cleft lip, alveolus and palate and did not undergo surgical treatment (Innis 1962). In a study on lateral cephalograms of untreated unilateral cleft patients with superimposed images of cleft and non-cleft side, the abnormal position of the maxilla could not confirmed, most probably due to the overprojection of the non-affected side (Capelozza et al. 1993).

Whether a combination of midfacial anomalies associated with a cleft alveolus and palate might represent a syndrome of craniofacial anomalies developing as reaction to a cleft was investigated in growing rabbits (Verwoerd et al. 1979a). Unilateral clefts of alveolus and palate, produced surgically in young growing rabbits, appeared to affect the further development of nose and (pre)maxilla into adulthood (Fig. 35.10a). On the cleft side the molar complex, lacking a connection with the growing septum, does not move forward and will show – in the adult stage – a retroposition (retrognathism) compared to the non-cleft side. Here, the premaxilla, maxilla and nasal bones will grow to normal length and gradually rotate and deviate to the non-cleft side as previously reported for human skulls (van Limborgh 1964). The results of these animal experiments indicate that the cleft syndrome as identified in 'untreated' human skulls with facial clefts should be considered an adaptation to the altered developmental mechanics in the developing midfacial skeleton.

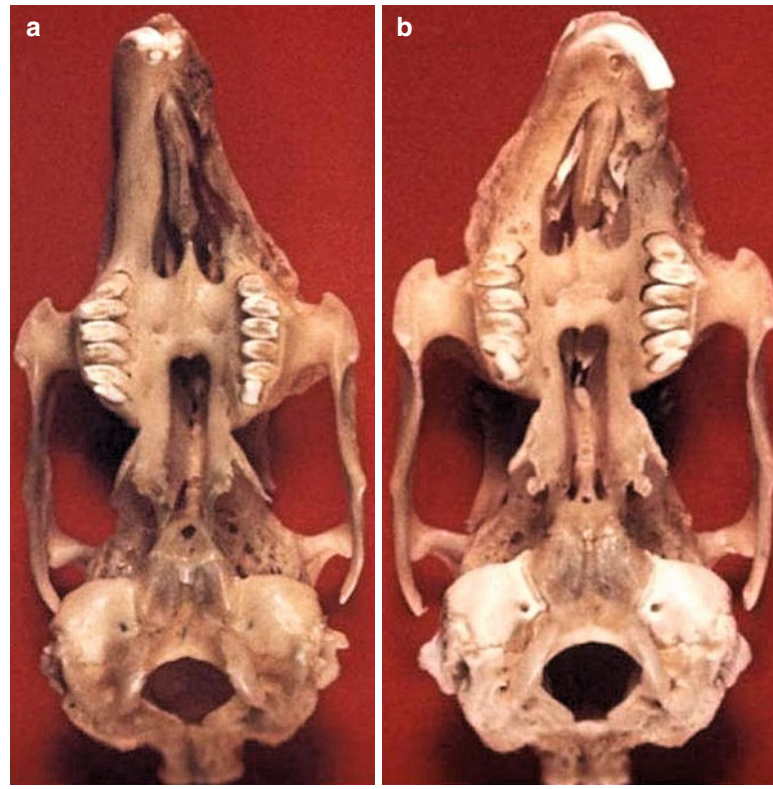


Fig. 35.10 Caudal aspect of the skulls of adult rabbits (24 weeks of age) with maldevelopment following surgical procedures at the age of 4 weeks: (**a**) following a surgical production of unilateral cleft lip and alveolus (resection of the premaxilla-maxillary suture): deviation of the premaxilla from the midline, retroposition of the maxilla, zygoma and pterygoid process on the cleft side; (**b**) after a similar cleft has been made and closed by primary osteoplasty: marked deviation to the operated side with shortening of the upper jaw, anteroposition of the maxilla including molar complex, zygoma and pterygoid process

The interaction between the growing cartilaginous and bony skeleton is modified when midfacial sutures are missing as in the presence of facial clefts; similar cleft syndromes were found in animals and untreated patients.

Another interesting observation has been done when in young rabbits the premaxillary-maxillary suture was resected and replaced by non-sutural bone (Fig. 35.10b). Following this intervention normal lengthening of the ipsilateral upper jaw failed. Secondary effects were a progressive deviation of the premaxilla to the nongrowing side and an excessive forward shift of the molar complex on the operated side. These observations confirm disappointing midfacial development as observed after osteoplasty of an alveolar cleft in young children. The outcome of the above-mentioned experiments refers to the role of the cartilaginous nasal septum in postnatal development of the upper jaw. The growing and lengthening of the cartilaginous nasal septum, connected on both sides to the premaxilla-maxilla, seems to be responsible for lengthening of the upper jaw and, secondly, for a shift in anterior direction of the upper jaw relative to the cranial base. In the presence of a unilateral cleft, the 'mechanical' balance between both sides is disturbed.

Although the results of orthodontic and surgical treatment of facial clefts are improving, the secondary cleft nose in these patients can demonstrate some of the following features: asymmetry of tip, columella, nostril, ala and nostril floor; deflection of the caudal part of the septum cartilage to the non-cleft side; stenosis of the vestibule on the cleft side; hypoplasia of the maxilla on the cleft side; variable collapse of the maxilla with asymmetry of the piriform aperture ; underdevelopment of the maxilla with retroposition of the anterior nasal spine; deviation of the cartilaginous and bony nasal dorsum; and deviation of the posterior part of the nasal septum to the cleft side (Verwoerd et al. 1995).

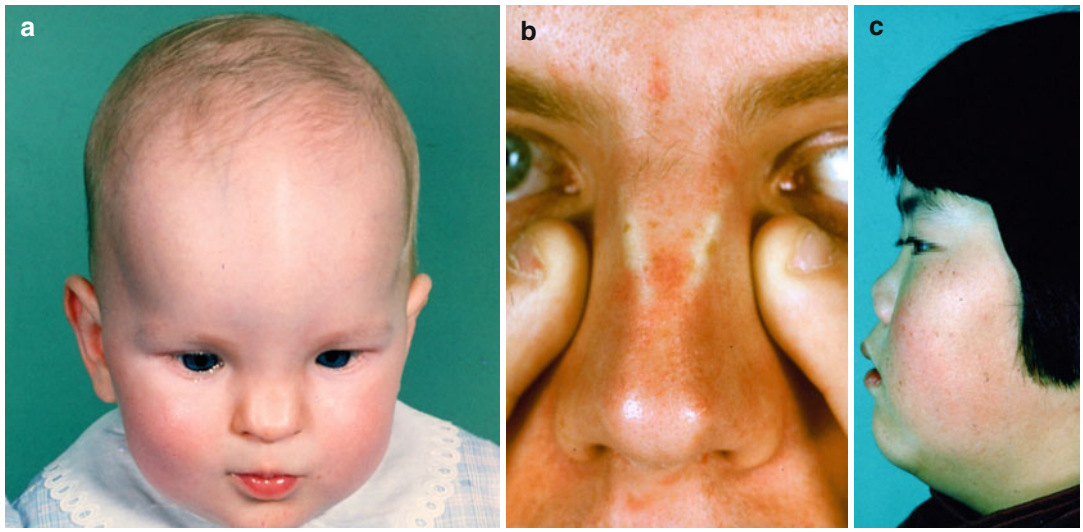


Fig. 35.11 Congenital anomalies of the nose. (**a**) Incomplete fusion of the left and right anlage of the cartilaginous and bony nasal skeleton in a 3-year-old girl and (**b**) an adult man. (**c**) Underdevelopment of the cartilaginous and bony nasal pyramid

35.2.1.2 Congenital Malformation of the Nose

Nasal congenital anomalies are extremely rare and range from bifidity of the nasal tip or dorsum to nasal aplasia with or without proboscis (Stricker et al. 1990). Reports on nasal dysplasia, which is mostly indicating a unilateral malformation, are scattered through the literature. The nasal cavity is missing and pneumatisation of the maxillary, ethmoidal and frontal sinuses has failed. Exploration reveals no cartilage, but just solid bone. The affected side of the maxilla is hypoplastic and regularly associated with other malformations such as cleft lip/palate or coloboma. The last variety to be mentioned is a duplication of the nasal dorsum, which can occur in different forms and as part of a syndrome (Fig. 35.11).

35.2.2 Acquired Anomalies of the Nose

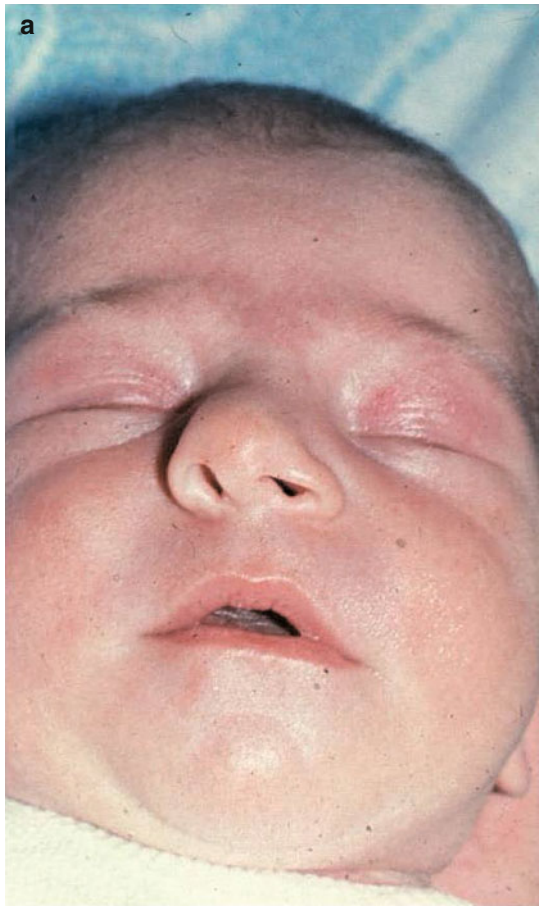
35.2.2.1 The Nose of the Neonate

Various studies refer to the importance of the nasal septum for midfacial development. In humans, intrauterine exposure to warfarin appeared to cause early calcification of the septal cartilage; subsequent nasal and midfacial hypoplasia was demonstrated in a cephalometric study, suggesting that even in utero midfacial growth is retarded by interference with the nasal septum (Howe et al. 2004).

The neonate's nose may show a slight or more pronounced deviation, with a luxation of the lower septal border into the nasal cavity, acquired during the passage through the birth canal (Fig. 35.12). In most cases this anomaly will restore spontaneously but infrequently the deformity has to be corrected by manipulation of the neonatal nasal septum which is still mostly cartilaginous from sphenoid to columella. Already in 1978, Gray found some type of septum anomaly in 57 % of 2,380 neonates (Gray 1978). Septal deformity was explained by Takahashi to be an inevitable condition resulting from the autonomic growth force of the septum cartilage (Takahashi 1988).

35.2.2.2 Trauma at a Young Age; Bone and Cartilage Lesions

Any kind of mechanical or surgical trauma at a young age, destroying the septodorsal cartilage, initiates an irreversible disturbance of the



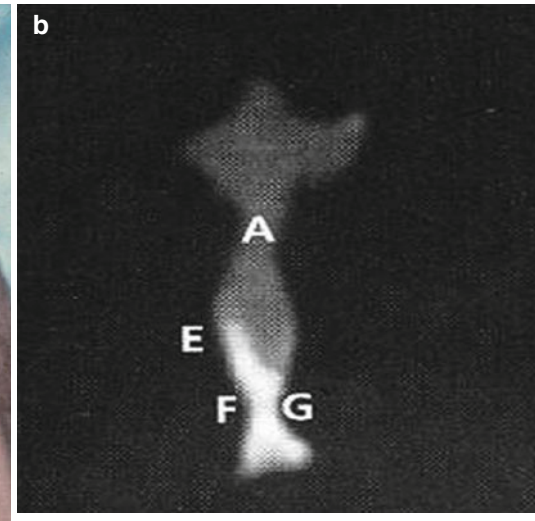


Fig. 35.12 A newborn baby with a deviation of the cartilaginous nasal dorsum and columella (**a**) due to a bending of the cartilaginous septum at the weak zone superior to the thick basal rim or a dislocation of the basal rim from the vomeral gutter, acquired during the passage through the birth canal. (**b**) Asymmetrical anlage of the vomer in a CT scan (frontal plane) of a neonatal septum. (*A*) Cartilaginous nasal septum, (*E*) ala vomeris, (*F*,*G*) inferior parts of the vomer

cartilage from its genetically based developmental orientation. A lesion may vary from fracture and dislocation, with later deviation, to haematoma and abscess formation and loss of septum cartilage, with various associated sequelae. The regional differences in thickness of the septum cartilage, described above, seem to explain that fractures preferably occur at sites with the least mechanical strength and thus the thinnest parts of the septum. Septal deviations could, therefore, be related to the 'weak' areas (Mladina 2000). Dislocation of the caudal end of the septum, the most frequent disorder in young children, is caused by a fracture running through the thin area lying cephalic of the columellar rim. The thin area above the thick basal rim is another vulnerable fracture-prone region. This preference of specific fracture lines was described by several authors in children as well as adult patients; it was demonstrated in the so-called C-fracture running horizontally and superiorly along the thick basal rim of the septum, then more horizontally through the thin portion of the perpendicular plate, while ending in the thinner zone just under the nasal dorsum (Harrison 1979; van Velzen et al. 1997). Another weak point is the area of thin cartilage, semi-parallel to the caudal rim and just anterior to the

connection between septum and upper lateral cartilages, which may easily fracture when the caudal end of the septum gets dislocated (viz. Fig. 35.2c).

35.2.2.3 Fractures: Direct Effects and Follow-Up

Although injuries of the nose appear to occur frequently in young children – and the incidence seems still to be growing – only a relative small number is seen by the general practitioner, and even less are diagnosed by an ORL specialist. Consequently the long-term follow-up of these cases is rare and certainly no routine. In the years following such a 'minor' trauma, however, a progressive deformity of the midface may be observed with increasing deviation or distortion of the nose, eventually in combination with an underdevelopment of the maxilla, while the final effects can only be defined after the adolescent growth spurt.

After a traumatic accident, fractured parts of the bony midface and the septum will lead to, often disproportionate, disfigurement of the facial profile. In particular, the less obvious lesions of the cartilaginous septum are seldom diagnosed and during further growth the fractured parts will bend and dislocate increasingly, thus leading to spine formations, local overlapping edges and finally to severe deviations (Manning 1999). A midfrontal trauma may cause multiple fractures with larger and smaller pieces of cartilage resulting in a highly distorted septum and finally an underdeveloped and distorted nose (Fig. 35.13). The direction of deviations is mostly unpredictable, because it depends on the direction of the deforming force and on the reaction of the traumatized tissues involved. Captivating evidence for the significance of the nasal septum in midfacial growth is supplied by a rather large study of 21 monozygotic twins ranging in age from 18 to 22 years by Grymer (Grymer et al. 1991). In only one of each twin pair, a deformity was found in the anterior part of the septum. The nose of the affected siblings was demonstrated by cephalometry to be shorter than in their 'normal' other half.

35.2.2.3.1 Animal Experiments

Poor wound healing of cartilage is the main reason for the occurrence of disorders of the nasal skeleton, with or without nasal airway obstruction. Experimental studies in young rodents and other mammals have consistently demonstrated that removal of full-thickness (cartilage + mucosal lining) portions of the growing nasal septum may result in growth retardation of nose, maxilla, premaxilla and palate (Kremenak and Searls 1971; Verwoerd et al. 1980; Sarnat 1983; Pinkston et al. 1995). Later studies with larger series of experiments in young rabbits using submucosal techniques could fill in some open ends of these earlier investigations as discussed in Sect. 35.2.2.4 (Verwoerd and Verwoerd-Verhoef 2011).

The growth of the rabbit skull was studied from 0 to 24 weeks after birth. The facial skeleton appeared to grow faster and over a longer period than the brain skull like in humans (Fig. 35.7). The growth rate increased rapidly in the first 8 weeks with a gradual decline thereafter till around the 22nd week of age. Twenty-four weeks was the final date of the experimental period. To achieve a complete image of the significance and developmental role of the bony and cartilaginous parts, the first experiments were performed on the nasal bones, maxilla and lateral nasal wall. Transverse osteotomy of the nasal bone anterior to the frontonasal suture on one or two sides did not disturb nasal growth in length nor did extirpation of the frontonasal suture alter the growth of the snout (Sarnat 2008). The snout showed no asymmetry, and a small bony defect remained only present in a small minority. Even subtotal resection of the nasal bone did not result in growth disorders as long as the underlying upper lateral cartilage was undamaged (Verwoerd et al. 1980). The same restriction applied to partial resection of the lateral nasal wall, which in rabbits can only be performed through an opening of the nasal cavity from above after mobilisation of the nasal bone without disturbing the upper lateral cartilage on that side (Verwoerd-Verhoef and Verwoerd 2003). Although the FESS procedure in children is not completely analogous, it was demonstrated that enlargement of the entrance to

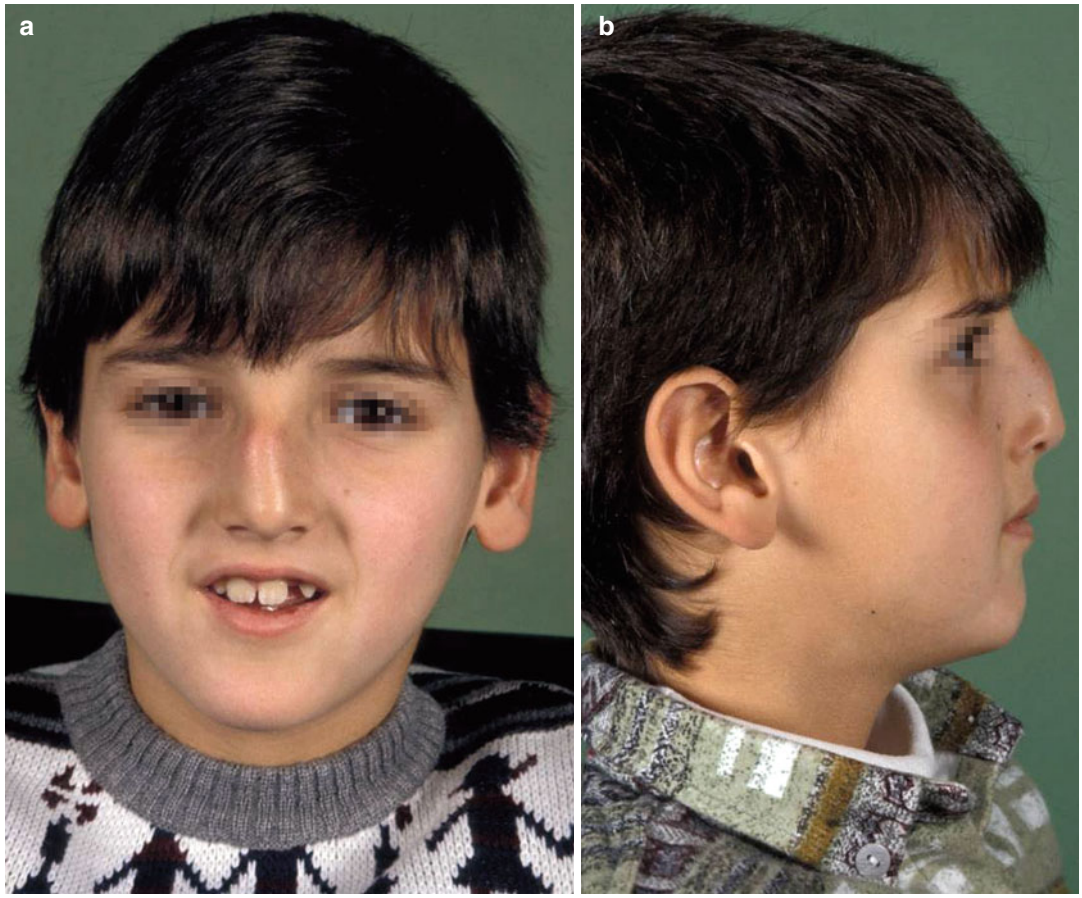


Fig. 35.13 Underdevelopment and deviation of the cartilaginous nasal pyramid, multiple and irregular deviations of the cartilaginous septum after a previous injury; (**a**) boy at the age of 8 years and (**b**) 13 years. Could a progressive anomaly have been prevented?

the maxillary sinus via this method did not disturb the normal growth of the rabbit's nose.

Experiments including resection of the premaxillo-maxillary suture(s), also in combination with resection of the midpalatal suture – comparable to the cleft upper jaw and palate – gave similar results as the cleft syndrome described for the human patients and skulls (see Sect. 35.2.1.1). The retroposition of the maxillary portion on the cleft side is explained by the failing connection to the growing septum at the anterior nasal spine. Consequently, the septum will only pull forward the premaxillary complex on the unaffected side and gradually deviate to that side. Malocclusion is the result. Closure of alveolar defect with non-sutural bone, like it was performed in children with cleft alveolus and palate in the 1970s and 1980s, demonstrated clearly that the development of the midface became severely disturbed (Verwoerd et al. 1979a).

35.2.2.4 Septum Haematoma and Abscess: Loss of Septum Cartilage

From many human case studies described in the literature, it is evident that the sequelae of a nasal injury are frequently a septum haematoma and, due to contamination and infection, a subsequent septum abscess. A haematoma may mostly, when not treated adequately, and an abscess may invariably cause destruction of the nasal cartilage leading to septum perforation or a submucosal

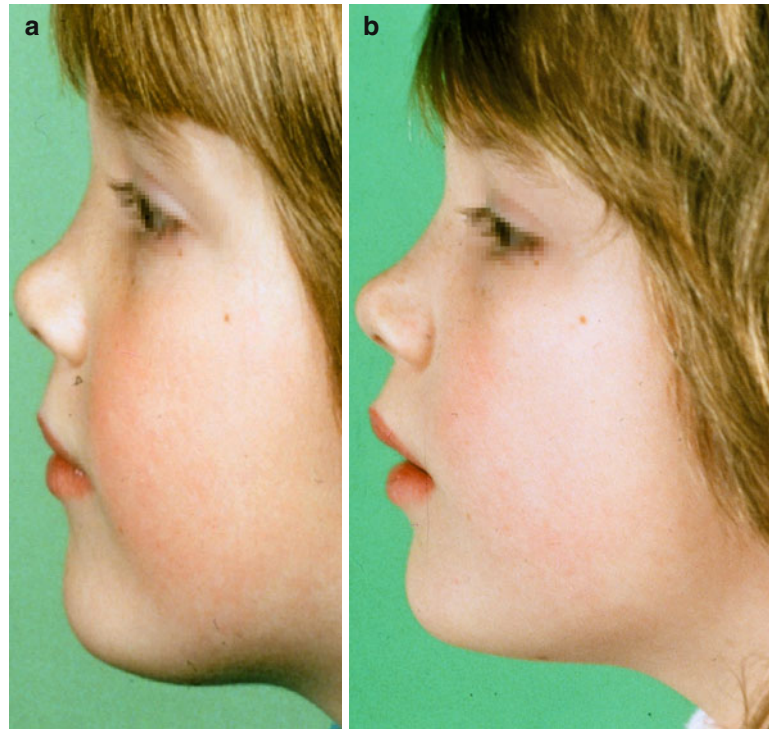


Fig. 35.14 Underdevelopment of the cartilaginous and bony nasal pyramid after a previous septal abscess; (**a**) girl at the age of 5 years and (**b**) 10 years. Increased nasolabial angle, with a prominent tip (supported by the alar cartilages)

defect of the septum cartilage. Saddling deformity with loss of tip support and growth retardation with a short nasal dorsum are then regular findings (Fig. 35.14a, b). Grymer and Bosch reported about one twin sibling, who endured septum destruction due to a septum abscess at the age of 7 years and was followed up with its twin for more than 10 years (Grymer and Bosch 1997). Despite the treatment with homologous cartilage from the tissue bank, the affected boy developed a severe saddle nose with upward displacement of the anterior part of the maxilla, decreased nasal projection and a retrognathical position of the maxilla compared to the unaffected sibling. This observation suggested that the nasal septum has a great influence on midfacial development determining vertical as well as anteroposterior maxillary growth. And secondly, that bank cartilage grafting is not adequate in preventing malformations of the midface during growth. Patients with a history of facial trauma develop progressive nasal deformation and/or nasal obstruction but the younger the age of the child the more impact such a lesion may have in the long run (Pirsig 2000). Also the extent of the injury – fracture, haematoma, abscess and perforation, surgical treatment – will play a role in the final result after the adolescent growth spurt. And these results are often disappointing, thus many of these patients have to undergo a second or even more surgical procedures later in life (Derkay 1999).

From a series of 241 children with a history of nasal injury, 40 % was diagnosed with pathological septal findings, with a longest follow-up period after trauma of 10 years (Blahova 1985). Septum deviation associated with snoring and abnormal rhinomanometric values appeared in 55 % of the patients. In a group of 16 paediatric patients, ranging from 2 to 14 years, major sequelae (62,5 %) like dorsum, tip or pyramid deformation, septum deviation with nasal obstruction, functional vault deformity and septum perforation were observed, whereas the other patients (37,5 %) all showed minor sequelae without any airway compromise (Alvarez et al. 2000). Another consecutive series of 20 children (2 months–15 years) were admitted to the hospital for treatment of nasal trauma followed by nasal abscess (12 patients) universally

associated with destruction of the septum cartilage (Canty and Berkowitz 1996). Nasal obstruction, however, was the most common symptom (19 patients). Recently a structured review of PubMed, EMBASE and the Cochrane Databases comprising 81 citations, dating from 1920 up to now, regarding nasal septal abscess was published (Alshaikh and Lo 2011). It was concluded that it is a serious condition that necessitates urgent surgical management in order to prevent severe complications, and even the growing child should be treated with early reconstruction essential for normal development of the midface. In this whole sequence, the lack of knowledge of the developmental mechanics is part of the problem.

35.2.2.4.1 Animal Experiments

35.2.2.4.1.1 Role of Cartilaginous Septum in Midfacial Growth; Experimental Evidence

To improve the definition of the role of the septo-dorsal cartilage for midfacial growth, a large series of animal experiments in which various parts of the cartilage were resected, resected and reimplanted, crushed and reimplanted and replaced by artificial materials or tissue-engineered cartilage was executed (Verwoerd and Verwoerd-Verhoef 2005). In this study, the most elementary and basic experiment of the former series was repeated in each new series. Surgical manipulation of the nasal septum with removal of cartilage resulted in midfacial malformations; the severity was depending on the extension of the cartilage defect.

> The dorsoseptal cartilage is the dominant growth centre of the midface. Specific growth zones are stimulating the development of the nasal skeleton and upper jaw.

35.2.2.4.1.2 Upper Laterals

In neonatal rabbits, the upper lateral cartilages are extending from the nasal tip to anterior cranial base, grossly comparable to the morphology in human newborns (viz. Fig. 35.8). Upper lateral cartilages and septum form an unpaired T-bar construct like in humans. This construction is supposed to possess much more mechanical strength and exert more 'pressure' in the period of growth than the septum alone. The growing septo-dorsal cartilage could therefore mechanically stimulate the lengthening of the upper jaw and nasal bones which are firmly connected. In the adult rabbit, the upper lateral cartilages, having lost the connection with anterior cranial base, have adapted a more triangular shape and extend only halfway under the nasal bones. Partial to subtotal resection of an upper lateral cartilage in young animals, on the other hand, would lead to specific anomalies: a decrease in length and curvature of the nasal bone, a deviation of the nasal tip to the nonoperated side and a considerable diminishing of the size of the turbinate on the operated side. This type of deformity could also be found in young patients with injury to one upper lateral cartilage at a young age (Pirsig 2000).

35.2.2.4.1.3 Mucosal Elevation

In the sequence of submucosal septal interventions, the first step was elevation of the mucosa on one or both sides, the so-called tunnelling; being executed carefully, it did not affect septal and nasal growth in rabbits (Verwoerd et al. 1979b). At microscopic level, however, a short period of swelling of the lamina propria of the perichondrium with exudate formation could be observed, followed by chondroblast proliferation, sometimes resulting in some extra cartilage production within the perichondrium (Verwoerd et al. 1990).

35.2.2.4.1.4 Release of Interlocked Stresses

Interruption of the septum cartilage over the antero-posterior length by a single and complete incision, comparable to a single total fracture, demonstrated an immediate overlap of the cut edges (Verwoerd et al. 1989b). It is explained by the release of interlocked stresses present in the hyaline cartilage, which was earlier described by Gibson for human rib cartilage and later by Fry for nasal septum cartilage in vitro (Gibson and Davis 1958; Fry 1967). Forces were supposed to be locked within the matrix of the cartilage; these should be in a state of balance between tension (in the three-dimensional collagen network) and pressure (evoked by water-binding hydrophilic proteins). Hyaline cartilage of the nasal septum contains a collagen

network of fibres aligned perpendicular to the surface and ending in alignment with the surface forming an inner and transitional layer of the perichondrium: the most proliferative cambium layer (Fig. 35.15a). The cartilage cells (chondroblasts-chondrocytes) with their surrounding proteoglycans-containing matrix are detained within the fibrous network. By fracture, incision or scoring of cartilage, the above-mentioned stresses might be released, thus altering the form of the cartilage . Also in the nasal cartilage of rabbits, this interlocked stress release resulting in a local duplicature of the cut ends could be found (Fig. 35.15b, c, d). This phenomenon could not be undone because within a short time, the overlapping ends were attached side to side by fibrous tissue originating from the perichondrium, and the interlocked stresses could then recur (Verwoerd and Verwoerd-Verhoef 2010).

The poor wound healing capacity of cartilage and the release of its interlocked stresses have definite effects on later development of the midface.

A relation between the depth of scoring and the immediate warping of cartilage in an isolated situation was studied separately (ten Koppel et al. 2003). The resected septa were immerged in a bath of saline. Scoring for less than 15 % of the total thickness was not followed by bending of the cartilage, but incisions up to 50 % of the thickness appeared to be directly related with the degree of warping; differences between young and mature cartilage could not be observed. Effects on the mechanical strength of resected cartilage or on midfacial development could, of course, not be measured.

35.2.2.4.1.5 Submucosal Resection of Parts of the Septum Cartilage: Effects on the Developing Nasal Skeleton

Submucosal resection of the middle one-third of the septum cartilage of 4-week-old rabbits (per series n = 10), interrupting the anteroposterior axis, had marked consequences for midfacial growth: a decreased length of the premaxilla and maxilla and a malocclusion of the molar complexes and incisors resulting in an underdevelopment of the midfacial skeleton (Fig. 35.16). Even when this surgical procedure was performed at a later stage, in rabbits at the age of 9 weeks with a follow-up of 16 weeks until the animals had reached adulthood, digital measurements (Screen Calipers version 3.3, Iconico.com Software) confirmed the above-mentioned observations(Wong et al. 2010). The septal defects in these experiments will interrupt both zones of thicker cartilage, earlier described as the sphenodorsal and sphenospinal zones (Fig. 35.17). Growth of the first is considered to contribute to lengthening of the bony nasal dorsum, whereas the second should 'push forward' the connected premaxilla-maxilla. Discontinuity of one or both zones can evidently explain different types of midfacial maldevelopment.

35.2.2.4.1.6 Histology

Histological examination of the septum after submucosal resection of the middle one-third of the septal cartilage demonstrates specific reactions of the elevated outer perichondrium, the transected cartilage and adhering cambium. The wound reaction of the cut ends of the cartilage implies a ± 3 mm deep zones of regressive changes and cell death bordering the cut surface, with an adjacent zone of high cellular activity with enlarged dedifferentiating chondrocytes and a few mitoses, as well as first signs of redifferentiation finally resulting in new cartilage . After the first 2–4 days, the necrotic area will be marked of the viable cartilage by a layer of fibres. The necrotic cartilage is invaded and resorbed by polymorphonuclear cells and macrophages originating from the outer perichondrium (Verwoerd et al. 1991). In the meantime cells migrating from the cambium layer grow over the cut cartilage, showing marked mitotic activity and redifferentiation into cartilage (Fig. 35.17). This new cartilage may even be recognised 20 weeks later in the adult stage by their large number of relatively small chondrocytes. Cells migrating from the outer perichondrium will soon cover the newly formed cartilage which shows hardly any further growth. The role of the outer and inner perichondrium in

wound healing of cartilage has been further analysed by in vivo and in vitro experiments and will be discussed later (Duynstee et al. 2002).

Where the septal cartilage has been resected, cells from the elevated (outer) perichondrium seem to migrate into the underlying 'free space' initially filled with exudates. In the following weeks, the 'free space' narrows and the elevated perichondrium from both sides will reconnect, locally enclosing islands of thin cartilage probably formed by migrating from parts of the cambium which might have been connected to the elevated perichondrium (Fig. 35.18).

Even in adult rabbits, in which submucosal resection of a central basal segment of the nasal septum (1.0×2.5 cm) was removed, islands of isogenic chondrocytes could be identified, 7 months later (Kaiser et al. 2006). This regrown

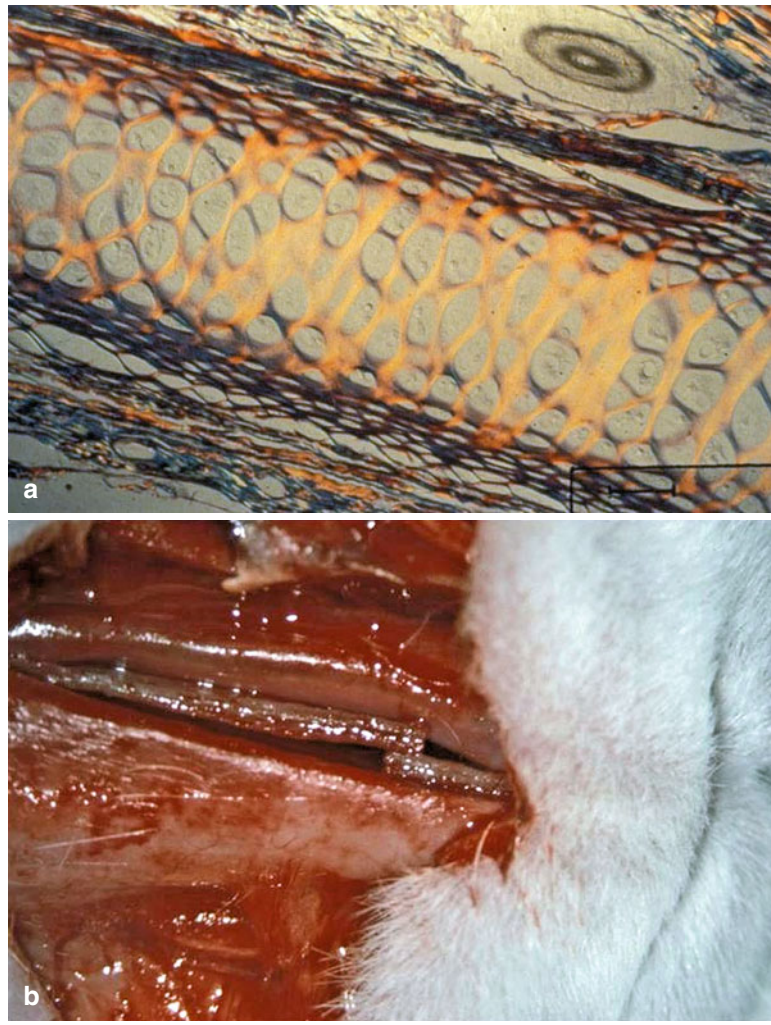
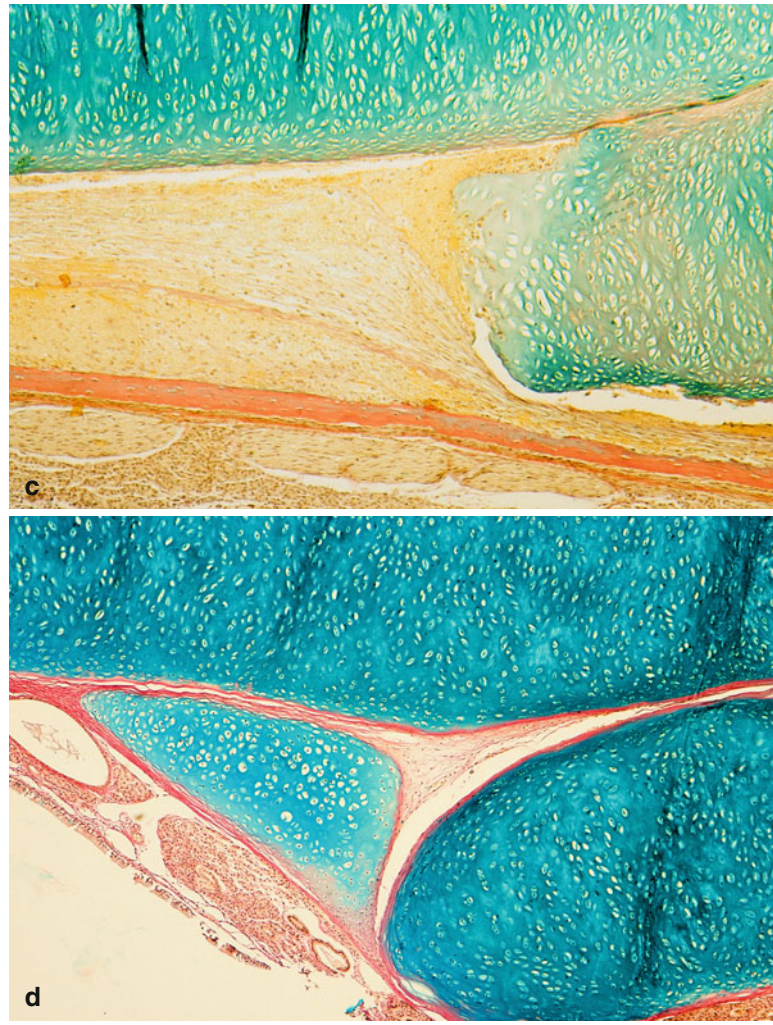


Fig. 35.15 Histological section of septum cartilage; (**a**) Sirius Red staining specifically demonstrating the dense layer of collagen fibres in the perichondrium and the network of collagen fibres in which the chondrocytres are locked; binding of water by intercellular proteins generates interlocked stresses within the collagen mantle and network. (**b**) After transection of the septal cartilage, release of interlocked stresses is responsible for an immediate overlap of the cut ends as observed in vivo. (**c**) Reaction at the wound surface with exsudate, necrosis and swelling of the elevated perichondrium, at the level of the vomer wing; (**d**) 20 weeks after a surgical intervention; the separated parts are reconnected side to side by their perichondrium (dehiscence is artefact); the 'free space' under the elevated perichondrium is filled with new cartilage (Pas Alcian blue staining)

Fig. 35.15 (continued)



cartilage morphologically resembled but was not identical to native septum cartilage. In contrast, healing of split cricoid cartilage did not occur easily in older rabbit: no mitotic activity or new cartilage formation was then observed (Verwoerd-Verhoef et al. 1998b). It was suggested that the potential of the septal perichondrium is much stronger than of the thinner perichondrium covering the cricoid.

Submucosal resection of the dorsal half of the middle part of the septum in young animals results in a shortening of the nasal bones in the adult stage due to the interruption of the sphenodorsal zone of thick cartilage (Rhys Evans and Brain 1981). Growth of the uninterrupted sphenospinal zone is responsible for the normal lengthening of the premaxilla and maxilla. If resection of the middle part of the septum is actually restricted to the sphenospinal zone, no growth disturbance of the nose and upper jaw could be demonstrated. The resected part appeared to be enclosed between the vomeral wings on both sides (Meeuwis et al. 1993). The outer perichondrium is here attached to the vomeral periosteum which may prevent their collapse after resection of cartilage leaving free space for cartilage new formation. Then, overgrowth of the amputated ends of the septum cartilage by the outer layer of the perichondrium may be retarded or prevented (Fig. 35.19). Geometrical measurements of this experimental series demonstrated no statistically significant

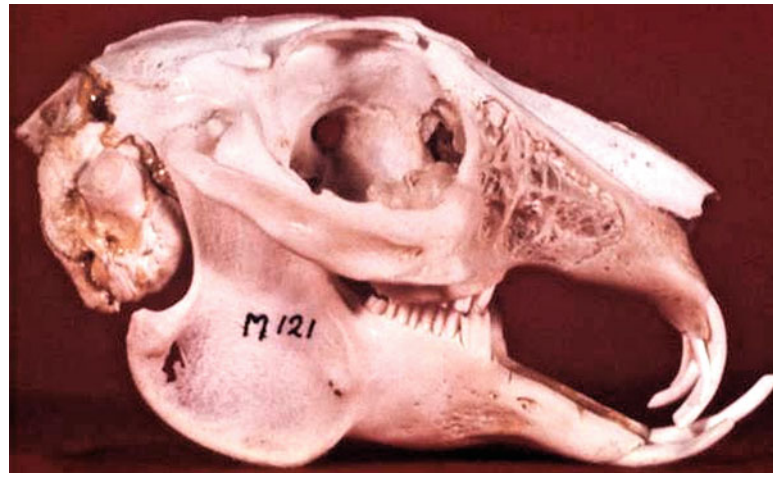


Fig. 35.16 Lateral view of an adult rabbit skull 20 weeks after resection of the middle one-third of the septum cartilage; shortened nasal dorsum with slight 'saddle'; malocclusion with crossbite of incisors

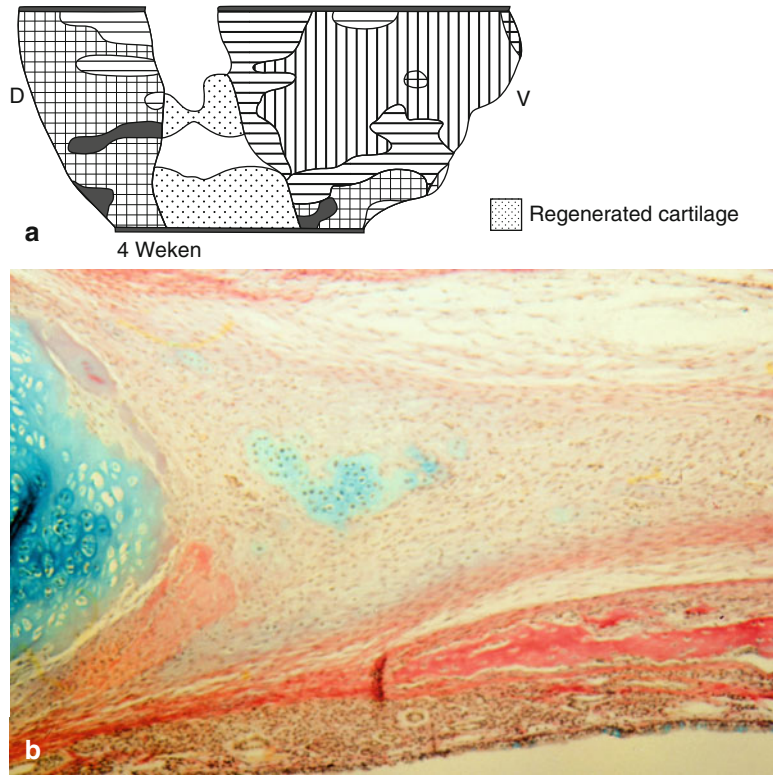


Fig. 35.17 (**a** and **b**) Schematic reconstruction of a septum 4 weeks after submucosal resection of 1cm in the middle part of the septum; (**a**) regenerated cartilage is observed which locally might bridge the defect; the majority of newly formed cartilage is found between the two vomer wings which keep the defect open (Courtesy of Dr C.A. Meeuwis). (**b**) Histologic section at the level of the vomer one week after surgery; precursor cells from the inner perichondrium (cambium) invade the open space and the first chondroblasts are formed; the original septum cartilage shows signs of necrosis: the chondrocytes have died, the intercellular matrix remains, the adjacent area shows highly activated cells

differences with the control group (Verwoerd and Verwoerd-Verhoef 1998). It may be concluded that the effects of septum resection in rabbits are depending on dimensions and location of the created defects. The larger the deficit of tissue the greater the interference with normal growth, in particular in the most important growth areas. The experimental results make clear that inadequate wound healing of cartilage is at the moment limiting the possibilities of surgery to restore the normal facial development.

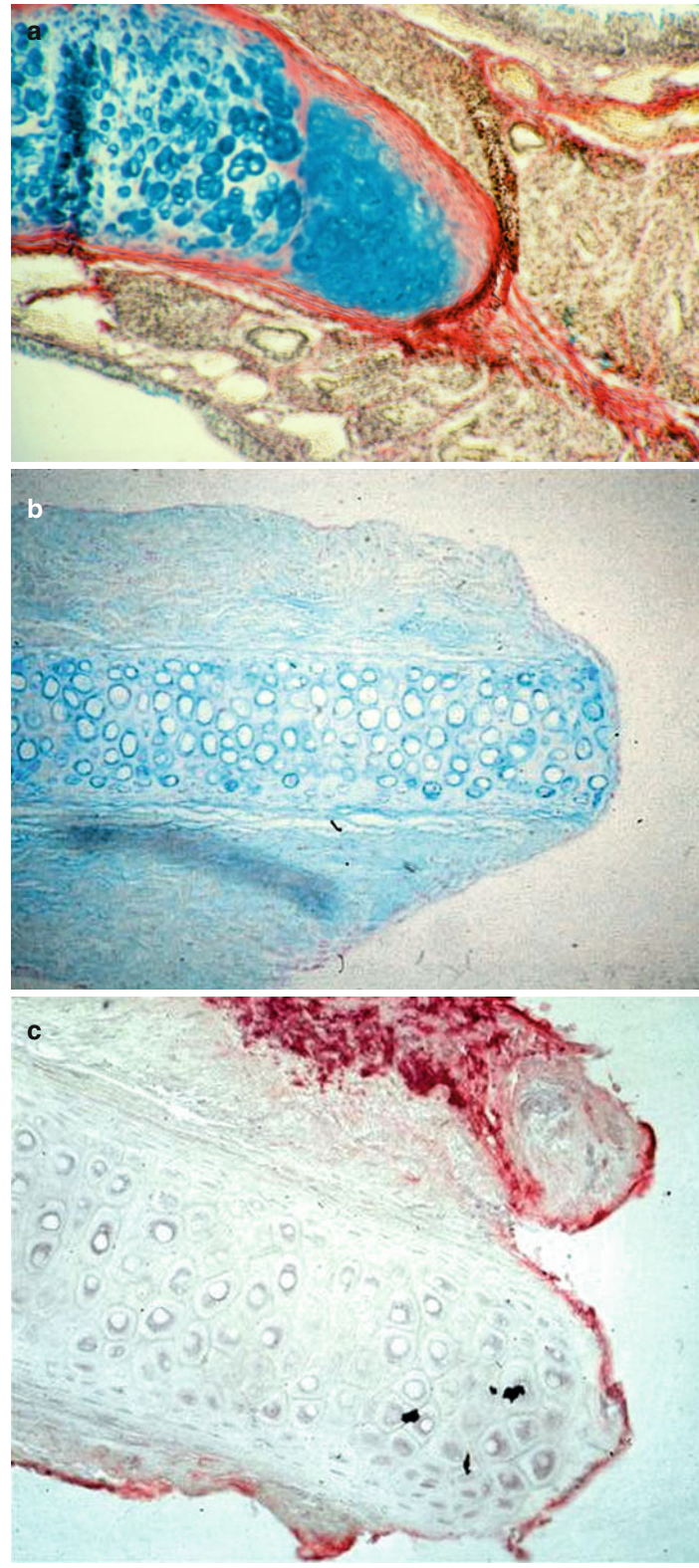


Fig. 35.18 Histologic section of a wound 6 weeks after resection of the middle part of the septum cartilage; (**a**) the cut end has been encapsulated by a fibrotic layer originating from the outer perichondrium; in the defect, the perichondrium layer of both sides has fused; (**b**) isolated piece of ear cartilage with intact perichondrium, cultured for 3 days, demonstrates fibrous cells originating from the outer perichondrium growing over the cut surface of the cartilage (Alcian blue staining; original magnification x75); (**c**) immunohistochemical staining for TGF ß1, present in the outer layer of the perichondrium and in the overgrowth, at day 7 of culturing

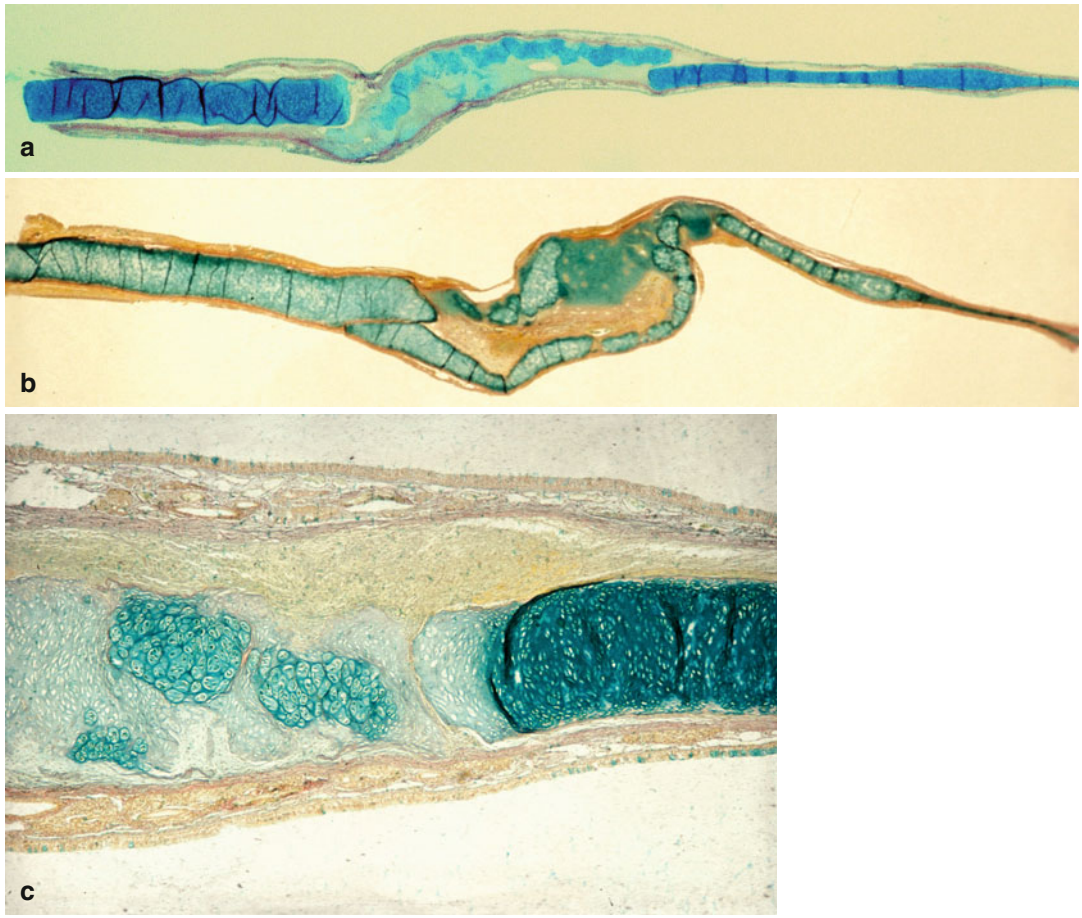


Fig. 35.19 Histologic sections of nasal septum with a crushed implant 2 days after surgery (**a**) and 20 weeks later (**b**) with deformation of the septum due to disorganised and insufficient repair of the cartilage; (**c**) detail at 7 days after crushing and grafting: the necrotic part of the stump is demarcated, invading cells from the perichondrium differentiate into chondroblasts, and proliferating viable cells form larger islands of cartilage through mitotic activity

35.2.3 Repair and Reconstruction of the Nasal Septum

35.2.3.1 Wound Healing of Hyaline Cartilage and Perichondrium

35.2.3.1.1 In Vitro Experiments

The wound healing capacity of hyaline cartilage and its perichondrium in the head and neck region, human as well as from animals, has been investigated since the midst of the last century (Peer 1941; Engkvist et al. 1979). The role of perichondrium was found to be twofold since it appeared to be composed of two layers: an inner layer (cambium) which is involved in the production of new cartilage cells and an outer, more fibrous, layer responsible for nutrition and protection (Duynstee et al. 2002). This was observed in explants of rabbit ear cartilage, cultured under various conditions up to 21 days, with perichondrium intact or after removal of the outer layer or both layers. After 3 days the cartilage explants with an intact perichondrium demonstrated fibroblasts, originating from the outer perichondrium layer, growing over the bare cut ends of the cartilage (Fig. 35.18b, c). When the outer layer was resected leaving the cambium layer in situ, fibrous overgrowth could not be observed and new cartilage was formed at the

cut ends. Pieces of cartilage denuded from inner and outer perichondrium did not show any reaction. It was concluded that the efficacy of neochondrogenesis lies in the inner perichondrium layer, the cambium. It seems evident that wound healing of cartilage would be improved when the overgrowth of fibres from the outer layer of perichondrium could be delayed or prevented favouring cartilage new formation by the cambium.

35.2.3.1.2 Animal Experiments

In experimental animals as rats, cats, guinea pigs, ferrets, beagles, chimpanzees and particularly in rabbits, reconstruction of the septum after cartilage resection with reimplantation of resected tissue or homologous cartilage or grafting with other materials was tested. As in most research models and series, not all outcomes are uniform. For example, in the cat with a very short nose, cephalometric measurements performed in the lateral sagittal plane after septoplasty did not show any growth disturbance, but septum deviations can only be made visible in the transversal plane. It might lead to incorrect conclusions and advice regarding septoplasty at a young age (Haye and Freng 1986). Experiments with 6-week-old rabbits and 8-week-old beagles revealed that following surgical creation of a cleft lip, alveolus and palate using identical experimental protocols, overall craniofacial aberrations were similar for both species (Bardach and Kelly 1988). From septoplasty procedures in chimpanzee monkeys of unknown age, it was concluded that by delaying the time of surgery, the impact of growth deceleration could be decreased (Siegel 1979).

35.2.3.1.3 Histology

In vivo cartilage wound healing is hindered by chondrocyte death at the lesion site (Verwoerd-Verhoef et al. 1998a; Tew et al. 2000; Bos et al. 2001). In injured cartilage dead cells and intercellular matrix at the lesion site are not easily eliminated. A band of avital tissue can hinder integrative repair of the lesion, even though the cells adjacent to the layer of necrosis increase the expression of growth factors and synthesis of matrix components as well as the mitotic activity. The hampered healing of cartilage wounds is the cause of deformation and growth disturbance. Positive results have been suggested on the use of a polydioxanone plate as a 'splint' between the perichondrial layers on both sides to prevent deformation (Boenisch et al. 2010). Using a very sharp scalpel might help to revive the wound edges since cell death is less at sharp cut edges (Tew et al. 2000). In experimental laboratory studies, the application of enzymes to degrade the avital tissue in the traumatised area has been demonstrated to improve integrative bonding of two pieces of cartilage , which thus far has not been tested in a clinical setting (Bos et al. 2002; van de Breevaart et al. 2004; Janssen et al. 2006). Furthermore, application of metabolically active cells at the lesion sites that can degrade the old matrix at the wound edge and lay down newly formed matrix has been proposed (Pabbruwe et al. 2010).

It should be understood that this newly generated cartilage is not always of the same quality as the original tissue. The matrix is often more fibrous and does not have the same fibre architecture and mechanical properties. Therefore, the repair tissue might be inadequate to bring forward normal nasal growth.

35.2.3.2 Implantation of Grafts

In general, cartilage grafts from nasal septum, auricle or cricoid will survive when embedded in a physiological condition (environment), the more so when the cartilage graft is covered by perichondrium. If the embedding is inadequate, necrosis cartilage resorption will take place. The majority of experimental investigations of the midface were performed in rabbits in different designs.

35.2.3.2.1 Animal Experiments

As discussed previously, submucoperichondrial resection of middle one-third of the nasal septum in young pure-bred rabbits resulted in all studies to retarded snout growth rather in length than in height (Nolst Trenité et al. 1987). Reimplantation of the resected, and thus autologous, cartilage could not prevent growth anomalies after a

follow-up of 20 weeks, when the animals are adult: reduced length, sometimes saddling of the nose and septal deformities were noted. Inadequate wound healing of the graft with a good binding to the original cartilage had resulted in septal spines and deviations. Crushing of resected pieces of septum cartilage followed by reimplantation showed similar sequelae: the crushed tissue may partially survive with dedifferentiation of new chondroblasts but is also the victim of necrosis and resorption (Fig. 35.19). Such a new construct appeared not to be suitable for reconstruction purposes in the growing animal (Verwoerd-Verhoef et al. 1991).

When insufficient material for grafting is available in the patient, alternatives should be considered. Artificial materials like proplast and Gore-Tex were tested and found absolutely not suitable for reconstruction because of their disastrous effect on the growing septum. Infection and rejection of the graft resulting in severe midfacial malformations were observed in the growing animals (Nolst Trenité et al. 1988).

35.2.3.2.2 Tissue Engineering

In addition to the use of artificial materials only, the combination of cells and carrier materials as used in the field of tissue engineering may offer advantages. New tissue can be formed by combining materials and cells in situ or by creating constructs with cells cultured on materials in the laboratory before implantation in the patient. Each year many new materials become available. To date none of the artificial materials, either with or without seeded cells, seems appropriate for cartilage reconstruction in the head and neck region because the risk of infection and rejection is particularly high. Therefore, natural materials seem a better choice for reconstruction of the nasal septum. One of the first natural materials investigated extensively for cartilage formation is demineralised bovine bone (Reddi et al. 1977; Bean et al. 1993; ten Koppel et al. 1998). This material is rich of natural growth factors that can attract cells and induce cartilage formation. A promising method for cartilage implantation in the head and neck region was found when a composite graft consisting of a piece of demineralised bovine bone matrix was enveloped in a flap of auricular perichondrium (Fig. 35.20a). In young rabbits, this compound graft was transformed into a piece of hyaline cartilage (Fig. 35.20b). This newly formed cartilage was then removed from the ear and transplanted into a septum or cricoid defect, apparently survived and could integrate well with the surrounding margins of the original cartilage (Bean et al. 1993). One case has been published in which a boy who lost most of his septum cartilage at a young age (around 3 years of age) was treated at the age of 9 with this method and showed a very good developed nose at the age of 19 years (Pirsig et al. 1995). Although positive results could be demonstrated, the irregular tendency of early ossification and above all the growing incidence of mad cow disease gave reason to interrupt research at that moment. Still, this process of engineering cartilage in vivo seems a promising method to be explored in the future.

The development of tailor-made scaffolds from natural materials such as collagen, collagen with glycosaminoglycans or hyaluronic acid-based materials might overcome some of the problems inherent to the bovine demineralised bone blocks. These materials can be combined with growth factors (Rosso et al. 2005). The disadvantage of these materials at the moment is their weak mechanical properties. Therefore, the materials have to be cultured with cells for several weeks in order to let these cells produce matrix that will provide mechanical stability.

The cells required to generate cartilage matrix can be harvested from several sources. Nasal septum would be the first choice. Nasal septal chondrocytes have been demonstrated to grow well in culture and to be able to form new cartilage matrix (van Osch et al. 2001a; Farhadi et al. 2006). In case the quantity of available cartilage in the septum itself is insufficient, the auricle could be a suitable source. A small biopsy will suffice to harvest cells and expand the number of cells in culture to obtain the number required to make a graft (van Osch et al. 2001b, 2004; Mandl et al. 2004). Chondrocytes from the auricle have proven to be very good cartilage matrix producers (Fig. 35.20c). The amount of cartilage matrix

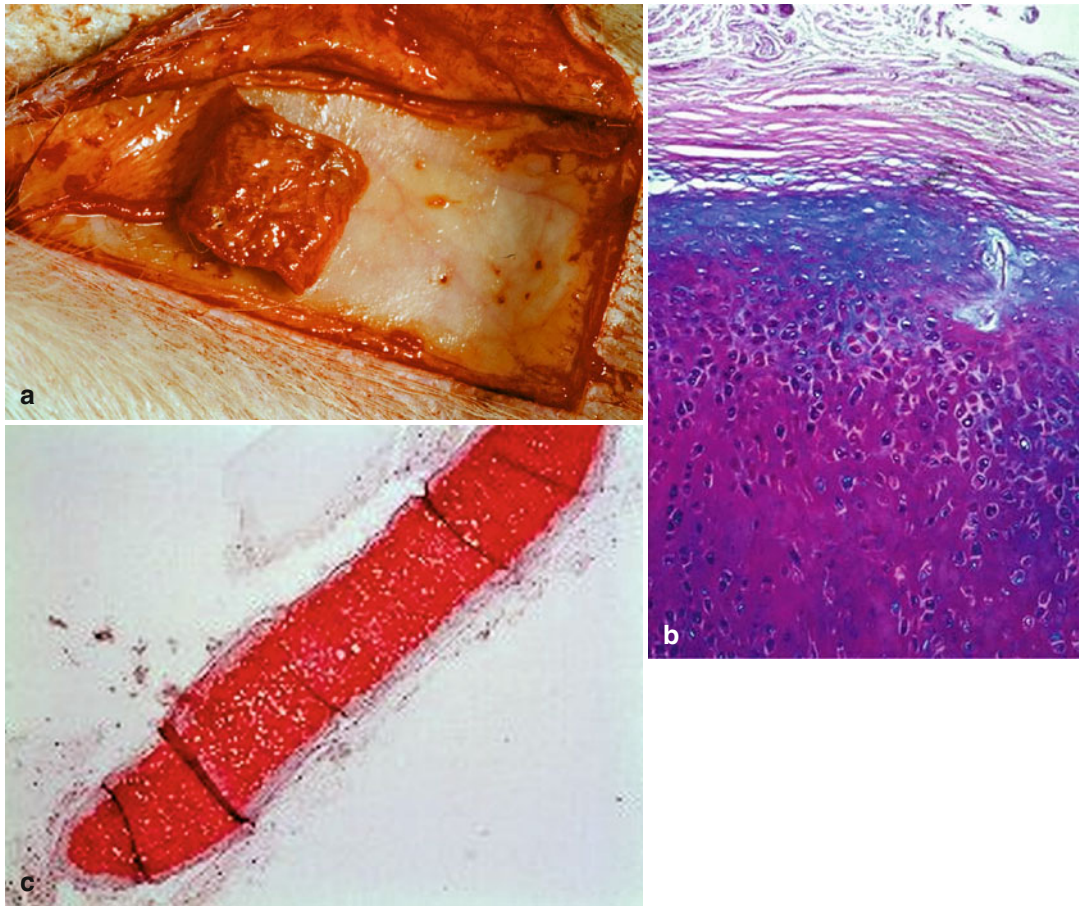


Fig. 35.20 Tissue engineering in vivo; (**a**) piece of demineralised bovine bone matrix is wrapped in elevated rabbit ear perichondrium for 6–8 weeks; (**b**) histology of human engineered cartilage in vivo (Courtesy of Prof. W. Pirsig). (**c**) Tissue engineering in vitro: construct generated from culture-expanded auricular chondrocytes of an 18-year-old donor; scaffold-free flat constructs were made by seeding the cells on a membrane and by culturing them for 14 days in the lab followed by implantation subcutaneously in an athymic mice for 6 weeks; a new piece of cartilage-like tissue, positive for collagen type II on this immunohistochemical staining, was produced

generated by these cells is higher than from cells derived from a nasal septum. Recently we have shown, however, that the molecular profiles of cells from auricle and septum are different, even after expansion of cells in the laboratory for several weeks (Hellingman et al. 2012). It is to be expected that the quality of the matrix and thus the functional behaviour of the graft produced by cells from nasal septum and auricle will differ as well, although this has never been investigated thoroughly. Moreover, it should be investigated whether this has clinical consequences. For the moment auricular cartilage grafts are being used frequently for nose reconstructions, with temporary success. In a growing nose, however, the long-term consequences have not yet been explored.

The harvest of cartilage for the isolation of cells will always cause donor-site morbidity; the defect will not heal due to the intrinsic limited repair capacity of cartilage. Stem cells may offer an alternative cell source. Stem cells can be isolated with relatively low donor-site morbidity from perichondrium of the ear, from bone marrow or from adipose tissue. Moreover, in contrast to cartilage cells, stem cells can be extensively expanded in number while retaining the potency to differentiate into cartilage. In spite all the

efforts, it appeared very challenging to produce stable cartilage using stem cells, as the generated cartilage is transient and will be remodelled into bone (Scotti et al. 2010; Farrell et al. 2011). Since stem cells are considered multipotential and capable of forming many different tissues, ongoing research efforts aim to unravel ways to stimulate stem cells to produce stable cartilage or even to form specifically nasal septum cartilage (Hellingman et al. 2011).

High costs and recently changed regulations concerning advanced-therapy medicinal products [Regulation EC, no. 1,394/2007] make long cell culture procedures less applicable for the use in patients. An alternative to improve mechanical properties would be to use a firm but flexible frame. Zhou et al. reported the use of a permanent support in the form of a coiled wire embedded into a porous collagen scaffold to maintain the construct's size and ear-specific shape in sheep (Zhou et al. 2011). But also other, more mechanically stable and newer formulations of materials are under investigation to be used to generate cartilage for reconstruction in the head and neck area such as polyurethane. For all materials it is required to tune the rate of formation of new tissue and degradation of the material in order to prevent too much foreign body reaction.

A key issue in research – in vivo and in vitro – is the promotion of healing of defects or fractures by tissue-engineered cartilage.

Lately the interest for decellularised cartilage grafts was renewed; most commonly involved allografts are of human origin. These decellularised grafts can be repopulated with cells by seeding the patient's own stem cells. This method has been successfully applied to reconstruct a trachea (Macchiarini et al. 2008). The use of decellularised cartilage grafts has several advantages including good mechanical properties and low foreign body reaction. Also when seeded with active stem cells, this might stimulate integration with the existing cartilage edges.

35.2.4 Conclusions and Clinical Epilogue

In the previous paragraphs, current data on normal growth of the nose in children have been presented:

- The development of the facial profile from baby to adult
- The evolution of the growth rate of the external nose in relation to age and sex
- The development of the cartilaginous and bony nasal skeleton
- The specific organisation of the cartilaginous nasal septum in thinner and thicker areas
- Growth and maturation of involved tissues, enchondral and mesenchymal ossification

In the latest decennia animal experiments have elucidated:

- The role of the septodorsal cartilage as dominant growth centre in the midface with specific growth zones within the cartilaginous septum, and upper lateral cartilages, responsible for growth of the nasal bones and premaxilla-maxilla.
- The effects of various lesions of the septodorsal cartilage, nasal bones and facial clefts on the developing midfacial skeleton, as well as the feasibility of surgical interventions to prevent these late effects.
- The potential of the cambium (inner perichondrium) layer to form new cartilage, which is restricted by overgrowing outer perichondrium.
- Prevention of untidy overgrowth by the outer perichondrium during repair of defects or fractures in cartilage is needed for restoration of the conditions for normal development.

In the clinical domain, nasal surgery in children has been practised for several years.

Septal haematoma and septal abscess are recognised as an acute indication for surgical treatment. Early drainage of a haematoma or abscess could save the septal cartilage from necrosis. In addition to drainage of the abscess and antibiotic treatment, the implantation of preserved bone has

been advocated to prevent saddling of the nasal dorsum. There is no evidence that preserved bone will restore normal growth. Occasionally a central submucosal defect is found leaving intact the thicker areas – growth and support zones – in the septal cartilage. The sequelae of nasal trauma in children are currently not sufficiently recognised, and the late effects of fractures on further growth are often not taken into full consideration. It seems that most children are not referred to an ORL specialist in case of an acute trauma.

When fractures and dislocation are diagnosed in children, reposition and realignment of dislocated fractured parts of the bony and cartilaginous nasal pyramid seems indicated at short notice. Uncertainties about further nasal growth should be discussed with patient and/or parents. This equally applies to the elective nasal surgery in case of progressive and severe functional or aesthetic problems.

Various studies of paediatric patients have reported successful results after rhinosurgical procedures at a young age (El Hakim et al. 2001; Dispenza et al. 2004; Menger et al. 2008; DeRosa and Smit 2009; Christophel and Gross 2009). The number of patients, however, is usually limited and the follow-up too short. To date, there is no consensus among clinicians with regard to the optimal age for surgical management of pathology of the nasal skeleton. Reconstruction with autologous cartilage (septal, costal or auricular) grafts in an open approach has been advocated as preferential for older children, although growth disturbances remain a risk (El Hakim et al. 2001).

Significant progress has been made in the preclinical domain – from human anatomy to experimental surgery in animal models – in recognising critical factors of cartilage wound healing. New developments might reveal methods that combine patient's own (stem) cells with scaffolds to reconstruct the growing nose in the future. For clinicians the next step should be to acquire more clinical evidence, differentiating for the age of the child and including an adequate follow-up, to evaluate the later nasal development in comparison with the outcome of the animal model studies (Alshaikh and Lo 2011; Verwoerd and Verwoerd-Verhoef 2011).

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Physiologic Concerns During Rhinoplasty

36

E.B. Kern

Keywords
Internal nasal valve • External nasal valve • Premaxillary wing • Piriform aperture • Head of the inferior turbinate • Upper lateral cartilage • Lower lateral cartilage • Breathing dysfunction after rhinoplasty

Core Messages

- The prime physiologic concern during cosmetic rhinoplasty centers on the breathing function, correcting a present breathing dysfunction or preventing a postoperative breathing disturbance while improving the patient's appearance.
- The nasal valve is the most important part of the nose (internal and external) causing breathing disturbances.
- Managing the entire nasal valve area is the main issue in protecting the patient's breathing function during cosmetic rhinoplasty.

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36.1 Introduction

Truth is as you see it, and as I see it, after evaluating thousands of rhinologic patients, the most common symptom that I observed after failed rhinoplasty was difficulty breathing. This statement is based on my almost 50 years of working in otorhinolaryngology (primarily rhinology) and the findings of almost 9,000 breathing test patients (anterior mask rhinomanometry) and numerous papers presented to the profession over many years from data collected on patients at the Mayo Clinic in Rochester, Minnesota, USA, between the years 1972 and 2003 (Gordon et al. 1989; Kern 1973, 1977b, 1979, 1988; Mertz et al. 1984; McCaffrey and Kern 1979, 1986; Pallanch et al. 1985, 1993; De Bonilla Santiago-Diez et al. 1986). After prolonged study and writing regarding nasal physiology, I choose to summarize (simplify) and emphasize four primary functions of the nose (Bridger 1970; Bridger and Proctor 1970; de Wit et al. 1965; Kern 1975, 1984; Knops et al. 1993; McCaffrey and Kern 1980; Whicker and Kern 1973a, b). These primary functions are listed as follows:

1. Olfaction
2. Defense (sneeze, mucociliary transport, defensive proteins, and the immune system)

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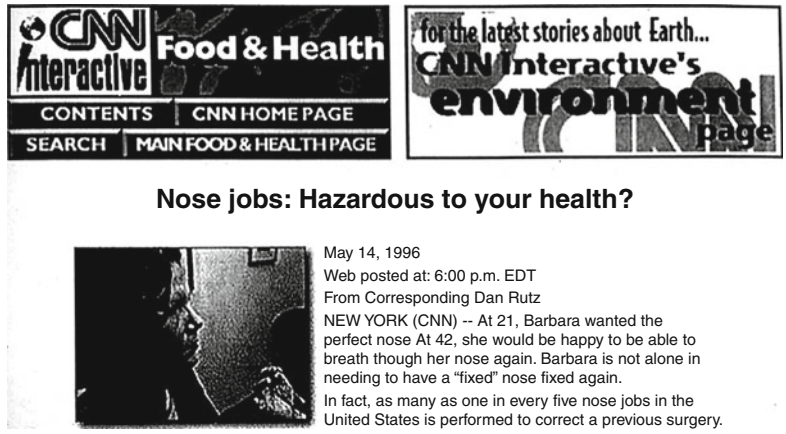

Fig. 36.1 Report from CNN (Cable News Network) Food and Health May 1996 claiming that one in five "nose jobs" (rhinoplasty operations) needs to be "fixed" again because of a postoperative breathing disturbance.

Realizing that the range of complications after rhinoplasty presented in literature varies somewhere from 6 to 10 % (approximate numbers) in experienced hands, after viewing web sites and contacting plastic, facial plastic, and cosmetic societies by phone, I estimate that the number of rhinoplasty operations performed in the USA is about 500,000 operations per year

3. Respiration (breathing, providing optimal nasal resistance and charging the inspired air with warmth and moisture, proper humidity, so oxygen and carbon dioxide exchange occurs optimally at the alveolar level)
4. Cosmesis (appearance)

Because a patient's symptoms can be so disturbing, my prime physiologic concern during cosmetic rhinoplasty centers on the breathing function. Of course, during rhinoplasty, cosmesis (appearance) is the usual first concern of the patient, yet for the surgeon the two essential concerns must be improving the appearance and correcting a present breathing dysfunction or preventing a postoperative breathing disturbance. The dictum of "do not sacrifice breathing function for appearance" is the mantra quietly singing in the back of the mind in my role as a "functional" nasal surgeon.

How many of us have experienced that sad and disquieting moment in our practice when the patient, even years after primary rhinoplastic surgery, complains bitterly about disturbed sleep (Olsen et al. 1981; Olsen and Kern 1990), mouth breathing, shortness of breath, or other symptoms of post-rhinoplasty nasal airway obstruction (Kern 1992) (Fig. 36.1)? In other words, it is the physiologic respiratory (breathing) concerns during rhinoplasty that I will address in this chapter with emphasis on those anatomic component parts of the nose that require meticulous attention during rhinoplasty to avoid producing a postoperative breathing disturbance. It is essential to preserve or improve nasal breathing and not impair any function while performing the rhinoplasty.

By definition, in my view, a rhinologist is a physician who is interested in patients who have disturbances of nose and paranasal sinuses. Surgery is but one treatment option for managing the varied symptoms seen in our rhinologic patients. I will review some of the important concepts concerning the nasal valve (internal and external nasal valve) since it is the nasal valve that is the most critical area for nasal breathing and by extension it is the nasal valve area which is the most important site of my physiologic concern while performing a primary cosmetic rhinoplasty.

36.2 Anatomy of the Nasal Valve Area

Since my primary physiologic concern during cosmetic rhinoplasty centers on the breathing function and the nasal valve is the most critical area for breathing, a review of both the anatomy

and physiology of the nasal valve area is imperative. Regarding the anatomy, an arbitrary subdivision of the nasal valve for practical clinical thinking has been forwarded in the literature, suggesting that we think of the nasal valve area as having two component parts. First, the internal nasal valve (most of our discussion will center around the internal nasal valve as it is composed of a number of diverse anatomic parts) and an external nasal valve, which is primarily composed of the lower lateral cartilages and surrounding soft tissues, which are covered both dorsally and ventrally by skin. Both valves (internal and external) are still subjected to the laws of fluid (air is the fluid) dynamics (Barelli et al. 1987; Bridger 1970; Bridger and Proctor 1970; Cole 2000, 2003; de Wit et al. 1965; Eccles 2000; Haight and Cole 1983; Hilberg et al. 1989; Hinderer 1971; Huizing and de Groot 2003; Kasperbauer and Kern 1987; O'Neill and Tolley 1988; Van Dishoeck 1942, 1965; Wexler and Davidson 2004).

36.2.1 Internal Nasal Valve

First, let's look at the anatomy of the external nose. The component parts of the external nose include a nasal skeletal structure (bone and cartilage) conveniently divided into three distinct and separate anatomic parts including:

1. Upper bony portion (paired nasal bones).
2. Middle third composed of the single upper lateral extension of the septal cartilage (the upper lateral cartilage is one cartilage and should not be thought of as two separate cartilages); this upper lateral cartilage is also termed the roof or triangular cartilage (Fig. 36.2). At its distal end (caudal end), the upper lateral cartilage is usually separated by a narrow cleft from the nasal septum and projects beneath the paired lower lateral cartilages.
3. Lower third of the external nose is composed of paired lower lateral cartilages (also called lobular, rim, alar, or great alar cartilages).

For emphasis, remember that this single upper lateral cartilage is attached proximally beneath the paired nasal bones and is attached distally beneath the lower lateral cartilages (Barelli et al. 1987; Hinderer 1971; Huizing and de Groot 2003). At its distal (caudal) end, the upper lateral cartilage frequently curls back upon itself forming a portion that is called the "scroll" also termed "returning" which is in contact with proximal (cephalic) end of the lower lateral cartilages (Barelli et al. 1987; Gray 1970; Hinderer 1971; Huizing and de Groot 2003). The upper lateral cartilage also extends laterally out to the bony margin of the piriform aperture formed, in part, by the frontal (ascending) process of the maxilla. This external nasal skeletal structure (bone and cartilage) is actually covered *externally* by the soft tissues of skin, muscles, perichondrium, periosteum, and neurovascular bundles. *Internally* (intranasal) these structures have mucocutaneous (skin and mucosa) coverings.

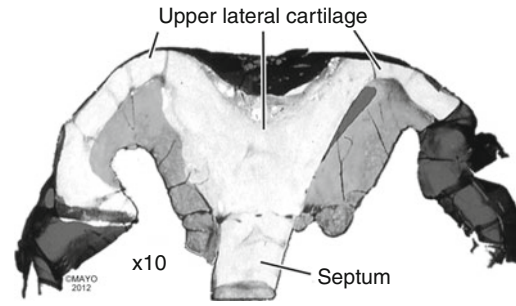

Fig. 36.2 Photograph showing that the upper lateral cartilage (roof cartilage) is an upper lateral extension of the septal cartilage in human. Photograph was taken after a rhinectomy that the author performed for a patient with an invasive nasal cancer (By permission of Mayo Foundation for Medical Education and Research. All Rights Reserved)

The entire internal nasal valve is more than the relationship between the distal end of the upper lateral cartilage and its angle formed with the nasal septum. Because of the complexity of the anatomy and the various papers on the subject, I think, for practical and functional reasons, the nasal valve should be thought of as an area. I think of the *nasal valve area* as a three-dimensional inverted cone-shaped structure that extends from the region of the distal (caudal) end of the upper lateral cartilage in its relationship to the nasal septum medially, including the premaxillary wing region, floor of the nose, and laterally to the bony

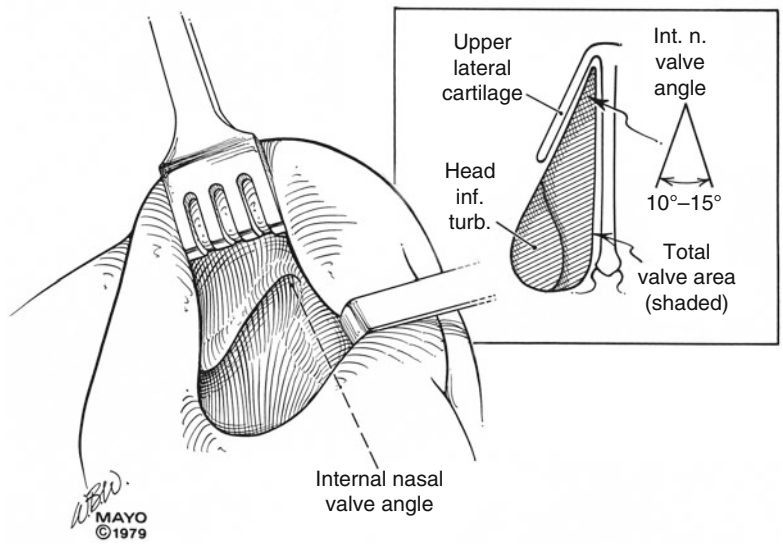

Fig. 36.3 This illustration demonstrates the clinical internal nasal valve angle and in the upper right corner of the illustration a representative view of the total internal nasal valve area which includes the upper lateral cartilage, the septal cartilage (the septal turbinate "swell body" is not shown here), the floor of the nose, the piriform aperture including the frontal (ascending) process of the maxilla, and the head of the inferior turbinate are all shown. The internal nasal valve angle is represented as ranging from 10 to 15 ° although some authors have different findings (Miman et al. 2006) (By permission of Mayo Foundation for Medical Education and Research. All Rights Reserved)

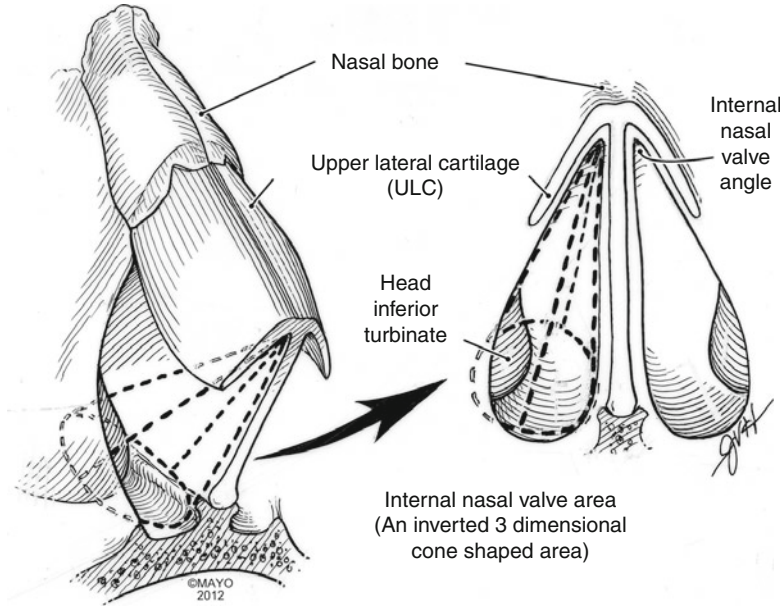

Fig. 36.4 Illustration demonstrates that the internal nasal valve area can be thought of as a three-dimensional structure (*an inverted cone*) with triangular portion (*bottom*) of cone fitting into the apex of the internal nasal valve angle (By permission of Mayo Foundation for Medical Education and Research. All Rights Reserved)

piriform aperture including the soft fibrofatty areolar tissue of this region of the internal nasal valve and is bounded posteriorly by the head of the inferior turbinate (Figs. 36.3 and 36.4).

Various workers have investigated the internal nasal valve and determined the approximate site using various methods, but the overwhelming consensus is that most of the upper airway

resistance is provided by the internal nasal valve and about one third of that resistance is due to the cartilaginous vestibule and approximately two thirds of that nasal resistance is due, in large measure, to the congestive capabilities of the anterior end (head) of the inferior turbinate. This turbinal "swell" body has a counterpart on the septum ("septal turbinate, swell body, or septal body") located on the nasal septum approximately adjacent to the anterior end (head) of the inferior turbinate (Miman et al. 2006; Wexler and Davidson 2004). The finding of the septal turbinate (swell body) was first described in the 1600s, and these findings have been reported and supported by investigations in humans (Barelli et al. 1987; Miman et al. 2006; Wexler and Davidson 2004). This entire *internal nasal valve area* ranges somewhere between 55 and 64 square millimeters.

The narrowest portion of the nasal airway is the apex of the internal nasal valve area at the nasal valve angle which is the specific triangular slit-like portion between the caudal (distal) end of the upper lateral cartilage and the nasal septum (Figs. 36.3 and 36.4). This nasal valve angle was first described over 100 years ago by Mink and is continuously re-reported to be approximately 10–15 ° in the leptorrhine (Caucasian) nose, as pointed out by Miman and coworkers (Miman et al. 2006). In their prospective comprehensive study of 248 nasal cavities using direct endoscopic examination along with acoustic rhinometry and rhinomanometry, they discovered different types of nasal valve angles, ranging "between 22.5 and 52 °" (Miman et al. 2006). Miman et al. studied normal asymptomatic control subjects and proposed a classification related to the upper lateral cartilage's caudal border stated as convex, concave, or twisted and the valve angle as blunt, sharp, or occupied by the septal body. The septal body has been noted and reported before with a prevalence ranging from 52 to 66 % of individuals (Arbour and Kern 1975; Wexler and Davidson 2004). Miman et al. also discussed another study whose authors used computed tomography to study the nasal valve angle and that was reported to be 11.4 ° +/− 2.6 °. After closer study of the other data obtained from computed tomography (while Miman et al. used direct endoscopic examination along with acoustic rhinometry and rhinomanometry), Miman et al. realized that positioning and placement of the lines for measurement are subjective and even a slight alteration of line placement could significantly alter the results by at least 15–20 °. In light of their findings, Miman et al. concluded that the literature's emphasis on a normal nasal valve angle of 10–15 ° needs challenge and must be open for further study and discussion.

It is the entire *internal nasal valve area* that is the primary airflow inflow regulator; accounting for the majority of the inspiratory resistance to inspiratory airflow and the head of the inferior turbinate is the posterior portion of the *internal nasal valve area*. The head of the inferior turbinate has a significant and at times a dominant role (think acute viral or acute allergic rhinitis) as an inflow regulator in the Caucasian (leptorrhine), Black (platyrrhine) nose, and in the Asian (mesorrhine) nose. Remember that the functional airway unit is the entire *internal nasal valve area* and any component anatomic part including the upper lateral cartilage; the anterior nasal septum, including the premaxillary wing region, floor of the nose, the piriform aperture, lateral fibrofatty areolar tissue, frontal (ascending) process of the maxilla and the head of the inferior turbinate, or the skin or mucosa (mucocutaneous coverings); or any combination of those structures when anatomically or pathologically altered from "normal" may contribute to dysfunction of the entire *internal nasal valve area*. *In other words*, *any anatomic part of the internal nasal valve area* may be surgically altered during primary rhinoplasty and therefore vulnerable to surgical alteration that could have negative consequences for breathing function postoperatively (Adamson et al. 1990; Araco et al. 2007; Becker et al. 2008; Beekhuis 1976; Berry 1981; Bruno et al. 2005; Constantian and Clardy 1996; Courtiss and Goldwyn 1983; Fischer and Gubisch 2006; Goode 1985; Hinderer 1970; Jenssen et al. 1988; Kern 1977a; Kern 1978, 1988b, 1991; Kern and Wang 1993; Kocer 2001; McCaffrey et al. 1983; McKee et al. 1994; Teichgraeber and Wainwright 1994).

36.2.2 External Nasal Valve

The external nasal valve is that portion of the nasal airway (ala of the nose) that is sprung open by the tensile strength of the paired lower lateral cartilages and the covering soft tissues and skin of the ala. The external nasal valve becomes a problem for the patient if the lower lateral cartilage is resorbed secondary to nonsurgical trauma, surgical trauma with over-resection of the lower lateral cartilages or changes in the tensile strength of the cartilage due to the atrophy of aging or loss of muscle tone secondary to facial palsy or other neurologic disorders (Constantian 1994; Huizing and de Groot 2003; Kern 1980b; Rizvi and Gauthier 2011; Schlosser and Park 1999).

36.3 Physiology of the Nasal Valve *Area*

Today, 40 years after Williams merely speculated that the nasal valve functions as a type of inflow device controlling the rate and depth of respiration, the complete function of the nasal valve is still unknown (Williams 1972). Hinderer suggested that the nasal valve controls inspiratory air currents changing them from a column to a sheet of air, thereby giving shape, velocity, direction, and resistance to the inspired air (Hinderer 1970, 1971). It has been previously suggested that the head of the inferior turbinate (Gray 1970) and the septal turbinate (Barelli et al. 1987; Cottle et al. 1958; Wexler and Davidson 2004) work in concert and both are important components of the internal nasal valve area because they provide the necessary resistance to breathing during inspiration. The nasal valve has been considered (Bridger 1970; Bridger and Proctor 1970) to function as a Starling resistor influenced by Bernoulli forces so that when the airflow increases (accelerates), the interior nasal pressure decreases allowing the lateral nasal walls to collapse inward (towards the nasal septum). Both the nose and a Starling resistor consist of a semirigid tube with a short collapsible segment (the internal and external nasal valve). The portion of the internal nasal valve at the head of the inferior

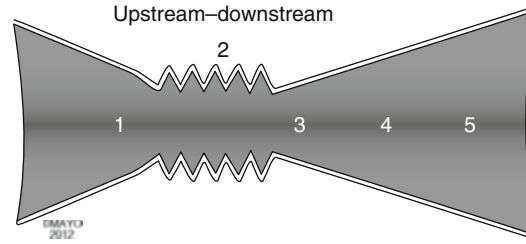

Fig. 36.5 Illustration is a graphic representation forwarding the idea that the nasal valve (internal and external) can potentially function as collapsible segment dividing the nose into upstream – cartilaginous portion (*Cottle areas 1 and 2*) – and downstream "bony portion" (*Cottle areas 3*,*4*, *and 5*). According to Cottle, the nasal septal areas are as follows: *area 1* refers to the nasal septum at the caudal end of the nasal septum. *Area 2* refers to the nasal septum at the valve area (now comprising the internal valve (including the anterior head of the inferior turbinate) and external valve (including the lower lateral cartilages)). *Area 3* refers to the nasal septum at the attic (the region of the septum beneath the nasal bones). *Area 4* refers to the nasal septum and its relationship to the turbinates (except for the most anterior head of the inferior turbinate, which is certainly part of the internal nasal valve and at the same time is the most posterior part of the internal nasal valve). *Area 5* refers to the nasal septum and its relationship to the choana (Barelli et al. 1987; Cottle et al. 1958; Hinderer 1971; Huizing and de Groot 2003) (By permission of Mayo Foundation for Medical Education and Research. All Rights Reserved.

turbinate can be considered the upstream segment, whereas that portion posterior to the head of the inferior turbinate and the septal body is the downstream segment (Fig. 36.5). In other words, the semirigid tube conducts pressure changes to the collapsible segment, which is influenced by several factors including the conducted pressure, the extramural pressure, Bernoulli forces, and the elasticity of the collapsible cartilaginous segment. In the nose, negative inspiratory pressure is transmitted from the nasopharynx to the internal nasal valve area, which then narrows. The degree of narrowing depends on three variables:

1. The pressure difference between the internal nasal pressure during breathing and the atmospheric pressure (transmural pressure)
2. The flexibility of the valve area's collapsible cartilaginous segment
3. The size of the valve area

In the normal nose, the nose does not collapse during quiet breathing because the tensile strength

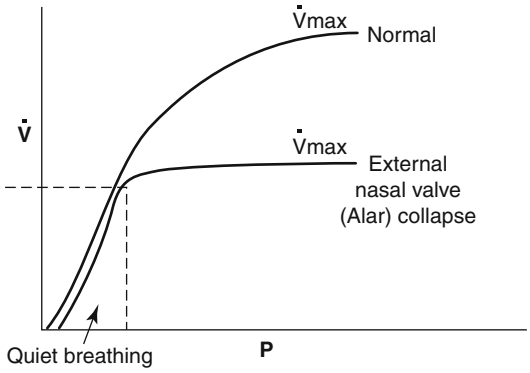

Fig. 36.6 Nasal pressure (*x*-axis) and nasal flow (*y*-axis) seen on idealized rhinomanometric curve in two situations.

A *normal* functioning nose. From a patient with *external nasal valve* (*alar*) *collapse* demonstrating limitation of flow at high inspiratory (negative to atmospheric) pressure.

At maximal inspiratory flow (Vmax), the nose collapses and no further increase in pressure (negative inspiratory pressure) can cause further increase in airflow through the nose. In other words, when the valve (internal and/or external) collapses, there is plateauing of the curve since no matter how hard a subject tries to increase the inspiratory effort (negative pressure during inspiration), there is a cessation of airflow secondary to (internal and/or external) nasal valve collapse

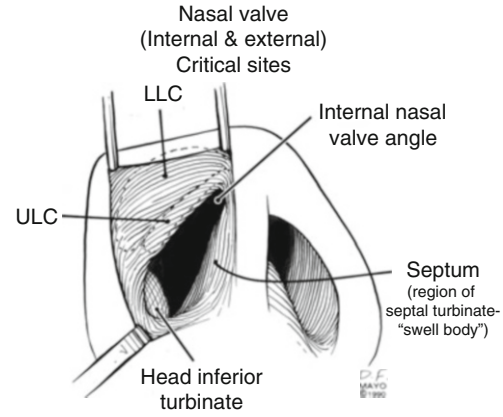

Fig. 36.7 Illustration depicts the most "critical sites" of "PHYSIOLOGIC CONCERN DURING RHINOPLASTY" that the surgeon must understand and avoid sacrificing structural support in these "critical sites"; otherwise breathing dysfunction will most probably occur postoperatively.

These "critical sites" include the following: the lower lateral cartilage (*LLC*), the major component of the *external nasal valve*; the *internal nasal valve* including the upper lateral cartilage (*ULC*), the septum, and the valve angle between the upper lateral cartilage (*ULC*) and the septum; and the head of the inferior turbinate.

If any of these "critical sites" are sacrificed for esthetic reasons, then the reconstruction must follow at the time of surgery; otherwise, a postoperative breathing dysfunction will often follow. If the internal nasal valve angle is blunted or scarred, then postoperative breathing dysfunction will almost invariably follow (By permission of Mayo Foundation for Medical Education and Research. All Rights Reserved)

of the cartilage (upper lateral cartilage, lower lateral cartilage, and septal cartilage) support of the nose offsets the closing forces of the transmural pressure and the Bernoulli effect. The resistance to airflow is dependent on the skeletal (cartilage and bone) and mucocutaneous nasal structures that are anterior (upstream) and posterior (downstream) to the head of the inferior turbinate. At maximal inspiratory flow rates, a greater inspiratory effort (increased negative pressure) fails to increase airflow because the external nasal valve (ala) is collapsed (Fig. 36.6). The external nasal valve does not remain collapsed as the process is reversed during expiration.

The external nasal valve (ala) is really the airway opening supported by the paired lower lateral (great alar or alar) cartilages. The critical sites for collapse are either at the external nasal valve (lower lateral cartilage) or at the internal nasal valve (nasal valve area composed of the upper lateral cartilage, nasal septum, including the premaxillary wing region, floor of the nose, piriform aperture, and the head of the inferior turbinate). Some observers believe that the septal turbinate (septal "swell" body) is part of the nasal valve area and I tend to agree, but these findings tend to support the notion that total understanding the valve area and its function is still far from fully understood (Haight and Cole 1983; Huizing and de Groot 2003; Miman et al. 2006; Wexler and Davidson 2004). Nonetheless, it is necessary to have some practical understanding of the nasal valve area and its critical sites in order to perform surgery without disturbing nasal breathing function.

These critical sites are seen in Fig. 36.7. A clinical un-instrumented view of many of the structures of the internal and external nasal valve can be seen in Fig. 36.8. The alar muscles are also involved in valvular function and aid in preventing

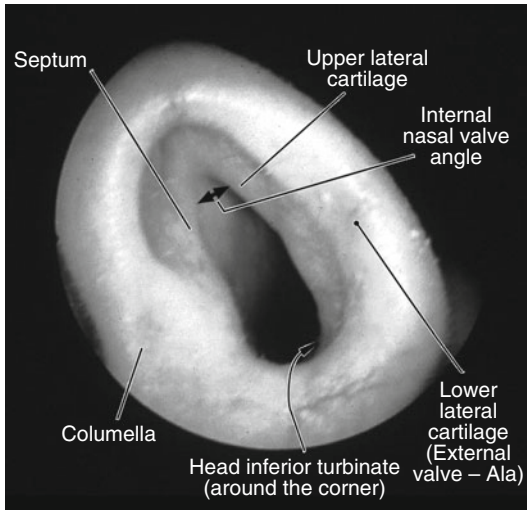

Fig. 36.8 Photograph is an un-instrumented clinical view of the left side of a person with a normal nose. Many structures of the internal and external nasal valve are seen and labeled (By permission of Mayo Foundation for Medical Education and Research. All Rights Reserved)

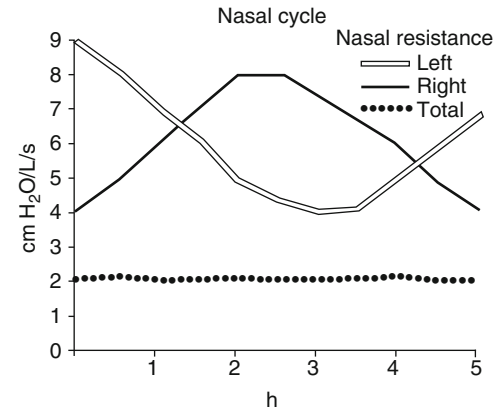

Fig. 36.9 The nasal cycle occurs in approximately 80 % of the adult population. It can be described as the normal physiologic alternating congestion and decongestion of the nasal turbinates producing changes in one-sided nasal (uninasal) resistance. Nasal resistance is calculated from the measurements of the trans-nasal pressure changes during breathing (inspiration and expiration) divided by the airflow during breathing (inspiration and expiration). In other words, resistance = pressure divided by flow. Note that each side (uninasal resistance right and left side) usually alternates (resistance values) with the other side, after the passage of time, while the total nasal resistance remains relatively constant. The patient experiences one side of the nose as obstructed (plugged) and after some period of time the other side becomes obstructed (plugged) while breathing through both sides (both noses) feels unobstructed

collapse of the valve at high inspiratory flow rates. Rigidity (scar) or flaccidity (over-resection) of cartilage structure including both the upper and the lower lateral cartilages and soft tissues would affect valvular function and breathing. Even minor changes in the diameter of the airway can significantly increase nasal airway resistance in concert with Poiseuille's laws where the airflow is proportional to the pressure changes times the radius to the fourth power divided by the length. In other words, small changes in the radius to the fourth power are extremely significant.

Using acoustic rhinometry and active anterior rhinomanometry, Zambetti and associates (Zambetti et al. 2001) proved and supported the long-held clinical observation that small deformities in the anterior portion of the nose (upstream) like a scar in the valve angle can more profoundly and adversely effect nasal breathing than larger deformities in the interior of the nose (downstream) when they said, "Modest nasal cross-sectional area reductions posterior to the nasal valve do not cause substantial variations in nasal resistance…" (Zambetti et al. 2001).

The nasal valve area must function in concert with the structures upstream and downstream to provide nasal pulmonary respiratory balance over the wide range of physiologic demands. Since the head of the inferior turbinate is part of the internal nasal valve, it is affected by the vascular changes of the capacitance vessels in the stroma, which is termed the nasal cycle (Arbour and Kern 1975; Hasegawa and Kern 1977; Kern 1981). Actually the nasal cycle is a normal physiologic phenomenon that includes the alternating congestion and decongestion of the turbinates with changes in uninasal resistance while the total nasal resistance remains relatively constant (Fig. 36.9).

36.4 Pathophysiology of the *Nasal Valve Area*

It is critical that nasal surgeons particularly rhinoplasty surgeons understand the pathophysiology of internal and external nasal valve since any

Table 36.1 Structures of the *external* nasal valve

1	Lower lateral cartilage (LLC)
2	Fibroareolar soft tissues of ala

Table 36.2 Structures of the *internal* nasal valve area

1	Nasal septum (including premaxillary wings)
2	Upper lateral cartilage (ULC)
3	Piriform aperture
4	Fibroareolar lateral soft tissues
5	Frontal (ascending) process of the maxilla
6	Head of the inferior turbinate
7	Mucosa and skin coverings of these structures

disturbance in any portion of the critical sites in the nasal valve area (external valve and/or internal valve) can produce disturbed nasal breathing during exercise and/or at rest resulting in a very unhappy patient. The abnormalities responsible for nasal airway dysfunction include:

1. The *external nasal valve*: dysfunction may be due to a flaccid external valve which collapses at low inspiratory (negative pressures) airflow rates which can occur when there is a loss of cartilage (lower lateral cartilage) support due to surgical or nonsurgical trauma, the effects of aging with atrophy of the lower lateral cartilages. A flaccid external nasal valve can also occur secondary to facial palsy. Avoid "over-resection" of the lower lateral cartilages since over-resection may lead to loss of structural support with early collapse during inspiration and postoperative breathing difficulties (Table 36.1).
2. The *internal nasal valve*: dysfunction may be due to valve area narrowing due to structural changes in the valve angle (upper lateral cartilage and/or septal cartilage) or any one of the structural components of the valve area (Table 36.2).
3. Combinations of structural skeletal (cartilage) changes and/or the absence of skeletal support (especially secondary to surgery) including avulsion of the upper lateral cartilage (Parkes and Kanodia 1981) which may be associated with early collapse of the valve during nasal airway breathing; however, often the airway obstruction is so severe that the patient is unable to breathe through the nose and becomes a mouth breather.

After blunt trauma (Barrs and Kern 1980), the second most likely cause of nasal valve abnormalities (with breathing problems) is nasal surgery (Barelli et al. 1987; Beekhuis 1976; Helal et al. 2010; Huizing and de Groot 2003; Nunez-Fernandez D 2999; Parkes and Kanodia 1981; Sheen 1983). Narrowing of the internal nasal valve angle by a medially displaced upper lateral cartilage after "hump" removal and infracture, additionally over-resection of the "hump" leaving an incomplete infracture, results in the "open roof" deformity (Barelli et al. 1987; Hinderer 1971; Javanbakht et al. 2012) and early collapse during inspiration in addition to posttraumatic neurogenic pain syndromes. Uncorrected septal pathology or over-resection of septal cartilage resulting in a "flaccid" septum with "flutter" is another cause of a collapsed internal nasal valve. Over-resection of the lower lateral cartilages may also result in "flaccid" collapse during inspiration. This "flaccid" collapse is also seen with loss of muscular action (as in facial paralysis) or with the atrophy of aging secondary to decreased tensile strength of the cartilages and soft tissues producing a "droopy tip" (Aksoy et al. 2010).

36.5 A Brief Word About the Preoperative Evaluation and Discussion

When rhinoplasty is considered, I take a considerable amount of time to develop a personal relationship (rapport) with the patient while obtaining a general medical history, supplemented with a rhinologic questionnaire (Kern 1972) which succinctly covers the essentials including a history of smoking and alcohol use, attention to allergic conditions (including seasonal and perennial allergic rhinitis, allergies to medications, soaps, surgical solutions, latex, tape), bleeding tendencies, use of steroids (topical and/or systemic), diabetes, hypertension, current and recent medications (including aspirin, aspirin-like drugs – nonsteroidal anti-inflammatory drugs), peripheral

vascular disease, and previous operations of any kind.

In addition to physical nasal examination (looking for a Cottle sign Heinberg and Kern 1973) also use the endoscope (0 ° 4 mm) for an intranasal examination before and after topical decongestion to study the mucosa and the interior of the nose back to the nasopharynx. I usually obtain the following tests and consultations (when medically indicated):

1. Minnesota Multiphasic Personality Inventory (MMPI) is obtained on all patients prior to surgery looking for evidence of personality disorders, schizophrenia, and psychosis (Goin and Goin 1981).
2. Olfaction testing is performed on *all* patients.
3. Rhinomanometry (anterior mask technique) is also performed on all patients prior to surgery based on techniques previously described (Broms 1982; Gordon et al. 1989; Kern 1973, 1977b; McCaffrey and Kern 1986; Pallanch et al. 1985). Other surgeons suggest the use of acoustic rhinometry (first introduced by Hilberg and associates in 1989) as an objective "evaluation of the nasal cavity geometry by acoustic reflections" (Corey 2006; Grymer 1995; Roithmann et al. 1997).
4. CT scanning (direct coronal) is ordered when indicated.
5. Preoperative photographs are ordered on ALL patients even prior to sinus surgery as the patients can occasionally "forget" how their face and nose appeared prior to surgery.
6. Blood studies and other medical consultations (including allergy evaluation) are ordered when indicated.

I always ask for the patient's parent(s) or significant other to be present before surgery, and I always welcome questions from the patient and family before ending the interview. The preoperative discussion is critical to establishing the necessary rapport with the patient and the family to better manage complications should they occur postoperatively. Succinctly, for cosmetic rhinoplasty, I ALWAYS discuss the following in detail:

1. Goal(s) of the operation
2. Risk(s) (to life) of the operation and the anesthesia
3. Possible complications of the operation
4. Possible need for nasal septal surgery (Kern 1980; Lipton and Kern 1990) to treat a current breathing disorder or the possible need for obtaining graft material from the patient such as cartilage and/or bone from the septum, ear, or rib for reconstruction and grafting (Breadon et al. 1979; Pirsig et al. 2004; Sherris and Kern 1998; Slavit et al. 1995)

It is also wise to prepare the patient for a possible revision surgery (second operation) before you perform the first operation as the patient may require secondary or "touch up" operation at some time in the future. Happily, most patients are more satisfied with the results of rhinoplasty perhaps even more than their surgeon (Hellings and Nolst Trenite 2007; Saleh et al. 2012). The important details of the preoperative discussion have been presented previously in the literature (Kern 2003):

> Trust your feelings. If the results of the MMPI are abnormal or you are concerned that the patient has significant emotional issues that preclude a "normal" doctor patient relationship, seek psychiatric consultation (because your inner voice tells you there is something "wrong" and you have an uncomfortable feeling about the patient, listen to your inner voice and trust your feelings). Obtain psychiatric consultation for your patient with a specific psychiatrist (who you have pre-selected, cultivated and is interested in cosmetic patients, to rule out body dysmorphic disorder (BDD) or other significant psychiatric illness. (Goin and Goin 1981; Javanbakht et al. 2012)

36.6 Prevention of Nasal Valve Area Breathing Complications During Rhinoplasty

In addition to esthetic improvements, the surgeon's challenge is preventing nasal valve (internal and/or external valve) collapse during the performance of the cosmetic rhinoplasty. That includes proper placement of incisions (Adamson 1987), which should always be placed in the skin (not in the mucosa). The surgeon must correct existing pathology when present, including all component parts of the nasal valve (internal and/

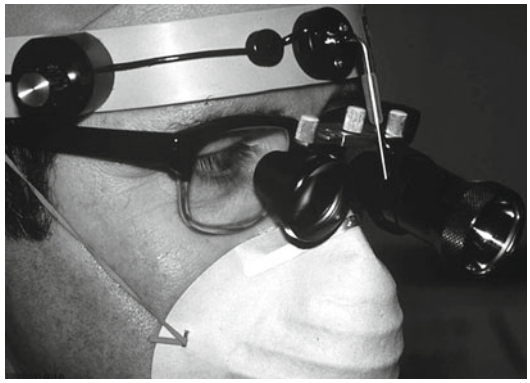

Fig. 36.10 Performing rhinoplasty using magnification with 2–2.5 power loops is extremely useful for the meticulous tissue handling required for surgery of the nasal valve (internal and external) area

or external), and the surgeon must prevent surgical maneuvers that could compromise the nasal airway postoperatively.

In my view, the goals of cosmetic rhinoplasty are to:

1. Improve appearance
2. Improve nasal breathing function (if needed)
3. Avoid postoperative iatrogenic breathing dysfunction

Small deformities in the internal valve region (upstream) can produce significant nasal airway symptoms. I strongly believe that nasal surgery must be exacting and precise especially when operating in the nasal valve area and magnification with 2–2.5 power loops are extremely useful for the meticulous tissue handling required for delicate surgery of the internal valve (Fig. 36.10).

It is well known, based on the post-rhinoplasty complications seen in the literature and from my own experience, that both the internal nasal valve and external nasal valve are at risk of being compromised during performance of a "routine" rhinoplasty. A successful outcome of cosmetic rhinoplasty includes both an esthetic improvement and a normal breathing nose, which includes correction of an abnormality or prevention of a breathing dysfunction. The pathophysiologic features of post-rhinoplasty breathing disturbances almost always involve the internal or external nasal valve.

I will cover specific surgical maneuvers that risk causing nasal valve area (internal and/or external nasal valve) breathing problems postoperatively.

36.6.1 Incisions

To gain adequate exposure and access to the skeletal structures (cartilage and bone), various incisions have been utilized including the transfixion (hemitransfixion and full or complete transfixion), *inter*cartilaginous (IC), i*ntra*cartilaginous, rim, marginal, "slot dome," trans-columellar (external approach), vestibular, or various external incisions for osteotomies (Barelli et al. 1987; Hinderer 1971; Huizing and de Groot 2003). Of these incisions, only the endonasal intercartilaginous incision, which is skin incision and not a mucosal incision, impinges directly on the internal nasal valve. This incision is created by eversion and exposure of the upper lateral cartilage and the lower lateral cartilage at the cartilaginous junction by incising the intervening vestibular skin. This incision is frequently joined to a transfixion incision to allow mobilization of the columella and access to the bony and cartilaginous dorsum. When performed with meticulous atraumatic technique and closed under accurate suture approximation, the ensuing healing scar does not adversely affect internal nasal valve function. However, should the tissues be handled roughly or closure performed imprecisely, the risk of subsequent scar contracture with stenosis of the valve angle is markedly increased (Adamson 1987). If indicated, detachment of the upper lateral cartilage from the nasal septum through parallel intranasal mucosal and skin incisions increases the risk of scarring if not performed carefully or closed meticulously. This is especially true of skin incisions at the apex of the internal nasal valve angle. Certainly, if it is necessary to separate the upper lateral cartilage from its septal attachment, detachment should be performed submucosally (intraseptally) beneath the underlying skin (sometimes called "junction tunnels") and beneath the more posteriorly placed mucosa to minimize postoperative scar

contracture. All intranasal skin incisions must be suture approximated to promote accurate healing by primary intention.

36.6.2 Approaches

Exposure of the nasal tip (lower lateral cartilages) and the nasal dorsum may be achieved through a variety of approaches including the retrograde, cartilage splitting, delivery (Hinderer 1971; Huizing and de Groot 2003; Parkes et al. 1988), or the external (trans-columellar) approach. The retrograde and delivery approaches exposing the lower lateral cartilages necessitate an intercartilaginous incision. In addition, these two approaches (retrograde and delivery) require severing the attachments between the upper lateral and the lower lateral cartilages. This maneuver has the potential to decrease the structural rigidity of the internal nasal valve. Dissection with meticulous atraumatic technique and precise suture closure of incisions ensure minimal tissue damage. The cartilage-splitting incision (probably less common today) and the incision for the external (trans-columellar) rhinoplasty approach (Anderson 1966) (probably more common today) are performed away from the valvular region and do not have an adverse potential impact on the internal or external valve area with secondary scarring.

36.6.3 Excisions

In the entire scope of nasal surgery, there are only a few surgical options:

1. Removal of tissue (bone and/or cartilage)
2. Adding tissue (biodegradable grafts of bone and/or cartilage are preferred over inorganic implants) (Barelli et al. 1987; Breadon et al. 1979; Hinderer 1971; Huizing and de Groot 2003; Mertz et al. 1984; Pirsig et al. 2004)
3. Repositioning of tissue (releasing tension)
4. Combinations of the above

With the goals of tip rotation, tip projection, and tip definition, the majority of cosmetic nasal operations require some degree of modification of the lower lateral cartilages (Huizing and de Groot 2003; Parkes et al. 1988). This change of the lower lateral cartilage usually involves excision of the cephalic border of these lower lateral cartilages. Extreme or total resection of the lateral crus of the lower lateral cartilages often leads to loss of structural support of the nasal ala with subsequent inspiratory collapse of the external valve. In addition, "excessive" cephalic trimming in this region can lead to the characteristic pinched appearance causing the tip to appear overly bulbous, thus distorting the symmetry of the nasal base. In addition, interruption of the intact strip of the lower lateral cartilage necessarily results in diminished structural support, increasing the risk of inspiratory collapse of the nasal ala in rhinoplasty. Therefore, unless absolutely necessary, cephalic removal of the lower lateral cartilages should be performed conservatively, meaning depending on the gender, age, skin quality, ethnicity, and thickness and resiliency of cartilage; "conservative" means leaving 6 to 8–10 mm of cartilage behind and/or combined with modeling of the lower lateral cartilages by suture techniques which minimizes risk for postoperative alar collapse of the external nasal valve. The dictum of "…it is not what you take, but what you leave behind that matters…" is applicable for nasal surgery in general and especially applicable to surgery of the lower lateral cartilages. While leaving an intact strip of lower lateral cartilage is advisable with tip modification, dome division (for narrowing) can be practiced especially when carried out medial to the dome (Huizing and de Groot 2003; Parkes et al. 1988). Should preservation of an intact strip of lower lateral cartilage be impossible and should it become necessary to disrupt the continuity of the lower lateral cartilage, then approximation of the cartilage remnants with permanent suture (5-0 or 6-0 nylon) is recommended to avoid alar collapse of the external nasal valve. Utilizing a columellar strut (autogenous septal cartilage) has been a very successful contribution to maintaining tip projection and rotation.

Excision of the caudal (inferior) edge of the upper lateral cartilage occasionally becomes necessary when the upper lateral cartilage is excessively protuberant, either in the native

(unoperated) state or after nasal shortening; if necessary, excision should always be performed conservatively since excessive resection of this region can result in loss of structural support and inspiratory collapse. Concomitant excision of the corresponding skin of the internal or external nasal valve along with the caudal (inferior) edge of the upper lateral cartilage should be avoided because skin excision markedly increases the likelihood of secondary cicatricial scarring and valvular stenosis leading to breathing dysfunction after surgery. When performing an "M" plasty to widen the internal valve angle (to compensate for infracture) in rhinoplasty (Schulte et al. 1999), the skin is incised (to open the internal valve angle), NOT excised. If skin excision is required for some reason, which is highly unlikely, in cosmetic rhinoplasty, suture approximation is always advisable.

Valve problems may therefore include structural changes causing fixed encroachment into the internal nasal valve region and/or a loss of structural support leading to flaccidity and collapse during inspiration.

Numerous papers have appeared in the literature to help the surgeon decide which approaches can best be utilized to "prevent" or "treat" (repair) valve collapse (Araco et al. 2007; Bottini et al. 2007; Camirand et al. 2004; Constantian 1994; Constantian and Clardy 1996; Fischer and Gubisch 2006; Goin and Goin 1981; Hage 1965; Khosh et al. 2004; Ozturan 2000; Paniello 1996; Park 1998; Slavit et al. 1990; Spielmann et al. 2009; Stucker et al. 2002; Toriumi et al. 1997; Wittkopf et al. 2008).

36.6.4 Hump Reduction

Dorsal nasal hump resection generally involves the nasal valve region in two frequent circumstances. First, excision of an excessive dorsal hump may involve removal of the attachment of the upper lateral cartilage to the septum, and this excision may be carried down into the valve angle (and area) in reduction rhinoplasty (Barelli et al. 1987; Huizing and de Groot 2003; Kienstra et al. 1999). Trimming this dorsal cartilaginous region may involve just the cartilage or both the cartilage and its underlying nasal mucosa and skin. In either instance, but particularly with dehiscence of the intranasal skin at the internal nasal valve angle, awareness and care is needed for the accurate repositioning and suturing (if possible) of the remaining upper lateral cartilage in continuity with the dorsal septum, and if "spreader" grafts are contemplated, then careful introduction, placement, and fixation with precise suturing are mandatory to avoid obstructing the internal nasal valve angle and producing postoperative breathing problems (Sheen 1983).

The second circumstance involves patients with short nasal bones and a dorsal hump requiring resection. Occasionally, hump resection effectively removes a significant portion of the important upper lateral cartilage supports allowing the upper lateral to "flail," which can lead to valvular and associated breathing dysfunction. Avoidance of this untoward result rests on appropriate preoperative diagnosis as well as careful approximation of the upper lateral cartilaginous back to the dorsal septum with a permanent suture (3-0 or 4-0 nylon suture with horizontal mattress placement). Approximation reestablishes support for the upper lateral cartilage, thereby minimizing potential postsurgical collapse. Most often, in my career, I performed dorsal nasal modification by either rasping the bony dorsum or lowering the cartilaginous dorsum by incremental shaving of the upper lateral cartilage (and dorsal septum when needed) using a number 15 or 15 C knife blade and when required a sharp pair of "super cut" scissors. I usually modified the combined bony and cartilaginous dorsal hump by the "push-down" or "let-down" operation supplemented by rasping of the bone and incremental shaving of the cartilage (when needed), and these procedures are covered in the literature (Barelli et al. 1987; Hinderer 1971; Huizing and de Groot 2003; Kienstra et al. 1999).

36.6.5 Osteotomies

Medial, intermediate, and lateral osteotomies of the nasal bone and the frontal (ascending) pro-

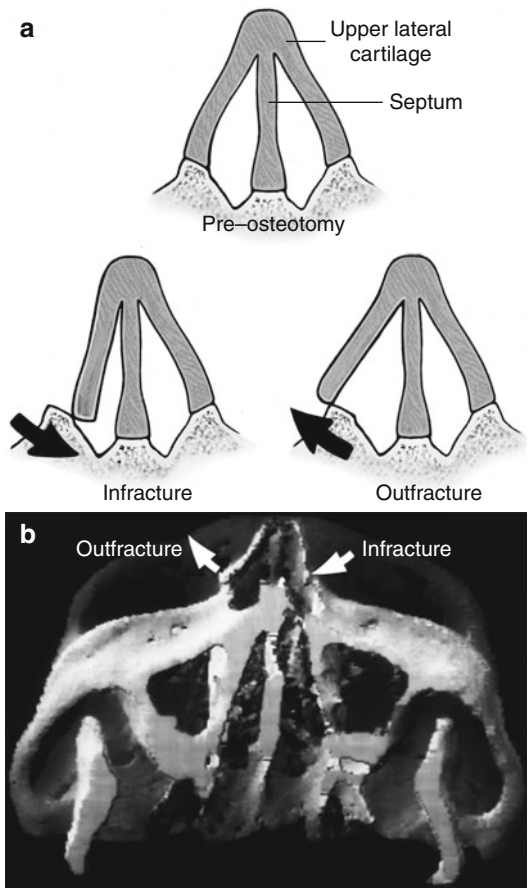

Fig. 36.11 (**a**) Illustration depicts the concepts of infracture and outfracture with the concomitant narrowing (infracture) of the internal nasal valve area and widening (outfracture) of the internal nasal valve area (By permission of Mayo Foundation for Medical Education and Research. All Rights Reserved.) (**b**) This reconstruction clearly demonstrates both an outfracture of the frontal (ascending) process of the maxilla with widening of the internal valve area and infracture of the frontal (ascending) process of the maxilla with narrowing of the internal valve area in a symptomatic patient (By permission of Mayo Foundation for Medical Education and Research. All Rights Reserved)

cess of the maxilla may all impact on the internal nasal valve area via alteration in the position of the upper lateral cartilage. In addition, lateral osteotomies with infracture may impact directly and result in narrowing of the internal nasal valve area; although, I have seen this complication of rhinoplasty on a number of occasions, the literature states that breathing disturbances after infracture in rhinoplasty are less common in practice than intuitive and theoretical reasoning would have you conclude (Adamson 1987; Adamson et al. 1990; Araco et al. 2007; Camirand et al. 2004; Corey 2006; Guenthner et al. 1984; Grymer 1995; Helal et al. 2010; Lewin 1954). Studies have shown that the risk to the upper lateral cartilage after lateral osteotomy with the inward collapse and narrowing of the internal nasal valve angle is real and the cross-sectional diameter of the nasal airway is altered (narrowed). If this occurs, then the surgeon may consider performing an outfracture (Pontell et al. 1998) as illustrated in Fig. 36.11a, b. Because lateral osteotomy with infracture, to close an open roof after hump removal, can narrow the valve angle producing symptoms, the frequency of this complication can be avoided or reduced by performing a curved lateral osteotomy as described by Webster and associates (Webster et al. 1977). By leaving an intact triangular piece of bone at the piriform aperture, just superior to the level of the inferior turbinate, the surgeon accomplishes the esthetic narrowing and closing of the open roof at the nasal dorsum while minimizing the risk of compromising the integrity of the internal valve region. I have used this technique successfully.

36.6.6 Turbinates

Surgeons have long been tempted, and many have succumbed to that temptation, to remove the inferior turbinate (or at least the head of the inferior turbinate in its position as the posterior guardian of the internal nasal valve) to improve the nasal airway after infracture to close the open roof after hump resection. Remember that *the mucosa is the organ of the nose* and removal of turbinate tissue carries with it the possibility of producing an "*empty nose*" *syndrome* (Chhabra and Houser 2009; Houser 2007; Martin C). Some authors have demonstrated that total inferior turbinectomy "carries significant morbidity and should be condemned" (Moore et al. 1985; Moore and Kern 2001; Rice et al. 2003; White et al. 1990). Other authors

Table 36.3 Range of symptoms seen in patients with the "*empty nose*" *syndrome*

1	Crusting
2	Bleeding
3	Anosmia or hyposmia
4	Difficulty breathing
5	Pain (localized posttraumatic neurogenic)
6	Headache
7	Nasal malodor
8	Disturbed sleep (associated fatigue and lethargy)
9	Aprosexia nasalis (inability to concentrate)
10	Disturbed sense of well-being
11	Emotional changes (anxiety, reactive depression)

think resecting turbinate tissues carries little or no morbidity whatsoever (Courtiss and Goldwyn 1983; Ophir et al. 1992). My experience with symptoms seen in patients with the "*empty nose*" *syndrome* (Table 36.3) has biased me in favor of very conservative treatment of turbinate mucosal hypertrophy, and I condemn aggressive removal of inferior turbinate tissue in nonmalignant cases (Moore and Kern 2001) (after allergic, vasomotor rhinitis and other more serious medical conditions have been ruled out, some of which may require biopsy (Kern 1991) with microscopic examination and other tests for accurate diagnosis of the cause of the turbinate hypertrophy).

Passali et al. (2003) in a randomized clinical trial divided 382 patients into six treatment groups who had therapy for their inferior turbinate hypertrophy including:

1. Turbinectomy
2. Laser cautery
3. Electrocautery
4. Cryotherapy
5. Submucosal resection
6. Submucosal resection with lateral displacement (outfracture)

After following patients for 6 years, these authors found that nasal patency, normalized breathing, restored mucociliary clearance, and local secretory IgA production (back to physiologic levels) with the fewest postoperative complications ($p < .001$) occurred with *conservative* submucosal resection combined with lateral displacement (outfracture) "as the first-choice technique for the treatment of nasal obstruction due to hypertrophy of the inferior turbinates." Turbinate surgery is indicated for obstruction after perennial allergic rhinitis and vasomotor rhinitis have been ruled out, and all other medical treatments have failed to successfully treat the inferior turbinate hypertrophy. As a general rule of approach, and because of the specter of very distraught "empty" nose symptomatic patient, I favor outfracture of the inferior turbinates, while maintaining intact mucosa using gauze packing (impregnated with steroid and antibiotic *solution*) to maintain the outfractured turbinate in the lateralized position for 1 week, effectively putting the nose to "rest" bathed in physiologic nasal secretions and away from the desiccating (drying) effects of nasal airflow.

36.7 Closing Thoughts

At this time, there are no final conclusions, merely observations and a current consensus of thinking regarding the surgical importance of the internal and external nasal valves to a patient's breathing function. With a better scientific understanding of nasal breathing and a classification of nasal valve abnormalities that has evolved over the past 35 years, surgeons are better able to successfully perform cosmetic rhinoplasty while minimizing the risks to breathing function. The weight of evidence and my clinical and surgical experience essentially states that complete physiologic understanding and systematic delicate handling of the structures of *both* the *external* and the *internal nasal valve* is crucial to avoiding postoperative breathing complications. The structures of the *internal nasal valve* include the upper lateral cartilage, the nasal septum (including the premaxillary wing region), the floor of the nose, the piriform aperture, the head of the inferior turbinate, and their mucocutaneous coverings. Various abnormalities in the diverse component parts of the internal nasal valve are summarized in Fig. 36.12.

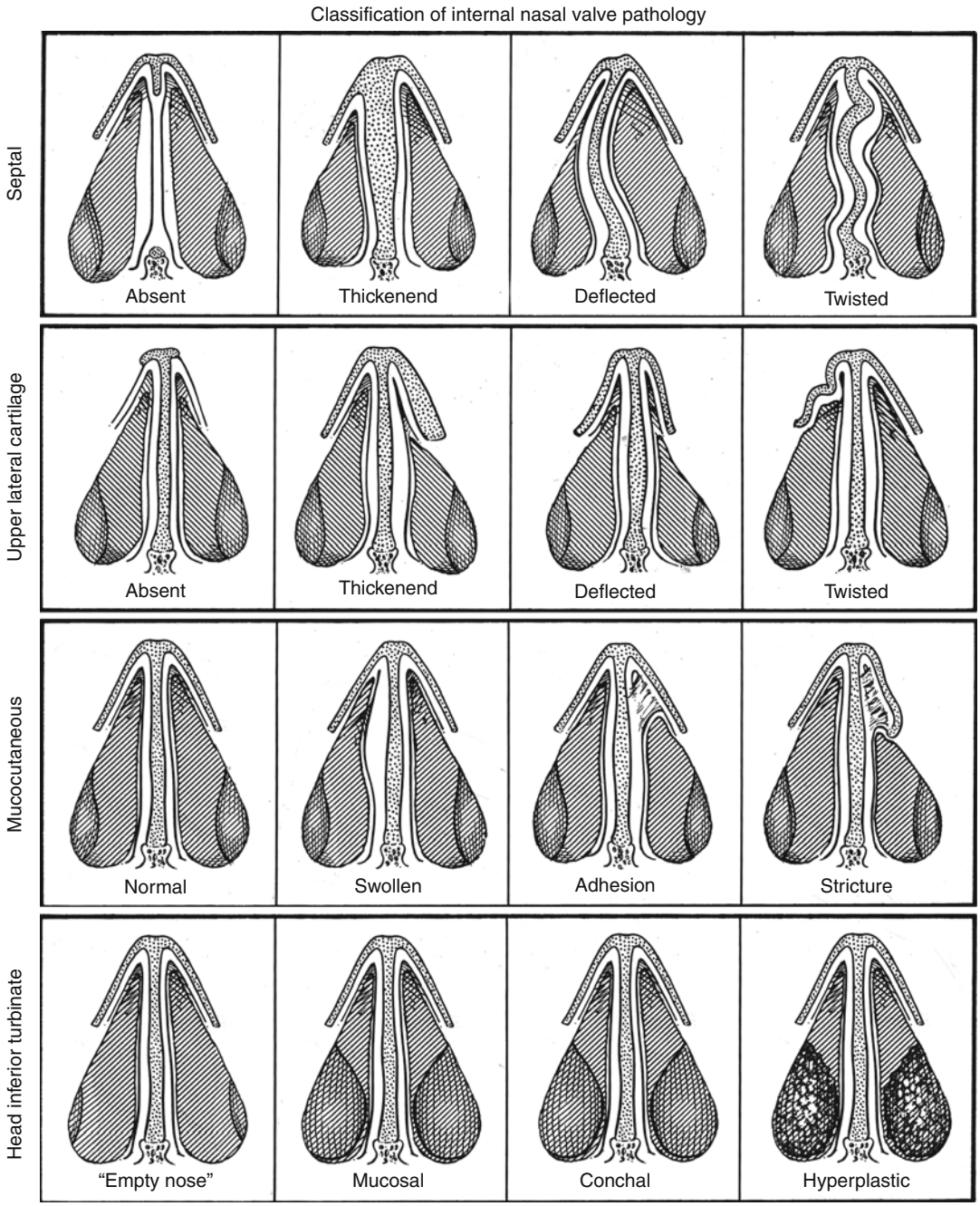

Fig. 36.12 Illustration is a summary and classification of some of the possible causes of internal nasal valve obstruction (By permission of Mayo Foundation for Medical Education and Research. All Rights Reserved)

Table 36.4 is a *classification* of the most current thinking regarding the causes of *nasal valve* (*internal and external*) obstruction and collapse. The surgical techniques and principles suggested in this chapter have evolved over the past half century of rhinologic surgery for nasal airway dysfunction by a variety of surgeons performing primary and secondary rhinoplasty operations.

Table 36.4 Classification of many causes of nasal valve (internal and external) obstruction and collapse

I. Internal nasal valve
1. Intramural
A. Anatomic
i. Mucosal
a. Inflammatory
b. Hypertrophy
ii. Submucosal
a. Scar
b. Hematoma
c. Abscess
iii. Cutaneous
a. Synechia (adhesions)
b. Stricture
iv. Cartilage
a. Septal
1. Absent (complete, incomplete)
2. Thickened
3. Deflected
4. Twisted
b. Upper lateral
1. Absent (complete, incomplete)
2. Thickened
3. Deflected
4. Twisted
5. Fixed collapse (secondary to pyramid trauma)
6. Physiologic collapse
v. Turbinate
a. Bone (concha)
b. Mucosal
1. Physiologic nasal cycle
2. Dependent (sleep positions)
3. Vasomotor rhinitis
4. Allergic rhinitis
5. Hyperplastic
6. Tumor
7. Systemic disease
2. Extramural
A. Fixed collapse (due to surgical, nonsurgical pyramid trauma)
B. External pressure glasses, goggles, etc.
C. Intranasal space occupying lesion
i. Foreign body
ii. Growth (poly, tumor)
II. External nasal valve
1. Anatomic
A. Lower lateral cartilage
i. Absent (complete, incomplete)
ii. Thickened
iii. Deflected
iv. Twisted
2. Pathophysiologic
A. Atrophy (aging)
B. Facial palsy
C. Neurologic disorders

The ultimate goal of rhinoplasty is producing an esthetically pleasing external nose without disturbing nasal breathing function. To achieve one without the other, or worse yet, at the expense of the other, represents a failed rhinoplasty. I strongly advise conservatism since most of the breathing complications treated over my past almost 50 years in otorhinolaryngology were secondary to over-resection of one or more of the varied components of the internal or external nasal valve including over-resection of functioning turbinate tissue.

After many years of experience in rhinology, and having read extensively in preparing the bibliography for this chapter, it is still humbling to realize that I did not study or read all of the literature, but I selected texts that I thought were important to construct a complete, honest, and meaningful understanding of the science and surgery of the nasal valve for the comprehensive writing of this chapter. With the exclusion of some texts from my bibliography, I have chosen to respect other serious authors and include a section entitled *Supplemental Readings*.

In nasal surgery as in life, it is not what you take, but what you leave behind that matters; therefore, I suggest that we all must strive to leave behind an enhanced (undisturbed) functional (breathing) nose with an esthetic improvement for our patients. One final suggestion is contained in this maxim "be a maximist in the office (developing rapport with the patient and the family) and a minimalist (in resecting tissue) in the operating room."

Conclusion

While the ultimate goal of cosmetic rhinoplasty is producing an esthetically pleasing external nose, it must be accomplished without

disturbing nasal breathing function and it is the location, dimensions, and functions of the nasal valve (internal and external) that have been covered in this chapter which provide the surgeon with the required understanding of the critical nasal valve area in order to accomplish the goals of improved appearance without producing a postoperative breathing disturbance.

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Nasal Pulmonary Interactions

37

James Bartley and Conroy Wong

Keywords
Airway inflammation • Nitric oxide • Carbon dioxide • Unified airway • Asthma • Chronic obstructive airway disease • Bronchiectasis • Allergic rhinitis • Chronic rhinosinusitis

Abbreviations

NO	Nitric oxide
CO2	Carbon dioxide
PaO2	Arterial oxygen levels
FEO2	Fraction of expired oxygen
FECO2	Fraction of expired carbon dioxide

Core Messages

- Physiological, epidemiological, and clinical evidence support an integrated upper and lower respiratory airway or "unified airway" model.
- Nasal breathing improves arterial oxygen concentrations and carbon dioxide excretion from the lungs.
- Nasal mucosal inflammation results in lower airway inflammation and vice versa.
- Many patients with asthma, chronic obstructive airway disease, and bronchiectasis have significant upper respiratory disease.
- Medical management of allergic rhinitis improves asthma.
- Nitric oxide from the nose and sinuses may have a role in the sterilization of incoming air and in improving ventilation-perfusion in the lungs.
- Nasal resistance is inversely related to end-tidal carbon dioxide levels.

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37.1 Introduction

Physiological, epidemiological, and clinical evidence support an integrated upper and lower respiratory airway or "unified airway" model (Krouse et al. 2007; Guilemany et al. 2009; Hurst 2009; Marple 2010). Important, well-known nasal

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functions include the filtering, warming, and humidification of inspired air before inhalation into the lungs. The nose and lungs potentially interact with each other in a number of ways (Fig. 37.1). Nasal mucosal inflammation results in lower airway inflammation and vice versa (Braunstahl et al. 2001a, b). Part of this mechanism is thought to be a generalized inflammatory response that amplifies the response to inflammatory stimuli in other parts of the respiratory tract (Braunstahl et al. 2001a, b). Inflammatory mediators and/or infectious pathogens may also be carried along the respiratory mucosa or along air currents (Hare et al. 2010). Neuronal responses may play a role, although the existence of nasobronchial reflexes remains controversial (Sarin et al. 2006). Nitric oxide (NO) from the nose and sinuses may have a role in the sterilization of incoming air (Lundberg et al. 1995) and in improving ventilation-perfusion in the lungs (Selimoglu 2005). An inverse relationship between nasal resistance and end-tidal carbon dioxide (CO_2) levels has been described (Mertz et al. 1984; Shi et al. 1988). CO_2 and NO may act as aerocrine messengers (Bartley 2005; Selimoglu 2005). Olfaction is also linked to the limbic system (Soudry et al. 2011), which can independently control our breathing pattern and rate (Plum 1992).

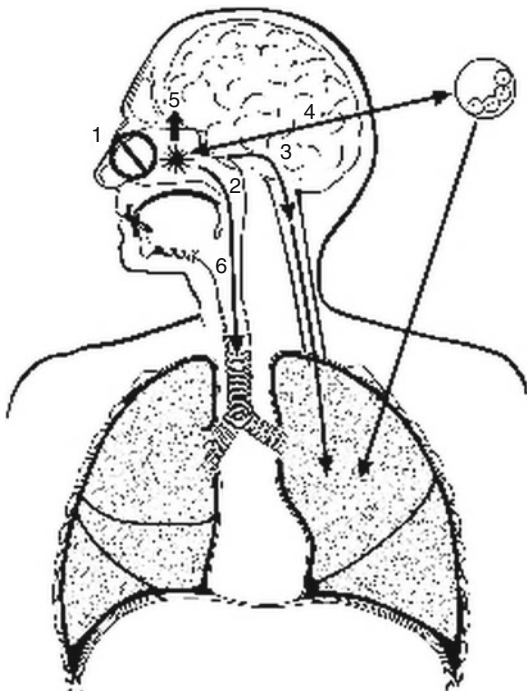

Fig. 37.1 Potential mechanisms for interaction between the upper and lower airways: (*1*) loss of nasal conditioning function, (*2*) direct passage of inflammatory mediators and/or microorganisms between the upper and lower airways, (*3*) nasobronchial reflexes, (*4*) stimulation at one point of the respiratory mucosal surface results in a pan-airway inflammatory response, (*5*) olfactory regulation of respiration, and (*6*) aerocrine messengers (CO_2 and NO)

Nasal breathing improves arterial oxygen concentrations and carbon dioxide excretion from the lungs.

37.2 Physiological Interactions

The nose has an important role in filtering, warming, and humidifying inspired air before inhalation into the lungs. The nose also provides a resistance to both inspiration and expiration that is twice that of the open mouth. This increased resistance appears to have a number of physiological benefits. In a study of arterial oxygen levels (PaO_2) before and after jaw wiring, which forced patients to breathe continuously through their noses, PaO_2 increased by nearly 10 % (Swift et al. 1988). Nasal packing after nasal surgery forcing patients to breathe through their mouths is associated with a reduction in arterial O_2 saturation (Ogretmenoglu et al. 2002). At rest, end-tidal CO_2 levels in expired air, which are considered to be a reliable indirect measure of CO_2 levels in the arterial blood, increase with nasal breathing indicating that nasal breathing improves the efficiency of CO_2 excretion from the lungs (Tanaka et al. 1988). During exercise, nasal breathing reduces the fraction of expired oxygen (F_EO_2), indicating that on expiration the percentage of O_2 extracted from the air by the lungs is increased, and increases the fraction of expired carbon dioxide (F_ECO_2), indicating an increase in the percentage of expired air that is CO_2 (Morton et al. 1995). This equates to more efficient O_2 extraction and CO_2 excretion during exercise.

Explanations for these observations still remain largely hypothetical. Nasal breathing increases total lung volume (Swift et al. 1988). The corresponding increase in functional residual capacity (volume of air present in the lungs present after passive expiration) is thought to improve gas exchange leading to improved PaO_2. NO derived from the nose and sinuses might also improve ventilation-perfusion relationships in the lungs (Della Rocca and Coccia 2005). The nose also provides an inspiratory resistance forcing the diaphragm to contract against a resistance. On a long-term basis, this might also have an important role in maintaining diaphragmatic muscle strength, although the role of inspiratory muscle training in a range of lung diseases continues to be debated (Padula and Yeaw 2007; Gosselink et al. 2011). Regardless, nasal breathing appears important in aiding O_2 absorption and in facilitating CO_2 excretion in the lungs.

Nasal breathing significantly improves oxygen extraction and carbon dioxide excretion during exercise.

The breathing cycle is divided into inspiratory and expiratory phases. When the respiratory rate increases, the expiratory phase shortens. Nasal breathing slows the respiratory rate increasing the length of the expiratory phase (Ayoub et al. 1997). Increasing the expiratory phase of the respiratory cycle is known to increase the body's relaxation response (Cappo and Holmes 1984). A number of ancient disciplines, such as yoga and tai chi, emphasize the importance of nasal breathing in relaxation and meditation.

37.3 Respiratory Inflammation

Upper and lower airway inflammatory processes often coexist and share common pathogenic mechanisms (Selimoglu 2005; Hare et al. 2010; Marple 2010). Based on the predominant cell type, chronic rhinosinusitis (CRS) has been classified as being either eosinophilic or neutrophilic (Meltzer and Hamilos 2011). The eosinophilic group includes CRS with polyps, a subset of CRS without polyps, aspirin hypersensitivity, asthma and nasal polyps (Samter's triad), and allergic fungal rhinosinusitis. Eosinophilic CRS and allergic rhinitis are associated with asthma (Marple 2010). Lower airway inflammation has also been classified according to the cell profile of induced sputum as being either eosinophilic or non-eosinophilic (Hargreave 2007). In asthma patients, eosinophils are the dominant inflammatory cells in middle meatal lavage (Ragab et al. 2005). In small airway disease patients, neutrophils are the dominant inflammatory cells in middle meatal lavage (Ragab et al. 2005).

Asthma and allergic rhinitis are strongly interrelated (Corren 1997; Krouse et al. 2007; Marple 2010). Corren reported nasal symptoms in 78 % of asthmatic patients and that 38 % of allergic and nonallergic rhinitis patients have asthma (Corren 1997). The severity of asthma symptoms correlates closely with rhinitis symptoms (Krouse et al. 2007). The presence of allergic rhinitis also increases the risk of subsequent asthma development nearly fourfold (Shaaban et al. 2008).

Asthma has also been associated with CRS. The prevalence of asthma is 20 % in CRS patients, which is higher than that seen in the general population (Jani and Hamilos 2005). Asthma severity also correlates with CRS disease severity, as determined by computed tomography (Bresciani et al. 2001). In patients having functional endoscopic sinus surgery, the asthma prevalence is 42 %, rising to 50 % in those with nasal polyps (Senior et al. 1999).

Neutrophilic inflammation is a feature of both chronic obstructive pulmonary disease (COPD) and bronchiectasis (Hargreave 2007). While tissue eosinophilia is an established feature of asthma, a neutrophilic picture can also be seen (Hargreave 2007). In COPD patients, inflammatory cells are found both in the sputum and in lung biopsy specimens (Hurst 2009). COPD patients commonly report nasal symptoms, the most common of which is rhinorrhea (Hurst et al. 2006). Nasal symptoms are also more common in COPD patients with chronic sputum production

(Hurst et al. 2006). Nasal symptoms double the risk over 8 years of patients developing COPD (Nihlén et al. 2008). Increased levels of the neutrophil chemoattractant protein IL-8 are found in the upper airways of COPD patients, when compared to control subjects (Hurst et al. 2006). Upper airway IL-8 concentrations correlate with those in the lower airway, and the concentration at both sites is related to indexes of bacterial colonization (Hurst et al. 2006). Many bronchiectatic patients also have nasal and sinus disease. Most bronchiectasis patients (77 %) meet the diagnostic criteria for CRS with 25 % of bronchiectasis patients having nasal polyps. Bronchiectasis severity also correlates with CRS severity (Guilemany et al. 2009).

Patients with asthma, chronic obstructive pulmonary disease, and bronchiectasis frequently have upper respiratory disease.

37.3.1 Inflammatory Interactions

Under the influence of serum IL-5 and eotaxin, eosinophils are released from the bone marrow into the systemic circulation. Depending on the local expression of a variety of adhesion molecules, cytokines, and chemokines, eosinophils then migrate to inflamed areas. Leukocytes migrate along a chemotactic gradient through the endothelium. Local cells upregulate endothelial adhesion molecules through the release of IL-1β, IL-4, and TNF-α. Leukocyte endothelial adherence is increased. Intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin are known endothelial adhesion molecules (Kita 2011). Increased local expression of these adhesion molecules occurs after experimental nasal and bronchial allergen challenge. Experimentally this results in increased eosinophilic allergic inflammation in the nasal and bronchial mucosa (Braunstahl et al. 2001a, b).

Even a single nasal allergen challenge administered to non-asthmatic subjects with seasonal allergy increases blood eosinophil levels and IL-5 in both the upper and lower airways (Corren 1997). Prior nasal stimulation using a nasal provocation antigen challenge increases bronchial hyperresponsiveness to methacholine challenge (Bonay et al. 2006). Similarly segmental bronchial provocation in patients with allergic rhinitis induces blood eosinophilia and mucosal inflammation in both the upper and lower airways. This inflammation is characterized by increased numbers of eosinophils, IL-5+ cells, and eotaxin-positive cells. Local allergen exposure in both the upper and lower airways results in generalized airway inflammation – this would appear to occur through vascular mechanisms.

A high level of similarity in bacterial cultures from the nasopharynx and from bronchoalveolar lavage is seen in children with bronchiectasis and protracted bacterial bronchitis as well as in patients with cystic fibrosis.

37.3.2 Microbial Aspiration

The silent aspiration of nasopharyngeal secretions has been hypothesized as important in relationships between upper and lower respiratory airway disease (Bardin et al. 1990; Kogahara et al. 2009). The possibility that *Staphylococcus aureus*-derived enterotoxins could also be inhaled into the lower airway has been raised (Hamilos 2000). COPD patients with lower airway bacterial colonization have a higher total nasal bacterial load (Hurst et al. 2005). Children with bronchiectasis have a high nasopharyngeal carriage of *Streptococcus pneumoniae,* nontypable *Haemophilus influenzae* (NTHi), and *Moraxella catarrhalis* and lower airway infection by NTHi. A high level of similarity in cultures from the nasopharynx and from bronchoalveolar lavage is seen (Hare et al. 2010). Similar agreement is also seen in children with protracted bacterial bronchitis (Hare et al. 2010) and in patients with cystic fibrosis (Godoy et al. 2011). In the critical care situation, the treatment of upper respiratory disease reduces the risk of ventilator-associated pneumonia (de Smet et al. 2009).

People with a high nasal bacterial load (and associated greater nasal inflammation) appear

more likely to pass bacteria into the lower respiratory tract. The evidence that gross aspiration of nasopharyngeal secretions into the lower respiratory airway occurs is controversial. Radionucleotide scanning in humans shows that it does not occur (Bonay et al. 2006); however, animal experiments suggest that it may occur during sleep (Kogahara et al. 2009). The similarity in microbiological cultures between the upper and lower respiratory tract suggests that some transmission occurs. Microaspiration of bacteria and inflammatory mediators could possibly occur, but this has yet to be demonstrated scientifically.

37.3.3 Influence of Upper Respiratory Interventions on the Lower Respiratory Tract

In the majority of trials, the treatment of allergic rhinitis with nasal steroids reduces asthma severity (Stelmach et al. 2005; Krouse et al. 2007). At the end of 3 years, the children treated with immunotherapy for grass and/or birch allergic rhinoconjunctivitis were less likely than the control group to develop asthma (Möller et al. 2002). Similarly, a number of studies have shown that the surgical treatment of CRS helps asthma patients through both an improvement in asthma symptoms and the decreased use of asthma medication (Krouse et al. 2007). Unfortunately these studies have been uncontrolled. There are also no randomized controlled studies that have investigated the effect of CRS medical therapy on asthma (Krouse et al. 2007).

Medical and surgical treatment of upper respiratory disease helps asthmatic patients.

37.4 Nasobronchial Reflexes

Nasobronchial reflexes have also been implicated in the interactions between the upper and lower respiratory airways. Mechanical or chemical stimulation of nasal, tracheal, and laryngeal receptors could produce sneezing, coughing, or bronchoconstriction, thus preventing deeper penetration of allergens or irritants into the airway (Sarin et al. 2006). Unilateral models of nasal provocation show that secretory responses can be measured in both nostrils (Sarin et al. 2006). The mechanism appears to be neural (Sarin et al. 2006).

When asthmatic patients exercise with their noses occluded, a 20 % decline in forced expiratory flow occurs, compared with less than a 5 % reduction among patients allowed to exercise while nose breathing (Shturman-Ellstein et al. 1978). Recent research has shown that bursts of cold air on the nasal mucosa increase nasal resistance. This effect was blocked by anesthetizing the nose or by inhaling atropine, an anticholinergic drug, before the provocation (Fontanari et al. 1996, 1997). Other researchers have not been able to confirm these results (Johansson et al. 2000). The existence of nasobronchial reflexes secondary to inflammatory exposure in the upper respiratory airway remains controversial (Sarin et al. 2006).

37.5 Olfaction and the Limbic System

Evolutionary theory teaches that in primitive life forms, the olfactory brain was probably a layer of cells above the brain stem that registered a smell and then simply categorized it. New layers of the olfactory brain then developed into what was initially called the rhinencephalon (nose brain) or limbic system (Le Doux 2003). Our limbic system coordinates the stress "fight or flight" response. As part of this response, not only does the heart rate increase, but the respiratory rate also goes up; the limbic system is able to override normal pCO_2 homeostasis (Plum 1992). The physiological evidence suggests that fragrances such as rosemary and lavender may have direct effects on human memory and mood (Herz 2009). Fragrances such as lavender by influencing the limbic system and the stress response could potentially affect breathing patterns and rate. The pheromone androstadienone when applied to women's nasovomerine organs slowed both their heart and breathing rates (Grosser et al. 2000).

37.6 Aerocrine Communication

37.6.1 Nitric Oxide

NO is a gas that is produced by the nose and paranasal sinuses. NO has bacteriostatic actions (Lundberg et al. 1995). NO may have a role in the sterilization of incoming air (Lundberg et al. 1995) and in improving ventilation-perfusion in the lungs (Selimoglu 2005).

37.6.2 Carbon Dioxide

An inverse relationship between nasal resistance and end-tidal pCO_2 levels has been described (Mertz et al. 1984; Shi et al. 1988). A reduction of end-tidal expired pCO_2 from 40 to 35 mmHg (5.3 to 4.7 kPa) corresponds to an increase in nasal resistance of 10 % (Mertz et al. 1984). Breathing is commonly taught as being controlled by independent voluntary and metabolic pathways. However, the limbic system is able to override metabolic respiratory control systems (Plum 1992). People practicing yoga would appear to set their pCO_2 receptors to a higher response level. End-tidal pCO_2 concentrations are nearly 4 mmHg higher in yogic breathers (Stanescu et al. 1981). In contrast, people who are prone to anxiety attacks would appear to have lower arterial pCO_2 levels (5 mmHg on average) as compared with controls (Papp et al. 1989). The mechanisms of the relationship between expired pCO_2 levels and nasal resistance are unknown. This could be either a systemic vascular effect or an aerocrine effect. Regardless, people who practice relaxed diaphragmatic breathing may be less likely to present complaining of nasal congestion, whereas anxious people are (Bartley 2006) (Fig. 37.2).

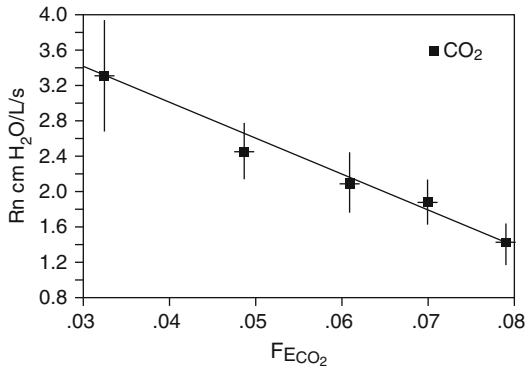

Fig. 37.2 Inverse linear relationship of nasal resistance to end-tidal expiratory CO_2 concentrations. An end-tidal pCO_2 reading of 0.05 corresponds to 38 mmHg. A reduction of end-tidal expired pCO_2 from 40 (0.053 kPa) to 35 mmHg (0.046 kPa) corresponds to an increase in nasal resistance of 10 % (Reproduced with permission from Mertz et al. 1984)

Conclusions

From a physiological perspective the nose has an important role in the preparation of inspired air before inhalation into the lungs. Other physiological effects such as improvements in O_2 transfer and CO_2 excretion would also appear to occur. Inflammation, both allergic and infective, affects both the upper and lower respiratory airways. These interactions would appear to occur through vascular mechanisms.

Both medical and surgical treatments of upper respiratory disease appear to help asthmatic patients. Both NO and CO_2 would appear to have roles in aerocrine communication. The influence of nasobronchial reflexes and microaspiration remains largely hypothetical. The current evidence indicates that optimal management of disease processes in both the upper and lower respiratory airways needs to consider a "unified airway" model.

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Physiologic and Dentofacial Effects of Mouth Breathing Compared to Nasal Breathing

38

Tulin Taner and Banu Saglam-Aydinatay

Keywords
Mouth breathing • Mode of respiration • Dentofacial changes • Physiologic changes • Upper airway obstruction • Adenoid facies • Malocclusion • Head extension

Core Messages

- Mouth breathing is a serious ailment which occurs in the presence of an obstruction in nasal and nasopharyngeal regions of the upper airway.
- Chronic mouth breathing can cause problems in facial structures and oral health.
- Changes in facial structures include long anterior facial height, narrow facial width, a retrognathic mandible, open-mouthed posture, an incompetent and short upper lip, loss of tonus in perioral muscles, a pinched looking nose and a dull appearance.
- The intraoral consequences of mouth breathing are openbite, a Class II molar occlusion with increased overjet, protruding maxillary anterior teeth, and a V-shaped maxillary arch.
- Not every patient has the same growth changes due to oral breathing. The heritable characteristics of anatomical structures also seems to play a role in determining which patients will be most affected.
- A careful evaluation of the patient by otolaryngologists, pediatricians and orthodontists is needed before treatment decisions.
- Medical, surgical and/or orthodontic treatment of the patients may be necessary depending on the cause of airway obstruction and severity of changes in dentofacial structures.

38.1 Introduction

Mouth breathing is the act of inhaling and exhaling using the mouth. This respiratory phenomenon is considered normal under increased physical activity because the increased need for oxygen under such circumstances can only be

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supplied by breathing through the mouth and nose simultaneously. However, using one's mouth to breathe in daily life or during sleep is a serious ailment which occurs in the presence of an obstruction in nasal and nasopharyngeal regions of the upper airway. Nasal obstructions can be due to physiologic factors like allergic rhinitis and polyps or anatomical factors such as a deviated septum and a narrow nasal area. Enlarged adenoids and tonsils are the most common causes of obstruction in the nasopharyngeal area, especially at ages 5–6 years.

If chronic mouth breathing develops due to obstruction of the airways, this can cause a multitude of problems in facial structures and oral health. Such patients have been described as having special facial characteristics generally referred to as *adenoid facies* (Emslie et al. 1952; Linder-Aronson 1970; Koski and Lähdemäki 1975), *long face syndrome* (Schendel et al. 1976), and *respiratory obstruction syndrome* (Ricketts 1968). This type of face reportedly features long anterior facial height, narrow facial width, a retrognathic mandible, open-mouthed posture, an incompetent and short upper lip, loss of tonus in perioral muscles, a pinched looking nose, and a dull appearance (Figs. 38.1 and 38.2). The intraoral consequences of mouth breathing are said to include open bite, a Class II molar occlusion with increased overjet, protruding maxillary anterior teeth, and a V-shaped maxillary arch with deep palatal vault (Figs. 38.3, 38.4, and 38.5). Mouth breathers may also extend their heads in order to maintain a patent airway (Figs. 38.6 and 38.7). In addition to these structural changes, mouth breathing can cause halitosis (breath malodor), increased incidence of caries, and marginal gingivitis around the maxillary anterior teeth. If diagnosed early, orthodontic and dentofacial orthopedic treatment of the patients is possible. However, in adult patients, orthognathic surgical treatment in addition to orthodontic treatment may be necessary.

Considering the potential serious side effects of mouth breathing, patients need to be carefully evaluated by an orthodontist and otolaryngologist to determine the etiology and proper treatment of nasal obstruction and the associated dentofacial changes.

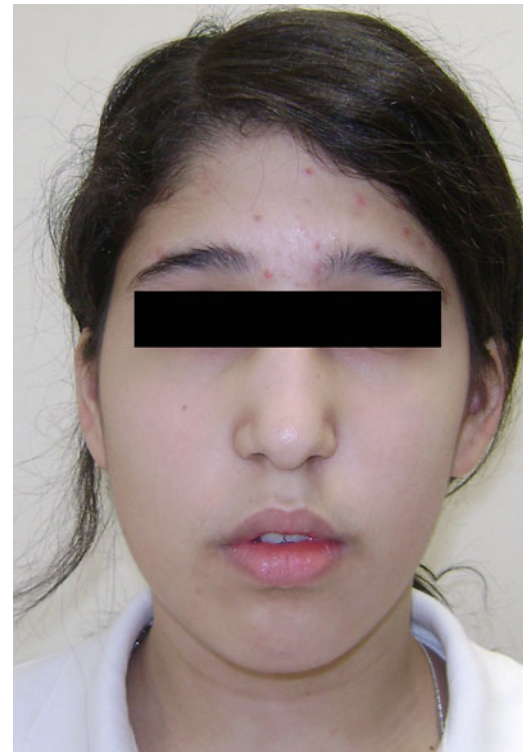

Fig. 38.1 The typical appearance of "adenoid facies" with increased anterior facial height, narrow facial width, open-mouthed posture, and an incompetent and short upper lip. However, these facial features are not always diagnostic of the respiratory pattern since patients who breathe with their lips separated may actually be oral-nasal or nasal breathers as well as oral breathers

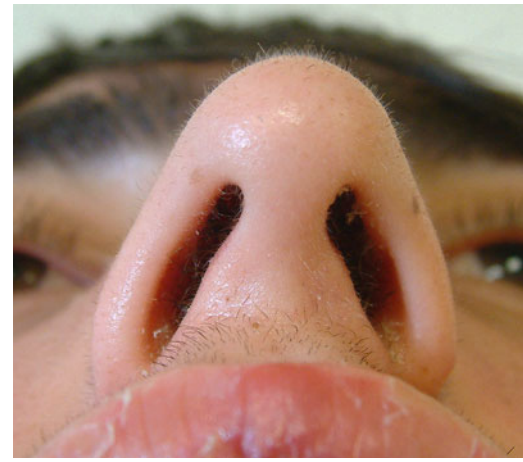

Fig. 38.2 The typical pinched nose appearance in a mouth-breathing patient

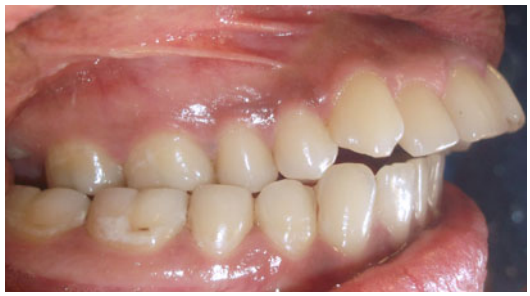

Fig. 38.3 Sagittal occlusal relationship in mouth-breathing patients is said to include a Class II molar occlusion with increased overjet and protruding maxillary anterior teeth

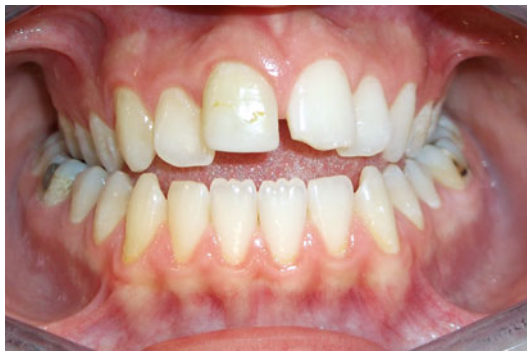

Fig. 38.4 A posterior crossbite and an anterior open-bite malocclusion in a mouth-breathing patient. The posterior crossbite is suggested to be due to transverse maxillary deficiency caused by an imbalance of forces between the muscle forces acting on these structures. The open bite is caused by extruded molar teeth due to an open-mouthed posture in response to an increased nasal resistance

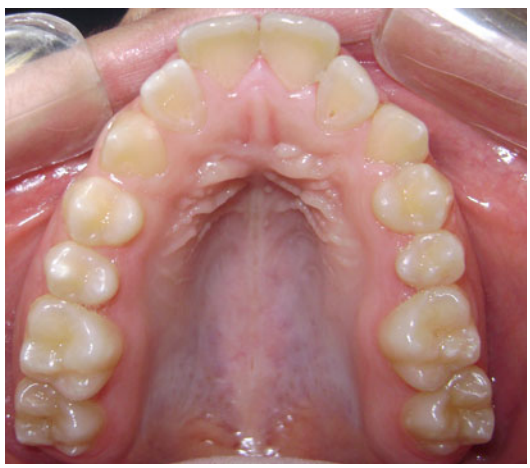

Fig. 38.5 The V-shaped maxillary arch with deep palatal vault

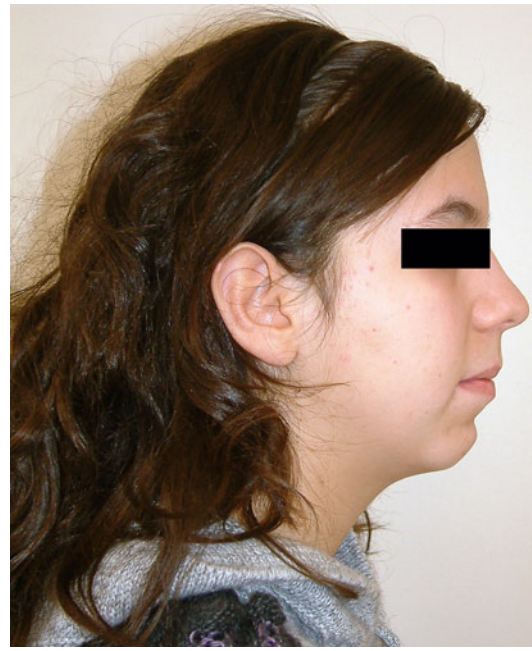

Fig. 38.6 The extended head position of a mouth-breathing child. Necessity of airway maintenance dictates the head and neck posture in these patients

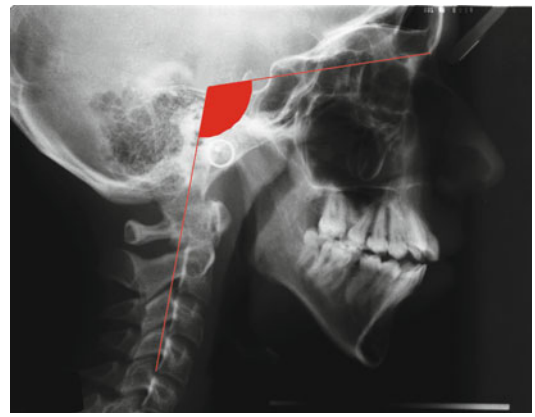

Fig. 38.7 Lateral cephalometric radiograph of the patient in Fig. 38.6. Note the dental protrusion and downward-backward rotation of the mandible in addition to the extended head position

Despite many attempts to establish a cause-and-effect relationship between nasal respiratory impairments and dentofacial deformities, the issue is still controversial within orthodontics and otolaryngology. The most prevalent view among clinicians is that a change in the mode of

respiration, such as mouth breathing due to an inadequate nasal airway, could cause changes in craniocervical posture, maxillomandibular relationship, and position of the tongue. This in turn could affect dentofacial growth and positions of the teeth. However, clinicians from both sides of controversy can find ample evidence in the literature supporting their opinions, and the results of studies relating dentofacial features with respiratory pattern are far from being conclusive.

Since there are treatment decisions that revolve around the degree of interplay between nasal obstruction and dentofacial development, the relationship must be further elucidated. If nasal obstruction has an effect on dentofacial development, early treatment for removal of the cause of this obstruction would be necessary. On the other hand, if dentofacial growth and development is not significantly affected by the respiratory mode, then treatment of nasal obstruction in order to prevent abnormal orofacial development would not be indicated.

In this chapter, we examine the possible interactions among respiratory mode and dentofacial growth and development by reviewing both sides of the controversy with special emphasis on questions such as:

- Does impaired nasal breathing always result in complete mouth breathing with possible negative effects for the dentofacial complex?
- What are the effects of mouth breathing on craniocervical posture, maxillomandibular relationships, facial morphology, tongue position, and occlusal features?
- Does reversing the mode of respiration from oral to nasal allow proper growth and of craniofacial and dentofacial complex?
- Do orthodontic treatment mechanics have a role in normalizing the breathing pattern?

38.2 Respiratory Pattern

The relationship between mouth breathing and dentofacial growth is still being debated after more than a century. Despite the existence of an extensive body of literature on this subject, the inconclusive results so far may be explained by different population selection criteria and the various diagnostic methods used for differentiating mouth breathers from nasal breathers. In order to determine this assumed relationship, the meaning of the term *mouth breathing* needs to be clearly established.

Human neonates are obligatory nasal breathers (Moss 1965). After birth, the maintenance of airway by correct posturing of the mandible and the tongue is necessary for survival. James and Hastings (1932) examined 53 infants, aged from 1 to 14 days, and found that most of the infants in their study with lips-apart posture achieved an oral seal by putting the tip of their tongue between the lips and their respiration was through the nose. Later, growth changes make it possible to breathe through the mouth. Although humans are primarily nasal breathers, when the need for air increases, mode of breathing changes from nasal to partially oral. In healthy adults, the switch from nasal to oronasal breathing occurs when ventilatory exchange rates above 40–45 L/min are reached (Niinimaa et al. 1981). This shift is transient, and when the need for air decreases back to normal, the individual goes back to nasal breathing. Human nasal passages also exhibit spontaneous changes in unilateral nasal airway resistance as a result of alternate nasal congestion and decongestion on opposing sides of the nose. This nasal cycle is said to last between 4 and 6 h, but fluctuations in nasal patency from 10 min to several days have been shown to occur (Huang et al. 2003; Chaaban and Corey 2011).

Mouth breathing can be defined as a shift from nasal respiration to oral respiration or mixed respiration due to obstruction or restriction on any part of the airway. Causes of such a nasal obstruction followed by a transition to mouth breathing can be adenoid or tonsil hypertrophy, chronic and allergic rhinitis, nasal traumas, congenital nasal deformities, foreign bodies, polyps, and neoplasms (Schlenker et al. 2000). It has been reported that when any of these factors increases the nasal resistance

and pressure, the patients sometimes break the anterior and posterior oral seals resulting in oral respiration (Rodenstein and Stanescu 1984). It is also possible for mouth breathing to occur as the result of habit, with or without any impairment of the upper airway (Fields et al. 1991).

Treatment of dentofacial deformities caused by mouth breathing should be preceded by a thorough ENT examination to determine whether the cause is *habitual* or *obstructive*. If the cause is habitual, the treatment goal is to obtain a lip seal and force the patient to breathe through the nose. However, in cases of mouth breathing due to respiratory obstruction, the treatment should focus on relieving the obstructive cause.

Various diagnostic methods have been used in research to determine respiratory mode (James and Hastings 1932; Paul and Nanda 1973; Humphreys and Leighton 1950; Rasmus and Jacobs 1969; Melsen et al. 1987; Woodside and Linder-Aronson 1979; Bresolin et al. 1983; Miller 1949). Others have used the presence of adenoids (Tarvonen and Koski 1987; Sosa et al. 1982) without determining the respiratory mode. Most of these diagnostic tests have been indicated to be inconsistent and lacking in sensitivity and specificity (Ung et al. 1990; Vig et al. 1991). With the improvements in physiologic diagnostic methods, rhinometric measurements such as nasal resistance came to be widely used in research. However, associations between nasal resistance and respiratory mode were reported to be variable and weak (Warren et al. 1991; Vig and Zajac 1993; Ellingsen et al. 1995). Advances in respirometric techniques made it possible to measure the volume of nasal and oral airflow simultaneously which provided valuable information in this controversial area. Gurley and Vig (1982) suggested a technique for the simultaneous measurement of nasal and oral respiration which is called Simultaneous Nasal and Oral Respirometric Technique (SNORT). This technique measured the ratio of oral to nasal airflow and made the quantification of normal and abnormal respiratory modes possible. Other techniques were used to determine the dimensions of nasal airway impairment (Warren et al. 1984, 1986, 1988). Hairfield et al. (1987) reported a mean cross-sectional nasal area of 0.65 cm^2 in adults. Warren et al. (1988) suggested that if nasal size falls below 0.4 cm^2, most individuals will become oral breathers to some extent. These values would probably be smaller in children since several studies have indicated that nasal cross-sectional area increases with growth (Vig and Zajac 1993; Laine and Warren 1991; Crouse et al. 1999).

Perhaps the most significant finding of these studies is that one should be careful when classifying patients as oral breathers. Even in a population referred with an impaired airway, there will be oral, nasal-oral, or total nasal breathers as well as habitual oral breathers with adequate nasal airways. There are no clear cutoff points to determine the mode of breathing, and oral or nasal respiration seems to be a transient phenomenon in many individuals (Shanker et al. 2004). Since the intensity of functional changes is important in the magnitude of growth alterations, the question becomes if partial airway obstruction can lead to reflex adaptive changes that cause dentofacial deformities.

Another important factor to consider is the age at which dentofacial growth changes and breathing mode are evaluated. In order for any functional change to have a significant effect on facial growth, it must start early and be effective for a long time, especially during the peak growth period. However, cross-sectional studies that investigate subjects before or a long time after their growth spurts may not show any differences between groups because in younger subjects the growth changes would not have occurred yet, whereas in older subjects nasal airway may no longer be compromised due to

growth changes in nasopharynx and lymphoid tissue.

Individuals also differ from each other in terms of adaptation and compensation processes. Several morphological factors may determine the extent of postural response to an inadequate airway. Subjects with compromised oropharyngeal airways due to size and shape of soft palate or tongue may give more exaggerated responses to a decrease in nasal airflow. The dentofacial changes observed in these individuals might be more pronounced. However, if the oropharyngeal airway is clear, only a slight parting of the lips may be enough to increase airflow (Bailey et al. 1996).

The extent of dentofacial changes due to any functional disturbance will be determined by multiple factors. Among these factors the age of the patient, the duration of the habit, and individual variations should be considered while making treatment decisions.

38.3 Physiologic and Dentofacial Effects

38.3.1 A Review of Early Literature

The influence of nasal respiratory function on the growth and development of craniofacial structures was first generated over a century ago by anecdotal reports describing the effects of "mouth breathing" on dental and facial morphology.

In 1872, Tomes (1872) described the dentofacial changes associated with chronic nasal airway obstruction, citing the lips-apart posture as the cause for decreased pressure on the incisors and proclined anterior teeth. He also coined the term "adenoid faces" to describe the associated facial changes.

In 1925, Dr. Edward H. Angle reprinted a book by George Catlin entitled "The Breath of Life (All Life on Earth is Breath, All Else on Earth is Death)." This book by Catlin advocated the superiority of nasal breathing over mouth breathing in sleep and described the consequences of habitual mouth breathing on teeth and facial features (Goldsmith and Stool 1994). Dr. Angle (1900) was also a firm believer in these concepts and stated in his textbook:

> When there is normal nasal respiration and normal relations of the dental arches, the teeth, and the muscles, the conditions are such as to perfectly maintain the equilibrium and the mutual support necessary to the normal development of the teeth and jaws. Should nasal obstruction occur in the developing child, inducing habitual mouth-breathing, immediately the equilibrium is disturbed, the lips and muscles are placed on a different tension, and pressure upon the arches, instead of being equal, is localized, being greater than normal at some points and less at others. No matter how strenuously it may be denied, malocclusion of the teeth and abnormalities in the formation of the bones of the jaws naturally follow. The undeveloped nose and adjacent region of the face, the vacant look, the short upper lip, the open mouth, and irregular teeth of the mouth-breather are common sights familiar to all.

Later other reports reiterated the relationship between altered dentofacial form and mouth breathing. Chronic nasal allergies were suggested to cause paranasal depression, V-shaped palate, and proclination of the maxillary incisors (Duke 1930; Balyeat and Bowen 1934). Cohen (1937) attributed mouth breathing due to allergies to high-arched and narrow palates, a flat and narrow face, and some type of orthodontic deformity (although he did not classify which type). Subtelny (1954) theorized that enlarged adenoids will cause a separation of the lips, downward and forward movement of the tongue away from the soft palate, depression in the position of the mandible, constriction of the maxillary arch, and a Class II division 1 type of malocclusion due to procumbent maxillary anterior teeth. Paul and Nanda (1973) also found a tendency toward Class II malocclusion with an increase in overbite and overjet in mouth-breathing subjects when compared to nasal breathers.

Different theories were proposed to explain the relationship between respiratory mode and possible dentofacial changes. Morrison (1931) suggested that the oral airstream in mouth-breathing individuals caused the negative pressure between the tongue and palate to be lost hindering normal downward palatal descent. James and Hastings

(1932) proposed that the loss of the normal pressure in the mouth due to an impairment of the airway is associated with impaired action of the tongue, lips, cheeks, and other forces acting on the jaws. They considered the impaired and misdirected action of these forces as the reason for the deformities of the jaws. A clearer understanding of these effects was possible when Moss (1962) developed the "functional matrix theory." This theory was based on the principle that the skeletal unit in the functional craniofacial component provides protection and mechanical support for its specific functional matrix and grows in response to the functional demands of surrounding tissues and structures. According to Moss's theory nasal breathing allowed proper growth and development of craniofacial and dentofacial complex (Moss 1969). Later, Solow and Tallgren (1976) found an association between the posture of the head and cervical column and craniofacial alterations seen in mouth-breathing patients. These results led to an alternative explanation known as "Soft Tissue Stretching Hypothesis" (Solow and Kreiberg 1977). This theory suggested that nasal obstruction caused extension of the head and that this postural change causes soft tissue stretching causing differential forces to act on skeleton causing morphological changes. Hence, the existence of a relationship between respiratory mode and dentofacial growth changes was widely accepted, and early treatment of allergies and removal of adenoid tissue before the eruption of permanent teeth were suggested to prevent the alterations in dental arches (Subtelny 1954; Marks 1965).

However, there were others who were skeptical of such wide acceptance of a possible relationship between oral respiration and growth changes. Kingsley (1889) considered the deep and narrow palate a congenital morphological trait rather than the results of a muscle imbalance due to mouth breathing. Gwynne-Evans and Ballard (1959) observed the relationship between jaw form, soft tissue morphology, and upper respiratory conditions for more than 15 years and concluded that mouth breathing does not result in deformities of the jaws, malocclusion, or adenoidal facies. Other authors reported that more than 50 % of the patients who were characterized as mouth breathers had Class I occlusions and no specific malocclusion pattern was correlated with mouth breathing (Howard 1932; Leech 1958; Huber and Reynolds 1946).

Since then, investigators have attempted to look more critically at the issue through experimental models and clinical research with objectively defined criteria for mouth breathing. Harvold (1968) used the rhesus monkey, *Macaca mulatta*, as a model in his experiments to test the connection between neuromuscular activity and skeletal morphogenesis. He anchored a piece of plastic in the palatal vault between the molars and found that the mandible moved lower and the tongue moved forward resulting in an anterior open bite. This study was followed by another one in which the animals were induced to lower their mandibles by fitting an acrylic block in the palatal vault (Harvold et al. 1972). After 6 months there was a significant increase in face height in experimental groups. They concluded that any factor, such as mouth breathing, that lowers the postural position of the mandible could also increase the face height. They tested their hypothesis by blocking nasal inhalation with silicone nose plugs in growing monkeys (Harvold et al. 1973, 1981). Radiographic, electromyographic, and dental cast measurements showed increased face height, decreased maxillary and mandibular intercanine distance, decreased maxillary dental arch length, steeper mandibular plane, larger gonial angle, altered muscle activity, and changes in the morphology of the tongue in the experimental group. The pattern of maintaining an airway differed between monkeys. Those that kept their mouths constantly open by lowering the mandible and protruding their tongues developed more severe malocclusions than those that rhythmically opened and closed their mouths with respiration.

The altered muscle activity in the rhesus monkeys due to forced oral breathing was further explored in other studies (Miller et al. 1982; 1984; Vargervik et al. 1984). These experiments documented changes in neuromuscular recruitment patterns resulting in changed function and posture of the mandible, tongue, and upper lip with considerable variation among the animals and concluded that nasal obstruction can induce neuromuscular changes which extend beyond the period of obstruction and remain even after nasal breathing is established.

More recent animal studies also found that nasopharyngeal respiratory obstruction was associated with downward and backward rotation of the mandible, upward and backward growth of the condyle, divergent gonial angle, anterior open bite, spaced dental arch in the lower anterior region, and a reduction in the height of the maxilla (Yamada et al. 1997; Scarano et al. 1998).

These experimental findings corroborated the previous data on the relationship between mouth breathing and an increase in facial height. However, it should be kept in mind that the results of these animal studies cannot be readily extrapolated to humans. Total nasal obstruction, as induced by researchers in these experiments, is extremely rare in humans. The oropharyngeal structures also differ between the species. Thus, the postural changes that occur in animals due to forced oral breathing may not be the same in humans.

Early clinical studies on humans generally used lateral cephalograms to evaluate dentofacial changes and the upper airway. Linder-Aronson (1970) studied 162 children aged 6–12 years. Half of these children were determined to need adenoidectomies, while the other half were controls. The patients were examined with respect to nasal airflow, breathing pattern, and dentofacial morphologic variables. He reported a significant relationship between enlarged adenoids determined by cephalometric x-rays and certain craniofacial changes, including low tongue position, mouth breathing, narrow maxillary arch, crossbite, and retroclined maxillary and mandibular incisors. In 1974, he examined a group of Swedish children before and after adenoidectomies and compared them to controls with respect to changes in cephalometric measurements. He reported that the patients in adenoidectomy group had increased anterior facial height, maxillary constriction, and retroclined incisors compared to controls. After their adenoidectomies, upper airway obstruction was resolved in these patients and their growth pattern became horizontal (Linder-Aronson 1974).

Hannuksela (1981) compared allergic and nonallergic children and reported a tendency toward clockwise rotation of the mandible and retroclined mandibular incisors. However, further evaluation of this population revealed no significant differences in the occlusion between groups (Hannuksela 1983). Other cephalometric studies also failed to show a relationship between the airway space or adenoid size and malocclusion (Sosa et al. 1982; Mergen and Jacobs 1970).

Lateral cephalograms were readily available to orthodontists and valuable in determining dentofacial changes. They were also recommended for assessing adenoid size (Shapiro and Shapiro 1984). However, since lateral cephalograms are two dimensional and unable to provide volumetric data, their reliability in determining airway size and adenoids have been criticized (Vig and Hall 1980; Maw et al. 1981).

With the development of respirometric techniques, a more objective classification of respiratory patterns became possible. Vig et al. (1981) reported higher nasal resistance in increased facial height groups compared with controls, but they found no significant differences in the nasal volume flow rate between groups. Fields et al. (1991) also concluded that subjects with long faces had a significantly smaller component of nasal airflow. Warren and Spalding (1991) suggested that high airway resistance due to nasal impairment may cause an exaggerated postural response if there is a low drape to the velum, the pillars form a posterior curtain, the tonsils are enlarged, or the posterior portion of the tongue is carried high.

The early clinical studies that used lateral cephalograms and/or other respirometric techniques showed that the relationship between dentofacial growth and development and respiratory mode is variable and multifactorial.

38.3.2 Current Perspective

Heredity and environmental factors are both effective in the development of dental arches and postnatal determination of craniofacial features. One of the most important environmental factors is the predominant respiratory pattern. Nasal breathing is associated with normal posture of the tongue and lips and normal muscle activity. If there is nasal obstruction, this would likely affect the muscle forces acting on the dentofacial region. This change in muscular action may cause abnormal facial growth and development. It has been shown that during oral breathing masseter muscle activity is inhibited (Ono et al. 1998). Increased airway resistance also

stimulates mechanoreceptors in the upper airway and increases the activities of the genioglossus and mylohyoid muscles due to forward positioning of the tongue and opening of the mouth to maintain the airway (Song and Pae 2001).

Today, it is accepted that growth occurs under the control of both genetic and environmental factors. Genetics act on cartilages and the bones respond to the changes in these cartilaginous structures. The growth and needs of the soft tissue matrix also cause reactive changes in both the bone and the cartilage.

Long-term mouth breathing seems to affect the occlusion and facial morphology during periods of rapid growth. However, not every patient has the same growth changes due to oral breathing. The heritable characteristics of anatomical structures also seem to play a role in determining which patients will be most affected. In some patients a slight opening of the lips may be enough to provide the necessary airway, while in others a more exaggerated postural response of the mandible, tongue, and head will be necessary. Children with narrow facial patterns also may be more susceptible to growth changes due to mouth breathing than children with broad facial features. It is also possible for patients with a vertical facial growth pattern to be more likely to be mouth breathers. The severity of the obstruction will also determine if the child is a chronic mouth breather or a partial one. If the obstruction is severe, the changed postural responses will be in place longer causing more extensive growth changes in dentofacial structures.

If the patient has morphologic risk factors in the oropharynx such as enlarged tonsils, a large tongue, or a long soft palate, the postural response necessary to open the airway will be more pronounced and the risk for developmental disturbance will be greater.

The most common cause of oral breathing in children is enlarged pharyngeal lymphoid tissue. The enlargement of these tissues may adversely affect pharyngeal patency (Gross and Harrison 2000). Normally, the size of the adenoid tissue is dependent on the associated skeletal structures. However, abnormal growth of this tissue may predispose the patient to upper airway obstruction causing oral respiration. As a matter of fact, any reason that causes nasal resistance to increase for long periods of time, such as allergies or nasal septal deformity, has the potential to cause chronic oral respiration.

When a tooth erupts in the mouth, it is subject to chewing forces as well as forces from soft tissues such as lips, cheeks, and tongue. This creates an equilibrium of forces acting on the dentition. When this equilibrium is disturbed, there are changes in tooth positions.

During oral respiration, the mandible rotates open and the tongue is positioned lower in the mouth and no longer contacts the palate causing eruption of the molars and transverse maxillary deficiency (Figs. 38.8 and 38.9). Thus, the mandible rotates in a clockwise direction, losing contact with the soft palate, causing open bite and mandibular retrognathism. However, this is only a

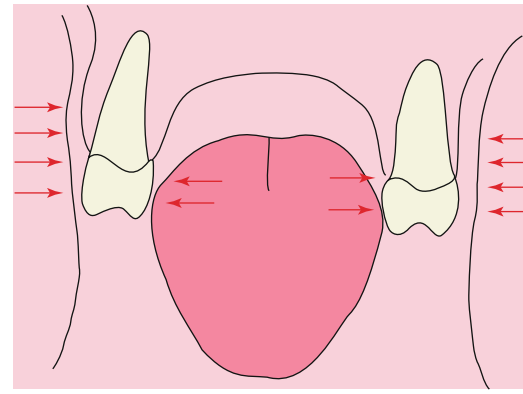

Fig. 38.8 When the tongue is in its correct position, it exerts transverse pressure on the teeth and alveolus, allowing proper growth

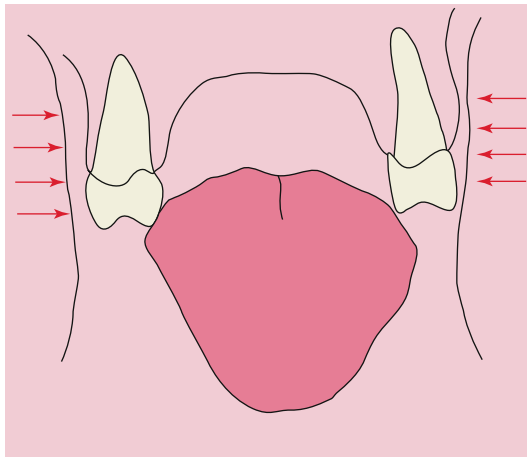

Fig. 38.9 If the tongue is in a lower position, equilibrium of forces is disturbed. As a result the palate becomes narrow

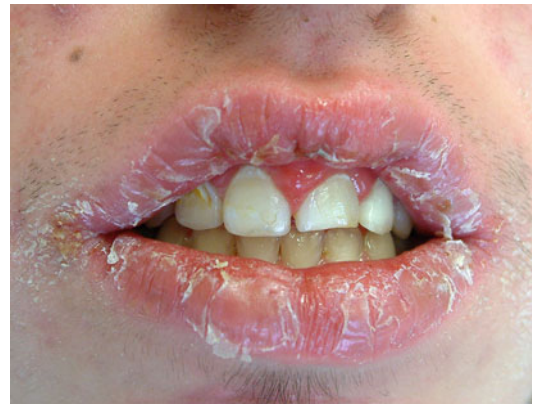

Fig. 38.10 At repose, the lips are open in mouth-breathing patients. This lack of lip seal causes the mouth to become dry. Maxillary anterior teeth and gingiva are most at risk for the negative effects of this open-mouthed posture

mechanistic view of the possible interactions between mandibular growth and oral breathing. Complex epigenetic events may also be responsible for the growth changes in the mandible. It has been hypothesized that children with significantly enlarged adenoids will develop obstructive sleep apnea causing abnormal nocturnal growth hormone secretion causing somatic growth impairment (Peltomaki 2007). Due to this abnormal hormonal balance, mandibular ramus growth may be less than in healthy subjects causing the observed mandibular rotation in these children. This mandibular rotation also causes backward and downward displacement of the tongue (L'Estrange et al. 1996). Postural changes of the tongue lead to altered muscle forces to act on maxillary arch causing a constricted maxillary arch, high palate, and posterior crossbite in the transverse direction. Maxillary retrusion (Linder-Aronson 1970) and an increase in palatinal inclination in relation to the cranial base (Linder-Aronson 1970; Trotman et al. 1997) have also been reported.

Craniocervical posture and oral breathing have also been the subject of various investigations. Oral breathing has been shown to be associated with head extension (Cuccia et al. 2008; Chaves et al. 2010; Neiva et al. 2009). This postural change moves the hyoid bone upward establishing an adequate airway (Gonzalez and Manns 1996). Since there is a relationship between head posture and altered muscle activity, long-term craniocervical changes may influence craniofacial growth as well as putting undue load on the neck and upper shoulders.

Mouth breathing in cleft palate patients is a clinically relevant subject as well (Hairfield et al. 1988). The airway size is reduced and nasal resistance is higher in cleft patients compared to non-cleft subjects (Warren et al. 1984, 1969). The large craniocervical angulation indicates an extended head position in these cases (Oosterkamp et al. 2007). The high prevalence of mouth breathing in these patients may be caused by various factors, such as septal deviation and effects of surgical techniques. Thus, a normal breathing pattern may not be established ever because of the open communication between the nose and mouth at birth (Warren et al. 1988).

In addition to these structural changes in the dentofacial region, mouth breathing may cause other oral diseases. Mouth-breathing patients often have inflamed labial gingival tissues around the maxillary incisors. The gingiva becomes inflamed and hyperplastic because the mouth remains open and the salivary flow is reduced. Since saliva performs essential roles including antimicrobial action and protection of oral tissues, a reduction in salivary flow will have negative impact on teeth and gingival tissues as well as generating odoriferous volatile compounds. Clinically, the gingiva appears swollen, red, and shiny with the classic rolled up appearance (Figs. 38.10 and 38.11). There can be bone loss and pocket formation in the interproximal area if

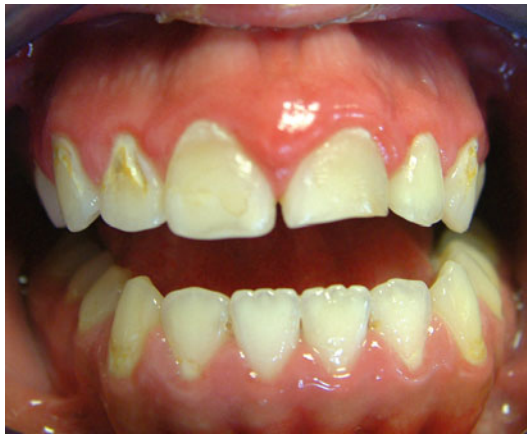

Fig. 38.11 Maxillary anterior region of the patient in Fig. 38.10. The gingiva is inflamed, and there are decalcifications on teeth due to poor oral hygiene and mouth breathing. Note the classic shiny red, swollen look of the gingiva

proper oral hygiene is not maintained. There is also an increased incidence of caries and halitosis (breath malodor). Correction of mouth breathing along with necessary dental treatments will improve the health of the oral cavity.

It is likely that the oral cavity becomes dry because the mouth remains open most of the time in chronic mouth breathers. Clinical manifestations of this negative impact will be halitosis, an increased incidence of caries, and gingivitis, especially around maxillary anterior teeth. These oral health problems will have significant negative social, economic, and psychological consequences causing a decrease in the quality of life.

It has been difficult to determine the relationship between dentofacial morphology and oral breathing because respiration is a complex act which cannot be easily classified with the current techniques. There are multiple factors which determine if dentofacial growth of a person will be affected by the changes in the nasal airway. Thus, a careful evaluation of the patient by otolaryngologists, pediatricians, and orthodontists is needed before treatment decisions.

38.3.3 Treatment

Treatment of patients with a diagnosis of mouth breathing needs to be preceded by an evaluation by otolaryngologist, pediatrician, and orthodontist. Treatment of upper airway obstruction may be provided by either of these specialists or by all, depending on etiology and severity of the clinical manifestations. The case report illustrated in Figs. 38.12, 38.13, 38.14, 38.15, 38.16, 38.17, and 38.18 demonstrates the type of treatment result that can be obtained for a patient with dentofacial deformity due to mouth breathing.

In cases of habitual mouth breathing without nasal, nasopharyngeal, or oropharyngeal obstruction, the treatment is directed toward establishing a lip seal and forcing the patient to breathe nasally. This is known as *myofunctional therapy*. If there are associated dentofacial changes in the patient, functional appliances can also be used.

If the cause of this pattern of breathing is obstructive, the location of obstruction and its cause must first be diagnosed and treatment must be directed accordingly. The surgical and medical treatments of such obstructions are beyond the scope of this chapter. However, the effects of treatments on dentofacial growth must be known before making any treatment decisions.

After adenoidectomy and establishment of nasal breathing, mandibular plane angle changes toward a more horizontal growth direction though individual variation in response has been reported (Linder-Aronson et al. 1986; Woodside et al. 1991). Peltomaki (2007), in a systematic review, reported that restoration of normal physiologic nasal breathing following adenotonsillectomy can induce acceleration in secretion of growth hormone. This may in part explain the mandibular growth changes in these children.

A flexion in head posture always occurs with a reduction in craniocervical angle in response to elimination of airway obstruction after adenoidectomy and has also been reported after medical treatment of children with asthma and perennial rhinitis (Solow and Sandham 2002; Wenzel et al. 1983, 1985) and after orthodontic rapid maxillary expansion (RME) (Tecco et al. 2005).

Rapid maxillary expansion is an orthopedic procedure that produces sutural expansion in the maxilla, and it is widely used in orthodontics to

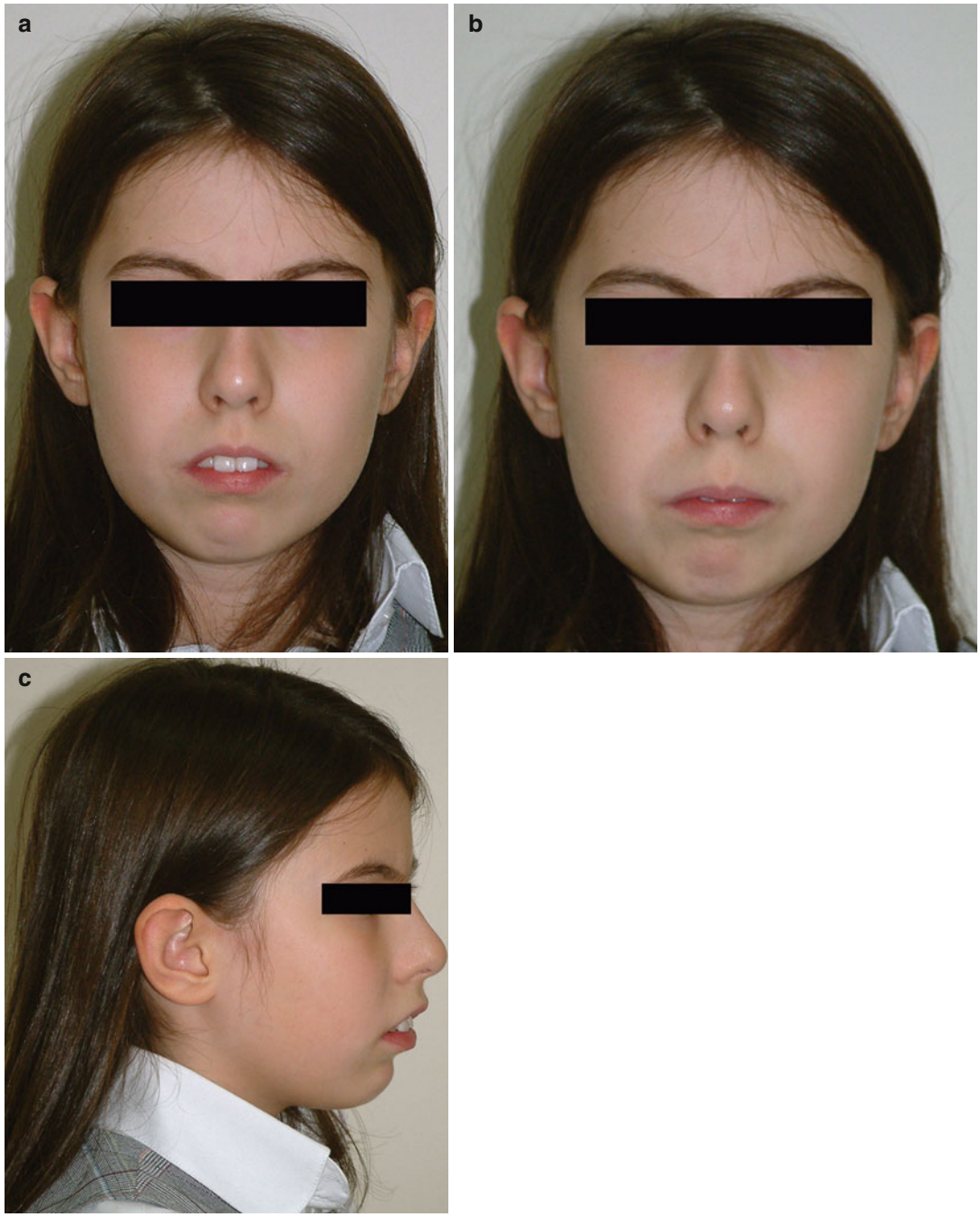

Fig. 38.12 Pretreatment (**a**) frontal view at rest, (**b**) frontal view with forced lip seal, and (**c**) profile view that indicates a high lip line, increased anterior lowerfacial height, and increased muscle activity during lip closure. Lower lip rests behind the protruded incisors during rest position

widen the palate without the movement of teeth through alveolar bone. Transverse dimensions of the maxilla can be effectively increased by RME appliances (Haas 1961). RME appliance has a screw in the middle and is applied on the maxillary arch. Separation of midpalatal suture is accomplished by turning the screw once a day for approximately a month. A retention period

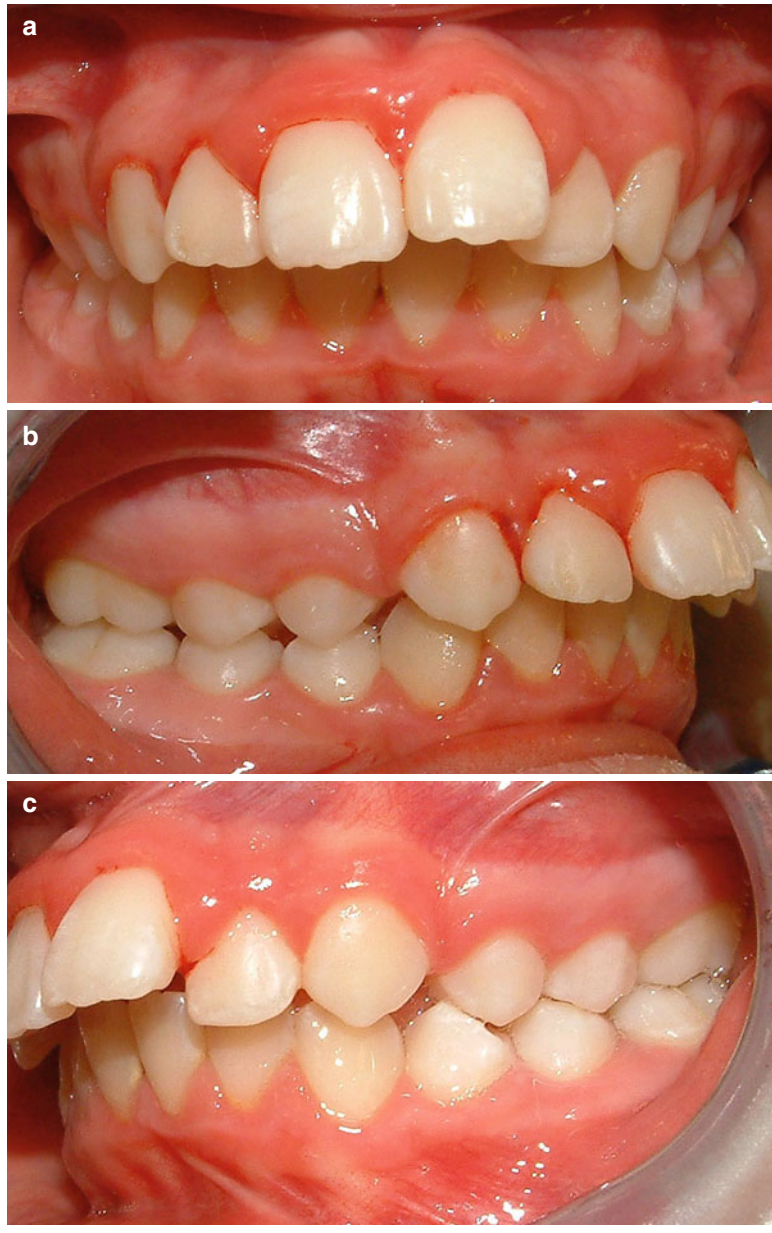

Fig. 38.13 (**a–e**) Pretreatment intraoral: (**a**) frontal, (**b**) right side, (**c**) left side, (**d**) upper arch, and (**e**) lower arch views of the patient demonstrating a Class II malocclusion with mild maxillary transverse deficiency and arch length deficiency

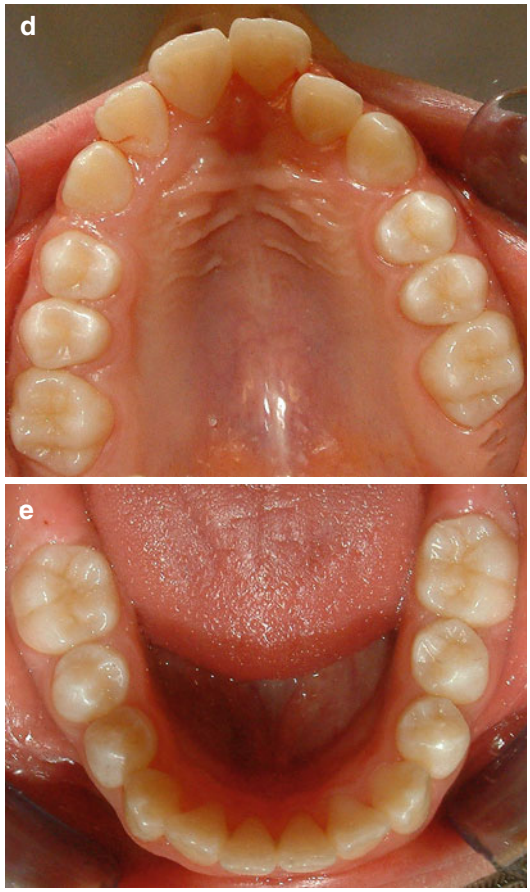

Fig. 38.13 (continued)

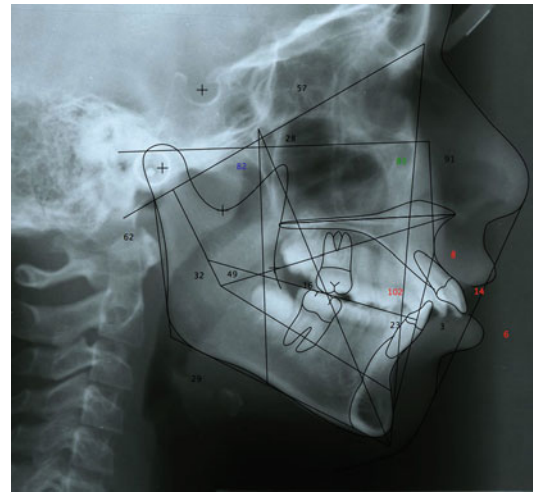

Fig. 38.14 Pretreatment lateral cephalometric view and analysis of the patient show protruded upper incisors, a retruded mandible and a Class II malocclusion

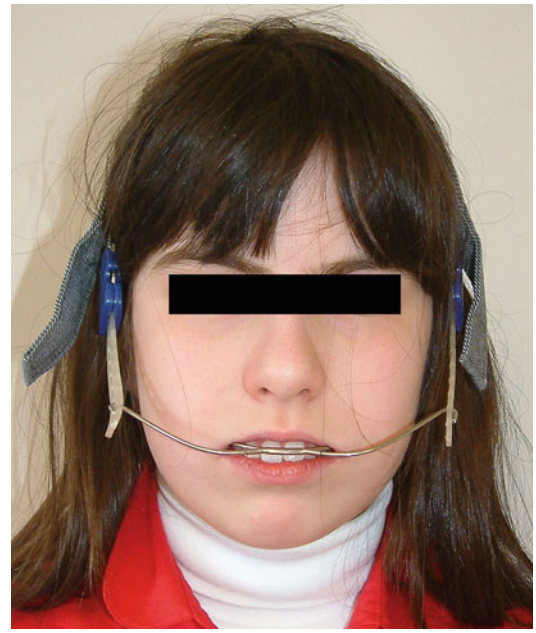

Fig. 38.15 The patient was treated with a high-pull headgear and fixed appliances. The high-pull headgear places a distal and upward force on the maxillary dentition and maxilla. This maintains the vertical position of the maxilla and inhibits eruption of the maxillary posterior teeth

of 3–6 months is recommended after active expansion is ended (Figs. 38.19, 38.20, 38.21, and 38.22).

In cases of maxillary constriction, when maxilla is expanded by RME treatment, an increase in nasal floor close to the midpalatal suture occurs as well. Numerous studies have radiographically investigated nasal cavity changes after maxillary expansion on posterior-anterior cephalometric films and reported an increase in nasal cavity width (Hershey et al. 1976; Cross and McDonald 2002; Basciftci et al. 2002).

Orthopedic expansion of maxilla by RME appliances plays an important role to improve the nasal airflow. A decrease in nasal resistance and a change in breathing pattern from oral to nasal have been reported after RME treatment (Hershey et al. 1976; Warren et al. 1987; Monini et al. 2009). A decrease in pharyngeal collapse was also

Fig. 38.16 Posttreatment (**a**) frontal view at rest, (**b**) frontal view during smile, and (**c**) profile view shows the improved aesthetic results obtained by orthodontic and orthopedic treatment

reported in patients with obstructive sleep apnea syndrome (OSAS) following RME treatment (Baik et al. 2002). However, in about one third to one half of the patients, mouth breathing could not be treated (Warren et al. 1987; Compadretti et al. 2006). Small clinical changes and wide individual variation were reported in other studies using acoustic rhinometry to test the differences in nasal volume before and after RME (Doruk et al. 2004; Bicakci et al. 2005; Babacan et al. 2006). It was

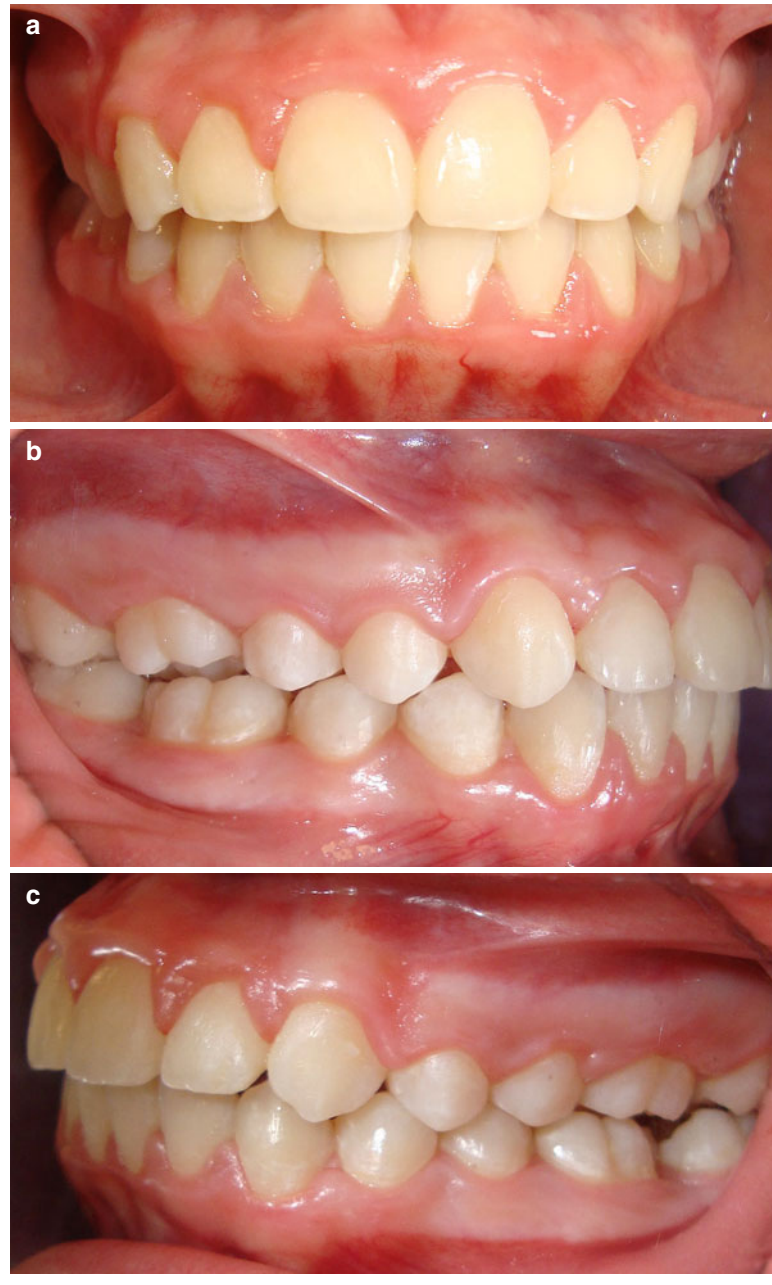

Fig. 38.17 (**a–e**) Posttreatment intraoral: (**a**) frontal, (**b**) right side, (**c**) left side, (**d**) upper arch, and (**e**) lower arch views of the patient demonstrating improved functional results with a Class I molar and canine occlusion as well as ideal overjet, overbite, and transverse relationship of the dentition

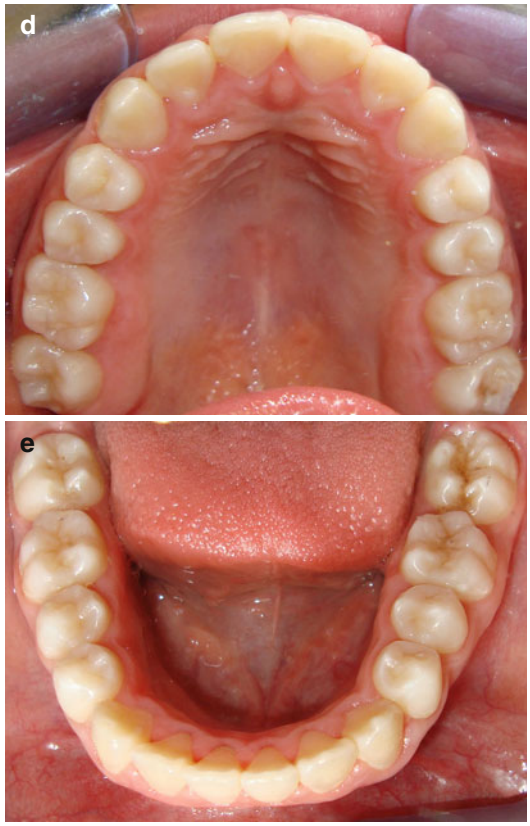

Fig. 38.17 (continued)

suggested that in the presence of nasal concha hyperplasia, nasal polyps, adenoidal hypertrophy, and septal deviation, increase in nasal airflow may not be enough to achieve nasal breathing (Warren et al. 1987). In general, RME is indicated in patients with maxillary constriction. Even if there is evidence that width of the nasal cavity increases and improvement in nasal airflow occurs to some extent, it cannot yet be offered solely for treatment of respiratory impairment (Warren et al. 1987; Compadretti et al. 2006; Doruk et al. 2004; Gordon et al. 2009).

Even though it has been shown that midpalatal sutural expansion increases nasal cavity width and nasal airflow, this may not be enough to change the respiratory pattern. Thus, the use of RME should be limited to patients with transverse maxillary deficiency.

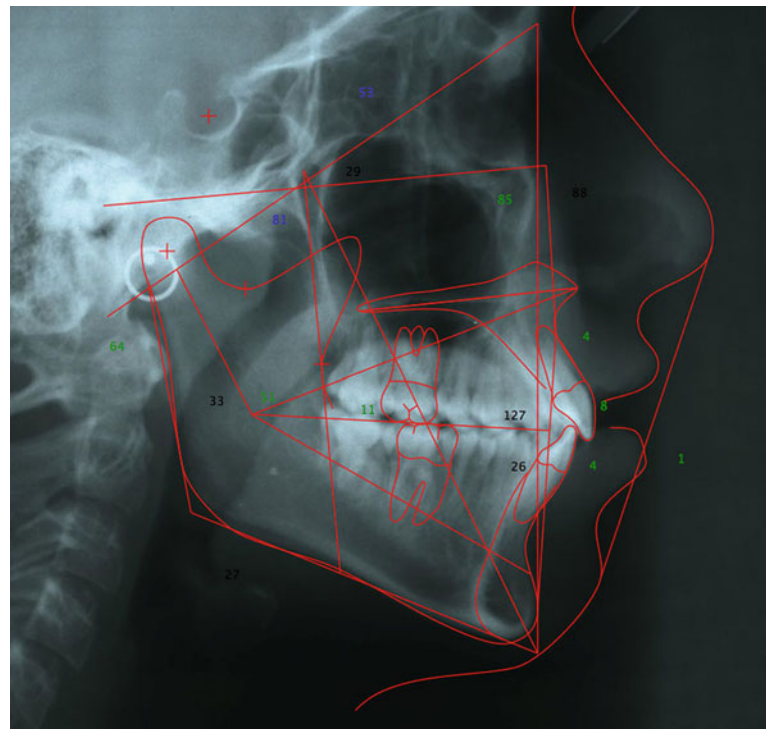

Fig. 38.18 Posttreatment lateral cephalometric view and analysis of the patient show uprighted upper incisors, mandible in a more forward position and a Class I occlusion

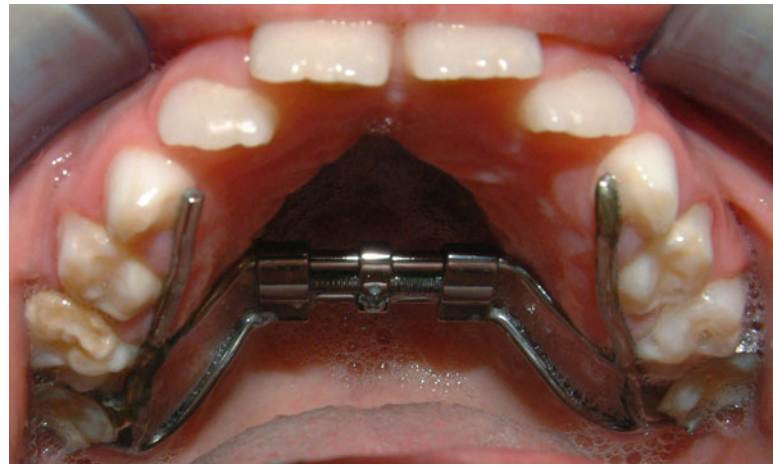

Fig. 38.19 The RME appliance in the maxillary arch is used to widen the maxilla

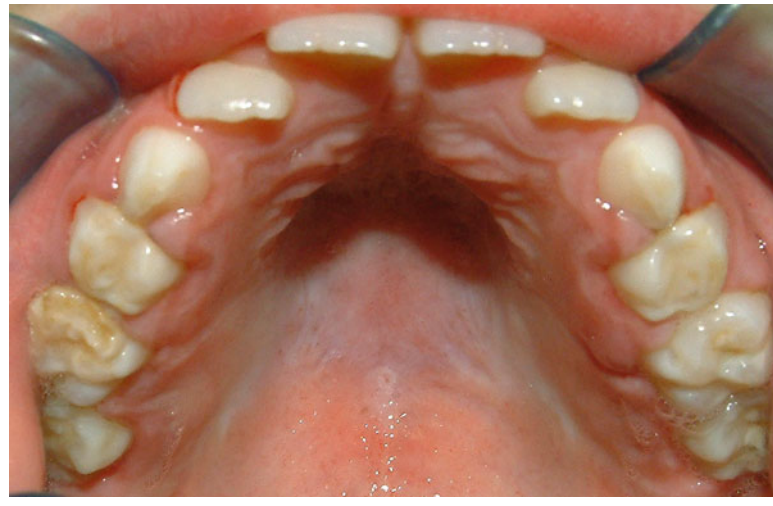

Fig. 38.20 Occlusal view of the maxillary arch after RME treatment

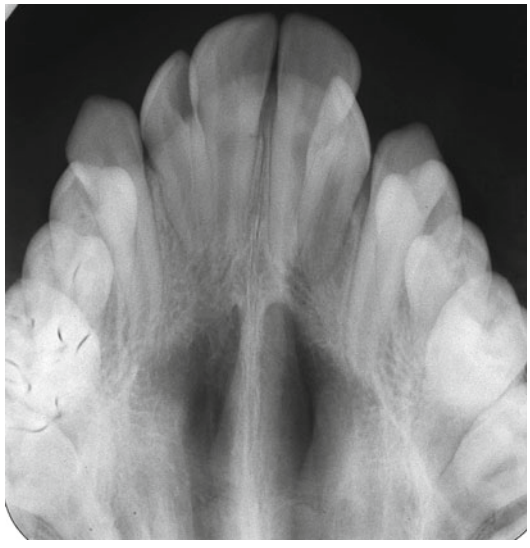

Fig. 38.21 Maxillary occlusal radiograph of a patient before RME

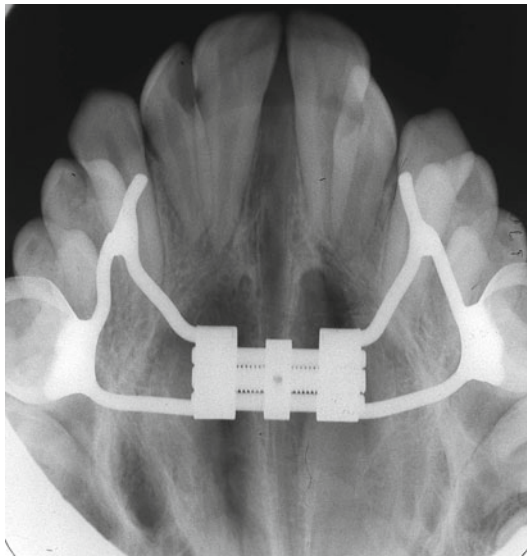

Fig. 38.22 The separation at the midpalatal suture is clearly seen in this occlusal film taken after RME is completed. A retention period of 3–6 months is needed to prevent relapse, while bone fills in the space between the right and left segments of the maxilla

Conclusion

Mouth breathing has the potential to adversely effect the growth and development of the individual, depending on the frequency, severity, and duration of the action with the inclusion of other confounding factors such as genetic features, variability in functional demands, and age. In the worst case scenario, an adenoid facies type of facial form can occur with a long face height, open-mouthed posture, short upper lip, small nostrils, a narrow maxillary arch, and extended head posture. To determine the etiology, objective evaluation of mouth breathing is important; techniques measuring the amount of oral and nasal airflow provide more valuable information compared to nasal resistance measurements and subjective evaluation of the patient. Mouth breathing may occur due to an obstruction in the nose and upper airway, but it is also possible for mouth breathing to be habitual without accompanying airway obstruction. Open-mouthed posture is not a good indicator of mouth breathing as people can breathe through their nose by creating a posterior seal. In treatment planning, correct diagnosis and defining the etiology of the problem will eliminate unnecessary treatment approaches.

In the presence of an obstruction that impedes physiologic nasal breathing, elimination of the obstruction is necessary to prevent abnormal facial and dental growth. In cases of obstructive adenoids and tonsils or allergic rhinitis, surgical or medical treatment is frequently indicated. Favorable changes in dentofacial structures and head posture are seen in these patients, especially when treatment is performed at an earlier age. Some of these patients may further need orthodontic treatment if they have already developed malocclusions.

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Nanomedicine and the Nose

39

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Keywords
Nanomedicine • Nanobiomaterials • Theragnostic • Nanosensors • Tissue engineering • Artificial nose • Nanonose

Core Messages

- Nanotechnology revealed that organic structures have different physical, chemical, and biological features in macroscopic and nanometric forms.
- "Nanomedicine" emerged as a new scientific area in nanotechnology and makes important conceptual changes in medical methods all over the world due to the different diagnostic and therapeutic alternatives.
- The use of nanomedicine in otorhinolaryngology is very important to meet the changing and increasing expectations of health.
- Today, the main three areas of experimental and clinical studies related to nanomedicine concentrates:
  (a) Nanotechnology-based imaging and diagnostic methods
  (b) Targeting delivery systems
  (c) Regenerative nanomedicine

39.1 Introduction

Developments in nanotechnology have revealed that macroscopic and nanometric forms of organic structures possess different features in physical, chemical, and biological aspects. By proving that nanodevices which are produced at the laboratory can interact with biomolecules, both physiological processes in healthy tissues and physiopathologic basis of diseases began to be understood in a more clear way.

"*Nanomedicine*" which appeared as a new scientific interest parallel to the above-mentioned

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developments in nanotechnology became one of the most studied topics in the world by the reason of the fact that it leads conceptual changes in accepted and applied medical methods up to now and presents different diagnosis-treatment alternatives.

Although nanotechnology is a commonly studied field all around the world, there is still no clear consensus about what nanoscala really is. One nanometer is calculated as one billionth (10^{-9}). It is possible to fit 5 carbon atoms in this scale as in three-dimensional forms. According to BSI (PAS 71) applications, less than 100 nm or even smaller scales are evaluated within the concept of nanotechnology. While at the beginning of 2000s, studies less than 200 nm and in smaller scale were considered as nanomedicine, today this range is accepted between 5 and100 nm.

Otorhinolaryngology is one of the basic disciplines of medicine which closely follows and implements medical innovations and advancements. In this regard, otorhinolaryngology is one of the leading areas which heavily utilizes microscopic and endoscopic treatments. Nowadays, treatment and rehabilitation methodologies like vocal prosthesis, cochlear implant, and brainstem implants are the top and best-known implementations examples of the micro-nanocircuits.

Nanomedicine will offer significant opportunities in meeting the treatment expectations of the otolaryngology patients with the new and advanced nanomedical diagnosis and treatment technologies in coming years. Such treatment solutions with advanced technologies will offer important treatment solutions for many different types of medical problems from hearing loss to facial paralysis, from nasal plastic surgery to early diagnosis and treatment of the head and neck cancers.

39.2 Clinical Nanomedicine Perspectives

Currently the most important aim to approach patients and diseases is to diagnose, if possible, when pathologic change is only at single-cell level and to start treatment. However, this could only be possible by increasing the efficiency of in vivo and in vitro diagnosis methods. Although nanomedicine is a field presenting great opportunities in this regard, it also brings along disadvantages because it is a new developing discipline.

Regarding the literature, it is possible to come across a wide range of research topics from the discovery of new nanobiomaterials to using these materials in clinics. While searching for physical, chemical, and biological principles for nanomaterials on one hand, on the other hand it is attempted to be understood how to use these materials on living creatures and what could be the adverse effects caused by the use of these materials and effects of nanomaterials on human health and environmental health. In addition, possible social and legal problems have been discussed and new ethical rules have been introduced.

A certain part of the studies is more in details, more specific, and more focusing on developing safer diagnosis devices. Also, there are studies for performing different biological measuring methods with one integrated device. By means of very precise biosensors which are tried to be developed with the use of nano-electronic circuits, it is attempted to establish micro-mobile laboratories which can be easily used by patients and, if necessary, can transmit multiple data to external user.

The other research topic in the related literature which requires advanced technology is about the combination of above-mentioned in vitro monitoring techniques and in vivo nanomedical devices. In those studies conducted within this regard, it is basically tried to be developed nanostructures which are able to carry specific contrast substance and be directed from the outside. Thus, it will be possible to take detailed molecular image of target tissues.

In another conducted group study, it is researched how to combine these nanostructures with pharmacological agents. By means of nanostructures which carry therapeutic and diagnostic agents at the same time, especially in cancer cases, it would be possible to administer a treatment on target tissue directly. With this approach defined as theragnostic (therapy + diagnose), again primarily for cancer patients, it is aimed to

follow up efficiency of the treatment by taking the images of the target tissue at different times.

Lastly, it has also been conducted intense studies on successful regeneration of diseased or injured tissues by means of nanografts and reproducing needed artificial organs by means of nanoscafolds in in vitro conditions and then replacing diseased or injured organs with the artificial ones.

Methods which have been developed by using nanotechnology have potential to be effective on all medical equipments. For example, developing new materials to be used in surgical implants, nanometric systems or minimal invasive sensors which can be used in monitoring metabolic activities can be considered within this regard. Nanopumps, injectable/implantable polymer systems, liposomal drug applications, and cell/gene therapy methods can be considered with regard to developed-controlled drug delivery systems (Wei et al. 2006). Currently half of the improvements related to new molecules all around the world are made by biotechnology companies. Therefore, over 4,000 companies in the world which work related to drug delivery systems, diseased part targeted therapy methods, drug carrying implants-patches and gels (Flynn and Wei 2005).

39.3 Interdisciplinary Frameworks

All those efforts for understanding the development of disease at molecular level and for treatment are very important to spread all the developments in nanomedicine to the society. Since the topic has a wide scale, different disciplines have to work together in nanomedicine area. It can be said that for now, neither any scientific field nor areas of expertise possesses capacity of scientific and technical infrastructure to conduct such a research by itself. To manage scientific research in such a field, it is a must to establish a well-organized "team." Within such team, conventional disciplines, such as basic-clinic medical scientists, pharmacologists, and physics-chemistry-electric-electronic-biomedical-computer engineers, and new fields, such as genom-proteom science, pharmacokinetic modeling, and microscope designing, should be included.

In addition to the self-disciplinary nature of nanomedicine, the more the number of studies increases in this field, the better new subdisciplines appear. Some of these subdisciplines are mentioned below and many studies have been conducted on each specific topic:

- Imaging: molecular, vascular, neurological, etc.
- In vitro diagnosis
- In vivo diagnosis and biosensors
- Advanced biomedical materials, including "smart"
- and functionalized materials and surfaces
- Regenerative medicine and tissue engineering
- Infection control
- Drug design and targeted drug delivery
- Gene and cell therapy
- Man–machine interfaces
- Nanotoxicology
- Nanomedicine and risk management
- Nanomedicine and ethics

39.4 Clinical Nanomedicine Applications

Today, big scaled centers which conduct experimental and clinical studies are focused mainly on three fields (Strategic Research Agenda for Nanomedicine, ETP-NM 2006).

39.4.1 Regenerative Nanomedicine

Current "traditional treatment" approaches lead to have limited results in many diseases or cause success of training to change from patient to patient. Both for improving the efficiency of the treatment and minimizing the side effects, methods to be used should be *patient-specific characteristics.*

As a result of "*tissue engineering*" studies, it has been started to form the basis of patient-specific treatments which can be used in regeneration and reparation of in situ tissues.

Main implementation fields of *tissue engineering*, which is an interdisciplinary field, are maintaining, improving, and repairing the functions of biological structures through collaboration of

engineering and life sciences. By means of *tissue engineering*, future therapy methods will be more focused on treatment of chronic disorders by the use of self-healing mechanisms of the body than targeting symptoms or reducing the development of diseases.

It is possible to evaluate regenerative nanomedicine studies into two topics as *therapy* and *biomimesis*.

39.4.1.1 Therapy

Within the scope of regenerative nanomedicine, studies have been conducted on protecting from such pathologies as diabetes, osteoarthritis, cardiovascular system diseases, and degenerative central neuronal system diseases and therapies for related disorders and functional loss after injuries. Regeneration of cartilage in an articulation with osteoarthritis, production of mechanically stable and elastic scaffolds, vascularization following implantation, and creating a physiologic oscillation in diabetic pancreas islets or starting self-reparation mechanisms in heart and nerve system are the other examples to give.

Both in terms of mortality-morbidity rates and prevalence, there have been more intensified researches on some certain disease groups. This is also the case for clinical studies within the scope of nanomedicine. The most researched diseases are primarily cardiovascular diseases, cancer, musculoskeletal disorders, neurodegenerative diseases, diabetes, and bacterial-viral infectious disease.

39.4.1.2 Cochlear Implants

There are many studies for the utilization of nanosystems in transmission of neural stimulants. Among those, cochlear and brainstem implants are the top areas to be implemented in clinical use. Nanotechnology offers significant alternative treatment opportunities in increasing hearing performances of the patients with sensory-neural hearing losses.

In this context, it is expected to see significant advancements both in increasing the technologic performance of the implants and in improvements in surgical implementations. This way, less invasive and more effective methods could be applied in treatment of patients with hearing loss. For example, using thin-film electrodes that have been manufactured by a study conducted at the University of Michigan, it is now possible to process sound from 128 different channels in comparison to standard 16–22 channel implants (Fig. 39.1). This, as a result, allows transmission of acoustic information with higher-quality frequency, amplitude, and pitch variables to the auditory cortex of the brain. This provides an opportunity in treatment of infants with hearing losses using high-quality acoustic stimulants. Nowadays, this system is in research phase on guinea pigs and cats, and in the coming years, it is expected that production of devices suitable for human use will be possible.

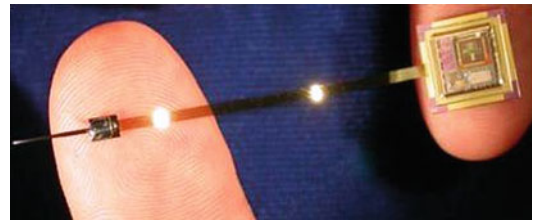


Fig. 39.1 Thin-film electrodes process to the sound from 128 different channels in comparison to standard 16–22 channel implants (Source: http://www.engadget.com/2006/02/09/new-type-of-cochlear-implant-to-improve-hearing/)

39.4.1.3 Design an Artificial Nose (Nanonose)

One of the areas with high-implementation potential for nanosensors is the artificial nose studies. Studies are continuing on systems to capture and process odor molecules (Fig. 39.2). Systems designed for this purpose involve use of receptors, transmitters, receivers, and a processor. Receptors used in these systems are manufactured with nanofabrication or MEMS (micro-electromechanical systems) technology. Nanowire and graphene sensors can also be used to produce nanonose (Figs. 39.3 and 39.4). Multisegmented nanowires via surface functionalization method can be used for detection of biological or odor molecules. P-type multisegmented nanostructures are in a back-to-back Schottky diode configuration. Au-part of the multisegment

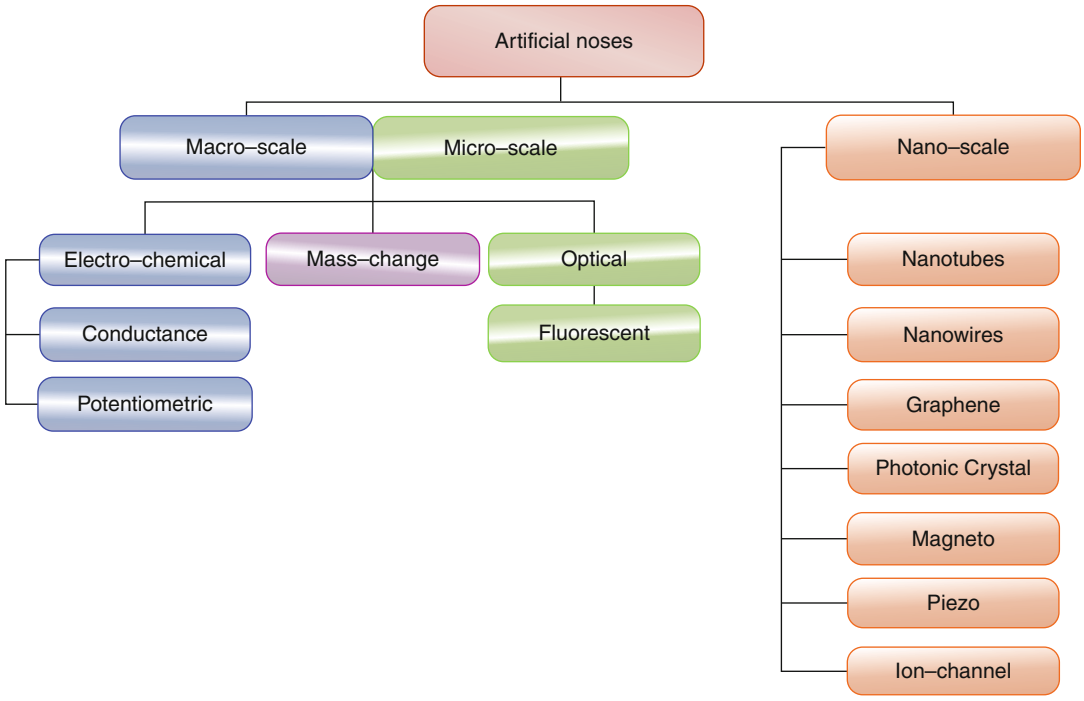
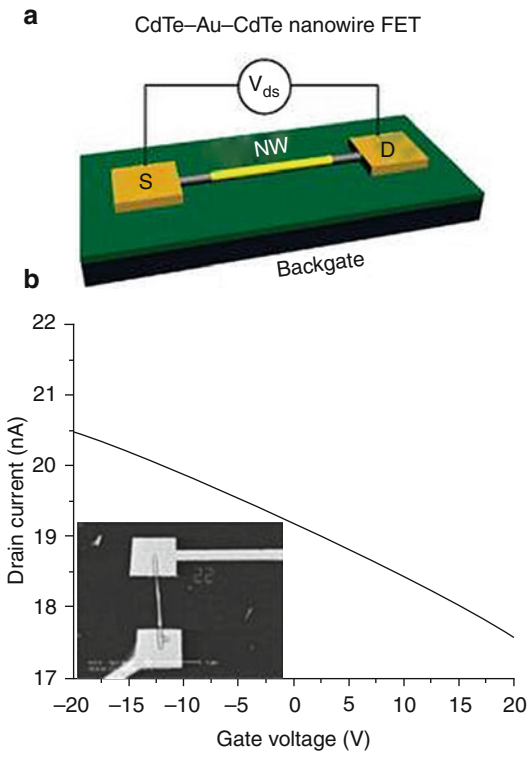


Fig. 39.2 Taxonomy of nose-like sensors (Adapted from The MITRE Corporation, McLean, ©1997–2006)



can be surface functionalized to increase the sensitivity of the nanowire sensor with specific sensing molecules. Attachment of odor molecules on Au-portion of the nanowire can modulate the Fermi level of the heterojunction device which leads to detection of the desired molecules. Such multisegmented nanowire sensors can be fabricated into an array format for detection of different types of odor molecules or biological agents.

Similarly, graphene field-effect transistors arrays can be used for sensing as well. Using graphene sensors, pH, DNA, and vapor detection have been demonstrated. Stability and reliability of such sensors became questionable due to graphene's fast response to its environment. For this purpose, extraordinary electrical property of a graphene transistor is combined with a cover of block copolymers where nanometer-scale

Fig. 39.3 (**a**) Schematic of CdTe-Au-CdTe nanowire field-effect transistor. (**b**) SEM image of CdTe-Au-CdTe nanowire FET (Source: Wang and Ozkan 2008)

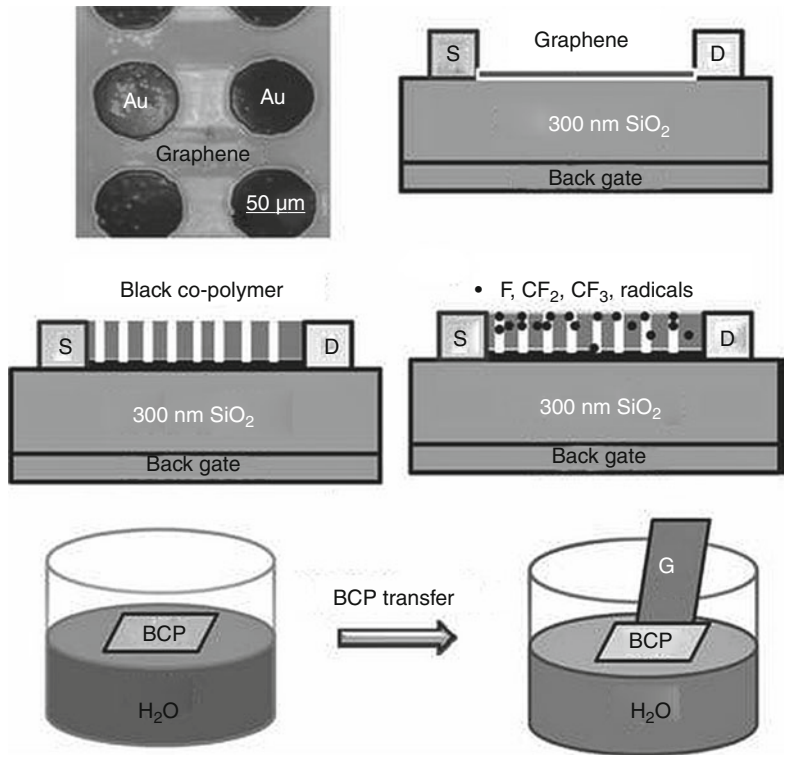


Fig. 39.4 Graphene-based electronic sensors are successfully used for chemical, biological, and gas sensing (Source: Guo et al. 2012)

openings provide access to the graphene surface where sensing can occur (Fig. 39.4). Gas/odor molecules can penetrate through the small holes across the block copolymer layer and reach to the graphene layer underneath. Interaction with these molecules and graphene surface leads to a shift in Dirac point of the transistor. Electrical shift in the signal is basically the senor output.

Arrays of graphene field-effect transistors with block copolymer on the surface can be fabricated and used for detection of different molecules. Block copolymers in appropriate volume fractions and molecular weights can provide control over the morphology and size/separation distance of cylindrical microdomains. These domains can be adjusted based on the size of the molecules or biological agents to be detected. As sensor output, the amount of Dirac point shift for different molecules is expected to be different which is important for the array-formatted sensors.

Today, electro-physiological basis of odor detection process is better understood, and in the upcoming period, the most important goal is to create a different type of nanosensors structure that will bring together an integrated system.

With the successful results obtained from studies based on this type of nanosensor will be able to develop an artificial nose.

39.4.1.4 Cancer

It has not gained enough success at the level of meeting the needs of the society regarding cancer, which has one of the highest mortality rates as a disease group in the world and on which billions of dollars are spent every year all around the world for understanding tumoral pathophysiology, for developing effective treatment agents, and for the treatment of patients. Without having the full understanding of chaotic dynamics of tumor tissue, it is not possible to administer an effective anticancer treatment. Today, it has been commonly discussed about the wrongs known as right on the topics of molecular oncology approaches

and cancer pathogenesis; accordingly, a new strategy in cancer therapy should be developed.

39.4.2 Diagnosis and Imaging Methods Based on Nanomedicine

The most important aim in diagnosis of diseases is to diagnose disease when it is at the earliest stage, at one-cell level. To reach this aim, it is required to develop new in vivo and in vitro diagnosis methods based on nanotechnology. Within the scope of in vitro applications, studies have been made on chemo-bio-nanosensors and ultrasensitive biochips ("lab-on-a-chip" and "cells-on-chips" devices) and products for routine medical applications have been prepared.

To-be-produced nano-analyzer devices can be used by patients and at the same time will be able to transmit multiple data to clinicians. More important than that, by means of nanobiosensors it will be possible to increase accuracy of already used test methods (Wang et al. 2010). Biosensors (*Photonic Crystal Nanobiosensors, Magneto Nano-immunosensor, Piezoelectric Nanosensors, Resonating Beam Sensors, Ion-channel Biosensors, etc.*) harness the immensely powerful molecular recognition properties of living systems and engineer these into electronic devices to provide easy-to-use sensing devices. The most successful biosensor developed to date is the home blood glucose sensor which is now ubiquitous worldwide. Biosensors can be used to measure disease markers, food safety, and environmental quality and to ensure safety and security.

Developments in microscopic scanning-imaging methods (*quantitative PET, MRS, d-MRI, f-MRI, etc.*) and spectroscopic techniques provide ultrahigh spatial resolutions and give detailed information about the complex "functionality" of cells (Zhang et al. 2012). Data acquired by use of quantum dots and fluorescent nanoparticles will lead to developments of more innovative and stronger in vivo diagnosis devices. Nanodevices produced as accompanying this functional molecular imaging will be more effective and much safer.

39.4.3 Targeting Delivery and Releasing

Long-term aims of controlled drug delivery systems are to develop diagnostic agents with high level of efficiency and safety and to perform treatment, application, and follow-up with the same nanosystem. "Find, fight, and follow," as is the concept determined, includes early diagnosis, treatment, and monitoring of the results, and also is stated as "theragnostic" (therapy+diagnose).

Drug delivery techniques suitable for theragnostic definition are prepared in accordance with two needs. First, one is drugs targeting more effectively where the disease is located, with high patient tolerance and cost effective, and the other is to detect new methods for distribution of new types of pharmacologic agents which cannot be distributed effectively by conventional methods.

The main aim of pharmaceutic studies in this regard is to address any medication to specific target tissue at the right time, in convenient amount and with safe-repeatable-controllable method. Today 13 % of products on the pharmaceutic market are related to controlled drug distribution systems. Nanoparticle formulations are still used to increase activity without increasing surface/volume proportion. In addition, nanoparticles act as drug carriers to effectively transmit therapeutics which have weak liquidity. If a therapeutic active substance is suitably encapsulated in a nanoparticle, carrying this drug anywhere requested, controlled oscillation of the drug, and protection from early stage activity decreases can be managed. These results will both increase the efficiency of drugs and decrease side effects dramatically. These types of nanoparticle delivery systems can be used for the treatment of cancer and many other diseases (Zhang et al. 2008).

Controlled drug delivery is based on the principle of turning pathophysiological changes, which appear basically in diseased tissue, into advantage for treatment. Because in tissues in which pathological process has already started, all physiological functionality disorders related to cell homeostasis are observed, accumulation of carriers which distribute drugs in a

controlled manner will be easier. Anatomic barrier between normal and pathologic tissues and vascularization differences will make it easier to reach of nanocarriers to diseased tissue. Thus, nanocarriers which carry therapeutic agents will reach much higher concentration in target tissue comparing to doses applied with normal drug treatment.

As a result of decrease in vascular permeability and lymphatic drainage appeared especially in tissue which developed tumor and inflammatory diseases, on one hand, reach of nanostructures to target tissue will be facilitated, on the other hand, it will be more difficult to withdraw. By means of the opportunity created by this pathophysiological change, nanostructures can easily be accumulated in extravasations and target tissue.

By means of localization tendency of nanocarrying systems, especially in RES, will be considered as a huge advantage in terms of both

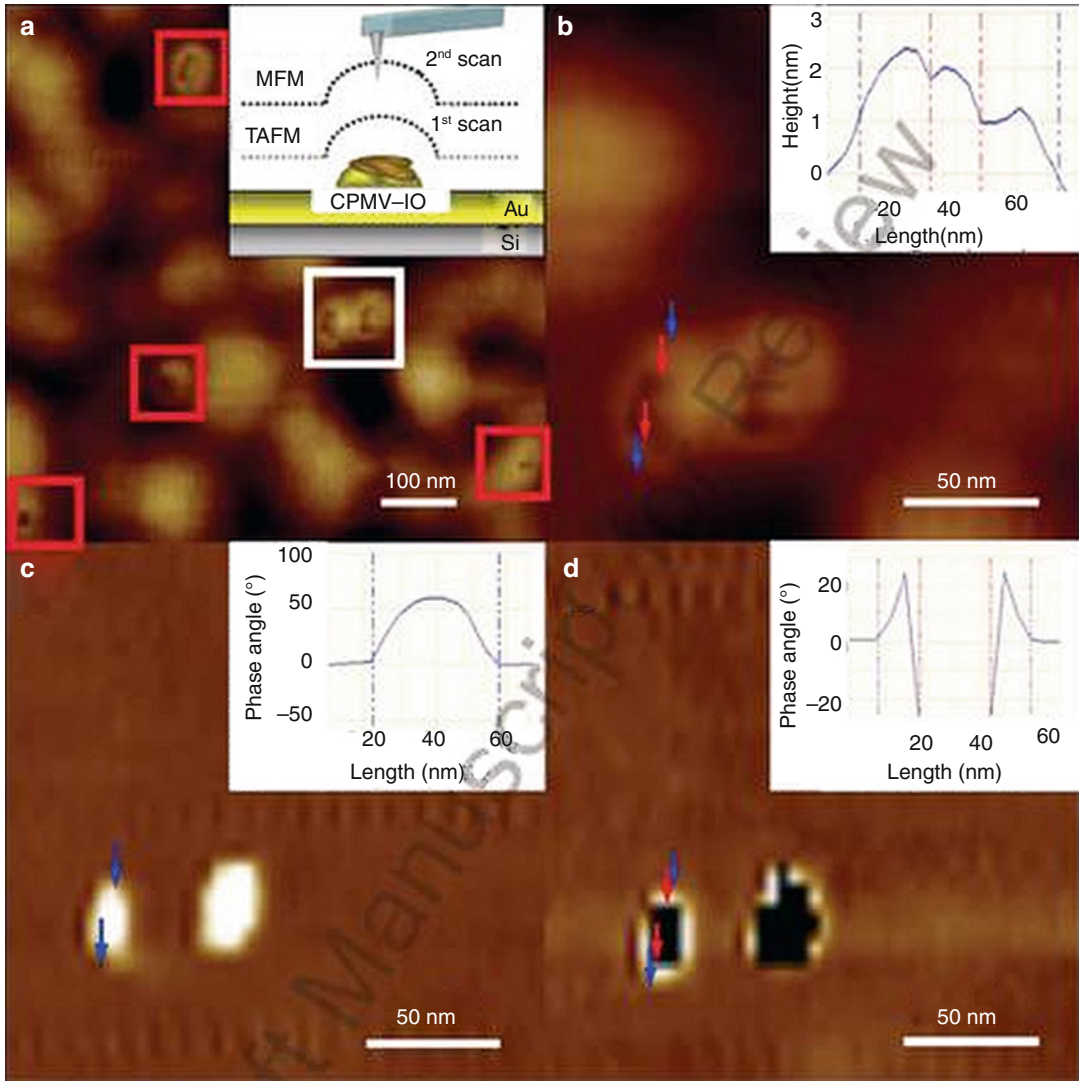


Fig. 39.5 Virus-like particles: AFM and MFM imaging of single CPMV-IO hybrids. (**a**) AFM topography showing single hybrids (*whites squares*). AFM/MFM schematic of dynamic lift-mode operation (*inset*), (**b**) AFM topography, (**c**) AFM phase detection, and (**d**) MFM phase detection of two adjacent CPMV-IO hybrids and their corresponding cross sections (Source: Martinez-Morales et al. 2008)

controlled and passive distribution of drugs. This natural distribution method managed by macrophages can be used for intracellular infections of liver and spleen.

Patient-specific therapies have a critical role on nanosystems performing controlled distributions to reach the target. It is possible to find many nanocarrying systems having such an aim in the literature (liposomes, micellar and microemulsion systems, liquid crystal-based formulations, nanocrystals, antibodies and conjugates, naturally occurring proteins as delivery systems, polymer conjugates and bio-conjugates, biodegradable nanoparticles/nanocapsules, virus-like particles for gene delivery, delivery of small nucleic acids or mimetics, delivery of vaccines, synthetic biomimetics, dendrimers, carbon nanotubes, etc.) (Fig. 39.5).

Although there have been many successful experimental studies on the topic existing today, strategies for developing new drug-carrying systems are not completely accepted yet. Efforts on this topic have been proceeding slowly because of the uncertainties about regulation and toxic side effects. It should be accepted that drug safety has to be attached as much importance as drug efficiency considering all nanoparticles.

Conclusions

As in all areas related to medicine, nanomedicine applications have many technological, legal, administrative, environmental, toxicological, social, and economic problems. However, in human health-related preventive and curative health services in achieving the objectives and the high-tech solutions on the whole of society through dissemination, nanomedicine will be one of the sciences to shape the world in the near future.

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The Nose and the Eustachian Tube

40

Özlem Önerci Çelebi and T. Metin Önerci

Keywords

Nasal physiology • Eustachian tube • Sniffing • Nose blowing • Sneezing • Otitic barotrauma • Sinus barotrauma • Toynbee phenomenon

Core Messages

- Normal functioning of the ear is closely related to the health status of the nose and paranasal sinuses.
- Pathologies of the nose, sinuses, and nasopharynx play an important role in the cause, treatment, and sequelae of ear disease.
- Sniffing creates negative pressure in the nose, in the nasopharynx, and in the middle ear, causing middle ear pathologies in patients with hyperpatent eustachian tube.
- Nose blowing increases intranasal propelling viscous fluid into the paranasal sinuses and middle ear.
- Sneezing elevates intranasal pressure tenfold times less compared to nose blowing. However, sneezing while the nasal passages are blocked may lead to an increase in nasopharyngeal pressure, causing a failure of the valve which protects the entrance to the eustachian tube.
- The positive middle ear pressures with bilateral nasal obstruction are caused by tubal openings synchronized into the positive phase of nasopharyngeal pressure generation.
- Increase in the environmental pressure in the presence of nasal obstruction interferes with eustachian tube functioning; thus, the tube may remain closed and may be "locked." Continued increase causes barotrauma.

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The nose is located in the middle of the face and acts as an air conditioning unit, making the air that we breathe harmless for the body. Awareness of the interrelationship between the nose, middle ear, and lower airways has increased; the respiratory tract is considered to be an integrated system, and any process that affects one part of the system affects the other parts as well.

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DOI 10.1007/978-3-642-37250-6_40,

The middle ear is connected to the other air-filled spaces of the upper respiratory tract via the eustachian tube. Politzer first suggested abnormal function of the ET as a cause of ear pathology more than 100 years ago. The eustachian tube is closed in its resting stage. It opens periodically during swallowing, yawning, and possibly at times during normal respiration, causing frequent alterations in middle ear pressure and thus equalizing middle ear pressure to atmospheric pressure.

Normal functioning of the ear is closely related to, and depends on, the health status of the nose, paranasal sinuses, and the throat. Pathologies of the nose, sinuses, and nasopharynx play a very important role in the cause, treatment, and sequelae of ear disease. Upper respiratory tract infection is the most frequent cause of otitis media (Shah 1999). In some patients with nasal septal deviation, ET function may be impaired. McNicholl (McNicoll 1982) reported that the equilibration of the middle ear pressure by Valsalva maneuver in patients with septal deviation may be difficult during diving or flying in an airplane, and this situation turns to normal after correcting the septal deviation. Anatomically, the nose and paranasal sinuses can affect the function of the eustachian tube (ET) due to its localization anterior to the nasopharynx (c).

The exact mechanism between the nose, the function of ET, and middle ear pathologies is not yet well understood. There are some explanations, all related to the nose (Shah 1999):

1. Nasal obstruction followed by sniffing results in ET dysfunction or blocking, causing high negative middle ear pressure and fluid accumulation.
2. Toynbee phenomenon (following swallowing in an obstructed nose) leads to the flow of secretions to the ET.
3. Vigorous nose blowing with increased nasopharyngeal pressure pushes the secretions up to the ET.

40.1 Sniffing

Recent investigations have demonstrated an association between sniffing, sniff-induced negative middle ear pressure, and otitis media with effusion. Sniffing creates negative pressure in the nose, in the nasopharynx, and in the middle ear. The negative nasopharyngeal pressure can close a hyperpatent eustachian tube, and abnormally negative middle ear pressures can occur. Sakakihara et al. found that most of the ETs with sniff-induced OME seemed to have excessive patency and poor active opening ability but may not be hypercompliant or “floppy” (Sakakihara et al. 1993). Bylander-Groth and Stentström (1998) reported that habitual sniffing in combination with closing failure and poor active function of ET may be a possible mechanism for the development of otitis media. Falk and Magnusson reported that sniffing can evacuate the middle ear, causing high negative intratympanic pressure (Falk and Magnuson 1984a).

The purpose of the tube should be considered primarily as protecting the middle ear from the extensive pressure variations that physiologically take place in the nasopharynx, for example, during sniffing. A number of studies of diseased ears have shown that tubal malfunction was characterized mainly by a reduced ability to withstand negative pressure in the nasopharynx. Eustachian tube malfunction in these subjects is characterized by a reduced protective function, a condition denoted as “eustachian tube closing failure” (Falk and Magnuson 1984b). On the other hand, Knight and Eccles found no evidence to support the hypothesis that negative middle ear pressures are associated with sniffing (Knight and Eccles 1993). Hauser and Münker (1989) stated that the traditional concept of opening failure of ET is no longer sufficient to explain tubal dysfunction. They suggested that sniffing can cause negative pressure in the middle ear space, and sniff-induced negative pressure is a further possible cause of tubal dysfunction and plays an important factor in the development of cholesteatoma. Dempster and Browning (1989) found that a high percentage of children with otitis media with effusion are capable of inducing a negative middle ear pressure by sniffing.

Miura et al. (1998) reported that the recovery of negative middle ear pressure in 5 min without swallowing was less than 10 mm H2O in the ears with sniff-induced middle ear disease, whereas in

the ears with normal eardrum, negative middle ear pressure recovered by more than 20 mm H2O in 5 min. They concluded that sniffing plays an important role on the development of ET dysfunction and middle ear disease.

Ohta et al. (2009) found that habitual sniffing was significantly higher in cholesteatoma than in COM and in otosclerosis. The coexistence of diseases on the contralateral side was significantly higher in cases with habitual sniffing than in those without habitual sniffing. After the canal wall up method, postoperative retraction of the eardrum was significantly related to habitual sniffing continuing after the surgery. They concluded that patulous eustachian tube and habitual sniffing might play a role in pathogenesis of middle ear cholesteatoma.

40.2 Nose Blowing

Nose blowing generates high nasopharyngeal and intranasal pressures. Rapid increases in middle ear pressure and the generation of a positive middle ear pressure were associated with nose blowing (Knight and Eccles 1993). Fluid dynamic simulations revealed that the high intranasal pressures generated by nose blowing would propel viscous fluid into the paranasal sinuses. The CT experiments confirmed fluid deposition in the paranasal sinuses after nose blowing (Gwaltney et al. 2000).

40.3 Sneezing

In contrast to nose blowing, sneezing (with the nostrils open) and coughing only elevated intranasal pressure slightly and tenfold less than the mean pressure produced by nose blowing. Fluid modeling indicated that sneezing and coughing would not result in nasal fluid deposition in the paranasal sinuses. This was supported by the negative findings in the CT scan experiments (Gwaltney et al. 2000).

However, sneezing while the nasal passages are blocked can increase nasopharyngeal pressure, causing a failure of the valve which protects the entrance to the eustachian tube. Fluid and pathogens can be forced into the tube by applying a strong positive pressure to the entrance of the tube during a sneeze, when the nasal passages are blocked by swelling or as we pinch our nose closed.

40.4 Valsalva

The Valsalva technique is the technique used to equalize pressure in the tympanic cavities. The technique is to close the mouth, to pinch the nose, and to try to breathe out through the nose. The Valsalva creates a strong positive pressure in the nasopharynx, sufficient to force air into our middle ear, thus equalizing pressure and allowing fluid to drain. The pressure has to be high enough to overcome the valve created by the redundant membrane of the nasopharyngeal orifice (Bluestone and Klein 1988).

40.5 Nasal Obstruction

Swallowing causes an initial positive meso- and hypopharyngeal pressure followed by a negative pressure resulting from the interactive motions of the pharyngeal wall, soft palate, and tongue (Gramiak and Kelley 1966). These pressures which are produced in the meso- and hypopharynx during swallowing are not reflected to the nasopharynx when the nose is open. However, when the nose is obstructed, these pressures which are reflected to the nasopharynx cannot be equalized through the nose because of the nasal obstruction. Finkelstein et al. (1988) reported that nasopharyngeal pressure can be increased from −340 to +450 mm H2O during swallowing in adults with complete nasal obstruction. The positive middle ear pressures with bilateral nasal obstruction are caused by tubal openings synchronized with the positive phase of nasopharyngeal pressure generation. Thus, the usual positive middle ear to nasopharyngeal pressure gradient established by the test methods is diminished or reversed in cases of bilateral nasal obstruction (Buchman et al. 1993). Alternatively, or

complementarily, the airflow resulting from the high nasopharyngeal pressures may affect the clearance function of the eustachian tube by opposing the prograde, middle ear–nasopharynx mucociliary clearance mechanism and thus forcing the materials back to their origin in the tympanum (Buchman et al. 1999). Therefore, bilateral nasal obstruction plays a very important role *on* the function of the eustachian tube. However, this is not true for unilateral nasal obstruction. Unilateral nasal obstruction causes only low positive pressures with swallowing and consequently a minimal effect on the pressure gradient (Buchman et al. 1999).

Toynbee maneuver manually equalizes ear pressure on ascent. While the nose is closed, swallowing creates a negative pressure and will help to suck extra air pressure out of the middle ear.

40.6 Toynbee Test

Measurement of middle ear pressures as the patient swallows with the nose pinched is called Toynbee test. This is a test of eustachian tube.

40.7 Toynbee Phenomenon

Swallowing causes an initial positive meso- and hypopharyngeal pressure followed by a negative pressure. These pressures which are produced in the meso- and hypopharynx during swallowing activity are reflected to the nasopharynx during swallowing with the nose closed/pinched. Therefore, swallowing while the nose is closed or obstructed causes an initial positive nasopharyngeal pressure followed by a negative pressure. Positive nasopharyngeal pressure might insufflate infected secretions into the middle ear, especially when the middle ear has high negative pressure. With negative pressure, a pliant tube could be impeded from opening and could be further obstructed functionally. This effect of swallowing when the nose is obstructed could be related to eustachian tube dysfunction and called as Toynbee phenomenon (Bluestone and Klein 1988; Bluestone 2005).

40.8 Otitic Barotrauma

Boyle's law states that the product of pressure times volume is constant for a given mass of confined gas as long as the temperature is constant. It is very important to understand the response of gases when subjected to pressure in order to know what happens during barotrauma because the tympanic cavity and the nasal sinuses are closed spaces full of gases. These closed spaces are aerated through the ostia in the sinuses and through the auditory tube in the middle ear. Unobstructed ventilation of the middle ear will produce no changes and no symptoms.

During an *ascent* there is a progressive reduction in pressure. According to Boyle's law when the pressure decreases, the volume becomes bigger. Therefore, during ascent, a given mass of gas contained within an elastic structure will expand. In the middle ear, this gaseous expansion will push the tympanic membrane laterally, and flow of air along the eustachian tube will follow (Benson and King 2008; Edmonds 2012a).

During a *descent*, due to an increase in the pressure, there is a decrease in volume of the middle ear gas. The eustachian tube must be opened by swallowing movements to adjust the volume. If this mechanism fails or if it is delayed, an increasing differential pressure will act on the soft nasopharyngeal end of the tube to close it. When this pressure is greater than can be generated by the tubal dilator muscles, the tube will stay closed and is said to be "locked." Thereafter, with continued descent the pathophysiological changes of barotrauma are inevitable (Benson and King 2008; Edmonds 2012a; Bluestone 2005).

To maintain equal pressure on both sides of the tympanic membrane (TM), gas must move freely between the nasopharynx and middle ear. When acute and chronic infections in the nose, nasal allergy and vasomotor rhinitis, and malformations of the nasal skeleton or other mechanisms interfere with eustachian tube functioning during changes in environmental pressure, the pressure in the middle ear either falls below ambient pressure, causing retraction of the TM, or rises above it, causing bulging. In the situation of a descent without ventilation of the middle ear, the vessels will become

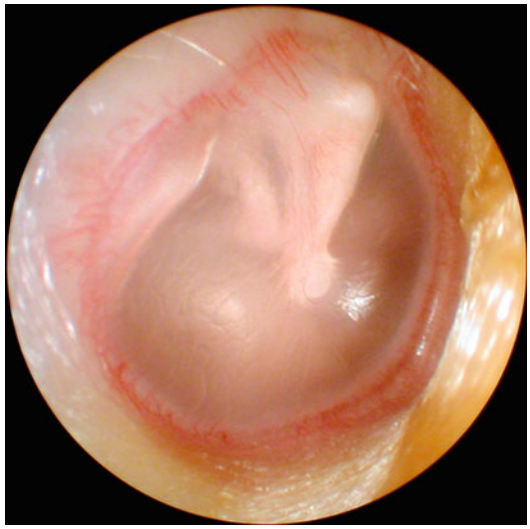

Fig. 40.1 Normal tympanic membrane, right ear

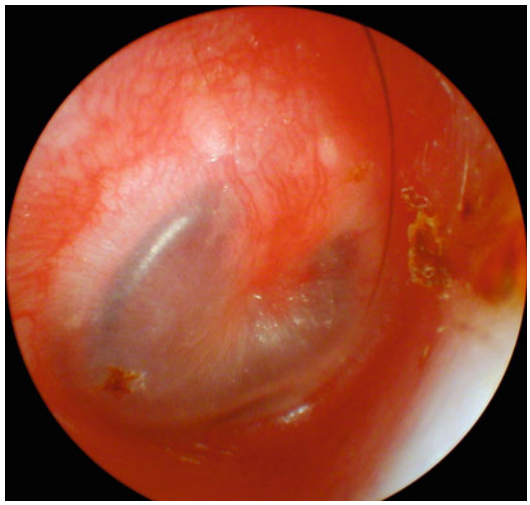

Fig. 40.2 Vascularization around the manubrium mallei due to Eustachian tube dysfunction, right ear

passively engorged due to the decreased pressure in the middle ear surrounding the vessels. As the middle ear pressure decreases, the congestion and swelling of the mucosa of the middle ear space increases. Ultimately, the blood vessels become over-distended and rupture, bleeding into the ear drum and the middle ear space. A very large pressure differential may cause bleeding into the middle ear (Bluestone 2005; Edmonds 2012a). See Figs. 40.1, 40.2, and 40.3.

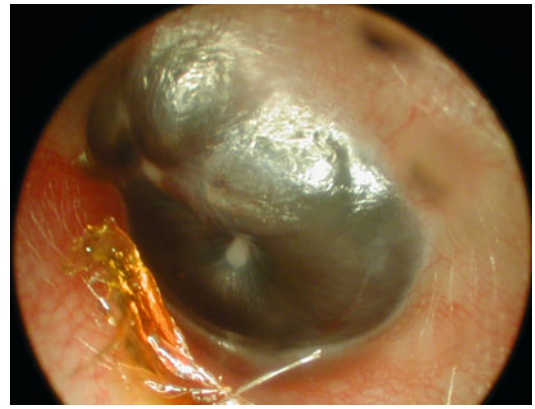

Fig. 40.3 Barotrauma during descent of the airplane, left ear, tympanic membrane is dark blue and bulging

40.9 Sinus Barotrauma

The paranasal sinuses also contain air, with the consequence that barotrauma of these structures may occur in flying and diving. As the water pressure changes during a dive, the sinuses normally equalize automatically by free passage of gas into or out of their openings. Problems are inevitable, however, if these openings become obstructed.

The production of pathology as a result of a change of pressure is directly related to the degree of patency of the sinus ostium and to the nasal function. Factors creating edema of the nasal mucosa are commonly found as predisposing causes, for example, chronic sinus inflammation (sinusitis), nasal inflammation (rhinitis), folds of tissue (polyps), coryza and its infective sequelae, vasomotor rhinitis, seasonal allergy, the effects of mechanical obstruction secondary to nasal injury, and deflection of the nasal septum. Unlike the middle ear, which can be ventilated through the eustachian tube voluntarily, there is no voluntary control over the diameter of the sinus ostium so that equalization of pressure may be difficult (Edmonds 2012b).

During descent (the compression phase) when the ostium is obstructed, the gas in the sinus will be compressed, causing barotrauma of descent (according to Boyles' law). The shrinking volume is replaced by swelling of the sinus lining, tissue fluid, or bleeding – partly filling the sinus.

If the descent continues mucosal vessels rupture and a subepithelial hematoma may develop.

If the sinus opening becomes obstructed during ascent, the gas contained in the sinus expands, causing the symptoms. This is called sinus barotrauma of ascent. Sinus barotrauma of descent is more common than ascent, but they often coexist. The degree of pathological change is proportional to the magnitude of the pressure differential and the period of time over which the pressure imbalance is unrelieved.

Conclusions

To maintain equal pressure on both sides of the tympanic membrane (TM), gas must move freely between the nasopharynx and middle ear. Sniffing, sneezing, and nose blowing may not have any significant effect on normal eustachian tubes; however, these may be the trigger factor and the cause of middle ear pathologies. Normal functioning of the ear is closely related to, and depends on, the health status of the nose, paranasal sinuses, and the throat. Pathology of the nose, sinuses, and nasopharynx has a very important role in the cause, treatment, and sequelae of ear disease. The pathologies of the nose should be treated to have a normal physiology of the ear. In other words, if the patient has an ear pathology, the nose and sinuses should be very carefully evaluated.

Bilateral nasal obstruction plays a very important role on the function of the eustachian tube. Nasal obstruction may cause high positive pressure in the middle ear and can also affect the clearance function of the eustachian tube and force the materials back to the tympanum. Nasal pathologies may interfere with eustachian tube function during changes in environmental pressure and may cause otitic barotrauma.

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