UNIVERSIDADE DE SÃO PAULO
HOSPITAL DE REABILITAÇÃO DE ANOMALIAS CRANIOFACIAIS

Natalia Bortotti Loureiro

Assessment of the internal nasal dimensions of individuals with cleft lip and/or palate and obstructive sleep apnea by computed tomography

Avaliação das dimensões internas nasais de indivíduos com fissuras labiopalatinas e apneia obstrutiva do sono por tomografia computadorizada

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Orientador: Prof. Dr. Sergio Henrique Kiemle Trindade

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“Talvez não tenha conseguido fazer o melhor, mas lutei para que o melhor fosse feito. Não sou o que deveria ser, mas Graças a Deus, não sou o que era antes”.

Martin Luther King

RESUMO

Introdução: A apneia obstrutiva do sono (AOS), tem como característica principal a obstrução mecânica intermitente das vias aéreas superiores. Estudos mostram possível associação entre obstrução nasal e risco de desordens respiratórias do sono, uma vez que, 50% dos pacientes diagnosticados com AOS, apresentaram queixas de obstrução nasal. Indivíduos com fissuras labiopalatinas (FLP) possuem alterações na morfofisiologia nasal, compondo grupo especialmente propenso a AOS. **Objetivos:** Avaliar os volumes, perímetros e áreas seccionais transversas (AST) das cavidades nasais de indivíduos com FLP e AOS ou ronco primário, por meio da análise de imagens tomográficas, comparativamente à indivíduos com AOS sem FLP (N-FLP). **Metodologia:** Os participantes foram divididos em dois grupos: G1) FLP+AOS ou ronco primário (n=11); e G2) N-FLP+AOS (n=13). A partir das tomografias computadorizadas de feixe cônico, as cavidades nasais foram segmentadas e reconstruídas por meio do software ITK- SNAP 3.8.0. No programa SpaceClaim, as geometrias 3D foram então utilizadas para a confecção de modelos CAD (Computed Aided Design), visando a mensurações de volumes, áreas e perímetros. **Resultados:** O volume total das cavidades nasais, da narina à região da válvula nasal (V1) e da válvula nasal ao limite superior da nasofaringe (V2), embora menores no grupo FLP+AOS, não diferiram significativamente do grupo N-FLP+AOS. A AST e o perímetro das regiões da válvula nasal, também não diferiram estatisticamente entre os grupos. Já, a AST e o perímetro do limite superior da nasofaringe nos pacientes do grupo FLP+AOS, foram significativamente maiores que no grupo N-FLP+AOS ($p \leq 0,05$). **Conclusão:** Em indivíduos adultos com FLP e apneicos as dimensões volumétricas, a área seccional transversa da válvula nasal e seu perímetro não parecem estar reduzidas quando comparadas as de adultos sem anomalias craniofaciais e com AOS. A influência da maior AST e perímetro na nasofaringe de pacientes com FLP+AOS em comparação aqueles sem anomalias, sobre as desordens respiratórias do sono, será o foco de estudos futuros.

Palavras-chave: Fissuras labiopalatinas. Obstrução nasal. Apneia do sono.

ABSTRACT

Background: Obstructive sleep apnea (OSA) is characterized by intermittent obstruction of the upper airways. The literature suggests a trend of association between nasal obstruction and sleep-disordered breathing, since 50% of adults with OSA report nasal obstruction symptoms. Individuals with cleft lip and/or palate (CL/P) due to an altered nasal morphophysiology, constitute a group especially prone to OSA development. **Aims:** To evaluate nasal cavity volumes, perimeters, and cross-sectional areas (CSA) of individuals with CL/P and OSA or primary snoring, by tomographic image analysis, compared to individuals with OSA without CL/P (N-CL/P). **Method**: Participants were divided into two groups: G1) CL/P+OSA or primary snoring (n=11); and G2) CL/P+OSA (n=13). From cone-beam computed tomography, the nasal cavities were segmented and reconstructed using the ITK-SNAP 3.8.0 software. In the SpaceClaim software, the 3D geometries were then used for computed aided design (CAD) models development, aiming at measuring volumes, areas, and perimeters of this anatomical structure. **Results:** Nasal cavities total volume, from the nostril to the nasal valve region (V1), and from the nasal valve to the upper limit of the nasopharynx (V2), although smaller in the CL/P+OSA group, did not differed from the CL/P+OSA group ($p>0.05$). The CSA and the perimeter of the nasal valve regions also did not differ statistically between groups ($p>0.05$). Otherwise, the CSA, and perimeter of the upper limit of the nasopharynx were significantly increased in those with CL/P+OSA than in the CL/P+OSA group ($p\leq0.05$). **Conclusions:** Nasal internal geometry of patients with CL/P and OSA did not present significant differences in relation to apneic patients without CL/P. The influence of larger cross-sectional areas and perimeters observed in the nasopharynx of patients with CL/P and OSA on sleep-disordered breathing will be the focus of future studies.

Keywords: Cleft lip and palate. Nasal obstruction. Sleep apnea.

LIST OF ILLUSTRATIONS

FIGURES

GRAPHIC

LIST OF TABLES

LIST OF ABBREVIATIONS

AHI	Apnea/Hypopnea Index
BMI	Body Mass Index
BCL/P	Bilateral Cleft Lip and/or Palate
CAD	Computer-Aided Design
CL/P	Cleft Lip and/or Palate
CBCT	Cone Beam Computed Tomography
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CP	Cleft palate
CSA	Cross-sectional area
DDS	Doctor in Dental Sciences
DICOM	Digital Imaging and Communications in Medicine
EEG	Electroencephalogram
EOG	Electrooculogram
EMG	Electromyogram
F	Frequency
FOV	Field of view
G1	Group 1
G2	Group 2
ICC	Intraclass Correlation Coefficient
Kv	Kilovoltage
mA	Milliamperage
Max	Maximum
MD	Medical Doctor
Min	Minimum
MSc	Master in Sciences
NC	Nasal Cavity
N-CL/P	With OSA without CL/P
NV	Nasal valve
NP	Nasal perimeter
OSA	Obstructive Sleep Apnea

ODI	Oxygen Desaturation Index
PhD	Philosophiae doctor
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SpO2	Oxygen Saturation
T1	First time point of assessment
T2	Second time point of assessment
UA	Upper Airway
UCL/P	Unilateral Cleft Lip and/or Palate
V1	Volumes of the nostril to the nasal valve
V2	Nasal valve to the superior limit of nasopharynx
.xstd	X-Band Stripline Tunnel Diode

SUMARY

1 General Introduction

1 INTRODUCTION

1.1 Obstructive sleep apnea

The sleep breathing disorders include the obstructive sleep apnea (OSA), whose main characteristic is the intermittent obstruction of the upper airway, caused by different mechanisms of pharyngeal collapse (GORUCU-COSKUNER et al., 2020; JENKINSON et al., 2020; JENKINSON et al. al., 1999). Due to the respiratory events, there are oxyhemoglobin desaturations and brief awakenings (MARIN et. al., 2005). Cyclic variations in oxygen saturation, combined with awakenings, constitute the basis for increased cardiovascular risk in apneic patients, due to the increase in adrenergic tone and release of free radicals, which, in summary, increases the inflammatory status and endothelial injury (PEKER et al., 2000).

However, due to the increased oxidative stress, OSA constitutes a risk factor for metabolic syndrome, since it alters the configuration of peripheral insulin receptors in adipocytes, changes the physiological control of hunger and satiety regulation, interfering with the action of leptin and ghrelin, thus increasing the cardiovascular risk (MARCUS et al., 2012). Also, frequent awakenings lead to sleep fragmentation, causing characteristic daytime symptoms, such as excessive sleepiness, decreased cognitive performance, irritability and depressive symptoms (MARCUS et al., 2012). Thus, OSA has different deleterious effects on individuals, increasing the risk of cardiovascular diseases and negatively impacting the population quality of life.

OSA is a highly prevalent disorder, affecting approximately 32% of the adult population in the city of São Paulo (TUFIK et al. 2010). However, this condition may be underdiagnosed in the general population (YOUNG et. al., 1997). The main risk factors for OSA include obesity, craniofacial malformations, hypothyroidism, male gender and individuals over 60 years of age (JENKINSON et al., 1999; MARIN et. al., 2005; TRINDADE et al. , 2020; SHADFAR et al., 2012).

The etiopathogenesis of OSA is multifactorial, with emphasis to the anatomical factors that lead to mechanical obstruction of the upper airway (UA); failure in the mechanisms of pharyngeal tonus control, due to progressively negative pressures in the upper airway lumen; low threshold for awakening and high “loop gain”, which determine different phenotypes of OSA. “Loop gain” can be understood as the response of the ventilatory control center to restrictions in respiratory volumes or changes in partial pressures of blood gases and hydrogen ions. Patients with high loop gain have a disproportionately high increase in ventilatory amplitude and flow volume in the presence of small flow restrictions or gas changes, which can lead to pharyngeal collapse and subsequent obstructive respiratory events (ECKERT et al., 2018; KOHLER; BLOCH; STRADLING, 2009; VÄRENDH et al., 2018).

For the “anatomical” phenotype, it is assumed that smaller internal nasal dimensions may constitute a risk factor for the occurrence of OSA. Studies have indicated an association between nasal obstruction and increased risk of sleep-disordered breathing (SDB), with a prevalence of this symptom in up to 50% of patients diagnosed with OSA (AN et. al., 2019; CUI et al., 2016; GEORGALAS, 2011; LOFASO et al, 2000). As a pathophysiological mechanism, it is proposed that the greater resistance to nasal airflow during sleep causes progressively more negative pressures in the upper airway, facilitating pharyngeal collapse and consequently snoring, obstructive respiratory events, sleep fragmentation and excessive daytime sleepiness (AWAD and KACKER, 2018).

Wellman et al. (2014) and Rodrigues et al. (2017) compared the upper airway to the Starling resistor model, describing the pharynx as the collapsible (flexible) region and the nasal cavities and larynx as the rigid ends of the resistor model. Greater resistance to airflow in the rigid segments (nasal cavity and larynx) would generate system instability, causing collapse of the collapsible segment, i.e., the pharynx. Thus, the association between nasal obstruction and OSA is biologically plausible. However, the relationship between the intensity of nasal obstruction, occurrence and greater severity of OSA remains controversial (TRINDADE et al., 2020).

1.2 Cleft lip and palate

Previous studies identified that individuals with cleft lip and palate (CLP) present changes in nasal morphophysiology, thus it is relevant to investigate the possible relationship with CLP as a risk factor for OSA (FUKUSHIRO et al, 2005; GANDEDKAR et al. 2017; KARIA ; SHRIVASTAV; KARIA, 2017; SOBRAL; FALLER; COLLARES, 2018; SILVESTRE et al., 2014; TRINDADE et al., 2020)

Cleft lip and palate is the most common congenital malformation in the craniofacial region, affecting 1:700 births (FREITAS et al., 2012). According to Spina et al. (1972) and Silva Filho et al. (1992), clefts can be classified into four distinct groups:

a) **Group 1 – Isolated cleft lip (pre-incisive foramen):** affect the upper lip, alveolar ridge and primary palate, reaching the incisive foramen, and can also be classified as complete (when affecting all structures involved) or incomplete (affecting only part of these structures). Concerning their location, they can be classified as unilateral, bilateral or median.
b) **Group 2 – Cleft lip and palate (trans-incisive foramen):** these affect both the upper lip, alveolar ridge, primary palate, crossing the incisive foramen and reaching the secondary palate, and can be classified as unilateral, bilateral or median.
c) **Group 3 – Isolated cleft palate (post-incisive foramen):** they exclusively affect the secondary palate, and can be complete, when they reach the entire extension of the secondary palate, involving up to the uvula; or incomplete, when they reach only a portion of this extension.
d) **Group 4:** These include clefts unrelated to the primary and secondary palate, also called rare facial clefts, which affect different orofacial structures, such as the skull, orbits, among other structures.

1.3 Cone-beam computed tomography

The evaluation of morphology and internal dimensions of the upper airway requires the use of complementary exams that allow the objective measurement

of areas and volumes. The most used methods include acoustic rhinometry, rhinomanometry, cephalometry, magnetic resonance imaging, and computed tomography (SCHWAB and GOLDBERG, 1998; ZINSLY et. al. 2010).

Computed tomography (CT) is a highly accurate method for morphological assessment of the upper airway. The modalities of this exam include the Cone Beam Computed Tomography (CBCT), which is widely used in Dentistry, because it is practical and allows visualization of different structures three-dimensionally, which was previously not possible in conventional dental radiographs (HAINTER NETO, 2013, p. 141; GARIB et. al., 2007). Lately, CBCT has been increasingly used to study the anatomy of the upper airway in patients with OSA (STEFFY E TANG 2018).

Alike CBCT, conventional CT uses X radiation for the achievement of images. Conversely, there are particularities inherent to CBCT that facilitate its use for examinations of the cephalic segment, highlighting: smaller dimensions of the equipment; conical shape of the X-ray beam, which allows the acquisition of images in volume; shorter time to acquire the image and consequently lower patient exposure to radiation (ZINSLY et al. 2010).

Routinely, the patient is positioned seated for the CBCT exam, unlike conventional CT, in which the images are obtained with the patient in supine position (SCARFE and FARMAN, 2008). However, the differences in positioning for image acquisition, for nasal volumetric evaluation, do not prevent comparison between the different methods, since unlike the pharyngeal segments, the nasal cavities, which are rigid structures, are not influenced by the action of gravity on their internal dimensions. Thus, both CBCT and conventional CT constitute a valuable tool for morphological assessment of the nasal cavities in different subgroups of patients.

1.4 Upper airway and cleft lip and palate

Fukushiro et al. (2005) demonstrated, by rhinomanometry, that the minimal nasal cross-sectional areas of adult patients with bilateral cleft lip and palate (BCLP) are smaller compared to individuals with isolated cleft palate (CP)

and without cleft. In the pediatric context, Trindade et al. (2015), evaluated, by acoustic rhinometry, the nasal internal dimensions of school-age patients with repaired unilateral cleft lip and palate (UCLP). In this study, they observed that, early in this age group, patients with UCLP had changes in the nasomaxillary complex and smaller internal nasal dimensions on the side affected by the cleft.

More recently, studies conducted by the HRAC Physiology Laboratory group demonstrated, by tomographic image analysis, that patients with UCLP and standard Class III malocclusion have smaller pharyngeal dimensions (TRINDADE-SUEDAM 2016). Subsequently, Campos et al. (2019) demonstrated that the pharyngeal dimensions of apneic patients with CLP are smaller compared to non-apneic patients with CLP.

Previously presented studies emphasize that patients with CLP have morphological changes in the upper airway that may predispose to OSA. However, the influence of anatomical changes in specific segments, especially the nasal cavities, has not yet been fully elucidated. The initial hypothesis of the present study was that patients with CLP with OSA and/or primary snoring would present smaller internal nasal dimensions than individuals with OSA without CLP. Additionally, it was hypothesized that smaller internal nasal dimensions, in both groups, could be related to greater OSA severity.

Therefore, studies that deepen the understanding of the influence of the morphophysiology of the upper airway in the genesis of OSA are necessary for a better understanding of this clinical disorder, in this special group of patients.

2 Objective

2 OBJECTIVES

- The main objective of this study was to evaluate the volumes, cross-sectional areas, and perimeters of different nasal and nasopharyngeal segments of adult individuals with cleft lip and palate who concomitantly had primary snoring and/or OSA, by tomographic image analysis, compared to individuals with apnea and without CLP.

- As a secondary objective, the study observed the occurrence of OSA in individuals with CLP, evaluating possible correlations between internal nasal dimensions and OSA severity.

3

Manuscript

3 MANUSCRIPT

The manuscript presented in this Dissertation was written according to **The Cleft Palate-Craniofacial Journal** instructions and guidelines for article submission.

Assessment of Internal Nasal Dimensions of Individuals with Cleft Lip and/or Palate and Obstructive Sleep Apnea by Computed Tomography

TITLE PAGE

Assessment of Internal Nasal Dimensions of Individuals with Cleft Lip and Palate and Obstructive Sleep Apnea Syndrome by Computed Tomography

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The Authors declare that there are no conflicts of interest.

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Running Title: Nasal dimensions in patients with CL/P and OSA

ABSTRACT

Objective: To evaluate nasal cavity (NC) dimensions of individuals with cleft lip and/or palate (CL/P) and obstructive sleep apnea (OSA), by tomographic image analysis, compared to individuals with OSA without CL/P (N-CL/P).

Design: Cross-sectional and retrospective.

Setting: Tertiary referral center.

Participants: They were divided into two groups: G1) CL/P+OSA or primary snoring, n=11; G2) N-CL/P+OSA, n=13.

Interventions: NC tomographic images were reconstructed using ITK-SNAP software and measurements were obtained from these three-dimensional models using SpaceClaim software.

Main Outcome Measures: Total NC volumes, right and left NC volumes and volumes of the nostril to the nasal valve (V1) and from nasal valve to the superior limit of nasopharynx (V2), cross-sectional areas and perimeters.

Results: NC volumes (total, right and left sides), V1, V2, though smaller in the CL/P+OSA, did not differ significantly from the N-CL/P+OSA. Cross-sectional areas and perimeters of the superior limit of the nasopharynx, in the CL/P+OSA, presented significantly higher values compared to the N-CL/P+OSA ($p \leq 0.05$).

Conclusions: Nasal internal geometry of patients with CL/P and OSA did not present significant differences in relation to apneic patients without CL/P (N-CL/P). The influence of larger cross-sectional areas and perimeters observed in the nasopharynx of patients with CL/P and OSA on sleep-disordered breathing will be the focus of future studies.

3.1 Introduction

Obstructive sleep apnea (OSA) is characterized by intermittent obstruction of the upper airways, caused by different mechanisms of pharyngeal collapse.[1,2] OSA negatively impacts the quality of life of individuals, triggering daytime symptoms, especially excessive sleepiness. Also, severe OSA is associated with greater cardiovascular morbidity and mortality, besides greater risk of car accidents and in the work environment.[3]

The risk factors for this sleep-disordered breathing include the following: obesity, craniofacial malformations, hypothyroidism, male gender and individuals over 60 years of age.[3-5] Its etiopathogenesis is multifactorial, especially involving anatomical characteristics, which can lead to mechanical obstruction of the upper airway (UA).[6-8] Individuals with OSA often present nasal obstruction. Thus, it is assumed that smaller internal nasal dimensions may constitute a risk factor for the occurrence of OSA.[9-12]

From a pathophysiological standpoint, it is proposed that the greater resistance to nasal airflow during sleep causes progressively more negative pressures in the UA, facilitating pharyngeal collapse and consequently snoring and obstructive respiratory events.[13] Comparing the UA to the Starling Resistor model, the pharynx would be the flexible (collapsible) region, while the nasal cavity and larynx would be the rigid ends; thus, a greater resistance to airflow in the rigid segments would cause system instability, leading to collapse of the flexible segment, thus biologically allowing the association between nasal obstruction and OSA.[14,15]

Since individuals with cleft lip and/or palate (CL/P) present changes in nasal morphophysiology, it is relevant to investigate the possible association between CL/P and OSA.[16-19] Despite previous studies indicating smaller internal nasal dimensions in patients with CL/P, their interrelation as a possible triggering factor for OSA in this specific group of patients has not been elucidated.

Thus, the main objective of this study was to evaluate the volumes, cross-sectional areas, and perimeters of different nasal and nasopharyngeal segments

of adult individuals with CL/P and who concomitantly had primary snoring and/or OSA, by analysis of tomographic images, compared to individuals with OSA without CL/P. As a secondary objective, the study observed the occurrence of OSA and its severity in individuals with CL/P, evaluating possible correlations between the intensity of OSA and smaller internal nasal and nasopharyngeal dimensions.

3.2 Methods

3.2.1 Design/ Setting

Retrospective cross-sectional study conducted at the Hospital for Rehabilitation of Craniofacial Anomalies – HRAC-USP, after approval by the Institutional Review Board (report n. 4.628.181).

3.2.2 Participants

The participants were divided in two distinct groups: G1 (CL/P+OSA) - the study group (n=11) consisted of patients with cleft lip and/or palate and OSA or primary snoring (4 mild/moderate OSA, 7 primary snoring); G2 (N-CL/P+OSA) - the control group (n=13) consisted of individuals with OSA (7 mild, 4 moderate, 2 severe OSA) without CL/P.

3.2.3 Interventions

Polysomnography

The exams in the G1 (CL/P+OSA) were selected from the database of Sleep Studies Unit of the Physiology Laboratory of HRAC-USP. Polysomnographic recordings were performed using an EMBLA N7000 polygraph, in type I setting, monitored by a polysomnography technician, with electroencephalogram (EEG), electrooculogram (EOG), submental electromyogram (EMG), right and left anterior tibial EMG, electrocardiogram, chest and abdominal effort plethysmographs, oronasal airflow sensors (thermistor and nasal cannula), oxygen saturation (SpO_2) and body position sensor.

The parameter used to score the intensity of OSA was the Apnea/Hypopnea Index (AHI). Patients with snoring complaints and AHI < 5 events/hour were scored as primary snoring; patients with AHI ≥ 5 and <15 events/hour as mild OSA, AHI ≥ 15 and <30 events/hour as moderate OSA, and ≥30 events/hour as severe OSA.

The exams of the G1 (CL/P+OSA) were performed before the COVID-19 pandemic; thus, they could be performed in the type I setting. The polysomnographic exams of the G2 (N-CL/P+OSA) group were performed prospectively, mostly during the COVID-19 pandemic. During this period, type I exams were interrupted in our institution. Thus, only the first 4 tests were type I. To continue the study, we selected to perform type IV polysomnography at the participants' homes (9 patients), to minimize the risk of contamination by SARS-CoV-2, using the Oxistart sensor (Biologix Sistemas Ltda., Brazil).

The Oxistart sensor is composed of an oximeter with a high sampling rate and sensitivity, which continuously analyzes data regarding oxyhemoglobin saturation, heart rate variation, patient positioning and snoring recording. Data obtained by Oxistart is continuously sent to a server for cloud storage. At completion of recording, an automated report is generated, whose main parameter analyzed is the Oxygen Desaturation Index (ODI), which measures the number of oxygen desaturations per hour of recording.[20]

A reduction of 3% or greater of the oximetry values prior to the respiratory event was considered as desaturation. Patients with a high chance of pre-test OSA, with snoring complaints and ODI < 5 events/hour were scored as primary snoring. Patients with ODI ≥ 5 and <15 events/hour were scored as mild OSA, ODI ≥15 and <30 events/hour as moderate OSA and ≥30 events/hour as severe OSA.

Cone Beam Computed Tomography (CBCT)

The CBCT scans of both groups were selected from the database of the Sleep Studies Unit, Physiology Laboratory of HRAC-USP and requested by members

of the Otolaryngology and/or Oral and Maxillofacial Surgery Sections of HRAC/USP, for different clinical indications.

The CBCT images were obtained using the i-CAT Next Generation tomograph (ISI-iCAT Imaging System – cone beam, Next Generation i-CAT®), with the following settings: field of view (FOV) of 16x13cm, exposure time of 26.9 seconds, 120Kv, 37.07mA, 0.25 voxel resolution. For image acquisition, the patients were comfortably seated on the CBCT device, being instructed to remain still, with the cephalic segment properly positioned.[21]

The images were originally generated with .xstd extension and then imported and saved in DICOM format (Digital Imaging and Communications in Medicine) to be viewed in the ITK-SNAP 3.8.0 image analysis software.

Inclusion and Exclusion Criteria

The inclusion criteria for the G1 (CL/P+OSA) were: adults with unilateral and bilateral complete cleft lip and palate or with isolated cleft palate, between 18 and 65 years old, of both genders, who underwent primary and/or secondary lip and/or palate surgeries, and who had primary snoring and OSA. The G2 (N-CL/P+OSA) included adults of both genders without cleft lip and/or palate, between 18 and 65 years old, with mild to severe OSA. Patients who underwent septoplasty, rhinoseptoplasty, turbinectomy, sinusectomy, pharyngoplasty, pharyngeal flap, or with a history of previous nasal fracture, nasal polyps or tumors were excluded from the study.

Morphometric Analysis

The nasal volumes were obtained from CBCT images in axial, sagittal and coronal planes, after delimitation of an anatomical polygon and a semiautomatic polygon (rectangle) (Figure 1 A-C). The ITK-SNAP software version 3.8.0[22] was used for semiautomatic segmentation (Figure 1 D-I) and obtention of 3D meshes (Figure 1 J). The nasal cavity limits were established according to the reference points described in Table 1.

Table 1: Anatomical boundaries of the nasal cavity considered for semi-automated segmentation.

Plane	Points or limits	Description
Axial	Posterior nasal spine	The most posterior point of the tip of the posterior nasal spine in the midsagittal plane (when present)
	Lateral pterygoid plate of the sphenoid	The most posterior point of the lateral pterygoid plates of the sphenoid, forming the medial wall of the infratemporal fossa.
	Lateral walls of the nasal cavity	The lateral wall of the right and left sides of nasal cavity, formed partly by the ethmoid bone, the perpendicular plate of the palatine bone, the medial plate of the pterygoid process of the sphenoid, medial faces of lacrimal and maxillary bones, and inferior nasal conchae bones.
	Alar crease	The most lateral point of the right and left nasal crease.
	Columella	The most anterior inferior point of the nose.
Sagittal	Sella – anterior superior	Representing the most anterior and superior point of the anterior wall of the pituitary fossa.
	Posterior nasal spine	The most posterior point of the tip of the posterior nasal spine in the midsagittal plane.
	Nasion	The most anterior point of the frontonasal suture, joining the frontal bone with nasal bones.
	Pronasale	The most anterior point of the nose.
	Columella	The most anterior and inferior point of the nose.
	Anterior nasal spine	The most anterior point of the tip of the anterior nasal spine in the midsagittal plane.
Coronal	Superior limit	A line passing through the crista Galli base, joining the mesial wall of the nasolacrimal canals.
	Lateral limits	Right and left lateral walls of the nasal cavity.
	Inferior limits	Nasal cavity floor (palatine processes of the maxilla and horizontal plates of the palatine bones).

Data were exported to the ANSYS SpaceClaim 2020 R2 software, [23] which uses the concept of reverse engineering for production of CAD (computer-aided design) models, thus allowing the achievement of solid 3D models of the 24 study participants.

The achievement of 3D models allowed measurement of the total nasal volumes (Figure 1 K), volumes of the nasal valve region (V1) and cavity body (V2) (Figure 1 L) and separate volume of the right and left cavities (Figure 1 M). Subsequently, the areas of nasal valves (right and left) and upper region of the nasopharynx were measured, as well as their respective perimeters (Figure 1 N,O).

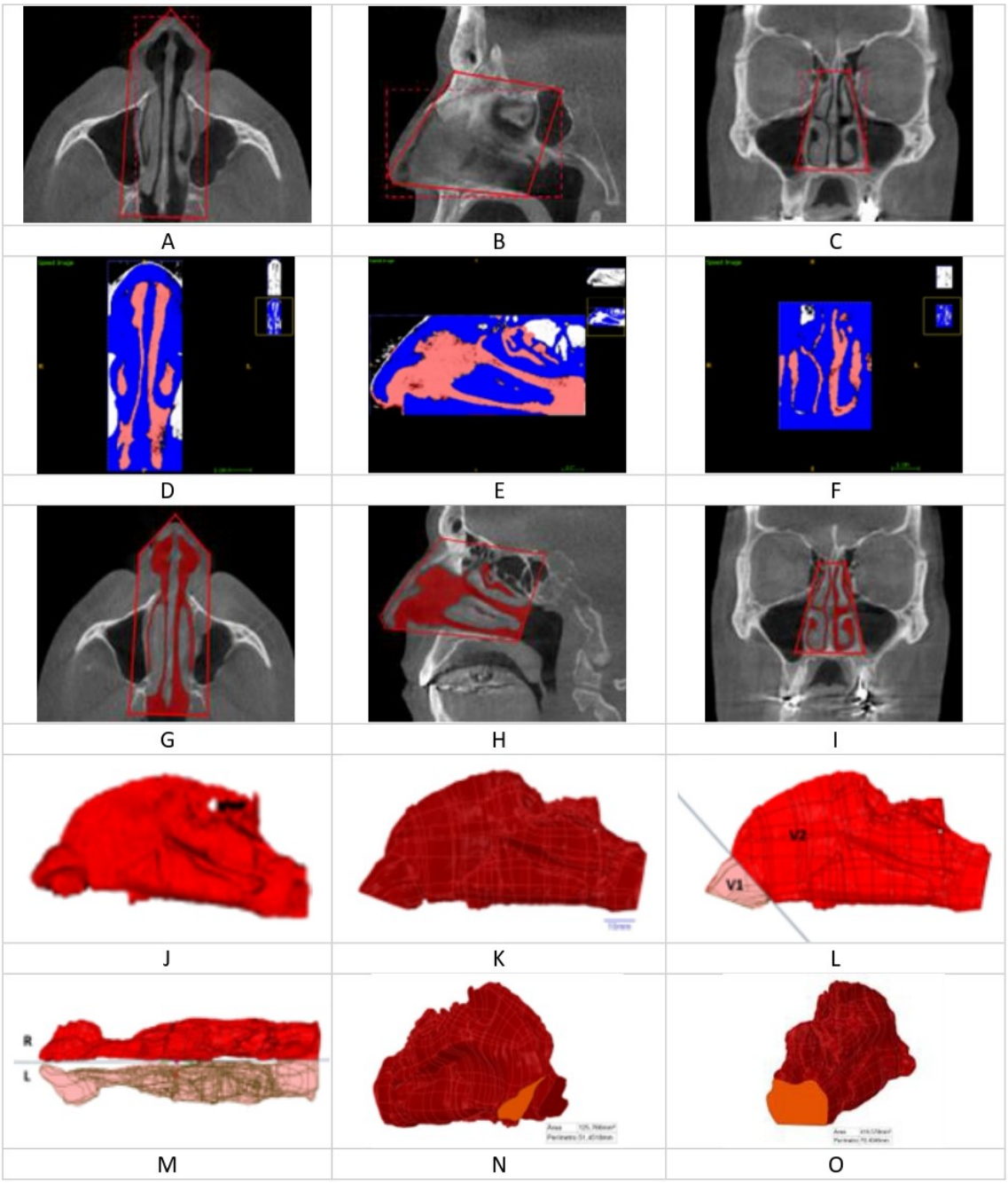


Figure 1. Delimitation of the region of interest (A-C) and semiautomatic segmentation in ITK-SNAP 3.8.0 (D-I) used for 3D meshes reconstruction (J), and computer-aided design geometries production in ANSYS SpaceClaim 2020 R2 software where measurements were obtained (K-O).

Analysis of Results

The reconstructions were performed by two trained and calibrated examiners, obtaining different nasal measurements. Examiner 1, more experienced, and examiner 2, less experienced, performed the nasal reconstructions and measurements of CBCT images at two different times (T1 and T2), with an

interval of 2 weeks between sessions. The intra- and interexaminer reproducibility was calculated using the Intraclass correlation coefficient (ICC), which adopts the following score: ICC<0.50 = weak agreement; ICC ≥0.50-0.75 = moderate agreement, ICC≥0.75-<0.90 good agreement, and ICC≥0.90 excellent agreement (Figure 2).

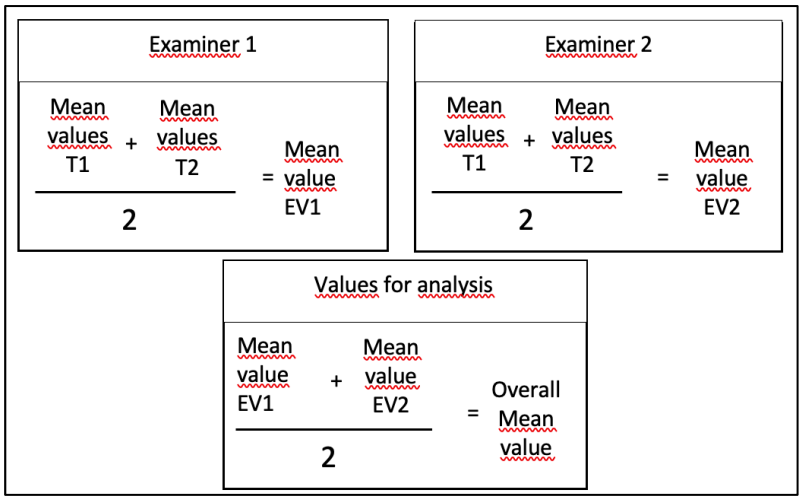


Figure 2. Method for calculation of final nasal volumes, cross-sectional areas, and perimeters, by two examiners in duplicate.

The mean values of the two examiners, obtained in the two measurements, were considered for statistical analysis. The variables were submitted to analysis of normality using the Kolmogorov-Smirnov test. For comparison of quantitative variables, data with normal distribution were presented as mean ± standard deviation and compared by the Student's t test. Variables with non-normal distribution were presented as median values and percentiles and evaluated by the Mann-Whitney test. Values of p≤0.05 were considered significant.

3.3 Results

Sample characterization

The study sample included 24 adult individuals. The G1 (CL/P+OSA) group was significantly younger, also showing a predominance of normotrophic individuals, whose body mass index (BMI) was statistically lower than the G2 (N-CL/P+OSA)

(p≤0.05). The most prevalent cleft type in the G1 (CL/P+OSA) was complete bilateral cleft lip and palate (63.3%) (Table 2).

Table 2: Characterization of the studied sample (N=24) and comparisons between groups.

Variables	Groups G1 (CL/P+OSA)	G2 (N-CL/P+OSA)	p-value
Sex (F; %)			
Male	9 (81.8%)	4 (30.8%)	-
Female	2 (18.2%)	9 (69.2%)	
BMI (kg/m²)			
Median	24.4	30.9	
25%	19.6	29.0	**≤0.05***
75%	28.0	41.3	
Cleft type (F; %)			
UCL/P	3 (27.3%)	-	
BCL/P	7 (63.3%)	-	-
CP	1 (9.1%)	-	
OSA (F; %)			
Primary snore (AHI or ODI <5 events/hour)	7 (63.6%)	0 (0.0%)	
Mild (AHI or ODI ≤5 to <15 events/hour)	3 (27.3%)	7 (53.8%)	
Moderate (AHI or ODI ≥15 to <30 events/hour)	1 (9.1%)	4 (30.8%)	-
Severe (AHI or ODI ≥30 events/hour)	0 (0.0%)	2 (15.4%)	

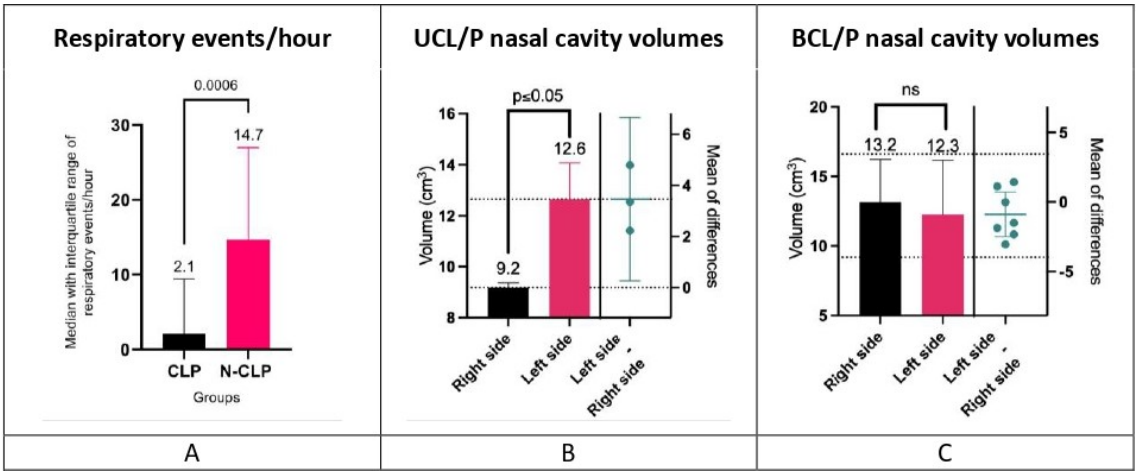
CL/P+OSA = group 1, individuals with cleft lip/palate; N-CL/P+OSA = group 2, individuals without cleft lip/palate; F = frequency; BMI = body mass index; UCL/P = unilateral cleft lip/palate; BCL/P = bilateral cleft lip/palate; CP = cleft palate; OSA = obstructive sleep apnea; AHI = apnea/hypopnea index (AHI); ODI = oxygen desaturation index; p-value ≤0.05* indicates a statistically significant difference.

Obstructive Sleep Apnea Syndrome

Table 2 summarizes the severity of OSA found in the groups. In the G1 (CL/P+OSA), there was predominance of individuals with primary snoring and mild OSA (median AHI = 2.1 events/hour; 25% = 1.7; 75% = 8.0; 95% CI min = 1.1 and max = 27.0). In the G2 (N-CL/P+OSA) there was a higher occurrence of mild, moderate, and severe OSA. Of the total number of individuals in this group (13), nine were evaluated by type IV polysomnography and four by type I polysomnography. The median ODI was 14.0 events/hour (25% = 8.4 events/hour; 75% = 23.2 events/hour; 95% CI min = 5.9 and max = 102.0), while the AHI was 16.0 events/hour (25% = 7.4; 75% = 38.1, 95% CI min = 5.0 and max = 45.0).

When considering the median values of AHI and ODI in combination for the G2 (N-CL/P+OSA), the median was 14.7 events/hour, 25% = 10.5, 75% =

24.50, 95% CI min = 5.0 and max = 102.0. The G2 (N-CL/P+OSA) had significantly higher AHI/ODI values than the G1 (CL/P+OSA) (Graph 1A; ≤0.05).



Graph 1. Boxplot graph of median values with interquartile range of respiratory events/hour in individuals with cleft lip and/or palate compared to individuals without cleft lip and/or palate (A). Comparison of right and left nasal cavity volumes in individuals with unilateral cleft lip and/or palate – UCL/P (B) and in those with bilateral cleft lip and/or palate – BCL/P (C). p-value ≤0.05* indicates a statistically significant difference.

Morphometric Analysis of the Nasal Cavity

The intra- and interexaminer reproducibility of measurements obtained to calculate the volumes, cross-sectional areas, and perimeters, showed intraexaminer ICC > 0.90 for both examiners. The interexaminer ICC was 0.85, confirming the high reproducibility of measurements.

The total volume of the nasal cavity and the right and left cavities, though smaller in the G1 (CL/P+OSA), did not differ statistically from the G2 (N-CL/P+OSA) (p>0.05). Similarly, the mean volume from the nostrils to the nasal valves (V1) and from the nasal valves to the upper limit of the nasopharynx (V2) did not differ between groups, although they were slightly lower in the G1 (CL/P+OSA) (p>0.05) (Table 3).

The areas and perimeters of the right and left nasal valves did not differ between groups (p>0.05). However, the area and perimeter of the upper limit of the nasopharynx, immediately posterior to the choanae, were statistically reduced in individuals of G2 (N-CL/P+OSA) (p≤0.05) (Table 3).

Among individuals in the G1 (CL/P+OSA), the nasal cavity volume did not differ between the right and left sides considering all types of clefts (p=0.687). However, when evaluated separately, individuals with unilateral cleft lip and palate (UCL/P) had a smaller mean volume on the right side (9.2±0.2cm^3) than on the left side (12.6±1.4cm^3) (p≤0.05) (Graph 1B).

Conversely, individuals with bilateral cleft lip and palate (BCL/P) did not show differences between volumes of the nasal cavities (right = 13.1±3.1 cm^3 vs. left = 12.3±3.9 cm^3, p=0.230) (Graph 1C). The areas of the right (UCL/P = 1.0±0.4cm^2, BCLP = 1.1±0.3cm^2) and left (UCL/P = 0.7±0.4cm^2, BCL/P= 1.0±0.4cm^2) nasal valves did not differ between each other (p>0.05) (Table 3).

Table 3: Nasal cavity mean (± standard deviation) volumes, areas, and perimeters in adults with cleft lip and/or palate and without craniofacial anomalies (N=24).

	Groups		
Variables	**G1 (CL/P+OSA)**	**G2 (N-CL/P+OSA)**	**p-value**
Volumes (cm^3)			
Total NC	25.2±6.3	28.4±5.0	0.186
Right NC	12.4±3.4	14.6±3.6	0.146
Left NC	12.7±3.3	13.7±3.1	0.473
V1	2.2±0.7	2.6±0.9	0.184
V2	23.1±5.9	25.8±4.9	0.235
Area (cm^2)			
Right NV	1.1±0.3	0.9±0.2	0.073
Left NV	0.9±0.3	0.9±0.2	0.829
NP	6.0±1.6	4.1±0.9	**0.05***
Perimeters (cm)			
Right NV	4.5±0.6	4.3±0.5	0.345
Left NV	4.1±1.1	4.4±0.5	0.356
NP	10.6±1.2	9.0±1.3	**0.05***

G1 (CL/P+OSA) = group 1, individuals with cleft lip/palate; G2 (N-CL/P+OSA) = group 2, individuals without cleft lip/palate; Total NC = total volume of the nasal cavity; Right NC = volume of the right side of the nasal cavity; Left = volume of the left side of the nasal cavity; V1 = volume from the nostril to the nasal valve; V2 = volume from the nasal valve region to the superior limit of the nasopharynx; Right NV = area/perimeter of the right nasal valve; Left NV = area/perimeter of the left nasal valve; NP = area/perimeter of the superior limit of the nasopharynx; p-value ≤0.05* indicates a statistically significant difference.

Three-dimensional CAD models of the nasal cavities of all study participants are shown in Figure 3. Qualitatively, the nasal cavities of the G1 (CL/P+OSA) were narrower in anteroposterior direction. The G2 (N-CL/P+OSA) exhibit nasal cavities with a wider aspect.

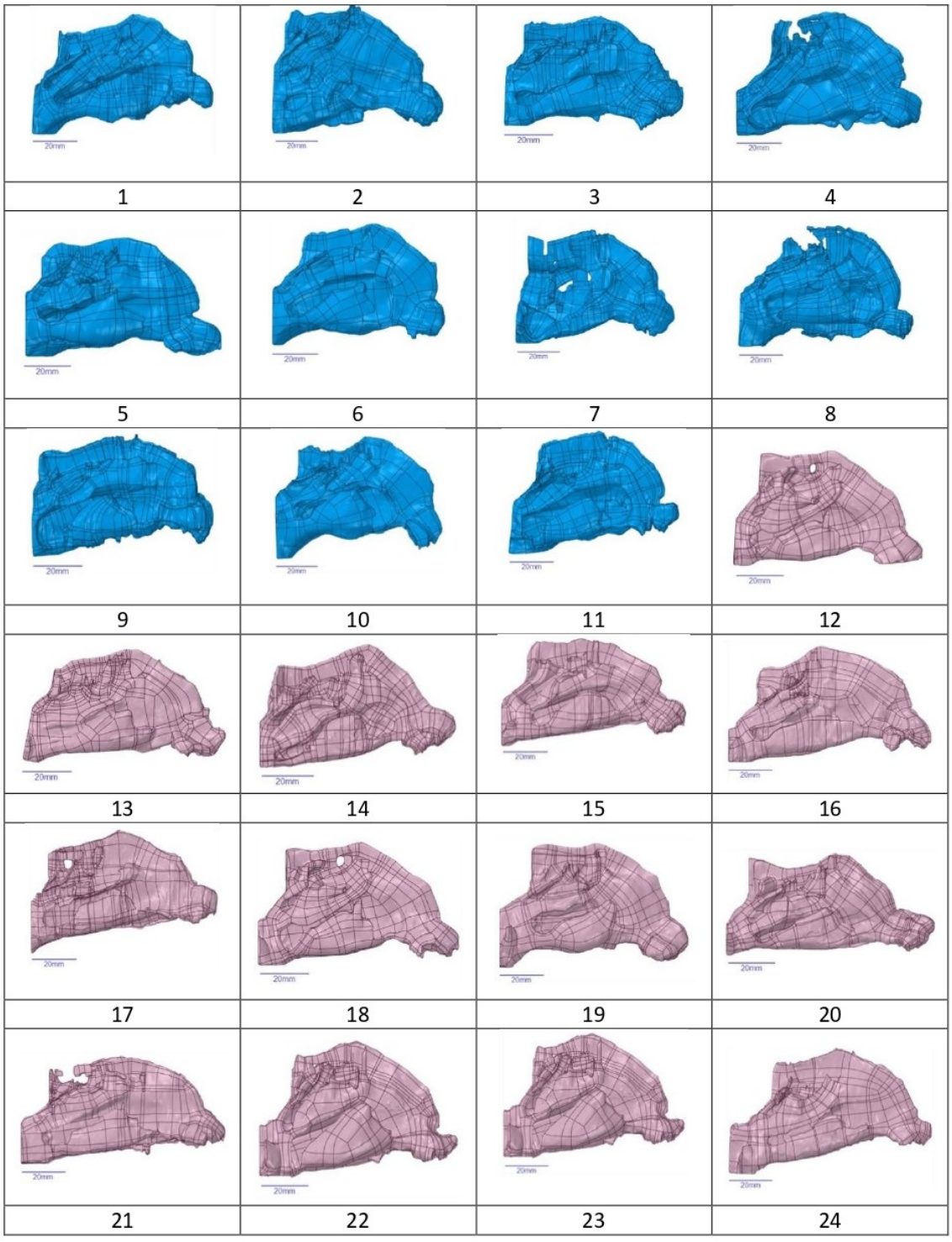


Figure 3. The CL/P+OSA group (blue computer-aided design geometries, 1-11) did not present a statistically significant different volume than the N-CL/P+OSA group (pink geometries, 12-24), as described in Table 3. However, nasal cavities geometries showed a widely variable interindividual morphology, especially among those with CL/P+OSA.

3.4 Discussion

The main objective of this study was to evaluate the internal dimensions of the nasal cavities of patients with CL/P and OSA, compared to individuals with OSA without CL/P. Also, possible associations between internal nasal dimensions and the severity of sleep-disordered breathing were evaluated.

The rationale for the study is that previous research has indicated a possible association between nasal obstruction and increased risk for OSA.[4,7-9] Studies conducted at the Physiology Laboratory of HRAC have shown that patients with CL/P have smaller internal nasal dimensions.[24-26] Thus, the initial hypothesis of the present study was that patients with CL/P would have smaller internal nasal dimensions, compared to a control group of patients with apnea without CL/P; also, that these smaller nasal dimensions would be associated with greater OSA severity.

Contradictorily, the results obtained did not demonstrate significant differences between groups for the following variables: total volume of the nasal cavities, separately volumes of right and left nasal fossae, cross-sectional areas, as well as the perimeters of different intranasal segments.

Detailed analysis of total nasal volumes showed lower values in the G1 (CL/P+OSA), yet without statistical significance. It is assumed that, with an eventual increase in the sample, this trend can be confirmed.[6-8]

The OSA severity was significantly higher in the G2 (N-CL/P+OSA) ($p \leq 0.05\%$), despite craniofacial anomalies being known to be associated with greater OSA intensity.[21,26-28] However, patients in the G2 (N-CL/P+OSA) had significantly higher BMI and age than the G1 (CL/P+OSA) ($p \leq 0.05\%$), which may justify this difference.[29]

Another factor that varied between study participants was gender, which might explain the morphological differences found between groups.[3,5] The G1 (CL/P+OSA) had predominance of males, while the G2 (N-CL/P+OSA) had a greater number of females ($p \leq 0.05\%$). Although men are more susceptible to the

development of OSA due to several factors,[30] concerning the nasal volumes, males have larger cavities than females.[31] The greater presence of females in the G2 (N-CL/P+OSA) may constitute a bias factor.

The severity of OSA was assessed and confirmed by polysomnography in both groups. In the G1 (CL/P+OSA), all patients underwent type I polysomnography, which is considered the gold standard for the diagnosis of OSA.[32] G2 (N-CL/P+OSA) was initially evaluated by type I polysomnography, according to the original study design. However, with the onset of the COVID-19 pandemic, it was decided to continue the study using type IV polysomnography. We considered this an important limitation of this study. However, as stated by Pinheiro et al.[22] there is a good correlation between AHI and ODI, which were the outcome variables used to categorize OSA severity in type I and IV polysomnography, respectively.

Cone-beam computed tomography is well recognized method to evaluate the morphology and internal geometry of the upper airway in different groups of patients,[33,34] such as rhinomanometry and acoustic rhinometry.[25,27] Thus, studies evaluating the nasal and upper airway morphology of patients with OSA and CL/P, by tomographic analysis, can contribute to a better understanding of the role of nasal cavities dimensions in the occurrence of OSA.

important finding in the present study was the difference found in relation to the area and perimeter of the upper limit of the nasopharynx. In the G1 (CL/P+OSA), greater nasopharynx area and perimeter were observed than in G2 (N-CL/P+OSA) ($p \leq 0.05\%$). It is assumed that this difference is due to the primary palatoplasty in G1 (CL/P+OSA). This procedure can lead to greater restriction of growth and development of the posterior palate, characteristically increasing the space between the soft palate and posterior wall of the nasopharynx in patients with CL/P.[35] Smaller dimensions in the nasopharyngeal region may be associated with greater severity of OSA.[27] Thus, the greater severity of OSA in the G2 (N-CL/P+OSA) may be additionally justified by these anatomical aspects.

The greater volumes of nasal cavities on the cleft side, found in patients with UCL/P may draw attention, as they oppose to results of previous studies.[25] Thus, the results of this analysis are still inconclusive.[36]

The present study has strengths and limitations. It is highlighted that the presence and severity of respiratory disorder was confirmed by polysomnographic examination, in the whole sample. Differences in demographic and morphological characteristics between groups must be considered when interpreting the results. Since most patients in the G1 (CL/P+OSA) had primary snoring and mild OSA, it must be considered whether the presence of the anomaly can be considered, in isolation, as a predisposing factor for the occurrence of OSA in its more severe forms. Studies longitudinally following patients with CL/P and sleep-disordered breathing may elucidate this complex question.

3.5 Conclusion

The analysis of nasal internal dimensions of patients with CLP and OSA did not show significant differences in relation to patients with apnea without CLP, except for the area and perimeter of the upper segment of the nasopharynx, which, contrary to the initial hypothesis, were greater in the CLP group. The internal nasal dimensions of patients with CLP do not seem to constitute a risk factor for the occurrence of OSA, as well as greater severity, in this special group of patients.

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4

General Conclusion

4 GENERAL CONCLUSION

Analysis of the nasal internal dimensions of patients with CLP and OSA showed no significant differences in relation to apneic patients without CLP, except for the area and perimeter of the upper segment of the nasopharynx, which, contrary to the initial hypothesis, were greater in the CLP group. The internal nasal dimensions of patients with CLP do not seem to constitute a risk factor for the occurrence of OSA, as well as its greater severity, in this special group of patients.

General References

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Appendix

APPENDIX A: This appendix presents, in an illustrative and complementary manner, data from the computational fluid dynamics analysis of three patients in the present study. The results presented are not the study objective of this dissertation. The present analyses were conducted on an exploratory basis and will be the object of future studies.

Introduction: Computational fluid dynamics (CFD) is a non-invasive method that simulates the flow of biological fluids. The results of CFD analyses are correlated with the findings of rhinomanometry and acoustic rhinometry. Therefore, this method may help to elucidate the biological and physical significance of the morphological characteristics of the airway in patients with CLP and OSA. **Objective:** The CFD simulation was conducted in three selected cases from a sample composed of adults with CLP+OSA (n=11) and N-CLP+OSA (n=13), to describe the airflow characteristics inside the nasal cavity. **Method:** The three cases studied were males, selected as follows: 1) bilateral CLP and primary snoring (AHI=1.1 events/hour; nasal cavity volume=29.3 cm^3), 2) bilateral CLP and moderate OSA (AHI=27.0 events/hour; nasal cavity volume=38.1 cm^3), 3) without CLP and with severe OSA (IDO=102.0 events/hour; nasal cavity volume=28.1 cm^3). The CADs of nasal cavities created in SpaceClaim (Ansys 2020R2) for the morphometric analysis were imported into the Fluent Meshing software (Ansys 2020R2), in which tetrahedral meshes with three prism layers on the wall were developed, using the Watertight Geometry model. Subsequently, in the Fluent solver (Ansys 2020R2), the physical model K-epsilon Realizable was used to simulate airflow (adiabatic and stationary) under resting ventilation conditions (15 l/min), using the finite volume method. The fluid properties were considered constant (density=1.225 kg/m^3, viscosity=$1.7894E^{-05}$ kg/m-s). The following variables were estimated: speed, pressure, wall stress and turbulent energy dissipation. **Results:** The adequate convergence and control of solution residues of the problem physics are shown in Figure 1. In the three cases, the most drastic drop in pressure values occurred from the nasal valve to the middle third of the nasal cavity (height of the middle and lower nasal concha) (Figure 2, Table 1), with greater difference in the case with CLP+OSA, even though this individual had the largest nasal cavity. Qualitative analysis suggests that the greatest gain in speed also occurs in this area (Figure 3), mainly in the same

individual. In the individual without CLP, there is a more pronounced speed gain in the upper limit of the nasopharynx than in those with CLP. The dissipation of turbulent energy followed the areas of greater pressure and speed, concentrating between the nasal valve and the middle third of the nasal cavity, in all three cases. Consequently, this generates greater stress on the wall, due to the transitional flow – from laminar to turbulent – in this region (Figure 4). **Conclusion:** The anterior region of the nasal cavity seems to be a site prone to changes in pressure, speed, dissipation of turbulent energy and stress, in the three cases. The individual with CLP+OSA seems to have more altered airflow, despite the greater internal nasal volume, and lower AHI values than those without the anomaly. Maybe, besides the nasal cavity dimensions, other aspects not investigated may have contributed to the development of OSA in this patient. Based on this analysis, it is not possible to establish cause-effect relationships, but the nasal cavity dimensions do not seem to be determinant for the occurrence of OSA.

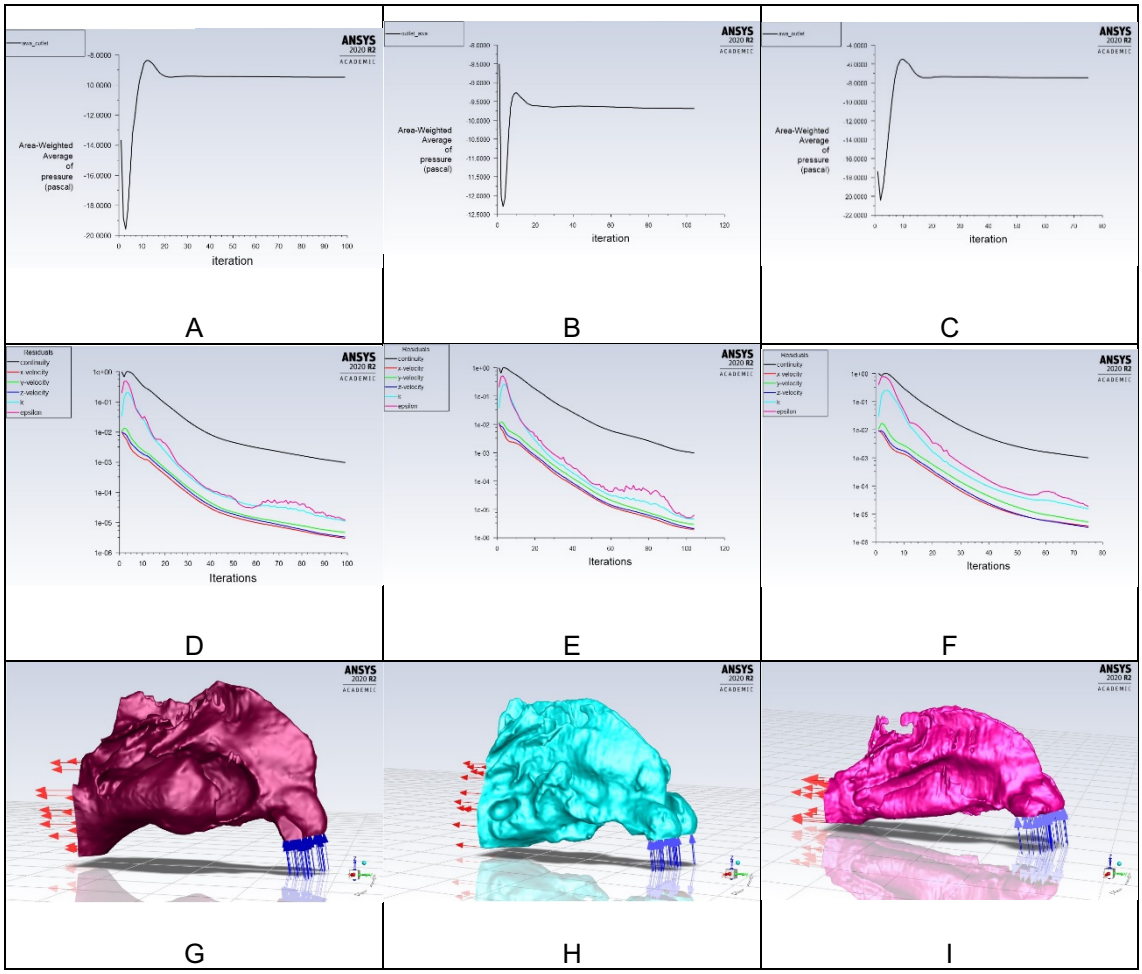


Figure 1: Statements of good practices in computational fluid dynamics analysis. Simulations iterated in time until a steady flow field was obtained, as indicated by monitors of area-weighted-average pressure set in the outlets (A-C). Residuals of equations of continuity; velocity in x, y and z plans; k and epsilon, directly quantified the error in the solution of the system equations, that were lesser than $1e^{-3}$ (D-F). Inlets and outlet of each hybrid mesh with walls of prisms and filled with tetrahedron are shown for illustrative purposes (G-I). In each case, solution imbalances were less than 1% of 0.00031 kg/s (G=$-5.1e^{-09}$, H=$4.6e^{-09}$ kg/s, I=$-3.0e^{-09}$ kg/s).

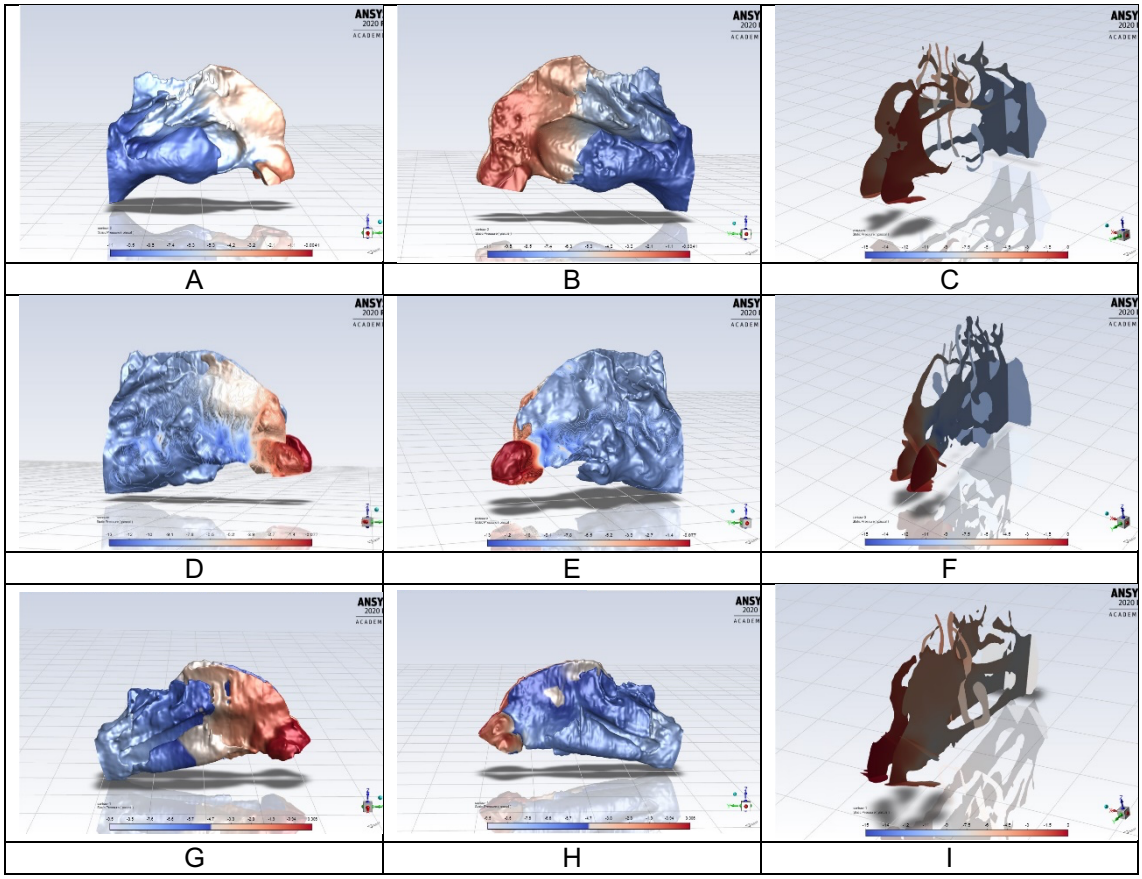
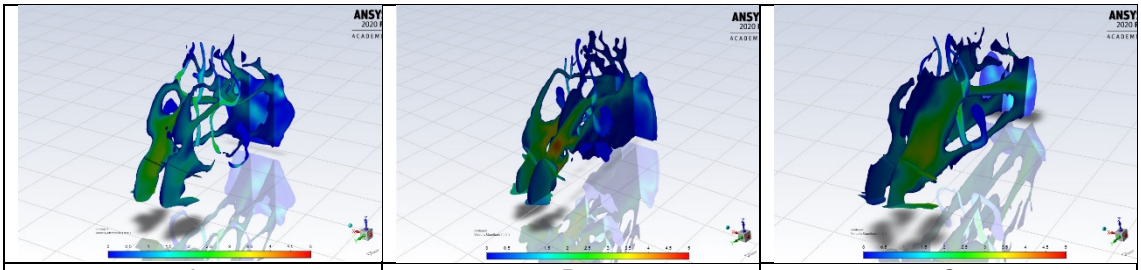


Figure 2: Qualitative computational fluid dynamics results. Walls and planes contours of static pressure in the nasal cavities of male individuals, with cleft lip palate and without obstructive sleep apnea (CL/P primary snore) (A-C; AHI = 1.1 events/hour), with cleft lip palate and obstructive sleep apnea (CL/P+OSA) (D-F; AHI = 27.0 events/hour), without cleft lip palate and with obstructive sleep apnea (N-CL/P+OSA) (G-I; ODI = 102.0 events/hour).

Table 1: Quantitative assessment of area-weighted-average static pressure (Pa) in three adults of the studied sample.

Area-weighted-average static pressure (Pa)	Fluid flow simulated cases		
	CL/P primary snore	**CL/P+OSA**	**N-CL/P+OSA**
Static pressure (Pa)			
Right inlet	-2.66	-2.57	-0.26
Left inlet	-1.04	-0.79	-2.61
Mean inlet (P1)	-1.85	-1.68	-1.43
Nasal valve	-3.13	-3.09	-2.89
Conchae	-7.33	-9.44	-5.46
Choanae	-9.56	-9.70	-7.55
Outlet (P2)	-9.47	-9.68	-7.47
Wall	-6.91	-8.55	-5.30
Right nasal cavity (yz plane)	-7.04	-8.23	-4.28
Left nasal cavity (yz plane)	-4.82	-8.65	-5.86
ΔP	7.62	8.00	6.04

CL/P primary snore = with cleft lip palate and without obstructive sleep apnea (AHI = 1.1 events/hour, nasal cavity volume = 29.31 cm^3); CL/P+OSA = with cleft lip palate and obstructive sleep apnea (AHI = 27.0 events/hour, nasal cavity volume = 38.13 cm^3); N-CL/P+OSA = without cleft lip palate and with obstructive sleep apnea (ODI = 102.0 events/hour, nasal cavity volume = 28.20 cm^3); *ΔP* = inlet pressure - outlet pressure (Pa).



A B C

Figure 3: Qualitative computational fluid dynamics results. Walls and planes contours of fluid flow velocity magnitude (m/s) in the nasal cavities of male individuals, with cleft lip palate and without obstructive sleep apnea (CL/P primary snore) (A; AHI = 1.1 events/hour), with cleft lip palate and obstructive sleep apnea (CL/P+OSA) (B; AHI = 27.0 events/hour), without cleft lip palate and with obstructive sleep apnea (N-CL/P+OSA) (C; ODI = 102.0 events/hour).

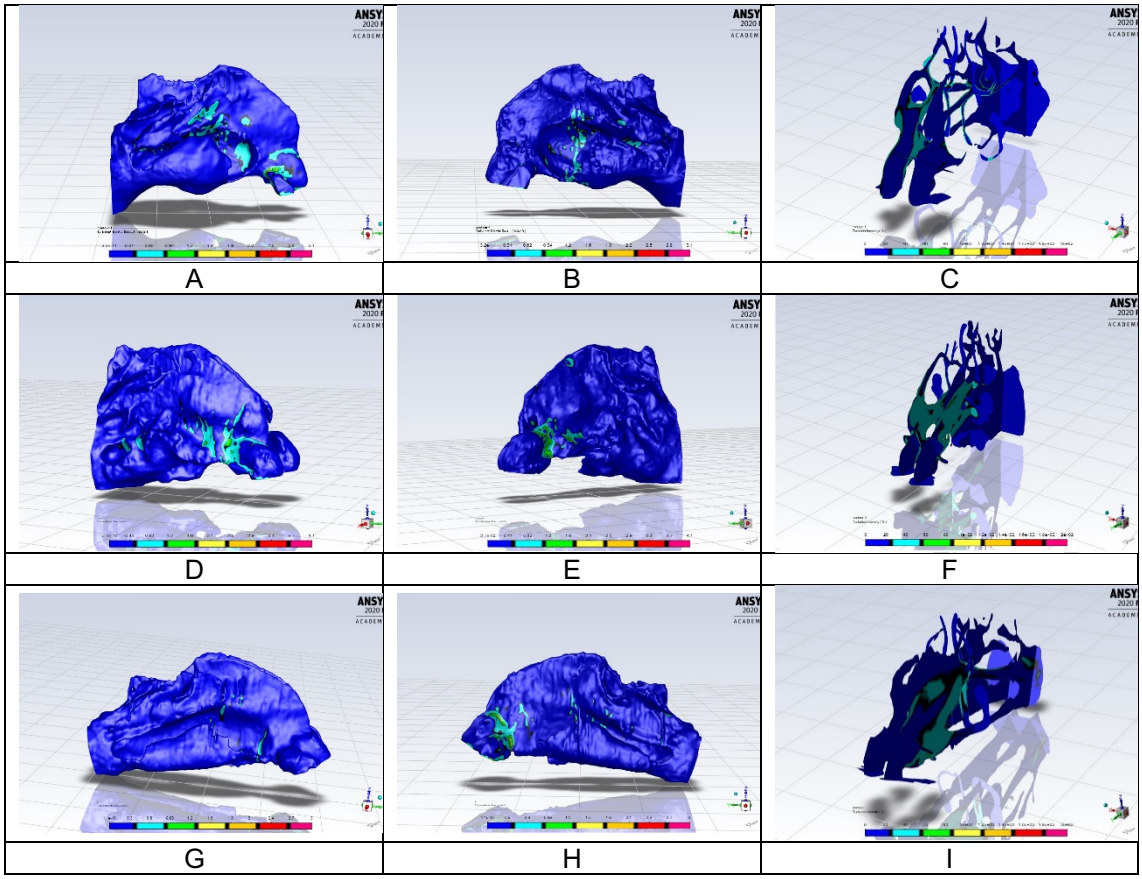


Figure 4: Qualitative computational fluid dynamics results. Contours of turbulent kinetic energy (m^2/s^2) (A,B,D,E,G,H) and turbulence intensity (%) (C,F,I) in the nasal cavities of male individuals, with cleft lip palate and without obstructive sleep apnea (CL/P primary snore) (A-C; AHI = 1.1 events/hour), with cleft lip palate and obstructive sleep apnea (CL/P+OSA) (D-F; AHI = 27.0 events/hour), without cleft lip palate and with obstructive sleep apnea (N-CL/P+OSA) (G-I; ODI = 102.0 events/hour).

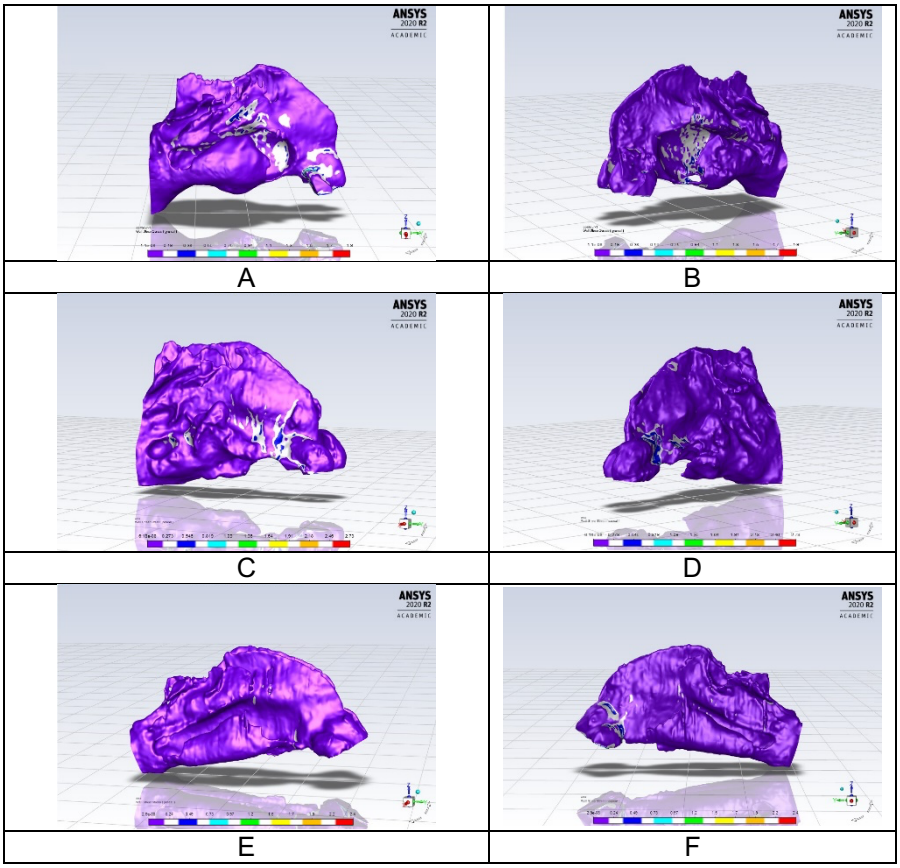


Figure 5: Qualitative computational fluid dynamics results. Contours of wall shear stress (Pa) in the nasal cavities of male individuals, with cleft lip palate and without obstructive sleep apnea (CL/P primary snore) (A,B; AHI = 1.1 events/hour), with cleft lip palate and obstructive sleep apnea (CL/P+OSA) (C,D; AHI = 27.0 events/hour), without cleft lip palate and with obstructive sleep apnea (N-CL/P+OSA) (E,F; ODI = 102.0 events/hour).

Attachments

ATTACHMENTS 1 – Declaração de uso exclusivo de artigo a ser publicado em periódico de língua inglesa

DECLARATION OF EXCLUSIVE USE OF THE ARTICLE IN DISSERTATION/THESIS

We hereby declare that we are aware of the article (Assessment of the internal nasal dimensions of individuals with cleft lip and/or palate and obstructive sleep apnea by computed tomography) will be included in Dissertation of the student Natalia Bortotti Loureiro was not used and may not be used in other works of Graduate Programs at the Bauru School of Dentistry, University of São Paulo.

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